WEBVTT

NOTE duration: ”00:29:00.160”

NOTE Confidence: 0.91246915

00:00:00.160 --> 00:00:02.000 Funding for Yale Cancer Answers

NOTE Confidence: 0.91246915

00:00:02.000 --> 00:00:03.840 is provided by Smilow Cancer

NOTE Confidence: 0.91246915

00:00:03.840 --> 00:00:04.340 Hospital.

NOTE Confidence: 0.93733364

00:00:06.399 --> 00:00:08.320 Welcome to Yale Cancer Answers

00;00;00;02 - 00;00;26;23 WNPR Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers. Director of the Yale Cancer Center is Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Dr. Winer.

00;00;27;00 - 00;00;53;02 Dr. Winer When it comes to cancer. Having the right information can make all the difference. Of course, it's critical to have the right diagnosis and as much information you can about that diagnosis. That's why researchers are constantly looking for new ways to better understand cancer and create tools that help doctors make the best treatment decisions for each and every patient. Today, we'll be talking about some exciting discoveries that are helping to do just that.

00;00;53;19 - 00;01;21;05 Dr. Winer One is a new tool that's making it easier to choose the best treatment options for women with breast cancer. The other relates to artificial intelligence and a breakthrough to improve how doctors studied the immune system and immune response in the treatment of melanoma, which I think is most of you know, is a type of skin cancer, the most worrisome type of skin cancer.

00;01;22;02 - 00;02;00;28 Dr. Winer Our guest tonight is Dr. David Rimm, who will explain how these tools work and how they're helping to make cancer care more personalized and precise. David is a pathologist, is the Anthony N. Brady professor of pathology at Yale School of Medicine, and he is perhaps first and foremost a cancer researcher at Yale Cancer Center. We'll be talking about some of his own work and we'll be talking about pathology and molecular pathology in general.

00;02;01;25 - 00;02;35;03 Dr. Winer So, David, welcome. Thanks for joining me here tonight.

Dr. Rimm Thanks for having me.

Dr. Winer So just to start off, I just want to ask you a couple of questions about pathology. And for the average listener, people are used to hearing about medical oncologists and surgeons and radiation oncologist. And they when someone's going through cancer treatment, they meet all those people.

00;02;35;03 - 00;03;12;16 Dr. Winer Pathologists are sort of back somewhere else, but they're really critical. And maybe you can just tell us for a minute about how important and you can teach your own horn how important pathology is when it comes to cancer treatment.

Dr. Rimm Thanks for this opportunity, because in fact, nobody has cancer until the pathologist says so. That is the definitive diagnosis of cancer is made by the pathologist, and any actions that are done by the oncologist or surgeons are based on that information from the pathologist.

00;03;12;16 - 00;03;49;24 Dr. Rimm So even though a patient may never see us, their treatment is highly dependent on what we say. That is absolutely the case. And I think that the best pathologists are the ones who are in in regular dialog with clinicians, with the people who are taking care of the patients, because without the right diagnosis and it's not just the diagnosis, sometimes it's questions that come up along the whole treatment course, but without that, we as clinicians are somewhat lost.

00;03;50;16 - 00;04;11;12 Dr. Winer So you all are really, really critical. How did you decide to become a pathologist?

Dr. Rimm It's a great question. I initially thought I would be a medical oncologist or even some other specialty in medicine, but then I took pathology in my second year of medicine. And back then when I was taking pathology, it was a major part of the second year.

00;04;11;23 - 00;04;31;13 Dr. Rimm I just really loved it and I thought, okay, this is what I think I'm going to I want to. I also thought it was the discipline that was closest to the patient that is that and mix science and patient care in that way that many other disciplines students and also allow time for the doctor to spend some time doing research.

00;04;31;13 - 00;05;01;28 Dr. Rimm And so that's why I chose pathology. And I'll just say to our listeners that as a clinician, I find working with great pathologists to be a complete joy.

Dr. Winer And it's something that helps so much when we when we take care of people and I just can't say how often it is that I speak to pathologists.So let's talk about the breast cancer test.

00;05;01;28 - 00;05;41;27 Dr. Winer And this is not the first that you have developed, but let's talk about your recent work in terms of looking at a new way of letting clinicians know perhaps what the best treatment approach would be.

Dr. Rimm Sure. So we've just developed an extension of a test that we've been doing for a while. And the idea is that instead of reading a tissue, which is what pathologists do when they look at it and give you their opinion, we're trying to measure, which is what happens in laboratory medicine when you get a blood glucose or something like that.

00;05;42;13 - 00;06;15;19 Dr. Rimm And that is we're trying to count the exact number of molecules for each for various drug targets that each tumor has. And so that's what we've developed. And initially we developed for one target that is HER2, which maybe many of your listeners have heard of before. So traditionally the way HER2 has been assessed is, is literally at the almost impression level.

00;06;15;28 - 00;06;42;00 Dr. Rimm So HER2 is scored on a 0 to 3 plus scale, zero one plus two plus three plus and how subjective is that? Well, we were really pathologist. Each pathologist does things a little bit differently and we're really good at telling positive from negative. But lately we've had to tell subtle differences in low range and we're really bad at that.

00;06;42;12 - 00;07;10;01 Dr. Rimm And so that's one of the reasons that we were working on this new test, is to try to answer questions about the levels of this protein when it's barely present, as opposed to when it's massively overexpressed. And in truth, even when it's clearly positive, it's turning out that there may be important clinical differences and actually having a little more quantification in theory at least, might be helpful.

00;07;10;15 - 00;07;30;28 Dr. Winer Absolutely. I agree. And that's another reason that we've been doing this. So we've got HER2, that's one part of this test. And then there's something else called TROP2. Tell us about that.

Dr. Rimm Right. So TROP2 and HER2 are both targets, and that is I like to call them like little tags on the cell and they might have functions.

00;07;30;28 - 00;07;50;06 Dr. Rimm But when you're using a new kind of therapy called an antibody drug conjugate, they're really just tags that we're not so concerned about their function but about their tagging. And so the thought behind antibody drug conjugates is the more tag you have, the more drug you can bring to the cancer cell. And so it's important to know how many tags you have.

00;07;50;16 - 00;08;08;25 Dr. Rimm And it's important, in my opinion, to know what color those tags are, if you will. That is it as a trope to tag or is it a HER2 tag? Because whichever one you have more of, theoretically that would be the one that should go with the two that patient first so that they can have the best chance of benefiting from the drug.

00;08;09;08 - 00;08;34;11 Dr. Rimm And so Trop two is one of the tags that has been less carefully assayed in the past compared to HER2. But what we've done is made an assay that can tell us essentially a number of molecules of chop to and the number of molecules of her to on cancer cells so that the oncologist

should be able to use that information to decide which of those two antibody drug conjugates to give first.

00;08;35;07 - 00;09;11;16 Dr. Winer And I realize you're not a medical oncologist, but all of this has become more important in the era of these antibody drug conjugates. And you want to just explain to our listeners what an antibody drug conjugate is.

Dr. Rimm Sure. An antibody drug conjugate I think is a real breakthrough in that it connects an antibody, which is a way of finding a specific tag on a cell to a drug that's so toxic that if you gave it to the patient without some sort of linkage, it would be too toxic to give and the patients would have a bad response.

00;09;11;16 - 00;09;35;04 Dr. Rimm So by connecting it to an antibody, you only deliver the drug just to the tumor cell that has the tag on it. And that method, as long as they drug doesn't get off of the antibody, allows you to deliver a lot of very toxic drug to just the tumor cells as opposed to having complications with that toxic drug reaching the whole patient's systems.

00;09;35;28 - 00;10;02;27 Dr. Rimm So it's a little bit like a Trojan horse and or a delivery truck. The antibody is the delivery truck. And when it gets inside the garage, the garage being inside the cell that it releases the payload or the chemotherapy drug that could be very toxic. And it's in that very specific place that it releases it. Am I getting that right?

00;10;03;09 - 00;10;26;13 Dr. Rimm And that's the exciting part about it, is that you can give it since you have that sort of delivery mechanism, you can give a much more toxic drug and much more likely to kill the cell and kill the cancer than you would otherwise be able to get by regular infusion. Now, to make this just a little bit more complicated and a little bit more confusing both for us and for patients at times.

00;10;27;09 - 00;11;10;15 Dr. Rimm Some of these antibodies in and of themselves have a therapeutic impact and some don't. So, for example, when we talk about antibody drug conjugates that are focused on HER2 antibodies to her to which are drugs like Herceptin, actually have a therapy value, whereas Trope two antibodies are just truly the passive delivery truck. Yeah, I think that that's a really important distinction, although, and I might point out that that delivery truck, there's about 260 of those delivery trucks in clinical trials now.

00;11;10;23 - 00;11;39;04 Dr. Rimm So I think this is going to be very important to be able to select the right the right address for the delivery trucks in the future.

Dr. Winer Yeah. This field has just absolutely exploded. So using this combine test, you have looking at her to intro to, how would you imagine that that would help doctors make decisions, help patients get better treatments?

00;11;39;19 - 00;12;06;03 Dr. Rimm Well, I think it's all about precision medicine or personalized medicine is that every cancer has a different biology and expresses more or less of her to or trope to. And so I think that in order to have truly personalized medicine, you need to know that patients what level of tag that patient's tumor expresses. And then if you know that level of tag, you can choose that the right drug that has in which the patient has the most tag.

00;12;06;23 - 00;12;35;09 Dr. Winer So with this one test, you could say there are a lot more trope to tags than HER2 tags, which would then prompt the clinician to give the drug the antibody drug conjugate that uses trip to as the delivery mechanism.

Dr. Rimm Exactly. Exactly. And in the future other we other pairwise tests to look at which tag is the most like the most frequent in the patient's tumor.

00;12;35;26 - 00;13;01;03 Dr. Winer And you know, this is talking about breast cancer but of course we're not just talking about breast cancer because of those hundreds of antibody drug conjugates only a small fraction of them are for women and occasionally men with breast cancer. And they're for all sorts of different diseases.

Dr. Rimm Right. So that's why we're this I think this assay will have utilization beyond breast cancer.

00;13;01;12 - 00;13;33;17 Dr. Winer But we're starting with breast cancer. And are you developing similar assays using other targets?

Dr. Rimm Yes, we've gotten a tag for EGFR is another tag we're looking at, or three is another tag had neck cancer and lung cancer have drugs in both of the for the both of those tags. So we're looking forward to expanding this kind. The concept of a specialized assay that's quantitative and can pick which tag is the correct tag for each patient's biology.

00;13;33;23 - 00;14;18;18 Dr. Rimm And not just in breast cancer, but in essentially every tumor type where there are antibody drug conjugates.

Okay. Well, we're going to have to take just a brief break. When we return, we'll continue our conversation with Dr. David Rimm, a pathologist at Yale School of Medicine and a very creative investigator who's been developing new tests. And we'll talk a little bit more when we come back about actually melanoma.

WNPR Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, which provides a multidisciplinary approach for treating appendix cancer, including advanced surgical techniques like hypothermic intraperitoneal chemotherapy.

00;14;18;29 - 00;14;57;21 WNPR Learn more at Smilow Cancer Hospital dot org. Over 230,000 Americans will be diagnosed with lung cancer this year, and in Connecticut alone, there will be over 2700 new cases. More than 85% of lung cancer diagnoses are related to smoking, and quitting, even after decades of use can significantly reduce your risk of developing lung cancer. Each day, patients

with lung cancer are surviving, thanks to increased access to advanced therapies and specialized care, new treatment options and surgical techniques are giving lung cancer survivors more hope than they have ever had before.

00;14;58;08 - 00;15;22;26 WNPR Clinical trials are currently underway at federally designated comprehensive cancer centers, such as the Battle to Trial at Yale Cancer Center and Smilow Cancer Hospital. To learn if a drug or combination of drugs based on personal biomarkers can help to control non-small cell lung cancer. More information is available at Yale Cancer Center dot org. You're listening to Connecticut Public Radio.

00;15;23;12 - 00;15;59;12 Dr. Winer Good evening again and welcome back to Yale Cancer Answers. I'm Eric Winer. And tonight I'm speaking with Dr. David Rimm, a cancer researcher and the Anthony N. Brady professor of pathology at Yale School of Medicine. We just spoke about a new personalized test that will help doctors choose therapies for women with advanced breast cancer and a test that in with some modifications could be useful in the treatment of a variety of different cancers.

00;16;00;02 - 00;16;42;22 Dr. Winer So we're now going to switch gears and we're going to talk about melanoma. David, you recently did some work that was published in JAMA Open Network about the use of artificial intelligence, which of course is just exploding in our lives and certainly in medicine. But using AI in helping to make decisions about the treatment for patients with melanoma and in fact, comparing to what I can do versus what a physiologist can do without and maybe you can tell us a little bit about this.

00;16;43;24 - 00;17;16;16 Dr. Rimm So the study was a study of melanoma tissue specimens on glass slides, and they were all scanned in so that we were looking at digital images. And then we had a machine that we built a little while ago that could identify using AI, the tumor cells versus the lymphocytes versus other stuff. And the hypothesis is that if you have more lymphocytes per tumor cell area are per line area, you're more likely to do better and have better outcomes.

00;17;17;01 - 00;18;04;15 Dr. Rimm And so what we did was had a bunch of pathologists do their reading as they normally would, to estimate the amount of lymphocytes. And then we had our machine operated by some pathologists, but sometimes operated by scientists, just run it on their machine, learning to run the machine to determine the number of lymphocytes. And what we found is that both that the machine was equivalently accurate to in terms of predicting outcome, but a lot more precise, meaning that all 60 of the people that used the machine had a very tight opinion about each slide, whereas the pathologists had somewhat more spread amongst the different the 30 different pathologists that read the slides, there was

00;18;04;15 - 00;18;43;29 Dr. Rimm more variance. And so, again, this is sort of a question about accuracy and precision given by get using a measurement as opposed to using a subjective estimate.

Dr. Winer Doesn't surprise me. Maybe you can explain to our listeners what tumor infiltrating lymphocytes are.

Dr. Rimm Sure. So whenever there's a tumor, the pathologist looks at the slide and they can see tumor cells, but they can also see a number of other kinds of cells on the slide that stained with just the routine hematoxylin of yes and stain.

00;18;44;12 - 00;19;01;08 Dr. Rimm And one of the most prominent other cell types are lymphocytes. And those are the cells that run the immune system and actually are thought to kill the tumor as well as being next to the tumor. And when there's a lot of them, needless to say that they're more likely to be successful than when there's only a few of them.

00;19;01;20 - 00;19;25;29 Dr. Winer So it's important to know how many there are, and that is useful information to determine the likelihood of the tumor being aggressive or recurring versus the tumor being cured by the resection. And does that also help us predict which patients are going to have a better or worse response to immunotherapy?

Dr. Rimm Yes, it's been used for that as well.

00;19;25;29 - 00;19;49;23 Dr. Rimm At our application in this case was the thought that is, should the patients after their surgery get immunotherapy, which is a pressing question in melanoma. Now that as they get their melanoma removed by the surgeon and then there's the option for the oncologist to give immunotherapy if they think the melanoma is going to return. But immunotherapy isn't without its toxic side effects.

00;19;50;04 - 00;20;13;19 Dr. Rimm And so if we could figure out a way with a high sensitivity and specificity to determine which patients need immunotherapy and which patients don't after their surgical resection, then that would be a valuable tool. And that's what we've done. We've just had a proof of concept at this point. And all the data is retrospective. So I think the data is sufficiently compelling that we should now try to use this test in a prospective setting.

00;20;14;16 - 00;20;43;17 Dr. Winer And you touched on the side effects of immunotherapy. And as I often tell patients, immunotherapy is either a total walk in the park and has very, very few side effects. But for a minority of patients, a relatively small minority, it can have really severe side effects. And I think that's the dilemma that many of us face, and particularly in in the hands of a melanoma doctor.

00;20;43;17 - 00;21;19;13 Dr. Winer This decision making is particularly challenging, partially because our treatment of melanoma has advanced so much that even if the melanoma recurs, patients can then often do extraordinarily well. And so it's a decision of do you give them the immunotherapy upfront, or do you wait to see if you're going to need it later? So does this mean that pathologists will be out of business and then they'll just be replaced by artificial intelligence tools?

00;21;19;25 - 00;21;50;11 Dr. Rimm So I've heard that comment from many people. And of course, any technologies that we're going to replace pathologists. But yet we're still here. And so my answer to that question is that pathologists will not be replaced by artificial intelligence, but they will be replaced by pathologists that use artificial intelligence. And so I think that it's a really it's important to understand that it's a tool, like many other tools that pathologists have in their toolbox and pathologists that don't use artificial intelligence will be replaced by those that do.

00;21;50;28 - 00;22;25;11 Dr. Winer I think that is extraordinarily well put. I think it's true of radiologists for that matter. I think it's true of medical oncologist. I think we can be way smarter using artificial intelligence than not using it. But there's still a need for the doctor in the room. And I think this is really, really a critical point. So what are the challenges that you see pathologists facing as they're beginning to use these new tools?

00;22;25;11 - 00;22;52;09 Dr. Winer And I imagine one of them is just there are some people who are resistant because as a friend of mine always says, all change is to be resisted, at least by some people.

Dr. Rimm Yeah, that's certainly true. And pathologists are not the most rapid discipline to pick up new tools, as you know. And so I think it's important that pathologists and especially junior pathologists are picking this up.

00;22;52;17 - 00;23;15;11 Dr. Rimm Certainly digital natives, the young pathologists that are now in training and early in their careers are a lot more amenable to the use of artificial intelligence because they've been using digital tools their whole life. Whereas us older guys, we didn't start using digital tools until later in our careers. But I think it's going to be critical. But again, it will never replace us because there you can't sue a machine.

00;23;15;20 - 00;23;45;28 Dr. Rim, There has to be someone that takes responsibility and has liability for patient care. And machines can't do that. You know, one of the things that's been said at times is that with AI, a pathologist can potentially sign out that many more cases in a given day. And I have no doubt that that might be the case when we worry about physician burnout and burnout of everyone in in our society.

00;23;46;15 - 00;24;19;16 Dr. Winer I think one of the concerns that's been expressed is that having this higher volume of work could in and of itself contribute to burnout. Any thoughts about that?

Dr. Rimm Yeah, so that's, I think, a really powerful use of AI and pathology that's just now coming online that allows us to only look at the interesting parts. So using AI…a number of companies have figured out a way to sort of color in the interesting parts that we need to look at and leave the other parts uncovered so that we can ignore anything except what's colored in.

00;24;19;16 - 00;24;39;29 Dr. Rim And then we focus in on that part. And by doing that, we might only have to look at 1/10 or 1/50 the number of cells that

we have to look at today. And so I think that's one of the most powerful tools will be sort of focusing the pathologists effort on where they most important pathologist judgments are required, as opposed to spending a lot of time looking at normal tissues.

00;24;40;14 - 00;25;37;11 Dr. Winer And, you know, I think that speaks to the fact that the real goal, I think with I might be a little bit to do work more efficiently, but it's also just to do work better. And if all we get out of it is doing work better, that in and of itself is is really huge. So both this work related to A.I. and the test we were talking about before in terms of quantifying HER2 and trope two are ways that we can begin to further personalize care for patients and how do you think that's going to play out over time and the whole role of more personalized, more individual lives, more tailored therapy in cancer?

00;25;38;12 - 00;25;58;06 Dr. Rimm Yeah, I think, you know, we've been seeing tailored therapy for 20 years now and it just keeps getting better and better. And I think initially, most of the most impactful, tailored, tailored therapy were when there were drugs for specific mutations. And then you test the patient by DNA sequence to see if they had that mutation. And if they did, they did well with that drug.

00;25;58;17 - 00;26;29;11 Dr. Rimm That's the first generation of personalized medicine, and it's been extremely successful and valuable to patients. I think the next generation will be you go beyond DNA sequencing and start looking at post-translational modifications or start looking at proteins or other things that also personalized tumors like ADE and can pick the right therapies like the tags on ADCs. And I think that's sort of the next generation of personalized medicine, and I predict it will have the same value that the first generation of personalized medicine had.

00;26;29;23 - 00;26;56;05 Dr. Winer And just following up on what you just said. Could you just explain what post-transplant translational work is about?

Dr. Rimm So there so the dogma is that DNA makes RNA and RNA makes protein, and that's sort of the central biology of all tumors. And so if you look at the DNA, that's kind of the first step, but it's the furthest away from function, but it's been the most successful for personalized medicine.

00;26;56;16 - 00;27;27;27 Dr. Rimm So now we get closer and closer to function using more and more sophisticated tools to measure things that are harder and harder to measure, like post-translational modifications and like protein quantities, which were now just now being able to measure accurately. As we discussed in the first half of the show.

Dr. Rimm Yeah. And then, you know, the other piece of personalized or tailored therapy is related to tailoring to the host, meaning the person, not just to the tumor.

00;27;28;11 - 00;27;57;06 Dr. Rimm Because, you know, the funny thing about

cancer is cancer is both self-meaning part of you and in some ways not self, because it's become this sort of monster, if you will. Not that all cancers are such monsters, but then there's this piece of the person themselves and the fact that different people react very differently to different therapies.

00;27;57;06 - 00;28;24;18 Dr. Rimm And I'm not talking about people's personalities, but people's DNA and RNA and what have you. Yeah, I think that it'll be very important in personalized medicine to not only personalize the medicine to the tumor, but personalize the medicine to the patient's response. And as you know, we all respond a little bit differently. That's why some patients suffer great toxicity and others less so for any given therapy.

00;28;24;29 - 00;28;49;01 Dr. Rimm And so we need to look at, again, looking at the response as well as the primary tumor for methods of personalizing medicine.

WNPR Dr. David Rimm is the Anthony N. Brady Professor of Pathology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.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.