

WNPR Radio Voice 00:00:00:02 - 00:00:27:09 Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers. The director of the Yale Cancer Center, 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.

Dr. Winer 00:00:27:26 - 00:01:02:13 I think most of you are familiar with vaccines on the topic of vaccines more generally. Vaccines, of course, are critical in preventing infectious diseases. But more recently, there's been discussion about the use of vaccines to help prevent or in some cases possibly treat cancer. And tonight, we're going to be touching on that subject with one of my colleagues, Dr. Daniel DiMaio. Dan, is the Wildfire von Edwards, professor of genetics and professor of molecular biophysics and biochemistry and of therapeutic radiology at Yale School of Medicine.

Dr. Winer 00:01:02:24 - 00:01:29:05 He's also a deputy director of the cancer center focusing on basic science. Tonight, we're going to be talking both about cancer vaccines. We're also going to be talking about the importance of basic science research as it relates to medical advances in general and more specifically, cancer advances. So, Dan, thanks so much for being with us today.

Dr. DiMaio 00:01:29:11 - 00:01:59:22 Well, thank you for having me, Eric.

Dr. Winer Could you just open up talking a little bit about vaccines in cancer and then maybe once you do that, we'll talk about some of the work that you've done or more specifically.

Dr. DiMaio So let me talk briefly about vaccines in general. First, that vaccines, I think, are really one of humanity's greatest accomplishments. They have been particularly in terms of infectious disease. They prevent thousands, millions of deaths. In fact, the only disease we've ever eradicated on Earth is smallpox. And that's because the vaccination.

Dr. DiMaio 00:01:59:22 - 00:02:31:23 So vaccines are a wonderful accomplishment of have saved many, many lives. And we hope now to apply them more towards cancer. So when we think about applying vaccines to cancer, I will say that I at least years ago was a real skeptic. The idea that we could somehow either prevent or treat cancer with vaccines seemed a little far-fetched. But what we've seen in recent years is there's been a tremendous amount of progress there.

Dr. Winer 00:02:31:27 - 00:03:00:06 And what's led to that progress?

Dr. DiMaio The topic we'll talk about later. Basic science has led to the progress in many ways, of course, and both technologically and also in terms of our understanding of cancer. There actually are two vaccines that are widespread use that prevent cancer. And these are vaccines that prevent infection by viruses that can cause cancer. Vaccine against hepatitis B virus that prevents a large fraction of liver cancers.

Dr. DiMaio 00:03:00:12 - 00:03:27:19 And there's a vaccine against human papillomavirus, HPV, that prevents a variety of cancers and could conceivably lead to the eradication of cervical cancer, which is all of which is caused by virus infection.

Dr. Winer 00:03:28:01 - 00:03:56:24 But those vaccines are a little different from vaccines that specifically target the prevention of cancer. They're doing it through what what we can achieve in terms of preventing infectious disease.

Dr. DiMaio 00:03:57:01 - 00:04:24:25 Yes. And most cancers, I mean, those are two cancers where, in fact, infection can over time directly lead to cancer. But most cancers aren't caused by infectious diseases, at least as best we know. A surprisingly large fraction are about 15% of all cancer is caused by virus infection and other than human papillomavirus and hepatitis B, there are others.

Dr. DiMaio 00:04:24:25 - 00:04:51:11 Yes, there are eight viruses that can cause cancer. The two we mentioned also hepatitis C virus causes liver cancer. Epstein-Barr virus. It's a common virus, but cause cancer in a small fraction of people and cause several different types of cancer. And there were a few others. And of course, HIV is an important cause of cancer by causing immune suppression in immune dysfunction.

Dr. Winer 00:04:51:11 - 00:05:19:06 When we moved to the topic of vaccines that actually prevent or treat cancer, what's happened there?

Dr. DiMaio 00:05:19:06 - 00:05:39:26 Conceptually, we have a better understood well that in order for the immune system to work, it has to recognize four foreign proteins. And it turns out that many cancer cells express foreign proteins because they contain alterations in the DNA sequence that contain mutations.

Dr. DiMaio 00:05:39:26 - 00:06:05:17 And now, thanks to technological advances, we can sequence determine the entire DNA sequence of the tumor and find all the new mutations that are there. And some tumors have thousands of mutations. And so these are all potential targets for immune response. And so now we know that and we actually know that for individual people, we can sequence everyone's every single person's their own tumor and say, okay, you have these mutations, and they might be mutations that no one else has, but they could be mutations that could be targeted by immune response.

Dr. Winer 00:06:05:17 - 00:06:33:17 So that's a real technological change in the last several years. So does that suggest that a vaccine might have to be individualized for each person's tumor?

Dr. DiMaio 00:06:33:18 - 00:07:07:20 In some cases, yes. And I think most work that I at least that I'm familiar with in this area, that's that's the approach people are taking. You know, their hope would be they might be off the shelf vaccines where there might be common mutations that are present in everybody or every one who has the same type of tumor. But I think in the near time, I think the personalized vaccines are more likely to be developed and those personalized as vaccines work by then activating the immune system.

Dr. Winer 00:07:07:20 - 00:07:36:12 Do you think that those vaccines could in and of themselves treat a cancer? Would they would they have to be given with other various types of treatments, whether they're chemotherapy or immunotherapy?

Dr. DiMaio 00:07:36:12 - 00:08:05:07 Sure. Sure. I think, you know, ideally vaccine would be enough. But I think what we've learned over the years is that combination therapies work really well, and that's because even the best therapies, sometimes cells escape. And if you can hit a tumor with many different weapons, it's less likely to to escape. And that was really shown very clearly, again, to use a virus example with HIV, that combination therapy that targets several viral proteins is much more effective than single.

Dr. DiMaio 00:08:05:07 - 00:08:31:24 And I think that's true also. And many cancers are treated by a combination combination of different drugs. So my guess is that will probably be a combination as required.

Dr. Winer 00:08:31:24 - 00:09:01:24 And to what extent is it a problem that any given cancer may have many different types of mutations? So there could be, you know, many potential targets? I mean, that's good news. Is it ever bad news, though, in terms of the cancer's liability to escape that?

Dr. DiMaio 00:09:01:24 - 00:09:39:26 No, I don't. I don't think so. And in fact, with with standard immunotherapy, which is not vaccination, it's a different type of way to activate the immune system. The more the more mutations in general, the better. The more more sensitive the tumors are. So I, I don't think the only problem with having too many mutations is picking the right one to vaccinate against. And we'll figure that out. So I might I'm not too concerned about that.

Dr. DiMaio 00:09:39:26 - 00:10:08:06 And we don't need to vaccinate against one. We could conceivably vaccinate against the whole cocktail of mutations.

Dr. Winer 00:10:08:06 - 00:10:31:23 And how is it that you would, you know, in a given tumor with multiple different mutations? How do you pick the the best mutation? I mean, it would seem that it should be obviously present on in all the cancer cells.

Dr. DiMaio 00:10:31:23 - 00:11:05:18 Yes. And so that that's important that obviously, if there are cells that lack the mutations, they won't respond to this sort of treatment. But there are ways now both from sequencing mutations and there are also more standard methods that pathologists use that can possibly look at. But fraction of the tumor cells express the mutations. And that's another advantage to targeting multiple mutations that hopefully every cell will express at least some of them.

Dr. Winer 00:11:05:18 - 00:11:36:02 And let's imagine for a minute that within a tumor that 80% of the cells have a given mutation because there is some variability or heterogeneity within tumors. So let's imagine 20% don't. Is it possible that by virtue of activating the immune system, using the vaccine, that

those 20% that aren't targeted by the vaccine could still be susceptible to the immune system?

Dr. DiMaio 00:11:36:02 - 00:12:30:17 Absolutely. Because those cells are the actual tumor cells that are killed by the vaccine will release other products, other proteins that will further stimulate the immune system. And in fact, that is the basis for another type of novel therapy. People are trying is called oncolytic virus therapy and the idea there is that a virus might specifically grow in the tumor cells, kill the tumor cells, but in the process recruit more immune cells that will be effective.

Dr. Winer 00:12:30:17 - 00:12:57:00 Maybe you could talk a little bit about the research you've done in this area.

Dr. DiMaio 00:12:57:00 - 00:13:36:04 Yes. So we recently published a paper, and I should say the lead people were not me in this paper. I was a late comer. It was led by City Chin, who's in Department of Genetics with some very important immune consultation and work by Kari Lucas, both here at Yale. And what we were trying to do was design a way to make proteins better at stimulating the immune system so the proteins that stimulate the immune system are called antigens. And we want those proteins to be recognized by by the immune cells.

Dr. DiMaio 00:13:36:04 - 00:14:13:25 And what we discovered really mostly said he and his team discovered, was that you need the proteins to be at the cell surface, at the outside of the cell to elicit a good immune response. And basically, he developed ways to improve the cell surface expression of these proteins. And so he was able to modify the proteins. So they got to the cell surface better and therefore were better at eliciting an immune response. And what we did was he focused on infectious disease and we helped him look at a cancer model, namely some cancer cells that express known antigens.

Dr. DiMaio 00:14:13:25 - 00:14:36:17 In this case, viral antigens, and show that this method also worked for those antigens.

Dr. Winer 00:14:36:17 - 00:15:08:25 And if the mutation is somehow buried in this cell, or would that be that would be a less attractive target?

Dr. DiMaio 00:15:08:25 - 00:15:59:22 Well, no, the hope the. Right. So two issues when you want to elicit the immune response. Which is? Which is which we worked on. But you also need the targets to be at the cell surface. So yes, the that might also influence what mutations you put into your vaccine that you want, ideally cell surface proteins to be more exposed and therefore make the cells a better target. Now, the other thing I might mention, we talked about the ability to sequence how to identify mutations as being a major technological advance.

Dr. DiMaio 00:15:59:22 - 00:16:33:00 The other one is actually the development of messenger RNA or M RNA vaccines, which really have been studied for many, many years, but really only came into use during the COVID 19 pandemic. And the messenger RNA vaccines are important because they can be developed very

quickly. That typically typically vaccines take years and years to develop. The messenger RNA vaccines can be developed within months.

Dr. Winer 00:16:33:00 - 00:17:19:17 So it's a it is a huge technological advance to be able to use this new technology. And is that why we, in fact, had a COVID vaccine so quickly?

Dr. DiMaio 00:17:19:17 - 00:17:59:09 Absolutely. If we had to rely on the standard methods which are all developed, by the way, by Louis Pasteur 150 years ago, if we had to rely on that, those vaccines would be coming online like now. But tracing that to cancer treatment, that would also suggest that if you have messenger RNA vaccines, you could develop the vaccine for a given patient where you're trying to individualize the treatment relatively quickly.

Dr. DiMaio 00:17:59:09 - 00:18:42:25 Absolutely. And that's important because cancer patients, you don't want to wait, have time. Yes. And so you can imagine sequencing can be done in a day. You can imagine the vaccines could be computationally designed within a day or two. And then a few weeks later, you conceivably could have a vaccine. It's really a remarkable thing that will allow us to rapidly get vaccines developed and and used in people.

Dr. Winer 00:18:42:25 - 00:19:08:29 Well, we're going to have to take a quick break. But when we come back, we will touch on this subject just a little bit more and then get on to talking about the importance of basic science research. Again, I'm joined by our guest, Dr. Daniel DiMaio. And we'll be back with your cancer answers in just a minute.

WNPR Radio Voice 00:19:08:29 - 00:19:36:17 Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where nationally renowned breast cancer specialists deliver a compassionate, cutting-edge care. Learn more about innovative treatment options at Smilow Cancer Hospital dot org.

WNPR Radio Voice 00:19:36:17 - 00:20:09:12 The American Cancer Society estimates that more than 65,000 Americans will be diagnosed with head and neck cancer this year, making up about 4% of all cancers diagnosed when detected early. However, head and neck cancers are easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and its Smilow Cancer Hospital to test innovative new treatments for head and neck cancers.

WNPR Radio Voice 00:20:09:12 - 00:20:33:26 Yale Cancer Center was recently awarded grants from the National Institutes of Health to fund the Yale Head and Neck Cancer Specialized Program of Research Excellence or SPORE to address critical barriers to treatment of head and neck squamous cell carcinoma due to resistance to immune DNA damaging and targeted therapy. More information is available at Yale Cancer Center dot org.

Dr. Winer 00:20:33:26 - 00:21:17:12 Good evening again and welcome back to the second half review. Into your answers, I'm joined tonight by our guest, Dr. Daniel DiMaio, professor of genetics at Yale School of Medicine and Yale Cancer

Center and also professor of biophysics and biochemistry, as well as therapeutic radiology. Dan, again, thanks so much for being with us. We've been talking about cancer vaccines, and I'm just curious about the likelihood that this will be something that we use somewhat routinely in the years ahead.

Dr. Winer 00:21:17:12 - 00:21:47:16 So maybe you could handicap this for us and tell us, you know, what do you think? I mean, will cancer vaccines be something that we use in the treatment of at least some number of cancers five years from now, ten years from now?

Dr. DiMaio 00:21:47:16 - 00:22:30:17 I think no question that that they will be I think there are some cancers as those work already well underway in, for example, at Yale and some form of kidney cancer. There are clinical trials that are being conducted, I think, be more likely to see use in treating cancer initially. And I think based on personalized vaccines, as I said, there already are vaccines that prevent cancer because the viruses.

Dr. DiMaio 00:22:30:17 - 00:23:30:09 But I think, you know, off the shelf, vaccines would be great. So you don't have to personalize it. But I think that's going to be a harder nut to crack. I think that's going to take more time and that's what you would need if you were going to use it to prevent cancer, because that's right. Now there's there are some and so a personalized vaccine to treat someone and someone is sick and so you can take their tumor. Yeah, you're going to want to treat rapidly and that treatment will be restricted to a few people, people that necessarily, you know, have the disease, you know, preventive vaccines.

Dr. DiMaio 00:23:30:09 - 00:23:59:05 You want to treat a lot of people. And so you have to be really, really sure that that it's appropriate to treat large numbers of people with a vaccine.

Dr. Winer 00:23:59:05 - 00:24:30:11 And let me make sure I'm getting this right. So with a personalized vaccine, you're personalizing to the tumor.

Dr. Winer 00:24:30:11 - 00:24:54:11 That's right. So the idea would be that a tumor or a biopsy would be collected from a patient and then characterized by DNA sequencing to determine what the mutations are and then a vaccine would be made. But that obviously couldn't be done in prevention where you don't have a tumor to personalize to.

Dr. Winer 00:24:54:11 - 00:25:30:09 And in terms of off-the-shelf vaccines, it would seem that those could be most useful if, you know, many, many individuals had tumors with the same characteristics.

Dr. DiMaio 00:25:30:09 - 00:26:02:24 Of course. And are there specific cancers where you think that that would be more likely to be the case? Sure. So, for example, there are some tumors that tend to have the same mutations like pancreatic cancers, for example, have a mutation in a gene called KRAS. So you could imagine using KRAS to prevent pancreatic cancer. I don't know how good an antigen it is because KRAS is not a T cell surface, but some of it might

get to the cell surface. That's what happens in cells. And so conceivably that could work, or you could have an off-the-shelf KRAS vaccine that could also be used for treatment, potentially.

Dr. DiMaio 00:26:02:24 - 00:26:30:05 Yes. The other thing is even for preventive vaccine, you can imagine it being used for specific populations, like there were mutations, for example, people well known in BRCA1 and BRCA2 that predispose people to breast and other cancers. So you can imagine people who have a genetic predisposition to tumors might benefit from a vaccine that you wouldn't necessarily want to give to the entire population.

Dr. Winer 00:26:30:05 - 00:26:59:09 But let me just ask you a question about that. So in the setting of somebody with a BRCA1 or BRCA2 mutation or there are other cancer-predisposing mutations, one of the issues is that every cell in that person's body has a BRCA1 or BRCA2 mutation. So would you be concerned that the vaccine could have effects beyond preventing cancer in terms of somehow causing damage to normal tissues?

Dr. DiMaio 00:26:59:09 - 00:27:30:05 Yes, I'm not suggesting that we would vaccinate against BRCA1 or BRCA2. I'm suggesting that we could use that to identify people who should be vaccinated with an antigen that is present in the cancer.

Dr. Winer 00:27:30:05 - 00:28:00:05 That is likely to be present in cancer.

Dr. DiMaio 00:28:00:05 - 00:28:29:09 Correct. So essentially identifying a very high-risk group exactly where, in fact, there would be that much more benefit. Yeah. So, for example, there's a common mutation in a gene called HER2 in breast cancer. And you could imagine that might be a better target for people who happen to have, although I don't know if that mutation's common in those people, but you can imagine some sort of scenario like that.

Dr. Winer 00:28:29:09 - 00:28:55:24 All right. So maybe we can transition a little bit at the moment and talk about the importance of basic science research. I think a lot of people, when they think about cancer research, think about clinical trials, they think about science and as being important underlying everything. But I think people at times don't understand how critical that science is in terms of developing new treatments.

Dr. DiMaio 00:28:55:24 - 00:29:52:03 Absolutely it is. It's everything is built on a foundation of basic science. Even the most applied, clinically relevant work is all based on decades of work, understanding how cells grow, how tumors form, how genes are expressed. It's all based on basic science. And the analogy I like to give is it's like sending a person to the moon that you have. You have the rocket scientists and engineers and the NASA people and the astronauts who actually get there. But it's all based on Newtonian mechanics and Kepler orbiting the planets. So it's all based on work that is often done. We don't know what its ultimate application will be.

Dr. Winer 00:29:52:03 - 00:30:20:17 Well, you know, I often say that no drug

goes from the laboratory to the pharmacy shelf without a clinical trials component. In the same way, though, there's no drug or at least no smart drug or drug that's likely to be very effective that's going to be developed without understanding the fundamental biology of the cancer, because otherwise it's just hit or miss.

Dr. DiMaio 00:30:20:17 - 00:31:23:00 Yeah, actually, I think a nice example actually goes back to M RNA vaccine story that people have been working on that for for many years. And in fact, many people thought it would would never work. And the key breakthrough which won a Nobel Prize was the discovery that you can make RNAs with modified subunits that make it work better as a vaccine. And this work was difficult to get funded if people thought it would never work. But some scientists stuck with it. And that's how basic science works that you don't know if it's going to work. You may spend years studying something that ends up being a dead end, but occasionally you make breakthroughs that have unanticipated consequences.

Dr. DiMaio 00:31:23:00 - 00:32:29:29 When people started working on M RNA vaccines, the virus that causes COVID 19 had not been discovered, and there are many examples here at Yale. We have a scientist, Leaping Chien, who is studying how the immune system is regulated, and he discovered some molecules and it turned out that led to the entire field of immunotherapy. And, you know, that was totally unpredictable at the time.

Dr. Winer 00:32:29:29 - 00:32:58:01 It's unpredictable, but not entirely accidental, not.

Dr. DiMaio 00:32:58:01 - 00:33:52:03 MATT Absolutely. No. Right. You know, it's because that science was done with a certain hypothesis and with trying to better understand how the immune system works and how cells respond to different types of stimuli. But some examples are even more. I'll give you an example. Less predictable is that when people studied a system of how bacteria prevent infection by by bacterial viruses, something very far from cancer, and what they discovered was a system we call now the CRISPR system in the CRISPR system now has many applications in cancer and elsewhere to to modify genes.

Dr. DiMaio 00:33:52:03 - 00:34:30:09 So it's a very powerful approach. Again, another Nobel Prize, and that work started studying bacteria and how they defend themselves totally unpredictable.

Dr. Winer 00:34:30:09 - 00:35:02:24 Well, you know, in cancer treatment and cancer clinical trials for years, I think it's fair to say we barely had advances. We would look at new drugs that weren't necessarily developed for any rational reason. And it was really hit or miss. And it's been the past 20 to 25 years where our understanding of fundamental cancer biology has improved so much, where we've seen this explosion of new treatments.

Dr. DiMaio 00:35:02:24 - 00:35:30:09 Yes, this is a direct relationship. Abso-



lutely. The the the era of targeted therapy where we if we understand the cause of the cancer, we can we can develop drugs that are specific for that particular type of cancer, particularly well known now in some forms of leukemia and in lung cancer, for example, we can develop drugs that specifically inhibit the protein that is mutant in the cancer.

Dr. DiMaio 00:35:30:09 - 00:36:02:24 It's very exciting. And these drugs tend to have fewer side effects because they don't they don't kill every cell. In the old days, most cancer chemotherapy was developed because it killed cells that were growing.

Dr. Winer 00:36:02:24 - 00:36:29:09 So it's sort of like an atomic bomb, like an atomic bomb being set off in each individual patient.

Dr. DiMaio 00:36:29:09 - 00:36:56:00 Absolutely. And do we have many cells in our body that normally like to grow a lot, like in our intestines and our blood forming cells, for example. And so that's why a lot of these early treatments had many side effects. And the newer treatments tend to have fewer side effects because they are more specific for the for the cancer. That's all based on basic research.

Dr. Winer 00:36:56:00 - 00:37:10:17 So in our last couple of minutes, maybe we can talk just a bit about young people and training scientists. You and I are both certainly in the last third of our careers, but we desperately need young doctors, clinical researchers and, of course, basic scientists to move the field forward.

Dr. Winer 00:37:10:17 - 00:37:30:12 And yet at the moment, there are real threats to that in terms of funding for these individuals. You want to just touch on that?

Dr. DiMaio 00:37:30:12 - 00:38:30:12 Yes, we're at the point we are now in terms of being able to make these new treatments, cure people, treat them with fewer side effects because of this fantastic 80-year history of science, scientific research in the United States and elsewhere that's now at risk. There are great concerns that federal funding will be slashed. That's going to have a huge impact. It's going to have the biggest impact on the young people because they're at the stage of deciding, do I want to have a career in research? Do I want to make discoveries? Is this a stable career?

Dr. DiMaio 00:38:30:12 - 00:39:06:07 And I think there'll be some people I know there are people who are very concerned about the current funding environment and the future of scientific research everywhere, but particularly right now in the United States. And there are people, for example, that I know who are applying for postdoctoral fellowships in Europe or for faculty positions. We had one faculty member leave our department to go to Germany. And this this is a real concern that we need to keep the momentum up because we know so much, but there's still so much more to learn.

WNPR Radio Voice 00:39:06:07 - 00:39:30:12 Dr. Daniel DiMaio is a professor

of genetics, molecular biophysics and biochemistry and of therapeutic radiology at the Yale School of Medicine. If you have questions, the address is cancer answers at Yale Dot edu and past editions of the program are available in audio and written form at Yale Cancer Center dot 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.