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Welcome to Yale Cancer Answers with doctors Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and cancer specialists who are on the forefront of the battle to fight cancer. This week Dr. Anees Chagpar welcomes Dr. David Rimm. Dr. Chagpar is Director of the Breast Center at Smilow Cancer Hospital and Dr. Rimm is Professor of Pathology and of Medicine in Medical Oncology, Director of Pathology Tissue Services and Director of Translational Pathology at Yale School of Medicine. Here is Dr. Chagpar.

Chagpar David, let's start off by talking a little bit about biomarkers. What are they? We hear a lot of about biomarkers, but what are they really?

Rimm That is a great question because biomarkers mean different things to different people. And biomarkers are things that we can obtain from a patient; it might be an x-ray, it might be something in the blood, but in my specialty, it is something that we look at in the tissue, that is, after we take a little tiny piece of tissue biopsy, then we look for biomarkers in the biopsy. And what a biomarker is, is it is an indication of the likelihood of a patient doing better or worse from the disease, that is called prognostic biomarker or responding or not responding to a drug. And those are the really important biomarkers because in this era of precision or personalized medicine, we want to make sure we are giving the right drugs to the right people, and it is the biomarker that is the key in the algorithm, the piece of that puzzle is to figure out which patient gets which drug and the way you do that is with biomarker.

Chagpar So, it is not like the same biomarker shows up in the same cancer all the time?

Rimm That is exactly right. Every cancer and every drug has a different biomarker. And there are a few biomarkers that are common, and sometimes there is a biomarker that works in multiple cancers, but more commonly the biomarkers are tightly linked to the biological process that is associated with the drug. So, a biomarker might be associated with a specific drug and more than one cancer, even though it is the same drug that is being given in both of those cancers.

Chagpar So, how do we figure out what biomarkers even exist? Because you can imagine that once you know what a biomarker is and where it is and what cancers it might be in, then some really smart scientists paired up with some really rich drug company and make a drug to target that biomarker. But how do we figure out what biomarkers exist to begin with?

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Rimm That is a great question. And let us start with your own specialty, breast cancer, because breast cancer was really the pioneer area of our tissue biomarkers. That is the kind of the biomarkers where you measure something in the tumor itself. And for example, either estrogen receptor or HER2 are known biological pathways that are used in the course of the cancer's progression and the growth of the cancer. And so, we understand that given a molecule is important for the growth of the cancer, then that molecule can be the target for a drug. But that molecule does not exist in equal amounts in all cancers in all patients. And so, measuring that molecule can tell us whether or not a patient is likely to respond to a drug that targets that molecule. And HER2 is perhaps one of the best examples in breast cancer.

Chagpar But how do we figure out that HER2 or estrogen receptor or any of the biomarkers were really expressed in a particular cancer, I mean, did people kind of look at a cancer, and say "aha, there is a marker there."

Rimm Well, in the beginning, the biomarkers are not biomarkers. In the beginning the protein that ultimately becomes the biomarker is just part of the machine or part of the process of the cancer. And then as we learn about the cancers and we figure out what processes we want to target with the drugs, those same processes become something that we want to assess and then they become a biomarker because a biomarker is simply a biological way to determine what sort of classification the disease is and that allows us to then say, "Oh, if it is this disease classification because it is expressing this protein, then it is likely to respond to this drug, because this drug targets that protein."

Chagpar So, essentially, we have known for a while the biology of how cells grow and that there are certain pathways that make them grow more than others, and cancer is essentially when these growth pathways go berserk and they start growing in aberrant ways and proliferating without any of the usual regulatory signals. Is that kind of it?

Rimm Exactly.

Chagpar But, if these regulatory pathways and these growth pathways and these signaling things exists in all cells, how come these biomarkers exist in some cancers and not in other cancers?

Rimm That is because not all cancers are the same. They are kind of like different animals in the zoo in some ways where there is a zebra cancer and there is a giraffe cancer and there is a dog cancer, and they all are similar, they all have 2 eyes, a head, a nose, and all that stuff, but they are all different in the way they look, the way they act and the way they behave in the patient. And so, even though there are some things that are in

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common in all patients or in all tumors, there are also many things that are different, and those differences are often the target for a drug. And so, in the

breast example, one of the differences is that HER2 target. That HER2 target is only present in 15% of breast cancers as you know. So, if to figure out if that breast cancer is that particular type, that is HER2 positive, and then we can give them a drug for that particular type that hits the HER2 targeted pathway. The biomarker is the way we figure that out. We actually measure that and there are different ways to measure that -- you can measure the protein or you can measure DNA amplification and there are different approaches to it, but that molecule is the core of what a biomarker is.

Chagpar But we do not look at HER2 necessarily in lung cancer or in colon cancer, and yet HER2 has a growth pathway. How come lung cancers do not have HER2?

Rimm Actually, they do.

Chagpar Well, they do, some of them.

Rimm 2% of lung cancer, not very many, but 2% of lung cancers actually over-express HER2 either by amplification or some other mechanism. So, actually we are starting to look at that, and in fact, it looks like there may be a small percentage of colon cancers that do as well. And so, that sort of is the essence of a biomarker, is that the different tumors like a giraffe and an elephant use different pathways. They are different and they look different and they have different properties, and so you have to sort of figure out which of those properties are. There are some things in common. They both have tails. So, if you had a tail-specific drug that would work on both of those animals but it would not work on a snail, for example. And so, that is the kind of thing that a biomarker is, where you have to figure out whether your disease is using that specific pathway and the biomarker is the mechanism for figuring out which pathway or which category of disease you have or which animal in the zoo example. And then once you know that, you can give the right drug.

Chagpar Historically, we used to treat, and I think this is still in large part true, although the paradigm may be changing, we used to treat the animals like animals. So, we would treat breast cancer like breast cancer. There are certain drugs that work for breast cancer, certain pathways that we know are particularly expressed in breast cancer, so for example, 80% express estrogen receptor and progesterone receptor, and then there are certain other drugs completely different drugs that work better in lung cancer, and other drugs that are better in colon cancer, and we used to treat these like different phenotypes based on the cell of origin, kind of like the giraffe is different from

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the monkey is different than the zebra. But is what you are saying that because all of these animals have tails and we may have a tail-targeted drug that with these biomarkers it may completely revolutionize the paradigm of how we treat cancer?

Rimm That is exactly what is happening and it is not happening so much with HER2 because HER2 is only in 2% in lung and maybe 1% in colon, even though it is 15% in breast, but there are other biomarkers, particularly some of the ones that we are studying now, PDL1, which is an immune pathway biomarker, and that may be present in lung and in bladder and in melanoma and possibly in breast and possibly in endometrium and ovarian cancers, and so it is one of those biomarkers that may stretch across many cancers, and in fact if that is true, then those drugs will also stretch across many cancers.

Chagpar When people get biopsies these days, we do standard kind of panels right? So, for the people who may be in the audience listening and who may have had or may know people who have had breast cancer, we always stain for ER and PR and HER2. It is kind of the standard panel because a lot of our therapies are based on that. Do you think that we are moving into an era where we are going to stain for a panel of things like PDL1 and KRAS and EGFR and VEGF because we may have drugs for these?

Rimm That is exactly what is happening, and in fact, it is happened in lung cancer already. As standard is to do ER and PR and HER2 in breast cancer, it is now that standard to look for EGFR mutations which is a DNA biomarker to look for RAS and ALK translocations, which are DNA biomarkers, and now every patient that comes in since June 1, we measure PDL1 which is a protein biomarker, and so it is happening now; breast was first, but now lung has followed along and I think we have this discussion 5 years from now, there might be 10 or 15 tumors where we have standard biomarkers that go with each tumor type.

Chagpar And do you think that that panel, as costs come down and we can talk a little bit about cost, but we have certainly seen the costs of tests and the costs of sequencing and costs of all kinds of things coming down with increasing technology and increasing knowledge, that maybe we would do that same panel on all cancers because even if HER2 is only expressed in 2% of lung cancer, if it is expressed and if those patients do have the kind of response that breast cancer patients have with dual-targeted HER2 therapies. That might be a good thing. Do you think that that is going to happen where we are going to have the standard biomarker panel and every cancer is going to get that and we are going to look at the profile and say, "well let us pick the potpourri of drugs to give you."

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Rimm I think that is happening too, especially in some of the more advanced cancers, where our molecular diagnostics lab do a panel of 50 different genes on every cancer that comes in, that sort of meets that criteria. Now, those are generally late stage cancers, but they are looking for any possible mutation and many of those are mutations that would be rare in that given cancer, but if they find that mutation, that gene alteration, then there is a drug that goes with it.

And so that is I believe the future is sort of single tests, like the 50-gene assay that can be an assay for many different drugs, there are about 25 or maybe as many as 30 different drugs that are associated with specific genetic mutations that could be found by that assay.

Chagpar And so, what generally comes first – the drug or the tests for the biomarker?

Rimm Generally the drug comes first, and actually, drug companies in some ways would rather not have a biomarker, because if there is a biomarker, then they cannot get their drug to everybody. Biomarkers inherently limit the scope, they more carefully define the effectiveness of the drug. So, if you have 100,000 patients and the biomarker says only 20% of those or 20,000 are going to respond to the drug, the drug company just sold a lot less drug, and they are not thrilled about that on one hand. On the other hand, they are happy that their drug is being used more effectively, and in fact, without that biomarker, their drug might not have gotten FDA approval because it was not sufficiently effective, whereas when they use it with the biomarker, then they have a very high response rate and the drug can rapid approval. So, it is a very careful balance that drug companies try to strike between the sensitivity of their marker and the specificity or the fact that their marker will or will not pick out the right patients.

Chagpar We are going to take a short break for a medical minute. Please stay tuned to learn more information from my guest, Dr. David Rimm, and when we get back, we are going to talk more about immunotherapy. Stay tuned.

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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. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale, New Haven. More information is available at YaleCancerCenter.org.

Chagpar Welcome back this is Dr. Anees Chagpar, and I am joined tonight

by my guest, Dr. David Rimm. We are talking about the use of biomarkers, particularly for lung cancer, but really for anything. And one of the things you said, David, right before the break was you were talking about some of the biomarkers that are used in lung cancer, one of which is PDL1 and you mentioned that this could be a biomarker that potentially has utility in all kinds of cancers and is an immune marker. Now, we hear a lot of immune markers. Tell us more about what exactly that is?

Rimm That is a really exciting new area in oncology, the fact that the patient's own immune system, all of our bodies immune systems, have all the tools they need to basically kill any cancer. The problem is that the cancer figures out a way around that immune system, and in fact, most cancers are never diagnosed because they are destroyed by the patient's own immune system. And the ones that are ultimately diagnosed are the ones that get around it. So, the question is, is there a way we can sort of re-jiggle the immune system to recognize those cancers that were not recognized? And one of the key components of the immune system that shuts the immune system off so that it does not attack the body's normal cells is called PDL1. The PDL1 molecule is also known as a checkpoint molecule, and what it does is it tells the immune systems cells, one of the key cells in the immune system that does the killing of tumors and other cells that are not supposed to be there or infected by a pathogen, it tells them to shut down, so the normal tissue; for example, in the course of a normal pregnancy, the placenta expresses PDL1 so that the mother's immune system does not destroy the placenta and the fetus. And that is an example of how you need to have some way to turn the immune system off even in a normal functioning human being. But somehow, cancers figure out "oh! that's a good idea!" and so the cancer starts expressing the same protein that is expressed in the placenta called PDL1 and that fools the immune system into thinking that "oh! this is just normal, we don't have to go and kill this funny-looking organ, that is the cancer," and so that sort of a trick that the cancer uses evolves to that state, where it can then turn off the immune system. So, recently a number of different pharmaceutical companies have thought "hmm, if we can block that signaling of that PDL1 molecule, maybe the immune system will turn back on and the cancer will then be killed by the patient's own immune system." And in fact, that works, and in fact, it works so well it works better than any other chemotherapy drug

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in history so far, particularly where it really first started was a melanoma, but now in lung cancer, we are seeing rates that are as high as 20 or 25% for long-term survival, and if you add two of these immune checkpoint drugs together, we are seeing rates as high as 50 or 60%, maybe even 70% long-term survival, which is amazing for patients in a class that would have otherwise died of disease in 6 to 9 months.

Chagpar That is really interesting, so do all cancers express this PDL1?

Rimm That is the problem. Not every cancer evolves that as its defense mechanism, and probably it is only somewhere between 20 and 30% of the cancers that actually use that pathway. There might be other checkpoints or other mechanisms of getting around the immune system and so what we need is a biomarker to determine whether or not that cancer is using that pathway. Now, we can give the drug to everybody and just hope for the best, but we probably only see a response rate of 20-30% of lung cancer and may be about the same in melanoma, and now it turns out maybe about the same in triple-negative breast cancer and maybe about the same in gastric cancer and maybe about the same in head and neck cancer, they are all sort of between that 15 and 25% range, but they are all using that mechanism of PDL1-mediated checkpoint inhibition for that subset. So, the biomarker test, that is to test for the presence of that PDL1 molecule suggested if it is present, then those are the patients that are likely to respond to the drug. And in two very interesting recent trials in lung cancer; in one case, they did a study where they looked for the presence of a lot of that biomarker and then if they found a lot of that biomarker, they put the patients on the study and when they got on the study, they had a 40% response rate, which is pretty phenomenal in high-stage lung cancer. Another company at the same time put the patients on if they had just barely a sniff of it, that is, just 5% or more, and those patients did not see any advantage. So, in fact that trial failed and their drug is not approved in first-line whereas the first company's drug is approved in first-line lung cancer. And so, that is an example of how a biomarker properly selected help the pharmaceutical company find the right patients for their drugs and now they have and have been selling them, you probably have seen their ads on TV, a very effective drug for lung cancer that can give as high as a 40% response rate and 4, 5, 6 and 7-year survival in patients who would have normally succumbed to disease in less than a year.

Chagpar So, that is only for the people who have that biomarker, who have a lot of that biomarker. But, what about the people who do not, how come their immune systems allow those other cancers to still exist, even though they do not have this PDL1. Rimm That is the 10-billion-dollar question, 64,000 dollars in the old school, what other pieces of the immune system can be blocked? And we are starting to see other checkpoints that are out there that are candidates, other ways of activating the

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Immune system and deactivating the immune system are all candidate therapies that would be tried either individually or in combination and there is literally 100s of, if not 1000s of, different clinical trials now, I had heard the number of 800 clinical trials of new checkpoint markers that are combined with the PDL1 inhibitor. So, if the PDL1 gets 20%, if we combine it with biomarker X for drug target X, can we bump that number up to 40 or 50%. And those trials are underway for a very broad range of other molecules that have been already proven to play some role in the immune system's mechanisms for cell death. But

the immune system is really, really complicated and in fact, it is so complicated that even sitting here today, we probably do not completely understand the whole thing, maybe only 50 or 80% of what really goes on in terms of the immune system mechanisms. So, as we learn more about the immune system and there are lots of people working on the basic sciences and mechanisms of the immune system, we find more and more mechanisms by which cell killing and cell checkpoints can occur, and those then become targets for therapy by new drug companies or old drug companies who are looking to enhance what we have already found with PDL1.

Chagpar Are there trials ongoing now that are looking at other checkpoints aside from PDL1, like you mentioned that there were combinations, but if their tumor does not express PDL1, that does not make a whole lot of sense to give them a drug to PDL1 if they do not have it.

Rimm One example of it is a molecule called CTLA4, and there is a drug called ipilimumab that blocks CTLA4, and CTLA4 is not expressed on the tumors, but it is a way of preventing the activation of the T-cell. And so, it works in a different way, but it might actually result in increased numbers of T-cells when it is inhibited being present in the tumor, and so, it is sort of a complicated mix, but the thought is that the combination of this drug, this another checkpoint inhibitor combined with PDL1 gives you a phenotype or gives a set of processes that increase the likelihood of PDL1 working, and so that is what happen when an ipilimumab or anti-CTLA4 was actually the first immune checkpoint that was discovered and predates PDL1 and was used in melanoma where they found a small percentage, maybe about 10 or 15% of patients who would have died from their stage IV melanoma were alive 6, 8, 10 years after that time. So, even went so far as to use that small percentage of patients was cured by a single checkpoint, but they needed to add something else, and so PDL1 which is also effective as a monotherapy in combination with anti-CTLA4 is even more effective, and that is what we have seen now in many trials. And so that model is sort of being used in these 800+ other trials where the idea is let us try some other checkpoint, maybe it was effective in monotherapy or maybe it was not so effective in monotherapy, but let us combine it and see if we get some sort of synergistic effect if we can get an effect that makes the PDL1 inhibitor more effective than it is by itself or potentially is effective as a

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brand new checkpoint blocker. The PDL1 checkpoint is a member of a family called the B7 family, and Lieping Chen here at Yale is one of the fathers of this whole field. And there are other B7 family members. There is one called PDL2 and one called B7H4 and B7H5 and B7H3. So, those are all potential other checkpoints that could be targeted as therapies. Now, it turns out some of them have already been tried in trials and they do not work so well. Others are showing promise, but it is still too early to tell whether or not those will be as effective as the PDL1 biomarker. And then, there is still other ways of

modulating the immune system bio-vaccine and other mechanisms that are also now reinvigorated because of the promise of the PDL1 and the success of the PDL1 therapies.

Chagpar So, could it be that when we were talking before about the importance of biomarkers and really fixing the target on that biomarker to be appropriate for therapy, so that when you have a lot of PDL expressed, then your inhibitor works really well, and when you have a little bit, not so much. Could it be that if you have a little bit of PDL1 expressed, that is the point at which the CTL4 would be most effective?

Rimm So, that is a great question and that is in fact what there is one other the thing going on in my lab now is to ask questions, can we characterize, can we sort of invent biomarkers that are not necessarily the drug targets but tell us about the immune state of the patient. So, are the T-cells activated or are they dormant and can that status of the immune cells helps us understand the likelihood of another checkpoint molecule or some other drug working. I think that is a key future direction for immunotherapy is that understanding better how the immune system works and how we can sort of monitor that and measure that using different, perhaps biomarkers that are not necessarily drug targets but biomarkers for the immune status itself, and then use those biomarkers to figure out which drugs will be appropriate at which times.

Chagpar So, all of these therapies, I mean it is great to think about all of these therapies that can get the immune system activated and targeting this cancer and, but one of the thing that you mentioned was vaccines, which seems to me to be a really promising kind of maneuver because it could be prevent cancers altogether. Can you talk a little bit about that?

Rimm Well, the vaccines that I am aware of are not really cancer prevention vaccines. We think about a vaccine for rubella or for mumps or for hepatitis, those are vaccines that prevent the disease entirely, whereas the vaccines that we are studying now or that some people are working on now, were vaccines to combat a specific cancer. And in fact, the vaccine may even be highly specific to that cancer itself, that is, the vaccine might be designed to amplify or awaken cells to the fact that this particular cancer

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signature is present. And so, they are making some vaccines from signals from the cancer itself. There are signals called the neo-antigen that a cancer produces, that stimulates the immune systems. And so, the vaccines that I think are most active in the immuno-oncology are not the preventive vaccines that we think of getting in childhood and preventing polio. These are vaccines that are disease specific and they are personalized medicine type or precision medicine type vaccine that actually might be no preventive but curative of these specific immune-mediated cancers.

Dr. David Rimm is Professor of Pathology and of Medical Oncology, Director of Pathology Tissue Services and Director of Translational Pathology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in both audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer. You are on WNPR, Connecticut's public media source for news and ideas.