

Yale CANCER CENTER *answers*

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The Nature of Cancer Cells

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you could submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about the nature of cancer cells and lung cancer research with Dr. Katie Politi. Dr. Politi is Assistant Professor of Medicine and Medical Oncology and of Pathology at Yale School of Medicine. Here is Dr. Steven Gore.

Gore The nature of cancer cells, that is quite a topic we have for tonight. Katie, why don't you start by telling me what you do here at Yale. I understand that you are a PhD and in pathology, so slightly different than many of our guests.

Politi Yes, I am a cancer biologist and my laboratory study is in lung cancer, so we are interested in understanding how lung cells become tumor cells and once they are tumor cells, the biology of these cells, why do they grow uncontrollably and how we can treat these cancer cells so that the tumor can shrink and go away.

Gore I see, so do you work primarily with cell lines or with animals, or primary materials from patients, how does that work?

Politi My laboratory interfaces basic science and clinical medicine. We do a lot of work in preclinical models which are cell lines and mouse models of lung cancer. We do studies in cell lines because the cell lines allow us to really understand what is happening to different signals within the cancer cells and they are a little bit easier to work with and one can do some experiments a little bit faster than in more complex systems. We also use animal models because the animal models allow us to understand what is happening in the cancer cells within the organ in which the cancer develops, so we have special models in which we can study a lung cancer that develops spontaneously in the lungs of mice and study these cancer cells within that tissue in which the tumor develops, in which there are blood vessels, in which there is an intact immune system, all of the different cell types that you would find in a patient with lung cancer. We also do a lot of work with specimens from patients, and our findings in the laboratory are really helpful, but we often want to see whether what we discover in the laboratory is applicable to patients who have lung cancer and so we also study the patient's specimens. And although I am a scientist, a biologist, who has not formally trained in the clinic, I work very closely with clinicians here at Yale and we have joint meetings so that together we can understand what things we need to prioritize to study in the laboratory to improve treatment for patients.

Gore It is fascinating, do your experiments and your research projects come basically from the lab or are they stimulated by your discussions with the clinicians, how does that work?

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Politi I would say it goes both ways. Some of the molecules that we study in the lab have a lot of different partners they work with and interact with and signal within cells and so one of the things that we are very interested in is understanding on a basic level how these molecules work, and so we will dig deep from a basic science way of doing experiments to understand how the molecules function, because we are really interested in understanding what is happening in those cancer cells. At the same time though, the ultimate objective of a lot of the work that we do in the lab is trying to improve therapies, so when we have meetings with the clinicians, we talk about the best way of trying to overcome some of the clinical problems. One of the issues that we are very interested in in the lab, for example, is studying resistance to different therapies, and we study a molecule called the epidermal growth factor receptor, EGF receptor which is very frequently mutated or altered in adenocarcinomas, a type of lung cancer, and there are really good drugs that can block the activity of this EGF receptor when it is mutated in these lung cancers and this has improved treatment of patients with this type of lung cancer, but we know that within a year, most of these patients will develop drug resistance, so most of the tumors will become resistant to this therapy and that is a huge clinical problem. So we are interested in understanding the nitty-gritty of what is happening to those resistant tumors and how we can alter that so that we can overcome drug resistance, and that is an example of something that we do in the lab that we study from a basic biology point of view but it has an ultimate application and it stems from a problem that is very real in the clinic.

Gore That sounds really interesting. Let's back track a minute for the audience members, which I would consider myself among on this topic, so this EGF receptor, is it like a receptor for a kind of hormone, would EGF be a kind of hormone?

Politi These are receptors. They are a family of receptors of the EGF receptor family. These are receptors for growth factors. Therefore, molecules will signal to a cell when it has to grow and divide and as you can imagine, that has to be a very controlled process because in a tissue, you only want cells to divide at a certain time point, so that is an external cue to the cell to grow and divide; however, when you have alterations in the EGF receptor itself, it does not respond to that growth factor stimulus anymore, it does not need that to signal to the cell to divide, so it is as if it really did not care about whether that growth factor was present or not and so then the cells can grow uncontrollably.

Gore So it is like the on switch is left on?

Politi Correct.

Gore And it is saying to divide, divide even without this growth signal or growth hormone.

Politi Exactly.

Gore And how do these drugs mitigate that on switch? Do they turn the switch off or?

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Politi These drugs that block the EGF receptor, that is exactly what they do; they will turn the off switch on, on the EGF receptor. One of the great things about these drugs and specifically this class of drugs which are called targeted therapies is that they will zero in on a specific molecule and they will turn the off switch on that one, so these are lung cancers that have the EGF receptor on switch on and the drugs are drugs that will only block EGF receptor and this is really helpful because it can limit toxicity that could be a big problem with some of the drugs that will target many different cells that are dividing, some of the more generic chemotherapies, for example, that are not specifically going to stop the on switch on that one molecule.

Gore Then are there some normal cells that would need this receptor?

Politi Correct, there could be some normal cells, and there is some toxicity associated with it. It is just much more limited than it is with some of the other more cytotoxic chemotherapies.

Gore Got it, and do all lung cancers have this mutated receptor?

Politi That is a very interesting question. There are many different subtypes of lung cancer and one of the main subtypes of lung cancer is called lung adenocarcinomas and these lung adenocarcinomas can have different types of mutations that are driving the cancer, so EGF receptor mutations account for about 10 to 15% of all lung adenocarcinomas. There are other on switches that are turned on in some of the other lung cancers, like KRAS mutations that can be present in another subset of lung adenocarcinomas or mutations and other drivers.

Gore You talk about resistance to these drugs that are targeting these mutated EGF receptors, is this kind of resistance present right from the get-go, so patients will not respond to the drug, or is this a resistance that would develop like when you give I guess antibiotics to an infection but you do not give enough or the right antibiotic and then the bugs become resistant?

Politi In the case of EGF receptor mutant lung cancer, over 70% of people who are treated with one of these targeted therapies that blocks EGF receptor activity will show an initial response to this drug. The problem is that even though the majority of patients initially respond, usually within a year of starting treatment, they develop what is called acquired resistance to this treatment, to this therapy. And in most of the cases, acquired resistance to these EGF receptor inhibitors is due to another change in EGF receptor that does not allow the drug to work well anymore and so it is as if the cancer cell has figured out a way of getting around the drug.

Gore So would that be an additional mutation?

Politi Exactly, that is an additional mutation. It is called the EGF receptor T790M mutation that is found in about over 50% of cases of acquired resistance. And in the other cases, we also see other ways in which the cells have found of getting around the drug treatment so that they can keep those pathways active that allow the continued uncontrolled growth of the cancer cells.

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- Gore What are some of those ways?
- Politi Some of those ways are higher levels of other genes that are similar to the EGF receptor and other ways are changes in pathways that are further down from the EGF receptor so that you have additional mutations that just turn on those growth signals.
- Gore Those cancer cells turn out to be pretty smart unfortunately?
- Politi Unfortunately they do turn out to be pretty smart, yes. The cancer cells are very complicated and I think that one of the things that is really problematic, but also fascinating about cancers in general, is that it is not only the cancer cells that will change but there is a whole tumor microenvironment and a whole environment in which those cancer cells are forming and developing that also contributes, and there is a whole interaction between the tumor cells and the environment that surrounds them.
- Gore How does that work?
- Politi For example, there is an immune system and one can have an interplay of signals that happen between the tumor cells themselves and the immune cells that recruit different types of immune cells or that make them not work very well, for example, and so if the cancer cells are there and they are sending a signal to the immune cells, not allowing them to function properly, it makes it harder for the immune system as a whole to battle the cancer cells and get rid of them. The other aspect of the environment that we have with cancer cells is also that they are blood vessels and so one of the interesting things is how do tumor cells recruit blood vessels and connect the tumor to the rest of the organism?
- Gore That is really fascinating, and I would like to take up some of these topics after our break. Right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about the nature of cancer cells, particularly in lung cancer, with Dr. Katie Politi.

Medical Minute

The American Cancer Society estimates that in 2014 over 45,000 new cases of pancreatic cancer will be diagnosed in the United States. Pancreatic cancer is the fourth most frequent cause of cancer death. Clinical trials are currently underway at federally designated comprehensive cancer centers, such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to make innovative new treatments available to patients. Clinical trial participation is offered for treatment of advanced stage metastatic pancreatic cancer using chemotherapy and other novel therapies for the disease. FOLFIRINOX, a combination of five different chemotherapies is the latest advancement in the treatment of metastatic pancreatic cancer. There is continued research being done at centers like Yale and around the world looking into targeted therapy and a recently discovered marker hENT1. This has been a medical minute brought to you as a public service by

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Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. For more information, go to yalecancercenter.org. You are listening to the WNPR, Connecticut's public media source for news and ideas.

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by our guest, Dr. Katie Politi and we are discussing cancer pathology and we have been discussing drugs which target mutant receptors and lung cancer. Before the break, Katie, you were telling me about the fascinating interaction between the tumor cells and the environment in which they live, including the immune system and blood vessels and so on. Are there other areas with these interconnections and these things which can be targeted for treatment as well?

Politi Yes, definitely, there is a lot of interest in understanding whether certain drugs that can reawaken or reactivate the immune system are useful in the treatment of lung cancer, not only in the case of EGF receptor mutant lung cancer but lots of other subsets of lung cancer. This is really a new area, there is a lot of exciting work and some very exciting clinical trial information that has shown that patients who do respond well to these drugs that target the immune system respond for a very long time. As I was telling you before about how we have resistance that develops within about a year to these targeted therapies, we are seeing something different in some cases in patients who are treated with immunotherapies where the responses can be very prolonged and so that is an exciting field of research, and we have a lot to learn still and we have to learn which immunotherapies or which drugs that target the immune system would be best depending on the nature of the cancer that is present. In the case of EGF receptor mutant lung cancer that we are talking about tonight, what does EGF receptor mutant lung cancer do to the immune system and how could we best harness the potential of the immune system in that case? It might be different for EGF receptor mutant lung cancer compared to lung cancers with other mutations and I think we still have a lot of work to do in that area.

Gore That sounds like you really need to work with people who have expertise in basic immunology as well as expertise in cancer biology and if you want to get into this microenvironment stuff and blood vessels, you have to really know a lot or interact with people who know a lot of different things.

Politi That is right. My lab has formed a partnership with Susan Kaech's lab here in the immunology department at Yale and we are bringing together both of our expertise, she is a T-cell biologist and I am a cancer biologist and bringing that together to really understand the basic biology, but then we also meet and we work with the clinicians like Dr. Scott Gettinger who is running many of the immunotherapy trials in lung cancer to figure out how we can best learn about the immune system in these lung cancers and then learn how to treat these tumors.

Gore What you are describing is really kind of a team medicine approach, or team science approach.

Politi Definitely, it is a team science approach and I think it is the only way that one can do this now-a-days. Everybody has different expertise and different models and different systems and different

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knowledge and if we all bring it to the table, we can start to make significant progress and make it fast. I think that one of the things that we would all like to see is some of our findings from the laboratory really translate into the clinic as fast as possible, and I think that has happened over the years with targeted therapies. I am thinking about one of the alterations that is found in a subset of lung cancer, rearrangement in the ALK gene, that was discovered in 2007 and the first targeted therapy to treat that subtype of lung cancer had accelerated approval by the FDA in 2011, only four years after its discovery, so just by bringing people together, we can really make rapid progress and get treatments to patients fast.

Gore What is really exciting is that we have these drugs which seem to be so promising in patients, say with this particular mutation that we have been discussing, but I am a little discouraged I guess to hear from you that resistance will develop for so many people in a relatively brief period of time. Is there anything that is going on that can prevent or delay the development of such resistance?

Politi I would say that there is promise and progress in several different areas here. Most of the work recently has been done in the area of developing therapies to overcome resistance and so the patients who develop resistance, and especially those who have the T790M mutation, this mutation changes the EGF receptor again so the drug does not work very well, so there have been new drugs that have been developed that can turn off EGF receptor when it has this resistance mechanism, and those drugs are in clinical trials and they are showing very good responses, so the patients are responding to those drugs. I think that that class of drugs holds a lot of promise for overcoming drug resistance. One of the other areas of interest is really studying how we can try to stave off the emergence of resistance and one of the studies that we are very interested in and that we will be opening here at Yale, is going to be a big cooperative group study looking at the drug combination that using our mouse model several years ago we found could overcome resistance and this is a combination of a drug called afatinib with another drug called cetuximab and both of these drugs target EGF receptor and so working with William Pao several years ago, we found that this drug combination could overcome resistance.

Gore In the mice.

Politi In the mice, and then also in a clinical trial in patients. It had really good responses in patients who already had resistance.

Politi Now what we have done is we have taken this drug combination and we have tested it in mice from the very beginning and compared it to using the single drug alone that blocks EGF receptor and we found that resistance takes much longer to occur and it occurs only in 50% of the mice, only in half of the mice, and so this is a proof of principle of the type of studies and the type of trials that we need to do in patients to see whether we can use drug combinations like this or even some of these newer drugs that block resistant disease, if we use them as the first drug and see whether that can delay the emergence of resistance, so these are all studies that are ongoing that people are interested in seeing whether we can stave off the emergence of resistance for as long as

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possible and of course, one of the other things that people are thinking about and studying is whether we can interface these studies with combining some of the newest and best drugs or drug combinations to EGF receptor together with immunotherapies, so if we do that from the very beginning, for example, is that an opportunity to eradicate, as much of the disease as possible and lengthen survival for patients with EGF receptor mutant lung cancer?

Gore Does that mean that we consider conventional cytotoxic chemotherapy or chemo drugs like most patients and our audience members might think about, are they done in this kind of lung cancer, they have no role to play?

Politi I think there might be a role for them in certain situations, in the resistant situation for example, but certainly if there is a patient with EGF receptor mutant lung cancer then you would want to treat them with one of these targeted therapies to EGF receptor.

Gore You are painting a picture where you'd be using non-chemo?

Politi Right, eventually.

Gore That is very exciting. It has got to be very exciting for you to have this observation you made in the laboratory in your animal models now, and you said a cooperative group study, which for the listeners means kind of a national study that is done by many centers together.

Politi Yes, correct, I think it is very exciting and when I started studying cancer biology, I never would have imagined that some of the things that we were working on in the lab would be used in the clinic and be so close to what is being studied and what can be done in the clinic.

Gore Have you always been interested in lung cancer in particular?

Politi I started working on lung cancer when I started my postdoctoral fellowship at Memorial Sloan Kettering. Before that, I was working on different models of cancer and trying to improve our mouse models of cancer but was not focused on lung cancer, I was mostly focused on breast cancer models and when I went to Memorial Sloan Kettering, I was working in Harold Varmus' group there and William Pao was one of the postdoctoral fellows and had just discovered EGF receptor mutations in parallel to some groups in Boston as well in lung cancer, and so that was fascinating to me and I started getting into developing models of this particular type of lung cancer and understanding how the cancer cells became addicted to these changes that were happening in them, like EGF receptor mutations because one of the interesting things is lung cells do not have EGF receptor mutations, they are not mutated. The mutations happen and lead to the tumor and these cells then change and they really need the continued signal of that on switch on continuously and so one of the things I was really interested in was why do those cells need that switched on because if you turn it off, they die now with these targeted therapies, so I was really interested in understanding how that happens and modeling that in animals and in cell lines.

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- Gore Some listeners may be concerned when we talk about mutations, that they have these mutations from birth. Is that how this arises?
- Politi That is a very important point because these are mutations that happen just in the cells of the tissue where the cancer develops, so they are not mutations that are present everywhere throughout the body; they are not inherited mutations, so if someone has lung cancer and they have an EGF receptor mutation, in the vast majority of cases, it is only in that lung tumor and it cannot be passed on to family or anything like that, so cancer is a genetic disease because at the basis of cancer, there are lots of changes in our genes, but it is not a hereditary disease all the time; actually, in most cases, it is not an inherited disease.
- Gore I think that is very confusing for many listeners because genetic to them means congenital or familial.
- Politi Right.
- Gore They hear you talking about genetic in terms of involving genes, but not necessarily acquired genetic abnormalities.
- Politi Correct, and in most cases, in cancer, that is what happens. The mutations, the changes, are acquired just in the tissue that is developing a tumor.
- Gore And why does that happen?
- Politi There can be lots of different reasons why that can happen. It can be due to environmental exposures, such as smoking for example, which can cause a lot of mutations. One of the things that is interesting though is EGF receptor mutations are most frequently found in people who have never smoked who develop lung cancer, so in that case, the reason is not so clear for which mutations happen, but mutations can happen because of environmental exposures, they can happen also because our cells are very complicated. They have to divide, they have to respond to signals, and when these things happen, mistakes can happen as well and changes can occur.

Dr. Katie Politi is Assistant Professor of Medicine and Medical Oncology and of Pathology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. As an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.