

Katerina Politi, PhD, The Biology of Lung Cancer October 17, 2010 Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson. I am Bruce Barber. Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Francine and Lynn are pleased to welcome Dr. Katerina Politi. Dr. Politi is an Assistant Professor of Pathology at Yale School of Medicine. Here is Francine Foss.

Foss Let us start off by having you tell our audience a little bit about what cancer biology is?

Politi Cancer biology is the science in which we try to understand which genes are involved in the process of tumor initiation, so what starts off the tumorigenic process? What genes are involved in tumor maintenance? What is required for a tumor to survive once it has already formed, and what leads to tumor progression? What leads to the development of metastases? In cancer biology, we also study the interplay of different cell types within the tumor. These cell types form what is called the tumor microenvironment that is made up, for example, of immune cells, blood vessels, and connective tissue.

Wilson This is obviously a fascinating field. Could you tell us a little bit about your background and how you became interested in studying cancer biology?

Politi I studied biological sciences at the University of Pavia in Italy, where I grew up, after which I came to the US and got my PhD in Genetics and Development at Columbia University in New York. After that I went to do a post doc at Memorial Sloan-Kettering Cancer Center in New York where I worked in Harold Varmus' lab, who is currently the Director of the National Cancer Institute. I became interested in cancer biology early on during my studies while I was in university, when I began to learn about genes involved in cancer and how these alterations in these genes and cancer cells really disrupted the circuitry within a cell.

Foss Katerina, you talk about cancer cells and tumor biology, could you tell our audience what the relationship is between cancer cells and tumors?

Politi Of course, cancer cells are what make up a tumor. So each tumor is made up of many-many different cancer cells.

Foss Is it true that those cancer cells may not all be exactly identical?

Politi That is true, one of the ideas is that you have a genetic event within a cell that gives an advantage, a survival advantage, and so that cell begins to grow and to proliferate, multiply, but then those other cells can also acquire other changes and this is actually one of the major problems in cancer biology. We will talk about it a little later on as well, but even when you have a tumor that is made 3:30 into mp3 file <http://yalecancercenter.org/podcast/oct1710-cancer-answers-politi.mp3>

Wilson Up of many cancer cells there may actually be different populations of cancer cells with different changes within each individual tumor.

Wilson Are there particular areas of cancer biology research that are happening now that are of great interest to lots of different investigators, or is it one or two areas, or many, can you talk to our audience about that?

Politi One of the things that we have seen emerge has been in the past 20 or so years. There was a focus on understanding the circuitry that I

was talking about before, within the cells, so how do the different pathways in a cell lead to proliferation and survival. What are the genes and proteins that make them up and how do they function? Now we understand much better how these are altered within cancer. What is happening now is that there is a lot of focus on understanding the full compliment of all of these changes that happen within each individual tumor. This goes into looking at the genomics, so sequencing the DNA, understanding all of the changes in individual tumors, and then one of the things that we can also do is we can work on interfering with these changes. A large focus of research right now is focusing on understanding how we can interfere with individual changes within each particular tumor and this is something that requires not only the cancer biologists sitting in their lab, working alone, but it also requires a team effort in which the cancer biologists are talking to the oncologist, talking to the surgeons, talking to the pathologist, so that we can study individual changes within each tumor. Foss That is one of the major changes that I have seen in cancer biology in the last 15 years or so. A long time ago we thought about a cancer cell and investigators focused on a single mutation or oncogene in that cell, and now when we talk about many of these cancers, we see these very complicated network diagrams that involve lots of different pathways, some of which are even normal cellular pathways and how they impact on the development of cancer, so we are at a completely different level of complexity now. Politi Absolutely, that is correct and one of the things that is happening is that now what has been done at various institutions and for certain tumor types, is that at the time when the tumor is diagnosed that tumor is then tested for a whole array of genetic changes, and then treatment strategies are then been devised to interfere specifically with the specific types of alterations that are found in that tumor. Wilson There is a tremendous amount of research going on here in cancer and cancer biology and obviously with the new construction of the Smilow Cancer Hospital there are lots of exciting things going on here. Was that part of the attraction for you to come to Yale? Obviously you have done a lot of your training and developed a lot of your career in New York. How long have you been here and what made you make the change to come to New Haven? Politi I actually arrived here in July, so just a couple of months ago, and I was really attracted to come to Yale because of the really great faculty and basic sciences and the great clinical faculty, and I felt 7:14 into mp3 file <http://yalecancercenter.org/podcast/oct1710-cancer-answers-politi.mp3> this commitment at Yale to further cancer research and treatment and it was a great place for me to start my lab as a junior investigator because this translates into a very dynamic scientific environment where communication between scientists and clinicians is encouraged, where there are cancer biology seminars that have been organized and there are also plans to train students in cancer biology and resources are being allocated to cancer biology. So for someone whose lab is in this field, this is a great moment to come here at a place where the foundation, the basic science, and clinical foundation is so strong. Foss Katerina, I understand that cancer biology isn't necessarily a silo organization that you cut across, as you point out, multiple other disciplines and other areas around the university. Can you talk a little

about how you integrate with other departments who perhaps aren't necessarily studying cancer biology, but are studying important pathways and mechanisms that could compliment your work?Politi There are two aspects to this, one of them is that I can work with people in various basic science departments, for example, one of the genes, and I will talk a little about it, that I work on is the Epidermal Growth Factor Receptor gene, and so when we study this gene and when we study mutations in this gene, we really have to understand how these mutations alter the structure of the protein, and so there we will interface with the structural biologist, for example. At the same time, some of the things that I work on, I develop genetically engineered mouse models of lung cancer based on these EGF receptor mutations and so we have to figure out ways in which we can actually visualize the tumor, so then we will talk to people from the imaging departments for MRI imaging, for CT imaging, PET imaging to see if we can visualize these tumors and even develop ways in which we can specifically view EGF receptor mutant tumors. So those are just a couple of examples of how the work that I do requires this really strong foundation in the basic sciences that there is here.Wilson You have mentioned lung cancer, be a little more specific with us about what types of cancers you study and within those, what sort of work you are doing?Politi I study lung cancer. Lung cancer can actually be divided into two main histological groups. Small cell lung cancer and non-small cell lung cancer. Now, non-small cell lung cancer makes up 80% of all lung cancers and this can be further subdivided into three histological subtypes; lung adenocarcinomas, squamous cell carcinomas, and large cell carcinomas. Lung adenocarcinomas actually develop at the periphery of the lung in contrast to squamous cell carcinomas, which instead develop more centrally in the central airways, and lung adenocarcinomas are rising in incidence and that is believed to be due to the increased use of filtered cigarettes which actually allow people to breath the smoke in more deeply, so carcinogens from the smoke reach the periphery of the lung more easily. My work focuses on studying genes that are mutated in lung cancer and so what we know is that even though lung adenocarcinomas may look very similar when you look at them under the microscope, they can actually be subdivided into different categories based on genes that we know are altered in these lung adenocarcinomas, and one of the11:38 into mp3 file <http://yalecancercenter.org/podcast/oct1710-cancer-answers-politi.mp3> genes that is altered in about 10% to 15% of lung adenocarcinomas in the US is called the Epidermal Growth Factor Receptor gene and this gene is actually mutated most frequently in lung adenocarcinomas that arise in people who have never smoked. Importantly, tumors with EGF receptor mutations are more sensitive to treatment with specific drugs that have been developed during the past several years that block the activity of the Epidermal Growth Factor Receptor protein.Foss So Katerina, the Epidermal Growth Factor Receptor is an important element on normal cells as well, and the distinguishing factor with the tumor cells is that this particular protein is mutated.Politi That is right, and so the Epidermal Growth Factor is present on human cells and it is one of these proteins that actually will sense cues from the external environment telling the cell whether the cell should survive and

multiply or whether it should not, and in the case where it is mutated, it does not know how to regulate these signals anymore and so it is always active. Foss Let me ask you the key question then, in nonsmokers who have an increased expression of this mutated receptor, how does that mutation happen outside of the setting of smoking which obviously exposes the lung to carcinogens? Politi The answer to that question is really not known at this point. Foss Is that something that you are looking at in your research as well, are you focusing on how those mutations happen? Politi I actually am not working on this in my laboratory, there are certainly groups that are trying to understand why this is happening and, for example, one of the things that we know is that there is a higher frequency of mutations in lung adenocarcinomas in Asians in the EGF receptor and so one of the possibilities is that there may be some environmental factors that may actually give a higher frequency of these mutations, but this is an area of active investigation, nobody knows the answer. Wilson Thank you Katerina. We are going to take a short break for a Medical Minute. Please stay tuned to learn more information about cancer biology with Dr. Katerina Politi. 15:04 into mp3 file <http://yalecancercenter.org/podcast/oct1710-cancer-answers-politi.mp3> of surgery at Yale Cancer Center is a video-assisted thoracoscopic surgery also known as VATS procedure, which is a minimally invasive technique. This has been a medical minute more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network. Wilson Welcome back to Yale Cancer Center Answers. This is Lynn Wilson, and I am joined by my co-host Dr. Francine Foss. Today, we are joined by Dr. Katerina Politi and we were discussing cancer biology. Katerina, tell us a little bit more about the mouse models with lung cancer that you have developed. Tell us what you do when you get into work or into the laboratory everyday. Politi When I developed the mouse models of lung cancer that I'll tell you about, we had just discovered EGF receptor mutations and the group I was working with it at Sloan-Kettering discovered these along with other groups in Boston, in particular, and Tom Lynch's group when he was at MGH as well, and so what I really wanted to do is I wanted to understand how the mutant EGF receptor is changing the biology of the tumor cells to cause cancer, and so to do this I decided to develop these mice in which I could actually turn on a copy of the mutant EGF receptor in the lung and see what happened, and in fact, what we can see is that these mice develop lung tumors and they closely resemble the lung tumors that have EGF receptor mutations in the case of human cancer. Importantly, what we can do is we can also visualize the tumor using imaging like Magnetic Resonance Imaging or CT scans and we can test the different drugs on mice that have tumors to see how effective they are at getting the tumor to go away. So the drugs that are used clinically now in humans, also work very effectively in these mouse models of cancer. One of the problems with drugs that are used to block the activity of mutant EGF receptor in the clinic, is that they work initially, but drug resistance inevitably emerges, so drug resistant tumors develop so we have used our mice to develop a model of resistance to these EGF receptor inhibitors. Foss Can you expand a little bit

on how you interact with the medical oncologists who are treating lung cancer patients? How do you connect your work on drug resistance to what is actually happening in the clinic in patients?

Politi Ever since I started working on lung cancer at Sloan-Kettering, we had a group there of thoracic oncologists, surgeons, pathologists, and scientists and we were trying to figure out what the important clinical questions related to lung cancer were and how we could answer those questions in the laboratory, and this type of approach will continue here at Yale as well. We're actually putting together a translational lung team to work on problems in lung cancer and so one of the examples of how our mouse models are very effective is that we, in collaboration with William Pao, a scientist and thoracic oncologist who is now at Vanderbilt, developed a mouse with EGF receptor mutant lung cancer that was resistant to treatment with these drugs that are used in the clinic, and we tested various different new drugs and drug combinations and we found one combination that works really well in the mouse models. The tumors shrink very rapidly and so this is the basis for a clinical trial that is now starting at sites that include Memorial Sloan-Kettering, Vanderbilt, and Yale, so this is how rapidly this translational lung cancer group

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tested things in the genetically engineered mice and are moving on to the clinic to help people who need effective treatments fast.

Foss The important thing about what you are saying is that historically when we've combined therapies in the treatment of cancer patients, we have not necessarily had a strong rationale for combining them. We have not had these kinds of molecular models where we have been able to show in a mouse tumor system that combination is better than either drug alone, so that is certainly a giant step forward.

Politi Now our knowledge of what is happening in the individual tumors is really helping us figure out what we need to do to block that tumor from growing.

Wilson Regarding the mice, do you have to do anything special to their immune system to make the model work, or are they completely normal mice?

Politi The mice that we use actually are immune-competent mice. So their immune systems are completely normal, and this is actually very important and is different from what has historically been done to test drugs, in fact, pharmaceutical companies historically use xenograft models and what that means is that human lung cancer cell lines are injected into mice that do not have a normal immune system, otherwise the mouse would reject the human cells, and the tumor is allowed to grow, and one of the problems is the immune system is a very important component of tumor formation, whether the immune system is functioning or not can modulate tumorigenesis, and so one of the advantages of using the genetically engineered mice that I am talking about is that we are doing these experiments in the context of an intact host, so everything is functioning.

Foss So again, a major step forward in cancer biology compared to the way we used to do things. Are there other major advances in cancer biology that you can tell us about?

Politi There are advances in terms of our knowledge of what is happening within the individual tumor. One of the big projects that was undertaken by the National Cancer Institute, I am thinking of the cancer genome atlas in which we sequenced tumors of different types and we

are not only sequencing them to see what mutations there are, but we are also looking at how the levels of genes change, how the levels of protein change and trying to integrate all of this information so that we can really get a full picture of what is happening in each individual tumor. One of the other big changes that has occurred is that formally a lot of drug discovery would happen within the drug companies and now as we are learning more about the molecular pathology of tumors and about the specific changes and we have very good models even within academia, and our technologies are better, we can actually do a lot of drugs screening even within an academic institution and so it is not unheard of for the development of drugs to actually start within universities. Wilson So you have mentioned lung cancers being related to smoking, people smoke the lung is exposed 23:38 into mp3 file <http://yalecancercenter.org/podcast/oct1710-cancer-answers-politi.mp3> to smoke, we can understand how cancer can develop in the lung, and you, in very basic terms describe for us what sort of differences are you aware of when we have a lung cancer that originates in the lung compared to a tumor somewhere else that may spread to the lung. You know, when I take care of a lung cancer patient often those cancers are generally in one place or may spread to the lymph nodes nearby, sometimes spread to other parts of the lungs, but in some patients I have taken care of who have a cancer elsewhere in their body, it may spread to many different parts of the lung. What is it about the cancer biology of these cells that makes one tend to behave itself sort of in an isolated way and another one perhaps spread very aggressively throughout the same kind of organ? Politi Even within lung cancer, for example, there are many different tumor types, so there is a situation in which there is a type of bronchioloalveolar carcinoma, which is a sub-type of lung and adenocarcinoma pneumonic BAC, which actually spreads throughout the whole lung field as opposed to, for example, focal tumors where there are cases in which you can have multiple primaries occur within the lungs. We really do not know very much about what the differences are molecularly between these different tumor types. Now that we have a better grasp on the molecular changes that occur within different tumors, we will see more of a focus on trying to understand these more complex issues in cancer biology that we could not understand or really even began to grapple with previously, like studying metastasis. Going back to your questions, one of the thoughts is that their may be a subpopulation, let us say within a breast tumor that metastasizes to the lung, there may be a subpopulation that goes through the blood stream that has acquired the ability to grow in the lungs, for example, and so that is what may be happening. It goes through the blood stream but it has acquired some genetic change or epigenetic change or something that allows it to spread through the blood and then survive in the lung. Foss That gets back to a point we made earlier in the show which is that tumors are not necessarily a homogenous groups of cells, as you mentioned there are multiple different aberrant pathways that could be expressed and they can be different within the same tumor. Politi Yes, that is right. Foss I wanted to ask you a little bit more about your EGF receptor work, and lung cancer of course isn't the only tumor that over expresses EGF receptor and I wonder if you could talk about some of the other tumor types

and how applicable your findings in lung cancer are going to be for some of these other tumors as well. Politi The EGF receptor mutations in these specific types of mutations, have really only been observed in lung adenocarcinomas and very-very rarely found in other types. Over expression of EGF receptor, on the other hand, has been found in other tumor types such as colon cancer and once again, there are drugs that target the EGF receptor that are used in colon cancer, for example the antibody to the EGF receptor, cetuximab, and so similarly there you have a specific change in a gene that is driving tumorigenesis and so when you block the activity of that specific gene, you27:45 into mp3 file <http://yalecancercenter.org/podcast/oct1710-cancer-answers-politi.mp3> are blocking the ability of that tumor to survive. That is very similar. The problem is that the EGF receptor inhibitors that work on mutant EGF receptors in lung cancer, do not work as well on high levels of EGF receptor. They have a better affinity for mutant EGF receptors. So, those drugs cannot be used, for example, in colon cancer. Foss That is an important point for our listeners who might be familiar with some of these drugs or read on the internet about some of these new agents. Even though it is EGF-receptor associated, it may not be applicable to their specific kind of cancer. Wilson You only been here a few months and obviously thought a lot about the future, what sorts of things are you looking forward to in your work here at Yale? What sort of opportunities do you see in the future or in the short term? Politi I am looking forward to working with the translational lung cancer team here. I am very excited. When I was in the process of choosing to come to Yale, I met a lot of people and there is great work in setting circulating tumors cells, stem cells inflammations, serum changes in lung cancer and so I am really looking forward to working together with this group, it is a very exiting time. There also have been, in the past couple of years, several cancer biologists recruited here, junior investigators, and so it has been exiting to get to meet them, and talk to them about research. I am very much looking forward to working together with them. Dr. Katerina Politi is an Assistant Professor of Pathology at Yale School of Medicine. If you have questions or would like to share your comments, visit yalecancercenter.org where you can also subscribe to our pod cast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.