Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss and 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 can 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 cancer metastasis with Dr. Don Nguyen. Dr. Nguyen is Associate Professor of Pathology at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar People always talk about cancer metastasis, so maybe we should start there in our demystification of this process. What exactly is a metastasis?

Nguyen It is funny that you mentioned that it is kind of a mystical process because it is a process that has been noted since antiquity and it really wasn't until I would say the last 10 to 20 years that we have kind of understood what it really means. Metastasis comes from Greek and means displacement. So it implies the displacement of tumor cells from one site, usually the organ where they originally arise, to another tissue and I would say that there is two sides of the coin of metastasis and they are both interdependent. One is of course the displacement of the tumor cells, but also their adaptability to their new surroundings and with recent advances in the last 10 to 20 years and a focus on biology and genetics, we are starting to in fact demystify the process of metastasis one step at a time in the hopes of being able to tackle that process.

Chagpar Why is it important that we understand cancer metastasis? I mean so a cancer goes from one place to another place, what are the implications of that in terms of treatment and prognosis, why do we care?

Nguyen I think you could argue it is the most critical part of cancer because most patients do not die of their primary tumor. They usually die of metastatic disease and the reasons for that are by the time the tumor has spread it is usually inoperable and also it is resistant to all forms of current therapy and so usually metastasis is equivalent to end stage disease for most cancer patients. I would say that usually it was a pretty grim prognosis, but recently there is hope to believe that we can tackle this stage of cancer progression.

Chagpar One other issue that I think people get confused about and certainly it is a confusing concept, is lymph node metastasis. We talk about

distant metastasis, but then we talk about regional metastasis are they different in terms of prognosis or in terms of how the cancer cells got there?

Nguyen That is a very good question. I think that in many cancers being able to detect the spread into regional lymph nodes is a prognostic step towards metastasis and distant organs. I think that there

3:25 into mp3 file http://yalecancercenter.org/podcasts/2014%201019%20YCC%20Answers%20-%20Dr%20Nguyen.mp3 are certainly different mechanism by which cells can enter lymph nodes, but ultimately what counts is that the cells enter the blood stream and then eventually distant organs and I think that is really the cause of poor outcome in patients.

Chagpar I do want to get to how this process works, but I thought, let's just tackle a few of the common questions that people ask. So, if you have a needle biopsy, for example, and you disrupt a cancer, can't you force that cancer then to spread and it will metastasize all over the body, and yet our doctors do that all the time to make diagnosis, what is going on there?

Nguyen That is one very fascinating aspect of metastasis, that although some cancers are more aggressive than others, generally speaking, we know that metastasis is actually very difficult to occur. For example, for breast cancer, we know from research that only one in 10,000 tumor cells that get into the blood stream can actually form a metastasis and that is actually good news, because that means that there is a window of time that can be very long before a metastasis can form and so if we can identify that window of time, I think that we could potentially prevent the disease from reaching its full stage and so it is really a very inefficient process in the first place and so just simply disrupting cells mechanically through certain surgical procedures, does not necessarily mean that the patient will develop metastasis.

Chagpar Yeah and I guess it is harkens back to something that you started to allude to earlier, which is that cancer cells also have to kind of set-up shop in their distant place.

Nguyen Absolutely.

Chagpar And they may not be in the appropriate soil for that seed to take hold.

Nguyen Absolutely, and you referred to a very longstanding concept from the 1800's, the seeding soil hypothesis and that is really a botanical analogy, which is that cancers are kind of like seeds and we know that you can spread seeds for different flowers all over the place, but they will only grow in certain climates and certain conditions and it is the same thing for cancer cells. And going back to my initial point about metastasis, there are two facets, one is the displacement of the tumor cells and secondly their adaptation to their new surroundings.

Chagpar And you know Don, the other question that I want to get to before we start talking about how exactly this process and metastasis work as we try to define what a metastasis is, you had mentioned that part of this whole process is cancer cells getting into the blood, what about people who have blood cancers? Is that automatically metastatic?

Nguyen Again, we know different types of cancers have different ways of metastasizing and have different disease prognosis. Cancers of the blood do not metastasize as frequently as solid tumors, for

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instance, and I think that has to do with the fact that metastasis is this multi-step process, so getting into the blood is only one of the steps necessary. One might argue that the more difficult step is as you mentioned, the ability for cells to set-up shop and this is a very different environment.

Chagpar So if cancers start from blood cells, that is kind of their original home as opposed to spreading other places. Now let's focus on what exactly we are talking about, because what we are really talking about is how cancers from a solid organ, something like lung, breast, colon, or prostate, get into the blood stream and set-up shop other places, which is really important in terms of prognosis. So take us through how exactly that happens. How does a cancer cell decide that it is going to metastasize? Are cancers cells kind of pre-programed to think that way or is that the mission of all cancer cells, is eventually they should metastasize?

Nguyen Cancer can be viewed more as a Darwinian process. I do not think the cancer cells want to go somewhere, I think that happens through natural selection and so if we take an example of breast cancer or lung cancer, which can spread to the brain and to the bone, I think what you would have, if we go through the steps of metastasis, the tumor will acquire a number of genetic changes. Some of which will allow the cells to outgrow their initial area. As a tumor grows, of course it uses up a lot of local nutrients and once some of those nutrients get depleted, some of these tumor cells might have the capacity to go to other areas to kind of take advantage of new environments and so a very small fraction of those tumor cells will be able to squeeze into the bloodstream and once they land in the bone or the brain, for instance, they will start to remodel their surroundings or take advantage of the available nutrients there for their growth and in the case of bone metastasis, that implies that the tumors are capable of destroying the surrounding bone to release a lot of nutrients and growth factors that they can take advantage of. So it has a lot to do with the process of adaptation and evolution of the tumor cells as they undergo a lot of genetic changes.

Chagpar How does a cancer cell acquire these genes that make them able to, or want to, metastasize in the first place? Because it would seem to me that if we could figure out how those genes are turned on and more importantly how to turn them off, we could potentially stop a lot of people from dying of metastatic disease?

Nguyen Yeah, and I think there are probably two schools of thought. On the one hand, in the type of cancer that we study in my lab, lung cancer, lung cancer is one of the most frequently mutated cancers. A lot of that has to do with exposure to smoke or environmental mutagens and so if you have a higher frequency of mutation in cancer, you might speculate that there is a higher frequency of genetic changes that will lead to a metastatic cancer. The other side of that question, and this is not mutually exclusive, we believe that one of the reasons why lung cancers have a tendency to metastasize is that some of the molecular circuits that increases the adaptability of the cell are kind of part of the initial cell types that are in the lung and that has to do with the fact that the lung, even under normal conditions, has to respond to different things that we breathe, and so therefore, when a cancer forms, it may already be predisposed to invade its local tissue or get into the blood

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stream and adapt to new surroundings, which we think is something that might

be predetermined in the initial cell type. So these two things, these two forces, I think are what drives the overall propensity for certain cancers to metastasize.

Chagpar Cancers may be automatically programmed with these genetic predispositions to be able to invade and that may or may not be just part of being a lung cell, but there must be something on the other side of that coin as to how a lung cell can break down bone, break down the actual calcium of bone and set-up shop there. If we could figure out how cancer cells do that, and prevent that from happening, maybe we could stop cancer metastases?

Nguyen Specifically referring to our own research again, we think that one of the reasons that cancer cells can adapt to, for instance, the bone or the brain is that part of the genetic changes that occur is in their ability to produce certain proteins that allow them to interact with their surroundings. Some of these are proteins that allow them to attach to certain surfaces in the bone matrix and then other changes have to do with the production of certain enzymes that can break down the bone matrix and what is very interesting, is that a lot of these changes in genes and proteins are changes that are normally seen in those tissues. For instance, in order to adapt to the bone microenvironment, the lung cancer cell will start to express proteins that other bone cells usually express in order to grow into the bone and those abnormal changes can happen very early and so we hope that by understanding those changes we might be able to detect lung cancer cells that have a propensity or are more likely to metastasize.

Chagpar What about taking it one step further, I mean I am sure that people who are listening are thinking, yeah that is great, so you can now tell me that my lung cancer has a propensity to metastasize, I would really rather you say, and we figured out a way to stop it from doing so.

Nguyen I think the research field is moving in both directions. I think that first of all there is a recognition that we can identify subtypes of patients that are more likely to metastasize, and that has two benefits. One is to be able to treat patients more aggressively that need to be and also spare the patients that do not need aggressive treatment. Aggressive treatments sometimes have detrimental side effects. The flip side is, of course, for patients that are diagnosed with late stage cancer, how do we treat those patients and that is where most of the challenge has been, but there has been some recent process. For instance, using the example of lung or breast cancer patients, especially those that develop bone metastasis, there are specific types of drugs that can be used to inhibit the growth of these tumor cells in the bone and what is very interesting is that those therapies are actually things that already exist. Some of the drugs that have shown benefit in the clinic are actually drugs that women that suffer from

osteoporosis use for treatment and these compounds have shown to be efficacious in breast cancer patients.

Chagpar We are going to pick up with how we treat bone metastasis and a little bit more on the genetics of cancer metastasis and what we can do about this mysterious problem. Right now we are going to

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take a short break for a Medical Minute, please stay tuned to learn more information about cancer metastasis with my guest, Dr. Don Nguyen.

Medical

Minute The American Cancer Society estimates that in 2014, there will be over 75,000 new cases of melanoma in this country with over 1000 of these patients living in Connecticut. While melanoma accounts for only about 4% of skin cancer cases it causes the most skin cancer deaths. Early detection is the key and when detected early melanoma is easily treated and highly curable. The patients with advanced melanoma have more hope than ever before. Each day patients are surviving the disease due to increased access to advanced therapies and specialized care. 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 test innovative new treatments for melanoma. The goal of the specialized programs for research excellence (SPORE) in skin cancer grant is to better understand the biology of skin cancer with the focus on discovering the targets that will lead to improved diagnosis and treatment. 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. You are listening to the WNPR, Connecticut's public media source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guest Dr. Don Nguyen. We are talking about cancer metastasis, particularly in lung cancer where he has a lab that is looking at how cancers metastasize, how they escape from where they are in a solid organ like the lung and get into the blood stream and take up shop in other places, which has a dismal prognosis for patients. Don, I want to take a step back, we talked a little bit before the break about the clinical implications of cancer metastases, but I want to now understand a bit more about how you go about the process of molecular discovery. How you figure out what genes are turned on and off to make cancers do what they do. Can you take us through that process a bit?

Nguyen In our lab, we start with the assumption that everything has to start from patient material. I think that is where the most useful information can be gleaned, so given the genetic complexity of cancer as a disease, we use a lot of high-end level computational analysis of human material. For instance, patients that undergo surgery, typically early stage patients where their tumors are removed, we have access to sample sets where those tumors have been analyzed at the gene level to look at broad ranges of abnormal patterns of genes that are either increased or decreased or genes that are mutated. And often we find that gene mutations alone are not sufficient to explain how tumor cells metastasize and so we start off by analyzing these different patterns of genetic changes and see how it associates with a patients prognosis, whether this patient went on to develop metastasis or went on to develop resistance to therapy or patients that responded to particular sets of therapies and starting from that very complex information, we kind of integrate it in such way that allows us to propose certain testable hypothesis that we then apply in a number of experiments in the lab.

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Chagpar Let me stop you there just for a couple clarifying questions. The first is, when people talk about cancers they often say that even within the cancer there are multiple different cells and there is really quite a heterogeneous environment, so how do you take advantage of that information, or are all lung cancers cells that are within a certain tumor going to behave identically or do you sample different areas to try to get a sense of that heterogeneity, how does that work?

Nguyen That is a really fascinating question from our perspective and the approach in my lab is we tend to steal a lot of information from other fields, and one of the most useful fields to understanding cancer is actually just normal biology, normal development, and I think that there is a rich body of scientific discovery to describe what normal cells in the lung look like, what genes they should be expressing and also what different cell types are within the lung and so using that information, we believe we can infer the composition of tumors and identify pathways that are linked to specific cell types and to simplify the problem and of course test those hypothesis in model systems that allows us to directly assess whether a certain molecule expressed in a certain cell contributes to metastasis.

Chagpar Tell us a little bit more about how you look at these cells and model systems. How does that work?

Nguyen There are a variety of model systems that we use in our lab. The first is that we can manipulate certain genes in cancer cells so we can use well established human cancer cell lines that we can grow in the lab and manipulate in such a way to affect their ability to metastasize and the way that we assay for these different capacities is actually by transplanting these cells into a mouse and the mouse models have actually proven to be very efficient and very useful at understanding the biology of cancer in general, and so that is a very good experimental model system to understand the different steps of metastasis. The other approach that we use also is to generate lung cancers in a mouse, so this would be tumors that are generated from the start in the mouse and this is using approaches that are referred to as genetically engineered mouse models.

Chagpar A lot of people talk about mouse models and a lot of science is actually based on mouse models, but I wonder, how much can you really translate from mice? I mean this is not really the story of mice and men, is there not a difference, you would think that the human model is much more complex? How tight is that linkage and can you really take discoveries that you find in a mouse or pathways that are working or not working in a mouse, and translate that into human biology?

Nguyen There is no doubt that scientific history tells us that is possible. But at the same time we do have to acknowledge limitations of the mouse model. One of the limitations of course is that even when you develop cancers in mice they are never as genetically complex as cancers in humans. This is why I think a complementary approach is to start with human material and see how it behaves. The mouse model, however, is essential to understand the process of metastasis because as we talked a little bit about in the first segment, what the process of metastasis is, it is a very complex

21:38 into mp3 file http://yalecancercenter.org/podcasts/2014%201019%20YCC%20Answers%20-%20Dr%20Nguyen.mp3 series of physiological advances and it starts with the tumors starting from a single cell in a lung growing in that environment and then escaping from the lung and then getting into circulation and then going through certain circulatory patterns and surviving that tortuous trip to lead to a distant organ and then getting out of the blood stream into a new organ and then growing out and so without an animal model system you cannot really recapitulate that and the mouse model is one of the best studied physiological systems that we have at the present moment.

Chagpar Tell us a little bit more about how you use that model, I mean when I think about this I think you have a series of steps and at each step you have got a light that goes on or goes off that allows certain genes to be turned

on or turned off that allows these cancer cells to move to the next step of okay, this particular gene if it is turned on, it is going to allow these cancer cells to get out into the circulation and when they finally get out of the circulation and into the bone you are going to have other genes that are turned on, that are going to help it chew down the bony structures, how do you figure out which genes do that?

Nguyen Essentially, and again getting back to the mouse model, we have ways to detect where and when the tumor cells are and one of the technologies we use is whole animal imaging, so whole body imaging, so that we can trace where the cells are, where they are growing and how fast they are growing.

Chagpar So you can trace these little cancer cells, cells are microns, right?

Nguyen Absolutely, there are a lot advances in terms of imaging so we can basically put a name tag onto a cancer and are able to find it and kind of scan it as it travels through an animal and so that really has been a major breakthrough in studying cancer metastasis, because previously it has been very difficult to detect small numbers of cells that are traveling throughout the blood stream and so I think that with these new technologies we will be able to detect small numbers of cells in different areas and that is going to help to unlock some of the different mechanisms of metastasis.

Chagpar And once you identify where these cancer cells are, where are they traveling? I mean, now you know that the cancer cell went from the lung, it is now in the blood stream and then five minutes later now it is knocking at the door of the bone, how do you know what genes are turned on even when you know where these cancer cells are?

Nguyen It is being able to detect when and where the cells are, and once we are able to do that, you can sample these tumors and use some of the genetic technologies that I described previously to identify what changes are associated with cells that are sitting in circulation and what changes are associated with cells sitting in the bone or the brain microenvironment and which of those changes appeared very early as a tumor grew in the lung, because one of the things that I want emphasize from our research that what we are finding is that a lot of the changes that are detected and required for these different later steps for cells to grow in different sites can be detected in early stage tumors and we think that provides an explanation for the fact that a significant proportion of

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Chagpar Speaking of how we translate what you are doing in the laboratory, which sounds fascinating, to what is going on in the clinic, I have a few questions. The first question is, we hear a lot about next generation whole gene sequencing and genetic mutations and all of these fancy alphabet soup genes that people are targeting, but how does that correlate with the genes that you are talking about?

Nguyen Often when we talk about all of these, like you said alphabet soup genes, we tend to forget that at its core in order to understand disease we have to understand its biology and so I think the challenge for the scientific community is to take all this alphabet soup and try to use that information, which really is just a roadmap, and try to piece it together, which part of this roadmap will lead to cancer metastasis or lead to resistance of therapy or lead to therapeutic response, which is what we really want to do. As I mentioned, our lab uses a very integrated approach, we have in my lab different people with different skill sets that can integrate these different types of information that we then go on to test in the biological model in order to simplify all this complex information to determine what of this information is relevant and what of this information is not.

Chagpar The other question that comes out is when people are thinking about, how you do this whole body imaging of this mouse and I am thinking about cancer cells having a flag as they run through the circulation and you are watching this thing putter about, does the same kind of technology exist for humans and can you actually tag a cancer cell and watch it circulate and then use that same technology to see what genes are turned on and off in the human system?

Nguyen I think that the technology is moving there, definitely. And one of the benefits of studying the basic biology of metastasis is, as you mentioned, we identify genes that are apparently expressed in certain tumors. Now, what we hope to do is to be able to use those same genes as markers to then develop imaging reagents towards those molecules and to then be able to trace tumor cells in a human being. There are other types of technology actually where we can detect tumor cells from the blood, and several of my colleagues here at the Cancer Center are interested in sampling blood from cancer patients to detect

what is called circulating tumor cells. There are a lot of different technologies on the cusp of being deployed and allowing us to image a patient's cancer cells.

Chagpar Another question that frequently comes up and I appreciate the fact that learning how cancer cells work, where they are going, what genes are expressed when they are in the circulation leads us to identify circulating tumor cells and get better imaging, which is fabulous, but I think for a lot of cancer patients is more than detection its, okay so once you detected then what? How do you search and actually kill cancer cells. In our last minute, can you tell us what you think are going to be the key therapeutic promises for metastatic disease?

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Nguyen Right, I think that again it is getting back to this notion of integration. I think that there have been a lot of technological advances and we have a clear understanding of the genetic changes that leads to a tumor and now I think a lot of the new therapies that are going to be deployed to treat metastasis have to do with how do we interfere with the tumor cells ability to interact with its surrounding, it is different, it is tissue and that implies, for instance immunotherapy that has become prominent. How do we tell your body to react to these tumor cells and vice verse how we tell the tumor cells to react differently to its environment to stop it from taking advantage of that surrounding, I think that is the key.

Dr. Don Nguyen is Associate Professor 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 and as an additional resource, archived programs are available in both audio and written form at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.