

Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. 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 1-888-234-4YCC. This week, Dr. Foss welcomes Dr. David Stern for a conversation about oncogenes and cancer. Dr. Stern is Professor of Pathology, Associate Director of Shared Resources and Leader of the Signal Transduction Research Program at Yale Cancer Center. Here is Francine Foss.

Foss Let's start by talking about what your role is in the Cancer Center, you are Director of Shared Resources and the Signal Transduction Program, can you tell our audience a little bit about how the Cancer Center is structured as far as the research programs?

Stern I am happy too. Yale Cancer Center is a federally sponsored comprehensive cancer center which serves to promote basic research and applied research that leads to effective new cancer therapies. The National Cancer Institute funds cancer center is all over the United States and Yale Cancer Center serves as a gathering point for cancer biologists and cancer clinicians at Yale to promote science and translation to the clinic. The Cancer Center does this in a couple of different ways, one way is by fostering research in targeted areas that are especially important for cancer biology and in this context, I am leader of the Signal Transduction Research Program, I will tell you more about that in a minute. The second way the Cancer Centers operate is by promoting activities of core facilities that would be too expensive or too complex for individual cancer investigators to run in their own laboratory operations. At Yale, these include a very large High Throughput DNA Sequencing Facility, and the Yale Center for Genome Analysis. They include a drug company like the High-Throughput Drug Screening Facility which is The Yale Center for Molecular Discovery and other similarly sized core resources that are used by many investigators, so in my role as Director of Shared Resources, I try to ensure that we have the right portfolio of Shared Resources at Yale and ensure that they are operating efficiently and cost effectively to serve the needs of Yale Cancer Center Investigators.

Foss David, can you tell us a little bit about signal transduction? What is signal transduction and how do you go about studying it?

Stern We now know that the fundamental processes that are dysregulated in all human cancers are what we call signal transduction processes. Cancer is fundamentally a disease of having too many cells in one place at one time and

this occurs either because cells are dividing when they should not or they are not committing suicide when they should. In normal tissues in organisms, cell division and cell survival are tightly regulated by the presence of hormones that stimulate cell division, promote differentiation or protect cells from committing suicide. These hormones are sometimes called growth factors. They work by binding to receptors on the cell surface and the receptors then actuate a cascade of signals and processes inside the cell that ultimately leads to cell division

3:53 into mp3 file <http://yalecancercenter.org/podcasts/2012%201202%20YCC%20Answers%20-%20Dr%20Stern%20copy.mp3> or survival. Collectively, these processes are known as signal transduction processes and generally speaking all human cancers are promoted by excessive activity or inactivity of components of these processes.

Foss So, this is a very complicated system that happens within the cell?

Stern It is the parts of the system that operate inside the cell that are somewhat complicated, but the basic system is very simple. Cells express many cell surface hormone receptors which are normally inactive. If a cell is to divide, a hormone will be made available at the surface of the cell, it will bind to the receptor on the cell surface and the receptor then initiates a cascade of signals into the cells. Often in human cancers, there are mutations that either turn the receptor on chronically, even when a hormone is not present, or turn on some components of the signal in pathways that the receptor normally activates. As a consequence, the cell thinks it should divide when in fact it should not and these are processes that are normally up regulated in cancers.

Foss So, normally these little messengers are floating around in the blood system looking for the right address so to speak and if they find the right address they land on that cell and they tell it to do something, but sometimes the cells decide to go off on their own and do what they want to do basically and that is when you get cancer.

Stern That is very nicely put Francine. The problem is the cell thinks that it has seen a signal to divide when it actually should not, again this can occur because the receptor is mutated and turned on when it should not be, or the receptor might be over expressed, or again one of the proteins normally activated by these receptors has a mutation or other change that causes it to be excessively active.

Foss So, these changes that are happening in cells, are they happening at the level of the DNA being mutated, or are they happening for other reasons? How do we understand that whole process of how a cell becomes a cancer cell?

Stern We do know and we have known for decades that cancer is often initiated by mutations which change the actual structure of the DNA and the structure of the proteins that are encoded by the DNA. Now we know that many of those mutations directly affect components of these signaling cascades, so generally speaking human cancers will often have mutations that change the structure of the receptor or the structure of a signaling protein, such that these proteins are active when they would normally be quiet. Likewise, there are other proteins that normally serve to prevent cells from dividing too often or promote cell suicide and these are mutations that either turn off expression of one of these cancer breaking proteins called tumors suppressors, or prevent production of one of these growth inhibitory proteins.

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Foss So basically you can have two things going on at the same time. You have got signals that make a cell grow and signals that make a cell stop growing?

Stern Yes, the cells have their own checks and balances much as our society does and there are many layers of controls to prevent cells from dividing when they should not and to ensure that the organism maintains its proper structure and pattern.

Foss The whole process of cell dividing happens all the time in our body because we have to replace cells that are dying like in our mouth and in our intestine where they come and go quickly, so the body does have a normal regulatory system for this?

Stern Yes, and because our bodies have very complex structures and as you say they are dynamically regulated, there is a great need to regulate division and differentiation of specific subsets of cells in different places in the body at different times, and that is why all of these regulatory systems exist.

Foss David, how often do you think that these regulatory systems go awry, in other words are there changes that are happening in our body all the time that we do not know about that do not turn into cancer, or do these always turn into cancer?

Stern We know that mutation itself is a chronic process that occurs in every cell as a direct consequence of metabolic processes and more mutations can be generated if individuals are exposed to environmental carcinogens including tobacco smoke or some industrial chemicals, but even without these environmental exposures the cells in the body are constantly encountering changes in their DNA. As a consequence, all living organisms have evolved very complicated systems to repair damage to DNA structures so that these mutations as they develop are quickly fixed, hopefully before the cell is divided and passes these changes on to the next generation of cells.

Foss A lot of people ask the question, how did I get this cancer? What did I do wrong? Why did this happen to me? It is difficult for people to understand what is happening at the very fundamental level of the cell and how these mutations occur. You mentioned chemicals and tobacco, are there other risks factors that you know of, other things that might be promoting cancer?

Stern As you mentioned, unfortunately a common question cancer patients will have is what they did to cause the cancer and the answer is that a major component of developing cancer is simply bad luck because these processes are occurring constantly in all individuals and because development of the cancer might take 6 or 12 major mutations. Unfortunately, we are all at risk over time for developing cancers. There are additional factors that can play into cancer risk and as we have discussed, exposure to environmental carcinogens or dietary carcinogens, especially tobacco smoke, are issues that the individual has some control over. Another important behavioral risk that

10:58 into mp3 file <http://yalecancercenter.org/podcasts/2012%201202%20YCC%20Answers%20-%20Dr%20Stern%20copy.mp3> we have learned about recently including studies at Yale is tanning in tanning facilities because we know that exposure to ultraviolet light which induces tanning of skin does so by damaging DNA and damaging cells and this promotes the development of skin cancer, so that is another important behavioral area individuals have some control over. Another kind of risk factor is a hereditary risk factor. We know that there are some cancers, fortunately relatively rare, that are in fact inherited from parent to child with variant degrees of risk and we have learned a lot

about cancer processes from studying the nature of individual hereditary cancer promoting genes.

Foss David, you mentioned that a lot of cancers require not one but more than one mutation, is this a process then that takes years and years to develop? Is the average cancer something that happens over time?

Stern There is very good evidence from the incidence of single large exposures to radiation, the atomic bombings in Japan during World War II being one example, and also changes in the rate of tobacco smoking among different populations in this country, and what these exposure studies have told us is that there is often a lag time of between 15 and 20 years between major environmental exposures that promote cancer and the onset of high risk for development of cancers.

Foss I know a lot of people in the audience are probably thinking, is there any way that I can find out whether I have any of these mutations? We talk a lot about genetic screening on this program, is there anything available now-a-days that would help someone to know whether or not they have mutations and are at risk?

Stern As I mentioned earlier, fortunately hereditary cancers are relatively rare in the population but certain types of hereditary cancer are more common than others. One example is hereditary mutations and the genes known as BRCA1 and BRCA2 that are associated with high risk over a lifetime for breast cancer and these now can be routinely screened through genetic counseling centers including one available at the Yale Medical School.

Foss David, we are going to have to take a break now for a medical minute. Please stay tuned to learn more information about oncogenes and signal transduction in cancer with Dr. David Stern.

Medical

Minute It is estimated that nearly 200,000 men in the U.S. will be diagnosed with prostate cancer this year and one in six American men will develop prostate cancer in the course of his lifetime. Fortunately, major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from the disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. With screening, early detection and a healthy

lifestyle, prostate cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers like

14:25 into mp3 file <http://yalecancercenter.org/podcasts/2012%201202%20YCC%20Answers%20-%20Dr%20Stern%20copy.mp3> the one at Yale to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is an option available for patient's at Yale that uses three dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined today by Dr. David Stern and we are discussing oncogenes and signal transduction in cancer. David, we talked a little bit in the first half of the show about these signaling proteins and mutations that happen in cells that lead to cancer, and we mentioned the word oncogene, but I do not know if the audience really understands what an oncogene is. Can you explain that word to us?

Stern As I mentioned earlier, we have known for decades that cancer is caused by changes in the DNA or gene mutations, and at that time before we knew what the genes were that were affected by those mutations, we just called them oncogenes, and oncogene is basically a gene that when mutated promotes the development of a cancer. Now the important thing about identifying and understanding how these genes work is that they can lead to cancer therapies and as I mentioned earlier we now know that many human cancers are characterized by mutations either in hormone receptors or components of the pathways they activate that promote the cancers and lead to the development of the cancers and because we understand a lot about these proteins, it is actually possible to devise therapeutic agents that interfere with this excessive activity of the receptors or the pathway proteins. There are a number of examples of this nature involving anticancer drugs that are in use in the clinics now. One of the first was a breast cancer drug called Herceptin which is an antibody that binds to and inhibits a hormone receptor called HER2 which is an important driver of about 20% or 25% of breast cancers. This was one of the first examples of an oncogene targeted anticancer drug and it illustrates an important point which is that this drug is very effective for the patients who have breast cancers that are associated with high level expression and activity of this hormone receptor HER2, but this drug probably will not have much impact on patients with other kinds of breast cancers. Likewise, there is another actually related receptor called the EGF receptor which is often activated in a subset of lung cancers and in the minority of lung cancer patients who have tumors that are driven by excessive activity caused by a mutation in the EGF receptor, those patients may benefit from treatment with drugs that inactivate that receptor and those drugs include Erbitux which is an antibody drug that binds to the EGF receptor on

the cell surface and another drug called Tarceva that inactivates the signaling activity of that same receptor and there several others either approved by the FDA or in the therapeutic development pipeline. In both of these instances, again it is important that the correct therapeutic agent be matched to patients with the right kinds of mutations because these agents will be largely ineffective on other cancer patients.

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Foss Along those lines, how important is it for us to be sequencing these tumors? We have talked a little bit on other shows on Yale Cancer Center Answers about a lot of the genomic work being done now to sequence patient's tumors and patient's DNA and I am wondering how important this really is both now and in the future to develop other targeted therapies for these mutations.

Stern Right now, thanks to incredible technological developments and reductions in cost in DNA sequencing, we are approaching an era in which it will become possible to determine the DNA sequence of the tumor for every patient that comes in for treatment. Already at Yale and elsewhere targeted re-sequencing is going on so that genes such as the EGF receptor or BRCA1 or HER2 are evaluated by DNA sequencing and other measurements so that the appropriate drugs can be matched. Unfortunately, this is just the beginning of a long complex process. At this point only a minority of cancers are associated with mutations for which we have good FDA approved drugs and a lot of the activity in the therapeutic development pipeline is bringing out drugs that target more and more of the signaling proteins that we know are potentially important. A second is that in some cases we learn from re-sequencing tumors that we cannot always identify mutations that drive these tumors and then for those patients it would be difficult to develop or identify the appropriate drug. One of the reasons is that not all cancers are driven by small changes in the DNA that we can recognize and understand, but rather they are driven by larger scale chromosomal changes that may even create new kinds of proteins and these are areas under intensive investigation in the research community, so for certain genes and drug targets we know a lot and we can make strong predications and we have good drugs. For the majority of tumor types, we're often in the learning and evaluation stages.

Foss David, you mentioned HER2 and how important that really has been in breast cancer and other cancers as well, but you actually were involved in some of the early research related to the development of HER2. Could you tell us a little about that?

Stern I am always happy to discuss HER2. When I started in this field in the 1980s that was the time when it was just becoming possible to identify human oncogenes. HER2 was actually first discovered as an oncogene not in humans, but in rat neuroblastomas in Bob Weinberg's lab at MIT, and I joined that project at a time when we knew that certain neuroblastoma cell lines had activity of a gene that was called NEU for neuroblastoma and we also had antibodies that could recognize that protein and that was really it, and my job as a fellow in the lab was to try and figure out what that protein did. In the course of my investigations with some of my colleagues in the lab we learned that the NEU protein was closely related to the hormone receptor already understood called the EGF receptor and that already told us a lot about the new protein and secondly I found that NEU could actually be activated by EGF but that strangely EGF did not bind directly to the NEU protein. We later learned that NEU, now known as HER2 or ERBB2, is a member of a four hormone receptor family, and that within the family there are 12 different hormones that can activate one or more of the receptors in the family and that when these receptors are activated they form complexes with other receptors in the family and they cross activate. That led to much of our

22:54 into mp3 file <http://yalecancercenter.org/podcasts/2012%201202%20YCC%20Answers%20-%20Dr%20Stern%20copy.mp3> early work done at Yale in understanding this somewhat complex hormone receptor system and it turns out that all four of the receptors in this family are involved and important in different human cancers.

Foss At the time that you are doing this work, did you envision that HER2 would become a therapy and would make the kind of impact that it has made in breast cancer therapy?

Stern Interestingly enough, at the time we were working on this rat oncogene it was only as a model system and that was because at that time we were doing this work it was not known that it was connected with a human cancer. In fact, in parallel to our work on the understanding of how this oncogene protein worked, our lab set up a collaboration with another group at the Dana-Farber Cancer Institute led by Mark Green, and Mark Green realized that since we were working on a hormone receptor that was exposed at the surface of the cell, it might be a good model system for evaluating whether antibodies could be injected into organisms and block the activity of an oncogenic protein, so working with our lab, Mark Green's lab developed monoclonal antibodies against this rat oncogene product and then the lab showed that when those antibodies were injected into rats bearing tumors induced by the new oncogene,

that these tumors were held in check and this was actually the first proof or principle that you could control a tumor with injection of an antibody that binds to hormone receptor . Then, about two years later, Dennis Slayman's group at UCLA discovered that the human relative of NEU, called HER2, is very important in human breast cancer and at that time all of the preclinical work that Mark Green's lab had done and our lab had done became very relevant and led in part to the rapid development of the antibody drug Herceptin by Genentech.

Foss And basically, what we do now with Herceptin is inject it into women the same way you did into the mice and it shrinks their breast cancer tumors, that is a tremendous story David about marrying basic cancer biology with translational research and that segue ways into the next question I was going to ask you which is, can you tell our audience why basic research in cancer biology is still critical and how you integrate on the clinical side of things to bring new treatments into the clinic?

Stern When I first started in cancer research the collaborations between basic scientists trying to understand cancer biology and genetics, and clinicians who were treating cancer patients, these connections were often fairly distant and that was because we did not have a conceptual framework or understanding of cancer to identify drug targets quickly, and so there was little common ground for connecting the clinicians, except within the areas of genotoxic and radiotherapies and that has changed dramatically now that we understand a lot about the systems that drive human cancers. Now-a-days it is routine even for the basic cancer scientist to work closely with clinical teams because even cancer genes that are identified in model systems like worms, flies or in rodent models, often the systems can be connected directly with specific

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human cancers. So now-a-days scientists like myself, and I still consider myself to be fundamentally a biologist, are working very closely with clinical translational teams in the cancers we're most interested in and right now those include breast cancers and melanoma and also because the signaling systems we study are important in all human cancers, we are beginning to develop collaborative relationships in other cancers including lung cancer and pancreatic cancer.

Foss You mentioned melanoma, and I know there is a lot of exciting work being done there with new targets as well. Can you speak a little bit

about your role in the development of those new therapies?

Stern There is great excitement in melanoma, which five years ago was regarded as an intractable disease, and that is occurring on two major fronts. One area is in signaling related drugs. It turns out that about 40% of human melanomas are driven by mutations in a gene called BRAF and BRAF is one of the components of the signaling chain that is activated by the growth factor receptors that we and others work on. A few years ago, a couple of drug companies became interested in developing therapeutics that selectively target BRAF when it is turned on and at least two of these agents, one is called vemurafenib have been FDA approved and these agents are having great impact on this subset of melanoma patients in the clinic. So, one exciting area in melanoma is the development of the signaling targeted drugs. Unfortunately, a subset of the BRAF mutated melanoma patients do not respond to this drug and other patients often develop resistance, so one area we're working on quite a bit is to look for combination signaling therapies that will have an impact on these BRAF mutated patients. The second area, which I am sure will be the subject of many Cancer Center Answers podcasts is the development of so called immunomodulation; therapeutic approaches for melanoma. This work was pioneered by individuals including Lieping Chen and Mario Sznol, who led some of the clinical trials on PD-1 inhibitors and these therapies ramp up the immune attack on cancers including melanoma and apparently renal cell carcinoma and lung cancer as well.

Dr. David Stern is Professor of Pathology, Associate Director of Shared Resources and leader of the Signal Transduction Research Program at Yale Cancer Center. If you have questions or would like to add your comments, visit yalecancercenter.org where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.