

Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. 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](mailto:canceranswers@yale.edu) and the phone number is 1-888-234-4YCC. This week, Francine is joined by Dr. David Stern. Dr Stern is Professor of Pathology at the Yale School of Medicine, Associate Director of the Shared Resources Program and Leader of the Signal Transduction and Research Program at Yale Cancer Center. Here is Francine Foss.

Foss: David, you primarily work as cancer biologist and so you are not in the clinic, you are actually in the research setting. Can you talk to us a little bit about what got you interested in cancer biology?

Stern: I became interested in biological sciences, in general, as a kid, and as I grew older and went to college, I entered college during the first provision of molecular genetics in understanding how animal cells operate, and around the same time the cancer problem, which had vexed clinicians and scientists for centuries, was becoming tractable through the study of viruses that caused cancer in animals. So, early on in my research experiences I became engaged in research to study how viruses that cause induce cancers, and as it turns out, that early area of research in the 1970s and 1980s turned out to be directly applicable to our understanding of human cancer.

Foss: Can you talk to us about what that connection was?

Stern: The connection turned out to be that many of the viruses that caused cancer in model animal systems, including mice and chickens, turn out to carry what are called oncogenes. These genes are introduced into cells they infect and take over normal cellular systems and in many cases induce them to grow abnormally in the same way cancer cells grow abnormally. Over a period of years, as these genes were identified and their functions were tracked down, it turned out that many of these same genes directly cause specific human cancers, or alternatively, regulate the same kinds of processes that human cancer genes regulate.

Foss: So are these oncogenes are genes that were carried by viruses, or are they primarily in viruses?

Stern: Actually, these families of oncogenes, although they were carried by viruses, were originally picked up by those viruses and their ancestors from cells that they infected, and this is why it turned out that many of those oncogenes were very closely related to genes that cause human cancer. For example, a virus called Harvey Sarcoma Virus had picked up a gene called RAS from a mouse cell that it had infected and then once that gene was captured by the virus and was slightly altered by mutation, the virus became capable of inducing cancers in other cells that it infected.

Foss: So these oncogenes, are they present in all humans?

Stern: 3:28 into mp3 file [http://yalecancercenter.org/podcasts/2011\\_0814\\_YCC\\_Answers\\_-\\_Dr.\\_Stern.mp3](http://yalecancercenter.org/podcasts/2011_0814_YCC_Answers_-_Dr._Stern.mp3)

Stern: Oncogenes are defined as genes that have sustained mutations in such a way that they promote the process of cancer, so oncogenes in humans are altered versions of normal cellular genes that because of mutations, or changes in regulation, can now promote the process

of developing cancers. Foss                      What percentages of cancers are actually caused by these oncogenes? Stern                      I would say that all human cancers are caused by genes that are sometimes called oncogenes, that is genes that are mutated so they promote cancer, and sometimes they are subdivided into oncogenes that promote cancer by advancing a normal cellular process such as cell division and other genes called tumor suppressor genes normally prevent cells from dividing or having other cancer like attributes and so when these tumor suppressor genes are mutated they lose their impeding functions and now cells are more likely to divide, or undergo some other cancer like changes. Foss                      Can you talk a little bit about how one gets an oncogene and how an oncogene gets activated or mutated to the point where it is going to cause cancer? Stern                      Unfortunately mutation itself is a process that is occurring chronically in all human cells as a byproduct of normal metabolic processes and mistakes that sometimes occur when cells divide. So, even though exposure to external agents like radiation or environmental carcinogens can enhance the likelihood that mutations will occur, everyone is susceptible to mutations in their genome that may turn out to affect genes that when mutated will promote cancer. Foss                      Thus the question that lot of patients ask, how did I get this cancer, was I exposed to something? And sometimes it is difficult for patients to understand that there may not have been a specific trigger. Stern                      Thanks Francine, that's a very important point. There is no way for individuals to avoid having some baseline mutation rate, which is actually a very high mutation rate, but individuals can of course prevent additional excessive risk by staying away from cigarettes and other activities such as radiation exposure that would accelerate mutagenesis. Foss                      Can a patient get screened for these oncogenes? Are there tests that we can do to tell whether the patient has one of these oncogenes? Stern                      There are two ways that we think about that right now. First of all, there are some families that are cancer prone; for example, in breast cancer maybe 5% or 10% of breast cancers in this country are associated with hereditary mutations and genes called BRCA1 and BRCA2. Individuals in families that are cancer prone may seek out genetic testing to determine if they have mutations in 6:51 into mp3 file [http://yalecancercenter.org/podcasts/2011\\_0814\\_YCC\\_Answers\\_-\\_Dr.\\_Stern.mp3](http://yalecancercenter.org/podcasts/2011_0814_YCC_Answers_-_Dr._Stern.mp3) those genes, since candidate genes have been identified. Nowadays, at a couple of institutions including Smilow Cancer Hospital, the patients who have already developed cancers are being tested for mutations in a certain subset of genes that are common possibly in their cancer subtypes, it might be breast cancer, perhaps lung cancer, and the patients will be tested for these mutations if there are medical treatments that are beneficial to the patient's who are known to have the mutations. Foss                      I am glad that you brought that up because you were actually involved in some of the early work on one of the major breakthroughs with respect to our developing a therapy specifically targeting a gene mutation, and that was the HER2/neu story in breast cancer. Can you talk a little bit about that? Stern                      I would be happy too. After I earned my PhD I went on to post doctoral training in the laboratory of Robert Weinberg at MIT and the project he

assigned me was to work on a peculiar rat oncogene that was called neu at that time but actually turned out to be the rat relative of the human gene now called HER2. So HER2 was first discovered as a rat oncogene and my project was to figure out what was wrong with his rat protein that enabled it to cause cancer in this rat model system. Over the years, I learned about many fundamental properties of the rat protein including the fact that they had an enzymatic activity that we now note to be associated with a large family of hormone receptors that can sometimes cause cancer, and a few years after I began this work, Dennis Slamon, working at UCLA, discovered that this gene is commonly duplicated in about 15% to 20% of breast cancers in this country, and that in those patients the product of this gene called HER2 is a major driving force in sustaining these tumors. Once Dr. Slamon had identified this change the question then was well how could one interfere with this change, this over activity of a hormone receptor that was driving these breast cancers? Also while I was at postdoctoral work we set up a collaboration with another laboratory led by Mark Green, and Mark Green was interested in the rat neu protein because it was a protein that we found was expressed at the surface of cancer cells and Mark thought that perhaps by injecting rats with monoclonal antibodies that would recognize this protein sticking out from the surface of the cell, he might be able to inhibit growth of those cells as tumors. So the Green Lab developed monoclonal antibodies that recognized the rat neu protein and I was a collaborator in these studies. We helped him characterize those antibodies and then Mark showed that in fact, if he had tumors caused by mutation in the neu oncogene, that those tumors were inhibited by injection of a monoclonal antibody that recognized this protein. This work was the pre-clinical foundation for the antibody work that eventually helped Genentech develop a drug that is called Herceptin, and Herceptin, like the original anti-neu antibodies that Mark Green's Lab developed, is an antibody that recognizes the portion of HER2 that projects from the cell surface and the antibody works in the same way as these original mouse experiments did. Foss That is really a fabulous bench to bedside story, how often did those kinds of things happen in cancer research? 10:53 into mp3 file [http://yalecancercenter.org/podcasts/2011\\_0814\\_YCC\\_Answers\\_-\\_Dr.\\_Stern.mp3](http://yalecancercenter.org/podcasts/2011_0814_YCC_Answers_-_Dr._Stern.mp3) Stern I moved to Yale about 22 years ago. At the time we did this work it was very unusual for scientific research to be translated into a human clinical application. In fact, the Herceptin drug targeting HER2 in breast cancer was the very first drug approved by the US Food and Drug Administration that targeted a known oncogene project, and in collaboration with having this drug work for these patients there was the necessity of having a test which would identify the subset of breast cancer patients whose cancers are driven by over expression of HER2. Now this test, which is done either by a technique called FISH or by another technique called immunohistochemistry, is routinely given to breast cancer patients entering our clinics and for women who turn out to have tumors that have excessive expression of HER2, Herceptin treatment is a very common and often effective therapy. Foss And often times the combination of Herceptin with chemotherapy prolongs the

survival of these women as well. Stern That's a really important point. In the early days of developing drugs, targeting signal transduction molecules in Herceptin was one of the first. The hope was that the signal transduction targeted drugs would completely replace the effective but rather difficult chemotherapies and radiation therapies that patients are still routinely treated with. In fact, as we have learned from clinical trials, most of the signaling targeted drugs are ineffectual without being used in combination with other conventional cancer therapies. So these groups of drugs are now used together with one another. Foss David, we started with antibodies binding to these receptors and now we have other small molecule drugs that inhibit some of these signal transduction molecules as well? Stern Yes, Herceptin was one of the prototypes, but in the later part of the 20th century investigators studying how cancer develops in humans found that the majority, if not all human cancers, are characterized by changes in the pathways that regulate cell division. Cell division is the process by which one cell divides to become two cells, and of course in all organisms, this process must be tightly regulated or cells will divide too often and cancers can ensue. It turns out that for mammals, like ourselves, the coordination of cell division at the organism level is achieved in part through intercellular communication, cells send signals to one another through a protein set of hormones and the hormones generally bind receptors on the cell surface and trigger a cascade of processes, a signaling pathway that moves inside the cell and eventually actuates the mechanism that causes cells to divide. Foss Let's talk a little bit more about that process of signal transduction when we come back after our short break for a Medical Minute. Stay tuned to learn about cancer biology with Dr. David Stern. MedicalMinute It is estimated that nearly 200,000 men in the US will be diagnosed with prostate cancer this year and over 2000 new cases will be diagnosed in Connecticut alone. One in six American men will 14:46 into mp3 file [http://yalecancercenter.org/podcasts/2011\\_0814\\_YCC\\_Answers\\_-\\_Dr.\\_Stern.mp3](http://yalecancercenter.org/podcasts/2011_0814_YCC_Answers_-_Dr._Stern.mp3) develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this 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. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is an option available for patients at Yale that uses 3 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](http://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 by my guest today by Dr. David Stern, and we are talking about the complicated area of cancer biology. David, you talked a little bit about how cells receive signals from the outside through these receptors and you call that signal transduction. Can you just define that a

little bit more specifically for the audience? Stern In this current text what we mean is that the cells are exposed to a hormone that instructs the cells to divide, or to survive, or to do any number of other things. The hormone will bind to a receptor and the receptor itself activates a series of changes like a pathway inside the cell and at the end point of the series of changes is an activation of the cell division mechanism. Now it turns out, that in human cancers, we can cause excessive cell division, for example, by excessive production of hormones that promote cell division or by putting mutations in the receptor genes so that the receptor is over expressed, or so that the receptor is signaling as if it had bound to the hormone that normally activates it, even in cases where the hormone isn't around. That's a very common cancer mechanism and the proteins that operate down stream are the pathways from these activated receptors that can also be mutated to likewise tell the cell to divide when it should not. Foss So these pathways inside the cells are very complicated? Stern The pathways are complicated when taken down to their smallest components, but in a general, they are just a series of signals handed off from protein to another protein and eventually communicating to various target proteins that either change expression of genes or activate a process like cell division. Foss So basically you switch a light switch on and then eventually the light bulb goes on? Stern Yes, that's an excellent analogy except instead of having wires to connect the switches, there is a relay of components involving several components in a series rather than just a single wire connecting the switch to the bulb. 18:10 into mp3 file [http://yalecancercenter.org/podcasts/2011\\_0814\\_YCC\\_Answers\\_-\\_Dr.\\_Stern.mp3](http://yalecancercenter.org/podcasts/2011_0814_YCC_Answers_-_Dr._Stern.mp3) Foss In the case of cancer cells, are there multiple areas where there are mutations or generally is there just a single mutation? Stern What we find is that there are a couple of pathways that are commonly activated in cancers, some of which promote cell division, some of which promote cell survival under circumstances where cells might be inclined otherwise to commit suicide and within these pathways almost any component can be mutated to activate the pathway and so in the pathways regulated by HER2, and its relative the epidermal growth receptor, both of which are often mutated in cancers. Below the receptors are genes called RAS, actually a family of three genes and these genes are mutated in many-many human cancers. Below RAS is another protein called BRAF that is often mutated in melanoma and mutated in renal cell carcinoma and sometimes in colon cancer and other proteins below that can be activated. Foss Identifying these proteins has led to the development of new drugs targeting those specific proteins and some of this work has been done at Yale, correct? Stern Yes, actually lot of this work has been done at Yale as well as at many leading research institutes internationally and the good news about understanding these pathways is that it is possible to develop drugs to intervene, for example, if there is a tumor that is driven by an activation of one of the receptors, including HER2 or the epidermal growth factor receptor, one can interfere with the growth of the these tumors in principles either by directing an antibody against the receptor that is activated or developing a small molecule drug that

inactivates what is called the warhead of the receptor, the component that signals to the next protein down the chain. There are many such drugs now including Tarceva and Tykerb which are in use in the clinics now, or one can interfere with the BRAF protein. There is a drug developed by a company called Plexxikon that was started by the chief of pharmacology here Yossi Schlessinger, who is also Director of our new Cancer Research Institute. All of these drugs in principle may help patients who have excessive activation of the pathways regulated by these receptors. Foss

And again, just to let patients know, none of these drugs would be out there if basic cancer biologists like yourself had not gone in and identified these pathways that were mutated. Stern

Thanks for bringing that up. The chain of events that led to the development of all of the new cancer therapies including the immune modulators, the PARP inhibitors, the signaling drugs such as Arissa, Tarceva, Herceptin, BRAF inhibitors, all of these drugs were developed as the result of a chain of basic research that began 25 to 30 years ago, and even earlier. Much of the scientific knowledge that the development of these drugs was built on has developed over an extended period of time, and every step was necessary for us to have the depth of understanding required to develop these therapies with having a good chance of them being effective and also being safe. Foss

That goes into the next part of the discussion which is your role at Yale Cancer Center and the Shared Resource Center. There have been a lot of new technologies that have been developed that 22:11 into mp3 file [http://yalecancercenter.org/podcasts/2011\\_0814\\_YCC\\_Answers\\_-\\_Dr.\\_Stern.mp3](http://yalecancercenter.org/podcasts/2011_0814_YCC_Answers_-_Dr._Stern.mp3) have helped in terms of this effort and one of those is genome-sequencing. Can you let our audience know a little bit about what that is and how that has been useful? Stern

First of all I should say my role in this has been minimal except that in my capacity as Director of Shared Resources for Yale Cancer Center I try and monitor and encourage core facilities at Yale that will benefit the development of cancer research and cancer therapies. One of the most important technologies that has been developed recently and has been invested in heavily by the University under the auspices of Rick Lifton and the Yale Center for Genome Research is high throughput DNA sequencing. This technology is an outgrowth of DNA sequencing technologies that were developed 20 or 30 years ago and first for you to understand this I should explain what DNA sequencing is. The genetic information in our chromosome is embodied in individual genes each of which has a specific function. The genes themselves are very much like words that are spelled out with four letters called nucleotides. It's the sequence of the nucleotides in each gene that spells out the word that is the gene and encodes the nature of the product of that gene. The product may be a protein or an RNA molecule, some kind of molecule that has a function in the cell. When a mutation develops in the genome, the DNA sequence changes and by comparing the series of letters in the gene from tumor tissue to the sequence of the same gene in normal tissue from the same patient, one can determine if a mutation has occurred. Ten years ago, this was possible only when one was interested in a particular candidate gene such as one of the RAS

genes, but the problem was that there are at least 30,000 genes in the human genome. New high throughput sequencing technologies make it possible to look for mutations, gene by gene, over this entire 30,000 gene complement in research samples, and soon in patient sample. To give you an idea of the cost at this point in a research setting it is possible to obtain this information for a few thousand dollars. The entire set of mutations in an entire genome. To perform a single DNA diagnostic test at the hospital nowadays also costs on the order of a few thousand dollars. So this is a revolutionary technology both in terms of discovering what kinds of genes are mutated in human cancers and in coming years we expect that these technologies will be applied as part of a routine clinical diagnostic workup for cancer patients. Foss

At this point in time, it is not part of a clinical routine? Stern

At this point in time, the technologies and cost are getting into the range where one can easily imagine that it will occur, but there are still huge practical problems first in developing approved clinical quality methods for doing this, and secondly in handling the enormous amount of information that comes with sequencing entire patient genomes or coding sequences. Foss

How long does it take to obtain the sequence from one tumor? Stern

In a research setting the analysis can be done at the Yale facility in a period of days after a wait on the queue, but at that point, having the DNA sequence is just the beginning of a long analytical process because this is such a large collection of information. As I said, it pertains to 30,000 genes 26:49 into mp3 file [http://yalecancercenter.org/podcasts/2011\\_0814\\_YCC\\_Answers\\_-\\_Dr.\\_Stern.mp3](http://yalecancercenter.org/podcasts/2011_0814_YCC_Answers_-_Dr._Stern.mp3) and there is quite a bit of analysis required by experts and bioinformatics to help weed out the most interesting changes. Foss

It sounds like the needle in the haystack story. Stern

In some tumors it is a needle in the haystack. One of the issues has been in the enormous variability in the human genome among individuals and as more individual human genomes are sequenced we're learning more about which changes are common in the human population and probably not connected with the cancers, and which are unusual. The other advantage of working with cancer patients is that most of the mutations that cause the tumors actually develop in the patient in the lifetime of the individual, and that means that any unusual sequence that is also found in normal DNA from that same patient, is unlikely to be interesting. Foss

That gets into another question and I think you alluded to this at the beginning, and that is the whole issue of DNA repair. You have got all these genes out there that may become mutated and then you have got a process to repair them, so what goes wrong in cancer? Stern

As I mentioned at the beginning DNA mutation is a corollary of life and all living organisms are constantly subjected to mutations in their DNA. In fact, the same DNA repair processes that are present in mammals many of them are also present in bacteria. As a result of the constant need of organisms to repair DNA, they have developed a number of DNA repair systems that seek out changes in the DNA and fix them before they are passed down to daughter cells. There are certain human hereditary cancers that are caused by alterations that inactivate one or more of these DNA repair systems. These

include a disease called xeroderma pigmentosum, which is a result of the mutation that prevents cells from repairing sunlight induced DNA damage and as a consequence these individuals are at very high risk for development of multiple skin cancers and we also mentioned earlier that there were two hereditary mutations, one in BRCA1 and one in BRCA2, each of which can cause a large minority of familial breast cancers. It turns out that mutations in these two genes interfere with another form of DNA repair called recombination of repair. Dr. David Stern is Professor of Pathology at Yale School of Medicine, Associate Director of the Shared Resources Program and leader of the Signal Transduction Research Program at Yale Cancer Center. If you have questions or would like to share your comments, visit [yalecancercenter.org](http://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.