

Yale CANCER
CENTER

answers

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**Pinpointing Oncogenes to
Destroy Cancer**

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Yale Cancer Center Answers

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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. Chagpar welcomes Dr. Frank Slack. Dr. Slack is Professor of Molecular, Cellular & Developmental Biology at Yale School of Medicine. Here is Anees Chagpar.

Chagpar Frank, we read all of the time about genomics and the genome and the whole Human Genome Project. Tell us a little bit about what exactly that is?

Slack The Human Genome Project was a very ambitious project conducted within the past 15 years or so, a very expensive project, but one that has definitely given us back so much valuable information, and opened so many avenues and doors. I liken the human genome project to the way that the skies opened up with the discovery of telescopes. Without the human genomes sequence, the string of all the letters that make up a human being, we really did not have a good map of what made us human, and what was similar amongst the different humans, and what was different in certain diseases, but having that human genome sequence really allowed us to go and explore the differences in the genomes of healthy individuals versus diseased individuals or healthy tissue versus diseased tissue and it has helped us pinpoint the key genes that are involved in many different diseases, and no disease has benefited more than cancer right now. So much so that the Human Genome Project has now morphed into the cancer genome project where people are basically sequencing individual cancer patients to find out how their genome is different from an uncancerous or noncancerous genome.

Chagpar Is this the same thing as when people have genetic testing? If they are at risk, they go and they see a genetic counselor and then they have genetic testing, is that the same thing as genomics or are they related, how does that work?

Slack They are definitely related. A genetic test in general would be the equivalent of having one of your genes looked, or just one position in one of your genes looked at, and one of those letters like A, the G, the C, or the T could be tested in one of those tests. Genomics is the sum of all the genes in a genome. Up until the Human Genome Project we really just had the ability to look at certain genes, for example, famous cancer genes like BRCA1 could be tested and you could see whether any of the letters A, C, Gs or T's were changed in a BRCA1 gene but of course many cancer patients do not have mutations in BRCA1. Now we are left with this challenge of trying to discover what is different about their genomes and genomics would allow us now to examine their entire genome and find out the differences in all the genes and if we are lucky we will find that there is one particular gene that stands out as being definitely mutated in those patients and that will be a gene we can then focus on for sensitive targeted therapeutic.

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- Chagpar That sounds like it is a ton of information, how many genes do people have?
- Slack The standard answer to that is that it is a moving target. Humans probably have about 25,000 recognized genes, so you can think of that as a haystack and we need to find that one little needle in the haystack. So the human genome is made up of three billion of those letters A, C, Gs and Ts and in some cases it is just one of those that can be mutated that can be the key in pushing itself into a cancer state, so finding that one particular change is equivalent to finding a needle in a haystack. We are getting better at identifying those needles more cheaply and more quickly to the point where it is not too far off that every cancer patient is likely to have their tumor genome sequenced as part of the workup that the oncologist would do for that patient.
- Chagpar When you say that they may have their tumor sequenced, that is different than the blood test for a normal patient and maybe looking at their risk, you are actually looking at the tumor itself, how does that work?
- Slack It is almost certain that tumors are going to be sequenced, but in order to make a valid comparison, you need to have something to actually compare it to because everybody's genome is slightly different from everybody else. Probably what will happen is that not only will the patient have their tumor DNA sequenced, but they also will have their germline DNA sequenced, that is DNA that is found in every cell presumably, every normal cell in their body. It usually comes from a cheek swab or from a blood draw or something like that. There are two broad classes of mutations that are thought to influence cancer, those that are derived in individual cells that lead to those cells becoming tumors, and those are tumor derived mutations, but then there are other mutations that we can inherit from our parents that give us an increased susceptibility to cancer and the most famous one of those is the BRCA1 gene in breast cancer. But there are other cancer susceptibilities that can be detected in a genome test or a genetic test from a blood draw, but it is generally accepted now that cancer is not a disease of just a single mutation, or one gene going awry, but it is really a combination of many thing coming together, the right combination, that can drive the cancers, so knowing the complete genome sequence is probably going to be imperative to truly understanding that individual's cancer.
- Chagpar People could have their tumor sequenced and find that they have multiple different mistakes in different genes.
- Slack Right.
- Chagpar And that leads me back to something that you said earlier, which is the whole idea of doing genomics is not just to find out where the mistake is, but to be able to target it, to be able to treat it, to be able to potentially prevent it, how does that happen?

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Slack That is the goal of a lot of cancer research. In fact, I would say that we are probably ahead of ourselves to some extent. We probably know more about the genome of the cancer patient than we know about how to actually fix that cancer patient, but having that information is a very important first step, it is a handle that allows us to now go and test for drugs that can affect those particular mutant genes, and that is the ultimate goal, once we have discovered the complement of different mutant genes in a cancer patient, we want to then be able to test drugs that can specifically affect those cancer cells without affecting the normal cells that are not mutated. That is the reason why cancer research is a fairly expensive operation and it definitely explains why cancer is a disease that still has not had a cure after 30 years of trying to solve this problem. We have had some major breakthroughs in our understanding of cancer over the last 30 years, do not get me wrong. One thing that we have realized is that because cancer is a disease of our own cells and our own genes for the most part and because everybody's genes are slightly different from everybody else's, I should say everybody's genome is slightly different, in general we all have the same genes but we might have different varieties of those genes, everybody's cancer is slightly different from everybody else's. That is a big realization that we came to in this decade and that means that ultimately every cancer patient is going to have to be personally treated for their complement of mutations and their complement of altered genes, and that can be very expensive. Lucky for us, the genome sequencing part is becoming a lot cheaper and there is definitely talk about a cancer patient being able to have their tumor DNA sequenced for about \$1000, and that will be something that will be happening over the next years. When that happens it will just become part of the medical record, I believe that everybody will have their tumor DNA sequenced, will have their germline DNA sequenced, it will be a computer program that will match and compare those to find the mutations that look different or the regions of the genomes that are different in the tumor relative to the normal cells and we will then be able, hopefully, to identify a handful of key genes where we know what drug will work against it, and quickly get those patients on a regimen of drugs that we have a pretty good idea will work against that particular set of genes.

Chagpar Tell us a little bit more about the genome, I mean all of us who are sitting here listening can remember back to grade 7 biology and learning about genes and DNA and RNA and so when we talk about a gene, are we are taking about the DNA sequence or we are talking about RNA or coding and noncoding regions, how does that all work?

Slack That is an excellent question, and things have dramatically changed since we were in high school that is for sure. The concept of a gene from a geneticist's point of view has not changed. The gene is a stretch of DNA that carries some hereditary information, some information that can get passed down from one cell to the next, from one parent to the children. But what we now understand of a gene in terms of how it looks structurally in the genome, that has changed quite dramatically. In the past, we thought of a gene as basically being a piece of DNA that is coded for some protein sequence and the gene generally was thought of as being the punctuation mark that tells you to start making the protein to the punctuation mark that told you to stop making the protein. We now

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know that there is a lot more information in the genome, even in the sequences or those letters that flank the punctuation mark start and stop, that should probably be considered part of the gene, they are the parts that will promote the use of the gene, will stop the use of the gene, they are also important parts of the gene. More importantly, we now know that not all genes in fact code for proteins, not all genes have these start and stop punctuation marks. There are genes that make other types of molecules that are equally important in the cell or the codes for other molecules. If you include our broader understanding of a gene, we probably have many more than 25,000 genes in our genome. We have 25,000 protein coding genes and many, many, more genes that code for other kinds or molecules, most commonly RNA molecules related to DNA but they also have the ability to actually do work within a cell and carry information around themselves.

Chagpar Are people looking at those RNAs, do they have any influence on cancer?

Slack I would say over the last 10 years things have dramatically changed and our view of genes and what gets made in a normal cell, and what is made in a cancerous cell. In fact, one of the great revelations, in fact it is a the research that my lab focuses on most intensely now, are these other kinds of RNAs that are being made within cells? The most famous of the cancer causing genes like BRCA1 and RAS, MEK which are commonly mutated genes in cancer, they do code for proteins and we know a lot about those particular proteins, those proteins do very very important things within cells. But over the past 20 years or so we have come to realize that cells make a lot of noncoding RNAs and these RNAs do not actually code for proteins, in fact they do play important roles in cancers and that is something that we are working on quite intensely.

Chagpar I would love to learn more about those microRNAs and how they are working in cancer, and we are going to do that right after we take a short break for a medical minute. Please stay tuned to learn more information about oncogenes, microRNAs, and cancer.

Medical Minute

The American Cancer Society estimates that the lifetime risk of developing colorectal cancer is about one in twenty, and that the risk is slightly lower in women than in men and when detected early colorectal cancer is easily treated and highly curable. Men and women over the age of 50 should have regular colonoscopies to screen for the disease. Each day more patients are surviving colorectal cancer due to increased access to advanced therapies and specialized care which is giving colorectal cancer survivors more hope than they have ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for colorectal cancer. New options include a Chinese herbal medicine being used in combination with chemotherapy to reduce side effects of treatment and help cancer drugs work more effectively. 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.

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Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by our guest, Dr. Frank Slack. Right before the break we were talking about oncogenes, we were talking about cancer and how genes can actually be influencing the development of cancer and you were telling us about these areas of RNA that have an influence on that. Tell us more about that.

Slack Over the past few years we have discovered that there are many RNAs being made within cells. I feel like we are still at the tip of the iceberg in understanding what these RNAs are doing. There are thousands of these little RNAs being made in cells and it is a real challenge and a real exciting area of research to try and figure out exactly what they are doing. One of those classes of RNAs are called microRNAs, something that we worked on for a long time. My lab initially studied them for roles in development, meaning the development of the embryo, the development is tightly linked to cancer, many of the genes involved in development are ultimately also found to be involved in cancer, and so we were drawn by an understanding of some of these microRNAs and their roles in cancer development and what they might be doing in cancer. microRNAs are small RNAs. If you can picture a typical RNA in a cell being about 2000 of these letters long, so 2000 A, Cs, Gs, or T's, microRNA is only about 20 of these letters long. So they are very small but their small size does not mean that they have little to do in the cell, in fact, they have a pretty important role in the cell. They act to regulate or to control the use of other genes, so their function is not to fold up into some sort of enzyme or some sort of structure that can catalyze the reaction, but rather they go and bind to other genes and determine whether that gene is going to be on or off. They act as these important switches and some of these microRNAs that we have discovered and other groups have found as well, act to turn on and off important oncogenes in a cell. So one thing to keep in mind about an oncogene is that it is a mutated gene, but that mutated gene actually in its normal role when it is un-mutated has a very-very important function but usually that function is during development, so oncogenes typically are involved in massive amounts of cell division that are required in the early embryo. Picture a single celled embryo, and that is how we all start out and we have to grow into an embryo of 200 trillion cells, so you need to have lots of cell division in the early embryo. These oncogenes are the genes that are driving that cell division. They get switched off over time as we get bigger and bigger and we need less and less cells. In a cancer, those oncogenes get reactivated again, or if they are somewhere you can mess up the block on those oncogenes, you can actually start a cell dividing again and it is sort of acts like it is in the early embryo and it starts to divide out of control. We have discovered that some of these microRNA genes control some of this cell division or proliferation activating genes. So that has been exciting for a few reasons, first of all we have discovered a new class of cancer genes and that is good information to have. Secondly, because these genes, these microRNAs, are only 20 of these nucleotides long they are so small that we can in fact synthesize them in a laboratory. We can make them in a test tube and we can give them to cancer cells and

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see whether they can suppress those oncogenes in a cancer cell and have a therapeutic benefit and that has been an area that we have been looking into over the last few years.

Chagpar If I understand this right, your body makes these microRNAs and the job of the microRNAs is to turn on and off genes, so normally they would potentially turn off genes that would otherwise, if left turned on, would go and make cancer. Is it ever that the microRNAs are mutated as well and so they do not stop the cancer genes from turning on as much as they should?

Slack We actually got into this particular area because we noticed that some of these microRNA genes just weren't being made at the same level in cancer cells as they were in normal cells and the very first example of that was a microRNA that we found to be very poorly expressed, very, very poorly made and made very low levels in lung cancer cells relative to normal lung cancer cells and so we suspected then that something was happening to that gene. Either it had been deleted from the cancer cells or in some way there were mutations within it leading to it being an unstable gene and it was just not functioning at the right level. Subsequent to that we now know that these microRNA genes are definitely altered in cancers. So they can be mutated, they can be deleted, they can be amplified, all those sorts of things that you might anticipate for other cancer genes can happen to these types of genes as well. This knowledge has increased the scope or the span of genes that we now know can be mutated and misregulated in cancer.

Chagpar So what turns on and off the production of microRNAs?

Slack The microRNA genes are very similar to our other genes, they have the same general promoting regions and regulatory regions that our normal genes do. There are proteins that will in fact bind to DNA and activate the use of genes. Some of the same proteins will activate and bind to genes like BRCA 1, for example, might also bind to inactivate one of these microRNA genes. So they are not that different from some of the well known cancer genes, it's just that they do not code for proteins in the end. Their function appears to be just to go and bind the other genes and shut them off or reduce the level of their use.

Chagpar Does their altered production only happen in tumor cells or would it also happen in normal cells?

Slack These microRNA genes are definitely not statically made. So it is not like in all times in our development the microRNAs are always on or they are always off. One of the key things that these microRNAs do is that they get turned on and off at precise times during our development so that we can allow cells to stop dividing so quickly, or to start to convert themselves from a stem cell or cell that can make many cells into a particular kind of cell within the early embryo. These microRNAs have functions in development and those are dynamic functions so they get made at particular times and then they get shut off again when that microRNA is no longer needed and so definitely that extends to the cancer cells as well as certain cancers will make reduced amounts of

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some of these microRNAs and other types of microRNAs will get up regulated in some other cancer cells, so it is definitely a dynamic state.

- Chagpar One of the things that is intriguing though, is that if you can make these microRNAs in a test tube then you can give them to people, do they actually get into the cancer cells to turn off those genes or do they get into normal cells, how does that work?
- Slack Good point, if you were to inject it into the blood stream or give a pill that would be taken early and go into the stomach of an RNA molecule, it does not last very well in our bodies. RNA is not a very stable molecule but over the past five years or so some very-very smart chemists and bioengineers have figured out ways to make these RNAs very stable. So they are still functional but they do not get degraded within our bodies and I think that is definitely accelerating the chances that these microRNAs are going to one day become therapeutics in other cancer patients. I should be clear here that, at this point, no cancer patient has taken a microRNA as a therapeutic. This is not something you can do yet, but clinical trials are definitely being planned for the next few years and a lot of work in mouse models of cancers have shown that these tricks, these stabilizing tricks, these ways to encapsulate RNAs and nanoparticles and other kinds of lipid particles that can survive within blood and can then target these things to cells, definitely work very well. So I do not think it is going to be a big leap for us to be able to show that these also function in humans.
- Chagpar We may be day dreaming towards the future, but do you foresee a way for these microRNA nanoparticles to be targeted to particular cancer cells so that that microRNA goes into the tumor cell and turns on or off particular genes that are oncogenes versus going into normal cells where you may need?
- Slack I did not answer your question fully last time, which was do they get into normal cells. With current technology, we do not yet have a way to exclude them from normal cells. However, we are collaborating, as I mentioned earlier, with some very smart bioengineers, some here at Yale such as Dr. Mark Saltzman, to make these nanoparticles specific for cancer cells or to target the cancer cells in their environment and I would say that we are getting some very encouraging success with those strategies. So basically we are trying to put on the surface of the nanoparticles warheads that will target just the cancer cells, that is the holy grail of the field right now is to try and get those to deliver the payload to the bad cells and avoid the good cells that are surrounding them.
- Chagpar That is so cool. Do you foresee a time when we could even use this in the preventative setting? Find genes that are mutated that increase your risk and put in the microRNAs upfront that prevent the oncogenes from turning on?

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Slack That would be an amazing thing if it could happen. At this point, I do not think anybody is realistically thinking of a preventative trial. People are definitely thinking about microRNAs in a therapeutic sense, once the patient already presents with a cancer, but I can imagine that in 20 years when we know enough about these types of genes and we have solved the whole therapy issue then we can divert our attention to actually preventing the cancer from happening in the first place. I would imagine that these would be fine cancer preventatives as well. Ultimately, what we have been talking about in the cancer genome has been in sequence, but I foresee a day when every child pretty much at birth is going to get a blood test and they will have their genome sequenced, the pediatrician will examine a gene and they will be able to say, well you have some predispositions to this disease or that disease and we actually have some things that we think might be able to help prevent those diseases and microRNAs could end up being preventative along those lines for sure and it would be a great day for medicine if that happens but I think it is a very long way off. It is not something my lab is even thinking about.

Chagpar In the last 30 seconds, tell us what you think will be the greatest advance in microRNAs and genomics in the next five years?

Slack I can say that having the human genome has opened up a whole new world to us. Before the human genome we knew about only one of these microRNA genes in the whole of biology. After the human genome sequence was done, we discovered at least 1500 of these microRNA genes and so this list just keeps growing and growing and as I mentioned earlier, getting to the bottom of this iceberg is going to be the most exciting thing, finding what is really out there, how many RNAs are really made and how we can harvest those for our own benefit, I think will be the most exciting thing.

Dr. Frank Slack is a Professor of Molecular, Cellular and Developmental Biology at the Yale School of Medicine. 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.