Cancer Genomics

Guest Expert:
Frank Slack, PhD and Joanne Weidhaas, MD, PhD

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Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Francine is joined by Dr. Frank Slack and Dr. Joanne Weidhaas for a conversation about cancer genomics. Dr. Slack is a Professor of Molecular, Cellular, and Developmental Biology and Dr. Weidhaas is an Assistant Professor of Therapeutic Radiology. Here is Francine Foss.

Foss Could we start off by asking you both for a basic description of what the cancer genome is?

Slack It’s a very exciting year as it's actually the 10th anniversary of the elucidation of a human genome. A human genome is essentially the complete set of letters in our DNA that codes for all of the things that make us human. It also includes the genes and pieces of DNA between the genes. We now have the ability to actually figure out the sequence of letters in every single human being and we can find in that sequence certain anomalous DNA changes, which we thought of as mutations, that have occurred that are often found in genes that are important for cell cycle control and cell mobility control, all things that are important for normal bodies, but when mutated, can lead to cancer. It’s a road map that let’s determine whether somebody has mutations in the DNA that might lead to cancer or may have caused the cancer.

Foss So, basically DNA is kind of like the reading code. Joanne, can you talk a little bit about how we actually get from DNA to the level of proteins actually in the cell? What happens between the DNA and the protein that exerts an affect in a cell?

Weidhaas I tell people that every cell has the same DNA, it’s kind of like the text book and if it’s a liver cell, it reads a chapter on being a liver cell. It will take the information from the DNA and basically build the building blocks of the cell to be the function of that cell. That's a very basic understanding of how we have understood DNA, how it turns ultimately into RNA, and then protein, although there is really a whole new level of understanding now with the discovery of microRNAs.

Foss Frank, you mentioned the importance of the Human Genome Project and studying these genes to understand cancer because of these mutations. How frequently do these mutations occur for a normal DNA, and how often do people get cancer if they develop a mutation? I know that’s a bit of a tough question.

Slack I will answer the first part. We are continually being bombarded with things that damage our DNA. I mean even if you lived in a cave, in a hermetically-sealed bubble, you would still be damaging your DNA in some way or another; there are just natural occurrences, every time

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a cell divides it has to replicate its DNA and there are just natural errors that occur in that process, but then we actually enhance that by exposing ourselves to environmental mutagens and carcinogens. These are compounds like UV light, cigarette smoke, or automobile exhaust that do damage DNA and when that occurs it occurs randomly, pretty much, throughout the genome, but if you get unlucky enough that it hits one of these important cancer genes that can contribute to a cancer, maybe Joanne can answer how frequent that is in the population.

Weidhass That's a great question. I think that everyone's damaged all the time and what we are starting to realize is that your risk for developing cancer may have something to do with your ability to repair that damage well. As an oncologist, I see patient's and everyone always wants to know, why me, why me? There are some very healthy people with cancer that have just done everything perfectly and we are starting to find some information that there could be things that just tip the scale a little bit where things might seem to be fine, you are a perfectly healthy individual, however, you may not do quite as well of a job in repairing your DNA. Some of the findings that Frank and I have found together have shed some new light on this. People have been interested in this for years, but there are really very few currently recognized syndromes where people get cancer and I would postulate that this is much more common.

Slack It's been predicted that about one in two males will get cancer in the United States, so that gives you a sense of how common it is right now, and one in three females.

Foss And that includes all different types of cancers, like somebody’s benign skin cancer that usually don’t cause a problem. We have talked on other shows about various cancer genes and family syndromes, but Joanne, you bring up an excellent point, which is that most patient's who develop cancer don't have one of these defined syndromes and that we’re really just scratching the surface in terms of understanding all the different mechanisms that lead to cancer.

Weidhass Exactly, and I think Frank can explain a little bit about how we have shed some new light on this with his understanding of some new biology. I will just say briefly that the syndromes we have known of were built on the paradigm that all DNA turns into protein and the areas of the genome that have been studied are those areas. With new understanding we have looked in different areas of the DNA and we found new markers of cancer risk.

Foss In particular, you mentioned microRNAs. That seems to be a hot topic; Frank could you talk a little bit about that?

Slack MicroRNAs are actually made from our own genes. They are very small RNAs, so as Joanne was mentioning earlier, most genes are made into RNA and then RNA gets translated into protein. But 15 years ago, it was discovered that there are certain kinds of genes that make an RNA that is not

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made into protein, in fact this RNA by itself has a function and that function is to go and negatively regulate other genes, so basically squelch the activity of other genes. About ten years ago, it was discovered that humans have many of these microRNA genes. We have about a thousand of these microRNA genes, and then about seven years ago, it was discovered that these little RNA genes get mis-regulated in cancer, so they get mutated in cancer, they get deleted in cancer, they get up-regulated in cancer, meaning you have too much of these products being made, and we now have the ability to use these little RNAs, these little microRNAs as very important diagnostics and prognostic tools and ultimately we hope therapeutic tools in the fight against cancer.

**Foss**  Why do you think it took us so long to find these microRNAs?

**Slack**  Well they have been referred to as the dark matter of the genome because they are so tiny. People for many years have this misconception that the genome was made up of about 25 thousand protein coding genes and everything else was junk. That work junk is fast finding itself on the junk heap. We now realize that much of this information between the genes is actually being used and in some cases being used to make these thousand microRNA genes. They were just very hard to find because the genes are so small and we did not really know they were going to exist like that, but working model organisms really paved the way in this case and proved that these little RNAs were in fact working and that they were useful and that they could be damaged. And when they were discovered in humans, it was not that big a leap to show the same was true in humans.

**Foss**  Joanne, can you tell us how these microRNAs have been important in specific cancers that we are studying now?

**Weidhass**  Frank was really a pioneer in the microRNA world, one of the first to show that microRNAs were important. The first cancer where it was really found was lung cancer and there has been a fair amount of work on microRNAs in lung cancer. First are the differences in microRNA levels, predicting response to treatment or outcome in lung cancer. There has been extensive work now showing microRNAs are abnormal in every cancer, and then Frank and I really joined forces and were some of the first to show that inherited changes in microRNAs and the regions where they bind and exert their influence can be important markers in developing cancer risk, really predictive markers, so that's kind of a new area for microRNAs.

**Foss**  Are there multiple of these microRNAs, multiple families of these?

**Weidhass**  There are probably about a thousand microRNAs known at this point, many are grouped together, but we think even though they look similar, they probably have unique functions and we are just beginning to understand that.

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You mentioned that these were important in a number of different types of cancer, pretty much all different types of cancer. Are there specific ones associated with specific tumor types?

Absolutely, it seems that each tissue really has its set of microRNAs it uses and in a tumor from that tissue it will be that set of microRNAs that are mis-regulated and important, some seem to be universal though. For example Let-7 is a very commonly mis-regulated microRNA in almost all forms of cancer, particularly solid tumors, but it really creates this similarity across tumor types. So inherited changes that might lead to one cancer type, will now tie together cancer types you would not normally group together, which is really changing how we as oncologists view cancer. Right now it's separated really by the sections of the body, for example, the thoracic cancers are in the chest. There are certain groups based on where things are, but biologically, they might be more similar, for example, a skin cancer might be more similar to lung cancer that we didn’t realize and some it’s just understanding the underlying biology, which microRNAs let us do.

Frank, that sounds very interesting. Can you tell us how you actually apply that in the lab, in your research? Do you look for these common microRNAs among these different tumor types or are you actually looking for unique ones, or both?

For example, in collaboration with Joanne, we will profile various different types of cancer. So we will take the tumor tissue from the wonderful donors that have donated their tumors here at Yale, and we will ask whether those tumors have a common set of microRNAs being made that, for example, are different from normal tissue taken from tissue surrounding that tumor. And we are trying to identify a signature for each type of tumor, and as Joanne was saying, we find that in general, every tumor type has its own signature and our goal is to build these signatures to the point where a physician one day might be able to read out the microRNA signature and know exactly what tumor type that patient has, and potentially what the response to therapy might be for that patient, and what the potential outcome for that patient would be. We are building that area. The second area is we identify these microRNAs that are mis-regulated in these cancer types. In general, we find two different classes of microRNAs. We find those that are lost, or down-regulated in the cancer, so invariably almost all the patients in that sub-class of cancer have a few of these microRNAs that have been lost. They also have a few microRNAs that have been up-regulated and our goal then is to try and replace the microRNAs that have been lost in those patients and somehow knock out the microRNAs that up-regulated. We first try and show that indeed in cell lines and tissue culture work that if you give microRNAs back that have been lost, or if you knock out microRNAs that are too expressed in those patients that we see an affect on cells; usually the cells die or the cells stop growing. Then we try the same experiments in the mouse model where we put the human cells into a mouse and we can show that those cells will now stop growing in the presence of the microRNAs, or we actually build the mouse model that mimics the human cancer and we show that those microRNAs are therapeutic in that mouse model with the
ultimate goal of going to clinical trials at some point in the next few years to actually deliver these agents as therapeutics, natural therapeutics.

Foss It sounds like now we are moving towards manipulating the level of these microRNAs and you think that's actually going to get into people from these animal models?

Weidhass We certainly hope so. What’s beautiful about microRNAs, because they are a natural element, they are not toxic, in general. You deliver them to the body, they’re something the body has, but they are not at regular levels in the tumor so there is a real potential to use them. And it’s not a chemical like much of the other therapies that we use, and it would be very specific to the cancer that has lost or has over expression of specific microRNAs that we are targeting.

Foss That sounds really exciting and I would like to talk a little bit more about that after the break. We are going to take a short break for a medical minute now. Please stay tuned to learn more about cancer genomics with our guests, Drs. Frank Slack and Joanne Weidhaas.

Medical Minute There are over 11 million cancer survivors in the US and the numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. Following treatment the return to normal activities and relationships may be difficult and cancer survivors may face other long-term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as the one at Yale Cancer Center, to keep cancer survivors well and focused on healthy living. This has been a medical minute brought to you as a public service by Yale Cancer Center. 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 here today with my guests Dr. Slack and Dr. Weidhaas to talk about cancer genomics. We talked before the break about some exciting advances with using these microRNAs to identify specific tumor types and also possibly to modulate those to affect cancer. I would like to go back to the point about using those as a signature for tumors. Frank, you had mentioned that we can now identify patterns of microRNAs and I am wondering, are those assays available yet in the clinic and will those be applicable to fresh tissue from patients? Or will we be able to use the archived tissue that we have in our tissue banks?

Slack Those sorts of assays are already for sale and we expect to see an explosion of those sorts of assays over the next few years. You can already purchase an assay that will allow a physician to operate.

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understand where a metastatic tumor arose from. In many cases oncologists have a difficult time identifying exactly where the primary tumor arose from in a metastatic patient, but because these metastatic tumors retain that signature of the originating tissue, it is possible just by profiling their microRNAs that we can determine what the primary tissue is and then of course the physician has an easier time getting and trying to identify where the primary tumor is.

Foss Joanne, you had mentioned that we are now understanding that some of these tumors are more related than we think they are based on the microRNA signature, so that certainly could change the way we treat some of these tumors.

Weidhaas Absolutely, and I think another thing that is tying it together with microRNAs and understanding the inner relationship between tumors is this new area where we, and others, have been looking at inherited changes in your germline DNA, not just in the tumor, that might predispose you to developing certain cancers and how they might be cancers that we wouldn’t necessarily group together, but there might be risks for both of them.

Foss This is really an important area that you bring up, actually looking at the germline mutations of these microRNAs and how that could potentially be a new marker for cancer risk.

Weidhaas Absolutely, so that’s an area we are very interested in. My sense has been that after finding some of the big protein coding sequence inherited mutations, people have somewhat given up on finding other markers of inherited cancer risk, while I think that is actually much more common then we realize. It's important to help predict who is going to develop cancer and understanding microRNAs and how important they are in cancer and as regulators, it was very logical to start looking in those regions of your DNA to see if there are changes you inherited from your parents, from your family that disrupted microRNAs and how they worked that put you at risk for cancers.

Foss Previously on another show we talked about the SNP analysis, genomic analysis to look at cancer risk. In those kinds of analyses do they look at these microRNAs, or is this is a completely different area?

Slack There are a number of studies, even some done here at Yale Cancer Center where SNP analysis has been performed in the microRNA genes themselves, and also in the places where the microRNAs tend to bind. Some very interesting results have already come from that. Our work has been slightly different in that we have looked for new types of genetic changes that aren't in the traditional SNP databases with the idea that all SNPs have not been discovered yet and that’s one of the wonderful advantages of having the human genome available to us, is that we can quickly compare back to the reference human genome any changes that we find and ask whether

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they are truly different from undiagnosed people. And so, yes, those SNP analysis have been useful but we think that they have to be limited and in fact there is more out there that needs to be discovered.

Foss Can you talk a little bit, both of you, about this whole area of cancer genomics and how much information is out there among all these different sites that are doing these studies and how that all gets integrated to help patients? I think, from a patient's point of view, it is hard to really figure out how this all comes together.

Weidhaas That’s a great question and it has been difficult. There have been approaches with SNP analysis where they do genome-wide SNP Association Studies and each marker is found to have just a little bit increased risk, and how would you combine that into meaningful information for a patient is I think undetermined. As Frank mentioned, we have taken approaches to look a little more carefully at certain regions of DNA and in doing so, we have found some markers that are more predictive of cancer risks, stronger markers, because they are functional. A lot of SNP work has looked at markers that are not themselves functional, so they might just be associated with something else and we think that is perhaps why they are not quite as powerful. Some of the markers that we have been studying are themselves the marker that predicts cancer risk and they are stronger. I think there is a lot of interest and it is really important how this is communicated to people and how it is used and plugged into the existing clinical paradigms. Our goal is to have the medical community weigh in heavily on this and to do it very responsibly because we think some of these markers are important and should really be plugged into the medical paradigms and communicated appropriately to patients. We are currently doing it from the top down starting with the physician community and having it move through that way.

Foss Certainly, as these microRNAs are used now for diagnosis, that will touch the patient in a more direct way.

Slack Yes, there are many areas from just risk assessment, through diagnosis, through prognosis, through ultimately treatment, where microRNAs are probably going to play a role.

Foss Could we switch gears a little bit now and talk about some other areas of cancer genomics, specifically I wanted to ask you guys if you could define an oncogene and tell us how an oncogene contributes to cancer?

Slack An oncogene is really just a mutated proto-oncogene. I will explain what a proto-oncogene is. We actually need these genes in our normal existence. It’s when they get mutated in such a way that they are not functioning correctly and can cause cancer, then they are called oncogenes. Think about how the single celled embryo needs to become the trillion cells that we have in our body,
well when we are sitting in our mother’s wombs, we actually use these proto-oncogenes to drive lots of cell division. We grow from a single cell to a trillion cells in about three months and we actually need these proto-oncogenes. But as we get more developed in the womb and our organs start to form and our limbs start to form, these proto-oncogenes get switched off slowly and cell division gets switched off to the point where when we are adults, we have very little cell division going on in our body. Only in certain places, like our skin and the lining of our intestine where we actually damage a lot of cells and we replace those cells on a frequent basis do we actually have lots of cell division. So these proto-oncogenes are very important for our development and for our normal existence. But when they get damaged, they no longer regulate appropriately and they are actually driving cell division inappropriately, then they become oncogenes. Now some of the traditional oncogenes have been considered to be the protein coding genes. Some famous ones include genes like MIC and ras but we are discovering that in fact microRNAs themselves can be oncogenes as well.

Foss That's really interesting. These oncogenes again are normal genes that have gone awry essentially?

Weidhaas Exactly.

Slack A bit of a misnomer, when the press refers to a person as having a gene for cancer, in fact everybody has got that gene. It’s just that it’s not mutated in everybody; it is mutated in the cancer patients.

Foss This mutation occurs at some point as the patient is basically evolving, not before the patient was born?

Weidhaas It depends, and that is a big controversy. Certainly there can be acquired mutations during life that could put you at cancer risk. We really think that there are inherited subtle changes in the regulation of some of these oncogenes or proto-oncogenes that somehow leads to an accumulation of damage or just a loss of control at some time in life that would put you at increased cancer risk.

Foss That’s an important point when you think about the issue of identical twins who basically have the same genetics, at least to start off with, and then one of them will go on to develop a cancer where the other one won't.

Weidhaas Cancer is very multi-factorial. That’s the thing about all of these even inherited risks, nothing is 100% and certainly there are the effects of living life, even a clean good life, which might interact in a certain way with some of what you are born with and lead to cancer for you and maybe not someone that is identical to you.

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Foss: We have talked a lot about the specific genetic issues in cancer and I know both of you are working in the lab on a number of these issues. Could you just tell us briefly what you are working on and what you think the most exciting areas are in cancer genetics? Frank, do you want to start?

Slack: I think if I had unlimited money, which is of course something that all scientists would love to have, I would start very quickly just getting the whole genome sequence of every single cancer patient that Yale could get their hands on and I think that is really the exciting part in genomics right now. It is trying to determine the entire set of changes within each individual and then trying to map those changes back to increased risks of various diseases. At the moment it's pretty expensive to sequence an entire person’s genome; it costs about $20,000, but that cost is declining and I think one of the really exciting areas in the next few years is going to be the fact that a lot of human genome sequencing is going to be done. In fact, there will be a time when almost everybody will have the genome sequence done just as part of their medical record and hopefully there will be a time when we can read out from that sequence of DNA exactly what risks these people will have coming down the road. I would really like to be moving in that direction if I could, but at this point, it is a little bit too expensive. In lieu of that we have taken the approach of trying to look at more limited parts of the human genome, the parts that we think contain some of that regulatory information where the microRNAs bind and in the microRNA gene. We are actually mapping all of the mutations in a whole set of different cancer patients for mutations in just those regions. We also have a few experiments going on in the lab where we are trying to build mouse models of cancer taking some of these microRNAs that we think are oncogenes and over expressing them in mice to try and prove that they can indeed cause cancer by themselves. Then using those mouse models then as models for therapy, we can try and treat those mice with therapies, maybe novel therapies that we might ultimately move into the clinic one day that could help patients that also have over expression of these same microRNAs. And then we also have mouse models where we try to cure the mice using these microRNA genes themselves both as genes and also just by giving them the RNAs. I am trying to inject these RNAs into either the tumor site or into the bloodstream or try and give it to them orally or intranasally and see if we can cure these particular mice.

Foss: And Joanne?

Weidhaas: There is a lot certainly that overlaps because Frank and I collaborate closely on many of these projects and have a lot of the same interests. One thing I would add is that there is certainly sequencing going on, although the focus has really been the sequence of tumors instead of normal germline DNA, and I feel very strongly that there is a wealth of information that is in your normal DNA and for people that develop cancer, it is searching for the hidden treasure. There is something there that is going to be meaningful for them, and for their children, not only in the development of cancer but ultimately in how that tumor biologically behaves, their outcome and
what therapy is the very best therapy for them. I do not think that is going to be in just trying to look at the tumor, which is so complicated by the time we look at it, there are so many events that take place as a tumor progresses, but instead, in what tipped the scales for them in the pathway that their tumor took to become a tumor, I think that is going to be the Achilles’ heel of those tumors. We do have some data suggesting that with some of these markers that we found that do predict for a cancer risk that those same markers tell them how those people are going to do, what therapies are going to work or not work for those patients. Ultimately that’s everybody’s goal, we can’t prevent all cancers, but to get this fundamental understanding we could certainly do a better job treating. I mean everyone does their best, and everyone gets standard of care, certainly, but there are some things that works differently and better for other people and there is such diversity across cancer.

Foss

It certainly does sound like there is a lot of exciting new research going on and that there will be a marrying of these two different aspects of the susceptibility of the patient as well as identifying specific mutations in the tumors that ultimately will hopefully lead to cure for more patients. It has been very exciting having this discussion with both of you today. Until next week, this is Dr. Francine Foss from Yale Cancer Center wishing you a safe and healthy week.

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