Yale CANCER CENTER answers

WNPR Connecticut Public Radio

Hosts

Anees Chagpar MD
Associate Professor of Surgical Oncology

Francine Foss MD
Professor of Medical Oncology

Hematopathology

Guest Expert:
Demetrios Braddock, MD, PhD
Associate Professor of Pathology, Yale School of Medicine

Yale Cancer Center Answers
is a weekly broadcast on
WNPR Connecticut Public Radio
Sunday Evenings at 6:00 PM

Listen live online at

OR

Listen to archived podcasts at

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 is joined by Dr. Demetrios Braddock. Dr. Braddock is Associate Professor of Pathology at Yale School of Medicine and he joins Dr. Foss for a conversation about hematopathology.

Foss Let's start off by having you tell us a little bit about yourself. How did you get interested in hematopathology?

Braddock I think it had to do with my teachers in medical school and my heroes, as it were, when I was training. I trained at the University of Chicago and at that time, and still today, there are a number of very eminent pathologists who study the basic science of disease and because Chicago is a very basic science kind of place, very similar to Yale, I was drawn to that and that led me naturally into pathology. During my training, I did a PhD and MD dual degree program, and my PhD was in the department of pathology in a lab that studied protein structure, very basic protein folding and protein design type questions.

Foss We often don't interview pathologists on this show, it is mostly clinical doctors. Can you just give our audience a little bit about background, about pathologists and what you do as a hospital pathologist and about the whole field of pathology and the kinds of research out there in that area?

Braddock Pathologists are involved in the classification of disease and it's evolved in the last century to become heavily involved in the classification of tumors of cancer. A pathologist's primary mission and job is to work with the treating physicians, the oncologists or the infectious disease physician, to provide the correct classification of either the infection or the disease process, be it a tumor, infection or viral illness that the patient is suffering from and the way the pathologist goes about giving that information is to look at tissue under the microscope, or now we look at tissue by looking at molecular tests and molecular diagnostic tests to give us a very detail molecular analysis of the disease process that were facing in patients.

Foss Pathology is changing as we are hearing more about molecular medicine, is that a part of what you are doing every day?

Braddock Absolutely, pathology in general and hematopathology in particular are integrating the molecular signatures of tumors into the diagnosis and so in hematopathology for instance, we are very interested in combining in one single report a top down analysis of the tumor from the way it appears under the microscope, all the way down to the specific genetic mutations that tumor has in order to assist the treating physician in choosing targeted therapy that the patient may benefit from.

3:56 into mp3 file http://yalecancercenter.org/podcasts/2013%200929%20YCC%20Answers%20-%20Dr%20Braddock.mp3

Foss Its sounds like there is now a lot of integration between the clinical part of the patient care and the pathological part if we are talking about genes and pathways and drugs that we are using. Can you talk a little bit about that interaction and how that has changed, and what we are doing now say in the hematologic malignancy group at Smilow?

Braddock Absolutely, the integration of the clinical details is absolutely essential to provide the correct interpretation of the patient's disease and oftentimes we are on the phone with each other or even sitting around the microscope together looking at the same tissue. For example, I am on service this week and Dr. Nikolai Podoltsev was down in the room with me as we were looking at a patient's bone marrow biopsy and trying to determine if this particular patient may be suffering a recurrence of his disease and Nikolai was providing some clinical details for us to help us interpret what we were seeing under the scope. So that process occurs on a daily basis with all the hematology/oncology attendings that are treating the patient's and hematopathologists working at Smilow. In addition, we have conferences throughout the week where we get together and we discuss in detail about specific patients. There is a lymphoma conference where we focus on those patients with lymphomas that are problematic and may not be responding adequately to therapy, maybe it was a surprise diagnosis that we were not expecting or a problem diagnosis that we cannot seem to arrive at a conclusive answer for and we will sit around a big table, we will look at the microscopic details of the tumor, we will look at the radiologic findings and we will discuss the clinical presentation of the patients and together we come to a consensus about how we are going to proceed with that patient's treatment. That occurs also for leukemia patients who have blood based malignancies and we do the exact same sort of thing and there is also now a coagulation conference where we discuss patients with bleeding disorders and bleeding diathesis or bleeding abnormalities that have presented and Albert Lee is heading that effort and he sees a number of these patients and it is a very interesting conference and Dr. Duffy is also there in attendance who is a wealth of knowledge as he has been at Yale for 30 some odd years and is nearing retirement unfortunately now, but these people are invaluable and they make Yale a very special place to be a physician at as well as to be a patient.

Foss I think from my side as a clinician, it is very important to patients that we have these conferences and oftentimes I will tell a patient that we are presenting your pathology in our multimodality conference and patients gets very excited and always remember to call me the day after or the day of the conference to get the results of that. I think it is really important to patients to know that multiple eyes are going on their specimen and we are talking about it as a group.

Braddock Right, and I think as a patient, as someone with malignancy in my family, it is very comforting to know that there are many heads thinking about the best way forward in some of these complex and difficult diseases that may not have clear answers yet, but when you are right at the edge of what you can do and trying to push that edge, it makes all the difference to have all these people around the table.

8:03 into mp3 file http://yalecancercenter.org/podcasts/2013%200929%20YCC%20Answers%20-%20Dr%20Braddock.mp3

Foss I also wanted to touch on the fact that you probably see a lot of cases that do not actually come to Yale as a consultation service since you have expertise in this area, could you comment a little bit on your role in some of these external cases?

Braddock Sure, so in the Hematopathology Department we see several different types of consults, one is consults brought in from an outreach effort that we have where we have established a reference laboratory to do full molecular testing and workup of a patient's tumor and that effort is called Precipio Diagnostics and we work with a number of oncologists throughout the country to provide a sort of top-down integrated report of those patient's diseases, usually they are leukemias and lymphomas, and again there is a lot of phone consultation with those physicians, probably more than one would anticipate in a private practice setting, but often these physicians are out in the community practicing community medicine, but they want an academic level intensive workup of certain patients so they will send us that material.

Foss How does the community physician and the patients out there in the community find out about this and is this the right thing to do for every patient with a hematologic malignancy?

Braddock It has primarily been by word of mouth, and we are just getting it off the ground, it has been less than a year, but the short answer is that in general oncologists treat patients and those patients can be very complicated just like we see here and you really have no idea when you are going to get a problem case and you are going to need a higher level of workup than one would typically have available to them in the community. So in those cases we offer services to assist the local pathologists or the local oncologists in the molecular analysis as well as a review of the histology. Not every patient may need this level of care, but the billing is the exact same, there is no mark up on these cases so there is no additional charge added. It is just that perhaps the level of analysis is at a greater detail. We also analyze solid tumors in this venture and this is a tumor profiling panel that was put together by Jeff Sklar in the Department of Pathology on the molecular analysis of the tumors and it tests for all of the oncogenes that are treatable so either there is a clinical trial or there is a small molecule that is targeted against that specific mutation in the patients tumors and for patients with solid tumors that may have a targeted therapy they can send us those tumors and we will do this molecular analysis within a week. So we are trying to turn that case around such that the treating oncologist can initiate treatment of the patient with this targeted therapy in mind if the correct mutation is available.

Foss That brings up an interesting point that we have talked about on the show, which is that we are not thinking about cancers as belonging to a specific organ site anymore, like lung or GI, we are starting to think more about these pathways from what we have learned from this kind of technique. Can you elaborate a little bit about that and where you think we are going in the future with that technology?

Braddock Certainly, I think that is an interesting observation. In the past, historically, because we have graded cancers by the way they appear under a microscope, we have grouped tumors into lung

12:18 into mp3 file http://yalecancercenter.org/podcasts/2013%200929%20YCC%20Answers%20-%20Dr%20Braddock.mp3

tumors and colon tumors and the site of origin, blood tumors. But now we get into the molecular age where we have sequenced these cancers to the level where we can see that some of these cancers share the same mutations and scientists and laboratories have developed very specific drugs that are very nontoxic, targeted against those specific mutations. Therefore, the way to approach these tumors is not to think about them and treat them as if they belong to a certain site of origin, but to think about them as an abnormality or tumor that has developed a mutation that can be treated effectively with certain drugs. So it is more of a treatment based approach to cancer rather than a classification based approach. The treatment is driving the classification now in a sense and the science behind these tumors is driving their classifications. For example, we have seen with incurable tumors, which would typically not respond to therapy and the patient would undergo very toxic chemotherapy that would carry with it a lot of morbidity, some of these tumors will occasionally, rarely, have a very specific mutation that we can target with one of these drugs and the patient responds remarkably to this treatment. For that reason we are beginning to realize that our classification based on morphology is naïve.

Foss I guess everything is changing in the future in the field of pathology?

Braddock That is right.

Foss We are going to take a break now for a medical minute. Stay tuned to learn more about hematopathology with Dr. Demetrios Braddock.

Medical Minute *There are over 12 millions cancer survivors in the US right now 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. 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 like 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 the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut's Public Broadcasting Network.*

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined tonight by my guest Dr. Demetrios Braddock. We are here today discussing the field of pathology and specifically hematopathology. We took a little tangent before the break to talk a little bit about molecular medicine and got into some fascinating topics about some of the new approaches in terms of identifying tissues and diseases based on genes that we have identified and I know

15:36 into mp3 file http://yalecancercenter.org/podcasts/2013%200929%20YCC%20Answers%20-%20Dr%20Braddock.mp3

Demetrios, that this probably leads into some of your research. Could you talk a little bit about some of the major projects that you are doing in the lab and how that segues into the whole field of pathology?

Braddock My lab studies are very interested in sort of the basic science behind blood disorders and diseases and recently we have been studying a family of enzymes that really nobody has looked at very closely and there is one particular member in that family that was unclassified, so people knew it was out there because we have sequenced the human genome so we know these proteins all exist, but nobody knew what its function was and researchers in my lab have been able to show over the last several years the enzymatic function of this enzyme, that it cleaves a small molecule that is released by platelets and the platelets release these molecules when they de-granulate so when they initiate clotting. This enzyme exists on the blood vessel surfaces of your brain and it promotes blood clotting by taking the chemical released by the platelets and converting it into another molecule called adenosine diphosphate of ADP. And ADP strongly stimulates platelet aggregation. People have known that the small molecules were in platelets for 30 years, but they have never really understood why they were there and why they were released and so it was a little bit gratifying to describe the enzyme that is on the blood vessel surfaces that can actually take that small molecule and make it into something that makes sense in the clotting reaction for us.

Foss Do you see that being implemented in the clinic in any way and how can it help us to treat patients who are developing clots?

Braddock The exciting thing about this finding is that it is very localized to the brain. So we have not seen the enzyme on the surface of the other blood vessels in the periphery, in the heart, or the lungs or any other tissues we have looked at and so we are really thinking that this may be important for helping us to treat strokes where patients will develop blood clots in their brain and clot off arteries and cause these terrible problems that occur during stroke. Part of the difficulty in treating patients with a clot is over treating them, and they will now bleed from sites other than the site that you are trying to prevent bleeding, but because this is a very localized enzyme to the brain and we can target it specifically during the platelet aggregation phase of the clotting, in other words, when we target the bleeding, we are not indiscriminately targeting all bleeding. We are just targeting bleeding at the site of platelet degranulation. So it is a very specific and anatomical location and it is very physiologically specific to the site of platelet degranulation. So we are hoping that we can take advantage of these two characteristics of the finding to specifically improve the treatment of stroke.

Foss That is really fascinating and that dovetails into the coagulation conference you talked about. I wanted to not pass by that because I think it is an important point for the audience as well. Can you talk about clotting problems in general and what the new advances are in that field?

19:27 into mp3 file http://yalecancercenter.org/podcasts/2013%200929%20YCC%20Answers%20-%20Dr%20Braddock.mp3

Braddock Often patients present with clotting problems and they are not aware of them and they may have a genetic predisposition for clotting that they may inherit mutations in certain proteins like von Willebrand factor and other enzymes that are involved in coagulation and not know of them and it is only during pregnancy or perhaps during elective surgery that the patient bleeds indiscriminately or unexpectedly or clots unexpectedly and that is a problem and to prevent future issues regarding future pregnancies or future surgeries, we work these patients up quite intensely and these are done in combined conferences as we discussed with both clinical pathologists, hematopathologists, and the treating hematologist that take care of these patients and we get into the genetics of their disease, we will go into sequencing, we will do specific clinical tests to determine the exact sites of the bleeding abnormalities, whether they are in platelets themselves or they are in the clotting cascade, the intrinsic or extrinsic clotting cascades, but we will try and isolate the exact problem and we will try and determine it genetically and develop a treatment plan around the exact classification of the disease.

Foss One question that the audience may have is, if you have a clotting problem, is it always genetic, do you need a genetic test? Does everybody out there who has a clotting problem or bleeding problem need a genetic test?

Braddock So the answer is no. Sometimes we can just treat the patient presumptively based on their clinical findings and not need to resort to that level of detail. There are other patients with clotting problems for which there is no genetic test available and those patients need to be treated on a presumptive basis, but these treatments are very effective in treating and taking care of their problems so that is why we do that.

Foss And I understand that there aren't many hospitals that actually have these clotting clinics that you are talking about, and the clotting conferences?

Braddock It is a fairly specialized branch of medicine and it takes a whole group of highly trained and highly experienced physicians to be able to quickly diagnose and treat these patients, I think it is a more subtle type of presentation of illness than most even large medical centers are able to field.

Foss And the kind of assays that you need to do and some of the tests that you need to do are fairly sophisticated. Are they available in many medical centers or are there limitations as far as where those tests can get done?

Braddock The equipment is another area that is evolving quickly and the equipment and the way we measure platelet aggregation and interactions between the platelets and the vessel walls is clinically changing with our knowledge of science. So the assays that are out there are very new and they are quite expensive and so often community hospitals would not be able to invest the money in

23:11 into mp3 file http://yalecancercenter.org/podcasts/2013%200929%20YCC%20Answers%20-%20Dr%20Braddock.mp3

these very highly specialized tests for which only a very few number of patients will use during a typical year, but here these tests are available and the hospital has invested in these tests so that we can accurately diagnose and treat these patients.

Foss As if that was not enough, in the lab I understand you are doing a number of other projects that are exciting. You have a Chemokine project and a project with micro RNA. Can you give us some information about both of those?

Braddock Both of these projects are with Yale researchers that I am assisting on and they both involve a lymphoma treatment. The Chemokine project is an interesting project because it is involved in the structures of these G coupled protein receptors, which exist on cell surfaces and the Nobel Prize in chemistry was awarded this year to an individual who first described the structure of these proteins after many-many years of failure and a lot of work and effort went into this remarkable discovery, but now we know the structures of these G-coupled protein receptors and there are several of them that are specific for T-cell lymphomas, which is your area of expertise Dr. Foss, and so we are working together with a structural biologist here at Yale, Elias Lolis, on actually determining the structure of these G-coupled protein receptors that are present in T-cell lymphomas. We are hopeful that combined with small molecule screening and our ability to make large quantities of these proteins, we will be able to screen these proteins through the Yale Small Molecule Discovery Center and develop new inhibitors and then with your database of patients with T-cell lymphomas and your interaction with these patients, we will be able to measure the clinical effect of some of these drugs in cell-based assays. So that is the long term hope of that proposal but again, it starts off from a very basic science perspective where we are going to start from the structure, develop inhibitors and then move into the clinic.

Foss So this is really translational medicine at its best, bench to bedside.

Braddock Exactly, that is the hope, that we can start from a strong foundation of really knowing the way these proteins look and how they work and then move into the unknown which is what they do in these incurable T-cell lymphomas.

Foss So once you learn something from this particular one, will you be able to extrapolate that to say other G protein-coupled receptors in this process of screening small molecules? Will we learn something from this they can be extrapolated to other kinds of cancer?

Braddock Absolutely, the G-coupled-protein receptors are very important for a number of cancers, and in fact, I think pharmacologically they are the most drugged protein out there and so we know starting out that it is very possible, not easy, but is it very possible to develop small molecule drugs that effectively inhibit these proteins. So that is why we are very interested in going after this approach. The second thing that we are taking advantage of is that these diseases are currently incurable, so the patients that have them eventually will succumb to their disease and there is no

27:00 into mp3 file http://yalecancercenter.org/podcasts/2013%200929%20YCC%20Answers%20-%20Dr%20Braddock.mp3

effective treatment. So something needs to be tried that is a little bit out of the box and a little bit drastic and so we are hopeful that we can start from the first principles of the process, the signaling receptors on these T-cell lymphomas, and arrive at effective treatments that will be nontoxic and if we are able to do that, then we can extend into other types of cancers and lymphomas with the same family of receptors.

Foss What about the other project that we are both involved in which is another way of trying to develop a model system to study another rare type of lymphoma? Can you talk a little bit about that and some of the technology that is involved in that particular project?

Braddock Sure, so this is a model that was developed by Frank Slack in the Department of Cell Biology at Yale and what Frank has done is induced micro RNA, a specific micro RNA called 155 which we know has been associated with B-cell lymphomas for a while, and he has made a transgenic mass that over expresses this micro RNA and he originally was anticipating that these mice would develop brain tumors, and as it so often happens in science, what you anticipate happening is not going to happen, but something even more important could happen, and that was that these mice instead developed lymphomas and although he was a little bit upset by it at first, it turns out to be very important because the kinds of lymphomas these mice developed are called Double hit lymphomas. These are a type of lymphoma in which the BCL-2 protein as well as the MYC oncogenes are both miss regulated. These lymphomas respond very poorly to treatment and there is no good model system on how we are going to develop new treatments, so what Frank has right now in his hands is a perfect model system for the development of new therapies for a very rare and incurable type of lymphoma, and that is an area of interest that we are both involved in and hopefully will be able to move forward with.

Dr. Demetrios Braddock is Associate Professor of Pathology at Yale School of Medicine. If you have questions or comments, we invite you to visit yalecancercenter.org where you can also get the podcast and find written transcripts of previously broadcast episodes. You are listening to the WNPR Connecticut Public Media Source.