

Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medicine in the section of Medical Oncology at Yale Cancer Center and is an internationally recognized clinician and clinical researcher. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. Yale Cancer Center Answers features weekly conversations about the most recent advances in the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions to canceranswers@yale.edu or leave a voice mail message at 1-888-234-4YCC. This week you will hear a conversation about hematopathology and lymphomas with Dr. Samuel Katz. Dr. Katz is Assistant Professor of Pathology at Yale School of Medicine and here is Anees Chagpar.

Chagpar        Tell us a little bit about what exactly hematopathology is?

Katz            So pathologists in general are a part of the medical team and I kind of think of them in a football analogy as kind of like an assistant coach during a game. You have on one side the other team being the disease and on the other side, the team being the treatment, the assistant coach, the pathologist's job is to look at that other team, the disease team, and figure out exactly what they are and what they are going to do, and inform the coach, your primary physician, as to what is going to happen and the way that we do that as pathologists is we look specifically at the cells that are taken out of the body of the patient and we match it up to images that we have studied over time in order to tell exactly what type of disease there is.

Chagpar        And so that is what a pathologist does, they tell us what kind of cancer it is and how it is going to behave and sometimes they can even tell us what treatment would work best. What is a hematopathologist?

Katz            A hematopathologist is a pathologist for heme, so heme are diseases involving the blood and so as a hematopathologist I look at organs that get involved by blood diseases, like lymph nodes or bone marrow or spleen and I diagnose different types of blood diseases. These can be classified broadly as lymphomas or leukemias, lymphoma being a solid manifestation of the disease, leukemia being it's happening within the circulation, within the bloodstream.

Chagpar        For our audience, and for me as well, to help us understand what exactly the difference is, because we oftentimes lump them together, we talk about societies for lymphoma and leukemia and I think that many of us may get them all confused, we get the fact that it is from a blood cell, and it is a white blood cell, right?

Katz                    Well, not necessarily. Yes, you can classify broadly into lymphoma and leukemia and I think it is reasonable to be confused about the two of them because they actually are very similar. One example would be, people might have heard of CLL or chronic lymphocytic leukemia, and that has another name, small lymphocytic lymphoma, so CLL and SLL are both leukemia and lymphoma. They are the same disease.

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Chagpar                So you are just trying to confuse us.

Katz                    Not trying to confuse, but trying to say that the same disease can manifest itself in different ways.

Chagpar                Okay, explain.

Katz                    If we first detect it in a lymph node as a solid, then we would call it small lymphocytic lymphoma. If we first detected it within the bloodstream then we would call it chronic lymphocytic leukemia. By underlying biology of the cell as far as we know and how we can detect it, it is the same.

Chagpar                So you are telling me that your diagnosis is going to be dependent on whether the doctor gives you a sample of blood or a sample of a lymph node?

Katz                    In part, as the disease goes on we see that sometimes what might come to us originally as in the blood, might actually wind up being in the lymph node.

Chagpar                And so that is why the name of the disease process can be different, even though it is the same disease process?

Katz                    Absolutely.

Chagpar                So are all lymphomas and leukemias part of the same disease process or are there some of them that are distinct entities? So like with CLL,

you just said it is also called a lymphoma, but it is also called leukemia, but are there some leukemias that are not lymphomas?

Katz            I think another way which is helpful is to classify not only as a lymphoma or leukemia, but there are two other ways I would think about, one is acute and chronic and the second is on the cell type that it came from. So for acute and chronic, if the disease is something that is meandering, taking a long time and does not hit the person right away, that is more of a chronic state. If it something that happens and the patient gets sick right away, that would acute. In terms of the cell type, there are many different cells within the blood and each one of them has the potential to become malignant. So you can have what we call myeloid cells that become malignant and these myeloid cells have several different types. There are ones that make red blood cells. There are ones that are platelets that help us with clotting. There are ones that helps us fight off infections like neutrophils or monocytes and each one of those has the potential to become malignant and so if those become malignant then we often get diseases such as CML or chronic myelogenous leukemia or acute myelogenous leukemia AML. On the other hand, there are also diseases that involve lymphoid cells or lymphocytes, which are B cells or T cells that also help us to fight infections and in this case you can have them in an acute state like an acute lymphoblastic

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leukemia or you can have them more chronic like we talked about with CLL which falls into the lymphoma type category. Lymphomas now also can be subdivided into Hodgkin lymphomas and non-Hodgkin lymphomas and then even further subdivided beyond that.

Chagpar        Wow, so as a pathologist you are looking at these different cells and trying to classify them to tell the treating physician what kind of lymphoma or leukemia it is, but do you rely in part on information that the treating physician gives you in order to figure out whether this is acute or chronic or is that something that you figure out under microscope?

Katz            There is somewhat of a differing of opinions among pathologists about how they like to do it but I think most people will start by trying to look just under the microscope to see what it is that it looks like, what it most resembles without being corrupted by any other part of the picture and from that you can get into sort of a narrow window of a differential of different possibilities. From there then most pathologists will go to the chart and talk

with the clinician and read up on everything that has happened to the patient and say okay, based on that information, plus the information I have from the microscope, we can put together the full story in this manner.

Chagpar      That is cool. As a pathologist, how do cancer cells look different from non-cancer cells? I mean it seems to me that you could look at blood and blood looks like blood so are there things that you look for that tells you, Aha, this is looking like it is a cancer cell and/or maybe this is how it got to be a cancer cell?

Katz              A lot of people like to talk about using genes and genetics to find the mutations and now people can look at thousands of genes at the same time. Well, when you are looking at a cell under the microscope and you are looking at its morphology, you are looking at the product of all of the genes at once and so each mutation will add up in such a way as to give a certain look to different type of cells and so you look specifically at the cell itself and you look to see maybe its nucleus is very large, maybe it has a very big what we call nucleolus structure within the nucleus, maybe the Chromatin that is the DNA within the nucleus looks a little bit more open. So these descriptors that I am giving are actually what we would describe as blasts, which are a particular type of cell that is a very primitive early hematopoietic cell that leads to AML or acute myelogenous leukemia and so seeing these types of features helps us identify that this is a very active moving cell, if the Chromatin or DNA is very open then perhaps it is making a lot of products that are helping this cell grow and move fast.

Chagpar      I mean for a lay person it kind of sounds like it is a lot of pattern recognition in that it really doesn't sound all that scientific, you are not like looking at special genes and using fancy equipment and x-rays and tracers. You are kind of telling me well, I am looking to see whether the nucleus is big or not big.

Katz              There is a fair amount of pattern recognition in pathology and it is a very I would say artistic field, a lot of people who like to look at images come into it, but that is one side of it and I think it is

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called immunohistochemistry where they use antibodies that recognize specific proteins within the cells, so what is the cell expressing and we know that some cancers express these markers and other cancers express these other proteins and so that can help us differentiate a little bit along the way too and we can do that on the tissue that is on a glass slide or we can even dissociate the tissue a bit and look at the individual cells by flow cytometry. We have gone further to where we can look at the genes within the cells using something called cytogenetics and we can take out and look at all the chromosomes within the cells and see if they are correct and is there any what we call translocations that are present, and that is where one part of the chromosomes breaks off and binds to a different chromosome and when that happens there are certain translocations that go with certain diseases. We can also do molecular analysis where we are looking for specific mutations and so we can take a lot of these other more scientific approaches in addition to our morphological judgment and integrate them all.

Chagpar        How often do you use all the fancy stuff?

Katz            For hematopathology it is actually quite frequent so for almost every case we are using immunohistochemistry and for a majority I would say we are using cytogenetics.

Chagpar        I loved your analogy at the beginning of the show where you talked about the hematopathologist as the assistant coach and the guy who looks at the field and says, I see that team, they are going to blitz right there I just know it. Do all of these fancy tests, the antibodies that look for certain proteins that are over expressed, or molecular finger printing, does that help the treating physician to know what drugs to use and how to fight these cancers?

Katz            Absolutely, I think part of our job is to be kind of a prognosticator and say they are going to blitz, they are very aggressive and we can tell that by looking at say markers for proliferation and if we see that there is a lot of proliferation that is going on we think they are very aggressive. We could also tell by morphology by looking for regions of death within the cancer and if we see a lot of death we also know that they are fairly aggressive. Knowing which type of molecular abnormalities can be very helpful for the physician as well, for example, translocations, we know in follicular lymphoma, another type of non-Hodgkin lymphoma, has a translocation that leads to an over expression of an anti-apoptotic protein, something that causes the cell to live, we can try to target that.

Chagpar        We are going to talk a lot more about how we target different therapies based on what you see under the microscope and with fancy tests right after we take a break for a medical minute. Please stay tuned to learn more information about hematopathology with my guest Dr. Sam Katz.

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Medical

Minute        It is estimated that one in six American men will develop prostate cancer in the course of his lifetime and that nearly 200,000 men in the United States will be diagnosed this year alone. The good news is that major advances in the detection and treatment of prostate cancer have dramatically decreased the numbers of men who die from the disease. Screening can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. With these screening methods early detection and a healthy lifestyle, prostate cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is as an option available for patients at Yale that uses three dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at [yalecancercenter.org](http://yalecancercenter.org). You are listening to the WNPR Connecticut's public media source for news and ideas.

Chagpar        Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guest, Dr. Sam Katz. We are discussing hematopathology and right before the break Sam you and I were talking about this really interesting role that the pathologist plays in trying to figure out what cancers are going to do and helping the treating physician to stop them from doing what they are going to do or to block them. You started to mention translocations looking at cell death. Talk to us a bit more about how exactly you look for that and what kinds of targeted therapies, or therapies in general, people can use based on the information that you provide?

Katz            Sure, let me back up a little bit to explain what cell death is, cells have in them a program whereby they normally can die, which is a little counterintuitive, we would not think that a cell would need to undergo suicide, but this program which has conserved all the way back to simple organism is one that normally occurs even through development, and so it turns out that this program that is used for development is also taken advantage of by the cell in order to survive. So if you have a program that can tell cells to die, what happens is as the cell accumulates mutations and becomes malignant, it finds ways to try to activate this program.

Chagpar        So in other words when a cancer cell becomes a cancer cell it has a program embedded in it that says, I have got too many mutations, I have to die.

Katz            Yes absolutely, it has this program that recognizes all these other cues and says, it is time for me to die.

Chagpar        So then cancer cells must kind of ignore that program when they continue to be cancer cells.

Katz            Absolutely, they must find a way around this program. They have to mutate things that either help them to keep them alive or that will make them die. It was a little bit of a paradox shift when it

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was first discovered, most people when they first thought about cancer is that it is a cell that is just proliferating really quickly and they did not realize there is another side to that equation, you can think of it like a bathtub with water in it, with the water being the number of cells. You have a faucet, that is the proliferation and you can keep adding in cells, but there is also a drain to that bathtub, right, and so if you close that drain it is also going to cause it to overflow.

Chagpar        Right.

Katz            And where the realization first came from was one of these translocations. About 30 years ago several different groups found within human lymphomas a translocation that if two different chromosomes came together and on one side was a region of the genome that causes large high expression of whatever has passed it, and on the other side was protein that they called BCL2 or B cell lymphoma 2 and BCL2 as it turns out is something that prevents cell death, prevents a apoptosis.

Chagpar        So now you have got this cell that is making a lot of strength that is preventing it from dying?

Katz Exactly.

Chagpar And that causes cancer.

Katz It can, and it turns out that BCL-2 was the first of many proteins within the cell that regulates this battle for its fates and you have essentially two types, ones that like BCL-2, stop the dying, that is they guard against it, and ones that are more like executioners that is they kill the cell and these proteins interact with each other and battle it out based on the signals that they are getting until one of them will ultimately win.

Chagpar So in the case of a cancer you want the executioners to win.

Katz Absolutely yes, and that does not always happen and the way that the cancer has to get around it is by either increasing the number of guardians like BCL-2 or decreasing the number of executioners.

Chagpar So then how do we as clinicians change the balance?

Katz What has been really exciting is that people, after learning a lot of this biology, have figured out that there are special touch points on the protein that you can target and bind to and break up this complex and get the executioners to activate, and so we now have the first of these small molecules that are designed to bind to BCL-2 family members, inhibit the guardians, and let the executioners take over.

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Chagpar That is really exciting, so are these small molecules being used right now in therapy?

Katz Yes. So the first few of them are being used in clinical trials for several different cancers and you can imagine that since cell death is critical to



all cancers, what the end game is that we want these cells gone, we want them to die, that this is very broadly applicable.

Chagpar        Wow, so are you telling me that these small molecules might actually be dare I say a cure for cancer?

Katz            No, I will not quite go that far. I would say that they might become a very important weapon in the arsenal against cancer and as I said, they are sort of the beginning stage because we have hit a couple of the points along the pathway, but there are many other points that we would want to be able to target and I think that what they might do is they might help shift the balance in this pathway and because there are only perhaps shifting this balance they will probably need to be combined with other forms of therapy.

Chagpar        Is BCL-2 the only guardian or are there other guardians too?

Katz            There are at least five total guardians, there is BCL-2, BCL-XL, BCL-W, those three are targeted by the first of these compounds that have been designed. There is also BFL1 and MCL1 two other guardians which are not touched at all by that.

Chagpar        It seems to me that you then need a new compound that targets them as well because if you tame the first three guardians, but the other two can proliferate, you still have not won the battle.

Katz            Absolutely and there are many people who are working on trying to get small molecules that target specifically those and not only that, but some cancers are more reliant on one of those five than another and so what would really be great is if we could target it so that we had a specific one for each single one of those five, so that way we could say, it turns out this time it is BCL-W that is up so let's give the anti BCL-W therapeutic.

Chagpar        And would you be able to know that by looking under the microscope or using those fancy tests that you were telling us about earlier?

Katz            Sure, there are two ways that one could do it, the way that is more currently used in practice today is under the microscope by using, as I was talking about, this immunostaining, where you use antibodies to recognize

what proteins are expressed. So for follicular lymphoma which has the BCL-2 translocation we have an antibody that recognizes BCL-2 and then we can see the over expression or the expression of BCL-2 in those cells. There is a second way that people are trying as well which is something that looks at the functional activity of the pathway and it isolates out the cells and you look to see which member of the pathway is more active by tickling it a little

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Chagpar      Might this be something that you would use in conjunction with standard chemotherapy or maybe even instead off?

Katz              Possibly, I think the first step would be in conjunction and as we learn more about it and as we get more targeted therapies, then we would start grouping it and pairing it with those.

Chagpar              When you mentioned what BCL-2 stands for, it was B cell lymphoma right, and it seems to me the other one that you mentioned was MCL, which is mantle cell right?

Katz              No, to be careful, MCL is actually myeloid cell leukemia, which is different from MCL or mantle cell lymphoma. They share the initials.

Chagpar              But regardless it seems to me that all of these really have their root in blood cancers.

Katz              Agreed, it is definitely where the story started and that is often the case because blood cancers are a very amenable system to work with in the laboratory compared to solid tumors.

Chagpar              Why is that?

Katz            Because we can get out the individual cells and culture them more easily within the lab. We have learned many more techniques and most of what we learned in blood early on, later got applied to the solid tumors.

Chagpar        And do you think that is traditionally going to be the case, that a lot of cancer research is going to start in the blood laboratories and then find its way into breast cancer and colon cancer and everything else?

Katz            I think that we are informed now from both sides. There is a lot of basic work that went on very early in the blood that then got pulled into solid cancers but then as time has evolved, lots of knowledge has been gained distinctly from solid tumors like breast cancer or colon cancer and that has circled back now and started to inform blood.

Chagpar        Let's talk a little bit about that because so often our guests on the show talk about targeted therapies and they talk about specific genes or specific markers in their specific cancer that is their favorite, and so when we talk about breast cancers they are talking about HER2 or estrogen

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Katz            There is an overlap but with the particular ones that you mentioned, not necessarily, so the apoptosis ones, this BCL-2 family, they do overlap from blood to all the other cancers as well and they sit at a point where as we said, remember these cells feel signals coming into them while the way they feel these signals is through these other pathways like EGFR or HER2, they impinge upon the apoptotic cascade telling the cell whether to live or die.

Chagpar        So it sounds to me like all of these pathways are really interconnected and the more we are learning about blood cancers, the more we are learning about cancer overall.

Katz            Absolutely.

Dr. Samuel Katz is Assistant Professor of Pathology at Yale School of Medicine. We would like to invite you to share your questions and comments with the doctors. You can send them to [canceranswers@yale.edu](mailto:canceranswers@yale.edu) or leave a voicemail message at 888-234-4YCC. Archived programs are available in both audio and written versions at [yalecancercenter.org/archives](http://yalecancercenter.org/archives). We would like to thank Yale Cancer Center for providing production support as part of the connecting our communities initiative from Connecticut's Public Broadcasting. I am Bruce Barber and I hope you join us again next Sunday evening for another addition of Yale Cancer Center Answers here on WNPR Connecticut's Public Media Source for News and Ideas.