

Yale CANCER CENTER *answers*

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale, New Haven. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation about immunobiology and hematopoiesis with Dr. Joao Pereira. Dr. Pereira is Assistant Professor of Immunobiology at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Could you start off by telling us what exactly immunobiology and hematopoiesis are?

Pereira Immunobiology is the study of the cells of the immune system and how these cells act to perform their jobs, basically. The immune system is involved in making sure that we can defend ourselves from microbial pathogens like bacteria, viruses, parasites, fungi and so on, but is also fundamentally important to make sure that we eliminate cells in our own body that are not performing adequately, for example, cancer cells, so the immune system has not just the job of fighting infectious diseases, but also acts as a sort of housekeeping function of keeping us somewhat healthy.

Chagpar There has been a lot of talk especially recently about immunotherapy in terms of cancer. Tell us a bit more about how that works, I mean, if the immune system really could fight off cancer cells, then nobody would get cancer, right?

Pereira Yes, that is a very good point. For several decades, cancer research has been focused on figuring out what kinds of mutations lead to cancer, what are the errors that happen in a cell that make a T-cell become a cancer cell and that research has been extremely important but for some decades now immunologists, and they are the folks interested in studying the immune system, have realized that cancer cells are themselves capable of activating the immune system, so with that discovery, it became clear that the immune system has a role in eliminating cancer cells in a natural manner, so in any healthy individual, a normal individual, genetic errors are constantly happening and occasionally these errors lead to the generation of a cancer cell, but in healthy individuals, that cancer cell is eliminated by the immune system such that we do not feel anything or even if you are going through routine medical exams, they do not show up in your medical exam. They are so rare that you cannot really find them, so the immune system does a pretty effective job most of the time. Now as immunologists are becoming aware of how the immune system works are trying to use the weapons the immune system uses normally to fight cancers that are developing in patients that for one reason or another, the immune system was not capable of eliminating that cancer cell.

Chagpar Do we know why in some people the immune system does not fight off these cancers? Is it a factor of the patient not having a robust enough immune system, somebody who is

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immunocompromised or is it a factor of the cancer tricking the immune system and not letting the immune system do its job in eliminating it?

Pereira It is both, so in immune deficient patients certainly cancers have a higher propensity to develop but also in individuals with a normal immune system, some cancer cells acquire properties that allow them to evade the immune system, so in those kinds of circumstances where the cancer cell has a turn off button to avoid immune recognition and immune mediated attack, then we can develop strategies to turn the off button off, basically, so that is the essence of cancer immunotherapy, to devise the immune system of the patient to more effectively reach out to the cancer cell and eliminate it directly.

Chagpar Kind of taking off the invisible cloak.

Pereira Yes, there are some strategies that cancer cells use, and that is one of them, the invisible cloak. The other is an active process where it turns the wrong button in the immune cell; by wrong I mean the button that tells the immune cell to turn itself off, so immune cells, they have to be able to be turned on to attack let us say a microbe that is infecting us but they also have to be able to be turned off such that the immune cell will not cause more damage than what is necessary for the individual. The turn on and the turn off mechanisms of immune cell regulation are somewhat known and so some cancer cells have the capacity to produce proteins that pretty much turn on the inhibitory function of the immune cell and then the immune cell is facing the cancer cell but just cannot do its job.

Chagpar Because the cancer cell turned it off?

Pereira Yes, it turned the inhibitory molecule in the immune system to switch itself off.

Chagpar Very interesting, so in the introduction I said that you were here to talk about both immunobiology and hematopoiesis, what is hematopoiesis?

Pereira Hematopoiesis is the process that generates all blood cells, so the cells that run through our veins in the blood system can be separated into two types, very simply, the red cells

and the white cells. The red cells as probably everybody knows are the cells that carry oxygen. They are not notoriously known for performing any type of immune defense but they play a vital role in the organ of carrying oxygen and it also produces white blood cells and white blood cells can be of various types. There are far too many types of blood cells for me to continue counting them but there is definitely 1000s of them and white blood cells can be of myeloid origin, cells that directly kill pathogens like macrophages, neutrophils and also lymphocytes. Lymphocytes are critical. These are the cells that have the memory that can actually remember that they have seen this microbe before and so these are the cells that are often targeted in vaccination, for example. Vaccination is basically trying to educate the body to recognize and destroy a virus or bacteria and that acts primarily on these lymphocytes, so hematopoiesis is the process that generates all of these blood cells.

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- Chagpar Tell us a little bit more about how the two fields are connected?
- Pereira Hematopoiesis is the process that generates the immune system. The white blood cells are the cells that form the immune system, so they are obviously interconnected.
- Chagpar Tell us a little bit more about the research that you have been doing.
- Pereira The research we are doing in my lab at Yale is focused on understanding how hematopoiesis is controlled. We know that all blood cells are formed from a single hematopoietic stem cell, a cell that is capable of differentiating into all blood cell types, but we do not really understand how a hematopoietic stem cell decides to become a red cell or a white cell and that is the primary focus of research in my lab. We really want to know what are the factors that allow these decisions to occur in the body and can the cell do these process alone, would it be able to do it anywhere or does it need the specific environment, the specific neighborhood, does it require a particular neighbor to help make this decision and if so, do they have to go through different neighborhoods to give rise to all blood cell types, is there a red cell neighborhood and a white cell neighborhood and so on and so forth, so that is the primary goal of our research.
- Chagpar Why is that important? You would think that if stem cell needs to differentiate that hopefully they differentiate into some of them becoming red cells and some of them becoming white cells because clearly we need both, but why is it important to understand what factors go into that decision?
- Pereira It is important at multiple levels, at a very practical level as we age as individuals, there are changes that occur in hematopoiesis that make us less capable of producing, for

example, lymphocytes and lymphocytes are extremely important. We need to keep producing them constantly throughout our life as much as possible because these are the cells that let us have memory against microbes and other entities that we faced before, so if we stop producing these cells, we run the risk of not being able to remember new pathogens that we have encountered, so in a globalized world, that is certainly important because we are constantly traveling overseas so we are constantly exposed to new environmental factors that 100 years ago would not have been such a problem, but currently it is. So it is really important to understand how cells make decisions at least to a certain level, so that hopefully, we can correct some of these shifts that occur throughout life. As we get old, we make less lymphocytes; can we stop that and make an individual produce the normal balanced proportion of blood cells constantly throughout life; that is certainly one aspect. The other aspect is hematopoiesis is a pretty complex process. It starts with a single cell that generates trillions of cells daily and a trillion cells is probably too large a number for people to really grasp but it certainly is a process that generates many chances of developing genetic errors in cells and so cancer cells. If we understand how the process is controlled normally, we are definitely equipped to understand when a blood cancer develops and the more we know how it forms the better we may be at correcting that mistake or eventually treating or curing that problem.

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- Chagpar I certainly can understand, if you have got a single cell that then makes trillions of cells every day that the rate at which it is making those cells is incredible and so it is clearly possible that errors occur, so what mechanisms are there in your body already that prevent you from accumulating these errors?
- Pereira There are multiple check points, so stages at which cells can be, let us say analyzed, for fitness and for any abnormality that might have occurred, and all cells have a certain internal program to die on their own in case some of these errors happen. The types of errors that occur that lead to the actual production of cancer usually is associated with failure at multiple levels, so it is kind of similar to if an airplane falls, it is not because one single problem occurred but mostly because of multiple sequences of problems and that is the combination that resulted in that, so cancer can also be seen in this way.
- Chagpar We are going to look more at how cancers develop and how this whole intersection between cancer and immunobiology works right after we take a short break for a medical minute.

*Medical
Minute*

Smoking can be a very strong habit that involves the potent drug nicotine and there are many obstacles to face when quitting smoking but smoking cessation is a very important lifestyle change especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments and to decrease the likelihood that the patients will develop second malignancies. Smoking cessation programs are currently being offered at federally designated comprehensive cancer centers, such as, Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven. The smoking cessation service at Smilow operates on the principles of the US Public Health Service Clinical Practice Guidelines. All treatment components are evidence based and therefore all patients are treated with FDA approved first line medications and smoking cessation counseling. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. For more information, go to yalecancercenter.org. You are listening to 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 tonight by my guest, Dr. Joao Pereira. We are talking about immunobiology and hematopoiesis. It is not every day that we talk about blood cells and cancer on the same show, but I want to get back to the link between all of these concepts. We talked a little bit before the break about immunotherapy, but are there other ways in which cancers and this whole hematopoietic system are intertwined?

Pereira

Certainly, there are I would say three levels at which cancer and hematopoiesis are interconnected. The first level as we have discussed, there are some blood cells that can give rise to cancers, leukemias and lymphomas, for example, are types of cancers that are hematopoietic of origin so they are cancers of the hematopoietic system. The second level is cancer cells that are not of

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hematopoietic origin, as we discussed are recognized by cells of the hematopoietic system, the immune system cells, so that is the second level but the third level is some cancers like lung cancer, breast cancer, prostate cancer that have the capacity to migrate out of where they were originally formed and colonize a distant organ, so those are known as metastasis and the organ where hematopoiesis is occurring is the bone marrow and bone is one of the preferred sites for cancer metastasis. For example, prostate cancer, bone is one of the primary if not the only place where prostate cancer cells metastasize, so there is something about that environment that sustains the production of all blood cell types that is also very

appealing for a cancer cell to thrive. It provides an environment that sustains some types of cancer cells, so that would be the third level.

Chagpar That is very interesting to me because a lot of your blood cells come from your bone marrow, but there are also other organs that are hematopoietic or that have a connection to the hematopoietic system like your spleen, but I do not really hear too much about cancer cells going to the spleen, what is the difference?

Pereira That is a really good question, so the spleen and the liver, they are not hematopoietic organs, although they once upon a time were, hematopoiesis comes from the fetal liver and from the fetal spleen, but in adults, humans, mammals in general, those organs do not support hematopoiesis for the most part. Now how do cells decide to go to the bone marrow instead of going to the spleen or to other organs? It has to do with what the cancer cell acquired as a property, so cancer cells can produce proteins that allow the cell to migrate to physically move from one organ to the other and some of these cancers, breast cancer, lung cancer, prostate cancer cells can produce a protein that recognizes another protein that is abundant in the marrow that attracts the cells there and this is more prevalent in the marrow than in other organs, so basically the bone marrow has a certain zip code for which the cancer cells can actually be directed to and that is what I think partitions metastasis to some organs versus not another organ.

Chagpar What is the deal with this protein that is in the bone marrow that attracts these cancer cells?

Pereira The deal is it is a protein that is part of a large family of proteins that help distribute the immune cells throughout the body into appropriate locations. For example, in the gut, we have trillions of bacteria, so there are immune cells that are poised in the gut to make sure that the bacteria that is inside the gut does not go outside the gut and start causing damage to the body and so how do the cells go to the gut instead of going to other organs? That has to do with the zip codes, the collection of proteins and molecules that help the cell, the site to stay in the gut and not to go into the spleen, for example, and so the same general properties are applicable to the bone marrow. This family of proteins contains dozens of proteins so you could imagine dozens of zip codes basically and bone marrow has a particular zip code.

Chagpar But what is it about that zip code? Is it like the wealthiest zip code that all of the cells want to go to? There has got to be something that says, come to the bone marrow, and I wonder whether that is related to how all of these immune cells actually develop since that is their home turf.

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- Pereira Yeah, that is a great connection, you are 100% right, so the zip code that makes cancer cells go to the marrow is the same zip code of hematopoietic cells used to actually develop in the bone marrow, so in essence it is just a collection of proteins and molecules that help the immune cells to stay in their appropriate locations.
- Chagpar So we do not know why it is that these cancer cells are attracted to that particular zip code?
- Pereira Well, during the process of cancer cell development, when cells acquire genetic errors, they carry a certain genomic instability that can result in abnormal production of proteins that they would normally not produce in such high amounts and also it can result in the acquisition of properties that the cells never had before, for example, the capacity to actually move from one place to the other. Many cancer cells are not cells known to be motile or capable of migrating from one place to the other and the transformation process enables the cell the ability to actually move, that ability is the simple acquisition of proteins that help the cell to read the zip codes, so now the cell can read a different zip code and so it goes there.
- Chagpar Interesting, so if we could turn off this migratory zip code reader, we could potentially do something about metastasis?
- Pereira That certainly is a very appealing strategy and it is being attempted, although there is a considerable amount of redundancy in the zip coding system of our body that makes it not the most attractive strategy so far, but it certainly would be fantastic if we could instruct cancer cells to go to the wrong zip code.
- Chagpar Or not to go to any zip code.
- Pereira Certainly, yeah.
- Chagpar Let's get back to a different layer that you were talking about because I liked the concept of many different layers where the immune system and cancer intersect and the second one that you had mentioned was the way that cancer cells develop actually from the immune system and this takes me back to our original conversation before the break where you were talking about how all of your blood cells essentially come from a stem cell and as this universal stem cell decides which way it is going to go and produces all of these other cells, that can then cause errors to form, so when you started talking about

how does a hematopoietic cell decide whether it is going to be a red cell or a white cell, is there some mechanism by which that gets screwed up so that then it does not turn into either of those but turns into a cancer cell or does that not work that way?

Pereira That is another very interesting question. There are problems with hematopoietic decisions of becoming a red or white cell that are known to be caused by the inability of the stem cell to produce a protein that helps the formation of a red cell, so in that case, the stem cell will not make

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the red cell but it could in theory make the other cells and I say in theory because if the stem cell cannot generate a red cell, then the organism does not really develop, so it does not even develop, so it is almost a problem that does not exist, but genetic errors are caused mostly by the fact that cells are constantly dividing and in the hematopoietic system, from the hematopoietic stem cell all the way to the generation of billions of cells, there are multiple check points when the cells are constantly dividing and when they divide they have to duplicate their entire DNA. Obviously, even the highest efficiency enzyme capable of duplicating the DNA is not 100% efficient, so errors are constantly introduced and so if the error occurs in the wrong gene, in the wrong place, then a cancer cell could be forming, but it is not only that that needs to occur, it is the failure of subsequent steps, the inability of the cell to correct the error that was introduced, that is the second level of regulation that our cells have, the enzyme may be writing the wrong code but we have other enzymes that correct for the wrong code, so it is a failure of all these multiple check points that results in the cancer cell. Now whether a stem cell that isn't able to go either left to the red or right to the white blood cell type now only has the option of becoming a cancer cell, I do not think that is exactly how it works.

Chagpar So it is more likely that it differentiates into one of the different types and then from there as it generates errors, if it is white blood cell and it generates a bunch of errors, it then turns into a white blood cell type of cancer.

Pereira That is correct.

Chagpar So it clearly made it through to being a white blood cell without errors but as it divides further, then the errors continue and so somehow this process of quality assurance and double checking gets fouled up down the line?

Pereira There are multiple stages where this could happen, yes.

Chagpar So it brings us back to what you are doing in the lab which seems to be really fundamental basic science, understanding how a stem cell decides, is it going to be a red cell or is it going to be a white cell. How does that affect cancer biologists and physicians? Tell us more about that and the importance of basic science.

Pereira That is certainly a very important discussion point that could fill in hours of conversation. In any human disease, cancer, autoimmunity any, there are obviously people interested in researching directly what is causing a certain problem and that research is fundamental and one can catalogue it as translational research if it has a clear role of defining a novel way to treat the disease or to test a new compound to treat the disease, but basic science is not defined in this way. Basic science is almost unbiased, unguided in the sense that it does not have permanent in the mind that there is a clear medical problem to be solved, yet the importance of basic science is enormous. Several decades ago several people were interested in studying how bacteria produced protein, the

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knowledge that came from that research that has obviously no clear connection with human diseases, made it possible for insulin, for example, to be produced in copious amounts these days and that is being used to treat many patients with diabetes, but in the 50s if you asked any of those researchers if their research could have direct impact in diabetes, I would say probably none of them would think that would be the case, I hope this illustrates how basic science is so important.

Dr. Joao Pereira is Assistant Professor of Immunobiology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.