



The Discovery of Renalase and its Role in Cancer

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May 7, 2017

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Welcome to Yale Cancer Answers with doctors Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week Dr. Gore welcomes Dr. Gary Desir for a conversation about the discovery of the growth factor renalase and its role in the development of certain cancers. Dr. Desir is the Paul B. Beeson Professor of Medicine and Chair of the Department of Medicine at Yale School of Medicine. Dr. Gore is Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore Gary, you are a nephrologist right?

Desir I am.

Gore For our listening audience, of course, nephrology is the medical study of kidney mostly right? And metabolism maybe a little bit?

Desir Yes, mostly kidney, kidney diseases.

Gore Kidney diseases, so that means if you are in a cancer shell, you just work on kidney cancers, that is how a nephrologist gets involved with cancer or what is the story there?

Desir Some nephrologists do work on kidney cancer, but most work on regular kidney disease; end-stage kidney failure, dialysis, diabetes and kidney disease. But the story I will tell you is unusual, in that I am a full-fledged nephrologist caught carrying and my work really has been with studying hypertension and kidney disease and the connection between the kidney disease and heart failure and heart disease.

Gore I have got kidneys and hypertension and blood pressure. I get blood pressure and heart disease, I do not get that in cancer.

Desir The way it began, our work on renalase, which is what we are going to be talking about, I was in the hospital with one of our renal fellows and seeing patients at the VA, and many of our patients have end-stage renal disease for which they get dialysis. Now, with dialysis, one of the good things is that it prolongs life. It was established in the 1960s and now patients who have end-stage renal disease can live much longer than they could before. But what has been found over the years is that when you put patients on dialysis, they develop really severe heart disease, cardiovascular disease.

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Gore And many die from the complications of heart disease and the question has been in the field, why is that. Why is that when you develop renal disease and renal failure, you have a much higher risk of heart disease?

Gore And that is not just because patients who have hypertension are at risk for both?

Desir Well partly, but what we have been doing is actually treating patients with kidney failure fairly aggressively for hypertension. So, many of them have normal blood pressure. And we also control for things like hyperlipidemia or high cholesterol levels. So, we treat them fairly aggressively. But in spite of our best efforts, they still get significantly higher incidence of heart disease. It is about six of seven-fold higher than the normal population.

Gore And it is just like heart attacks or heart failure?

Desir It is both. So, when they get heart attacks, it is much more severe than the person without renal disease and a quarter of them die suddenly, presumably from disorder of heart rhythm and the rest die from heart failure and strokes and peripheral vascular.

Gore That must be very frustrating if you are a nephrologist really keeping somebody like that alive with your best dialysis and medical care and then they just kind of drop dead on you.

Desir Exactly. So, essentially the fellow was complaining that he felt we were doing the best we could, but it really was not good enough. So, the question was, why? And he was a very enterprising fellow, and this is a question I have to say that has been plaguing the renal field for many years and there have been many hypotheses as why that would be, why you develop more heart disease and part of it may have to do with anemia for instance. So, in the 1980s, when I was a fellow, we thought that the development of erythropoietin which is something that helps you build your red blood cells would really make a huge difference in how patients survive and whether the outcome would be better. It turns out that erythropoietin is good, but it really had made no difference in terms of survival.

Gore That helps treat the anemia right?

Desir It treats anemia but does not really help survival. So, one of the hypothesis has been that perhaps the kidney behaves as an organ that makes things that affect the cardiovascular system. And the question has been, how do you find what the kidney is making, presumably, that is unknown. So, we developed a hypothesis that perhaps the kidney is making a protein that circulates in blood and that affects cardiac function. And the issue was, how do you find that protein?

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Gore How do you convince somebody who may want to fund your research.

Desir Well, that is another thing.

Gore I have got a good idea, give me money.

Desir Give me some money to do that, and I will get to that in a second. So, we decided to look at that question. And it is a high-risk project as you mentioned, perhaps funding would not be forthcoming for such a project, but we decided to do it anyway. And we used a couple of new methods that were becoming available. One of them was, an ability to look for proteins based on certain specification that could be secreted in plasma even if they were unknown. So, we used that. We also used computer-generated algorithms to screen for large numbers of genes and proteins.

Gore Even back in the 80s?

Desir Actually back in the late 80s and mid-90s when the NIH, National Institute of Health, was funding research labs who actually sequence and characterize genes that were expressing a number of cells. So, they are the special database called the Mammalian Gene Collection Project, and we looked into the database, we screened about 18,000 genes and looked for very specific clues for proteins that were unknown but that could be secreted. The way proteins are secreted is that they have to sneak through the membrane and they have a special tag on them that allows them to go through the membrane to get out of the cell. So, we used that knowledge to screen for those tags. So, we identified about 100 proteins that fit the bill, that could be secreted but that were unknown.

Gore And you did not know if they were in the kidney or not.

Desir We did not. And then we used different methods to make sure that they were in kidney and we focused on those that were only present in kidney.

Gore Well this is really a needle in the haystack kind of project.

Desir Yes. So, we were looking for one out of 15 million. And then we found about 9 or so that were in the kidney. And then we isolated all 9 and then expressed them in cells just to make sure that they were actually secreted and then focused on one. And the reason we focused on one was that it was highly expressed in the kidney. The kidney made a lot of it. But also it could metabolize what we call epinephrine and catecholamine, adrenaline.

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Gore Adrenaline, well people know about that.

Desir Adrenaline is something that in the renal field seems to drive or cause hypertension. So, it is elevated in patients with kidney disease.

Gore This is the fight or flight hormone.

Desir Exactly, adrenaline. And we thought if a protein, or an enzyme, metabolize adrenaline and if you develop kidney disease and if the level of it goes down, then perhaps that could be related to why one gets lower levels.

Gore So, the adrenaline might go higher because you did not have this thing to metabolize the adrenal. Am I understanding that correctly?

Desir Exactly. And we know that in patients with chronic kidney disease, adrenal levels tend to be higher. So, that made perfect sense. So, we studied the protein further. We called it renalase because we thought it was an enzyme that was made by the kidney, hence the name renalase. And so we studied it. One of the way to study is to delete in animal model, we used mice to do that and we showed that if you remove the protein from mice, they become hypertensive and they have very catecholamine levels and they are very sensitive to kidney damage and to heart damage, and that made sense. And then we started working on the mechanism. Is it really metabolizing catecholamine or is it something else. I am summarizing a lot of work.

Gore I bet. This is not easy folks, do not try this at home.

Desir Not in your basement. And what we found was, that instead of being just an enzyme, renalase is a protein that gets secreted into the blood and the blood and then it attaches itself to the membrane of cells, and then it sends signals inside the cell that allows the cells to survive when stressed. So, for instance, if you reduce blood flow to an organ, let us say the kidney, this cell becomes stressed and could potentially die, it increases levels of renalase to survive by activating these pathways. So, that is the major mechanism of renalase. And we have studied its structure in significant detail and we know exactly what it binds and how it binds to the cell. So, that is my role as a nephrologist. Now the question is, how do I get to cancer from there?

Gore Let me just try here. As an oncologist, I know that genes which help cells to survive can contribute to cancer because such cells who have their genes damaged, they should kill

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themselves off because they are not healthy; and if they have a survival advantage, may turn into cancer cells. That is just my guess.

Desir That is your guess. Well that was our guess.

Gore Great minds thinking alike.

Desir So, we thought perhaps something for most cell survival and the stress might be hijacked by cancer cells to allow them to survive longer. And so we began looking in the human cancers to see whether or not renalase expression was higher or lower or different comparing to normal tissue and cancer tissue. And what we found to our great surprise was that there were several cancers where renalase levels were highly elevated in cancer compared to normal tissue.

Gore Was renal cell one of them?

Desir It was not.

Gore Ironically.

Desir Ironically it was not. So, the cancers that came out were pancreatic cancer, melanoma, breast cancer and bladder cancer. So, bladder is close to the kidney but not exactly kidney. And so we had to make a decision at this point I had no experience in cancer research and should we pursue this?

Gore How it would look to your fellow nephrologists?

Desir They were not happy I have to tell you. But we decided to work on pancreatic cancer and melanoma for two reasons. Pancreatic cancer is one where mortality is quite high and treatment has not advanced significantly over the years, and melanoma, although we have made significant advances in treatment quite recently, we could do better, and Yale has great resources for melanoma research, and we thought that this was a good cancer to work on. So, we started working on that. We partnered with Dr. Harriet Kluger, who is a melanoma expert and started looking at whether or not blocking renalase action in cancer might be a therapeutic option for patients. And so that is where we are. And what we began to do is to develop drugs that inhibit renalase action and in particular we have been focusing on antibodies that can do that.

Gore Wow. This is a very fascinating story. And even though I have heard you talk about this before, it is really, really interesting to hear how science leads us in interesting directions. We are going to need to take a break for medical minute, we will pick this

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up after the break. So, please stay tuned to learn more information about renalase with Dr. Gary Desir.

*Medical
Minute*

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The American Cancer Society estimates that more than 60,000 Americans will be diagnosed with head and neck cancer this year. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancers and their treatment. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to test innovative new treatments for head and neck cancers. In many cases less radical surgeries are able to preserve nerves, arteries and muscles in the neck, enabling patients to move, speak, breathe, and eat normally after surgery. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital. More information is available at YaleCancerCenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.

Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore, and I am joined tonight by my guest, Dr. Gary Desir. We have been discussing his work on an interesting protein called renalase. So, Gary before the break you were telling me that you teamed up Dr. Harriet Kluger who deals with melanoma and you are trying to design drugs to inhibit this protein which you think may be contributing to melanoma.

Desir So to continue, what we decided to do is to develop antibodies, monoclonal antibodies that bind to renalase and block it from activating the cancer cell and surviving. We have done extensive studies in mice and shown that the antibodies actually work really well.

Gore Do you think that the melanoma itself is secreting the renalase that is sort of feedback, self-feedback to protect itself. Is that what is happening.

Desir Yeah partly. So, melanoma do make renalase and renalase secreted by cells can bind back to the cell membrane, the surface of the cell, and signal into the cell. But what we found most importantly is that it is made by immune cells, in particular macrophages that invade the melanoma tumors.

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Gore So, these macrophages, they are cells like Pac-man, to gobble up the garbage and kill cancer cells sometimes.

Desir Correct. Sometimes, they kill cancer cells and sometimes they help cancer cells survive. In this particular case, making a lot of renalase allows the cells to grow. So, if you block secretion of renalase from macrophages, you actually kill cancer cells. So, it has a direct effect on cancer cells themselves but also on what is called the microenvironment of the tumor where it inhibits the action of cells that invade the tumor.

Gore So, what happens when you give these antibodies to the mice? Are the mice carrying melanoma?

Desir They are carrying melanoma and you give them the antibody, and the melanoma in most cases disappear completely.

Gore Wow.

Desir It has been really amazing results.

Gore And that is just this antibody and you are not combining with these other super-duper new immune drugs that they use in melanoma?

Desir We are not. So, just by itself renalase can make a melanoma go away. But in addition, if you have a melanoma that is resistant to those new super-duper drugs, renalase is effective against them, and if you combine them, it has got a synergistic action.

Gore I know that we are going to get a bunch of e-mails saying "okay, how do I get myself some renalase." So, how does one get from this really fascinating story to delivering it to our patients?

Desir Well, the first thing we have to do and which we are doing right now is to make the antibodies suitable for human use. So, the antibodies are originally made in animals and we have to convert it to something that will work in people.

Gore Because otherwise the human body may not tolerate those antibodies.

Desir Correct. So, we are currently doing that and should be completed within the next few months, and then we have to convince the FDA that it is safe to use in humans and then plan for human trials, and we hope to be able to do that in the next couple of years.

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- Gore Wow. That's really a fantastic story. But besides this really genius science hat that you wear, you also serve as a Chairman of the Department of Medicine, which is a very big department here.
- Desir It is. It has been a wonderful experience. We have about 500 faculty members and 12 sections and it is a very vibrant clinical department and research-based department. It has been great.
- Gore Yeah, so that is really two very different hats that you are wearing.
- Desir Yes, and people ask me how do I find time to do that, I say it comes out of sleep.
- Gore Better you than me I guess. I like sleep. I guess I should not be telling that to my boss. I do like my sleep. So, Gary, one of the things we know you are passionate about is this issue of diversity, and I think it is so important in such a big department, I mean diversity is important in all of our society right now. How do you see diversity as a challenge and a benefit in departments of medicine or in medicine in general, and what are your approaches?
- Desir Right. You can make several arguments for diversity. One is just a moral argument that is just fair, and you should involve others in what is being done. I like to make the argument about diversity based on utility. So, my belief is that medicine is really a team sport, team science and we take care of patients in teams. And I think the data about how teams behave is fairly consistent in that if you have diversity in making a decision, you usually make the better decision than if you have homogenous team. In that, I am thinking about diversity in terms of gender, race and ethnicity and also cognitive diversity – how you think about things. So, there are several papers published in PNAS for instance where they have shown that if you have a team that has some diversity in terms of thinking and life experience, they tend to make much better decision about buying stocks, or if you have a team thinking about how much to pay for something, and you can avoid price bubble if you have a diverse team. So, that is my approach to diversity when we are taking care of patients and deciding on big programs and doing research, we really need that diverse input from diverse groups of people. And I think that is for me the point of making the department great is we really need to make it more diverse. And so how do you do that in the very large department?
- Gore Right, because you have been in the chair for about 2 years and you inherited a large majority of these people right?

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- Desir Yes. So, going forward I think what we have decided to do is a few things: One, I think to make a significant change, you need agents and the most valuable agents would be program leaders and section chiefs. So, the question was, how do you bring the issue of diversity into the daily conversation? One of the first things I did was to provide leadership training and evaluation for all the leaders in the program and the section leaders and get a sense of how they think and where they are and provide advice and provide some leadership development support for the leaders. In addition, we commissioned a company to do a culture survey in the department and see how we think, what we think the culture is, what it should be and how we can make it better. And the issue of diversity came up repeatedly.
- Gore So far we were not diverse enough?
- Desir Not diverse enough. And people who represented medicine felt that they were being supported as well as others. So an issue of fairness and inclusion, and that is what we are working on. And we also believe that recruiting a diverse house staff, residents and fellows, is important because many of them will become faculty. So, we are focusing on that. And to help in that work, I have appointed an Associate Chair of Diversity and Inclusion in Medicine who works very close with the program directors in medicine and the faculty to try to put in program that helps people already here feel included and supported and programs to track the more diverse resident pool and faculty pool. So, those are ongoing projects.
- Gore These are really wonderful initiatives and I wonder sort of going back of course because our whole society is so slanted traditionally in a way that it does not necessarily help develop people from minority communities and less advantaged economic communities getting back to the talent pool, that is something that as a director of medicine you do not really have control over right?
- Desir That is true. We do not have control. So, we basically essentially have to compete for the small talented pool of people, and we have not done a good enough job competing with them. So, part of the work that the associate chair of diversities do is actually trying to make it much more competitive in that process. So, we go to historically black colleges and medical school and we are much visible than we used to be.
- Gore That's great. It has been my impression, of course, I came here from Baltimore a few years ago, 3 years ago as you know, and it is my impression that we have, especially in the house staff, quite a diverse house staff, both racially and in terms of multi-national. I think it is an apparently quite a rainbow house staff as far as I am concerned.

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Desir We are getting there.

Gore A lot of women?

Desir Yes. Actually, this year, we recruited more women than men. So, one of the issues we have to try to solve is that we have a fairly diverse medical school student body and slightly less diverse residency program and a much less diverse faculty. So, how do you recruit and convince students and/or residents to stay here as faculty members>

Gore One of the things I have been impressed with and I hope I am not divulging any confidences, which I do not think I will, is that I was once sitting in a promotions discussion among the professors and one female candidate was being presented for promotion to whatever rank it was, and the person presenting her was really quite clear that this person had several children during the early part of her career, had prioritized that as part of her life and not to say that there was a mommy track, but to hold such a person to what might otherwise be mostly for male faculty would not be appropriate, and I thought that was quite a beautiful and important representation of the fact that there has got to be different pathways for men and women who have other issues in their life, right? The work-life balance is very important.

Desir It is. And I think the University and the school recognize that and they make certain allowances. Let us say, you have a child when you are a young faculty member, you can get an extension for promotion because of that and that is also truthful for this. If you take time off work to take care of your child, then you will get extra time for it, and I think that is really important. And I think that is good and that has been quite helpful.

Gore The listeners may not know Gary that I think you are originally from Haiti, is that right?

Desir I am, yes.

Gore Do you feel like your Haitian background or your immigrant status gives you a different perspective than many faculty might have?

Desir I am sure it does. I grew up in Haiti and went to elementary and high school there and then came to the US to go to college, and I go back quite often to Haiti and I actually do work in Haiti. I have a very different life experience and if I go to a hospital in Haiti and I see how things are and I come here and I see how things are, my perspective is quite different. The things I would complain about here, I would never complain about it in Haiti.

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Gore First world problems, right?

Desir Right, exactly. But I think that I have remained connected to Haiti, so I think as an institution we have a duty to help others.

Dr. Gary Desir is the Paul B. Beeson Professor of Medicine and Chair of the Department of Medicine at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer. You are on WNPR, Connecticut's public media source for news and ideas.