Transcript for Marcus Ruscetti's Podcast – to publish on Jan 30., 2024.

Marcus Ruscetti, PhD, assistant professor of molecular, cell & cancer biology, describes his research into senescent cells and the role they play in prostate cancer. Having spent most of his life avoiding becoming a scientist, Dr. Ruscetti describes how the research bug bit him and resulted in the path he is now on.

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Voice over artist
Thank you for listening to the Voices of UMass Chan, featuring the people, ideas and advances of UMass Chan Medical School.

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Jennifer Berryman
From UMass Chan Medical School, this is the Voices of UMass Chan. I am your host, Jennifer Berryman. It is a sobering statistic, one in every eight men in the United States will at some point in their life be diagnosed with prostate cancer according to the American Cancer Society. Our guest today is a scientist here at UMass Chan Medical School who is investigating a certain type of cell and its role in prostate cancer. Marcus Ruscetti is an assistant professor of molecular, cell, and cancer biology. Thanks so much for making time to speak with us, Dr. Ruscetti.

Marcus Ruscetti
Thanks, Jen, for having us and having this platform to really share some of the research we're doing here at UMass.

Jennifer Berryman
We are really interested in learning more about this. So, as an aside, you recently received a large $800,000 Research Scholar grant from the Cancer Society to advance your research specifically into senescent cells. And so, can we start right there and tell the folks who are listening, what are senescent cells? And what do you see is their role in the progression of prostate tumors?

Marcus Ruscetti

Thanks for asking one in eight men are diagnosed with prostate cancer. And many of these happen late in life and really don't need to be treated, and then some other ones actually become very aggressive and need to be treated. And so, one thing we're trying to understand is why some become aggressive and need treatment and others don't. And so, one thing we're studying is senescence. So, what is senescence? Senescence is sort of a Greek word for aging. So, when any cells in our body get damaged, so say, from sunlight, or things we're eating, they instead of dying, they can sort of become this damaged cell, this senescent cell and it sort of sticks around. The reason there is to sort of alert your body that there's some damage, and usually what will happen is your immune system will find these damaged senescent cells and clear them out and sort of restore your health and your organs and your tissues. But a lot of times, especially when you age, these senescent cells linger, and they can actually do damage to your tissues over time, really, we're trying to understand the role of senescence in cancer. We and other people actually found in human prostate cancer and also other prostate cancer markers of these senescent cells. We're trying to understand what is this good senescence cell that can activate immune response against cancer versus a bad senescent cell that can really promote tumor genesis and be a biomarker of this more aggressive disease.

Jennifer Berryman

And maybe to put a finer point on one thing you said, not all senescent cells are necessarily bad. Not all senescence cells necessarily lead to cancer. But when they linger in the body, and they don't get flushed out by the immune system, that is when you would want to start monitoring them because it would potentially be an indicator of a higher risk?

Marcus Ruscetti

Yeah, that's a great point. Yeah. So. the other thing we're thinking, you know, so naturally, the immune system, your immune system should be able to clear these out. But over time, as you age, a lot of times, they don't. And so, we and others are working on a whole sort of type of therapeutic called Seno, therapeutic grade, or senolytics. And so senolytics just kills a senescenct cell. So, we and others are interested in these these senolytics therapies as a way to design a drug to specifically kill these senescent cells that might be potentially bad, that might be leading to disease progression.

Jennifer Berryman

So, is there a way to find out like, can you do a blood test to determine if there are senescent cells in a person's body?

Marcus Ruscetti

So, there's sort of two hallmarks of senescent cells, right. One is that they don't grow. Right. So, they sort of stopped growing. So right, in some ways that can be good for cancer, cancer conceptually, is just your cells keep growing and they don't stop. Right. So naturally, senescence, if it causes them not to grow, should be a good thing. But the second hallmark of senescence, that leads to why it can be sort of tumor promoting is that senescent cells secrete lots of molecules. So these are proteins that can signal to other cells in your body. One way the secreted proteins can activate immune responses, but in other ways they can actually, you know, promote progression or actually inhibit immune responses. So, getting back to your point, because these are secreted factors, right? They're secreted into the bloodstream. So, there is potential to use these factors, these proteins secreted by senescenct cells, and potentially use that as sort of a blood test to say, oh, this patient has very high levels of the secreted factors that may be coming from a senescent cell. Maybe this is suggesting that they might have aggressive disease. or it might suggest, oh, we could treat with maybe a therapy to kill these senescent cells.

Jennifer Berryman

So, I'm really curious and I'm hoping you'll take a couple minutes to describe the research that you're doing now into these senolytic therapies, and specifically how those therapies can really target prostate cancer maybe, hopefully better than current therapies.

Marcus Ruscetti

So, the way we're approaching this and a great thing about being at UMass is we're very collaborative on the research side. So we're working with Christina Baer who runs an imaging core facility here, Dory Schafer, as well, who does a lot of neuroinflammation, to do this sort of newish technique called spatial transcriptomics that allows us to do at the single cell level use different markers that we and others have described as senescent cells to understand the difference in senescent populations. Some of these are good senescent cells. Some are bad, meaning some promote tumor growth, some suppress it. So, we're using spatial transcriptomics as a way to pick out markers of the different senescent populations. And so, we're hoping to use this sort of new technology to find these sorts of bad senescent cells and

markers they express, molecules they express and design new therapies to target just sort of the bad senescent cells while leaving the good ones intact. And getting back to therapy, so most prostate cancer patients that have advanced cancer, get hormone therapy, and many respond very well, but unfortunately, many relapse on that and they form what's called castration resistant prostate cancer. And there, there's really not many effective treatments. There's some chemotherapy that works for a few months. There are other antigen receptor antagonists that work, you know, for a little bit, but there's nothing really curative at that stage. And so, a big thing in cancer biology in treatment over the last decade has been the advent of immunotherapy. Immunotherapy is sort of using a drug or an antibody to activate your own immune system to target cancer. And this has worked amazingly, in melanoma, it's worked in lung cancer extremely well, there's set of especially solid tumors, prostate cancer being one of them, that they just don't have a lot of immune cells in there. So even when you treat with these immunotherapies, nothing happens. A big part of our lab is understanding why these immunotherapies don't work in cancers like prostate cancer and trying to find combinations with immunotherapy that do work. We're finding as these sort of bad senescent cells that linger, actually suppress types of immune cells. So, one immune cell type that immunotherapy targets your T cells and your T cells in your body are very good if they can recognize a cancer cell and killing it. And we think that senescent cells in these molecules they secrete have a lot to do with that, and so what we're hoping is that not only to design these senolytics therapies to kill these senescent cells, but we're hoping that that will, by doing that, that will bring in more immune cells into these tumors. And now when we combine that with immunotherapy that are approved for other cancer types, can this immunotherapy now function much better? So, we're basically using targeting senescence is also a way to reactivate the immune system, and combined with other immunotherapies that are already on the market.

Jennifer Berryman

That is so interesting. would be sort of the ultimate good news outcome from the research that you have ongoing?

Marcus Ruscetti

Yeah, so I think by there, there are two things right one in localized disease early on, could senescence biomarkers or perhaps they're secreted molecules in the blood be used as a diagnostic or prognostic tool to say, this patient might be developing a more aggressive cancer, right? And two, more at the late stage, right? Once they develop this castration resistant prostate cancer, that doesn't have a lot of

effective therapies, could this be tell us new effective therapy combinations, in particular, to activate the immune system to clear out the very aggressive cancer.

Jennifer Berryman

And I know this is sometimes a dangerous question to ask, but is there any sort of timeline as to how long these research studies will be going on?

Marcus Ruscetti

Yeah, so in terms of the timeline, the good news is we've already tested in some of our animal models, we actually shown that treating with senolytics. And these mouse models of prostate cancer can actually have some therapeutic benefits. So, what we're doing now is we're trying to sort of design I mentioned some of the spatial transcriptomics new biomarkers of these senescence cells and new drugs. So this might take the order of two to three years sort of to do this analysis in our mouse models. And the hope is that we find something effective. The great thing about being here at UMass as we also have a lot of interactions with the clinical side to bring this in the clinic either as biomarkers or as sort of early phase trials. And the good news is that a lot of one of the therapies we are sort of trying had been FDA approved as single agents for other cancer types that allows us to more easily potentially translate that into patients.

Jennifer Berryman

That's such an exciting time. And so, we'll be following the progress of your research with a watchful eye. I want to talk a little bit more about your time outside the lab. Besides dedicating your career to oncological research, you also spend some of your personal time raising money to support cancer related research, particularly taking part in the annual UMass Cancer Walk. I'm just curious, what drives you and your family to participate in that way,

Marcus Ruscetti

I think all of us know someone, a family member, friend affected by cancer, I think it's really something that brings the community together. And you know, what we do in the lab is important, but eventually we want to, you know, raise awareness, tell people sort of what we're doing, and eventually get this into patients, right. So, I think it's important, these cancer walks are amazing events, to bring together community, to share our research, to come together. And also, for us, as researchers to realize people are really excited about the research about new drugs and new ways to treat these devastating diseases for them and their family members.

Jennifer Berryman

Thank you. Yeah, there's so many patients out there just holding on to hope. And there's no better place to look for hope and research. Because even though it takes time, it's moving faster than it ever has. And you also come from a family of scientists, as I understand it. Was this always, was this your destiny? Was this always something that was in the cards for you?

Marcus Ruscetti

It's funny you asked? Yes. So, both of my parents were researchers at the National Cancer Institute, they were biologists and immunologists. And they were starting an interesting time where these ideas of viruses could directly cause cancer. And they investigated many of these cancer types that were virally induced. So as a kid, I sort of wanted to do something different. So, I basically tried everything I could, I was thinking of going into law school, I was thinking of becoming a teacher, and I tried all these different things. But eventually, I sort of caught the same bug that they had to do research. And I tried to sort of differentiate myself by doing more cancer biology. But you know, the interesting cycle of life and research is that now a big thing in cancer biology is immunology. So it's sort of, in a way come full circle, now studying something that my parents studied decades ago, immune responses and how they can affect cancer. What my parents taught me about research, you know, it's an amazing thing to be able to benefit people in society. But it's also just very intellectually stimulating. And you get to meet people all over the world who are doing research. And it's just really a great way to connect with different people. So, since I've been at UMass, it's been really great being here, the community has been fabulous. Everyone's been so nice and welcoming, and very collaborative. And doing both great basic research and also research that I think has a lot of potential to translate into helping people which is ultimately what our goal is, and what has always been my goal and research to actually benefit people.

Jennifer Berryman

When did you come to UMass [Chan]?

Marcus Ruscetti

We came up here during the pandemic, actually in March of 2020. Because my wife's family lives up here, thinking we'd be here for two weeks, and we're here for three months. And we got to get the position that UMass and move bought a house, close the area and been here ever since. But yeah, it's been great. I mean, you know, the communities mentioned has been great. And I love sort of living in

Massachusetts, and we have two little kids and you know, having a backyard and some nature around us. It's been great.

Jennifer Berryman

There's no better place to be if you're going to do science. So, you talked a little bit about making how science is great academia is great for making connections all over the world. One of those connections that you made, and that had an impact on your life is with somebody named Michael Green. And you two had quite a special connection. Michael

Marcus Ruscetti

Michael was my department chair. He's the person who brought me to UMass, actually. And he, me and myself, another professor Will Flavahan, and we're the last people he hired actually, yeah. Michael has just been, you know, it was fantastic about his vision about bringing people together. I mean, this is a person you mentioned him wearing many different hats. You know, he was the head of our department, Vice Provost, a research director of the Cancer Center. So he had really this vision to build up the Cancer Center. You know, UMass is really known for RNA therapeutics, treatment of rare genetic diseases, but cancer not as much right? And then something that we're sort of building and it was really Michael's vision, you know, to build this at UMass bring in, you know, fantastic new researchers to build bridges between basic and clinical and also other expertise at UMass. So, he was an amazing visionary person. And so yeah, one of our goals unfortunately since his passing in February, is really sort of continue his vision of building the Cancer Center building these bridges and collaborations at UMass.

Jennifer Berryman

As you said he passed away quite unexpectedly in February of 2023. And his impact and his presence and his wit, and his laughter and his knowledge are sorely missed by so many in our community. But we're delighted that the mission continues and that the cancer team is getting stronger and stronger by the day. So. All right, well, Dr. Ruscetti, this has been fascinating to hear more about your work and we wish you well with the ongoing studies. Thank you so much for making time.

Marcus Ruscetti

Thanks, Jen for taking time and for you know, this platform to allow us to share research with the broader community. Really appreciate it.

Jennifer Berryman

Of course, and thank you for joining us. I'm your host, Jennifer Berryman. If you like the voices of UMass Chan podcast, think about subscribing on the platform where you listen to podcasts and if you have a topic idea or a suggestion for a future episode, we hope you'll email us at UMassChanCommunications@umassmed.edu

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