TELOMERE SUMMIT

A Paradigm Shift in Cancer Therapy: Focus on metastisis not just the primary tumor

Dr. Joseph M. Raffaele, M.D.
Mark Rosenberg, M.D.

Dr. Joseph M. Raffaele, M.D.
Welcome to the Telomere Summit. I'm your host, Dr. Joseph Raffaele. And today I'm very pleased to have Dr. Mark Rosenberg along to talk about his work in really a new approach to oncology and treatment of cancer patients. We're gonna have a very interesting discussion about his recent work and a new phase one trial that is being initiated that will be initiated in the first quarter of this year. Oh welcome, Dr. Rosenberg.

Mark Rosenberg, M.D.
Thank you.

Dr. Joseph M. Raffaele, M.D.
Dr. Mark Rosenberg received his undergraduate degree from the University of Pennsylvania and his medical degree from Georgetown University School of Medicine in 1988. He completed his residency in emergency medicine where he was awarded resident and teacher of the year. Dr. Rosenberg has been an assistant director of several emergency departments, including Walter Reed army medical center, and approximately 17 years ago, after diagnosing his mother with metastatic lung cancer, Dr. Rosenberg began treating patients with advanced stage cancer and became a cancer researcher. Dr. Rosenberg started a pharmaceutical company, which merged with a spin out of Harvard and a phase one trial will be initiated, as I mentioned in the first quarter of 2022 with a new drug that targets cancer stem cells. Dr. Rosenberg recently filed a patent on a device that I'm really interested to hear about that will decrease the ability of cancer cells to leave the circulation, thereby reducing metastatic seeding. I'd like to just have you start by talking about your journey into becoming, going from emergency medicine into cancer research and cancer treatment. Why don't you tell us a little about your, your journey?

Mark Rosenberg, M.D.
Sure. So as you mentioned, my board certification was emergency medicine and I was also a consultant for poisons and overdoses throughout Walter Reed Army Medical Center. So whenever there was a toxicology emergency or a suspected overdose, I was consulted on the case. I had written a book back in residency for the treatment, for novel treatments for toxicology and overdoses. And so, while I was working in the emergency department approximately 17 years ago, my mom walked in complaining of chest pain and shortness of breath. A plain chest x-ray showed a large right upper lobe mass. We ended up doing a CT, chest, abdomen, pelvis, and I had the misfortune of diagnosing her with metastatic non-small cell lung cancer to liver, spleen, bilateral adrenal glands, and left hip.

Dr. Joseph M. Raffaele, M.D.
Oh my God.

Mark Rosenberg, M.D.
At that time, I didn't know anything about treating cancer. I brought my mom up to Philadelphia, as you know, I went to Penn undergrad, and that's where they explained to me because they knew I was a doctor. And they said, well the truth is conventional chemotherapy had extended survival for advanced stage solid tumors by about two months, so we're doing nothing.

Dr. Joseph M. Raffaele, M.D.
Yeah.

Mark Rosenberg, M.D.
And I was appalled. I really couldn't believe that in all this time with all of our advancements in medicine, that's all we achieved. And so, that's where my journey began.

Dr. Joseph M. Raffaele, M.D.
Yeah, and that there is often stories like that makes somebody switch their focus and find a passion for something. So what happened after that?

Mark Rosenberg, M.D.
Well, I was told, or we were told that my mom could do chemotherapy. Maybe she'd live six months. No chemotherapy, maybe four months, but who knows? So I hit the internet and this is back in 2004. So yeah, 17 years ago. And I came across the name Ralph Moss who's a famous journalist in cancer since science writer. And he sent me about a 400 page dissertation on all the treatments available throughout the world on non-small cell lung cancer. So after going

through all of that, I asked my mother what she was willing to do and she said, IV vitamin C, nothing else. And that was my first time dealing with intravenous vitamin C. My mom lived 11 months.

Dr. Joseph M. Raffaele, M.D.
Wow.

Mark Rosenberg, M.D.
And And then, what I started doing is, you know, my treatment has evolved. So I consider myself a cancer researcher, generally spending, after I finish office hours, three to four hours a night researching the literature and it goes on and on and on. What I... The best way to sum up what I do, I'm gonna tell you what I tell most of my patients now when I have a consultation and I kid around and say, I have no friends. And the reason I say that is I don't like both sides. I don't like the fact that most conventional oncologists do not want to step outside of the NCCN, National Comprehensive Cancer Network Guidelines. Even if the treatment's not working. You follow the rules and if you want to leave the rules, even if it's not working, you either do a clinical trial or you go to hospice. And that's the way it's being practiced. I don't like that. And I don't think they're receiving the best treatment they can. On the other hand, I'm gonna be honest and tell you that I'm not happy with most of the alternative cancer doctors. I've yet to meet one that is a cancer researcher or scientist. And most of them that I've met are not aware of the data and they don't seem... They have their rules that they live by.

Dr. Joseph M. Raffaele, M.D.
Right.

Mark Rosenberg, M.D.
And everybody gets hydrogen peroxide and UVBI and ozone, and they just do their thing. And so, that's why I say I have no friends. So what I do is I present all the patients all the different options with the available data. And so, I've kind of become well known around the world for using repurposed drugs, but also using conventional chemotherapy in a different fashion. So I'll, for example, I'm a big fan of using polychemotherapy. So for example, if you use, instead of two drugs, if you use four or five or six, you can increase synergy. There's a lot of synergy. Now the conventional oncologists will say, well, of course, that makes sense, but you'll kill the patient with chemotherapy. And my response will be, we'll lower the dose of each of the drugs. And they'll say, no, no, no. The guidelines tell you, you don't lower the dose.

Dr. Joseph M. Raffaele, M.D.
Right.

Mark Rosenberg, M.D.
So I use chemotherapy and I'll do literature searches. And I will come up with very unique combinations. I will also use the immunotherapy drugs now, except again, I'll often use lower dose. And I use a lower dose based on data, even though the standard guidelines are, no, you use this high dose, but when you look at the data, you have to say to yourself, why are we using a dose higher than what the data suggests is effective? And so, in addition to that, I do, you know, I use supplements, but I tell patients for most of the supplements, I don't have data. So I... For example, we know there are a lot of supplements that may be helpful, like high dose curcumin, like melatonin, but then you have to say to yourself, what is the effective dose? And there again lies the problem. I have to tell patients, I'm not saying there's not an effective dose, but nobody's gonna fund a study on a supplement and lose all this money because it's very expensive to do a large clinical trial. So we don't have that data.

Dr. Joseph M. Raffaele, M.D.
Right.

Mark Rosenberg, M.D.
And probably the other thing that I would say that I started really over the past couple of years is I have aligned myself with an interventional radiologist and what we're doing together is injecting drugs, such as the immunotherapy drugs directly into the tumors. And so, when we combine all these modalities, and by the way, I also do use local hyperthermia, local, to potentiate a lot of what I'm doing. And the device will penetrate five to seven centimeters deep and achieve temperatures of anywhere between 107 and 111 degrees Fahrenheit. So... But again, that's only getting where I'm applying it.

Dr. Joseph M. Raffaele, M.D.
Right.

Mark Rosenberg, M.D.
And it's sparing the skin. It's only getting deep to the tumor. So, you know, the success has been remarkable, and I will tell you some interesting things. I treat a lot of patients from Sloan Kettering. I won't name drop, but the chief of one of the divisions of Sloan Kettering has been sending me patients for 13 years. And, I am, you know... Another very interesting anecdote, there is a local neuro-oncologist who... Most of what he treats is glioblastoma and glioblastoma has a median survival, with the best of standard of care of about 14 months. And I get patients from him and I asked the last patient who came to me and I said, how did this all go that you got referred to me from, you know, from the neuro-oncologist? And he's an electrical engineer and

he's very well-educated. And he... So he went to the neuro-oncologist and he said, look, I get it. I've read the data and I have an expected survival about 14 months. And the oncologist said, yeah. And he said, but, you know, we have the best equipment here and we'll do everything we can. And the engineer said, I wanna do better. And he said, okay, let me have you see Dr. Rosenberg. And he said, wait a minute, I'm sorry? You tell me that you offer the best, but you're gonna send me to someone else 'cause I wanna do better. And that's where he got an explanation. Well, Dr. Rosenberg has creative ideas and he's very successful, but we are not allowed to step outside the guidelines.

Dr. Joseph M. Raffaele, M.D.
Yeah, it's crazy.

Mark Rosenberg, M.D.
And I realize and I'm sure everybody realizes, it's not that you're not allowed. The FDA approves or disapproves drugs, but they don't make the protocols. But you understand is, you're working within a system.

Dr. Joseph M. Raffaele, M.D.
Yup.

Mark Rosenberg, M.D.
And everybody's following the rules. So it's not that you're not allowed. But we need to step outside the box, there's a price to pay for that.

Dr. Joseph M. Raffaele, M.D.
Yeah. I'm sure you've been living it. But I think your, from what I understand, your approach is born out of a different paradigm for what cancer is. This whole idea of the cancer stem cell and treating the soil rather than the seed.

Mark Rosenberg, M.D.
Yeah.

Dr. Joseph M. Raffaele, M.D.
There've been some remarkable books written about chasing down that last cancer cell and you don't have to do that. You have to just make sure that metastasis doesn't occur and that's what kills the patient. So tell us a little bit about that different paradigm, which I think others have written about,

Mark Rosenberg, M.D.
Sure, sure.

Dr. Joseph M. Raffaele, M.D.
This whole seed thing, but I found it fascinating, and it makes a lot of sense and it probably informs your lower dose treatment and your multi-modality treatment too. And then I'd love to hear some about the, you know, the actual diagnosis tests for the cancer stem

Mark Rosenberg, M.D.
Sure, sure.

Dr. Joseph M. Raffaele, M.D.
Sorry.

Mark Rosenberg, M.D.
Circulating the... circulating tumor cells.

Dr. Joseph M. Raffaele, M.D.
Circulating tumor cells.

Mark Rosenberg, M.D.
Yeah. So yeah, you make an excellent point, you know, this seed and soil hypothesis, and basically, you know, you have cells that are circulating and then they look for the appropriate soil and then they see, and what we're aware of now is that each tumor micro-environment is unique and it's unique within each individual. So you can have two individuals with the same exact type of cancer and genotypically, I mean, it doesn't happen, but even if they're genotypically identical, there's going to be unique environments in one individual versus another. And of course, you know, that for example, this individual's gut microbiome looks like this and that individual's gut microbiome looks like that, and they're gonna have completely different immune responses. So the micro environment is unique to each individual, but it's also unique within each organ. So for example, the tumor micro environment in the liver is different than the tumor microenvironment in bone. And a great example. I have a lady that's being seen at Johns Hopkins that I spoke with today, and she's been on a chemotherapy regimen. And her bony disease has been steadily decreasing on this regimen. Her tumor marker's coming down. And she feels great. But the liver lesions are growing and that's not uncommon because the microenvironment in the liver is different. As a matter of fact, there's a lot of data and a lot of publications written on the resistance... The resistant milieu in the liver. And as a matter of fact, a recent article talked about the liver, literally filtering out T-cells,

filtering out the immune cells. So it can't do its job. And so her oncologist at Johns Hopkins says, we'll give you one more month. If the liver lesions are still growing, We're gonna change your chemotherapy. And I said, well, that doesn't make a lot of sense to me. So you have a nice response in your bones to this treatment, but the liver lesions are grown. So what I would do is I would continue that treatment, but we'll add liver directed therapy. So for example, there are different techniques like it's a type of radiation called Y90, that goes right into the arterial supply and wherever that's supplying the part of the liver, it will kill that tumor. You can do chemoembolization right there. You can do cryoablation. And I said, it makes no sense to me to throw something out that's working when you could continue that and take care of the bones and get liver directed therapy.

And we can possibly achieve NED or No Evidence of Disease. And she said, I don't know why my oncologist didn't say that. And, you know, unfortunately the thinking has gone from oncology and in medicine because we have algorithms to follow. And it's very unfortunate. Now, as far as circulating tumor cells, if you don't mind, I'm gonna get into this whole conversation. So how does cancer go from being a focal disease to a systemic disease? Well, the key is that cells break off from their primary location and these cells, when they start to break off, very often, they become genotypically unique and then phenotypically unique. And so as they start to change, it allows them to migrate and we call that EMT or epithelial to mesenchymal transition. So they stop resembling the epithelial cells that like to stay home and be adhered to a basement membrane. And they act more like mesenchymal cells traveling. And then these cells intravasate into circulation and they are predestined to go to their new homes. So, you know, cells are earmarked.

Dr. Joseph M. Raffaele, M.D.
Based on their markers.

Mark Rosenberg, M.D.
To go to the liver. I'm sorry.

Dr. Joseph M. Raffaele, M.D.
Based on their markers.

Mark Rosenberg, M.D.
Based on their markers. And we're learning about that now. So we know, some cells are predetermined to go to brain. Predetermined to go to liver. Predetermined to go to lungs. Now, if you talk to an oncologist and say, I want to look for circulating tumor cells, as I've learned from them. Oh, that's a late finding. That's... You wouldn't look for it in stage three or stage two or

stage one. We only see that in stage four. Well, that is incorrect. And there's a very interesting study that was performed where they took patients with colorectal cancer, with metastasis to the liver. And the goal of this study was to find out when did those cells get to the liver? So they studied the lineages of those cells, and they found out that 80% of the cells in the liver arrived there before the primary colon lesion was large enough to see.

Dr. Joseph M. Raffaele, M.D.
Wow.

Mark Rosenberg, M.D.
So it was an early phenomenon, but we couldn't see it on a scan and to put it in perspective, it takes approximately one million cancer cells to form a one millimeter lesion. So, you know, we have, you know, you may have 300,000 cells here, 750,000 cells here, a couple hundred thousand cells here. And we say, there's no evidence of disease. But it's incorrect.

Dr. Joseph M. Raffaele, M.D.
So it sounds like what you're saying is that metastasis occurs early on in a lot of tumors, but then the immune system takes care of it or they, you know, they don't survive in their milieu.

Mark Rosenberg, M.D.
Good point.

Dr. Joseph M. Raffaele, M.D.
They're gonna sort of one of the ideas behind. I know other physicians approaches to this where they wanna change the milieu. So there's... Glycolysis is less, capable of being performed by the cells, the tumor cells. So, that does change it all on its head. I mean, that cancer is metastasis, not a late phenomenon, and you just have to accept that the cells are coming out. And so what does that mean for us in terms of, you know, all the diagnostic tests that we have now too for early detection of cancer?

Mark Rosenberg, M.D.
Sure. So, you know, we are heading somewhat in the right direction. Now, I wanna clear that, you know, not all cancers have circulating tumor cells early. But the ones, even the early stages, when they do, when they... When we do find circulating tumor cells, they are very likely to recur and have metastatic disease. But there are some cancers that are sitting at home. And it is a very late finding. But what we need to do is we need to be more proactive and find out, you know, who is actually seeding already. So for example, how many times has an oncologist... How many times have I seen what we think is stage two or stage three cancer? So you take a stage

three cancer patient, colorectal cancer, and you go to Memorial Sloan Kettering, and you get your six months, you... They resect the colon lesion. You get your six months of adjuvant chemotherapy. And they say you're gonna be fine. And then they scan you and say, sorry, it's all over the place. Well, you know, if we were really proactive, we should have known that probably much earlier. So how do we start detecting that? Well, number one, there is a test that's been out for quite a while now called CellSearch. Now, it's not a great test but it looks for circulating tumor cells that express what's called... An antigen called EpCAM or epithelial cell adhesion molecule. Now, even though there's a lot of data showing that the number of circulating tumor cells is a much better prognostic factor with regards to survival than even a scan, even the imaging study and the tumor markers.

So why are our physicians not ordering that? It's simply not part of the NCCN guidelines. Now, in addition to that, we have a new diagnostic technique and there's a company called Natera and they have a test called Signatera. And what they do is they access some of the patient's tissue from their cancer, and they sequence the genome, so they know exactly what that genome looks like. And then they isolate any circulating tumor DNA that's floating in the bloodstream that matches that genome. And then they quantify it. And they'll say, we found 10 molecules of circulating DNA. And I apologize my dog is barking in the background. I don't know if you hear that. But they'll say we saw 10 molecules of circulating tumor DNA per ml of blood, or now we retest it. It's up to 15. It's up to 20. That is turning out to be a very early finding. So for example, again, remember 1 million cancer cells makes a one millimeter tumor. So we often will see circulating... Not only circulating tumor cells, but circulating cell-free tumor DNA, going up in the blood before you see anything on scan. Now, what would a conventional oncologist do with that? Nothing, because you have to wait for the scan.

Dr. Joseph M. Raffaele, M.D.
Right.

Mark Rosenberg, M.D.
Now, in my opinion, that's not acceptable. Now, what I'm... The way I handle this, this will change in the future. But as you know, it takes a lot of money and a lot of years to change the guidelines.

Dr. Joseph M. Raffaele, M.D.
Yup.

Mark Rosenberg, M.D.
So anyway, that's, you know, that's the direction we're headed. Now, can you... Do you mind if I break for a second, just get my wife to stifle my dog 'cause.

Dr. Joseph M. Raffaele, M.D.
It's not that bad but is it bothering you?

Mark Rosenberg, M.D.
Oh, no. If you're okay, I'm okay.

Dr. Joseph M. Raffaele, M.D.
Yeah it's not that bad, I don't think people are hearing it that much.

Mark Rosenberg, M.D.
Okay, thank you. So do you want me to get into my work that... My new research project?

Dr. Joseph M. Raffaele, M.D.
Yeah. I mean, absolutely, that's the thing. It's time to move in that direction. I just want to help for the, for the listeners that aren't as savvy about oncology, you know, what the cancer stem cell is and how it works and it's not, you know, it's this sort of different from the vast majority of the tumor. Maybe a little bit about that and then move into your work from there.

Mark Rosenberg, M.D.
Sure. So there's argument about whether the cancer stem cell exists but there's no argument about this. You can call it whatever you want. It's all about nomenclature. The bottom line is there are cells that have stem like features and these stem-like cells have the ability to self-renew. So not all the cancer cells have the ability to self renew. These cells do. And these cells are inherently resistant to our treatments, including radiation therapy and chemotherapy. So these cells are genetically unique. And the problem... One of the problems is we don't have a drug or treatment that targets the cancer stem cells. And as you can imagine, if we get rid of almost all the tumor or even everything we can see. When you have stage four disease for almost every cancer, even if you get a patient to any NED, which means No Evidence of Disease, we all know that there's cancer still there, because we don't know how to kill those stem cells. And then with time, those stem cells will repopulate the tumor. So there was a company that started called Verastem, where they wanted to target. There are many companies trying to target cancer stem cells. And so what I... As you mentioned, what I did is I looked at a drug that in vitro and animal studies showed to really target cancer stem cells. And we ended up merging

with a spin out of Harvard that developed a novel nano particle technology that allowed us to put this drug in there and preferentially target cancer and preferentially target cancer stem cells. So now that doesn't stop, of course, all of the seeding from the bloodstream, but to compliment standard treatment, it really should be, you know, if not a home run, certainly a double or triple.

Dr. Joseph M. Raffaele, M.D.
Oh, and can you say what the drug is that's in there?

Mark Rosenberg, M.D.
Well, so what we did, yeah, what it's... Now it only has a number, but we took the drugs salinomycin, and now salinomycin is really a macrolide that is used as an antibiotic in chicken and pig feed to treat coccidiosis. And the problem with it is, inadequate doses. It's very neurotoxic. And so what we did is we figured out a way to get it right to using the nanoparticle, get it just to the cancer. So it's not neurotoxic to the entire system. And it allowed us to lower the dose very significantly while getting great results. So, you know, in our mouse studies at Harvard, we treated ovarian, metastatic ovarian, breast, prostate, pancreatic, lung, sarcomas, glioblastoma, the results were phenomenal on every single model we studied.

Dr. Joseph M. Raffaele, M.D.
Wow, that's... Sounds like it could be and you're having a trial... Is this a trial that's coming up in first quarter of 2022?

Mark Rosenberg, M.D.
Phase 1, correct.

Dr. Joseph M. Raffaele, M.D.
Phase 1 , yeah. Should be... Could be potentially groundbreaking.

Mark Rosenberg, M.D.
Yeah, I'm... We're certainly all very excited about that.

Dr. Joseph M. Raffaele, M.D.
And you have a device that also can.

Mark Rosenberg, M.D.
So, yeah. Over the past year and a half, I, you know, I've been for many years thinking about, you know, the concept of circulating tumor cells. And to explain a little more of that and you had

actually hit on this, the individual circulating tumor cells very often floating in the bloodstream, they'll get... They can succumb to the hydrostatic forces of the blood flow and often get killed. The immune system may kill it. So most of the circulating individual tumor cells don't make it. On the other hand, the clusters are what causes this problem. And what's been demonstrated is that clustering doesn't happen in the circulation. It happens from the primary tissue where some of the cells will leave as a cluster. Now it turns out that, so.

Dr. Joseph M. Raffaele, M.D.
How does that happen that a large cluster of cells leaves 'cause it's hard enough for one cell to you know, intravasate. Is there some other.

Mark Rosenberg, M.D.
Yeah.

Dr. Joseph M. Raffaele, M.D.
I mean, how big are these clusters.

Mark Rosenberg, M.D.
Well. So, by definition a cluster is a minimum of two cells.

Dr. Joseph M. Raffaele, M.D.
Okay.

Mark Rosenberg, M.D.
Now you can have 15, 20, 30 cells. You know, to give you an idea of size, one cell would probably average around 15 microns. So you're talking to at least 30 microns in size but very often you'll have 50, 75, 100 microns. So now, and you say, how does this happen? The amount of crosstalk, the amount of communication that goes on between the cancer cells and our own cells is mind boggling. See they come from us and they literally instruct our own cells to get help. And I don't want to waste you people's time. Talk for, you know, I'll just give you one example. There's constant crosstalk between these tumor cells and platelets and they will exchange exosomes and RNA and they will call up the platelets to work for them. And for example, there's a site on platelets called the P-selectin site where cancer cells can ride on their backs and travel around.

Dr. Joseph M. Raffaele, M.D.
Wow.

Mark Rosenberg, M.D.
There's so much communication and again, we look at it as the enemy but the problem is the enemy arises from within us.

Dr. Joseph M. Raffaele, M.D.
Right. They speak the language.

Mark Rosenberg, M.D.
And. So, yeah, that's perfect. They speak the same language. And so, yeah, go ahead, I'm sorry.

Dr. Joseph M. Raffaele, M.D.
No you're gonna talk about the device as some kind of a filter or something or.

Mark Rosenberg, M.D.
Well, so. The clusters now, when I talk about clusters, it's not only the cancer... The tumor clusters but neutrophil clusters. So if you were to google neutrophil to lymphocyte ratio in cancer progression, you'll see, as cancer progresses, neutrophils goes up and lymphocytes go down, their ratio goes up. When you have neutrophil clusters, they they will follow the tumor clusters, the tumor cell clusters, and help them. Very often we'll see a combination cluster of tumor cell cluster with neutrophil clusters. And those neutrophils will protect them and accompany them to their new homes and help them set up shop. Now, there are also many other types of clusters. There are macrophage clusters. We call them, you know, cancer associated macrophages like cells.

And they form large clusters. There are cancer associated fibroblasts clusters, and they're important for nourishing. There are approximately eight significant clusters that have been identified and they all help set up shop and build the milieu or environment that the cancer needs. So I, you know, I came up with a concept that if I can eliminate these clusters, this could be a game changer. Well, it turns out that people have looked at filtering some cells off. Actually, not even clusters, but individual cells. It's been very difficult. It's been very difficult. And so what I decided to do after drawing many, many, many different diagrams is to develop a filtration device that you can hook your arterial supply up to this filtration device and we will break up every cluster and it's complicated to filter, and I'm not gonna get into the details and actually they don't want me to get into the details.

Dr. Joseph M. Raffaele, M.D.
Right.

Mark Rosenberg, M.D.
But the bottom line is I will make sure that everything that leaves that filter when it... Now that there's an inlet and outlet, so arterial supply will feed into this filter. The filter will eliminate the clustering of everything. And now only individual cells can return to circulation, which are harmless. And that is basically, you know, the concept behind it. Now to support this concept, there was one mouse study that was done. And what they did is they didn't look at clusters, but they injected green fluorescent protein into circulating tumor cells. And they injected Rose Bengal. And when you shine a 430. Actually, I don't remember the number. I better back on that but it's a specific laser with a specific frequency. It will activate the green fluorescent protein with the Rose Bengal stain. So it causes massive oxidative stress to the circulating tumor cells and they'll die. And when they did that, the mice lived so much longer and all much less metastasis. So that is the first proof of concept in an animal. If you can eliminate circulating tumor cells, well then the patient will live a lot longer.

And so to extrapolate that further, think about this concept. If I no longer allow clusters to leave circulation, then there's no more seeding. In essence, what we'll do is we'll turn a systemic disease into a focal disease because it can't seed anymore. So now your chemotherapy and immunotherapy and radiation and surgical resection works better because there's no longer seeding. So what I ended up doing is I filed a patent about two months ago. A provisional patent about two months ago. We just brought on an engineering team. And one of the groups is that has a lot of experience in circulating tumor cells is at University of Michigan. But they've been only on the diagnostic side. They've been looking at isolating circulating tumor cells so we can come up with a drug to treat it better. So they got very excited when we... They heard what I wanted to do.

And so, as a matter of fact, I have to send the NDA back today and we have an agreement. Any IP that we develop on the diagnostic side, we'll give to them. Any IP we develop on the therapeutic side comes to me. And so what we're going to do is we're going to start building this prototype device and we're gonna take animal blood with many clusters in the lab at University of Michigan. They have all the equipment we need to measure these clusters before and after. So we'll measure the clusters before. We'll run it through the filter and we'll measure them after. And there's a lot of tweaking until we can say, okay, after one pass or three passes or five passes, clusters are gone. And so that is the basic concept. And the idea is that going ahead in the future, certainly you can have your blood cleaned as often as you need. You know, we may say, you know, we'll measure, you know, once a month, we'll measure your circulating tumor clusters. And we'll say, you know, you're good this month. Next month, come in. You know what? We found two clusters per, you know, 7.5 milliliters of blood. We need to clean your

blood again. And so we're extremely excited about that. And that's version 1.0. Now, I will tell you, honestly what happens. You know it costs a lot of money to bring this into practice. Likely a large device company will buy us out. Once we, you know, we'll publish the first animal study. But there'll be milestones. In other words, it can't show this.

Dr. Joseph M. Raffaele, M.D.
Right

Mark Rosenberg, M.D.
If that company doesn't meet milestones, it comes back to me

Dr. Joseph M. Raffaele, M.D.
Right.

Mark Rosenberg, M.D.
Version 2.0, you shrink this device down, insert it in the inferior vena cava, superior vena cava with a chip and an app to your phone. So you can constantly receive feedback. You look at your phone and say, okay, let's see this month I've captured 30 clusters. And it's time to change the filter in two weeks. So this.

Dr. Joseph M. Raffaele, M.D.
Wow.

Mark Rosenberg, M.D.
This is this is very doable. And now this is all conceived by my mind. But, I really don't have to develop new science. I can use everything we have to make this happen.

Dr. Joseph M. Raffaele, M.D.
So, it's like home cancer dialysis.

Mark Rosenberg, M.D.
Yeah and that's funny you said that. Nothing is an accident because the company we formed, one of the people we brought on wanted to call this cancer dialysis. I nixed that idea, but you're right. That's what we're talking about.

Dr. Joseph M. Raffaele, M.D.
Well I mean, it's you know it's kind of like an apheresis kind of thing but, you know, so... And dialysis has bad connotations to it. So that's why you put a nix. 'Cause that's.

Mark Rosenberg, M.D.
Yeah.

Dr. Joseph M. Raffaele, M.D.
Basically a short life sentence. You know, but yeah, it's a very, you know interesting concept. So you can, in fact, I mean, this kind of brings us sort of, to the larger question of this whole idea, curing cancer. It sounds more like what we're talking about is managing it as a chronic disease that doesn't kill you, you know, and you know, maybe that... Certainly you can have cures and we have successes like that we believe et cetera. But if you can keep the person alive, just like with HIV, you know, if there's no evidence of cluster circulating, no evidence of viral load, it is that success, I mean.

Mark Rosenberg, M.D.
Exactly, exactly. Now again, I think it is possible to... This could lead to curing because if it's no longer able to seed and then you can wipe everything out, you know, we'll now add a drug that targets cancer stem cells, and we wipe everything out. We can see and there's no longer seeding going on. You know, then you use, like, I also use a repurposed drug called ammonium tetrathiomolybdate, which is a drug that lowers copper and prevents angiogenesis. So I think, you know, initially this could lead of course, to managing this as a chronic disease indefinitely, but it really can lead to a cure.

Dr. Joseph M. Raffaele, M.D.
That's really, that's fascinating, I mean. We've been trying to have that cure for cancer for a long time. We got to the moon before then, which most people wouldn't have predicted. It's a pretty complicated... I think our paradigm has been wrong for a long time. And you're right about the... I mean, I understand why the guidelines are in there because the studies are done. You have to have a large enough study to get the significant results and then you stick by it. But I'm always very kind of disappointed when patients come back to me and they're like, well, you know, they want to do this. And you know, somebody has breast cancer or prostate cancer, and it really is not tailored to the individual situation. And what we're learning is that cancer is a unique disease in each person, not only.

Mark Rosenberg, M.D.
Exactly.

Dr. Joseph M. Raffaele, M.D.
Because of the genetics of the tumor, but because of the soil of the person.

Mark Rosenberg, M.D.
You're exactly right.

Dr. Joseph M. Raffaele, M.D.
And that's, I think important. I also tell patients that... And this is kind of interesting for me, which I don't do any cancer therapy in my practice, obviously. Patients are always worried and their doctors are always worried and oncologists are always worried about you wanna prevent cancer at all costs, you know, and the truth is, that cancer and aging are two sides of the same coin. Your ability to regenerate tissues is what happens. You know, that's the seed for cancer potentially, but maintaining optimal performance means not completely shutting down and for, you know, because you don't have a growth phase with things.

Mark Rosenberg, M.D.
Of course, yeah.

Dr. Joseph M. Raffaele, M.D.
And so if we can, you know, allow for therapies, like for instance, you know, I don't think hormone replacement therapy causes cancer, but that was a big worry. But, you know, estrogen is an important molecule. So.

Mark Rosenberg, M.D.
Absolutely.

Dr. Joseph M. Raffaele, M.D.
You have therapies for allowing patients to have the benefits of those, and then being able to deal with it when it becomes a problem that then... That's just have longer and very, you know, healthy lives. I mean, somebody who sees patients with androgen deprivation, I know you use that sometimes in metastatic prostate cancer, but, it does a number on the rest of the body.

Mark Rosenberg, M.D.
You're right?

Dr. Joseph M. Raffaele, M.D.
And they often.

Mark Rosenberg, M.D.
And you may even be aware, and this is... It's getting, more press even at Johns Hopkins. So for example, there's something called Bipolar Androgen Therapy. And what they do is patients who have metastatic prostate cancer who have failed all the guidelines, then what they do is they slam them with huge amounts of testosterone every month. And I won't get, I mean, I can get into my theory on how it works, but very often cancer starts receding.

Dr. Joseph M. Raffaele, M.D.
Probably I think... So maybe it's just hard to say because it gets aromatized into estrogen. And then estradiol, you know, I think I recall that could potentially stop it... Slow it down.

Mark Rosenberg, M.D.
Well, you know, that's been shown not to be the mechanism, but you're right. As a matter of fact. So, in a third world country, instead of using the powerful second generation androgen antagonist, that we use now, they still use DES Diethylstilbestrol. And so you're absolutely right, but very likely the way the high dose testosterone works is what you end up doing is, as cancer progresses and the prostate cancer becomes what we call castrate-resistant.

Dr. Joseph M. Raffaele, M.D.
Right.

Mark Rosenberg, M.D.
Meaning, it doesn't respond to androgen deprivation anymore, but you still have a few cells that still responded to testosterone, but, they're now, they're overwhelmed by the resistant cells that don't care. And in my opinion, you know, how I think giving testosterone is working? I think you start recruiting back those cells that are more sensitive and less aggressive. And so by giving testosterone you can recruit the relatively benign cells as opposed to the resistance cells. And they do the same thing with estrogen. So with breast cancer, same concept patients and this is old medicine, but when patients had metastatic breast cancer is nothing working. You give them a lot of estrogen and a portion of those patients, will start to regress.

Dr. Joseph M. Raffaele, M.D.
Yeah. So maybe they're getting a selective advantage because they're getting... They can respond to the estrogen and outcompete.

Mark Rosenberg, M.D.
And interestingly, along those lines, with both breast and prostate, when you give them all the testosterone and it works for a while, and then it stops working, what do you do? You block the testosterone and it works again.

Dr. Joseph M. Raffaele, M.D.
Yeah.

Mark Rosenberg, M.D.
And you can go back and forth and back and forth.

Dr. Joseph M. Raffaele, M.D.
Very interesting. Well, it's been a fascinating discussion. I mean, and this whole area of medicine I think, is really changing in a way that makes more sense, biologically and physiologically. It's exciting work that you do, any closing words.

Mark Rosenberg, M.D.
Well, you know, I just... You and I have been doing... We've been in medicine for a long time. And, you know, I think it's your role and my role to try to make positive changes. I think probably many of us are not happy about the direction, and I'm not... I'm gonna go past cancer now. I think many of us are not happy with the direction that medicine is going in. And I get it. You know, the pharmaceutical industry is really writing medicine. It's writing the algorithms for medicine and I'm on both sides now. I see, I get it.

Dr. Joseph M. Raffaele, M.D.
True.

Mark Rosenberg, M.D.
But what's really sad is that, the thinking part is kind of going away. So for example, Dr. DeVita, wrote a book on cancer, and he was in the seventies. He was the Chief of Oncology at Yale and Chief of the NCI. And in his book, he talks about perhaps the biggest obstacle to curing cancer, our oncologists ourselves, and it's, you know, we're hoping, and it's your role and my role to help spur this movement on, to bring thinking back and not simply follow algorithms. And so my parting words would be to encourage everybody, to use what you've been given and to think, and when a rule doesn't make sense, you know, it's... And it's scary for someone like me to say, I'm not going to follow the rules, but we owe it to our patients because that's why we became doctors.

Dr. Joseph M. Raffaele, M.D.
That's fantastic parting words. That's a very Sage advice mean when it doesn't make sense, then it doesn't make sense. And you gotta let it go. It's been a pleasure talking to you, look forward to maybe seeing it at the next meeting, or if you're ever in New York city on drop by.

Mark Rosenberg, M.D.
Excellent, thank you so much show. I appreciate the time.