Targeting Stem Cells in Multiple Myeloma for Improved Outcomes

Multiple myeloma remains incurable despite improved remissions with novel agents. Relapse eventually occurs in the form of drug-resistant disease that carries a dismal prognosis. Relapse is dependent on stem cell functions. We are talking to Dr. William Matsui of Johns Hopkins University School of Medicine to get a better understanding of the drivers of these functions and how they may lead to novel therapies for relapsed disease.

Full Transcript:

Priya Menon: Good evening everyone and welcome to CureTalks. This is Priya Menon joining you from India and today we are talking about multiple myeloma. The patient panel is led by Gary Petersen, myeloma survivor and editor of myelomasurvival.com, he is today's co-host. Joining Gary on the panel are survivors and advocates Jack Aiello, Cynthia Chmielewski and Yelak Biru. The featured expert on the talk today is Dr William Matsui, hematologist oncologist from Johns Hopkins University School of Medicine. Welcome to Cure Talks everyone, it's a pleasure to have you all with us once again. As we know multiple myeloma remains incurable despite improved remissions with novel agents. Relapse eventually occurs in the form of drug resistant disease that carries a dismal prognosis. Relapse is dependent on stem cell function. We're talking with Dr Matsui to get a better understanding of the drivers of these functions and how they may lead to novel therapy for relapsed disease. We will be taking questions towards the discussion and if you have a question for Dr Matsui, please e-mail them to Priya@trialx.com or post on CureTalks website. You can also press one on your telephone keypad and we will bring you on air to ask the question. With that I will hand over to Gary Peterson to begin with the discussion. Gary, its over to you.

Gary Petersen: Thank you Priya and thank you so much for bringing this forum for all of us who are myeloma patients to better understand and what we need in order to survive it. With that I would like to introduce Dr. Matsui and what I'll do is I'll give the clipped notes version because we have a quite an extensive number of questions. Dr William Matsui is a professor of oncology at Johns Hopkins University School of Medicine within the division of hematologic malignancies. He directs the multiple myeloma program at the Johns Hopkins Kimmel Cancer Center and I think the next sentence is pretty much a significant amount about what we're going to talk about today and also what his focus is and his primary focus is research to better understand the role of cancer stem cells and hematologic malignancies and develop novel therapies, therapeutic strategies to target these cells so welcome Dr Matsui again to Cure Talks.

Dr Matsui: Thank you thanks so much for having me.

Gary: I'd say the rest of it but it would take the entire hour and we have more to talk about because you do have an extensive background. But we brought you back because I think it was 2016 when we talked last on this program and earlier than that I think with Jenny on another program. But back then you were kind of the lone ranger as far as the CAR T and stem cells but now pretty much CAR T has taken center stage and you are now in the limelight and all things in we were talking to Dr June about the CAR T program a few weeks ago and he explained that although CD19 is not present on myeloma cells CD19 CAR T cells work in 20% of the patients. He was followed by highlighting your work at Johns Hopkins on myeloma stem cells is one of the reasons that perhaps this has been as successful as it has been. So with that I was wondering if you

might be able to talk to our patients who are listening who would like to learn a little bit about what the stem cell is and how it differs from the normal cells and specifically myeloma and also maybe if you could clear something up for me because I'm a little confused because I thought stem cells were something created if you want to call it that you know white and red blood cells plus B cells and in your analysis I had read that you had separated B cells from the myeloma cells and myeloma cells won't reproduce themselves but in the B cells introduced in rats or whatever will in fact result in in myeloma so are myeloma cells then B cells or is there a way to differentiate a stem cell from a myeloma stem cell, or how do you do that. So as a result if it's a B cell, is a B cell a stem cell so that's what was my confusion so if you can as you go through this clear that up for me…

Dr Matsui: Sure… sure so I think that there are a couple of disclaimers. I think one is that I've not really been a part of the CAR T cell story I think that's really been championed by many groups mostly most prominently I think Dr June's group and I think it's been very kind to highlight our work in terms of what they've done for us it's really when I started out when I was in medical school and when I was training the one thing that always puzzled me was why do patients relapse, like you can take cancers many cancers not exclusively myeloma but treat them until they're just about you can't find them see any evidence or any trace of them and yet there are some diseases where in just about every patient unfortunately the disease is going to come back and myeloma is one of those diseases to a great extent there are other leukemias and lymphomas that have the same sorts of patterns and so for me when I started out the whole question was what is the problems or what are the processes that are going on there leading to cancers returning. Because I thought in a very simple way that if you can prevent them from coming back then essentially you can make people live longer and potentially cure them because that's really curing them as is not having them come back so the way that we addressed this was trying to figure out, are all myeloma cells the same, are they all the same, do they all sort of have the same properties and the same potential for growth and you brought up a great point which is this idea of stem cells and one I think example of how cells are all not the same is in the bone marrow so you have different types of cells you have stem cells and then you have more mature cells and those mature cells actually really do the job that they're supposed to do.

They protect you from an infection in the case of white cells they carry around oxygen in the case of red cells and so those mature cells have a job to do and one of their jobs is not to make more of themselves so in the bone marrow it's really a stem cell, a haematopoietic stem cell that gives rise to all those other cells but that stem cell if you just had those stem cells you'd still be susceptible to infections you'd still be anemic because those cells can't do those jobs and so there's a compartmentalisation of different functions that different cells can do. So one, in stem cell biology, stem cells have a bunch of different attributes and so in the case of haematopoietic stem cells I think is a great example so one of their jobs is to make all of the other cells and to give rise to daughter cells that become all these mature cells. The other job that they have is to actually stay around because if you if you don't have enough stem cells then at some point you're not making blood and that is not a good thing so in us as humans if we think about the normal bone marrow stem cells we probably have about one hundred thousand of those cells and those cells end up having to make about ninety billion cells a day to replace all of the red cells and white cells that we lose. So there's an incredible expansion a long way but one of the most important things is that you're making blood your entire life and so you must have some stem cells that are around for your entire life. So if you think about it in those terms one aspect is for sure stem cells being able to give rise to other cells that are maturing and then the second is that they need to hang around forever.

Because if they don't, then you can't make new cells and then that becomes a problem. So when we talk about cancer stem cells or stem cells and cancer I think that it's not necessary that we have to have to ascribe all of the properties to those cells and so I think that in the case of cancers we do care about what kind of cells they make because that might lead to specific medical problems but I think that in terms of thinking about relapse what we care about is that, are there cells they're able to give rise to new cells and how long can they do that for. Because if they can do that no longer when you're alive then you're never going to be cured. So one part of the thought about stem cells and especially in cancer is really focusing on this one property called self-renewal which allows the stem cells to be maintained over time so there's always a pool of cells to grow new tumor cells and so in myeloma it ends up being that the stem cells are not

the same thing as haematopoietic stem cells they're actually more like the cells and I think you asked a great question which is like how can B cells be stem cells, well B cells give rise to a mature population of cells those are plasma cells and then the other thing is that B cells and also T cells have this very unique property in that they are actually able to last for a long long long long time in your body and part of that is that if you think about it they're there to provide immunity against certain things and so if we vaccinate someone against polio when they're an infant that immune protection actually last almost just about the entire lifespan of that individual. So if one great example is that there was a study done about ten years ago where there was a lot of concern about bioterrorism and one of the viral sort of one of the pathogens was smallpox and nobody gets immunized against smallpox and more if you're of a certain age you got immunized but there's smallpox has been eradicated so there's no reason why you need to maintain immunity to smallpox because you never see it but in those patients who are immunized years and years and years ago if you look now you still have immunity to smallpox.

That that has lasted forever and so I think one of the thoughts about why is myeloma such a difficult thing to cure and to prevent it from coming back is that if B cells are involved and B cells normally are going to last forever to provide you with immunity then it makes sense that the cancerous counterpart of that it's going to last forever as well. But that's its job it's not gotten some magical property it's just doing the normal job that it's supposed to do. So in terms of stem cells and myeloma I think that it is been an incredibly controversial field. And I think that it's I always realize this, I have never really understood what the major issues that have actually been, why people are so opposed to this idea but I think that part of it is the distinction between what do the cells look like and what can they do. So in for me right what I wanted to figure out is are the plasma cells the things that are maintaining that growth potential over a long period of time or is it something else, is it B cells and that was the first experiment that you described where we took patients samples and either to B cells or plasma cells. Plasma cells couldn't form tumors in mice. But the B cells could in our hands and I think it hit a nerve with a lot of people in the field because most people spend their time if they're doing research studying plasma cells and if you go up to someone and say look it's great that you're studying that because that's the tumor cell that's truly the cell that's causing people to have bone problems, renal problems, problems with anaemia but those are not really the things that are responsible for the patient relapsing people have have a contention with that because you're implying that they're studying sort of the wrong thing. I think that over time one of the things is so so there's this big yes so that the big distinction is what people I think have a problem with is the way that cells look right so that it does it look like a B-cell or does it look like a plasma cell and what can it do?

And so one analogy I think that's a good one is that I'm in Baltimore and Baltimore has a football team and the Ravens and if you go to a game at the stadium on Sunday and you said to someone who didn't know anything you said well tell me who the football players are and you can tell who the football players are because they're all wearing Jerseys. If you go to the stadium on Sunday every single person is wearing a jersey but they're not all necessarily football players and so part of the issue is that can we completely link what a cell looks like to what it can actually do and in our original work we thought that B cells were very important and in some patients we think that that's still important that maybe the 20% of patients who are actually benefited by targeting CD19 with CAR-T cells but what we found over the last couple of years is that not in every single myeloma patient are the B cells the important cells because this property of being able to survive for a long time and produce mature cells or more tumor cells over time that can also be plasma cells as well, it depends on a number of things it depends on where you are in your your therapy like if you are in MGUS, I think that it's more important the B-cells are more important I think that if you have unfortunately something like a plasma cell leukemia I think that plasma cells actually have that property. I think that it depends on a lot of times on which your genetics are. So there are a lot of variables that dictate what the cell exactly that we're trying to target might be and what I tell people is that don't get so hung up on whether to B cell or a plasma cell, what we should try to figure out is what are the biological properties or what are the processes that allow cells whether they are B cells or myeloma cells to just maintain themselves over time. Because if we can target those things then maybe what we can do is inhibit those pathways or processes that maybe will prevent relapses but I think that it's really important when you know that to be to think about stem cells as a function and not as what do they look like, because it's the function that kills you and brings the disease back it's not actually what they look like and so that is one of the messages we've been trying

to get across for the last few years is to be a little bit careful about what they look like and what they do. In terms of CAR T cells you have to be actually pretty precise about what they look like because you're targeting a specific protein on the surface of cells and like I said I think that in some cells some patients CD19 is important and in other patients maybe something like BCMA may be more important so I think that there what we're trying to do is figure out a way of figuring out in an individual person what exactly is the what is the cell that is causing extended growth, what does that cell look like and can we target it with CD19, can we target it with BCMA, can we target it with NYE so what are actually. Can we figure out for an individual patient and personalize it to figure out what exact either CAR or antibody or other approach might be best for them.

Gary: So you know I guess one of the questions then would also be is are you suggesting that you really can't, you can see I believe, stem cells we already know what a stem cell is you can take a look at it but you can't see or you haven't been able to differentiate myeloma stem cell?

Dr Matsui: So what we can do is we can tell like if you said look I have this tube of cells do they have chemical properties, no matter what they looked like I could tell you that because we have assays to do that so that's a functional assay. If you said in this particular person they have B cells that are related to their myeloma and they have plasma cells related to their myeloma which one of those cells is responsible for the patient relapse thing, I would say it could it could actually be either one and I think that we could tease that out but we would have to do one of these tests for we said look let's just take the different cells, grow them up in different environments and see which one does it because that's the one we should target but like I said at this point in time I try to steer people little bit away from what exactly is a cell what does it look like is it to B cells or a plasma cell, I think that it's more important to say look what are the things that are allowing you to to hang around forever because that's what we should be targeting not what it looks like but what it actually does.

Gary: OK, one last point I'll turn it over to the rest of the folks, is that if you're talking about functions so, but originally you were talking about stem cells as something that it wasn't a function necessarily, it was an actual cell that you were working with, and my question would have been if you in fact take your stem cells out and do your transplant and then reintroduce them, are you also reintroducing these myeloma stem cells if they are such a thing?

Dr Matsui: But I think that I think that there's a potential for that but it may be dependent upon the actual nature of the cell to some extent. I think that there've been a couple of studies during autologous transplantation. One study one set of studies and this is this experiments have been done multiple times is that once you get a stem cell graft what you do is you try to enrich for the haematopoietic stem cells and you do that using usually like an antibody in a magnet and things like that, what you can do by that is collect those stem cells and then all of the other cells will get purged they just won't collect them right so what you're giving back in a product that is really just pure haematopoietic stem cells so if you do that experiment if you do that versus just giving an unmanipulated graft you just collect the graft from the person's blood and you don't collect it you don't enrich for any stem cells, any haematopoietic stem cells that actually would think that you're not that since you're not introducing back any tumour cells that the patient should do a lot better but it ends up being that the patients do exactly the same as if they got just a plain old graft where they just collected it and then just gave it back. What that suggests to me is that basically it's not as important it may not be as important if you are reinfusing myeloma stem cells back, it's probably that the stem cells, the myeloma stem cells are not actually not eradicated by the blend that you're giving people. So I think that during the transplant, I think the major reason why people potentially relapse is probably not because you're putting bad stem cells back in, it's probably because there's stem cells in the patient and you're not able to actually get rid of them using high dose chemotherapy.

Gary: Ok, and so I guess the next question is the second half of that, is are we targeting the wrong thing, we identify these characters that we can just look at them and say well they express CD19, they express BCMA, they express this so we target that, if you take care of those stem cells then you take care of the disease.

Dr Matsui: I think that that is I would hope that that's the case that's what I believe and that's why we do what we do. I think that if you were to say well if we think about how we develop medications for specific cancers, so when we first give someone let's say we discovered some chemical and we say we think that it's going to work against cancer. So the first study that one clinical trial that one would do is to give it to patients and for sure, number one show that it's safe right but then the second thing we do is we try to see whether or not you can take patients with active cancer and make some of that go away. So when you do that and you do things like look at the M. protein or your light chains or even if you go into the bone marrow and look for plasma cells those are all the mature cells, those are not potentially the stem cells and so if it ends up being that like in our calculations it ends up being better a myeloma stem cell is probably for every myeloma stem cell there's probably one hundred thousand to a million plasma cells or mature cells. So if you even if you get rid of everything it looks like everything is gone, you can still have stem cells that protect, if you're developing drugs if you're really looking for chemicals or medicines that actually make the plasma cells go away and if the stem cells are different than the plasma cells then those drugs may not target the stem cells. And the other is that if you actually had a drug that targeted the stem cells and you gave it to someone and one hundred thousands of the tumor went away you would never ever be able to detect that right away. Your M-protein would be the same, your plasma cells would be the same, your light chains would be the same. It would only be after a reasonable amount of time because you're not making any more tumor cells that you might now start to see those numbers get better.

So I think that it's great to be where we've gotten in myeloma and I think that it's amazing how far the field has come. There's a ton of new medications, there's always new medications coming out and it truly has helped patients with myeloma like I run the myeloma program here I have a lot of myeloma patients and the drugs for sure are a true advance from what we used to do 15-20 years ago. But at the same time I think that it is potentially are we targeting the right things or not. I would say as if we're not able to cure the disease and I think that that potential exists and that is sort of I think been like I said I'm more than happy and interested in like how can you develop drugs to make plasma cells go away, but at the same time if you do that and patients relapse then I don't know how much more bang for the buck we're going to get by continuing to do that.

Gary: The story of your work is so very important. Jack do you have some questions for the doctor?

Jack Aiello: I do thanks Gary and thank you Dr Matsui for this call. We as patients always hear about the bone marrow microenvironment is surrounding the myeloma tumor cells, the plasma cells. Is that also the case if the bone marrow microenvironment important surrounding myeloma stem cells?

Dr Matsui: Yes so I think that it is very important so if you think about any stem cells like I provided the example of hematopoietic stem cells, there's a hundred thousand you have for your entire life, they have to make ninety billion blood cells a day. So that process of how much they make and what they make has to be incredibly tightly controlled. If you make even one percent more you're going to have leukemia if you make one percent less you're not going to have enough blood cells so it's really a finely tuned system. So stem cells are actually really really good at listening and sensing their environment. So stem cells are really highly regulated by environmental cues, so there are cues in the bone marrow let's say for hematopoietic stem cells for example that tell them you've got to make more neutrophils, or you got to make more red blood cells, like those are all cues that are given by the environment. So in every every tissue, the stem cells in every tissue your skin your brain your bone marrow all of those are regulated by clues from the outside you don't have a stem cell just deciding on its own that it's going to start dividing or not, it's got to be tightly regulated and so that for sure I think has to be the same case with myeloma and I think that that the two pieces of evidence why I would think that that's the case is that if you, what we found is that, if you treat patients let's say you treat them with something like Lenalidomide, the stem cell and you get rid of plasma cells, the stem cell number actually starts going up and it's going up because your body thinks that your plasma cells and your B cells are an organ.

So if you get rid of the mature cells then the immature cells say look we need to make more mature cells so the only way we can do that is by starting to expand and so that's why there is I think a balance between or

communication between plasma cells and B cells in the normal situation because you only have a certain number plasma cells in a normal person you only have a certain amount of immunoglobulin in a person and all that is super highly regulated and I think most of that regulation is through the microenvironment. So in the case of myeloma stem cells what we've found is that we've looked at this and there are a couple of factors that we found in the bone marrow, one of them is a factor that was originally studied by a group in France called growth differentiation factor fifteen or GDF-15, it's a signaling molecule and what you find is that what this French group from which was amazing was that if you take bone marrow, what are called bone marrow stromal cells, which are thought to be important in myeloma, if you take those from myeloma patients or normal patients and you compare them, the myeloma patient ones will make this signaling molecule GDF-15 while normal ones don't and what they found was that you can measure the amount of this protein in the blood and if you had high amounts that was associated with you relapsing faster and actually not living as long. So this group had tried for many many years to figure out what does it do to plasma cells because it's a myeloma thing we find it in myeloma patients but they could never ever really find anything of note and so we had studied the bone marrow stromal cells, we were interested in factors that might regulate stem cells and if you have this property where the levels of this thing predict things like relapse and survival, to me that is not a plasma cell thing to me that is a stem cell thing.

Whether you relapse or not is a stem cell thing, so we looked and we found that this molecule GDF-15 actually had a profound effect on myeloma stem cells where it had almost no effect on plasma cells, so I think this explained what the French group was seeing. And so I think that's an example of something that gets turned on when you have myeloma and it's I think a great example of how the environment actually is regulating what tumour stem cells are doing and there's been sort of notable findings in things like leukemia and colon cancer and breast cancer that showed very similar things that the microenvironment changing is really a part of fueling what cancer stem cells might do in each of those diseases. I think that the tumor micro environment is super important and I think that if you said well this is some abnormal thing and maybe what we can do is target that. I think for us it doesn't really matter if they're plasma cells or B cells, GDF-15 just seems to fuel cells growing faster and growing more profoundly and so what we think is targeting GDF-15 should impact regrowth of tumors no matter what the stem cell looks like and so I think that's a great example of how the environment may play some role in the regulation of cancer stem cells.

Jack: Several of us just came back from ASH and typically I can see the presentations are phase 2 and phase 3 trials for myeloma. Have there been other people working on the myeloma stem cell, were they asked presentations even if they were at the biological level or…

Dr Matsui: Actually I would say that the one notable study was a because of you know the Penn groups I think had really done a great job like I think there was like I said there was a high degree of skepticism. I think that there are initial findings using CD19 CARs was really I think very intriguing evidence that what we've been studying a law all along might have some relevance. And one of the studies that was presented was actually a CAR-T cell study where they combined a CAR-T cell against BCMA which is primarily expressed by plasma cells with a CAR against CD19 so they're trying to get both things. And I thought that was they said they're doing that because they want to target myeloma stem cells and so I thought that that was actually a really clever approach. I think that there's some thoughts at Penn where Dr June and another person, L Garfall and he was the person who reported the CD19 story with CAR-T cells originally from Penn and so I think they have thoughts of doing a trial where they're doing combinations and I think that that is actually a great way to go. I think that you cover a lot of bases by doing that. And so I thought that the it was not I would say it was not super easy to figure out what was going on in that trial that was presented. People responding you can really tell why there was a because of the CD19 or because of the BCMA but we're doing studies now with the Penn group, with Dr June's group to try to figure out in individual patients, does targeting CD19 or targeting BCMA or actually targeting both have have a better therapeutic effect and there are trying to couple that with a clinical trial where they're actually going to combine CARs with against CD19 and BCMA.

Jack: For a given individual, the actionable mutations on a regular plasma myeloma cell are not necessarily the same as would be on their myeloma stem cells, is that correct?

Dr Matsui: That is correct so I think that you know and there's this whole idea again I think it makes some sense because if you think about like there's this been this ongoing sort of discovery of Holly Connell disease and what I mean by that is that if you let's say you have a mutation in Ras which is pretty common. And it may not be that every single myeloma cell has that mutation. But might not it may be that it's interesting because if you look at myeloma patients that diagnosis of about 10% of them you can find a Ras mutation but in patients who have more advanced disease it might be more than half of them actually and so if you go back and you look actually those those 90% of patients where you couldn't find a Ras mutation if you look carefully enough in most of those patients you can find it. So for each of these different clones as they're called that pops up, it's a stem cell that makes those things appear and so I think that there's a couple of interesting things from that.

I think that one is that if you use go in you go in sequence the tumor and the stem cells are one one hundred thousandth of the tumor you're never going to pick up the mutation in that one cell, because it's swamped up by the thousand nine hundred and ninety nine cells or you're never going to be able to pick that up. and so I think that part of why you see the mutation sort of pop up, I think part of it is because the stem cell that has that mutation is just resistant to the chemotherapy that's there. And that sort of explains why you see sort of different clones in an individual person and so I think for us what we're trying to do is to figure out if we can find the stem cells in a person and we identified the mutations in those stem cells, can we actually predict what mutations are going to arise when patients relapse. And so we have a little bit of data suggesting that if you isolate the stem cells when someone gets diagnosed with the B cells when someone gets diagnosed, knows they have different mutations than the plasma cells, the myeloma plasma cells, so if you wait long enough and the patient relapses oftentimes you can see those mutations in the relapse disease that we originally found in myeloma stem cells and so we're trying to figure out can we use that as a tool to predict what mutations are going to arise and if those are mutations that we can target maybe what we should do is try to target them very very early. Instead of just waiting for the person to relapse, so that is one of the thoughts that we have about how to use stem cells to sort of inform how do we treat patients over a longer period of time.

Jack: Thank you very much Dr Matsui, back to you Gary

Gary: Ok thank you Jack. Cindy your questions.

Cindy Chmielewski: This is a fascinating topic, I really think this idea of myeloma stem cells. What we are talking is going a little bit over my head so, I don't know if my questions makes sense so I'll ask them anyway. So myeloma cells are plasma cells, and plasma cells come from B cells, so myeloma stem cells can be coming from B cells – from what I am understanding. So are there tests that we could do from bone marrow that can track and count myeloma stem cells? Can we identify them yet?

Dr Matsui: Yes. So that is an awesome question. So you would think that if you were able to monitor them and let's say that you were monitoring them during treatment in your modern treatment and after treatment, if you were to say that they were responsible for you relapsing maybe they would start to increase the number before you relapse. That might be a solution and so we actually have data that that's the case so if we monitor people over time what we can find is that if we see changes in the myeloma stem cells and we don't know what causes them to start growing but if we follow patients and we monitor them and we counted and the way we count as we actually count them by using a test in the blood rather than having to do bone marrows and if we follow patients over time usually anywhere between six and twelve months we can actually predict when someone is going to relapse. So one question is that can we use that in the clinical way to let's say start treating patients earlier before they relapse so we have some thoughts about doing that and then the other thing is that can we use that test since we can't use the M-protein we can't use the number of plants in the cells can we use that test to count the stem cells as a way of figuring out if a therapy that we're giving let's say like CD19 CARs, or something targeting B cells whether that actually is going to work in the person.

And one way we could see is that do the stem cells go down because like I said earlier I don't think that you

could sort of say look we targeted the stem cells and then the next day the M-protein is probably going to be exactly the same. So I think it's a way of monitoring the efficacy of things that we're trying to use to target stem cells in sort of a more real time fashion but as you were saying I think that or we're trying to refine these tests but like I said I think that in most patients where we've done this we've been able to predict when are people going to actually relapse before you see their M-proteins change before you see their light chains change I think we can predict least a few months beforehand that that's going to happen.

Cindy: Are those tests available at Johns Hopkins laboratory or are they available for other people to use?

Dr Matsui: So the way that we're doing it is we haven't been with clinical testing you have to have tests be done a certain way and they have to be done in a certain kind of lab and they're called CLIA approved labs and so if you get like your M-protein checked, your M-protein gets checked in a CLIA approved lab and what that does is that that means that a clinician like me can actually use those results to make some sort of decision. Do you need more treatment, can you stop your treatment we need to change treatment like we can do that because we know that the value that we're getting is been qualified by being done technically in a certain with a certain level of scrutiny. In our case what we do is we do this test we've developed this test but we don't have it in a way that we can use it clinically So right now what we're doing is primarily using it as a way of monitoring different clinical trials that we're doing but we haven't ever used it as a way of in a normal clinical way where we would say look let's monitor your stem cells if they're going up we're going to start you on mAB, CD19 or something. We would like to get there at some point but right now the testing that we do is just in a regular plain old lab that's not a clinical lab and so we can't use that information to inform anyone what we should do but like I said what we're doing in using it now is this to try and use it as sort of a result to try to help us figure out whether we're on the right track or not what we do clinical trials where we attempt to target cancer stem cells.

Cindy: Ok that makes sense. So eventually you are trying to validate that, so you would find something that would help predict relapse?

Dr Matsui: I would love to do that because I think that it's it's better to try and prevent relapse from happening rather than waiting for it to happen and then try to get on top of it. It would be great if we could develop it into something where we can really monitor patients over time. And so we have some funding from the National Institutes of Health and the National Cancer Institute to do those types of study to sort of validate or earlier findings but there is a lot of work to do that so we're trying to figure that out.

Cindy: Ok sounds good. I know we have been talking about CD19 as, I guess one of the markers on the myeloma stem cells. You did talk about UPenn's first CAR – T cell trial. I kind of remember that coming of age, because at that age I got treated at Upenn. So long before, the only drawback for me on that was it had to be done within a stem cell transplant. I guess the rationale was that CD19 is not really aimed at the myeloma cells because there are not not only myeloma stem cell as you were saying. So my question I think that was Dr. Collin was telling,…Is there a trial now going on that at first uses something like BCMA or a stem cell transplant or something to get you on complete remission…hopefully, MRD negativity and then using like a CD19 antibody as a maintenance therapy, to start telling, now that you got rid of myeloma cells, now let us take care of those stem cells that may help you with relapse.

Dr Matsui: So you should come and we should work together because that's exactly what we should do and so right now what we have is we have a trial, we had done a trial previously with an antibody against CD19 from a company called MedImmune and the antibody is called MEDI-551 and we use that in patients where we had given them Revlimid and then we added the antibody to it and what we were measuring really was using our assays to see what happened to myeloma stem cells and in that study what we found is that patients initially after they were diagnosed a combination of Revlimid and Dexamethasone and they got that for two rounds and what we could see after two rounds in just about all the patients the number of myeloma stem cells started going up even though their M-proteins were going down and then we gave them three doses of this antibody and we could see those increasing numbers now starting to go down and compared to other studies we've done before that what we just gave people Revlimid and dexamethasone over a number

of months we never ever saw those numbers really decreasing so we thought at the antibody had activity. We talked to the company for a long long time about doing some sort of follow up study. There was a lot of back and forth and what we decided in the end to do was to do something that I think is also surprising to a lot of people, we decided to do allogeneic stem cell transplants.

And after an allogeneic stem cell transplant then give people this antibody against CD19 and give it to them for a year so that trial actually just opened we've just enrolled our second patient and so what patients will do is if patients have high risk disease and they've been recently diagnosed or if patients have relapsed or have refractory disease, we will do an allogeneic transplant in them it's one of these mini transplants where you get cells from a donor; one thing we found in our studies of transplantation here at Hopkins is that the age of your donor matters a lot so the younger the donor the better the outcome and that's for leukemia, lymphoma, myeloma whatever and so what we do is the other thing we've done over the years is made it developed strategies so that you could use half matched instead of fully matched relatives so if you have a fully matched relative then that person is almost always going to be a sibling so if you are older unfortunately and you have myeloma then it's likely that your sibling is going to be older as well so if we use half managed donors basically all of your kids can donate for you so if you take patients who are a little bit older and they have kids, those kids are typically younger and so what we do is we've been doing a lot of transplants where there are mini transplants these are all done as an outpatient, you get chemotherapy and then you get either blood stem cells or bone marrow stem cells from a child and then following that transplant our plan has been to about three or four months after that transplant is completed, to start people on this antibody.

So we have people now who are just now going through the transplant phase and they're getting allogeneic transplants. We had on back at our state our study of allotransplant because it is a very controversial thing and we just published this about three months ago and so what we found is that up about. We had looked at about 40 patients at 39 patients, all the way going back to 2003 from 2003 to 2011, what we found in those patients were that about a quarter of them a little more than a quarter of them were still alive and didn't have any relapse. So it doesn't cure everyone but there's a portion of pretty people we think are cured I think that the other is that one of the knocks against allogeneic transplantation is that it is really dangerous and so the danger comes from this complication called Graft versus host disease where your donors immune system starts to attack you and the way that we do the transplants here at Hopkins, the risk of getting very bad graft vs host disease is pretty minimal; like back in twenty years ago when I was actually a resident in Seattle and trained at the Fred Hutch we were doing allotransplants and there about at least a half to two thirds of individuals patients would get really bad graft vs host disease, bad enough that it could potentially kill them and in the way that we've modified things over the years in this group of patients from 2003 to 2011, patients who got serious graft vs host disease was in the single digits, it was like around 4%. Yes So I think we can make it safer, the relapse is still the major problem most of the patients relapse so that's why we think if we build in this thing to target the stem cells using CD19 after an allotransplant our hopes are to prevent more, to try to reduce the relapse rate in more individuals, because we think we can safely get them through the transplant and we think that the very beneficial for people to have a new immune system and we're trying to harness that by adding in this antibody to try to go after the stem cells so that's a trial like I said we just opened about a month ago, we just enrolled our second patient.

Gary: Fantastic. Cindy we'll need to move on so if you don't mind we will move to Yelak.

Yelak Biru: Thanks Gary. Thank you Dr Matsui for that question. You have answered two of my questions which is the MEDI-551, for untreated myeloma patients and the allotransplant or the mini allotransplant. I think my third question is related to something you discussed which is the circulating cancer stem cells and how they correlate with either disease burden or showing relapse or alternatively also showing response to treatment. Is that considered a basis for what we are calling liquid biopsy?

Dr Matsui: So I guess so I would say that it's not I think that when people talk about liquid biopsies it's more like they take your blood and then they do sequencing on it to look for mutation so they might be able to tell you oh now you have a raft mutation just by sampling your blood because as the cancer cells die they'll release their DNA and that will go into your circulation so they can find mutations in your blood. That

you don't know whether it comes from stem cells or from mature cells it's just DNA. They don't know where it comes from but that is something that especially in solid tumors are difficult to be biopsy patients you can sort of see what mutations are present in potentially in the tumor just by looking at someone's blood so that's usually what a liquid biopsy sort of is thought to be.

As a side note it's an interesting thing where like it there was a study just published here at Hopkins what people were doing liquid biopsies for patients with prostate cancers and looking for specific mutations and what they found was that if they took blood from an individual patient with prostate cancer they sent the liquid biopsy test to one company and then at the same time they sent it to a different company, you would get most of the time very different results right so that the whole liquid biopsy thing I think is is going to be great in the future because then you don't have to go back and get more tumor but I think that it's still in its infancy and so there's like everything there are kinks to work out I think as far as us for circulating cells what we find is that they oftentimes actually do the opposite of what you see with other parameters and so if you treat someone with RVD their plasma cells go down but paradoxically their myeloma stem cells start to increase and like I said I think that the reason for this is because if you get rid of the mature cells somehow the stem cells sense that and they want to start growing it's just like if you burn your skin, your skin has stem cells in it if you burn your skin your skin stem cells turn on right away so that it can repair your skin. If we give you a high dose chemotherapy and we put stem cells in you those stem cells are going to go right away because they need to make blood for you as quickly as possible so I think it's the paradox between the stem cells want to maintain that compartment all those mature cells and if all those mature cells aren't there, then they start to freak out a little bit and say look we've got to start making more cells so I think that that's why we see what we see in patients who undergo therapy, it's almost like the opposite of of what one might expect I'll give you making your M-protein better than you should be making your stem cells better as well but in actuality they most patients that we've looked at it's been the exact opposite.

Yelak: Gary I'm done, thank you.

Gary: Alright well thank you, if we could go on to some of the questions from the audience. Priya

Priya: Thank you Gary. Yes, we just actually we've almost done with our time but we have to probably take just one caller. Dana you are live, please ask your question.

Dana: Priya thanks so much Hi Gary. Dr Matsui thanks so much for joining us tonight. I was listening and trying to follow and I do find the science quite daunting and so my questions may be very very lay person based but I'm going to give it a shot. I was listening to a recent patient power video and some of the panelists one included Dr Tricot and he mentioned that at diagnosis you actually have a trillion myeloma cells and you have about a billion or so left after treatment is given. So that to me is just a daunting quantification and then now I'm adding in these myeloma stem cells that apparently don't respond to treatment so it's very very sobering to contemplate that if we haven't actually yet identified these extended growth cells responsible for the function of relapse that we may likely not be able to cure myeloma or so I'm just trying to really understand are myeloma stem cells actually dividing or rising at all times or do they primarily do this under treatment pressure, in other words the standard of care treatment including Melphalan clearing the playing field for them in essence?

Dr Matsui: So I think it probably depends from person to person and might be a little bit different. I think normally the most the most systems themselves grow actually slower than the mature cells. And in terms of the rate at which they grow I think that if you stimulate them then they can grow very very quickly I think that t is a for sure I think that in in our hands which used to be you see that relative increase in the number of stem cells over time following treatment that may level out over time but I think that it's for sure we want to figure out what are the things that are actually stimulating those cells, because I think that that might be a way rather than targeting CD19 or sequence that may be a way of targeting some pathway that's important that we can do with a pill or something like that I think that would be something we would like to do because it my guess is that you have to do something to target that population now which is one fell swoop like a transplant but you're going to need to do that over long periods of time so we would like to find drugs that are very safe

that you can give over long periods of time and that would be one of the hopes but I think one of the things is that what I for sure like to offer is that if you have questions just let me know I'd be happy to talk to you, I'd be happy to answer e-mails and I guess the one other thing I would say in terms of that is I've spent twenty years here at Johns Hopkins and loved every minute of it but I'm actually moving to Austin Texas to take a job at a new cancer center, the Live Strong Cancer Center that's at the University of Texas, so I'll do that in June but I think I'll be pretty easy to get in touch with them so if you have questions please feel free to just reach out.

Dana: Will you be also working on this research in your new position?

Dr Matsui: I will, my job is a little bit different because there's no blood cancer program because the medical school is new and the cancer center is new and so my job is to actually build a blood cancer program but as far as my research goes and as far as the patients that I'll see, it all still primarily center around myeloma. I'll find other people to see lymphoma patients that's not what I do, I do myeloma and so I'll find I think I'll be able to find great people to help me take care of all blood cancer patients but I would still I am devoted to spending my time working on myeloma.

Dana: Oh I wish you well thank you so much and yes my last question I remember listening to Dr Rodger Tiedemann from Canada a couple years ago and he was explaining progenitor cells, are those the same as myeloma stem cells or is it just a different term?

Dr Matsui: They are exactly the same thing I think Rodger and I study exactly the same thing I think Rodger is a wonderful person and I think that their findings his group's findings actually mesh super well with our finding. And I think that on top of that the work that was done at Penn using CD19 CAR-T. cells I think really buttresses so I think we've been very fortunate that other really good groups have really recapitulated some of our ideas and brought light to some of our ideas because I think that being alone and out there with the weird idea that nobody likes is not easy but I think we've gotten great support as time has gone on.

Dana: Well your theory makes perfect sense to me because obviously there are cells that stay behind that are responsible for relapse and it's seen in all of the treatments in the quadruplets and you're hitting it with the kitchen sink if it's still not eradicating it, somebody is missing something so I'm grateful to you and your and your ideas because they may end up leading to see the answers someday so I wish you the best of luck and thanks so much for taking my call.

Priya: Thank you Dana

Gary: Dr Matsui you're no longer a lone ranger.

Dr Matsui: That's nice, its nice not to be alone, that's tough.

Priya: So we are well over our time today Dr Matsui, thank you so very much for all the information you shared with us and we wish you very well in your new position and hope to get you back with us some time soon then, in the New Year some time. Gary, Jack, Cindy and Yelak as usual, thank you so much for participation, you are the pillars of this program and this talk will be made available on the Cure Talks website. Please join us in the New Year when we are talking to Anne Quinn Young of MMRF on Jan 25th 2018, please visit curetalks.com for details on upcoming talks thank you very much.