Preventing Relapse in Multiple Myeloma

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However, cures remain rare in myeloma and most people may eventually relapse.

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William Matsui of Johns Hopkins University School of Medicine on why relapses occur after several years of remission and how they can be prevented.

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Full Transcript:

Priya Menon – Good afternoon and welcome to CureTalks. I am Priya Menon, Scientific Media Editor of CureTalks, joining you from India. This is CureTalks' 107th episode; and today, we are talking about multiple myeloma. On the myeloma panel today, we have patient experts and myeloma advocates, Jack Aiello and Matt Goldman. My co-host for the evening is myeloma survivor and advocate, Gary Petersen, editor of myelomasurvival.com. Welcome to CureTalks.

Priya Menon – Recent introduction of new therapies has significantly improved outcomes for patients diagnosed with multiple myeloma; however, cure remained rare in myeloma and most people may eventually relapse. If we want to better understand how and why myeloma goes back, there is hope that relapse can be prevented and thereby eventually improve long-term outlook for myeloma patients. The myeloma panel is talking to Dr. William Matsui of Johns…, John-Hopkins University School of Medicine on why relapses occur after several years of remission and how they can be prevented. Dr. Matsui is Professor and Director, Multiple Myeloma Program, Sidney Kimmel Comprehensive Cancer Center at John-Hopkins University School of Medicine. Welcome to CureTalks, doctor.

Dr. William Matsui – Hello! Thanks for having me.

Priya Menon – We will be addressing questions from the audience towards the end of the discussion. If you have a question for our panel, please press 1 on your keypads to let us know and we will bring you on air.

You can also email your questions to priya@trialx.com or post them on curetalks.com. With that, I will hand over to Gary to begin with the discussion. Gary, over to you.

Gary Petersen – Yes. Thank you very much, Priya, as always for providing this very important forum and Dr. Matsui for, you know, being kind and generous with your time. Dr. Matsui has a degree from Harvard College; and he has a doctorate from the University of California, San Francisco. He has also completed his internship and residency in internal medicine at the University of Washington in Seattle and a fellowship training in medical oncology at John Hopkins University. All of these names of these universities have an excellent history in the world of multiple myeloma. At the completion of his fellowship in 2002, he joined the facility as an assistant professor at Sidney Kimmel Comprehensive Cancer History, John Hopkins University School of Medicine. He was subsequently promoted to the rank of associate professor in 2008. His current research is focused on normal and cancer stem cell biology in his laboratory; and he has his own laboratory named after him, which is an honor. His laboratory identified tumor-initiating cells in plasma cell malignancy in multiple myeloma in 2004. He has subsequently found these cells share similar cellular characteristics with normal stem cells. Dr. Matsui has been awarded the George Santos Research Award from the Leukemia and Lymphoma Society; and there are so many other things that he has done and accomplished over his career that it would take entirely too long to…, to mention all of them. So, we do welcome you, doctor, for taking part in this presentation; and we have got a number of people who are going to find this new and exciting. So, thank you.

Dr. William Matsui – Thank you.

Gary Petersen – Dr. Matsui. You are doing some cutting edge research in the identifying myeloma stem cells as a main cause of myeloma relapse. You believe we can cure myeloma if we can focus treatments to this cancer stem cell? Could you please explain this theory?

Dr. William Matsui – Sure. So, the theory is, is that there are certain tumor cells that are different from all the other tumor cells, so…, and the way that you can distinguish them is that some of the tumor cells have a specific function and that's not shared with all the tumor cells. So, the function that we are interested in is the ability to maintain growth over long periods of time. So, that's one property of normal stem cell and so, for example, in your bone marrow, you have hematopoietic stem cells and they are…, they are for your entire life and their job is to make blood for your entire life. So, in tumors, what we believe is that there are cells that actually fuel the tumor and fuel growth of the tumor and its not a property that is shared by all other cells. Its actually just a minority of cells, just like in the bone marrow with normal stem cells, there is a vast minority, a very small percentage of all the cells in the bone marrow. So, what we have been trying to do is figure out what these cells are and how they are different from the rest of the myeloma cells and ways of trying to target them and our hopes are that if these are the…, sort of the factory that lead to relapse, so if we control those, then after we achieve remission, then maybe what we can do is prevent relapse from occurring.

Gary Petersen – So, is there a way of determining whether, you know, like, for example, they have minimal residual disease measures which people were believing would, you know, if you had a low level of residual disease that, you know, you can pretty much cure myeloma, whereas I think what you are saying is that it doesn't matter what you do with residual disease if you still have latent stem cells or would these stem cells show up as residual disease as well?

Dr. William Matsui – Oh, no. I think that we don't know. I think that with new technology you can detect very small numbers of tumor cells. The primary way that's done these days is by doing DNA sequencing and that's probably the most sensitive way to do it and the stem cells and the plasma cells that make up the tumor, you know, they share the same genetic components, so you couldn't tell just by DNA sequencing whether or not you are dealing with a stem cell as MRD or as just residual occult tumor cell. So, its…, there is a relationship. I think that, you know, one of the properties…., one of the…, the thoughts is that in myeloma, stem cells may be very different in the way that they act from the rest of the tumor and so they may be deferentially sensitive to certain chemotherapies, though if we think about the chemotherapy that we use in myeloma and if we think about ones that are curative, then, you know, stem cells, even if you go into

remission, they have to survive that chemotherapy somehow. So, even if they are very low in number, you know, they have this potency to grow back the entire tumor and so one of the things we have thought about…, we thought of very early on was how are they more resistant to the drugs that we normally give myeloma patients and, you know, if there is some other way that we could attack it.

Gary Petersen – And did you find other ways?

Dr. William Matsui – So, one of the thoughts is that plasma cells which are the differentiated, you know, which are the cells that are the myeloma cells occurring as normal. They are, you know, they are not an anomaly of the disease. You just.., you have many more of them in the disease. The plasma cells themselves normally don't make new plasma cells. They come from an earlier compartment, which are B cells. So, B cells are the components that arm of your immune system where antibodies are made and in myeloma that manifests as your M protein. So one way to think about it is is that like in your skin, you have an upper layer skin and then you have skin stem cells which are deeper down in the skin and the upper layer of…, of skin cells is there to protect you and they are actually not even alive, but they come from a deeper compartment of stem cells that…, that remain until its not as if, you know, the dead skin cells on the surface can make more cells. They…, they do their job which is protecting, but they come from a different source.

Dr. William Matsui – So, what we think is is that in myeloma the plasma cells may not be making more plasma cells and maybe just…, just as in the normal system. It may be B cells that make plasma cells and B cells are actually the cell type that is the prominent tumor cell type in lymphomas, in many lymphomas. So, there are many things that have been designed, too many drugs have been designed to treat lymphomas. So, one of the things we have been actively doing is to see whether the cancer therapies that can treat lymphomas are also something that we can use to treat myeloma because we think that the stem cells in myeloma and the…., look very similar to those that of lymphoma cells. So, that's one of the ways we have been trying to get at this question and, you know, one…, one of the things is that there's the…, there's a lot of controversy in the field about myeloma stem cells and there are couple things…, there are few things that people agree on and there are things that people disagree on. I think most people agree that there must be something like a stem cell that leads and drives relapse of the disease and the…, but the controversial part is what is it that they actually look like. Do they look like B cells? Do they look like plasma cells? Do they look like something in between? That's where most of the controversy lies, is… is what is their phenotypic appearance, but I think that everyone believes there is some stem cell somewhere, no matter what it looks like, because if you didn't have that, then you likely wouldn't relapse.

Gary Petersen – You know, and its probably my ignorance, but I had thought originally that the stem cells were like this mother cell, if you want to call it that, that it was something that was unique. A stem cell was a hematological stem cell and it could then hang out and be anything. If you want it to be a blood cell, it could be a blood cell. If you want it to be a…, a liver cell, it could be a liver cell. If you want it to be and as a result, you know, I recently looked at the EuroStemCell.org. They wrote an article, saying there's different theories to explain tumor growth and they said, one is cancer stem cell theory and the other is a stochastic model of cancer growth and the stochastic model assumes kind of this normal change if you want to call it that, stem cell that can be anything, as in it can create plasma cells or anything else, has an equal chance at becoming cancerous and there is…, there are no cancer stem cells. Why do the stem cells exist and is it the correct approach….

Dr. William Matsui – Right and I think that…, I think….

Gary Petersen – ….and not just a stochastic model?

Dr. William Matsui – Right. I think that there are two ways to think about it. One is that…, one is really just the functional sort of definition and its something, like in…, in normal stem cells, in normal systems, right, there are multiple different kinds of stem cells. There are pluripotent stem cells and like the pluripotent stem cell is the cell that gets made when an egg and sperm come together because that cell has to make everything a part of your body. Right? So, it has sort of that differentiation potential. During…, normally during

adult life, each…, its thought that each sort of organ has its own stem cell. So, like in the brain, there are neuro stem cells that continually make different parts…, different cells that make a potential nervous system. The hematopoietic system, I think, is the easiest one to understand where there are stem cells that make all the different lineages in the blood. In the skin, there are stem cells. In the liver, there are stem cells and its not yet clear during, you know, adult life whether or not stem cells from your liver can now become heart stem cells. Like, that's never really been shown and so its not that every organ has their own complements of stem cells and that…, and that complement is responsible for maintaining that organ and repairing it if the organ is injured.

Dr. William Matsui – So, one…, one controversy about…, and I think its a misunderstanding about cancer stem cells is…, is…, its not…. they are not cancerous stem cells, meaning that it doesn't mean that you…, you need to have cancers that start in stem cells. Like even in leukemia, let's say, most leukemias do not start in a hematopoietic stem cell, the true hematopoietic stem cell, because if you get AML or myeloid leukemia, that…, that if it was in a…., a hematopoietic stem cell, then it should make lymphoid or B cells and T cells as well. So, if you…, so…, so, one part of the theory I think that is…, is misunderstood is that…, is…, is talking about the origin of cancer, like the cancers originate in stem cells. Its an attractive thing to think that that happens because they are the cells that are actually around long enough to acquire the mutations that you need to form a tumor, but in fact, we don't have much evidence. We don't have a great deal of evidence suggesting that.., that cancers arrive in the stem cells, either in the lung or the liver or the colon or the…, the bone marrow actually. So, the other way to think about it is is that cancer stem cells are an entity, but it…, it doesn't describe sort of where they arise. It just describes their functional properties and…, and I think that the two greatest functional properties that are different from the other tumor cells are, one is.., is withstanding chemotherapy because they will survive that chemotherapy and then the other is, they have this tremendous capacity to re-grow tumors. So, if it wasn't for them, right, and their special ability to grow, then, you know, you wouldn't have relapsed. So…, so, I think that, like I said, I think that there are…, there are many theory things about cancer, where cancer arise from. I think that the…, the…, the cancer stem cell theory doesn't describe where they come from within a normal organ. It just describes sort of the…, the properties that contribute to the activity or…, or the natural history of a cancer in a person.

Gary Petersen – Okay. Well, you've…, you've had some, I think, proof that they exist, right, by doing some research that showed that when you go after something that shouldn't work, like after a B cell, that when you look…, you can actually see these stem cells, I assume, somehow and you can see whether or not they… they are reduced because one of the things that you mentioned was, there was like a 50% reduction in one of the experiments or trials that you had completed or something like that.

Dr. William Matsui – Right. So basically we have done…, we have done a couple of clinical trials and those clinical trials have been… There have been a couple clinical trials that have used antibodies that are useful in lymphoma to try and test them in multiple myeloma. So, the first one we did was a number of years ago, and it was using an antibody called rituximab which is very commonly used in lymphomas as well as leukemia and that was…, it was not successful. We did not prolong the time that people were…, remained in remission and what…, but one of the things we learned from that trial is, we developed a couple of different methods to count the number of stem cells in a person. So, one was during the bone marrow where we take the bone marrow and we just see how many sort of myeloma stem cells can grow and that would be in.., in incubator in the lab and then the other is an assay where we actually use flow cytometry which is this way of…, of marking different cells and we do this in the blood. So, we try to identify myeloma stem cells in the blood and so in the first trial which was a trial with rituximab, like I said, we didn't…, we weren't clinically successful, but what we learned in that is that if you had myeloma stem cells that we were counting and they went up over time so you are increasing the number of stem cells, those patients relapse much, much quicker than if you had stem cells that stayed the same in their number or they went down over time.

Dr. William Matsui – So, we thought that there was some…, you know, there is some relationship between what we are measuring and the time that people were in a remission. So, then, most recently we did a trial using a…, a different antibody against B cells called MEDI-551, its an…, its an antibody used in clinical trials in lymphomas and leukemia and what we found there was that we could actually see the stem cells go down in

most patients unlike who are experienced with rituximab, but in this trial we only gave three doses of the antibody over two months and so the…, the trial itself was not designed to see how long the patients would be in a remission or whether they would go into a complete remission over time. It was basically just to see whether or not if we gave this antibody, was it safe to do in individuals with myeloma and could we see evidence that the number of myeloma stem cells were going down. So, that's what we are able to…, to show and that's the trial that we reported as at the most recent AACR meeting and what we are trying to do now is build upon that and actually use that antibody for a longer period of time and in the first trial, the trial we just completed, it was done in conjunction with Revlimid and so what we would like to do is to use something more than that and so the trial that we are thinking of doing is something where we do some type of transplant, really get the patient into remission, and then to use the antibody after that to see whether we can keep them in remission.

Dr. William Matsui – So, I think that the proof that we have is really the correlation between or disassociation between, do the numbers of them go up or down in an individual and can that predict when the patients relapse because if you think, well, they are going up and they are growing, then you should see relapse happening quicker and if you see them going down, then you should say, it should take a longer time before the patients relapse. So, that's the relationship we found, and I think the most compelling evidence that B cells are important in myeloma actually doesn't come from our lab at all. It comes from a group at the University of Pennsylvania and what they have done is they have used T cells and they have engineered them to target a protein called CD19 which is only on B cells. Its not on myeloma plasma cells at all and they have used these things called chimeric antigen receptor T cells or CART cells in patients with leukemia and they have shown that you could eradicate leukemias using these cells. Its an immune-based therapy. So, what they did was they actually tried to use these cells in myeloma and so they gave patients a transplant and then they gave them these cells right afterward and in a number of patients who had had a previous transplant, who did go into a complete remission and had very short remission, doing another transplant plus…, plus giving these cells actually made them go into very deep remission and so there they are using a very powerful and a very precise way of targeting just B cells and they are able to…, they were able to generate sustained and complete remissions in a number of patients. So, really I think that there are…, something's been very correlative or very associative, but I think that, you know, the truth is you get rid of the cells and then you see what happens to the patient and I think that the…, the…, the University of Pennsylvania group has actually been the strongest evidence that B cells are important in the disease.

Gary Petersen – Yeah, it sounds like it. The early research you were talking about was at the University of California in San Francisco with leukemia and has…, have they made inroads into the cure using cancer stem cell theory and…, and would they, you know, look at using these antibodies…, leukemia and then able to determine whether or not, you know, they have gone up or down and improved outcomes.

Dr. William Matsui – So, its funny because the cancer stem cells sort of hypothesis, though the theory is really old actually, quite old. It goes back to the 50s and really the proof of the existence of cancer stem cells was in acute leukemia…, in acute myeloid leukemia and that was done by a group in Toronto run by an investigator names John Dick and that was…, he…, he reported that they identified B cells in 1994 and subsequent to that, you know, we have identified them in myeloma, there have been other diseases, brain tumors, breast cancer, head and neck cancer. There have been many diseases where these things have been identified, but one of the major issues is is that none of that has been really translated out into clinical practice. So, what I would say is is that like our job…, part of our job is to try to study these cells and understand how they grow and to regulate it, but another big part of what we should do is to actually prove that they are important in individuals and so, I think that is the cancer stem cell field. I think that we in myeloma are probably the most advanced to trying to figure out whether this theory is correct or not. I think that in breast cancer there have been some trials; in leukemia, there have been some trials, but I don't think any…, anyone's come close to the data that we have in myeloma. So, I think we are…, we are far ahead of the curve and…, but, you know, it is ironic…, its interesting that…, or just I think its just that that its very difficult to take ideas from the lab and actually convert them into clinical trials and then from clinical trials into something that is standardly used and so, you know, big part of our program is to try to get these ideas from the clinic into the…, from the lab into the clinic and I think try to get as much data as we can so we can do

more definitive trials moving forward and…, and that's sort of where we are right now.

Gary Petersen – Okay and that kind of leads to my…, my next and last question before we go on to the other panel members. For myeloma, you know, you say its very difficult to take it from the lab into the clinic and have there…, has this approach made it out of the lab and into the clinic yet and if so, what have you found and what are the plans for the future?

Dr. William Matsui – So, we've done, you know, so we've done, like I said, some early phase trials. We did the trial with rituximab. We did the trial with MEDI-551. We have done one other trial using inhibitor against the pathway called Hedgehog and, you know, the…, the…, the difficulty as it being is that for most drugs that we test for myeloma, the initial barrier to overcome, right, if you have a drug and you want to figure out whether that worked, the initial thing you do is you give it to patients with advanced myeloma and you see whether or not their tumor version goes down, so whether their M proteins go down, their light chains go down, whether the plasma cells are decreased in the bone marrow. So, that is sort of the first hurdle to drug development in the disease. So, if you said, look, I gave someone the drug and it didn't change their M protein, it didn't change the number of plasma cells, then I think most people would say, look, that drug is not going to work in the disease. Right? So, for us, one challenge is is that the…, we think that the stem cells in myeloma are like 1 in a 100,000 to 1 in a million of the tumor cells. So…, so that…, that frequency is so low that even if you targeted those cells, its going to take you a while before you start to see things like the M protein go down and the plasma cells go down in number because if you are cutting off the factory, you still have to wait for all those other…, other progeny or all of the mature cells to go away. So, it may take a lot of time and so one very big hurdle in drug development for cancer stem cells is having to know that they are working. Right?

Dr. William Matsui – Because the traditional methods that we use like in myeloma, those things don't change for a long, long time. So, trying to find partners or trying to find the trials where you say, look, even if we are not making the M protein go down, we should continue to treat the patient, like that is a difficult sort of conceptual hurdle to overcome and the same goes for all other cancer stem cell trials and other diseases that, you know, the things that are important to us, the things like the relapse rate, right, those are not the things that are traditionally looked at very early on in drug development, that allow you to sort of say, well, there is…, there is a compound and we think it has some…, some potential benefit in the disease because you are going to…, if you give these compounds that…, that target 1 in a million cells, you are not going to see the M proteins go down in a couple of weeks. Its just never going to happen and so I think a lot of it is trying to convince, you know, the government like the FDA or drug companies that help us with our studies, some group of companies that help us with our studies to…, to devise specific clinical trials where we can actually go and we can see whether or not there is an effect and whether or not we can try to look at that over a longer period of time. So, that's sort of where we are right now and, you know, one of the thoughts now is is that if these cells are important in relapse, then what we should do is we should give patients medications in the setting where they might relapse, so after…, let's say, after transplant and see whether or not you can prolong the time before…, before that occurs.

Gary Petersen – And see whether or not you can reduce those stem cells?

Dr. William Matsui – Yes. Exactly!

Gary Petersen – And somehow measure that. All right. Well, thank you so much, doctor.

Dr. William Matsui – Sure.

Gary Petersen – Jack, are you online?

Jack Aiello- Yeah, I am online, Gary.

Gary Petersen – Okay, then with your question.

Jack Aiello – Dr. Matsui, thank you so much for being here. This is fascinating! I…, I am glad… also, I was going to ask you the question about kind of correlating the number of myeloma stem cells to plasma tumor cells, but you mentioned 1 in a million and golly, sounds really difficult to find. When…, when I attend myeloma conferences these days, I am always struck by one of the slides that shows the plasma tumor cell being a circle made up of a pie, slices of different colors and maybe the predominant colors are blue and…, and as it progresses to cloning itself, the predominant color then becomes green and…, and those colors represent the characteristics that are somehow changed for a…, for a plasma cell and perhaps explains why a treatment which didn't work originally becomes…, is…, is no longer effective. So, my question is, can myeloma cells…, stem cells do the same thing or are we already talking about myeloma stem cells when we are referring to myeloma clones? Can you expand on that?

Dr. William Matsui – Yeah, so I think that, so one of the things for sure that's been a very interesting finding because we…, we developed the…, the technology has been developed that allows you to…, to sequence every gene in itself. Right? Allows you to sort of see over time, are you dealing with the same genetic…, genetically defined tumor. So, if you are diagnosed and we sequence the tumor, you find specific mutations, you treat and then when the patient relapses, you sequence again and then when they go back…, after they go back into remission and relapse again, you sequence again. So, its actually…, its interesting to see that…, that every time you relapse, it may be a different clone that arises and in some cases what you see is is that the.., the…, the clone that relapses is exactly the same as what you had in the beginning. In some patients, its exactly the same except that there are extra mutations when you relapse and then in some patients, its actually not a completely different set, but its…, its sort of a different set of mutations suggesting that there was some other thing hiding out in the beginning that was just suppressed and when you cleared out the tumor using some therapy, that that thing was now allowed to grow because it was resistant. So, I think the way that stem cells fit into that is that I…, I think that every clone probably has a stem cell and…, and that allows it to be…, to be…, to expand over time. I think that we don't know when you progress over time, so let's say over many different rounds of therapy or different kinds of therapy, if your.., if your…, if tumors become more drug resistant, is that because you are gaining more mutations or you just have stem cell now that is resistant to everything. That is…, that is something we don't know at this point in time. I think that one of the things that…, that's super interesting, that comes out of…, of looking at these clonal dynamics is that there's…, there's usually one that is dominant. Right?

Jack Aiello- Yeah.

Dr. William Matsui – And so, it ends up being that.. like, like the question is like why is that one dominant, like what is it. Is it…, is it simply that it grows faster than the other one to become the predominant one or is it that, like one other theory, the theory that we have is is that, one clone can actually actively suppress the other one. So, its not just a matter of who is cloning the fastest that wins, its a matter of who can suppress the other clone so that's until…, sometimes what you see in myeloma patients when they are newly diagnosed is they can have very incredibly smoldering disease and you could use something like, you know, lenalidomide alone or with some dexamethasone and…, and it may not create a complete remission, but it keeps things at bay for a long, long, long, long time, but then when you try to sort of get rid of everything, something comes back and when it comes back, it grows much, much quicker than it sort of originally did and I think that it may be that the…, the competition between clones is something that we should…, we should try to figure out how we can study because it may be that if we figure out the mechanisms that suppress clones, maybe what we can do is generate those in people and…, and keep all the clones down over time, but we…, we just don't understand…, we don't understand how clones interact with one another. Right now, all we understand is is that you see them there, you know you take a picture in time and its one clone, you do something and you take a picture at a different set…, at a different time and its a different clone, so we know that clones change, but we have no idea how they interact with one another and…

Jack Aiello- Okay.

Dr. William Matsui – …so I think that that is one layer of biologic complexity that most individuals have not thought it out.

Jack Aiello- If these B cells are myeloma stem cells, do these B cells have targets for myeloma treatment? For example, you know, we are always looking at surface antigens for which a drug can be developed that might cause the cancer cell death and such. Can… I think you said you isolated some myeloma stem cells. Can drugs be developed to attack markers on these cells as well?

Dr. William Matsui – Yes, so…, so that was, you know… When I was talking about these two antibodies that we have used, those are really specifically designed to go after the B cells and not the plasma cells. I think that what we are…, what we are trying to do now is we are trying to find cell surface proteins that are on plasma cells as well as B cells, so you can get rid of both compartments at the same time using a single approach and so we've…, we've been trying to figure that out. The…, the…., you know, there are very specific biologic characteristics that I think lead to differential drug sensitivity. So, one…, one sort of prominent one is the use of something like bortezomib which is a proteasome inhibitor. So, that drugs works the best in cells that are making a lot of protein, which are plasma cells. Plasma cells: They are designed, they are little faster and they are designed to make antibodies or the M protein. So, they work really well against cells that are making a lot of protein.

Dr. William Matsui – Well, B cells don't make a lot of protein, right? Their job is not to make antibodies. Their job is to make plasma cells and so with bortezomib, bortezomib is typically not very active against B cells in myeloma and we showed that a few years ago, but its also not very effective in most lymphomas because, you know, the…, the mechanism by which they kill is not something that's really super important in B cell. So, there are differences just based upon being a different cell type that lends to drug sensitivity or drug resistance and as you were saying, I…, I think that there are surface antigens available and it may be that if there are CART cells as can be used against B cells and you combine those with CART cells against something that has had myeloma cells and there's a couple of different trials using CART cells against this antigen called BCMA. So, maybe what…, if what we do is combine CART cells and maybe what we do is we get rid of multiple components or compartments in the disease and maybe that will lead to longer remission. So, that's something that we are very interested in…, in pursuing.

Jack Aiello- Yes. CD19 example as to why the CART might have worked for a myeloma patient and CD19 being part of a B cell. Since B cells are kind of higher up in the, you know, tree, if you will, are there risks where other non-myeloma-related B cells also have CD19 and therefore you might be killing good stem cells as well?

Dr. William Matsui – Yep. So, in the trials that are ongoing now and…, and with CART 19 T cell, one of the side effects, if you…, you know, if you use them for…, for leukemia where CD19 is expressed or for lymphomas, if it works it gets rid of all CD19 positive cells which are, as you were saying, they are both the malignant cells and they are the normal cells, like one of the…, one of the…, the…, the good things about the system…, about the B cell system is that you don't really need B cells because what we can do is we can give you, you know, antibodies back and that's giving people IVIG back and so even if you got rid of all the normal B cells, you can still provide some of that immunity back in the form of, you know, an immune treatment. So, there are other things, you know, where people have thought about using immune approaches where that's probably the not as reasonable, like if you get rid of, you know, brain cancer stem cells but you also get rid of brain…, normal brain stem cells, that's probably not such a good thing. So, we are lucky in the disease that we are studying because if you got rid of B cells, if you got rid of all good plasma cells, you would still be okay, like there is still a way that we could rescue that, but in many other cancers, that's not necessarily unfortunately the case.

Jack Aiello – Right. Thanks so much and now turn it back to Gary.

Gary Petersen – Jack, great questions! Matt Goldman, are you online?

Matt Goldman – Yes, I am. Hi, Gary!

Gary Petersen – Hi, Matt! Welcome.

Matt Goldman – Hey! Thank you very much. Doctor, thanks for your time. I guess just some basic questions and you are talking about relapse. Are you…, are you putting relapse and refractory into the…, into the same pool or is there a difference there to that approach towards each of those?

Dr. William Matsui – So, I think that…., I think it depends on the phase of the disease, though I think that very early on when you can…, when you can generate complete remissions in patients, then I think that…, that, you know, the…, the growth back is…, is…, is relapse. I think that as you go on in time and the drugs becomes less effective, that's when you develop resistance and what we don't know in particular is what do stem cells do and what do they look like in very resistant patients. We know that the frequency…., there are many more stem cells that we can find in patients who are much, much more advanced than those, let's say, who have smoldering myeloma, but we don't know yet what are the differences in stem cells in patients who have advanced disease that are refractory to…, to many therapies versus those that are…, we think are responsible for relapse early on, like one of the thoughts is that CD19 is…, is perhaps a good target early on for…, for more patients but may not be such a good target way down the road, when you have cancer stem cells that may look less like B cells than they did in the beginning.

Matt Goldman – Okay and…, and you…, you touched on this just a little bit before, earlier. In terms of when a patient does relapse, what's…, what's the thing that you are really looking for? Is it that they are symptomatic or is it just purely what their numbers are looking like?

Dr. William Matsui – So, right now that…., you know, as a myeloma physician, what we look for is, we look for…., early on we look for biochemical evidence of relapse and that's why we check M proteins and light chains periodically. When patients are in a complete remission, the…, you know, everyone has their own sort of trigger point when you need to be treated. I think that if you are…. Just the evidence that the M protein is sort of coming back, yet there is no end organ damage, it may be prudent to just wait a little while before you…, you start to treat. You definitely want to start treating before…, before there are, you know, things like kidney damage or bone damage, but typically you don't need to treat at the first time that the M protein is back and I think that trying to figure out what the pace of the disease coming back is and sort of how long its been since, you know, you initially got therapy, those things comes into play when…, when we are deciding whether or not to…, to re-treat and when to re-treat and…, what specifically we have to treat with. That is totally different than the whole idea of stem cells. The idea of stem cells would be that if you are in a complete remission, what we are going to do, we are going to try to track your stem cells rather than tracking M proteins and light chains because those are the components that are more indicative of the differentiated cells and if we are going to use stem cell therapy, its probably…, the time to use them is when you are in a complete remission, not when you are…, you are relapsing, but that remains to be seen.

Matt Goldman – Okay. We talked about being… This approach, is it…, is it sort of taking us away from transplants as a…, as in the past as a treatment for relapse patients potentially or does that not really come into play?

Dr. William Matsui – I think that's sort of, you know, like, part of…, you know, part…, an important part of treatment for many myeloma patients is an…, is an autologous stem cell transplant. I think that there are…, there are other types of transplants, specifically allogeneic transplants and, you know, allogeneic transplants, you have a track record of being curative, but its in a small proportion of patients and one of the things we try to do at Hopkins is develop safer ways of doing allogeneic transplants and we've…, we've come quite a long way. We…, we…., one of the big problems with allo transplantation is…, is graft versus host disease and we have reduced that down considerably. We have made it so that we do most of our transplants as outpatients now. We used to have an upper age limit of transplantation using allos and then we got rid of that because we can make this procedure safer. So, we have done those things in many diseases like AML, ALL, and lymphomas and so, we are starting to study those approaches in myeloma and the hope is, is that…, what we can do is we can save…, I think we…, we pretty… I think its likely that we can pretty safely get patients to do the transplant and then the issue becomes what do we to try to keep it from coming back and I think that's where the idea of stem cells comes into play and…, so we are trying to develop clinical trials where we do allo transplants in patients and we are following up with some sort of maintenance strategy after the transplant to

prevent relapse. So, those things are things that we are getting up and running and hopefully we will have a myeloma-specific allo trial up in the next year, but I think that the big hurdle for allo transplantation was really its safety and I think we've…, we have pretty much overcome that. So, now I think that we can use the biggest benefit of an allo transplant, which is an entirely new immune system to try to help fight myeloma and try to figure out ways where we can coax that immune system to be active against a recipient's myeloma.

Matt Goldman – Okay and with…, with an autologous transplant, is there a chance that when…, and pardon my ignorance here, but when you…, when you are harvesting your stem cells, is there a chance that…, that these myeloma cells are sort of with that harvest and you are simply going to…., you are putting them back in?

Dr. William Matsui – Yep and so, there…, there was a…, there is a…, there is a nice study that was done by a colleague of mine, Paul at MD Anderson. What they did was they took stem cell graft from myeloma patients and you could find evidence of myeloma by sort of genetic testing and what they did was they actually treated the…, those stem cell grafts in the lab with two things. They treated it with bortezomib to try to get rid of any plasma cells if plasma cells were there and then they used the molecule antibody rituximab as well to try to clear any stray myeloma B cells. What they found were that they could clean up the graft where you didn't see any evidence of myeloma in the graft, but what we don't know is we don't know that that truly prolonged the time a patient stays in remission after an autologous transplant or does it…, does it prevent people from relapsing after an autologous transplant because one of the things we…, we found is that for sure we can detect myeloma stem cells after an auto transplant and we specifically don't know whether it comes from the graft, whether the melphalan that we use doesn't kill them all, but we could certainly see them afterwards and…, and in…., as another situation when we…, when we track them, often times what we see is they start to go up in number before you detect an increase in the M spike or recurrence in the M spike or abnormalities in the light chains. So, we think that they sort of hang out for a while, that for whatever reasons is trying to become active again and start to grow and so we are trying to figure out what keeps them dormant because if you can keep them dormant for ever, that would be great.

Matt Goldman – Right.

Dr. William Matsui – So, we are trying to figure out those…, those sorts of partners of biology right now.

Matt Goldman – Right. Okay and then…, and then, this is my last question here. Did…, did you say that with each new relapse if patient has multiple relapses that the intensity of the relapse or the speed of…, of the myeloma increasing is…, is more intense with each relapse. Does that make sense?

Dr. William Matsui – It can be, like if you, I…, I think that the…, the biggest thing I think is that, that the life of the remission tend to be shorter between…, between sort of later lines of therapy than they are after the first line of therapy. We can keep patients in remissions for…., often times for quite a long time. The repetivity that they come back…, that the…, that the tumors grow back is…, you know, is…, is super variable and…, and I don't…, I don't understand why that is. Often times when you get more advanced cases of myeloma, they make much less M protein than they did at the beginning. So, they are becoming less sort of mature in their plasma cell phenotype because making protein is part of that…, of that phenotype, but the…, the pace that they…, that typically when patients relapse later on is a little bit faster, but that's not a universal thing.

Matt Goldman – Okay. Okay. That's…, that's all I have. I will throw it back to Gary. Thanks again, doctor. Appreciate your time.

Dr. William Matsui – Sure.

Gary Petersen – Yeah. Thank you, Matt. Really appreciate and, doctor, what we really do right now is…, is see if we have some caller questions. So, Priya Menon, will you please see if we have any callers on line?

Priya Menon – Thank you, Gary. We have some questions sent in from our…, by our audience, Dr. Matsui.

So, I'll just…, I'll just go through them and maybe we can get some answers here. One of our listeners writes in, what are the available clinical trials related to relapse prevention that I can enroll in?

Dr. William Matsui – So, we have…, I think we have trials that are specifically targeting myeloma stem cells that are starting up within the next…, probably the next six months or so. They are…, they are transplant-related trials. I think that there are other…, other places that…, that have very much tried to focus on preventing relapse and…, and in a non-stem cell way, which is also I think an important strategy and so there are…, there are many trials looking at maintenance strategies following induction therapy or following a transplant and I think all of these are potentially ways of…, of…, of slowing down relapse and hopefully extending overall survival in the end. So, we have a few, but there are many trials that are not, you know, outwardly or demonstratively going after myeloma stem cells, but those are ones that are maintenance trials and I think that those are potentially important as well.

Priya Menon – Thank you, doctor. Another question is, could you please explain in layman terms how can telomerase pathway be useful in developing a drug that may prevent myeloma relapse? Do we have a molecule in the pipeline that can target this pathway?

Dr. William Matsui – Yes. So, we actually did a small…, a very small trial with a drug called imetelstat and it is a drug that inhibits the…, the enzyme that makes telomeres and so it inhibits telomerase and that drug is… What we found was that if you gave the drug, we found no effect on someone's myeloma and these were pretty early stage patients. They had detectable myeloma. We gave the drug. The myeloma didn't really change as part of M spiked or light chains, but if you…, so since there…, there was no change, the patient stopped the drug and what we found was that if you waited a while, waited a few months, they can now see the M proteins kind of going down by themselves in a number of patients. So, what we think is is that maybe we were targeting the stem cells, but it would take a while to see that effect because its sort of a 1 in a million cell type of effect. It ends up being that…, that…, that inhibitor has been tried in breast cancer, its been tried in another hematologic malignancies called myelofibrosis and there are efforts to… The company, I think, has some difficulties that was…, that had generated the drug and I think that its been picked up by another pharmaceutical company and I think that they are interested in…, in pursuing that therapy in several diseases and, you know, we are hopeful that myeloma might be one of them.

Dr. William Matsui – So, there is a compound that people have used. There are some vaccines that are targeted against telomerase which is this enzyme that makes telomeres, but I think its a very attractive target, but it is one that we don't have great drugs to get with… Like I said, we have this one drug, its been in the clinic. Its not entirely without toxicity and I think trying to find better drugs against telomerase is…, I think its a viable approach. I think that…, that many cancer stem cells depend on telomerase. Many cancers depend on telomerase and so I think its…, it is…, it could be a very potent anti-tumor approach, but i think we…, we need to find sort of the right drugs and the right cancers to try…, try the idea of it.

Priya Menon – Thank you, doctor. Another… The next question is, could you please address research in curcumin and the supposedly more bioavailable Meriva in stabilizing disease and maintaining remission?

Dr. William Matsui – So, there's a lot of data for the use of curcumin in many cancers. There's been a little bit of data studying it in…, against pancreatic cancer stem cells and or the cancer stem cells and pancreatic cancer and breast cancer would never look and myeloma. I think that it is not exactly clear what the mechanism of action is. I think that there are so many trials ongoing. I don't know if there are any in myeloma in particular, but, I think that in general there is a lot of potential for natural compounds to be used anti-tumor agents and I think that its the challenges are similar to the challenges for any other drug is can you develop them and do like clinical trials and get the right support to do those clinical trials and I think that that's, you know, definitely an avenue that is attractive, but I think its been difficult to find funding to do those trials.

Priya Menon – Thank you, doctor. That's all the questions that we have for you today, and I have to say this is very interesting and very hopeful for the myeloma community. We will be following your work here on

CureTalks. Thank you so much for sharing this with us today and Gary, Jack…

Dr. William Matsui – Great! Thank you.

Priya Menon – Yeah. Gary, Jack, and Matt, thank you so much for your participation. The transcript and the recorded talk will be made available on CureTalks' website. Please visit curetalks.com for details of our upcoming talks. Thank you very much.

Gary Petersen – Thank you. Thank you very much.

Matt Goldman – Thank you.

Dr. William Matsui – Thank you.

Gary Petersen – Excellent!

Jack Aiello- Thank you.

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