

Dr. Stuart Seropian, What is a Stem Cell Transplantation? January 6 , 2008
Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center, and Dr. Miller specializes in pain and palliative care. If you would like to join the discussion you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening, Dr. Chu and Dr. Miller are joined by Dr. Stuart Seropian, Associate Professor of Medical Oncology and an integral member of the Yale Cancer Center Leukemia, Lymphoma, and Myeloma Program. Dr. Seropian's clinical and research interests are in the area of stem cell transplantation. Miller Let us start off by talking about the basics of what a stem cell transplant and bone marrow transplant are. Seropian A stem cell transplant, which now a days I think is the preferred term, is a procedure where we use stem cells, either from the blood or from the bone marrow, in support of chemotherapy, often in high doses, to treat certain cancers; mostly hematologic malignancies or cancers of the blood marrow or lymph system. Miller There is a lot of controversy about stem cells, are these the same stem cells we're talking about? Seropian No, and that is an important point to emphasize. We are talking about stem cells that are more grown up than the embryonic stem cells that you hear about a lot in the news. These are cells that make blood. They make the cells that are part of the immune system. They are not the kind of cells that there is controversy about. These cells have been used for more than 20 years to support patients who have cancer. Chu Where do these cells come from specifically? Seropian A lot of people are familiar with the term bone marrow transplant, which had its origins in the late 1960s, early 1970s. Things have evolved to the point where a lot of the cells that we used to get out of the bone marrow for this procedure, can now be taken out of the blood stream. It is more common to get these cells out of the blood stream now, but many of them originate in bone marrow. Chu The original perception of bone marrow transplantation was that it would be painful to get cells out of the bone marrow, but with the new technology, there really is no pain involved. Seropian It is easier to get the type of cells we need out of the blood stream than out of the bone marrow, so the experience for donors, if we are doing a transplant from a brother or sister for instance to the patient, is easier than it used to be. The methods are different. There are sometimes side effects from the treatments, but donors do not have to go to the operating room and have multiple bone marrow aspirates under general or spinal anesthesia anymore. 3:02 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jan-06-08.mp3 Miller If someone is considering being a donor, there are donor drives throughout the state and elsewhere. What is involved, do you have to give blood or have a physical exam if you want to consider being a donor? Seropian Before we launch into that let's get into a little background about the different kinds of transplants. There are transplants where there are donors involved and then there are also transplants where the patient is donating stem cells to themselves. For example, a patient with the disease multiple myeloma, we have known for a long time that higher doses of chemotherapy can be

more effective in treating this disease, but there are limits to the doses of chemotherapy we can administer because the blood counts drop and take a long time to recover. We can harvest the patient's own stem cells out of the blood stream and freeze them, then give the high doses of chemotherapy and return their stem cells to the body. Their blood counts will get better in 9 or 10 days, whereas without those stem cells, without that support, it might take 3 weeks or even longer; which would be quite dangerous. This is called an autologous transplant. It is really just a safer way to give a more effective dose of chemotherapy to patients with less side effects, discomfort or risk to the patient. An autologous transplant is a very commonly performed procedure where the patient is donating to themselves. In follow-up to that, is there ever any concern that there may be minimal numbers of tumor cells that are in that collection of cells? Seropian Sure, in fact, that is one of the factors when deciding what kind of transplant to perform. We might switch to a different donor than the patient. For a patient who has a disease like leukemia, which is a disease of the blood and the bone marrow, that is a major concern. It is one of the original reasons why the other kind of transplant, allogeneic transplant, became popular. Allogeneic transplant is where we take a brother or sister's stem cells and use them to support the procedure. If we are using a patient's own stem cells to support a transplant there are ways to check and see if they are contaminating tumor cells in the graft. The best way to know is the remission status of the patient. In other words, if a patient receives chemotherapy, has a good response and goes into remission, then we know that we have reduced the burden of cancer in the body and when we collect the stem cells we know there are not going to be a lot of tumor cells in there. For a disease like myeloma, with the understanding that sometimes there are tumor cells still in there, giving a higher dose of chemotherapy benefits the patient. Miller Let's stick to the autologous transplant, how difficult a process is it for a patient? Seropian There are potential side effects and risks that are possible with the patient's high-dose chemotherapy, which is really the purpose of using a patient's own stem cells. It is a supportive way of giving high-dose chemotherapy. When we used to use bone marrow for that purpose, which in the autologous setting does not appear to work as well as using the stem cells out of the blood stream, patients had to undergo the procedure in the hospital and it could take 2 weeks or longer for the blood counts to get better, so patients would get quite ill. High-dose chemotherapy can irritate the lining of the mouth and the bowels, people lose their appetite when the blood counts are low, and get fevers and infections. Miller Have you been able to do this procedure, autologous transplant, without a patient having to be admitted? Seropian With peripheral blood stem cells, which are the grafts that are used for autologous transplant, at Yale, we do not admit people to the hospital unless they have a problem such as a fever, or if they are not feeling well after a transplant. In that case we will put them in the hospital quickly, but this is an outpatient procedure at our institution and in many institutions now. With the antibiotics we have and the supportive care and the rapidity

with which the blood counts get better using the patient's own blood stem cells, there is not a clear reason why people have this procedure in the hospital. Chu That is a very important point that you just raised Stuart. We've certainly gotten a lot better in terms of the supportive care of patients who undergo intense chemotherapy and autologous transplants. Seropian We have much better antibiotics to prevent viral infections, bacterial infections and fungal infections. We have drug growth factors like Neupogen, or filgrastim, a medicine that helps to speed up the recovery of the blood counts after transplant, which can make a big difference of 3 or 4 days in terms of the patient's white blood cell count recovering after this kind of procedure. It helps patients feel better more quickly, and it prevents a lot of our patients from needing to be admitted to the hospital. Right now, after an autologous transplant, probably about half of the patients will end up being admitted to the hospital at some point, but half of them are seen in our outpatient clinic where they get fluids and antibiotics. It is fair to say that most patients prefer not to be in the hospital for a long period of time if they can avoid it. Chu When do you typically recommend an autologous transplant to a patient? Seropian There are pretty well agreed upon criteria for performing autologous transplant, and I should emphasize that these procedures in general are for patients who have cancers of the lymph nodes, blood, and the bone marrow. Diseases like multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's disease and testicular cancers are examples. These are diseases that respond well to chemotherapy. For patients who go into remission where we know there is very high risk of relapse at some point in the future, transplantation can help to either keep the patients in remission longer, or sometimes cure them. Multiple myeloma is an illness where there are a lot of good drugs to get people into remission. There are not standard therapies that cure patients of myeloma. Transplantation is often performed in first remission and has the benefit of keeping people in remission for a longer period of time where they don't have to take chemotherapy or other medicines. Non-Hodgkin's lymphoma is cured sometimes with standard therapy, but 40% to 50% of patients will have a relapse and many of those patients are cured if they have a transplant in a second remission. That is a typical indication for an autologous stem cell transplant. Miller It sounds like for some patients it is a curative form of therapy and for others it at least helps give them a longer remission. Seropian That is right, and because the side effects and the risks of autologous transplant have been reduced greatly over the last 10-15 years, we are more likely to consider performing that procedure for patients. We like to do this procedure when we are trying to cure a patient, but if we know we can transplant a patient, and they will be off therapy for 1 year or 2 years because of the transplant procedure, which is a 4- to 6-week commitment, then that is often the best thing for the patient. Miller We would like to remind you to e-mail your questions to canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more information about stem cell transplantation with Dr. Stuart Seropian from the Yale Cancer Center. Miller Welcome back to Yale Cancer Center Answers. This Dr. Ken

Miller, I am here with my co-host Dr. Ed Chu and Dr. Stuart Seropian who is an expert in stem cell transplantation at the Yale Cancer Center. Chu Before the break we were talking about autologous transplants. Maybe we can turn to the other transplant known as allogeneic stem cell transplantation. Can you give our listeners a brief description of what that involves? Seropian The same principal applies to allogeneic transplant as the autologous transplant; we use 13:32 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jan-06-08.mp3 stem cells to support the administration of chemotherapy. However, there are a lot of differences. An allogeneic transplant is performed using a donor other than the patient, ideally a brother or a sister who is matched for the genes. Sometimes, the donor is an unrelated person and the cells are obtained with the help of the National Marrow Donor Program. This is a different kind of transplant in that we are treating malignancy in part by giving chemotherapy, but also by replacing the patient's blood in the immune system with somebody else's. In contrast to the autologous transplant, we're after the benefits of getting a new immune system in some cases, so it may be a more powerful therapy, but because we are replacing the patient's immune system, this is a more complicated procedure. Chu For other diseases in organ transplantation we always hear concerns about long waiting lists and waiting times for someone to actually find a potential donor, is that the same for bone marrow transplantation, stem cell transplantation? Seropian It is a little different. When we are looking for a donor for an allogeneic transplant, it is within the family, the brothers and sisters typically are the eligible donors. It is quite rare for a child or a parent of the patient to be a donor. It is not entirely unheard of, but the genetics of the HLA genes, which are the genes that are important, predict that typically it is only going to be a brother or sister who is matched. If a brother or sister is matched, then transplant often can be performed very quickly. When we need to find a donor who is unrelated, we search through the National Marrow Donor Program which can take longer. It typically takes somewhere in the order of three months to secure a donor, but the National Marrow Donor Program actually has made some advances in the way the typing is performed. There are patients in the registry where sometimes we can get grafts as quickly as 6 to 8 weeks. Chu What is the importance of looking at the underlying genetics in the HLA haplotypes? Seropian In order to perform an allogeneic transplant we have to have a donor who matches either 100% or 90% of the genes that we know are predictive of success with the transplant. Patients often want to type a lot of their friends or cousins, but genes are much more complex in comparison to the ABO blood system. You don't need to be matched for your blood type with the donor, because you are not going to acquire the donor's blood type, but you really have to be matched for these genes. Our requirement is that the patient and the donor be matched for 9/10 genes that we test for, otherwise the risks of transplant are really quite high. Miller What is the role of the donor's immune system in trying to prevent the disease from coming back? Seropian As I mentioned that is one of the things we try and take advantage of. It is a little different depending on the disease that we are forming a transplant to try and eradicate. Chronic myelogenous

leukemia, for example, which is an illness where transplant has17:15into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jan-06-08.mp3 been performed for many years, less commonly now because of other new therapies, is a disease where it has been well demonstrated that the major manner in which patients are cured is by donor lymphocytes killing the leukemic cells in the patient. We call that a graft versus tumor, or graft versus leukemia, effect. We know that the immune systems between the patient and a donor, unless we have an identical twin, are not really identical. We hope they are minor differences because we don't want to have complications if the donor's immune cells react badly to the patient. Those differences probably account for donor cells recognizing leukemic cells in the body and killing them in many instances. This is a very strong effect for patients who have chronic myelogenous leukemia, but we think that this effect is there for other leukemias and for lymphomas. When we are trying to decide what kind of transplant to perform, we take into account a number of things. One of them is whether or not a patient's own stem cells could be contaminated with tumor cells. If a patient has a cancer that is not in a good remission, and giving them a high-dose of chemotherapy is not going to do the trick, we look for the extra benefit of the donor's immune system trying to eradicate the tumor cells.Chu What are the types of diseases that you consider for allogeneic transplant?Seropian Similar hematologic malignancies, more in the way of acute leukemia's. This is where we would tend to perform an allogeneic transplant as opposed to an autologous transplant, in part because we think there is more benefit to this graft versus tumor effect and also because those diseases originate in the bone marrow. It is harder to eradicate tumor cells from a graft if we were to use the patient's own cells to try and support a transplant procedure. So similar diseases, mainly hematologic malignancies.Chu So you would really never think about using this for colon cancer, lung cancer or breast cancer? That is a common question that I get.Seropian No you wouldn't. It is not a standard therapy because the graft versus tumor effect has been demonstrated in the hematologic malignancies. There are transplant programs that have done research asking the question; could this graft versus tumor effect apply to solid tumors? In fact, there is some evidence in certain diseases that this can occur. Renal cell cancer is the solid tumor where there is the most evidence of that. There are patients who have had this kind of transplant with renal cell cancer and have gone into remission and clearly it was the donor cells that did the trick. So, there is research being done for renal cell cancer and for breast cancer. There has been some research for ovarian cancer as well, but in terms of the solid tumors it is still in its infancy. We have not figured out how to apply allogeneic transplant to those diseases effectively.Miller We have an e-mail question from George who lives in Stamford. He asks, "I am 68 years old and have chronic myelogenous leukemia. My doctors have talked about a transplant. Am I too old to get a transplant?Seropian That is a good question. If you go back 10 or 15 years, the answer would have been yes.20:54into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jan-06-08.mp3 The age cut-off in some centers used to be 55 years of age, at others, 60 years of age.

That has changed now. In fact, the oldest patient that we have transplanted in our program with an allogeneic transplant was 72. He is 76 now and doing well. The reason this changed is because of our recognition of this graft versus tumor effect that goes along with allogeneic transplant. Once that was recognized, we took a step back and said, well if the graft can do a lot of the work, do we have to give the high doses of chemotherapy in the very beginning prior to giving the donor cells? The answer to that question is no, we don't have to do that. There are occasions where chemotherapy really is very important, but for older patients, where that may be too risky, there are some newer chemotherapy drugs and other medicines that allow us to perform the procedure and give them donor cells that will not be rejected. This is because we know a little more about matching patients with donors and which chemotherapy drugs are good at suppressing the patient's immune system so they don't reject the cell. With a gentler treatment that is safe, we can get a graft from a brother, sister or unrelated donor into a patient even if they are older, and then hope for a graft versus tumor effect. Particularly for a patient with CML, if they are not doing well despite all the wonderful new drugs for that disease, we would consider it. Certainly other medical issues apply to all patients that need to be investigated, but just on the basis of age, no. Chu We are obviously quite proud of the fact that the Yale Cancer Center is the only accredited center here in the state of Connecticut that is performing allogeneic stem cell transplantation. Maybe you could tell our listeners how were we able to get that accreditation designation. How many transplants are being done and what research are you folks doing in the transplant center? Seropian The current version of the transplant program at Yale has been around since the mid 1990s. We perform over 100 transplants a year. A little more than half of them are autologous transplant type, the rest are allogeneic transplants. We are accredited by FACT (Federation for the Accreditation of stem cell therapy, or Cell Therapy. This is a national organization that inspects transplant programs and makes sure they are following the standard safe policies and procedures from top to bottom in terms of the way we collect cells, the way we administer our therapies, the areas where our patients are taken care of and the laboratory techniques. It is a pretty rigorous inspection that happens every 3 or 4 years. We were accredited initially in 2003, and just got reaccredited recently. Miller In terms of research, what are some of the things that are interesting that you are working on now? Seropian In terms of allogeneic stem cell transplant, I mentioned the benefits of that type of procedure, graft versus tumor effects, but we did not touch much on the potential side effects or risks yet. The benefits of getting a new immune system from a donor, we hope, translate into a better outcome in terms of curing cancer, but there is also the possibility that the donor's immune cells will recognize the patient's tissues as different, and there can be reactions there, that is what graft versus host disease is. Graft versus host disease 25:16 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jan-06-08.mp3 is an illness that can occur after an allogenic transplant. Going back to how we decide what kind of transplant we might perform for a patient, we have to keep

in mind the risks and side effects of both procedures. The extra benefits we might get from an allogenic transplant can be offset by higher risks of graft versus host disease which is the most important complication when we consider those factors. This is an illness that can cause a rash, it could be relatively minor and treated readily, but it can also affect the bowels and liver. A lot of our research is directed at trying to reduce those complications. Miller If a patient or their family wants to learn more about bone marrow transplant, how do they contact the transplant program? Seropian They can get information on the Yale Cancer Center website, yalecancercenter.org, or they can call 1-866-Yale Cancer, which is the direct number to the cancer center. Miller Terrific. Stuart, I want to thank you very-very much for joining us. Chu This has been great, we look forward to having you on a future session to hear more about transplantation. Until next week, this is Dr. Ed Chu and Dr. Ken Miller from the Yale Cancer Center wishing you a safe and healthy week. If you have questions, comments, or would like to subscribe to our podcast, go to yalecancercenter.org, where you will also find transcripts of past broadcasts in written form. Next week, we will examine supportive care options for cancer patients.