

Dr. Richard Edelson, Using Immunotherapy to Treat Cancer December 19, 2010 Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. I am Bruce Barber. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening, Francine and Lynn are pleased to welcome Dr. Richard Edelson. Dr. Edelson is Aaron and Marguerite Lerner Professor of Dermatology and Chair and Professor of the Department of Dermatology at Yale School of Medicine. Here is Francine Foss. Foss Since we are talking about immunotherapy, let us start off by defining immunotherapy for the audience. Edelson Immunotherapy is really one of those relatively few aptly named terms. It actually involves manipulation of the immune system to the benefit of patients. It can be an important tool in the defense against cancer, even in the prevention of cancer, but it can also be a valuable tool when the immune system is an enemy in autoimmunity. Foss Your interest in immunotherapy dates way back and the first disease that you addressed with immunotherapy was a disease called cutaneous T-cell lymphoma. Could you take us back and tell us how this all got started? Edelson Thank you for saying that it goes way, way back, but it does, and it goes back to the time when very early in my career I was at the National Cancer Institute and it was the year that human T-cells, the cells that are at the actual center of immune responses, were first identified. So it first became possible, all the way back as you say in 1972, to apply the new principles of immune cell recognition and demonstrate that the first malignancy of white blood cells shown to be a malignancy of T-cells, was cutaneous T-cell lymphoma, which was named cutaneous because it involves the skin, and because the cells that are malignant are T-cells. Foss It really is interesting when you think about it that we really did not understand much about immunology until the 1970s when the T-cell was identified and that so much has happened since that time. Edelson Right, if you take cutaneous T-cell lymphoma, here was a disease which was a malignancy starting as all malignancies do, from a normal counterpart cell. So a single normal T-cell, which has a propensity to circulate from the blood to the skin and back, becomes malignant and many, many copies of that cell wind up amplifying the localization patterns of the cell. So a cell that normally helps defend against infections in the skin, for example, when it becomes malignant, shows up as tumors in the skin. Wilson Tell our listeners a little bit about the thought process you had in the development of photopheresis and what photopheresis is and what was happening during this exciting time. 3:48 into mp3 file <http://yalecancercenter.org/podcast/dec1910-cancer-answers-edelson.mp3> Edelson Photopheresis was introduced by our group when I was still at Columbia University School of Medicine in 1982, and first became FDA approved as a therapy for cutaneous T-cell lymphoma in 1988. I am happy to say we were on our toes because it certainly was not discovered on purpose and I would actually make the point that relatively few

really important therapies are discovered on purpose, but the idea behind photopheresis at the beginning was not as immunotherapy but as what we thought was neat at the time, maybe trivial in retrospect, a chemotherapeutic drug that could be turned on by a light switch and only have its activity exactly where the light and the drug came together. The goal was to be palliative, not curative but help patients decrease severe symptomatology. In the absence of systemic side effects, the very first patients with a leukemic form of the disease, which is really devastating, had not responded to conventional chemotherapy and had total skin infiltration. Your listeners can imagine what that would be like of these malignant cells. As well as the malignant cells in the blood, we treated only 2% of the patient's malignant cells by passing the blood through an apparatus to see that it was safe, and the goal was, if we could show that those cells could be safely returned and then removed by the filtration in the body, the liver, spleen, lymph nodes, then we would go ahead and treat the patient more frequently and simply try to decrease the number of cells by removing them faster than they were being made. The astonishing thing was that by treating such a small percentage of the cells and returning them, the other cells disappeared. So it was clear, all the way back in the first patient, that somehow, mysteriously, this was fortuitously causing an immune reaction that was treating the rest of the disease and one could argue that we're not that good because it took from 1982 all the way until 2010, 28 years, to gain a handle on many of the clues which I must say, came from my two interviewers, Lynn Wilson and Francine Foss, but we have got a pretty good handle on this now. Wilson Can you elaborate on that a little bit for our listeners, and some of the mechanisms or the understanding of how this works in terms the listeners could understand? Edelson The drug that was used, and is used, has a name that is abbreviated to 8-MOP, because we do not even have to bother your listeners with the real long name. That drug is actually a naturally occurring substance found in small quantities in figs, lime, and in larger quantities in the root of a weed that grows in most of our backyards called Queen Anne's lace. It does nothing by itself, but if you take it, as dermatologists have known for a long time, by mouth, although it's excreted without any activity, any effect in 24 hours, if you shine light on any tissue that temporarily have it in it, which is usually two hours after a person has ingested the drug, this inactive drug gets instantaneously converted to a very potent chemotherapeutic agent which binds in an active H-DNA. So the mechanism, as we fast forward, does relate to the original suggestion that it is such a finely tunable drug because it only is active where the light and the drug come together for literally a millionth of a second, but what actually happens is something very surprising, which is why it was not discovered on purpose. As the blood is passed from one arm vein through a machine where the light is shined on the blood, as we had always planned, before it is returned to another arm vein, a very abundant protein in the blood, generally involved in blood clotting, fibrinogen, sticks to the plastic in the ultraviolet exposure system and within seconds completely coats that plastic surface. So the cells that are passed through that surface including the leukemic cells and

edelson.mp3 cutaneous T-cell lymphoma, never actually encounter the plastic surface. Those that are closest to the surface encounter the platelets, also typically involved in clotting, which have stuck to the fibrinogen just as they do in clotting, and now a white blood cell called a monocyte which was also not the cell we were targeting at first, but a so-called antigen-presenting cell but not that good an antigen-presenting cell in the form that it circulates in the blood as a monocyte, now sticks and unsticks and literally jumps from platelet to platelet on that plate, and it is that interaction with the platelets, probably just as happens in wound healing and in sites of inflammation, converts these monocytes to dendritic cells within a single day and those dendritic cells, named because of their shape, normally are only one-tenth of 1% of the circulating white blood cells, but 70% of the monocytes that pass through this apparatus within one day become dendritic cells, which are the most potent trigger of immune reaction. So to very briefly summarize that, this treatment has had its impact on the immune system because all these years, secretly, by mechanisms that had not been recognized before, this treatment is converting monocytes into dendritic cells that stimulate immune reactions, probably because that is the way it really happens. Foss You recently published this in the highest-tier journal in the field of hematologic malignancies, the journal *Blood*, and this paper elucidates this mechanism that you described to us. Can you talk a little bit about the impact of those findings, particularly with respect to the fact that there are other ways to view these antigen-presenting cells and to prepare these antigen-presenting cells, and there are other immunotherapies out there? Can you talk a little bit about the impact of your findings in this paper? Edelson One of the really puzzling and even disappointing features of immunotherapy for cancer, which has always had so much promise because it is really such a powerful intricate system, and we know that the immune system, even as we speak is protecting us against cancers we will never see. We know that people that get immunosuppressed as part of an organ transplant have a much higher incidence particularly of cancers of the skin. They presumably are normally being destroyed before they ever get to that point of being clinically evident. So the question has always been, why can't immunotherapy in the face of clinical cancer do just as well? It does often induce clinical responses, but they have been generally disappointing. Then why would a treatment that was not even designed as an immunotherapy turn out to have such a good record? Part of it is that the immune system is incredibly complicated and in a way, certainly we in our own group fall prey to this, we tend to think that we can create immunologic responses because we are smart enough to do that. Well, we are generally not, and we learn from experiences like this. So the answer to your question in a very succinct way is that the way the dendritic cells have been manufactured, which has been a great advance pioneered largely originally from Rockefeller University, were breakthroughs, but if you look closely at them, that is not the way the body could possibly ever do it. The amounts of growth factors that are used over a full week to induce the conversion is a thousand fold what is normally present in the body. So the question will be, since we fell into this by actually, probably co-opting of the way it may normally happen in one day without any added growth factors,

maybe now one can take that knowledge and try to use it in other kinds of cancer.13:59 into mp3 file <http://yalecancercenter.org/podcast/dec1910-cancer-answers-edelson.mp3>Wilson

Rick, this is really a fascinating story. We are going to take a short break for a medical minute. Please stay tuned to learn more information about immunotherapy with Dr. Richard Edelson. Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my co-host Dr. Francine Foss. Today we are joined by Dr. Richard Edelson and we are discussing photopheresis and immunotherapy. Rick, this is a fascinating story that you were obviously spearheading during the majority of your career, and we do a lot of photopheresis at Yale. Is this done at other centers, and how commonly is this done around the world? The second part of the question is, could you discuss what other malignancies or other clinical problems that you think this treatment could be applicable to?Edelson Lynn, photopheresis, which really was started here, was used for the first time at Yale Cancer Center. So it is a Yale home-grown therapy on the basis of clinical responses and an excellent safety profile. In fact, I am not aware of a single patient who had to stop the treatment after responding because of side effects. The issue originally was, how do you explain how this treatment works? But here we fast forward again to 2010, the treatment is used throughout Europe and the United States, and it has become the most widely used cellular immunotherapy, even though the mechanism has only just now become elucidated. It is widely used and the question about what other cancers it could be used for begins to become a very interesting question, because now that we know that this simple treatment which a patient receives over a two-hour period as an outpatient procedure lying comfortably on a blood drawing type of couch, even watching television, is something that might be applicable to other kinds of cancers, solid tumors, that cannot be cured surgically. The key to the way photopheresis works in T-cell lymphoma is that the drug that we mentioned damages in the blood stream, the malignant cells, and essentially feeds them to the new immunogenic dendritic cells that we talked about. So the dendritic cells loaded with digested parts or antigens that are distinctive of the malignant T-cells, go back into the body as essentially a cellular vaccine. Well, if that is the actual way that this is happening as it appears, then other kinds of cancers become susceptible, at least in concept. If you can get your hands18:06 into mp3 file <http://yalecancercenter.org/podcast/dec1910-cancer-answers-edelson.mp3>

surgically, for example, on a lung cancer or a breast cancer, if that cancer is capable of stimulating an immune reaction at all, then those cells could be damaged in a different way, and then incubated or placed together over night with the new dendritic cells, which then can perhaps become a vaccine for those cells in that cancer. In collaboration with Dr. Foss, and Thomas Rutherford in gynecologic oncology and his close colleague Dr. Gil Mor, and several people in our group, one of the first cancers that we will try to treat that way is ovarian cancer, because there is a cancer that is quite severe often in an initial diagnosis because it is already advanced, and in those cases, we will try to immunize those patients against a cancer. I emphasize that these kinds of studies are very preliminary. In fact, that study has not even yet be-

gun.Foss We are talking about these antigen-loaded dendritic cells stimulating an immune response against the tumor, is that what normally happens in a cancer patient, is that recapitulating, say, a normal process in the patient?Edelson It is very tough to know and it would be very nice if that is the case, but by the time we actually diagnose a cancer, if the immune system had originally slowed its progression or prevented cases like it, by the time we see that cancer, the immune system has already been overrun. So what really is confronting the clinician who was attempting to then turn the immune system back on, is that you are really trying to get the horses back into the barn, and you are running in reverse.Foss Do you think that these kinds of immunotherapies that we are talking about would be most useful for patients, say after they have received their chemotherapy and their disease is at a minimal level, or perhaps early on in the course of their disease?Edelson What you want to do, of course, if you are going to marshal the strength of the immune system to fight cancer is you also have to have an immune system that is fully functional. So chemotherapy, and the certain kinds of chemotherapy that you both know better than I, can suppress the immune system. So you would not want to use a treatment like this in a patient whose immune system could not respond, but a lot of the other more biologic modern therapies that both of you have pioneered do not involve suppression of the immune system. For example, a great way to limit the number of malignant cells it would need to be attacked by an immune system that you turn back on, would be the kind of radiotherapy that Lynn Wilson does, because by and large it does not suppress the immune reactions, and several other treatments that you developed also circumvent suppression of the immune system. I would favor those in association with this treatment as opposed to conventional therapies.Wilson Rick, you had mentioned that photopheresis is very safe for patients and that you have not been aware of even one patient who has had to discontinue therapy assuming they are responding because of toxicity, could you just briefly describe for our listeners what is involved? You had mentioned lying down on a comfortable blood-drawing couch, venous access, what are the side effects of the treatment, if there indeed are any, because I agree it is very well tolerated.22:08 into mp3 file <http://yalecancercenter.org/podcast/dec1910-cancer-answers-edelson.mp3>Edelson The side effects of the treatment involve the same kind of side effects that blood drawing itself for a blood donor might have. If you donate a unit of blood, most people can tolerate that very well. That is approximately the amount of blood which is outside the body at any given time being processed through the apparatus and then returned to the patient, but some people with low blood volumes or with cardiac insufficiency might have some difficulty because of temporary volume depletion, so their blood pressure might drop, and that would be reversed quickly by attentive nurses and the overseeing physicians, by then returning that blood. The other kinds of reactions that can occur can be in a circumstance where the treatment actually is working too fast, where the photoactivatable drug is injuring the cells that are particularly susceptible to it, a little too fast so that over the first few hours when the blood goes back, a lot of the cells, a lot of the malignant cells, might be dying and releasing their products. These are not very dangerous,

typically, but one has to be on their toes. Wilson Patients get this treatment as an outpatient, is that correct, and they go home? Edelson That is right. Wilson Do they have to have precautions when they leave your center in terms of exposure to light or anything else that could happen to them when they walk outside? Edelson There is one very important thing, and that is as the blood passes through the machine, it is important that it not clot in the machine. We certainly have many protections against it that eliminate the possibility of accidentally returning a clot so that does not happen, but these patients have to have their blood thinned with a drug called heparin. That drug does not wear off for a few hours after they leave. We highly advise individuals who leave not to have an automobile accident. Foss Rick, can we go back to talk a little bit about this new technique that you are developing to take photopheresis to the next step, which is to try to introduce tumor cells to these antigen-presenting cells that have gone through the machine. Are there some new ways that you are developing now in collaboration with other areas, or expertise, at Yale that would help us to better deliver those tumor cells to these antigen-presenting cells? Edelson These are areas of very active investigation. One area, for example, as Lynn Wilson and other colleagues and I have discussed over a number of years, is in areas like the lung. One could radiate and damage, not necessarily in a curative way, classical, non-small cell lung cancer, and then introduce these new dendritic cells intravenously where they then pass directly, with a very simple introduction the same way we always do, back to the right side of the heart which pumps blood through the lung and to the lung. That was a very attractive way of getting these new dendritic cells directly to the site of damaged malignant cells, and hoping that that encounter could accomplish the goal of immunizing the patients. In other kinds of solid tumors, there are a number of different approaches that can be taken, building on the scientific advances. For example, one of 26:03 into mp3 file <http://yalecancercenter.org/podcast/dec1910-cancer-answers-edelson.mp3> the most interesting and intriguing to us is, in fact, as you know, one of the approaches that we are planning to take in ovarian cancer for the first time, and that is to do a single photopheresis treatment, hold on to the new dendritic cells that come out, and there are actually typically now up to 500,000,000 of them, and freeze them, in a way, in small test tubes, aliquots of only 10,000,000 each. So, 500,000,000 would lead to 50 different aliquots that could be frozen and saved, and instead of giving the cells back to the patient after adding the ovarian cancer antigens, have 50 different vials of such cells and immunize them by injecting it into their skin. So one could boost the immunity in an oncologist's office, for example, and even tell whether the patient has truly been immunized against a cancer by whether they develop a little bump at that site, just like a tuberculin reaction. So these are the kinds of exciting new advances, and time will tell. Foss Basically, all of these techniques involve a patient's own tumor cells being introduced to the antigen-presenting cells, and that is a little bit different than say some of the other vaccine strategies out there where they are using proteins like Mac-1, for instance, which is a protein expressed on a number of tumors for many different patients and trying to immunize a patient against that. In this case, you are immunizing

a patient against their own tumor cells. Edelson That is right. This is an ultimate example of personalized therapy but it is also important to emphasize that we are always dealing, as physicians, with practical considerations. So there are so-called markers or antigens that can stimulate immune reactions against the tumor type in general, like a melanoma, like ovarian cancer, but the most important antigens may be the ones that are very unique to that person's malignant cells, and you cannot have a preparation that is put into a bottle for every single patient that really knows and identifies each patient's individual array of antigens, but the immune system and their own dendritic cells can do that sorting for you if you give them, as a source, the malignant cells. So, what you say is exactly correct Francine, and that is that the attraction of this treatment is that it is so unique and so simple to apply to the individual patient. Dr. Richard Edelson is Aaron and Marguerite Lerner Professor of Dermatology and Professor and Chair of the Department of Dermatology at Yale School of Medicine. If you have questions or would like to share your comments, visit YaleCancerCenter.org, where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.