

Dr. Richard Edelson, Using your Body's Immune System to Fight Cancer July 26, 2009 Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. 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 Ed and Francine welcome Dr. Richard Edelson. Dr. Edelson is the Chairman and Aaron B. and Marguerite Lerner Professor of Dermatology. He is also an internationally known expert in the treatment of cutaneous T-cell lymphomas using immunotherapy. Chu Tell us a little bit about what got you interested in focusing on this disease of cutaneous T-cell lymphoma and focusing on developing immunotherapies? Edelson Thanks Ed. From all the way back in my days as a medical student at Yale, then as a fellow at the National Institutes of Health, and National Cancer Institute, and then as a faculty member at Columbia and then Yale, the common theme has been a fascination with the possibility of using the immune system to understand, diagnose, and treat cancer. Cutaneous T-cell lymphoma was an extremely good model for that and a very important disease and dangerous disease in its own right. Foss I remember back from the National Cancer Institute days that many of us were focusing on attacking the tumor cells and thinking about ways to kill the tumor cells, but we forgot about the other part of the system, which are the normal immune cells and how they play a role in cancer. Can you explain for our listeners a little bit about what the normal immune system does and how it impacts on cancer? Edelson Thank you Francine, because that's a great lead in to frame the entire story. The immune system is a wonderfully intricate, complicated, and well organized, and I say organized much better than we even appreciate, system that helps us fight infection, defend ourselves against all sorts of noxious or dangerous external agents and internal agents including the distinctively bad cancer cells. So the real challenge has been to try to understand how the many millions of different clones of T-cells at the core of the immune system do their job, and they basically are as complicated as the neurons in the brain, but even more complicated because they float around looking for the enemy. Chu One concept that we were brought up with is that cancer may in part arise from a dysfunction or defective immune surveillance system. How do you bring that concept within the concept of trying to harness the immune system to attack the tumor? Edelson We now understand that while the three of us are sitting here and talking, and while the folks 3:23 into mp3 file <http://yalecancercenter.org/podcast/july2609-immune-system-fight-cancer.mp3> are listening, our immune systems are silently and very efficiently defending ourselves, all of us, against incipient cancers that are too small for us to ever diagnose. One of the great examples is in the easily examined skin, where we know now, because of perhaps 60 years of experience from immunosuppression following organ transplant, particularly kidney, that a high percentage, in fact the majority of those patients who have had long-term immunosuppression to prevent the rejection of an organ transplanted from a dif-

ferent person, developed enormous numbers of those skin cancers such as basal and squamous cell carcinomas that normally occur from sun exposure or other exposure, but these people, because their immune system was not able to rid them of those incipient cancers, can be loaded and they are particularly dangerous in those individuals. Foss Rick, can you clarify for our listeners, we are talking about immune surveillance and the immune system and there are different kinds of cells out there, T-cells and the B-cells, and other so called antigen-presenting cells, can you just explain a little bit about how those different populations of cells interact? Edelson There are three broad categories of cells at the center of the immune system. The center of an immune system is intended to pick needles out of haystacks and destroy them if they are undesirable. There are the T-cells, very broadly, and there are millions of different sub-clones, or types, of each one of these, but we are just talking in generalities right now. The T- cells are at the core of directing the immune system as so called effector cells or the cells that make things happen. The B-cells are the ones that produce antibody, ultimately. The T- cells can directly kill cancer cells if they are specifically targeted to a particular chemical in the cancer cells that distinguish them. But the cells that are the ignition of the immune system, like the ignition in your car, are the dendritic antigen-presenting cells. An antigen is just a term that refers to those distinctive molecules that the immune system is geared to attack. So, the antigen-presenting cells are ones that take in, process, and present the distinctive chemicals, the targets, that the immune system then becomes directed to attack. That can be parts of proteins that are very distinctive that separate cancer cells in general from normal counterparts, and in fact, in each patient, a cancer apparently many have, probably has, patient specific tumor antigens, or license plates. Foss So these dendritic cells also are very important, can you tell us where we find these in the body? Edelson You find them acting in lymph nodes, which are the hubs where immune cells interact. It is part of the draining system called the lymphatic draining system, and direct contact with the blood and cells circulate or percolate through the tissues where most of the action needs to be. That's where you really need the immune active cells if they are going to do their task of 7:10 into mp3 file <http://yalecancercenter.org/podcast/july2609-immune-system-fight-cancer.mp3> destroying cancer cells or defending against bacteria and the like. They circulate through the blood to get to their site. In the case of antigen presenting cells, largely as a population called monocytes, we didn't mention them before, but approximately 20% of a normal person's white blood cells are in the form of monocytes. When they get into the tissues and get the right signals, they can become antigen-presenting cells, the ignitions of the immune system. Chu Are there ways, strategies, in which one can activate or induce the number of these dendritic cells to fight off, in our case, to fight off the tumors? Edelson Ed and Francine are leading me to the key question, and that is, how do you get an immune system that has been overrun by a cancer, and you wouldn't have identified the cancer because by the time we can recognize that the patient has a cancer, the cancer or the cancerous cells have already accumulated to a point where they have evaded the initial immunoprotection, or the sentinel anti-cancer T-cells, B-cells, macrophages, monocytes, and antigen-

presenting cells. So, the real question is, how do you take an antigen-presenting cell, such as the so called key dendritic cell which is normally circulating in the blood as less then one out of the thousand of the white blood cells? That's not really as bad as it sounds because you don't really need them in the blood, you need them to transit the blood the same way I don't really have the capacity to have conversations with people in the next car on the highway. You need to get them to the site where you need them to do their job of kick starting the immune system, and the question that Ed is asking is how does that actually happen, how does a transformation of a trafficking monocyte into that ignition cell, the dendritic cell, happen? That's been a very key question that goes to the core of perhaps why the immune system, as exciting and the number of opportunities it has presented, in large measure hasn't fully realized them. We have to learn how to do it the same way that the body does it and what's happened so far in large measure is to try to find ways to artificially, in laboratory, turn the monocytes into dendritic cells and humans have not gotten nearly as good at this as the body itself. The ways we have collectively approached that has been to take so called chemical factors, factors that make cells mature into one type or another and use literally industrial quantities of those, and we can clobber the monocytes and turn them into dendritic cells with levels of this factor that are really a thousand times what have ever been found in the body. That's not exactly a good trick.Foss I understand that using those kinds of techniques haven't been very successful, so generating those dendritic cells with these growth factors really hasn't been successful thus far, but you have actually pioneered of a novel way of doing this and you have provided tremendous10:57 into mp3 file <http://yalecancercenter.org/podcast/july2609-immune-system-fight-cancer.mp3>insight into perhaps how the body is doing this, could you talk a little bit about your development?Edelson Sure, so one of the things that happens to us as clinician/scientists is that we take a lot of clues from what happens in the actual patient. I tell you how we have had some success, but it really came from careful observation, and I should mention that Dr. Francine Foss, to my right, has been central. These are actually not questions that are pulled out of thin air.Foss Only under the tutelage of the master.Edelson That's very kind, but this malignancy of T-cells, cutaneous T-cell lymphoma, which we now recognize as approximately as common as Hodgkin's disease, not a terribly common disease, but much more common than we have previously recognized, of course it couldn't be identified until we could identify human T-cells in the 70s, which is why it is still a relatively new name. In our efforts to treat patient's who had failed all conventional therapy, it's just a devastating disease in advanced stages, we found out that we had accidentally landed on a way to truly immunize them against their cancer even after their cancer had expanded so much, and the key in a nutshell was this. By using a drug that's naturally existing in nature, actually found in small quantity in lime, figs, even celery root, but does nothing by itself called 8-MOP and is well know in dermatologic circles because it can be activated by the kind of ultraviolet light that passes through window glass and normally doesn't even causes sunburn, to become a very pin pointed chemotherapeutic drug only active where the light and the drug

meet. We found out that if we injured malignant T-cells in the patient's blood by passing it through a very narrow field between two plastic sheets that allows the ultraviolet light to pass, a remarkable thing happened, if you return only 2% of the patient's malignant cells, damaged this way, they now often manifested a response, an immune response, that could go out and attack the other 98%. Foss This sounds really exiting and I cant wait to hear the rest of the story, but we have to take a break now. You are listening to Yale Cancer Center Answers and we are here with Dr. Richard Edelson discussing the use of the immune system to treat cancer. 14:24 into mp3 file <http://yalecancercenter.org/podcast/july2609-immune-system-fight-cancer.mp3> Foss Welcome back to Yale Cancer Center Answers, this is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu, and Dr. Rick Edelson, an expert in the treatment of cutaneous T-cell lymphoma and immunotherapy. So Rick, before the break you were telling us about this discovery that you made to treat cutaneous T-cell lymphoma, which was really the first immunotherapy that was used in cancer, and is called photophoresis. Can you go on with your story and tell us how the development of this has led to the discoveries that we have recently made with respect to the dendritic cell? Edelson The first astonishing clinical result occurred all the way back in 1982, and was reported by an international group that we led in the New England Journal of Medicine in the late 1980s, and as you pointed out, the treatment in 1988 became the first FDA approved immunotherapy for any cancer. What happened was that we of course tried to develop a chemotherapy that would have none of the classical side effects, because it would only be active where the light and drug came together and classical side effects of chemotherapy, such as bone marrow suppression and even immunosuppression, hair loss, and intestinal problems, wouldn't happen, but the big surprise was that when we returned those 2% of the treated cells to the patient in the first test run, thinking that we were just testing safety, the first two patients had a complete clearing of their disease; that only happens in a large a minority of the patients. Perhaps 80% of those patients' immune systems were intact, which was a clue that we were somehow marshaling the power of the immune system. The key then and is has taken all of this time for science to catch up and give the tools it allow this to really be deciphered. Fast-forwarding to 2009, it's become quite an exciting story. First, this treatment has been used more than a million times worldwide driven by the power of the clinical response and the safety of the treatment. It's being used now in the largest number of patients on both sides of the immunologic coin. To turn the immune system on, to treat the cancer, cutaneous T-cell lymphoma, and in work that was pioneered by Dr. Foss, the same treatment, initially in a very puzzling way, and in fact this is now two thirds of the use of the treatment world wide, has been used as a major therapy to reverse an undesirable immune reaction called graft-versus-host disease, which is the major side effect following bone marrow transplant from a person other than oneself or an identical twin. The question has been, what happened? The bottom line is this, and after all of this time it's really only two years old and rapidly evolving and that is when monocytes are passed through the same 18:15 into mp3 file <http://yalecancercenter.org/podcast/july2609-immune->

system-fight-cancer.mp3system outside the body where the light activates the drug, which attacks the malignant T- cells, or the T-cells that can be causing a disease, the monocytes interact with the plastic surface in a way which we now recognize mimics the normal way that monocytes become dendritic cells and tissue and we could not have discovered that except by accident.Chu Is there any way to be able to identify which patients may or may not respond to your photophoresis treatment?Edelson Yes. The patients that respond, and the patient that don't respond, can be segregated largely on the basis of how intact their immune system is. An immune system can be injured of course by chemotherapeutic agents that are being used to treat cancer patients, or by the cancer itself. So, the numbers are rather clear-cut. If you take the patients with cutaneous T-cell lymphoma, whose immune system is not intact, there is almost no chance that this treatment, this immunotherapy photophoresis will work. If you take the patients who represent about 25% of the patients with advance disease, whose immune system is intact, 80% of them will. Clearly the immune system has to be intact.Foss Its sounds to me Rick like we need to start thinking about immunotherapies prior to thinking about chemotherapy, many of us as oncologists instinctively go to chemotherapy, but what we are learning from this certainly is that we need to look at the patient from an immunological point of view and perhaps if there is immunotherapy to be administered, then that should be thought about earlier rather than later.Edelson Exactly, it's a different paradigm because there are certain therapies that are biologically based, particularly a marshaling of the strength and power of the immune system which requires that they be early interventions, in fact they are most effective at a time when the total number of cancer cells is small and the immune system is not injured by prior therapy.Foss What about the application of this to other kinds of cancers? This has been very successful with CTCL, but can you see ways that this kind of strategy might be useful in say solid tumors?Edelson From the very beginning it was clear that something extraordinary was happening biologically, and the biggest question was could the mystery be deciphered, could you figure out how this treatment was becoming such an effective immunotherapy in that cancer, and could you then apply, as you suggest, those principals if you understood them to other cancers including solid tumors? The advantage in cutaneous T-cell lymphoma at the outset is that the malignant cells are circulating the blood where there are accessible to a treatment like this and you can injure those cells and use them as their own kind of vaccine, but how do21:37 into mp3 file <http://yalecancercenter.org/podcast/july2609-immune-system-fight-cancer.mp3> you do that with solid tumors? Now that we know that this treatment converts more than 50% of the blood monocytes into these igniting cells, these dendritic antigen presenting cells, within in a single day in a way that leaves the immune system intact and doesn't involve any major contortions requiring special laboratory activity just the apparatus, the possibility exists that one can begin to use those cells to treat solid tumor. The way that one can do that, at least in concept, and we're beginning to test, is that those malignant cells and cancers such as lung cancer, prostate, breast or colon cancer can be obtained from the surgeon after the tissue is used that has

been removed for diagnosis, you can take those cells and you can treat them so that they are now obtainable in single cell suspension, in saline, or salt water, and then use them in combination, theoretically at least it merits major testing, with these antigen-presenting cells to mimic perhaps what happens in cutaneous T-cell lymphoma.

Foss I understand there has been some very sophisticated work done in your lab in collaboration with other labs at Yale to try to take these tumor lysates and use these nano-particles to help to introduce those antigens into the dendritic cells, could you just talk a little bit about that?

Edelson One of the primary reasons for having a cancer center is the way it brings together so many different experts from different disciplines under the broad umbrella of biology and cancer. We have, together with my two partners here, eight different groups of these experts and every one of those groups has contributed to the story. So, the science that was done involved finding out that five thousand genes out of the slightly more than twenty five thousand in the human genome are involved in a very orchestrated way in this response.

Chu To kind of get back to the use of photophoresis for other cancers, other solid tumors, there is in fact a clinical study at Yale Cancer Center looking at this approach to treat lung cancer, as I understand.

Edelson This is a treatment that was driven over literally 20 years empirically by its successes, and so clinical trails were leading the way and observations that were made from them as we all tried around Yale and around the world to figure out how this was working. A study was initiated, a clinical trial in lung cancer several years ago, but then the science began to truly answer, solve the puzzle, and begin to really open the door. So at the current time, what we are doing is consolidating those scientific gains, and completely revising those studies because we can hopefully do them much-much better and smarter.

Foss We talked about photophoresis as being an available treatment and you said that there have been a million treatments. How available is this for patients and is this now available for solid tumor patients?

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Edelson The first answer is easier and the answer is that it's present throughout the United States and Europe, and virtually all geographic areas are at least represented by one major tertiary care center in that region. In Connecticut, the single place this is done with a lot of expertise is right here at Yale, but one can find it virtually any place in Europe and in the United States. In terms of the question about solid tumors, it's not yet available for that purpose.

Edelson It's always a little embarrassing once a puzzle begins to come together of any type, to admit that it took so long to see it, because this will sound very simple. It turns out that if the components as they appear to be of this treatment success are really simply, number one, slightly damaging the cancer cells so that the immune system cells can recognize them as damaged and allow them to be used. Turning on the monocytes to become dendritic cells and then bringing them together so that together they can form a cellular vaccine, and if takes one day for the damaged cells to really show the damage, and one day for the monocytes to become dendritic cells, it was a simple key. Why not just hold them together for one day in a controlled environment to make it easier for them to come together, rather than squirting them back into the

body and making them find each other, and that's what transimmunization is, it's a simple but major step forward. Chu You have been a pioneer in this whole field of immunotherapy for the past 25 to 30 years, where do you see the field developing, evolving, over the next say 10 to 15 years? Edelson The real quick answer is that right now the level of knowledge about the fundamental ways of how the immune system works has got to such a level that we can do this and a number of other therapies, we can evolve more therapies more rapidly than never before, but it's really a story that's coming together very nicely. I would not hold the past promises that have been unrealized against immunotherapy for cancer, but the future is now. Chu Rick, we certainly appreciate you joining us on the show this evening and we look forward to having you come back and tell us how the story evolves. Edelson Thank you Ed and Francine. Chu You have been listening to Yale Cancer Center Answers and we would like to thank our 28:36 into mp3 file <http://yalecancercenter.org/podcast/july2609-immune-system-fight-cancer.mp3> special guest expert Dr. Richard Edelson for joining us this evening. Until next time, I am Ed Chu from the Yale Cancer Center wishing you a safe and healthy week. If you have questions or would like to share your comments, go to 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 from Connecticut Public Radio.