CONVERSATIONS WITH MIKE MILKEN

Steven A. Rosenberg

Chief, Surgery Branch, National Cancer Institute

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Mike Milken: Good morning, Steve. Thank you for joining us.

Steven Rosenberg: My pleasure.

Steve, we are in our fifth decade of working together in the field of cancer and medical research. You were our very first young investigator many, many years ago, and I remember our dinner vividly when you told me you were trying to raise enough money to rent a Winnebago, to take your wife, your mother-in-law, and your three daughters to visit the national parks. And you remember I told you that I didn't think you had to take a vow of poverty when you made the decision to join the NCI. And my feeling at that time is the greatest contribution that you can make to the world was if you could stay at the NCI and not go into private practice or a specific area. And that started our young scientist research program at the Milken Family Foundation and eventually led to our funding of almost a thousand young scientists over the years. You arrived at the NCI 45 years ago, and I'd love to understand your journey that led you to the national cancer Institute and led you to the field of immunology research.

I came to the NCI for the first time in 1970 as a member of the U.S. Public Health Service and spent two years here in the immunology branch doing research before I went back to the Peter Bent Brigham Hospital in Boston to complete my residency. But

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This interview has been lightly edited for clarity and readability.

the National Cancer Institute is a remarkable place, and as soon as I had an opportunity to come back, I did. The last day of my residency in surgery was June 30th, 1974, and July 1 I was appointed chief of the surgery branch, a position I've held now for over 45 years and it's been a great honor to be able to work at the NCI and do my research here.

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As soon as I came here, there were two patients I heard about when I was at the Peter Bent Brigham hospital finishing my residency. One was a patient who 12 years earlier had come into the hospital with a gastric cancer, a stomach cancer that had spread widely throughout his body. He had been operated on. They could do nothing. They closed the belly after biopsy, and 12 years later when I was a resident covering the emergency ward, this fellow came back in. I looked at his chart. It was quite remarkable. He had clear biopsy evidence of disseminated cancer and yet here, 12 years later, in the absence of any treatments, all of this cancer was gone. Somehow his body had destroyed the cancer in the absence of any treatment. It's one of the rarest events in all of medicine, the spontaneous regression of cancer, but it planted the seed within me that in fact somehow the body had the properties to get rid of a cancer.

A second patient also impressed me greatly, and that was a patient who underwent a renal transplant and received a kidney that inadvertently had a cancer in it. It was not recognized at the time, but the recipient of that kidney then developed a widespread renal cancer from that transplanted kidney. When his immunosuppression for the kidney transplant was stopped, all of this disseminated cancer disappeared, again demonstrating that the body has the capacity, if it could recognize an immune signal, to cause the regression of large, vascularized cancers.

It was those two patients that set me on this path to try to develop ways to utilize the immune system to treat cancer. And when I came to the NCI, that became my sole endeavor. I attempted to immerse myself in modern immunology and cancer research to see if we couldn't develop effective immunotherapies for cancer.

You've seen the advances in bioscience over so many decades. What has changed the most as we reflect over this period of time?

In the last 45 years there's been an explosion of information. The whole development of the field of molecular biology was taking place during that time. The sequencing of the human genome has had enormous impact. The development of the three major areas of

cancer treatment have all shown incremental improvements over these last 45 years, and patients can now survive much longer than they could before this.

The major problem, however, we continue to face is major solid cancers – the epithelial cancers that start in the ducts of the major organs – which result in 90% of all cancer deaths in this country. Those tumors, once they spread – that is, form metastases outside their site of origin – we can prolong life by treating those patients with chemotherapy, radiation therapy, surgery, but it's virtually impossible today to cure patients with the solid epithelial cancers. I believe that based on what has been accomplished already and especially in the last decade, that immunotherapy – that is, stimulating the body's immune system to react against the cancer – represents today our best hope for developing these curative treatments that can get rid of the last cancer cell rather than just delay the progression of the disease.

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There have been inklings now that immunotherapy can, in fact, cure some patients. The first patient we treated with interleukin 2 back in 1984, that first patient is still alive now 30 years later; she had a widespread metastatic melanoma. The first patients that we treated with cell transfers – that is, using their own lymphocytes that we could isolate from the body, identify those lymphocytes that could recognize the cancer and then give them back in large numbers –several of the first patients we treated with that approach in 1988 are still alive. That led to what I think is a major step forward in the development of immunotherapy, and that is the ability to use genetically modified lymphocytes that can attack lymphomas and leukemias and result in their disappearance in half of all treated patients.

In the middle of a coronavirus crisis, what is the link to cancer? The minute we started thinking about what is a potential solution, we turned immediately back in February of this year to focus on cancer research. You were among the very first researchers to see the cytokine release syndrome or the cytokine storms as a reaction to immunology, and so our thought was let's go identify those successful immunology treatments in cancer research, which maybe had controlled this cytokine storm, in order for them to be successful. Talk to us about what this is and how it came on to your radar so many years ago.

The first treatments that we developed utilized a T cell growth factor, something that could stimulate lymphocytes inside the body called interleukin 2 administered to

patients. And in 1985 we published in the *New England Journal* that in fact interleukin 2 could cause major regressions of widespread disease in patients with melanoma and kidney cancer. And in fact that became the first FDA-approved immunotherapy for cancer – for renal cancer in 1992 and melanoma in 1998. In trying to explain how interleukin 2 worked, we identified a kind of cell called a tumor infiltrating lymphocyte – a lymphocyte that infiltration to the stroma of tumors and intuitively what better place to look for cells doing battle against the cancer than within the cancer itself.

And in 1988 we published in *Science* the first examples, and then a year later in the *New England Journal*, the first examples of the ability to remove cells from the body, identify the cells that could recognize the cancer, grow them to large numbers and give them back. That was the origin of the field of adoptive cell therapy.

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Well, we worked on ways to prove this and that's when we came into contact with the cytokine release syndrome because we developed approaches where we could take very active T cell receptors – that is, the molecules on a lymphocyte that recognize an antigen on the cancer – we can take those molecules and genetically engineer a patient's own lymphocytes to give them this remarkable ability to recognize a cancer by using retroviruses to introduce a receptor that gave the lymphocytes the ability to attack the malignancy. And when we did that very strong immunologic approach for the first time, we saw very unexpected toxicities that we now recognize as a kind of cytokine release syndrome – the first time that anyone had seen that. And that's a result of a strong immune reaction that causes the release of hormones from lymphocytes. Hormones like interferon gamma, like tumor necrosis factor, like other interleukins that had profound effects on the body. It caused fluid release from the capillaries within organs. It could cause fever because it caused the release of interleukin one. It could cause muscle aches and pains. It was a dramatic impact sometimes on blood pressure of patients as fluid shifts occurred. It was that cytokine release syndrome that we recognized as part of a very strong immune reaction taking place.

Now when it comes to COVID and the reactions against that virus, we've learned that the viral infection causes damage in the body by two mechanisms. One, when it inhabits the respiratory epithelium in the lung, it can damage the linings of the lung and cause severe side effects. But also, the strong immune reaction that occurs against the virus leads to the release of a lot of cytokines, a lot of hormones from lymphocytes that we call the cytokine release syndrome. And so the damage from the COVID virus is not only

directly the virus itself, but in fact the body's reaction to the virus in much of the same way that the body secreted these large numbers of molecules when lymphocytes recognized the antigens that we had targeted with our genetic engineering.

There's another side of this coronavirus crisis that's particularly affecting cancer patients and others. Recently the U.K. pointed out that they expect a substantial increase in deaths from cancer patients due to the reduction in research and treatment, as a side effect of the coronavirus. What has happened at the NCI and your research efforts and treating patients? Are you seeing similar things that the U.K. has been warning against?

The impact of the COVID crisis is in two different areas. First, by virtue of the treatments that they receive – chemotherapy, radiation therapy – cancer patients are immunosuppressed. This immunosuppression makes patients far more susceptible to serious side effects of the COVID virus. That has impacted us at the NCI directly. We have an active hospital. I have normally dozens of patients in the hospital that are receiving treatment by us and by other groups, and it was vitally important that COVID be excluded from hospitals that took care of cancer patients because of their increased susceptibility to severe side effects and death from the virus. And that's led us now to very highly restrict the number of cancer patients that we can bring into the hospital. I would say we're perhaps working now at 10% of where we were working before the COVID infections. It's heartbreaking to think of what cancer patients are going through as they're watching their cancers grow and yet to have to deal with this threat of the virus and problems in getting access to care because so many hospitals including the NCI have had to limit admissions to prevent the virus from infecting patients that are here.

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The second impact, of course, has been the impact on cancer research. We have in my own lab perhaps 30 fellows and staff who are actually doing research on immunotherapy, and they are now only allowed into the hospital laboratory to continue their research when it is absolutely vital to keep animals alive or tissue cultures alive. But this has had a dramatic impact on restricting research, and every day counts when it comes to a disease that kills 600,000 Americans every year, and that's also heartbreaking to see our fellows unable to travel sufficiently to continue their work. It's going to be a temporary setback for progress in cancer research as well.

Steve, one of the cancers that I had turned to early with was melanoma. My father had been diagnosed in the early seventies, and as you know, no matter who I visited and

what was going on, we could not move science along fast enough to save his life. When I see the enormous success that's occurred in recent years in melanoma with immunology, it makes me feel that if it could have happened 30 years ago, we could have saved my father's life. And that's obviously the issue with so much cancer research. It's a question of time and acceleration. You have to be energized when you see the results of your work and immunology working in cancer patients today.

Well, you mentioned melanoma, which of course has been the poster child for the development of immunotherapy. And very recently – the last five years – we finally understand what it is about melanoma that makes it susceptible to these immunotherapy approaches. It looks like, again as a result of just the research in the last few years, that the final common pathway for all immunotherapy in patients is the development of immune reactions against the very mutations that occur within the cancer. Effective immunotherapies against melanoma and other diseases result from the ability to attack the products of the very mutations that caused the cancer in the first place. Somewhat ironic that the very things that caused the cancer will turn out to be the Achilles heel for cancer and certainly has for melanoma. Melanoma seems to be so susceptible to immunotherapy because it has many more mutations due to UV irradiation on the skin than most other cancers.

We now know that to develop effective immunotherapies for these other common cancers, we actually have to attack the targets of the DNA mutations that led to the cancer. In fact, we published recently developing T-cells that can recognize these mutations in patients with bile duct cancers, with colon cancer, with breast cancer. And we published these examples in the *New England Journal*. It can result in cancer regression.

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But the price for these very vigorous immune reactions is cytokine release syndrome. And as we learn to control that using certain drugs, then I believe that those can be very much applied to the treatment of cytokine release syndrome that causes many of the side effects from the COVID infection. And so we're taking information that we've learned from cancer treatment and learning to at least control some of the morbidity that occurs from a viral infection, which comes from the vigorous immune reaction and the release of hormones that causes many of the side effects of COVID.

Well, we look forward as many of these therapies we've worked on for decades are now being applied to COVID-19 patients with the idea of controlling this storm. Steve, you've served our country. Our decision to invest in you was one of the best decisions I ever made in my life. It has changed the world for cancer patients. So many of your

mentees have gone out, built biotech companies and have been successfully treating patients. What about your own family? How has your own family reacted to coronavirus?

Well, first off, Mike, I have to offer you my particular thanks for all of the support you've given me over the years, especially very early on when I joined the National Cancer Institute. I've had many opportunities to leave here and join academic institutions and certainly biotech companies, but the National Cancer Institute is such a remarkable place. I feel so honored to be able to stay here. And your early help impacted upon me substantially.

I have three daughters. One of them, my youngest, Naomi is actually on the frontlines of this COVID epidemic. She went to medical school, went into emergency medicine, and is now an attending physician in the emergency department at Temple University in Philadelphia. A very difficult area of Philadelphia. She's seeing COVID patients daily, has had to intubate patients. It's very high risk and is a huge concern for me as I talk with her daily on the front lines of this attempting to treat patients with COVID infections. My other two daughters are doing well. One lives in Anchorage, Alaska, and the second one lives in Los Angeles, and so they're doing well. Unfortunately I can't get together with them but we try to stay in touch on a daily basis, but our family is doing okay and I appreciate your asking about them. Thank you.

Steve, it sounds like Naomi, your youngest has followed in your footsteps, her commitment in putting herself in harm's way in one of the most difficult areas to work, in an emergency room. And Steve, I think recognizing your decision to stay at the NCI in the last 45 years was one of the decisions that you made to serve the world. And we can't thank you enough for it, and we wish you and your entire family good health.

Thank you, Mike. I return that to you and your family as well.
