Dr. Steven Rosenberg Oral History

Steven Rosenberg, MD, PhD, Chief of Surgery, National Cancer Institute (NCI)

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PA: Dr. Rosenberg, thank you so much for making time; I know as much as anybody how busy you are because I have sat next to you and watched how hard and how tirelessly you work. It really means a lot that you would make the time to sit and talk today. I almost don't know where to begin, but I would like to begin chronologically with your life story because you're probably the most focused person I have ever met, and that focus seems to have started at a very young age. Let's talk a little about your childhood. If I am not mistaken, you grew up in the Bronx.

SR: Correct, that's correct, I was born in the Bronx

PA: If I recall we're coming up to your 81st birthday; you were born, I think, on August 2nd, 1940. What are your earliest memories of childhood as they pertain both to your love of science and perhaps more importantly your obsession with cancer?

SR: Up until about the age of five or six I wanted to be a cowboy. I have an older brother and we would talk about going out west and riding horses. But the first things that I remember other than wanting to be a cowboy, occurred when I was about five or six years old. I have given a lot of thought to how that came to pass. Living at our home at the end of World War II when all the remarkable tragedies of the Holocaust sort of came home, as my parents received one postcard after another. I remember this, they were suffering as they got notified of relatives that died in the death camps during the war. I remember being so horrified by that in terms of how evil people could be towards one another. Somewhere around that time I developed an almost spiritual desire to become a doctor, to do research and make progress in helping people in alleviating suffering, rather than causing suffering, and that persisted. I began to keep scrapbooks about anything I could find about medicine or research. I think it was in response to the horrors of that particular time that inspired me to not only become a doctor, but to become a doctor who not only helped alleviate suffering now but alleviate potential suffering in the future by doing research and I stuck with that right through my education.

PA: You did very well in high school, although you have never spoken about it. I can only assume you did, because you were accepted to the best medical school, and not only that, but

you did the combined Bachelor and MD degrees and you managed to get into the six-year program, we are talking about Johns Hopkins Medical School. What was the impression that Hopkins left on you, in what would have been the late 1950s and early 1960s?

SR: I went into this six-year program—it was three years of college and three years of medical school—knowing that I would want to get further education and that I would take additional time. I knew from the very beginning that I would go on to get a PhD in one of the sciences. It turned out to be biophysics. Hopkins was a very nurturing environment in this respect, so as soon as I got to Hopkins I started working in a biology laboratory in the afternoons and evenings doing some very simple projects, but I knew from the very beginning that I wasn't just going to practice today's science or practice today's medicine but rather try to create the medicine of tomorrow, and that stuck with me for these last 60 or 70 years.

PA: Who was the Chief of Surgery when you were there, was Alfred Blalock still the Chief of Surgery?

SR: Yes, it was Alfred Blalock, and the medical school was not necessarily a terribly nurturing environment. You were thrown in there and at rounds there seemed to be a spirit of calling people to task in front of others. It wasn't the way that I thought education should happen, but there were brilliant people around and that's what I think is probably one of the single most important components of a good education. Being surrounded by people who know a lot, know more than you, can inspire you and that kind of people were at Hopkins.

PA: I remember when I was in medical school and spending time with you. One night we got talking and you explained that the reason you chose to do your PhD at Harvard in biophysics, and this is as close to what I remember as a direct quote, you said that you never wanted to be intimidated by a differential equation. Which presumably was a bit of a shortcut for you to say that you wanted the broadest education possible. But at that point in time, did you know you had an interest in immunology, had that piqued your curiosity or were you still thinking more broadly?

SR: **I** knew that I was interested in the mysteries of cancer through high school biology and my college classes. I got a PhD because I wanted more formal learning. I never wanted to be intimidated by what I did not know and wanted to be able to grasp any area of science and use it to answer questions and maybe differential equations were in the source of that. I ended up doing a lot of math in graduate school but it was more than that. I wanted to have the feeling that I had a good enough broad background in the sciences. When I got that PhD in biophysics, I was doing physical chemistry, quantum mechanics, thermodynamics, it was a lot of non-biology in biophysics and I wanted to have a background in the sciences such that if I encountered a problem, I could get a good book, read some papers, and understand it. This was that base of knowledge that I tried to acquire.

PA: When you were doing your PhD, had you already applied to residency, or did you take time out between medical school and the application to residency?

SR: I went immediately into the surgical residency at the Peterborough Brigham Hospital right out of medical school. Then took off four years to get a PhD in in biophysics, so it was a year of internship, took off four years and then went back to the residency and then came down to the NIH for several years to join the immunology branch here, before going back to finish the residency in 1974. This was during the Vietnam War.

PA: Was Francis Moore, the Chief of Surgery the most significant figure in your life at that point in time as a mentor?

SR: Frannie Moore was the Chief of Surgery and an incredibly smart person—there are an awful lot of smart people in that educational system, but he stood out in that when discussing a problem, discussing a patient, it wouldn't be at all surprising for him to come up with an idea or an outlook or a perspective on a problem that most people had not considered. So, in that sense he was an important figure. He was not so much loved as respected, which is a feature that I think can be very inspiring to young people.

PA: Was it unusual for someone to leave their internship or leave after their internship and go into a PhD program?

SR: At that time, it was as a matter of fact and the Brigham encouraged you to take off a year or sometimes two years in the middle of the residency program generally after two or three years. But at that point I was just itching to learn more. I was just not satisfied after college and medical school that I really knew enough to do creditable, meaningful, impactful research. So again, this was a real program and for two years I did nothing but study, nothing but take classes and study and learn. Then the latter two years I spent in the research laboratory doing physical chemistry and protein chemistry research of cell membranes.

PA: And the Chief of Surgery was supportive of this?

SR: He was, to an extent. To take that time off after internship required a few meetings and ultimately, I remember sending him a note saying, look I'm 23 years old, I have just finished the residency and I need to do what I am excited about. He gave in and I have enormous respect for him for that, and he was quite patient because I came back for a year, and then went down to the NIH [this was part of the Vietnam war draft obligation]. He kept taking me back each time, which was very nice, but it turns out I set some kind of record at the Brigham; it took me 11 years from the time that I started my internship to the time I actually finished the residency.

PA: You would have been old for a Chief Resident at that time, I guess.

SR: Yes, I was 33 or 34 by the time I had my first job.

PA: But of course, you made up for it because you progressed so early at the outset, as you know well. The book that you wrote with John Barry in 1992, 'The Transformed Cell' is a book

that I may have the record for most times reading it and may also possess the record for most copies owned. I know you get a kick out of that, every time I say something to that effect. You basically say I am one of the few people who read it, which I know is not true. You know, I still remember the first time I read it and it's a remarkable story. I suspect many people will go on to read it after this interview. It is in many ways one of the best books about science, which I think was your motivation for writing it, and we'll come back to that. In the book you talk about an important moment in your training which occurred in 1968 with a patient who you met one day in the Emergency Room. Can you tell us a little bit about that story and why it altered the course of your career.

SR: Well, there were actually two patients that I saw early on or become familiar with early on that influenced my thinking about cancer. The first was a patient I saw when I was a junior resident at the West Roxbury, Veteran Affairs (VA) hospital (we rotated through for three or four months at a time during the residency). It was a 68-year-old fellow who came in complaining of right upper quadrant pain. It looked like a typical gallbladder attack, and I got pretty excited because it might be a patient that I might be able to perform one of the first operations I was allowed to do. So, I looked into his chart and encountered a remarkable story. It turned out that 11 or 12 years earlier that patient had been seen at the West Roxbury VA hospital and had a gastric cancer of stomach. He had undergone a laparotomy. I looked at the surgeon's note saying that he opened the belly he saw a tumor that was encompassing about three quarters of the stomach, there were multiple liver metastases deposits that were biopsied shown to be the gastric cancer that had spread, multiple enlarged hardened nodes and he took out part of the stomach, I guess that as a palliative measure. The surgeon left the rest of the disease in place and the patient recovered and about a week later went home. Well, as I turned the page of the chart, the patient comes back three months later, he was doing fine, he was gaining weight, six months later he was back working. And here he was, 12 years later, having lived the past 10 or 11 years completely normally. I took part in removing his gallbladder, under supervision of course, and his belly was completely clean of cancer. There was no evidence of cancer of any kind, and we went back and looked at his chart to be sure it was the same patient. We re-reviewed the pathology, sure enough it was a cancer that had spontaneously disappeared over time in the absence of any therapy. One of the rarest events in medicine, that is to have the spontaneous regression of cancer without any treatments being given. Somehow his body had rejected the cancer.

I then did what turned out, of course, to be a very naive experiment, but I was wondering whether this patient, who had somehow cured his own cancer could be somehow taken advantage of to treat other patients. It turned out we had another patient in the hospital with a gastric cancer, a veteran who happened to have the same blood type. So, I called up the head of the surgery department and said, “I want to take a blood transfusion from this patient who spontaneously was cured and give it to this other patient”, and he said “OKAY”, that was the Institutional Review Board (IRB) as it existed at that at that time. So, we got blood from this one patient and infused it into the other veteran but, of course, it didn't do anything, and the other patient ended up dying of his gastric cancer, but at least planted the seed that in fact maybe there was something in the immune system that caused the rejection of that cancer, as much

as it would reject a foreign transplant. As the body's major defense mechanism against foreign invaders is of course the immune system, it got me thinking about potential immune manipulations.

There was a second patient that also influenced me a great deal that had been seen about a year before I came to the Brigham as an intern, and this was a patient who had received one of the early kidney transplants that were developed and innovated at the Brigham Hospital. He had received a kidney from a young individual who died in a motorcycle accident and that kidney was transplanted into the recipient and the recipient developed a widespread renal cell cancer. It turned out after study that the transplanted kidney inadvertently had contained a renal cancer that then in this other patient, under the influence of immunosuppressive medications, had spread widely through his body. In an attempt to control this, the immunosuppressive medications were stopped; of course, the kidney was rejected and had to be removed, but the patient's cancer then went away as well, because it too was allogeneic, it too came from the genome of the of the original donor. So, what did that teach one? Well, it showed that a large invasive vascularized cancer could be caused to be rejected completely by the immune system, if you had a strong enough stimulus that could mediate that rejection. And so it was that spontaneous regression, maybe this demonstration that the immune system more directly, by removing immunosuppressive medications, could result in tumor collapse and regression. That put me on the path towards cancer, but I was already pretty much there, because of what I had seen as a doctor in cancer patient.

PA: In the late 1960s, what was understood about the human immune system as it pertained even to viruses, let alone cancer? Had Major Histocompatibility Complex [MHC] Class 1 and Class 2 been identified yet? I don't think they were identified until the mid-1970s.

SR: Right, Class 1 in the 1970s and in the early 1980s Class 2, but when I started in 1974 the idea of immunotherapy was a dream. There were anecdotes way back into the late 1980s of tumors going away when people got an infection but really nothing stable. There was no ability to measure an immune reaction against any cancer there was no such thing as a cancer antigen that had ever been found. There were no manipulations you could give that worked. It was a sort of a dark period when it came to knowledge about the immune system against cancer. It's a little hard to understand just how immunologic information developed. In the 1957 issue of the Journal of Immunology the word “lymphocyte” was not in the index. We did not understand what small lymphocytes did and how they were circulating the 1950s. That information only came to pass in the early 1960s when it became clear that you could transfer immunity by transferring lymphocytes, not by transferring blood or serum. Even in experimental animals there was no manipulation that could cause an existing cancer to disappear. You could immunize a mouse against a tumor by letting it grow and then removing it and cause that mouse to resist an implantation of the same tumor again, but once the tumor was growing there was no maneuver that could keep it from growing, no immunologic maneuver that could keep it from growing, so the field was desperately in need of more information.

PA: Before we get to how you arrived at the NCI, well, let's talk about that. It's a very unusual first job. How did it come about and what did you assume you would do at the completion of this otherwise very long residency?

SR: As you're indicating I finished my residency June 30, 1974, and the next day I was appointed Chief of Surgery at the National Cancer Institute, a position that I still hold. I'm still Chief of the Surgery Branch now, what is 47 years later. The NIH, when I came here, I knew it was a remarkable place, it had resources and a commitment, a mandate to make progress. It's a state-of-the-art hospital that provides outstanding care to patients, but it exists not only to practice the best of today's medicine, but ***to create the medicine of tomorrow.*** That always intrigued me, from my first knowledge of the NIH, when I came here in the midst of the residency during the Vietnam War.

PA: You did have an offer to stay at Harvard, correct? Was Dana Farber Hospital in existence at the time?

SR: Dana Farber was just being built, and Francis Moore, who was chief of surgery offered me a position as the head of surgery in that new Dana-Farber Institution. The director and head of medical oncology also offered me the position and I had tentatively accepted it, although we were amid some negotiations about whether there would be individual and independent operating rooms in the hospital and so on. But in the course of that, I heard from one of the division directors here at the NIH who I had gotten to know when I was a fellow, who came at the time to Brigham to interview me, as he was wondering whether I would be interested in the position. I was expecting to stay at the at the Brigham at Harvard, but one day I got a phone call from him saying that the Chief of Surgery, Alfred Ketcham, decided to retire, and the position was open July 1st. Was I interested? I knew I was, but I had to call my wife Alice. Told her about it, she said just pack and let's go, and off we went.

PA: Was the Chief of Surgery at Brigham disappointed?

SR: Oh, it was a really shocking encounter that I had with him, when I went in to tell him I decided to go to the NIH, as I thought it was a place where I could best utilize my interests and knowledge, and he said no. And I said, “Look, I’ve decided to do it.” He said, “You have to stay here, it's too great an opportunity to turn down” and I said no. He wasn't an easy guy to say no to, but I knew I wanted to come back to the NIH. Finally, after almost an hour I said, “Dr. Moore, I am going down to Bethesda, Maryland” and I offered my hand to shake his as I was going to leave and he refused to shake my hand, which was a little shocking. But he got over it finally. I left and we became good friends, and he said all kinds of nice things about me when he needed to. So, it worked out well. You see, at that point I knew I wanted to study cancer. I had already made that absolute commitment and the National Cancer Institute seemed like the right way to do it. And in some sense, it was a logical decision for me, given my childhood experience that got me interested in medicine and science. Cancer is such a devastating disease; it attacks innocent people through no fault of their own, it makes them, and their

families watch impotently as they progress and then die of cancer. It is a holocaust and just seemed like the kind of thing I wanted to study.

PA: It was around this time I guess that Richard Nixon and that administration had declared a war on cancer. I believe it was just a year prior to that. How did that resonate with you? Did you view that with great optimism, or did you think that it was naïve to think that in a matter of years cancer would be eradicated in the same way that man had gone to the moon?

SR: Well, I had great hopes for making progress, perhaps naively, even at that point not fully understanding all the complexities that the National Cancer Act mainly influenced funding outside of the NIH. The NIH was already, I thought, well-funded, had a building that had been built in 1953 one of the largest buildings in this area dedicated to doing research. It had hospital beds and so that National Cancer Act didn't have much impact on the intramural NIH that I could see. But again remember, I am a worker bee, I became Chief of the Surgery Branch and have never advanced in the hierarchy. I was where I wanted to be. I turned down a fair number of positions and when it came to the influence of the National Cancer Act on the country as a whole, I really wasn't involved that much at all. [What] I focused on was the work that I wanted to do intramurally at the NIH.

PA: How did you lay out a research agenda when you arrived in 1974? You're now finally able to not only with the resources of money, but perhaps more importantly with the resources of time, to lay out an agenda for hypotheses that you want to test, to effectively build a program to systematically narrow down the set of questions. So, what was the process by which you went about doing that?

SR: When I came to the NIH knowing I wanted to study cancer, I started reading everything I possibly could about therapeutic approaches, which at that point were simply surgery, radiation therapy, and chemotherapy, mostly used alone. It was clear to me at that point that although incremental advances had been made over the years, surgery is 3000 years old. Radiation therapy began immediately after Roentgen discovered x-rays in 1895 and chemotherapy arose in biological and chemical warfare laboratories here at Fort Dietrich in Maryland, to attempt to develop these agents. It was in a laboratory accident in 1942, when inadvertently exposed to nitrogen mustard, laboratory technicians developed a lymphopenia throughout their body, with their lymph nodes shrinking. That led a Yale physician to attempt to use nitrogen mustard, now known as melphalan, as a chemotherapy agent. That was the birth of chemotherapy in 1942 and that started search for chemicals to treat cancer. But the advances that were being made were slow and incremental.

I wanted something big that would make a big difference. As I read about the immune system, I realized how little was known about it. But, with the examples that I had and the intuition that I had developed (which is so important in science) I thought that this might be something valuable and I decided to study immunology. I looked at everything I could read about, and it seemed to me that the immune cells that were then being recognized as the mediators of organ rejection, were the agents that one needed to stimulate. And why not use an immune

cell as a drug? That is: Take advantage of a patient's own immune reactions to try to treat the disease—that is immunotherapy. I started with some unbelievably naive experiments. There was no way at that point to keep lymphocytes alive outside the body. We're talking about 1974, you could take them out, they would die in a day or two, and you had no way to keep them alive. You could mix them with other cells, and they would stimulate for a few days, but they would die after about a week. Yet, I was desperate to try to use lymphocytes with immune reactivity to treat patients and so I began implanting human tumors into the mesentery of mini pigs. A good friend of mine, David Sacks, here, had developed a mini pig colony that was partially inbred at major histocompatibility (MHC) loci, and so I would embed a tumor in the mesentery of these mini pigs wait about two weeks, operate, and remove the inflamed lymph nodes that were draining that tumor and gave those lymphocytes to six patients whose tumors I had taken out, implanted in pigs to generate lymphocytes reactive against that tumor tissue, and then harvested lymphocytes from that pig and administered them intravenously to patients. Of course, nothing happened, but it's just a sign of how desperate I was at that point to have some impact, to be doing something. I have a saying on the door of my lab, you probably remember it, it's a modification of a Louis Pasteur's saying: "Chance favors the prepared mind' and what I added to it was "Chance favors the prepared mind, only if the mind is at work." So, I was trying things, and it was only with the discovery of T-cell growth factor in 1976 by Drs. Doris Morgan and Robert Gallo that opened the door to be able to manipulate lymphocytes outside the body by adding a growth factor called Interleukin-2 (IL-2). That was something I began to study quite intensively to see if one couldn't then grow lymphocytes that had anti-tumor activity and would retain it as they grew. None of that was known, those were the first experiments I was doing along those lines.

PA: Before we go further, I think it is worth making sure people understand the semantics because obviously you and I can take much for granted. Let's start with some basics about cancer: how does one define cancer, what separates a cancer cell from a non-cancer cell?

SR: If you look at the broadest properties, there are two properties that separate cancer from other cells in the body: the first is uncontrolled growth. Virtually all the tissues we have, fingernails or eyebrows or you name it, they'll grow to a given amount and then they'll stop. Cancers don't have that signal to stop; they'll keep growing. The second [property is], cancer is the only cell that can arise in one part of the body and spread and live and divide and grow in another part of the body, and that's not true of virtually any other kind of kind of cell. So, cells with uncontrolled growth that can spread and grow elsewhere, these are the biologic properties. Now we can dig down layer by layer by layer and get to the point of why a normal cell ultimately becomes a cancer cell, and we now understand that that's due to the accumulation of mutations in DNA of these cells. Cells divide, which explains why it's the common organs of the body, all of which have ducts, the linings of those ducts are constantly turning over. As DNA is turning over, mistakes are made, called mutations. It is that accumulation of mutations that results in the cancer itself. So, we can take it all away from the biology of uncontrolled growth, down to the very molecules that are involved. That we can describe it, doesn't mean we really understand it all, but we can describe it.

PA: Then let's also explain to people the difference between the epithelial tumors and the hematologic tumors and let's frame it as it was in 1974 in terms of what were a person's odds of surviving. Maybe tell folks what the common epithelial tumors are and explain a little bit about the difference between local tumor versus metastatic tumor and what's the impact that had on a person's survival at the time you arrived at NCI.

SR: The hematologic cancers, of course, are the blood cancers, and they start from progenitors in the hematopoietic system because after all the metabolic system starts from an individual stem cell that then divides into multiple different characteristics, much as we all grow from a single fertilized egg, from one cell that makes us what we are. Even back then and a little more so now, if you developed a cancer of the blood, which were about 10% of all cancer deaths, 90% of cancer deaths are due to epithelial cancers, which start in the solid organs of the body, and that is all the way from the rectum up through the gastrointestinal tract through the stomach through the esophagus, the pancreas, the testis, the ovary, the prostate. All these solid organs have ducts and, as I've mentioned, it's the epithelial linings of the ducts that are continuously turning over that become the cancer. In blood cancers, it's the more primordial cells that develop into neutrophils and lymphocytes and other types of cells.

Let us talk about the solid tumors which are 90% of all cancer deaths. Last year in the United States of about 600,000 deaths due to cancer, 550 000 were due to the solid epithelial cancers. If you operate on a patient who develops a cancer to remove that cancer, well over half the time, that patient will be cured and live their normal lifespan, but the half, a little less than half of patients that cannot be cured result in this enormous tragedy of 600,000 innocent people dying of cancer every year once the cancer spreads.

However, and this is my view, the dirty little secret of oncology is that if a cancer spreads from its local site and cannot be surgically removed, then the death rate in that patient is a hundred percent. That is, we have virtually no treatments that can cure systemic cancer, that can cure a patient with a metastatic solid cancer [that is one that has spread to a different site] that cannot be surgically resected. Now there are a couple of exceptions to that. There are two solid tumor exceptions that have existed for several decades, one is choriocarcinomas, these are cancers that start in the placenta of pregnant women that then spread, and you can have 90% of the lung replaced by that tumor, receive methotrexate [a chemotherapy drug] and it will all disappear, I still don't understand exactly how. Germ cell tumors in the male, tumors of the testis like Lance Armstrong, who had brain metastases and lung metastases, no matter how much they've spread, if you give patients platinum-derived chemotherapy regimens, you can cause complete durable regression of that metastatic disease. Until 1985 those were the only cancers that could be cured. We can now add to that list of solid cancers melanoma and renal cancer because interleukin-2 administered to patients back in the mid-1980s, caused complete regressions of widely metastatic cancer in patients that are still alive today. But that's it: choriocarcinoma, germ cell tumors, melanoma, and renal cancer. Other than those, everyone who develops a spread cancer will die of it despite all the best treatments that we have. We read in the paper that a celebrity has cancer and they're going to fight it and they're going to beat it, but nobody beats it. We are in such desperate need of better treatments for patients

with metastatic cancers, because we just can beat them back a little bit, we can improve survival by months and for some cancers maybe a few years, like breast cancer and colon cancer, but everybody ultimately will succumb to the disease.

PA: That's what I was going to ask you about. If you think about the past 50 years in cancer and what you just said, I still starkly remember having those discussions as a medical student with you and the main point was, we've basically just extended median survival of metastatic cancer but haven't increased overall survival and what would be the extent to which even median survival has changed? If we are just talking about stage four of the common breast, colorectal, lung, pancreatic cancers, how much has the needle been moved with respect to median and survival, notwithstanding the fact that overall survival hasn't changed?

SR: If you look at current papers and advertisements most regimens that ultimately get approved by the Food and Drug Administration prolong survival by months. Probably the best example in modern oncology is the treatment of metastatic colorectal cancer. When I started median survival would have been maybe eight to ten months; now it's two and a half years, so there's an example where life has been extended by years. Breast cancer patients can go from one regimen to another, each one causing some temporary regression of the cancer or limitation of its growth, but the cancer will ultimately grow, and the patient will have to move on to something else. That's why cancer care is so remarkably expensive, people just move from one treatment that can prolong life by a few weeks, like in lung and pancreatic cancers; a six week improvement in survival for $40,000, with enormous toxicity and huge, huge life-altering expense. The most frequently prescribed drug in oncology today is bevacizumab [Avastin], which can impact blood vessels' formation in tumors. The trials of that regimen in combination with others will prolong survival in patients with colorectal cancer by about four and a half months, but those are the tiny increments which can provide substantial benefit to some patients, but none are curative, and people are always living under the cloud of that cancer that is going to regrow. We need something more dramatic than the application of surgery radiation and chemotherapy, barring some enormous advances in those fields.

PA: One other point worth making for folks with respect to chemotherapy, I was just on the phone yesterday with one of my patients whose wife is currently recovering from cancer surgery, and he asked about the efficacy of chemotherapy and how good is chemotherapy at killing cancer cells, which I thought was an interesting question that led to a discussion. I said you know, the challenge with chemotherapy is not finding chemotherapeutic agents that can kill cancer cells. I made a point that he probably has 20 chemicals in his home and garage that could kill every cancer cell remaining in his wife. The issue is how can you do that selectively, how could you do that and not at the same time kill the normal cells. I think therein lies the arbitrage that needs to be exploited with chemotherapy and ultimately what we're going to talk about, which is immunotherapy. But I think that's an important point that many people don't understand, which is how difficult it is to thread the needle of chemotherapy, it's not the killing of cancer that's hard. It's the killing of cancer and not killing the non-cancer.

SR: The point you make is incredibly important. It's the selective killing of cancer without killing normal cells, which is not the case for virtually any chemotherapy or radiation therapy. Even in surgery you have to remove some normal tissue and so it's that selectivity against the cancer that's so important and in fact, that's almost the perfect explanation, the reason, that I think immunotherapy has importance. It is because of its immense selectivity and sensitivity of recognition, ability to recognize single amino acid changes in a protein and develop an immune response against trivial differences that can distinguish normal from tumor. Or if you get a viral infection, destroy the virus in the respiratory system without destroying the respiratory epithelium. It's the exquisite sensitivity and specificity of the immune reaction that I think makes it such a seductively interesting approach to trying to develop new cancer treatments.

PA: Let's take a moment and have people get a little bit deeper on how the immune system works. I remember for me personally in medical school it was one of the most interesting sets of courses, were the courses in immunology. Particularly, how T-cells worked was fascinating, it seemed to lend itself to a story with generals and soldiers. Explain to people, let's maybe start with a virus as the example, because in the era of coronavirus that's on everybody's mind and we can talk about how the body defeats a virus, but then pivot to how in the case of cancer that exact same immune system can accomplish what you just said.

SR: Let's take viral infection as an example. whether it's a common cold or coronavirus. The virus comes into the body and infects the respiratory epithelium in the pharynx and the bronchi and the lung, the virus replicates, and the infected cells then express the viral proteins, which the immune system has evolved to detect proteins or other molecules that are not part of the normal “self” of the body. As the immune system evolves, in the thymus immune cells that can recognize foreign invaders get spared, whereas cells that can attack normal tissue get eliminated and so, except for autoimmune diseases, we don't have cells that can recognize normal tissues, they've been eliminated in the evolution of our immune system. So, you have lymphocytes; B cells that make antibodies and T-cells that act directly by interacting with other cells. So, the immune system via antibodies or T-cells recognizes viral proteins that are being displayed by the respiratory cell. The lymphocytes are constantly patrolling the body, every 14 or 15 seconds your heart is pumping out lymphocytes that are circulating through the vascular system, sometimes extravasating into tissues coming back into the lymphoid system and returning to the heart via the thoracic duct. When the lymphocyte encounters a foreign antigen to which it has reactivity and is not self…

PA: Please define an antigen for folks to tell people what an antigen is, how long is it and what's it made of.

SR: An antigen is a molecule that is not normally being expressed in the body by tissues. Antigens are generally proteins, but they can be other molecules, and what makes that molecule an antigen is its ability to be recognized by a T-lymphocyte or a B lymphocyte. That is a T lymphocyte that can directly recognize an infected cell or a B-lymphocyte that can make antibodies against it in plasma cells, and so if a molecule is identified as foreign, the immune system can recognize that antigen. Lymphocytes are patrolling the body, when they encounter

this viral antigen in the respiratory epithelium they stop at that location, and you can visualize this in tissues with instrumentation called two photon microscopy. Lymphocytes stop at that location, and you can see them extravasate into the tissue. When they're there, they then begin to divide, as they divide the dividing cells can also recognize the viral protein and start making molecules that can destroy the infected cells. They also summon other cells to that arena; macrophages, neutrophils, and so on and that's what an immune reaction is. As the antigen is eliminated by these mechanisms, there's no reason for those cells to stay around anymore; they're not stimulated. They enter the circulation but now you have them patrolling the body for the rest of your life. These long-lived lymphocytes can recognize those foreign molecules and that's why when you get immunized against smallpox you have that immunization for the rest of your life and hopefully for coronavirus. Although we don't know that yet for coronavirus, we don't know the extent to which those lymphocytes survive.

PA: At the outset you said there are two things about cancer that make it different from self, it has these two properties that individually wouldn't be the end of the world but when you combine them they're devastating. It's this failure to respond to cell cycle signaling which results in unregulated growth and it's this capacity to leave the site of origin and go and grow in an unregulated manner elsewhere. You also mention that this is the result of, although you didn't use the word, somatic mutations and we can clarify for people that these aren't typically mutations that people are born with—although in diseases like Lynch Syndrome that might be the case—these are acquired mutations. So, the natural question would be why is it that a cell that has these acquired mutations that clearly produce a phenotype that is different from self, why that wouldn’t be foreign enough for the immune system to act? In other words, why does cancer even exist in the first place, why doesn't it get squashed out in its infancy?

SR: So, these mutations, these changes in DNA that are random events. As the cell is dividing it can produce proteins that can be recognized by the immune system and cells do it in complex ways by breaking down into small molecules, peptides, and putting them on the cell surface, and the immune system can recognize these mutations. It's only been in the last three or four years that we now recognize these mutations as commonly recognized by the immune system. In about 80 percent of patients with the common epithelial cancers, it turns out as a result of the research done in recent years, the products of the mutations that can be recognized exist, but the immune system against them is too small. It's not vigorous enough. What does that mean? Not enough cells create receptors that have a high enough avidity for recognition of the tumor. The immune reaction is not very strong, and the growth of the tumor can overcome the small impact that an immune reaction might have in killing some tumor cells.

Plus, for a tumor cell to survive and grow, it develops certain properties that can suppress the local immune reaction. It can make molecules like transforming growth factor beta (TGF-beta), it can make cytokines like interleukin 10, which can cause the development of lymphocytes that inhibit immune reactions. I mean virtually every physiologic system in the body has stimulatory elements and inhibitory elements. You have hormones that can increase gastric secretion, and some that can decrease it. You have a sympathetic nervous system a parasympathetic nervous system. The immune system is the same: it has effector cells that can be very aggressive in

recognizing antigens, and it has regulatory T cells that deliberately suppress immune reactions, and that's one of the things that keeps us from developing autoimmune disease. But there are many of these regulatory elements recently described, like myeloid derived suppressor cells that can suppress immune reactions and so it's the balance of the aggressive immune reaction against the inhibitory molecules that can prevent that immune reaction. That is the holy grail of trying to find effective treatments, and effective treatments come in both directions. Interleukin-2 stimulates immune reactions, and we now have checkpoint modulators like ipilimumab or PD-1 inhibitors that can inhibit these inhibitory factors and thereby stimulate the immune reaction by taking away the breaks on the immune system. So, the more we understand the more we can take advantage of the biology.

PA: Let's go back to the first of those because that seems to have been the first big break you got at NCI, after Gallo's discovery of Interleukin-2. Now you had both, a cytokine that could allow you to grow lymphocytes in vitro, but also something that could be given to patients in vivo, to stimulate the immune system, so how did that propel your work?

SR: With the advent of Interleukin-2 what had been shown was that some bone marrow cells could make a substance which would keep lymphocytes alive outside the body. The minute I heard about that a series of questions arose: Well, if it kept lymphocytes alive, could it keep lymphocytes alive and dividing in a format that enabled them to have all of their immune recognition, or as they grew would they just lose that property? So, we would try to demonstrate that by developing cells that could recognize what we call allo-antigens, that is very strong antigens that are present in one person that inhibit the ability to transplant organs. Our initial studies were to see whether we could develop lymphocytes, grow them in culture and cause experimental skin grafts in mice to disappear faster. We are not talking about tumor, only normal tissue, and we showed that in fact we could grow lymphocytes that retain their function in the laboratory and then retain their function in vivo. Well, with that knowledge we didn't want to cause skin grafts to disappear more quickly.

With that knowledge we had to try to develop cells that could react against the cancer and very early on when we grew cells in interleukin-2, we found that in fact they could destroy tissue cultured cancer cells, have some impact on normal cultured cells as well, just by virtue of exposure to interleukin-2. We call them Lymphokine-activated killer cells (LAKs) and we studied them for three or four years. Turned out to be a false alarm because they could impact tiny little tumors in mice before they become vascularized, but by the time tumors were vascularized they would not work in mice at all. But interleukin-2 seemed like a molecule that might be able to stimulate those rare cells in the body that could recognize the cancerous foreign or develop cells in the laboratory that could do that recognition.

That then led us to many years of experiments in the laboratory and clinical trials trying to see whether either interleukin-2 administration alone, or cells that you could devise in vitro, that could recognize a tumor and administer those. That was a very frustrating time, it wasn't until 1984 that we finally figured out a way to use interleukin-2 to mediate regression. We treated over 70 patients with either interleukin-2 or cells that we grew in interleukin without seeing a

response, until we modified the schedule of interleukin-2 administration, after learning its pharmacokinetics, that is a half-life inside the body of about seven minutes. So, we had to alter the schedule, we had to give higher and higher doses which mediated toxicity until finally a patient that we treated in 1984, who had widespread melanoma, was administered interleukin-2 and was the first patient finally, after over 70 other patients, to show us a tumor regression. The first time that a deliberate immunological maneuver could reproducibly cause cancer regression. It was one of the few eureka moments that I have had in doing research, but the realization finally that after all those patient deaths due to advanced cancer, all would go on to die of their cancer, a patient survived and that the patient now alive, over 35 years later free of disease.

PA: You know it reminds me a lot of Thomas Starzl's work in the 1960s with liver transplantation, where the number of patients who died was hard to keep track of before finally achieving the technical success that was necessary, both the perioperative care and the post-operative care and the technical skill necessary plus the immunosuppressive regimen. All of those four things had to be firing on all cylinders for patients to finally undergo liver transplantation. This patient in 1984, if I recall, was the 67th patient treated, meaning 67 consecutive patients died of metastatic cancer and were unresponsive to interleukin-2. The first question is really just a logistics question, how many different histologies were in that group, how many different types of cancers were you treating at that time?

SR: We were treating all cancers, metastatic cancers with the idea that although they each arose from different organs, had somewhat different properties and methods of spread, there would be commonalities that could be attacked. The first patient that we treated with this revised regimen happened to have a melanoma, the third and fourth patients had renal cancer. As we continued to use interleukin-2 , we found that patients with those two histologic types of cancer could respond and ultimately response rates in those two diseases turned out to be about 15 to 20 percent of patients, with about a third of those patients having complete durable regressions. But it was a little different than the liver transplant situation, because in that situation, there were technical problems that had to be overcome and it was a genius of Tom Starzl to stick with it and figure out those technical problems. When it came to immunotherapy for cancer, it was a little different, we didn't know that it would ever work, we didn't know that there was ever going to be an immune system that could cause a cancer to disappear. In contrast, if you can work out the technical problems [with liver transplantation], how to sew the vessels together, you could get this thing to work. That first patient had an enormous impact on me and on the field because it showed that it was possible, and until you know it's possible, you never know that it's ever going to occur. So that changed everything because it showed that simply administering this one molecule, a T-cell growth factor, could cause a cancer regression in a patient and that then led us to studies to understand how that was occurring, and that then led to a lot of different directions, cell transfer, gene modification and so on.

PA: How did you keep going in the face of all those failures up until this patient's miraculous remission in 1984. How did you, because again, if you were working as a surgical oncologist at

the time, you would not have been exposed to that death. The surgical oncologist's work would have been done after the primary resection, typically the medical oncologist would be the one that would be at that patient's bedside as they progress through treatment, but you were seeing something that you would not have seen, had you chosen a different arc to your surgical career. I just wonder how you coped with that, what were those drives home like, what was it like to be alone in your thoughts?

SR: Well, as I look at it, seems remarkable that there were so many patients one after another, everyone died eventually of their cancer because we did not have any impact in the manipulations that we were applying. You are a doctor, and you know that it's not the patients that do well that you remember, it's the patients that you fail to help that you remember, and there was just a remarkable number of tragedies, young people dying of cancer, people of all ages, but I had this intuition based on everything I knew about biology and everything I had studied in biophysics. I had an intuition also influenced by these inklings of the first two patients I mentioned that this would work. You know, I recently saw a quote by Abraham Lincoln that said success consists of moving from failure to failure without loss of enthusiasm, and that actually happened to me. I just saw that quote a few months ago but I always felt it was going to work, and it did eventually in a small number of patients, still a long way to go. But at least now we have effective immunotherapies for a variety of diseases, and when that first patient responded, it all exploded in my brain; it does work, this can work and now we'll figure out ways to make it better.

PA: I imagine that Alice was a big part of that support for you, again I have the privilege of meeting her and knowing how important she is. Do you think you could have got through this alone without the support of your family? I mean you had to do this very difficult thing, which was basically this remarkable obligation to your family, which every father does and at the same time felt like you were carrying the weight of your world on your shoulders trying to take care of these patients who were otherwise really left with no hope. Do you see that as sort of a synergy between those two?

SR: There were probably, and I am not exaggerating, 40 days in the first 40 years of my work here that I was in town not traveling, that I was not in this hospital. I would come in every day of course, I would come in every Saturday, Sundays I would come in to go over research with some of the fellows, you probably remember that, or see some patients, and that kind of life requires support. There are not a lot of wives who I think would tolerate that kind of commitment outside the home and Alice was such a person. Never hassled me about it, always understood. I remember once she said, “Look, I know what you're doing is important and so what I am going to do, as much as I can, is relieve you of the burdens that we commonly face as part of daily living.” I haven't written a check in 20 years; Alice pays our bills and really takes care of so much that enabled me to work at that level. But it was a family thing, I have three daughters who were growing up as all of this was happening and I remember when my oldest daughter applied to college, she opened her college essay with a sentence somewhat along the lines of “at our dinner table at home we're much more likely to be talking about cancer and AIDS, than the Washington Redskins.” It made me understand how much the kids had been

affected by all of this talk of death and suffering from these diseases, so it takes a family and I doubt I could have done it without that kind of support.

PA: Once you identified this patient number 67, did you have an inkling what it was about melanoma and renal cell cancer that made them particularly immunogenic relative to the whole host of other epithelial cancers that were less reactive?

SR: The answer is no, but the answer would be yes 35 years later because I think now we do understand what's different about melanoma, but we didn't at the time. We were seeing responses to interleukin-2 in patients with melanoma and kidney cancer. However, no other diseases would respond to interleukin-2, and we learned that the hard way treating over 600 patients with interleukin-2, here at the Clinical Center. It turns out those two diseases were uniquely responsive, and we now know at least for melanoma why that's the case. That is, the immune system is recognizing the products of mutations and if one looks at the frequency of mutations among different cancer types, melanoma has more mutations than any other cancer type with the exception of lung cancer. There're about equivalent of 400 mutations per tumor as a median, and that's very likely because melanoma is induced by a carcinogen, ultraviolet light, lung cancer by the carcinogens largely in cigarette smoke or the environment, that leads to an increased number of mutations and that at least is part of the answer. That is, the more mutations you have in the cancer, the more likelihood that you'll develop a particular foreign protein that can be recognized by the immune system.

PA: Did you ever see patients with Lynch Syndrome respond, they would typically have many mutations.

SR: You're exactly right, so there are some situations like the microsatellite instability colon cancer, other cancer types, Lynch Syndrome. But we didn't understand at that point that mutations were involved, and I don't remember ever treating a patient with Lynch Syndrome. You're right, they would have a very large number of mutations. For comparison, if we talk about a standard, you can't even use the word standard, there's no such thing as a standard cancer. Right now, we know so much about cancer, that every cancer is different. You would probably encompass 80 percent of these common cancers if you considered mutation frequency between 60 to 70 and 150 that would be the range, the median would probably be somewhere about 110, but it would vary from cancer type to a cancer type. Some pediatric cancers have very few mutations, some cancers have more, but I would say the median very likely to be about 110.

PA: How many of those mutations would be driver mutations, so they are oncogenes, tumor suppressor genes, that are playing a functional role in the cancer versus what we might call passenger mutations that can still produce antigens, they could still generate a peptide that could be recognized by MHC, but they're not playing a functional role in those two properties of cancer that we spoke about.

SR: About six years ago, we described an assay that would enable us to actually identify the exact molecular nature of these antigens that are recognized by T-cells and that came from the understanding that it was the products of this unique cancer, these new cancer mutations that were being recognized by the immune system. Well, it turns out that some of these antigens that are recognized by T-cells derive from driver mutations that caused the cancer in the first place like p53, present in half of all cancers. But only about two percent of patients develop immune reactions against it. K-Ras, about 90% of pancreatic cancers will have that as a driver mutation, but what's stunning to me about oncology and the biology of cancer, is that how few of these shared cancer mutations exist. There's p53, there's K-Ras, to some extent PIK3CA in breast cancer, maybe b-raf mutations in melanoma. Other than that, the incidence of driver mutations as a cause of cancer is in low single digits. You'd think there would be many mutations that would change the cell so dramatically. But it turns out it's not only those few driver mutations, but the accumulation of mutations, each with its own property that in and of itself appears unlikely to cause cancer, but in concert with the action of other genes, other mutations, does cause a cancer. And more recently shown in a breast cancer patient (that we published a few years ago) that we could mediate complete durable regression, now over six years later, by targeting four, what appeared to be, random somatic mutations. None of which had a driver function but in concert caused cancer and by attacking them you could cause cancers to disappear.

PA: I am still struggling to understand why it is that a p53 mutation or a K-Ras mutation is not immunogenic. Is that simply due to the evolution of cancer, that because of the ubiquity of these mutations in cancer has come up with enough evolutionary tricks to evade detection of those mutations, that's a teleologic question, but do we have biologic insight into this?

SR: We have to dig a little deeper into the biology; for a mutation to give rise to a change in a protein, first DNA is transcribed into RNA, which is translated into a protein. For that protein, even though it has now a string of amino acids that are not seen as normal by the body, that abnormal amino acid, a result of non-synonymous mutation, is recognized by the immune system only if the protein in which it occurs is broken down inside the cell into small peptides, that is, short sequences of amino acids. So the tumor cell or the antigen presenting cell breaks the changed protein into small peptides that are displayed on the surface, and then one of those peptides has to fit onto the surface of the patient's own human leukocyte antigen (HLA), a molecule that is the kind of molecule that we call transplantation molecules. For a mutation to be recognized by the immune system it has to be broken into these 9-11 amino acid peptides and fit on that patient's own transplantation molecule. That transplantation molecule is highly polymorphic, there are hundreds of them, and so if you had a mutation and your cells made small peptides but they did not fit on your HLA molecule, it wouldn't be recognized by the immune system. So, as we've learned more in the last five to six years about what cancer antigens are, it's these abnormal proteins that are broken down and put on the surface of a patient's presenting cells or tumor cells and that turns out to be only between one and a half to two percent of all mutations. When you look at melanoma it's 1.3 percent, when you look at the gastrointestinal cancers 1.6 percent, in breast cancer 2.1 percent of mutations are immunogenic because they happen to fit into that individual patient's HLA molecule, and the

most stunning finding of recent years in my view in this field is that virtually every patient recognizes a unique antigen. We are in the process of writing a report involving 195 consecutive patients, that we've identified the exact antigenic nature of what the T-cell can recognize in about 80 histologies, and that turned out to be 363 individual antigens that were recognized in these 195 patients and no two patients shared the exact same antigen with the exception of two patients that had a K-Ras mutation that was recognized on a very rare class 1 molecule (Cw 802 HLA).

PA: Just to make sure I understand, you're saying that in this series of nearly 200 patients, the first interesting finding is that each of them produces at least one neoantigen that is immunogenic.

SR: Yes, eighty percent of patients will.

PA: And second, outside of the K-Ras overlap they were novel across the board.

SR: That's right, of those 393 antigens, 392 of them were unique, not shared by any patients with the exception of K-Ras. That's not to say that p53 or other driver genes can't be recognized, but they aren't naturally recognized. You might be able to raise those very rare cells but that's correct, it's good news and it is bad news.

PA: Explain why that is, because I was just about to say that's really good but creates a huge problem for scale.

SR: You got it, that's exactly right. It's good news because we finally understand after all those decades what a cancer antigen is. Back in 1985 I knew one existed, yet I didn't know what it was, whether it would be shared, and we spent an enormous amount of time trying to identify shared antigens, especially in melanoma. These melanocyte antigens are shared by normal pigment producing cells, but now that we understand what an antigen is and we understand that most cancers contain multiple mutations, which give rise to the antigens. Since almost all cancers have mutations, if we can figure out ways to target these mutations that are foreign, we potentially have a treatment applicable to all cancer histologies. Since almost all cancers have mutations, let's recognize them and now you don't have to worry whether it's a breast cancer or a colon cancer or a brain tumor. The T-cells are there, so the possibilities of developing broadly applicable treatments exist. The bad news is, as you point out, to target these mutations highly individualized treatments are needed, unless you can fully unleash the immune system against even the most minor antigens, which we can't do. Now, checkpoint modulators have virtually no impact on the overwhelming majority of the solid epithelial cancers, it means that if you're going to stimulate immune reactions via a vaccine or a T-cell as a drug, it has to be individualized to target that cancer because that antigen is present only in that patient but not in any other patient and that's going to make it very complex to develop. But when we develop this other form of T-cells, Chimeric Antigen Receptor (CAR) T-cells. CAR-T cells is a whole other story. People said that it could never be applied, but in fact, if you have

something that works and can cure people, the genius of modern industry will figure out ways to make it available.

PA: I wanted to go back to 1985 to pick up the story with both, Ronald Reagan, but before we do, because you brought up CAR T-cells, let's tell the story about the diffuse B-cell lymphomas that ultimately led to Kite Pharma. I think that most people listening to this will have heard of a CAR-T, but I think it's an important illustrative case to explain how they came about, how they differ from a regular T-cell receptor and, as you said, how industry basically came in to solve a problem that at the outset looked daunting. So, pick it up wherever it makes sense with respect to lymphoma.

SR: We have to understand the biology; that normal T-cells have receptors that can recognize antigens on the surface of a cancer cell and how the immune system recognizes antigens. Well, there's a way to create an alternate way for a lymphocyte to recognize an antigen. That was created by scientists at the Weizmann Institute about 10 or 12 years ago, Zelig Eshhar and Gideon Gross. They took advantage of antibody recognition. Now, antibody recognition is very different than that of T-cell recognition. Antibodies recognize the three-dimensional structure of a molecule on the surface of a cancer cell or any cell, not a processed peptide brought to the surface, but an actual molecule on the surface, and that antibody like a lock and a key will latch onto that antigen. Well, T-cells can't do that. But by creating a chimeric T-cell you put antibody recognition domains into a lymphocyte that converts the lymphocyte from its normal recognition from its own receptor into the recognition of this antibody that you've put into the lymphocyte and that expands the number of molecules that can be recognized by T-cells. It's this chimeric antigen receptor which is part normal receptor but with antibodies attached to it, that enables the lymphocyte to now recognize molecules that it never was able to recognize in the course of evolution, based on antibody recognition. It turns out that there are very few molecules on the cell surface—I could name the few I know on the fingers of one hand—that are unique to a cancer that are not on normal cells. We learnt the hard way that the immune system will destroy a normal cell just as quickly as it will a cancer cell and we've mediated cancer deaths by targeting antigens that are present even in very low levels on normal cells. Well, it turns out there's a molecule on B lymphocytes called CD19 (cluster differentiation 19). We don't exactly know what its function is, but when B cells turn into lymphomas and leukemias they continue to express CD19. So with this understanding, and as soon as I heard about these chimeric T-cells, I invited Zelig Eshhar to come for a sabbatical in my lab, he spent three years working in the Surgery Branch and we worked out ways to use CAR-T cells to attack cancers, but we could never get cancers to disappear because the molecules that we were giving could not be used in large enough numbers because of their ability to recognize normal CD19. We developed a technique to introduce these anti-CD19 chimeric antigen receptors into T cells to create a CAR-T cell that when administered to patients would kill every cell in the body that expressed CD19, so all the normal B cells were eliminated, but so too were lymphomas and leukemias, and that became the first actual cell in gene therapy ever approved by the FDA.

So, how did that happen? Well, we studied the ability of these anti-CD19 CAR-T cells to kill B-cells in experimental animals and they did. One can live without normal B cells because you can give antibodies by antibody infusions. We used these CAR-T cells to treat the first patient ever to receive a CAR-T cell. This was in 2009, a patient that had a lymphoma that had spread throughout his chest had been through four different chemotherapy regimens, had enormous kilogram tumor burdens in his body, we treated with CAR-T cells that could recognize a CD19 molecule on the surface of normal B cells and all this tumor disappeared. He is well 12 years later and completely disease-free. We published a series of those treatments over the course of the next two years, and we had seven or eight patients who had a complete disappearance of all of their lymphoma. Diffuse large B-cell lymphoma is the most aggressive form of and lethal form of lymphomas that people develop, and they had complete regressions that were ongoing for at least several years. Well, once we did this incidentally all the patients' normal B cells disappeared, but again you can live without B cells. We published several of these cases and a year later Carl June at the University of Pennsylvania used these CD19 CAR-T cells to treat leukemia patients. Two years after our description of multiple lymphoma patients undergoing a complete regression, I was contacted by a former fellow, Arie Belldegrun who had worked in my lab 25 years earlier, he just finished his urology training became a professor of urology at UCLA. We become friends and he came to see me in 2011 saying, I want to commercialize this; I want to start a company to do this. We had several companies come through, like Johnson and Johnson, brought in 12 people [who] examined everything we had done and said, "If we have a lymphoma, we'll come back and get treated by you, but we don't see how we can make any money doing this at Johnson and Johnson." Well Arie had a different vision, he said we can figure out a way to make this available and in 2012 formed what's called a Cooperative Research and Development Agreement (CRADA) that enabled us in the lab to work with this biotech company, started Kite Pharma, they were able to give us funds to help support the research and so we just started that in 2012; we signed the CRADA and worked together. We treated over 50 patients, showed that this could happen and over half of patients will undergo durable regressions. He then did a multi-institutional study, and Novartis was doing this in leukemia patients almost simultaneously. His multi-institutional study reproduced the results exactly with about a 70% objective response rate with 50% durable complete regressions and in 2017 five years after Kite Pharma started working with us, it was sold to Gilead for 11.9 billion dollars. That all happened in the course of five years and that treatment is now available thanks to Kite and Novartis for use in patients in the US and Europe and parts of Asia that can effectively treat B-cell lymphomas and leukemias. It's really an incredible story that evolved so rapidly.

PA: Yes, it is. Do you think that CAR-T cells can have efficacy against non-hematologic cancers?

SR: Right now, the answer is no. We have no way to use them against solid cancers, again because for the solid cancer to be treated with a CAR-T cell, you have to have a molecule on the cell surface that's unique to cancer. We originally didn't fully realize quite how sensitive they could be and when we targeted molecules that were on normal cells, patients died, devastating

events in the development of the treatment. But monoclonal antibodies were first described about 45 years ago, and no one has found unique monoclonal antibodies against molecules uniquely on cancer cells and not normal cells, and that's what you need to make a chimeric T cell receptor. You need an antibody that you can put into a lymphocyte that has specificity and antibodies just have not evolved to recognize individual cell surface molecules on cancer, which are not shared by normal cells, whereas conventional T-cells do. Right now, there's very little prospect for CAR-T cells being useful for the treatment of solid tumors, but that's not to say that some brilliant ideas will come forth in the years to come that will make them available, right now they're not useful.

PA: What about for organs that are not essential, so you could waive the need to recognize or differentiate between cancer and non-cancer? For example, breast or even pancreas, I mean if a person had metastatic pancreatic cancer and you were willing to completely lose both normal and non-normal pancreatic cells and render that person a type 1 diabetic, it would still be worth it. Are there any antigens that are present on exclusively pancreas or exclusively breast or colon? Obviously, this wouldn't work for liver and lung, but is that a slightly easier problem to solve or is it just as hard?

SR: It's just as hard because for the past 45 years some of the best immunologists in the world have tried to develop these monoclonal antibodies that can uniquely recognize cancer and they have not found any, either because they haven't done it right or there just aren't these molecules on the cell surface. Even very recently in last several months, you probably heard about this, two deaths of patients that were targeting what was thought to be a prostate-specific molecule, PSMA, but it's not, it was present on normal cells and that can result in death of patients. So yes, if you could find a molecule unique to prostate cancer, breast cancer, that is expendable organs, you could develop more effective cell-based therapies against them, but right now none of those molecules have been identified.

PA: Let's now go back in time to the post-interleukin-2 insight, you had this other amazing realization, which is that there are certain types of lymphocytes that are attracted to tumors, T-cells that infiltrate the tumor, called tumor infiltrating lymphocytes (TILs). How did you come to understand these, understand the efficiency with which they could detect tumors?

SR: Looking back on it, things seemed to move very slowly, although we had an explosion of ideas, but when it comes to scientific advance it moved along pretty quickly. Because interleukin-2 as a T-cell growth factor was mediating reproducible regressions, it seemed reasonable that it is being mediated by the ability of interleukin-2 to stimulate lymphocytes in vivo. In melanoma patients we looked for T-cells that could recognize the tumor deposit itself. We didn't know what it was recognizing, so, what is a better place intuitively to look for a cell battling against the cancer than within the cancer stroma itself? We grew those cells out of peripheral blood, and also grew cells invading into tumor called tumor infiltrating lymphocytes or TILs, we grew them in vitro and in animals and then very quickly in human experiments. We grew those lymphocytes to large numbers in vitro, and administered them to patients with metastatic melanoma, and now instead of the 15% response rate that we got from giving

interleukin-2 alone, by giving lymphocytes that we grew in interleukin 2, we got response rates 30-35% in melanoma patients. It represented a substantial improvement. But they were pretty short durations; they were real but did not appear to be durable. Yet it was the first demonstration that lymphocyte transfer as a sole modality could cause tumor regression in patients with melanoma and to some lesser extent kidney cancer. So that intuition then became a reality of a biologic finding in that lymphocytes were the cause of these regressions or could be the cause of regressions.

And then things moved along fairly slowly and quickly, depending on your point of view. It immediately became apparent that if we had these lymphocytes naturally maybe we could genetically modify them to be more potent. If they were making factors that drew other cells, well, let's introduce that gene into them, but no one had ever introduced a gene into human cells. I teamed up with the two scientists at the NIH, French Anderson and Mike Blaise, who were trying to develop gene therapies to replace adenosine deaminase deficiencies, a lethal deficiency in young children, to see if they could introduce those genes. But of course, no genes had ever been introduced into people. We decided to see if we could break the ice about putting foreign genes into humans by putting a marker gene into the lymphocytes we're administering to patients. We picked a bacterial gene called neomycin phosphate transferase, inserted that gene into a patient's normal lymphocytes and our plan was to administer them, so we could track where these lymphocytes were going inside the body because they would have this unique bacterial gene being expressed. We proposed that to institutional review boards. At that point, the government had established what's called the Recombinant DNA Advisory Committee, the RAC (adequately named), that had to review any clinical proposals. We went through, we tabulated 117 different review groups having to go back and forth as they made changes until RAC finally voted, it was a painful time, 13 to 4 to allow us to do it. But the director of the NIH, James Wyngaarden, insisted that before we would start tampering with the human genome, we needed unanimous consent. Back and forth, making changes. Finally there was a vote of the RAC, 13 to zero with one abstention, which was unanimous and so we got permission to proceed with the clinical trial. Activists filed lawsuits against the NIH saying we shouldn't be tampering with the human genome, it was immoral, it was ungodly. But we finally got permission to do it and inserted these lymphocytes that were genetically modified with this bacterial gene that enabled us to track the cells inside the body when we did biopsies. It was a paper we published in the New England Journal of Medicine, and that then led to the gene modifications of lymphocytes that we attempted to use to improve them. We put in the gene for interleukin-2 that didn't improve them because we couldn't regulate it. But it just started our endeavors to genetically modify cells that finally came to fruition in the CAR-T cells by inserting the genes that would encode these new receptors that could recognize molecules on lymphomas and leukemias.

That started us on the track of trying to improve the cells and then there were a variety of advances. We learned that you had to first wipe out all these inhibitory regulatory T-cells before you gave the modified cells, and that jumped the response rates up to 55% in melanoma patients with about 25% being durable, complete remissions. We then started developing ways to use T-cells to do cancer treatments. In 2013, we finally realized that it was the unique

mutations and developed techniques that enabled us to develop T-cells specifically targeting mutations and published the first report in 2014. It was a patient with a bile duct cancer, cholangiocarcinoma, that was widespread in the lungs and liver. We gave her bulk of TILs; it did not work; then we gave cells that were uniquely directed against her mutations, and she's undergone a dramatic regression and is now disease-free.

PA: Those were TILs that were not genetically modified?

SR: Yes, our work went in two directions: genetically modifying TILs or figuring out ways to use natural TILs. These were natural TILs that were selected for mutation reactivity and given to a patient whose natural immune system was temporarily eliminated. She's living disease free now, eight years later all her liver and lung disease is gone. We subsequently have published on these T-cells that recognize unique mutations and their ability to cause regression in cervical cancer induced by human papilloma virus, in colon cancer, that patient recognized K-Ras protein, and in breast cancer recognized four random somatic mutations. We're now struggling to figure out ways to more efficiently target the products of unique mutations that cause the cancer. It's sort of ironic that the Achilles heel of the cancer is going to be the very abnormalities that caused it in the first place. And that brings us to 2021. We can now take advantage of all this new biologic information about the role of mutations and T-cells that target them and about the ability to genetically modify cells in large numbers using retroviruses. Can we take advantage of that technology, that biologic information to develop more effective immuno-therapies in the years to come and that's what we're working on today in the lab, as we speak.

PA: I want to go back and talk about a few other things, both for posterity, I suppose and also because I think there are some other things we've glossed over quickly. In 1985, you had this this opportunity to operate on the then President of the United States who had colon cancer. Why is it that you were a part of the team that would take care of the President, why is it that the surgery chief from the National Cancer Institute would be involved in the president's care? Was that something that's sort of mandated at the federal level?

SR: No, it's part of the aberrancy involved in treating high government officials. It turns out that there is a set of modules in the in Walter Reed or Bethesda Naval Hospital that are set aside for the treatment of the President. It's an isolated set of rooms, I learned this as it happened. I didn't know it ahead of time, what kind of equipment and availability of technologies was in place, so the President could run the country from his hospital bed. But it turned out that it was the physicians in this particular case at Bethesda Naval Hospital (they have marvelous doctors there) that would be treating the President and it turned out that the Chief of Surgery had just rotated off an aircraft carrier to be the Chief of Surgery at Bethesda Naval Hospital. It would change very commonly as officers in the Navy had different assignments and he happened to be an expert in vascular surgery, not oncology. He was the one responsible for calling the shots about the patient's cancer and it turned out he was an excellent vascular surgeon but not an oncologist, never really operating on cancer patients in any volumes, and so they needed an expert in oncology to take part. Just out of the blue on one

Friday evening, I got a call saying. “Would you come over to Bethesda Naval Hospital, we have a patient we need your help with.” It turned out to be President [Ronald] Reagan. It was simply because I was nearby, I had previously gotten a security clearance because I had tentatively been assigned to be part of a medical team that would take care of high government officials in the case of calamitous nuclear emergencies. So, it was because vascular surgeon was in charge and I was across the street, that I got that call and took part in that surgery.

PA: If I recall at the press conference following the surgery, you explained point blank that the president had colorectal cancer and if I recall Nancy Reagan wasn't too pleased about that.

SR: No, and I'm not telling stories here about a patient. Because of Larry Speakes the press secretary, it was public information, and he wrote a memoir that describes some of this. When we had a press conference they were a little concerned about having a vascular surgeon handle the questions [and] I had been in as an operating surgeon, as part of the operating team. Before I went on to hold a press conference, I remember standing backstage and Nancy Regan said, “You cannot use the word cancer in describing this because if foreign officials know, think the President has cancer, they won't pay any attention to him anymore thinking he would not be around.” And I said, “I am sorry I can't do that, if I have to go out, I have to just tell the truth.” It was Don Regan who was the Chief of Staff who finally talked her off that ledge and said, “Look we've just got to let him do what he wants to do.” So, we went out and the surgeon who led the discussion just basically read off the pathology report: there's an adenocarcinoma in distal portion of the colon and so on, and nobody understood what he said and so they asked me to explain it. So, I said, “The President has cancer”, which got me into all kinds of trouble. I later learned that when Vincent DeVita, who was the director of the NCI resigned to become chief at Memorial Sloan Kettering, I was on a short list to become the director of the NCI. Not a position I would have thought of accepting. I was told at that point, when I wrote this book in 1992 that my name got taken off the list, as someone who had become the director of the NCI, was very upset that I used the word “has” cancer and not “had” cancer—that is past tense. But we got over it and the President did very well and recovered and his early colon cancer never recurred.

PA: You mentioned in passing earlier that although you've been in the post you're in now for 47 years, along the way you've had a few jobs offers that have tempted you. I'm sure you've had many job offers. What are some of the ones that tempted you, at least where you thought you could even do better work or continue your work because obviously, you're so mission focused, it would be a special opportunity that I would imagine would get you to leave NCI. What were some of those other opportunities that you even contemplated?

SR: There were only three that I looked at, one was here at Georgetown because of a relationship I had with a surgeon, in terms of collaborating on things and it was sort of a favor to him to look at the job. I was also invited to look at a job as Chief of Surgery at Hopkins and ultimately, I was told, it boiled down to John Cameron and me on the shortlist. I went back a second time but refused to go back a third time because I knew I would not go to Johns Hopkins and leave the NIH. I was also asked to look at the job at the Brigham where Murray Brennan, a friend of mine, and I was again being pursued to accept that position, but again I backed out. I

knew that I didn't want to take an administrative job, I wanted to be in the lab, I wanted to be mentoring fellows, I wanted to be trying to make progress. I didn't want to guide other people making it. I wanted to be there to be doing it. I want to be guiding it because I thought I could do it well. I refused those offers, never looked at another job and actually turned down opportunities to advance in the hierarchy here at the NCI, because I wanted to remain at the level that I'm at the control of resources that enabled me to pursue the kinds of research that I thought needed to be done in an environment of enormous resources.

PA: Let's talk a little bit about checkpoint inhibitors. They've come up now a couple of times in this discussion, you've mentioned anti-CTLA-4 and anti-PD-1. Certainly, in my time at the NCI I got very familiar with anti-CTLA-4, and it was an exciting time and of course James Allison would go on to receive the Nobel prize a couple of years ago for his work in the discovery of this. Maybe go back and explain how that system works how the removal of brakes in the immune system works and of course, as a part of the undercurrent of this, it only works if there's a tumor antigen to be recognized. In other words, taking the brakes off when there's no stimuli doesn't do anything, but how does that system work and how is it a two-edged sword?

SR: So again, there are stimulants and there are inhibitors of virtually every physiologic system that we have. One of the inhibitors are molecules on the cell surface, on the surface of a lymphocyte that when engaged by a receptor will inhibit a lymphocyte from developing an immune reaction and surprisingly there were two molecules that have been found on the cell surface. Now, many more that when targeted by an antibody will not kill the cell but actually turn off the brakes that are keeping that cell's activity from inhibiting itself. It's releasing the brakes that turns out to have a very important function in the body, because there are some cells that can react against normal tissues, that do not react because they're being inhibited by these brakes and when you release those brakes, the T-cell can be very active. It turns out that cancer has manipulated those and by taking the brakes off you can attack certain cancers. This explains why melanoma is one of the more common cancers to be attacked, as it has many antigens generated by the many mutations. It was a startling discovery that simply attacking a molecule, a single molecule on the cell surface could take the brakes off a lymphocyte and let it attack cancer. When it comes to melanoma, kidney cancer, and cancers that have large numbers of mutations, because they have repair gene deficiency, Lynch syndrome or microsatellite instability (MSI) generated tumors, T-cells can very strongly react against cancer. But the common epithelial cancers that result in 90% of patients' deaths have very little reactivity against the checkpoint modulators, so although they can be lifesaving and potentially curative for some cancer patients, the overwhelming majority of cancer patients just do not respond to taking off the brakes. Because when you take off the brakes there's not a strong enough reaction to take advantage of, but hopefully combinations of treatments using checkpoint modulators will be more effective in the future. It was a major step forward and the beauty that is easy to apply because all that required was the injection of an antibody.

PA: When you think about these amazing conceptual advances in the field: the ability of CAR-T cells to recognize CD19 on B cells and eradicate any lymphomas originating from that lineage, the checkpoint modulators anti-CTLA-4 and anti-PD-1 and the durable effect that they

can have on patients who have enough mutagenic burden that relieving the checkpoint is enough to initiate it and what you described earlier with interleukin-2, I don't want to sound disparaging, but let's just call that the low-hanging fruit of immunotherapy, which is of course completely ridiculous given that's 50 years of work and countless lives. But if for the sake of being cheeky the low-hanging fruit of immunotherapy are those pillars. Do you believe that the final frontier to go from where we are in 2021 until the point where all of those 550,000 patients with solid organ metastatic cancer who have neoantigens, or 80% of them have neoantigens that are unique to them but not occurring in high enough frequencies that they will respond to a checkpoint inhibitor in isolation and or in combination with cytokines? Do you believe that there is a path for these people to be cured using adoptive cell therapy either genetically or naturally occurring in some sort of a customized format, do you think that that is the path forward from here?

SR: My intuition is very strong that the answer to that is yes, for a variety of reasons: one, we know it can work for multiple tumor types and as I've mentioned, we've described it and published a treatment of liver tumors, bile duct cancers, breast cancer, colon cancer, and cervical cancer. We have responses in ovarian cancer that were published, and so it's no longer a question of can it work, in these other cancers the answer is yes. It can work and that's a world of difference. Before interleukin-2 we never knew that immunotherapy would work, but once it did, we knew that the immune system could do it. Now we know that antigens recognized by T-cells are present on 80 percent of the common cancers and if you can develop unique reactivities, lymphocytes select reactivities against them and administering them can cause those regressions. In fact, now because we know the exact T-cell receptor sequences that we've cloned and isolated, it's almost an engineering problem. Since we identified the receptors, we've isolated libraries of receptors against p53 and k-ras that we can now use to genetically modify lymphocytes to turn a normal lymphocyte into a lymphocyte that can attack the cancer. We have our first example that we submitted for publication of targeting p53 by genetically altering a lymphocyte, by giving it a receptor that could recognize some of these driver antigens, so we know it can work, and to tell you the truth, I finally feel like I have the hang of this kind of research and that with sufficient work and creativity, this is going to be a problem that is that is solvable. We know the antigens are there, we know that T-cells are there; it should work, and it can work, and I believe, it will work as the years go on. That is 100 percent of what I am working on today; how to utilize these unique mutational reactivities to cause these solid common epithelial cancers that result in 90 percent of all cancer deaths, how to get them to respond to immunotherapy.

PA: I mean of all the eureka moments in your career of which you've had several, this one seems to be the most promising. Of course, maybe they always seem that way when you're glowing in them, but do you see it that way, that while every one of these milestones that came before this was vital, but this has the greatest potential. This recognition that virtually every solid tumor out there, has novel peptides that can be recognized by a patient's own immune system.

SR: Right now, just realize how current this is, we published a lot of these individual cases that can respond, we published the first 40 or so colorectal cancers showing that mutations were all unique, but we haven't published much of what I've told you. For example, none of the breast cancer work has been published. We now have looked at these 195 individual cancers and found regardless of histology they're there. So, it's very recent, this realization that mutations are the antigens and now that T-cells can recognize these mutations, it's really a new world. But that happens every time you make an advance. You find the immune system can be stimulated, okay, well, let's get to work on figuring out how cells can do it, and science works that way by incremental advances. We know this can work and I have every confidence that scientists around the world will figure out ways to make it work.

PA: That kind of reminds me of some of the important lessons that that those of us who've been privileged enough to work alongside you have learned along the way and I don't think you ever sort of pounded the table to make these lessons, but it was it was abundantly clear. One of them was no secrecy, there was never any secrecy. I remember working on my experiments and before data were published you would encourage me to reach out to people from different labs all over the country to share my results with them, even running the risk that they would scoop me, but none of that mattered to you. Your goal was what is the fastest path to the accumulation of collective knowledge in the field. Am I accurately representing that? I don't think I am overstating that.

SR: No, I've always been horrified by the secrecy that exists in medicine and it's an ongoing problem. The need for biotech companies, pharmacologic pharma, pharmaceutical companies to protect their intellectual property given current patent laws, will often prevent them from sharing information, sharing reagents and this is holding back progress. If we could somehow overcome this secrecy that results from either people's own personal jealousies about wanting to be the one who does it, or intellectual property that companies have to protect, to preserve themselves and raise funds to continue to do their work. We need kinds of regulations that will bring lawyers and doctors together to figure out ways to prevent that kind of secrecy from being a part of modern science. It's not like we're trying to create a better air conditioner, we're trying to save the life of another human being and I think that when you take care of cancer patients, it puts a lot of things in perspective. And the idea of having a policy or a rule that you live by that inhibits your ability to help people who could potentially be helped is abhorrent to me. I wrote a perspective in New England Journal of Medicine trying to change things. But they haven't changed, they're every bit as common today as they were back then. As you know the first thing a fellow hears in my lab when they start the first day is anything you know, you share; any experimental result you have, you can tell somebody; any experiment you plan to do tomorrow, you can tell somebody about. I mean our goal is to help people that are involved in the suffering of cancer and there is no excuse for not doing everything you can to try to help and that means sharing what you know.

PA: I remember, on one side of your office is the lab, on the other side of your office is the clinic. The other lesson that you've infused into the literally hundreds, might even be into the thousands, of people who have come through and trained with you is basically this idea that

one never retreats from the bedside. One of the things that struck me, especially in medical school, because I spent the entire time in the clinic, I lived in the clinical ward you may recall, I had rented an apartment in Bethesda, where I never went, except on Sundays to get new clothes, but I slept in the ward.

SR: I remember that you were quite a legend at the NIH. With respect to that, people thought I never left, but you never left. It was really quite an experience to see you in action.

PA: But the thing that was hard to believe and hard to process, until you experienced it, was that eight or nine out of ten people that walked in the door died. Because again what I think most people don't maybe understand, because it's implicit, but it should be stated: the patients who are coming to NIH have progressed through every standard therapy, people aren't coming here for whom there are standard options elsewhere. By definition, these are patients who have the most advanced, the most aggressive, the most recalcitrant cancers imaginable . These are people who would probably be expected to live no more than six months without a miracle, and they come to the NCI for those Hail Marys and if 20 percent of them are saved that's remarkable. But it means 80 percent of them don't. I think what I remember most, was the way in which you described taking care of those 80% and fighting the urge to retreat from them, because of the failure we saw in ourselves. How did you develop that? I assume it came naturally to you. But how deliberate has it been in how you taught those of us that came through.

SR: You know I have enormous respect for practicing oncologists who face this every day in their practice. It's difficult as you point out, especially when you give treatments that not only don't work but actually cause some harm. This has happened in the course of the development of these treatments, as we try to figure out exactly what we are doing in the right ways and the right ways to do it. But I always had the feeling that I was working and working hard to try to improve the situation, to try to somehow repair this holocaust, and that kept me going. I don't know what it must be like to be taking care of cancer patients knowing you have limited tools at your disposal that are not good enough, and yet that's all you have and that's what you do day in and day out. I mean that must be even more trying, and so I think, one of the things that keeps me going at least, is the fact that I'm doing everything I possibly can within reason to improve the situation. Without that, I think it would be much more difficult.

PA: Yes, there are so many patients that I still remember from more than 20 years ago who were those ones that didn't make it. I can't imagine how haunting it is for you sometimes, because I can see their faces, I remember their names, I remember their voices, and I remember their stories. You know, the newlywed girl who came to clinic one day and I mean she had literally been married for maybe three months, a beautiful 25-year-old woman with metastatic melanoma and she was not one of the survivors. A young man whose name and face I remember in every detail. A single guy, metastatic melanoma and what was most tragic in his case, I remember, everybody kind of abandoned him at the end of his life. I always, and I've said this before, I feel like cancer takes families that are close and brings them closer and takes families that are fractured and fractures them more. And I got the sense that his was fractured

to begin with, and you know, he was maybe 26 years old. So, I certainly understand the motivation for how you do what you do. I guess you talked about how the immune system has the stimulatory and the inhibitory components. Well, it might be similar that in taking care of patients like this, there's the motivation that comes from it to do more, but at some level there's the depression of the death toll. I'm not sure everybody could do that. You seem to have found that balance.

SR: Well, you know when I lie awake at night, it's not the successes that I think about, it's the tragedies, patients that you're remembering even now that I'm sure are impacting on you and it gets even worse because there are patients that we've killed by doing the wrong thing to them, not understanding some of the underlying biology, that's the hardest thing to deal with. But again, given the fact that I'm doing everything that I can reasonably do to help them, certainly eases the burden some, and if you know being a doctor, what an unbelievable privilege it is to have the opportunity to help people like that given the skills that you've, that you've developed. One of the first lines of the prayer of Maimonides goes, "You have been given the wisdom to alleviate the suffering of your brothers", and that's true in medicine because you know we spend a lot of time just learning how to help people. It's a unique opportunity in the world and in life in general, so there are the satisfactions that you're trying hard, even if most often things don't work out, but there clearly are sleepless nights involved in that process.

PA: You know, the good news is you have wonderful longevity in your family so despite being 81, I have every confidence that you're going to be doing this for many more years. I know you don't like golf enough to hang up what you're doing for the golf course. I found this photo, I wasn't sure if you would still recognize these guys, here, this is us. I think this is 16 years ago. We both look quite a bit younger, and this is the only picture of me in my office. This picture speaks to what an influence you've been in my life; I think the list of people who have had a greater impact on the course of my life than you is somewhere between zero and epsilon, a decidedly small list, so I feel forever in your debt and though I have not been able to follow in your footsteps, your impact is greater than you could ever recognize.

SR: Thank you for saying that. That means a lot to me knowing that someone of your incredible intellect and perseverance feels that way, so thank you.

PA: Again, I know what a sacrifice it was for you to take time today to speak, and I know that every minute you spent talking with me was literally a moment you were not working on this problem, so I'm beyond grateful and I know that the people listening to this are equally grateful. So, thank you so much Dr. Rosenberg for everything.

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