On behalf of myself and Doctor Weiner and the team here at Yale Cancer Center, it's really my honor to introduce our 15th Calabresi Memorial Lecture and I think I've been here for about 12 of them in honor of Doctor Paul Calabresi. We always are proud to welcome the Calabresi family with us in person or online. We have actually in the front row Judge Guido Calbresi, and I'll have him say a few words at some point and just received a week ago with the honor and another Yale degree.
He’s already had several and you know Paul’s younger brother and I’ve been very fortunate to know Guido for a long time as well.

We also have Steven Calabresi on his way from Rhode Island and we have several other Calabresi family online and we’re really honored to have Steven Rosenberg. This year’s Cal Brazi lecturer and we’ve been Vince and I have been trying to get Steven for years and the offer of doing it virtually was fine because that is such timely work.

It’s the type of work that we want to build here at Yale.

We actually have Mario Snow here who’s...
NOTE Confidence: 0.9201268
00:01:11.770 --> 00:01:13.164 will show up at some point, Steve.
NOTE Confidence: 0.9201268
00:01:13.164 --> 00:01:15.288 So we’re really happy you’re here.
NOTE Confidence: 0.9201268
00:01:15.290 --> 00:01:18.044 But let me say a few words about Paul.
NOTE Confidence: 0.9201268
00:01:18.050 --> 00:01:19.976 Paul Cal Brazi is often referred
NOTE Confidence: 0.9201268
00:01:19.976 --> 00:01:22.049 to as the father of oncology
NOTE Confidence: 0.9201268
00:01:22.050 --> 00:01:24.000 and as influence here at Yale.
NOTE Confidence: 0.9201268
00:01:24.000 --> 00:01:25.372 Remains to this day.
NOTE Confidence: 0.9201268
00:01:25.372 --> 00:01:27.087 He’s a former faculty member
NOTE Confidence: 0.9201268
00:01:27.087 --> 00:01:29.077 of Yale School of Medicine.
NOTE Confidence: 0.9201268
00:01:29.080 --> 00:01:29.674 In fact,
NOTE Confidence: 0.9201268
00:01:29.674 --> 00:01:32.198 he I believe he held one of the jobs I hold.
NOTE Confidence: 0.9201268
00:01:32.200 --> 00:01:34.207 He built medical oncology at a time when I
NOTE Confidence: 0.9201268
00:01:34.207 --> 00:01:36.195 don’t think it really was medical oncology.
NOTE Confidence: 0.9201268
00:01:36.200 --> 00:01:39.280 So he really, he really built the field.
NOTE Confidence: 0.9201268
00:01:39.280 --> 00:01:41.320 He was internationally recognized for
NOTE Confidence: 0.9201268
the pharmacology of anti cancer agents.

And if you walk through the B wing, you still feel his influence, the people he worked with, the people he recruited.

And he also serves as the director of Yale Cancer Centers Advisory Board. Until 2003.

Unfortunately, he himself passed away from cancer, showing us how while we're making progress, we still have so much more we need to do.

I have a good fortune to meet Paul. I hate to say it, 43 years ago. I don’t think I’ll talk about that too much here.
But his son Peter was my freshman roommate at Yale, and I met Peter and.

What better for someone who wanted to be a doctor to have as a roommate, you know, the father of oncology.

It was very nice.

They didn’t like me at first too much. But I’ve the family has warmed up to me over the years and actually I’ve I was looking through some photos last night.

You know it was an error without iPhone, so it’s hard to find photos like it is now.

But I’ve spent many memorable times with the Cal Brazi family over the
Yale Paul was an advisor, a mentor, and a really good friend to me. Actually Vince and I, I still we know we helped him with his disease as well. And having this job here means so much to me. One of the reasons I’m back at Yale is Paul had always told me Yale is a great place for you. I think you’d be happy there. So joining us today we have Guido Calbresi as I mentioned Doctor Calgary’s brother, his wife Anne I believe is online. His wife Mimi and Paul’s daughter Janice and son Peter are online. So this is a very special grand rounds.
We have a plaque for you, Steve. I don’t know if it arrived yet. It has to get to NCI security. But what I’m going to do now is I’m going to turn it over to Vince De Vita who needs a little introduction here, but certainly another father of oncology and actually Paul’s good friend. And I’m going to let Vince come up, introduce the you Steven, and then we’ll do a quick photo with you in the background. We’ll figure out how to do a hybrid photo and then we’ll give the time to you for your talk.
00:03:44.620 --> 00:03:44.940 Vince.
NOTE Confidence: 0.40746477
00:03:57.500 --> 00:04:00.660 Yeah, My welcome to the Calabresi family.
NOTE Confidence: 0.938995675
00:04:00.660 --> 00:04:03.120 It’s always a pleasure to see
NOTE Confidence: 0.938995675
00:04:03.120 --> 00:04:05.608 you here and reminisce about my
NOTE Confidence: 0.938995675
00:04:05.608 --> 00:04:08.140 old friend and my mentor, Paul.
NOTE Confidence: 0.938995675
00:04:08.140 --> 00:04:09.924 I’m sure he’s up there looking
NOTE Confidence: 0.938995675
00:04:09.924 --> 00:04:11.054 down saying this is great.
NOTE Confidence: 0.926288107142857
00:04:14.260 --> 00:04:16.114 And it’s a real pleasure to
NOTE Confidence: 0.926288107142857
00:04:16.114 --> 00:04:17.350 introduce my longtime friend
NOTE Confidence: 0.926288107142857
00:04:17.405 --> 00:04:19.057 and colleague Steve Rosenberg.
NOTE Confidence: 0.926288107142857
00:04:19.060 --> 00:04:22.840 I met Steve in 1974 when
NOTE Confidence: 0.926288107142857
00:04:22.840 --> 00:04:25.120 he arrived fully formed.
NOTE Confidence: 0.926288107142857
00:04:25.120 --> 00:04:27.240 As the new chief of the surgery brands
NOTE Confidence: 0.926288107142857
00:04:27.240 --> 00:04:29.160 right out of his training program,
NOTE Confidence: 0.926288107142857
00:04:29.160 --> 00:04:32.250 this caused quite a stir because
NOTE Confidence: 0.926288107142857
00:04:32.250 --> 00:04:34.690 the old administration of surgeons
were oldfashioned and their motto was if you can’t go wide, go deep.

And and Steve was a thinking surgeon, which immediately changed the ability to collaborate and to consult with the surgery department. It was a fun time for the he also came with his passion for immunotherapy. It was a patient he operated on in 1968 who came in with right up a quadrant pain, had a non visualizing gallbladder, was all set to go to operation.

And in the book he was to write a lot later he describes the the source of his passion in immunotherapy. It was a patient he operated on in 1968 who came in with right up a quadrant pain,
And Steve reviewed his old charts and he had come in 12 years earlier with belly pain. He was operated on a big masses of tumor with metastasis to the liver. And here he was 12 years later he was supposed to die. Few months later he was 12 years later he was fine. Steve thought this was a powerful expression of the immunotherapy and he wanted to find out how we could harness this work. And since then, with fierce intensity, he has worked in the immunotherapy field and he has unwavering focus and stayed on this. Doing work in vitro and then in...
00:05:53.895 --> 00:05:55.826 animals and then repeating the animal
00:05:55.826 --> 00:05:58.192 studies in humans to the point where
00:05:58.259 --> 00:06:00.219 he's become the lead investigator
00:06:00.220 --> 00:06:03.220 in the world in immunotherapy,
00:06:03.220 --> 00:06:05.200 having either discovered or developed
00:06:05.200 --> 00:06:07.963 all of the things that have been
00:06:07.963 --> 00:06:10.099 done in immunotherapy that are now
00:06:10.099 --> 00:06:13.420 making us very excited in the clinic.
00:06:13.420 --> 00:06:15.045 And since we're talking about
00:06:15.045 --> 00:06:16.020 fathers of programs,
00:06:16.020 --> 00:06:18.468 I would sort of view Steve as the
00:06:18.468 --> 00:06:21.147 father of the immunotherapy of cancer.
00:06:21.150 --> 00:06:24.298 He got his bachelor's degree and
00:06:24.298 --> 00:06:26.146 his MD degree from Johns Hopkins.
00:06:26.150 --> 00:06:29.420 He’s got his PhD from biophysics
00:06:29.420 --> 00:06:31.666
from Harvard, and he spent his time in Boston at the Peter Ben Brigham getting a surgical training under the famous Brandy Moore. And then during that time he’d spent two years coming to the clinical associate at the National Cancer Institute. I also started as a clinical associate. We used to refer to ourselves as the Yellow Berets. Because it was a Vietnam War and we got our military credit without any of the gunfire. Steve may forgive me for not going over his honors and awards. They’re just too many.
00:07:04.550 --> 00:07:07.810 I stopped counting 80.

00:07:08.598 --> 00:07:10.997 And finally,

00:07:10.997 --> 00:07:13.132 I've been working with Steve on

00:07:13.132 --> 00:07:15.540 the textbook answer Principles of

00:07:15.540 --> 00:07:19.095 Practice of Oncology for 42 years.

00:07:19.100 --> 00:07:21.214 He and I are two of the three editors,

00:07:21.220 --> 00:07:24.060 making sure that we each,

00:07:24.060 --> 00:07:27.452 the other guy,

00:07:27.452 --> 00:07:30.242 was doing all the things he had to do.

00:07:30.242 --> 00:07:32.774 And of all the editors,

00:07:32.780 --> 00:07:34.940 the editors in preparing the book,

00:07:34.940 --> 00:07:35.708 making sure that we each,

00:07:35.708 --> 00:07:37.899 the other guy,

00:07:37.900 --> 00:07:39.500 was doing all the things he had to do.
Steve was the most competitive and not just a little story about to illustrate that.

The publishers took us away, reached new addition a one week before to set the table of contents and pick the authors and invite them and at the end the second week.

And so we work very hard during those days, getting up at 7:00 in the morning work until five and at the end of the day we would, you know, do our exercise and relax.

And Sam Helman, at that time you played tennis. I jogged and Steve, not so much.

Steve wasn’t really into exercise.
00:08:20.540 --> 00:08:22.856 or healthy diet at the time.

00:08:22.860 --> 00:08:24.820 So much to my surprise at the end of one day when he said you mind if I jog with you?

00:08:27.100 --> 00:08:28.820 And so I said no with a little smile on my face.

00:08:30.549 --> 00:08:32.706 Off we went, me and my running shorts and my New Balance shoes.

00:08:34.116 --> 00:08:35.898 Steve and his khaki pants and tennis or sneakers more than and we started running and after a little while I ratcheted it up and Steve ratcheted it up. And a little while I did some more and Steve ratcheted up some more and
00:08:52.744 --> 00:08:54.912 pretty soon we were sprinting as
NOTE Confidence: 0.944566418571428
00:08:54.912 --> 00:08:57.328 fast as we could with our heads down,
NOTE Confidence: 0.94427896
00:08:57.330 --> 00:08:59.850 not to some specified gold,
NOTE Confidence: 0.94427896
00:08:59.850 --> 00:09:02.725 but clearly to see who
NOTE Confidence: 0.94427896
00:09:02.725 --> 00:09:04.450 would collapse first.
NOTE Confidence: 0.94427896
00:09:04.450 --> 00:09:06.852 And Steve Rosenberg.
NOTE Confidence: 0.94427896
00:09:06.852 --> 00:09:11.357 The unconditioned Steve Rosenberg.
NOTE Confidence: 0.94427896
00:09:11.360 --> 00:09:13.578 Collapsed about four seconds
NOTE Confidence: 0.94427896
00:09:13.578 --> 00:09:15.276 before the conditioned.
NOTE Confidence: 0.94427896
00:09:15.280 --> 00:09:16.080 Vince Devita.
NOTE Confidence: 0.941691165714286
00:09:18.400 --> 00:09:19.758 And I tell you, ladies and gentlemen,
NOTE Confidence: 0.941691165714286
00:09:19.760 --> 00:09:21.632 that’s the last time I beat
NOTE Confidence: 0.941691165714286
00:09:21.632 --> 00:09:22.880 Steve Rosenberg at anything.
NOTE Confidence: 0.93019015
00:09:25.000 --> 00:09:28.440 His talk today is entitled The Lymphocyte,
NOTE Confidence: 0.93019015
00:09:28.440 --> 00:09:30.672 the Living Drug for the Treatment
NOTE Confidence: 0.93019015
00:09:30.672 --> 00:09:32.160 of Cancer Doctor Rosenberg.
Well, this is a unique pleasure for me for several reasons. It's a pleasure to honor Paul Calabresi and his family. Paul a giant in the field of medical oncology, but also to present in front of Vince De Vita who has played such an important role in my ability to do a lot of this work. Vince is a true giant in the field of oncology and his contributions are known to you all. But when I started working at the NCI trying to develop immunotherapies for treatment of cancer,
there was not a lot of enthusiasm for it.

But as I initially began to get results, I remember going to Vince De Vita and saying, look, I think there’s something here and I’m going to need more resources. And in a remarkably generous way, I was given by Vince De Vita probably over the objection of many, I know over the objection of some others, was given the space and money and resources to conduct the kinds of studies that I’ll be talking about today. And it made a huge difference. To me, we became friends for the past 47 years we worked in a textbook, Vince’s the soul of that textbook and
00:11:15.035 --> 00:11:18.835 has led the the process for now through

00:11:18.840 --> 00:11:21.675 1212 generations of the of the book.

00:11:21.680 --> 00:11:25.118 And so to be here to honor Paul Calabresi,

00:11:25.120 --> 00:11:28.250 to honor Vince De Vita.

00:11:28.250 --> 00:11:28.944 Doctor Weiner,

00:11:28.944 --> 00:11:31.720 thank you so much for the invitation to

00:11:31.793 --> 00:11:34.369 to come and deliver these remarks today.

00:11:37.330 --> 00:11:39.562 So I’ll be talking about lymphocytes as a

00:11:39.562 --> 00:11:41.650 living drug for the treatment of cancer,

00:11:41.650 --> 00:11:44.138 The use of lymphocytes in much the same

00:11:44.138 --> 00:11:47.309 way that we might use chemotherapy or other

00:11:47.309 --> 00:11:49.813 targeted agents to administer the to the

00:11:49.813 --> 00:11:53.616 patient to try to impact on the on the tumor.

00:11:53.620 --> 00:11:56.320 And I’ll be talking about this

00:11:56.320 --> 00:11:58.550 particular kind of immunotherapy and
that is cell transfer immunotherapy that has many advantages. One, if we’re going to use a lymphocyte as a drug, we can grow lymphocytes easily to 10 of the 11 cells or more and administer very high large numbers of highly selected cells because we can potentially identify the exact subpopulations and effector functions that are required for the cancer regression. And 3rd and very importantly, we can manipulate the host prior to the cell transfer in a way that you cannot do with other forms of
immunotherapy because the cells to be used are outside the body and we can therefore alter the microenvironment of the tumor in ways that will enable immune cells to enter into those tumors and destroy them. And so it’s the cell therapy that I’m going to emphasize this morning. Now cells carry a conventional T cell receptor and the entire function of the lymphocyte is dependent on that T cell receptor to recognize its antigen. Which in conventional forms for CD8 cells, is a processed peptide coming from inside the cell and put.
on the patient’s own MHC molecule.

But a little over a decade ago, chimeric antigen receptors were described and at the Weitzman Institute. And that converts a lymphocyte into the recognition of an antibody not based on the conventional T cell receptor. But by making a single chain of the heavy and light chains of an antibody and connecting it to intracellular signaling domains, we can then use that lymphocyte to become recognition based on an antibody rather than on a T cell receptor. It can recognize cell surface molecules based on this antibody.
And so it provides us with a whole other way to identify, identify targets. And I’d like to spend just a moment on CAR T cells because although they’ve had substantial activity in the treatment of the hematologic cancers, they have not had activity against the solid tumors. And what’s the reason for that? Well, CAR T cells require the use of monoclonal antibodies that recognize molecules on the cell surface. And they were described by Kohler and Milstein over 45 years ago.
And despite extraordinary work, there’s not been found a monoclonal antibody that can distinguish A malignant from a normal cell. The antibodies can have a lot of influence by reacting with cells. Surface molecules that can affect cell signaling can affect cell growth. But we do not have antibodies that are unique to a cancer. And that’s a problem, because it’s just as easy to kill a normal cell as a cancer cell, and we’ve seen deaths due to the application of cells that do not clearly distinguish.
NOTE Confidence: 0.938017398888889
00:15:14.510 --> 00:15:17.279 between a tumor in a normal cell.
NOTE Confidence: 0.938017398888889
00:15:17.280 --> 00:15:19.808 Normal cells are highly,
NOTE Confidence: 0.938017398888889
00:15:19.808 --> 00:15:22.740 exquisitely sensitive to.
NOTE Confidence: 0.938017398888889
00:15:22.740 --> 00:15:24.852 The expression of monoclonal
NOTE Confidence: 0.938017398888889
00:15:24.852 --> 00:15:27.164 antibodies and using ones that
NOTE Confidence: 0.938017398888889
00:15:27.164 --> 00:15:29.394 can attack normal cells have
NOTE Confidence: 0.938017398888889
00:15:29.394 --> 00:15:31.971 major clinical toxicities and
NOTE Confidence: 0.938017398888889
00:15:31.971 --> 00:15:34.797 thus the limitation of cars for
NOTE Confidence: 0.938017398888889
00:15:34.797 --> 00:15:37.420 solid tumors is substantial,
NOTE Confidence: 0.938017398888889
00:15:37.420 --> 00:15:40.815 and there are as yet now no
NOTE Confidence: 0.938017398888889
00:15:40.815 --> 00:15:43.280 known CAR T cell treatments that
NOTE Confidence: 0.938017398888889
00:15:43.280 --> 00:15:45.884 are capable of treating in a
NOTE Confidence: 0.938017398888889
00:15:45.884 --> 00:15:48.180 reproducible fashion malignant cells.
NOTE Confidence: 0.946962533333333
00:15:50.300 --> 00:15:52.448 They are, however.
NOTE Confidence: 0.946962533333333
00:15:52.450 --> 00:15:54.605 Potentially very valuable for the
treatment of humanologic malignancies.

And back in 2009, we reported the first patient to be treated with a cell therapy that finally got approved by the Food and Drug Administration. The only cell therapy now approved and I'll just spend a moment talking about it. We had developed models showing we could treat syngenetic tumors by targeting CD19. A molecule on virtually all B cells and B cell malignancies. We saw a patient with an aggressive lymphoma in the way it behaved as you can as you'll see his Xrays, he's had multiple chemotherapies, vaccines, checkpoint modulators,
more chemotherapy and finally came to us in May in 2009 for treatment with.

His own T cells that were genetically modified with a chimeric antigen receptor that could recognize CD19 and this is what his X-ray look like when we treated him.

You can see large masses directed by these yellow arrows in his axilla. Large mediastinal mass, huge spleens, lymph nodes surrounding his vena cava and aorta, huge iliac vessels.

We treated him. All of his tumor disappeared over 27 days.
In the course of a few months and he remains disease free to the present.

He had bone marrow replaced which also disappeared. But you pay the price because normal cells can also be killed and B cells disappeared at a time when normal T cells and natural killer cells were returning over the course of the week and 1/2 after the cell infusion. It took eight or nine months for the precursors that were not destroyed to restore B cells in the patient. But patients can survive for long periods of time in the absence of any B cells.
Well, we treated the 1st 10 patients, six of them responded.

Five of them are still responding to the present day over 10 years later.

And in the surgery branch we received these kinds of results.

We had objective responses by 47 percent.

42% are ongoing and have never recurred out, with median survivals now beyond eight years.

A good friend of mine, Ari Beldegrand, had been in my lab 20 years earlier.

We had remained friends and he heard about some of these responses and after we had had six complete responders, he contacted me and said he
wanted to start a company,
Kite Pharma, who went on to do a multiinstitutional study that almost exactly reproduced our results.
We began interacting with Kite in 2012 through a research agreement.
A research and development agreement.
A crater to transfer our technology to Kite Pharma.
Five years later, they received FDA approval, along with Novartis, who had begun working on this a year later.
And in October 2017, Kite, who has started to do this from nothing, was told to Gilead Sciences for $11.9
billion and it’s now widely available.

This treatment is now widely available through the United States and Europe and now beginning in Asia as well.

I think a very proud example of how findings in an academic and a government institution can then get translated to help people in need.

This remains, however, the only T cell treatment that has been approved by the FDA, although there were several others that have shown effectiveness against multiple myeloma.
00:19:52.054 --> 00:19:54.630 are have actually just very
NOTE Confidence: 0.93421556
00:19:54.630 --> 00:19:57.229 recently been been approved.
NOTE Confidence: 0.945285226
00:20:01.950 --> 00:20:03.990 So here’s the problem of
NOTE Confidence: 0.945285226
00:20:03.990 --> 00:20:06.030 oncology in the United States,
NOTE Confidence: 0.945285226
00:20:06.030 --> 00:20:09.000 there are about 600,000 cases.
NOTE Confidence: 0.945285226
00:20:09.000 --> 00:20:11.850 The solid cancers, epithelial cancers
NOTE Confidence: 0.945285226
00:20:11.850 --> 00:20:14.919 comprise about 90% of all cancers
NOTE Confidence: 0.945285226
00:20:14.919 --> 00:20:17.637 that cause death in this country,
NOTE Confidence: 0.945285226
00:20:17.640 --> 00:20:20.916 about 10% of the humanologic cancers.
NOTE Confidence: 0.945285226
00:20:20.920 --> 00:20:22.840 And the devastating impact of this,
NOTE Confidence: 0.945285226
00:20:22.840 --> 00:20:23.692 as you can see,
NOTE Confidence: 0.945285226
00:20:23.692 --> 00:20:25.623 is that one in every two or three
NOTE Confidence: 0.945285226
00:20:25.623 --> 00:20:27.411 Americans of us will develop an
NOTE Confidence: 0.945285226
00:20:27.411 --> 00:20:28.919 invasive cancer during our life,
NOTE Confidence: 0.945285226
00:20:28.920 --> 00:20:29.860 and unless we can find
NOTE Confidence: 0.945285226
00:20:29.860 --> 00:20:30.800 better ways to treat it,
00:20:30.800 --> 00:20:32.640 about one in five will die of the cancer.

And so the major challenge confronting cancer immunotherapy today is the development of effective immunotherapies for patients with metastatic epithelial solid cancers that cannot be cured by any available treatment and result in 90% of all cancer deaths, the checkpoint modulators have had major impact on some solid tumors like Melanoma renal cell cancer patients that have mismatched repair genes. But the overwhelming majority of
patients with the solid epithelial cancers do not respond with only single digit levels of response to the combined use of checkpoint inhibitors.

So how can we attack these solid epithelial cancers and I'll talk mainly about them and but here's a general cartoon of how we do this.

We excise a tumor. If you follow me along clockwise, we follow it excise a tumor. We grow cells to try to identify cells with anti-tumor activity if we can, we grow them selectively to large numbers. We generally infuse $5 \times 10^9$ to $10^10$ cells.
and reinfuse them following A.

Non myeloblade of lymphoid depleting regimen with cyclophosphonine or fludarabine that will eliminate T cells for about 8 days before they normally recover.

I'm going to talk primarily about the epithelial cancers, but we learned a lot from Melanoma, so let me spend a moment.

With this lesson, we treated 192 patients with metastatic Melanoma with some of these results that I first showed Vince Stavita when we had our first lymphocyte
transfer that mediated aggression of a Melanoma patient in 1988.

As you can see, we've treated 192 patients with their own cells, their own tumor infiltrating lymphocytes that we would grow out of the tumor. Those cells are a sink for tumor reactive cells. You can see our objective response rate by classic recess criteria, which is the criteria I'll use throughout this talk with 56% with a quarter of patients having complete regressions, only two patients that ever had a complete regression ever gone on to recur.
The rest of the main disease free and of these 48 complete responders, only two patients required more than a single treatment. The cells are alive, they can divide up to 10,000 fold in the first two weeks and that’s they patrol the body, wherever the circulation exists. Well here are our results in those the overall. Survival race, progression free.
survival race or were about 37%, but notice the complete responders very rarely ever recur. Somehow adoptive cell therapy appears to eliminate the last Melanoma cell and so the rest of the presentation will be on trying to find factors that we can use to treat not only Melanoma but the solid epithelial cancers. And the first question? That we’ll discuss or what are the characteristics of the cells that mediated cancer regression in vivo, especially to these patients with Melanoma that have undergone
durable complete regressions.
And to do that we used a high dimensional single cell transcriptome analysis of up to 10,000 cells per patient, a single very elegant single cell analysis available 10X from alumina.
Well, because we had a group of patients that could respond and not respond, we utilize the single cell approach to identify the transcriptome analysis of patients, comparing responders from non responders. Because for the first time we had a group of immunotherapy patients that were showing this distinction and
when we break all of the lymphocytes.

And their transcriptome analysis using this these UMAP,

UMAP or typically analysis using a near neighbor analysis,

you can identify 22 different kinds of lymphocytes based on their transcriptome,

the messages that they express into proteins.

And there turned out to be one cluster that seemed to differentiate responders from non responders.

And when we looked at the transcriptomic analysis it turned out that only that cluster cluster number one could distinguish responding.
from non responding patients.

If we looked at the expressed genes in each of the other 21 clusters, the responders and the non responders were virtually identical except in this cluster that was largely non responders. It was only cluster number one that could distinguish.

Responders from non responders and it turned out that cluster one was highly enriched in stem like lymphocytes that do not express CD39 and CD69, two molecules of lymphocyte activation and differentiation. Well,
it appeared therefore that maybe these CD3969 stem like lymphocytes were the ones that were most responsible. For the Melanoma regressions, because when we looked at the survival there was no statistical difference between the cells that were respond, the patients that were responding to
not responding based on the number of these double navigative cells that they received highly statistically significant well.

When we looked at the properties of these cells, they were true stem cells. If you divide a lymphocyte population of till and facts based on CD39 and 69 expection, the double positive cells. When isolated and grow will only reconstitute themselves double positive. But when you take the double negative cells they reconstitute themselves whereas the double positive cells do not.
They are true stem like cells when you take cells in one of our trials targeting Nye cell, one antigen you can see. In red, the double negative cells from the infusion continued to sustain themselves as they grew in vitro and were re stimulated one time after another, whereas the double positive cells disappeared as they grew. They were not stem like, they could not reproduce their themselves with their own. Native reactivities and in fact if you look at the actual transcriptomes,
it is a stem like markers like K.

LF2TCF7CD62L that were expressed in the response associated culture.

And if you then took this back to the mouse models that we had initially studied female mouse model of Melanoma, you can see that in fact.

These cells when implanted and allowed to grow for 10 days before treatment, they grew.

If you gave double positive cells, they had some weak reactivity.

But if you gave double negative cells at two different concentrations including this very low concentration of 500,000 cells,
the double negative cells could mediate dramatic anti tumor effects compared to the bulk populations and so we could thus identify. These stem like cells that had a profound reactivity and published that about two years ago and have been utilizing it. We'll talk about some of the results in the epithelial cancers. But very recently and in this unpublished data, we found that we could actually make the double positive cells that were fairly weak work much better if we could give them a vaccine that could target the same antigens.
00:29:02.180 --> 00:29:03.930 that the cells were targeting.
00:29:03.930 --> 00:29:05.946 And you can see here if we take the double positive cells which are the most exhausted of the cells and give them, they do have some reactivity compared to the control.
00:29:08.011 --> 00:29:10.010 exhausted of the cells and give them,
00:29:10.010 --> 00:29:12.165 But when you give the double positive, the double neck, these double positive cells in conjunction with a vaccine, you can now make them very active and take even 1 centimeter tumors, 20% of the total.
00:29:13.890 --> 00:29:16.165 But when you give the double positive,
00:29:16.170 --> 00:29:17.172 the double neck,
00:29:17.172 --> 00:29:18.508 these double positive cells
00:29:18.508 --> 00:29:20.089 in conjunction with a vaccine,
00:29:20.090 --> 00:29:22.295 you can now make them very active and take even 1 centimeter tumors, 20% of the total.
00:29:22.295 --> 00:29:24.650 and take even 1 centimeter tumors,
00:29:24.650 --> 00:29:25.570 20% of the total.
00:29:27.990 --> 00:29:30.438 5% of the total body weight of the mouse to disappear completely and
00:29:30.438 --> 00:29:32.650 mouse to disappear completely and
that’s something that we’re now clinical trial that we’re now initiating.

So we know the kind of cell we want to use. But what did the till actually recognize that enables the in vivo control in the last Melanoma cell And the fact that we have seen specific regression of cancer in the absence of any on target but off tumor toxicities led us to believe. That we were targeting something completely unique to cancers and those were the targets of cancer mutations that we suspected were the CAR targets of the till. And so again, to identify the target, we have to identify this small peptide that comes from an intracellular
molecule or a molecule that’s been ingested by the cell that can then be presented to the T cell receptor.

And so about five years ago, we developed this particular blueprint for the identification. Of cells that were recognized by Till that could mediate tumor regressions. And what do we do? If you follow me counterclockwise, we excise a tumor, isolate the TILL and extract DNA and RNA from that till and do whole exome sequencing so that we could identify every cancer mutation that was present in that cell.
And we do RN A/C to identify all the mRNA molecules as well. We then take those. Cancer mutations as 25 more molecules and either as peptides or as mini genes put together in a tandem structure to form a tandem mini gene and put it into a patient’s own antigen presenting cell. Now that antigen presenting cell contains all of the MHC molecules of the patient and if any of these cancer mutations can then be presented. On the antigen presenting cell and recognized by the T cell receptor.
of till that forms a signal in
NOTE Confidence: 0.943847613571429
the lymphocyte that enables us to
NOTE Confidence: 0.943847613571429
identify it because of upregulation
NOTE Confidence: 0.943847613571429
of activation markers and we could
NOTE Confidence: 0.943847613571429
then grow those cells selectively.
NOTE Confidence: 0.943847613571429
So again the key is to make a 25 more
NOTE Confidence: 0.943847613571429
peptide with the mutation in the middle
NOTE Confidence: 0.943847613571429
so that any peptide that could be
NOTE Confidence: 0.943847613571429
presented on the MHC surface is concluded.
NOTE Confidence: 0.943847613571429
It could either be the last.
NOTE Confidence: 0.943847613571429
Amino acid of the peptide that's presented,
NOTE Confidence: 0.943847613571429
or the first one,
NOTE Confidence: 0.943847613571429
but it has to be in this 25.
NOTE Confidence: 0.943847613571429
And the advantage of this is there's no
NOTE Confidence: 0.943847613571429
need to do any predicted peptide binding.
NOTE Confidence: 0.943847613571429
Every candidate peptide and all
MHC loci are included in the screen because both have to be recognized the peptide on the MHC and there’s no tumor cell lines necessary. And as you know, it’s very hard to grow tumor cell lines for most of the epithelial cancers. This can be done within about two to three weeks, takes 10 days to do the to identify all of the cancer mutation sequences, another few days to do the bioinformatic analyses.
And so one has all this information available within two weeks of the tumor resection. We started in Melanoma and evaluated 86 patients. Those tumors have more mutations in most 556 as a median. We screened every mutation that was expressed in RNA/C 15,000 mutations in these 86 patients to see if any could be recognized by the patient’s own autologous T cell. So we looked at 218 immunogenic epitopes 85% of patients could recognize their own tumor cells based on. Interestingly,
only 1.4% of the mutations could be recognized because they had been cleaved and also presented on the Mac molecule. Of that particular patient, 92% were CD8 cells rather than CD4 cells. And our first surprise every NEO antigen that we recognized, all 218 were unique to the individual patient. Patient’s cancer and recognized by that patient, none were shared between 2 Melanoma patients. Well, we then did this for 130
consecutive gastrointestinal cancers

NOTE Confidence: 0.951574925

screened over 15,000.

NOTE Confidence: 0.951574925

Of the expressed mutations, 1.3% were recognized interestingly half by CD8 and CD4 cells.

NOTE Confidence: 0.951574925

And for the first time we found an antigen that was recognized in more than one patient.

NOTE Confidence: 0.951574925

It was a KRAS mutation restricted by a fairly unusual CW8O2 Class 1 molecule.

NOTE Confidence: 0.941921875

The other hundred 209 epitopes that were found were all unique to the individual individual patient.

NOTE Confidence: 0.941921875

True in breast cancer that we just published last year, 43 consecutive patients 100 immunogenic
epitopes 2.1% were recognized of the mutations recognized half by mainly by CD Fours and all were absolutely unique. And here is an updated as of last September study of 205 consecutive patients and note we’re talking about the GI cancers, breast cancer, lung cancer, Gastro, across the board as you can see about 70 to 80% of the patients contain Neo antigens their own cancer mutations that were presented on their autologous cancer cells and of this 363 neo antigens we found, we only found this one K Ras that was
recognized by more than one patient found on this particular screen.

Now an advantage of targeting mutations is its applicability to target multiple cancer types, because we're targeting mutations and most cancers have mutations, some more than others. But let me show you examples of what we've been able to see an individual patient's cancers that can respond. Interestingly, the first patient that responded to T cells that were unique, identified as uniquely.
Responsive to our own mutation, it was under a B2 mutation, was a 4045 year old woman with a clangiocarcinoma. Bile duct cancer had undergone A hepatectomy, multiple chemotherapy regimens, developed lung and liver metastases. We treated her with unselected till much as we did in Melanoma that does not work for the epithelial cancers. Unselected till do work in Melanoma, but you have to select the specific ones which are much rarer in the epithelial cancers. We gave her those,
she didn’t respond. However, when we use our Tandeminy gene approach, she had 26 mutations. We could found that her B2IP mutation that she recognized it contained almost 90% the infusion bag of cells recognized as mutation. And she underwent a complete regression of all of her cancer. You can see her lung cancers gone. She had three liver metastatic deposits that disappeared and she remains now disease free. Almost 10 years, 10 years later, this woman who had a metastatic breast cancer, had been through seven
different treatments for her metastatic disease to multiple groups, chest, wall, bone, multiple nodal groups. She came to us, received cells for treatment. She received four different what appeared to be random somatic mutations. There's no driver function involved in these. And there was redundancy in the T cell receptors that we used to treat her. But by treating these four now random somatic mutations, she underwent a complete regression of this lesion beginning to grow through the cell wall. You can see multiple liver metastases. She had many more which disappeared.
And she’s over five years later now completely disease, disease free.

This patient with a metastatic cervical cancer that was very aggressive and fungating into her vagina. Underwent resection radiation and cisplatin chemotherapy. Underwent our hysterectomy and excision of both ovaries. She developed liver, lymph node, intra abdominal Mets including one that was obstructing her ureter. Came to us for treatment with our own till. You can see these lymph nodes which disappeared. This chest wall lesion disappearing
This node was obstructing her ureter.

We put in a urinary catheter.

A ureteral catheter.

When our tumor went away we could take it out.

She remains disease free.

Now over seven years later this patient with colorectal cancer was the one in which we found the KRS receptor.

It had a colectomy was invading her bladder so it was very aggressive.

We resected 2 lung metastasis.

She had seven others treated her and.

Almost all of our tumors disappeared.
She had seven lesions, six of which disappeared. This one did not disappear and continued to grow and where we resected it. We learned that in fact, by looking at copy number analysis of the chromosomes, she had lost one chromosome from chromosome 6 and that chromosome codes MHC molecules, including her restricting element. Therefore, that tumor could escape. And when we then went on to resect her that one lesion, she has not occurred since and remains disease free over six years later.
We can see responses in pancreatic cancer as you can see this very dramatic. Response which I show you. It was a very recent patient who had what appeared to be almost a complete regression of multiple liver metastasis disease. But unfortunately within three months this patient didn't recur. And when we biopsied one of the lesions, he had lost expression of his target molecule which turned out to be P53 and a molecule that we'll hear about in a few moments longer.
100 patients with epithelial cancers.

Again, it’s the ducts in these organs that provide the source of mutations that are turning over constantly and as mistakes are made, mutations appear and those are the ones we’re targeting.

If you use bulk till in patients with epithelial cancers who are chemo, fract, chemo refractory, we do not see responses in 21 patients, but when we started to select these till. And treated 81 patients, 17% of them have responded.

I’ve shown you some of them. These are all patients.
that are chemo refractory.

Many had had checkpoint modulators which do not work in these tumors and had not responded and.

We have a long ways to go, but these 17 patients at least show us that this is possible as we continue to refine and learn how to treat these patients.

For the refractory epithelial cancers, there were two hypotheses that come from this.

First, it appears to be the recognition of random somatic mutations.
It’s a final common pathway that explains cancer aggression for most, if not all immuno therapies. We finally understand what a cancer antigen is and as we now look at the variety of chemother of immunotherapies, it’s now been shown for anti C2A4, we’re studying it fertil tumor infiltrating lymphocytes as well. About one in every seventy of these
mutated NEO epitopes are NEO antigens and there's good news and bad news. The bad news is that this will have to be a very highly personalized treatment after over taking a patient’s own cells. We’re targeting A mutation that’s unique to his own tumor and will therefore be complex to administer. The good news is that virtually all cancer patients are potentially eligible because they all have mutations. And some more than others. So the opportunity does exist to further deliver this treatment and the complexity will be difficult.
But then again, I heard that in the early days of our development of CAR T cells, several groups came through large pharmaceutical companies saying, hey, if we had this disease, we’d come to you, but we don’t see how to make money doing it. But I have every confidence that if we can figure out ways to make it work and large numbers of patients, the genius of American industry will figure out a way to deliver it. Well there are two main approaches to using lymphos type transfer and we’ve talked about expanding
00:43:13.121 --> 00:43:15.050 naturally occurring anti cancer cells.

00:43:15.050 --> 00:43:18.210 But because now it becomes so readily usable

00:43:18.210 --> 00:43:21.288 to easy to identify T cell receptors,

00:43:21.290 --> 00:43:23.966 we can actually identify T cell

00:43:23.966 --> 00:43:25.750 receptors into autologous lymphocytes

00:43:25.819 --> 00:43:27.997 and expand normal cells and convert

00:43:27.997 --> 00:43:32.726 them into anti tumor anti tumor T cells.

00:43:35.350 --> 00:43:37.318 We’ve talked about these non mutated

00:43:37.318 --> 00:43:39.708 proteins that are not on normal tissues,

00:43:39.710 --> 00:43:42.750 CD19, the unique somatic mutations,

00:43:42.750 --> 00:43:45.546 but there are mutations in cancer

00:43:45.550 --> 00:43:48.405 driver oncogenes or tumor suppressors

00:43:48.405 --> 00:43:52.190 that can be shared among patients.

00:43:52.190 --> 00:43:54.234 It’s remarkable now that so many different

00:43:54.234 --> 00:43:55.870 cancer genomes have been sequenced,
how few of these actually exist that are shared. Far and away the most common are KK, RASS, and P53. KRS expressing 30% of all cancers, 70% of pancreatic cancer, and half of all cancers. And so we've made efforts to identify TCRS from patients that contain these mutations to find T cell receptors by doing a highly directed screening using very high concentrations of these molecules or by especially by in vitro sensitization. To identify T cells, that do exist in patients that...
00:44:36.729 --> 00:44:40.790 can recognize K Ras in P53.

00:44:40.790 --> 00:44:43.886 And we published about a year and a half ago a library of T cell receptors that

00:44:47.275 --> 00:44:51.230 are CD8 and CD4 that can recognize K Ras,

00:44:51.230 --> 00:44:54.770 the common K Ras hotspot mutations.

00:44:54.770 --> 00:45:00.330 Over 80% of OK Ras mutations

00:45:00.330 --> 00:45:05.678 occur at three different hotspots,

00:45:05.678 --> 00:45:08.650 amino acid almost all of them.

00:45:08.650 --> 00:45:10.450 However the great majority are

00:45:10.450 --> 00:45:15.612 at this K12 and 13 position and

00:45:15.612 --> 00:45:18.958 you can see for a variety now of

00:45:18.958 --> 00:45:22.494 restriction elements we can identify.

00:45:22.494 --> 00:45:26.360 sequences of them that can recognize

NOTE Confidence: 0.949542781538462

72
tumors mutations based on the recognition of K Ras mutations and a similar library now of mutations in K Ras can be recognized by CD4 cells using a variety of different Class 2 restriction elements. And if you look at the two libraries that we've now developed, 33% of all patients with K Ras mutations can potentially be eligible for treatment. These T cell receptors if we can learn to use them well, that led us to the issue of, well, what kinds of receptors do we really want because we can find dozens of redundant receptors recognizing the
same exact molecules and there are a variety of tests that one can use to test these receptors lytic.

Function, cytokine secretion, the avidity, the affinity catch bond techniques. And so we’ve gone to try to understand what T cells do we need so that we can select the right ones among the redundant number. And this brings us back to that patient with KRAS who was treated with four different receptors all that recognized KRAS, you can look here at their avidity,
That is they all recognize about the same concentration of peptide. But one of these receptors disappeared immediately upon infusion and this was a majority receptor given. Where are three of these receptors persisted well out beyond the year? Here are measurements out to 290 days. There was something very different about this receptor compared to these. What was the difference? The avidity was the same. We looked at a variety of criteria, especially surface plasmon resistance, to measure the exact KD, the association constant of that receptor.
What we did is identify the receptor, clone it, purified it, and put it into human cells that were then used to treat the human tumor and immunosuppressed mice and Notices 1 receptor had the highest affinity. If you look now at this highest affinity receptor using a mouse, a human receptor to treat a human tumor in a highly immunosuppressed mouse, it was these lower affinity receptors which were the most effective. And so it appears that it’s not only the fitness state of the lymphocyte itself,
but the quality of its receptor that play a role in anti tumor. Effectiveness well knowing the receptor that was developed by Eric Tran who was a fellow in the laboratory who about the three years ago moved to Portland. With Eric, we use this receptor that had the low affinity that seemed to have that sweet spot of the recognition to treat a patient with pancreatic cancer. It was published in the New England Journal. What about six months ago and you can see the regression that was reported with follow up out to six months of multiple lung metastases which shrank in that patient to perform.
a substantial partial regression. We have additional follow up now that patient did recur at one year but spent one year disease free of his pancreatic cancer and we recently just four months ago. Treated a patient with pancreatic cancer utilizing a different set of key res receptors restricted by a eleven O 1 which is a class 1MHC molecule and you can see here this liver metastases which is almost disappeared by three months this large one smaller and by three months almost gone. We’re continuing to follow this
patient but this is an approach.

Using T cell receptors into normal cells that can potentially be effective,
Peter Kim in the Surgery Branch a fellow has developed a library mainly using in vitro sensitization to target P53 molecules.
This was published about six months ago in Clinical Clinical Cancer Immunology
Research and again these receptors.
Now with some common Class 1 molecules, O2, O1 can potentially treat about 5
1/2% of all patients with K Ras
mutations and again 50% of all cancer
patients have K Ras mutations.
Well, we could again identify the T cell receptors that were most common in recognizing P53 and recognizing tumors that contain P53. We isolated those T cell receptors that you uniquely recognize P53 recognizing tumors and again studied each one of these 5-6 receptors that we could find to see which were most effective and one of them was more effective than the rest. Although at high concentrations many others began to work as well in terms of causing in the regression of a human tumor in a mouse.
Using human receptors at 27 cells, you could see many, several of the receptors were active. But when you went down to 1/5 of that a 2E6A tiny number of cells, this one receptor was most effective and it was the receptor with an intermediate affinity. And so as we continue these experiments, we’re beginning to learn which kind of receptors we need. Having identified that a patient who came in with breast cancer, we’ve been through multiple chemotherapies with the highly advanced disease was
00:51:34.610 --> 00:51:38.280 treated with our own cells that were

00:51:38.280 --> 00:51:41.513 transduced with a high affinity.

00:51:41.513 --> 00:51:42.219 Excuse me,

00:51:42.219 --> 00:51:44.690 a high avidity but not a high

00:51:44.764 --> 00:51:46.528 affinity T cell receptor.

00:51:46.530 --> 00:51:49.380 She had very aggressive disease including

00:51:49.380 --> 00:51:52.250 a pericardium that was replaced by tumor.

00:51:52.250 --> 00:51:53.951 We know that because a week before

00:51:53.951 --> 00:51:56.096 we treated her we had to perform a

00:51:56.096 --> 00:51:57.461 pericardial window to release fluid

00:51:57.511 --> 00:52:00.902 of the biopsies here were positive.

00:52:00.902 --> 00:52:02.126 She had pleural effusions.

00:52:02.130 --> 00:52:05.530 She had tumor covering her her breast

00:52:05.530 --> 00:52:08.670 and extending into the into the other breast.
She was treated with our own cells that had been transduced to express an anti P53 receptor, this 175 H receptor that I just mentioned. Every one of these nodules is a separate tumor deposit at a large necrotic lesion in our breasts. All of this, everything visible. Disappeared and you can see here at 60 days the way this breast looked at six months. However, she did recur with a nodule that we biopsied that had an LOHA loss of heterozygosity at her MHC locust which enabled this and other lesions to
00:52:49.065 --> 00:52:52.298 escape and so she did recur at six months.
00:52:58.270 --> 00:53:00.166 So we can use T cell receptors to treat patients.
00:53:00.166 --> 00:53:01.430 And I’ll finish with this very latest finding we just published about six months ago in the science and are beginning to exploit.
00:53:03.739 --> 00:53:05.484 And that is a very rapid method to identify cancer reactive T cell receptors directly from a resected tumor without having to do all of the testing to see what they recognize.
00:53:09.590 --> 00:53:12.534 And how do we do this?
00:53:12.534 --> 00:53:14.720 We use a single cell transcriptome analysis of lymphocytes.
00:53:14.720 --> 00:53:17.010 receptors directly from a resected tumor without having to do all of the testing to see what they recognize.
00:53:17.010 --> 00:53:19.871 tumor without having to do all of the testing to see what they recognize.
00:53:19.871 --> 00:53:22.468 So how do we do this?
00:53:24.850 --> 00:53:27.454 We use a single cell transcriptome analysis of lymphocytes.
from freshly resected tumor.

In this analysis, each cell is bar coded with an individual DNA sequence and when that individual cell is sequenced and you can sequence up to 10,000 cells at a given time, the transcriptome all the messenger RNA's can be analyzed and the T cell resequence identified and each. Identified in an individual cell and so we did that. And if you then break those lymphocytes into all of the different clusters, what you can do is the following because we have the transcriptome
00:54:15.418 --> 00:54:19.508 sequence for every individual cell.

00:54:19.510 --> 00:54:21.544 And we’ve identified the T cell receptors in that patient that

00:54:21.544 --> 00:54:23.312 can recognize the tumor because

00:54:23.312 --> 00:54:25.067 every time we identify a cell and

00:54:25.067 --> 00:54:27.402 all the patients I’ve showed you,

00:54:27.402 --> 00:54:29.142 we can very easily then get to the T cell receptor using PCR techniques

00:54:29.150 --> 00:54:31.517 to clone it out only takes about

00:54:31.517 --> 00:54:33.282 the about two weeks if we look

00:54:33.282 --> 00:54:35.826 at this cluster and look at the T cell receptor sequences that we’ve

00:54:35.826 --> 00:54:38.064 identified for this rectal cancer

00:54:38.064 --> 00:54:40.847 patient and see what cells they’re in.

00:54:40.847 --> 00:54:43.190 They quite astonishingly all appear
in a single transcriptome culture

was true for this breast cancer patient.

In this cluster, we take nine cancer patients from many different histologies.

You can see they all fit in these clusters and So what that enables us to do is identify the gene signature.

Of cells in that cluster because we know the whole transcriptome, all the MRN A’s expressed and could identify and report on a gene signature which we published in Science led interestingly by a B cell antigen CX, CL13.

And when we take now an unknown patient cluster, look for that transcriptome sequencing.
that we look for those T cell receptors. Sequences that fit this gene signature we could then identify. For unknown samples, we could identify cells that contain that gene signature. And because the cells are bar coded, we can immediately get to the T cell receptor sequence and know that within a few weeks of the resection. And when we test each of the TC R’s in that signature right now and we’re trying to define that signature of the CDH cells. CD62 percent of all of the T cell
receptors that are present in
that cluster are tumor reactive
and we can identify within weeks.
And CD4 cells it’s not quite as good
as about 1/3 of the T cell receptors.
Thus anti tumor T cell receptors
can be quickly identified without
extensive screening.
And use for cell therapy and we haven’t
haven’t published much of this yet
but in fact are working hard now
to try to improve our ability to use
T cell receptors for for treatment.
Well, I might conclude with this final,
this final slide and leave you with
these few general conclusions.
Cell transfer therapy can mediate durable regression in patients with metastatic cancer refractory to all other treatments that T cells recognize unique somatic mutations and targeting these mutations unique to each cancer or sometimes shared. Have the potential to extend cell therapy to patients with the common epithelial cancers using either these naturally occurring or T cell receptor transduced cells. And finally gene signatures can be.
generified generated to identify anti
tumor T cell receptors in fresh tumors
as well as identify the phenotype
functions in eliminating tumor in vivo.
Well, I thank you for your very kind,
Thanks, Steve.
That was inspiring and certainly I know
there were a good number of questions.
I know Diane Krauss has a few online.
But as is our tradition
at the Cal Brazi lecture,
we will often turn to Judge
Cal Brazi or Steven to please
ask the first question.
Doctor Colleridge: Son or I’m a law professor. But I wondered, would the you’re talking about have any applicability to glioma brain cancer which I know of especially hard to treat and which may become much more common in the future? Because there is does seem to be some evidence that cell phone use. Increases the risk of coming down with brain cancer. So I just wondered, is this applicable to glioma brain, brain cancers.
Glioblastoma is the most aggressive form of brain cancers do express mutations. We have identified mutations in glioblastomas. In fact, we published a paper on that by VED Leiko who is a fellow in the surgery branch. Of a mutation in a glioblastoma, but we have not treated any glioblastoma patients with these uniquely reactive cells. We have treated glioblastomas with CAR T cells targeting a shared mutation. And so no responses again because their tumors might express normal
antigens and in a separate study that I won’t go into, we actually saw substantial toxicities by targeting a shared antigen and glioblastomas. But using this new cancer antigens that result from cancer mutations, I think should be tried in glioblastoma. But we have not begun those studies yet and are concentrating on the more common. Well, common epithelial cancers. But it’s a wonderful idea and something that I hope to to get to in a serious way soon.
While we’re doing that, I’ll just ask a question from an anonymous attendee. I have a patient with one of the targetable Rasmutations with the appropriate actual a. What can I do for them? How do I send them to you? We’re actively seeking those patients. And if you e-mail me sar@nih.gov, I’ll see that you get contacted immediately about that patient to evaluate the eligibility of that patient for our studies. Yeah, I’m guessing that was Diane Kraus. So that Eric would see that he has
to put more resource into this so that we’ll keep them here. He’s laughing. OK Diane, are you able to ask your question online or do you want me to? I can ask it. I can ask my question was why? The selected till work when the bulk till do not for some of these patients with solid tumors, is it a matter of the large dose of the effective till or potentially inhibition by other till that aren’t targeting the cancer. We have evidence for both and I think
both are important in the animal models.

In the number of cells you give is very highly related to its effectiveness.

In the human, although we generally give us very large numbers of cells,
even within the numbers of cells we give, which generally are between 10 of the 10 and 10 of the 11,

we do see an influence of the number of cells in the likelihood of having complete regressions.

And we just published that about a year and a half ago.

But we have evidence in animal models.

That the normal cells that you give can inhibit.
Now if you’re giving normal cells that contain T regulatory cells that would be hurtful, but also these other cells that you give that are non tumor reactive compete for the cytokines that are result of the lympho depletion. When you lympho deplete, you increase circulating levels of I L15IL7 which normally do not circulate and. Those circulating cytokines then can impact on the cells we administer and if we’re administering normal cells they compete with the good ones. So you’ve hit your your your question.
01:02:22.300 --> 01:02:23.848 actually hit on the exactly the
NOTE Confidence: 0.94226628
01:02:23.848 --> 01:02:25.420 right answer that you mentioned.
NOTE Confidence: 0.94226628
01:02:25.420 --> 01:02:27.022 You need the right cells and
NOTE Confidence: 0.94226628
01:02:27.022 --> 01:02:28.500 none of the wrong cells.
NOTE Confidence: 0.94226628
01:02:28.500 --> 01:02:30.540 I know we’re
NOTE Confidence: 0.9372034875
01:02:30.540 --> 01:02:31.896 little over but just two more
NOTE Confidence: 0.9372034875
01:02:31.896 --> 01:02:33.065 questions because some of your
NOTE Confidence: 0.9372034875
01:02:33.065 --> 01:02:34.349 old friends Mario Snow is online
NOTE Confidence: 0.9372034875
01:02:34.349 --> 01:02:35.777 and would like to ask a question.
NOTE Confidence: 0.9372034875
01:02:35.780 --> 01:02:37.220 Mario you should have come
NOTE Confidence: 0.9372034875
01:02:37.220 --> 01:02:38.372 here in person Mario.
NOTE Confidence: 0.9372034875
01:02:38.380 --> 01:02:41.005 Mario. I’m sorry, Steve,
NOTE Confidence: 0.9372034875
01:02:41.005 --> 01:02:42.835 I’m just curious for all the
NOTE Confidence: 0.9372034875
01:02:42.835 --> 01:02:43.836 reactive TCR’s that you found
NOTE Confidence: 0.9372034875
01:02:43.836 --> 01:02:45.500 in the epithelium malignancies,
NOTE Confidence: 0.9372034875
01:02:45.500 --> 01:02:47.668 are those internally differentiated cells,
are there any in the stem cell pool that you say work well and is that different between epithelium malignancies and Melanoma? We can find them easily in Melanoma and they are very difficult to find in, in the epithelial cancers because the incidence of those cells are likely 100,000 fold less in our measurements in the epithelial cancers than in the melanomas because we generally try to find them in circulating cells. But they do exist, they just very hard to identify. And my suspicion as we continue
to study and find better ways to identify tiny numbers of them, we will find them in the patients that did respond. But it’s a particular delight to hear Mario, who worked closely with us for several years, as are several others of your fellows. We now have Nick Clement on our staff, and it reminds me to say that in fact, especially all of this work, except for the first five to seven years, was actually done not by me, but by fellows who come to the surgery branch to train.
Fellows like Nick Lemon, like Mario, who come to the NCI to gain experience in doing clinical and laboratory research for two to three years. And I owe them a great debt, as I do to Mario, for all the contributions he made when he was here, when he was here with us, you know, Steve, that might be a good way to end. We're going to move into the other room with some of our fellows to talk with you and with the judge and others. Let me just say in hearing you say that the Paul Calabresi I knew would
have loved this lecture because it was innovative and it was patient focused.
You’re bringing new therapies to clinic and Guido’s going to say a word, but the fact that you mentored, that was what Paul is all about. And I’m going to go the final word. Judge Guido Calbresi. And then we’ll retire to the other room. course, one people who developed chemotherapy first, he said there was no doubt that where one went was not with chemotherapy but with immune. And he said that was where...
it would have to be.

And that's why I'm particularly delighted to a very. Well, on that note, thank you all. Thank you, Steve. We'll retire and we'll be 5 minutes and we'll get you back. Thank you, everyone.