WEBVTT

NOTE duration:"01:05:32"

NOTE recognizability:0.937

NOTE language:en-us

NOTE Confidence: 0.9201268

00:00:00.000 --> 00:00:03.883 On behalf of myself and Doctor Weiner and

NOTE Confidence: 0.9201268

00:00:03.883 --> 00:00:06.519 the the team here at Yale Cancer Center,

NOTE Confidence: 0.9201268

00:00:06.520 --> 00:00:09.064 it's really my honor to introduce our

NOTE Confidence: 0.9201268

00:00:09.064 --> 00:00:12.182 15th Calabresi Memorial Lecture and I

NOTE Confidence: 0.9201268

00:00:12.182 --> 00:00:14.670 think I've been here for about 12 of

NOTE Confidence: 0.9201268

00:00:14.748 --> 00:00:17.639 them in honor of Doctor Paul Calabresi.

NOTE Confidence: 0.9201268

00:00:17.640 --> 00:00:20.984 We always are proud to welcome the Calabresi

NOTE Confidence: 0.9201268

00:00:20.984 --> 00:00:24.920 family with us in person or online.

NOTE Confidence: 0.9201268

00:00:24.920 --> 00:00:27.422 We have actually in the front

NOTE Confidence: 0.9201268

00:00:27.422 --> 00:00:29.136 row Judge Guido Calbresi,

NOTE Confidence: 0.9201268

00:00:29.136 --> 00:00:31.862 and I'll have him say a few words at

NOTE Confidence: 0.9201268

00:00:31.862 --> 00:00:34.353 some point and just received a week ago

NOTE Confidence: 0.9201268

00:00:34.353 --> 00:00:36.799 with the honor and another Yale degree.

NOTE Confidence: 0.9201268

00:00:36.800 --> 00:00:39.520 He's already had several and you

NOTE Confidence: 0.9201268

00:00:39.520 --> 00:00:42.100 know Paul's younger brother and I've

NOTE Confidence: 0.9201268

00:00:42.100 --> 00:00:43.180 been very fortunate to know Guido

NOTE Confidence: 0.9201268

00:00:43.180 --> 00:00:44.238 for a long time as well.

NOTE Confidence: 0.9201268

00:00:44.240 --> 00:00:47.760 We also have Steven Calabresi on his way

NOTE Confidence: 0.9201268

00:00:47.760 --> 00:00:50.133 from Rhode Island and we have several

NOTE Confidence: 0.9201268

00:00:50.133 --> 00:00:52.352 other Calbresi family online and we're

NOTE Confidence: 0.9201268

00:00:52.352 --> 00:00:54.728 really honored to have Steven Rosenberg.

NOTE Confidence: 0.9201268

00:00:54.730 --> 00:00:56.961 This year's Cal Brazi lecturer and

NOTE Confidence: 0.9201268

00:00:56.961 --> 00:00:59.138 we've been Vince and I have been

NOTE Confidence: 0.9201268

00:00:59.138 --> 00:01:01.761 trying to get Steven for years and the

NOTE Confidence: 0.9201268

00:01:01.761 --> 00:01:03.938 offer of doing it virtually was fine

NOTE Confidence: 0.9201268

00:01:03.938 --> 00:01:06.087 because that this is such timely work.

NOTE Confidence: 0.9201268

00:01:06.090 --> 00:01:07.987 It's the type of work that we

NOTE Confidence: 0.9201268

00:01:07.987 --> 00:01:09.688 want to build here at Yale.

NOTE Confidence: 0.9201268

00:01:09.690 --> 00:01:11.769 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

00:01:41.320 --> 00:01:43.840 the pharmacology of anti cancer agents.

NOTE Confidence: 0.9201268

00:01:43.840 --> 00:01:45.440 And if you walk through the B wing,

NOTE Confidence: 0.9201268

00:01:45.440 --> 00:01:46.560 you still feel his influence,

NOTE Confidence: 0.9201268

00:01:46.560 --> 00:01:47.480 the people he worked with,

NOTE Confidence: 0.9201268

00:01:47.480 --> 00:01:48.532 the people he recruited.

NOTE Confidence: 0.9201268

00:01:48.532 --> 00:01:50.879 And he also serves as the director of

NOTE Confidence: 0.9201268

00:01:50.879 --> 00:01:52.649 Yale Cancer Centers Advisory Board.

NOTE Confidence: 0.9201268

00:01:52.650 --> 00:01:55.650 Until 2003.

NOTE Confidence: 0.9201268

00:01:55.650 --> 00:01:56.187 Unfortunately,

NOTE Confidence: 0.9201268

00:01:56.187 --> 00:01:59.409 he himself passed away from cancer,

NOTE Confidence: 0.9201268

00:01:59.410 --> 00:02:02.049 showing us how while we're making progress,

NOTE Confidence: 0.9201268

00:02:02.050 --> 00:02:04.570 we still have so much more we need to do.

NOTE Confidence: 0.9201268

00:02:04.570 --> 00:02:06.650 I have a good fortune to meet Paul.

NOTE Confidence: 0.9201268

00:02:06.650 --> 00:02:09.150 I hate to say it, 43 years ago.

NOTE Confidence: 0.9201268

00:02:09.150 --> 00:02:11.025 I don't think I'll talk about

NOTE Confidence: 0.9201268

00:02:11.025 --> 00:02:12.125 that too much here.

NOTE Confidence: 0.9201268

00:02:12.130 --> 00:02:14.410 But his son Peter was my

NOTE Confidence: 0.9201268

00:02:14.410 --> 00:02:15.930 freshman roommate at Yale,

NOTE Confidence: 0.9201268

00:02:15.930 --> 00:02:18.030 and I met Peter and.

NOTE Confidence: 0.9201268

00:02:18.030 --> 00:02:19.320 What better for someone who wanted

NOTE Confidence: 0.9201268

00:02:19.320 --> 00:02:21.189 to be a doctor to have as a roommate,

NOTE Confidence: 0.9201268

00:02:21.190 --> 00:02:22.750 you know, the father of oncology.

NOTE Confidence: 0.9201268

00:02:22.750 --> 00:02:23.670 It was very nice.

NOTE Confidence: 0.9201268

00:02:23.670 --> 00:02:25.550 They didn't like me at first too much.

NOTE Confidence: 0.9201268

00:02:25.550 --> 00:02:27.446 But I've the family has warmed up to

NOTE Confidence: 0.9201268

00:02:27.446 --> 00:02:29.905 me over the years and actually I've I I

NOTE Confidence: 0.9201268

00:02:29.905 --> 00:02:31.990 was looking through some photos last night.

NOTE Confidence: 0.9201268

00:02:31.990 --> 00:02:33.390 You know it was an error without iPhone,

NOTE Confidence: 0.9201268

00:02:33.390 --> 00:02:35.190 so it's hard to find photos like it is now.

NOTE Confidence: 0.9201268

00:02:35.190 --> 00:02:37.206 But I've spent many memorable times

NOTE Confidence: 0.9201268

00:02:37.206 --> 00:02:39.870 with the Cal Brazi family over the

NOTE Confidence: 0.9201268

00:02:39.870 --> 00:02:42.962 Yale Paul was an advisor, a mentor,

NOTE Confidence: 0.9201268

00:02:42.962 --> 00:02:46.084 and a really good friend to me.

NOTE Confidence: 0.936701811764706

00:02:46.090 --> 00:02:48.097 Actually Vince and I, I still we know we

NOTE Confidence: 0.936701811764706

00:02:48.097 --> 00:02:50.247 we helped him with his disease as well.

NOTE Confidence: 0.936701811764706

00:02:50.250 --> 00:02:53.050 And having this job here means so much to me.

NOTE Confidence: 0.936701811764706

00:02:53.050 --> 00:02:55.482 One of the reasons I I'm back at

NOTE Confidence: 0.936701811764706

00:02:55.482 --> 00:02:57.355 Yale is Paul had always told me

NOTE Confidence: 0.936701811764706

00:02:57.355 --> 00:02:59.130 Yale is a great place for you.

NOTE Confidence: 0.936701811764706

00:02:59.130 --> 00:03:01.008 I think you'd be happy there.

NOTE Confidence: 0.936701811764706

00:03:01.010 --> 00:03:03.514 So joining us today we have Guido Calbresi

NOTE Confidence: 0.936701811764706

00:03:03.514 --> 00:03:05.950 as I mentioned Doctor Calgary's brother,

NOTE Confidence: 0.936701811764706

00:03:05.950 --> 00:03:08.450 his wife Anne I believe is online.

NOTE Confidence: 0.936701811764706

00:03:08.450 --> 00:03:10.728 I talked about Steven, Paul's son.

NOTE Confidence: 0.936701811764706

00:03:10.728 --> 00:03:13.482 His wife Mimi and Paul's daughter

NOTE Confidence: 0.936701811764706

00:03:13.482 --> 00:03:15.939 Janice and son Peter are online.

NOTE Confidence: 0.936701811764706

00:03:15.939 --> 00:03:19.420 So this is a very special grand rounds.

NOTE Confidence: 0.936701811764706

00:03:19.420 --> 00:03:21.615 We have a plaque for you, Steve.

NOTE Confidence: 0.936701811764706

00:03:21.615 --> 00:03:23.260 I don't know if it arrived yet.

NOTE Confidence: 0.936701811764706

00:03:23.260 --> 00:03:25.220 It has to get to NCI security.

NOTE Confidence: 0.936701811764706

00:03:25.220 --> 00:03:26.561 But what I'm going to do now is I'm

NOTE Confidence: 0.936701811764706

00:03:26.561 --> 00:03:27.909 going to turn it over to Vince De Vita

NOTE Confidence: 0.936701811764706

00:03:27.909 --> 00:03:29.620 who needs a little introduction here,

NOTE Confidence: 0.936701811764706

00:03:29.620 --> 00:03:32.968 but certainly another father of oncology

NOTE Confidence: 0.936701811764706

00:03:32.968 --> 00:03:34.653 and actually Paul's good friend.

NOTE Confidence: 0.936701811764706

00:03:34.660 --> 00:03:36.620 And I'm going to let Vince come up,

NOTE Confidence: 0.936701811764706

00:03:36.620 --> 00:03:37.628 introduce the you Steven,

NOTE Confidence: 0.936701811764706

00:03:37.628 --> 00:03:39.460 and then we'll do a quick photo

NOTE Confidence: 0.936701811764706

00:03:39.460 --> 00:03:40.815 with you in the background.

NOTE Confidence: 0.936701811764706

00:03:40.820 --> 00:03:42.115 We'll figure out how to do a

NOTE Confidence: 0.936701811764706

00:03:42.115 --> 00:03:43.290 hybrid photo and then we'll give

NOTE Confidence: 0.936701811764706

00:03:43.290 --> 00:03:44.620 the time to you for your talk.

NOTE Confidence: 0.936701811764706

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

NOTE Confidence: 0.926288107142857

00:04:34.690 --> 00:04:36.915 were oldfashioned and their motto

NOTE Confidence: 0.926288107142857

00:04:36.915 --> 00:04:39.092 was if you can't go wide, go deep.

NOTE Confidence: 0.926288107142857

00:04:39.092 --> 00:04:41.514 And and Steve was a thinking surgeon,

NOTE Confidence: 0.926288107142857

00:04:41.520 --> 00:04:43.576 which immediately changed the

NOTE Confidence: 0.926288107142857

00:04:43.576 --> 00:04:45.714 ability to collaborate and to

NOTE Confidence: 0.926288107142857

00:04:45.714 --> 00:04:47.199 consult with the surgery department.

NOTE Confidence: 0.926288107142857

00:04:47.200 --> 00:04:51.504 It was a fun time for the he also came

NOTE Confidence: 0.926288107142857

00:04:51.504 --> 00:04:54.342 with his passion for immunotherapy.

NOTE Confidence: 0.926288107142857

00:04:54.342 --> 00:04:58.549 And in the book he was to write a

NOTE Confidence: 0.926288107142857

00:04:58.549 --> 00:05:02.194 lot later he describes the the source

NOTE Confidence: 0.926288107142857

00:05:02.194 --> 00:05:03.679 of his passion in immunotherapy.

NOTE Confidence: 0.926288107142857

00:05:03.680 --> 00:05:06.840 It was a patient he operated on in 1968

NOTE Confidence: 0.926288107142857

00:05:06.840 --> 00:05:09.840 who came in with right up a quadrant pain,

NOTE Confidence: 0.926288107142857

00:05:09.840 --> 00:05:12.080 had a non visualizing gallbladder,

NOTE Confidence: 0.926288107142857

00:05:12.080 --> 00:05:13.676 was all set to go to operation.

NOTE Confidence: 0.926288107142857

00:05:13.680 --> 00:05:16.931 And Steve reviewed his old charts and he had

NOTE Confidence: 0.926288107142857

00:05:16.931 --> 00:05:19.650 come in 12 years earlier with belly pain.

NOTE Confidence: 0.926288107142857

00:05:19.650 --> 00:05:22.410 He was operated on a big masses of

NOTE Confidence: 0.926288107142857

00:05:22.491 --> 00:05:25.119 tumor with metastasis to the liver.

NOTE Confidence: 0.926288107142857

00:05:25.120 --> 00:05:26.326 And here he was 12 years

NOTE Confidence: 0.926288107142857

00:05:26.326 --> 00:05:27.480 later he was supposed to die.

NOTE Confidence: 0.926288107142857

00:05:27.480 --> 00:05:28.962 Few months later he was 12

NOTE Confidence: 0.926288107142857

00:05:28.962 --> 00:05:30.280 years later he was fine.

NOTE Confidence: 0.926288107142857

00:05:30.280 --> 00:05:33.360 Steve thought this was a powerful expression

NOTE Confidence: 0.926288107142857

00:05:33.360 --> 00:05:35.874 of the immunotherapy and he wanted to

NOTE Confidence: 0.926288107142857

00:05:35.874 --> 00:05:38.400 find out how we could harness this

NOTE Confidence: 0.9402535425

00:05:38.400 --> 00:05:42.040 work. And since then, with

NOTE Confidence: 0.944566418571428

00:05:42.040 --> 00:05:44.950 fierce intensity, he has worked in

NOTE Confidence: 0.944566418571428

00:05:44.950 --> 00:05:49.112 the immunotherapy field and he has

NOTE Confidence: 0.944566418571428

00:05:49.112 --> 00:05:51.896 unwavering focus and stayed on this.

NOTE Confidence: 0.944566418571428

00:05:51.900 --> 00:05:53.895 Doing work in vitro and then in

NOTE Confidence: 0.944566418571428

00:05:53.895 --> 00:05:55.826 animals and then repeating the animal

NOTE Confidence: 0.944566418571428

00:05:55.826 --> 00:05:58.192 studies in humans to the point where

NOTE Confidence: 0.944566418571428

00:05:58.259 --> 00:06:00.219 he's become the lead investigator

NOTE Confidence: 0.944566418571428

00:06:00.220 --> 00:06:03.220 in the world in immunotherapy,

NOTE Confidence: 0.944566418571428

00:06:03.220 --> 00:06:05.200 having either discovered or developed

NOTE Confidence: 0.944566418571428

00:06:05.200 --> 00:06:07.963 all of the things that have been

NOTE Confidence: 0.944566418571428

00:06:07.963 --> 00:06:10.099 done in immunotherapy that are now

NOTE Confidence: 0.944566418571428

00:06:10.099 --> 00:06:13.420 making us very excited in the clinic.

NOTE Confidence: 0.944566418571428

00:06:13.420 --> 00:06:15.045 And since we're talking about

NOTE Confidence: 0.944566418571428

00:06:15.045 --> 00:06:16.020 fathers of programs,

NOTE Confidence: 0.944566418571428

00:06:16.020 --> 00:06:18.468 I would sort of view Steve as the

NOTE Confidence: 0.944566418571428

00:06:18.468 --> 00:06:21.147 father of the immunotherapy of cancer.

NOTE Confidence: 0.944566418571428

00:06:21.150 --> 00:06:24.298 He got his bachelor's degree and

NOTE Confidence: 0.944566418571428

00:06:24.298 --> 00:06:26.146 his MD degree from Johns Hopkins.

NOTE Confidence: 0.944566418571428

00:06:26.150 --> 00:06:29.420 He's got his PhD from biophysics

NOTE Confidence: 0.944566418571428

00:06:29.420 --> 00:06:30.510 from Harvard,

NOTE Confidence: 0.944566418571428

00:06:30.510 --> 00:06:33.363 and he spent his time in Boston at the

NOTE Confidence: 0.944566418571428

00:06:33.363 --> 00:06:35.648 Peter Ben Brigham getting a surgical

NOTE Confidence: 0.944566418571428

00:06:35.648 --> 00:06:37.809 training under the famous Brandy Moore.

NOTE Confidence: 0.944566418571428

00:06:37.809 --> 00:06:40.718 And then during that time he'd spent two

NOTE Confidence: 0.944566418571428

00:06:40.718 --> 00:06:42.950 years coming to the clinical associate

NOTE Confidence: 0.944566418571428

00:06:42.950 --> 00:06:45.230 at the National Cancer Institute.

NOTE Confidence: 0.944566418571428

00:06:45.230 --> 00:06:47.344 I also started as a clinical associate.

NOTE Confidence: 0.944566418571428

00:06:47.350 --> 00:06:49.330 We used to refer to ourselves

NOTE Confidence: 0.944566418571428

00:06:49.330 --> 00:06:50.650 as the Yellow Berets.

NOTE Confidence: 0.944566418571428

00:06:50.650 --> 00:06:53.104 Because it was a Vietnam War

NOTE Confidence: 0.944566418571428

00:06:53.104 --> 00:06:56.006 and we got our military credit

NOTE Confidence: 0.944566418571428

00:06:56.006 --> 00:06:58.926 without any of the gunfire.

NOTE Confidence: 0.944566418571428

00:06:58.930 --> 00:07:01.352 Steve may forgive me for not

NOTE Confidence: 0.944566418571428

00:07:01.352 --> 00:07:02.924 going over his honors and awards.

NOTE Confidence: 0.944566418571428

00:07:02.930 --> 00:07:04.550 They're just too many.

NOTE Confidence: 0.944566418571428

00:07:04.550 --> 00:07:07.810 I stopped counting 80.

NOTE Confidence: 0.944566418571428

00:07:07.810 --> 00:07:08.598 And finally,

NOTE Confidence: 0.944566418571428

00:07:08.598 --> 00:07:10.997 I've been working with Steve on

NOTE Confidence: 0.944566418571428

00:07:10.997 --> 00:07:13.132 the textbook answer Principles of

NOTE Confidence: 0.944566418571428

00:07:13.132 --> 00:07:15.540 Practice of Oncology for 42 years.

NOTE Confidence: 0.944566418571428

00:07:15.540 --> 00:07:19.095 He and I are two of the three editors,

NOTE Confidence: 0.944566418571428

00:07:19.100 --> 00:07:21.214 and it has been quite an experience.

NOTE Confidence: 0.944566418571428

00:07:21.220 --> 00:07:24.060 The reason the book has risen to the

NOTE Confidence: 0.944566418571428

00:07:24.060 --> 00:07:27.452 most popular Kansas text in the world is

NOTE Confidence: 0.944566418571428

00:07:27.452 --> 00:07:30.242 of the fierce competitiveness amongst

NOTE Confidence: 0.944566418571428

00:07:30.242 --> 00:07:32.774 the editors in preparing the book,

NOTE Confidence: 0.944566418571428

00:07:32.780 --> 00:07:34.940 making sure that we each,

NOTE Confidence: 0.944566418571428

00:07:34.940 --> 00:07:35.708 the other guy,

NOTE Confidence: 0.944566418571428

00:07:35.708 --> 00:07:37.899 was doing all the things he had to do.

NOTE Confidence: 0.944566418571428

00:07:37.900 --> 00:07:39.500 And of all the editors,

NOTE Confidence: 0.944566418571428

00:07:39.500 --> 00:07:42.642 Steve was the most competitive and not

NOTE Confidence: 0.944566418571428

00:07:42.642 --> 00:07:45.610 just a little story about to illustrate that.

NOTE Confidence: 0.944566418571428

00:07:45.610 --> 00:07:49.290 The publishers took us away,

NOTE Confidence: 0.944566418571428

00:07:49.290 --> 00:07:52.098 reached new addition a one week

NOTE Confidence: 0.944566418571428

00:07:52.098 --> 00:07:55.048 before to set the table of contents

NOTE Confidence: 0.944566418571428

00:07:55.050 --> 00:07:56.670 and pick the authors and invite

NOTE Confidence: 0.944566418571428

00:07:56.670 --> 00:07:58.969 them and at the end the second week.

NOTE Confidence: 0.944566418571428

00:07:58.970 --> 00:08:02.236 And so we work very hard during those days,

NOTE Confidence: 0.944566418571428

00:08:02.236 --> 00:08:04.350 getting up at 7:00 in the morning

NOTE Confidence: 0.944566418571428

00:08:04.416 --> 00:08:06.106 work until five and at the end

NOTE Confidence: 0.944566418571428

00:08:06.106 --> 00:08:08.054 of the day we would, you know,

NOTE Confidence: 0.944566418571428

00:08:08.054 --> 00:08:10.364 do our exercise and relax.

NOTE Confidence: 0.944566418571428

00:08:10.370 --> 00:08:11.813 And Sam Helman,

NOTE Confidence: 0.944566418571428

00:08:11.813 --> 00:08:14.699 at that time you played tennis.

NOTE Confidence: 0.944566418571428

00:08:14.700 --> 00:08:17.976 I jogged and Steve, not so much.

NOTE Confidence: 0.944566418571428

00:08:17.980 --> 00:08:20.540 Steve wasn't really into exercise

NOTE Confidence: 0.944566418571428

00:08:20.540 --> 00:08:22.856 or healthy diet at the time.

NOTE Confidence: 0.944566418571428

00:08:22.860 --> 00:08:24.820 So much to my surprise at the

NOTE Confidence: 0.944566418571428

00:08:24.820 --> 00:08:27.100 end of one day when he said you

NOTE Confidence: 0.944566418571428

00:08:27.100 --> 00:08:28.820 mind if I jog with you?

NOTE Confidence: 0.944566418571428

00:08:28.820 --> 00:08:30.549 And so I said no with a

NOTE Confidence: 0.944566418571428

00:08:30.549 --> 00:08:31.859 little smile on my face.

NOTE Confidence: 0.944566418571428

00:08:31.860 --> 00:08:32.706 Off we went,

NOTE Confidence: 0.944566418571428

00:08:32.706 --> 00:08:34.116 me and my running shorts

NOTE Confidence: 0.944566418571428

00:08:34.116 --> 00:08:35.898 and my New Balance shoes.

NOTE Confidence: 0.944566418571428

00:08:35.900 --> 00:08:39.456 Steve and his khaki pants and tennis

NOTE Confidence: 0.944566418571428

00:08:39.456 --> 00:08:42.429 or sneakers more than and we started

NOTE Confidence: 0.944566418571428

00:08:42.429 --> 00:08:44.690 running and after a little while I.

NOTE Confidence: 0.944566418571428

00:08:44.690 --> 00:08:47.890 Ratcheted it up and Steve ratcheted it up.

NOTE Confidence: 0.944566418571428

00:08:47.890 --> 00:08:50.226 And a little while I did some more

NOTE Confidence: 0.944566418571428

00:08:50.226 --> 00:08:52.744 and Steve ratcheted up some more and

NOTE Confidence: 0.944566418571428

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 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.

NOTE Confidence: 0.941930721666667

00:09:37.570 --> 00:09:41.248 Well, this is a unique pleasure

NOTE Confidence: 0.941930721666667

00:09:41.250 --> 00:09:43.890 for me for several reasons.

NOTE Confidence: 0.940253495

00:09:46.170 --> 00:09:49.806 It's a pleasure to honor Paul

NOTE Confidence: 0.940253495

00:09:49.810 --> 00:09:51.638 Calabresi and his family.

NOTE Confidence: 0.940253495

00:09:51.638 --> 00:09:55.910 Paul a giant in the field of medical

NOTE Confidence: 0.940253495

00:09:55.910 --> 00:10:00.890 oncology, but also to present

NOTE Confidence: 0.940253495

00:10:00.890 --> 00:10:04.250 in front of Vince De Vita who.

NOTE Confidence: 0.940253495

00:10:04.250 --> 00:10:06.490 Has played such an important role in

NOTE Confidence: 0.940253495

00:10:06.490 --> 00:10:08.930 my ability to do a lot of this work.

NOTE Confidence: 0.940253495

00:10:08.930 --> 00:10:11.849 Vince is a true giant in the

NOTE Confidence: 0.940253495

00:10:11.849 --> 00:10:14.690 field of of oncology and his

NOTE Confidence: 0.940253495

00:10:14.690 --> 00:10:18.170 contributions are known to to you all.

NOTE Confidence: 0.938815971428571

00:10:20.290 --> 00:10:23.063 But when I started working at the NCI

NOTE Confidence: 0.938815971428571

00:10:23.063 --> 00:10:24.875 trying to develop immunotherapies

NOTE Confidence: 0.938815971428571

00:10:24.875 --> 00:10:26.687 for treatment of cancer,

NOTE Confidence: 0.938815971428571

00:10:26.690 --> 00:10:29.489 there was not a lot of enthusiasm for it.

NOTE Confidence: 0.938815971428571

00:10:29.490 --> 00:10:33.410 But as I initially began to get results.

NOTE Confidence: 0.938815971428571

00:10:33.410 --> 00:10:36.362 I remember going to Vince De Vita and saying,

NOTE Confidence: 0.938815971428571

00:10:36.370 --> 00:10:39.406 look, I think there's something here

NOTE Confidence: 0.938815971428571

00:10:39.410 --> 00:10:41.888 and I'm going to need more resources.

NOTE Confidence: 0.938815971428571

00:10:41.890 --> 00:10:46.244 And in a a remarkably generous way,

NOTE Confidence: 0.938815971428571

00:10:46.250 --> 00:10:49.764 I was given by Vince De Vita

NOTE Confidence: 0.938815971428571

00:10:49.770 --> 00:10:52.368 probably over the objection of many,

NOTE Confidence: 0.938815971428571

00:10:52.370 --> 00:10:55.330 I know over the objection of some others,

NOTE Confidence: 0.938815971428571

00:10:55.330 --> 00:10:57.367 was given the space and money and

NOTE Confidence: 0.938815971428571

00:10:57.367 --> 00:10:59.170 resources to conduct the kinds of

NOTE Confidence: 0.938815971428571

00:10:59.170 --> 00:11:01.207 studies that I'll be talking about today.

NOTE Confidence: 0.938815971428571

00:11:01.210 --> 00:11:03.358 And it made a huge difference.

NOTE Confidence: 0.938815971428571

00:11:03.360 --> 00:11:07.908 To me, we became friends for the past

NOTE Confidence: 0.938815971428571

00:11:07.908 --> 00:11:10.680 47 years we worked in a textbook,

NOTE Confidence: 0.938815971428571

00:11:10.680 --> 00:11:15.035 Vince's the soul of that textbook and

NOTE Confidence: 0.938815971428571

00:11:15.035 --> 00:11:18.835 has led the the process for now through

NOTE Confidence: 0.938815971428571

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

NOTE Confidence: 0.938815971428571

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

NOTE Confidence: 0.938815971428571

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

NOTE Confidence: 0.938815971428571

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

NOTE Confidence: 0.938815971428571

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

NOTE Confidence: 0.938815971428571

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

NOTE Confidence: 0.943607957333333

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

NOTE Confidence: 0.943607957333333

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

NOTE Confidence: 0.943607957333333

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

NOTE Confidence: 0.943607957333333

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

NOTE Confidence: 0.943607957333333

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

NOTE Confidence: 0.943607957333333

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

NOTE Confidence: 0.943607957333333

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

NOTE Confidence: 0.943607957333333

00:11:56.320 --> 00:11:58.550 particular kind of immunotherapy and

NOTE Confidence: 0.943607957333333

00:11:58.550 --> 00:12:02.180 that is cell transfer immunotherapy

NOTE Confidence: 0.943607957333333

00:12:02.180 --> 00:12:03.652 that has many advantages.

NOTE Confidence: 0.943607957333333

00:12:03.652 --> 00:12:05.148 One, if we're going to use a

NOTE Confidence: 0.943607957333333

00:12:05.148 --> 00:12:05.900 lymphocyte as a drug,

NOTE Confidence: 0.943607957333333

00:12:05.900 --> 00:12:07.916 we can grow lymphocytes easily to

NOTE Confidence: 0.943607957333333

00:12:07.916 --> 00:12:10.950 10 of the 11 cells or more and

NOTE Confidence: 0.943607957333333

00:12:10.950 --> 00:12:12.960 administer very high large numbers

NOTE Confidence: 0.943607957333333

00:12:12.960 --> 00:12:15.768 of highly selected cells because we

NOTE Confidence: 0.943607957333333

00:12:15.768 --> 00:12:18.526 have the reagent in the test tube.

NOTE Confidence: 0.943607957333333

00:12:18.530 --> 00:12:21.422 We can potentially identify the exact

NOTE Confidence: 0.943607957333333

00:12:21.422 --> 00:12:23.823 subpopulations and effector functions that

NOTE Confidence: 0.943607957333333

00:12:23.823 --> 00:12:26.247 are required for the cancer regression.

NOTE Confidence: 0.943607957333333

00:12:26.250 --> 00:12:27.770 And 3rd and very importantly,

NOTE Confidence: 0.943607957333333

00:12:27.770 --> 00:12:30.074 we can manipulate the host prior

NOTE Confidence: 0.943607957333333

00:12:30.074 --> 00:12:32.738 to the cell transfer in a way that

NOTE Confidence: 0.943607957333333

00:12:32.738 --> 00:12:34.941 you cannot do with other forms of

NOTE Confidence: 0.943607957333333

00:12:34.941 --> 00:12:37.384 immunotherapy because the cells to be

NOTE Confidence: 0.943607957333333

00:12:37.384 --> 00:12:40.160 used are outside the body and we can

NOTE Confidence: 0.943607957333333

00:12:40.249 --> 00:12:43.282 therefore alter the microenvironment

NOTE Confidence: 0.943607957333333

00:12:43.282 --> 00:12:48.090 of the tumor in ways that will enable.

NOTE Confidence: 0.943607957333333

00:12:48.090 --> 00:12:50.754 Immune cells to enter into those

NOTE Confidence: 0.943607957333333

00:12:50.754 --> 00:12:52.530 tumors and destroy them.

NOTE Confidence: 0.943607957333333

00:12:52.530 --> 00:12:56.086 And so it's the cell therapy that

NOTE Confidence: 0.943607957333333

00:12:56.090 --> 00:12:58.766 I'm going to emphasize this morning.

NOTE Confidence: 0.943066896153846

00:13:02.730 --> 00:13:05.320 Now cells carry a conventional T cell

NOTE Confidence: 0.943066896153846

00:13:05.320 --> 00:13:07.659 receptor and the entire function of

NOTE Confidence: 0.943066896153846

00:13:07.659 --> 00:13:10.347 the lymphocyte is dependent on that T

NOTE Confidence: 0.943066896153846

00:13:10.422 --> 00:13:13.098 cell receptor to recognize its antigen.

NOTE Confidence: 0.943066896153846

00:13:13.100 --> 00:13:15.152 Which in conventional forms for CD8

NOTE Confidence: 0.943066896153846

00:13:15.152 --> 00:13:18.008 or CD4 cells, is a processed peptide

NOTE Confidence: 0.943066896153846

00:13:18.008 --> 00:13:21.300 coming from inside the cell and put

NOTE Confidence: 0.943066896153846

00:13:21.300 --> 00:13:24.060 on the patient's own MHC molecule.

NOTE Confidence: 0.943066896153846

00:13:24.060 --> 00:13:25.894 But a little over a decade ago,

NOTE Confidence: 0.943066896153846

00:13:25.900 --> 00:13:28.860 chimeric antigen receptors were described

NOTE Confidence: 0.884955534

00:13:31.460 --> 00:13:33.620 and at the Weitzman Institute.

NOTE Confidence: 0.884955534

00:13:33.620 --> 00:13:36.812 And that converts A lymphocyte into the

NOTE Confidence: 0.884955534

00:13:36.812 --> 00:13:39.520 recognition of an antibody not based

NOTE Confidence: 0.884955534

00:13:39.520 --> 00:13:42.480 on the conventional T cell receptor.

NOTE Confidence: 0.884955534

00:13:42.480 --> 00:13:44.692 But by making a single chain of

NOTE Confidence: 0.884955534

00:13:44.692 --> 00:13:47.451 the heavy and light chains of an

NOTE Confidence: 0.884955534

00:13:47.451 --> 00:13:49.626 antibody and connecting it to

NOTE Confidence: 0.884955534

00:13:49.626 --> 00:13:51.400 intracellular signaling domains,

NOTE Confidence: 0.884955534

00:13:51.400 --> 00:13:55.091 we can then use that lymphocyte to

NOTE Confidence: 0.884955534

00:13:55.091 --> 00:13:58.757 become recognition based on an antibody

NOTE Confidence: 0.884955534

00:13:58.757 --> 00:14:02.039 rather than on a T cell receptor.

NOTE Confidence: 0.884955534

00:14:02.039 --> 00:14:04.434 It can recognize cell surface

NOTE Confidence: 0.884955534

00:14:04.434 --> 00:14:07.120 molecules based on this antibody.

NOTE Confidence: 0.884955534

00:14:07.120 --> 00:14:07.468 Recognition.

NOTE Confidence: 0.884955534

00:14:07.468 --> 00:14:10.252 And so it provides us with a whole

NOTE Confidence: 0.884955534

00:14:10.252 --> 00:14:14.800 other way to identify, identify targets.

NOTE Confidence: 0.884955534

00:14:14.800 --> 00:14:16.942 And I'd like to spend just a moment on

NOTE Confidence: 0.884955534

00:14:16.942 --> 00:14:19.262 CAR T cells because although they've

NOTE Confidence: 0.884955534

00:14:19.262 --> 00:14:21.120 had substantial activity in the

NOTE Confidence: 0.884955534

00:14:21.120 --> 00:14:22.720 treatment of the hematologic cancers,

NOTE Confidence: 0.884955534

00:14:22.720 --> 00:14:26.026 they have not had activity against

NOTE Confidence: 0.884955534

00:14:26.026 --> 00:14:27.679 the solid tumors.

NOTE Confidence: 0.884955534

00:14:27.680 --> 00:14:28.958 And what's the reason for that?

NOTE Confidence: 0.884955534

00:14:28.960 --> 00:14:31.840 Well, CAR T cells require the use of

NOTE Confidence: 0.884955534

00:14:31.840 --> 00:14:33.423 monoclonal antibodies that recognize

NOTE Confidence: 0.884955534

00:14:33.423 --> 00:14:35.418 molecules on the cell surface.

NOTE Confidence: 0.884955534

00:14:35.420 --> 00:14:37.508 And they were described by Kohler

NOTE Confidence: 0.884955534

00:14:37.508 --> 00:14:39.620 and Milstein over 45 years ago.

NOTE Confidence: 0.884955534

00:14:39.620 --> 00:14:41.308 And despite extraordinary work,

NOTE Confidence: 0.884955534

00:14:41.308 --> 00:14:43.840 there's not been found a monoclonal

NOTE Confidence: 0.884955534

00:14:43.908 --> 00:14:45.984 antibody that can distinguish A

NOTE Confidence: 0.884955534

00:14:45.984 --> 00:14:48.494 malignant from a normal cell.

NOTE Confidence: 0.884955534

00:14:48.500 --> 00:14:50.145 The antibodies can have a lot of

NOTE Confidence: 0.884955534

00:14:50.145 --> 00:14:51.380 influence by reacting with cells.

NOTE Confidence: 0.884955534

00:14:51.380 --> 00:14:54.068 Surface molecules that can affect cell

NOTE Confidence: 0.884955534

00:14:54.068 --> 00:14:56.420 signaling can affect cell growth.

NOTE Confidence: 0.884955534

00:14:56.420 --> 00:14:58.442 But we do not have antibodies

NOTE Confidence: 0.884955534

00:14:58.442 --> 00:15:00.499 that are unique to a cancer.

NOTE Confidence: 0.938017398888889

00:15:03.040 --> 00:15:04.372 And that's a problem,

NOTE Confidence: 0.938017398888889

00:15:04.372 --> 00:15:06.740 because it's just as easy to kill

NOTE Confidence: 0.938017398888889

00:15:06.740 --> 00:15:08.840 a normal cell as a cancer cell,

NOTE Confidence: 0.938017398888889

00:15:08.840 --> 00:15:11.090 and we've seen deaths due to

NOTE Confidence: 0.938017398888889

00:15:11.090 --> 00:15:13.038 the application of cells that

NOTE Confidence: 0.938017398888889

00:15:13.038 --> 00:15:14.510 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

NOTE Confidence: 0.946962533333333

00:15:54.605 --> 00:15:56.329 treatment of humanologic malignancies.

NOTE Confidence: 0.946962533333333

00:15:56.330 --> 00:15:59.760 And back in 2009, we reported the

NOTE Confidence: 0.946962533333333

00:15:59.760 --> 00:16:03.058 first patient to be treated with a

NOTE Confidence: 0.946962533333333

00:16:03.058 --> 00:16:04.546 cell therapy that finally got approved

NOTE Confidence: 0.946962533333333

00:16:04.546 --> 00:16:06.489 by the Food and Drug Administration.

NOTE Confidence: 0.946962533333333

00:16:06.490 --> 00:16:08.856 The only cell therapy now approved and

NOTE Confidence: 0.946962533333333

00:16:08.856 --> 00:16:11.569 I'll just spend a moment talking about it.

NOTE Confidence: 0.946962533333333

00:16:11.570 --> 00:16:15.598 We had developed models showing we could

NOTE Confidence: 0.946962533333333

00:16:15.598 --> 00:16:18.880 treat syngenetic tumors by targeting CD19.

NOTE Confidence: 0.946962533333333

00:16:18.880 --> 00:16:20.626 A molecule on virtually all B

NOTE Confidence: 0.946962533333333

00:16:20.626 --> 00:16:22.680 cells and B cell malignancies.

NOTE Confidence: 0.946962533333333

00:16:22.680 --> 00:16:25.508 We saw a patient with an aggressive

NOTE Confidence: 0.946962533333333

00:16:25.508 --> 00:16:28.170 lymphoma in the way it behaved as

NOTE Confidence: 0.946962533333333

00:16:28.170 --> 00:16:29.920 you can as you'll see his Xrays,

NOTE Confidence: 0.946962533333333

00:16:29.920 --> 00:16:32.960 he's had multiple chemotherapies,

NOTE Confidence: 0.946962533333333

00:16:32.960 --> 00:16:34.572 vaccines, checkpoint modulators,

NOTE Confidence: 0.946962533333333

00:16:34.572 --> 00:16:37.128 more chemotherapy and finally came to

NOTE Confidence: 0.946962533333333

00:16:37.128 --> 00:16:39.896 us in May in 2009 for treatment with.

NOTE Confidence: 0.946962533333333

00:16:39.896 --> 00:16:42.697 His own T cells that were genetically

NOTE Confidence: 0.946962533333333

00:16:42.697 --> 00:16:45.931 modified with a chimeric antigen receptor

NOTE Confidence: 0.946962533333333

00:16:45.931 --> 00:16:48.966 that could recognize CD19 and this is

NOTE Confidence: 0.946962533333333

00:16:48.966 --> 00:16:52.600 what his X-ray look like when we treated him.

NOTE Confidence: 0.946962533333333

00:16:52.600 --> 00:16:55.806 You can see large masses directed

NOTE Confidence: 0.946962533333333

00:16:55.806 --> 00:16:58.842 by these yellow arrows in his

NOTE Confidence: 0.946962533333333

00:16:58.842 --> 00:17:01.423 media stymum in his axilla.

NOTE Confidence: 0.946962533333333

00:17:01.423 --> 00:17:03.814 Large mediastinal mass, huge spleens,

NOTE Confidence: 0.946962533333333

00:17:03.814 --> 00:17:05.050 lymph nodes surrounding

NOTE Confidence: 0.946962533333333

00:17:05.050 --> 00:17:07.110 his vena cava and aorta,

NOTE Confidence: 0.946962533333333

00:17:07.110 --> 00:17:09.189 huge iliac vessels.

NOTE Confidence: 0.946962533333333

00:17:09.189 --> 00:17:11.268 We treated him.

NOTE Confidence: 0.946962533333333

00:17:11.270 --> 00:17:14.788 All of his tumor disappeared over

NOTE Confidence: 0.946962533333333

00:17:14.788 --> 00:17:17.332 the course of a few months and he

NOTE Confidence: 0.946962533333333

00:17:17.332 --> 00:17:20.434 remains disease free to the present.

NOTE Confidence: 0.946962533333333

00:17:20.434 --> 00:17:22.946 To the present time.

NOTE Confidence: 0.946962533333333

00:17:22.950 --> 00:17:25.190 He had bone marrow replaced which also

NOTE Confidence: 0.99057055

00:17:27.750 --> 00:17:31.940 disappeared. But you pay the price

NOTE Confidence: 0.99057055

00:17:31.940 --> 00:17:34.410 because normal cells can also be killed

NOTE Confidence: 0.99057055

00:17:34.410 --> 00:17:37.068 and B cells disappeared at a time when

NOTE Confidence: 0.99057055

00:17:37.068 --> 00:17:39.279 normal T cells and natural killer cells

NOTE Confidence: 0.99057055

00:17:39.279 --> 00:17:41.575 were returning over the course of the

NOTE Confidence: 0.99057055

00:17:41.575 --> 00:17:44.059 week and 1/2 after the cell infusion.

NOTE Confidence: 0.99057055

00:17:44.060 --> 00:17:46.900 It took eight or nine months for the

NOTE Confidence: 0.99057055

00:17:46.900 --> 00:17:49.390 precursors that were not destroyed to to

NOTE Confidence: 0.99057055

00:17:49.390 --> 00:17:51.740 restore B cells in the in the patient.

NOTE Confidence: 0.99057055

00:17:51.740 --> 00:17:54.284 But patients can be can survive

NOTE Confidence: 0.99057055

00:17:54.284 --> 00:17:57.100 for long periods of time in the

NOTE Confidence: 0.99057055

00:17:57.100 --> 00:18:01.250 absence of any of any B cells.

NOTE Confidence: 0.99057055

00:18:01.250 --> 00:18:03.084 Well, we treated the 1st 10 patients,

NOTE Confidence: 0.99057055

00:18:03.090 --> 00:18:04.658 six of them responded.

NOTE Confidence: 0.99057055

00:18:04.658 --> 00:18:07.406 Five of them are still responding to

NOTE Confidence: 0.99057055

00:18:07.406 --> 00:18:09.695 the present day over 10 years later.

NOTE Confidence: 0.99057055

00:18:09.695 --> 00:18:11.885 And in the surgery branch we

NOTE Confidence: 0.99057055

00:18:11.885 --> 00:18:13.770 received these kinds of results.

NOTE Confidence: 0.99057055

00:18:13.770 --> 00:18:17.298 We had objective responses by 47 percent.

NOTE Confidence: 0.99057055

00:18:17.298 --> 00:18:21.490 42% are ongoing and have never recurred out,

NOTE Confidence: 0.99057055

00:18:21.490 --> 00:18:24.087 with median survivals now beyond eight years.

NOTE Confidence: 0.93421556

00:18:26.340 --> 00:18:27.808 A good friend of mine, Ari Beldegrand,

NOTE Confidence: 0.93421556

00:18:27.808 --> 00:18:30.645 had been in my lab 20 years earlier.

NOTE Confidence: 0.93421556

00:18:30.645 --> 00:18:33.130 We had remained friends and he heard

NOTE Confidence: 0.93421556

00:18:33.205 --> 00:18:35.508 about some of these responses and after

NOTE Confidence: 0.93421556

00:18:35.508 --> 00:18:37.421 we had had six complete responders,

NOTE Confidence: 0.93421556

00:18:37.421 --> 00:18:39.263 he contacted me and said he

NOTE Confidence: 0.93421556

00:18:39.263 --> 00:18:40.617 wanted to start a company,

NOTE Confidence: 0.93421556

00:18:40.620 --> 00:18:44.124 Kite Pharma, who went on to do a

NOTE Confidence: 0.93421556

00:18:44.124 --> 00:18:46.115 multiinstitutional study that almost

NOTE Confidence: 0.93421556

00:18:46.115 --> 00:18:48.695 exactly reproduced our our results.

NOTE Confidence: 0.93421556

00:18:48.700 --> 00:18:50.900 We began interacting with Kite

NOTE Confidence: 0.93421556

00:18:50.900 --> 00:18:53.884 in 2012 through a. A.

NOTE Confidence: 0.93421556

00:18:53.884 --> 00:18:55.856 A research agreement.

NOTE Confidence: 0.93421556

00:18:55.856 --> 00:18:59.196 A research and development agreement.

NOTE Confidence: 0.93421556

00:18:59.200 --> 00:19:01.546 A crater to transfer our technology

NOTE Confidence: 0.93421556

00:19:01.546 --> 00:19:02.719 to Kite Pharma.

NOTE Confidence: 0.93421556

00:19:02.720 --> 00:19:06.136 Five years later, they received FDA approval,

NOTE Confidence: 0.93421556

00:19:06.136 --> 00:19:07.720 along with Novartis,

NOTE Confidence: 0.93421556

00:19:07.720 --> 00:19:10.330 who had begun working on this a year later.

NOTE Confidence: 0.93421556

00:19:10.330 --> 00:19:12.650 And in October 2017, Kite,

NOTE Confidence: 0.93421556

00:19:12.650 --> 00:19:14.690 who has started to do this from nothing,

NOTE Confidence: 0.93421556

00:19:14.690 --> 00:19:17.610 was told to Gilead Sciences for $11.9

NOTE Confidence: 0.93421556

00:19:17.610 --> 00:19:20.490 billion and it's now widely available.

NOTE Confidence: 0.93421556

00:19:20.490 --> 00:19:22.512 This treatment is now widely available

NOTE Confidence: 0.93421556

00:19:22.512 --> 00:19:24.450 through the United States and Europe

NOTE Confidence: 0.93421556

00:19:24.450 --> 00:19:27.580 and now beginning in Asia as well.

NOTE Confidence: 0.93421556

00:19:27.580 --> 00:19:30.440 I think a very proud example of how

NOTE Confidence: 0.93421556

00:19:30.440 --> 00:19:33.205 findings in an academic and a government

NOTE Confidence: 0.93421556

00:19:33.205 --> 00:19:35.209 institution can then get translated

NOTE Confidence: 0.93421556

00:19:35.210 --> 00:19:40.988 to help to help people in in need.

NOTE Confidence: 0.93421556

00:19:40.990 --> 00:19:41.904 This remains,

NOTE Confidence: 0.93421556

00:19:41.904 --> 00:19:42.361 however,

NOTE Confidence: 0.93421556

00:19:42.361 --> 00:19:44.800 the only T cell treatment that

NOTE Confidence: 0.93421556

00:19:44.800 --> 00:19:46.630 has been approved by the FDA,

NOTE Confidence: 0.93421556

00:19:46.630 --> 00:19:48.540 although there were several others

NOTE Confidence: 0.93421556

00:19:48.540 --> 00:19:50.068 that have shown effectiveness

NOTE Confidence: 0.93421556

00:19:50.070 --> 00:19:52.054 against multiple myeloma that

NOTE Confidence: 0.93421556

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,

NOTE Confidence: 0.945285226

00:20:30.800 --> 00:20:32.640 about one in five will

NOTE Confidence: 0.945285226

00:20:32.640 --> 00:20:34.800 die of the of the cancer.

NOTE Confidence: 0.936035507

00:20:38.070 --> 00:20:40.015 And so the major challenge

NOTE Confidence: 0.936035507

00:20:40.015 --> 00:20:41.182 confronting cancer immunotherapy

NOTE Confidence: 0.936035507

00:20:41.182 --> 00:20:43.948 today is the development of effective

NOTE Confidence: 0.936035507

00:20:43.948 --> 00:20:45.872 immunotherapies for patients with

NOTE Confidence: 0.936035507

00:20:45.872 --> 00:20:47.593 metastatic epithelial solid cancers

NOTE Confidence: 0.936035507

00:20:47.593 --> 00:20:50.036 that cannot be cured by any available

NOTE Confidence: 0.936035507

00:20:50.036 --> 00:20:53.420 treatment and result in 90% of all.

NOTE Confidence: 0.936035507

00:20:53.420 --> 00:20:55.244 Of all cancer deaths,

NOTE Confidence: 0.936035507

00:20:55.244 --> 00:20:57.524 the checkpoint modulators have had

NOTE Confidence: 0.936035507

00:20:57.524 --> 00:21:00.670 major impact on some solid tumors like

NOTE Confidence: 0.936035507

00:21:00.670 --> 00:21:02.840 Melanoma renal cell cancer patients

NOTE Confidence: 0.936035507

00:21:02.917 --> 00:21:05.337 that have mismatched repair genes.

NOTE Confidence: 0.936035507

00:21:05.340 --> 00:21:07.550 But the overwhelming majority of

NOTE Confidence: 0.936035507

00:21:07.550 --> 00:21:09.760 patients with the solid epithelial

NOTE Confidence: 0.936035507

00:21:09.832 --> 00:21:12.010 cancers do not respond with only

NOTE Confidence: 0.936035507

00:21:12.010 --> 00:21:14.974 single digit levels of response to the

NOTE Confidence: 0.936035507

00:21:14.974 --> 00:21:17.259 combined use of checkpoint inhibitors.

NOTE Confidence: 0.945620639333333

00:21:19.570 --> 00:21:22.328 So how can we attack these solid

NOTE Confidence: 0.945620639333333

00:21:22.328 --> 00:21:24.365 epithelial cancers and I'll talk

NOTE Confidence: 0.945620639333333

00:21:24.365 --> 00:21:26.602 mainly about them and but here's a

NOTE Confidence: 0.945620639333333

00:21:26.602 --> 00:21:28.570 general cartoon of how we do this.

NOTE Confidence: 0.945620639333333

00:21:28.570 --> 00:21:29.882 We excise A tumor.

NOTE Confidence: 0.945620639333333

00:21:29.882 --> 00:21:31.850 If you follow me along clockwise,

NOTE Confidence: 0.945620639333333

00:21:31.850 --> 00:21:33.728 we follow it excise A tumor.

NOTE Confidence: 0.945620639333333

00:21:33.730 --> 00:21:36.490 We grow cells to try to identify cells

NOTE Confidence: 0.945620639333333

00:21:36.490 --> 00:21:39.048 with anti tumor activity if we can,

NOTE Confidence: 0.945620639333333

00:21:39.050 --> 00:21:41.927 we grow them selectively to large numbers.

NOTE Confidence: 0.945620639333333

00:21:41.930 --> 00:21:44.170 We generally infuse 5 * 10 to

NOTE Confidence: 0.945620639333333

00:21:44.170 --> 00:21:45.710 the 10th 10 to the 11 cells

NOTE Confidence: 0.945620639333333

00:21:45.710 --> 00:21:47.897 and reinfuse them following A.

NOTE Confidence: 0.945620639333333

00:21:47.897 --> 00:21:50.532 Non myeloblade of lymphoid depleting

NOTE Confidence: 0.945620639333333

00:21:50.532 --> 00:21:52.640 regimen with cyclophosphonine or

NOTE Confidence: 0.945620639333333

00:21:52.715 --> 00:21:54.615 fludarabine that will eliminate

NOTE Confidence: 0.945620639333333

00:21:54.615 --> 00:21:58.810 T cells for about 8 days before

NOTE Confidence: 0.945620639333333

00:21:58.810 --> 00:22:01.402 they normally normally recover.

NOTE Confidence: 0.945620639333333

00:22:01.410 --> 00:22:02.875 I'm going to talk primarily

NOTE Confidence: 0.945620639333333

00:22:02.875 --> 00:22:04.047 about the epithelial cancers,

NOTE Confidence: 0.945620639333333

00:22:04.050 --> 00:22:05.527 but we learned a lot from Melanoma,

NOTE Confidence: 0.945620639333333

00:22:05.530 --> 00:22:07.138 so let me spend a moment.

NOTE Confidence: 0.945620639333333

00:22:07.140 --> 00:22:08.364 With this lesson,

NOTE Confidence: 0.945620639333333

00:22:08.364 --> 00:22:10.908 we treated 192 patients with metastatic

NOTE Confidence: 0.945620639333333

00:22:10.908 --> 00:22:13.500 Melanoma with some of these results

NOTE Confidence: 0.945620639333333

00:22:13.575 --> 00:22:15.532 that I first showed Vince Stavita

NOTE Confidence: 0.945620639333333

00:22:15.532 --> 00:22:17.548 when we had our first lymphocyte

NOTE Confidence: 0.945620639333333

00:22:17.548 --> 00:22:18.980 transfer that mediated aggression

NOTE Confidence: 0.945620639333333

00:22:18.980 --> 00:22:22.340 of a Melanoma patient in 1988.

NOTE Confidence: 0.945620639333333

00:22:22.340 --> 00:22:23.508 As you can see,

NOTE Confidence: 0.945620639333333

00:22:23.508 --> 00:22:25.260 we've treated that we did treat

NOTE Confidence: 0.945620639333333

00:22:25.260 --> 00:22:27.900 192 patients with their own cells,

NOTE Confidence: 0.945620639333333

00:22:27.900 --> 00:22:29.895 their own tumor infiltrating lymphocytes

NOTE Confidence: 0.945620639333333

00:22:29.895 --> 00:22:32.778 that we would grow out of the tumor.

NOTE Confidence: 0.945620639333333

00:22:32.780 --> 00:22:34.952 Those cells are a sink for

NOTE Confidence: 0.945620639333333

00:22:34.952 --> 00:22:36.038 tumor reactive cells.

NOTE Confidence: 0.945620639333333

00:22:36.040 --> 00:22:37.690 You can see our objective response

NOTE Confidence: 0.945620639333333

00:22:37.690 --> 00:22:39.280 rate by classic recess criteria,

NOTE Confidence: 0.945620639333333

00:22:39.280 --> 00:22:41.485 which is the criteria I'll use throughout

NOTE Confidence: 0.945620639333333

00:22:41.485 --> 00:22:44.280 this talk with 56% with a quarter

NOTE Confidence: 0.945620639333333

00:22:44.280 --> 00:22:46.440 of patients having complete regressions,

NOTE Confidence: 0.945620639333333

00:22:46.440 --> 00:22:48.890 only two patients that ever had a

NOTE Confidence: 0.945620639333333

00:22:48.890 --> 00:22:51.027 complete regression ever gone on to recur.

NOTE Confidence: 0.945620639333333

00:22:51.030 --> 00:22:53.326 The rest of the main disease free

NOTE Confidence: 0.945620639333333

00:22:53.326 --> 00:22:56.028 and of these 48 complete responders,

NOTE Confidence: 0.945620639333333

00:22:56.030 --> 00:22:57.182 only two patients required

NOTE Confidence: 0.945620639333333

00:22:57.182 --> 00:22:58.622 more than a single treatment.

NOTE Confidence: 0.945620639333333

00:22:58.630 --> 00:22:59.790 The cells are alive,

NOTE Confidence: 0.945620639333333

00:22:59.790 --> 00:23:01.530 they can divide up to 10,000

NOTE Confidence: 0.945620639333333

00:23:01.594 --> 00:23:03.724 fold in the first two weeks

NOTE Confidence: 0.945620639333333

00:23:03.724 --> 00:23:05.144 after they've been administered.

NOTE Confidence: 0.945620639333333

00:23:05.150 --> 00:23:06.710 And that's they patrol the body,

NOTE Confidence: 0.945620639333333

00:23:06.710 --> 00:23:07.974 they find,

NOTE Confidence: 0.945620639333333

00:23:07.974 --> 00:23:10.910 they find deposits wherever they

NOTE Confidence: 0.945620639333333

00:23:10.910 --> 00:23:12.990 wherever the circulation exists.

NOTE Confidence: 0.942490022222222

00:23:15.830 --> 00:23:17.830 Well here are our results

NOTE Confidence: 0.942490022222222

00:23:17.830 --> 00:23:19.430 in those the overall.

NOTE Confidence: 0.942490022222222

00:23:19.430 --> 00:23:22.094 Survival race, progression free

NOTE Confidence: 0.942490022222222

00:23:22.094 --> 00:23:26.870 survival race or were about 37%,

NOTE Confidence: 0.942490022222222

00:23:26.870 --> 00:23:30.150 but notice the complete responders

NOTE Confidence: 0.942490022222222

00:23:30.150 --> 00:23:32.230 very rarely ever recur.

NOTE Confidence: 0.942490022222222

00:23:32.230 --> 00:23:34.018 Somehow adoptive cell therapy

NOTE Confidence: 0.942490022222222

00:23:34.018 --> 00:23:36.253 appears to eliminate the last

NOTE Confidence: 0.942490022222222

00:23:36.253 --> 00:23:38.465 Melanoma cell and so the rest of

NOTE Confidence: 0.942490022222222

00:23:38.465 --> 00:23:40.259 the presentation will be on trying

NOTE Confidence: 0.942490022222222

00:23:40.259 --> 00:23:42.310 to find factors that we can use

NOTE Confidence: 0.942490022222222

00:23:42.310 --> 00:23:44.556 to treat not only Melanoma but

NOTE Confidence: 0.942490022222222

00:23:44.556 --> 00:23:46.148 the solid epithelial cancers.

NOTE Confidence: 0.942490022222222

00:23:46.150 --> 00:23:47.486 And the first question?

NOTE Confidence: 0.942490022222222

00:23:47.486 --> 00:23:49.953 That we'll discuss or what are the

NOTE Confidence: 0.942490022222222

00:23:49.953 --> 00:23:52.260 characteristics of the cells that

NOTE Confidence: 0.942490022222222

00:23:52.260 --> 00:23:55.860 mediated cancer regression in vivo,

NOTE Confidence: 0.942490022222222

00:23:55.860 --> 00:23:57.452 especially to these patients

NOTE Confidence: 0.942490022222222

00:23:57.452 --> 00:23:59.442 with Melanoma that have undergone

NOTE Confidence: 0.942490022222222

00:23:59.442 --> 00:24:01.100 durable complete regressions.

NOTE Confidence: 0.942490022222222

00:24:01.100 --> 00:24:04.097 And to do that we used a high dimensional

NOTE Confidence: 0.942490022222222

00:24:04.097 --> 00:24:06.200 single cell transcriptome analysis of

NOTE Confidence: 0.942490022222222

00:24:06.200 --> 00:24:09.355 up to 10,000 cells per per patient,

NOTE Confidence: 0.942490022222222

00:24:09.355 --> 00:24:12.265 a single very elegant single cell

NOTE Confidence: 0.942490022222222

00:24:12.265 --> 00:24:15.860 analysis available 10X from alumina.

NOTE Confidence: 0.943847671428572

00:24:18.310 --> 00:24:21.014 Well, because we had a group of patients

NOTE Confidence: 0.943847671428572

00:24:21.014 --> 00:24:23.350 that could respond and not respond,

NOTE Confidence: 0.943847671428572

00:24:23.350 --> 00:24:25.970 we utilize the single cell

NOTE Confidence: 0.943847671428572

00:24:25.970 --> 00:24:28.066 approach to identify the

NOTE Confidence: 0.943847671428572

00:24:28.070 --> 00:24:30.538 transcriptome analysis of patients,

NOTE Confidence: 0.943847671428572

00:24:30.538 --> 00:24:33.623 comparing responders from non responders.

NOTE Confidence: 0.943847671428572

00:24:33.630 --> 00:24:35.734 Because for the first time we had a

NOTE Confidence: 0.943847671428572

00:24:35.734 --> 00:24:37.566 group of immunotherapy patients that

NOTE Confidence: 0.943847671428572

00:24:37.566 --> 00:24:39.631 were showing this distinction and

NOTE Confidence: 0.943847671428572

00:24:39.631 --> 00:24:42.257 when we break all of the lymphocytes.

NOTE Confidence: 0.943847671428572

00:24:42.260 --> 00:24:44.260 And their transcriptome analysis

NOTE Confidence: 0.943847671428572

00:24:44.260 --> 00:24:46.260 using this these UMAP,

NOTE Confidence: 0.943847671428572

00:24:46.260 --> 00:24:48.464 UMAP or typically analysis

NOTE Confidence: 0.943847671428572

00:24:48.464 --> 00:24:51.219 using a near neighbor analysis,

NOTE Confidence: 0.943847671428572

00:24:51.220 --> 00:24:54.440 you can identify 22 different kinds of

NOTE Confidence: 0.943847671428572

00:24:54.440 --> 00:24:57.460 lymphocytes based on their transcriptome,

NOTE Confidence: 0.943847671428572

00:24:57.460 --> 00:25:00.436 the messages that they that

NOTE Confidence: 0.943847671428572

00:25:00.436 --> 00:25:02.260 they express into proteins.

NOTE Confidence: 0.943847671428572

00:25:02.260 --> 00:25:04.682 And there turned out to be one

NOTE Confidence: 0.943847671428572

00:25:04.682 --> 00:25:06.895 cluster that seemed to differentiate

NOTE Confidence: 0.943847671428572

00:25:06.895 --> 00:25:09.107 responders from non responders.

NOTE Confidence: 0.943847671428572

00:25:09.110 --> 00:25:11.644 And when we looked at the transcriptomic

NOTE Confidence: 0.943847671428572

00:25:11.644 --> 00:25:13.959 analysis it turned out that only

NOTE Confidence: 0.943847671428572

00:25:13.959 --> 00:25:15.894 that cluster cluster number one

NOTE Confidence: 0.943847671428572

00:25:15.894 --> 00:25:17.222 could distinguish responding

NOTE Confidence: 0.943847671428572

00:25:17.222 --> 00:25:19.186 from non responding patients.

NOTE Confidence: 0.943847671428572

00:25:19.190 --> 00:25:22.186 If we looked at the expressed genes

NOTE Confidence: 0.943847671428572

00:25:22.190 --> 00:25:25.182 in each of the other 21 clusters,

NOTE Confidence: 0.943847671428572

00:25:25.182 --> 00:25:27.798 the responders and the non responders

NOTE Confidence: 0.943847671428572

00:25:27.798 --> 00:25:30.400 were virtually identical except in this

NOTE Confidence: 0.943847671428572

00:25:30.400 --> 00:25:32.918 cluster that was largely non responders.

NOTE Confidence: 0.943847671428572

00:25:32.918 --> 00:25:36.164 It was only cluster number ones

NOTE Confidence: 0.943847671428572

00:25:36.164 --> 00:25:38.796 transcriptome that could distinguish.

NOTE Confidence: 0.943847671428572

00:25:38.800 --> 00:25:41.098 Responders from non responders and it

NOTE Confidence: 0.943847671428572

00:25:41.098 --> 00:25:43.831 turned out that cluster one was highly

NOTE Confidence: 0.943847671428572

00:25:43.831 --> 00:25:45.716 enriched in stem like lymphocytes

NOTE Confidence: 0.943847671428572

00:25:45.720 --> 00:25:49.606 that do not express CD39 and CD69,

NOTE Confidence: 0.943847671428572

00:25:49.606 --> 00:25:52.990 two molecules of lymphocyte

NOTE Confidence: 0.943847671428572

00:25:52.990 --> 00:25:56.600 activation and differentiation.

NOTE Confidence: 0.943847671428572

00:25:56.600 --> 00:25:57.091 Well,

NOTE Confidence: 0.943847671428572

00:25:57.091 --> 00:26:00.037 it appeared therefore that maybe these

NOTE Confidence: 0.943847671428572

00:26:00.040 --> 00:26:01.795 CD3969 stem like lymphocytes were

NOTE Confidence: 0.943847671428572

00:26:01.795 --> 00:26:04.350 the ones that were most responsible.

NOTE Confidence: 0.943847671428572

00:26:04.350 --> 00:26:05.818 For the Melanoma regressions,

NOTE Confidence: 0.943847671428572

00:26:05.818 --> 00:26:08.549 because when we looked at the survival

NOTE Confidence: 0.943847671428572

00:26:08.549 --> 00:26:10.766 of patients receiving either very

NOTE Confidence: 0.943847671428572

00:26:10.766 --> 00:26:13.622 high or low total numbers of cells,

NOTE Confidence: 0.943847671428572

00:26:13.630 --> 00:26:15.870 there was no statistical difference

NOTE Confidence: 0.943847671428572

00:26:15.870 --> 00:26:18.270 in the outcome of those patients.

NOTE Confidence: 0.943847671428572

00:26:18.270 --> 00:26:20.622 But if we now looked at patients

NOTE Confidence: 0.943847671428572

00:26:20.622 --> 00:26:22.468 that got either high or low

NOTE Confidence: 0.943847671428572

00:26:22.470 --> 00:26:25.196 double negative CD6939,

NOTE Confidence: 0.943847671428572

00:26:25.196 --> 00:26:27.226 double negative stem like cells.

NOTE Confidence: 0.943847671428572

00:26:27.230 --> 00:26:29.630 There was a highly significant difference

NOTE Confidence: 0.943847671428572

00:26:29.630 --> 00:26:32.109 between the cells that were respond,

NOTE Confidence: 0.943847671428572

00:26:32.110 --> 00:26:34.306 the patients that were responding to

NOTE Confidence: 0.943847671428572

00:26:34.306 --> 00:26:36.542 not responding based on the number

NOTE Confidence: 0.943847671428572

00:26:36.542 --> 00:26:38.312 of these double navigative cells

NOTE Confidence: 0.943847671428572

00:26:38.312 --> 00:26:41.683 that they that they received highly

NOTE Confidence: 0.943847671428572

00:26:41.683 --> 00:26:44.826 statistically significant well.

NOTE Confidence: 0.943847671428572

00:26:44.826 --> 00:26:46.478 When we looked at the properties of

NOTE Confidence: 0.943847671428572

00:26:46.478 --> 00:26:48.390 these cells, they were true stem cells.

NOTE Confidence: 0.943847671428572

00:26:48.390 --> 00:26:50.565 If you divide a lymphocyte

NOTE Confidence: 0.943847671428572

00:26:50.565 --> 00:26:53.175 population of till and facts based

NOTE Confidence: 0.943847671428572

00:26:53.175 --> 00:26:55.350 on CD39 and 69 expection,

NOTE Confidence: 0.943847671428572

00:26:55.350 --> 00:26:56.798 the double positive cells.

NOTE Confidence: 0.943847671428572

00:26:56.798 --> 00:26:58.970 When isolated and grow will only

NOTE Confidence: 0.943847671428572

00:26:59.034 --> 00:27:01.490 reconstitute themselves double positive.

NOTE Confidence: 0.943847671428572

00:27:01.490 --> 00:27:04.759 But when you take the double negative

NOTE Confidence: 0.943847671428572

00:27:04.759 --> 00:27:07.010 cells they reconstitute themselves

NOTE Confidence: 0.943847671428572

00:27:07.010 --> 00:27:09.404 whereas the double positive cells do not.

NOTE Confidence: 0.943847671428572

00:27:09.410 --> 00:27:11.456 They are true stem like cells

NOTE Confidence: 0.943847671428572

00:27:11.456 --> 00:27:13.943 when you take cells in one of

NOTE Confidence: 0.943847671428572

00:27:13.943 --> 00:27:15.683 our trials targeting Nye cell,

NOTE Confidence: 0.943847671428572

00:27:15.690 --> 00:27:18.896 one antigen you can see.

NOTE Confidence: 0.943847671428572

00:27:18.896 --> 00:27:19.620 In red,

NOTE Confidence: 0.943847671428572

00:27:19.620 --> 00:27:22.050 the double negative cells from the

NOTE Confidence: 0.943847671428572

00:27:22.050 --> 00:27:24.085 infusion continued to sustain themselves

NOTE Confidence: 0.943847671428572

00:27:24.085 --> 00:27:26.869 as they grew in vitro and were re

NOTE Confidence: 0.943847671428572

00:27:26.869 --> 00:27:28.739 stimulated one time after another,

NOTE Confidence: 0.943847671428572

00:27:28.740 --> 00:27:31.940 whereas the double positive cells

NOTE Confidence: 0.90532105

00:27:34.060 --> 00:27:35.356 disappeared as they grew.

NOTE Confidence: 0.90532105

00:27:35.356 --> 00:27:36.976 They were not stem like,

NOTE Confidence: 0.90532105

00:27:36.980 --> 00:27:39.120 they could not reproduce their

NOTE Confidence: 0.90532105

00:27:39.120 --> 00:27:40.832 themselves with their own.

NOTE Confidence: 0.90532105

00:27:40.840 --> 00:27:42.676 Native reactivities and in fact if

NOTE Confidence: 0.90532105

00:27:42.676 --> 00:27:45.320 you look at the actual transcriptomes,

NOTE Confidence: 0.90532105

00:27:45.320 --> 00:27:47.040 it is a stem like markers like K

NOTE Confidence: 0.952553311111111

00:27:50.080 --> 00:27:52.532 LF2TCF7CD62L that were expressed

NOTE Confidence: 0.952553311111111

00:27:52.532 --> 00:27:55.597 in the response associated culture.

NOTE Confidence: 0.952553311111111

00:27:55.600 --> 00:27:58.066 And if you then took this back to the

NOTE Confidence: 0.952553311111111

00:27:58.066 --> 00:28:00.196 mouse models that we had initially

NOTE Confidence: 0.952553311111111

00:28:00.200 --> 00:28:04.200 studied female mouse model of Melanoma,

NOTE Confidence: 0.952553311111111

00:28:04.200 --> 00:28:06.798 you can see that in fact.

NOTE Confidence: 0.952553311111111

00:28:06.800 --> 00:28:08.624 These cells when implanted and allowed

NOTE Confidence: 0.952553311111111

00:28:08.624 --> 00:28:11.142 to grow for 10 days before treatment

NOTE Confidence: 0.952553311111111

00:28:11.142 --> 00:28:13.064 started peripheral blood, they grew.

NOTE Confidence: 0.952553311111111

00:28:13.064 --> 00:28:15.320 If you gave double positive cells,

NOTE Confidence: 0.952553311111111

00:28:15.320 --> 00:28:17.640 they had some weak reactivity.

NOTE Confidence: 0.952553311111111

00:28:17.640 --> 00:28:20.232 But if you gave double negative cells at

NOTE Confidence: 0.952553311111111

00:28:20.232 --> 00:28:22.353 two different concentrations including this

NOTE Confidence: 0.952553311111111

00:28:22.353 --> 00:28:25.048 very low concentration of 500,000 cells,

NOTE Confidence: 0.952553311111111

00:28:25.048 --> 00:28:27.068 the double negative cells could

NOTE Confidence: 0.952553311111111

00:28:27.068 --> 00:28:29.124 mediate dramatic anti tumor effects

NOTE Confidence: 0.952553311111111

00:28:29.124 --> 00:28:31.074 compared to the bulk populations

NOTE Confidence: 0.952553311111111

00:28:31.080 --> 00:28:34.200 and so we could thus identify.

NOTE Confidence: 0.952553311111111

00:28:34.200 --> 00:28:38.392 These stem like cells that had a profound

NOTE Confidence: 0.952553311111111

00:28:38.392 --> 00:28:41.920 reactivity and published that about two

NOTE Confidence: 0.952553311111111

00:28:41.920 --> 00:28:45.804 years ago and have been utilizing it.

NOTE Confidence: 0.952553311111111

00:28:45.804 --> 00:28:47.310 We'll talk about some of the

NOTE Confidence: 0.952553311111111

00:28:47.359 --> 00:28:48.999 results in the epithelial cancers.

NOTE Confidence: 0.952553311111111

00:28:49.000 --> 00:28:51.070 But very recently and in this

NOTE Confidence: 0.952553311111111

00:28:51.070 --> 00:28:51.760 unpublished data,

NOTE Confidence: 0.952553311111111

00:28:51.760 --> 00:28:53.992 we found that we could actually

NOTE Confidence: 0.952553311111111

00:28:53.992 --> 00:28:56.171 make the double positive cells that

NOTE Confidence: 0.952553311111111

00:28:56.171 --> 00:28:58.208 were fairly weak work much better if

NOTE Confidence: 0.952553311111111

00:28:58.208 --> 00:29:00.485 we could give them a vaccine that

NOTE Confidence: 0.952553311111111

00:29:00.485 --> 00:29:02.115 was targeting the same antigens

NOTE Confidence: 0.952553311111111

00:29:02.180 --> 00:29:03.930 that the cells were targeting.

NOTE Confidence: 0.952553311111111

00:29:03.930 --> 00:29:05.946 And you can see here if we take the

NOTE Confidence: 0.952553311111111

00:29:05.946 --> 00:29:08.011 double positive cells which are the most

NOTE Confidence: 0.952553311111111

00:29:08.011 --> 00:29:10.010 exhausted of the cells and give them,

NOTE Confidence: 0.952553311111111

00:29:10.010 --> 00:29:12.165 they do have some reactivity

NOTE Confidence: 0.952553311111111

00:29:12.165 --> 00:29:13.889 compared to the control.

NOTE Confidence: 0.952553311111111

00:29:13.890 --> 00:29:16.165 But when you give the double positive,

NOTE Confidence: 0.952553311111111

00:29:16.170 --> 00:29:17.172 the double neck,

NOTE Confidence: 0.952553311111111

00:29:17.172 --> 00:29:18.508 these double positive cells

NOTE Confidence: 0.952553311111111

00:29:18.508 --> 00:29:20.089 in conjunction with a vaccine,

NOTE Confidence: 0.952553311111111

00:29:20.090 --> 00:29:22.295 you can now make them very active

NOTE Confidence: 0.952553311111111

00:29:22.295 --> 00:29:24.650 and take even 1 centimeter tumors,

NOTE Confidence: 0.952553311111111

00:29:24.650 --> 00:29:25.570 20% of the total.

NOTE Confidence: 0.941371755555556

00:29:27.990 --> 00:29:30.438 5% of the total body weight of the

NOTE Confidence: 0.941371755555556

00:29:30.438 --> 00:29:32.650 mouse to disappear completely and

NOTE Confidence: 0.941371755555556

00:29:32.650 --> 00:29:35.356 that's something that we're now clinical

NOTE Confidence: 0.941371755555556

00:29:35.356 --> 00:29:36.986 trial that we're now initiating.

NOTE Confidence: 0.929275345454545

00:29:50.130 --> 00:29:52.250 So we know the kind of cell we want to use.

NOTE Confidence: 0.929275345454545

00:29:52.250 --> 00:29:54.882 But what did the till actually recognize

NOTE Confidence: 0.929275345454545

00:29:54.882 --> 00:29:57.729 that enables the in vivo control in the

NOTE Confidence: 0.929275345454545

00:29:57.729 --> 00:30:00.402 last Melanoma cell And the fact that we

NOTE Confidence: 0.929275345454545

00:30:00.402 --> 00:30:02.430 have seen specific regression of cancer

NOTE Confidence: 0.929275345454545

00:30:02.499 --> 00:30:05.358 in the absence of any on target but off

NOTE Confidence: 0.929275345454545

00:30:05.358 --> 00:30:07.740 tumor toxicities led us to believe.

NOTE Confidence: 0.929275345454545

00:30:07.740 --> 00:30:10.482 That we were targeting something completely

NOTE Confidence: 0.929275345454545

00:30:10.482 --> 00:30:13.268 unique to cancers and those were the

NOTE Confidence: 0.929275345454545

00:30:13.268 --> 00:30:15.380 targets of cancer mutations that we

NOTE Confidence: 0.929275345454545

00:30:15.452 --> 00:30:18.260 suspected were the CAR targets of the till.

NOTE Confidence: 0.929275345454545

00:30:18.260 --> 00:30:20.738 And so again, to identify the target,

NOTE Confidence: 0.929275345454545

00:30:20.740 --> 00:30:22.756 we have to identify this small peptide

NOTE Confidence: 0.929275345454545

00:30:22.756 --> 00:30:24.356 that comes from an intracellular

NOTE Confidence: 0.929275345454545

00:30:24.356 --> 00:30:26.378 molecule or a molecule that's been

NOTE Confidence: 0.929275345454545

00:30:26.378 --> 00:30:28.281 ingested by the cell that can then

NOTE Confidence: 0.929275345454545

00:30:28.281 --> 00:30:31.980 be presented to the T cell receptor.

NOTE Confidence: 0.929275345454545

00:30:31.980 --> 00:30:33.420 And so about five years ago,

NOTE Confidence: 0.929275345454545

00:30:33.420 --> 00:30:35.432 we developed this particular

NOTE Confidence: 0.929275345454545

00:30:35.432 --> 00:30:37.444 blueprint for the identification.

NOTE Confidence: 0.929275345454545

00:30:37.450 --> 00:30:40.040 Of cells that were recognized by Till

NOTE Confidence: 0.929275345454545

00:30:40.040 --> 00:30:42.410 that could mediate tumor regressions.

NOTE Confidence: 0.929275345454545

00:30:42.410 --> 00:30:43.250 And what do we do?

NOTE Confidence: 0.929275345454545

00:30:43.250 --> 00:30:45.290 If you follow me counterclockwise,

NOTE Confidence: 0.929275345454545

00:30:45.290 --> 00:30:47.210 we excise A tumor,

NOTE Confidence: 0.929275345454545

00:30:47.210 --> 00:30:52.282 isolate the TILL and extract DNA&RNA from

NOTE Confidence: 0.929275345454545

00:30:52.282 --> 00:30:54.774 that till and do whole exome sequencing

NOTE Confidence: 0.929275345454545

00:30:54.774 --> 00:30:57.559 so that we could identify every cancer

NOTE Confidence: 0.929275345454545

00:30:57.559 --> 00:31:00.048 mutation that was present in that cell.

NOTE Confidence: 0.929275345454545

00:31:00.050 --> 00:31:02.192 And we do RN A/C to identify

NOTE Confidence: 0.929275345454545

00:31:02.192 --> 00:31:05.290 all the mRNA molecules as well.

NOTE Confidence: 0.929275345454545

00:31:05.290 --> 00:31:07.518 We then take those.

NOTE Confidence: 0.929275345454545

00:31:07.518 --> 00:31:10.585 Cancer mutations as 25 more molecules

NOTE Confidence: 0.929275345454545

00:31:10.585 --> 00:31:13.840 and either as peptides or as mini

NOTE Confidence: 0.929275345454545

00:31:13.934 --> 00:31:16.205 genes put together in a tandem

NOTE Confidence: 0.929275345454545

00:31:16.205 --> 00:31:18.440 structure to form a tandem mini

NOTE Confidence: 0.929275345454545

00:31:18.440 --> 00:31:20.876 gene and put it into a patient's

NOTE Confidence: 0.929275345454545

00:31:20.876 --> 00:31:22.789 own antigen presenting cell.

NOTE Confidence: 0.929275345454545

00:31:22.790 --> 00:31:24.400 Now that antigen presenting cell

NOTE Confidence: 0.929275345454545

00:31:24.400 --> 00:31:26.659 contains all of the MHC molecules of

NOTE Confidence: 0.929275345454545

00:31:26.659 --> 00:31:29.003 the patient and if any of these cancer

NOTE Confidence: 0.929275345454545

00:31:29.067 --> 00:31:30.907 mutations can then be presented.

NOTE Confidence: 0.943847613571429

00:31:33.030 --> 00:31:35.532 On the antigen presenting cell and

NOTE Confidence: 0.943847613571429

00:31:35.532 --> 00:31:38.097 recognized by the T cell receptor

NOTE Confidence: 0.943847613571429

00:31:38.097 --> 00:31:40.655 of till that forms a signal in

NOTE Confidence: 0.943847613571429

00:31:40.655 --> 00:31:42.891 the lymphocyte that enables us to

NOTE Confidence: 0.943847613571429

00:31:42.891 --> 00:31:44.996 identify it because of upregulation

NOTE Confidence: 0.943847613571429

00:31:44.996 --> 00:31:47.565 of activation markers and we could

NOTE Confidence: 0.943847613571429

00:31:47.565 --> 00:31:49.590 then grow those cells selectively.

NOTE Confidence: 0.943847613571429

00:31:49.590 --> 00:31:52.394 So again the key is to make a 25 more

NOTE Confidence: 0.943847613571429

00:31:52.394 --> 00:31:55.068 peptide with the mutation in the middle

NOTE Confidence: 0.943847613571429

00:31:55.070 --> 00:31:57.667 so that any peptide that could be

NOTE Confidence: 0.943847613571429

00:31:57.667 --> 00:32:00.707 presented on the MHC surface is concluded.

NOTE Confidence: 0.943847613571429

00:32:00.710 --> 00:32:02.516 It could either be the last.

NOTE Confidence: 0.943847613571429

00:32:02.520 --> 00:32:05.320 Amino acid of the peptide that's presented,

NOTE Confidence: 0.943847613571429

00:32:05.320 --> 00:32:06.128 or the first one,

NOTE Confidence: 0.943847613571429

00:32:06.128 --> 00:32:07.840 but it has to be in this 25.

NOTE Confidence: 0.943847613571429

00:32:07.840 --> 00:32:10.472 And the advantage of this is there's no

NOTE Confidence: 0.943847613571429

00:32:10.472 --> 00:32:13.516 need to do any predicted peptide binding.

NOTE Confidence: 0.943847613571429

00:32:13.520 --> 00:32:15.165 Every candidate peptide and all

NOTE Confidence: 0.943847613571429

00:32:15.165 --> 00:32:17.542 MHC loci are included in the screen

NOTE Confidence: 0.943847613571429

00:32:17.542 --> 00:32:19.552 because both have to be recognized

NOTE Confidence: 0.943847613571429

00:32:19.552 --> 00:32:21.838 the peptide on the MHC and there's

NOTE Confidence: 0.943847613571429

00:32:21.838 --> 00:32:23.393 no tumor cell lines necessary.

NOTE Confidence: 0.943847613571429

00:32:23.400 --> 00:32:24.368 And as you know,

NOTE Confidence: 0.943847613571429

00:32:24.368 --> 00:32:26.168 it's very hard to grow tumor cell

NOTE Confidence: 0.943847613571429

00:32:26.168 --> 00:32:27.878 lines for most of the epithelial

NOTE Confidence: 0.943847613571429

00:32:27.880 --> 00:32:31.820 epithelial cancers.

NOTE Confidence: 0.943847613571429

00:32:31.820 --> 00:32:33.596 This can be done within about

NOTE Confidence: 0.943847613571429

00:32:33.596 --> 00:32:34.780 two to three weeks,

NOTE Confidence: 0.943847613571429

00:32:34.780 --> 00:32:36.658 takes 10 days to do the

NOTE Confidence: 0.951574925

00:32:38.820 --> 00:32:40.470 to identify all of the

NOTE Confidence: 0.951574925

00:32:40.470 --> 00:32:41.460 cancer mutation sequences,

NOTE Confidence: 0.951574925

00:32:41.460 --> 00:32:43.884 another few days to do the

NOTE Confidence: 0.951574925

00:32:43.884 --> 00:32:45.096 bioinformatic informatic analyses.

NOTE Confidence: 0.951574925

00:32:45.100 --> 00:32:48.364 And so one has all this information available

NOTE Confidence: 0.951574925

00:32:48.364 --> 00:32:51.377 within two weeks of the tumor resection.

NOTE Confidence: 0.951574925

00:32:51.380 --> 00:32:53.540 Well, we started in Melanoma

NOTE Confidence: 0.951574925

00:32:53.540 --> 00:32:55.624 and evaluated 86 patients.

NOTE Confidence: 0.951574925

00:32:55.624 --> 00:32:58.229 Those tumors have more mutations

NOTE Confidence: 0.951574925

00:32:58.229 --> 00:33:01.420 in most 556 as a median.

NOTE Confidence: 0.951574925

00:33:01.420 --> 00:33:04.108 We screened every mutation that was

NOTE Confidence: 0.951574925

00:33:04.108 --> 00:33:07.020 expressed that was expressed in RN A/C

NOTE Confidence: 0.951574925

00:33:07.020 --> 00:33:09.066 15,000 mutations in these 86 patients

NOTE Confidence: 0.951574925

00:33:09.066 --> 00:33:11.650 to see if any could be recognized by

NOTE Confidence: 0.951574925

00:33:11.717 --> 00:33:14.135 the patient's own autologous T cell.

NOTE Confidence: 0.951574925

00:33:14.140 --> 00:33:17.602 So we looked at 218 immunogenic

NOTE Confidence: 0.951574925

00:33:17.602 --> 00:33:20.170 epitopes 85% of patients could recognize

NOTE Confidence: 0.951574925

00:33:20.170 --> 00:33:22.430 their own tumor cells based on.

NOTE Confidence: 0.951574925

00:33:22.430 --> 00:33:24.606 Recognition of these mutations.

NOTE Confidence: 0.951574925

00:33:24.606 --> 00:33:25.150 Interestingly,

NOTE Confidence: 0.951574925

00:33:25.150 --> 00:33:28.115 only 1.4% of the mutations could

NOTE Confidence: 0.951574925

00:33:28.115 --> 00:33:30.136 be recognized because they had it

NOTE Confidence: 0.951574925

00:33:30.136 --> 00:33:31.696 been cleaved and also presented

NOTE Confidence: 0.951574925

00:33:31.696 --> 00:33:32.944 on the Mac molecule.

NOTE Confidence: 0.951574925

00:33:32.950 --> 00:33:35.550 Of that particular patient,

NOTE Confidence: 0.951574925

00:33:35.550 --> 00:33:39.350 92% were CD8 cells rather than CD Fours.

NOTE Confidence: 0.951574925

00:33:39.350 --> 00:33:41.610 And our first surprise every

NOTE Confidence: 0.951574925

00:33:41.610 --> 00:33:43.870 NEO antigen that we recognized,

NOTE Confidence: 0.951574925

00:33:43.870 --> 00:33:47.206 all 218 were unique to the

NOTE Confidence: 0.951574925

00:33:47.206 --> 00:33:48.318 individual patient.

NOTE Confidence: 0.951574925

00:33:48.320 --> 00:33:49.988 Patient's cancer and recognized

NOTE Confidence: 0.951574925

00:33:49.988 --> 00:33:51.239 by that patient,

NOTE Confidence: 0.951574925

00:33:51.240 --> 00:33:54.677 none were shared between 2 Melanoma patients.

NOTE Confidence: 0.951574925

00:33:54.680 --> 00:33:54.940 Well,

NOTE Confidence: 0.951574925

00:33:54.940 --> 00:33:56.820 we then did this for 130

NOTE Confidence: 0.951574925

00:33:56.820 --> 00:33:58.560 consecutive gastrointestinal cancers

NOTE Confidence: 0.951574925

00:33:58.560 --> 00:34:00.344 screened over 15,000.

NOTE Confidence: 0.951574925

00:34:00.344 --> 00:34:02.840 Of the expressed mutations,

NOTE Confidence: 0.951574925

00:34:02.840 --> 00:34:05.000 1.3% were recognized interestingly

NOTE Confidence: 0.951574925

00:34:05.000 --> 00:34:08.240 half by CD8 and CD4 cells.

NOTE Confidence: 0.951574925

00:34:08.240 --> 00:34:09.864 And for the first time we found

NOTE Confidence: 0.951574925

00:34:09.864 --> 00:34:11.184 an antigen that was recognized

NOTE Confidence: 0.951574925

00:34:11.184 --> 00:34:12.599 in more than one patient.

NOTE Confidence: 0.951574925

00:34:12.600 --> 00:34:15.800 It was a KRAS mutation restricted by a

NOTE Confidence: 0.951574925

00:34:15.800 --> 00:34:17.960 fairly unusual CW8O2 Class 1 molecule.

NOTE Confidence: 0.941921875

00:34:20.310 --> 00:34:22.210 The other hundred 209 epitopes

NOTE Confidence: 0.941921875

00:34:22.210 --> 00:34:25.199 that were found were all unique to

NOTE Confidence: 0.941921875

00:34:25.199 --> 00:34:27.227 the individual individual patient.

NOTE Confidence: 0.930852555

00:34:29.870 --> 00:34:31.590 True in breast cancer that

NOTE Confidence: 0.930852555

00:34:31.590 --> 00:34:33.310 we just published last year,

NOTE Confidence: 0.930852555

00:34:33.310 --> 00:34:37.310 43 consecutive patients 100 immunogenic

NOTE Confidence: 0.930852555

00:34:37.310 --> 00:34:40.310 epitopes 2.1% were recognized of the

NOTE Confidence: 0.930852555

00:34:40.310 --> 00:34:42.956 mutations recognized half by mainly by

NOTE Confidence: 0.930852555

00:34:42.956 --> 00:34:46.057 CD Fours and all were absolutely unique.

NOTE Confidence: 0.930852555

00:34:46.060 --> 00:34:49.723 And here is an updated as of last September

NOTE Confidence: 0.930852555

00:34:49.723 --> 00:34:52.032 study of 205 consecutive patients and

NOTE Confidence: 0.930852555

00:34:52.032 --> 00:34:55.032 note we're talking about the GI cancers,

NOTE Confidence: 0.930852555

00:34:55.032 --> 00:34:57.380 breast cancer, lung cancer, Gastro,

NOTE Confidence: 0.930852555

00:34:57.380 --> 00:35:00.260 Gu cancers like ovarian and prostate.

NOTE Confidence: 0.930852555

00:35:00.260 --> 00:35:03.660 And across the board as you can see

NOTE Confidence: 0.930852555

00:35:03.660 --> 00:35:08.070 about 70 to 80% of the patients contain

NOTE Confidence: 0.930852555

00:35:08.070 --> 00:35:10.940 T cells that would recognize their own.

NOTE Confidence: 0.951500929411765

00:35:12.990 --> 00:35:16.105 Neo antigens their own cancer mutations that

NOTE Confidence: 0.951500929411765

00:35:16.105 --> 00:35:18.784 were presented on their autologous cancer

NOTE Confidence: 0.951500929411765

00:35:18.784 --> 00:35:22.630 cells and of this 363 neo antigens we found,

NOTE Confidence: 0.951500929411765

00:35:22.630 --> 00:35:25.798 we only found this one K Ras that was

NOTE Confidence: 0.951500929411765

00:35:25.798 --> 00:35:29.030 recognized by more than one patient found on

NOTE Confidence: 0.951500929411765

00:35:29.030 --> 00:35:32.550 this particular on this particular screen.

NOTE Confidence: 0.951500929411765

00:35:32.550 --> 00:35:35.077 Now an advantage of targeting mutations is

NOTE Confidence: 0.951500929411765

00:35:35.077 --> 00:35:37.538 its applicability to target multiple cancer.

NOTE Confidence: 0.951500929411765

00:35:37.540 --> 00:35:39.520 Types, because we're targeting mutations

NOTE Confidence: 0.951500929411765

00:35:39.520 --> 00:35:41.500 and most cancers have mutations,

NOTE Confidence: 0.951500929411765

00:35:41.500 --> 00:35:43.100 some more than others.

NOTE Confidence: 0.951500929411765

00:35:43.100 --> 00:35:47.012 But let me show you examples of what we've

NOTE Confidence: 0.951500929411765

00:35:47.012 --> 00:35:50.540 been able to see an individual patients.

NOTE Confidence: 0.951500929411765

00:35:50.540 --> 00:35:52.036 Most do not respond.

NOTE Confidence: 0.951500929411765

00:35:52.036 --> 00:35:54.700 I'll show you the overall results soon,

NOTE Confidence: 0.951500929411765

00:35:54.700 --> 00:35:57.832 but here are examples of individual

NOTE Confidence: 0.951500929411765

00:35:57.832 --> 00:35:59.920 cancers that can respond.

NOTE Confidence: 0.951500929411765

00:35:59.920 --> 00:36:01.675 Interestingly, the first patient that

NOTE Confidence: 0.951500929411765

00:36:01.675 --> 00:36:04.159 responded to T cells that were unique,

NOTE Confidence: 0.951500929411765

00:36:04.160 --> 00:36:06.060 that were identified as uniquely

NOTE Confidence: 0.951500929411765

00:36:06.060 --> 00:36:07.960 responsive to our own mutation,

NOTE Confidence: 0.951500929411765

00:36:07.960 --> 00:36:10.036 it was under a B2 mutation,

NOTE Confidence: 0.951500929411765

00:36:10.040 --> 00:36:12.758 was a 4045 year old woman

NOTE Confidence: 0.951500929411765

00:36:12.758 --> 00:36:14.117 with a clangiocarcinoma.

NOTE Confidence: 0.951500929411765

00:36:14.120 --> 00:36:16.717 Bile duct cancer had undergone A hepatectomy,

NOTE Confidence: 0.951500929411765

00:36:16.720 --> 00:36:18.355 multiple chemotherapy regimens,

NOTE Confidence: 0.951500929411765

00:36:18.355 --> 00:36:21.080 developed lung and liver metastases.

NOTE Confidence: 0.951500929411765

00:36:21.080 --> 00:36:22.862 We treated her with unselected till

NOTE Confidence: 0.951500929411765

00:36:22.862 --> 00:36:25.488 much as we did in Melanoma that does

NOTE Confidence: 0.951500929411765

00:36:25.488 --> 00:36:27.552 not work for the epithelial cancers.

NOTE Confidence: 0.926237971666667

00:36:29.590 --> 00:36:33.706 Unselected till do work in Melanoma,

NOTE Confidence: 0.926237971666667

00:36:33.710 --> 00:36:35.684 but you have to select the

NOTE Confidence: 0.926237971666667

00:36:35.684 --> 00:36:37.477 specific ones which are much

NOTE Confidence: 0.926237971666667

00:36:37.477 --> 00:36:39.507 rarer in the epithelial cancers.

NOTE Confidence: 0.926237971666667

00:36:39.510 --> 00:36:40.490 We gave her those,

NOTE Confidence: 0.926237971666667

00:36:40.490 --> 00:36:41.575 she didn't respond. However,

NOTE Confidence: 0.926237971666667

00:36:41.575 --> 00:36:43.990 when we use our Tandeminy gene approach,

NOTE Confidence: 0.926237971666667

00:36:43.990 --> 00:36:45.198 she had 26 mutations.

NOTE Confidence: 0.926237971666667

00:36:45.198 --> 00:36:47.438 We could found that her B2IP

NOTE Confidence: 0.926237971666667

00:36:47.438 --> 00:36:50.921 mutation that she recognized it

NOTE Confidence: 0.926237971666667

00:36:50.921 --> 00:36:53.776 contained almost 90% the infusion

NOTE Confidence: 0.926237971666667

00:36:53.776 --> 00:36:57.300 bag of cells recognized as mutation.

NOTE Confidence: 0.926237971666667

00:36:57.300 --> 00:36:58.950 And she underwent a complete

NOTE Confidence: 0.926237971666667

00:36:58.950 --> 00:37:01.100 regression of all of her cancer.

NOTE Confidence: 0.926237971666667

00:37:01.100 --> 00:37:03.938 You can see her lung cancers

NOTE Confidence: 0.94025373

00:37:06.140 --> 00:37:10.235 gone. She had three liver metastatic

NOTE Confidence: 0.94025373

00:37:10.235 --> 00:37:12.540 deposits that disappeared and

NOTE Confidence: 0.94025373

00:37:12.540 --> 00:37:16.340 she remains now disease free.

NOTE Confidence: 0.94025373

00:37:16.340 --> 00:37:19.496 Almost 10 years, 10 years later,

NOTE Confidence: 0.94025373

00:37:19.500 --> 00:37:21.810 this woman who had a metastatic

NOTE Confidence: 0.94025373

00:37:21.810 --> 00:37:24.392 breast cancer, had been through seven

NOTE Confidence: 0.94025373

00:37:24.392 --> 00:37:26.635 different treatments for her metastatic

NOTE Confidence: 0.94025373

00:37:26.635 --> 00:37:29.080 disease to multiple groups, chest,

NOTE Confidence: 0.94025373

00:37:29.080 --> 00:37:32.380 wall, bone, multiple nodal groups.

NOTE Confidence: 0.94025373

00:37:32.380 --> 00:37:36.179 She came to us, received cells for treatment.

NOTE Confidence: 0.94025373

00:37:36.179 --> 00:37:38.340 She received four different what

NOTE Confidence: 0.94025373

00:37:38.340 --> 00:37:40.380 appeared to be random somatic mutations.

NOTE Confidence: 0.94025373

00:37:40.380 --> 00:37:42.858 There's no driver function involved in these.

NOTE Confidence: 0.93059757

00:37:45.100 --> 00:37:48.284 And there was redundancy in the T cell

NOTE Confidence: 0.93059757

00:37:48.284 --> 00:37:50.736 receptors that we used to treat her.

NOTE Confidence: 0.93059757

00:37:50.740 --> 00:37:53.694 But by treating these four now random

NOTE Confidence: 0.93059757

00:37:53.694 --> 00:37:55.503 somatic mutations, she underwent a

NOTE Confidence: 0.93059757

00:37:55.503 --> 00:37:57.108 complete regression of this lesion

NOTE Confidence: 0.93059757

00:37:57.108 --> 00:37:59.178 beginning to grow through the cell wall.

NOTE Confidence: 0.93059757

00:37:59.180 --> 00:38:01.100 You can see multiple liver metastases.

NOTE Confidence: 0.93059757

00:38:01.100 --> 00:38:02.660 She had many more which disappeared.

NOTE Confidence: 0.93059757

00:38:02.660 --> 00:38:05.516 And she's over five years later now

NOTE Confidence: 0.93059757

00:38:05.516 --> 00:38:07.290 completely disease, disease free.

NOTE Confidence: 0.93059757

00:38:07.290 --> 00:38:10.140 This patient with a metastatic cervical

NOTE Confidence: 0.93059757

00:38:10.140 --> 00:38:12.895 cancer that was very aggressive and

NOTE Confidence: 0.93059757

00:38:12.895 --> 00:38:15.481 fungating into her into her vagina.

NOTE Confidence: 0.93059757

00:38:15.490 --> 00:38:19.466 Underwent resection radiation

NOTE Confidence: 0.93059757

00:38:19.466 --> 00:38:21.610 therapy and cisplatin chemotherapy.

NOTE Confidence: 0.93059757

00:38:21.610 --> 00:38:23.350 Underwent our hysterectomy

NOTE Confidence: 0.93059757

00:38:23.350 --> 00:38:26.250 and excision of both ovaries.

NOTE Confidence: 0.93059757

00:38:26.250 --> 00:38:28.170 She developed liver, lymph node,

NOTE Confidence: 0.93059757

00:38:28.170 --> 00:38:29.730 intra abdominal Mets including one

NOTE Confidence: 0.93059757

00:38:29.730 --> 00:38:31.290 that was obstructing her ureter.

NOTE Confidence: 0.93059757

00:38:31.290 --> 00:38:33.963 Came to us for treatment with our own till.

NOTE Confidence: 0.93059757

00:38:33.970 --> 00:38:35.770 You can see these lymph nodes

NOTE Confidence: 0.93059757

00:38:35.770 --> 00:38:36.370 which disappeared.

NOTE Confidence: 0.93059757

00:38:36.370 --> 00:38:38.810 This chest wall lesion disappearing

NOTE Confidence: 0.93059757

00:38:38.810 --> 00:38:40.138 this one as well.

NOTE Confidence: 0.93059757

00:38:40.138 --> 00:38:42.130 This node was obstructing her ureter.

NOTE Confidence: 0.93059757

00:38:42.130 --> 00:38:44.950 We put in a urinary catheter.

NOTE Confidence: 0.93059757

00:38:44.950 --> 00:38:46.142 A a ureteral catheter.

NOTE Confidence: 0.93059757

00:38:46.142 --> 00:38:47.930 When our tumor went away we

NOTE Confidence: 0.93059757

00:38:47.995 --> 00:38:49.067 could take it out.

NOTE Confidence: 0.93059757

00:38:49.070 --> 00:38:50.790 She remains disease free.

NOTE Confidence: 0.93059757

00:38:50.790 --> 00:38:55.306 Now over seven years later this patient

NOTE Confidence: 0.93059757

00:38:55.306 --> 00:38:56.974 with colorectal cancer was the one

NOTE Confidence: 0.93059757

00:38:56.974 --> 00:38:58.869 in which we found the KRS receptor.

NOTE Confidence: 0.93059757

00:38:58.870 --> 00:39:01.635 It had a colectomy was invading her

NOTE Confidence: 0.93059757

00:39:01.635 --> 00:39:04.470 bladder she so it was very aggressive.

NOTE Confidence: 0.93059757

00:39:04.470 --> 00:39:06.310 We resected 2 lung metastasis.

NOTE Confidence: 0.93059757

00:39:06.310 --> 00:39:09.352 She had seven others treated her and.

NOTE Confidence: 0.93059757

00:39:09.352 --> 00:39:12.244 Almost all of our tumors disappeared.

NOTE Confidence: 0.93059757

00:39:12.250 --> 00:39:14.070 She had seven lesions,

NOTE Confidence: 0.93059757

00:39:14.070 --> 00:39:15.890 six of which disappeared.

NOTE Confidence: 0.93059757

00:39:15.890 --> 00:39:19.746 This one did not disappear and continued

NOTE Confidence: 0.93059757

00:39:19.746 --> 00:39:22.322 to grow and where we resected it.

NOTE Confidence: 0.93059757

00:39:22.330 --> 00:39:23.610 We learned that in fact,

NOTE Confidence: 0.93059757

00:39:23.610 --> 00:39:25.520 by looking at copy number

NOTE Confidence: 0.93059757

00:39:25.520 --> 00:39:27.048 analysis of the chromosomes,

NOTE Confidence: 0.93059757

00:39:27.050 --> 00:39:29.834 she had lost one chromosome from chromosome 6

NOTE Confidence: 0.93059757

00:39:29.834 --> 00:39:32.849 and that chromosome and codes MHC molecules,

NOTE Confidence: 0.93059757

00:39:32.850 --> 00:39:34.738 including her restricting element.

NOTE Confidence: 0.93059757

00:39:34.738 --> 00:39:35.210 Therefore,

NOTE Confidence: 0.93059757

00:39:35.210 --> 00:39:37.458 that tumor could escape.

NOTE Confidence: 0.93059757

00:39:37.460 --> 00:39:41.460 And when we then went on to

NOTE Confidence: 0.93059757

00:39:41.460 --> 00:39:44.300 resect her that one lesion,

NOTE Confidence: 0.93059757

00:39:44.300 --> 00:39:47.002 she has not occurred since and remains

NOTE Confidence: 0.93059757

00:39:47.002 --> 00:39:49.339 disease free over six years later.

NOTE Confidence: 0.93059757

00:39:49.340 --> 00:39:51.566 We can see responses in pancreatic cancer

NOTE Confidence: 0.93059757

00:39:51.566 --> 00:39:53.998 as you can see this very dramatic.

NOTE Confidence: 0.93059757

00:39:54.000 --> 00:39:55.880 Response which I show you.

NOTE Confidence: 0.93059757

00:39:55.880 --> 00:39:58.556 It was a very recent patient

NOTE Confidence: 0.93059757

00:39:58.560 --> 00:40:00.228 who had what appeared to be

NOTE Confidence: 0.93059757

00:40:00.228 --> 00:40:01.728 almost a complete regression of

NOTE Confidence: 0.93059757

00:40:01.728 --> 00:40:03.076 multiple liver methass disease.

NOTE Confidence: 0.93059757

00:40:03.080 --> 00:40:05.112 But unfortunately within three

NOTE Confidence: 0.93059757

00:40:05.112 --> 00:40:07.184 months this patient didn't recur.

NOTE Confidence: 0.93059757

00:40:07.184 --> 00:40:09.360 And when we biopsied one of the lesions,

NOTE Confidence: 0.93059757

00:40:09.360 --> 00:40:12.293 he had lost expression of his target

NOTE Confidence: 0.93059757

00:40:12.293 --> 00:40:14.280 molecule which turned out to be

NOTE Confidence: 0.93059757

00:40:14.280 --> 00:40:16.758 P53 and a molecule that we'll hear

NOTE Confidence: 0.93059757

00:40:16.758 --> 00:40:19.400 about in a few moments longer.

NOTE Confidence: 0.954510083333333

00:40:21.460 --> 00:40:23.693 Well, we've now treated a little over

NOTE Confidence: 0.954510083333333

00:40:23.693 --> 00:40:25.819 100 patients with epithelial cancers.

NOTE Confidence: 0.954510083333333

00:40:25.820 --> 00:40:27.920 Again, it's the ducts in these

NOTE Confidence: 0.954510083333333

00:40:27.920 --> 00:40:30.159 organs that provide the source of

NOTE Confidence: 0.954510083333333

00:40:30.159 --> 00:40:32.074 mutations that are turning over

NOTE Confidence: 0.954510083333333

00:40:32.074 --> 00:40:34.458 constantly and as mistakes are made,

NOTE Confidence: 0.954510083333333

00:40:34.460 --> 00:40:36.252 mutations appear and those

NOTE Confidence: 0.954510083333333

00:40:36.252 --> 00:40:38.492 are the ones we're targeting.

NOTE Confidence: 0.954510083333333

00:40:38.500 --> 00:40:42.084 If you use bulk till in patients with

NOTE Confidence: 0.954510083333333

00:40:42.084 --> 00:40:44.179 epithelial cancers who are chemo,

NOTE Confidence: 0.954510083333333

00:40:44.180 --> 00:40:45.170 fract, chemo refractory,

NOTE Confidence: 0.954510083333333

00:40:45.170 --> 00:40:48.100 we do not see responses in 21 patients,

NOTE Confidence: 0.954510083333333

00:40:48.100 --> 00:40:52.036 but when we started to select these till.

NOTE Confidence: 0.954510083333333

00:40:52.040 --> 00:40:55.360 And treated 81 patients,

NOTE Confidence: 0.954510083333333

00:40:55.360 --> 00:40:56.920 17% of them have responded.

NOTE Confidence: 0.954510083333333

00:40:56.920 --> 00:40:58.396 I've shown you some of them.

NOTE Confidence: 0.954510083333333

00:40:58.400 --> 00:40:59.980 These are all patients

NOTE Confidence: 0.954510083333333

00:40:59.980 --> 00:41:01.560 that are chemo refractory.

NOTE Confidence: 0.954510083333333

00:41:01.560 --> 00:41:03.195 Many had had checkpoint modulators

NOTE Confidence: 0.954510083333333

00:41:03.195 --> 00:41:05.232 which do not work in these

NOTE Confidence: 0.954510083333333

00:41:05.232 --> 00:41:08.850 tumors and had not responded and.

NOTE Confidence: 0.954510083333333

00:41:08.850 --> 00:41:10.565 We have a long ways to go,

NOTE Confidence: 0.954510083333333

00:41:10.570 --> 00:41:13.765 but these 17 patients at least

NOTE Confidence: 0.954510083333333

00:41:13.765 --> 00:41:16.362 show us that this is possible as

NOTE Confidence: 0.954510083333333

00:41:16.362 --> 00:41:18.610 we continue to refine and learn

NOTE Confidence: 0.954510083333333

00:41:18.610 --> 00:41:20.210 how to treat these patients.

NOTE Confidence: 0.954510083333333

00:41:20.210 --> 00:41:24.170 For the refractory epithelial cancers,

NOTE Confidence: 0.954510083333333

00:41:24.170 --> 00:41:25.345 well, there were two hypotheses

NOTE Confidence: 0.954510083333333

00:41:25.345 --> 00:41:26.285 that come from this.

NOTE Confidence: 0.954510083333333

00:41:26.290 --> 00:41:26.615 First,

NOTE Confidence: 0.954510083333333

00:41:26.615 --> 00:41:28.565 it appears to be the recognition

NOTE Confidence: 0.954510083333333

00:41:28.565 --> 00:41:30.170 of random somatic mutations.

NOTE Confidence: 0.954510083333333

00:41:30.170 --> 00:41:32.270 It's a final common pathway that

NOTE Confidence: 0.954510083333333

00:41:32.270 --> 00:41:34.010 explains cancer aggression for most,

NOTE Confidence: 0.954510083333333

00:41:34.010 --> 00:41:37.460 if not all immuno therapies.

NOTE Confidence: 0.954510083333333

00:41:37.460 --> 00:41:39.518 We finally understand what a cancer

NOTE Confidence: 0.954510083333333

00:41:39.518 --> 00:41:42.868 antigen is and as we now look at the

NOTE Confidence: 0.954510083333333

00:41:42.868 --> 00:41:44.778 variety of chemother of immunotherapies,

NOTE Confidence: 0.954510083333333

00:41:44.780 --> 00:41:47.124 it's now been shown for anti C2A4,

NOTE Confidence: 0.954510083333333

00:41:47.124 --> 00:41:50.044 we're studying it fertil tumor

NOTE Confidence: 0.954510083333333

00:41:50.044 --> 00:41:52.380 infiltrating lymphocytes as well.

NOTE Confidence: 0.954510083333333

00:41:52.380 --> 00:41:53.820 What is a cancer antigen?

NOTE Confidence: 0.954510083333333

00:41:53.820 --> 00:41:55.628 It's any intracellular protein

NOTE Confidence: 0.954510083333333

00:41:55.628 --> 00:41:58.340 that could potentially be a cancer

NOTE Confidence: 0.954510083333333

00:41:58.410 --> 00:42:01.164 antigen if it's mutated and processed

NOTE Confidence: 0.954510083333333

00:42:01.164 --> 00:42:03.517 intracellulally to a peptide that

NOTE Confidence: 0.954510083333333

00:42:03.517 --> 00:42:06.199 combined to the autologous MHC molecule.

NOTE Confidence: 0.954510083333333

00:42:06.200 --> 00:42:09.098 About one in every seventy of these

NOTE Confidence: 0.954510083333333

00:42:09.098 --> 00:42:11.598 mutated NEO epitopes are NEO antigens

NOTE Confidence: 0.954510083333333

00:42:11.600 --> 00:42:14.358 and there's good news and bad news.

NOTE Confidence: 0.954510083333333

00:42:14.360 --> 00:42:16.331 The bad news is that this will have to

NOTE Confidence: 0.954510083333333

00:42:16.331 --> 00:42:18.365 be a very highly personalized treatment

NOTE Confidence: 0.954510083333333

00:42:18.365 --> 00:42:20.720 after over taking a patient's own cells.

NOTE Confidence: 0.954510083333333

00:42:20.720 --> 00:42:23.520 We're targeting A mutation that's

NOTE Confidence: 0.954510083333333

00:42:23.520 --> 00:42:27.496 unique to his own tumor and will

NOTE Confidence: 0.954510083333333

00:42:27.496 --> 00:42:30.436 therefore be complex to administer.

NOTE Confidence: 0.954510083333333

00:42:30.440 --> 00:42:32.421 The good news is that virtually all

NOTE Confidence: 0.954510083333333

00:42:32.421 --> 00:42:34.100 cancer patients are potentially eligible

NOTE Confidence: 0.954510083333333

00:42:34.100 --> 00:42:36.045 because they all have mutations.

NOTE Confidence: 0.954510083333333

00:42:36.050 --> 00:42:37.650 And some more than others.

NOTE Confidence: 0.954510083333333

00:42:37.650 --> 00:42:41.005 So the opportunity does exist to

NOTE Confidence: 0.954510083333333

00:42:41.005 --> 00:42:44.180 further deliver this treatment and

NOTE Confidence: 0.954510083333333

00:42:44.180 --> 00:42:46.269 the complexity will be difficult.

NOTE Confidence: 0.954510083333333

00:42:46.269 --> 00:42:47.088 But then again,

NOTE Confidence: 0.954510083333333

00:42:47.090 --> 00:42:48.946 I heard that in the early days of

NOTE Confidence: 0.954510083333333

00:42:48.946 --> 00:42:50.167 our development of CAR T cells,

NOTE Confidence: 0.954510083333333

00:42:50.170 --> 00:42:51.995 several groups came through large

NOTE Confidence: 0.954510083333333

00:42:51.995 --> 00:42:53.090 pharmaceutical companies saying,

NOTE Confidence: 0.954510083333333

00:42:53.090 --> 00:42:54.686 hey, if we had this disease,

NOTE Confidence: 0.954510083333333

00:42:54.690 --> 00:42:55.534 we'd come to you,

NOTE Confidence: 0.954510083333333

00:42:55.534 --> 00:42:57.890 but we don't see how to make money doing it.

NOTE Confidence: 0.954510083333333

00:42:57.890 --> 00:42:59.458 But I have every confidence that if

NOTE Confidence: 0.954510083333333

00:42:59.458 --> 00:43:01.201 we can figure out ways to make it

NOTE Confidence: 0.954510083333333

00:43:01.201 --> 00:43:02.690 work and large numbers of patients,

NOTE Confidence: 0.954510083333333

00:43:02.690 --> 00:43:03.870 the genius of American industry

NOTE Confidence: 0.954510083333333

00:43:03.870 --> 00:43:05.728 will figure out a way to deliver it.

NOTE Confidence: 0.922228133333333

00:43:07.770 --> 00:43:09.552 Well there are two main approaches

NOTE Confidence: 0.922228133333333

00:43:09.552 --> 00:43:11.186 to using lymphos type transfer

NOTE Confidence: 0.922228133333333

00:43:11.186 --> 00:43:13.121 and we've talked about expanding

NOTE Confidence: 0.922228133333333

00:43:13.121 --> 00:43:15.050 naturally occurring anti cancer cells.

NOTE Confidence: 0.922228133333333

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

NOTE Confidence: 0.922228133333333

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

NOTE Confidence: 0.922228133333333

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

NOTE Confidence: 0.922228133333333

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

NOTE Confidence: 0.922228133333333

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

NOTE Confidence: 0.922228133333333

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

00:43:54.234 --> 00:43:55.870 cancer genomes have been sequenced,

NOTE Confidence: 0.949542781538462

00:43:55.870 --> 00:43:58.814 how few of these actually exist that are

NOTE Confidence: 0.949542781538462

00:43:58.814 --> 00:44:02.195 shared Far and away the most common are KK,

NOTE Confidence: 0.949542781538462

00:44:02.195 --> 00:44:04.250 RASS and P53.

NOTE Confidence: 0.949542781538462

00:44:04.250 --> 00:44:07.336 KRS expressing 30% of all cancers,

NOTE Confidence: 0.949542781538462

00:44:07.336 --> 00:44:08.704 70% of pancreatic cancer,

NOTE Confidence: 0.949542781538462

00:44:08.710 --> 00:44:12.266 it's P53 and half of all cancers.

NOTE Confidence: 0.949542781538462

00:44:12.270 --> 00:44:14.844 And so we've made efforts to

NOTE Confidence: 0.949542781538462

00:44:14.844 --> 00:44:16.914 identify TCRS from patients that

NOTE Confidence: 0.949542781538462

00:44:16.914 --> 00:44:19.411 contain these mutations to find T

NOTE Confidence: 0.949542781538462

00:44:19.411 --> 00:44:21.733 cell receptors by doing a highly

NOTE Confidence: 0.949542781538462

00:44:21.733 --> 00:44:24.169 directed screening using very high

NOTE Confidence: 0.949542781538462

00:44:24.169 --> 00:44:27.450 concentrations of these molecules or by

NOTE Confidence: 0.949542781538462

00:44:27.450 --> 00:44:30.150 especially by in vitro sensitization.

NOTE Confidence: 0.949542781538462

00:44:30.150 --> 00:44:31.822 To identify T cells,

NOTE Confidence: 0.949542781538462

00:44:31.822 --> 00:44:34.330 to identify that very tiny number

NOTE Confidence: 0.949542781538462

00:44:34.407 --> 00:44:36.729 that do exist in patients that

NOTE Confidence: 0.949542781538462

00:44:36.729 --> 00:44:40.790 can recognize K Ras in P53.

NOTE Confidence: 0.949542781538462

00:44:40.790 --> 00:44:43.886 And we published about a year and a half

NOTE Confidence: 0.949542781538462

00:44:43.886 --> 00:44:47.275 ago a library of T cell receptors that

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

00:44:54.770 --> 00:44:57.572 Over 80% of OK Ras mutations

NOTE Confidence: 0.949542781538462

00:44:57.572 --> 00:45:00.330 occur at three different hotspots,

NOTE Confidence: 0.949542781538462

00:45:00.330 --> 00:45:05.678 GG12DG12V and G6 and the 60 oneth

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

00:45:10.450 --> 00:45:12.667 at this K12 and 13 position and

NOTE Confidence: 0.949542781538462

00:45:12.667 --> 00:45:15.612 you can see for a variety now of

NOTE Confidence: 0.949542781538462

00:45:15.612 --> 00:45:18.958 restriction elements we can identify.

NOTE Confidence: 0.949542781538462

00:45:18.960 --> 00:45:22.494 T cell receptors and publish the

NOTE Confidence: 0.949542781538462

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

NOTE Confidence: 0.949542781538462

00:45:26.360 --> 00:45:29.915 tumors mutations based on the

NOTE Confidence: 0.949542781538462

00:45:29.915 --> 00:45:34.781 recognition of K Ras mutations and a

NOTE Confidence: 0.949542781538462

00:45:34.781 --> 00:45:37.514 similar library now of mutations in

NOTE Confidence: 0.949542781538462

00:45:37.514 --> 00:45:40.250 K Ras can be recognized by CD4 cells

NOTE Confidence: 0.949542781538462

00:45:40.250 --> 00:45:43.302 using a variety of different Class 2

NOTE Confidence: 0.949542781538462

00:45:43.302 --> 00:45:45.560 restriction elements And if you look at.

NOTE Confidence: 0.949542781538462

00:45:45.560 --> 00:45:48.199 The two libraries that we've now developed,

NOTE Confidence: 0.949542781538462

00:45:48.200 --> 00:45:51.176 33% of all patients with K Ras mutations

NOTE Confidence: 0.949542781538462

00:45:51.176 --> 00:45:53.692 can potentially be eligible for treatment.

NOTE Confidence: 0.949542781538462

00:45:53.692 --> 00:45:56.608 These T cell receptors if we

NOTE Confidence: 0.949542781538462

00:45:56.608 --> 00:45:59.006 can learn to use them well,

NOTE Confidence: 0.949542781538462

00:45:59.006 --> 00:46:01.330 that led us to the issue of,

NOTE Confidence: 0.949542781538462

00:46:01.330 --> 00:46:01.675 well,

NOTE Confidence: 0.949542781538462

00:46:01.675 --> 00:46:04.090 what kinds of receptors do we really

NOTE Confidence: 0.949542781538462

00:46:04.159 --> 00:46:07.225 want because we can find dozens of

NOTE Confidence: 0.949542781538462

00:46:07.225 --> 00:46:09.005 redundant muceptors recognizing the

NOTE Confidence: 0.949542781538462

00:46:09.005 --> 00:46:11.001 same exact molecules and there are

NOTE Confidence: 0.949542781538462

00:46:11.001 --> 00:46:12.870 a variety of tests that one can

NOTE Confidence: 0.949542781538462

00:46:12.931 --> 00:46:14.947 use to test these receptors lytic.

NOTE Confidence: 0.949542781538462

00:46:14.950 --> 00:46:16.438 Function, cytokine secretion,

NOTE Confidence: 0.949542781538462

00:46:16.438 --> 00:46:17.430 the avidity,

NOTE Confidence: 0.949542781538462

00:46:17.430 --> 00:46:20.230 the affinity catch bond techniques.

NOTE Confidence: 0.949542781538462

00:46:20.230 --> 00:46:22.734 And so we've gone to try to understand

NOTE Confidence: 0.949542781538462

00:46:22.734 --> 00:46:25.184 what T cells do we need so that

NOTE Confidence: 0.949542781538462

00:46:25.184 --> 00:46:27.745 we can select the right ones among

NOTE Confidence: 0.949542781538462

00:46:27.745 --> 00:46:29.065 the redundant number.

NOTE Confidence: 0.949542781538462

00:46:29.070 --> 00:46:31.670 And this brings us back to that patient

NOTE Confidence: 0.949542781538462

00:46:31.670 --> 00:46:34.547 with KRAS who was treated with four

NOTE Confidence: 0.949542781538462

00:46:34.547 --> 00:46:37.110 different receptors all that recognized KRAS,

NOTE Confidence: 0.949542781538462

00:46:37.110 --> 00:46:39.720 you can look here at their.

NOTE Confidence: 0.949542781538462

00:46:39.720 --> 00:46:40.181 Avidity,

NOTE Confidence: 0.949542781538462

00:46:40.181 --> 00:46:42.947 that is they all recognize about

NOTE Confidence: 0.949542781538462

00:46:42.947 --> 00:46:45.199 the same concentration of peptide.

NOTE Confidence: 0.949542781538462

00:46:45.200 --> 00:46:48.800 But one of these receptors disappeared

NOTE Confidence: 0.949542781538462

00:46:48.800 --> 00:46:51.365 immediately upon infusion and this

NOTE Confidence: 0.949542781538462

00:46:51.365 --> 00:46:53.640 was a majority receptor given.

NOTE Confidence: 0.949542781538462

00:46:53.640 --> 00:46:55.962 Where are three of these receptors

NOTE Confidence: 0.949542781538462

00:46:55.962 --> 00:46:58.159 persisted well out beyond the year?

NOTE Confidence: 0.949542781538462

00:46:58.160 --> 00:47:00.814 Here are measurements out to 290 days.

NOTE Confidence: 0.949542781538462

00:47:00.814 --> 00:47:03.249 There was something very different

NOTE Confidence: 0.949542781538462

00:47:03.249 --> 00:47:06.160 about this receptor compared to these.

NOTE Confidence: 0.949542781538462

00:47:06.160 --> 00:47:08.224 What was the difference?

NOTE Confidence: 0.949542781538462

00:47:08.224 --> 00:47:10.804 The avidity was the same.

NOTE Confidence: 0.949542781538462

00:47:10.810 --> 00:47:12.924 We looked at a variety of criteria,

NOTE Confidence: 0.961638325

00:47:15.810 --> 00:47:18.170 especially surface plasmon resistance,

NOTE Confidence: 0.961638325

00:47:18.170 --> 00:47:20.901 to measure the exact KD,

NOTE Confidence: 0.961638325

00:47:20.901 --> 00:47:23.127 the association constant of that receptor.

NOTE Confidence: 0.961638325

00:47:23.130 --> 00:47:25.209 What we did is identify the receptor,

NOTE Confidence: 0.961638325

00:47:25.210 --> 00:47:27.050 clone it, purified it,

NOTE Confidence: 0.961638325

00:47:27.050 --> 00:47:30.410 and put it into human cells that were

NOTE Confidence: 0.961638325

00:47:30.410 --> 00:47:33.360 then used to treat the human tumor

NOTE Confidence: 0.961638325

00:47:33.360 --> 00:47:36.070 and immunosuppressed mice and Notices

NOTE Confidence: 0.961638325

00:47:36.070 --> 00:47:38.890 1 receptor had the highest affinity.

NOTE Confidence: 0.961638325

00:47:38.890 --> 00:47:44.090 And was the least active in treating mice.

NOTE Confidence: 0.961638325

00:47:44.090 --> 00:47:46.610 If you look now at this highest

NOTE Confidence: 0.961638325

00:47:46.610 --> 00:47:48.289 affinity receptor using a mouse,

NOTE Confidence: 0.961638325

00:47:48.290 --> 00:47:50.690 a human receptor to treat a human tumor

NOTE Confidence: 0.961638325

00:47:50.690 --> 00:47:53.408 in a highly immunosuppressed mouse,

NOTE Confidence: 0.961638325

00:47:53.410 --> 00:47:56.404 it was these lower affinity receptors

NOTE Confidence: 0.961638325

00:47:56.404 --> 00:47:59.370 which were the most effective.

NOTE Confidence: 0.961638325

00:47:59.370 --> 00:48:01.458 And so it appears that it's not only the

NOTE Confidence: 0.961638325

00:48:01.458 --> 00:48:03.246 fitness state of the lymphocyte itself,

NOTE Confidence: 0.961638325

00:48:03.250 --> 00:48:05.386 but the quality of its receptor

NOTE Confidence: 0.961638325

00:48:05.386 --> 00:48:07.928 that play a role in anti tumor.

NOTE Confidence: 0.961638325

00:48:07.930 --> 00:48:10.690 Effectiveness well knowing the

NOTE Confidence: 0.929647369565217

00:48:12.890 --> 00:48:15.826 receptor that was developed by Eric Tran who

NOTE Confidence: 0.929647369565217

00:48:15.826 --> 00:48:19.023 was a fellow in the laboratory who about

NOTE Confidence: 0.929647369565217

00:48:19.023 --> 00:48:22.009 the three years ago moved to Portland.

NOTE Confidence: 0.929647369565217

00:48:22.010 --> 00:48:25.082 With Eric, we use this receptor that had

NOTE Confidence: 0.929647369565217

00:48:25.082 --> 00:48:27.638 the low affinity that seemed to have

NOTE Confidence: 0.929647369565217

00:48:27.638 --> 00:48:29.588 that sweet spot of the recognition to

NOTE Confidence: 0.929647369565217

00:48:29.588 --> 00:48:31.364 treat a patient with pancreatic cancer.

NOTE Confidence: 0.929647369565217

00:48:31.370 --> 00:48:33.130 It was published in the New England Journal.

NOTE Confidence: 0.87752148

00:48:36.320 --> 00:48:41.318 What about six months ago and you can

NOTE Confidence: 0.87752148

00:48:41.318 --> 00:48:44.594 see the regression that was reported

NOTE Confidence: 0.87752148

00:48:44.600 --> 00:48:47.568 with follow up out to six months

NOTE Confidence: 0.87752148

00:48:47.568 --> 00:48:50.319 of multiple lung metastases which

NOTE Confidence: 0.87752148

00:48:50.320 --> 00:48:52.750 shrank in that patient to perform

NOTE Confidence: 0.87752148

00:48:52.750 --> 00:48:54.447 a substantial partial regression.

NOTE Confidence: 0.87752148

00:48:54.447 --> 00:48:57.021 We have additional follow up now

NOTE Confidence: 0.87752148

00:48:57.021 --> 00:48:59.316 that patient did recur at one year

NOTE Confidence: 0.87752148

00:48:59.316 --> 00:49:01.343 but spent one year disease free

NOTE Confidence: 0.87752148

00:49:01.343 --> 00:49:03.694 of his pancreatic cancer and we

NOTE Confidence: 0.87752148

00:49:03.694 --> 00:49:05.729 recently just four months ago.

NOTE Confidence: 0.87752148

00:49:05.730 --> 00:49:08.065 Treated a patient with pancreatic

NOTE Confidence: 0.87752148

00:49:08.065 --> 00:49:10.400 cancer utilizing a different set

NOTE Confidence: 0.87752148

00:49:10.479 --> 00:49:12.477 of key res receptors restricted by

NOTE Confidence: 0.87752148

00:49:12.477 --> 00:49:15.865 a eleven O 1 which is a class 1MHC

NOTE Confidence: 0.87752148

00:49:15.865 --> 00:49:18.935 molecule and you can see here this

NOTE Confidence: 0.87752148

00:49:18.935 --> 00:49:21.760 liver metastases which is almost

NOTE Confidence: 0.87752148

00:49:21.760 --> 00:49:24.924 disappeared by three months this large

NOTE Confidence: 0.87752148

00:49:24.924 --> 00:49:28.326 one smaller and by three months almost gone.

NOTE Confidence: 0.87752148

00:49:28.330 --> 00:49:29.730 We're continuing to follow this

NOTE Confidence: 0.87752148

00:49:29.730 --> 00:49:31.650 patient but this is an approach.

NOTE Confidence: 0.87752148

00:49:31.650 --> 00:49:34.476 Using T cell receptors into normal

NOTE Confidence: 0.87752148

00:49:34.476 --> 00:49:37.449 cells that can potentially be effective,

NOTE Confidence: 0.87752148

00:49:37.450 --> 00:49:41.130 Peter Kim in the Surgery Branch

NOTE Confidence: 0.87752148

00:49:41.130 --> 00:49:44.154 a fellow has developed a library

NOTE Confidence: 0.87752148

00:49:44.154 --> 00:49:47.138 mainly using in vitro sensitization

NOTE Confidence: 0.87752148

00:49:47.138 --> 00:49:49.490 to target P53 molecules.

NOTE Confidence: 0.87752148

00:49:49.490 --> 00:49:53.630 This was published about six months ago

NOTE Confidence: 0.87752148

00:49:53.630 --> 00:49:56.705 in Clinical Clinical Cancer Immunology

NOTE Confidence: 0.87752148

00:49:56.705 --> 00:49:59.508 Research and again these receptors.

NOTE Confidence: 0.87752148

00:49:59.508 --> 00:50:03.750 Now with some common Class 1 molecules,

NOTE Confidence: 0.87752148

00:50:03.750 --> 00:50:04.190 O2,

NOTE Confidence: 0.87752148

00:50:04.190 --> 00:50:06.752 O1 can potentially treat about 5

NOTE Confidence: 0.87752148

00:50:06.752 --> 00:50:09.286 1/2% of all patients with K Ras

NOTE Confidence: 0.87752148

00:50:09.286 --> 00:50:11.735 mutations and again 50% of all cancer

NOTE Confidence: 0.87752148

00:50:11.735 --> 00:50:13.310 patients have K Ras mutations.

NOTE Confidence: 0.944446623333334

00:50:15.430 --> 00:50:17.782 Well, we could again identify the

NOTE Confidence: 0.944446623333334

00:50:17.782 --> 00:50:20.070 T cell receptors that were most

NOTE Confidence: 0.944446623333334

00:50:20.070 --> 00:50:25.172 common in recognizing P53 and

NOTE Confidence: 0.944446623333334

00:50:25.172 --> 00:50:28.916 recognizing tumors that contain P53.

NOTE Confidence: 0.944446623333334

00:50:28.916 --> 00:50:30.946 We isolated those T cell.

NOTE Confidence: 0.944446623333334

00:50:30.950 --> 00:50:34.110 Receptors that you uniquely recognize

NOTE Confidence: 0.944446623333334

00:50:34.110 --> 00:50:39.230 P53 recognizing tumors and again

NOTE Confidence: 0.944446623333334

00:50:39.230 --> 00:50:42.756 studied each one of these 5-6 receptors

NOTE Confidence: 0.944446623333334

00:50:42.756 --> 00:50:45.297 that we could find to see which

NOTE Confidence: 0.944446623333334

00:50:45.297 --> 00:50:48.705 were most effective and one of them

NOTE Confidence: 0.944446623333334

00:50:48.705 --> 00:50:51.990 was more effective than the rest.

NOTE Confidence: 0.944446623333334

00:50:51.990 --> 00:50:54.445 Although at high concentrations many

NOTE Confidence: 0.944446623333334

00:50:54.445 --> 00:50:56.852 others began to work as well in terms

NOTE Confidence: 0.944446623333334

00:50:56.852 --> 00:50:58.556 of cursing in the regression of a

NOTE Confidence: 0.944446623333334

00:50:58.556 --> 00:51:01.420 human tumor in a in a in a mouse.

NOTE Confidence: 0.944446623333334

00:51:01.420 --> 00:51:03.832 Using human receptors at 27 cells,

NOTE Confidence: 0.944446623333334

00:51:03.832 --> 00:51:05.088 you could see many,

NOTE Confidence: 0.944446623333334

00:51:05.090 --> 00:51:07.568 several of the receptors were active.

NOTE Confidence: 0.944446623333334

00:51:07.570 --> 00:51:09.682 But when you went down to 1/5 of

NOTE Confidence: 0.944446623333334

00:51:09.682 --> 00:51:12.010 that a 2E6A tiny number of cells,

NOTE Confidence: 0.944446623333334

00:51:12.010 --> 00:51:13.960 this one receptor was most effective

NOTE Confidence: 0.944446623333334

00:51:13.960 --> 00:51:16.318 and it was the receptor with

NOTE Confidence: 0.944446623333334

00:51:16.318 --> 00:51:17.809 an intermediate affinity.

NOTE Confidence: 0.944446623333334

00:51:17.810 --> 00:51:20.449 And so as we continue these experiments,

NOTE Confidence: 0.944446623333334

00:51:20.450 --> 00:51:22.070 we're beginning to learn which

NOTE Confidence: 0.944446623333334

00:51:22.070 --> 00:51:24.050 kind of receptors we we need.

NOTE Confidence: 0.944446623333334

00:51:24.050 --> 00:51:24.497 Well,

NOTE Confidence: 0.944446623333334

00:51:24.497 --> 00:51:28.073 having identified that a patient who came in.

NOTE Confidence: 0.944446623333334

00:51:28.080 --> 00:51:29.460 With breast cancer,

NOTE Confidence: 0.944446623333334

00:51:29.460 --> 00:51:31.760 we've been through multiple chemotherapies

NOTE Confidence: 0.944446623333334

00:51:31.760 --> 00:51:34.610 with the highly advanced disease was

NOTE Confidence: 0.944446623333334

00:51:34.610 --> 00:51:38.280 treated with our own cells that were

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

00:51:57.511 --> 00:51:59.173 from inside the pericardium and all

NOTE Confidence: 0.944446623333334

00:51:59.173 --> 00:52:00.902 of the biopsies here were positive.

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

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

NOTE Confidence: 0.944446623333334

00:52:05.530 --> 00:52:08.670 and extending into the into the other breast.

NOTE Confidence: 0.944446623333334

00:52:08.670 --> 00:52:11.889 She was treated with our own cells that.

NOTE Confidence: 0.944446623333334

00:52:11.890 --> 00:52:14.230 Had been transduced to express

NOTE Confidence: 0.944446623333334

00:52:14.230 --> 00:52:15.994 an anti P53 receptor,

NOTE Confidence: 0.944446623333334

00:52:15.994 --> 00:52:19.290 this 175 H receptor that I just mentioned.

NOTE Confidence: 0.944446623333334

00:52:19.290 --> 00:52:21.950 Every one of these nodules is a

NOTE Confidence: 0.944446623333334

00:52:21.950 --> 00:52:24.050 separate tumor deposit at a large

NOTE Confidence: 0.944446623333334

00:52:24.050 --> 00:52:25.650 necrotic lesion in our breasts.

NOTE Confidence: 0.944446623333334

00:52:25.650 --> 00:52:30.296 All of this, everything visible.

NOTE Confidence: 0.944446623333334

00:52:30.296 --> 00:52:32.835 Disappeared and you can see here

NOTE Confidence: 0.944446623333334

00:52:32.835 --> 00:52:35.253 at the 60 days the way this breast

NOTE Confidence: 0.944446623333334

00:52:35.253 --> 00:52:36.657 looked at six months.

NOTE Confidence: 0.944446623333334

00:52:36.660 --> 00:52:37.156 However,

NOTE Confidence: 0.944446623333334

00:52:37.156 --> 00:52:41.124 she did recur with a nodule that we

NOTE Confidence: 0.944446623333334

00:52:41.124 --> 00:52:43.930 biopsied that had an LOHA loss of

NOTE Confidence: 0.944446623333334

00:52:43.930 --> 00:52:46.431 heterozygosity at her MHC locust which

NOTE Confidence: 0.944446623333334

00:52:46.431 --> 00:52:49.065 enabled this and other lesions to

NOTE Confidence: 0.944446623333334

00:52:49.065 --> 00:52:52.298 escape and so she did recur at six months.

NOTE Confidence: 0.93924726

00:52:58.270 --> 00:53:00.166 So we can use T cell

NOTE Confidence: 0.93924726

00:53:00.166 --> 00:53:01.430 receptors to treat patients.

NOTE Confidence: 0.93924726

00:53:01.430 --> 00:53:03.739 And I'll finish with this very

NOTE Confidence: 0.93924726

00:53:03.739 --> 00:53:05.484 latest finding we just published

NOTE Confidence: 0.93924726

00:53:05.484 --> 00:53:07.934 about six months ago in the science

NOTE Confidence: 0.93924726

00:53:07.934 --> 00:53:09.589 and are beginning to exploit.

NOTE Confidence: 0.93924726

00:53:09.590 --> 00:53:12.534 And that is a very rapid method to

NOTE Confidence: 0.93924726

00:53:12.534 --> 00:53:14.720 identify cancer reactive T cell

NOTE Confidence: 0.93924726

00:53:14.720 --> 00:53:17.010 receptors directly from a resected

NOTE Confidence: 0.93924726

00:53:17.010 --> 00:53:19.871 tumor without having to do all of the

NOTE Confidence: 0.93924726

00:53:19.871 --> 00:53:22.468 testing to see what they recognize.

NOTE Confidence: 0.93924726

00:53:22.470 --> 00:53:24.846 So how do we do this?

NOTE Confidence: 0.93924726

00:53:24.850 --> 00:53:27.454 We use a single cell transcriptome

NOTE Confidence: 0.93924726

00:53:27.454 --> 00:53:29.490 analysis of lymphocytes

NOTE Confidence: 0.93924726

00:53:29.490 --> 00:53:32.690 from freshly resected tumor.

NOTE Confidence: 0.93924726

00:53:32.690 --> 00:53:33.650 In this analysis,

NOTE Confidence: 0.93924726

00:53:33.650 --> 00:53:35.570 each cell is bar coded with

NOTE Confidence: 0.93924726

00:53:35.570 --> 00:53:37.721 an individual DNA sequence and

NOTE Confidence: 0.93924726

00:53:37.721 --> 00:53:39.921 when that individual cell is

NOTE Confidence: 0.93924726

00:53:39.921 --> 00:53:41.898 sequenced and you can sequence up

NOTE Confidence: 0.93924726

00:53:41.898 --> 00:53:44.272 to 10,000 cells at a given time,

NOTE Confidence: 0.93924726

00:53:44.272 --> 00:53:46.527 the transcriptome all the messenger

NOTE Confidence: 0.93924726

00:53:46.527 --> 00:53:50.288 RN A's can be analyzed and the T

NOTE Confidence: 0.93924726

00:53:50.288 --> 00:53:53.160 cell resequence identified and each.

NOTE Confidence: 0.93924726

00:53:53.160 --> 00:53:56.835 Identified in an individual cell

NOTE Confidence: 0.93924726

00:53:56.840 --> 00:54:00.400 and so we did that.

NOTE Confidence: 0.93924726

00:54:00.400 --> 00:54:03.158 And if you then break those lymphocytes

NOTE Confidence: 0.93924726

00:54:03.158 --> 00:54:06.200 into all of the different clusters,

NOTE Confidence: 0.93924726

00:54:06.200 --> 00:54:09.917 what you can do is the following

NOTE Confidence: 0.93924726

00:54:09.920 --> 00:54:15.418 because we have the transcriptome

NOTE Confidence: 0.93924726

00:54:15.418 --> 00:54:19.508 sequence for every individual cell.

NOTE Confidence: 0.93924726

00:54:19.510 --> 00:54:21.544 And we've identified the T cell

NOTE Confidence: 0.93924726

00:54:21.544 --> 00:54:23.312 receptors in that patient that

NOTE Confidence: 0.93924726

00:54:23.312 --> 00:54:25.067 can recognize the tumor because

NOTE Confidence: 0.93924726

00:54:25.067 --> 00:54:27.402 every time we identify a cell and

NOTE Confidence: 0.93924726

00:54:27.402 --> 00:54:29.142 all the patients I've showed you,

NOTE Confidence: 0.93924726

00:54:29.150 --> 00:54:31.517 we can very easily then get to the T

NOTE Confidence: 0.93924726

00:54:31.517 --> 00:54:33.282 cell receptor using PCR techniques

NOTE Confidence: 0.93924726

00:54:33.282 --> 00:54:35.826 to clone it out only takes about

NOTE Confidence: 0.93924726

00:54:35.826 --> 00:54:38.064 the about two weeks if we look

NOTE Confidence: 0.93924726

00:54:38.064 --> 00:54:40.847 at this cluster and look at the T

NOTE Confidence: 0.93924726

00:54:40.847 --> 00:54:43.190 cell receptor sequences that we've

NOTE Confidence: 0.93924726

00:54:43.190 --> 00:54:45.490 identified for this rectal cancer

NOTE Confidence: 0.93924726

00:54:45.490 --> 00:54:48.878 patient and see what cells they're in.

NOTE Confidence: 0.93924726

00:54:48.880 --> 00:54:51.380 They quite astonishingly all appear

NOTE Confidence: 0.93924726

00:54:51.380 --> 00:54:53.880 in a single transcriptome culture

NOTE Confidence: 0.901119807142857

00:54:56.040 --> 00:54:57.874 was true for this breast cancer patient.

NOTE Confidence: 0.901119807142857

00:54:57.880 --> 00:55:00.743 In this cluster, we take nine cancer

NOTE Confidence: 0.901119807142857

00:55:00.743 --> 00:55:03.097 patients from many different histologies.

NOTE Confidence: 0.901119807142857

00:55:03.097 --> 00:55:06.113 You can see they all fit in these

NOTE Confidence: 0.901119807142857

00:55:06.120 --> 00:55:11.362 clusters and So what that enables us

NOTE Confidence: 0.901119807142857

00:55:11.362 --> 00:55:15.819 to do is identify the gene signature.

NOTE Confidence: 0.901119807142857

00:55:15.820 --> 00:55:17.500 Of cells in that cluster because

NOTE Confidence: 0.901119807142857

00:55:17.500 --> 00:55:19.460 we know the whole transcriptome,

NOTE Confidence: 0.901119807142857

00:55:19.460 --> 00:55:23.012 all the MRN A's expressed and could

NOTE Confidence: 0.901119807142857

00:55:23.012 --> 00:55:25.784 identify and report on a gene signature

NOTE Confidence: 0.901119807142857

00:55:25.784 --> 00:55:28.170 which we published in Science led

NOTE Confidence: 0.901119807142857

00:55:28.170 --> 00:55:31.646 interestingly by a B cell antigen CX, CL13.

NOTE Confidence: 0.901119807142857

00:55:31.646 --> 00:55:34.604 And when we take now an

NOTE Confidence: 0.901119807142857

00:55:34.604 --> 00:55:36.500 unknown patient cluster,

NOTE Confidence: 0.901119807142857

00:55:36.500 --> 00:55:39.460 look for that transcriptome sequencing

NOTE Confidence: 0.901119807142857

00:55:39.460 --> 00:55:42.380 that we look for those T cell receptors.

NOTE Confidence: 0.901119807142857

00:55:42.380 --> 00:55:45.945 Sequences that fit this gene

NOTE Confidence: 0.901119807142857

00:55:45.945 --> 00:55:48.900 signature we could then identify.

NOTE Confidence: 0.901119807142857

00:55:48.900 --> 00:55:50.580 For unknown samples,

NOTE Confidence: 0.901119807142857

00:55:50.580 --> 00:55:52.265 we could identify cells that

NOTE Confidence: 0.901119807142857

00:55:52.265 --> 00:55:53.613 contain that gene signature.

NOTE Confidence: 0.901119807142857

00:55:53.620 --> 00:55:55.258 And because the cells are bar coded,

NOTE Confidence: 0.901119807142857

00:55:55.260 --> 00:55:57.535 we can immediately get to the T

NOTE Confidence: 0.901119807142857

00:55:57.535 --> 00:55:59.473 cell receptor sequence and know that

NOTE Confidence: 0.901119807142857

00:55:59.473 --> 00:56:01.580 within a few weeks of the resection.

NOTE Confidence: 0.901119807142857

00:56:01.580 --> 00:56:03.332 And when we test each of the TC

NOTE Confidence: 0.901119807142857

00:56:03.332 --> 00:56:05.141 R's in that signature right now

NOTE Confidence: 0.901119807142857

00:56:05.141 --> 00:56:07.385 and we're trying to define that

NOTE Confidence: 0.901119807142857

00:56:07.385 --> 00:56:10.410 signature of the CDH cells.

NOTE Confidence: 0.901119807142857

00:56:10.410 --> 00:56:12.514 CD62 percent of all of the T cell

NOTE Confidence: 0.901119807142857

00:56:12.514 --> 00:56:13.969 receptors that are present in

NOTE Confidence: 0.901119807142857

00:56:13.969 --> 00:56:15.419 that cluster are tumor reactive

NOTE Confidence: 0.901119807142857

00:56:15.419 --> 00:56:17.487 and we can identify within weeks.

NOTE Confidence: 0.901119807142857

00:56:17.490 --> 00:56:19.706 And CD4 cells it's not quite as good

NOTE Confidence: 0.901119807142857

00:56:19.706 --> 00:56:22.047 as about 1/3 of the T cell receptors.

NOTE Confidence: 0.901119807142857

00:56:22.050 --> 00:56:24.480 Thus anti tumor T cell receptors

NOTE Confidence: 0.901119807142857

00:56:24.480 --> 00:56:26.825 can be quickly identified without

NOTE Confidence: 0.901119807142857

00:56:26.825 --> 00:56:28.129 extensive screening.

NOTE Confidence: 0.901119807142857

00:56:28.130 --> 00:56:31.520 And use for cell therapy and we haven't

NOTE Confidence: 0.901119807142857

00:56:31.520 --> 00:56:34.220 haven't published much of this yet

NOTE Confidence: 0.901119807142857

00:56:34.220 --> 00:56:36.902 but but in fact are working hard now

NOTE Confidence: 0.901119807142857

00:56:36.902 --> 00:56:39.419 to try to improve our ability to use

NOTE Confidence: 0.901119807142857

00:56:39.419 --> 00:56:41.327 T cell receptors for for treatment.

NOTE Confidence: 0.944566485714286

00:56:46.300 --> 00:56:48.939 Well, I might conclude with this final,

NOTE Confidence: 0.944566485714286

00:56:48.940 --> 00:56:51.929 this final slide and leave you with

NOTE Confidence: 0.944566485714286

00:56:51.929 --> 00:56:54.260 these few general conclusions.

NOTE Confidence: 0.944566485714286

00:56:54.260 --> 00:56:56.330 Cell transfer therapy can mediate

NOTE Confidence: 0.944566485714286

00:56:56.330 --> 00:56:58.400 durable regression in patients with

NOTE Confidence: 0.944566485714286

00:56:58.460 --> 00:57:00.353 metastatic cancer refractory to

NOTE Confidence: 0.944566485714286

00:57:00.353 --> 00:57:02.939 all other treatments that T cells

NOTE Confidence: 0.944566485714286

00:57:02.939 --> 00:57:05.059 recognize unique somatic mutations

NOTE Confidence: 0.944566485714286

00:57:05.060 --> 00:57:07.255 and common cancers that identification

NOTE Confidence: 0.944566485714286

00:57:07.255 --> 00:57:09.450 and targeting these mutations unique

NOTE Confidence: 0.944566485714286

00:57:09.516 --> 00:57:11.448 to each cancer or sometimes shared

NOTE Confidence: 0.944566485714286

00:57:11.448 --> 00:57:13.550 mutations such as K, RASM, P53.

NOTE Confidence: 0.944566485714286

00:57:13.550 --> 00:57:15.980 Have the potential to extend cell

NOTE Confidence: 0.944566485714286

00:57:15.980 --> 00:57:18.972 therapy to patients with the common

NOTE Confidence: 0.944566485714286

00:57:18.972 --> 00:57:20.870 epithelial cancers using either

NOTE Confidence: 0.944566485714286

00:57:20.870 --> 00:57:22.970 these naturally occurring or T

NOTE Confidence: 0.944566485714286

00:57:22.970 --> 00:57:24.670 cell receptor transduced cells.

NOTE Confidence: 0.944566485714286

00:57:24.670 --> 00:57:27.970 And finally gene signatures can be

NOTE Confidence: 0.944566485714286

00:57:27.970 --> 00:57:30.698 generified generated to identify anti

NOTE Confidence: 0.944566485714286

00:57:30.698 --> 00:57:33.785 tumor T cell receptors in fresh tumors

NOTE Confidence: 0.944566485714286

00:57:33.790 --> 00:57:37.060 as well as identify the phenotype

NOTE Confidence: 0.944566485714286

00:57:37.060 --> 00:57:40.070 of lymphocytes that can improve

NOTE Confidence: 0.944566485714286

00:57:40.070 --> 00:57:43.910 functions in eliminating tumor in vivo.

NOTE Confidence: 0.944566485714286

00:57:43.910 --> 00:57:46.030 Well, I thank you for your very kind,

NOTE Confidence: 0.944566485714286

00:57:46.030 --> 00:57:46.950 kind attention.

NOTE Confidence: 0.956067514285714

00:57:53.950 --> 00:57:55.138 Thanks, Steve.

NOTE Confidence: 0.956067514285714

00:57:55.138 --> 00:57:58.518 That was inspiring and certainly I know

NOTE Confidence: 0.956067514285714

00:57:58.518 --> 00:57:59.946 there were a good number of questions.

NOTE Confidence: 0.956067514285714

00:57:59.950 --> 00:58:02.110 I know Diane Krauss has a few online.

NOTE Confidence: 0.956067514285714

00:58:02.110 --> 00:58:03.390 But as is our tradition

NOTE Confidence: 0.956067514285714

00:58:03.390 --> 00:58:04.670 at the Cal Brazi lecture,

NOTE Confidence: 0.956067514285714

00:58:04.670 --> 00:58:06.386 we will often turn to Judge

NOTE Confidence: 0.956067514285714

00:58:06.386 --> 00:58:08.112 Cal Brazi or Steven to please

NOTE Confidence: 0.956067514285714

00:58:08.112 --> 00:58:09.310 ask the first question.

NOTE Confidence: 0.68143945

00:58:14.510 --> 00:58:17.810 Doctor Colleridge Son or I'm a law

NOTE Confidence: 0.68143945

00:58:17.810 --> 00:58:19.710 professor Doctor But I wondered,

NOTE Confidence: 0.95283285

00:58:20.750 --> 00:58:23.270 would the you're talking about have

NOTE Confidence: 0.95283285

00:58:23.270 --> 00:58:27.270 any applicability to glioma brain

NOTE Confidence: 0.95283285

00:58:27.270 --> 00:58:29.810 cancer which I know of especially

NOTE Confidence: 0.95283285

00:58:29.810 --> 00:58:31.790 hard to treat and which may

NOTE Confidence: 0.950317

00:58:32.270 --> 00:58:33.990 become much more common

NOTE Confidence: 0.908854072727273

00:58:33.990 --> 00:58:34.812 in the future?

NOTE Confidence: 0.908854072727273

00:58:34.812 --> 00:58:36.730 Because there is does seem to be

NOTE Confidence: 0.908854072727273

00:58:36.796 --> 00:58:39.002 some evidence that cell phone use.

NOTE Confidence: 0.908854072727273

00:58:39.002 --> 00:58:40.940 Increases the risk of coming

NOTE Confidence: 0.908854072727273

00:58:40.940 --> 00:58:42.240 down with brain cancer.

NOTE Confidence: 0.943272513

00:58:42.640 --> 00:58:44.824 So I just wondered, is this applicable

NOTE Confidence: 0.943272513

00:58:44.824 --> 00:58:46.480 to gliola brain, Brain cancers

NOTE Confidence: 0.949310557

00:58:49.560 --> 00:58:51.060 plus brain cancers.

NOTE Confidence: 0.949310557

00:58:51.060 --> 00:58:54.560 Glioblastoma is the most aggressive form of

NOTE Confidence: 0.949310557

00:58:54.560 --> 00:58:57.675 of the brain cancers do express mutations.

NOTE Confidence: 0.949310557

00:58:57.680 --> 00:59:00.424 We have identified mutations

NOTE Confidence: 0.949310557

00:59:00.424 --> 00:59:02.464 in glioblastomas. In fact,

NOTE Confidence: 0.949310557

00:59:02.464 --> 00:59:04.788 we published a paper on that by

NOTE Confidence: 0.949310557

00:59:04.788 --> 00:59:07.466 VED Leiko who is a fellow in the

NOTE Confidence: 0.949310557

00:59:07.466 --> 00:59:09.050 in the surgery branch.

NOTE Confidence: 0.949310557

00:59:09.050 --> 00:59:11.288 Of a mutation in a glioblastoma,

NOTE Confidence: 0.949310557

00:59:11.290 --> 00:59:14.755 but we have not treated any glioblastoma

NOTE Confidence: 0.949310557

00:59:14.755 --> 00:59:18.818 patients with these uniquely reactive cells.

NOTE Confidence: 0.949310557

00:59:18.818 --> 00:59:21.266 We have treated glioblastomas with CAR

NOTE Confidence: 0.949310557

00:59:21.266 --> 00:59:23.729 T cells targeting a shared mutation.

NOTE Confidence: 0.949310557

00:59:23.730 --> 00:59:26.992 And so no responses again because

NOTE Confidence: 0.949310557

00:59:26.992 --> 00:59:29.670 of the the weakness of of cars

NOTE Confidence: 0.949310557

00:59:29.670 --> 00:59:31.720 and the potential danger that.

NOTE Confidence: 0.949310557

00:59:31.720 --> 00:59:33.560 Their tumors might express normal

NOTE Confidence: 0.949310557

00:59:33.560 --> 00:59:35.400 antigens and in a separate

NOTE Confidence: 0.949310557

00:59:35.463 --> 00:59:37.119 study that I won't go into,

NOTE Confidence: 0.949310557

00:59:37.120 --> 00:59:39.652 we actually saw substantial toxicities by

NOTE Confidence: 0.949310557

00:59:39.652 --> 00:59:42.519 targeting a shared antigen and glioblastomas.

NOTE Confidence: 0.949310557

00:59:42.520 --> 00:59:47.954 But using this new the new cancer antigens

NOTE Confidence: 0.949310557

00:59:47.954 --> 00:59:50.239 that result from cancer mutations,

NOTE Confidence: 0.949310557

00:59:50.240 --> 00:59:52.074 I think should be tried in glioblastoma.

NOTE Confidence: 0.949310557

00:59:52.080 --> 00:59:54.624 But we have not begun those studies yet

NOTE Confidence: 0.949310557

00:59:54.624 --> 00:59:57.557 and are concentrating on the more common.

NOTE Confidence: 0.949310557

00:59:57.560 --> 00:59:59.140 Well, common epithelial cancers.

NOTE Confidence: 0.949310557

00:59:59.140 --> 01:00:00.720 But it's a wonderful,

NOTE Confidence: 0.949310557

01:00:00.720 --> 01:00:02.580 wonderful idea and something that I

NOTE Confidence: 0.949310557

01:00:02.580 --> 01:00:04.960 hope to to get to in a serious way soon.

NOTE Confidence: 0.936899233333333

01:00:08.480 --> 01:00:10.370 Question. I wonder if we can unmute

NOTE Confidence: 0.936899233333333

01:00:10.370 --> 01:00:12.680 her so she can ask it herself.

NOTE Confidence: 0.936899233333333

01:00:12.680 --> 01:00:14.416 While we're doing that, I'll just ask

NOTE Confidence: 0.936899233333333

01:00:14.416 --> 01:00:16.238 a question from an anonymous attendee.

NOTE Confidence: 0.936899233333333

01:00:16.240 --> 01:00:18.018 I have a patient with one of

NOTE Confidence: 0.936899233333333

01:00:18.018 --> 01:00:18.780 the targetable Rasmutations

NOTE Confidence: 0.936899233333333

01:00:18.834 --> 01:00:20.199 with the appropriate actual a.

NOTE Confidence: 0.936899233333333

01:00:20.200 --> 01:00:21.478 What can I do for them?

NOTE Confidence: 0.936899233333333

01:00:21.480 --> 01:00:22.240 How do I send them

NOTE Confidence: 0.95031704

01:00:22.240 --> 01:00:24.330 to you? We're actively seeking,

NOTE Confidence: 0.95031704

01:00:24.330 --> 01:00:25.866 we're actively seeking those

NOTE Confidence: 0.95031704

01:00:25.866 --> 01:00:27.610 patients. And if you e-mail me

NOTE Confidence: 0.948944718181818

01:00:29.650 --> 01:00:32.128 sar@nih.gov, I'll see that you get

NOTE Confidence: 0.948944718181818

01:00:32.128 --> 01:00:34.213 contacted immediately about about that

NOTE Confidence: 0.948944718181818

01:00:34.213 --> 01:00:36.403 patient to evaluate the eligibility of

NOTE Confidence: 0.948944718181818

01:00:36.403 --> 01:00:38.570 that patient for our studies. Yeah,

NOTE Confidence: 0.888763083333333

01:00:38.570 --> 01:00:39.728 I'm guessing that was Diane Kraus.

NOTE Confidence: 0.888763083333333

01:00:39.730 --> 01:00:40.874 So that Eric would see that he has

NOTE Confidence: 0.888763083333333

01:00:40.874 --> 01:00:41.938 to put more resource into this

NOTE Confidence: 0.888763083333333

01:00:41.938 --> 01:00:43.048 so that we'll keep them here.

NOTE Confidence: 0.888763083333333

01:00:43.050 --> 01:00:45.050 He's he's laughing. OK Diane,

NOTE Confidence: 0.888763083333333

01:00:45.050 --> 01:00:46.058 are you able to ask your question

NOTE Confidence: 0.888763083333333

01:00:46.058 --> 01:00:46.969 online or do you want me to

NOTE Confidence: 0.926416425

01:00:46.970 --> 01:00:48.529 read it for you? I can ask it. I can ask

NOTE Confidence: 0.9402536

01:00:49.730 --> 01:00:51.698 my question was why?

NOTE Confidence: 0.9402536

01:00:51.700 --> 01:00:53.717 The selected till work when the

NOTE Confidence: 0.9402536

01:00:53.717 --> 01:00:55.530 bulk till do not for some of

NOTE Confidence: 0.9402536

01:00:55.595 --> 01:00:57.900 these patients with solid tumors,

NOTE Confidence: 0.9402536

01:00:57.900 --> 01:01:00.196 is it a matter of the large dose of

NOTE Confidence: 0.9402536

01:01:00.196 --> 01:01:02.240 the effective till or potentially

NOTE Confidence: 0.9402536

01:01:02.240 --> 01:01:03.880 inhibition by other till that

NOTE Confidence: 0.9402536

01:01:03.880 --> 01:01:04.980 aren't targeting the cancer.

NOTE Confidence: 0.94226628

01:01:07.700 --> 01:01:10.962 We have evidence for both and I think

NOTE Confidence: 0.94226628

01:01:10.962 --> 01:01:13.160 both are important in the animal models

NOTE Confidence: 0.94226628

01:01:13.228 --> 01:01:16.282 in the number of cells you give is very

NOTE Confidence: 0.94226628

01:01:16.282 --> 01:01:19.137 highly related to its effectiveness.

NOTE Confidence: 0.94226628

01:01:19.140 --> 01:01:21.156 In the human, although we generally

NOTE Confidence: 0.94226628

01:01:21.156 --> 01:01:23.618 give us very large numbers of cells,

NOTE Confidence: 0.94226628

01:01:23.620 --> 01:01:25.700 even within the numbers of cells we give,

NOTE Confidence: 0.94226628

01:01:25.700 --> 01:01:26.895 which generally are between 10

NOTE Confidence: 0.94226628

01:01:26.895 --> 01:01:28.660 of the 10 and 10 of the 11,

NOTE Confidence: 0.94226628

01:01:28.660 --> 01:01:31.490 we do see an influence of the

NOTE Confidence: 0.94226628

01:01:31.490 --> 01:01:33.500 number of cells in the likelihood

NOTE Confidence: 0.94226628

01:01:33.500 --> 01:01:35.312 of having complete regressions.

NOTE Confidence: 0.94226628

01:01:35.312 --> 01:01:37.922 And we just published that about

NOTE Confidence: 0.94226628

01:01:37.922 --> 01:01:39.974 a year and a half ago.

NOTE Confidence: 0.94226628

01:01:39.980 --> 01:01:42.899 But we have evidence in animal models.

NOTE Confidence: 0.94226628

01:01:42.900 --> 01:01:44.740 That the normal cells that

NOTE Confidence: 0.94226628

01:01:44.740 --> 01:01:46.212 you give can inhibit.

NOTE Confidence: 0.94226628

01:01:46.220 --> 01:01:48.844 Now if you're giving normal

NOTE Confidence: 0.94226628

01:01:48.844 --> 01:01:50.764 cells that contain T regulatory

NOTE Confidence: 0.94226628

01:01:50.764 --> 01:01:52.900 cells that would be hurtful,

NOTE Confidence: 0.94226628

01:01:52.900 --> 01:01:54.937 but also these other cells that you

NOTE Confidence: 0.94226628

01:01:54.937 --> 01:01:56.949 give that are non tumor reactive

NOTE Confidence: 0.94226628

01:01:56.949 --> 01:01:59.091 compete for the cytokines that are

NOTE Confidence: 0.94226628

01:01:59.091 --> 01:02:00.939 result of the lympho depletion.

NOTE Confidence: 0.94226628

01:02:00.940 --> 01:02:02.684 When you lympho deplete,

NOTE Confidence: 0.94226628

01:02:02.684 --> 01:02:05.300 you increase circulating levels of I

NOTE Confidence: 0.94226628

01:02:05.300 --> 01:02:10.060 L15IL7 which normally do not circulate and.

NOTE Confidence: 0.94226628

01:02:10.060 --> 01:02:12.690 Those circulating cytokines then can

NOTE Confidence: 0.94226628

01:02:12.690 --> 01:02:14.936 impact on the cells we administer and

NOTE Confidence: 0.94226628

01:02:14.936 --> 01:02:16.386 if we're administering normal cells

NOTE Confidence: 0.94226628

01:02:16.386 --> 01:02:17.934 they compete with the good ones.

NOTE Confidence: 0.94226628

01:02:17.940 --> 01:02:22.294 So you've hit your your your question

NOTE Confidence: 0.94226628

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,

NOTE Confidence: 0.9372034875

01:02:47.668 --> 01:02:49.740 are there any in the stem cell

NOTE Confidence: 0.9372034875

01:02:49.740 --> 01:02:51.712 pool that you say work well and is

NOTE Confidence: 0.9372034875

01:02:51.712 --> 01:02:53.339 that different between epithelium

NOTE Confidence: 0.967089333333333

01:02:53.340 --> 01:02:54.699 malignancies and Melanoma?

NOTE Confidence: 0.922710933333333

01:02:56.740 --> 01:02:59.436 We can find them easily in Melanoma and

NOTE Confidence: 0.922710933333333

01:02:59.436 --> 01:03:02.020 they are very difficult to find in,

NOTE Confidence: 0.922710933333333

01:03:02.020 --> 01:03:06.890 in the epithelial cancers because the.

NOTE Confidence: 0.922710933333333

01:03:06.890 --> 01:03:09.080 Incidence of those cells are likely

NOTE Confidence: 0.922710933333333

01:03:09.080 --> 01:03:11.390 100,000 fold less in our measurements

NOTE Confidence: 0.922710933333333

01:03:11.390 --> 01:03:14.127 in the epithelial cancers than in the

NOTE Confidence: 0.922710933333333

01:03:14.130 --> 01:03:16.035 melanomas because we generally try

NOTE Confidence: 0.922710933333333

01:03:16.035 --> 01:03:18.370 to find them in circulating cells.

NOTE Confidence: 0.922710933333333

01:03:18.370 --> 01:03:19.554 But they do exist,

NOTE Confidence: 0.922710933333333

01:03:19.554 --> 01:03:21.330 they just very hard to identify.

NOTE Confidence: 0.922710933333333

01:03:21.330 --> 01:03:23.112 And my suspicion as we continue

NOTE Confidence: 0.922710933333333

01:03:23.112 --> 01:03:25.385 to study and find better ways to

NOTE Confidence: 0.922710933333333

01:03:25.385 --> 01:03:27.090 identify tiny numbers of them,

NOTE Confidence: 0.922710933333333

01:03:27.090 --> 01:03:29.260 we will find them in the in the

NOTE Confidence: 0.922710933333333

01:03:29.260 --> 01:03:31.090 patients that did that did respond.

NOTE Confidence: 0.941371755555556

01:03:33.400 --> 01:03:35.577 But it's a particular delight to to

NOTE Confidence: 0.941371755555556

01:03:35.577 --> 01:03:37.868 hear Mario, who worked closely with

NOTE Confidence: 0.941371755555556

01:03:37.868 --> 01:03:40.910 us for for several years, as are

NOTE Confidence: 0.941371755555556

01:03:40.910 --> 01:03:44.424 several others of your of your fellows.

NOTE Confidence: 0.941371755555556

01:03:44.424 --> 01:03:49.852 We we now have Nick Clement on our on our

NOTE Confidence: 0.941371755555556

01:03:49.852 --> 01:03:57.888 staff, and it reminds me to say that in fact.

NOTE Confidence: 0.941371755555556

01:03:57.890 --> 01:03:59.050 Especially all of this work,

NOTE Confidence: 0.941371755555556

01:03:59.050 --> 01:04:01.650 except for the first five to seven years,

NOTE Confidence: 0.941371755555556

01:04:01.650 --> 01:04:04.248 was actually done not by me,

NOTE Confidence: 0.941371755555556

01:04:04.250 --> 01:04:05.566 with my own hands in the lab,

NOTE Confidence: 0.941371755555556

01:04:05.570 --> 01:04:07.496 but by fellows who come to

NOTE Confidence: 0.941371755555556

01:04:07.496 --> 01:04:09.250 the surgery branch to train.

NOTE Confidence: 0.941371755555556

01:04:09.250 --> 01:04:10.914 Fellows like Nick Lemon,

NOTE Confidence: 0.941371755555556

01:04:10.914 --> 01:04:13.570 like like Mario,

NOTE Confidence: 0.941371755555556

01:04:13.570 --> 01:04:16.154 who come to the NCI to gain experience

NOTE Confidence: 0.941371755555556

01:04:16.154 --> 01:04:18.159 in doing clinical and laboratory

NOTE Confidence: 0.941371755555556

01:04:18.159 --> 01:04:20.727 research for two to three years.

NOTE Confidence: 0.941371755555556

01:04:20.730 --> 01:04:24.194 And I owe them a great debt, as I do to.

NOTE Confidence: 0.941371755555556

01:04:24.194 --> 01:04:25.798 Mario, for all the contributions

NOTE Confidence: 0.941371755555556

01:04:25.798 --> 01:04:27.550 he made when he was here,

NOTE Confidence: 0.941371755555556

01:04:27.550 --> 01:04:29.270 when he was here with us, you

NOTE Confidence: 0.920199787

01:04:29.270 --> 01:04:30.590 know, Steve, that might be a good way to end.

NOTE Confidence: 0.920199787

01:04:30.590 --> 01:04:32.340 We're going to move into the other

NOTE Confidence: 0.920199787

01:04:32.340 --> 01:04:34.264 room with some of our fellows to talk

NOTE Confidence: 0.920199787

01:04:34.264 --> 01:04:36.309 with you and with the judge and others.

NOTE Confidence: 0.920199787

01:04:36.310 --> 01:04:38.238 Let me just say in hearing you say

NOTE Confidence: 0.920199787

01:04:38.238 --> 01:04:40.434 that the Paul Calabresi I knew would

NOTE Confidence: 0.920199787

01:04:40.434 --> 01:04:42.775 have loved this lecture because it was

NOTE Confidence: 0.920199787

01:04:42.775 --> 01:04:44.665 innovative and it was patient focused.

NOTE Confidence: 0.920199787

01:04:44.670 --> 01:04:46.530 You're bringing new therapies to clinic

NOTE Confidence: 0.920199787

01:04:46.530 --> 01:04:48.389 and Guido's going to say a word,

NOTE Confidence: 0.920199787

01:04:48.390 --> 01:04:49.986 but the fact that you mentored,

NOTE Confidence: 0.920199787

01:04:49.990 --> 01:04:50.984 that was what Paul is all about.

NOTE Confidence: 0.920199787

01:04:50.990 --> 01:04:52.606 And I'm going to go the final word.

NOTE Confidence: 0.920199787

01:04:52.610 --> 01:04:53.465 Judge Guido Calbresi.

NOTE Confidence: 0.920199787

01:04:53.465 --> 01:04:55.770 And then we'll retire to the other room.

NOTE Confidence: 0.920199787

01:04:55.770 --> 01:04:56.250 Judge of

NOTE Confidence: 0.9603804

01:05:04.590 --> 01:05:07.682 course, one people who

NOTE Confidence: 0.9603804

01:05:07.682 --> 01:05:09.544 developed chemotherapy first,

NOTE Confidence: 0.9603804

01:05:09.544 --> 01:05:11.820 he said there was no doubt that

NOTE Confidence: 0.9603804

01:05:11.820 --> 01:05:14.174 where one went was not with

NOTE Confidence: 0.9603804

01:05:14.174 --> 01:05:16.670 chemotherapy but with immune.

NOTE Confidence: 0.9603804

01:05:16.670 --> 01:05:18.926 And he said that was where

NOTE Confidence: 0.9603804

01:05:18.926 --> 01:05:20.790 it would have to be.

NOTE Confidence: 0.9603804

01:05:20.790 --> 01:05:22.870 And that's why I'm particularly

NOTE Confidence: 0.9603804

01:05:22.870 --> 01:05:24.109 delighted to a very.

NOTE Confidence: 0.883691071428572

01:05:25.990 --> 01:05:27.509 Well, on that note, thank you all.

NOTE Confidence: 0.883691071428572

01:05:27.510 --> 01:05:28.095 Thank you, Steve.

NOTE Confidence: 0.883691071428572

01:05:28.095 --> 01:05:29.265 We'll retire and we'll be 5

NOTE Confidence: 0.883691071428572

01:05:29.265 --> 01:05:30.347 minutes and we'll get you back.

NOTE Confidence: 0.883691071428572

01:05:30.350 --> 01:05:32.000 Thank you, everyone.