WEBVTT

00:00:00.000 --> 00:00:03.204 Funding for Yale Cancer Answers is NOTE Confidence: 0.9416965 00:00:03.204 --> 00:00:06.240 provided by Smilow Cancer Hospital. NOTE Confidence: 0.9416965 00:00:06.240 --> 00:00:08.440 Welcome to Yale Cancer Answers NOTE Confidence: 0.9416965 $00:00:08.440 \rightarrow 00:00:10.200$ with Doctor Anees Chappar. NOTE Confidence: 0.9416965 $00:00:10.200 \rightarrow 00:00:11.985$ Yale Cancer Answers features the NOTE Confidence: 0.9416965 00:00:11.985 --> 00:00:13.760 latest information on cancer care NOTE Confidence: 0.9416965 00:00:13.760 -> 00:00:15.147 by welcoming oncologists and NOTE Confidence: 0.9416965 $00:00:15.147 \rightarrow 00:00:17.019$ specialists who are on the forefront NOTE Confidence: 0.9416965 $00:00:17.019 \longrightarrow 00:00:18.917$ of the battle to fight cancer. NOTE Confidence: 0.9416965 $00:00:18.920 \rightarrow 00:00:21.160$ This week it's a conversation about the NOTE Confidence: 0.9416965 $00{:}00{:}21.160 \dashrightarrow 00{:}00{:}22.875$ role of break through the rapeutics in NOTE Confidence: 0.9416965 $00:00:22.875 \longrightarrow 00:00:24.957$ fighting cancer with Doctor Sidi Chen. NOTE Confidence: 0.9416965 00:00:24.960 --> 00:00:26.510 Doctor Chen is an associate NOTE Confidence: 0.9416965 $00{:}00{:}26.510 \dashrightarrow 00{:}00{:}28.425$ professor of genetics at the Yale NOTE Confidence: 0.9416965 00:00:28.425 --> 00:00:29.950 School of Medicine where Dr. NOTE Confidence: 0.9416965

00:00:29.950 --> 00:00:32.547 Chagpar as a professor of surgical oncology.

NOTE Confidence: 0.933137500000001

00:00:34.070 --> 00:00:36.464 Maybe we can start off by you

NOTE Confidence: 0.933137500000001

 $00{:}00{:}36{.}464 \dashrightarrow 00{:}00{:}38{.}500$ telling us a little bit more about

NOTE Confidence: 0.933137500000001

 $00:00:38.500 \rightarrow 00:00:40.310$ yourself and what it is you do.

NOTE Confidence: 0.9331375

 $00{:}00{:}40{.}910 \dashrightarrow 00{:}00{:}43{.}550$ Yeah, sure. I'm a faculty member at Yale

 $00:00:45.656 \rightarrow 00:00:47.909$ and a professor of genetics Genetics,

NOTE Confidence: 0.9331375

 $00{:}00{:}47{.}909 \dashrightarrow 00{:}00{:}49{.}869$ Systems Biology Institute, and Yale Cancer Center.

NOTE Confidence: 0.9331375

 $00:00:49.870 \longrightarrow 00:00:53.110$ My role in the field is trying to

NOTE Confidence: 0.9331375

 $00{:}00{:}53.110 \dashrightarrow 00{:}00{:}55.779$ understand the biological systems of

NOTE Confidence: 0.9331375

 $00:00:55.779 \rightarrow 00:00:58.302$ cancer and the biological systems of the

NOTE Confidence: 0.9331375

 $00{:}00{:}58.302 \dashrightarrow 00{:}01{:}00.550$ immune system of our cells and therefore

NOTE Confidence: 0.9331375

 $00{:}01{:}00{.}550 \dashrightarrow 00{:}01{:}02{.}530$ leverage immune system to fight cancer.

NOTE Confidence: 0.9209762

00:01:03.130 --> 00:01:07.027 So I mean that all sounds very high tech

NOTE Confidence: 0.9209762

 $00:01:07.027 \dashrightarrow 00:01:10.607$ and new and novel and exciting.

NOTE Confidence: 0.9209762

00:01:10.610 --> 00:01:12.610 Tell us more about

NOTE Confidence: 0.9209762

 $00:01:12.610 \longrightarrow 00:01:14.024$ how exactly that works.

- NOTE Confidence: 0.9209762
- 00:01:14.024 --> 00:01:15.559 How did you get interested
- NOTE Confidence: 0.9209762
- $00{:}01{:}15{.}559 \dashrightarrow 00{:}01{:}17{.}494$ in the field and what
- NOTE Confidence: 0.9209762
- 00:01:17.494 --> 00:01:19.404 exactly is your research doing?
- NOTE Confidence: 0.9209762
- $00{:}01{:}20{.}010 \dashrightarrow 00{:}01{:}23{.}766$ Sure. I'll be happy to elaborate.
- NOTE Confidence: 0.9209762
- 00:01:23.770 --> 00:01:27.578 As you know, our own
- NOTE Confidence: 0.9209762
- $00:01:27.578 \longrightarrow 00:01:30.026$ body consists of the many,
- NOTE Confidence: 0.9209762
- $00:01:30.026 \longrightarrow 00:01:31.250$ many different organs.
- NOTE Confidence: 0.9209762
- $00{:}01{:}31{.}250 \dashrightarrow 00{:}01{:}33{.}754$ And the system that protect our own organs
- NOTE Confidence: 0.9209762
- $00:01:33.754 \dashrightarrow 00:01:36.485$ or our own health is the immune system.
- NOTE Confidence: 0.9209762
- 00:01:36.490 --> 00:01:38.690 It's our own defense system.
- NOTE Confidence: 0.9209762
- 00:01:38.690 --> 00:01:41.810 For example, if we get infected,
- NOTE Confidence: 0.9209762
- $00:01:41.810 \dashrightarrow 00:01:45.290$ we have cells that produce antibody,
- NOTE Confidence: 0.9209762
- $00{:}01{:}45.290 \dashrightarrow 00{:}01{:}48.006$ we have cells that clear the infection.
- NOTE Confidence: 0.9209762
- 00:01:48.010 --> 00:01:50.470 Likewise for cancer,
- NOTE Confidence: 0.9209762
- $00{:}01{:}50.470 \dashrightarrow 00{:}01{:}54.050$ when a patient gets cancer and
- NOTE Confidence: 0.9209762

 $00:01:54.050 \longrightarrow 00:01:56.720$ the first reaction of the body

NOTE Confidence: 0.9209762

 $00{:}01{:}56{.}720 \dashrightarrow 00{:}01{:}58{.}980$ is the immune system trying to

NOTE Confidence: 0.9209762

 $00:01:58.980 \rightarrow 00:02:01.080$ distinguish which is the cancer cell,

NOTE Confidence: 0.9209762

 $00:02:01.080 \dashrightarrow 00:02:03.840$ which is our own healthy cells.

NOTE Confidence: 0.9209762

00:02:03.840 --> 00:02:05.640 But very often our system

NOTE Confidence: 0.9209762

 $00:02:05.640 \longrightarrow 00:02:07.080$ is fooled by cancer.

NOTE Confidence: 0.9209762

00:02:07.080 --> 00:02:08.900 The immune system cannot recognize

NOTE Confidence: 0.9209762

 $00{:}02{:}08{.}900 \dashrightarrow 00{:}02{:}11{.}382$ cancer or cannot clear them and our

NOTE Confidence: 0.9209762

 $00{:}02{:}11.382 \dashrightarrow 00{:}02{:}13.037$ research is trying to understand

NOTE Confidence: 0.9209762

 $00{:}02{:}13.037 \dashrightarrow 00{:}02{:}15.971$ why is that the case and how we can NOTE Confidence: 0.9209762

 $00:02:15.971 \rightarrow 00:02:17.922$ educate the immune system or help NOTE Confidence: 0.9209762

 $00:02:17.922 \rightarrow 00:02:21.238$ the immune system to detect cancer NOTE Confidence: 0.9209762

00:02:21.238 --> 00:02:24.815 better and equip them with the tools

NOTE Confidence: 0.9209762

 $00:02:24.815 \longrightarrow 00:02:27.377$ to fight cancer and clear cancer

NOTE Confidence: 0.9209762

 $00{:}02{:}27.377 \dashrightarrow 00{:}02{:}29.370$ cells and restore our own health.

NOTE Confidence: 0.93518937

 $00{:}02{:}31{.}730 \dashrightarrow 00{:}02{:}33{.}780$ You know that sounds a

- NOTE Confidence: 0.93518937
- $00{:}02{:}33.780 \dashrightarrow 00{:}02{:}35.010$ lot like immuno therapy,
- NOTE Confidence: 0.93518937
- $00{:}02{:}35{.}010 \dashrightarrow 00{:}02{:}36{.}690$ which is something that we've
- NOTE Confidence: 0.93518937
- $00:02:36.690 \rightarrow 00:02:39.850$ discussed on this show previously.
- NOTE Confidence: 0.93518937
- 00:02:39.850 --> 00:02:41.578 How is your research either the
- NOTE Confidence: 0.93518937
- $00:02:41.578 \longrightarrow 00:02:43.050$ same or different than that?
- NOTE Confidence: 0.93518937
- 00:02:43.050 -> 00:02:45.090 I thought that immunotherapy
- NOTE Confidence: 0.93518937
- $00:02:45.090 \longrightarrow 00:02:46.722$ is already being used.
- NOTE Confidence: 0.93518937
- $00:02:46.730 \longrightarrow 00:02:49.089$ Is your work trying to extend that?
- NOTE Confidence: 0.9396244
- $00:02:50.590 \longrightarrow 00:02:52.336$ You're absolutely right.
- NOTE Confidence: 0.9396244
- 00:02:52.336 --> 00:02:54.664 Immunotherapy is the current
- NOTE Confidence: 0.9396244
- $00{:}02{:}57.150 \dashrightarrow 00{:}02{:}59.802$ major the rapeutic for cancer.
- NOTE Confidence: 0.9396244
- 00:02:59.802 --> 00:03:01.791 Immunotherapy involving immune
- NOTE Confidence: 0.9396244
- 00:03:01.791 -> 00:03:04.324 checkpoint blockage has been
- NOTE Confidence: 0.9396244
- $00{:}03{:}04{.}324 \dashrightarrow 00{:}03{:}07{.}066$ approved by over 30 indications now.
- NOTE Confidence: 0.9396244
- $00{:}03{:}07{.}070$ --> $00{:}03{:}08{.}654$ But unfortunately immunotherapy only
- NOTE Confidence: 0.9396244

 $00:03:08.654 \rightarrow 00:03:11.630$ works for a small fraction of patients,

NOTE Confidence: 0.9396244

 $00{:}03{:}11{.}630 \dashrightarrow 00{:}03{:}14{.}150$ about 20 to 30% overall.

NOTE Confidence: 0.9396244

 $00:03:14.150 \rightarrow 00:03:15.866$ Some cancer have a better response,

NOTE Confidence: 0.9396244

 $00:03:15.870 \rightarrow 00:03:20.238$ some cancer have literally no responses.

NOTE Confidence: 0.9396244

 $00:03:20.240 \longrightarrow 00:03:23.048$ So our goal is to understand

NOTE Confidence: 0.9396244

 $00:03:23.048 \longrightarrow 00:03:24.920$ why some cancers respond,

NOTE Confidence: 0.9396244

 $00:03:24.920 \longrightarrow 00:03:28.940$ why some don't and then try to either

NOTE Confidence: 0.9396244

 $00:03:28.940 \longrightarrow 00:03:33.000$ help the cells to improve the

NOTE Confidence: 0.9396244

 $00{:}03{:}33{.}000 \dashrightarrow 00{:}03{:}35{.}547$ immuno therapy response or on the other

NOTE Confidence: 0.9396244

 $00{:}03{:}35{.}547 \dashrightarrow 00{:}03{:}38{.}130$ hand we're thinking why don't we just

NOTE Confidence: 0.9396244

 $00{:}03{:}38{.}205 \dashrightarrow 00{:}03{:}40{.}788$ take the immune cells out and engineer

NOTE Confidence: 0.9396244

00:03:40.788 --> 00:03:43.520 them in the lab or in the factory

NOTE Confidence: 0.9396244

 $00{:}03{:}43.520 \dashrightarrow 00{:}03{:}45.515$ and then give them back to the patient.

NOTE Confidence: 0.9396244

 $00:03:45.520 \rightarrow 00:03:48.004$ That's what we call cell therapy

NOTE Confidence: 0.9396244

 $00:03:48.004 \rightarrow 00:03:49.246$ or cellular immunotherapy,

NOTE Confidence: 0.9396244

 $00:03:49.250 \longrightarrow 00:03:51.375$ which is another type of

- NOTE Confidence: 0.9396244
- 00:03:51.375 00:03:52.650 major cancer immunotherapy.

 $00:03:52.650 \rightarrow 00:03:54.930$ So unlike immune checkpoint blockade,

NOTE Confidence: 0.9396244

 $00:03:54.930 \rightarrow 00:03:59.074$ I used to utilize a therapeutic antibody,

NOTE Confidence: 0.9396244

 $00:03:59.074 \longrightarrow 00:04:01.346$ cell therapy utilizes cells

NOTE Confidence: 0.9396244

 $00:04:01.346 \longrightarrow 00:04:03.210$ instead of compounds.

NOTE Confidence: 0.9176469

 $00{:}04{:}05{.}410 \dashrightarrow 00{:}04{:}07{.}746$ So that's very interesting and I want to

NOTE Confidence: 0.9176469

 $00:04:07.746 \longrightarrow 00:04:10.170$ kind of discuss both of those angles.

NOTE Confidence: 0.9176469

 $00:04:10.170 \longrightarrow 00:04:13.418$ So the first is why is it that

NOTE Confidence: 0.9176469

 $00{:}04{:}13.418 \dashrightarrow 00{:}04{:}15.716$ some cancers respond better

NOTE Confidence: 0.9176469

 $00:04:15.716 \longrightarrow 00:04:18.488$ to immunotherapy than others?

NOTE Confidence: 0.9176469

 $00:04:18.490 \longrightarrow 00:04:20.930$ We know that for example,

NOTE Confidence: 0.9176469

 $00{:}04{:}20{.}930 \dashrightarrow 00{:}04{:}23{.}202$ there are some cancers,

NOTE Confidence: 0.9176469

 $00{:}04{:}23.202 \dashrightarrow 00{:}04{:}26.210$ melanoma being one of the

NOTE Confidence: 0.9176469

 $00:04:26.210 \longrightarrow 00:04:28.162$ mainstays that's very

NOTE Confidence: 0.9176469

 $00{:}04{:}28.170 \dashrightarrow 00{:}04{:}30.602$ receptive to immunotherapy and

 $00:04:30.602 \longrightarrow 00:04:33.642$ other cancers not so much.

NOTE Confidence: 0.9176469

 $00:04:33.650 \longrightarrow 00:04:35.650$ So what is it?

NOTE Confidence: 0.9176469

 $00{:}04{:}35{.}650 \dashrightarrow 00{:}04{:}38{.}650$ Is it something about the cancer

NOTE Confidence: 0.9176469

 $00:04:38.762 \longrightarrow 00:04:41.728$ itself or is it the way that the

NOTE Confidence: 0.9176469

 $00:04:41.728 \longrightarrow 00:04:43.438$ cancer evades the immune system?

NOTE Confidence: 0.9176469

 $00{:}04{:}43{.}440 \dashrightarrow 00{:}04{:}46{.}268$ Or is it just that the immune

NOTE Confidence: 0.9176469

 $00{:}04{:}46.268 \dashrightarrow 00{:}04{:}49.196$ system is better able to fight

NOTE Confidence: 0.9176469

 $00:04:49.196 \rightarrow 00:04:51.356$ cancers in particular organs?

NOTE Confidence: 0.9176469

 $00:04:51.360 \longrightarrow 00:04:52.518$ Why the difference?

NOTE Confidence: 0.9346789

 $00:04:53.760 \dashrightarrow 00:04:55.440$ This is a billion dollar question,

NOTE Confidence: 0.9346789

 $00{:}04{:}55{.}440 \dashrightarrow 00{:}04{:}57{.}324$ great question. In fact,

NOTE Confidence: 0.9346789

 $00:04:57.324 \rightarrow 00:04:59.679$ the answer is very complicated.

NOTE Confidence: 0.9346789

00:04:59.680 --> 00:05:01.857 I don't think I can even address

NOTE Confidence: 0.9346789

 $00:05:01.857 \longrightarrow 00:05:03.960$ in half an hour or a year.

NOTE Confidence: 0.9346789

 $00{:}05{:}03{.}960 \dashrightarrow 00{:}05{:}07{.}360$ So the reason,

NOTE Confidence: 0.9346789

 $00:05:07.360 \longrightarrow 00:05:09.632$ to put it short, cancer cells

- NOTE Confidence: 0.9346789
- $00:05:09.632 \rightarrow 00:05:11.712$ can evade the immune systems and attack

 $00{:}05{:}11.712 \dashrightarrow 00{:}05{:}13.798$ and the immune cells sometimes

NOTE Confidence: 0.9346789

 $00:05:13.798 \longrightarrow 00:05:16.084$ it's weak or enabled to find

NOTE Confidence: 0.9346789

 $00:05:16.084 \rightarrow 00:05:18.120$ cancer or eradicate cancer.

NOTE Confidence: 0.9346789

 $00{:}05{:}18{.}120 \dashrightarrow 00{:}05{:}19{.}280$ So in order

NOTE Confidence: 0.92279476

 $00{:}05{:}21{.}360 \dashrightarrow 00{:}05{:}23{.}882$ to help the immune system there are a

NOTE Confidence: 0.92279476

00:05:23.882 --> 00:05:26.054 lot of different ways, for example,

NOTE Confidence: 0.92279476

 $00{:}05{:}26.054 \dashrightarrow 00{:}05{:}27.854$ using the monoclonal antibody to

NOTE Confidence: 0.92279476

 $00{:}05{:}27.854 \dashrightarrow 00{:}05{:}30.115$ hit the brake that cancer uses to

NOTE Confidence: 0.926691493333333

00:05:32.360 --> 00:05:35.677 to put on cancer. For example PD1,

NOTE Confidence: 0.926691493333333

 $00:05:35.677 \rightarrow 00:05:37.813$ PDL one therapy which is well known now

NOTE Confidence: 0.926691493333333

 $00{:}05{:}37{.}813 \dashrightarrow 00{:}05{:}40{.}167$ I don't want to go too much into and

NOTE Confidence: 0.926691493333333

 $00{:}05{:}40{.}167 \dashrightarrow 00{:}05{:}42{.}383$ on the other hand it could be there's

NOTE Confidence: 0.926691493333333

 $00{:}05{:}42{.}383 \dashrightarrow 00{:}05{:}45{.}037$ not enough immune cells in the tumor

NOTE Confidence: 0.926691493333333

 $00:05:45.037 \rightarrow 00:05:47.016$ micro environment or there's simply

 $00:05:47.016 \longrightarrow 00:05:50.490$ not enough T cells to clear the cancer.

NOTE Confidence: 0.926691493333333

 $00:05:50.490 \longrightarrow 00:05:53.840$ So that's why cell therapy

NOTE Confidence: 0.926691493333333

 $00{:}05{:}53.840 \dashrightarrow 00{:}05{:}55.850$ provides another solution.

NOTE Confidence: 0.926691493333333

 $00:05:55.850 \longrightarrow 00:05:58.629$ You take the cells out from the

NOTE Confidence: 0.926691493333333

 $00{:}05{:}58{.}629 \dashrightarrow 00{:}06{:}01{.}534$ patient and then you amplify them to

NOTE Confidence: 0.926691493333333

 $00:06:01.534 \dashrightarrow 00:06:03.358$ billions and billions of cells and

NOTE Confidence: 0.926691493333333

 $00:06:03.358 \longrightarrow 00:06:05.706$ then you give it back to the patient.

NOTE Confidence: 0.926691493333333

 $00{:}06{:}05{.}710 \dashrightarrow 00{:}06{:}07{.}774$ And in addition you can equip

NOTE Confidence: 0.926691493333333

 $00{:}06{:}07.774 \dashrightarrow 00{:}06{:}09.981$ the cells because you already

NOTE Confidence: 0.926691493333333

 $00:06:09.981 \longrightarrow 00:06:12.083$ took them out, right.

NOTE Confidence: 0.926691493333333

00:06:12.083 --> 00:06:15.860 So now you can install things like

NOTE Confidence: 0.926691493333333

00:06:15.860 --> 00:06:18.590 chimeric antigen receptor or CAR T that

NOTE Confidence: 0.926691493333333

 $00:06:18.590 \longrightarrow 00:06:21.052$ can recognize specific cancer antigens

NOTE Confidence: 0.926691493333333

 $00:06:21.052 \rightarrow 00:06:23.998$ to distinguish cancer from the healthy

NOTE Confidence: 0.926691493333333

 $00:06:23.998 \rightarrow 00:06:26.677$ cells and you can amplify those cells

NOTE Confidence: 0.926691493333333

 $00{:}06{:}26.677 \dashrightarrow 00{:}06{:}28.290$ to billions and billions of them

- NOTE Confidence: 0.926691493333333
- $00:06:28.290 \rightarrow 00:06:30.149$ and then give it back to patient.
- NOTE Confidence: 0.926691493333333
- $00:06:30.150 \longrightarrow 00:06:34.340$ So this is a solution to
- NOTE Confidence: 0.926691493333333
- $00:06:34.340 \longrightarrow 00:06:37.380$ amplify the immune system.
- NOTE Confidence: 0.9260515
- $00:06:39.300 \longrightarrow 00:06:41.322$ So in that case, right,
- NOTE Confidence: 0.9260515
- $00:06:41.322 \longrightarrow 00:06:43.614$ that seems to make sense.
- NOTE Confidence: 0.9260515
- $00:06:43.620 \longrightarrow 00:06:47.524$ If you have a cancer and it has
- NOTE Confidence: 0.9260515
- $00:06:47.524 \rightarrow 00:06:50.322$ particular antigens on its surface and
- NOTE Confidence: 0.9260515
- $00{:}06{:}50{.}322 \dashrightarrow 00{:}06{:}53{.}378$ it's the job of the immune system to
- NOTE Confidence: 0.9260515
- $00:06:53.378 \rightarrow 00:06:56.216$ recognize things that shouldn't be there.
- NOTE Confidence: 0.9260515
- $00:06:56.220 \longrightarrow 00:06:58.920$ And you can take out a
- NOTE Confidence: 0.9260515
- $00:06:58.920 \longrightarrow 00:07:00.720$ patient's own immune cells,
- NOTE Confidence: 0.9260515
- $00{:}07{:}00.720 \dashrightarrow 00{:}07{:}02.904$ kind of engineer them so that
- NOTE Confidence: 0.9260515
- $00:07:02.904 \rightarrow 00:07:04.360$ they recognize those antigens,
- NOTE Confidence: 0.9260515
- $00:07:04.360 \dashrightarrow 00:07:07.066$ essentially give them a targeting
- NOTE Confidence: 0.9260515
- $00{:}07{:}07{.}066 \dashrightarrow 00{:}07{:}10.524$ system so that they can go after this
- NOTE Confidence: 0.9260515

00:07:10.524 --> 00:07:13.685 cancer and then give them back to the

NOTE Confidence: 0.9260515

 $00:07:13.685 \rightarrow 00:07:17.278$ patient in billions and billions of cells,

NOTE Confidence: 0.9260515

 $00:07:17.280 \dashrightarrow 00:07:19.645$ essentially giving the immune system

NOTE Confidence: 0.9260515

 $00:07:19.645 \dashrightarrow 00:07:22.600$ an unfair advantage over the cancer.

NOTE Confidence: 0.9260515

 $00{:}07{:}22.600 \dashrightarrow 00{:}07{:}24.216$ Presumably that would help

NOTE Confidence: 0.9260515

 $00{:}07{:}24.216 \dashrightarrow 00{:}07{:}26.236$ to wipe the cancer out.

NOTE Confidence: 0.9260515

00:07:26.240 --> 00:07:30.090 So #1 is, has that been tried?

NOTE Confidence: 0.9260515

 $00:07:30.090 \longrightarrow 00:07:31.635$ Does it work?

NOTE Confidence: 0.9260515

00:07:31.635 --> 00:07:34.210 And #2 if it does,

NOTE Confidence: 0.9260515

 $00:07:34.210 \dashrightarrow 00:07:36.247$ why are we still talking about cancer?

NOTE Confidence: 0.9260515

 $00{:}07{:}36.250 \dashrightarrow 00{:}07{:}38.374$ Wouldn't that be the fundamental answer

NOTE Confidence: 0.9260515

 $00:07:38.374 \longrightarrow 00:07:40.570$ that would kill off all cancers?

NOTE Confidence: 0.93521374

 $00{:}07{:}41.410 \dashrightarrow 00{:}07{:}42.902$ Those are great questions.

NOTE Confidence: 0.93521374

00:07:42.902 --> 00:07:47.112 And #1, it has been approved

NOTE Confidence: 0.93521374

 $00:07:47.112 \longrightarrow 00:07:49.154$ for several different diseases,

NOTE Confidence: 0.93521374

 $00:07:49.154 \longrightarrow 00:07:50.722$ for example, leukemia,

00:07:50.722 --> 00:07:53.090 lymphoma, and multiple myeloma.

NOTE Confidence: 0.93521374

00:07:53.090 --> 00:07:56.765 And the FDA has approved six different cell

NOTE Confidence: 0.93521374

 $00:07:56.765 \longrightarrow 00:07:58.638$ therapies for treating these diseases.

NOTE Confidence: 0.93521374

 $00:07:58.638 \dashrightarrow 00:08:02.270$ And in fact, the overall response

NOTE Confidence: 0.93521374

 $00:08:02.270 \longrightarrow 00:08:05.450$ for these cell therapies are amazing.

NOTE Confidence: 0.93521374

 $00:08:05.450 \dashrightarrow 00:08:08.768$ And for example, in multiple myeloma,

NOTE Confidence: 0.93521374

 $00{:}08{:}08{.}770 \dashrightarrow 00{:}08{:}09{.}938$ the overall response rate

NOTE Confidence: 0.93521374

 $00:08:09.938 \longrightarrow 00:08:12.010$ can be in the high 90% digit.

NOTE Confidence: 0.9355516

 $00:08:14.170 \longrightarrow 00:08:16.840$ But the challenge is that #1 the

NOTE Confidence: 0.9355516

 $00:08:16.840 \dashrightarrow 00:08:19.210$ cancer still can still come back.

NOTE Confidence: 0.9355516

 $00{:}08{:}19{.}210 \dashrightarrow 00{:}08{:}21{.}730$ They can become resistant to cell the rapy.

NOTE Confidence: 0.9355516

00:08:21.730 --> 00:08:25.190 And #2 for solid tumors,

NOTE Confidence: 0.9355516

00:08:25.190 --> 00:08:26.243 not leukemia, lymphoma,

NOTE Confidence: 0.9355516

 $00{:}08{:}26{.}243 \dashrightarrow 00{:}08{:}28{.}349$ those are what we call blood cancers.

NOTE Confidence: 0.9355516

 $00:08:28.350 \dashrightarrow 00:08:32.470$ Solid tumors are for example a breast cancer,

- $00:08:32.470 \longrightarrow 00:08:34.438$ lung cancer, melanoma,
- NOTE Confidence: 0.9355516
- 00:08:34.438 --> 00:08:36.736 pancreatic cancer, brain cancer.
- NOTE Confidence: 0.9355516
- $00:08:36.736 \longrightarrow 00:08:38.708$ Those are solid tumors.
- NOTE Confidence: 0.9355516
- 00:08:38.710 00:08:40.774 They are more resistant to cell
- NOTE Confidence: 0.9355516
- $00{:}08{:}40.774 \dashrightarrow 00{:}08{:}42.949$ the rapy for a number of reasons.
- NOTE Confidence: 0.9355516
- $00:08:42.950 \longrightarrow 00:08:43.566$ For example,
- NOTE Confidence: 0.9355516
- $00:08:43.566 \longrightarrow 00:08:46.030$ the cell can't get in the solid tumor,
- NOTE Confidence: 0.9355516
- $00:08:46.030 \rightarrow 00:08:47.950$ the cells can get in,
- NOTE Confidence: 0.9355516
- $00{:}08{:}47{.}950 \dashrightarrow 00{:}08{:}49{.}950$ but they fail to proliferate.
- NOTE Confidence: 0.9355516
- $00{:}08{:}49{.}950 \dashrightarrow 00{:}08{:}52{.}314$ They can't grow because the solid
- NOTE Confidence: 0.9355516
- 00:08:52.314 --> 00:08:54.304 tumor micro environment is very
- NOTE Confidence: 0.9355516
- $00:08:54.304 \longrightarrow 00:08:56.356$ hostile for the immune cells or
- NOTE Confidence: 0.9355516
- $00:08:56.356 \dashrightarrow 00:08:58.959$ the cells can get in and proliferate,
- NOTE Confidence: 0.9355516
- $00:08:58.960 \rightarrow 00:09:00.600$ but then they become exhausted,
- NOTE Confidence: 0.9355516
- 00:09:00.600 -> 00:09:02.256 which means they're too tired of
- NOTE Confidence: 0.9355516
- $00:09:02.256 \rightarrow 00:09:03.720$ killing so many cancer cells.

- NOTE Confidence: 0.9355516
- $00:09:03.720 \longrightarrow 00:09:06.933$ So there's still a lot of problems

00:09:06.933 --> 00:09:09.520 hindering the success of this type

NOTE Confidence: 0.9355516

 $00:09:09.520 \rightarrow 00:09:12.400$ of cell therapy for curing cancer.

NOTE Confidence: 0.9355516

00:09:12.400 - 00:09:14.688 That's why we are trying very hard to

NOTE Confidence: 0.9355516

 $00:09:14.688 \rightarrow 00:09:17.439$ find new solutions to improve cell therapy.

NOTE Confidence: 0.938678

 $00:09:19.840 \longrightarrow 00:09:22.904$ So we don't have a magic bullet

NOTE Confidence: 0.938678

 $00:09:22.904 \dashrightarrow 00:09:25.584$ although it sounds like we have

NOTE Confidence: 0.938678

 $00:09:25.584 \rightarrow 00:09:27.844$ something very effective for the

NOTE Confidence: 0.938678

 $00{:}09{:}27.844 \dashrightarrow 00{:}09{:}29.934$ the liquid tumors, the leukemias.

NOTE Confidence: 0.938678

 $00{:}09{:}29{.}934 \dashrightarrow 00{:}09{:}33{.}389$ So tell us more about your work in terms

NOTE Confidence: 0.938678

 $00:09:33.389 \dashrightarrow 00:09:36.041$ of how you optimize cellular therapy

NOTE Confidence: 0.938678

00:09:36.041 --> 00:09:38.700 for solid tumors because presumably when

NOTE Confidence: 0.938678

 $00{:}09{:}38{.}700 \dashrightarrow 00{:}09{:}41{.}995$ most of us think about cancer we

NOTE Confidence: 0.938678

 $00{:}09{:}41.995 \dashrightarrow 00{:}09{:}44.480$ tend to think about those solid tumors,

NOTE Confidence: 0.938678

00:09:44.480 --> 00:09:46.132 breast cancer, lung cancer,

00:09:46.132 --> 00:09:48.278 colon cancer, prostate cancer,

NOTE Confidence: 0.938678

 $00:09:48.278 \longrightarrow 00:09:49.596$ pancreatic cancer.

NOTE Confidence: 0.938678

 $00:09:49.596 \dashrightarrow 00:09:55.107$ And so it would be really nice if we had

NOTE Confidence: 0.938678

 $00{:}09{:}55{.}107 \dashrightarrow 00{:}09{:}58{.}578$ a way for us to target these cancers

NOTE Confidence: 0.938678

 $00:09:58.578 \dashrightarrow 00:10:02.149$ and eliminate them with high efficacy.

NOTE Confidence: 0.938678

 $00{:}10{:}02{.}150 \dashrightarrow 00{:}10{:}04.688$ So what have you been trying and

NOTE Confidence: 0.938678

 $00:10:04.688 \dashrightarrow 00:10:07.343$ how well or not has it been working?

NOTE Confidence: 0.92647344

 $00{:}10{:}09{.}230 \dashrightarrow 00{:}10{:}12{.}307$ Another great question in fact when

NOTE Confidence: 0.92647344

 $00{:}10{:}12{.}307 \dashrightarrow 00{:}10{:}15{.}169$ the cell the rapy stopped working or

NOTE Confidence: 0.92647344

 $00{:}10{:}15{.}169 \dashrightarrow 00{:}10{:}18{.}802$ didn't even start working, the few ways NOTE Confidence: 0.92647344

00:10:18.802 --> 00:10:21.706 we can naturally think about it,

NOTE Confidence: 0.92647344

 $00{:}10{:}21.710 \dashrightarrow 00{:}10{:}23.590$ imagine this is a car,

NOTE Confidence: 0.92647344

 $00{:}10{:}23.590 \dashrightarrow 00{:}10{:}26.680$ well it is car kinematic antigen

NOTE Confidence: 0.92647344

 $00:10:26.680 \rightarrow 00:10:28.662$ receptor but pun intended.

NOTE Confidence: 0.92647344

 $00{:}10{:}28.662 \dashrightarrow 00{:}10{:}32.846$ So for a car, you can push the gas on you

NOTE Confidence: 0.92647344

 $00:10:32.846 \longrightarrow 00:10:35.478$ can release the brake or you can

- NOTE Confidence: 0.92647344
- $00:10:35.478 \longrightarrow 00:10:37.990$ change the structure of the car.

 $00:10:37.990 \longrightarrow 00:10:39.374$ So there's three different

NOTE Confidence: 0.92647344

 $00:10:39.374 \longrightarrow 00:10:43.230$ ways to make it run faster.

NOTE Confidence: 0.92647344

 $00:10:43.230 \rightarrow 00:10:46.110$ So in order to put the gas pedal on,

NOTE Confidence: 0.92647344

00:10:46.110 --> 00:10:51.808 we develop things we call a hyper

NOTE Confidence: 0.92647344

 $00{:}10{:}51{.}808 \dashrightarrow 00{:}10{:}57{.}208$ boost or like functional booster or

NOTE Confidence: 0.92647344

 $00:10:57.208 \longrightarrow 00:11:01.618$ functional augmentation factors so that

NOTE Confidence: 0.92647344

 $00:11:01.618 \rightarrow 00:11:05.618$ we can allow the T cells to kill better,

NOTE Confidence: 0.92647344

00:11:05.618 --> 00:11:09.962 become tireless and remember the cancer

NOTE Confidence: 0.92647344

 $00:11:09.962 \rightarrow 00:11:12.850$ cells, but sometimes T cells can

NOTE Confidence: 0.92647344

00:11:12.850 --> 00:11:15.173 be blocked by cancer cells, right,

NOTE Confidence: 0.92647344

00:11:15.173 --> 00:11:18.077 cancer cells put those brakes on and we

NOTE Confidence: 0.92647344

 $00{:}11{:}18.077 \dashrightarrow 00{:}11{:}21.356$ can use a thing called gene editing,

NOTE Confidence: 0.92647344

00:11:21.360 --> 00:11:24.195 or CRISPR that we hear about a

NOTE Confidence: 0.92647344

 $00:11:24.195 \longrightarrow 00:11:27.176$ lot to eliminate those brakes,

 $00:11:27.176 \longrightarrow 00:11:30.396$ those we call cellular checkpoints

NOTE Confidence: 0.92647344

00:11:30.400 --> 00:11:33.478 like PD1 but not exactly PD1.

NOTE Confidence: 0.92647344

 $00:11:33.480 \longrightarrow 00:11:37.456$ So you can remove or at least

NOTE Confidence: 0.92647344

 $00:11:37.456 \rightarrow 00:11:40.120$ stampen those blocked or like the

NOTE Confidence: 0.92647344

 $00{:}11{:}40.209 \dashrightarrow 00{:}11{:}43.198$ hurdles the T cell has to overcome.

NOTE Confidence: 0.92647344

 $00:11:43.200 \rightarrow 00:11:46.088$ So that's another way of modifying the cells.

NOTE Confidence: 0.92647344

00:11:46.090 --> 00:11:47.294 And finally

NOTE Confidence: 0.92647344

 $00:11:47.294 \rightarrow 00:11:49.808$ the newer way is that why don't we

NOTE Confidence: 0.92647344

00:11:49.808 --> 00:11:52.048 make the car shape a little better,

NOTE Confidence: 0.92647344

 $00:11:52.050 \rightarrow 00:11:55.072$ so a little more smooth so they

NOTE Confidence: 0.92647344

 $00{:}11{:}55{.}072 \dashrightarrow 00{:}11{:}57{.}178$ can run more smoothly and that's

NOTE Confidence: 0.92647344

 $00{:}11{:}57{.}178 \dashrightarrow 00{:}11{:}59{.}502$ called the structural design of the

NOTE Confidence: 0.92647344

 $00:11:59.502 \rightarrow 00:12:02.086$ car to make it run more smoothly.

NOTE Confidence: 0.92647344

 $00:12:02.090 \rightarrow 00:12:04.556$ So we're doing all three different

NOTE Confidence: 0.92647344

 $00{:}12{:}04.556 \dashrightarrow 00{:}12{:}07.388$ approaches and we published a few pieces

NOTE Confidence: 0.92647344

 $00:12:07.388 \rightarrow 00:12:11.606$ for the gas pedal and the brake.

 $00:12:11.610 \longrightarrow 00:12:14.266$ And the recent piece of work is a

NOTE Confidence: 0.92647344

 $00:12:14.266 \longrightarrow 00:12:16.170$ structural design of the car that

NOTE Confidence: 0.92647344

00:12:16.170 --> 00:12:19.083 makes the car work more tirelessly

NOTE Confidence: 0.92647344

00:12:19.083 --> 00:12:21.338 against cancer and avoid self

NOTE Confidence: 0.92647344

00:12:21.338 --> 00:12:23.637 destruction like avoid the crashes

NOTE Confidence: 0.92647344

 $00{:}12{:}23.637 \dashrightarrow 00{:}12{:}25.405$ between the cars themselves.

NOTE Confidence: 0.9245574

 $00:12:27.250 \longrightarrow 00:12:29.450$ So I want to dig into each of

NOTE Confidence: 0.9245574

 $00:12:29.450 \longrightarrow 00:12:31.887$ those in a little bit more detail.

NOTE Confidence: 0.9245574

 $00{:}12{:}31.890 \dashrightarrow 00{:}12{:}34.648$ And let's start with CAR T therapy,

NOTE Confidence: 0.9245574

 $00:12:34.650 \longrightarrow 00:12:36.432$ which is something that some of

NOTE Confidence: 0.9245574

00:12:36.432 --> 00:12:38.160 our audience might have heard of,

NOTE Confidence: 0.9245574

 $00{:}12{:}38{.}160 \dashrightarrow 00{:}12{:}40{.}554$ but others might still be unaware of.

NOTE Confidence: 0.9245574

00:12:40.560 --> 00:12:43.170 Can you tell us a little bit more about

NOTE Confidence: 0.9245574

 $00{:}12{:}43{.}170$ --> $00{:}12{:}45{.}840$ what exactly that is and how that works? NOTE Confidence: 0.9351585

00:12:46.400 --> 00:12:50.236 Yeah, sure. To take two steps back,

 $00:12:50.240 \rightarrow 00:12:53.942$ CAR T therapy means chimeric

NOTE Confidence: 0.9351585

 $00:12:53.942 \dashrightarrow 00:12:56.997$ antigen receptor T cell therapy.

NOTE Confidence: 0.9351585

00:12:57.000 --> 00:13:01.568 So T cells, sometimes they recognize cancer,

NOTE Confidence: 0.9351585

 $00:13:01.568 \rightarrow 00:13:03.164$ sometimes they don't.

NOTE Confidence: 0.9351585

 $00{:}13{:}03{.}170 \dashrightarrow 00{:}13{:}05{.}722$ And in order to make all the T

NOTE Confidence: 0.9351585

00:13:05.722 --> 00:13:07.725 cells recognize the cancer

NOTE Confidence: 0.9351585

 $00:13:07.725 \longrightarrow 00:13:10.287$ we want to target,

NOTE Confidence: 0.9351585

 $00:13:10.290 \longrightarrow 00:13:12.110$ we install chimeric endogen

NOTE Confidence: 0.9351585

 $00{:}13{:}12{.}110 \dashrightarrow 00{:}13{:}13{.}930$ receptor on their surface.

NOTE Confidence: 0.9351585

 $00{:}13{:}13{.}930 \dashrightarrow 00{:}13{:}16{.}410$ Those are CAR for short.

NOTE Confidence: 0.9351585

 $00{:}13{:}16{.}410 \dashrightarrow 00{:}13{:}18{.}447$ So by putting those cars on their

NOTE Confidence: 0.9351585

 $00{:}13{:}18{.}447 \dashrightarrow 00{:}13{:}20{.}233$ surface then every T cell can

NOTE Confidence: 0.9351585

 $00{:}13{:}20{.}233 \dashrightarrow 00{:}13{:}21{.}943$ recognize those cancer cells and we

NOTE Confidence: 0.9351585

 $00:13:21.943 \rightarrow 00:13:23.970$ hope they can kill the cancer cell.

NOTE Confidence: 0.9351585

 $00:13:23.970 \rightarrow 00:13:25.338$ But sometimes they don't.

 $00:13:26.370 \longrightarrow 00:13:28.488$ That's why we're doing all this,

 $00:13:28.490 \longrightarrow 00:13:30.970$ the three different tricks,

NOTE Confidence: 0.9351585

 $00{:}13{:}30{.}970 \dashrightarrow 00{:}13{:}32{.}830$ the gas pedal,

NOTE Confidence: 0.9351585

00:13:32.830 --> 00:13:34.576 hitting the brake, and changing the

NOTE Confidence: 0.9351585

 $00:13:34.576 \longrightarrow 00:13:36.749$ shape in order to make them better.

NOTE Confidence: 0.93413925

00:13:37.950 --> 00:13:40.750 OK, well, we're going to pick up this

NOTE Confidence: 0.93413925

 $00{:}13{:}40{.}750 \dashrightarrow 00{:}13{:}42{.}745$ conversation right after we take a NOTE Confidence: 0.93413925

00:13:42.745 -> 00:13:44.581 short break for a medical minute.

NOTE Confidence: 0.93413925

00:13:44.590 --> 00:13:46.810 Please stay tuned to learn more

NOTE Confidence: 0.93413925

 $00{:}13{:}46{.}810 \dashrightarrow 00{:}13{:}48{.}290$ about break through the rapeutics and NOTE Confidence: 0.93413925

 $00:13:48.349 \rightarrow 00:13:50.590$ cancer with my guest, Dr. Sidi Chen.

NOTE Confidence: 0.93413925

00:13:51.110 --> 00:13:53.090 Funding for Yale Cancer Answers

NOTE Confidence: 0.93413925

00:13:53.090 --> 00:13:55.070 comes from Smilow Cancer Hospital,

NOTE Confidence: 0.93413925

 $00{:}13{:}55{.}070 \dashrightarrow 00{:}13{:}57{.}000$ where their hematology program offers

NOTE Confidence: 0.93413925

 $00:13:57.000 \rightarrow 00:13:59.430$ diagnosis and treatment of blood cancers,

NOTE Confidence: 0.93413925

 $00:13:59.430 \rightarrow 00:14:02.690$ including lymphoma, leukemia, and myeloma.

NOTE Confidence: 0.93413925

 $00:14:02.690 \rightarrow 00:14:05.724$ More at smilowcancerhospital.org or

- NOTE Confidence: 0.93413925
- $00{:}14{:}05{.}724 \dashrightarrow 00{:}14{:}08{.}363$ e-mail Cancer Answers at Yale dot Edu.
- NOTE Confidence: 0.92270476
- 00:14:10.490 --> 00:14:12.374 Genetic testing can be useful for
- NOTE Confidence: 0.92270476
- $00:14:12.374 \rightarrow 00:14:14.222$ people with certain types of cancer
- NOTE Confidence: 0.92270476
- $00:14:14.222 \rightarrow 00:14:16.084$ that seem to run in their families.
- NOTE Confidence: 0.92270476
- $00{:}14{:}16.090 \dashrightarrow 00{:}14{:}17.985$ Genetic counseling is a process
- NOTE Confidence: 0.92270476
- $00{:}14{:}17{.}985 \dashrightarrow 00{:}14{:}19{.}880$ that includes collecting a detailed
- NOTE Confidence: 0.92270476
- 00:14:19.943 --> 00:14:21.527 personal and family history,
- NOTE Confidence: 0.92270476
- $00:14:21.530 \longrightarrow 00:14:22.874$ a risk assessment,
- NOTE Confidence: 0.92270476
- $00:14:22.874 \rightarrow 00:14:26.010$ and a discussion of genetic testing options.
- NOTE Confidence: 0.92270476
- 00:14:26.010 --> 00:14:28.596 Only about 5 to 10% of all cancers
- NOTE Confidence: 0.92270476
- $00{:}14{:}28.596 \dashrightarrow 00{:}14{:}30.306$ are inherited and genetic testing
- NOTE Confidence: 0.92270476
- $00{:}14{:}30{.}306 \dashrightarrow 00{:}14{:}32{.}618$ is not recommended for every one.
- NOTE Confidence: 0.92270476
- $00{:}14{:}32{.}620 \dashrightarrow 00{:}14{:}34{.}585$ Individuals who have a personal
- NOTE Confidence: 0.92270476
- $00{:}14{:}34{.}585 \dashrightarrow 00{:}14{:}37{.}077$ and or family history that includes
- NOTE Confidence: 0.92270476
- $00:14:37.077 \rightarrow 00:14:39.337$ cancer at unusually early ages,
- NOTE Confidence: 0.92270476

 $00:14:39.340 \rightarrow 00:14:41.344$ multiple relatives on the same side

NOTE Confidence: 0.92270476

 $00:14:41.344 \rightarrow 00:14:43.738$ of the family with the same cancer,

NOTE Confidence: 0.92270476

00:14:43.740 --> 00:14:46.020 more than one diagnosis of cancer

NOTE Confidence: 0.92270476

 $00:14:46.020 \rightarrow 00:14:47.540$ in the same individual,

NOTE Confidence: 0.92270476

 $00:14:47.540 \longrightarrow 00:14:48.342$ rare cancers,

NOTE Confidence: 0.92270476

 $00{:}14{:}48{.}342 \dashrightarrow 00{:}14{:}51{.}149$ or family history of a known altered

NOTE Confidence: 0.92270476

 $00:14:51.149 \longrightarrow 00:14:53.660$ cancer predisposing gene could be

NOTE Confidence: 0.92270476

 $00{:}14{:}53.660 \dashrightarrow 00{:}14{:}55.700$ candidates for genetic testing.

NOTE Confidence: 0.92270476

 $00{:}14{:}55{.}700 \dashrightarrow 00{:}14{:}57{.}705$ Resources for genetic counseling and

NOTE Confidence: 0.92270476

 $00{:}14{:}57.705 \dashrightarrow 00{:}14{:}59.710$ testing are available at federally

NOTE Confidence: 0.92270476

 $00{:}14{:}59{.}774 \dashrightarrow 00{:}15{:}01{.}427$ designated comprehensive cancer

NOTE Confidence: 0.92270476

 $00{:}15{:}01{.}427 \dashrightarrow 00{:}15{:}03{.}760$ centers such as Yale Cancer Center

NOTE Confidence: 0.92270476

 $00:15:03.760 \longrightarrow 00:15:05.540$ and Smilow Cancer Hospital.

NOTE Confidence: 0.92270476

 $00{:}15{:}05{.}540 \dashrightarrow 00{:}15{:}07{.}908$ More information is available

NOTE Confidence: 0.92270476

 $00{:}15{:}07{.}908 \dashrightarrow 00{:}15{:}08{.}934$ at yale cancercenter.org.

NOTE Confidence: 0.92270476

00:15:08.934 --> 00:15:11.538 You're listening to Connecticut Public Radio.

 $00:15:12.180 \longrightarrow 00:15:14.298$ Welcome back to Yale Cancer Answers.

NOTE Confidence: 0.92193615

 $00{:}15{:}14{.}300 \dashrightarrow 00{:}15{:}15{.}900$ This is Dr. Anees Chagpar,

NOTE Confidence: 0.92193615

 $00:15:15.900 \dashrightarrow 00:15:18.421$ and I'm joined to night by my guest, Dr.

NOTE Confidence: 0.92193615

 $00:15:18.421 \dashrightarrow 00:15:20.587$ Sidi Chen. We're talking about the

NOTE Confidence: 0.92193615

 $00{:}15{:}20.587 \dashrightarrow 00{:}15{:}22.193$ role of break through the rapeutics

NOTE Confidence: 0.92193615

 $00{:}15{:}22{.}193 \dashrightarrow 00{:}15{:}24{.}017$ in fighting cancer.

NOTE Confidence: 0.92193615

 $00:15:24.020 \longrightarrow 00:15:25.972$ Right before the break,

NOTE Confidence: 0.92193615

 $00{:}15{:}25{.}972 \dashrightarrow 00{:}15{:}28{.}900$ we were talking about this concept

NOTE Confidence: 0.92193615

00:15:28.991 --> 00:15:31.615 of the interplay between cancers in

NOTE Confidence: 0.92193615

00:15:31.615 --> 00:15:34.070 the immune system and essentially

NOTE Confidence: 0.92193615

 $00{:}15{:}34{.}151 \dashrightarrow 00{:}15{:}36{.}724$ the fact that cancers try to get

NOTE Confidence: 0.92193615

 $00{:}15{:}36{.}724$ --> $00{:}15{:}39{.}652$ the upper hand on the immune system NOTE Confidence: 0.92193615

 $00{:}15{:}39{.}652 \dashrightarrow 00{:}15{:}42{.}075$ and do that with a number of tricks NOTE Confidence: 0.92193615

 $00{:}15{:}42.075 \dashrightarrow 00{:}15{:}44.597$ that try to evade the immune system.

NOTE Confidence: 0.92193615

 $00{:}15{:}44.600 \dashrightarrow 00{:}15{:}46.885$ There's now been some the rapeutics

- 00:15:46.885 --> 00:15:48.713 like CAR T therapy,
- NOTE Confidence: 0.92193615
- $00:15:48.720 \rightarrow 00:15:53.040$ which essentially tries to arm the T cells,
- NOTE Confidence: 0.92193615
- $00:15:53.040 \longrightarrow 00:15:55.512$ those fighting cells that are in
- NOTE Confidence: 0.92193615
- $00{:}15{:}55{.}512 \dashrightarrow 00{:}15{:}58{.}098$ the immune system so that they can
- NOTE Confidence: 0.92193615
- $00{:}15{:}58.098 \dashrightarrow 00{:}16{:}00.510$ recognize these cancers and go after them.
- NOTE Confidence: 0.92193615
- $00:16:00.510 \longrightarrow 00:16:02.374$ But even with that,
- NOTE Confidence: 0.92193615
- $00{:}16{:}02{.}374 \dashrightarrow 00{:}16{:}04{.}704$ not all cellular the rapeutics or
- NOTE Confidence: 0.92193615
- 00:16:04.704 --> 00:16:07.430 CAR T therapies are effective,
- NOTE Confidence: 0.92193615
- $00:16:07.430 \longrightarrow 00:16:10.374$ particularly for solid tumors.
- 00:16:11.598 --> 00:16:14.038 Sidi, if I understand it correctly
- NOTE Confidence: 0.92193615
- $00:16:14.038 \longrightarrow 00:16:15.990$ that being the case,
- NOTE Confidence: 0.92193615
- 00:16:15.990 --> 00:16:19.080 you have 3 strategies really to
- NOTE Confidence: 0.92193615
- 00:16:19.080 --> 00:16:21.547 try to make things better,
- NOTE Confidence: 0.92193615
- $00:16:21.547 \longrightarrow 00:16:24.421$ give the immune system kind
- NOTE Confidence: 0.92193615
- $00{:}16{:}24{.}421 \dashrightarrow 00{:}16{:}27{.}838$ of an upper edge on these tumor cells.
- NOTE Confidence: 0.92193615
- $00{:}16{:}27.840 \dashrightarrow 00{:}16{:}30.612$ So the first one you talked about
- NOTE Confidence: 0.92193615

 $00:16:30.612 \longrightarrow 00:16:33.960$ was kind of like giving

NOTE Confidence: 0.92193615

 $00{:}16{:}33{.}960 \dashrightarrow 00{:}16{:}37{.}200$ the immune system a hyper boost.

NOTE Confidence: 0.92193615

00:16:37.200 --> 00:16:38.859 Can you talk a little bit more

NOTE Confidence: 0.92193615

 $00:16:38.859 \longrightarrow 00:16:40.040$ about what that entails?

NOTE Confidence: 0.92193615

 $00{:}16{:}40.040 \dashrightarrow 00{:}16{:}42.833$ I mean is that simply making more

NOTE Confidence: 0.92193615

00:16:42.833 --> 00:16:46.518 of these T cells that are armed to

NOTE Confidence: 0.92193615

 $00{:}16{:}46{.}518 \dashrightarrow 00{:}16{:}48{.}796$ recognize the cancer cells or

NOTE Confidence: 0.92193615

00:16:48.796 --> 00:16:51.540 do you try to engineer them in some

NOTE Confidence: 0.92193615

00:16:51.540 --> 00:16:53.640 way to make them more effective,

NOTE Confidence: 0.92193615

 $00{:}16{:}53.640 \dashrightarrow 00{:}16{:}56.496$ make them be more able to

NOTE Confidence: 0.92193615

 $00:16:56.496 \longrightarrow 00:16:58.400$ get into solid tumors?

NOTE Confidence: 0.9253724

 $00:16:59.200 \longrightarrow 00:17:02.240$ The first strategy as we

NOTE Confidence: 0.9253724

 $00{:}17{:}04{.}320 \dashrightarrow 00{:}17{:}07{.}400$ term as hyper boost is with an analogy

NOTE Confidence: 0.9253724

 $00:17:07.400 \longrightarrow 00:17:11.077$ to putting the gas pedal on the CAR.

NOTE Confidence: 0.9253724

00:17:11.080 --> 00:17:14.008 So we're trying to engineer the car so

NOTE Confidence: 0.9253724

 $00:17:14.008 \rightarrow 00:17:17.080$ that the gas pedals are more efficient,

- NOTE Confidence: 0.9253724
- $00{:}17{:}17{.}080 \dashrightarrow 00{:}17{:}19{.}366$ like a more fuel efficient car.

00:17:19.370 --> 00:17:22.202 So as you know, T cells kill cancer

NOTE Confidence: 0.9253724

00:17:22.202 --> 00:17:25.556 cells by recognizing them and then

NOTE Confidence: 0.9253724

 $00{:}17{:}25{.}556$ --> $00{:}17{:}28{.}541$ produce cancer killing cytokines and NOTE Confidence: 0.9253724

 $00:17:28.541 \rightarrow 00:17:31.247$ all trigger the cell death signal.

NOTE Confidence: 0.9253724

 $00{:}17{:}31{.}250 \dashrightarrow 00{:}17{:}37{.}445$ And our approach is trying to install

NOTE Confidence: 0.9253724

 $00{:}17{:}37{.}450 \dashrightarrow 00{:}17{:}41{.}804$ the modification to our normal T cells,

NOTE Confidence: 0.9253724

 $00{:}17{:}41.810 \dashrightarrow 00{:}17{:}46.570$ which often fail to kill cancer cells

NOTE Confidence: 0.9253724

 $00{:}17{:}46.570 \dashrightarrow 00{:}17{:}49.660$ by equipping with these T cells

NOTE Confidence: 0.9253724

 $00{:}17{:}49.660 \dashrightarrow 00{:}17{:}52.214$ better tools or better modifications.

NOTE Confidence: 0.9253724

 $00{:}17{:}52.214 \dashrightarrow 00{:}17{:}55.728$ For example, in one of the scenarios,

NOTE Confidence: 0.9253724

 $00{:}17{:}55{.}730 \dashrightarrow 00{:}17{:}59{.}118$ we're trying to see which of our

NOTE Confidence: 0.9253724

00:17:59.118 --> 00:18:01.794 own 20,000 genes when you install NOTE Confidence: 0.9253724

 $00{:}18{:}01{.}794 \dashrightarrow 00{:}18{:}05{.}214$ or overexpress on a T cell can help NOTE Confidence: 0.9253724

 $00{:}18{:}05{.}214 \dashrightarrow 00{:}18{:}08{.}028$ the T cells produce more cytokines NOTE Confidence: 0.9253724

 $00:18:08.028 \rightarrow 00:18:10.050$ to cure cancer cells.

NOTE Confidence: 0.9253724

 $00:18:10.050 \rightarrow 00:18:14.580$ And we did a scanning of the 20,000 and then

NOTE Confidence: 0.9253724

 $00:18:14.686 \rightarrow 00:18:18.268$ we found a few that are working very well.

NOTE Confidence: 0.9253724

00:18:18.270 --> 00:18:22.441 This is one of the examples that we can

NOTE Confidence: 0.9253724

 $00{:}18{:}22{.}441 \dashrightarrow 00{:}18{:}26{.}281$ find the modification genes and hook you

NOTE Confidence: 0.9253724

 $00{:}18{:}26{.}281 \dashrightarrow 00{:}18{:}29{.}023$ up with the chimeric endogen receptor.

NOTE Confidence: 0.9253724

 $00{:}18{:}29{.}030 \dashrightarrow 00{:}18{:}32{.}082$ So now we have a substantially improved

NOTE Confidence: 0.9253724

00:18:32.082 --> 00:18:34.734 CAR T cells to fight cancer cells.

NOTE Confidence: 0.9253724

 $00{:}18{:}34{.}734 \dashrightarrow 00{:}18{:}36{.}750$ This is approach number one.

NOTE Confidence: 0.9362019

 $00:18:37.230 \longrightarrow 00:18:40.408$ So just on that, if these T

NOTE Confidence: 0.9362019

00:18:40.408 --> 00:18:43.430 cells are making more cytokines,

NOTE Confidence: 0.9362019

 $00:18:43.430 \rightarrow 00:18:45.628$ could that be problematic for some patients?

NOTE Confidence: 0.9362019

00:18:45.630 --> 00:18:49.235 I mean, we've just lived through the

NOTE Confidence: 0.9362019

 $00:18:49.235 \longrightarrow 00:18:52.047$ COVID-19 pandemic and one of the

NOTE Confidence: 0.9362019

 $00:18:52.047 \longrightarrow 00:18:55.798$ things that came up as a result of

NOTE Confidence: 0.9362019

 $00:18:55.798 \rightarrow 00:18:58.900$ that experience was that we learned

- NOTE Confidence: 0.9362019
- 00:18:58.900 --> 00:19:01.785 about things like cytokine storm.
- NOTE Confidence: 0.9362019
- $00:19:01.790 \longrightarrow 00:19:04.710$ So is that a possibility?
- NOTE Confidence: 0.9362019
- $00:19:04.710 \longrightarrow 00:19:06.876$ Is there any downside to having
- NOTE Confidence: 0.9362019
- 00:19:06.876 --> 00:19:09.510 your T cells make more cytokines?
- NOTE Confidence: 0.928788
- $00{:}19{:}10.230 \dashrightarrow 00{:}19{:}11.184$ Yeah, of course.
- NOTE Confidence: 0.928788
- $00:19:11.184 \longrightarrow 00:19:12.774$ This is a great point.
- NOTE Confidence: 0.928788
- $00:19:12.780 \longrightarrow 00:19:15.755$ In fact, one of the major cell
- NOTE Confidence: 0.928788
- 00:19:15.755 --> 00:19:18.199 therapy drawbacks is
- NOTE Confidence: 0.928788
- 00:19:18.199 00:19:19.819 cytokine release syndrome.
- NOTE Confidence: 0.928788
- $00:19:19.820 \longrightarrow 00:19:21.938$ We certainly want to avoid that.
- NOTE Confidence: 0.928788
- 00:19:21.940 --> 00:19:25.605 So it's a balance of how much cytokine
- NOTE Confidence: 0.928788
- 00:19:25.605 --> 00:19:28.800 you want to produce by enabling T cell
- NOTE Confidence: 0.928788
- $00{:}19{:}28{.}800 \dashrightarrow 00{:}19{:}31{.}584$ to produce but not over do it so that
- NOTE Confidence: 0.928788
- $00{:}19{:}31{.}584 \dashrightarrow 00{:}19{:}34{.}499$ you create the unwanted side effect.
- NOTE Confidence: 0.928788
- $00:19:34.500 \longrightarrow 00:19:36.663$ So we're doing a lot of work
- NOTE Confidence: 0.928788

 $00:19:36.663 \rightarrow 00:19:39.050$ trying to find the balance

NOTE Confidence: 0.928788

00:19:39.050 --> 00:19:41.140 of efficacy versus toxicity. And

NOTE Confidence: 0.93611157

 $00{:}19{:}41{.}140 \dashrightarrow 00{:}19{:}44{.}161$ that balance I mean is that, I don't know,

NOTE Confidence: 0.93611157

 $00:19:44.161 \longrightarrow 00:19:45.883$ I'm thinking that might be

NOTE Confidence: 0.93611157

 $00{:}19{:}45{.}883 \dashrightarrow 00{:}19{:}47{.}842$ something that is very personal, right.

NOTE Confidence: 0.93611157

 $00:19:47.842 \longrightarrow 00:19:50.614$ That depends on the individual,

NOTE Confidence: 0.93611157

 $00:19:50.620 \longrightarrow 00:19:51.950$ it depends on how much

NOTE Confidence: 0.93611157

 $00:19:51.950 \rightarrow 00:19:53.014$ cancer they might have,

NOTE Confidence: 0.93611157

 $00:19:53.020 \dashrightarrow 00:19:55.176$ the type of cancer they might have.

NOTE Confidence: 0.93611157

 $00:19:55.180 \longrightarrow 00:19:56.993$ Is that right or is that balance

NOTE Confidence: 0.93611157

00:19:56.993 --> 00:19:59.299 going to be kind of a one size fits all?

NOTE Confidence: 0.9392858

 $00{:}19{:}59{.}980 \dashrightarrow 00{:}20{:}02{.}446$ Yes and no. There are certainly patient

NOTE Confidence: 0.9392858

 $00{:}20{:}02{.}446 \dashrightarrow 00{:}20{:}05{.}258$ to patient and disease to disease variations.

NOTE Confidence: 0.9392858

 $00{:}20{:}05{.}260 \dashrightarrow 00{:}20{:}07{.}732$ But the T cells on the other hand

NOTE Confidence: 0.9392858

 $00:20:07.732 \longrightarrow 00:20:11.060$ can be modified so that they can be

NOTE Confidence: 0.9392858

 $00{:}20{:}11.060 \dashrightarrow 00{:}20{:}14.020$ tuned to shift towards better cancer

- NOTE Confidence: 0.9392858
- $00:20:14.020 \rightarrow 00:20:16.900$ killing and not being too toxic.
- NOTE Confidence: 0.9392858
- $00{:}20{:}16{.}900 \dashrightarrow 00{:}20{:}19{.}700$ And the other approach we're talking
- NOTE Confidence: 0.9392858
- $00:20:19.700 \rightarrow 00:20:22.060$ about is modified indulgent genes
- NOTE Confidence: 0.9392858
- $00:20:22.060 \rightarrow 00:20:25.180$ so they can remember cancer better,
- NOTE Confidence: 0.9392858
- $00{:}20{:}25{.}180 \dashrightarrow 00{:}20{:}27{.}304$ so they last longer without having
- NOTE Confidence: 0.9392858
- 00:20:27.304 --> 00:20:29.380 to produce too much cytokine.
- NOTE Confidence: 0.93125427
- $00:20:29.670 \longrightarrow 00:20:31.902$ Yeah, So let's talk about
- NOTE Confidence: 0.93125427
- $00{:}20{:}31{.}902 \dashrightarrow 00{:}20{:}33{.}390$ the second strategy.
- NOTE Confidence: 0.93125427
- $00{:}20{:}33{.}390 \dashrightarrow 00{:}20{:}35{.}340$ So the second strategy you
- NOTE Confidence: 0.93125427
- $00:20:35.340 \longrightarrow 00:20:37.602$ talked about was kind of hitting
- NOTE Confidence: 0.93125427
- $00:20:37.602 \longrightarrow 00:20:40.150$ the brakes on the car.
- NOTE Confidence: 0.93125427
- $00{:}20{:}40.150 \dashrightarrow 00{:}20{:}41.482$ Help us to understand
- NOTE Confidence: 0.93125427
- $00{:}20{:}41{.}482 \dashrightarrow 00{:}20{:}43{.}147$ that piece a bit better.
- NOTE Confidence: 0.93125427
- 00:20:43.350 --> 00:20:46.486 As you know we have 20,000 different
- NOTE Confidence: 0.93125427
- $00{:}20{:}46.486 \dashrightarrow 00{:}20{:}49.342$ genes and a lot of different proteins,
- NOTE Confidence: 0.93125427

 $00:20:49.350 \longrightarrow 00:20:52.300$ some are suppressive because nature

NOTE Confidence: 0.93125427

 $00{:}20{:}52{.}300 \dashrightarrow 00{:}20{:}54{.}892$ evolves so that our immune system

NOTE Confidence: 0.93125427

 $00:20:54.892 \longrightarrow 00:20:57.567$ is not always on so that the

NOTE Confidence: 0.93125427

 $00:20:57.567 \rightarrow 00:20:59.625$ immune system keeps damaging the body.

NOTE Confidence: 0.93125427

 $00{:}20{:}59{.}630 \dashrightarrow 00{:}21{:}02{.}582$ So in order to avoid that our body and

NOTE Confidence: 0.93125427

 $00{:}21{:}02{.}590 \dashrightarrow 00{:}21{:}05{.}662$ billion years of evolution evolve the

NOTE Confidence: 0.93125427

 $00:21:05.662 \rightarrow 00:21:07.710$ molecule that are immunosuppressive.

NOTE Confidence: 0.93125427

00:21:07.710 --> 00:21:09.666 For example, a PD1 PDL one,

NOTE Confidence: 0.93125427

00:21:09.670 --> 00:21:12.222 which is one of the most famous pathway

NOTE Confidence: 0.93125427

 $00{:}21{:}12{.}222 \dashrightarrow 00{:}21{:}14{.}774$ and there are many others and some

NOTE Confidence: 0.93125427

 $00{:}21{:}14.774 \dashrightarrow 00{:}21{:}18.230$ are on the surface like PD1 PDL 1,

NOTE Confidence: 0.93125427

 $00:21:18.230 \rightarrow 00:21:19.361$ some are internal,

NOTE Confidence: 0.93125427

 $00{:}21{:}19{.}361 \dashrightarrow 00{:}21{:}22{.}000$ like we call this cellular checkpoint or

NOTE Confidence: 0.93125427

 $00{:}21{:}22{.}070 \dashrightarrow 00{:}21{:}25{.}770$ internal checkpoints and those genes hold

NOTE Confidence: 0.93125427

 $00:21:25.770 \longrightarrow 00:21:30.608$ the T cells back from being too active.

NOTE Confidence: 0.93125427

 $00:21:30.608 \rightarrow 00:21:33.628$ But those genes sometimes create

- NOTE Confidence: 0.93125427
- 00:21:33.628 --> 00:21:37.195 a hurdle to block the efficacy of
- NOTE Confidence: 0.93125427
- $00:21:37.195 \longrightarrow 00:21:40.488$ the T cell therapy and we can use
- NOTE Confidence: 0.93125427
- 00:21:40.488 --> 00:21:42.600 gene editing to modify or dampen
- NOTE Confidence: 0.93125427
- $00{:}21{:}42.682 \dashrightarrow 00{:}21{:}44.936$ those pathways so that we let the
- NOTE Confidence: 0.93125427
- 00:21:44.936 --> 00:21:47.968 T cell be a little more active in
- NOTE Confidence: 0.93125427
- $00{:}21{:}47.968 \dashrightarrow 00{:}21{:}50.251$ getting an upper hand against cancer,
- NOTE Confidence: 0.93125427
- 00:21:50.251 > 00:21:51.997 wiping them out first and then
- NOTE Confidence: 0.93125427
- 00:21:51.997 --> 00:21:53.400 we can turn it down.
- NOTE Confidence: 0.93125427
- $00{:}21{:}53.400 \dashrightarrow 00{:}21{:}55.488$ That's the hitting the brake strategy
- NOTE Confidence: 0.93125427
- 00:21:55.488 --> 00:21:58.000 like you can release the brake and then
- NOTE Confidence: 0.93125427
- $00{:}21{:}58{.}000 \dashrightarrow 00{:}22{:}00{.}187$ when the T cells kill the cancer cell
- NOTE Confidence: 0.93125427
- $00{:}22{:}00{.}187 \dashrightarrow 00{:}22{:}02{.}581$ and then you can put a brake back on.
- NOTE Confidence: 0.93125427
- $00{:}22{:}02{.}581 \dashrightarrow 00{:}22{:}03{.}736$ So those are the strategies
- NOTE Confidence: 0.93125427
- $00{:}22{:}03.736 \dashrightarrow 00{:}22{:}04.429$ we're talking about.
- NOTE Confidence: 0.9242995
- 00:22:05.230 --> 00:22:08.250 Sidi, I can see how you can
- NOTE Confidence: 0.9242995

 $00:22:08.339 \rightarrow 00:22:11.444$ combine those two initial strategies,

NOTE Confidence: 0.9242995

00:22:11.444 --> 00:22:14.746 making the T cells more

NOTE Confidence: 0.9242995

 $00:22:14.746 \rightarrow 00:22:17.844$ effective in terms of releasing those NOTE Confidence: 0.9242995

 $00:22:17.844 \rightarrow 00:22:20.894$ cytokines that hyper boost strategy NOTE Confidence: 0.9242995

00:22:20.894 --> 00:22:24.456 with this other strategy which kind

NOTE Confidence: 0.9242995

00:22:24.456 --> 00:22:27.522 of dampens their brake system

NOTE Confidence: 0.9242995

 $00{:}22{:}27{.}522 \dashrightarrow 00{:}22{:}31{.}254$ and so you can create a kind of a

NOTE Confidence: 0.9242995

 $00{:}22{:}31{.}254 \dashrightarrow 00{:}22{:}33{.}621$ more effective T cell to kill cancer

NOTE Confidence: 0.9242995

 $00{:}22{:}33{.}621 \dashrightarrow 00{:}22{:}36{.}372$ cells but by combining those two

NOTE Confidence: 0.9242995

 $00{:}22{:}36{.}372 \dashrightarrow 00{:}22{:}39{.}547$ you can kind of modulate the response.

NOTE Confidence: 0.9242995

00:22:39.550 --> 00:22:41.706 My question then is you know one

NOTE Confidence: 0.9242995

 $00{:}22{:}41.706 \dashrightarrow 00{:}22{:}43.659$ would think that would need

NOTE Confidence: 0.9242995

 $00{:}22{:}43.659 \dashrightarrow 00{:}22{:}45.269$ to be tempered over time.

NOTE Confidence: 0.9242995

 $00{:}22{:}45{.}270 \dashrightarrow 00{:}22{:}47{.}706$ So for example you might say well

NOTE Confidence: 0.9242995

 $00:22:47.706 \longrightarrow 00:22:50.818$ we need to really go after and kill

NOTE Confidence: 0.9242995

 $00{:}22{:}50{.}818 \dashrightarrow 00{:}22{:}53{.}596$ all the cancer cells full throttle

- NOTE Confidence: 0.9242995
- $00:22:53.596 \rightarrow 00:22:56.123$ initially and then we need to ease up
- NOTE Confidence: 0.9242995
- $00:22:56.123 \rightarrow 00:22:58.860$ a bit and start actually using
- NOTE Confidence: 0.9242995
- $00:22:58.860 \longrightarrow 00:23:01.891$ that brake pedal that was there to
- NOTE Confidence: 0.9242995
- $00{:}23{:}01{.}891 \dashrightarrow 00{:}23{:}04{.}033$ alleviate some of the side effects
- NOTE Confidence: 0.9242995
- $00{:}23{:}04{.}033 \dashrightarrow 00{:}23{:}07{.}500$ that might come from an overabundance
- NOTE Confidence: 0.9242995
- $00:23:07.500 \dashrightarrow 00:23:11.310$ of cytokines or T cell response.
- NOTE Confidence: 0.9242995
- $00:23:11.310 \longrightarrow 00:23:14.607$ So how do you do that with
- NOTE Confidence: 0.9242995
- 00:23:14.607 --> 00:23:15.549 cellular the rapeutics?
- NOTE Confidence: 0.9242995
- $00:23:15.550 \rightarrow 00:23:18.628$ My understanding of how cellular
- NOTE Confidence: 0.9242995
- 00:23:18.628 --> 00:23:22.254 therapies work and granted my
- NOTE Confidence: 0.9242995
- $00{:}23{:}22{.}254 \dashrightarrow 00{:}23{:}24{.}536$ understanding is very pedestrian, is
- NOTE Confidence: 0.9242995
- 00:23:24.536 --> 00:23:27.392 really that you take these cells out,
- NOTE Confidence: 0.9242995
- $00{:}23{:}27{.}400 \dashrightarrow 00{:}23{:}28{.}965$ you genetically engineer them and NOTE Confidence: 0.9242995
- $00:23:28.965 \rightarrow 00:23:31.279$ you give them back to the patient.
- NOTE Confidence: 0.9242995
- $00:23:31.280 \longrightarrow 00:23:34.808$ So is there a need to tailor this
- NOTE Confidence: 0.9242995

 $00:23:34.808 \rightarrow 00:23:38.752$ over time to kind of give patients

NOTE Confidence: 0.9242995

 $00{:}23{:}38{.}752 \dashrightarrow 00{:}23{:}41{.}485$ different sets of T cells with

NOTE Confidence: 0.9242995

 $00:23:41.485 \longrightarrow 00:23:43.530$ different either hyper boost or

NOTE Confidence: 0.9242995

 $00:23:43.614 \rightarrow 00:23:46.079$ brake pedal capacity over time?

NOTE Confidence: 0.9313311

 $00{:}23{:}46{.}720 \dashrightarrow 00{:}23{:}48{.}960$ This is another excellent question.

NOTE Confidence: 0.9313311

00:23:48.960 - 00:23:51.680 In fact, by taking the T cells out,

NOTE Confidence: 0.9313311

 $00:23:51.680 \longrightarrow 00:23:53.552$ there are a lot of ways

NOTE Confidence: 0.9313311

 $00:23:53.552 \rightarrow 00:23:54.800$ you can engineer them.

NOTE Confidence: 0.9313311

 $00{:}23{:}54{.}800 \dashrightarrow 00{:}23{:}57{.}116$ So you can change the brake,

NOTE Confidence: 0.9313311

 $00:23:57.120 \longrightarrow 00:23:58.480$ put the gas pedal on,

NOTE Confidence: 0.9313311

 $00{:}23{:}58{.}480 \dashrightarrow 00{:}24{:}00{.}880$ and in addition you can change the structure.

NOTE Confidence: 0.9313311

 $00:24:00.880 \rightarrow 00:24:03.365$ You can also put in control elements

NOTE Confidence: 0.9313311

00:24:03.365 --> 00:24:05.520 so that you can wipe them out when

NOTE Confidence: 0.9313311

 $00:24:05.520 \longrightarrow 00:24:07.550$ you no longer need them. For example,

NOTE Confidence: 0.9313311

 $00{:}24{:}07{.}550 \dashrightarrow 00{:}24{:}10{.}988$ if you put a queue switch in the T cells,

NOTE Confidence: 0.9313311

 $00:24:10.988 \longrightarrow 00:24:12.473$ let them do the job,

- NOTE Confidence: 0.9313311
- $00:24:12.480 \longrightarrow 00:24:14.560$ and when the CAR T clear the cancer,

00:24:14.560 --> 00:24:16.352 you no longer need so much CAR

NOTE Confidence: 0.9313311

 $00{:}24{:}16.352 \dashrightarrow 00{:}24{:}18.079 \ {\rm T}$ that could be problematic.

NOTE Confidence: 0.9313311

 $00:24:18.080 \longrightarrow 00:24:22.132$ Later on you can give the

NOTE Confidence: 0.9313311

 $00:24:22.132 \longrightarrow 00:24:24.986$ patient a small molecule

NOTE Confidence: 0.9313311

 $00{:}24{:}24{.}986 \dashrightarrow 00{:}24{:}27{.}472$ that can turn on the Q switch so

NOTE Confidence: 0.9313311

 $00{:}24{:}27{.}472 \dashrightarrow 00{:}24{:}29{.}593$ to eliminate the T cells later on.

NOTE Confidence: 0.9313311

 $00{:}24{:}29{.}600 \dashrightarrow 00{:}24{:}31{.}520$ Those are some of the strategies

NOTE Confidence: 0.9313311

 $00{:}24{:}31{.}520 \dashrightarrow 00{:}24{:}35{.}902$ and in addition we now create a

NOTE Confidence: 0.9313311

00:24:35.902 --> 00:24:38.309 new strategy by protein design

NOTE Confidence: 0.9313311

 $00:24:38.309 \longrightarrow 00:24:40.990$ by fusing a small piece of tail

NOTE Confidence: 0.9313311

 $00{:}24{:}41.073 \dashrightarrow 00{:}24{:}43.417$ to the T cell so that they are

NOTE Confidence: 0.92892903

 $00:24:45.620 \longrightarrow 00:24:47.126$ more long lasting,

NOTE Confidence: 0.92892903

 $00{:}24{:}47{.}126 \dashrightarrow 00{:}24{:}49{.}134$ they persist for longer.

NOTE Confidence: 0.92892903

 $00{:}24{:}49{.}140 \dashrightarrow 00{:}24{:}51{.}372$ So those are the several different

 $00{:}24{:}51{.}372 \dashrightarrow 00{:}24{:}54{.}393$ strategies we can utilize to make the

NOTE Confidence: 0.92892903

00:24:54.393 --> 00:24:57.459 T cell more sophisticated in order

NOTE Confidence: 0.92892903

 $00{:}24{:}57{.}460 \dashrightarrow 00{:}24{:}59{.}485$ for us to utilize the T cell to

NOTE Confidence: 0.92892903

 $00{:}24{:}59{.}485 \dashrightarrow 00{:}25{:}01{.}015$ treat cancer better without

NOTE Confidence: 0.92892903

00:25:01.015 - 00:25:03.220 doing too much damage to the body,

NOTE Confidence: 0.93666536

 $00:25:04.350 \longrightarrow 00:25:07.110$ so that changing the structure

NOTE Confidence: 0.93666536

 $00:25:07.110 \longrightarrow 00:25:08.390$ to make them last longer.

NOTE Confidence: 0.93666536

 $00:25:08.390 \rightarrow 00:25:10.567$ That sounds like that third strategy that

NOTE Confidence: 0.93666536

 $00{:}25{:}10.567 \dashrightarrow 00{:}25{:}12.947$ you were talking about redesigning the car,

NOTE Confidence: 0.93666536

 $00:25:12.950 \longrightarrow 00:25:16.190$ is that right? Absolutely.

NOTE Confidence: 0.93666536

 $00{:}25{:}16.190 \dashrightarrow 00{:}25{:}19.070$ And so again, I can see how many

NOTE Confidence: 0.93666536

 $00{:}25{:}19.070 \dashrightarrow 00{:}25{:}21.799$ of these are complementary, right?

NOTE Confidence: 0.93666536

 $00{:}25{:}21.799 \dashrightarrow 00{:}25{:}24.431$ You want the T cells to last longer

NOTE Confidence: 0.93666536

 $00{:}25{:}24{.}431 \dashrightarrow 00{:}25{:}26{.}630$ and to maintain their memory.

NOTE Confidence: 0.93666536

 $00:25:26.630 \rightarrow 00:25:28.724$ Presumably that could even have an

NOTE Confidence: 0.93666536

 $00:25:28.724 \rightarrow 00:25:31.509$ impact in terms of reducing recurrence.

- NOTE Confidence: 0.93666536
- 00:25:31.510 --> 00:25:33.785 So, you know, maybe the T cells
- NOTE Confidence: 0.93666536
- $00{:}25{:}33{.}785 \dashrightarrow 00{:}25{:}35{.}920$ wipe out your initial cancer,
- NOTE Confidence: 0.93666536
- $00:25:35.920 \longrightarrow 00:25:38.200$ but you'll always have this
- NOTE Confidence: 0.93666536
- 00:25:38.200 --> 00:25:39.720 residual risk of recurrence.
- NOTE Confidence: 0.93666536
- $00:25:39.720 \rightarrow 00:25:42.411$ And so if the T cells retain some memory
- NOTE Confidence: 0.93666536
- 00:25:42.411 -> 00:25:45.160 and if enough of them are still around,
- NOTE Confidence: 0.93666536
- $00:25:45.160 \rightarrow 00:25:47.450$ then presumably they can monitor
- NOTE Confidence: 0.93666536
- $00{:}25{:}47{.}450 \dashrightarrow 00{:}25{:}50{.}675$ the situation and get rid of cancer
- NOTE Confidence: 0.93666536
- $00{:}25{:}50.675 \dashrightarrow 00{:}25{:}53.231$ cells early before they even become
- NOTE Confidence: 0.93666536
- $00{:}25{:}53{.}231 \dashrightarrow 00{:}25{:}56{.}304$ a cancer recurrence down the line.
- NOTE Confidence: 0.93666536
- $00:25:56.304 \longrightarrow 00:25:58.096$ On the other hand,
- NOTE Confidence: 0.93666536
- 00:25:58.100 --> 00:26:01.277 I do like the idea of the kill switch
- NOTE Confidence: 0.93666536
- 00:26:01.277 --> 00:26:03.770 because we want to make sure that NOTE Confidence: 0.93666536
- $00:26:03.770 \longrightarrow 00:26:05.858$ we're not having an overabundance
- NOTE Confidence: 0.93666536
- $00{:}26{:}05{.}858 \dashrightarrow 00{:}26{:}08{.}188$ of this cellular activity that
- NOTE Confidence: 0.93666536

 $00:26:08.188 \longrightarrow 00:26:10.538$ could cause other side effects.

NOTE Confidence: 0.93666536

00:26:10.540 --> 00:26:13.760 So how do you kind of engineer

NOTE Confidence: 0.93666536

 $00:26:13.760 \longrightarrow 00:26:15.140$ this delicate balance?

NOTE Confidence: 0.93666536

 $00:26:15.140 \rightarrow 00:26:17.504$ It's almost like a Symphony where

NOTE Confidence: 0.93666536

 $00{:}26{:}17.504 \dashrightarrow 00{:}26{:}19.992$ you need certain parts of the

NOTE Confidence: 0.93666536

00:26:19.992 --> 00:26:22.072 orchestra playing at certain levels

NOTE Confidence: 0.93666536

 $00{:}26{:}22.072 \dashrightarrow 00{:}26{:}24.659$ in certain times and not in others.

NOTE Confidence: 0.93507236

 $00:26:26.110 \longrightarrow 00:26:27.902$ That's a nice analogy.

NOTE Confidence: 0.93507236

00:26:27.902 --> 00:26:31.790 I like symphonies too and the

NOTE Confidence: 0.93507236

 $00{:}26{:}31.790 \dashrightarrow 00{:}26{:}34.850$ balance between the persistence and

NOTE Confidence: 0.93507236

 $00:26:34.850 \longrightarrow 00:26:37.910$ the durability is absolutely the

NOTE Confidence: 0.93507236

 $00:26:37.910 \longrightarrow 00:26:41.746$ the goal for solid tumors.

NOTE Confidence: 0.93507236

 $00{:}26{:}41.750 \dashrightarrow 00{:}26{:}43.829$ The problem is that they don't last

NOTE Confidence: 0.93507236

 $00:26:43.829 \longrightarrow 00:26:45.715$ long enough and or at least last

NOTE Confidence: 0.93507236

 $00:26:45.715 \rightarrow 00:26:47.750$ long enough in the tumor environment.

NOTE Confidence: 0.93507236

 $00:26:47.750 \longrightarrow 00:26:50.662$ So by a new strategy we now

- NOTE Confidence: 0.93507236
- $00:26:50.662 \rightarrow 00:26:53.139$ call the protein fusion tail,

 $00:26:53.140 \longrightarrow 00:26:55.716$ we allow the T cell to be more

NOTE Confidence: 0.93507236

 $00:26:55.716 \rightarrow 00:26:57.732$ memory like which means they

NOTE Confidence: 0.93507236

 $00{:}26{:}57.732 \dashrightarrow 00{:}27{:}00.312$ can remember the cancer cells or

NOTE Confidence: 0.93507236

 $00{:}27{:}00{.}312 \dashrightarrow 00{:}27{:}02{.}740$ cancer cells antigen for longer.

NOTE Confidence: 0.93507236

00:27:02.740 --> 00:27:04.492 And by doing so,

NOTE Confidence: 0.93507236

 $00:27:04.492 \longrightarrow 00:27:07.120$ we enable the T cell therapy

NOTE Confidence: 0.93507236

 $00{:}27{:}07{.}225 \dashrightarrow 00{:}27{:}09{.}180$ to have more durable effect,

NOTE Confidence: 0.93507236

 $00{:}27{:}09{.}180 \dashrightarrow 00{:}27{:}11{.}820$ suppress the cancer growth for longer,

NOTE Confidence: 0.93507236

 $00:27:11.820 \longrightarrow 00:27:16.746$ preventing the relapse and

NOTE Confidence: 0.93507236

 $00:27:16.746 \longrightarrow 00:27:19.683$ therefore prolonged survival benefit.

NOTE Confidence: 0.93507236

 $00{:}27{:}19.683 \dashrightarrow 00{:}27{:}21.838$ So those are the strategies

NOTE Confidence: 0.93507236

 $00:27:21.838 \longrightarrow 00:27:23.389$ we're testing right now.

NOTE Confidence: 0.93813497

 $00{:}27{:}24.390 \dashrightarrow 00{:}27{:}26.346$ In terms of testing these strategies,

NOTE Confidence: 0.93813497

 $00{:}27{:}26.350 \dashrightarrow 00{:}27{:}29.346$ have these been taken into the clinic?

 $00:27:29.350 \longrightarrow 00:27:31.762$ Do we have human data on

NOTE Confidence: 0.93813497

 $00:27:31.762 \longrightarrow 00:27:33.910$ whether or not these work?

NOTE Confidence: 0.93813497

 $00{:}27{:}33{.}910 \dashrightarrow 00{:}27{:}35{.}355$ Is this something that patients

NOTE Confidence: 0.93813497

 $00{:}27{:}35{.}355 \dashrightarrow 00{:}27{:}37{.}689$ can go in and talk to their doctor

NOTE Confidence: 0.93813497

 $00{:}27{:}37{.}689 \dashrightarrow 00{:}27{:}39{.}628$ about today or when do you think

NOTE Confidence: 0.93813497

 $00:27:39.691 \longrightarrow 00:27:41.306$ that might be the situation?

NOTE Confidence: 0.93813497

 $00:27:41.710 \longrightarrow 00:27:45.478$ For now, the FDA has approved 6 cell therapy

NOTE Confidence: 0.93813497

 $00:27:45.478 \longrightarrow 00:27:48.574$ products for the patients

NOTE Confidence: 0.93813497

 $00:27:48.574 \longrightarrow 00:27:50.750$ within those indications,

NOTE Confidence: 0.93813497

 $00{:}27{:}50.750 \dashrightarrow 00{:}27{:}53.822$ the doctor will see if they fit the

NOTE Confidence: 0.93813497

 $00{:}27{:}53.822 \dashrightarrow 00{:}27{:}56.469$ criteria to receive those the rapies.

NOTE Confidence: 0.93813497

 $00{:}27{:}56.470 \dashrightarrow 00{:}27{:}58.150$ But unfortunately for solid tumors,

NOTE Confidence: 0.93813497

 $00{:}27{:}58{.}150 \dashrightarrow 00{:}28{:}01{.}270$ no cell therapy has been approved

NOTE Confidence: 0.93813497

00:28:01.270 -> 00:28:06.143 yet by the FDA and there are many,

NOTE Confidence: 0.93813497

 $00{:}28{:}06{.}143 \dashrightarrow 00{:}28{:}08{.}908$ many clinical trials ongoing over

NOTE Confidence: 0.93813497

00:28:08.908 --> 00:28:11.964 1000 cell therapy clinical trials now

- NOTE Confidence: 0.93813497
- $00:28:11.964 \rightarrow 00:28:15.200$ and the patient can see if they are

 $00{:}28{:}15{.}200 \dashrightarrow 00{:}28{:}17{.}625$ right for enrollment of the clinical trials.

NOTE Confidence: 0.93813497

 $00:28:17.630 \rightarrow 00:28:20.324$ In the newer strategy we're talking

NOTE Confidence: 0.93813497

 $00:28:20.324 \rightarrow 00:28:23.064$ about of course the goal is

NOTE Confidence: 0.93813497

00:28:23.064 --> 00:28:25.790 to balance efficacy to safety

NOTE Confidence: 0.93813497

 $00:28:25.790 \longrightarrow 00:28:28.870$ and hopefully this can become the

NOTE Confidence: 0.93813497

 $00:28:28.870 \longrightarrow 00:28:30.470$ clinical product in the future.

NOTE Confidence: 0.93813497

 $00:28:30.470 \longrightarrow 00:28:32.336$ But as of now they're not

NOTE Confidence: 0.93813497

 $00:28:32.336 \longrightarrow 00:28:33.269$ approved products yet.

NOTE Confidence: 0.9233917

 $00{:}28{:}33{.}830 \dashrightarrow 00{:}28{:}36{.}526$ Doctor Sidi Chen is an associate professor of

NOTE Confidence: 0.9233917

 $00{:}28{:}36{.}526 \dashrightarrow 00{:}28{:}38{.}990$ genetics at the Yale School of Medicine.

NOTE Confidence: 0.9233917

 $00{:}28{:}38{.}990 \dashrightarrow 00{:}28{:}41{.}114$ If you have questions, the address

NOTE Confidence: 0.9233917

00:28:41.114 --> 00:28:43.439 is Cancer Answers at Yale dot Edu,

NOTE Confidence: 0.9233917

 $00{:}28{:}43{.}440 \dashrightarrow 00{:}28{:}45{.}690$ and past editions of the program

NOTE Confidence: 0.9233917

 $00:28:45.690 \rightarrow 00:28:47.911$ are available in audio and written

 $00{:}28{:}47{.}911 \dashrightarrow 00{:}28{:}48{.}857$ form at yale cancercenter.org.

NOTE Confidence: 0.9233917

00:28:48.857 --> 00:28:51.233 We hope you'll join us next week to

NOTE Confidence: 0.9233917

 $00{:}28{:}51{.}233 \dashrightarrow 00{:}28{:}53{.}042$ learn more about the fight against

NOTE Confidence: 0.9233917

 $00{:}28{:}53.042 \dashrightarrow 00{:}28{:}54.840$ cancer here on Connecticut Public Radio.

NOTE Confidence: 0.9233917

 $00{:}28{:}54{.}840 \dashrightarrow 00{:}28{:}57{.}492$ Funding for Yale Cancer Answers is

NOTE Confidence: 0.9233917

 $00{:}28{:}57{.}492 \dashrightarrow 00{:}29{:}00{.}000$ provided by Smilow Cancer Hospital.