WEBVTT

00:00:00.000 --> 00:00:01.965 Funding for Yale Cancer Answers NOTE Confidence: 0.9549644 00:00:01.965 --> 00:00:03.930 is provided by Smilow Cancer NOTE Confidence: 0.9549644 00:00:03.997 --> 00:00:05.697 Hospital and AstraZeneca. NOTE Confidence: 0.977658900000001 $00:00:07.720 \rightarrow 00:00:09.658$ Welcome to Yale Cancer Answers with NOTE Confidence: 0.977658900000001 00:00:09.658 --> 00:00:11.817 your host doctor Anees Chagpar. NOTE Confidence: 0.97765890000001 $00:00:11.817 \rightarrow 00:00:13.817$ Yale Cancer Answers features the NOTE Confidence: 0.977658900000001 $00:00:13.817 \rightarrow 00:00:16.193$ latest information on cancer care by NOTE Confidence: 0.977658900000001 $00:00:16.193 \rightarrow 00:00:17.677$ welcoming oncologists and specialists NOTE Confidence: 0.977658900000001 00:00:17.677 -> 00:00:20.266 who are on the forefront of the NOTE Confidence: 0.97765890000001 00:00:20.266 --> 00:00:22.480 battle to fight cancer. This week, NOTE Confidence: 0.977658900000001 00:00:22.480 --> 00:00:24.325 it's a conversation about DNA NOTE Confidence: 0.977658900000001 00:00:24.325 --> 00:00:26.170 repair with Doctor Megan King. NOTE Confidence: 0.977658900000001 00:00:26.170 --> 00:00:28.300 Doctor King is an associate professor NOTE Confidence: 0.977658900000001 00:00:28.300 --> 00:00:30.599 of cell biology and of molecular, NOTE Confidence: 0.977658900000001 $00:00:30.600 \rightarrow 00:00:32.076$ cellular, and developmental biology NOTE Confidence: 0.97765890000001

00:00:32.076 --> 00:00:34.290 at the Yale School of Medicine,

NOTE Confidence: 0.977658900000001

00:00:34.290 --> 00:00:36.504 where Doctor Chagpar is a

NOTE Confidence: 0.977658900000001

00:00:36.504 --> 00:00:37.980 professor of surgical oncology.

NOTE Confidence: 0.98509663

 $00{:}00{:}39{.}430 \dashrightarrow 00{:}00{:}42.014$ Megan, maybe we can start off with you

NOTE Confidence: 0.98509663

 $00{:}00{:}42.014 \dashrightarrow 00{:}00{:}44.550$ telling us a little bit about yourself

NOTE Confidence: 0.98509663

00:00:44.550 --> 00:00:47.493 and about your research and how you got NOTE Confidence: 0.98509663

 $00{:}00{:}47{.}493 \dashrightarrow 00{:}00{:}49{.}605$ involved in this research project to

NOTE Confidence: 0.98509663

 $00:00:49.610 \longrightarrow 00:00:50.314$ begin with.

NOTE Confidence: 0.98509663

 $00{:}00{:}50{.}314 \dashrightarrow 00{:}00{:}52{.}426$ Yeah, so it's very interesting thinking

NOTE Confidence: 0.98509663

 $00:00:52.426 \dashrightarrow 00:00:54.869$ back to what drew me towards science.

NOTE Confidence: 0.98509663

00:00:54.870 -> 00:00:56.976 I'm from a family of engineers,

NOTE Confidence: 0.98509663

 $00:00:56.980 \rightarrow 00:00:59.086$ actually including both of my parents,

NOTE Confidence: 0.98509663

 $00:00:59.090 \dashrightarrow 00:01:01.540$ but I always gravitated towards science,

NOTE Confidence: 0.98509663

 $00:01:01.540 \rightarrow 00:01:04.348$ and in particular as a high school student,

NOTE Confidence: 0.98509663

00:01:04.350 --> 00:01:06.110 I took anatomy and Physiology,

NOTE Confidence: 0.98509663

 $00:01:06.110 \longrightarrow 00:01:07.945$ and it was actually the

- NOTE Confidence: 0.98509663
- $00:01:07.945 \longrightarrow 00:01:09.413$ section of my textbook
- NOTE Confidence: 0.98509663
- $00{:}01{:}09{.}420 \dashrightarrow 00{:}01{:}11{.}835$ on cancer that really provided for me,
- NOTE Confidence: 0.98509663
- $00{:}01{:}11{.}840 \dashrightarrow 00{:}01{:}14{.}088$ I think the first kind of window into
- NOTE Confidence: 0.98509663
- $00:01:14.088 \dashrightarrow 00:01:16.587$ how a scientist could have a positive
- NOTE Confidence: 0.98509663
- 00:01:16.587 --> 00:01:19.986 impact on human health in a way that was
- NOTE Confidence: 0.98509663
- $00:01:19.986 \rightarrow 00:01:22.182$ different from becoming a medical doctor,
- NOTE Confidence: 0.98509663
- $00:01:22.190 \longrightarrow 00:01:24.574$ which I think all of us are a
- NOTE Confidence: 0.98509663
- $00:01:24.574 \longrightarrow 00:01:26.670$ little bit more familiar with,
- NOTE Confidence: 0.98509663
- $00:01:26.670 \longrightarrow 00:01:27.708$ certainly as children.
- NOTE Confidence: 0.98509663
- $00{:}01{:}27.708 \dashrightarrow 00{:}01{:}29.784$ And so I've been reflecting on
- NOTE Confidence: 0.98509663
- $00:01:29.784 \longrightarrow 00:01:31.805$ that recently because it's been a
- NOTE Confidence: 0.98509663
- $00{:}01{:}31{.}805 \dashrightarrow 00{:}01{:}33{.}839$ bit of a circuitous route that's
- NOTE Confidence: 0.98509663
- $00:01:33.839 \dashrightarrow 00:01:35.987$ brought me back to Cancer Research.
- NOTE Confidence: 0.98509663
- $00{:}01{:}35{.}990 \dashrightarrow 00{:}01{:}37{.}745$ I really trended towards very
- NOTE Confidence: 0.98509663
- $00{:}01{:}37.745 \dashrightarrow 00{:}01{:}39.500$ fundamental kind of basic science.
- NOTE Confidence: 0.98509663

 $00:01:39.500 \rightarrow 00:01:41.750$ Questions for my initial training

NOTE Confidence: 0.98509663

 $00{:}01{:}41.750 \dashrightarrow 00{:}01{:}44.000$ as an undergraduate and graduate

NOTE Confidence: 0.98509663

 $00:01:44.068 \longrightarrow 00:01:46.595$ student and even into my

NOTE Confidence: 0.98509663

 $00:01:46.595 \rightarrow 00:01:48.500$ postdoc period where one typically

NOTE Confidence: 0.98509663

 $00:01:48.500 \dashrightarrow 00:01:51.125$ is defining the kind of areas of

NOTE Confidence: 0.98509663

 $00:01:51.125 \rightarrow 00:01:53.100$ research that they will pursue,

NOTE Confidence: 0.98509663

 $00:01:53.100 \rightarrow 00:01:55.100$ and in their independent laboratory.

NOTE Confidence: 0.98509663

 $00{:}01{:}55{.}100 \dashrightarrow 00{:}01{:}57{.}440$ But I discovered a connection between

NOTE Confidence: 0.98509663

 $00{:}01{:}57{.}440 \dashrightarrow 00{:}01{:}59{.}899$ the cell biology of the nucleus,

NOTE Confidence: 0.98509663

 $00:01:59.900 \longrightarrow 00:02:02:02.300$ which is something that I had

NOTE Confidence: 0.98509663

 $00:02:02.300 \longrightarrow 00:02:03.900$ been training with

NOTE Confidence: 0.98509663

00:02:03.900 --> 00:02:05.500 Gunter Blobel at Rockefeller

NOTE Confidence: 0.98509663

00:02:05.500 --> 00:02:07.100 University in Genome Integrity,

NOTE Confidence: 0.98509663

 $00{:}02{:}07{.}100 \dashrightarrow 00{:}02{:}09{.}590$ so that is the mechanisms that

NOTE Confidence: 0.98509663

 $00:02:09.590 \longrightarrow 00:02:11.708$ maintain the DNA blueprint

NOTE Confidence: 0.98509663

 $00:02:11.708 \longrightarrow 00:02:14.231$ as it should be and that was

- NOTE Confidence: 0.98509663
- $00:02:14.231 \rightarrow 00:02:16.307$ really just something that I had

 $00:02:16.307 \longrightarrow 00:02:18.349$ not focused on before

NOTE Confidence: 0.98509663

 $00:02:18.350 \longrightarrow 00:02:20.989$ but it really changed the direction of

NOTE Confidence: 0.98509663

 $00:02:20.989 \rightarrow 00:02:23.530$ my research and I became very interested

NOTE Confidence: 0.98509663

00:02:23.530 - 00:02:26.380 in how aspects of how a cell works,

NOTE Confidence: 0.98509663

 $00{:}02{:}26.380 \dashrightarrow 00{:}02{:}28.858$ are able to contribute to the mechanisms

NOTE Confidence: 0.98509663

 $00:02:28.858 \dashrightarrow 00:02:30.760$ that maintain that genetic code.

NOTE Confidence: 0.98509663

 $00{:}02{:}30.760 \dashrightarrow 00{:}02{:}32.590$ So tell us more about

NOTE Confidence: 0.988603650000001

 $00:02:32.590 \longrightarrow 00:02:35.430$ that. I think some of us can

NOTE Confidence: 0.988603650000001

 $00:02:35.430 \longrightarrow 00:02:37.804$ remember back to junior high biology

NOTE Confidence: 0.988603650000001

 $00:02:37.804 \rightarrow 00:02:41.069$ where we kind of know what a cell is.

NOTE Confidence: 0.988603650000001

 $00{:}02{:}41.070 \dashrightarrow 00{:}02{:}43.622$ And we know what a nucleus is and

NOTE Confidence: 0.988603650000001

 $00{:}02{:}43.622 \dashrightarrow 00{:}02{:}45.771$ housed within that nucleus is the

NOTE Confidence: 0.988603650000001

 $00{:}02{:}45{.}771 \dashrightarrow 00{:}02{:}47{.}931$ DNA which is responsible for that

NOTE Confidence: 0.988603650000001

 $00{:}02{:}48.000 \dashrightarrow 00{:}02{:}49.970$ genetic blueprint as you say.

 $00:02:49.970 \longrightarrow 00:02:52.189$ So tell us more about the connection

NOTE Confidence: 0.988603650000001

 $00{:}02{:}52.189 \dashrightarrow 00{:}02{:}54.790$ that you found between how a cell

NOTE Confidence: 0.988603650000001

00:02:54.790 --> 00:02:56.374 functions and genomic integrity.

NOTE Confidence: 0.988603650000001

 $00:02:56.380 \longrightarrow 00:02:57.800$ Yeah, so I was

NOTE Confidence: 0.9847528

 $00{:}02{:}57{.}800 \dashrightarrow 00{:}02{:}59{.}894$ also fascinated with this

NOTE Confidence: 0.9847528

 $00:02:59.894 \longrightarrow 00:03:02.428$ idea of the the nucleus which

NOTE Confidence: 0.9847528

 $00:03:02.428 \rightarrow 00:03:04.920$ is the organelle that houses the DNA,

NOTE Confidence: 0.9847528

 $00:03:04.920 \longrightarrow 00:03:07.056$ being kind of the brain.

NOTE Confidence: 0.9847528

 $00{:}03{:}07{.}056 \dashrightarrow 00{:}03{:}09{.}192$ Having all of the kind of

NOTE Confidence: 0.9847528

 $00:03:09.192 \longrightarrow 00:03:11.080$ control and that plan

NOTE Confidence: 0.9847528

 $00{:}03{:}11.080 \dashrightarrow 00{:}03{:}13.870$ for the cell, but I think one of the

NOTE Confidence: 0.9847528

 $00:03:13.870 \rightarrow 00:03:16.177$ things that maybe isn't always captured

NOTE Confidence: 0.9847528

 $00{:}03{:}16.177 \dashrightarrow 00{:}03{:}19.423$ when we kind of make that diorama during

NOTE Confidence: 0.9847528

 $00:03:19.423 \rightarrow 00:03:22.356$ you know grade school is that actually

NOTE Confidence: 0.9847528

 $00:03:22.360 \longrightarrow 00:03:25.368$ it's not just a big ball of yarn,

NOTE Confidence: 0.9847528

 $00:03:25.370 \longrightarrow 00:03:28.010$ but actually the DNA has lots of different

 $00{:}03{:}28{.}010 \dashrightarrow 00{:}03{:}30{.}393$ regions and these regions are important

NOTE Confidence: 0.9847528

 $00:03:30.393 \rightarrow 00:03:32.883$ for different aspects of that blueprint.

NOTE Confidence: 0.9847528

 $00:03:32.890 \longrightarrow 00:03:35.898$ And they're not all created equal.

NOTE Confidence: 0.9847528

 $00:03:35.900 \rightarrow 00:03:38.644$ There are specific regions of the DNA

NOTE Confidence: 0.9847528

 $00:03:38.644 \longrightarrow 00:03:41.550$ that are far more prone to damage.

NOTE Confidence: 0.9847528

 $00{:}03{:}41.550 \dashrightarrow 00{:}03{:}43.727$ And there are also mechanisms to repair

NOTE Confidence: 0.9847528

 $00:03:43.727 \dashrightarrow 00:03:45.949$ that damage that may be quite specific,

NOTE Confidence: 0.9847528

 $00{:}03{:}45{.}950 \dashrightarrow 00{:}03{:}48{.}960$ so if you have a leak

NOTE Confidence: 0.9847528

00:03:49.046 --> 00:03:51.914 in a pipe you may need a plumber, right?

NOTE Confidence: 0.9847528

00:03:51.914 --> 00:03:53.798 But if you're siding

NOTE Confidence: 0.9847528

00:03:53.798 --> 00:03:54.740 has gone downhill,

NOTE Confidence: 0.9847528

00:03:54.740 --> 00:03:57.248 maybe you need someone who is

NOTE Confidence: 0.9847528

 $00{:}03{:}57{.}248 \dashrightarrow 00{:}03{:}58{.}818$ more like a Carpenter.

NOTE Confidence: 0.9847528

 $00{:}03{:}58.820 \dashrightarrow 00{:}03{:}59.696$ Or for any

NOTE Confidence: 0.9847528

00:03:59.696 --> 00:04:01.740 new paint you're going

 $00:04:01.808 \longrightarrow 00:04:04.160$ to have a different kind of approach

NOTE Confidence: 0.9847528

 $00:04:04.160 \longrightarrow 00:04:06.038$ depending on what the issue is.

NOTE Confidence: 0.9847528

00:04:06.040 --> 00:04:07.924 And it turns out for cells,

NOTE Confidence: 0.9847528

 $00{:}04{:}07{.}924 \dashrightarrow 00{:}04{:}08{.}866$ that's similar.

NOTE Confidence: 0.9847528

 $00{:}04{:}08{.}870 \dashrightarrow 00{:}04{:}10{.}154$ There are actually different

NOTE Confidence: 0.9847528

 $00{:}04{:}10{.}154 \dashrightarrow 00{:}04{:}11{.}759$ DNA repair mechanisms and you

NOTE Confidence: 0.9847528

 $00:04:11.760 \longrightarrow 00:04:14.301$ really need to use the right mechanism

NOTE Confidence: 0.9847528

 $00:04:14.301 \longrightarrow 00:04:16.509$ for the right kind of damage,

NOTE Confidence: 0.9847528

 $00{:}04{:}16{.}510$ --> $00{:}04{:}19{.}255$ and it turns out that much of that is NOTE Confidence: 0.9847528

 $00{:}04{:}19.255 \dashrightarrow 00{:}04{:}21.141$ actually dictated by these different

NOTE Confidence: 0.9847528

 $00{:}04{:}21{.}141 \dashrightarrow 00{:}04{:}23{.}876$ flavors of the regions of DNA and

NOTE Confidence: 0.9847528

 $00{:}04{:}23.876 \dashrightarrow 00{:}04{:}25.866$ also physically where those different

NOTE Confidence: 0.9847528

 $00{:}04{:}25.866 \dashrightarrow 00{:}04{:}28.555$ regions of the DNA blueprint are

NOTE Confidence: 0.9847528

 $00{:}04{:}28.555 \dashrightarrow 00{:}04{:}30.380$ organized inside the nucleus,

NOTE Confidence: 0.9847528

00:04:30.380 --> 00:04:33.040 because it's a much more

NOTE Confidence: 0.9847528

 $00:04:33.040 \rightarrow 00:04:34.569$ compartmentalized kind of network

 $00:04:36.564 \longrightarrow 00:04:39.420$ than when we just again think of

NOTE Confidence: 0.9847528

00:04:39.508 --> 00:04:42.524 this string that has all of that

NOTE Confidence: 0.9847528

 $00:04:42.530 \longrightarrow 00:04:43.258$ coding material,

NOTE Confidence: 0.9847528

 $00{:}04{:}43.258 \dashrightarrow 00{:}04{:}44.350$ so it's not

NOTE Confidence: 0.98854697

 $00{:}04{:}44{.}350 \dashrightarrow 00{:}04{:}47{.}052$ just where the break occurs in the

NOTE Confidence: 0.98854697

 $00{:}04{:}47.052 \dashrightarrow 00{:}04{:}50.149$ DNA or what kind of a break it is,

NOTE Confidence: 0.98854697

 $00:04:50.150 \dashrightarrow 00:04:51.915$ whether it's a single strand

NOTE Confidence: 0.98854697

00:04:51.915 --> 00:04:54.150 break or a double strand break,

NOTE Confidence: 0.98854697

 $00{:}04{:}54{.}150 \dashrightarrow 00{:}04{:}55{.}598$ but where exactly it's

NOTE Confidence: 0.98854697

 $00{:}04{:}55{.}598 \dashrightarrow 00{:}04{:}57{.}046$ located within the nucleus.

NOTE Confidence: 0.98920226

 $00{:}04{:}57.760 \dashrightarrow 00{:}05{:}00.357$ We think about two components.

NOTE Confidence: 0.98920226

 $00:05:00.360 \rightarrow 00:05:02.580$ One exactly as you say physically,

NOTE Confidence: 0.98920226

 $00:05:02.580 \dashrightarrow 00:05:05.548$ where is that DNA break in the nucleus?

NOTE Confidence: 0.98920226

 $00{:}05{:}05{.}550 \dashrightarrow 00{:}05{:}07{.}405$ And then there's also the

NOTE Confidence: 0.98920226

 $00{:}05{:}07{.}405 \dashrightarrow 00{:}05{:}09{.}260$ other attributes of the DNA.

NOTE Confidence: 0.98920226

 $00:05:09.260 \dashrightarrow 00:05:12.599$ So DNA doesn't live on its own.

 $00:05:12.600 \rightarrow 00:05:14.910$ It's actually wrapped up and packaged

NOTE Confidence: 0.98920226

 $00{:}05{:}14.910 \dashrightarrow 00{:}05{:}16.896$ around proteins that are called

NOTE Confidence: 0.98920226

 $00{:}05{:}16.896 \dashrightarrow 00{:}05{:}19.170$ histones and this packaging is

NOTE Confidence: 0.98920226

 $00:05:19.170 \longrightarrow 00:05:21.712$ really important for whether a

NOTE Confidence: 0.98920226

 $00:05:21.712 \rightarrow 00:05:24.079$ particular gene may be expressed or not.

NOTE Confidence: 0.98920226

 $00{:}05{:}24.079 \dashrightarrow 00{:}05{:}26.522$ It turns out that a DNA break

NOTE Confidence: 0.98920226

 $00:05:26.522 \longrightarrow 00:05:29.190$ in a region of the genome

NOTE Confidence: 0.98920226

 $00:05:29.190 \longrightarrow 00:05:31.326$ that is coding for a protein,

NOTE Confidence: 0.98920226

 $00{:}05{:}31{.}330 \dashrightarrow 00{:}05{:}33{.}376$ so it's going to be transcribed

NOTE Confidence: 0.98920226

 $00:05:33.376 \dashrightarrow 00:05:35.543$ into the messenger RNA and then

NOTE Confidence: 0.98920226

 $00:05:35.543 \rightarrow 00:05:37.015$ translated into a protein.

NOTE Confidence: 0.98920226

 $00{:}05{:}37{.}020 \dashrightarrow 00{:}05{:}39{.}144$ Those regions of the genome are

NOTE Confidence: 0.98920226

 $00{:}05{:}39{.}144 \dashrightarrow 00{:}05{:}41{.}332$ a bit different than regions of

NOTE Confidence: 0.98920226

 $00:05:41.332 \rightarrow 00:05:43.426$ the genome that may be silent,

NOTE Confidence: 0.98920226

 $00{:}05{:}43{.}430 \dashrightarrow 00{:}05{:}46{.}364$ and so that also just leads to both some

 $00{:}05{:}46{.}364 \dashrightarrow 00{:}05{:}48{.}288$ challenges for DNA repair mechanisms

NOTE Confidence: 0.98920226

 $00{:}05{:}48.288 \dashrightarrow 00{:}05{:}50.586$ and also some activities that

NOTE Confidence: 0.98920226

 $00:05:50.657 \rightarrow 00:05:53.072$ may actually make it more prone to

NOTE Confidence: 0.98920226

 $00:05:53.072 \dashrightarrow 00:05:54.806$ the accumulation of DNA damage.

NOTE Confidence: 0.98920226

 $00{:}05{:}54.806 \dashrightarrow 00{:}05{:}57.242$ And so we think of both

NOTE Confidence: 0.98920226

 $00{:}05{:}57{.}242 \dashrightarrow 00{:}05{:}59{.}219$ where the break is

NOTE Confidence: 0.98920226

00:05:59.220 --> 00:05:59.581 physically,

NOTE Confidence: 0.98920226

 $00:05:59.581 \dashrightarrow 00:06:02.108$ and also where it is in context

NOTE Confidence: 0.98920226

 $00{:}06{:}02.108 \dashrightarrow 00{:}06{:}04.287$ of what else is happening in

NOTE Confidence: 0.98920226

 $00:06:04.287 \longrightarrow 00:06:06.017$ that region of the DNA.

 $00{:}06{:}06{.}400 \dashrightarrow 00{:}06{:}09{.}248$ So we know that DNA can incur various

NOTE Confidence: 0.98681915

 $00:06:09.248 \rightarrow 00:06:12.180$ forms of damage that can be in coding

NOTE Confidence: 0.98681915

 $00:06:12.180 \longrightarrow 00:06:14.849$ regions or in non coding regions.

NOTE Confidence: 0.98681915

 $00{:}06{:}14.850 \dashrightarrow 00{:}06{:}17.154$ How does that then evolve into

NOTE Confidence: 0.98681915

 $00:06:17.154 \longrightarrow 00:06:18.690$ your research with cancer?

NOTE Confidence: 0.98681915

 $00{:}06{:}18.690 \dashrightarrow 00{:}06{:}21.175$ So initially as I mentioned our

 $00:06:21.175 \longrightarrow 00:06:23.887$ interest was the idea that these

NOTE Confidence: 0.98681915

 $00{:}06{:}23.887 \dashrightarrow 00{:}06{:}25.857$ different locations in the nucleus

NOTE Confidence: 0.98681915

 $00:06:25.857 \dashrightarrow 00:06:28.654$ might be important for making sure that NOTE Confidence: 0.98681915

 $00:06:28.654 \rightarrow 00:06:31.401$ those breaks are repaired by the right NOTE Confidence: 0.98681915

 $00:06:31.401 \dashrightarrow 00:06:34.631$ process and in order to study that we NOTE Confidence: 0.98681915

00:06:34.631 --> 00:06:37.559 really need to be able to watch DNA NOTE Confidence: 0.98681915

00:06:37.560 -> 00:06:39.961 repair in a cell that's living while

NOTE Confidence: 0.98681915

 $00{:}06{:}39{.}961 \dashrightarrow 00{:}06{:}42{.}460$ it's happening and that as it turns out

NOTE Confidence: 0.98681915

 $00{:}06{:}42.460 \dashrightarrow 00{:}06{:}44.560$ is actually quite a difficult problem,

NOTE Confidence: 0.98681915

00:06:44.560 --> 00:06:47.710 and so over the past ten years or so, NOTE Confidence: 0.98681915

00:06:47.710 --> 00:06:50.254 one of the things that my group has NOTE Confidence: 0.98681915

 $00:06:50.254 \rightarrow 00:06:52.478$ invested in, is building so called

NOTE Confidence: 0.98681915

 $00{:}06{:}52{.}478 \dashrightarrow 00{:}06{:}54{.}752$ as says where we can actually watch

NOTE Confidence: 0.98681915

 $00:06:54.823 \longrightarrow 00:06:56.107$ a single DNA break,

NOTE Confidence: 0.98681915

 $00:06:56.110 \longrightarrow 00:06:57.566$ which we actually control.

NOTE Confidence: 0.98681915

 $00{:}06{:}57{.}566 \dashrightarrow 00{:}07{:}00{.}478$ So we induce the break to occur in

00:07:00.478 - 00:07:03.110 exactly the place where we want it to,

NOTE Confidence: 0.98681915

 $00{:}07{:}03.110 \dashrightarrow 00{:}07{:}05.342$ and then we actually follow the

NOTE Confidence: 0.98681915

 $00:07:05.342 \longrightarrow 00:07:08.127$ repair of that break in real time and

NOTE Confidence: 0.98681915

 $00:07:08.130 \longrightarrow 00:07:09.970$ once we built this system,

NOTE Confidence: 0.98681915

 $00:07:09.970 \longrightarrow 00:07:12.602$ we became very interested in how we might

NOTE Confidence: 0.98681915

 $00:07:12.602 \rightarrow 00:07:14.867$ leverage it to answer some important

NOTE Confidence: 0.98681915

 $00:07:14.867 \rightarrow 00:07:16.792$ questions that were really arising

NOTE Confidence: 0.98681915

 $00{:}07{:}16.792 \dashrightarrow 00{:}07{:}19.168$ in the field of cancer treatments.

NOTE Confidence: 0.98681915

00:07:19.170 --> 00:07:19.914 And really,

NOTE Confidence: 0.98681915

 $00:07:19.914 \longrightarrow 00:07:22.146$ I was driven towards those questions

NOTE Confidence: 0.98681915

 $00{:}07{:}22.146 \dashrightarrow 00{:}07{:}24.128$ through my interactions with my

NOTE Confidence: 0.98681915

00:07:24.128 --> 00:07:26.474 fantastic colleagues here

NOTE Confidence: 0.98681915

 $00{:}07{:}26{.}474 \dashrightarrow 00{:}07{:}29{.}226$ at the School of Medicine and at

NOTE Confidence: 0.98681915

00:07:29.226 --> 00:07:31.794 Yale Cancer Center who really brought

 $00:07:32.850 \rightarrow 00:07:35.522$ a way of connecting the kind of questions

NOTE Confidence: 0.98681915

 $00:07:35.522 \rightarrow 00:07:38.000$ that I had become interested in,

00:07:38.000 --> 00:07:40.808 again as a postdoc and kind of just

NOTE Confidence: 0.98681915

00:07:40.808 --> 00:07:42.198 looking through the microscope

NOTE Confidence: 0.98681915

 $00{:}07{:}42.198 \dashrightarrow 00{:}07{:}44.670$ to where we had a real need to

NOTE Confidence: 0.98681915

 $00{:}07{:}44.746 \dashrightarrow 00{:}07{:}46.490$ understand specific questions in

NOTE Confidence: 0.98681915

 $00:07:46.490 \longrightarrow 00:07:48.670$ the field of DNA repair,

NOTE Confidence: 0.98681915

 $00{:}07{:}48.670 \dashrightarrow 00{:}07{:}50.455$ and particularly those that were

NOTE Confidence: 0.98681915

 $00{:}07{:}50.455 \dashrightarrow 00{:}07{:}52.688$ relevant to the kind of the rapies

NOTE Confidence: 0.98681915

 $00:07:52.688 \dashrightarrow 00:07:55.327$ that might be used in the context

NOTE Confidence: 0.98681915

 $00{:}07{:}55{.}327 \dashrightarrow 00{:}07{:}56{.}400$ where patients have

NOTE Confidence: 0.986171

 $00:07:56.400 \longrightarrow 00:07:58.969$ defects in DNA repair within their tumors.

NOTE Confidence: 0.986171

 $00:07:58.970 \longrightarrow 00:08:00.065$ So first question,

NOTE Confidence: 0.986171

 $00:08:00.065 \dashrightarrow 00:08:02.620$ how exactly do you watch DNA being

NOTE Confidence: 0.986171

 $00:08:02.693 \rightarrow 00:08:05.272$ repaired in real time?

NOTE Confidence: 0.986171

 $00{:}08{:}05{.}272 \dashrightarrow 00{:}08{:}08{.}530$ I'm kind of blown away by that concept.

NOTE Confidence: 0.986171

00:08:08.530 --> 00:08:10.858 I remember back in junior high

 $00:08:10.858 \rightarrow 00:08:13.265$ biology looking down a microscope at

NOTE Confidence: 0.986171

00:08:13.265 - 00:08:15.995 a cell and looking at the nucleus.

NOTE Confidence: 0.986171

00:08:16.000 --> 00:08:18.919 And sometimes you could even see DNA

NOTE Confidence: 0.986171

00:08:18.919 --> 00:08:21.499 separating into mitotic figures and so on.

NOTE Confidence: 0.986171

 $00:08:21.500 \rightarrow 00:08:24.244$ But to actually see DNA being repaired?

NOTE Confidence: 0.986171

 $00{:}08{:}24.250 \dashrightarrow 00{:}08{:}27.580$ I mean presumably that occurs at a base pair NOTE Confidence: 0.986171

 $00:08:27.580 \rightarrow 00:08:30.538$ level and that's just fascinating to me.

NOTE Confidence: 0.986171

 $00:08:30.540 \longrightarrow 00:08:32.906$ So how exactly do you do that

NOTE Confidence: 0.986171

 $00{:}08{:}32{.}906 \dashrightarrow 00{:}08{:}35{.}340$ and what kind of magnification

NOTE Confidence: 0.986171

 $00:08:35.340 \rightarrow 00:08:37.069$ would you need even to see that?

NOTE Confidence: 0.9868847

 $00{:}08{:}37{.}770 \dashrightarrow 00{:}08{:}39{.}877$ Yeah, that's a great question and honestly,

NOTE Confidence: 0.9868847

 $00:08:39.880 \dashrightarrow 00:08:42.890$ this is why I'm a cell biologist at the end

NOTE Confidence: 0.9868847

 $00{:}08{:}42.960 \dashrightarrow 00{:}08{:}45.900$ of the day because we love to just look.

NOTE Confidence: 0.9868847

 $00:08:45.900 \longrightarrow 00:08:48.258$ If we have a way we can look at

NOTE Confidence: 0.9868847

 $00:08:48.258 \rightarrow 00:08:50.256$ something happening in real time that

NOTE Confidence: 0.9868847

 $00:08:50.256 \rightarrow 00:08:52.818$ is always the best thing in the world.

- NOTE Confidence: 0.9868847
- $00:08:52.820 \rightarrow 00:08:53.780$ However, as you say,
- NOTE Confidence: 0.9868847
- $00{:}08{:}53.780 \dashrightarrow 00{:}08{:}56.258$ it's not easy and so our work is built
- NOTE Confidence: 0.9868847
- $00:08:56.258 \rightarrow 00:08:57.888$ on really critical discoveries that
- NOTE Confidence: 0.9868847
- $00:08:57.888 \rightarrow 00:09:00.040$ have driven cell biology, in particular,
- NOTE Confidence: 0.9868847
- $00:09:00.040 \dashrightarrow 00:09:01.937$ and I'll just tell you about two
- NOTE Confidence: 0.9868847
- $00{:}09{:}01{.}937 \dashrightarrow 00{:}09{:}03{.}802$ of those that are critical for
- NOTE Confidence: 0.9868847
- $00:09:03.802 \longrightarrow 00:09:05.457$ the assays that we've built.
- NOTE Confidence: 0.9868847
- $00{:}09{:}05{.}460 \dashrightarrow 00{:}09{:}07{.}350$ The first is the advent of
- NOTE Confidence: 0.9868847
- $00:09:07.350 \dashrightarrow 00:09:08.295$ these fluorescent proteins.
- NOTE Confidence: 0.9868847
- 00:09:08.300 --> 00:09:09.335 Green fluorescent proteins
- NOTE Confidence: 0.9868847
- $00{:}09{:}09{.}335 \dashrightarrow 00{:}09{:}10.715$ and red fluorescent proteins.
- NOTE Confidence: 0.9868847
- $00:09:10.720 \longrightarrow 00:09:12.790$ Now we have an entire rainbow
- NOTE Confidence: 0.9868847
- $00:09:12.790 \longrightarrow 00:09:14.170$ of these fluorescent proteins,
- NOTE Confidence: 0.9868847
- $00:09:14.170 \longrightarrow 00:09:16.150$ and so these are proteins that
- NOTE Confidence: 0.9868847
- $00{:}09{:}16.150 \dashrightarrow 00{:}09{:}18.604$ fold up and they're able to make
- NOTE Confidence: 0.9868847

 $00:09:18.604 \rightarrow 00:09:20.379$ what's called a chromophore

NOTE Confidence: 0.9868847

 $00{:}09{:}20{.}380 \dashrightarrow 00{:}09{:}22{.}240$ and we can actually follow that

NOTE Confidence: 0.9868847

 $00:09:22.240 \longrightarrow 00:09:24.170$ specific molecule in a microscope.

NOTE Confidence: 0.9868847

 $00:09:24.170 \dashrightarrow 00:09:26.770$ And what we do is we basically stitch

NOTE Confidence: 0.9868847

 $00{:}09{:}26.770 \dashrightarrow 00{:}09{:}28.569$ that fluorescent protein onto a

NOTE Confidence: 0.9868847

 $00{:}09{:}28.569 \dashrightarrow 00{:}09{:}30.374$ protein that we're interested in,

NOTE Confidence: 0.9868847

 $00{:}09{:}30{.}380 \dashrightarrow 00{:}09{:}32{.}718$ and now we can follow our favorite

NOTE Confidence: 0.9868847

 $00:09:32.718 \longrightarrow 00:09:34.753$ protein of interest in a live

NOTE Confidence: 0.9868847

00:09:34.753 --> 00:09:36.363 cell on a fluorescence microscope

NOTE Confidence: 0.9868847

 $00{:}09{:}36{.}363 \dashrightarrow 00{:}09{:}38{.}309$ that can specifically detect

NOTE Confidence: 0.9868847

 $00:09:38.310 \longrightarrow 00:09:39.291$ that fluorescent protein,

NOTE Confidence: 0.9868847

 $00{:}09{:}39{.}291 \dashrightarrow 00{:}09{:}41{.}253$ and so that's one technology

NOTE Confidence: 0.9868847

 $00{:}09{:}41.253 \dashrightarrow 00{:}09{:}42.629$ that's absolutely critical.

NOTE Confidence: 0.9868847

 $00:09:42.630 \longrightarrow 00:09:43.278$ The other,

NOTE Confidence: 0.9868847

 $00{:}09{:}43.278 \dashrightarrow 00{:}09{:}45.546$ and I think this really speaks to

NOTE Confidence: 0.9868847

 $00:09:45.546 \longrightarrow 00:09:47.892$ the importance of kind of basic

- NOTE Confidence: 0.9868847
- $00{:}09{:}47.892 \dashrightarrow 00{:}09{:}49.847$ science discoveries and what

 $00{:}09{:}49{.}920 \dashrightarrow 00{:}09{:}52{.}026$ really has impacts on human

NOTE Confidence: 0.9868847

 $00:09:52.026 \longrightarrow 00:09:54.714$ health these days is that we use

NOTE Confidence: 0.9868847

 $00:09:54.714 \longrightarrow 00:09:56.640$ tricks to insert a region that's

NOTE Confidence: 0.9868847

00:09:56.711 -> 00:09:58.826 actually taken from a bacteria,

NOTE Confidence: 0.9868847

 $00:09:58.830 \longrightarrow 00:10:01.035$ so it's not native to the cells

NOTE Confidence: 0.9868847

00:10:01.035 - 00:10:02.790 that we are modifying,

NOTE Confidence: 0.9868847

 $00{:}10{:}02{.}790 \dashrightarrow 00{:}10{:}05{.}310$ and we essentially take that little sequence,

NOTE Confidence: 0.9868847

 $00{:}10{:}05{.}310 \dashrightarrow 00{:}10{:}09{.}030$ and we put it into the place in the genome

NOTE Confidence: 0.9868847

 $00{:}10{:}09{.}030 \dashrightarrow 00{:}10{:}10{.}992$ we're interested in and then we

NOTE Confidence: 0.9868847

 $00:10:10.992 \longrightarrow 00:10:13.431$ have a protein that can bind to

NOTE Confidence: 0.9868847

00:10:13.431 --> 00:10:15.196 that very specific DNA sequence,

NOTE Confidence: 0.9868847

 $00:10:15.200 \dashrightarrow 00:10:17.672$ and so we can monitor any kind of

NOTE Confidence: 0.9868847

 $00{:}10{:}17.672 \dashrightarrow 00{:}10{:}20.021$ region of the genome that we want

NOTE Confidence: 0.9868847

 $00{:}10{:}20{.}021 \dashrightarrow 00{:}10{:}22{.}870$ just by doing a little bit of editing

 $00:10:22.870 \rightarrow 00:10:25.114$ to that genome and putting these

NOTE Confidence: 0.9868847

 $00:10:25.114 \rightarrow 00:10:26.862$ in bacterial gene sequences

NOTE Confidence: 0.9868847

00:10:26.862 --> 00:10:28.234 into our eukaryotic cell,

NOTE Confidence: 0.9868847

 $00:10:28.240 \rightarrow 00:10:30.976$ because that's what we want to be studying.

NOTE Confidence: 0.9868847

 $00:10:30.980 \longrightarrow 00:10:33.038$ In terms of the magnification,

NOTE Confidence: 0.9868847

 $00:10:33.040 \longrightarrow 00:10:34.129$ you're absolutely right.

NOTE Confidence: 0.9868847

 $00:10:34.129 \longrightarrow 00:10:37.197$ We are able to do a pretty good

NOTE Confidence: 0.9868847

00:10:37.197 --> 00:10:39.017 job following these events

NOTE Confidence: 0.9868847

 $00{:}10{:}39{.}020 \dashrightarrow 00{:}10{:}40{.}656$ even with a magnification,

NOTE Confidence: 0.9868847

 $00{:}10{:}40.656 \dashrightarrow 00{:}10{:}43.504$ usually between 100 and 1000 fold over

NOTE Confidence: 0.9868847

 $00{:}10{:}43.504 \dashrightarrow 00{:}10{:}46.104$ what you could see with the naked eye.

NOTE Confidence: 0.98792106

 $00:10:46.700 \rightarrow 00:10:49.493$ Wow, so essentially you can clip the

NOTE Confidence: 0.98792106

 $00{:}10{:}49{.}493 \dashrightarrow 00{:}10{:}52{.}448$ DNA where you want to make a break.

NOTE Confidence: 0.98792106

 $00{:}10{:}52.450 \dashrightarrow 00{:}10{:}54.742$ Insert a bacterial strand of genetic

NOTE Confidence: 0.98792106

 $00:10:54.742 \rightarrow 00:10:56.850$ material, flag it with a particular

NOTE Confidence: 0.98792106

 $00:10:56.850 \rightarrow 00:11:00.228$ flag so you know where the break is and

 $00{:}11{:}00{.}228 \dashrightarrow 00{:}11{:}02{.}598$ then have these chromophores which can

NOTE Confidence: 0.98792106

 $00{:}11{:}02.670 \dashrightarrow 00{:}11{:}05.470$ light up when they approach that break.

 $00{:}11{:}08{.}770$ --> $00{:}11{:}10{.}642$ That's right, so another critical aspect is NOTE Confidence: 0.9764157

 $00:11:10.642 \rightarrow 00:11:13.337$ we have to know a lot about DNA repair,

NOTE Confidence: 0.9764157

 $00:11:13.340 \longrightarrow 00:11:14.548$ and fortunately,

NOTE Confidence: 0.9764157

 $00{:}11{:}14.548 \dashrightarrow 00{:}11{:}16.723$ DNA repair has been a really rich

NOTE Confidence: 0.9764157

00:11:16.723 --> 00:11:18.529 area of research for many decades,

NOTE Confidence: 0.9764157

 $00:11:18.530 \rightarrow 00:11:20.679$ and so building again on the knowledge

NOTE Confidence: 0.9764157

 $00{:}11{:}20.679 \dashrightarrow 00{:}11{:}22.779$ of many others we know pretty well

NOTE Confidence: 0.9764157

 $00{:}11{:}22.779 \dashrightarrow 00{:}11{:}25.152$ about the kind of timing and the events

NOTE Confidence: 0.9764157

 $00{:}11{:}25{.}152 \dashrightarrow 00{:}11{:}27{.}066$ that are taking place and repair.

NOTE Confidence: 0.9764157

00:11:27.070 --> 00:11:29.198 So protein X shows up,

NOTE Confidence: 0.9764157

 $00:11:29.200 \dashrightarrow 00:11:31.640$ and it always shows up before protein Y.

NOTE Confidence: 0.9764157

00:11:31.640 --> 00:11:32.864 And as you said,

NOTE Confidence: 0.9764157

 $00:11:32.864 \rightarrow 00:11:34.700$ we want to know what's happening

NOTE Confidence: 0.9764157

 $00:11:34.768 \longrightarrow 00:11:36.520$ at the base pair level,

- NOTE Confidence: 0.9764157
- $00:11:36.520 \longrightarrow 00:11:38.668$ like the smallest unit of DNA.
- NOTE Confidence: 0.9764157
- 00:11:38.670 --> 00:11:40.545 We can't really see something
- NOTE Confidence: 0.9764157
- $00:11:40.545 \longrightarrow 00:11:42.420$ that small in this assay,
- NOTE Confidence: 0.9764157
- $00:11:42.420 \longrightarrow 00:11:44.412$ so we're using proxies of factors
- NOTE Confidence: 0.9764157
- $00{:}11{:}44{.}412 \dashrightarrow 00{:}11{:}47{.}087$ that we know will show up at different
- NOTE Confidence: 0.9764157
- $00{:}11{:}47.087 \dashrightarrow 00{:}11{:}49.001$ points and that allows us to
- NOTE Confidence: 0.9764157
- $00:11:49.072 \rightarrow 00:11:51.420$ essentially monitor distinct events,
- NOTE Confidence: 0.9764157
- $00{:}11{:}51{.}420 \dashrightarrow 00{:}11{:}53{.}788$ because if we build up our
- NOTE Confidence: 0.9764157
- $00{:}11{:}53.788 \dashrightarrow 00{:}11{:}56.214$ library of these different flags that
- NOTE Confidence: 0.9764157
- $00:11:56.214 \rightarrow 00:11:58.419$ indicate different times and repair
- NOTE Confidence: 0.9764157
- $00:11:58.419 \rightarrow 00:12:01.168$ them more able to monitor those events,
- NOTE Confidence: 0.9764157
- $00{:}12{:}01{.}170 \dashrightarrow 00{:}12{:}03{.}045$ and we're also able to
- NOTE Confidence: 0.9764157
- $00{:}12{:}03.045 \dashrightarrow 00{:}12{:}04.545$ monitor them in single,
- NOTE Confidence: 0.9764157
- $00{:}12{:}04.550 \dashrightarrow 00{:}12{:}05.750$ individual cells,
- NOTE Confidence: 0.9764157
- $00:12:05.750 \longrightarrow 00:12:08.150$ and it's turned out that that's
- NOTE Confidence: 0.9764157

- $00:12:08.150 \longrightarrow 00:12:09.280$ really important.
- NOTE Confidence: 0.9764157
- $00:12:09.280 \longrightarrow 00:12:11.728$ Because if we look at a million
- NOTE Confidence: 0.9764157
- $00{:}12{:}11.728 \dashrightarrow 00{:}12{:}13.368$ cells doing something they all kind
- NOTE Confidence: 0.9764157
- $00{:}12{:}13.368 \dashrightarrow 00{:}12{:}15.805$ of do it on a little bit different
- NOTE Confidence: 0.9764157
- $00:12:15.805 \rightarrow 00:12:18.304$ time over a little bit different time,
- NOTE Confidence: 0.9764157
- $00{:}12{:}18{.}310 \dashrightarrow 00{:}12{:}20{.}109$ then the cell next
- NOTE Confidence: 0.9764157
- 00:12:20.109 --> 00:12:21.983 door and so by actually watching
- NOTE Confidence: 0.9764157
- $00:12:21.983 \rightarrow 00:12:23.728$ these events in single cells,
- NOTE Confidence: 0.9764157
- $00{:}12{:}23.730 \dashrightarrow 00{:}12{:}25.560$ that really gives us a resolution
- NOTE Confidence: 0.9764157
- $00:12:25.560 \rightarrow 00:12:26.780$ that's really important for
- NOTE Confidence: 0.9764157
- $00:12:26.839 \rightarrow 00:12:28.939$ being able to make very
- NOTE Confidence: 0.9764157
- $00:12:28.939 \longrightarrow 00:12:30.349$ mechanistic conclusions from the data.
- NOTE Confidence: 0.9873662
- $00:12:31.140 \longrightarrow 00:12:33.276$ So we understand that you've got
- NOTE Confidence: 0.9873662
- $00{:}12{:}33{.}276 \dashrightarrow 00{:}12{:}36{.}122$ DNA that can get injured and it can
- NOTE Confidence: 0.9873662
- $00:12:36.122 \longrightarrow 00:12:38.570$ get injured in a variety of ways
- NOTE Confidence: 0.9873662
- $00:12:38.570 \rightarrow 00:12:41.048$ at a variety of places,

- NOTE Confidence: 0.9873662
- $00:12:41.050 \longrightarrow 00:12:42.820$ each of which requires a

 $00:12:42.820 \rightarrow 00:12:44.590$ specific mechanism to repair it.

NOTE Confidence: 0.9873662

 $00:12:44.590 \rightarrow 00:12:46.654$ And we now understand that you've

NOTE Confidence: 0.9873662

 $00:12:46.654 \rightarrow 00:12:49.171$ built this model to kind of see

NOTE Confidence: 0.9873662

00:12:49.171 --> 00:12:50.956 how DNA repairs itself overtime,

NOTE Confidence: 0.9873662

 $00:12:50.960 \longrightarrow 00:12:53.432$ so tell us more about how this gets

NOTE Confidence: 0.9873662

 $00:12:53.432 \rightarrow 00:12:55.570$ into cancer and into the rapeutics

NOTE Confidence: 0.9873662

 $00{:}12{:}55{.}570 \dashrightarrow 00{:}12{:}58{.}594$ And we'll have to do that as soon as

NOTE Confidence: 0.9873662

 $00{:}12{:}58{.}594 \dashrightarrow 00{:}13{:}01{.}945$ we take a break for a medical minute.

NOTE Confidence: 0.9873662

00:13:01.950 --> 00:13:05.406 So please stay tuned to learn more about

NOTE Confidence: 0.9873662

 $00{:}13{:}05{.}406 \dashrightarrow 00{:}13{:}08{.}480$ DNA repair and cancer with my guest

NOTE Confidence: 0.9873662

00:13:08.480 --> 00:13:08.910 Doctor Megan King.

NOTE Confidence: 0.9213101

 $00{:}13{:}08{.}910 \dashrightarrow 00{:}13{:}11{.}586$ Funding for Yale Cancer Answers

NOTE Confidence: 0.9213101

00:13:11.586 --> 00:13:14.281 comes from AstraZeneca, working

NOTE Confidence: 0.9213101

 $00{:}13{:}14.281 \dashrightarrow 00{:}13{:}17.609$ to eliminate cancer as a cause of death.

 $00{:}13{:}17.610 \dashrightarrow 00{:}13{:}19.350$ Learn more at a strazeneca-us.com.

NOTE Confidence: 0.990294

00:13:21.410 --> 00:13:24.098 Breast cancer is one of the most common

NOTE Confidence: 0.990294

00:13:24.098 --> 00:13:26.659 cancers in women. In Connecticut alone,

NOTE Confidence: 0.990294

 $00:13:26.660 \rightarrow 00:13:28.550$ approximately 3500 women will be

NOTE Confidence: 0.990294

 $00{:}13{:}28.550 \dashrightarrow 00{:}13{:}30.790$ diagnosed with breast cancer this year,

NOTE Confidence: 0.990294

 $00:13:30.790 \longrightarrow 00:13:32.290$ but there is hope,

NOTE Confidence: 0.990294

 $00:13:32.290 \longrightarrow 00:13:33.790$ thanks to earlier detection,

NOTE Confidence: 0.990294

 $00:13:33.790 \rightarrow 00:13:35.640$ noninvasive treatments and the development

NOTE Confidence: 0.990294

 $00{:}13{:}35{.}640 \dashrightarrow 00{:}13{:}38{.}289$ of novel the rapies to fight breast cancer.

NOTE Confidence: 0.990294

 $00{:}13{:}38{.}290 \dashrightarrow 00{:}13{:}40{.}195$ Women should schedule a baseline

NOTE Confidence: 0.990294

 $00:13:40.195 \rightarrow 00:13:42.508$ mammogram beginning at age 40 or

NOTE Confidence: 0.990294

 $00:13:42.508 \longrightarrow 00:13:44.572$ earlier if they have risk factors

NOTE Confidence: 0.990294

 $00{:}13{:}44{.}572 \dashrightarrow 00{:}13{:}46{.}160$ associated with the disease.

NOTE Confidence: 0.990294

 $00:13:46.160 \rightarrow 00:13:47.660$ With screening, early detection,

NOTE Confidence: 0.990294

 $00:13:47.660 \longrightarrow 00:13:49.160$ and a healthy lifestyle,

NOTE Confidence: 0.990294

 $00:13:49.160 \longrightarrow 00:13:51.610$ breast cancer can be defeated.

- NOTE Confidence: 0.990294
- $00:13:51.610 \rightarrow 00:13:53.818$ Clinical trials are currently

00:13:53.818 --> 00:13:56.026 underway at federally designated

NOTE Confidence: 0.990294

00:13:56.026 --> 00:13:57.916 Comprehensive cancer centers such

NOTE Confidence: 0.990294

00:13:57.916 --> 00:14:00.429 as Yale Cancer Center and Smilow

NOTE Confidence: 0.990294

00:14:00.429 --> 00:14:02.776 Cancer Hospital to make innovative

NOTE Confidence: 0.990294

 $00{:}14{:}02.776$ --> $00{:}14{:}05.176$ new treatments available to patients.

NOTE Confidence: 0.990294

 $00{:}14{:}05{.}180 \dashrightarrow 00{:}14{:}07{.}405$ Digital breast tomosynthesis, or 3D

NOTE Confidence: 0.990294

 $00:14:07.405 \rightarrow 00:14:09.630$ mammography is also transforming breast

NOTE Confidence: 0.990294

 $00{:}14{:}09{.}698 \dashrightarrow 00{:}14{:}11{.}670$ cancer screening by significantly

NOTE Confidence: 0.990294

 $00:14:11.670 \longrightarrow 00:14:13.149$ reducing unnecessary procedures

NOTE Confidence: 0.990294

 $00{:}14{:}13.149 \dashrightarrow 00{:}14{:}15.479$ while picking up more cancers.

NOTE Confidence: 0.990294

 $00{:}14{:}15{.}480 \dashrightarrow 00{:}14{:}18{.}240$ More information is available at

NOTE Confidence: 0.990294

00:14:18.240 --> 00:14:19.896 yalecancercenter.org. You're listening

NOTE Confidence: 0.990294

00:14:19.896 --> 00:14:21.920 to Connecticut Public Radio.

NOTE Confidence: 0.990294

00:14:21.920 --> 00:14:22.300 Welcome

 $00:14:22.300 \longrightarrow 00:14:24.200$ back to Yale Cancer Answers.

NOTE Confidence: 0.9793338

 $00{:}14{:}24{.}200 \dashrightarrow 00{:}14{:}27{.}341$ This is doctor Anees Chagpar and I'm

NOTE Confidence: 0.9793338

00:14:27.341 --> 00:14:30.656 joined to
night by my guest doctor Megan King.

NOTE Confidence: 0.9793338

 $00{:}14{:}30.660 \dashrightarrow 00{:}14{:}33.320$ We're talking about DNA repair and cancer,

NOTE Confidence: 0.9793338

 $00{:}14{:}33{.}320 \dashrightarrow 00{:}14{:}35{.}854$ and right before the break we had

NOTE Confidence: 0.9793338

 $00:14:35.854 \rightarrow 00:14:38.557$ gotten to the point in the story

NOTE Confidence: 0.9793338

 $00{:}14{:}38{.}557 \dashrightarrow 00{:}14{:}41{.}323$ where we were talking about the fact

NOTE Confidence: 0.9793338

 $00{:}14{:}41{.}323 \dashrightarrow 00{:}14{:}43{.}962$ that DNA gets injured and it can

NOTE Confidence: 0.9793338

 $00{:}14{:}43.962 \dashrightarrow 00{:}14{:}46.620$ get damaged in a variety of places.

NOTE Confidence: 0.9793338

 $00:14:46.620 \longrightarrow 00:14:49.231$ And each of these breaks may be

NOTE Confidence: 0.9793338

 $00{:}14{:}49{.}231 \dashrightarrow 00{:}14{:}51{.}908$ specific and may require a specific

NOTE Confidence: 0.9793338

 $00{:}14{:}51{.}910 \dashrightarrow 00{:}14{:}54{.}956$ mechanism to repair it and we also

NOTE Confidence: 0.9793338

 $00{:}14{:}54{.}956 \dashrightarrow 00{:}14{:}58{.}000$ talked about the fact that Doctor King's

NOTE Confidence: 0.9793338

 $00{:}14{:}58.000 \dashrightarrow 00{:}15{:}01.101$ laboratory had figured out a way to

NOTE Confidence: 0.9793338

 $00{:}15{:}01{.}101 \dashrightarrow 00{:}15{:}03{.}657$ actually watch how DNA gets repaired.

NOTE Confidence: 0.9793338

 $00:15:03.660 \longrightarrow 00:15:06.250$ right under a microscope,

- NOTE Confidence: 0.9793338
- $00:15:06.250 \longrightarrow 00:15:07.694$ which was just fascinating.

00:15:07.694 --> 00:15:08.777 But now Megan,

NOTE Confidence: 0.9793338

 $00:15:08.780 \rightarrow 00:15:10.915$ maybe you can help us to understand

NOTE Confidence: 0.9793338

 $00:15:10.915 \longrightarrow 00:15:12.622$ how this really evolves into

NOTE Confidence: 0.9793338

 $00{:}15{:}12.622 \dashrightarrow 00{:}15{:}14.447$ understanding a little bit more

NOTE Confidence: 0.9793338

 $00:15:14.447 \dashrightarrow 00:15:16.380$ about cancer and the rapeutics.

NOTE Confidence: 0.9793338

 $00:15:16.380 \longrightarrow 00:15:19.276$ We built the capability now of

NOTE Confidence: 0.9799037

00:15:19.280 --> 00:15:21.807 monitoring DNA repair and these single cells.

NOTE Confidence: 0.9799037

 $00{:}15{:}21{.}810 \dashrightarrow 00{:}15{:}24{.}420$ And now we get to the point

NOTE Confidence: 0.9799037

 $00{:}15{:}24{.}420 \dashrightarrow 00{:}15{:}27{.}243$ in a basic scientist life where you

NOTE Confidence: 0.9799037

 $00{:}15{:}27{.}243 \dashrightarrow 00{:}15{:}29{.}779$ think about, I've built this assay,

NOTE Confidence: 0.9799037

 $00{:}15{:}29{.}780 \dashrightarrow 00{:}15{:}32{.}668$ it took us many years to do it.

NOTE Confidence: 0.9799037

 $00:15:32.670 \longrightarrow 00:15:35.256$ What do we want to study?

NOTE Confidence: 0.9799037

 $00{:}15{:}35{.}260 \dashrightarrow 00{:}15{:}38{.}140$ And it's about this time that I had

NOTE Confidence: 0.9799037

 $00{:}15{:}38{.}140 \dashrightarrow 00{:}15{:}39{.}767$ been interacting increasingly

 $00:15:39.767 \longrightarrow 00:15:42.263$ with members of Yale Cancer

NOTE Confidence: 0.9799037

 $00{:}15{:}42{.}263 \dashrightarrow 00{:}15{:}44{.}266$ Center and hearing about their

NOTE Confidence: 0.9799037

00:15:44.266 --> 00:15:46.835 work in the clinic and their work

NOTE Confidence: 0.9799037

 $00:15:46.840 \longrightarrow 00:15:48.770$ that is more translational.

NOTE Confidence: 0.9799037

 $00{:}15{:}48.770 \dashrightarrow 00{:}15{:}51.250$ So that's when we kind of apply basic

NOTE Confidence: 0.9799037

 $00:15:51.250 \rightarrow 00:15:53.399$ science and fundamental principles,

NOTE Confidence: 0.9799037

 $00:15:53.400 \longrightarrow 00:15:55.716$ directly to new treatments.

NOTE Confidence: 0.9799037

 $00{:}15{:}55{.}720 \dashrightarrow 00{:}15{:}58{.}378$ And through these interactions we became

NOTE Confidence: 0.9799037

 $00:15:58.378 \rightarrow 00:16:01.643$ very interested in how we might use this

NOTE Confidence: 0.9799037

 $00{:}16{:}01{.}643 \dashrightarrow 00{:}16{:}04{.}580$ as say to answer a question that has arisen NOTE Confidence: 0.9799037

 $00:16:04.580 \rightarrow 00:16:06.869$ that was clearly critical to the treatment NOTE Confidence: 0.9799037

 $00:16:06.869 \rightarrow 00:16:09.237$ of breast and ovarian cancer that is

NOTE Confidence: 0.9799037

 $00{:}16{:}09{.}240 \dashrightarrow 00{:}16{:}11{.}586$ tied to this familial cancer susceptibility

NOTE Confidence: 0.9799037

 $00:16:11.586 \longrightarrow 00:16:14.196$ genes BRCA one and 2.

NOTE Confidence: 0.9799037

 $00:16:14.196 \longrightarrow 00:16:16.438$ I allways have a soft spot in my heart

NOTE Confidence: 0.9799037

00:16:16.438 --> 00:16:18.532 for BRCA 1 because it

00:16:18.532 --> 00:16:20.442 was discovered by Mary Claire King.

NOTE Confidence: 0.9799037

 $00{:}16{:}20{.}442 \dashrightarrow 00{:}16{:}22{.}627$ No relation but we have the same

NOTE Confidence: 0.9799037

 $00{:}16{:}22.627 \dashrightarrow 00{:}16{:}24.748$ initials and last name and in fact

NOTE Confidence: 0.9799037

00:16:24.748 --> 00:16:26.957 over the years I've gotten emails

NOTE Confidence: 0.9799037

00:16:26.957 --> 00:16:28.882 intended for Mary Claire King.

NOTE Confidence: 0.9799037

 $00{:}16{:}28{.}890 \dashrightarrow 00{:}16{:}31{.}116$ So we've struck up already a kind

NOTE Confidence: 0.9799037

 $00:16:31.116 \longrightarrow 00:16:33.304$ of back and forth just because

NOTE Confidence: 0.9799037

 $00:16:33.304 \rightarrow 00:16:35.614$ of people getting us mixed up.

 $00{:}16{:}36{.}727 \dashrightarrow 00{:}16{:}40{.}154$ And so BRCA one really had

NOTE Confidence: 0.9799037

00:16:40.154 --> 00:16:42.842 become a success story of an approach

NOTE Confidence: 0.9799037

 $00{:}16{:}42.842 \dashrightarrow 00{:}16{:}45.940$ to the rapy called synthetic lethality.

NOTE Confidence: 0.9799037

 $00{:}16{:}45{.}940 \dashrightarrow 00{:}16{:}48{.}196$ And so the idea is that

NOTE Confidence: 0.9799037

00:16:48.196 --> 00:16:50.670 BRCA one is very important,

NOTE Confidence: 0.9799037

 $00{:}16{:}50.670 \dashrightarrow 00{:}16{:}53.659$ particularly in a type of DNA repair

NOTE Confidence: 0.9799037

 $00{:}16{:}53.659 \dashrightarrow 00{:}16{:}55.450$ called homologous or combination

NOTE Confidence: 0.9799037

 $00{:}16{:}55{.}450 \dashrightarrow 00{:}16{:}58{.}054$ and in individuals who have a

- NOTE Confidence: 0.9799037
- 00:16:58.054 --> 00:17:00.558 loss of function and BRCA one,
- NOTE Confidence: 0.9799037
- $00{:}17{:}00{.}560 \dashrightarrow 00{:}17{:}03{.}350$ this leads to an increased susceptibility
- NOTE Confidence: 0.9799037
- $00:17:03.350 \longrightarrow 00:17:05.810$ to breast and ovarian cancer in women.
- $00:17:06.520 \rightarrow 00:17:08.650$ And so you are probably quite familiar
- NOTE Confidence: 0.9799037
- $00:17:08.650 \rightarrow 00:17:10.739$ with this because it's become very well known.
- 00:17:13.390 --> 00:17:15.290 And it's also well known
- NOTE Confidence: 0.9799037
- $00:17:15.290 \longrightarrow 00:17:17.635$ even on the scientific front
- NOTE Confidence: 0.9799037
- 00:17:17.635 00:17:20.284 because of the advent of a therapy
- NOTE Confidence: 0.9799037
- $00{:}17{:}20.284 \dashrightarrow 00{:}17{:}22.254$ which is called PARP inhibitor
- NOTE Confidence: 0.9799037
- $00{:}17{:}22.254 \dashrightarrow 00{:}17{:}23.899$ the rapies that specifically kill
- NOTE Confidence: 0.9799037
- $00{:}17{:}23.899 \dashrightarrow 00{:}17{:}26.657$ tumor cells that are defective in the
- NOTE Confidence: 0.9799037
- 00:17:26.660 --> 00:17:29.306 functions of BRCA one or two,
- NOTE Confidence: 0.9799037
- $00:17:29.310 \longrightarrow 00:17:31.530$ and actually more broadly in DNA
- NOTE Confidence: 0.9799037
- $00:17:31.530 \longrightarrow 00:17:33.010$ repair through this mechanism
- NOTE Confidence: 0.9799037
- 00:17:33.077 --> 00:17:34.988 called homologous recombination.
- NOTE Confidence: 0.9799037
- $00:17:34.990 \longrightarrow 00:17:36.770$ And so this is fantastic.
- NOTE Confidence: 0.9799037

 $00:17:36.770 \longrightarrow 00:17:39.248$ What does that mean for a patient?

NOTE Confidence: 0.9799037

 $00{:}17{:}39{.}250 \dashrightarrow 00{:}17{:}41{.}651$ It means that all of their normal

NOTE Confidence: 0.9799037

 $00{:}17{:}41.651 \dashrightarrow 00{:}17{:}43.509$ tissues can tolerate these drugs.

NOTE Confidence: 0.9799037

 $00{:}17{:}43.510 \dashrightarrow 00{:}17{:}45.640$ They really only attack the cells

NOTE Confidence: 0.9799037

 $00{:}17{:}45.640 \dashrightarrow 00{:}17{:}47.769$ that don't have functional DNA repair.

NOTE Confidence: 0.9799037

 $00{:}17{:}47{.}770 \dashrightarrow 00{:}17{:}50{.}437$ So DNA repair is this kind of

NOTE Confidence: 0.9799037

00:17:50.437 -> 00:17:52.739 double edged sword, on the one hand,

NOTE Confidence: 0.9799037

 $00{:}17{:}52{.}740 \dashrightarrow 00{:}17{:}54{.}959$ a defect in DNA repair can lead

NOTE Confidence: 0.9799037

 $00{:}17{:}54{.}959 \dashrightarrow 00{:}17{:}56{.}790$ an individual to be vulnerable

NOTE Confidence: 0.9799037

 $00{:}17{:}56{.}790 \dashrightarrow 00{:}17{:}58{.}418$ to developing a cancer.

NOTE Confidence: 0.9799037

 $00{:}17{:}58{.}420 \dashrightarrow 00{:}18{:}00{.}550$ But if the cancer is defective

NOTE Confidence: 0.9799037

 $00:18:00.550 \longrightarrow 00:18:01.615$ in DNA repair,

NOTE Confidence: 0.9799037

 $00:18:01.620 \longrightarrow 00:18:03.804$ it also opens up a window

NOTE Confidence: 0.9799037

00:18:03.804 --> 00:18:05.260 for the rapies and PARP

NOTE Confidence: 0.9799037

 $00{:}18{:}05{.}260 \dashrightarrow 00{:}18{:}06{.}636$ Inhibitors were something that

NOTE Confidence: 0.9799037

00:18:06.636 --> 00:18:09.180 could kind of fit into that window,

- NOTE Confidence: 0.9799037
- $00:18:09.180 \longrightarrow 00:18:11.581$ so this was really a very exciting
- NOTE Confidence: 0.9799037
- 00:18:11.581 --> 00:18:14.355 time and continues to be a really new
- NOTE Confidence: 0.9799037
- 00:18:14.355 --> 00:18:16.481 approach to treating cancers that are
- NOTE Confidence: 0.9799037
- $00{:}18{:}16{.}481 \dashrightarrow 00{:}18{:}18{.}356$ tied to homologous or combination
- NOTE Confidence: 0.9799037
- $00{:}18{:}18{.}356 \dashrightarrow 00{:}18{:}21{.}024$ defects which we now know include a
- NOTE Confidence: 0.9799037
- $00{:}18{:}21.024 \dashrightarrow 00{:}18{:}23.740$ number of contexts that do not involve
- NOTE Confidence: 0.9799037
- $00:18:23.820 \longrightarrow 00:18:26.238$ just BRCA 1 and 2.
- NOTE Confidence: 0.9799037
- 00:18:26.240 --> 00:18:26.566 However,
- NOTE Confidence: 0.9799037
- $00:18:26.566 \longrightarrow 00:18:28.522$ we also knew quite early on
- NOTE Confidence: 0.9799037
- $00:18:28.522 \longrightarrow 00:18:29.500$ that these patients
- NOTE Confidence: 0.9861332
- $00{:}18{:}29{.}562 \dashrightarrow 00{:}18{:}31{.}090$ would often have acquired
- NOTE Confidence: 0.9861332
- $00{:}18{:}31.090 \dashrightarrow 00{:}18{:}33.000$ resistance to the PARP inhibitiors.
- NOTE Confidence: 0.9861332
- $00:18:33.000 \rightarrow 00:18:35.136$ They would initially respond very well,
- NOTE Confidence: 0.9861332
- $00{:}18{:}35{.}140 \dashrightarrow 00{:}18{:}37{.}168$ but the response would not
- NOTE Confidence: 0.9861332
- $00:18:37.168 \longrightarrow 00:18:39.693$ be as durable as they and their
- NOTE Confidence: 0.9861332

00:18:39.693 --> 00:18:41.895 physicians would like it to be,

NOTE Confidence: 0.9861332

 $00{:}18{:}41{.}900 \dashrightarrow 00{:}18{:}43{.}910$ and investigators had gone in to

NOTE Confidence: 0.9861332

 $00:18:43.910 \longrightarrow 00:18:46.826$ try to ask how is it that these

NOTE Confidence: 0.9861332

 $00:18:46.826 \rightarrow 00:18:48.315$ tumors are evolving, essentially,

NOTE Confidence: 0.9861332

 $00:18:48.315 \rightarrow 00:18:50.445$ to become resistant to PARP inhibitors,

NOTE Confidence: 0.9861332

 $00:18:50.450 \rightarrow 00:18:52.935$ and particularly in the case of BRCA 1

NOTE Confidence: 0.9861332

 $00:18:52.940 \longrightarrow 00:18:54.780$ they found that there

NOTE Confidence: 0.9861332

 $00:18:54.780 \longrightarrow 00:18:56.620$ seemed to be secondary loss

NOTE Confidence: 0.9861332

00:18:56.620 --> 00:18:59.326 of other repair factors that were

NOTE Confidence: 0.9861332

 $00{:}18{:}59{.}326$ --> $00{:}19{:}01{.}677$ involved and we became excited

NOTE Confidence: 0.9861332

 $00{:}19{:}01{.}677 \dashrightarrow 00{:}19{:}04{.}431$ about the potential of our assay NOTE Confidence: 0.9861332

 $00:19:04.431 \longrightarrow 00:19:06.687$ to maybe provide some insight

NOTE Confidence: 0.9861332

 $00{:}19{:}06{.}687 \dashrightarrow 00{:}19{:}09{.}452$ into how is it that these tumors

NOTE Confidence: 0.9861332

 $00{:}19{:}09{.}452 \dashrightarrow 00{:}19{:}11{.}614$ are getting around this the rapy,

NOTE Confidence: 0.9861332

 $00:19:11.614 \rightarrow 00:19:13.378$ and even more importantly,

NOTE Confidence: 0.9861332

 $00:19:13.380 \longrightarrow 00:19:16.369$ might there be ways that we could

- NOTE Confidence: 0.9861332
- $00:19:16.369 \rightarrow 00:19:18.670$ actually target these cells again?
- NOTE Confidence: 0.9861332
- $00:19:18.670 \longrightarrow 00:19:21.316$ So kind of re-sensitize them
- NOTE Confidence: 0.9861332
- 00:19:21.316 --> 00:19:22.639 to PARP inhibitors,
- NOTE Confidence: 0.9861332
- $00:19:22.640 \rightarrow 00:19:25.727$ and so we modeled these mutations,
- $00:19:28.999 \rightarrow 00:19:31.707$ so that cells no longer express a number
- NOTE Confidence: 0.9861332
- $00:19:31.707 \longrightarrow 00:19:34.149$ of other factors called 53BP1
- NOTE Confidence: 0.9861332
- $00:19:34.150 \longrightarrow 00:19:37.090$ on a complex called shieldin.
- NOTE Confidence: 0.9861332
- $00{:}19{:}37{.}090 \dashrightarrow 00{:}19{:}39{.}718$ And somehow this allows cells that
- NOTE Confidence: 0.9861332
- $00{:}19{:}39{.}718 \dashrightarrow 00{:}19{:}41{.}944$ don't have functional BRCA one
- NOTE Confidence: 0.9861332
- $00:19:41.944 \longrightarrow 00:19:44.320$ to still survive in the presence
- NOTE Confidence: 0.9861332
- 00:19:44.320 --> 00:19:45.508 of PARP inhibitors,
- NOTE Confidence: 0.9861332
- $00{:}19{:}45{.}510 \dashrightarrow 00{:}19{:}47{.}958$ and so we investigated those using
- NOTE Confidence: 0.9861332
- $00{:}19{:}47{.}958 \dashrightarrow 00{:}19{:}50{.}948$ this assay and we discovered that the
- NOTE Confidence: 0.9861332
- $00:19:50.948 \longrightarrow 00:19:53.916$ loss of these factors that drove
- NOTE Confidence: 0.9861332
- $00:19:54.000 \rightarrow 00:19:57.376$ this PARP inhibitor to no longer work were
- NOTE Confidence: 0.9861332
- 00:19:57.380 --> 00:19:59.138 affecting DNA repair in a very

- NOTE Confidence: 0.9861332
- $00:19:59.138 \rightarrow 00:20:01.007$ specific way by unleashing

 $00{:}20{:}01{.}007 \dashrightarrow 00{:}20{:}02{.}927$ a DNA repair factor that really

NOTE Confidence: 0.9861332

00:20:02.927 --> 00:20:04.955 shouldn't be functioning and this is

NOTE Confidence: 0.9861332

 $00{:}20{:}04{.}955 \dashrightarrow 00{:}20{:}06{.}941$ a protein called the bloom's helicase NOTE Confidence: 0.9861332

 $00{:}20{:}06{.}950 \dashrightarrow 00{:}20{:}09{.}620$ and it was able to kind of step in for NOTE Confidence: 0.9861332

 $00{:}20{:}09{.}694 \dashrightarrow 00{:}20{:}12{.}058$ BRCA one when these other factors

NOTE Confidence: 0.9861332

 $00{:}20{:}12.058 \dashrightarrow 00{:}20{:}14.548$ are silenced and take over and so

NOTE Confidence: 0.9861332

 $00{:}20{:}14.548 \dashrightarrow 00{:}20{:}17.160$ in a sense that seems like a bad thing.

NOTE Confidence: 0.9861332

 $00{:}20{:}17.160 \dashrightarrow 00{:}20{:}19.400$ Some other protein can come in and NOTE Confidence: 0.9861332

 $00:20:19.400 \rightarrow 00:20:21.619$ and take the place of BRCA one,

NOTE Confidence: 0.9861332

 $00{:}20{:}21{.}620 \dashrightarrow 00{:}20{:}24{.}392$ but it turns out one of the things we

NOTE Confidence: 0.9861332

 $00{:}20{:}24{.}392 \dashrightarrow 00{:}20{:}26{.}386$ learned in our experiments was that

NOTE Confidence: 0.9861332

 $00{:}20{:}26{.}386 \dashrightarrow 00{:}20{:}29{.}029$ there was kind of a new liability.

NOTE Confidence: 0.9861332

 $00{:}20{:}29{.}030 \dashrightarrow 00{:}20{:}31{.}370$ That this activation of this

NOTE Confidence: 0.9861332

 $00{:}20{:}31{.}370 \dashrightarrow 00{:}20{:}33{.}242$ bloom's helicase brought along,

 $00:20:33.250 \longrightarrow 00:20:35.590$ and it's actually now this

NOTE Confidence: 0.9861332

 $00:20:35.590 \longrightarrow 00:20:37.462$ angle that we're targeting,

NOTE Confidence: 0.9861332

 $00{:}20{:}37{.}470 \dashrightarrow 00{:}20{:}40{.}515$ with the idea that there will be

NOTE Confidence: 0.9861332

 $00{:}20{:}40.515 \dashrightarrow 00{:}20{:}42.759$ new combination the rapies that will

NOTE Confidence: 0.9861332

 $00{:}20{:}42.759 \dashrightarrow 00{:}20{:}45.327$ re sensitize these tumors to PARP

NOTE Confidence: 0.9861332

 $00{:}20{:}45{.}327 \dashrightarrow 00{:}20{:}47{.}863$ inhibitors in combination with either NOTE Confidence: 0.9861332

 $00:20:47.863 \rightarrow 00:20:51.067$ inhibitors of the bloom helicase itself,

NOTE Confidence: 0.9861332

 $00{:}20{:}51.070 \dashrightarrow 00{:}20{:}53.640$ but also some other additional

NOTE Confidence: 0.9861332

 $00{:}20{:}53.640 \dashrightarrow 00{:}20{:}56.706$ treatments that have already been being

NOTE Confidence: 0.9861332

 $00:20:56.706 \longrightarrow 00:20:59.583$ pushed forward.

NOTE Confidence: 0.9861332

 $00:20:59.590 \rightarrow 00:21:01.786$ Things like the DNA damage checkpoint,

NOTE Confidence: 0.9861332

00:21:01.790 --> 00:21:03.620 which is something that acts

NOTE Confidence: 0.9861332

 $00{:}21{:}03.620 \dashrightarrow 00{:}21{:}05.450$ downstream of unresolved DNA damage,

NOTE Confidence: 0.9861332

 $00{:}21{:}05{.}450 \dashrightarrow 00{:}21{:}07{.}616$ so we're pretty excited that these

NOTE Confidence: 0.9861332

 $00{:}21{:}07.616 \dashrightarrow 00{:}21{:}09.516$ kind of very fundamental insights

NOTE Confidence: 0.9861332

 $00:21:09.516 \rightarrow 00:21:11.832$ from this assay that I've described

- NOTE Confidence: 0.9861332
- $00:21:11.832 \rightarrow 00:21:14.067$ are really leading us to consider

 $00:21:14.067 \longrightarrow 00:21:15.752$ new combinations of drugs that

NOTE Confidence: 0.9861332

 $00{:}21{:}15.752 \dashrightarrow 00{:}21{:}17.862$ may allow for

NOTE Confidence: 0.9861332

 $00:21:17.862 \rightarrow 00:21:20.456$ not necessarily to make the PARP inhibitor

NOTE Confidence: 0.9861332

 $00:21:20.456 \longrightarrow 00:21:23.750$ but be a good therapy on its own for longer,

NOTE Confidence: 0.9861332

 $00:21:23.750 \longrightarrow 00:21:25.910$ but how we might use combinations

NOTE Confidence: 0.9861332

 $00:21:25.910 \longrightarrow 00:21:28.190$ that will allow for a very

NOTE Confidence: 0.9861332

 $00:21:28.190 \rightarrow 00:21:29.730$ durable response for these patients.

NOTE Confidence: 0.98652893

 $00:21:30.330 \longrightarrow 00:21:33.018$ Let me make sure that we've got

NOTE Confidence: 0.98652893

 $00:21:33.018 \longrightarrow 00:21:35.446$ that straight for all of our listeners.

NOTE Confidence: 0.98652893

 $00{:}21{:}35{.}450 \dashrightarrow 00{:}21{:}37{.}770$ So normally every body has functional

NOTE Confidence: 0.98652893

 $00{:}21{:}37{.}770$ --> $00{:}21{:}41{.}418$ BRCA but when you have a mutation in NOTE Confidence: 0.98652893

 $00:21:41.418 \rightarrow 00:21:43.914$ that it no longer becomes effective

NOTE Confidence: 0.98652893

 $00{:}21{:}43{.}914$ --> $00{:}21{:}47{.}168$ and the function of that BRCA gene is NOTE Confidence: 0.98652893

 $00:21:47.168 \rightarrow 00:21:49.858$ really to repair DNA because DNA we

 $00{:}21{:}49.858 \dashrightarrow 00{:}21{:}53.175$ have in all of our cells and sometimes

NOTE Confidence: 0.98652893

 $00{:}21{:}53.175 \dashrightarrow 00{:}21{:}56.549$ it can just get damaged and BRCA

NOTE Confidence: 0.98652893

 $00{:}21{:}56{.}549$ --> $00{:}21{:}59{.}598$ actually forms is a very important gene NOTE Confidence: 0.98652893

 $00:21:59.598 \rightarrow 00:22:03.006$ that can help us to repair that DNA,

NOTE Confidence: 0.98652893

 $00{:}22{:}03.006 \dashrightarrow 00{:}22{:}05.640$ but when that's defective we get cancers.

NOTE Confidence: 0.98652893

 $00{:}22{:}05{.}640 \dashrightarrow 00{:}22{:}08{.}525$ But these PARP inhibitors

NOTE Confidence: 0.98652893

 $00:22:08.525 \rightarrow 00:22:11.410$ are very effective against tumors

NOTE Confidence: 0.98652893

00:22:11.499 - 00:22:14.509 that have DNA damage that is not

NOTE Confidence: 0.98652893

 $00:22:14.509 \longrightarrow 00:22:16.410$ being repaired by BRCA.

NOTE Confidence: 0.98652893

 $00:22:16.410 \rightarrow 00:22:20.260$ But then you've got this bloom helicase

NOTE Confidence: 0.98652893

 $00:22:20.260 \longrightarrow 00:22:24.110$ which can step in for BRCA.

NOTE Confidence: 0.98652893

 $00{:}22{:}24.110 \dashrightarrow 00{:}22{:}27.246$ It's almost like a fail

NOTE Confidence: 0.98652893

 $00{:}22{:}27{.}246 \dashrightarrow 00{:}22{:}30{.}778$ safe kind of belt and suspenders

NOTE Confidence: 0.98652893

 $00:22:30.780 \longrightarrow 00:22:33.894$ where if one

NOTE Confidence: 0.98652893

 $00{:}22{:}33{.}894 \dashrightarrow 00{:}22{:}35{.}970$ repair mechanism doesn't work,

NOTE Confidence: 0.98652893

 $00:22:35.970 \rightarrow 00:22:38.256$ then another repair mechanism can work,

- NOTE Confidence: 0.98652893
- $00:22:38.260 \rightarrow 00:22:40.486$ but in cancer cells you really
- NOTE Confidence: 0.98652893
- $00{:}22{:}40{.}486 \dashrightarrow 00{:}22{:}42{.}450$ don't want it to work.
- NOTE Confidence: 0.98652893
- 00:22:42.450 --> 00:22:44.893 So what you're now doing is trying
- NOTE Confidence: 0.98652893
- $00:22:44.893 \rightarrow 00:22:47.154$ to find inhibitors to that secondary
- NOTE Confidence: 0.98652893
- $00{:}22{:}47.154 \dashrightarrow 00{:}22{:}49.828$ repair mechanism to ensure that the PARP
- NOTE Confidence: 0.98652893
- $00:22:49.896 \rightarrow 00:22:52.724$ inhibitors can kill off those cancer cells.
- $00:22:53.500 \longrightarrow 00:22:55.400$ Yes, that's exactly right,
- NOTE Confidence: 0.9839927
- $00:22:55.400 \rightarrow 00:22:58.208$ and it had been known for a while that
- NOTE Confidence: 0.9839927
- 00:22:58.208 --> 00:23:01.321 there might be these two kind of parallel
- NOTE Confidence: 0.9839927
- $00{:}23{:}01{.}321 \dashrightarrow 00{:}23{:}03{.}945$ mechanisms to carry out a specific
- NOTE Confidence: 0.9839927
- $00{:}23{:}03{.}945 \dashrightarrow 00{:}23{:}06{.}250$ step in homologous recombination and
- NOTE Confidence: 0.9839927
- $00:23:06.250 \longrightarrow 00:23:08.194$ indeed, it was known already that
- NOTE Confidence: 0.9839927
- $00{:}23{:}08{.}194 \dashrightarrow 00{:}23{:}09{.}490$ these two mechanisms existed,
- NOTE Confidence: 0.9839927
- $00:23:09.490 \longrightarrow 00:23:11.674$ but actually we didn't know very much
- NOTE Confidence: 0.9839927
- $00{:}23{:}11.674 \dashrightarrow 00{:}23{:}14.665$ about how a cell could decide to use one
- NOTE Confidence: 0.9839927
- $00:23:14.665 \rightarrow 00:23:17.270$ mechanism that would be this kind of BRCA

- NOTE Confidence: 0.9839927
- $00:23:17.270 \longrightarrow 00:23:18.890$ one mechanism which works with
- 00:23:20.510 00:23:22.130 this blooms' helicase pathway,

 $00:23:22.130 \longrightarrow 00:23:24.074$ which as you said is kind

NOTE Confidence: 0.9839927

 $00:23:24.074 \longrightarrow 00:23:25.370$ of a backup mechanism.

NOTE Confidence: 0.9839927

 $00{:}23{:}25{.}370 \dashrightarrow 00{:}23{:}27{.}642$ One of the things we've discovered is that

NOTE Confidence: 0.9839927

 $00{:}23{:}27{.}642 \dashrightarrow 00{:}23{:}30{.}230$ we think that the bloom's helicase mechanism,

NOTE Confidence: 0.9839927

00:23:30.230 --> 00:23:31.466 although it's a backup,

NOTE Confidence: 0.9839927

 $00:23:31.466 \rightarrow 00:23:33.011$ it's really not supposed to

NOTE Confidence: 0.9839927

 $00{:}23{:}33{.}011 \dashrightarrow 00{:}23{:}34{.}760$ be working in normal cells,

NOTE Confidence: 0.9839927

 $00:23:34.760 \longrightarrow 00:23:37.955$ and that's why there are a number of factors

NOTE Confidence: 0.9839927

 $00{:}23{:}37{.}960 \dashrightarrow 00{:}23{:}39{.}988$ that keep it off and that

NOTE Confidence: 0.9839927

 $00:23:39.988 \longrightarrow 00:23:41.002$ includes these proteins,

NOTE Confidence: 0.9839927

 $00:23:41.010 \longrightarrow 00:23:43.038$ the loss of which can drive

NOTE Confidence: 0.9839927

00:23:43.038 --> 00:23:44.052 PARP inhibitor resistance.

NOTE Confidence: 0.9839927

 $00{:}23{:}44.060 \dashrightarrow 00{:}23{:}46.094$ So we think that actually there's

NOTE Confidence: 0.9839927

 $00:23:46.094 \rightarrow 00:23:47.450$ kind of a gain.

- NOTE Confidence: 0.9839927
- $00{:}23{:}47{.}450 \dashrightarrow 00{:}23{:}49{.}434$ We would call it a gain of function

 $00:23:49.434 \rightarrow 00:23:51.773$ of the bloom's helicase that underlies

NOTE Confidence: 0.9839927

 $00{:}23{:}51{.}773 \dashrightarrow 00{:}23{:}53{.}549$ the PARP inhibitor resistance.

NOTE Confidence: 0.9839927

 $00{:}23{:}53{.}550 \dashrightarrow 00{:}23{:}56{.}118$ Why might cells not want to be using

NOTE Confidence: 0.9839927

 $00{:}23{:}56{.}118 \dashrightarrow 00{:}23{:}58{.}300$ this bloom's helicase all the time?

NOTE Confidence: 0.9839927

 $00{:}23{:}58{.}300 \dashrightarrow 00{:}24{:}00{.}526$ We think that it's because actually it's

NOTE Confidence: 0.9839927

 $00:24:00.526 \rightarrow 00:24:03.390$ not a very well controlled enzyme,

NOTE Confidence: 0.9839927

 $00:24:03.390 \rightarrow 00:24:05.756$ so its activity in the repair process

NOTE Confidence: 0.9839927

 $00{:}24{:}05{.}760 \dashrightarrow 00{:}24{:}08{.}728$ kind of goes wild a bit.

NOTE Confidence: 0.9839927

 $00{:}24{:}08{.}730 \dashrightarrow 00{:}24{:}11{.}040$ And even though this allows the cells

NOTE Confidence: 0.9839927

00:24:11.040 --> 00:24:13.329 to get around the PARP inhibitor,

NOTE Confidence: 0.9839927

 $00:24:13.330 \rightarrow 00:24:15.454$ it actually may make them susceptible to

 $00:24:16.520 \longrightarrow 00:24:17.932$ additional targets

NOTE Confidence: 0.9839927

 $00:24:17.932 \longrightarrow 00:24:19.344$ that are being developed,

NOTE Confidence: 0.9839927

 $00{:}24{:}19{.}350 \dashrightarrow 00{:}24{:}21{.}468$ and so we think

NOTE Confidence: 0.9839927

 $00:24:21.470 \longrightarrow 00:24:23.498$ just like a DNA repair defect

- NOTE Confidence: 0.9839927
- 00:24:23.498 --> 00:24:25.370 opens up a therapeutic window,

 $00{:}24{:}25{.}370 \dashrightarrow 00{:}24{:}27{.}680$ we think this kind of rewiring from

NOTE Confidence: 0.9839927

 $00{:}24{:}27.680 \dashrightarrow 00{:}24{:}30.088$ BRCA one to the bloom's helicase may

NOTE Confidence: 0.9839927

 $00{:}24{:}30.088 \dashrightarrow 00{:}24{:}32.965$ also open up new ways that we could

NOTE Confidence: 0.9839927

 $00:24:32.965 \longrightarrow 00:24:34.930$ go about treating these tumors.

NOTE Confidence: 0.9785853

 $00:24:34.930 \longrightarrow 00:24:37.048$ So then the next question is,

NOTE Confidence: 0.9785853

 $00:24:37.050 \longrightarrow 00:24:40.416$ is there a way for us to

NOTE Confidence: 0.9785853

 $00:24:40.420 \longrightarrow 00:24:42.250$ figure out either upfront before

NOTE Confidence: 0.9785853

 $00{:}24{:}42{.}250 \dashrightarrow 00{:}24{:}44{.}490$ we give any the rapy whether a

NOTE Confidence: 0.9785853

00:24:44.490 --> 00:24:46.572 particular patient is going to have

NOTE Confidence: 0.9785853

 $00:24:46.572 \rightarrow 00:24:48.718$ this bloom's helicase turned on or not,

NOTE Confidence: 0.9785853

 $00{:}24{:}48{.}720 \dashrightarrow 00{:}24{:}51{.}233$ so that up front we can decide whether

NOTE Confidence: 0.9785853

 $00:24:51.233 \rightarrow 00:24:53.908$ we should just give up our PARP inhibitor,

NOTE Confidence: 0.9785853

 $00:24:53.908 \longrightarrow 00:24:56.220$ or whether we need to give dual

NOTE Confidence: 0.9785853

 $00:24:56.220 \rightarrow 00:24:58.374$ therapy or in a productive manner

 $00:24:58.374 \rightarrow 00:25:00.830$ where we can say, well,

NOTE Confidence: 0.9785853

 $00{:}25{:}00{.}830 \dashrightarrow 00{:}25{:}02{.}714$ if some body hasn't responded to the

NOTE Confidence: 0.9785853

 $00:25:02.714 \rightarrow 00:25:04.990$ PARP inhibitor as we would anticipate,

NOTE Confidence: 0.9785853

 $00:25:04.990 \longrightarrow 00:25:07.951$ is there a way for us to figure out

NOTE Confidence: 0.9785853

 $00{:}25{:}07{.}951 \dashrightarrow 00{:}25{:}11{.}048$ if this is the mechanism by which

NOTE Confidence: 0.9785853

 $00{:}25{:}11.050 \dashrightarrow 00{:}25{:}13.234$ the cell is getting around that

NOTE Confidence: 0.9785853

 $00:25:13.234 \rightarrow 00:25:14.878$ PARP inhibitor and developing resistance

NOTE Confidence: 0.9785853

 $00:25:14.878 \longrightarrow 00:25:17.462$ so that we can add in another drug.

NOTE Confidence: 0.9785853

 $00{:}25{:}17{.}470 \dashrightarrow 00{:}25{:}19{.}717$ Do we have those kinds of diagnostics?

NOTE Confidence: 0.98452777

 $00:25:21.070 \rightarrow 00:25:22.072$ You're absolutely right,

NOTE Confidence: 0.98452777

 $00{:}25{:}22{.}072 \dashrightarrow 00{:}25{:}24{.}919$ this is exactly what we would like to have,

NOTE Confidence: 0.98452777

 $00:25:24.920 \rightarrow 00:25:26.846$ but we don't have it yet,

NOTE Confidence: 0.98452777

 $00{:}25{:}26.850 \dashrightarrow 00{:}25{:}29.418$ so we would like to be able to take a

NOTE Confidence: 0.98452777

 $00{:}25{:}31.562 \dashrightarrow 00{:}25{:}33.589$ tumor sample and ask the question,

NOTE Confidence: 0.98452777

 $00:25:33.590 \longrightarrow 00:25:36.479$ what is happening in this tumor?

NOTE Confidence: 0.98452777

 $00:25:36.480 \longrightarrow 00:25:38.085$ Is this patient likely to

- NOTE Confidence: 0.98452777
- 00:25:38.085 --> 00:25:39.690 respond to the PARP inhibitor?
- NOTE Confidence: 0.98452777
- $00:25:39.690 \longrightarrow 00:25:41.460$ We know that if they have
- NOTE Confidence: 0.98452777
- 00:25:41.460 --> 00:25:43.220 a defect in DNA repair,
- NOTE Confidence: 0.98452777
- $00:25:43.220 \longrightarrow 00:25:44.504$ they're likely to respond.
- NOTE Confidence: 0.98452777
- $00:25:44.504 \longrightarrow 00:25:46.908$ We know, as I told you, this bloom's
- NOTE Confidence: 0.98452777
- $00{:}25{:}46{.}908 \dashrightarrow 00{:}25{:}49{.}320$ helicase tends to go kind of overboard,
- NOTE Confidence: 0.98452777
- $00{:}25{:}49{.}320 \dashrightarrow 00{:}25{:}51{.}665$ and we think that we can design
- NOTE Confidence: 0.98452777
- $00{:}25{:}51{.}670 \dashrightarrow 00{:}25{:}53{.}395$ what we would call a
- NOTE Confidence: 0.98452777
- 00:25:53.395 00:25:54.775 biomarker of that activity,
- NOTE Confidence: 0.98452777
- $00:25:54.780 \longrightarrow 00:25:57.104$ because it generates far too much of
- NOTE Confidence: 0.98452777
- $00{:}25{:}57{.}104 \dashrightarrow 00{:}25{:}58{.}790$ this single stranded DNA generating
- NOTE Confidence: 0.98452777
- $00{:}25{:}58{.}790 \dashrightarrow 00{:}26{:}00{.}988$ single strand of DNA is a critical
- NOTE Confidence: 0.98452777
- 00:26:00.988 --> 00:26:03.057 part of homologous or combination,
- NOTE Confidence: 0.98452777
- $00:26:03.060 \longrightarrow 00:26:03.734$ but again,
- NOTE Confidence: 0.98452777
- $00:26:03.734 \rightarrow 00:26:06.850$ bloom's helicase seems to do too much of this,
- NOTE Confidence: 0.98452777

 $00:26:06.850 \rightarrow 00:26:08.852$ and we think that we might be

NOTE Confidence: 0.98452777

 $00{:}26{:}08.852 \dashrightarrow 00{:}26{:}11.008$ able to use proteins that bind

NOTE Confidence: 0.98452777

 $00:26:11.008 \rightarrow 00:26:13.053$ to that single stranded DNA,

NOTE Confidence: 0.98452777

00:26:13.060 --> 00:26:14.059 kind of quantitatively,

NOTE Confidence: 0.98452777

 $00:26:14.059 \longrightarrow 00:26:16.390$ and that may be an indication

NOTE Confidence: 0.98452777

 $00{:}26{:}16.452 \dashrightarrow 00{:}26{:}18.706$ that this is the mechanism by which NOTE Confidence: 0.98452777

 $00{:}26{:}18.706 \dashrightarrow 00{:}26{:}20.650$ these cells elevated PARP inhibitors.

NOTE Confidence: 0.98452777

00:26:20.650 - 00:26:21.853 Another major mechanism

NOTE Confidence: 0.98452777

 $00{:}26{:}21.853 \dashrightarrow 00{:}26{:}23.056$ of PARP inhibitor resistance

NOTE Confidence: 0.98452777

 $00{:}26{:}23.060 \dashrightarrow 00{:}26{:}24.690$ are so called reversion mutations.

NOTE Confidence: 0.98452777

 $00{:}26{:}24.690 \dashrightarrow 00{:}26{:}26.556$ This is where there's actually a

NOTE Confidence: 0.98452777

00:26:26.556 --> 00:26:28.599 second mutation in the BRCA gene,

NOTE Confidence: 0.98452777

 $00{:}26{:}28{.}600 \dashrightarrow 00{:}26{:}29{.}900$ which essentially can reconstitute

NOTE Confidence: 0.98452777

 $00:26:29.900 \rightarrow 00:26:30.875$ its normal function.

NOTE Confidence: 0.98452777

00:26:30.880 --> 00:26:31.762 In this case,

NOTE Confidence: 0.98452777

 $00:26:31.762 \longrightarrow 00:26:33.526$ the tumor no longer has

- NOTE Confidence: 0.98452777
- 00:26:33.526 --> 00:26:35.119 a DNA repair defect,
- NOTE Confidence: 0.98452777
- $00:26:35.120 \longrightarrow 00:26:36.704$ and so we'd really like to
- NOTE Confidence: 0.98452777
- $00:26:36.704 \longrightarrow 00:26:39.039$ be able to tell is there a
- NOTE Confidence: 0.98452777
- $00:26:39.039 \rightarrow 00:26:40.655$ reconstitution of normal repair.
- NOTE Confidence: 0.98452777
- $00{:}26{:}40.660 \dashrightarrow 00{:}26{:}42.568$ But may be that repair still has
- NOTE Confidence: 0.98452777
- $00{:}26{:}42.568 \dashrightarrow 00{:}26{:}44.580$ some defects that we can target,
- NOTE Confidence: 0.98452777
- $00:26:44.580 \longrightarrow 00:26:46.855$ or is repair kind of totally normal,
- NOTE Confidence: 0.98452777
- 00:26:46.860 --> 00:26:48.883 in which case we know we're going
- NOTE Confidence: 0.98452777
- $00{:}26{:}48.883 \dashrightarrow 00{:}26{:}50.916$ to have to think about another
- NOTE Confidence: 0.98452777
- $00:26:50.916 \rightarrow 00:26:53.106$ type of therapy to treat that patient.
- $00{:}26{:}53{.}434 \dashrightarrow 00{:}26{:}55{.}378$ So these are in development and
- NOTE Confidence: 0.98452777
- $00:26:55.378 \rightarrow 00:26:57.281$ this is something we're really
- NOTE Confidence: 0.98452777
- $00:26:57.281 \longrightarrow 00:26:58.589$ interested in,
- NOTE Confidence: 0.98452777
- $00:26:58.590 \longrightarrow 00:27:00.050$ particularly again with our
- NOTE Confidence: 0.98452777
- $00{:}27{:}00{.}050 \dashrightarrow 00{:}27{:}02{.}240$ colleagues here and at Yale Cancer Center.
- NOTE Confidence: 0.98452777
- $00:27:02.240 \longrightarrow 00:27:04.496$ To continue to push forward by

 $00{:}27{:}04{.}496 \dashrightarrow 00{:}27{:}06{.}406$ partnering with those clinicians who

NOTE Confidence: 0.98452777

 $00{:}27{:}06{.}406 \dashrightarrow 00{:}27{:}08{.}807$ are running clinical trials in this space.

NOTE Confidence: 0.98452777

 $00{:}27{:}08{.}810$ --> $00{:}27{:}10{.}640$ In patients with BRCA or NOTE Confidence: $0{.}98452777$

 $00{:}27{:}10.640 \dashrightarrow 00{:}27{:}11.738$ other homologous recombination

NOTE Confidence: 0.98452777

 $00{:}27{:}11.738 \dashrightarrow 00{:}27{:}13.457$ defects who have been enrolled

NOTE Confidence: 0.98452777

 $00{:}27{:}13.457 \dashrightarrow 00{:}27{:}15.305$ on PARP inhibitors and looking at

NOTE Confidence: 0.98452777

 $00{:}27{:}15{.}305 \dashrightarrow 00{:}27{:}16{.}840$ those resistance mechanisms.

NOTE Confidence: 0.98452777

 $00{:}27{:}16.840 \dashrightarrow 00{:}27{:}19.024$ And if we can develop these

NOTE Confidence: 0.98452777

 $00:27:19.024 \rightarrow 00:27:20.116$ types of biomarkers.

NOTE Confidence: 0.98960394

 $00:27:20.870 \longrightarrow 00:27:23.018$ I mean it's so fascinating

NOTE Confidence: 0.98960394

 $00{:}27{:}23.018 \dashrightarrow 00{:}27{:}25.675$ thinking about the fact that

NOTE Confidence: 0.98960394

 $00:27:25.675 \rightarrow 00:27:27.595$ when we started this conversation,

NOTE Confidence: 0.98960394

 $00{:}27{:}27{.}600 \dashrightarrow 00{:}27{:}29{.}992$ we started by saying that you know DNA

NOTE Confidence: 0.98960394

00:27:29.992 --> 00:27:33.100 can be damaged in different ways and each

NOTE Confidence: 0.98960394

 $00:27:33.100 \longrightarrow 00:27:35.460$ requires a specific repair mechanism.

00:27:35.460 --> 00:27:38.082 But now thinking about how you're

NOTE Confidence: 0.98960394

00:27:38.082 --> 00:27:39.830 actually taking your science

NOTE Confidence: 0.98960394

00:27:39.905 --> 00:27:41.809 and in a way kind of again,

NOTE Confidence: 0.98960394

 $00:27:41.810 \rightarrow 00:27:43.310$ moving towards personalized medicine,

NOTE Confidence: 0.98960394

 $00:27:43.310 \longrightarrow 00:27:44.434$ figuring out, well,

NOTE Confidence: 0.98960394

 $00:27:44.434 \rightarrow 00:27:46.678$ if somebody develops resistance,

NOTE Confidence: 0.98960394

 $00:27:46.680 \longrightarrow 00:27:48.540$ how exactly is that resistance

NOTE Confidence: 0.98960394

 $00:27:48.540 \longrightarrow 00:27:49.284$ mechanism functioning?

NOTE Confidence: 0.98960394

 $00:27:49.290 \longrightarrow 00:27:51.660$ And how can we get around it?

NOTE Confidence: 0.98436666

 $00{:}27{:}53{.}530 \dashrightarrow 00{:}27{:}56{.}085$ Absolutely, and I want to highlight

NOTE Confidence: 0.98436666

00:27:56.090 - 00:27:57.908 we can do this really efficiently

NOTE Confidence: 0.98436666

 $00:27:57.908 \longrightarrow 00:27:59.890$ in cells in a laboratory that's

NOTE Confidence: 0.98436666

 $00{:}27{:}59{.}890 \dashrightarrow 00{:}28{:}02{.}333$ never going to tell us about what

NOTE Confidence: 0.98436666

 $00{:}28{:}02{.}333 \dashrightarrow 00{:}28{:}04{.}879$ is happening in individual patients.

NOTE Confidence: 0.98436666

00:28:04.880 --> 00:28:07.088 So really, this discovery requires the

NOTE Confidence: 0.98436666

 $00:28:07.088 \rightarrow 00:28:08.969$ commitment of patients who've been

- NOTE Confidence: 0.98436666
- $00:28:08.969 \rightarrow 00:28:10.729$ enrolled on these clinical trials.
- NOTE Confidence: 0.98436666
- $00{:}28{:}10.730 \dashrightarrow 00{:}28{:}12.854$ That's not an easy thing to
- NOTE Confidence: 0.98436666
- $00:28:12.854 \longrightarrow 00:28:15.120$ ask of patients in this case.
- NOTE Confidence: 0.98436666
- $00:28:15.120 \rightarrow 00:28:17.280$ For example, they've signed up for
- NOTE Confidence: 0.98436666
- 00:28:17.280 --> 00:28:19.150 serial biopsies of their tumor,
- NOTE Confidence: 0.98436666
- $00:28:19.150 \longrightarrow 00:28:21.040$ but that is absolutely essential
- NOTE Confidence: 0.98436666
- $00:28:21.040 \longrightarrow 00:28:23.630$ for us to continue to discover
- NOTE Confidence: 0.98436666
- $00:28:23.630 \rightarrow 00:28:25.734$ the mechanisms that are at play and for
- NOTE Confidence: 0.98436666
- $00{:}28{:}25{.}734 \dashrightarrow 00{:}28{:}28{.}128$ us to come up with better treatments.
- NOTE Confidence: 0.93307334
- 00:28:28.760 --> 00:28:30.908 Doctor Megan King is an associate
- NOTE Confidence: 0.93307334
- $00:28:30.908 \rightarrow 00:28:33.439$ professor of cell biology and of molecular,
- NOTE Confidence: 0.93307334
- $00:28:33.440 \longrightarrow 00:28:34.880$ cellular, and developmental biology
- NOTE Confidence: 0.93307334
- $00{:}28{:}34{.}880 \dashrightarrow 00{:}28{:}37{.}040$ at the Yale School of Medicine.
- NOTE Confidence: 0.93307334
- $00{:}28{:}37{.}040 \dashrightarrow 00{:}28{:}38{.}596$ If you have questions,
- NOTE Confidence: 0.93307334
- $00{:}28{:}38{.}596 \dashrightarrow 00{:}28{:}40{.}541$ the address is cancer answers at
- NOTE Confidence: 0.93307334

 $00{:}28{:}40{.}541 \dashrightarrow 00{:}28{:}42{.}698$ yale.edu and past editions of the

NOTE Confidence: 0.93307334

 $00{:}28{:}42.698 \dashrightarrow 00{:}28{:}44.793$ program are available in audio and

NOTE Confidence: 0.93307334

 $00{:}28{:}44.793 \dashrightarrow 00{:}28{:}47.117$ written form at yale cancercenter.org.

NOTE Confidence: 0.93307334

 $00{:}28{:}47{.}120 \dashrightarrow 00{:}28{:}49{.}440$ We hope you'll join us next week to

NOTE Confidence: 0.93307334

 $00{:}28{:}49{.}440 \dashrightarrow 00{:}28{:}51{.}676$ learn more about the fight against

NOTE Confidence: 0.93307334

00:28:51.676 --> 00:28:53.661 cancer here on Connecticut Public Radio.

NOTE Confidence: 0.93307334

00:28:53.661 --> 00:28:55.643 Funding for Yale Cancer

NOTE Confidence: 0.93307334

00:28:55.643 --> 00:28:57.533 Answers is provided by Smilow

NOTE Confidence: 0.93307334

 $00{:}28{:}57{.}533 \dashrightarrow 00{:}29{:}00{.}072$ Cancer Hospital and Astra Zeneca.