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 --> 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: 0.977658900000001

00:00:11.817 --> 00:00:13.817 Yale Cancer Answers features the

NOTE Confidence: 0.977658900000001

00:00:13.817 --> 00:00:16.193 latest information on cancer care by

NOTE Confidence: 0.977658900000001

00:00:16.193 --> 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: 0.977658900000001

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 --> 00:00:32.076 cellular, and developmental biology

NOTE Confidence: 0.977658900000001

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 --> 00:00:42.014 Megan, maybe we can start off with you

NOTE Confidence: 0.98509663

00:00:42.014 --> 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 --> 00:00:49.605 involved in this research project to

NOTE Confidence: 0.98509663

00:00:49.610 --> 00:00:50.314 begin with.

NOTE Confidence: 0.98509663

00:00:50.314 --> 00:00:52.426 Yeah, so it's very interesting thinking

NOTE Confidence: 0.98509663

00:00:52.426 --> 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 --> 00:00:59.086 actually including both of my parents,

NOTE Confidence: 0.98509663

00:00:59.090 --> 00:01:01.540 but I always gravitated towards science,

NOTE Confidence: 0.98509663

00:01:01.540 --> 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 --> 00:01:07.945 and it was actually the

NOTE Confidence: 0.98509663

00:01:07.945 --> 00:01:09.413 section of my textbook

NOTE Confidence: 0.98509663

00:01:09.420 --> 00:01:11.835 on cancer that really provided for me,

NOTE Confidence: 0.98509663

00:01:11.840 --> 00:01:14.088 I think the first kind of window into

NOTE Confidence: 0.98509663

00:01:14.088 --> 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 --> 00:01:22.182 different from becoming a medical doctor,

NOTE Confidence: 0.98509663

00:01:22.190 --> 00:01:24.574 which I think all of us are a

NOTE Confidence: 0.98509663

00:01:24.574 --> 00:01:26.670 little bit more familiar with,

NOTE Confidence: 0.98509663

00:01:26.670 --> 00:01:27.708 certainly as children.

NOTE Confidence: 0.98509663

00:01:27.708 --> 00:01:29.784 And so I've been reflecting on

NOTE Confidence: 0.98509663

00:01:29.784 --> 00:01:31.805 that recently because it's been a

NOTE Confidence: 0.98509663

00:01:31.805 --> 00:01:33.839 bit of a circuitous route that's

NOTE Confidence: 0.98509663

00:01:33.839 --> 00:01:35.987 brought me back to Cancer Research.

NOTE Confidence: 0.98509663

00:01:35.990 --> 00:01:37.745 I really trended towards very

NOTE Confidence: 0.98509663

00:01:37.745 --> 00:01:39.500 fundamental kind of basic science.

NOTE Confidence: 0.98509663

00:01:39.500 --> 00:01:41.750 Questions for my initial training

NOTE Confidence: 0.98509663

00:01:41.750 --> 00:01:44.000 as an undergraduate and graduate

NOTE Confidence: 0.98509663

00:01:44.068 --> 00:01:46.595 student and even into my

NOTE Confidence: 0.98509663

00:01:46.595 --> 00:01:48.500 postdoc period where one typically

NOTE Confidence: 0.98509663

00:01:48.500 --> 00:01:51.125 is defining the kind of areas of

NOTE Confidence: 0.98509663

00:01:51.125 --> 00:01:53.100 research that they will pursue,

NOTE Confidence: 0.98509663

00:01:53.100 --> 00:01:55.100 and in their independent laboratory.

NOTE Confidence: 0.98509663

00:01:55.100 --> 00:01:57.440 But I discovered a connection between

NOTE Confidence: 0.98509663

00:01:57.440 --> 00:01:59.899 the cell biology of the nucleus,

NOTE Confidence: 0.98509663

00:01:59.900 --> 00:02:02.300 which is something that I had

NOTE Confidence: 0.98509663

00:02:02.300 --> 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 --> 00:02:09.590 so that is the mechanisms that

NOTE Confidence: 0.98509663

00:02:09.590 --> 00:02:11.708 maintain the DNA blueprint

NOTE Confidence: 0.98509663

00:02:11.708 --> 00:02:14.231 as it should be and that was

NOTE Confidence: 0.98509663

00:02:14.231 --> 00:02:16.307 really just something that I had

NOTE Confidence: 0.98509663

00:02:16.307 --> 00:02:18.349 not focused on before

NOTE Confidence: 0.98509663

00:02:18.350 --> 00:02:20.989 but it really changed the direction of

NOTE Confidence: 0.98509663

00:02:20.989 --> 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 --> 00:02:28.858 are able to contribute to the mechanisms

NOTE Confidence: 0.98509663

00:02:28.858 --> 00:02:30.760 that maintain that genetic code.

NOTE Confidence: 0.98509663

00:02:30.760 --> 00:02:32.590 So tell us more about

NOTE Confidence: 0.988603650000001

00:02:32.590 --> 00:02:35.430 that. I think some of us can

NOTE Confidence: 0.988603650000001

00:02:35.430 --> 00:02:37.804 remember back to junior high biology

NOTE Confidence: 0.988603650000001

00:02:37.804 --> 00:02:41.069 where we kind of know what a cell is.

NOTE Confidence: 0.988603650000001

00:02:41.070 --> 00:02:43.622 And we know what a nucleus is and

NOTE Confidence: 0.988603650000001

00:02:43.622 --> 00:02:45.771 housed within that nucleus is the

NOTE Confidence: 0.988603650000001

00:02:45.771 --> 00:02:47.931 DNA which is responsible for that

NOTE Confidence: 0.988603650000001

00:02:48.000 --> 00:02:49.970 genetic blueprint as you say.

NOTE Confidence: 0.988603650000001

00:02:49.970 --> 00:02:52.189 So tell us more about the connection

NOTE Confidence: 0.988603650000001

00:02:52.189 --> 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 --> 00:02:57.800 Yeah, so I was

NOTE Confidence: 0.9847528

00:02:57.800 --> 00:02:59.894 also fascinated with this

NOTE Confidence: 0.9847528

00:02:59.894 --> 00:03:02.428 idea of the the nucleus which

NOTE Confidence: 0.9847528

00:03:02.428 --> 00:03:04.920 is the organelle that houses the DNA,

NOTE Confidence: 0.9847528

00:03:04.920 --> 00:03:07.056 being kind of the brain.

NOTE Confidence: 0.9847528

00:03:07.056 --> 00:03:09.192 Having all of the kind of

NOTE Confidence: 0.9847528

00:03:09.192 --> 00:03:11.080 control and that plan

NOTE Confidence: 0.9847528

00:03:11.080 --> 00:03:13.870 for the cell, but I think one of the

NOTE Confidence: 0.9847528

00:03:13.870 --> 00:03:16.177 things that maybe isn't always captured

NOTE Confidence: 0.9847528

00:03:16.177 --> 00:03:19.423 when we kind of make that diorama during

NOTE Confidence: 0.9847528

00:03:19.423 --> 00:03:22.356 you know grade school is that actually

NOTE Confidence: 0.9847528

00:03:22.360 --> 00:03:25.368 it's not just a big ball of yarn,

NOTE Confidence: 0.9847528

00:03:25.370 --> 00:03:28.010 but actually the DNA has lots of different

NOTE Confidence: 0.9847528

00:03:28.010 --> 00:03:30.393 regions and these regions are important

NOTE Confidence: 0.9847528

00:03:30.393 --> 00:03:32.883 for different aspects of that blueprint.

NOTE Confidence: 0.9847528

00:03:32.890 --> 00:03:35.898 And they're not all created equal.

NOTE Confidence: 0.9847528

00:03:35.900 --> 00:03:38.644 There are specific regions of the DNA

NOTE Confidence: 0.9847528

00:03:38.644 --> 00:03:41.550 that are far more prone to damage.

NOTE Confidence: 0.9847528

00:03:41.550 --> 00:03:43.727 And there are also mechanisms to repair

NOTE Confidence: 0.9847528

00:03:43.727 --> 00:03:45.949 that damage that may be quite specific,

NOTE Confidence: 0.9847528

00:03:45.950 --> 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 --> 00:03:58.818 more like a Carpenter.

NOTE Confidence: 0.9847528

00:03:58.820 --> 00:03:59.696 Or for any

NOTE Confidence: 0.9847528

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

NOTE Confidence: 0.9847528

00:04:01.808 --> 00:04:04.160 to have a different kind of approach

NOTE Confidence: 0.9847528

00:04:04.160 --> 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 --> 00:04:08.866 that's similar.

NOTE Confidence: 0.9847528

00:04:08.870 --> 00:04:10.154 There are actually different

NOTE Confidence: 0.9847528

00:04:10.154 --> 00:04:11.759 DNA repair mechanisms and you

NOTE Confidence: 0.9847528

00:04:11.760 --> 00:04:14.301 really need to use the right mechanism

NOTE Confidence: 0.9847528

00:04:14.301 --> 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 --> 00:04:21.141 actually dictated by these different

NOTE Confidence: 0.9847528

00:04:21.141 --> 00:04:23.876 flavors of the regions of DNA and

NOTE Confidence: 0.9847528

00:04:23.876 --> 00:04:25.866 also physically where those different

NOTE Confidence: 0.9847528

00:04:25.866 --> 00:04:28.555 regions of the DNA blueprint are

NOTE Confidence: 0.9847528

00:04:28.555 --> 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 --> 00:04:34.569 compartmentalized kind of network

00:04:36.564 --> 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 --> 00:04:43.258 coding material,

NOTE Confidence: 0.9847528

00:04:43.258 --> 00:04:44.350 so it's not

NOTE Confidence: 0.98854697

00:04:44.350 --> 00:04:47.052 just where the break occurs in the

NOTE Confidence: 0.98854697

00:04:47.052 --> 00:04:50.149 DNA or what kind of a break it is,

NOTE Confidence: 0.98854697

00:04:50.150 --> 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 --> 00:04:55.598 but where exactly it's

NOTE Confidence: 0.98854697

00:04:55.598 --> 00:04:57.046 located within the nucleus.

NOTE Confidence: 0.98920226

00:04:57.760 --> 00:05:00.357 We think about two components.

NOTE Confidence: 0.98920226

00:05:00.360 --> 00:05:02.580 One exactly as you say physically,

NOTE Confidence: 0.98920226

00:05:02.580 --> 00:05:05.548 where is that DNA break in the nucleus?

NOTE Confidence: 0.98920226

00:05:05.550 --> 00:05:07.405 And then there's also the

NOTE Confidence: 0.98920226

00:05:07.405 --> 00:05:09.260 other attributes of the DNA.

NOTE Confidence: 0.98920226

00:05:09.260 --> 00:05:12.599 So DNA doesn't live on its own.

NOTE Confidence: 0.98920226

00:05:12.600 --> 00:05:14.910 It's actually wrapped up and packaged

NOTE Confidence: 0.98920226

00:05:14.910 --> 00:05:16.896 around proteins that are called

NOTE Confidence: 0.98920226

00:05:16.896 --> 00:05:19.170 histones and this packaging is

NOTE Confidence: 0.98920226

00:05:19.170 --> 00:05:21.712 really important for whether a

NOTE Confidence: 0.98920226

00:05:21.712 --> 00:05:24.079 particular gene may be expressed or not.

NOTE Confidence: 0.98920226

00:05:24.079 --> 00:05:26.522 It turns out that a DNA break

NOTE Confidence: 0.98920226

00:05:26.522 --> 00:05:29.190 in a region of the genome

NOTE Confidence: 0.98920226

00:05:29.190 --> 00:05:31.326 that is coding for a protein,

NOTE Confidence: 0.98920226

00:05:31.330 --> 00:05:33.376 so it's going to be transcribed

NOTE Confidence: 0.98920226

00:05:33.376 --> 00:05:35.543 into the messenger RNA and then

NOTE Confidence: 0.98920226

00:05:35.543 --> 00:05:37.015 translated into a protein.

NOTE Confidence: 0.98920226

00:05:37.020 --> 00:05:39.144 Those regions of the genome are

NOTE Confidence: 0.98920226

00:05:39.144 --> 00:05:41.332 a bit different than regions of

NOTE Confidence: 0.98920226

00:05:41.332 --> 00:05:43.426 the genome that may be silent,

NOTE Confidence: 0.98920226

00:05:43.430 --> 00:05:46.364 and so that also just leads to both some

NOTE Confidence: 0.98920226

00:05:46.364 --> 00:05:48.288 challenges for DNA repair mechanisms

NOTE Confidence: 0.98920226

00:05:48.288 --> 00:05:50.586 and also some activities that

NOTE Confidence: 0.98920226

00:05:50.657 --> 00:05:53.072 may actually make it more prone to

NOTE Confidence: 0.98920226

00:05:53.072 --> 00:05:54.806 the accumulation of DNA damage.

NOTE Confidence: 0.98920226

00:05:54.806 --> 00:05:57.242 And so we think of both

NOTE Confidence: 0.98920226

00:05:57.242 --> 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 --> 00:06:02.108 and also where it is in context

NOTE Confidence: 0.98920226

00:06:02.108 --> 00:06:04.287 of what else is happening in

NOTE Confidence: 0.98920226

00:06:04.287 --> 00:06:06.017 that region of the DNA.

00:06:06.400 --> 00:06:09.248 So we know that DNA can incur various

NOTE Confidence: 0.98681915

00:06:09.248 --> 00:06:12.180 forms of damage that can be in coding

NOTE Confidence: 0.98681915

00:06:12.180 --> 00:06:14.849 regions or in non coding regions.

NOTE Confidence: 0.98681915

00:06:14.850 --> 00:06:17.154 How does that then evolve into

NOTE Confidence: 0.98681915

00:06:17.154 --> 00:06:18.690 your research with cancer?

NOTE Confidence: 0.98681915

00:06:18.690 --> 00:06:21.175 So initially as I mentioned our

NOTE Confidence: 0.98681915

00:06:21.175 --> 00:06:23.887 interest was the idea that these

NOTE Confidence: 0.98681915

00:06:23.887 --> 00:06:25.857 different locations in the nucleus

NOTE Confidence: 0.98681915

00:06:25.857 --> 00:06:28.654 might be important for making sure that

NOTE Confidence: 0.98681915

00:06:28.654 --> 00:06:31.401 those breaks are repaired by the right

NOTE Confidence: 0.98681915

00:06:31.401 --> 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 --> 00:06:42.460 it's happening and that as it turns out

NOTE Confidence: 0.98681915

00:06:42.460 --> 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 --> 00:06:52.478 invested in, is building so called

NOTE Confidence: 0.98681915

00:06:52.478 --> 00:06:54.752 assays where we can actually watch

NOTE Confidence: 0.98681915

00:06:54.823 --> 00:06:56.107 a single DNA break,

NOTE Confidence: 0.98681915

00:06:56.110 --> 00:06:57.566 which we actually control.

NOTE Confidence: 0.98681915

00:06:57.566 --> 00:07:00.478 So we induce the break to occur in

NOTE Confidence: 0.98681915

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

NOTE Confidence: 0.98681915

00:07:03.110 --> 00:07:05.342 and then we actually follow the

NOTE Confidence: 0.98681915

00:07:05.342 --> 00:07:08.127 repair of that break in real time and

NOTE Confidence: 0.98681915

00:07:08.130 --> 00:07:09.970 once we built this system,

NOTE Confidence: 0.98681915

00:07:09.970 --> 00:07:12.602 we became very interested in how we might

NOTE Confidence: 0.98681915

00:07:12.602 --> 00:07:14.867 leverage it to answer some important

NOTE Confidence: 0.98681915

00:07:14.867 --> 00:07:16.792 questions that were really arising

NOTE Confidence: 0.98681915

00:07:16.792 --> 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 --> 00:07:22.146 I was driven towards those questions

NOTE Confidence: 0.98681915

00:07:22.146 --> 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 --> 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 --> 00:07:35.522 a way of connecting the kind of questions

NOTE Confidence: 0.98681915

00:07:35.522 --> 00:07:38.000 that I had become interested in,

NOTE Confidence: 0.98681915

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 --> 00:07:44.670 to where we had a real need to

NOTE Confidence: 0.98681915

00:07:44.746 --> 00:07:46.490 understand specific questions in

NOTE Confidence: 0.98681915

00:07:46.490 --> 00:07:48.670 the field of DNA repair,

NOTE Confidence: 0.98681915

00:07:48.670 --> 00:07:50.455 and particularly those that were

NOTE Confidence: 0.98681915

00:07:50.455 --> 00:07:52.688 relevant to the kind of therapies

NOTE Confidence: 0.98681915

00:07:52.688 --> 00:07:55.327 that might be used in the context

NOTE Confidence: 0.98681915

00:07:55.327 --> 00:07:56.400 where patients have

NOTE Confidence: 0.986171

00:07:56.400 --> 00:07:58.969 defects in DNA repair within their tumors.

NOTE Confidence: 0.986171

00:07:58.970 --> 00:08:00.065 So first question,

NOTE Confidence: 0.986171

00:08:00.065 --> 00:08:02.620 how exactly do you watch DNA being

NOTE Confidence: 0.986171

00:08:02.693 --> 00:08:05.272 repaired in real time?

NOTE Confidence: 0.986171

00:08:05.272 --> 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

NOTE Confidence: 0.986171

00:08:10.858 --> 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 --> 00:08:24.244 But to actually see DNA being repaired?

NOTE Confidence: 0.986171

00:08:24.250 --> 00:08:27.580 I mean presumably that occurs at a base pair

NOTE Confidence: 0.986171

00:08:27.580 --> 00:08:30.538 level and that's just fascinating to me.

NOTE Confidence: 0.986171

00:08:30.540 --> 00:08:32.906 So how exactly do you do that

NOTE Confidence: 0.986171

00:08:32.906 --> 00:08:35.340 and what kind of magnification

NOTE Confidence: 0.986171

00:08:35.340 --> 00:08:37.069 would you need even to see that?

NOTE Confidence: 0.9868847

00:08:37.770 --> 00:08:39.877 Yeah, that's a great question and honestly,

NOTE Confidence: 0.9868847

00:08:39.880 --> 00:08:42.890 this is why I'm a cell biologist at the end

NOTE Confidence: 0.9868847

00:08:42.960 --> 00:08:45.900 of the day because we love to just look.

NOTE Confidence: 0.9868847

00:08:45.900 --> 00:08:48.258 If we have a way we can look at

NOTE Confidence: 0.9868847

00:08:48.258 --> 00:08:50.256 something happening in real time that

NOTE Confidence: 0.9868847

00:08:50.256 --> 00:08:52.818 is always the best thing in the world.

NOTE Confidence: 0.9868847

00:08:52.820 --> 00:08:53.780 However, as you say,

NOTE Confidence: 0.9868847

00:08:53.780 --> 00:08:56.258 it's not easy and so our work is built

NOTE Confidence: 0.9868847

00:08:56.258 --> 00:08:57.888 on really critical discoveries that

NOTE Confidence: 0.9868847

00:08:57.888 --> 00:09:00.040 have driven cell biology, in particular,

NOTE Confidence: 0.9868847

00:09:00.040 --> 00:09:01.937 and I'll just tell you about two

NOTE Confidence: 0.9868847

00:09:01.937 --> 00:09:03.802 of those that are critical for

NOTE Confidence: 0.9868847

00:09:03.802 --> 00:09:05.457 the assays that we've built.

NOTE Confidence: 0.9868847

00:09:05.460 --> 00:09:07.350 The first is the advent of

NOTE Confidence: 0.9868847

00:09:07.350 --> 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 --> 00:09:10.715 and red fluorescent proteins.

NOTE Confidence: 0.9868847

00:09:10.720 --> 00:09:12.790 Now we have an entire rainbow

NOTE Confidence: 0.9868847

00:09:12.790 --> 00:09:14.170 of these fluorescent proteins,

NOTE Confidence: 0.9868847

00:09:14.170 --> 00:09:16.150 and so these are proteins that

NOTE Confidence: 0.9868847

00:09:16.150 --> 00:09:18.604 fold up and they're able to make

NOTE Confidence: 0.9868847

00:09:18.604 --> 00:09:20.379 what's called a chromophore

NOTE Confidence: 0.9868847

00:09:20.380 --> 00:09:22.240 and we can actually follow that

NOTE Confidence: 0.9868847

00:09:22.240 --> 00:09:24.170 specific molecule in a microscope.

NOTE Confidence: 0.9868847

00:09:24.170 --> 00:09:26.770 And what we do is we basically stitch

NOTE Confidence: 0.9868847

00:09:26.770 --> 00:09:28.569 that fluorescent protein onto a

NOTE Confidence: 0.9868847

00:09:28.569 --> 00:09:30.374 protein that we're interested in,

NOTE Confidence: 0.9868847

00:09:30.380 --> 00:09:32.718 and now we can follow our favorite

NOTE Confidence: 0.9868847

00:09:32.718 --> 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 --> 00:09:38.309 that can specifically detect

NOTE Confidence: 0.9868847

00:09:38.310 --> 00:09:39.291 that fluorescent protein,

NOTE Confidence: 0.9868847

00:09:39.291 --> 00:09:41.253 and so that's one technology

NOTE Confidence: 0.9868847

00:09:41.253 --> 00:09:42.629 that's absolutely critical.

NOTE Confidence: 0.9868847

00:09:42.630 --> 00:09:43.278 The other,

NOTE Confidence: 0.9868847

00:09:43.278 --> 00:09:45.546 and I think this really speaks to

NOTE Confidence: 0.9868847

00:09:45.546 --> 00:09:47.892 the importance of kind of basic

NOTE Confidence: 0.9868847

00:09:47.892 --> 00:09:49.847 science discoveries and what

NOTE Confidence: 0.9868847

00:09:49.920 --> 00:09:52.026 really has impacts on human

NOTE Confidence: 0.9868847

00:09:52.026 --> 00:09:54.714 health these days is that we use

NOTE Confidence: 0.9868847

00:09:54.714 --> 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 --> 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 --> 00:10:05.310 and we essentially take that little sequence,

NOTE Confidence: 0.9868847

00:10:05.310 --> 00:10:09.030 and we put it into the place in the genome

NOTE Confidence: 0.9868847

00:10:09.030 --> 00:10:10.992 we're interested in and then we

NOTE Confidence: 0.9868847

00:10:10.992 --> 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 --> 00:10:17.672 and so we can monitor any kind of

NOTE Confidence: 0.9868847

00:10:17.672 --> 00:10:20.021 region of the genome that we want

NOTE Confidence: 0.9868847

00:10:20.021 --> 00:10:22.870 just by doing a little bit of editing

NOTE Confidence: 0.9868847

00:10:22.870 --> 00:10:25.114 to that genome and putting these

NOTE Confidence: 0.9868847

00:10:25.114 --> 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 --> 00:10:30.976 because that's what we want to be studying.

NOTE Confidence: 0.9868847

00:10:30.980 --> 00:10:33.038 In terms of the magnification,

NOTE Confidence: 0.9868847

00:10:33.040 --> 00:10:34.129 you're absolutely right.

NOTE Confidence: 0.9868847

00:10:34.129 --> 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 --> 00:10:40.656 even with a magnification,

NOTE Confidence: 0.9868847

00:10:40.656 --> 00:10:43.504 usually between 100 and 1000 fold over

NOTE Confidence: 0.9868847

00:10:43.504 --> 00:10:46.104 what you could see with the naked eye.

NOTE Confidence: 0.98792106

00:10:46.700 --> 00:10:49.493 Wow, so essentially you can clip the

NOTE Confidence: 0.98792106

00:10:49.493 --> 00:10:52.448 DNA where you want to make a break.

NOTE Confidence: 0.98792106

00:10:52.450 --> 00:10:54.742 Insert a bacterial strand of genetic

NOTE Confidence: 0.98792106

00:10:54.742 --> 00:10:56.850 material, flag it with a particular

NOTE Confidence: 0.98792106

00:10:56.850 --> 00:11:00.228 flag so you know where the break is and

NOTE Confidence: 0.98792106

00:11:00.228 --> 00:11:02.598 then have these chromophores which can

NOTE Confidence: 0.98792106

00:11:02.670 --> 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 --> 00:11:13.337 we have to know a lot about DNA repair,

NOTE Confidence: 0.9764157

00:11:13.340 --> 00:11:14.548 and fortunately,

NOTE Confidence: 0.9764157

00:11:14.548 --> 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 --> 00:11:20.679 and so building again on the knowledge

NOTE Confidence: 0.9764157

00:11:20.679 --> 00:11:22.779 of many others we know pretty well

NOTE Confidence: 0.9764157

00:11:22.779 --> 00:11:25.152 about the kind of timing and the events

NOTE Confidence: 0.9764157

00:11:25.152 --> 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 --> 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 --> 00:11:34.700 we want to know what's happening

NOTE Confidence: 0.9764157

00:11:34.768 --> 00:11:36.520 at the base pair level,

NOTE Confidence: 0.9764157

00:11:36.520 --> 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 --> 00:11:42.420 that small in this assay,

NOTE Confidence: 0.9764157

00:11:42.420 --> 00:11:44.412 so we're using proxies of factors

NOTE Confidence: 0.9764157

00:11:44.412 --> 00:11:47.087 that we know will show up at different

NOTE Confidence: 0.9764157

00:11:47.087 --> 00:11:49.001 points and that allows us to

NOTE Confidence: 0.9764157

00:11:49.072 --> 00:11:51.420 essentially monitor distinct events,

NOTE Confidence: 0.9764157

00:11:51.420 --> 00:11:53.788 because if we build up our

NOTE Confidence: 0.9764157

00:11:53.788 --> 00:11:56.214 library of these different flags that

NOTE Confidence: 0.9764157

00:11:56.214 --> 00:11:58.419 indicate different times and repair

NOTE Confidence: 0.9764157

00:11:58.419 --> 00:12:01.168 them more able to monitor those events,

NOTE Confidence: 0.9764157

00:12:01.170 --> 00:12:03.045 and we're also able to

NOTE Confidence: 0.9764157

00:12:03.045 --> 00:12:04.545 monitor them in single,

NOTE Confidence: 0.9764157

00:12:04.550 --> 00:12:05.750 individual cells,

NOTE Confidence: 0.9764157

00:12:05.750 --> 00:12:08.150 and it's turned out that that's

NOTE Confidence: 0.9764157

00:12:08.150 --> 00:12:09.280 really important.

NOTE Confidence: 0.9764157

00:12:09.280 --> 00:12:11.728 Because if we look at a million

NOTE Confidence: 0.9764157

00:12:11.728 --> 00:12:13.368 cells doing something they all kind

NOTE Confidence: 0.9764157

00:12:13.368 --> 00:12:15.805 of do it on a little bit different

NOTE Confidence: 0.9764157

00:12:15.805 --> 00:12:18.304 time over a little bit different time,

NOTE Confidence: 0.9764157

00:12:18.310 --> 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 --> 00:12:23.728 these events in single cells,

NOTE Confidence: 0.9764157

00:12:23.730 --> 00:12:25.560 that really gives us a resolution

NOTE Confidence: 0.9764157

00:12:25.560 --> 00:12:26.780 that's really important for

NOTE Confidence: 0.9764157

00:12:26.839 --> 00:12:28.939 being able to make very

NOTE Confidence: 0.9764157

00:12:28.939 --> 00:12:30.349 mechanistic conclusions from the data.

NOTE Confidence: 0.9873662

00:12:31.140 --> 00:12:33.276 So we understand that you've got

NOTE Confidence: 0.9873662

00:12:33.276 --> 00:12:36.122 DNA that can get injured and it can

NOTE Confidence: 0.9873662

00:12:36.122 --> 00:12:38.570 get injured in a variety of ways

NOTE Confidence: 0.9873662

00:12:38.570 --> 00:12:41.048 at a variety of places,

NOTE Confidence: 0.9873662

00:12:41.050 --> 00:12:42.820 each of which requires a

NOTE Confidence: 0.9873662

00:12:42.820 --> 00:12:44.590 specific mechanism to repair it.

NOTE Confidence: 0.9873662

00:12:44.590 --> 00:12:46.654 And we now understand that you've

NOTE Confidence: 0.9873662

00:12:46.654 --> 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 --> 00:12:53.432 so tell us more about how this gets

NOTE Confidence: 0.9873662

00:12:53.432 --> 00:12:55.570 into cancer and into therapeutics

NOTE Confidence: 0.9873662

00:12:55.570 --> 00:12:58.594 And we'll have to do that as soon as

NOTE Confidence: 0.9873662

00:12:58.594 --> 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 --> 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 --> 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 --> 00:13:17.609 to eliminate cancer as a cause of death.

NOTE Confidence: 0.9213101

00:13:17.610 --> 00:13:19.350 Learn more at astrazeneca-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 --> 00:13:28.550 approximately 3500 women will be

NOTE Confidence: 0.990294

00:13:28.550 --> 00:13:30.790 diagnosed with breast cancer this year,

NOTE Confidence: 0.990294

00:13:30.790 --> 00:13:32.290 but there is hope,

NOTE Confidence: 0.990294

00:13:32.290 --> 00:13:33.790 thanks to earlier detection,

NOTE Confidence: 0.990294

00:13:33.790 --> 00:13:35.640 noninvasive treatments and the development

NOTE Confidence: 0.990294

00:13:35.640 --> 00:13:38.289 of novel therapies to fight breast cancer.

NOTE Confidence: 0.990294

00:13:38.290 --> 00:13:40.195 Women should schedule a baseline

NOTE Confidence: 0.990294

00:13:40.195 --> 00:13:42.508 mammogram beginning at age 40 or

NOTE Confidence: 0.990294

00:13:42.508 --> 00:13:44.572 earlier if they have risk factors

NOTE Confidence: 0.990294

00:13:44.572 --> 00:13:46.160 associated with the disease.

NOTE Confidence: 0.990294

00:13:46.160 --> 00:13:47.660 With screening, early detection,

NOTE Confidence: 0.990294

00:13:47.660 --> 00:13:49.160 and a healthy lifestyle,

NOTE Confidence: 0.990294

00:13:49.160 --> 00:13:51.610 breast cancer can be defeated.

NOTE Confidence: 0.990294

00:13:51.610 --> 00:13:53.818 Clinical trials are currently

NOTE Confidence: 0.990294

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 --> 00:14:07.405 Digital breast tomosynthesis, or 3D

NOTE Confidence: 0.990294

00:14:07.405 --> 00:14:09.630 mammography is also transforming breast

NOTE Confidence: 0.990294

00:14:09.698 --> 00:14:11.670 cancer screening by significantly

NOTE Confidence: 0.990294

00:14:11.670 --> 00:14:13.149 reducing unnecessary procedures

NOTE Confidence: 0.990294

00:14:13.149 --> 00:14:15.479 while picking up more cancers.

NOTE Confidence: 0.990294

00:14:15.480 --> 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

NOTE Confidence: 0.9793338

00:14:22.300 --> 00:14:24.200 back to Yale Cancer Answers.

NOTE Confidence: 0.9793338

00:14:24.200 --> 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 tonight by my guest doctor Megan King.

NOTE Confidence: 0.9793338

00:14:30.660 --> 00:14:33.320 We're talking about DNA repair and cancer,

NOTE Confidence: 0.9793338

00:14:33.320 --> 00:14:35.854 and right before the break we had

NOTE Confidence: 0.9793338

00:14:35.854 --> 00:14:38.557 gotten to the point in the story

NOTE Confidence: 0.9793338

00:14:38.557 --> 00:14:41.323 where we were talking about the fact

NOTE Confidence: 0.9793338

00:14:41.323 --> 00:14:43.962 that DNA gets injured and it can

NOTE Confidence: 0.9793338

00:14:43.962 --> 00:14:46.620 get damaged in a variety of places.

NOTE Confidence: 0.9793338

00:14:46.620 --> 00:14:49.231 And each of these breaks may be

NOTE Confidence: 0.9793338

00:14:49.231 --> 00:14:51.908 specific and may require a specific

NOTE Confidence: 0.9793338

00:14:51.910 --> 00:14:54.956 mechanism to repair it and we also

NOTE Confidence: 0.9793338

00:14:54.956 --> 00:14:58.000 talked about the fact that Doctor King's

NOTE Confidence: 0.9793338

00:14:58.000 --> 00:15:01.101 laboratory had figured out a way to

NOTE Confidence: 0.9793338

00:15:01.101 --> 00:15:03.657 actually watch how DNA gets repaired.

NOTE Confidence: 0.9793338

00:15:03.660 --> 00:15:06.250 right under a microscope,

NOTE Confidence: 0.9793338

00:15:06.250 --> 00:15:07.694 which was just fascinating.

NOTE Confidence: 0.9793338

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

NOTE Confidence: 0.9793338

00:15:08.780 --> 00:15:10.915 maybe you can help us to understand

NOTE Confidence: 0.9793338

00:15:10.915 --> 00:15:12.622 how this really evolves into

NOTE Confidence: 0.9793338

00:15:12.622 --> 00:15:14.447 understanding a little bit more

NOTE Confidence: 0.9793338

00:15:14.447 --> 00:15:16.380 about cancer and therapeutics.

NOTE Confidence: 0.9793338

00:15:16.380 --> 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 --> 00:15:24.420 And now we get to the point

NOTE Confidence: 0.9799037

00:15:24.420 --> 00:15:27.243 in a basic scientist life where you

NOTE Confidence: 0.9799037

00:15:27.243 --> 00:15:29.779 think about, I've built this assay,

NOTE Confidence: 0.9799037

00:15:29.780 --> 00:15:32.668 it took us many years to do it.

NOTE Confidence: 0.9799037

00:15:32.670 --> 00:15:35.256 What do we want to study?

NOTE Confidence: 0.9799037

00:15:35.260 --> 00:15:38.140 And it's about this time that I had

NOTE Confidence: 0.9799037

00:15:38.140 --> 00:15:39.767 been interacting increasingly

NOTE Confidence: 0.9799037

00:15:39.767 --> 00:15:42.263 with members of Yale Cancer

NOTE Confidence: 0.9799037

00:15:42.263 --> 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 --> 00:15:48.770 that is more translational.

NOTE Confidence: 0.9799037

00:15:48.770 --> 00:15:51.250 So that's when we kind of apply basic

NOTE Confidence: 0.9799037

00:15:51.250 --> 00:15:53.399 science and fundamental principles,

NOTE Confidence: 0.9799037

00:15:53.400 --> 00:15:55.716 directly to new treatments.

NOTE Confidence: 0.9799037

00:15:55.720 --> 00:15:58.378 And through these interactions we became

NOTE Confidence: 0.9799037

00:15:58.378 --> 00:16:01.643 very interested in how we might use this

NOTE Confidence: 0.9799037

00:16:01.643 --> 00:16:04.580 assay to answer a question that has arisen

NOTE Confidence: 0.9799037

00:16:04.580 --> 00:16:06.869 that was clearly critical to the treatment

NOTE Confidence: 0.9799037

00:16:06.869 --> 00:16:09.237 of breast and ovarian cancer that is

NOTE Confidence: 0.9799037

00:16:09.240 --> 00:16:11.586 tied to this familial cancer susceptibility

NOTE Confidence: 0.9799037

00:16:11.586 --> 00:16:14.196 genes BRCA one and 2.

NOTE Confidence: 0.9799037

00:16:14.196 --> 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

NOTE Confidence: 0.9799037

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

NOTE Confidence: 0.9799037

00:16:20.442 --> 00:16:22.627 No relation but we have the same

NOTE Confidence: 0.9799037

00:16:22.627 --> 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 --> 00:16:31.116 So we've struck up already a kind

NOTE Confidence: 0.9799037

00:16:31.116 --> 00:16:33.304 of back and forth just because

NOTE Confidence: 0.9799037

00:16:33.304 --> 00:16:35.614 of people getting us mixed up.

00:16:36.727 --> 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 --> 00:16:45.940 to therapy called synthetic lethality.

NOTE Confidence: 0.9799037

00:16:45.940 --> 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 --> 00:16:53.659 particularly in a type of DNA repair

NOTE Confidence: 0.9799037

00:16:53.659 --> 00:16:55.450 called homologous or combination

NOTE Confidence: 0.9799037

00:16:55.450 --> 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 --> 00:17:03.350 this leads to an increased susceptibility

NOTE Confidence: 0.9799037

00:17:03.350 --> 00:17:05.810 to breast and ovarian cancer in women.

00:17:06.520 --> 00:17:08.650 And so you are probably quite familiar

NOTE Confidence: 0.9799037

00:17:08.650 --> 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 --> 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 --> 00:17:22.254 which is called PARP inhibitor

NOTE Confidence: 0.9799037

00:17:22.254 --> 00:17:23.899 therapies that specifically kill

NOTE Confidence: 0.9799037

00:17:23.899 --> 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 --> 00:17:31.530 and actually more broadly in DNA

NOTE Confidence: 0.9799037

00:17:31.530 --> 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 --> 00:17:36.770 And so this is fantastic.

NOTE Confidence: 0.9799037

00:17:36.770 --> 00:17:39.248 What does that mean for a patient?

NOTE Confidence: 0.9799037

00:17:39.250 --> 00:17:41.651 It means that all of their normal

NOTE Confidence: 0.9799037

00:17:41.651 --> 00:17:43.509 tissues can tolerate these drugs.

NOTE Confidence: 0.9799037

00:17:43.510 --> 00:17:45.640 They really only attack the cells

NOTE Confidence: 0.9799037

00:17:45.640 --> 00:17:47.769 that don't have functional DNA repair.

NOTE Confidence: 0.9799037

00:17:47.770 --> 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 --> 00:17:54.959 a defect in DNA repair can lead

NOTE Confidence: 0.9799037

00:17:54.959 --> 00:17:56.790 an individual to be vulnerable

NOTE Confidence: 0.9799037

00:17:56.790 --> 00:17:58.418 to developing a cancer.

NOTE Confidence: 0.9799037

00:17:58.420 --> 00:18:00.550 But if the cancer is defective

NOTE Confidence: 0.9799037

00:18:00.550 --> 00:18:01.615 in DNA repair,

NOTE Confidence: 0.9799037

00:18:01.620 --> 00:18:03.804 it also opens up a window

NOTE Confidence: 0.9799037

00:18:03.804 --> 00:18:05.260 for therapies and PARP

NOTE Confidence: 0.9799037

00:18:05.260 --> 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 --> 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 --> 00:18:18.356 tied to homologous or combination

NOTE Confidence: 0.9799037

00:18:18.356 --> 00:18:21.024 defects which we now know include a

NOTE Confidence: 0.9799037

00:18:21.024 --> 00:18:23.740 number of contexts that do not involve

NOTE Confidence: 0.9799037

00:18:23.820 --> 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 --> 00:18:28.522 we also knew quite early on

NOTE Confidence: 0.9799037

00:18:28.522 --> 00:18:29.500 that these patients

NOTE Confidence: 0.9861332

00:18:29.562 --> 00:18:31.090 would often have acquired

NOTE Confidence: 0.9861332

00:18:31.090 --> 00:18:33.000 resistance to the PARP inhibitiors.

NOTE Confidence: 0.9861332

00:18:33.000 --> 00:18:35.136 They would initially respond very well,

NOTE Confidence: 0.9861332

00:18:35.140 --> 00:18:37.168 but the response would not

NOTE Confidence: 0.9861332

00:18:37.168 --> 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 --> 00:18:43.910 and investigators had gone in to

NOTE Confidence: 0.9861332

00:18:43.910 --> 00:18:46.826 try to ask how is it that these

NOTE Confidence: 0.9861332

00:18:46.826 --> 00:18:48.315 tumors are evolving, essentially,

NOTE Confidence: 0.9861332

00:18:48.315 --> 00:18:50.445 to become resistant to PARP inhibitors,

NOTE Confidence: 0.9861332

00:18:50.450 --> 00:18:52.935 and particularly in the case of BRCA 1

NOTE Confidence: 0.9861332

00:18:52.940 --> 00:18:54.780 they found that there

NOTE Confidence: 0.9861332

00:18:54.780 --> 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 --> 00:19:04.431 about the potential of our assay

NOTE Confidence: 0.9861332

00:19:04.431 --> 00:19:06.687 to maybe provide some insight

NOTE Confidence: 0.9861332

00:19:06.687 --> 00:19:09.452 into how is it that these tumors

NOTE Confidence: 0.9861332

00:19:09.452 --> 00:19:11.614 are getting around this therapy,

NOTE Confidence: 0.9861332

00:19:11.614 --> 00:19:13.378 and even more importantly,

NOTE Confidence: 0.9861332

00:19:13.380 --> 00:19:16.369 might there be ways that we could

NOTE Confidence: 0.9861332

00:19:16.369 --> 00:19:18.670 actually target these cells again?

NOTE Confidence: 0.9861332

00:19:18.670 --> 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 --> 00:19:25.727 and so we modeled these mutations,

00:19:28.999 --> 00:19:31.707 so that cells no longer express a number

NOTE Confidence: 0.9861332

00:19:31.707 --> 00:19:34.149 of other factors called 53BP1

NOTE Confidence: 0.9861332

00:19:34.150 --> 00:19:37.090 on a complex called shieldin.

NOTE Confidence: 0.9861332

00:19:37.090 --> 00:19:39.718 And somehow this allows cells that

NOTE Confidence: 0.9861332

00:19:39.718 --> 00:19:41.944 don't have functional BRCA one

NOTE Confidence: 0.9861332

00:19:41.944 --> 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 --> 00:19:47.958 and so we investigated those using

NOTE Confidence: 0.9861332

00:19:47.958 --> 00:19:50.948 this assay and we discovered that the

NOTE Confidence: 0.9861332

00:19:50.948 --> 00:19:53.916 loss of these factors that drove

NOTE Confidence: 0.9861332

00:19:54.000 --> 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 --> 00:20:01.007 specific way by unleashing

NOTE Confidence: 0.9861332

00:20:01.007 --> 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 --> 00:20:06.941 a protein called the bloom's helicase

NOTE Confidence: 0.9861332

00:20:06.950 --> 00:20:09.620 and it was able to kind of step in for

NOTE Confidence: 0.9861332

00:20:09.694 --> 00:20:12.058 BRCA one when these other factors

NOTE Confidence: 0.9861332

00:20:12.058 --> 00:20:14.548 are silenced and take over and so

NOTE Confidence: 0.9861332

00:20:14.548 --> 00:20:17.160 in a sense that seems like a bad thing.

NOTE Confidence: 0.9861332

00:20:17.160 --> 00:20:19.400 Some other protein can come in and

NOTE Confidence: 0.9861332

00:20:19.400 --> 00:20:21.619 and take the place of BRCA one,

NOTE Confidence: 0.9861332

00:20:21.620 --> 00:20:24.392 but it turns out one of the things we

NOTE Confidence: 0.9861332

00:20:24.392 --> 00:20:26.386 learned in our experiments was that

NOTE Confidence: 0.9861332

00:20:26.386 --> 00:20:29.029 there was kind of a new liability.

NOTE Confidence: 0.9861332

00:20:29.030 --> 00:20:31.370 That this activation of this

NOTE Confidence: 0.9861332

00:20:31.370 --> 00:20:33.242 bloom's helicase brought along,

NOTE Confidence: 0.9861332

00:20:33.250 --> 00:20:35.590 and it's actually now this

NOTE Confidence: 0.9861332

00:20:35.590 --> 00:20:37.462 angle that we're targeting,

NOTE Confidence: 0.9861332

00:20:37.470 --> 00:20:40.515 with the idea that there will be

NOTE Confidence: 0.9861332

00:20:40.515 --> 00:20:42.759 new combination therapies that will

NOTE Confidence: 0.9861332

00:20:42.759 --> 00:20:45.327 re sensitize these tumors to PARP

NOTE Confidence: 0.9861332

00:20:45.327 --> 00:20:47.863 inhibitors in combination with either

NOTE Confidence: 0.9861332

00:20:47.863 --> 00:20:51.067 inhibitors of the bloom helicase itself,

NOTE Confidence: 0.9861332

00:20:51.070 --> 00:20:53.640 but also some other additional

NOTE Confidence: 0.9861332

00:20:53.640 --> 00:20:56.706 treatments that have already been being

NOTE Confidence: 0.9861332

00:20:56.706 --> 00:20:59.583 pushed forward.

NOTE Confidence: 0.9861332

00:20:59.590 --> 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 --> 00:21:05.450 downstream of unresolved DNA damage,

NOTE Confidence: 0.9861332

00:21:05.450 --> 00:21:07.616 so we're pretty excited that these

NOTE Confidence: 0.9861332

00:21:07.616 --> 00:21:09.516 kind of very fundamental insights

NOTE Confidence: 0.9861332

00:21:09.516 --> 00:21:11.832 from this assay that I've described

NOTE Confidence: 0.9861332

00:21:11.832 --> 00:21:14.067 are really leading us to consider

NOTE Confidence: 0.9861332

00:21:14.067 --> 00:21:15.752 new combinations of drugs that

NOTE Confidence: 0.9861332

00:21:15.752 --> 00:21:17.862 may allow for

NOTE Confidence: 0.9861332

00:21:17.862 --> 00:21:20.456 not necessarily to make the PARP inhibitor

NOTE Confidence: 0.9861332

00:21:20.456 --> 00:21:23.750 but be a good therapy on its own for longer,

NOTE Confidence: 0.9861332

00:21:23.750 --> 00:21:25.910 but how we might use combinations

NOTE Confidence: 0.9861332

00:21:25.910 --> 00:21:28.190 that will allow for a very

NOTE Confidence: 0.9861332

00:21:28.190 --> 00:21:29.730 durable response for these patients.

NOTE Confidence: 0.98652893

00:21:30.330 --> 00:21:33.018 Let me make sure that we've got

NOTE Confidence: 0.98652893

00:21:33.018 --> 00:21:35.446 that straight for all of our listeners.

NOTE Confidence: 0.98652893

00:21:35.450 --> 00:21:37.770 So normally everybody 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 --> 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 --> 00:21:49.858 really to repair DNA because DNA we

NOTE Confidence: 0.98652893

00:21:49.858 --> 00:21:53.175 have in all of our cells and sometimes

NOTE Confidence: 0.98652893

00:21:53.175 --> 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 --> 00:22:03.006 that can help us to repair that DNA,

NOTE Confidence: 0.98652893

00:22:03.006 --> 00:22:05.640 but when that's defective we get cancers.

NOTE Confidence: 0.98652893

00:22:05.640 --> 00:22:08.525 But these PARP inhibitors

NOTE Confidence: 0.98652893

00:22:08.525 --> 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 --> 00:22:16.410 being repaired by BRCA.

NOTE Confidence: 0.98652893

00:22:16.410 --> 00:22:20.260 But then you've got this bloom helicase

NOTE Confidence: 0.98652893

00:22:20.260 --> 00:22:24.110 which can step in for BRCA.

NOTE Confidence: 0.98652893

00:22:24.110 --> 00:22:27.246 It's almost like a fail

NOTE Confidence: 0.98652893

00:22:27.246 --> 00:22:30.778 safe kind of belt and suspenders

NOTE Confidence: 0.98652893

00:22:30.780 --> 00:22:33.894 where if one

NOTE Confidence: 0.98652893

00:22:33.894 --> 00:22:35.970 repair mechanism doesn't work,

NOTE Confidence: 0.98652893

00:22:35.970 --> 00:22:38.256 then another repair mechanism can work,

NOTE Confidence: 0.98652893

00:22:38.260 --> 00:22:40.486 but in cancer cells you really

NOTE Confidence: 0.98652893

00:22:40.486 --> 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 --> 00:22:47.154 to find inhibitors to that secondary

NOTE Confidence: 0.98652893

00:22:47.154 --> 00:22:49.828 repair mechanism to ensure that the PARP

NOTE Confidence: 0.98652893

00:22:49.896 --> 00:22:52.724 inhibitors can kill off those cancer cells.

00:22:53.500 --> 00:22:55.400 Yes, that's exactly right,

NOTE Confidence: 0.9839927

00:22:55.400 --> 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 --> 00:23:03.945 mechanisms to carry out a specific

NOTE Confidence: 0.9839927

00:23:03.945 --> 00:23:06.250 step in homologous recombination and

NOTE Confidence: 0.9839927

00:23:06.250 --> 00:23:08.194 indeed, it was known already that

NOTE Confidence: 0.9839927

00:23:08.194 --> 00:23:09.490 these two mechanisms existed,

NOTE Confidence: 0.9839927

00:23:09.490 --> 00:23:11.674 but actually we didn't know very much

NOTE Confidence: 0.9839927

00:23:11.674 --> 00:23:14.665 about how a cell could decide to use one

NOTE Confidence: 0.9839927

00:23:14.665 --> 00:23:17.270 mechanism that would be this kind of BRCA

NOTE Confidence: 0.9839927

00:23:17.270 --> 00:23:18.890 one mechanism which works with

00:23:20.510 --> 00:23:22.130 this blooms' helicase pathway,

NOTE Confidence: 0.9839927

00:23:22.130 --> 00:23:24.074 which as you said is kind

NOTE Confidence: 0.9839927

00:23:24.074 --> 00:23:25.370 of a backup mechanism.

NOTE Confidence: 0.9839927

00:23:25.370 --> 00:23:27.642 One of the things we've discovered is that

NOTE Confidence: 0.9839927

00:23:27.642 --> 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 --> 00:23:33.011 it's really not supposed to

NOTE Confidence: 0.9839927

00:23:33.011 --> 00:23:34.760 be working in normal cells,

NOTE Confidence: 0.9839927

00:23:34.760 --> 00:23:37.955 and that's why there are a number of factors

NOTE Confidence: 0.9839927

00:23:37.960 --> 00:23:39.988 that keep it off and that

NOTE Confidence: 0.9839927

00:23:39.988 --> 00:23:41.002 includes these proteins,

NOTE Confidence: 0.9839927

00:23:41.010 --> 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 --> 00:23:46.094 So we think that actually there's

NOTE Confidence: 0.9839927

00:23:46.094 --> 00:23:47.450 kind of a gain.

NOTE Confidence: 0.9839927

00:23:47.450 --> 00:23:49.434 We would call it a gain of function

NOTE Confidence: 0.9839927

00:23:49.434 --> 00:23:51.773 of the bloom's helicase that underlies

NOTE Confidence: 0.9839927

00:23:51.773 --> 00:23:53.549 the PARP inhibitor resistance.

NOTE Confidence: 0.9839927

00:23:53.550 --> 00:23:56.118 Why might cells not want to be using

NOTE Confidence: 0.9839927

00:23:56.118 --> 00:23:58.300 this bloom's helicase all the time?

NOTE Confidence: 0.9839927

00:23:58.300 --> 00:24:00.526 We think that it's because actually it's

NOTE Confidence: 0.9839927

00:24:00.526 --> 00:24:03.390 not a very well controlled enzyme,

NOTE Confidence: 0.9839927

00:24:03.390 --> 00:24:05.756 so its activity in the repair process

NOTE Confidence: 0.9839927

00:24:05.760 --> 00:24:08.728 kind of goes wild a bit.

NOTE Confidence: 0.9839927

00:24:08.730 --> 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 --> 00:24:15.454 it actually may make them susceptible to

00:24:16.520 --> 00:24:17.932 additional targets

NOTE Confidence: 0.9839927

00:24:17.932 --> 00:24:19.344 that are being developed,

NOTE Confidence: 0.9839927

00:24:19.350 --> 00:24:21.468 and so we think

NOTE Confidence: 0.9839927

00:24:21.470 --> 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,

NOTE Confidence: 0.9839927

00:24:25.370 --> 00:24:27.680 we think this kind of rewiring from

NOTE Confidence: 0.9839927

00:24:27.680 --> 00:24:30.088 BRCA one to the bloom's helicase may

NOTE Confidence: 0.9839927

00:24:30.088 --> 00:24:32.965 also open up new ways that we could

NOTE Confidence: 0.9839927

00:24:32.965 --> 00:24:34.930 go about treating these tumors.

NOTE Confidence: 0.9785853

00:24:34.930 --> 00:24:37.048 So then the next question is,

NOTE Confidence: 0.9785853

00:24:37.050 --> 00:24:40.416 is there a way for us to

NOTE Confidence: 0.9785853

00:24:40.420 --> 00:24:42.250 figure out either upfront before

NOTE Confidence: 0.9785853

00:24:42.250 --> 00:24:44.490 we give any therapy 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 --> 00:24:48.718 this bloom's helicase turned on or not,

NOTE Confidence: 0.9785853

00:24:48.720 --> 00:24:51.233 so that upfront we can decide whether

NOTE Confidence: 0.9785853

00:24:51.233 --> 00:24:53.908 we should just give up our PARP inhibitor,

NOTE Confidence: 0.9785853

00:24:53.908 --> 00:24:56.220 or whether we need to give dual

NOTE Confidence: 0.9785853

00:24:56.220 --> 00:24:58.374 therapy or in a productive manner

NOTE Confidence: 0.9785853

00:24:58.374 --> 00:25:00.830 where we can say, well,

NOTE Confidence: 0.9785853

00:25:00.830 --> 00:25:02.714 if somebody hasn't responded to the

NOTE Confidence: 0.9785853

00:25:02.714 --> 00:25:04.990 PARP inhibitor as we would anticipate,

NOTE Confidence: 0.9785853

00:25:04.990 --> 00:25:07.951 is there a way for us to figure out

NOTE Confidence: 0.9785853

00:25:07.951 --> 00:25:11.048 if this is the mechanism by which

NOTE Confidence: 0.9785853

00:25:11.050 --> 00:25:13.234 the cell is getting around that

NOTE Confidence: 0.9785853

00:25:13.234 --> 00:25:14.878 PARP inhibitor and developing resistance

NOTE Confidence: 0.9785853

00:25:14.878 --> 00:25:17.462 so that we can add in another drug.

NOTE Confidence: 0.9785853

00:25:17.470 --> 00:25:19.717 Do we have those kinds of diagnostics?

NOTE Confidence: 0.98452777

00:25:21.070 --> 00:25:22.072 You're absolutely right,

NOTE Confidence: 0.98452777

00:25:22.072 --> 00:25:24.919 this is exactly what we would like to have,

NOTE Confidence: 0.98452777

00:25:24.920 --> 00:25:26.846 but we don't have it yet,

NOTE Confidence: 0.98452777

00:25:26.850 --> 00:25:29.418 so we would like to be able to take a

NOTE Confidence: 0.98452777

00:25:31.562 --> 00:25:33.589 tumor sample and ask the question,

NOTE Confidence: 0.98452777

00:25:33.590 --> 00:25:36.479 what is happening in this tumor?

NOTE Confidence: 0.98452777

00:25:36.480 --> 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 --> 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 --> 00:25:44.504 they're likely to respond.

NOTE Confidence: 0.98452777

00:25:44.504 --> 00:25:46.908 We know, as I told you, this bloom's

NOTE Confidence: 0.98452777

00:25:46.908 --> 00:25:49.320 helicase tends to go kind of overboard,

NOTE Confidence: 0.98452777

00:25:49.320 --> 00:25:51.665 and we think that we can design

NOTE Confidence: 0.98452777

00:25:51.670 --> 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 --> 00:25:57.104 because it generates far too much of

NOTE Confidence: 0.98452777

00:25:57.104 --> 00:25:58.790 this single stranded DNA generating

NOTE Confidence: 0.98452777

00:25:58.790 --> 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 --> 00:26:03.734 but again,

NOTE Confidence: 0.98452777

00:26:03.734 --> 00:26:06.850 bloom's helicase seems to do too much of this,

NOTE Confidence: 0.98452777

00:26:06.850 --> 00:26:08.852 and we think that we might be

NOTE Confidence: 0.98452777

00:26:08.852 --> 00:26:11.008 able to use proteins that bind

NOTE Confidence: 0.98452777

00:26:11.008 --> 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 --> 00:26:16.390 and that may be an indication

NOTE Confidence: 0.98452777

00:26:16.452 --> 00:26:18.706 that this is the mechanism by which

NOTE Confidence: 0.98452777

00:26:18.706 --> 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 --> 00:26:23.056 of PARP inhibitor resistance

NOTE Confidence: 0.98452777

00:26:23.060 --> 00:26:24.690 are so called reversion mutations.

NOTE Confidence: 0.98452777

00:26:24.690 --> 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 --> 00:26:29.900 which essentially can reconstitute

NOTE Confidence: 0.98452777

00:26:29.900 --> 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 --> 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 --> 00:26:36.704 and so we'd really like to

NOTE Confidence: 0.98452777

00:26:36.704 --> 00:26:39.039 be able to tell is there a

NOTE Confidence: 0.98452777

00:26:39.039 --> 00:26:40.655 reconstitution of normal repair.

NOTE Confidence: 0.98452777

00:26:40.660 --> 00:26:42.568 But maybe that repair still has

NOTE Confidence: 0.98452777

00:26:42.568 --> 00:26:44.580 some defects that we can target,

NOTE Confidence: 0.98452777

00:26:44.580 --> 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 --> 00:26:50.916 to have to think about another

NOTE Confidence: 0.98452777

00:26:50.916 --> 00:26:53.106 type of therapy to treat that patient.

00:26:53.434 --> 00:26:55.378 So these are in development and

NOTE Confidence: 0.98452777

00:26:55.378 --> 00:26:57.281 this is something we're really

NOTE Confidence: 0.98452777

00:26:57.281 --> 00:26:58.589 interested in,

NOTE Confidence: 0.98452777

00:26:58.590 --> 00:27:00.050 particularly again with our

NOTE Confidence: 0.98452777

00:27:00.050 --> 00:27:02.240 colleagues here and at Yale Cancer Center.

NOTE Confidence: 0.98452777

00:27:02.240 --> 00:27:04.496 To continue to push forward by

NOTE Confidence: 0.98452777

00:27:04.496 --> 00:27:06.406 partnering with those clinicians who

NOTE Confidence: 0.98452777

00:27:06.406 --> 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 --> 00:27:11.738 other homologous recombination

NOTE Confidence: 0.98452777

00:27:11.738 --> 00:27:13.457 defects who have been enrolled

NOTE Confidence: 0.98452777

00:27:13.457 --> 00:27:15.305 on PARP inhibitors and looking at

NOTE Confidence: 0.98452777

00:27:15.305 --> 00:27:16.840 those resistance mechanisms.

NOTE Confidence: 0.98452777

00:27:16.840 --> 00:27:19.024 And if we can develop these

NOTE Confidence: 0.98452777

00:27:19.024 --> 00:27:20.116 types of biomarkers.

NOTE Confidence: 0.98960394

00:27:20.870 --> 00:27:23.018 I mean it's so fascinating

NOTE Confidence: 0.98960394

00:27:23.018 --> 00:27:25.675 thinking about the fact that

NOTE Confidence: 0.98960394

00:27:25.675 --> 00:27:27.595 when we started this conversation,

NOTE Confidence: 0.98960394

00:27:27.600 --> 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 --> 00:27:35.460 requires a specific repair mechanism.

NOTE Confidence: 0.98960394

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 --> 00:27:43.310 moving towards personalized medicine,

NOTE Confidence: 0.98960394

00:27:43.310 --> 00:27:44.434 figuring out, well,

NOTE Confidence: 0.98960394

00:27:44.434 --> 00:27:46.678 if somebody develops resistance,

NOTE Confidence: 0.98960394

00:27:46.680 --> 00:27:48.540 how exactly is that resistance

NOTE Confidence: 0.98960394

00:27:48.540 --> 00:27:49.284 mechanism functioning?

NOTE Confidence: 0.98960394

00:27:49.290 --> 00:27:51.660 And how can we get around it?

NOTE Confidence: 0.98436666

00:27:53.530 --> 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 --> 00:27:59.890 in cells in a laboratory that's

NOTE Confidence: 0.98436666

00:27:59.890 --> 00:28:02.333 never going to tell us about what

NOTE Confidence: 0.98436666

00:28:02.333 --> 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 --> 00:28:08.969 commitment of patients who've been

NOTE Confidence: 0.98436666

00:28:08.969 --> 00:28:10.729 enrolled on these clinical trials.

NOTE Confidence: 0.98436666

00:28:10.730 --> 00:28:12.854 That's not an easy thing to

NOTE Confidence: 0.98436666

00:28:12.854 --> 00:28:15.120 ask of patients in this case.

NOTE Confidence: 0.98436666

00:28:15.120 --> 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 --> 00:28:21.040 but that is absolutely essential

NOTE Confidence: 0.98436666

00:28:21.040 --> 00:28:23.630 for us to continue to discover

NOTE Confidence: 0.98436666

00:28:23.630 --> 00:28:25.734 the mechanisms that are at play and for

NOTE Confidence: 0.98436666

00:28:25.734 --> 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 --> 00:28:33.439 professor of cell biology and of molecular,

NOTE Confidence: 0.93307334

00:28:33.440 --> 00:28:34.880 cellular, and developmental biology

NOTE Confidence: 0.93307334

00:28:34.880 --> 00:28:37.040 at the Yale School of Medicine.

NOTE Confidence: 0.93307334

00:28:37.040 --> 00:28:38.596 If you have questions,

NOTE Confidence: 0.93307334

00:28:38.596 --> 00:28:40.541 the address is cancer answers at

NOTE Confidence: 0.93307334

00:28:40.541 --> 00:28:42.698 yale.edu and past editions of the

NOTE Confidence: 0.93307334

00:28:42.698 --> 00:28:44.793 program are available in audio and

NOTE Confidence: 0.93307334

00:28:44.793 --> 00:28:47.117 written form at yalecancercenter.org.

NOTE Confidence: 0.93307334

00:28:47.120 --> 00:28:49.440 We hope you'll join us next week to

NOTE Confidence: 0.93307334

00:28:49.440 --> 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 --> 00:29:00.072 Cancer Hospital and AstraZeneca.