WEBVTT

NOTE duration:"00:53:35"

NOTE recognizability:0.597

NOTE language:en-us

NOTE Confidence: 0.75512505

 $00:00:00.000 \rightarrow 00:00:02.394$  Morning. For those of you who don't know me,

NOTE Confidence: 0.75512505

00:00:02.400 --> 00:00:03.471 I'm Rachel Greenup.

NOTE Confidence: 0.75512505

 $00{:}00{:}03{.}471 \dashrightarrow 00{:}00{:}06{.}396$  I'm Chief of Breast surgery and newly named

NOTE Confidence: 0.75512505

 $00{:}00{:}06{.}396 \dashrightarrow 00{:}00{:}08{.}916$  Co director of the SMILO Breast Program.

NOTE Confidence: 0.75512505

 $00:00:08.920 \rightarrow 00:00:11.800$  And I have the honor today of introducing Dr.

NOTE Confidence: 0.75512505

 $00{:}00{:}11.800 \dashrightarrow 00{:}00{:}15.620$  Megan King. Doctor King is an associate

NOTE Confidence: 0.75512505

 $00:00:15.620 \longrightarrow 00:00:18.160$  professor of cell biology and of molecular,

NOTE Confidence: 0.75512505

 $00:00:18.160 \rightarrow 00:00:19.820$  cellular and development biology.

NOTE Confidence: 0.75512505

 $00:00:19.820 \rightarrow 00:00:23.236$  She's also the Co leader of radio Biology

NOTE Confidence: 0.75512505

 $00{:}00{:}23.236$  -->  $00{:}00{:}25.804$  and Genome Integrity Research program at NOTE Confidence: 0.75512505

 $00{:}00{:}25{.}804 \dashrightarrow 00{:}00{:}28{.}832$  the Yale Cancer Center and an Associate NOTE Confidence: 0.75512505

00:00:28.832 --> 00:00:31.256 Cancer Center Director for Basic Science.

NOTE Confidence: 0.75512505

 $00{:}00{:}31.260 \dashrightarrow 00{:}00{:}33.276$  She did undergrad at Brandeis and

 $00{:}00{:}33.276 \dashrightarrow 00{:}00{:}36.614$  then went on to receive her PhD in

NOTE Confidence: 0.75512505

 $00:00:36.614 \dashrightarrow 00:00:38.534$  Biochemistry and molecular Biophysics

NOTE Confidence: 0.75512505

00:00:38.540 --> 00:00:40.730 from the University of Pennsylvania

NOTE Confidence: 0.75512505

 $00:00:40.730 \rightarrow 00:00:43.327$  under the mentorship of Doctor Mark NOTE Confidence: 0.75512505

 $00:00:43.327 \dashrightarrow 00:00:46.076$  Lemon and went on to get a post doc

NOTE Confidence: 0.75512505

00:00:46.076 --> 00:00:48.396 training with at Rockefeller University NOTE Confidence: 0.75512505

00:00:48.396 --> 00:00:51.420 where she discovered new mechanisms for NOTE Confidence: 0.75512505

 $00:00:51.500 \rightarrow 00:00:54.572$  the targeting and function of integral

NOTE Confidence: 0.75512505

 $00{:}00{:}54.572 \dashrightarrow 00{:}00{:}56.620$  inter nuclear membrane proteins.

NOTE Confidence: 0.75512505

 $00:00:56.620 \rightarrow 00:00:59.028$  Since founding her own group in 2009,

NOTE Confidence: 0.75512505

 $00{:}00{:}59{.}028$  -->  $00{:}01{:}01{.}236$  Megan has continued to investigate the NOTE Confidence: 0.75512505

00:01:01.236 --> 00:01:03.266 broad array of biological functions

NOTE Confidence: 0.75512505

 $00{:}01{:}03.266 \dashrightarrow 00{:}01{:}05.846$  that are integrated at the nuclear

NOTE Confidence: 0.75512505

 $00{:}01{:}05{.}846 \dashrightarrow 00{:}01{:}08{.}412$  envelope from impacts on DNA repaired

NOTE Confidence: 0.75512505

 $00{:}01{:}08{.}412 \dashrightarrow 00{:}01{:}10{.}457$  to nuclear and cellular mechanisms.

NOTE Confidence: 0.75512505

00:01:10.460 --> 00:01:13.292 She was named a Sarah Scholar in 2011

- NOTE Confidence: 0.75512505
- $00{:}01{:}13.292 \dashrightarrow 00{:}01{:}16.108$  and is the recipient of the NIH New
- NOTE Confidence: 0.75512505
- 00:01:16.108 --> 00:01:19.138 Innovator Award and is currently an
- NOTE Confidence: 0.75512505
- 00:01:19.138 --> 00:01:20.698 Allen Distinguished Investigator.
- NOTE Confidence: 0.75512505
- 00:01:20.700 --> 00:01:22.660 She's been at Yale for 15 years,
- NOTE Confidence: 0.75512505
- $00{:}01{:}22.660 \dashrightarrow 00{:}01{:}24.396$  and we're excited to hear about her
- NOTE Confidence: 0.75512505
- 00:01:24.396 --> 00:01:26.500 work today. So thank you, Doctor King.
- NOTE Confidence: 0.9675821
- $00:01:31.540 \longrightarrow 00:01:32.692$  Thank you so much.
- NOTE Confidence: 0.9675821
- $00:01:32.692 \longrightarrow 00:01:34.420$  It's a pleasure to be here.
- NOTE Confidence: 0.9675821
- 00:01:34.420 --> 00:01:37.636 And I think, you know,
- NOTE Confidence: 0.9675821
- $00:01:37.636 \longrightarrow 00:01:38.140$  hearing that bio,
- NOTE Confidence: 0.9675821
- $00{:}01{:}38{.}140 \dashrightarrow 00{:}01{:}40{.}396$  it always reminds me of how far I've
- NOTE Confidence: 0.9675821
- $00:01:40.396 \dashrightarrow 00:01:42.878$  come to what I'm going to be talking
- NOTE Confidence: 0.9675821
- $00{:}01{:}42.878 \dashrightarrow 00{:}01{:}45.196$  about today and how much that is
- NOTE Confidence: 0.9675821
- 00:01:45.196 --> 00:01:46.896 a consequence of the environment
- NOTE Confidence: 0.9675821
- $00:01:46.896 \dashrightarrow 00:01:49.092$  at Yale and the interactions that
- NOTE Confidence: 0.9675821

 $00:01:49.092 \rightarrow 00:01:50.982$  really have been driven initially

NOTE Confidence: 0.9675821

 $00:01:50.982 \longrightarrow 00:01:53.323$  by joining what was on the Radio

NOTE Confidence: 0.9675821

 $00:01:53.323 \rightarrow 00:01:55.627$  biology and genome and radio biology

NOTE Confidence: 0.9675821

 $00:01:55.627 \dashrightarrow 00:01:57.575$  and radio therapy research program,

NOTE Confidence: 0.9675821

00:01:57.580 --> 00:01:59.780 which was connected to me by Patrick Sung,

NOTE Confidence: 0.9675821

 $00{:}01{:}59.780 \dashrightarrow 00{:}02{:}00.976$  who's no longer here.

NOTE Confidence: 0.9675821

 $00{:}02{:}00{.}976 \dashrightarrow 00{:}02{:}02{:}02{.}770$  But he kind of immediately roped

NOTE Confidence: 0.9675821

 $00:02:02.829 \dashrightarrow 00:02:05.136$  me into that program and then all

NOTE Confidence: 0.9675821

00:02:05.136 --> 00:02:07.458 of the relationships I made through

NOTE Confidence: 0.9675821

 $00{:}02{:}07{.}458 \dashrightarrow 00{:}02{:}08{.}816$  that particularly with Joanne,

NOTE Confidence: 0.9675821

00:02:08.816 $\operatorname{-->}$ 00:02:10.748 Sweezy and Pat Larusso and really

NOTE Confidence: 0.9675821

 $00:02:10.748 \longrightarrow 00:02:12.414$  it's that transition that is

NOTE Confidence: 0.9675821

 $00:02:12.414 \dashrightarrow 00:02:13.702$  really spurred everything that

NOTE Confidence: 0.9675821

00:02:13.702 --> 00:02:15.410 I'm going to talk about today.

NOTE Confidence: 0.9675821

 $00:02:15.410 \dashrightarrow 00:02:17.673$  And so I'm really appreciative of

NOTE Confidence: 0.9675821

 $00:02:17.673 \rightarrow 00:02:19.731$  that because I think it's really

- NOTE Confidence: 0.9675821
- 00:02:19.731 $\operatorname{-->}$ 00:02:22.419 going to broaden the the scope of

 $00:02:22.419 \rightarrow 00:02:24.003$  where this fundamental biology,

NOTE Confidence: 0.9675821

 $00:02:24.010 \longrightarrow 00:02:26.284$  which hopefully you'll see today about

NOTE Confidence: 0.9675821

 $00{:}02{:}26.284 \dashrightarrow 00{:}02{:}28.969$  the nuclear envelope is really related to,

NOTE Confidence: 0.9675821

00:02:28.970 --> 00:02:29.634 you know,

NOTE Confidence: 0.9675821

 $00{:}02{:}29{.}634 \dashrightarrow 00{:}02{:}31{.}294$  a chemotherapy approach that's being

NOTE Confidence: 0.9675821

 $00:02:31.294 \dashrightarrow 00:02:33.200$  broadly used in which we're hoping

NOTE Confidence: 0.9675821

 $00:02:33.200 \rightarrow 00:02:35.020$  could be used and even more context.

NOTE Confidence: 0.9675821

 $00{:}02{:}35{.}020 \dashrightarrow 00{:}02{:}36{.}460$  And so that's what I'm going

NOTE Confidence: 0.9675821

 $00:02:36.516 \longrightarrow 00:02:37.460$  to talk about today.

NOTE Confidence: 0.9675821

 $00{:}02{:}37{.}460 \dashrightarrow 00{:}02{:}38{.}783$  And then the surprise to us has

NOTE Confidence: 0.9675821

00:02:38.783 --> 00:02:39.922 been a connection between this

NOTE Confidence: 0.9675821

 $00:02:39.922 \longrightarrow 00:02:40.978$  and innate immune signaling,

NOTE Confidence: 0.9675821

 $00{:}02{:}40{.}980 \dashrightarrow 00{:}02{:}43{.}260$  which is also not our expertise.

NOTE Confidence: 0.9675821

 $00{:}02{:}43.260 \dashrightarrow 00{:}02{:}46.236$  And so I really appreciate anyone

 $00:02:46.236 \longrightarrow 00:02:48.559$  here online now later thoughts

NOTE Confidence: 0.9675821

 $00{:}02{:}48.559 \dashrightarrow 00{:}02{:}50.593$  on that because there's so many

NOTE Confidence: 0.9675821

00:02:50.593 --> 00:02:52.830 people at Yale who do have more

NOTE Confidence: 0.9675821

 $00:02:52.830 \longrightarrow 00:02:54.820$  expertise in that area than we do.

NOTE Confidence: 0.9675821

00:02:54.820 --> 00:02:55.244 OK.

NOTE Confidence: 0.9675821

 $00:02:55.244 \rightarrow 00:02:56.940$  So just my disclosure,

NOTE Confidence: 0.9675821

 $00{:}02{:}56{.}940 \dashrightarrow 00{:}02{:}59{.}156$  some of this work is funded through the

NOTE Confidence: 0.9675821

 $00:02:59.156 \rightarrow 00:03:00.580$  strategic alliance with AstraZeneca.

NOTE Confidence: 0.539626

00:03:03.150 --> 00:03:06.118 So as as many of you are familiar

NOTE Confidence: 0.539626

 $00{:}03{:}06.118 \dashrightarrow 00{:}03{:}09.107$  with PARP inhibitors are really the

NOTE Confidence: 0.539626

 $00{:}03{:}09{.}110 \dashrightarrow 00{:}03{:}12{.}030$  canonical example of synthetic lethality.

NOTE Confidence: 0.539626

 $00{:}03{:}12{.}030$  -->  $00{:}03{:}14.746$  And it's such a powerful concept because NOTE Confidence: 0.539626

NOTE Confidence. 0.553020

 $00{:}03{:}14.746 \dashrightarrow 00{:}03{:}17.381$  it really highlights how we might use

NOTE Confidence: 0.539626

 $00{:}03{:}17{.}381 \dashrightarrow 00{:}03{:}19{.}131$  approaches that are really specific

NOTE Confidence: 0.539626

 $00{:}03{:}19{.}131 \dashrightarrow 00{:}03{:}21{.}613$  to tumor cells and otherwise do not

NOTE Confidence: 0.539626

 $00:03:21.613 \rightarrow 00:03:23.854$  affect all the normal cells of the body.

- NOTE Confidence: 0.539626
- $00:03:23.854 \rightarrow 00:03:25.904$  And and what is you know, fabulous approach,

 $00:03:25.904 \rightarrow 00:03:27.789$  right that that would be.

NOTE Confidence: 0.539626

 $00{:}03{:}27.790 \dashrightarrow 00{:}03{:}31.254$  And so the idea is that PARP inhibitors

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 $00:03:31.260 \rightarrow 00:03:33.035$  in particular cause single stranded

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 $00{:}03{:}33{.}035 \dashrightarrow 00{:}03{:}35{.}481$  DNA damage to persist or at least

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 $00{:}03{:}35{.}481 \dashrightarrow 00{:}03{:}37{.}595$  that's one of the mechanisms that we

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 $00:03:37.595 \dashrightarrow 00:03:39.736$  think about as being important here.

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 $00:03:39.740 \longrightarrow 00:03:41.894$  And that typically cells can tolerate

NOTE Confidence: 0.539626

00:03:41.894 --> 00:03:44.659 this kind of damage because they have

NOTE Confidence: 0.539626

 $00{:}03{:}44.659 \dashrightarrow 00{:}03{:}46.769$  a functional homologous or combination

NOTE Confidence: 0.539626

00:03:46.769 --> 00:03:48.885 DNA repair mechanism that can act

NOTE Confidence: 0.539626

 $00{:}03{:}48.885 \dashrightarrow 00{:}03{:}51.161$  in SNG 2 and repair these breaks.

NOTE Confidence: 0.539626

 $00{:}03{:}51{.}161 \dashrightarrow 00{:}03{:}53{.}927$  And this leads to cell survival.

NOTE Confidence: 0.539626

00:03:53.930 --> 00:03:55.845 However, in the consequence of

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 $00{:}03{:}55{.}845 \dashrightarrow 00{:}03{:}57{.}377$  defects and homologous recombination

 $00:03:57.377 \dashrightarrow 00:03:59.754$  and kind of the classic example of

NOTE Confidence: 0.539626

 $00:03:59.754 \rightarrow 00:04:01.553$  this are pathogenic mutations in the

NOTE Confidence: 0.539626

 $00{:}04{:}01{.}553 \dashrightarrow 00{:}04{:}02{.}885$  BRCA one and BRCA 2 genes.

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 $00:04:02.890 \rightarrow 00:04:05.746$  There's a defect in tolerating this damage

NOTE Confidence: 0.539626

 $00:04:05.746 \longrightarrow 00:04:08.646$  and this will lead to cell death,

NOTE Confidence: 0.539626

 $00:04:08.650 \longrightarrow 00:04:08.962$  right.

NOTE Confidence: 0.539626

 $00{:}04{:}08{.}962 \dashrightarrow 00{:}04{:}11{.}146$  And so this is the mechanism where

NOTE Confidence: 0.539626

 $00{:}04{:}11.146 \dashrightarrow 00{:}04{:}13.216$  it's the combination of the HR

NOTE Confidence: 0.539626

00:04:13.216 --> 00:04:15.280 defect on the PARP inhibitor that

NOTE Confidence: 0.539626

 $00:04:15.344 \longrightarrow 00:04:16.969$  drives a tumor cell death.

NOTE Confidence: 0.539626

00:04:16.970 --> 00:04:18.950 So I want to just set the stage for

NOTE Confidence: 0.539626

00:04:18.950 --> 00:04:20.853 what I'm going to talk about today

NOTE Confidence: 0.539626

00:04:20.853 --> 00:04:22.730 by by reminding you about how P53

NOTE Confidence: 0.539626

00:04:22.730 --> 00:04:24.410 works because I'm going to use this

NOTE Confidence: 0.539626

 $00{:}04{:}24{.}410 \dashrightarrow 00{:}04{:}26{.}679$  as an example of of our kind of

NOTE Confidence: 0.539626

 $00:04:26.679 \rightarrow 00:04:28.391$  framework for thinking about the story

- NOTE Confidence: 0.539626
- $00:04:28.391 \longrightarrow 00:04:30.134$  that I'm going to tell the debt.

 $00:04:30.140 \longrightarrow 00:04:33.482$  So in interface in normal cells, right,

NOTE Confidence: 0.539626

00:04:33.482 - > 00:04:35.294 we have when there's DNA damage,

NOTE Confidence: 0.539626

 $00{:}04{:}35{.}300 \dashrightarrow 00{:}04{:}37{.}912$  there is the activation of P53 and

NOTE Confidence: 0.539626

 $00:04:37.912 \longrightarrow 00:04:40.614$  P53 is is really this decision point,

NOTE Confidence: 0.539626

 $00{:}04{:}40{.}620 \dashrightarrow 00{:}04{:}44{.}330$  It's both activating mechanisms to

NOTE Confidence: 0.539626

 $00:04:44.330 \rightarrow 00:04:45.662$  repair that damage, right.

NOTE Confidence: 0.539626

 $00{:}04{:}45.662 \dashrightarrow 00{:}04{:}48.337$  So that the first response of the cell

NOTE Confidence: 0.539626

 $00:04:48.337 \rightarrow 00:04:50.769$  is try to tolerate and repair this damage,

NOTE Confidence: 0.539626

 $00:04:50.770 \longrightarrow 00:04:52.314$  stall the cell cycle,

NOTE Confidence: 0.539626

 $00{:}04{:}52{.}314 \dashrightarrow 00{:}04{:}55{.}584$  fix the genome and then go into mitosis

NOTE Confidence: 0.539626

 $00{:}04{:}55{.}584 \dashrightarrow 00{:}04{:}58{.}643$  and and have normal cell growth.

NOTE Confidence: 0.539626

 $00:04:58.650 \dashrightarrow 00:05:02.010$  But but if this damage is too deleterious,

NOTE Confidence: 0.539626

00:05:02.010 --> 00:05:02.850 if it persists,

NOTE Confidence: 0.539626

 $00{:}05{:}02.850 \dashrightarrow 00{:}05{:}04.250$  if it can't be tolerated,

 $00:05:04.250 \longrightarrow 00:05:06.168$  then this is going to lead to

NOTE Confidence: 0.539626

 $00{:}05{:}06{.}170 \dashrightarrow 00{:}05{:}07{.}674$  the stimulation of apoptosis.

NOTE Confidence: 0.539626

 $00{:}05{:}07{.}674 \dashrightarrow 00{:}05{:}09{.}930$  And so really this is this

NOTE Confidence: 0.539626

 $00:05:09.999 \dashrightarrow 00:05:12.652$  combination of repair and then when

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00:05:12.652 --> 00:05:15.220 we can't repair driving cell death,

NOTE Confidence: 0.539626

 $00{:}05{:}15{.}220 \dashrightarrow 00{:}05{:}15{.}528$  however,

NOTE Confidence: 0.539626

00:05:15.528 --> 00:05:16.144 you know,

NOTE Confidence: 0.539626

 $00{:}05{:}16{.}144 \dashrightarrow 00{:}05{:}18{.}300$  we know that this is a mechanism

NOTE Confidence: 0.539626

 $00{:}05{:}18.367 \dashrightarrow 00{:}05{:}20.581$  that is dys regulated in the vast

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 $00{:}05{:}20.581 \dashrightarrow 00{:}05{:}22.503$  majority of tumors including those

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 $00{:}05{:}22.503 \dashrightarrow 00{:}05{:}24.418$  that respond to PARP inhibitors.

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 $00{:}05{:}24{.}420 \dashrightarrow 00{:}05{:}26{.}697$  And so this is not the mechanism, right.

NOTE Confidence: 0.539626

 $00:05:26.697 \dashrightarrow 00:05:29.233$  So we know we can get the synthetic

NOTE Confidence: 0.539626

00:05:29.233 --> 00:05:30.610 lethality of PARP inhibitors

NOTE Confidence: 0.539626

 $00{:}05{:}30{.}610 \dashrightarrow 00{:}05{:}32{.}590$  with HR defects even in the

NOTE Confidence: 0.539626

 $00:05:32.590 \rightarrow 00:05:34.201$  context of dysregulated P53.

- NOTE Confidence: 0.539626
- $00:05:34.201 \longrightarrow 00:05:35.706$  So what is this mechanism

 $00{:}05{:}35{.}706 \dashrightarrow 00{:}05{:}37{.}731$  actually and you might think that

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 $00{:}05{:}37{.}731 \dashrightarrow 00{:}05{:}39{.}247$  we understand this mechanism,

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 $00:05:39.250 \dashrightarrow 00:05:41.106$  but what I'm going to tell you about

NOTE Confidence: 0.539626

 $00{:}05{:}41{.}106 \dashrightarrow 00{:}05{:}43{.}150$  today is that we we don't and I'm

NOTE Confidence: 0.539626

 $00{:}05{:}43.150 \dashrightarrow 00{:}05{:}45.250$  going to focus today disclaimer on

NOTE Confidence: 0.539626

 $00{:}05{:}45{.}250 \dashrightarrow 00{:}05{:}47{.}768$  the tumor cell intrinsic mechanisms.

NOTE Confidence: 0.539626

 $00{:}05{:}47.770 \dashrightarrow 00{:}05{:}49.554$  That is not to negate the fact that

NOTE Confidence: 0.539626

 $00{:}05{:}49{.}554 \dashrightarrow 00{:}05{:}51{.}673$  there are other roles for the immune

NOTE Confidence: 0.539626

 $00:05:51.673 \rightarrow 00:05:53.288$  system for the tumor microenvironment.

NOTE Confidence: 0.539626

 $00{:}05{:}53.290 \dashrightarrow 00{:}05{:}55.282$  But what we know is that in in

NOTE Confidence: 0.539626

 $00{:}05{:}55{.}282 \dashrightarrow 00{:}05{:}57{.}405$  HR deficient cells in a dish PARP

NOTE Confidence: 0.539626

 $00:05:57.405 \dashrightarrow 00:05:58.970$  inhibitors can cause cell deaths.

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 $00{:}05{:}58{.}970 \dashrightarrow 00{:}06{:}01{.}786$  So we know that there is at least

NOTE Confidence: 0.531500307142857

 $00:06:01.786 \longrightarrow 00:06:04.074$  a sufficiency in in cells and

 $00:06:04.074 \longrightarrow 00:06:06.324$  culture for a tumor cell intrinsic

NOTE Confidence: 0.531500307142857

 $00{:}06{:}06{.}404 \dashrightarrow 00{:}06{:}09{.}438$  mechanism of cell death and IT and

NOTE Confidence: 0.531500307142857

 $00:06:09.440 \longrightarrow 00:06:11.896$  and how do we think about what kind NOTE Confidence: 0.531500307142857

 $00{:}06{:}11.896 \dashrightarrow 00{:}06{:}13.548$  of surveillance mechanisms might be

NOTE Confidence: 0.531500307142857

 $00:06:13.548 \longrightarrow 00:06:17.080$  akin to P53 that that drive this.

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00:06:17.080 --> 00:06:18.856 So I just want to highlight a few

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 $00{:}06{:}18.856 \dashrightarrow 00{:}06{:}20.838$  of the challenges that we face in

NOTE Confidence: 0.531500307142857

 $00:06:20.838 \dashrightarrow 00:06:22.664$  the use of HARP inhibitors because

NOTE Confidence: 0.531500307142857

 $00:06:22.664 \rightarrow 00:06:24.434$  really this is our motivation for

NOTE Confidence: 0.531500307142857

 $00:06:24.434 \rightarrow 00:06:26.100$  the kind of fundamental studies

NOTE Confidence: 0.531500307142857

 $00{:}06{:}26{.}100 \dashrightarrow 00{:}06{:}28{.}440$  that I'm going to talk about.

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00:06:28.440 --> 00:06:30.504 You know, it's very clear that

NOTE Confidence: 0.531500307142857

00:06:30.504 --> 00:06:31.536 PARP inhibitors specifically

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00:06:31.536 --> 00:06:32.958 kill HR deficient cells,

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 $00:06:32.960 \longrightarrow 00:06:33.860$  but we don't understand

NOTE Confidence: 0.531500307142857

 $00:06:33.860 \longrightarrow 00:06:34.760$  the cell death mechanism.

- NOTE Confidence: 0.531500307142857
- 00:06:34.760 --> 00:06:36.588 As I already highlighted,
- NOTE Confidence: 0.531500307142857
- 00:06:36.588 --> 00:06:38.873 acquired resistance is a major
- NOTE Confidence: 0.531500307142857
- 00:06:38.873 --> 00:06:41.234 challenge and it's really well
- NOTE Confidence: 0.531500307142857
- $00:06:41.234 \rightarrow 00:06:43.062$  explored in preclinical models
- NOTE Confidence: 0.531500307142857
- $00:06:43.062 \rightarrow 00:06:45.439$  through things like CRISPR screens.
- NOTE Confidence: 0.531500307142857
- $00{:}06{:}45{.}440 \dashrightarrow 00{:}06{:}47{.}550$  But actually the insights from
- NOTE Confidence: 0.531500307142857
- 00:06:47.550 --> 00:06:49.660 patient samples is really still
- NOTE Confidence: 0.531500307142857
- $00:06:49.733 \longrightarrow 00:06:51.499$  rather limited and understanding
- NOTE Confidence: 0.531500307142857
- $00{:}06{:}51{.}499 \dashrightarrow 00{:}06{:}54{.}194$  the cell death mechanism that
- NOTE Confidence: 0.531500307142857
- $00:06:54.194 \rightarrow 00:06:56.350$  PARP inhibitors precipitate could
- NOTE Confidence: 0.531500307142857
- $00:06:56.420 \longrightarrow 00:06:58.376$  really help in in this area.
- NOTE Confidence: 0.531500307142857
- $00{:}06{:}58{.}380 \dashrightarrow 00{:}07{:}01{.}609$  A major challenge is that we lack a
- NOTE Confidence: 0.531500307142857
- $00:07:01.609 \longrightarrow 00:07:04.052$  robust biomarker that can tell us that
- NOTE Confidence: 0.531500307142857
- $00:07:04.052 \dashrightarrow 00:07:06.496$  PARP inhibitors are likely to be effective.
- NOTE Confidence: 0.531500307142857
- $00{:}07{:}06{.}500 \dashrightarrow 00{:}07{:}08{.}018$  So this can either be that
- NOTE Confidence: 0.531500307142857

00:07:08.018 --> 00:07:08.777 cells are reconstituted,

NOTE Confidence: 0.531500307142857

 $00{:}07{:}08.780 \dashrightarrow 00{:}07{:}10.412$  homologous recombination or there

NOTE Confidence: 0.531500307142857

 $00{:}07{:}10.412 \dashrightarrow 00{:}07{:}13.258$  could be other contexts outside of the

NOTE Confidence: 0.531500307142857

 $00{:}07{:}13.258 \dashrightarrow 00{:}07{:}15.238$  genetic kind of germline mutations and

NOTE Confidence: 0.531500307142857

00:07:15.238 --> 00:07:17.794 BRCA one and BRCA 2 or even somatic

NOTE Confidence: 0.531500307142857

00:07:17.794 --> 00:07:19.687 mutations where it could be there

NOTE Confidence: 0.531500307142857

 $00{:}07{:}19.687 \dashrightarrow 00{:}07{:}22.009$  is an HR defect that's actionable.

NOTE Confidence: 0.531500307142857

 $00{:}07{:}22.010 \dashrightarrow 00{:}07{:}23.991$  But because we don't have a biomarker

NOTE Confidence: 0.531500307142857

 $00{:}07{:}23.991 \dashrightarrow 00{:}07{:}26.290$  for HR status that is at least dynamic,

NOTE Confidence: 0.531500307142857

00:07:26.290 --> 00:07:26.650 right,

NOTE Confidence: 0.531500307142857

 $00:07:26.650 \longrightarrow 00:07:28.450$  There are kind of sequencing

NOTE Confidence: 0.531500307142857

 $00:07:28.450 \longrightarrow 00:07:29.170$  based approaches,

NOTE Confidence: 0.531500307142857

 $00{:}07{:}29{.}170 \dashrightarrow 00{:}07{:}31{.}900$  but we don't have a classic kind

NOTE Confidence: 0.531500307142857

 $00:07:31.900 \longrightarrow 00:07:33.070$  of pathological straightforward

NOTE Confidence: 0.531500307142857

 $00:07:33.134 \longrightarrow 00:07:34.678$  psychology kind of approach

NOTE Confidence: 0.531500307142857

 $00{:}07{:}34.678 \dashrightarrow 00{:}07{:}36.608$  and that's a real limitation.

- NOTE Confidence: 0.623311
- $00:07:38.730 \longrightarrow 00:07:41.180$  And and lastly, there's a lot of

 $00:07:41.180 \longrightarrow 00:07:42.693$  enthusiasm about combining PARP

NOTE Confidence: 0.623311

00:07:42.693 --> 00:07:44.305 inhibitors with immune checkpoint

NOTE Confidence: 0.623311

 $00{:}07{:}44.305 \dashrightarrow 00{:}07{:}46.719$  blockades and indeed a number of

NOTE Confidence: 0.623311

 $00:07:46.719 \longrightarrow 00:07:48.399$  trials that are exploring this.

NOTE Confidence: 0.623311

 $00{:}07{:}48.400 \dashrightarrow 00{:}07{:}50.680$  But we don't actually understand the

NOTE Confidence: 0.623311

 $00{:}07{:}50.680 \dashrightarrow 00{:}07{:}52.702$  underlying mechanisms of why those

NOTE Confidence: 0.623311

 $00:07:52.702 \rightarrow 00:07:54.478$  combinations might be effective.

NOTE Confidence: 0.623311

 $00:07:54.480 \longrightarrow 00:07:55.640$  And to really understand that,

NOTE Confidence: 0.623311

 $00{:}07{:}55{.}640 \dashrightarrow 00{:}07{:}57{.}341$  we have to understand how how carpenters

NOTE Confidence: 0.623311

 $00{:}07{:}57{.}341 \dashrightarrow 00{:}07{:}59{.}360$  are working and and This is why we're

NOTE Confidence: 0.623311

 $00{:}07{:}59{.}360 \dashrightarrow 00{:}08{:}00{.}600$  really interested in the crosstalk.

NOTE Confidence: 0.623311

 $00{:}08{:}00{.}600 \dashrightarrow 00{:}08{:}02{.}497$ I'll talk about today with the innate

NOTE Confidence: 0.623311

 $00{:}08{:}02{.}497 \dashrightarrow 00{:}08{:}04{.}198$  immune system and how that might be

NOTE Confidence: 0.623311

 $00:08:04.200 \dashrightarrow 00:08:06.678$  contribute to the the rationale for

 $00:08:06.678 \rightarrow 00:08:08.760$  these combinations and might point

NOTE Confidence: 0.623311

 $00{:}08{:}08{.}760 \dashrightarrow 00{:}08{:}10{.}920$  to what the right approaches are.

NOTE Confidence: 0.623311

00:08:10.920 --> 00:08:12.040 So as I said,

NOTE Confidence: 0.623311

 $00{:}08{:}12{.}040 \dashrightarrow 00{:}08{:}14{.}535$  I'm going to focus on this cell death

NOTE Confidence: 0.623311

00:08:14.535 --> 00:08:17.878 mechanism in my talk today and to 1st

NOTE Confidence: 0.623311

00:08:17.878 --> 00:08:20.265 to introduce how we've kind of how

NOTE Confidence: 0.623311

 $00{:}08{:}20.265 \dashrightarrow 00{:}08{:}22.150$  we've been thinking about this problem.

NOTE Confidence: 0.623311

 $00:08:22.150 \rightarrow 00:08:25.486$  I want to just introduce you to this

NOTE Confidence: 0.623311

00:08:25.486 --> 00:08:27.230 canonical innate immune surveillance

NOTE Confidence: 0.623311

00:08:27.230 --> 00:08:30.310 mechanism in which C Gas shown here NOTE Confidence: 0.623311

 $00:08:30.381 \longrightarrow 00:08:32.505$  is they are really key player.

NOTE Confidence: 0.623311

00:08:32.510 --> 00:08:35.334 So C gas is an innate immune sensor

NOTE Confidence: 0.623311

00:08:35.334 --> 00:08:38.065 protein that is in the cytoplasm of cells

NOTE Confidence: 0.623311

 $00{:}08{:}38.065 \dashrightarrow 00{:}08{:}40.909$  and it binds to double stranded DNA.

NOTE Confidence: 0.623311

 $00:08:40.910 \longrightarrow 00:08:43.278$  And the idea is that it can surveil

NOTE Confidence: 0.623311

 $00:08:43.278 \rightarrow 00:08:45.520$  4 viruses and bacterial pathogens,

- NOTE Confidence: 0.623311
- $00:08:45.520 \rightarrow 00:08:47.600$  but there's increasing evidence that

00:08:47.600 --> 00:08:50.759 C gas is also capable of surveilling

NOTE Confidence: 0.623311

 $00{:}08{:}50.760 \dashrightarrow 00{:}08{:}53.496$  self DNA that's present within cells

NOTE Confidence: 0.623311

 $00:08:53.496 \rightarrow 00:08:55.320$  within eukaryotic cells themselves.

NOTE Confidence: 0.623311

 $00:08:55.320 \longrightarrow 00:08:56.400$  So for example,

NOTE Confidence: 0.623311

 $00{:}08{:}56{.}400 \dashrightarrow 00{:}08{:}58{.}560$  a distregated mitochondria can lead to

NOTE Confidence: 0.623311

 $00{:}08{:}58{.}560 \dashrightarrow 00{:}09{:}00{.}722$  leaking of mitochondrial DNA into the

NOTE Confidence: 0.623311

 $00:09:00.722 \dashrightarrow 00:09:02.760$  cytoplasm which can activate C gas.

NOTE Confidence: 0.623311

00:09:02.760 --> 00:09:05.240 And today I'm going to be talking about NOTE Confidence: 0.623311

 $00:09:05.240 \longrightarrow 00:09:07.262$  how actually the chromosomes or the

NOTE Confidence: 0.623311

 $00{:}09{:}07{.}262 \dashrightarrow 00{:}09{:}09{.}621$  chromatin or DNA from the nucleus can

NOTE Confidence: 0.623311

 $00{:}09{:}09{.}621 \dashrightarrow 00{:}09{:}11.658$  be exposed and surveilled by C gas.

NOTE Confidence: 0.623311

00:09:11.660 --> 00:09:15.413 C gas works by when it binds to DNA.

NOTE Confidence: 0.623311

 $00{:}09{:}15{.}420 \dashrightarrow 00{:}09{:}16{.}820$  Just I'm going to say very clearly,

NOTE Confidence: 0.623311

 $00:09:16.820 \longrightarrow 00:09:18.740$  when it binds to naked DNA,

 $00{:}09{:}18{.}740 \dashrightarrow 00{:}09{:}20{.}952$  this drives a change and and molecules

NOTE Confidence: 0.623311

00:09:20.952 --> 00:09:23.994 of C gas come together and they produce

NOTE Confidence: 0.623311

00:09:23.994 --> 00:09:26.420 the second messenger called C gamp.

NOTE Confidence: 0.623311

00:09:26.420 --> 00:09:29.140 But actually binding of C gas to DNA

NOTE Confidence: 0.623311

 $00:09:29.140 \longrightarrow 00:09:32.099$  does not always lead to this response.

NOTE Confidence: 0.623311

00:09:32.100 --> 00:09:33.815 And so there's regulation of this that

NOTE Confidence: 0.623311

 $00{:}09{:}33.815 \dashrightarrow 00{:}09{:}35.819$  I'll talk about in more detail in a moment.

NOTE Confidence: 0.623311

 $00{:}09{:}35{.}820 \dashrightarrow 00{:}09{:}37{.}338$  So just recruiting C gas somewhere

NOTE Confidence: 0.623311

 $00{:}09{:}37{.}338 \dashrightarrow 00{:}09{:}39{.}141$  does not mean that it's actually

NOTE Confidence: 0.623311

 $00:09:39.141 \dashrightarrow 00:09:40.609$  producing this second messenger,

NOTE Confidence: 0.623311

 $00{:}09{:}40.610 \dashrightarrow 00{:}09{:}42.416$  but the second messenger is thought to

NOTE Confidence: 0.623311

 $00:09:42.416 \dashrightarrow 00:09:44.650$  be key to its downstream mechanisms.

NOTE Confidence: 0.623311

 $00:09:44.650 \dashrightarrow 00:09:48.088$  The recipient of the C gamp signal is sting.

NOTE Confidence: 0.623311

 $00{:}09{:}48.090 \dashrightarrow 00{:}09{:}50.190$  Sting is a membrane protein that

NOTE Confidence: 0.623311

 $00:09:50.190 \dashrightarrow 00:09:52.740$  is key to the canonical signaling

NOTE Confidence: 0.623311

 $00:09:52.740 \dashrightarrow 00:09:55.405$  pathway that C gas activates.

 $00:09:55.410 \rightarrow 00:09:58.056$  And that is by driving the phosphorylation

NOTE Confidence: 0.623311

 $00{:}09{:}58.056 \dashrightarrow 00{:}10{:}00.660$  of a kinase called TBK one once

NOTE Confidence: 0.623311

 $00:10:00.660 \rightarrow 00:10:03.128$  it's traffic to the Golgi and then

NOTE Confidence: 0.623311

 $00:10:03.128 \rightarrow 00:10:05.282$  this phosphorylates IRF 3 which is

NOTE Confidence: 0.623311

 $00{:}10{:}05{.}282 \dashrightarrow 00{:}10{:}07{.}229$  a transcription factor that when

NOTE Confidence: 0.623311

 $00{:}10{:}07{.}229 \dashrightarrow 00{:}10{:}09{.}563$  phosphorylated goes into the nucleus and

NOTE Confidence: 0.623311

 $00:10:09.563 \rightarrow 00:10:12.329$  drives interferon stimulated gene expression.

NOTE Confidence: 0.623311

 $00:10:12.330 \longrightarrow 00:10:14.367$  So that's the kind of canonical pathway.

NOTE Confidence: 0.623311

00:10:14.370 $\operatorname{-->}$ 00:10:16.911 There's also a non canonical roles in

NOTE Confidence: 0.623311

00:10:16.911 --> 00:10:19.186 activating NF Kappa B signaling and

NOTE Confidence: 0.623311

 $00{:}10{:}19{.}186 \dashrightarrow 00{:}10{:}22{.}514$  and any of these may in addition to

NOTE Confidence: 0.623311

 $00{:}10{:}22.514 \dashrightarrow 00{:}10{:}24.768$  inflammatory genes cause apoptosis.

NOTE Confidence: 0.623311

 $00{:}10{:}24.770 \dashrightarrow 00{:}10{:}26.548$  So this could be a mechanism that

NOTE Confidence: 0.623311

 $00:10:26.548 \longrightarrow 00:10:27.690$  can drive cell death,

NOTE Confidence: 0.623311

 $00:10:27.690 \longrightarrow 00:10:30.040$  although we really don't understand

- $00:10:30.040 \rightarrow 00:10:31.450$  this terribly well.
- NOTE Confidence: 0.623311
- 00:10:31.450 --> 00:10:32.056 In addition,
- NOTE Confidence: 0.623311
- $00:10:32.056 \longrightarrow 00:10:33.874$  sting is also involved in some
- NOTE Confidence: 0.623311
- $00{:}10{:}33.874 \dashrightarrow 00{:}10{:}35.825$  other non canonical mechanisms that
- NOTE Confidence: 0.623311
- $00{:}10{:}35{.}825 \dashrightarrow 00{:}10{:}37{.}970$  could also precipitate cell death,
- NOTE Confidence: 0.5575379
- $00:10:37.970 \rightarrow 00:10:39.858$  which as I mentioned is what I'm going
- NOTE Confidence: 0.5575379
- $00{:}10{:}39.858 \dashrightarrow 00{:}10{:}42.485$  to be focusing on today and part of this
- NOTE Confidence: 0.5575379
- $00:10:42.485 \rightarrow 00:10:44.569$  actually involves the autophagy mechanisms.
- NOTE Confidence: 0.5575379
- $00{:}10{:}44.570 \dashrightarrow 00{:}10{:}47.108$  There appears to be some autophagy
- NOTE Confidence: 0.5575379
- 00:10:47.108 --> 00:10:48.800 dependent cell death mechanism
- NOTE Confidence: 0.5575379
- $00{:}10{:}48.873 \dashrightarrow 00{:}10{:}51.177$  downstream of sting and this is
- NOTE Confidence: 0.5575379
- $00{:}10{:}51{.}177 \dashrightarrow 00{:}10{:}53{.}398$  independent perhaps of this canonical
- NOTE Confidence: 0.5575379
- $00:10:53.398 \rightarrow 00:10:55.850$  interferon stimulated gene signaling.
- NOTE Confidence: 0.5575379
- 00:10:55.850 --> 00:10:57.994 And so while I'm going to focus kind
- NOTE Confidence: 0.5575379
- $00:10:57.994 \rightarrow 00:11:00.330$  of on these upstream steps today,
- NOTE Confidence: 0.5575379
- $00:11:00.330 \rightarrow 00:11:02.722$  we really don't know what the key downstream

- NOTE Confidence: 0.5575379
- $00:11:02.722 \rightarrow 00:11:04.819$  steps are in terms of which signaling
- NOTE Confidence: 0.5575379
- $00:11:04.819 \rightarrow 00:11:07.370$  pathways are going to be most most relevant.
- NOTE Confidence: 0.5575379
- $00{:}11{:}07{.}370 \dashrightarrow 00{:}11{:}09{.}786$  And so that's really kind of ongoing work.
- NOTE Confidence: 0.5575379
- 00:11:09.790 --> 00:11:11.722 And I'll just close this slide
- NOTE Confidence: 0.5575379
- $00{:}11{:}11{.}722 \dashrightarrow 00{:}11{:}13{.}337$  by highlighting that actually AC
- NOTE Confidence: 0.5575379
- $00{:}11{:}13{.}337 \dashrightarrow 00{:}11{:}14{.}945$  gas is a really ancient protein.
- NOTE Confidence: 0.5575379
- $00:11:14.950 \longrightarrow 00:11:16.492$  It actually goes all the way
- NOTE Confidence: 0.5575379
- $00:11:16.492 \longrightarrow 00:11:17.263$  back to prokaryotes.
- NOTE Confidence: 0.5575379
- $00{:}11{:}17{.}270 \dashrightarrow 00{:}11{:}19{.}566$  And so it's played a role in
- NOTE Confidence: 0.5575379
- 00:11:19.566 --> 00:11:21.004 surveilling foreign DNA long
- NOTE Confidence: 0.5575379
- $00:11:21.004 \rightarrow 00:11:22.949$  before the innate immune system.
- NOTE Confidence: 0.5575379
- $00:11:22.950 \longrightarrow 00:11:24.028$  And so that kind of makes sense,
- NOTE Confidence: 0.5575379
- $00:11:24.030 \longrightarrow 00:11:25.530$  this idea that it's actually
- NOTE Confidence: 0.5575379
- $00:11:25.530 \rightarrow 00:11:26.730$  multiple signaling pathways that
- NOTE Confidence: 0.5575379
- $00{:}11{:}26.730 \dashrightarrow 00{:}11{:}28.508$  lie downstream of C gas activation.
- NOTE Confidence: 0.5958521

 $00:11:30.750 \longrightarrow 00:11:33.242$  So. So how do we get thinking

NOTE Confidence: 0.5958521

00:11:33.242 --> 00:11:34.310 about innate immunity?

NOTE Confidence: 0.5958521

00:11:34.310 --> 00:11:36.950 There's abundant evidence in the

NOTE Confidence: 0.5958521

 $00{:}11{:}36{.}950 \dashrightarrow 00{:}11{:}40{.}110$  literature that HR defects on this.

NOTE Confidence: 0.5958521

 $00:11:40.110 \longrightarrow 00:11:42.147$  In this particular case on the left,

NOTE Confidence: 0.5958521

 $00{:}11{:}42.150 \dashrightarrow 00{:}11{:}43.050$  we're looking at bracket.

NOTE Confidence: 0.5958521

 $00:11:43.050 \longrightarrow 00:11:43.950$  In both these cases,

NOTE Confidence: 0.5958521

 $00:11:43.950 \longrightarrow 00:11:46.290$  we're looking at bracket to knock

NOTE Confidence: 0.5958521

00:11:46.290 --> 00:11:48.538 down models that HR defects are

NOTE Confidence: 0.5958521

 $00{:}11{:}48.538 \dashrightarrow 00{:}11{:}50.373$  sufficient to trigger an innate

NOTE Confidence: 0.5958521

00:11:50.373 --> 00:11:53.157 immune response and this is a response

NOTE Confidence: 0.5958521

 $00{:}11{:}53{.}157 \dashrightarrow 00{:}11{:}55{.}163$  that's actually further pushed by

NOTE Confidence: 0.5958521

 $00{:}11{:}55{.}163 \dashrightarrow 00{:}11{:}57{.}008$  the addition of PARP inhibitors.

NOTE Confidence: 0.5958521

00:11:57.010 --> 00:11:58.501 So let me just walk you through

NOTE Confidence: 0.5958521

 $00:11:58.501 \rightarrow 00:11:59.649$  the example of this data.

NOTE Confidence: 0.5958521

 $00{:}11{:}59.650 \dashrightarrow 00{:}12{:}00.274$  As I mentioned,

- NOTE Confidence: 0.5958521
- $00{:}12{:}00{.}274 \dashrightarrow 00{:}12{:}01{.}730$  these are BRCA 2 knock down cells.
- NOTE Confidence: 0.5958521
- $00:12:01.730 \longrightarrow 00:12:03.330$  So with doxycycline we have
- NOTE Confidence: 0.5958521
- 00:12:03.330 --> 00:12:05.213 suppression A BRCA 2 expression and
- NOTE Confidence: 0.5958521
- $00{:}12{:}05{.}213 \dashrightarrow 00{:}12{:}06{.}802$  you can see that there's a gain
- NOTE Confidence: 0.5958521
- $00{:}12{:}06{.}802 \dashrightarrow 00{:}12{:}08{.}796$  in IRF 3 phosphorylation which is
- NOTE Confidence: 0.5958521
- $00{:}12{:}08.796 \dashrightarrow 00{:}12{:}10.641$  one of that canonical downstream
- NOTE Confidence: 0.5958521
- 00:12:10.641 --> 00:12:12.446 outcomes of C gas signaling.
- NOTE Confidence: 0.5958521
- $00{:}12{:}12{.}446 \dashrightarrow 00{:}12{:}14.600$  And this also leads in this
- NOTE Confidence: 0.5958521
- $00{:}12{:}14.682 \dashrightarrow 00{:}12{:}17.127$  model to Stat 1 phosphorylation.
- NOTE Confidence: 0.5958521
- $00{:}12{:}17{.}130 \dashrightarrow 00{:}12{:}19{.}299$  And a similar thing is seen in the in
- NOTE Confidence: 0.5958521
- $00:12:19.299 \rightarrow 00:12:21.889$  in breast cancer cells in this 231 model.
- NOTE Confidence: 0.5958521
- 00:12:21.890 --> 00:12:22.335 Again,
- NOTE Confidence: 0.5958521
- $00{:}12{:}22{.}335 \dashrightarrow 00{:}12{:}25{.}005$  this is a artificial system of
- NOTE Confidence: 0.5958521
- $00{:}12{:}25{.}005 \dashrightarrow 00{:}12{:}27{.}488$  the knock down of BRCA 2 with
- NOTE Confidence: 0.5958521
- 00:12:27.488 --> 00:12:28.928 regards to how PARP inhibitors
- NOTE Confidence: 0.5958521

 $00:12:28.928 \rightarrow 00:12:30.080$  then synergize with this.

NOTE Confidence: 0.5958521

00:12:30.080 --> 00:12:32.078 I've just pulled out this data

NOTE Confidence: 0.5958521

00:12:32.080 --> 00:12:33.636 from BRCA 1 deficient,

NOTE Confidence: 0.5958521

00:12:33.636 --> 00:12:35.970 BRCA 1 deficient breast cancer line

NOTE Confidence: 0.5958521

 $00:12:36.041 \longrightarrow 00:12:37.931$  that's commonly used in the lab

NOTE Confidence: 0.5958521

 $00{:}12{:}37{.}931$  -->  $00{:}12{:}40{.}268$  to study a BRCA 1 deficiency and NOTE Confidence: 0.5958521

 $00:12:40.268 \longrightarrow 00:12:42.613$  this is now in a xenograft model.

NOTE Confidence: 0.5958521

 $00{:}12{:}42.620 \dashrightarrow 00{:}12{:}44.654$  So these are actually now xenographs

NOTE Confidence: 0.5958521

 $00{:}12{:}44.654 \dashrightarrow 00{:}12{:}47.200$  looking at how PARP inhibitors affect NOTE Confidence: 0.5958521

 $00:12:47.200 \rightarrow 00:12:49.460$  interferon stimulated gene expression.

NOTE Confidence: 0.5958521

 $00{:}12{:}49{.}460 \dashrightarrow 00{:}12{:}51{.}556$  And you can see that all of these

NOTE Confidence: 0.5958521

00:12:51.556 --> 00:12:53.427 genes that are downstream of C

NOTE Confidence: 0.5958521

 $00{:}12{:}53{.}427 \dashrightarrow 00{:}12{:}55{.}353$  gas activation are up regulated in

NOTE Confidence: 0.5958521

 $00{:}12{:}55{.}422 \dashrightarrow 00{:}12{:}57{.}307$  the with PARP inhibitor treatment

NOTE Confidence: 0.5958521

 $00{:}12{:}57{.}307 \dashrightarrow 00{:}12{:}58{.}815$  in the xenograft model.

NOTE Confidence: 0.5958521

 $00{:}12{:}58{.}820 \dashrightarrow 00{:}13{:}00{.}745$  So there's been these observations

- NOTE Confidence: 0.5958521
- 00:13:00.745 --> 00:13:02.816 of innate immune stimulation in
- NOTE Confidence: 0.5958521
- $00{:}13{:}02{.}816 \dashrightarrow 00{:}13{:}05{.}564$  the context of HR deficient cells
- NOTE Confidence: 0.5958521
- $00{:}13{:}05{.}564 \dashrightarrow 00{:}13{:}07{.}925$  that's further pushed by PARP
- NOTE Confidence: 0.5958521
- $00:13:07.925 \longrightarrow 00:13:09.820$  inhibitors in a number of cases.
- NOTE Confidence: 0.5958521
- $00:13:09.820 \longrightarrow 00:13:13.019$  But what is the cause of this?
- NOTE Confidence: 0.5958521
- $00:13:13.020 \longrightarrow 00:13:13.305$  Right.
- NOTE Confidence: 0.5958521
- $00:13:13.305 \longrightarrow 00:13:14.160$  So what the,
- NOTE Confidence: 0.5958521
- $00:13:14.160 \longrightarrow 00:13:15.300$  what the signal is,
- NOTE Confidence: 0.5958521
- $00{:}13{:}15{.}300 \dashrightarrow 00{:}13{:}18{.}092$  How we go from HR deficiency to innate
- NOTE Confidence: 0.5958521
- $00:13:18.092 \rightarrow 00:13:20.380$  immune signaling has been really unclear.
- NOTE Confidence: 0.5958521
- $00{:}13{:}20{.}380 \dashrightarrow 00{:}13{:}22{.}151$  One other thing that I want to
- NOTE Confidence: 0.5958521
- $00{:}13{:}22{.}151 \dashrightarrow 00{:}13{:}23{.}872$  just a lert you to is that when
- NOTE Confidence: 0.5958521
- $00:13:23.872 \longrightarrow 00:13:25.620$  there is an HR defect in cells,
- NOTE Confidence: 0.5958521
- $00{:}13{:}25.620 \dashrightarrow 00{:}13{:}27.640$  one of the consequences is
- NOTE Confidence: 0.5958521
- $00:13:27.640 \longrightarrow 00:13:29.256$  that we accumulate cells,
- NOTE Confidence: 0.5958521

 $00:13:29.260 \longrightarrow 00:13:30.253$  accumulate mitotic errors.

NOTE Confidence: 0.5958521

00:13:30.253 --> 00:13:32.570 So this is just one paper I've

NOTE Confidence: 0.5958521

00:13:32.638 --> 00:13:34.208 pulled out from Steve West,

NOTE Confidence: 0.5958521

 $00{:}13{:}34{.}210 \dashrightarrow 00{:}13{:}36{.}254$  actually from more than a decade or

NOTE Confidence: 0.5958521

 $00{:}13{:}36{.}254 \dashrightarrow 00{:}13{:}38{.}049$  probably more than 15 years ago now

NOTE Confidence: 0.5958521

 $00:13:38.050 \rightarrow 00:13:40.170$  where it's been recognized for a long time.

NOTE Confidence: 0.5958521

 $00:13:40.170 \longrightarrow 00:13:42.485$  If there are challenges in

NOTE Confidence: 0.5958521

 $00:13:42.485 \rightarrow 00:13:44.800$  maintaining integrity of the genome,

NOTE Confidence: 0.5958521

 $00{:}13{:}44{.}800 \dashrightarrow 00{:}13{:}46{.}948$  then in mitosis you have these

NOTE Confidence: 0.5958521

 $00{:}13{:}46{.}948 \dashrightarrow 00{:}13{:}48{.}380$  intermediates that lead to

NOTE Confidence: 0.5958521

 $00{:}13{:}48.446 \dashrightarrow 00{:}13{:}50.516$  persistent bridges of DNA and DNA

NOTE Confidence: 0.5958521

00:13:50.516 --> 00:13:52.720 breaks and these kind of breakage,

NOTE Confidence: 0.5958521

 $00:13:52.720 \longrightarrow 00:13:54.910$  fusion breakage cycles that can

NOTE Confidence: 0.5958521

 $00:13:54.910 \rightarrow 00:13:57.879$  actually be precipitated by an HR defect,

NOTE Confidence: 0.5958521

 $00{:}13{:}57{.}880 \dashrightarrow 00{:}14{:}00{.}316$  by a radiation, by taxol treatments.

NOTE Confidence: 0.5958521

 $00:14:00.320 \longrightarrow 00:14:01.730$  You can arrive at these kind

- NOTE Confidence: 0.5958521
- $00:14:01.730 \longrightarrow 00:14:02.960$  of structures in many ways.

00:14:02.960 --> 00:14:04.418 But I would say HR deficiency

NOTE Confidence: 0.5958521

 $00:14:04.418 \longrightarrow 00:14:06.406$  is not the way that most people

NOTE Confidence: 0.5958521

 $00:14:06.406 \rightarrow 00:14:08.006$  have thought about arriving at

NOTE Confidence: 0.5958521

 $00:14:08.006 \rightarrow 00:14:09.480$  these kind of structures.

NOTE Confidence: 0.7051682

00:14:11.530 --> 00:14:13.245 I also just want to remind you,

NOTE Confidence: 0.7051682

 $00:14:13.250 \rightarrow 00:14:15.410$  'cause I'm a cell biologist,

NOTE Confidence: 0.7051682

 $00:14:15.410 \rightarrow 00:14:18.410$  that actually the nuclear envelope,

NOTE Confidence: 0.7051682

 $00:14:18.410 \longrightarrow 00:14:20.432$  not only the nuclear envelope is

NOTE Confidence: 0.7051682

00:14:20.432 --> 00:14:22.440 breaks down every cell cycle. OK.

NOTE Confidence: 0.7051682

00:14:22.440 --> 00:14:24.510 So I just wanted to keep this in your

NOTE Confidence: 0.7051682

 $00{:}14{:}24{.}571$  -->  $00{:}14{:}26{.}643$  mind too as I talk about this because NOTE Confidence: 0.7051682

1011 Connactice: 0.1001002

00:14:26.650 --> 00:14:29.114 I just told you there's an innate

NOTE Confidence: 0.7051682

 $00{:}14{:}29{.}114 \dashrightarrow 00{:}14{:}30{.}822$  immune surveillance protein that is

NOTE Confidence: 0.7051682

 $00{:}14{:}30{.}822 \dashrightarrow 00{:}14{:}32{.}887$  looking for DNA and yet every mitosis,

 $00:14:32.890 \rightarrow 00:14:35.529$  the chromosomes are exposed to the cytoplasm.

NOTE Confidence: 0.7051682

 $00{:}14{:}35{.}530 \dashrightarrow 00{:}14{:}37{.}970$  So we we know that that's not sufficient

NOTE Confidence: 0.7051682

 $00{:}14{:}37{.}970 \dashrightarrow 00{:}14{:}40{.}258$  to drive an innate immune response.

NOTE Confidence: 0.7051682

 $00:14:40.260 \longrightarrow 00:14:42.186$  So we know in mitosis there

NOTE Confidence: 0.7051682

 $00:14:42.186 \longrightarrow 00:14:43.860$  are mechanisms to down rate,

NOTE Confidence: 0.7051682

 $00{:}14{:}43.860 \dashrightarrow 00{:}14{:}45.565$  down regulate this surveillance mechanisms

NOTE Confidence: 0.7051682

 $00{:}14{:}45{.}565 \dashrightarrow 00{:}14{:}48{.}215$  are a way to shield these chromosomes

NOTE Confidence: 0.7051682

 $00:14:48.215 \rightarrow 00:14:50.420$  from actually activating this pathway.

NOTE Confidence: 0.7051682

 $00{:}14{:}50{.}420 \dashrightarrow 00{:}14{:}52{.}725$  And so these recombination intermediates

NOTE Confidence: 0.7051682

 $00:14:52.725 \longrightarrow 00:14:55.030$  are interesting in part because

NOTE Confidence: 0.7051682

00:14:55.103 --> 00:14:57.215 they don't just occur in mitosis,

NOTE Confidence: 0.7051682

 $00{:}14{:}57{.}220 \dashrightarrow 00{:}14{:}59{.}980$  they persist into the following interface.

NOTE Confidence: 0.7051682

 $00:14:59.980 \longrightarrow 00:15:01.688$  And that's going to be important here

NOTE Confidence: 0.7051682

 $00:15:01.688 \rightarrow 00:15:03.550$  because we need to get to the next

NOTE Confidence: 0.7051682

 $00{:}15{:}03.550 \dashrightarrow 00{:}15{:}05.408$  interphase in order for this innate immune

NOTE Confidence: 0.7051682

 $00:15:05.408 \longrightarrow 00:15:07.218$  surveillance mechanism to be reactivated.

- NOTE Confidence: 0.44108427
- $00{:}15{:}09{.}330 \dashrightarrow 00{:}15{:}11{.}556$  And indeed, there is also evidence in

 $00:15:11.556 \rightarrow 00:15:13.621$  the literature that for PARP inhibitors

NOTE Confidence: 0.44108427

 $00:15:13.621 \rightarrow 00:15:15.366$  to actually induce cell death,

NOTE Confidence: 0.44108427

 $00:15:15.370 \rightarrow 00:15:17.848$  cells have to transit through mitosis.

NOTE Confidence: 0.44108427

 $00:15:17.850 \rightarrow 00:15:19.845$  This is additional evidence that you know,

NOTE Confidence: 0.44108427

 $00:15:19.850 \longrightarrow 00:15:22.034$  unlike P53, which as I mentioned

NOTE Confidence: 0.44108427

 $00:15:22.034 \rightarrow 00:15:23.490$  is acting an interphase,

NOTE Confidence: 0.44108427

 $00:15:23.490 \rightarrow 00:15:25.650$  that it is essential for cells to go

NOTE Confidence: 0.44108427

 $00{:}15{:}25{.}650 \dashrightarrow 00{:}15{:}27{.}168$  through mitosis for PARP inhibitors

NOTE Confidence: 0.44108427

 $00:15:27.168 \longrightarrow 00:15:29.004$  to actually cause the cell death.

NOTE Confidence: 0.44108427

 $00{:}15{:}29{.}010 \dashrightarrow 00{:}15{:}30{.}714$  This is actually some work again

NOTE Confidence: 0.44108427

 $00{:}15{:}30{.}714 \dashrightarrow 00{:}15{:}32{.}582$  in a xenograph model and the

NOTE Confidence: 0.44108427

 $00{:}15{:}32{.}582 \dashrightarrow 00{:}15{:}33{.}938$  absence of functional bracket,

NOTE Confidence: 0.44108427

 $00{:}15{:}33{.}940 \dashrightarrow 00{:}15{:}36{.}060$  two and cells treated with a laparib and

NOTE Confidence: 0.44108427

 $00:15:36.060 \rightarrow 00:15:38.376$  what you can see is kind of these events.

 $00:15:38.380 \longrightarrow 00:15:42.133$  So we have a cell that is likely in G2,

NOTE Confidence: 0.44108427

 $00{:}15{:}42{.}133 \dashrightarrow 00{:}15{:}43{.}777$  it goes into mitosis.

NOTE Confidence: 0.44108427

 $00{:}15{:}43{.}780 \dashrightarrow 00{:}15{:}45{.}820$  You can see this is an this is an anaphase. NOTE Confidence: 0.44108427

 $00{:}15{:}45{.}820 \dashrightarrow 00{:}15{:}48{.}256$  So there are an aphase bridges here and

NOTE Confidence: 0.44108427

00:15:48.256 --> 00:15:50.903 actually most cells have some degree of

NOTE Confidence: 0.44108427

00:15:50.903 --> 00:15:52.823 entanglement of chromosomes in anaphase NOTE Confidence: 0.44108427

 $00:15:52.823 \rightarrow 00:15:55.495$  that are going to be resolved dynamically.

NOTE Confidence: 0.44108427

 $00:15:55.500 \rightarrow 00:15:57.738$  However, if that does not happen,

NOTE Confidence: 0.44108427

 $00{:}15{:}57{.}740 \dashrightarrow 00{:}16{:}00{.}026$  if cells are unable to resolve

NOTE Confidence: 0.44108427

 $00:16:00.026 \rightarrow 00:16:01.550$  these entanglements of chromosomes,

NOTE Confidence: 0.44108427

 $00{:}16{:}01{.}550 \dashrightarrow 00{:}16{:}03{.}860$  So what happens is that these cells

NOTE Confidence: 0.44108427

 $00:16:03.860 \rightarrow 00:16:05.750$  will biochemically come out of mitosis.

NOTE Confidence: 0.44108427

 $00{:}16{:}05{.}750 \dashrightarrow 00{:}16{:}07{.}534$  So they're back in interface and you can

NOTE Confidence: 0.44108427

 $00:16:07.534 \rightarrow 00:16:09.667$  see that because the nucleus is intact again.

NOTE Confidence: 0.44108427

 $00{:}16{:}09{.}670 \dashrightarrow 00{:}16{:}11{.}110$  But what you can see in this cell is

NOTE Confidence: 0.44108427

 $00:16:11.110 \rightarrow 00:16:12.550$  you now have a doublet essentially,

00:16:12.550 --> 00:16:12.856 right?

NOTE Confidence: 0.44108427

 $00:16:12.856 \rightarrow 00:16:14.998$  You have a cell that actually failed

NOTE Confidence: 0.44108427

 $00{:}16{:}14.998 \dashrightarrow 00{:}16{:}16.929$  in cytokinesis and it failed because

NOTE Confidence: 0.44108427

 $00{:}16{:}16{.}929 \dashrightarrow 00{:}16{:}18{.}509$  you couldn't actually generate 2

NOTE Confidence: 0.44108427

 $00{:}16{:}18{.}509 \dashrightarrow 00{:}16{:}20{.}174$  cells because there was bridging

NOTE Confidence: 0.44108427

 $00{:}16{:}20{.}174 \dashrightarrow 00{:}16{:}21{.}784$  DNA between these two cells.

NOTE Confidence: 0.44108427

 $00:16:21.790 \longrightarrow 00:16:23.350$  But the cell has biochemically

NOTE Confidence: 0.44108427

 $00{:}16{:}23.350 \dashrightarrow 00{:}16{:}25.492$  come back into interface and so we

NOTE Confidence: 0.44108427

 $00{:}16{:}25{.}492 \dashrightarrow 00{:}16{:}27{.}076$  can imagine that the innate immune

NOTE Confidence: 0.44108427

 $00:16:27.076 \longrightarrow 00:16:28.350$  system is active again.

NOTE Confidence: 0.44108427

 $00:16:28.350 \longrightarrow 00:16:29.614$  And the question is,

NOTE Confidence: 0.44108427

 $00{:}16{:}29.614 \dashrightarrow 00{:}16{:}31.927$  is this somehow aware of the fact

NOTE Confidence: 0.44108427

 $00{:}16{:}31{.}927 \dashrightarrow 00{:}16{:}34{.}027$  that this is a defective mitosis?

NOTE Confidence: 0.44108427

 $00{:}16{:}34{.}030 \dashrightarrow 00{:}16{:}35{.}703$  Is there some mechanism to know that

NOTE Confidence: 0.44108427

 $00:16:35.703 \dashrightarrow 00:16:37.429$  and that this would ultimately Dr.

 $00{:}16{:}37{.}430 \dashrightarrow 00{:}16{:}38{.}725$  the cell death and that's what we

NOTE Confidence: 0.44108427

 $00{:}16{:}38{.}725 \dashrightarrow 00{:}16{:}40{.}133$  see happening on the right with

NOTE Confidence: 0.44108427

 $00{:}16{:}40{.}133 \dashrightarrow 00{:}16{:}40{.}946$  this chromosome condensation.

NOTE Confidence: 0.9336245

 $00:16:43.590 \longrightarrow 00:16:45.676$  I just want to highlight that this

NOTE Confidence: 0.9336245

 $00:16:45.676 \rightarrow 00:16:47.630$  is not really new information,

NOTE Confidence: 0.9336245

 $00:16:47.630 \longrightarrow 00:16:48.710$  so we can go back.

NOTE Confidence: 0.9336245

 $00{:}16{:}48.710 \dashrightarrow 00{:}16{:}52.374$  This is from 2001 and there has been

NOTE Confidence: 0.9336245

 $00{:}16{:}52{.}374 \dashrightarrow 00{:}16{:}56{.}290$  long been the understanding that these,

NOTE Confidence: 0.9336245

 $00{:}16{:}56{.}290 \dashrightarrow 00{:}16{:}57{.}770$  the changes in nuclear shape,

NOTE Confidence: 0.9336245

 $00{:}16{:}57{.}770 \dashrightarrow 00{:}17{:}00{.}930$  nuclear atypia which are used all the time

NOTE Confidence: 0.9336245

 $00:17:00.930 \dashrightarrow 00:17:03.287$  by pathologists to diagnose and stays,

NOTE Confidence: 0.9336245

 $00:17:03.290 \longrightarrow 00:17:06.510$  cancers are tied to these kind of

NOTE Confidence: 0.9336245

 $00{:}17{:}06{.}510 \dashrightarrow 00{:}17{:}08{.}810$  aberrations that I've mentioned.

NOTE Confidence: 0.9336245

 $00{:}17{:}08.810 \dashrightarrow 00{:}17{:}10.736$  So I just want to you know that they've

NOTE Confidence: 0.9336245

 $00:17:10.736 \dashrightarrow 00:17:12.409$  been called many things over time.

NOTE Confidence: 0.9336245

 $00:17:12.410 \longrightarrow 00:17:14.480$  What I want to point out is that all

- NOTE Confidence: 0.9336245
- $00:17:14.480 \longrightarrow 00:17:16.998$  of these kind of mitotic errors that

00:17:16.998 --> 00:17:18.963 are typically associated with altered

NOTE Confidence: 0.9336245

 $00{:}17{:}18.963 \dashrightarrow 00{:}17{:}21.270$  nuclear shape are all things that we're

NOTE Confidence: 0.9336245

 $00:17:21.270 \rightarrow 00:17:22.750$  observing in interphase cells again,

NOTE Confidence: 0.9336245

 $00:17:22.750 \longrightarrow 00:17:24.458$  so not in cells just in mitosis

NOTE Confidence: 0.9336245

 $00:17:24.458 \longrightarrow 00:17:25.910$  that have an anaphase bridge

NOTE Confidence: 0.9336245

 $00:17:25.910 \longrightarrow 00:17:27.590$  but they're in in interphase.

NOTE Confidence: 0.9336245

 $00:17:27.590 \longrightarrow 00:17:29.970$  So these were called what the structures

NOTE Confidence: 0.9336245

 $00{:}17{:}29{.}970 \dashrightarrow 00{:}17{:}32{.}211$  that I just described that you can

NOTE Confidence: 0.9336245

 $00{:}17{:}32{.}211 \dashrightarrow 00{:}17{:}34{.}402$  have persistent DNA that then is still

NOTE Confidence: 0.9336245

 $00{:}17{:}34{.}402 \dashrightarrow 00{:}17{:}36{.}208$  there as cells reform their nucleus

NOTE Confidence: 0.9336245

 $00{:}17{:}36{.}208 \dashrightarrow 00{:}17{:}38{.}310$  and go into the next cell cycle.

NOTE Confidence: 0.9336245

00:17:38.310 --> 00:17:39.598 And this, you know,

NOTE Confidence: 0.9336245

 $00{:}17{:}39{.}598 \dashrightarrow 00{:}17{:}41{.}530$ 25 years ago were called inter

NOTE Confidence: 0.9336245

 $00:17:41.598 \rightarrow 00:17:42.630$  nuclear strings,

 $00:17:42.630 \rightarrow 00:17:45.180$  but you can also have micronuclei.

NOTE Confidence: 0.9336245

00:17:45.180 --> 00:17:46.800 And I just want to point out one of

NOTE Confidence: 0.9336245

00:17:46.800 --> 00:17:48.195 the differences between these two

NOTE Confidence: 0.9336245

00:17:48.195 - 00:17:49.941 types of structures is that these

NOTE Confidence: 0.9336245

 $00:17:49.992 \rightarrow 00:17:51.422$  inter nuclear strings are because

NOTE Confidence: 0.9336245

 $00{:}17{:}51{.}422 \dashrightarrow 00{:}17{:}53{.}277$  of an inability to segregate the

NOTE Confidence: 0.9336245

 $00{:}17{:}53.277 \dashrightarrow 00{:}17{:}54.945$  chromosomes because the chromosomes

NOTE Confidence: 0.9336245

 $00:17:54.945 \rightarrow 00:17:56.613$  are literally entangled and

NOTE Confidence: 0.9336245

 $00{:}17{:}56.613 \dashrightarrow 00{:}17{:}58.500$  cannot be physically segregated.

NOTE Confidence: 0.9336245

 $00:17:58.500 \rightarrow 00:18:01.224$  Micronuclei are different and that they

NOTE Confidence: 0.9336245

00:18:01.224 --> 00:18:03.860 predominantly arise from lagging chromosomes,

NOTE Confidence: 0.9336245

 $00:18:03.860 \longrightarrow 00:18:05.405$  acentrosomal chromosome fragments

NOTE Confidence: 0.9336245

 $00{:}18{:}05{.}405 \dashrightarrow 00{:}18{:}07{.}980$  and perhaps extra chromosomal DNA,

NOTE Confidence: 0.9336245

 $00:18:07.980 \longrightarrow 00:18:08.218$  right.

NOTE Confidence: 0.9336245

 $00{:}18{:}08{.}218 \dashrightarrow 00{:}18{:}09{.}646$  So they really are a different

NOTE Confidence: 0.9336245

 $00{:}18{:}09{.}646 \dashrightarrow 00{:}18{:}11{.}011$  structure than these two structures

- NOTE Confidence: 0.9336245
- $00:18:11.011 \rightarrow 00:18:12.215$  are actually quite different.
- NOTE Confidence: 0.9336245
- $00:18:12.220 \longrightarrow 00:18:14.266$  And I'll come back to that.
- NOTE Confidence: 0.9336245
- $00:18:14.270 \longrightarrow 00:18:15.470$  The consequence of this can
- NOTE Confidence: 0.9336245
- $00{:}18{:}15{.}470 \dashrightarrow 00{:}18{:}16{.}430$  lead to BI nucleation.
- NOTE Confidence: 0.9336245
- 00:18:16.430 $\operatorname{-->}$ 00:18:18.453 That's what I just showed you in
- NOTE Confidence: 0.9336245
- $00:18:18.453 \longrightarrow 00:18:19.790$  that particular bracket 2 model.
- NOTE Confidence: 0.9336245
- 00:18:19.790 --> 00:18:21.390 And I won't really talk about it today,
- NOTE Confidence: 0.9336245
- $00:18:21.390 \rightarrow 00:18:23.700$  but you can also get nuclear ruptures
- NOTE Confidence: 0.9336245
- $00:18:23.700 \longrightarrow 00:18:26.189$  that happen in interface due to a
- NOTE Confidence: 0.9336245
- $00:18:26.189 \longrightarrow 00:18:27.984$  defect in the nuclear integrity.
- NOTE Confidence: 0.9336245
- $00:18:27.990 \longrightarrow 00:18:29.334$  But that is not an event that's
- NOTE Confidence: 0.9336245
- $00{:}18{:}29{.}334 \dashrightarrow 00{:}18{:}29{.}910$  tied to mitosis.
- NOTE Confidence: 0.9336245
- $00{:}18{:}29{.}910 \dashrightarrow 00{:}18{:}31{.}350$  So I'm not going to talk
- NOTE Confidence: 0.9336245
- $00:18:31.350 \longrightarrow 00:18:32.367$  more about that today.
- NOTE Confidence: 0.9336245
- 00:18:32.367 -> 00:18:32.664 OK.
- NOTE Confidence: 0.9336245

 $00:18:32.664 \rightarrow 00:18:35.040$  So let me just show you kind of

NOTE Confidence: 0.9336245

 $00:18:35.113 \longrightarrow 00:18:37.128$  the amazing cell biology that

NOTE Confidence: 0.9336245

 $00:18:37.128 \longrightarrow 00:18:39.143$  is tied and specifically to

NOTE Confidence: 0.9336245

 $00{:}18{:}39{.}218 \dashrightarrow 00{:}18{:}41{.}270$  these persistent DNA bridges.

NOTE Confidence: 0.9336245

 $00{:}18{:}41{.}270 \dashrightarrow 00{:}18{:}43{.}790$  So here I'm showing you a movie.

NOTE Confidence: 0.9336245

 $00:18:43.790 \rightarrow 00:18:45.506$  These are cells that are expressing

NOTE Confidence: 0.9336245

00:18:45.506 --> 00:18:46.650 a nuclear localization signal

NOTE Confidence: 0.9336245

 $00:18:46.699 \rightarrow 00:18:48.109$  tagged to a fluorescent protein.

NOTE Confidence: 0.9336245

00:18:48.110 --> 00:18:50.228 So it's exclusively in the nucleus.

NOTE Confidence: 0.9336245

 $00{:}18{:}50{.}230 \dashrightarrow 00{:}18{:}52{.}150$  And we're going to look at this cell

NOTE Confidence: 0.9336245

 $00:18:52.150 \rightarrow 00:18:54.050$  that is just going through mitosis,

NOTE Confidence: 0.9336245

 $00{:}18{:}54.050 \dashrightarrow 00{:}18{:}55.190$  if it will.

NOTE Confidence: 0.9209971

 $00{:}18{:}57{.}830 \dashrightarrow 00{:}18{:}59{.}478$  Maybe I'm not allowed to do that while

NOTE Confidence: 0.9209971

 $00{:}18{:}59{.}478 \dashrightarrow 00{:}19{:}01{.}350$  I have the pointer on, Is that possible?

NOTE Confidence: 0.9209971

00:19:05.310 --> 00:19:07.425 Yep, that's possible.

NOTE Confidence: 0.9209971

00:19:07.425 --> 00:19:09.670 OK, so we're gonna look at the cell
- NOTE Confidence: 0.9209971
- $00:19:09.670 \longrightarrow 00:19:11.289$  that is trying to transit mitosis.
- NOTE Confidence: 0.9209971
- 00:19:11.290 --> 00:19:12.730 We're gonna see it come out of mitosis.
- NOTE Confidence: 0.9209971
- $00:19:12.730 \longrightarrow 00:19:14.020$  These cells are still linked by
- NOTE Confidence: 0.9209971
- $00:19:14.020 \longrightarrow 00:19:15.649$  one of these DNA bridges and you
- NOTE Confidence: 0.9209971
- $00:19:15.649 \rightarrow 00:19:17.083$  can see there are these flashes,
- NOTE Confidence: 0.9209971
- $00{:}19{:}17{.}090 \dashrightarrow 00{:}19{:}18{.}460$  there are these transient ruptures
- NOTE Confidence: 0.9209971
- $00{:}19{:}18{.}460 \dashrightarrow 00{:}19{:}20{.}473$  of the nucleus and all the nuclear
- NOTE Confidence: 0.9209971
- $00{:}19{:}20{.}473 \dashrightarrow 00{:}19{:}21{.}943$  localization signal will spill out
- NOTE Confidence: 0.9209971
- $00{:}19{:}21{.}943 \dashrightarrow 00{:}19{:}23{.}978$  and then there seems to be some repair
- NOTE Confidence: 0.9209971
- $00{:}19{:}23{.}978 \dashrightarrow 00{:}19{:}25{.}822$  of that event and then the the the
- NOTE Confidence: 0.9209971
- $00{:}19{:}25.822 \dashrightarrow 00{:}19{:}27.286$  protein can start to accumulate again.
- NOTE Confidence: 0.9209971
- $00{:}19{:}27{.}290 \dashrightarrow 00{:}19{:}30{.}076$  So it's kind of these cycles of
- NOTE Confidence: 0.9209971
- $00:19:30.076 \dashrightarrow 00:19:32.490$  ruptures and then repair events.
- NOTE Confidence: 0.9209971
- $00{:}19{:}32{.}490 \dashrightarrow 00{:}19{:}34{.}290$  So this is just looking in this case,
- NOTE Confidence: 0.9209971
- $00{:}19{:}34{.}290 \dashrightarrow 00{:}19{:}37{.}050$  this is actually a model where there's
- NOTE Confidence: 0.9209971

00:19:37.050 --> 00:19:39.288 a dicentric chromosome, however one.

NOTE Confidence: 0.9209971

 $00{:}19{:}39{.}288 \dashrightarrow 00{:}19{:}41{.}451$  So one of the questions is what's

NOTE Confidence: 0.9209971

 $00{:}19{:}41{.}451 \dashrightarrow 00{:}19{:}43{.}561$  the consequence of this innate

NOTE Confidence: 0.9209971

 $00{:}19{:}43.561 \dashrightarrow 00{:}19{:}45.293$  immune surveillance mechanism when

NOTE Confidence: 0.9209971

 $00:19:45.293 \rightarrow 00:19:47.587$  you have one of these ruptures.

NOTE Confidence: 0.9209971

 $00{:}19{:}47.590 \dashrightarrow 00{:}19{:}49.366$  So these kind of transient ruptures

NOTE Confidence: 0.9209971

 $00:19:49.366 \rightarrow 00:19:50.794$  of the nuclear envelopes, right.

NOTE Confidence: 0.9209971

 $00:19:50.794 \rightarrow 00:19:52.746$  So the nucleus, we've come out of mitosis,

NOTE Confidence: 0.9209971

 $00{:}19{:}52.750 \dashrightarrow 00{:}19{:}55.830$  it should be intact, but it's it's unstable.

NOTE Confidence: 0.9209971

 $00:19:55.830 \longrightarrow 00:19:57.958$  And so here I'm going to show

NOTE Confidence: 0.9209971

 $00:19:57.958 \longrightarrow 00:19:58.870$  you similarly cells,

NOTE Confidence: 0.9209971

 $00{:}19{:}58{.}870 \dashrightarrow 00{:}20{:}01{.}990$  but these cells are actually now

NOTE Confidence: 0.9209971

 $00{:}20{:}01{.}990 \dashrightarrow 00{:}20{:}03{.}725$  expressing AC gas that's tagged and

NOTE Confidence: 0.9209971

 $00:20:03.725 \longrightarrow 00:20:05.840$  that's going to be in this panel here.

NOTE Confidence: 0.9209971

 $00{:}20{:}05{.}840 \dashrightarrow 00{:}20{:}07{.}149$  And I just want to again point

NOTE Confidence: 0.9209971

 $00:20:07.149 \longrightarrow 00:20:08.558$  out this is not just anaphase.

- NOTE Confidence: 0.9209971
- $00:20:08.560 \longrightarrow 00:20:10.120$  This is far after anaphase.
- NOTE Confidence: 0.9209971
- $00:20:10.120 \longrightarrow 00:20:11.240$  These cells have this bridge.
- NOTE Confidence: 0.9209971
- 00:20:11.240 --> 00:20:13.520 They're trying to break their DNA
- NOTE Confidence: 0.9209971
- $00:20:13.520 \longrightarrow 00:20:15.554$  and and and segregate it, right,
- NOTE Confidence: 0.9209971
- $00:20:15.554 \rightarrow 00:20:16.958$  Not break it, but segregate it.
- NOTE Confidence: 0.9209971
- $00{:}20{:}16{.}960 \dashrightarrow 00{:}20{:}18{.}731$  And what I hope you can appreciate
- NOTE Confidence: 0.9209971
- $00:20:18.731 \longrightarrow 00:20:20.344$  is that late in this movie,
- NOTE Confidence: 0.9209971
- $00:20:20.344 \longrightarrow 00:20:22.727$  all of a sudden what we see is
- NOTE Confidence: 0.9209971
- $00{:}20{:}22{.}727 \dashrightarrow 00{:}20{:}24{.}367$  that there's recruitment of sea
- NOTE Confidence: 0.9209971
- $00{:}20{:}24.367 \dashrightarrow 00{:}20{:}26.637$  gas all over this strand of DNA.
- NOTE Confidence: 0.9209971
- $00:20:26.640 \rightarrow 00:20:28.632$  OK. So it's not something that
- NOTE Confidence: 0.9209971
- $00{:}20{:}28.632 \dashrightarrow 00{:}20{:}29.628$  happens in mitosis.
- NOTE Confidence: 0.9209971
- 00:20:29.630 --> 00:20:30.866 It's far after mitosis.
- NOTE Confidence: 0.9209971
- $00{:}20{:}30{.}866 \dashrightarrow 00{:}20{:}33{.}094$  There is this bridge of DNA the
- NOTE Confidence: 0.9209971
- $00:20:33.094 \rightarrow 00:20:35.264$  nuclear was trying to form around it,
- NOTE Confidence: 0.9209971

00:20:35.270 --> 00:20:38.150 but we get these ruptures and see gases

NOTE Confidence: 0.9209971

 $00{:}20{:}38.150 \dashrightarrow 00{:}20{:}40.466$  recruited and this is a persistent bridge.

NOTE Confidence: 0.9209971

 $00{:}20{:}40.470 \dashrightarrow 00{:}20{:}42.207$  I just want to point out you also get

NOTE Confidence: 0.9209971

 $00{:}20{:}42{.}207 \dashrightarrow 00{:}20{:}43{.}788$  this kind of thing to Micronuclei.

NOTE Confidence: 0.9209971

 $00{:}20{:}43.790 \dashrightarrow 00{:}20{:}46.023$  Here's a micronucleus and we can actually

NOTE Confidence: 0.9209971

 $00{:}20{:}46.023 \dashrightarrow 00{:}20{:}48.068$  see that that micronucleus is intact

NOTE Confidence: 0.9209971

 $00:20:48.068 \rightarrow 00:20:50.382$  and then it's going to rupture and

NOTE Confidence: 0.9209971

 $00:20:50.382 \rightarrow 00:20:51.954$  then there's massive C gas recruitment,

NOTE Confidence: 0.9209971

 $00{:}20{:}51{.}960 \dashrightarrow 00{:}20{:}52{.}297$  OK.

NOTE Confidence: 0.9209971

 $00{:}20{:}52{.}297 \dashrightarrow 00{:}20{:}54{.}993$  So any of these losses of nuclear integrity,

NOTE Confidence: 0.9209971

 $00{:}20{:}55{.}000 \dashrightarrow 00{:}20{:}56{.}932$  whether it's one of these persistent

NOTE Confidence: 0.9209971

00:20:56.932 --> 00:20:58.998 Dania bridges or it's a micronucleus

NOTE Confidence: 0.9209971

 $00{:}20{:}58{.}998 \dashrightarrow 00{:}21{:}00{.}840$  can recruit the C gas protein.

NOTE Confidence: 0.27129424

 $00:21:05.240 \longrightarrow 00:21:07.704$  So I'm going to focus today on these

NOTE Confidence: 0.27129424

00:21:07.704 --> 00:21:10.242 DNA bridges and I'm going to just give

NOTE Confidence: 0.27129424

 $00:21:10.242 \rightarrow 00:21:12.319$  you the rationale for why that is.

- NOTE Confidence: 0.27129424
- $00:21:12.320 \rightarrow 00:21:16.650$  Now, one of them is that actually
- NOTE Confidence: 0.27129424
- $00:21:16.650 \longrightarrow 00:21:19.100$  many perturbations will cause both
- NOTE Confidence: 0.27129424
- 00:21:19.100 --> 00:21:22.040 these DNA bridges and micronuclei.
- NOTE Confidence: 0.27129424
- $00{:}21{:}22.040 \dashrightarrow 00{:}21{:}23.792$  But there's evidence in the literature
- NOTE Confidence: 0.27129424
- $00{:}21{:}23.792 \dashrightarrow 00{:}21{:}26.083$  that DNA bridges are actually much more
- NOTE Confidence: 0.27129424
- $00{:}21{:}26.083 \dashrightarrow 00{:}21{:}27.873$  potent activators of Segamp production.
- NOTE Confidence: 0.27129424
- 00:21:27.880 --> 00:21:28.720 If you remember, I told you,
- NOTE Confidence: 0.27129424
- $00:21:28.720 \longrightarrow 00:21:30.911$  the recruitment of of C gas is
- NOTE Confidence: 0.27129424
- $00{:}21{:}30{.}911 \dashrightarrow 00{:}21{:}33{.}043$  not sufficient to activate it to
- NOTE Confidence: 0.27129424
- 00:21:33.043 --> 00:21:34.918 generate high levels of Segamp.
- NOTE Confidence: 0.27129424
- 00:21:34.920 --> 00:21:36.600 You know why might that be?
- NOTE Confidence: 0.27129424
- 00:21:36.600 --> 00:21:38.868 There's evidence actually that one of
- NOTE Confidence: 0.27129424
- 00:21:38.868 --> 00:21:41.083 the mechanisms that keeps cells from
- NOTE Confidence: 0.27129424
- 00:21:41.083 --> 00:21:43.309 over<br/>reacting to its own genome is the
- NOTE Confidence: 0.27129424
- $00{:}21{:}43{.}309 \dashrightarrow 00{:}21{:}45{.}463$  fact that nucleosomal or chromatized DNA NOTE Confidence: 0.27129424

 $00:21:45.463 \rightarrow 00:21:48.292$  is a poor stimulator of Segamp production.

NOTE Confidence: 0.27129424

 $00{:}21{:}48.292 \dashrightarrow 00{:}21{:}49.870$  Whereas naked DNA,

NOTE Confidence: 0.27129424

00:21:49.870 --> 00:21:51.870 what you would have in a virus or a bacteria,

NOTE Confidence: 0.27129424

 $00:21:51.870 \longrightarrow 00:21:54.150$  is a far more potent activator

NOTE Confidence: 0.27129424

00:21:54.150 --> 00:21:55.670 of C gamp activation.

NOTE Confidence: 0.27129424

 $00{:}21{:}55.670 \dashrightarrow 00{:}21{:}57.944$  And so this would suggest that

NOTE Confidence: 0.27129424

 $00{:}21{:}57{.}944 \dashrightarrow 00{:}22{:}00{.}749$  really the state of the DNA matters.

NOTE Confidence: 0.27129424

00:22:00.750 --> 00:22:02.806 And what I'm going to argue here is

NOTE Confidence: 0.27129424

 $00{:}22{:}02{.}806 \dashrightarrow 00{:}22{:}04{.}474$  that actually micronuclei for the

NOTE Confidence: 0.27129424

 $00{:}22{:}04{.}474 \dashrightarrow 00{:}22{:}06{.}309$  most part are chromatized substrate.

NOTE Confidence: 0.27129424

 $00{:}22{:}06{.}310 \dashrightarrow 00{:}22{:}07{.}810$  It was a lagging chromosome

NOTE Confidence: 0.27129424

 $00:22:07.810 \longrightarrow 00:22:09.310$  that formed its own nucleus.

NOTE Confidence: 0.27129424

00:22:09.310 --> 00:22:12.988 It's unstable but still it's nucleosomal

NOTE Confidence: 0.27129424

 $00{:}22{:}12{.}990 \dashrightarrow 00{:}22{:}14.766$  whereas this DNA in these persistent

NOTE Confidence: 0.27129424

 $00{:}22{:}14.766 \dashrightarrow 00{:}22{:}16.869$  bridges as you saw in those movies,

NOTE Confidence: 0.27129424

 $00:22:16.870 \longrightarrow 00:22:18.868$  the DNA is being pulled apart.

 $00:22:18.870 \longrightarrow 00:22:20.814$  And so one of the ideas is that it

NOTE Confidence: 0.27129424

 $00{:}22{:}20{.}814 \dashrightarrow 00{:}22{:}22{.}715$  there's so much tension on the DNA

NOTE Confidence: 0.27129424

00:22:22.715 --> 00:22:24.531 that actually the histones that make

NOTE Confidence: 0.27129424

 $00{:}22{:}24.531$  -->  $00{:}22{:}26.678$  nucleosomes are being evicted and then NOTE Confidence: 0.27129424

 $00{:}22{:}26.678 \dashrightarrow 00{:}22{:}30.326$  the DNA that's left is naked and that

NOTE Confidence: 0.27129424

 $00{:}22{:}30{.}326$  -->  $00{:}22{:}33{.}590$  that is a more potent activator C camp.

NOTE Confidence: 0.27129424

 $00{:}22{:}33{.}590 \dashrightarrow 00{:}22{:}35{.}770$  And additional evidence from that

NOTE Confidence: 0.27129424

 $00{:}22{:}35{.}770 \dashrightarrow 00{:}22{:}37{.}950$  for that comes from observations

NOTE Confidence: 0.27129424

00:22:38.017 --> 00:22:40.243 that Apobac activity it is actually

NOTE Confidence: 0.27129424

00:22:40.243 --> 00:22:42.100 very high over overstretched DNA

NOTE Confidence: 0.27129424

 $00:22:42.100 \longrightarrow 00:22:43.950$  that is present in bridges,

NOTE Confidence: 0.27129424

 $00{:}22{:}43.950 \dashrightarrow 00{:}22{:}46.113$  which suggests that it can also become

NOTE Confidence: 0.27129424

 $00:22:46.113 \rightarrow 00:22:48.109$  single stranded and acted on by APOBEC.

NOTE Confidence: 0.27129424

 $00{:}22{:}48.110 \dashrightarrow 00{:}22{:}49.845$  Such as additional evidence that

NOTE Confidence: 0.27129424

 $00{:}22{:}49.845 \dashrightarrow 00{:}22{:}52.000$  the structure in these in these

 $00:22:52.000 \rightarrow 00:22:53.795$  persistent DNA bridges is different

NOTE Confidence: 0.27129424

 $00{:}22{:}53.795 \dashrightarrow 00{:}22{:}56.190$  than what might be in Micronuclei.

NOTE Confidence: 0.27129424

 $00:22:56.190 \longrightarrow 00:22:56.401$  OK.

NOTE Confidence: 0.27129424

00:22:56.401 --> 00:22:57.878 And then last bit of cell biology

NOTE Confidence: 0.27129424

00:22:57.878 --> 00:22:59.617 before I get into our own data that

NOTE Confidence: 0.27129424

 $00{:}22{:}59{.}617 \dashrightarrow 00{:}23{:}01{.}243$  I need to introduce you to is the NOTE Confidence: 0.27129424

 $00:23:01.243 \longrightarrow 00:23:02.677$  idea that like in that NLS movie,

NOTE Confidence: 0.27129424

 $00{:}23{:}02{.}677 \dashrightarrow 00{:}23{:}04{.}312$  there's also a nuclear envelope

NOTE Confidence: 0.27129424

00:23:04.312 --> 00:23:05.980 repair mechanism that is looking

NOTE Confidence: 0.27129424

 $00{:}23{:}05{.}980 \dashrightarrow 00{:}23{:}07{.}816$  for these breaks in the nuclear

NOTE Confidence: 0.27129424

 $00{:}23{:}07{.}816 \dashrightarrow 00{:}23{:}09{.}310$  envelope and trying to fix it.

NOTE Confidence: 0.27129424

00:23:09.310 --> 00:23:11.095 And this is something that's been of

NOTE Confidence: 0.27129424

 $00{:}23{:}11.095 \dashrightarrow 00{:}23{:}12.986$  interest to our group for a long time.

NOTE Confidence: 0.27129424

 $00{:}23{:}12{.}990 \dashrightarrow 00{:}23{:}14{.}510$  So remember as I said,

NOTE Confidence: 0.27129424

 $00{:}23{:}14.510 \dashrightarrow 00{:}23{:}15.662$  in a normal mitosis,

NOTE Confidence: 0.27129424

 $00:23:15.662 \rightarrow 00:23:17.390$  the nuclear envelope has broken down,

- NOTE Confidence: 0.27129424
- $00:23:17.390 \longrightarrow 00:23:18.578$  the chromosomes are exposed,

 $00:23:18.578 \longrightarrow 00:23:20.063$  but they don't activate the

NOTE Confidence: 0.27129424

00:23:20.063 --> 00:23:21.069 innate immune system.

NOTE Confidence: 0.27129424

 $00:23:21.070 \longrightarrow 00:23:23.020$  Then we reform the nuclear

NOTE Confidence: 0.27129424

 $00:23:23.020 \longrightarrow 00:23:24.580$  envelope at mitotic exit.

NOTE Confidence: 0.27129424

 $00{:}23{:}24{.}580 \dashrightarrow 00{:}23{:}26{.}140$  When the nuclear envelope is reformed,

NOTE Confidence: 0.27129424

 $00:23:26.140 \longrightarrow 00:23:28.140$  you have sheets of endoplasmic

NOTE Confidence: 0.27129424

 $00:23:28.140 \longrightarrow 00:23:29.740$  reticulum around the chromosomes,

NOTE Confidence: 0.27129424

 $00:23:29.740 \longrightarrow 00:23:31.258$  but it's full of holes actually.

NOTE Confidence: 0.27129424

 $00:23:31.260 \rightarrow 00:23:32.870$  And those holes are particularly

NOTE Confidence: 0.27129424

 $00{:}23{:}32{.}870 \dashrightarrow 00{:}23{:}34{.}480$  where there are still microtubules

NOTE Confidence: 0.27129424

 $00{:}23{:}34{.}537 \dashrightarrow 00{:}23{:}35{.}982$  from the spindle that are

NOTE Confidence: 0.27129424

 $00:23:35.982 \longrightarrow 00:23:37.138$  attached to the chromosomes.

NOTE Confidence: 0.27129424

 $00{:}23{:}37{.}140 \dashrightarrow 00{:}23{:}38{.}890$  So there is a machinery that has

NOTE Confidence: 0.27129424

 $00{:}23{:}38{.}890 \dashrightarrow 00{:}23{:}40{.}957$  to come in and fix all these holes

 $00:23:40.957 \longrightarrow 00:23:42.740$  at the end of every mitosis.

NOTE Confidence: 0.27129424

 $00:23:42.740 \longrightarrow 00:23:45.050$  And that machinery is made-up of the

NOTE Confidence: 0.27129424

 $00{:}23{:}45.050 \dashrightarrow 00{:}23{:}46.740$  components that I've shown here.

NOTE Confidence: 0.27129424

 $00:23:46.740 \rightarrow 00:23:48.522$  There is an abundant DNA binding

NOTE Confidence: 0.27129424

 $00:23:48.522 \longrightarrow 00:23:49.413$  protein called bath,

NOTE Confidence: 0.73344946

 $00{:}23{:}49{.}420 \dashrightarrow 00{:}23{:}52{.}444$  not to be confused with the chromatin

NOTE Confidence: 0.73344946

 $00{:}23{:}52{.}444 \dashrightarrow 00{:}23{:}54{.}998$  remodeler bath and this brings in

NOTE Confidence: 0.73344946

 $00:23:54.998 \longrightarrow 00:23:57.688$  a protein called LEM 2 which is

NOTE Confidence: 0.73344946

 $00{:}23{:}57{.}688 \dashrightarrow 00{:}23{:}59{.}133$  an integral membrane protein and

NOTE Confidence: 0.73344946

 $00{:}23{:}59{.}133 \dashrightarrow 00{:}24{:}00{.}789$  that's shown here in the cartoon.

NOTE Confidence: 0.73344946

 $00{:}24{:}00{.}790 \dashrightarrow 00{:}24{:}02{.}806$  So this LEM Two is recruited to these

NOTE Confidence: 0.73344946

 $00{:}24{:}02{.}806 \dashrightarrow 00{:}24{:}05{.}478$  holes in the nuclear envelope and LEM Two

NOTE Confidence: 0.73344946

 $00{:}24{:}05{.}478 \dashrightarrow 00{:}24{:}07{.}830$  is an adapter for the escort machinery,

NOTE Confidence: 0.73344946

00:24:07.830 --> 00:24:09.798 particularly CHIM 7 which is a

NOTE Confidence: 0.73344946

 $00{:}24{:}09{.}798 \dashrightarrow 00{:}24{:}11{.}110$  nuclear envelope specific escort.

NOTE Confidence: 0.73344946

 $00:24:11.110 \rightarrow 00:24:13.483$  So the escorts are a membrane remodeling

- NOTE Confidence: 0.73344946
- $00{:}24{:}13.483 \dashrightarrow 00{:}24{:}15.437$  machinery that basically can take a hole

 $00{:}24{:}15{.}437 \dashrightarrow 00{:}24{:}17{.}279$  in a membrane and they can close it.

NOTE Confidence: 0.73344946

 $00:24:17.280 \rightarrow 00:24:20.040$  And so this machinery is recruiting,

NOTE Confidence: 0.73344946

 $00:24:20.040 \rightarrow 00:24:21.858$  is recruiting escorts to the nuclear

NOTE Confidence: 0.73344946

 $00:24:21.858 \rightarrow 00:24:23.920$  envelope they form these spiral polymers,

NOTE Confidence: 0.73344946

 $00{:}24{:}23{.}920 \dashrightarrow 00{:}24{:}25{.}872$  and you need this to have one nuclear

NOTE Confidence: 0.73344946

 $00:24:25.872 \longrightarrow 00:24:27.357$  envelope at the end of mitosis.

NOTE Confidence: 0.73344946

 $00:24:27.360 \longrightarrow 00:24:28.998$  So this is the normal thing

NOTE Confidence: 0.73344946

 $00:24:29.000 \longrightarrow 00:24:30.245$  that's always happening.

NOTE Confidence: 0.73344946

 $00{:}24{:}30{.}245 \dashrightarrow 00{:}24{:}32{.}735$  But there's abundant evidence that this

NOTE Confidence: 0.73344946

 $00:24:32.735 \rightarrow 00:24:35.130$  same exact machinery is recruited anytime

NOTE Confidence: 0.73344946

 $00{:}24{:}35{.}130 \dashrightarrow 00{:}24{:}37{.}720$  there's a defect in nuclear integrity.

NOTE Confidence: 0.73344946

00:24:37.720 --> 00:24:38.692 And so I'm just showing you

NOTE Confidence: 0.73344946

 $00{:}24{:}38.692 \dashrightarrow 00{:}24{:}39.560$  an example of this here.

NOTE Confidence: 0.73344946

 $00:24:39.560 \rightarrow 00:24:41.548$  This is actually where a rupture in

 $00{:}24{:}41{.}548 \dashrightarrow 00{:}24{:}43{.}320$  the nuclear envelope has been induced.

NOTE Confidence: 0.73344946

 $00{:}24{:}43{.}320 \dashrightarrow 00{:}24{:}45{.}630$  And you can see that there's recruitment

NOTE Confidence: 0.73344946

 $00:24:45.630 \longrightarrow 00:24:48.180$  of this escort chimp 7 as well as

NOTE Confidence: 0.73344946

 $00:24:48.180 \rightarrow 00:24:49.740$  recruitment of sea gas, right.

NOTE Confidence: 0.73344946

 $00{:}24{:}49{.}740 \dashrightarrow 00{:}24{:}52{.}008$  So one way of thinking about this

NOTE Confidence: 0.73344946

 $00:24:52.008 \longrightarrow 00:24:54.262$  kind of similar to the P53 story,

NOTE Confidence: 0.73344946

 $00{:}24{:}54{.}262 \dashrightarrow 00{:}24{:}56{.}117$ you know, you can repair,

NOTE Confidence: 0.73344946

 $00:24:56.120 \longrightarrow 00:24:58.280$  you can repair DNA or the cell can

NOTE Confidence: 0.73344946

 $00{:}24{:}58{.}280 \dashrightarrow 00{:}25{:}00{.}555$  die and you can give up on things.

NOTE Confidence: 0.73344946

 $00{:}25{:}00{.}560 \dashrightarrow 00{:}25{:}01{.}868$  We have this machinery that sees

NOTE Confidence: 0.73344946

 $00:25:01.868 \rightarrow 00:25:03.600$  a hole in the nuclear envelope.

NOTE Confidence: 0.73344946

 $00:25:03.600 \rightarrow 00:25:05.497$  It can try to fix the hole,

NOTE Confidence: 0.73344946

 $00:25:05.500 \longrightarrow 00:25:06.697$  but if it can't fix the hole,

NOTE Confidence: 0.73344946

 $00:25:06.700 \longrightarrow 00:25:08.050$  there's a surveillance by the

NOTE Confidence: 0.73344946

00:25:08.050 --> 00:25:08.860 innate immune system.

NOTE Confidence: 0.73344946

 $00:25:08.860 \longrightarrow 00:25:10.085$  And so there's actually a

- NOTE Confidence: 0.73344946
- $00:25:10.085 \rightarrow 00:25:10.820$  competition potentially that's

 $00{:}25{:}10.820 \dashrightarrow 00{:}25{:}12.178$  going on between these factors.

NOTE Confidence: 0.73344946

00:25:12.180 --> 00:25:13.866 And I'll show you some evidence

NOTE Confidence: 0.73344946

 $00{:}25{:}13.866 \dashrightarrow 00{:}25{:}15.500$  for that in a moment.

NOTE Confidence: 0.73344946

00:25:15.500 --> 00:25:15.739 Right.

NOTE Confidence: 0.73344946

 $00:25:15.739 \longrightarrow 00:25:16.456$  So here is,

NOTE Confidence: 0.73344946

 $00:25:16.456 \rightarrow 00:25:18.792$  and I'm just going to lay out why we've

NOTE Confidence: 0.73344946

 $00:25:18.792 \rightarrow 00:25:20.484$  done the experiments that I'm going

NOTE Confidence: 0.73344946

 $00{:}25{:}20{.}484 \dashrightarrow 00{:}25{:}22{.}618$  to describe in the rest of the talk.

NOTE Confidence: 0.73344946

 $00:25:22.620 \longrightarrow 00:25:24.732$  I've already walked through

NOTE Confidence: 0.73344946

 $00{:}25{:}24.732 \dashrightarrow 00{:}25{:}27.140$  Interphase and the idea, P 53.

NOTE Confidence: 0.73344946

 $00{:}25{:}27{.}140 \dashrightarrow 00{:}25{:}29{.}155$  So I just want to make the argument

NOTE Confidence: 0.73344946

 $00{:}25{:}29{.}155 \dashrightarrow 00{:}25{:}32{.}300$  up front for the hypothesis of a

NOTE Confidence: 0.73344946

 $00{:}25{:}32{.}300 \dashrightarrow 00{:}25{:}34{.}040$  similar surveillance mechanism that's

NOTE Confidence: 0.73344946

00:25:34.040 --> 00:25:36.390 active post mitosis to Surveil,

 $00:25:36.390 \rightarrow 00:25:38.790$  the integrity of the mitotic process.

NOTE Confidence: 0.73344946

 $00{:}25{:}38{.}790 \dashrightarrow 00{:}25{:}41{.}261$  So if cells go into mitosis with

NOTE Confidence: 0.73344946

 $00{:}25{:}41{.}261 \dashrightarrow 00{:}25{:}43{.}430$  under replicated DNA or unresolved

NOTE Confidence: 0.73344946

00:25:43.430 --> 00:25:44.990 DNA repair intermediates,

NOTE Confidence: 0.73344946

 $00{:}25{:}44{.}990 \dashrightarrow 00{:}25{:}46{.}220$  these are things which we're going

NOTE Confidence: 0.73344946

00:25:46.220 --> 00:25:47.868 to see in an HR deficient cell,

NOTE Confidence: 0.73344946

 $00:25:47.870 \longrightarrow 00:25:49.458$  particularly one that's been

NOTE Confidence: 0.73344946

 $00{:}25{:}49{.}458 \dashrightarrow 00{:}25{:}51{.}443$  treated with PARP inhibitors or

NOTE Confidence: 0.73344946

 $00{:}25{:}51{.}443 \dashrightarrow 00{:}25{:}52{.}948$  chromosomes that are entangled.

NOTE Confidence: 0.73344946

 $00:25:52.950 \rightarrow 00:25:54.906$  This will initially activate mechanisms that

NOTE Confidence: 0.73344946

 $00{:}25{:}54{.}906 \dashrightarrow 00{:}25{:}57{.}149$  try to help segregate these chromosomes.

NOTE Confidence: 0.73344946

 $00:25:57.150 \rightarrow 00:25:59.598$  This involves proteins like the Bloom

NOTE Confidence: 0.73344946

 $00:25:59.598 \rightarrow 00:26:01.810$  helicase on the pitch healer case,

NOTE Confidence: 0.73344946

00:26:01.810 --> 00:26:04.482 Paul Theta, You know,

NOTE Confidence: 0.73344946

 $00:26:04.482 \rightarrow 00:26:06.486$  mediated and joining,

NOTE Confidence: 0.73344946

 $00{:}26{:}06{.}490 \dashrightarrow 00{:}26{:}09{.}526$  as well as other topo isomerases.

- NOTE Confidence: 0.73344946
- 00:26:09.530 --> 00:26:10.926 But if those repair,
- NOTE Confidence: 0.73344946
- $00{:}26{:}10{.}926 \dashrightarrow 00{:}26{:}12{.}671$  you know those attempts to
- NOTE Confidence: 0.73344946
- 00:26:12.671 --> 00:26:14.129 segregate chromosomes fail,
- NOTE Confidence: 0.73344946
- $00{:}26{:}14.130 \dashrightarrow 00{:}26{:}15.691$  then one of the consequences I've shown
- NOTE Confidence: 0.73344946
- $00{:}26{:}15.691 \dashrightarrow 00{:}26{:}17.696$  you is that you can have defects in
- NOTE Confidence: 0.73344946
- $00:26:17.696 \rightarrow 00:26:18.910$  nuclear integrity and now the cell
- NOTE Confidence: 0.73344946
- $00:26:18.910 \longrightarrow 00:26:20.249$  has to kind of decide what to do.
- NOTE Confidence: 0.73344946
- $00:26:20.250 \longrightarrow 00:26:21.560$  So there's a nuclear envelope
- NOTE Confidence: 0.73344946
- $00{:}26{:}21.560 \dashrightarrow 00{:}26{:}23.404$  repair network And so I showed you
- NOTE Confidence: 0.73344946
- $00{:}26{:}23{.}404 \dashrightarrow 00{:}26{:}25{.}070$  this bath LEM two chimp 7 access
- NOTE Confidence: 0.73344946
- $00:26:25.070 \rightarrow 00:26:26.524$  that as I've mentioned our group
- NOTE Confidence: 0.73344946
- $00{:}26{:}26{.}524 \dashrightarrow 00{:}26{:}28{.}730$  has worked on for a long time
- NOTE Confidence: 0.73344946
- $00{:}26{:}28{.}730 \dashrightarrow 00{:}26{:}30{.}810$  understanding the mechanisms of
- NOTE Confidence: 0.29974625
- $00{:}26{:}30{.}810 \dashrightarrow 00{:}26{:}33{.}645$  and that this can promote cell survival
- NOTE Confidence: 0.29974625
- $00:26:33.650 \rightarrow 00:26:36.490$  and possibly genome integrity.
- NOTE Confidence: 0.29974625

 $00:26:36.490 \longrightarrow 00:26:38.688$  On the other hand if they're unable

NOTE Confidence: 0.29974625

 $00{:}26{:}38.688 \dashrightarrow 00{:}26{:}40.677$  to repair these breaks in the

NOTE Confidence: 0.29974625

 $00{:}26{:}40.677 \dashrightarrow 00{:}26{:}42.645$  nucleus then this will expose DNA.

NOTE Confidence: 0.29974625

 $00{:}26{:}42.650 \dashrightarrow 00{:}26{:}44.827$  This can activate C gas and perhaps

NOTE Confidence: 0.29974625

00:26:44.827 --> 00:26:47.187 this is the mechanism of cell death

NOTE Confidence: 0.29974625

00:26:47.187 --> 00:26:50.109 that is tied to mitosis and is tied

NOTE Confidence: 0.29974625

 $00:26:50.109 \rightarrow 00:26:52.581$  to these observations of innate immune

NOTE Confidence: 0.29974625

 $00{:}26{:}52{.}581 \dashrightarrow 00{:}26{:}55{.}418$  signaling that occur as a consequence of

NOTE Confidence: 0.29974625

 $00{:}26{:}55{.}418 \dashrightarrow 00{:}26{:}58{.}359$  PARP inhibitors in HR deficient cells.

NOTE Confidence: 0.29974625

 $00{:}26{:}58{.}360 \dashrightarrow 00{:}27{:}00{.}784$  And I just want to point out that, right,

NOTE Confidence: 0.29974625

 $00{:}27{:}00{.}784$  -->  $00{:}27{:}03{.}880$  we're going to push these further if we any, NOTE Confidence: 0.29974625

 $00{:}27{:}03.880 \dashrightarrow 00{:}27{:}05.855$  any time we disrupt the checkpoint, right. NOTE Confidence: 0.29974625

00:27:05.855 --> 00:27:07.640 So if cells are going into mitosis

NOTE Confidence: 0.29974625

 $00:27:07.640 \rightarrow 00:27:09.600$  when they have not repaired their DNA,

NOTE Confidence: 0.29974625

 $00:27:09.600 \longrightarrow 00:27:11.833$  these are more likely to happen if

NOTE Confidence: 0.29974625

 $00{:}27{:}11.833 \dashrightarrow 00{:}27{:}14.387$  you have an HR defect and if you

 $00{:}27{:}14.387 \dashrightarrow 00{:}27{:}16.680$  treat cells with a PARP inhibitor.

NOTE Confidence: 0.29974625

 $00{:}27{:}16.680 \dashrightarrow 00{:}27{:}18.880$  The very last thing I'll talk about is,

NOTE Confidence: 0.29974625

00:27:18.880 --> 00:27:21.895 is there a way that we might use this

NOTE Confidence: 0.29974625

 $00{:}27{:}21.895 \dashrightarrow 00{:}27{:}24.246$  nuclear integrity defects as a biomarker

NOTE Confidence: 0.29974625

 $00{:}27{:}24.246 \dashrightarrow 00{:}27{:}27.655$  of HR defects or of of contacts

NOTE Confidence: 0.29974625

 $00{:}27{:}27{.}655 \dashrightarrow 00{:}27{:}30{.}439$  where PARP inhibitors might be effective.

NOTE Confidence: 0.29974625

 $00{:}27{:}30{.}440 \dashrightarrow 00{:}27{:}32{.}420$  So I'll come back to that at the end.

NOTE Confidence: 0.29974625

 $00{:}27{:}32{.}420 \dashrightarrow 00{:}27{:}34{.}100$  And also might this nuclear envelope

NOTE Confidence: 0.29974625

 $00{:}27{:}34.100 \dashrightarrow 00{:}27{:}36.224$  repair network be a new target, right.

NOTE Confidence: 0.29974625

 $00{:}27{:}36{.}224 \dashrightarrow 00{:}27{:}38{.}648$  These are factors which actually limit

NOTE Confidence: 0.29974625

 $00{:}27{:}38.648 \dashrightarrow 00{:}27{:}40.572$  the action potentially of agents

NOTE Confidence: 0.29974625

 $00{:}27{:}40.572 \dashrightarrow 00{:}27{:}42.708$  that are driving these defects that

NOTE Confidence: 0.29974625

 $00:27:42.708 \longrightarrow 00:27:44.180$  we're using clinically.

NOTE Confidence: 0.29974625

 $00{:}27{:}44.180 \dashrightarrow 00{:}27{:}44.446$  OK.

NOTE Confidence: 0.29974625

 $00{:}27{:}44.446 \dashrightarrow 00{:}27{:}46.574$  So now I'm just going to show you

 $00:27:46.574 \rightarrow 00:27:48.617$  some of the data from our group.

NOTE Confidence: 0.29974625

 $00:27:48.620 \rightarrow 00:27:50.972$  This initial data is using actually

NOTE Confidence: 0.29974625

 $00:27:50.972 \longrightarrow 00:27:52.540$  an ovarian cancer model,

NOTE Confidence: 0.29974625

 $00{:}27{:}52{.}540 \dashrightarrow 00{:}27{:}55{.}096$  UWB 1280 nines which are a BRCA 1 deficient,

NOTE Confidence: 0.29974625

 $00{:}27{:}55{.}100 \dashrightarrow 00{:}27{:}56{.}604$  HR deficient cell line.

NOTE Confidence: 0.29974625

 $00{:}27{:}56{.}604 \dashrightarrow 00{:}27{:}59{.}732$  And so I'm just showing you an example

NOTE Confidence: 0.29974625

 $00{:}27{:}59{.}732 \dashrightarrow 00{:}28{:}02{.}120$  of what one of these persistent

NOTE Confidence: 0.29974625

00:28:02.120 --> 00:28:03.730 DNA bridges look like.

NOTE Confidence: 0.29974625

 $00{:}28{:}03.730 \dashrightarrow 00{:}28{:}04.228$  This is.

NOTE Confidence: 0.29974625

 $00{:}28{:}04{.}228 \dashrightarrow 00{:}28{:}06{.}220$  You can think of this as very much

NOTE Confidence: 0.29974625

 $00:28:06.279 \longrightarrow 00:28:08.064$  as the end point of that movie

NOTE Confidence: 0.29974625

 $00{:}28{:}08.064 \dashrightarrow 00{:}28{:}10.247$  that I showed you that we also see

NOTE Confidence: 0.29974625

 $00{:}28{:}10.247 \dashrightarrow 00{:}28{:}12.342$  specifically in HR in this HR deficient

NOTE Confidence: 0.29974625

 $00:28:12.342 \rightarrow 00:28:14.172$  line that's further precipitated by

NOTE Confidence: 0.29974625

 $00{:}28{:}14.172 \dashrightarrow 00{:}28{:}16.249$  the addition of PARP inhibitors.

NOTE Confidence: 0.29974625

 $00:28:16.250 \rightarrow 00:28:18.762$  And so like in that example you can

- NOTE Confidence: 0.29974625
- $00:28:18.762 \longrightarrow 00:28:21.335$  see that this bridge which is all
- NOTE Confidence: 0.29974625
- 00:28:21.335 --> 00:28:23.280 along connecting these two nuclei
- NOTE Confidence: 0.29974625
- $00:28:23.350 \longrightarrow 00:28:25.228$  is highly enriched in C gas.
- NOTE Confidence: 0.29974625
- $00{:}28{:}25{.}230 \dashrightarrow 00{:}28{:}27{.}232$  And so we would speculate from this
- NOTE Confidence: 0.29974625
- $00{:}28{:}27{.}232 \dashrightarrow 00{:}28{:}29{.}344$  that this is the region of the
- NOTE Confidence: 0.29974625
- $00{:}28{:}29{.}344 \dashrightarrow 00{:}28{:}31{.}132$  nucleus where the DNA is exposed
- NOTE Confidence: 0.29974625
- $00:28:31.192 \longrightarrow 00:28:33.298$  to the cytoplasm and where we're
- NOTE Confidence: 0.29974625
- 00:28:33.298 --> 00:28:34.702 getting C gas recruitment.
- NOTE Confidence: 0.29974625
- $00:28:34.710 \longrightarrow 00:28:36.980$  And so this is just showing you here what
- NOTE Confidence: 0.29974625
- $00:28:36.980 \rightarrow 00:28:38.880$  happens when we treat with PARP inhibitor.
- NOTE Confidence: 0.29974625
- 00:28:38.880 --> 00:28:39.924 Sorry, I've lost.
- NOTE Confidence: 0.29974625
- $00{:}28{:}39{.}924 \dashrightarrow 00{:}28{:}41{.}316$  Yes, here we go.
- NOTE Confidence: 0.29974625
- 00:28:41.320 --> 00:28:41.602 Yeah.
- NOTE Confidence: 0.29974625
- $00{:}28{:}41.602 \dashrightarrow 00{:}28{:}44.140$  So the on the on the left is just
- NOTE Confidence: 0.29974625
- $00{:}28{:}44{.}212 \dashrightarrow 00{:}28{:}46{.}240$  the UWB one, this UW one cell line.
- NOTE Confidence: 0.29974625

 $00:28:46.240 \longrightarrow 00:28:48.358$  And then when we add elaporib,

NOTE Confidence: 0.29974625

 $00{:}28{:}48{.}360 \dashrightarrow 00{:}28{:}50{.}076$  interestingly one of the things that

NOTE Confidence: 0.29974625

 $00{:}28{:}50{.}076 \dashrightarrow 00{:}28{:}52{.}033$  we see is the elaporib increases

NOTE Confidence: 0.29974625

 $00:28:52.033 \longrightarrow 00:28:54.295$  the percent of cells that have

NOTE Confidence: 0.29974625

 $00{:}28{:}54{.}295 \dashrightarrow 00{:}28{:}55{.}799$  these persistent DNA bridges.

NOTE Confidence: 0.29974625

00:28:55.800 --> 00:28:59.475 But UWB ONE cells have abundant micronuclei

NOTE Confidence: 0.29974625

00:28:59.475 --> 00:29:02.798 as many tumor cells do in vitro.

NOTE Confidence: 0.29974625

00:29:02.800 --> 00:29:03.722 And actually,

NOTE Confidence: 0.29974625

 $00:29:03.722 \rightarrow 00:29:06.800$  this is not precipitated by PARP inhibitors,

NOTE Confidence: 0.29974625

 $00:29:06.800 \longrightarrow 00:29:08.850$  at least in this context.

NOTE Confidence: 0.29974625

 $00:29:08.850 \rightarrow 00:29:10.453$  And so this is another reason why

NOTE Confidence: 0.29974625

 $00:29:10.453 \rightarrow 00:29:11.890$  we're very interested in these bridges,

NOTE Confidence: 0.29974625

 $00{:}29{:}11{.}890 \dashrightarrow 00{:}29{:}13{.}626$  because they seem to be the structure

NOTE Confidence: 0.29974625

 $00{:}29{:}13.626 \dashrightarrow 00{:}29{:}15.169$  that's most precipitated by PARP inhibitors,

NOTE Confidence: 0.29974625

 $00:29:15.170 \longrightarrow 00:29:17.300$  whereas there's just a high rate

NOTE Confidence: 0.29974625

 $00:29:17.300 \longrightarrow 00:29:18.834$  of micronuclei all of the time.

- NOTE Confidence: 0.29974625
- $00{:}29{:}18.834 \dashrightarrow 00{:}29{:}20.070$  But that does not seem to

 $00{:}29{:}20{.}123 \dashrightarrow 00{:}29{:}21{.}448$  respond to the addition of,

NOTE Confidence: 0.6971082

 $00:29:21.450 \longrightarrow 00:29:24.408$  in this case, a lab rib.

NOTE Confidence: 0.6971082

 $00{:}29{:}24{.}410 \dashrightarrow 00{:}29{:}26{.}754$  So we also think that for the vast

NOTE Confidence: 0.6971082

 $00{:}29{:}26.754 \dashrightarrow 00{:}29{:}28.553$  majority of these persistent bridges

NOTE Confidence: 0.6971082

 $00{:}29{:}28{.}553 \dashrightarrow 00{:}29{:}30{.}845$  that we observe in response to

NOTE Confidence: 0.6971082

 $00:29:30.845 \rightarrow 00:29:33.207$  PARP inhibitors that there is that,

NOTE Confidence: 0.6971082

 $00{:}29{:}33{.}210 \dashrightarrow 00{:}29{:}34{.}895$  that there has been a

NOTE Confidence: 0.6971082

 $00:29:34.895 \longrightarrow 00:29:36.243$  loss of nuclear integrity.

NOTE Confidence: 0.6971082

 $00{:}29{:}36{.}250 \dashrightarrow 00{:}29{:}37{.}930$  And so one thing I just want to

NOTE Confidence: 0.6971082

 $00:29:37.930 \longrightarrow 00:29:39.527$  point out here is that you know,

NOTE Confidence: 0.6971082

00:29:39.530 --> 00:29:41.840 one challenge I think in general is

NOTE Confidence: 0.6971082

00:29:41.840 --> 00:29:44.352 that you cannot see that these

NOTE Confidence: 0.6971082

00:29:44.352 --> 00:29:46.530 nuclei have a persistent DNA bridge.

NOTE Confidence: 0.6971082

00:29:46.530 --> 00:29:48.538 If you just look at DNA stain because

 $00:29:48.538 \rightarrow 00:29:50.547$  it's too thin essentially or there's

NOTE Confidence: 0.6971082

 $00{:}29{:}50{.}547 \dashrightarrow 00{:}29{:}52{.}352$  something about the DNA structure

NOTE Confidence: 0.6971082

 $00{:}29{:}52{.}352 \dashrightarrow 00{:}29{:}54{.}642$  that disrupts the ability of the DNA

NOTE Confidence: 0.6971082

 $00{:}29{:}54.642 \dashrightarrow 00{:}29{:}56.302$  stain to intercalate into the bases.

NOTE Confidence: 0.6971082

00:29:56.302 --> 00:29:57.126 One or the other,

NOTE Confidence: 0.6971082

 $00:29:57.130 \longrightarrow 00:29:59.030$  we don't actually know yet.

NOTE Confidence: 0.6971082

 $00{:}29{:}59{.}030 \dashrightarrow 00{:}30{:}00{.}374$  So actually in order to know

NOTE Confidence: 0.6971082

 $00:30:00.374 \rightarrow 00:30:01.590$  that there's a bridge there,

NOTE Confidence: 0.6971082

 $00{:}30{:}01{.}590 \dashrightarrow 00{:}30{:}03{.}424$  you need a marker for a bridge.

NOTE Confidence: 0.6971082

 $00:30:03.430 \longrightarrow 00:30:04.739$  And actually it turns out that one

NOTE Confidence: 0.6971082

 $00{:}30{:}04{.}739 \dashrightarrow 00{:}30{:}06{.}196$  of the best markers for a bridge

NOTE Confidence: 0.6971082

 $00:30:06.196 \longrightarrow 00:30:07.468$  is this protein called man one,

NOTE Confidence: 0.6971082

 $00:30:07.470 \longrightarrow 00:30:10.389$  which is a specific nuclear envelope protein.

NOTE Confidence: 0.6971082

00:30:10.390 --> 00:30:11.270 And so you know,

NOTE Confidence: 0.6971082

 $00:30:11.270 \rightarrow 00:30:13.148$  you can see quite a beautifully that it is,

NOTE Confidence: 0.6971082

00:30:13.150 --> 00:30:13.550 you know,

- NOTE Confidence: 0.6971082
- $00:30:13.550 \rightarrow 00:30:14.950$  in the nuclear envelope of all cells,
- NOTE Confidence: 0.6971082
- $00:30:14.950 \rightarrow 00:30:16.826$  but it really nicely decorates these bridges.
- NOTE Confidence: 0.6971082
- $00:30:16.830 \longrightarrow 00:30:18.504$  And so this has been a really important tool.
- NOTE Confidence: 0.6971082
- $00:30:18.510 \rightarrow 00:30:19.386$  It seems very simple,
- NOTE Confidence: 0.6971082
- $00:30:19.386 \longrightarrow 00:30:20.952$  but the ability to see the things
- NOTE Confidence: 0.6971082
- $00:30:20.952 \longrightarrow 00:30:22.387$  that you want to look for is,
- NOTE Confidence: 0.6971082
- $00:30:22.390 \rightarrow 00:30:23.227$  is pretty important.
- NOTE Confidence: 0.6971082
- $00:30:23.227 \longrightarrow 00:30:25.180$  So we've been using this antibody to
- NOTE Confidence: 0.6971082
- $00:30:25.234 \rightarrow 00:30:26.999$  this inner nuclear membrane protein,
- NOTE Confidence: 0.6971082
- $00:30:27.000 \dashrightarrow 00:30:29.359$  MAN one in order to surveil this.
- NOTE Confidence: 0.6971082
- $00:30:29.360 \longrightarrow 00:30:33.336$  And so we can then look at the
- NOTE Confidence: 0.6971082
- $00{:}30{:}33{.}336 \dashrightarrow 00{:}30{:}35{.}193$  coincidence of other factors on
- NOTE Confidence: 0.6971082
- 00:30:35.193 --> 00:30:37.979 these bridges and I want to focus
- NOTE Confidence: 0.6971082
- $00{:}30{:}37{.}979 \dashrightarrow 00{:}30{:}39{.}973$  specifically on the other elements
- NOTE Confidence: 0.6971082
- $00:30:39.973 \longrightarrow 00:30:41.873$  of that DNA repair pathway.
- NOTE Confidence: 0.6971082

 $00:30:41.880 \rightarrow 00:30:43.736$  So not only is is C gas recruited

NOTE Confidence: 0.6971082

 $00{:}30{:}43.736 \dashrightarrow 00{:}30{:}45.823$  and yet we we interpret that

NOTE Confidence: 0.6971082

 $00:30:45.823 \longrightarrow 00:30:46.759$  as ruptured bridges,

NOTE Confidence: 0.6971082

 $00{:}30{:}46.760 \dashrightarrow 00{:}30{:}48.200$  but there's also the recruitment

NOTE Confidence: 0.6971082

 $00{:}30{:}48.200 \dashrightarrow 00{:}30{:}49.640$  of LEM two and bath.

NOTE Confidence: 0.6971082

 $00{:}30{:}49{.}640$  -->  $00{:}30{:}51{.}212$  These are these factors that are NOTE Confidence: 0.6971082

 $00:30:51.212 \rightarrow 00:30:52.871$  involved in trying to repair these

NOTE Confidence: 0.6971082

00:30:52.871 - 00:30:54.437 breaks in in the nuclear envelope

NOTE Confidence: 0.6971082

 $00{:}30{:}54{.}437 \dashrightarrow 00{:}30{:}56{.}347$  and so this is evidence that that

NOTE Confidence: 0.6971082

 $00{:}30{:}56{.}347 \dashrightarrow 00{:}30{:}57{.}949$  same kind of antagonism that I

NOTE Confidence: 0.6971082

 $00{:}30{:}58{.}000 \dashrightarrow 00{:}30{:}59{.}958$  showed you in a induced rupture of

NOTE Confidence: 0.6971082

 $00{:}30{:}59{.}958 \dashrightarrow 00{:}31{:}02{.}730$  the nucleus is also going on here.

NOTE Confidence: 0.6971082

 $00{:}31{:}02{.}730 \dashrightarrow 00{:}31{:}04.865$  If we identify bridges using this man

NOTE Confidence: 0.6971082

 $00:31:04.865 \longrightarrow 00:31:07.137$  1 antibody what what we can see is

NOTE Confidence: 0.6971082

 $00{:}31{:}07{.}137 \dashrightarrow 00{:}31{:}09{.}529$  that all bridges have limb 2 which we expect.

NOTE Confidence: 0.6971082

 $00:31:09.530 \dashrightarrow 00:31:11.636$  Those are two different inter nuclear

00:31:11.636 - 00:31:13.120 membrane proteins but more than

NOTE Confidence: 0.6971082

 $00{:}31{:}13.120 \dashrightarrow 00{:}31{:}14.940$  half of them have C gas recruitment

NOTE Confidence: 0.6971082

 $00:31:14.994 \rightarrow 00:31:16.614$  and so this suggests again that

NOTE Confidence: 0.6971082

 $00:31:16.614 \dashrightarrow 00:31:18.563$  the majority of the bridges that we NOTE Confidence: 0.6971082

00:31:18.563 --> 00:31:20.183 detect are ruptured and that DNA

NOTE Confidence: 0.6971082

 $00:31:20.183 \dashrightarrow 00:31:22.460$  is likely exposed to the cytoplasm.

NOTE Confidence: 0.4833358

 $00{:}31{:}25.060 \dashrightarrow 00{:}31{:}26.537$  I also want to point out that

NOTE Confidence: 0.4833358

 $00:31:26.537 \longrightarrow 00:31:28.582$  one of the ideas in that nuclear

NOTE Confidence: 0.4833358

 $00{:}31{:}28.582 \dashrightarrow 00{:}31{:}30.272$  envelope reformation is that there's

NOTE Confidence: 0.4833358

 $00{:}31{:}30{.}272 \dashrightarrow 00{:}31{:}32{.}124$  local recruitment of LEM two and

NOTE Confidence: 0.4833358

 $00{:}31{:}32{.}124 \dashrightarrow 00{:}31{:}34{.}362$  these escort proteins to try to to

NOTE Confidence: 0.4833358

 $00{:}31{:}34{.}362 \dashrightarrow 00{:}31{:}36{.}317$  actually seal the nuclear envelope.

NOTE Confidence: 0.4833358

 $00{:}31{:}36{.}320 \dashrightarrow 00{:}31{:}38{.}007$  And if we kind of zoom in

NOTE Confidence: 0.4833358

00:31:38.007 --> 00:31:39.711 particularly on LEM two, LEM 2 here,

NOTE Confidence: 0.4833358

 $00:31:39.711 \rightarrow 00:31:41.709$  you can see that there are regions where

- $00:31:41.709 \rightarrow 00:31:43.997$  there's a really high accumulation of LEM 2.
- NOTE Confidence: 0.4833358
- $00{:}31{:}44.000 \dashrightarrow 00{:}31{:}45.617$  And so this is likely the region
- NOTE Confidence: 0.4833358
- 00:31:45.617 --> 00:31:46.909 of this bridge where there's
- NOTE Confidence: 0.4833358
- $00:31:46.909 \longrightarrow 00:31:48.279$  been a loss of integrity.
- NOTE Confidence: 0.4833358
- $00{:}31{:}48{.}280 \dashrightarrow 00{:}31{:}50{.}360$  And that kind of explains why sea gas
- NOTE Confidence: 0.4833358
- $00{:}31{:}50{.}360 \dashrightarrow 00{:}31{:}52{.}530$  is also seen in this patchy pattern
- NOTE Confidence: 0.4833358
- $00:31:52.530 \longrightarrow 00:31:54.930$  because there probably is a local effect.
- NOTE Confidence: 0.4833358
- $00:31:54.930 \rightarrow 00:31:57.290$  And I'm just showing you here line profiles,
- NOTE Confidence: 0.4833358
- $00{:}31{:}57{.}290 \dashrightarrow 00{:}31{:}58{.}410$  just showing that there's
- NOTE Confidence: 0.4833358
- 00:31:58.410 --> 00:31:59.810 specific recruitment of LEM two,
- NOTE Confidence: 0.4833358
- $00:31:59.810 \longrightarrow 00:32:00.518$  this man one protein,
- NOTE Confidence: 0.4833358
- $00:32:00.518 \longrightarrow 00:32:01.580$  even though it's in a nuclear
- NOTE Confidence: 0.4833358
- 00:32:01.619 --> 00:32:02.209 membrane protein,
- NOTE Confidence: 0.4833358
- $00:32:02.210 \longrightarrow 00:32:03.595$  it's kind of distributed throughout
- NOTE Confidence: 0.4833358
- $00{:}32{:}03{.}595 \dashrightarrow 00{:}32{:}05{.}694$  the bridge and that it's not part of
- NOTE Confidence: 0.4833358
- $00:32:05.694 \rightarrow 00:32:07.241$  the same repair network as LEM twos.

- NOTE Confidence: 0.4833358
- $00{:}32{:}07{.}250 \dashrightarrow 00{:}32{:}08{.}370$  This makes sense to us.
- NOTE Confidence: 0.36765093
- 00:32:10.890 --> 00:32:13.738 I also want to point out that while
- NOTE Confidence: 0.36765093
- 00:32:13.738 --> 00:32:16.047 though that work is in UWB ones,
- NOTE Confidence: 0.36765093
- $00:32:16.050 \rightarrow 00:32:18.642$  UDO in the lab has also been looking
- NOTE Confidence: 0.36765093
- $00:32:18.642 \longrightarrow 00:32:21.394$  at a model of BRCA 1 deficient
- NOTE Confidence: 0.36765093
- $00:32:21.394 \dashrightarrow 00:32:23.010$  triple negative breast cancer.
- NOTE Confidence: 0.36765093
- $00:32:23.010 \longrightarrow 00:32:24.258$  And so these again are cells
- NOTE Confidence: 0.36765093
- $00{:}32{:}24.258 \dashrightarrow 00{:}32{:}25.090$  treated with a laparib.
- NOTE Confidence: 0.36765093
- $00:32:25.090 \rightarrow 00:32:27.250$  This is just showing you the Dappy staining.
- NOTE Confidence: 0.36765093
- $00:32:27.250 \longrightarrow 00:32:29.383$  I just want to this I think is a
- NOTE Confidence: 0.36765093
- $00{:}32{:}29{.}383 \dashrightarrow 00{:}32{:}31{.}204$  beautiful example of pointing out that
- NOTE Confidence: 0.36765093
- $00:32:31.204 \rightarrow 00:32:33.067$  even when we can't really perceive
- NOTE Confidence: 0.36765093
- 00:32:33.067 > 00:32:35.089 these bridges in the DNA stain,
- NOTE Confidence: 0.36765093
- $00{:}32{:}35{.}090 \dashrightarrow 00{:}32{:}36{.}168$  these ones are a little bit earlier.
- NOTE Confidence: 0.36765093
- $00:32:36.170 \longrightarrow 00:32:37.843$  So you can still kind of see
- NOTE Confidence: 0.36765093

 $00{:}32{:}37{.}843 \dashrightarrow 00{:}32{:}39{.}250$  faintly that there's DNA staining.

NOTE Confidence: 0.36765093

 $00{:}32{:}39{.}250 \dashrightarrow 00{:}32{:}41{.}128$  You can appreciate the changes in

NOTE Confidence: 0.36765093

00:32:41.128 --> 00:32:43.168 nuclear shape that are tied to this, NOTE Confidence: 0.36765093

 $00:32:43.170 \dashrightarrow 00:32:44.595$  just like those heart-shaped nuclei NOTE Confidence: 0.36765093

00:32:44.595 --> 00:32:46.963 in that first movie that I showed you

NOTE Confidence: 0.36765093

 $00{:}32{:}46{.}963 \dashrightarrow 00{:}32{:}48{.}448$  with the nuclear localization signal.

NOTE Confidence: 0.36765093

 $00{:}32{:}48{.}450 \dashrightarrow 00{:}32{:}50{.}320$  So there's there's actually 2

NOTE Confidence: 0.36765093

 $00:32:50.320 \dashrightarrow 00:32:52.707$  hallmarks we think that we can use

NOTE Confidence: 0.36765093

00:32:52.707 --> 00:32:54.730 as essentially I know proxies for

NOTE Confidence: 0.36765093

 $00{:}32{:}54{.}730 \dashrightarrow 00{:}32{:}56{.}530$  the presence of these bridges.

NOTE Confidence: 0.36765093

 $00{:}32{:}56{.}530 \dashrightarrow 00{:}32{:}58{.}469$  One of them is the kind of

NOTE Confidence: 0.36765093

 $00:32:58.469 \dashrightarrow 00:33:00.009$  orientation of these two nuclei.

NOTE Confidence: 0.36765093

00:33:00.010 --> 00:33:01.762 But the other is that there are these

NOTE Confidence: 0.36765093

 $00:33:01.762 \longrightarrow 00:33:03.122$  classic changes in nuclear shape that

NOTE Confidence: 0.36765093

 $00{:}33{:}03{.}122 \dashrightarrow 00{:}33{:}04{.}690$  we see that are coincident with this.

NOTE Confidence: 0.36765093

 $00{:}33{:}04.690 \dashrightarrow 00{:}33{:}06.184$  And this may become relevant if

- NOTE Confidence: 0.36765093
- $00{:}33{:}06{.}184 \dashrightarrow 00{:}33{:}07{.}924$  we think about whether we can use

 $00{:}33{:}07{.}924 \dashrightarrow 00{:}33{:}09{.}079$  the prevalence of these structures

NOTE Confidence: 0.36765093

 $00:33:09.079 \longrightarrow 00:33:10.050$  as a biomarker,

NOTE Confidence: 0.36765093

 $00{:}33{:}10.050 \dashrightarrow 00{:}33{:}12.507$  which is one of our kind of

NOTE Confidence: 0.36765093

00:33:12.507 --> 00:33:13.560 long term interests.

NOTE Confidence: 0.36765093

 $00:33:13.560 \longrightarrow 00:33:15.300$  This is just showing you that

NOTE Confidence: 0.36765093

 $00:33:15.300 \longrightarrow 00:33:16.750$  in this MDA 436 line,

NOTE Confidence: 0.36765093

 $00:33:16.750 \dashrightarrow 00:33:18.490$  preliminarily what we see is that

NOTE Confidence: 0.36765093

 $00{:}33{:}18{.}490 \dashrightarrow 00{:}33{:}19{.}962$  there's a dose dependent increase

NOTE Confidence: 0.36765093

 $00{:}33{:}19{.}962 \dashrightarrow 00{:}33{:}21{.}991$  in the number of cells with these

NOTE Confidence: 0.36765093

 $00{:}33{:}21.991 \dashrightarrow 00{:}33{:}23.755$  bridges in response to a laparib,

NOTE Confidence: 0.36765093

 $00{:}33{:}23{.}760 \dashrightarrow 00{:}33{:}25{.}923$  whereas we don't see this in a

NOTE Confidence: 0.36765093

 $00{:}33{:}25{.}923 \dashrightarrow 00{:}33{:}27{.}571$  different triple negative line that's

NOTE Confidence: 0.36765093

 $00{:}33{:}27.571 \dashrightarrow 00{:}33{:}29.557$  BRCA 1 proficient and HR proficient.

NOTE Confidence: 0.5707516

 $00{:}33{:}32{.}040 \dashrightarrow 00{:}33{:}34{.}744$  So I've shown you this that we likely

- $00:33:34.744 \rightarrow 00:33:36.839$  have these persistent bridges,
- NOTE Confidence: 0.5707516
- $00:33:36.840 \longrightarrow 00:33:38.960$  they accumulate in the context of a laparib,
- NOTE Confidence: 0.5707516
- $00:33:38.960 \longrightarrow 00:33:40.104$  they recruit C gas.
- NOTE Confidence: 0.5707516
- $00{:}33{:}40{.}104 \dashrightarrow 00{:}33{:}41{.}534$  But is there actually activation
- NOTE Confidence: 0.5707516
- $00:33:41.534 \rightarrow 00:33:43.228$  of the innate immune pathway?
- NOTE Confidence: 0.5707516
- 00:33:43.230 --> 00:33:45.372 Just to remind you that the canonical
- NOTE Confidence: 0.5707516
- 00:33:45.372 --> 00:33:47.457 pathway is that C gas produces
- NOTE Confidence: 0.5707516
- $00{:}33{:}47{.}457 \dashrightarrow 00{:}33{:}49{.}302$  C gamp which activates sting
- NOTE Confidence: 0.5707516
- $00{:}33{:}49{.}302 \dashrightarrow 00{:}33{:}51{.}006$  which phosphorylates TDK one and
- NOTE Confidence: 0.5707516
- $00{:}33{:}51.006 \dashrightarrow 00{:}33{:}52.806$  IRF 3 and leads to interferon
- NOTE Confidence: 0.5707516
- $00{:}33{:}52.806 \dashrightarrow 00{:}33{:}55.310$  stimulated gene expression.
- NOTE Confidence: 0.5707516
- $00{:}33{:}55{.}310 \dashrightarrow 00{:}33{:}57{.}515$  So if we look at the GWB one cells
- NOTE Confidence: 0.5707516
- $00:33:57.515 \longrightarrow 00:33:59.772$  in the presence of a lab rib
- NOTE Confidence: 0.5707516
- $00:33:59.772 \dashrightarrow 00:34:01.670$  compared to the vehicle control,
- NOTE Confidence: 0.5707516
- $00:34:01.670 \longrightarrow 00:34:03.638$  we don't actually see the level
- NOTE Confidence: 0.5707516
- 00:34:03.638 --> 00:34:04.950 of TBK one phosphorylation,

- NOTE Confidence: 0.5707516
- $00:34:04.950 \longrightarrow 00:34:05.870$  much of an effect.
- NOTE Confidence: 0.5707516
- $00:34:05.870 \rightarrow 00:34:08.349$  But if we look at IRF 3 phosphorylation,
- NOTE Confidence: 0.5707516
- $00{:}34{:}08{.}350 \dashrightarrow 00{:}34{:}11{.}724$  we see that there is a stimulation
- NOTE Confidence: 0.5707516
- $00:34:11.724 \rightarrow 00:34:14.020$  of the phosphorylation of IRF 3.
- NOTE Confidence: 0.5707516
- $00:34:14.020 \rightarrow 00:34:15.940$  And if we look at the downstream consequence,
- NOTE Confidence: 0.5707516
- $00:34:15.940 \longrightarrow 00:34:18.005$  which is interferon stimulated gene
- NOTE Confidence: 0.5707516
- $00:34:18.005 \rightarrow 00:34:20.058$  expression, just picking two of those genes,
- NOTE Confidence: 0.5707516
- $00{:}34{:}20.060 \dashrightarrow 00{:}34{:}21.775$  we do see that we can stimulate.
- NOTE Confidence: 0.5707516
- $00{:}34{:}21.780 \dashrightarrow 00{:}34{:}23.664$  We can see stimulation of interferon
- NOTE Confidence: 0.5707516
- $00:34:23.664 \rightarrow 00:34:25.297$  stimulated genes with the addition
- NOTE Confidence: 0.5707516
- $00:34:25.297 \longrightarrow 00:34:27.268$  of ELABORA in this cell line.
- NOTE Confidence: 0.5707516
- $00{:}34{:}27{.}268 \dashrightarrow 00{:}34{:}29{.}260$  And just to point out this,
- NOTE Confidence: 0.5707516
- 00:34:29.260 --> 00:34:31.861 how much of A signal we get does depend
- NOTE Confidence: 0.5707516
- $00{:}34{:}31{.}861 \dashrightarrow 00{:}34{:}34{.}699$  on how intact the C gasting pathway is.
- NOTE Confidence: 0.5707516
- $00{:}34{:}34{.}700 \dashrightarrow 00{:}34{:}36{.}800$  And many tumors have an activated
- NOTE Confidence: 0.5707516

00:34:36.800 --> 00:34:38.648 C gas expression likely because

NOTE Confidence: 0.5707516

 $00{:}34{:}38{.}648 \dashrightarrow 00{:}34{:}40{.}578$  there is selection against the

NOTE Confidence: 0.5707516

 $00{:}34{:}40{.}578 \dashrightarrow 00{:}34{:}42{.}560$  pathway that I'm talking about.

NOTE Confidence: 0.5707516

 $00{:}34{:}42.560 \dashrightarrow 00{:}34{:}44.315$  But these cells do as you can see here,

NOTE Confidence: 0.5707516

 $00{:}34{:}44{.}320 \dashrightarrow 00{:}34{:}47{.}120$  they do express sea gas and sting.

NOTE Confidence: 0.5707516

 $00{:}34{:}47{.}120$  -->  $00{:}34{:}48{.}877$  But this is about as much stimulation NOTE Confidence: 0.5707516

 $00{:}34{:}48.877 \dashrightarrow 00{:}34{:}50.868$  as we can probably get in this

NOTE Confidence: 0.5707516

 $00{:}34{:}50.868 \dashrightarrow 00{:}34{:}52.632$  line because this is an experiment

NOTE Confidence: 0.5707516

00:34:52.692 --> 00:34:54.242 where we've just transfected DNA

NOTE Confidence: 0.5707516

 $00:34:54.242 \dashrightarrow 00:34:56.047$  to drive an innate immune response.

NOTE Confidence: 0.5707516

 $00{:}34{:}56{.}047 \dashrightarrow 00{:}34{:}57{.}776$  This is the two people using this

NOTE Confidence: 0.5707516

 $00:34:57.776 \longrightarrow 00:34:59.239$  in this field all the time.

NOTE Confidence: 0.5707516

 $00{:}34{:}59{.}240 \dashrightarrow 00{:}35{:}01{.}116$  And we get a pretty similar degree

NOTE Confidence: 0.5707516

 $00:35:01.116 \longrightarrow 00:35:02.909$  of stimulation as we get with

NOTE Confidence: 0.5707516

 $00{:}35{:}02{.}909 \dashrightarrow 00{:}35{:}03{.}839$  the elaborate treatment.

NOTE Confidence: 0.5707516

 $00:35:03.840 \longrightarrow 00:35:05.870$  So that may be kind of the top of what

 $00:35:05.928 \rightarrow 00:35:08.056$  we can get in this particular cell line.

NOTE Confidence: 0.5707516

 $00:35:08.056 \rightarrow 00:35:10.360$  So we do think although this is only

NOTE Confidence: 0.5707516

 $00:35:10.360 \longrightarrow 00:35:12.265$  about four fold increase longitude

NOTE Confidence: 0.5707516

 $00{:}35{:}12.265 \dashrightarrow 00{:}35{:}15.209$  full change of two that this is that

NOTE Confidence: 0.5707516

 $00{:}35{:}15{.}209 \dashrightarrow 00{:}35{:}17{.}141$  this is a pretty strong response

NOTE Confidence: 0.5707516

 $00:35:17.141 \longrightarrow 00:35:18.520$  for this cell type.

NOTE Confidence: 0.5707516

 $00{:}35{:}18.520 \dashrightarrow 00{:}35{:}22.152$  So does the you know does this the

NOTE Confidence: 0.5707516

 $00:35:22.152 \dashrightarrow 00:35:24.825$  response actually require C gas that

NOTE Confidence: 0.5707516

 $00{:}35{:}24.825 \dashrightarrow 00{:}35{:}26.600$  I'm showing you this stimulation

NOTE Confidence: 0.5707516

00:35:26.600 --> 00:35:28.919 of this innate immune pathway.

NOTE Confidence: 0.5707516

 $00:35:28.920 \rightarrow 00:35:31.188$  So now we're just doing an experiment

NOTE Confidence: 0.5707516

00:35:31.188 --> 00:35:32.906 where we're knocking down C gas

NOTE Confidence: 0.5707516

 $00{:}35{:}32{.}906 \dashrightarrow 00{:}35{:}34{.}783$  and you can see the knock down by

NOTE Confidence: 0.5707516

 $00{:}35{:}34{.}783 \dashrightarrow 00{:}35{:}36{.}295$  qPCR to the C gas gene Here.

NOTE Confidence: 0.5707516

00:35:36.300 --> 00:35:37.338 I'll just walk you through this.

 $00:35:37.340 \dashrightarrow 00:35:38.966$  This is the same stimulation that

NOTE Confidence: 0.5707516

00:35:38.966 --> 00:35:40.865 we saw of these two genes with

NOTE Confidence: 0.5707516

 $00{:}35{:}40.865 \dashrightarrow 00{:}35{:}42.377$  the addition of a lab rib.

NOTE Confidence: 0.5707516

 $00:35:42.380 \longrightarrow 00:35:45.138$  If we now knock down C gas,

NOTE Confidence: 0.5707516

 $00{:}35{:}45{.}140 \dashrightarrow 00{:}35{:}47{.}606$  what we can see is that this does to

NOTE Confidence: 0.5707516

 $00{:}35{:}47.606 \dashrightarrow 00{:}35{:}49.820$  some extent limit the activation.

NOTE Confidence: 0.5707516

 $00:35:49.820 \rightarrow 00:35:52.020$  But to what extent that is we're not,

NOTE Confidence: 0.5707516

 $00:35:52.020 \rightarrow 00:35:53.544$  we're not where I would say

NOTE Confidence: 0.5707516

00:35:53.544 --> 00:35:55.300 where it's unclear yet whether C

NOTE Confidence: 0.5707516

 $00:35:55.300 \dashrightarrow 00:35:56.660$  gas is completely responsible.

NOTE Confidence: 0.5707516

 $00:35:56.660 \rightarrow 00:35:58.428$  We're trying to be kind of very agnostic

NOTE Confidence: 0.5707516

 $00:35:58.428 \dashrightarrow 00:35:59.780$  about what is lying downstream.

NOTE Confidence: 0.5707516

 $00{:}35{:}59{.}780 \dashrightarrow 00{:}36{:}01{.}600$  And so one of the things we're

NOTE Confidence: 0.5707516

00:36:01.600 --> 00:36:03.269 doing is generating C gas knock out

NOTE Confidence: 0.5707516

 $00{:}36{:}03.269 \dashrightarrow 00{:}36{:}04.925$  Isagenix of these cell lines to

NOTE Confidence: 0.5707516

 $00:36:04.925 \longrightarrow 00:36:06.699$  really look at how much sea gas

- NOTE Confidence: 0.5707516
- $00:36:06.699 \longrightarrow 00:36:07.659$  is important for this

 $00:36:07.660 \longrightarrow 00:36:09.740$  response and also of course

NOTE Confidence: 0.531161

 $00{:}36{:}09{.}740 \dashrightarrow 00{:}36{:}11.820$  for the cell death mechanism.

NOTE Confidence: 0.531161

 $00:36:11.820 \longrightarrow 00:36:13.720$  One of the ideas that I set up was that

NOTE Confidence: 0.531161

 $00:36:13.768 \dashrightarrow 00:36:15.568$  this nuclear envelope repair network

NOTE Confidence: 0.531161

 $00{:}36{:}15{.}568 \dashrightarrow 00{:}36{:}17{.}368$  could be ant agonizing surveillance by

NOTE Confidence: 0.531161

 $00{:}36{:}17{.}421 \dashrightarrow 00{:}36{:}19{.}290$  the innate immune system and we have

NOTE Confidence: 0.531161

 $00:36:19.290 \dashrightarrow 00:36:20.970$  some evidence that that's the case.

NOTE Confidence: 0.531161

 $00:36:20.970 \longrightarrow 00:36:22.420$  So just to remind you,

NOTE Confidence: 0.531161

 $00:36:22.420 \longrightarrow 00:36:24.093$  the idea is that Bath and this

NOTE Confidence: 0.531161

 $00{:}36{:}24.093 \dashrightarrow 00{:}36{:}25.905$  LEM two protein come in to recruit

NOTE Confidence: 0.531161

 $00{:}36{:}25{.}905 \dashrightarrow 00{:}36{:}27{.}805$  escorts to seal these breaks in the

NOTE Confidence: 0.531161

 $00:36:27.805 \dashrightarrow 00:36:29.235$  nuclear envelope and this limits

NOTE Confidence: 0.531161

 $00{:}36{:}29{.}235 \dashrightarrow 00{:}36{:}30{.}966$  sea gas access and activation.

NOTE Confidence: 0.531161

 $00{:}36{:}30{.}966 \dashrightarrow 00{:}36{:}34{.}482$  So here is an experiment where

 $00{:}36{:}34{.}482 \dashrightarrow 00{:}36{:}37{.}488$  we have used siRNA to knock down

NOTE Confidence: 0.531161

 $00{:}36{:}37{.}488 \dashrightarrow 00{:}36{:}39{.}360$  the bath protein to test this.

NOTE Confidence: 0.531161

 $00:36:39.360 \longrightarrow 00:36:41.684$  So again here you can see the

NOTE Confidence: 0.531161

 $00{:}36{:}41.684 \dashrightarrow 00{:}36{:}43.057$  interferon stimulated gene expression

NOTE Confidence: 0.531161

 $00{:}36{:}43.057 \dashrightarrow 00{:}36{:}45.319$  in a lab with elaborative treatment.

NOTE Confidence: 0.531161

 $00:36:45.320 \longrightarrow 00:36:47.854$  This is again in the UWB 1289 cells.

NOTE Confidence: 0.531161

00:36:47.854 --> 00:36:48.241 Interestingly,

NOTE Confidence: 0.531161

 $00:36:48.241 \rightarrow 00:36:50.176$  and consistent with another study

NOTE Confidence: 0.531161

 $00{:}36{:}50{.}176 \dashrightarrow 00{:}36{:}51{.}650$  in the literature,

NOTE Confidence: 0.531161

00:36:51.650 --> 00:36:53.168 if you just knock down Bath,

NOTE Confidence: 0.531161

 $00:36:53.170 \longrightarrow 00:36:55.432$  you also get a stimulation of

NOTE Confidence: 0.531161

 $00{:}36{:}55{.}432 \dashrightarrow 00{:}36{:}56{.}563$  an immune signaling,

NOTE Confidence: 0.531161

 $00:36:56.570 \longrightarrow 00:36:58.100$  which suggests that just knocking

NOTE Confidence: 0.531161

 $00{:}36{:}58{.}100 \dashrightarrow 00{:}36{:}59{.}979$  down bath and removing it can

NOTE Confidence: 0.531161

00:36:59.979 --> 00:37:01.449 always stimulate some sea gas.

NOTE Confidence: 0.531161

 $00:37:01.450 \longrightarrow 00:37:03.858$  And that may be as cells are reforming
- NOTE Confidence: 0.531161
- $00{:}37{:}03.858 \dashrightarrow 00{:}37{:}05.919$  their nuclear envelope or some other

 $00:37:05.919 \rightarrow 00:37:08.007$  aspect of the normal cell Physiology.

NOTE Confidence: 0.531161

00:37:08.010 --> 00:37:08.270 However,

NOTE Confidence: 0.531161

 $00{:}37{:}08{.}270 \dashrightarrow 00{:}37{:}10{.}090$  if we now add a lab rib,

NOTE Confidence: 0.531161

00:37:10.090 - 00:37:11.770 we can boost this even further,

NOTE Confidence: 0.531161

 $00{:}37{:}11.770 \dashrightarrow 00{:}37{:}14.010$  suggesting that there's a synergy

NOTE Confidence: 0.531161

00:37:14.010 --> 00:37:15.662 synergistic effect of knocking

NOTE Confidence: 0.531161

 $00{:}37{:}15.662 \dashrightarrow 00{:}37{:}18.510$  down Bath and adding a lab rib,

NOTE Confidence: 0.531161

 $00{:}37{:}18{.}510 \dashrightarrow 00{:}37{:}20{.}883$  which suggests that a lab rib actually

NOTE Confidence: 0.531161

 $00:37:20.883 \rightarrow 00:37:22.612$  precipitates these kind of breaks

NOTE Confidence: 0.531161

 $00{:}37{:}22.612 \dashrightarrow 00{:}37{:}24.252$  in the nuclear envelope because

NOTE Confidence: 0.531161

 $00{:}37{:}24.252 \dashrightarrow 00{:}37{:}25.950$  of these entangled chromosomes.

NOTE Confidence: 0.531161

 $00{:}37{:}25{.}950 \dashrightarrow 00{:}37{:}27{.}390$  And then normally Bath would

NOTE Confidence: 0.531161

 $00:37:27.390 \dashrightarrow 00:37:28.542$  be suppressing the signaling

NOTE Confidence: 0.531161

 $00:37:28.542 \longrightarrow 00:37:29.470$  downstream of that event.

 $00:37:29.470 \longrightarrow 00:37:30.270$  But when it's not there,

NOTE Confidence: 0.531161

00:37:30.270 -> 00:37:32.466 we get more C gas expression.

NOTE Confidence: 0.531161

 $00{:}37{:}32{.}470 \dashrightarrow 00{:}37{:}34{.}110$  So this is consistent with

NOTE Confidence: 0.531161

 $00{:}37{:}34{.}110 \dashrightarrow 00{:}37{:}35{.}422$  that kind of antagonism.

NOTE Confidence: 0.633801

 $00{:}37{:}37{.}470 \dashrightarrow 00{:}37{:}40{.}364$  So I just want to show you just briefly

NOTE Confidence: 0.633801

 $00:37:40.364 \dashrightarrow 00:37:41.860$ I because it's just you know we're cell NOTE Confidence: 0.633801

 $00:37:41.905 \dashrightarrow 00:37:43.345$  biologists so we love to look at things.

NOTE Confidence: 0.633801

 $00:37:43.350 \longrightarrow 00:37:44.745$  This is this really cool

NOTE Confidence: 0.633801

 $00{:}37{:}44.745 \dashrightarrow 00{:}37{:}46.140$  reconstruction of what one of

NOTE Confidence: 0.633801

 $00:37:46.193 \dashrightarrow 00:37:47.945$  these bridges looks like up close.

NOTE Confidence: 0.633801

00:37:47.950 --> 00:37:50.062 And I bring it up because the protein

NOTE Confidence: 0.633801

 $00{:}37{:}50.062 \dashrightarrow 00{:}37{:}52.456$  man one which is in yellow is actually

NOTE Confidence: 0.633801

 $00{:}37{:}52{.}456 \dashrightarrow 00{:}37{:}54{.}778$  localized to the mid body and the protein

NOTE Confidence: 0.633801

 $00{:}37{:}54.778 \dashrightarrow 00{:}37{:}56.710$  LEM 2 which is that nuclear repair

NOTE Confidence: 0.633801

 $00:37:56.769 \dashrightarrow 00:37:58.869$  protein you can see along this bridge.

NOTE Confidence: 0.633801

 $00:37:58.870 \longrightarrow 00:38:00.290$  But you can see they're

 $00:38:00.290 \longrightarrow 00:38:01.426$  actually in distinct regions.

NOTE Confidence: 0.633801

 $00{:}38{:}01{.}430 \dashrightarrow 00{:}38{:}04{.}014$  As I mentioned LEM two is likely to

NOTE Confidence: 0.633801

 $00:38:04.014 \dashrightarrow 00:38:06.582$  be along the regions of the bridge

NOTE Confidence: 0.633801

00:38:06.582 --> 00:38:08.835 that that are ruptured and actually

NOTE Confidence: 0.633801

 $00{:}38{:}08{.}835 \dashrightarrow 00{:}38{:}11{.}739$  man one is sitting on the mid body.

NOTE Confidence: 0.633801

 $00{:}38{:}11.740 \dashrightarrow 00{:}38{:}14.276$  And so one other area that that

NOTE Confidence: 0.633801

00:38:14.276 --> 00:38:16.292 we're interested in looking into is

NOTE Confidence: 0.633801

 $00{:}38{:}16{.}292 \dashrightarrow 00{:}38{:}18{.}827$  there is a known checkpoint that

NOTE Confidence: 0.633801

 $00{:}38{:}18.827 \dashrightarrow 00{:}38{:}21.257$  controls whether cells do abscission.

NOTE Confidence: 0.633801

00:38:21.260 --> 00:38:23.354 That's does seems to be downstream

NOTE Confidence: 0.633801

 $00:38:23.354 \longrightarrow 00:38:24.750$  of surveilling whether there's

NOTE Confidence: 0.633801

00:38:24.809 --> 00:38:26.185 been chromosome entanglements and

NOTE Confidence: 0.633801

 $00:38:26.185 \rightarrow 00:38:28.249$  this is regulated by Aurora B,

NOTE Confidence: 0.633801

 $00{:}38{:}28{.}250 \dashrightarrow 00{:}38{:}29{.}458$  which is interesting because

NOTE Confidence: 0.633801

 $00{:}38{:}29{.}458 \dashrightarrow 00{:}38{:}30{.}968$  the Aurora kinases have also

00:38:30.968 - 00:38:32.449 been interesting clinically,

NOTE Confidence: 0.633801

00:38:32.450 --> 00:38:35.434 although I think I've not been so far

NOTE Confidence: 0.633801

 $00:38:35.434 \rightarrow 00:38:37.810$  really terribly successful clinically.

NOTE Confidence: 0.633801

 $00:38:37.810 \dashrightarrow 00:38:40.458$  But I think that this is one context NOTE Confidence: 0.633801

00:38:40.458 --> 00:38:42.516 where thinking about how Aurora B

NOTE Confidence: 0.633801

 $00{:}38{:}42{.}516$  -->  $00{:}38{:}44{.}502$  might impact these events and be NOTE Confidence: 0.633801

 $00:38:44.574 \rightarrow 00:38:46.849$  involved would be very interesting.

NOTE Confidence: 0.633801

 $00{:}38{:}46{.}850 \dashrightarrow 00{:}38{:}49{.}685$  So that and that is a reason why you

NOTE Confidence: 0.633801

 $00{:}38{:}49.685 \dashrightarrow 00{:}38{:}51.971$  get these doublet cells that are

NOTE Confidence: 0.633801

00:38:51.971 --> 00:38:53.693 binucleate is because there has been NOTE Confidence: 0.633801

 $00{:}38{:}53{.}693 \dashrightarrow 00{:}38{:}55{.}669$  an obscision failure downstream of

NOTE Confidence: 0.633801

 $00{:}38{:}55{.}669 \dashrightarrow 00{:}38{:}57{.}709$  the failure to segregate chromosomes.

NOTE Confidence: 0.633801

 $00{:}38{:}57{.}710 \dashrightarrow 00{:}38{:}59{.}730$  And so that's something that

NOTE Confidence: 0.633801

 $00:38:59.730 \dashrightarrow 00:39:01.750$  we're interested in in pursuing.

NOTE Confidence: 0.633801

00:39:01.750 --> 00:39:02.245 OK.

NOTE Confidence: 0.633801

00:39:02.245 --> 00:39:06.388 So I just wanted to come back to this

- NOTE Confidence: 0.633801
- $00:39:06.388 \longrightarrow 00:39:08.422$  idea that these nuclear integrity defects

 $00{:}39{:}08{.}422 \dashrightarrow 00{:}39{:}11{.}031$  are the OR and these mitotic errors

NOTE Confidence: 0.633801

 $00:39:11.031 \rightarrow 00:39:12.901$  and then nuclear integrity defects.

NOTE Confidence: 0.633801

 $00:39:12.910 \longrightarrow 00:39:13.514$  Could this,

NOTE Confidence: 0.633801

 $00:39:13.514 \rightarrow 00:39:15.628$  could this be something that we actually

NOTE Confidence: 0.633801

 $00:39:15.628 \rightarrow 00:39:17.656$  take advantage of as a biomarker?

NOTE Confidence: 0.633801

 $00:39:17.656 \longrightarrow 00:39:19.366$  This is something that we're

NOTE Confidence: 0.633801

 $00:39:19.366 \longrightarrow 00:39:21.199$  really is very preliminary,

NOTE Confidence: 0.633801

 $00:39:21.200 \longrightarrow 00:39:23.200$  but we're very interested in.

NOTE Confidence: 0.633801

 $00{:}39{:}23.200 \dashrightarrow 00{:}39{:}24.880$  So you know as I've already pointed out,

NOTE Confidence: 0.633801

 $00:39:24.880 \dashrightarrow 00:39:26.840$  when you have these persistent DNA bridges,

NOTE Confidence: 0.633801

 $00{:}39{:}26{.}840 \dashrightarrow 00{:}39{:}28{.}160$  there is this relationship

NOTE Confidence: 0.633801

 $00{:}39{:}28.160 \dashrightarrow 00{:}39{:}29.480$  between the two nuclei,

NOTE Confidence: 0.633801

 $00{:}39{:}29{.}480 \dashrightarrow 00{:}39{:}32{.}189$  the result from that mitosis and there

NOTE Confidence: 0.633801

 $00{:}39{:}32{.}189 \dashrightarrow 00{:}39{:}34{.}600$  are these changes in nuclear shape.

 $00{:}39{:}34.600 \dashrightarrow 00{:}39{:}39.160$  These are actually H& amp;E from the

NOTE Confidence: 0.633801

00:39:39.160 --> 00:39:42.346 10020 trial headed by Pat Larusso

NOTE Confidence: 0.633801

 $00{:}39{:}42{.}350 \dashrightarrow 00{:}39{:}44{.}990$  and as well as Kurt Shopper.

NOTE Confidence: 0.633801

 $00{:}39{:}44{.}990 \dashrightarrow 00{:}39{:}46{.}908$  And one of the things we've been

NOTE Confidence: 0.633801

 $00:39:46.908 \longrightarrow 00:39:49.196$  looking at is if we look at these

NOTE Confidence: 0.633801

 $00:39:49.196 \rightarrow 00:39:51.070$  tumors in patients that are bracket

NOTE Confidence: 0.633801

00:39:51.070 - 00:39:53.110 deficient treated with a laparib,

NOTE Confidence: 0.633801

 $00:39:53.110 \longrightarrow 00:39:55.110$  can we see these structures.

NOTE Confidence: 0.633801

 $00{:}39{:}55{.}110 \dashrightarrow 00{:}39{:}57{.}030$  And I think what we've been,

NOTE Confidence: 0.633801

 $00:39:57.030 \rightarrow 00:39:59.232$  we did not expect to be able to see any of

NOTE Confidence: 0.633801

00:39:59.232 --> 00:40:01.184 these structures in H&<br/>amp; E just to be honest.

NOTE Confidence: 0.633801

 $00{:}40{:}01{.}190 \dashrightarrow 00{:}40{:}04{.}435$  But but we're kind of excited that we

NOTE Confidence: 0.633801

 $00{:}40{:}04{.}435 \dashrightarrow 00{:}40{:}06{.}654$  think that we can see these kind of

NOTE Confidence: 0.633801

 $00:40:06.654 \rightarrow 00:40:08.109$  arrangements that are between cells.

NOTE Confidence: 0.633801

00:40:08.110 --> 00:40:08.458 You know,

 $00:40:08.458 \longrightarrow 00:40:09.502$  they were not the first people

NOTE Confidence: 0.633801

 $00{:}40{:}09{.}502 \dashrightarrow 00{:}40{:}10{.}468$  to ever comment on this,

NOTE Confidence: 0.633801

 $00{:}40{:}10.470 \dashrightarrow 00{:}40{:}12.756$  but I think we're connecting these

NOTE Confidence: 0.633801

00:40:12.756 --> 00:40:14.280 observations to an underlying

NOTE Confidence: 0.633801

 $00:40:14.347 \rightarrow 00:40:16.387$  mechanism that may highlight why we

NOTE Confidence: 0.633801

 $00:40:16.387 \longrightarrow 00:40:18.625$  should be paying more attention to

NOTE Confidence: 0.633801

 $00{:}40{:}18.625 \dashrightarrow 00{:}40{:}20.670$  the prevalence of these structures.

NOTE Confidence: 0.633801

 $00:40:20.670 \rightarrow 00:40:22.495$  I think particularly because micronuclei

NOTE Confidence: 0.633801

00:40:22.495 --> 00:40:24.590 really cannot be perceived in H&E,

NOTE Confidence: 0.633801

 $00:40:24.590 \longrightarrow 00:40:27.054$  this may be a mitotic error

NOTE Confidence: 0.633801

 $00{:}40{:}27.054 \dashrightarrow 00{:}40{:}28.110$  that's much more

NOTE Confidence: 0.74551356

 $00:40:28.193 \longrightarrow 00:40:30.068$  easy to perceive in the

NOTE Confidence: 0.74551356

 $00:40:30.068 \longrightarrow 00:40:31.943$  tissue and so might this.

NOTE Confidence: 0.74551356

00:40:31.950 --> 00:40:33.570 I think and one really interesting

NOTE Confidence: 0.74551356

 $00{:}40{:}33{.}570 \dashrightarrow 00{:}40{:}35{.}849$  part of this to me is that you

NOTE Confidence: 0.74551356

 $00:40:35.849 \longrightarrow 00:40:37.279$  know these there's already an

00:40:37.279 - 00:40:39.021 increase in these bridges just in

NOTE Confidence: 0.74551356

00:40:39.021 --> 00:40:40.803 HR defective cells that you can

NOTE Confidence: 0.74551356

 $00{:}40{:}40{.}803 \dashrightarrow 00{:}40{:}42{.}668$  push further with PARP inhibitors.

NOTE Confidence: 0.74551356

 $00{:}40{:}42.670 \dashrightarrow 00{:}40{:}44.518$  But this could be a kind of non

NOTE Confidence: 0.74551356

 $00:40:44.518 \rightarrow 00:40:46.260$  genomic way of assessing is there

NOTE Confidence: 0.74551356

 $00{:}40{:}46.260 \dashrightarrow 00{:}40{:}48.096$  a homologous or combination or just

NOTE Confidence: 0.74551356

00:40:48.155 --> 00:40:49.733 DNA repair defect in this cell

NOTE Confidence: 0.74551356

 $00{:}40{:}49{.}733 \dashrightarrow 00{:}40{:}51{.}498$  line Because I see these mitotic

NOTE Confidence: 0.74551356

 $00:40:51.498 \longrightarrow 00:40:53.268$  errors that actually are such,

NOTE Confidence: 0.74551356

 $00:40:53.270 \longrightarrow 00:40:55.286$  so large that they can be

NOTE Confidence: 0.74551356

 $00:40:55.286 \longrightarrow 00:40:56.630$  perceived even in HNA.

NOTE Confidence: 0.74551356

 $00:40:56.630 \longrightarrow 00:40:58.835$  To really validate that we

NOTE Confidence: 0.74551356

 $00:40:58.835 \longrightarrow 00:41:02.030$  have to be able to actually,

NOTE Confidence: 0.74551356

00:41:02.030 --> 00:41:02.588 you know,

NOTE Confidence: 0.74551356

 $00{:}41{:}02.588 \dashrightarrow 00{:}41{:}03.704$  convince ourselves that these

 $00:41:03.704 \longrightarrow 00:41:05.087$  really are the structures that

NOTE Confidence: 0.74551356

00:41:05.087 --> 00:41:06.377 I've been talking about that we

NOTE Confidence: 0.74551356

 $00:41:06.377 \longrightarrow 00:41:07.669$  see in tissue culture cells.

NOTE Confidence: 0.74551356

 $00:41:07.670 \longrightarrow 00:41:09.030$  And so to be able to do that,

NOTE Confidence: 0.74551356

 $00{:}41{:}09{.}030 \dashrightarrow 00{:}41{:}10{.}927$  we are working on validating some of

NOTE Confidence: 0.74551356

 $00{:}41{:}10.927 \dashrightarrow 00{:}41{:}12.825$  the antibodies that we've raised to

NOTE Confidence: 0.74551356

 $00:41:12.825 \rightarrow 00:41:14.550$  these specific nuclear envelope proteins.

NOTE Confidence: 0.74551356

 $00:41:14.550 \longrightarrow 00:41:16.083$  I mentioned it's really hard to see

NOTE Confidence: 0.74551356

 $00{:}41{:}16.083 \dashrightarrow 00{:}41{:}17.390$  these bridges even with DNA stain.

NOTE Confidence: 0.74551356

 $00:41:17.390 \longrightarrow 00:41:19.126$  You really have to have the right

NOTE Confidence: 0.74551356

 $00{:}41{:}19{.}126 \dashrightarrow 00{:}41{:}20{.}642$  molecule that you're looking for and

NOTE Confidence: 0.74551356

 $00{:}41{:}20.642 \dashrightarrow 00{:}41{:}22.126$  we think that these integral and a

NOTE Confidence: 0.74551356

 $00{:}41{:}22.126 \dashrightarrow 00{:}41{:}23.588$  nuclear membrane proteins are exactly that.

NOTE Confidence: 0.74551356

00:41:23.590 --> 00:41:27.114 And so we're hoping to validate

NOTE Confidence: 0.74551356

 $00:41:27.114 \longrightarrow 00:41:28.810$  that these structures indeed

NOTE Confidence: 0.74551356

00:41:28.810 --> 00:41:30.930 are representative of these DNA

- NOTE Confidence: 0.74551356
- $00:41:30.996 \rightarrow 00:41:33.146$  bridges because we can specifically

 $00{:}41{:}33.146 \dashrightarrow 00{:}41{:}35.105$  identify them with these antibodies.

NOTE Confidence: 0.74551356

 $00:41:35.105 \longrightarrow 00:41:36.565$  And then in addition,

NOTE Confidence: 0.74551356

 $00:41:36.570 \rightarrow 00:41:38.163$  I think just to be a bit agnostic also,

NOTE Confidence: 0.74551356

 $00{:}41{:}38{.}170 \dashrightarrow 00{:}41{:}41{.}035$  but other mitotic errors like

NOTE Confidence: 0.74551356

00:41:41.035 --> 00:41:43.200 Micronuclei LEM two in addition to

NOTE Confidence: 0.74551356

00:41:43.200 --> 00:41:44.790 being recruited to the ruptured

NOTE Confidence: 0.74551356

00:41:44.858 --> 00:41:46.982 regions of DNA breaks is also

NOTE Confidence: 0.74551356

00:41:46.982 --> 00:41:49.170 recruited strongly to ruptured Micronuclei.

NOTE Confidence: 0.74551356

00:41:49.170 - 00:41:50.770 And so if we had this molecular tool,

NOTE Confidence: 0.74551356

 $00{:}41{:}50{.}770 \dashrightarrow 00{:}41{:}53{.}605$  we might also be able to more

NOTE Confidence: 0.74551356

00:41:53.605 --> 00:41:55.255 accurately quantitate the prevalence

NOTE Confidence: 0.74551356

 $00{:}41{:}55{.}255 \dashrightarrow 00{:}41{:}57{.}330$  of micronuclei and chemical samples,

NOTE Confidence: 0.74551356

 $00{:}41{:}57{.}330 \dashrightarrow 00{:}41{:}58{.}650$  which would be fant astic.

NOTE Confidence: 0.5170579

 $00{:}42{:}01{.}290 \dashrightarrow 00{:}42{:}03{.}058$  And you know why I think that's so

00:42:03.058 --> 00:42:04.928 important and I just picked out one example,

NOTE Confidence: 0.5170579

00:42:04.930 --> 00:42:06.694 I could have picked out many of

NOTE Confidence: 0.5170579

 $00{:}42{:}06{.}694 \dashrightarrow 00{:}42{:}09{.}198$  them is that there of course is an

NOTE Confidence: 0.5170579

 $00{:}42{:}09{.}198 \dashrightarrow 00{:}42{:}10{.}888$  interest in expanding PARP inhibitors

NOTE Confidence: 0.5170579

 $00{:}42{:}10.945 \dashrightarrow 00{:}42{:}12.949$  beyond you know breast and ovarian,

NOTE Confidence: 0.5170579

 $00{:}42{:}12{.}950 \dashrightarrow 00{:}42{:}15{.}148$ Braca 1 and Braca 2 deficient patients,

NOTE Confidence: 0.5170579

00:42:15.150 --> 00:42:16.564 right. So I just pick and picked

NOTE Confidence: 0.5170579

 $00:42:16.564 \longrightarrow 00:42:18.213$  out one of these examples of the

NOTE Confidence: 0.5170579

 $00{:}42{:}18.213 \dashrightarrow 00{:}42{:}19.707$  fact that there really are some

NOTE Confidence: 0.5170579

 $00:42:19.754 \rightarrow 00:42:21.068$  amazing clinical responders.

NOTE Confidence: 0.5170579

 $00{:}42{:}21.070 \dashrightarrow 00{:}42{:}23.778$  This is in pancreatic cancer here.

NOTE Confidence: 0.5170579

 $00{:}42{:}23.778 \dashrightarrow 00{:}42{:}26.346$  There has been selection for BRACA

NOTE Confidence: 0.5170579

00:42:26.346 --> 00:42:27.630 associated pancreatic cancer,

NOTE Confidence: 0.5170579

 $00:42:27.630 \longrightarrow 00:42:28.870$  but I think an ecdotally,

NOTE Confidence: 0.5170579

 $00{:}42{:}28.870 \dashrightarrow 00{:}42{:}31.089$  we know there are triple negative breast

NOTE Confidence: 0.5170579

 $00:42:31.089 \rightarrow 00:42:32.913$  cancers that respond to PARP inhibitors

- NOTE Confidence: 0.5170579
- $00:42:32.913 \rightarrow 00:42:35.009$  even if we don't understand why.

 $00{:}42{:}35{.}010 \dashrightarrow 00{:}42{:}37{.}120$  There are right very aggressive

NOTE Confidence: 0.5170579

00:42:37.120 --> 00:42:37.964 prostate cancers,

NOTE Confidence: 0.5170579

 $00:42:37.970 \rightarrow 00:42:40.354$  A subset of which respond to PARP inhibitors

NOTE Confidence: 0.5170579

 $00:42:40.354 \rightarrow 00:42:42.290$  even though we don't understand why.

NOTE Confidence: 0.5170579

 $00{:}42{:}42{.}290 \dashrightarrow 00{:}42{:}44{.}474$  And so we're hoping that these kind

NOTE Confidence: 0.5170579

00:42:44.474 --> 00:42:45.879 of biomarkers could potentially

NOTE Confidence: 0.5170579

 $00{:}42{:}45.879 \dashrightarrow 00{:}42{:}47.894$  indicate where PARP inhibitors might

NOTE Confidence: 0.5170579

 $00{:}42{:}47.894 \dashrightarrow 00{:}42{:}50.416$  be effective even when the molecular

NOTE Confidence: 0.5170579

 $00:42:50.416 \longrightarrow 00:42:52.526$  or genetic signature isn't understood.

NOTE Confidence: 0.7353201

 $00{:}42{:}54{.}610 \dashrightarrow 00{:}42{:}57{.}816$  OK. So just to just to restate

NOTE Confidence: 0.7353201

 $00{:}42{:}57.816 \dashrightarrow 00{:}43{:}00.310$  what I've told you today,

NOTE Confidence: 0.7353201

 $00:43:00.310 \longrightarrow 00:43:01.890$  while Laparov enhances the prevalence

NOTE Confidence: 0.7353201

 $00{:}43{:}01{.}890 \dashrightarrow 00{:}43{:}03{.}470$  of these persistent DNA bridges,

NOTE Confidence: 0.7353201

 $00:43:03.470 \longrightarrow 00:43:04.710$  there's already more in

00:43:04.710 --> 00:43:05.950 an HR deficient context.

NOTE Confidence: 0.7353201

 $00{:}43{:}05{.}950 \dashrightarrow 00{:}43{:}08{.}169$  But you can push this further with

NOTE Confidence: 0.7353201

 $00{:}43{:}08{.}169$  -->  $00{:}43{:}10{.}641$  PARP inhibitors and this does lead to

NOTE Confidence: 0.7353201

 $00{:}43{:}10.641$  -->  $00{:}43{:}12.466$  activation of innate immune signaling.

NOTE Confidence: 0.7353201

 $00{:}43{:}12{.}470 \dashrightarrow 00{:}43{:}14{.}710$  Their recruitment of bath and

NOTE Confidence: 0.7353201

00:43:14.710 --> 00:43:16.950 C gas may be antagonistic,

NOTE Confidence: 0.7353201

 $00{:}43{:}16.950 \dashrightarrow 00{:}43{:}19.218$  but both are seem to be recruited

NOTE Confidence: 0.7353201

 $00:43:19.218 \longrightarrow 00:43:20.190$  to these bridges.

NOTE Confidence: 0.7353201

 $00{:}43{:}20{.}190 \dashrightarrow 00{:}43{:}21{.}910$  So that suggests that there

NOTE Confidence: 0.7353201

 $00:43:21.910 \longrightarrow 00:43:23.630$  many of them are ruptured.

NOTE Confidence: 0.7353201

 $00{:}43{:}23.630 \dashrightarrow 00{:}43{:}25.574$  We're interested in whether

NOTE Confidence: 0.7353201

 $00{:}43{:}25{.}574 \dashrightarrow 00{:}43{:}27{.}518$  just regulating disrupting this

NOTE Confidence: 0.7353201

00:43:27.518 --> 00:43:29.521 nuclear envelope repair network

NOTE Confidence: 0.7353201

 $00:43:29.521 \rightarrow 00:43:31.441$  could actually further stimulate

NOTE Confidence: 0.7353201

 $00{:}43{:}31{.}441 \dashrightarrow 00{:}43{:}33{.}361$  the innate immune signaling

NOTE Confidence: 0.7353201

 $00:43:33.429 \rightarrow 00:43:35.669$  downstream of these mitotic errors.

- NOTE Confidence: 0.7353201
- $00:43:35.670 \rightarrow 00:43:37.952$  And we're excited about the idea of

 $00{:}43{:}37{.}952 \dashrightarrow 00{:}43{:}39{.}996$  these persistent bridges could be an

NOTE Confidence: 0.7353201

00:43:39.996 --> 00:43:41.354 accessible hallmark of HR deficiency,

NOTE Confidence: 0.7353201

 $00{:}43{:}41{.}354 \dashrightarrow 00{:}43{:}42{.}266$  which as I said,

NOTE Confidence: 0.7353201

 $00:43:42.270 \longrightarrow 00:43:45.922$  we poorly need in terms of what

NOTE Confidence: 0.7353201

 $00{:}43{:}45{.}922 \dashrightarrow 00{:}43{:}47{.}666$  our next steps are and what

NOTE Confidence: 0.7353201

 $00:43:47.666 \rightarrow 00:43:49.340$  we're focusing on at the moment,

NOTE Confidence: 0.7353201

 $00:43:49.340 \rightarrow 00:43:51.074$  where we really need to understand

NOTE Confidence: 0.7353201

 $00{:}43{:}51{.}074 \dashrightarrow 00{:}43{:}53{.}019$  if this is really the canonical

NOTE Confidence: 0.7353201

 $00{:}43{:}53.020 \dashrightarrow 00{:}43{:}55.174$  ISG expression is relevant here or

NOTE Confidence: 0.7353201

 $00{:}43{:}55{.}174 \dashrightarrow 00{:}43{:}57{.}092$  perhaps there's some other downstream

NOTE Confidence: 0.7353201

 $00{:}43{:}57.092 \dashrightarrow 00{:}43{:}58.784$  consequence that's running in

NOTE Confidence: 0.7353201

 $00{:}43{:}58{.}784 \dashrightarrow 00{:}44{:}01{.}260$  parallel with the production of Isgs.

NOTE Confidence: 0.7353201

 $00{:}44{:}01{.}260 \dashrightarrow 00{:}44{:}01{.}822$  That's important.

NOTE Confidence: 0.7353201

00:44:01.822 --> 00:44:02.103 Again,

 $00:44:02.103 \longrightarrow 00:44:04.070$  you get cell killing in a tumor

NOTE Confidence: 0.7353201

 $00{:}44{:}04{.}123 \dashrightarrow 00{:}44{:}05{.}575$  cell intrinsic way in a dish.

NOTE Confidence: 0.7353201

 $00:44:05.580 \longrightarrow 00:44:07.869$  So we don't know if that's really

NOTE Confidence: 0.7353201

 $00:44:07.869 \rightarrow 00:44:09.550$  a consequence directly of anything

NOTE Confidence: 0.7353201

 $00{:}44{:}09{.}550 \dashrightarrow 00{:}44{:}11{.}135$  to do with ISG expression.

NOTE Confidence: 0.7353201

 $00:44:11.140 \rightarrow 00:44:13.926$  And so that's something that we're exploring.

NOTE Confidence: 0.7353201

 $00{:}44{:}13.930 \dashrightarrow 00{:}44{:}16.110$  We're also taking both candidate

NOTE Confidence: 0.7353201

 $00:44:16.110 \rightarrow 00:44:18.290$  approaches and unbiased screens to

NOTE Confidence: 0.7353201

 $00{:}44{:}18.357 \dashrightarrow 00{:}44{:}20.583$  identify what are the factors required

NOTE Confidence: 0.7353201

 $00{:}44{:}20{.}583 \dashrightarrow 00{:}44{:}22{.}850$  for the cell death in culture.

NOTE Confidence: 0.7353201

 $00:44:22.850 \longrightarrow 00:44:24.383$  You in some ways you would have

NOTE Confidence: 0.7353201

 $00{:}44{:}24{.}383 \dashrightarrow 00{:}44{:}26{.}014$  thought this would have come out of

NOTE Confidence: 0.7353201

 $00{:}44{:}26.014 \dashrightarrow 00{:}44{:}27.406$  CRISPR screens which have been done.

NOTE Confidence: 0.7353201

 $00:44:27.410 \longrightarrow 00:44:28.538$  But actually I think there are

NOTE Confidence: 0.7353201

 $00{:}44{:}28{.}538 \dashrightarrow 00{:}44{:}29{.}954$  a lot of reasons to think that

NOTE Confidence: 0.7353201

 $00:44:29.954 \rightarrow 00:44:30.994$  those screens weren't really set

- NOTE Confidence: 0.7353201
- $00:44:30.994 \rightarrow 00:44:32.410$  up to identify this mechanism.

 $00{:}44{:}32{.}410 \dashrightarrow 00{:}44{:}34{.}842$  And so that's one of the things that

NOTE Confidence: 0.7353201

 $00:44:34.842 \rightarrow 00:44:36.909$  we're setting up to do at the moment.

NOTE Confidence: 0.7353201

00:44:36.910 --> 00:44:38.238 Again, we're cell biologists,

NOTE Confidence: 0.7353201

 $00:44:38.238 \rightarrow 00:44:39.898$  so we're using correlative light

NOTE Confidence: 0.7353201

 $00:44:39.898 \rightarrow 00:44:41.702$  and electron microscopy to really

NOTE Confidence: 0.7353201

 $00{:}44{:}41.702 \dashrightarrow 00{:}44{:}43.467$  understand what's happening in these

NOTE Confidence: 0.7353201

 $00{:}44{:}43{.}467 \dashrightarrow 00{:}44{:}45{.}686$  DNA bridges and also to and get

NOTE Confidence: 0.7353201

 $00{:}44{:}45.686 \dashrightarrow 00{:}44{:}47.826$  information about the DNA structure.

NOTE Confidence: 0.7353201

 $00{:}44{:}47.830 \dashrightarrow 00{:}44{:}49.998$  We can do that by looking at accessibility

NOTE Confidence: 0.7353201

 $00{:}44{:}49{.}998 \dashrightarrow 00{:}44{:}52{.}428$  to the TN 5 transpose ACE as an example,

NOTE Confidence: 0.7353201

 $00{:}44{:}52{.}430 \dashrightarrow 00{:}44{:}54{.}670$  which is the basis for ATAC experiments,

NOTE Confidence: 0.7353201

00:44:54.670 - 00:44:57.342 but you can use that in a microscopy

NOTE Confidence: 0.7353201

 $00{:}44{:}57{.}342 \dashrightarrow 00{:}44{:}58{.}579$  based experiment as well.

NOTE Confidence: 0.7353201

 $00:44:58.580 \rightarrow 00:45:01.058$  And then we're working with our

 $00:45:01.058 \rightarrow 00:45:03.022$  partners at AstraZeneca to really

NOTE Confidence: 0.7353201

 $00:45:03.022 \longrightarrow 00:45:05.549$  try to test whether we can use

NOTE Confidence: 0.7353201

 $00{:}45{:}05{.}549 \dashrightarrow 00{:}45{:}08{.}152$  these bridges as a sa biomarker,

NOTE Confidence: 0.7353201

 $00{:}45{:}08{.}152 \dashrightarrow 00{:}45{:}10{.}980$  you know at the very initial stages NOTE Confidence: 0.7353201

 $00:45:10.980 \longrightarrow 00:45:12.258$  in a really well controlled system.

NOTE Confidence: 0.7353201

 $00{:}45{:}12{.}260 \dashrightarrow 00{:}45{:}14{.}004$  So one of the things that they have NOTE Confidence: 0.7353201

00:45:14.004 --> 00:45:15.918 is that they have xenograft models of

NOTE Confidence: 0.7353201

 $00{:}45{:}15{.}918$  -->  $00{:}45{:}17{.}961$  of BRCA 1 deficient tumors which they

NOTE Confidence: 0.7353201

 $00{:}45{:}17{.}961$  -->  $00{:}45{:}19{.}935$  then treated those mice with a laparib.

NOTE Confidence: 0.7353201

 $00{:}45{:}19{.}940 \dashrightarrow 00{:}45{:}22{.}132$  And so we have really nice kind of

NOTE Confidence: 0.7353201

00:45:22.132 --> 00:45:24.468 ground truth data of HR deficient,

NOTE Confidence: 0.7353201

00:45:24.468 --> 00:45:25.460 HR proficient,

NOTE Confidence: 0.7353201

 $00{:}45{:}25{.}460 \dashrightarrow 00{:}45{:}26{.}106$  you know,

NOTE Confidence: 0.7353201

 $00{:}45{:}26.106 \dashrightarrow 00{:}45{:}28.044$  with and without treatment with a

NOTE Confidence: 0.7353201

 $00{:}45{:}28.044 \dashrightarrow 00{:}45{:}29.394$  laparib or other PARP inhibitors.

NOTE Confidence: 0.7353201

 $00{:}45{:}29{.}394 \dashrightarrow 00{:}45{:}31{.}662$  And so looking at the H and AE of

- NOTE Confidence: 0.7353201
- $00:45:31.662 \rightarrow 00:45:33.578$  those data sets and doing that in a

 $00:45:33.578 \rightarrow 00:45:35.587$  blinded way will really help us to

NOTE Confidence: 0.7353201

 $00{:}45{:}35{.}587 \dashrightarrow 00{:}45{:}36{.}809$  understand whether this is something

NOTE Confidence: 0.7353201

 $00:45:36.809 \rightarrow 00:45:38.087$  that's going to be worth pursuing.

NOTE Confidence: 0.3837364

 $00:45:40.210 \longrightarrow 00:45:42.314$  All right. So I just like to thank

NOTE Confidence: 0.3837364

 $00{:}45{:}42.314 \dashrightarrow 00{:}45{:}44.405$  the people who did the work and then

NOTE Confidence: 0.3837364

 $00:45:44.405 \rightarrow 00:45:46.290$  I'm happy to take any questions.

NOTE Confidence: 0.3837364

 $00:45:46.290 \rightarrow 00:45:48.593$  We have a really great group working

NOTE Confidence: 0.3837364

 $00:45:48.593 \longrightarrow 00:45:50.288$  on genome integrity in the lab.

NOTE Confidence: 0.3837364

00:45:50.290 --> 00:45:53.040 Yuduo is a is a fellow much of what much

NOTE Confidence: 0.3837364

 $00{:}45{:}53{.}109 \dashrightarrow 00{:}45{:}55{.}701$  of what I showed you today is work from

NOTE Confidence: 0.3837364

00:45:55.701 --> 00:45:58.610 AJ Kozak who's a PhD student in the lab.

NOTE Confidence: 0.3837364

 $00{:}45{:}58.610 \dashrightarrow 00{:}45{:}59.985$  Carrie recently joined the team

NOTE Confidence: 0.3837364

 $00{:}45{:}59{.}985 \dashrightarrow 00{:}46{:}02{.}005$  and she's going to be working on

NOTE Confidence: 0.3837364

 $00{:}46{:}02.005 \dashrightarrow 00{:}46{:}03.485$  these screens for DNA repair.

00:46:03.490 --> 00:46:05.940 So we're we're we're almost getting sorry

NOTE Confidence: 0.3837364

 $00{:}46{:}05{.}940 \dashrightarrow 00{:}46{:}08{.}489$  not DNA repair screens to identify the

NOTE Confidence: 0.3837364

 $00{:}46{:}08{.}490 \dashrightarrow 00{:}46{:}10{.}494$  the mechanisms of cell death downstream NOTE Confidence: 0.3837364

 $00:46:10.494 \dashrightarrow 00:46:12.768$  of PARP inhibitors in the cell models.

NOTE Confidence: 0.3837364

 $00:46:12.770 \longrightarrow 00:46:14.754$  And I'll say just joined the lab and

NOTE Confidence: 0.3837364

 $00:46:14.754 \longrightarrow 00:46:16.601$  he's going to try to get our our

NOTE Confidence: 0.3837364

 $00:46:16.601 \rightarrow 00:46:18.210$  tissue part of this up and going.

NOTE Confidence: 0.3837364

 $00{:}46{:}18{.}210 \dashrightarrow 00{:}46{:}21{.}130$  I'd also like to acknowledge Pat

NOTE Confidence: 0.3837364

00:46:21.130 --> 00:46:22.870 Larusso who who has really been

NOTE Confidence: 0.3837364

 $00:46:22.870 \longrightarrow 00:46:24.784$  essential and in all aspects of

NOTE Confidence: 0.3837364

 $00{:}46{:}24.784 \dashrightarrow 00{:}46{:}26.752$  getting us involved in this direction.

NOTE Confidence: 0.3837364

 $00{:}46{:}26.760 \dashrightarrow 00{:}46{:}29.315$  It would not have happened without her

NOTE Confidence: 0.3837364

 $00{:}46{:}29{.}320 \dashrightarrow 00{:}46{:}31{.}357$  and I'm happy to take any questions.

NOTE Confidence: 0.3837364

 $00:46:31.360 \longrightarrow 00:46:31.960$  Thanks.

NOTE Confidence: 0.26034585

 $00:46:38.460 \longrightarrow 00:46:42.252$  Yeah. Have you seen this

NOTE Confidence: 0.26034585

 $00:46:42.252 \rightarrow 00:46:44.899$  type outside of other HRD

00:46:46.980 --> 00:46:48.900 such as what do you thinking

NOTE Confidence: 0.3960918375

00:46:51.740 --> 00:46:56.738 Yeah I yeah I think we have not some

NOTE Confidence: 0.3960918375

00:46:56.738 --> 00:46:58.610 of the some of the data that I showed

NOTE Confidence: 0.3960918375

 $00:46:58.660 \rightarrow 00:47:00.412$  you from the literature is strongly

NOTE Confidence: 0.3960918375

 $00{:}47{:}00{.}412 \dashrightarrow 00{:}47{:}02{.}433$  suggestive that also in the contents of NOTE Confidence: 0.3960918375

 $00:47:02.433 \rightarrow 00:47:04.554$  bracket two we need mitosis to get cell

NOTE Confidence: 0.3960918375

 $00:47:04.554 \rightarrow 00:47:06.610$  death you get innate immune signaling.

NOTE Confidence: 0.3960918375

 $00{:}47{:}06.610 \dashrightarrow 00{:}47{:}08.464$  We have not, I should ask

NOTE Confidence: 0.3960918375

00:47:08.464 --> 00:47:10.170 Connor actually but I don't,

NOTE Confidence: 0.3960918375

 $00{:}47{:}10.170 \dashrightarrow 00{:}47{:}12.060$  I don't even think Connor we haven't

NOTE Confidence: 0.3960918375

 $00{:}47{:}12.060 \dashrightarrow 00{:}47{:}13.730$  stained bracket 2 deficient cells.

NOTE Confidence: 0.3960918375

 $00:47:13.730 \longrightarrow 00:47:15.464$  So I don't think we've explicitly

NOTE Confidence: 0.3960918375

 $00:47:15.464 \rightarrow 00:47:17.462$  done that just cause we've we've been NOTE Confidence: 0.3960918375

00:47:17.462 --> 00:47:19.510 focused more on BRCA one in our lab.

NOTE Confidence: 0.3960918375

00:47:19.510 --> 00:47:21.708 But I would be highly surprised if

 $00:47:21.708 \longrightarrow 00:47:23.823$  it wasn't the same in a probably

NOTE Confidence: 0.3960918375

 $00{:}47{:}23.823 \dashrightarrow 00{:}47{:}25.870$ 2 or a BRCA 2 deficient line.

NOTE Confidence: 0.3960918375

 $00{:}47{:}25{.}870 \dashrightarrow 00{:}47{:}28{.}190$  And and just to make the point you

NOTE Confidence: 0.3960918375

 $00{:}47{:}28.190 \dashrightarrow 00{:}47{:}30.404$  know others have also seen similar

NOTE Confidence: 0.3960918375

00:47:30.404 --> 00:47:32.750 downstream effects for example of Taxol

NOTE Confidence: 0.3960918375

 $00{:}47{:}32.820$  -->  $00{:}47{:}35.046$  treatment and actually have shown that NOTE Confidence: 0.3960918375

 $00:47:35.046 \rightarrow 00:47:37.390$  you know tumor cells that respond

NOTE Confidence: 0.3960918375

 $00:47:37.390 \longrightarrow 00:47:40.110$  to Taxol have intact C gas stings

NOTE Confidence: 0.3960918375

 $00{:}47{:}40.110$  -->  $00{:}47{:}42.350$  signaling and those that don't do not.

NOTE Confidence: 0.3960918375

 $00{:}47{:}42.350 \dashrightarrow 00{:}47{:}44.780$  So that I think that if this is not going

NOTE Confidence: 0.3960918375

 $00{:}47{:}44.842 \dashrightarrow 00{:}47{:}47.286$  to be even limited just to HR deficiency,

NOTE Confidence: 0.3960918375

 $00:47:47.286 \longrightarrow 00:47:50.135$  it's just one of the ways that honestly

NOTE Confidence: 0.3960918375

 $00{:}47{:}50{.}135 \dashrightarrow 00{:}47{:}52{.}685$  TAXOL HR deficiencies of HARP inhibitors

NOTE Confidence: 0.3960918375

 $00{:}47{:}52.685 \dashrightarrow 00{:}47{:}55.680$  and and even a radiation probably could

NOTE Confidence: 0.3960918375

 $00{:}47{:}55{.}680 \dashrightarrow 00{:}47{:}58{.}350$  all be stimulating the same pathway.

NOTE Confidence: 0.3960918375

 $00:47:58.350 \longrightarrow 00:48:00.694$  Yeah, as a fault.

 $00:48:00.694 \longrightarrow 00:48:03.141$  So I mean if if you're having an

NOTE Confidence: 0.3960918375

 $00:48:03.141 \longrightarrow 00:48:04.955$  inhibition of the main signaling,

NOTE Confidence: 0.3960918375

 $00{:}48{:}04{.}955 \dashrightarrow 00{:}48{:}07{.}385$  would these cancers be potentially more

NOTE Confidence: 0.3960918375

 $00:48:07.385 \rightarrow 00:48:09.350$  sensitive to alcoholic viruses or kind

NOTE Confidence: 0.3960918375

 $00:48:09.350 \rightarrow 00:48:11.593$  of a you know alternative fall strategy?

NOTE Confidence: 0.3960918375

 $00{:}48{:}11.593 \dashrightarrow 00{:}48{:}14.239$  I think that's a great question.

NOTE Confidence: 0.3960918375

 $00{:}48{:}14{.}240 \dashrightarrow 00{:}48{:}15{.}829$  And I think that as you can

NOTE Confidence: 0.3960918375

 $00:48:15.829 \longrightarrow 00:48:16.840$  see what we've done,

NOTE Confidence: 0.3960918375

 $00:48:16.840 \longrightarrow 00:48:19.376$  we've completely ignored right,

NOTE Confidence: 0.3960918375

 $00:48:19.376 \longrightarrow 00:48:22.896$  any of that, any of that crosstalk.

NOTE Confidence: 0.3960918375

00:48:22.896 --> 00:48:25.892 And I and I think it's if you look

NOTE Confidence: 0.3960918375

 $00{:}48{:}25{.}892 \dashrightarrow 00{:}48{:}27{.}676$  in the literature it's been kind of

NOTE Confidence: 0.3960918375

00:48:27.676 --> 00:48:29.041 challenging and people who've tried

NOTE Confidence: 0.3960918375

00:48:29.041 --> 00:48:31.036 to use this even even not even to

NOTE Confidence: 0.3960918375

 $00:48:31.036 \rightarrow 00:48:32.616$  the depth of what you just asked.

00:48:32.616 --> 00:48:34.984 But if you look at you know is

NOTE Confidence: 0.3960918375

00:48:34.984 --> 00:48:37.033 sting actually is sting signaling

NOTE Confidence: 0.3960918375

 $00{:}48{:}37{.}033 \dashrightarrow 00{:}48{:}39{.}553$  actually a tumor suppressive or a

NOTE Confidence: 0.3960918375

00:48:39.626 --> 00:48:41.703 tumor driving mechanism, right,

NOTE Confidence: 0.3960918375

 $00{:}48{:}41.703 \dashrightarrow 00{:}48{:}43.818$  Because inflammation driven by sting

NOTE Confidence: 0.3960918375

 $00:48:43.818 \rightarrow 00:48:46.517$  has also been suggested to be a driver,

NOTE Confidence: 0.3960918375

00:48:46.520 --> 00:48:46.793 right.

NOTE Confidence: 0.3960918375

 $00:48:46.793 \rightarrow 00:48:49.680$  Is, is actually a tumor driver C gas I think.

NOTE Confidence: 0.3960918375

 $00{:}48{:}49{.}680 \dashrightarrow 00{:}48{:}52{.}980$  And actually if you look at the number

NOTE Confidence: 0.3960918375

 $00{:}48{:}52{.}980 \dashrightarrow 00{:}48{:}54{.}880$  of tumors that have inactivated

NOTE Confidence: 0.3960918375

 $00{:}48{:}54{.}880 \dashrightarrow 00{:}48{:}56{.}400$  C gas versus sting,

NOTE Confidence: 0.3960918375

 $00:48:56.400 \rightarrow 00:48:57.992$  very few inactivate sting,

NOTE Confidence: 0.3960918375

 $00:48:57.992 \rightarrow 00:49:00.740$  the vast majority have inactivated C gas

NOTE Confidence: 0.3960918375

 $00:49:00.740 \rightarrow 00:49:03.359$  if you just look across you know that map.

NOTE Confidence: 0.3960918375

 $00{:}49{:}03{.}360 \dashrightarrow 00{:}49{:}05{.}889$  And so I do wonder if some of the

NOTE Confidence: 0.3960918375

 $00:49:05.889 \rightarrow 00:49:08.337$  signaling we're seeing is C gas dependent,

- NOTE Confidence: 0.3960918375
- $00:49:08.340 \longrightarrow 00:49:09.765$  but maybe not strictly through
- NOTE Confidence: 0.3960918375
- 00:49:09.765 --> 00:49:11.586 sting or sting is more complicated
- NOTE Confidence: 0.3960918375
- $00{:}49{:}11.586 \dashrightarrow 00{:}49{:}13.590$  because it's multiple roles and I
- NOTE Confidence: 0.3960918375
- $00:49:13.590 \longrightarrow 00:49:15.477$  think that might be important to
- NOTE Confidence: 0.3960918375
- $00{:}49{:}15{.}477 \dashrightarrow 00{:}49{:}16{.}857$  tease out to think about.
- NOTE Confidence: 0.3960918375
- $00:49:16.860 \rightarrow 00:49:19.940$  Then how is this going to intersect
- NOTE Confidence: 0.3960918375
- $00:49:19.940 \longrightarrow 00:49:22.460$  with approaches like oncolytic viruses.
- NOTE Confidence: 0.3960918375
- $00:49:22.460 \longrightarrow 00:49:24.628$  So I think that's still one of the
- NOTE Confidence: 0.3960918375
- $00{:}49{:}24.628 \dashrightarrow 00{:}49{:}26.365$  confusions at the moment because
- NOTE Confidence: 0.3960918375
- $00{:}49{:}26{.}365 \dashrightarrow 00{:}49{:}28{.}633$  honestly there's very high profile papers
- NOTE Confidence: 0.3960918375
- $00{:}49{:}28.633 \dashrightarrow 00{:}49{:}30.634$  saying you know sting agonists would be
- NOTE Confidence: 0.3960918375
- $00{:}49{:}30{.}634 \dashrightarrow 00{:}49{:}32{.}379$  great and sting agonists are terrible.
- NOTE Confidence: 0.3960918375
- $00:49:32.380 \longrightarrow 00:49:33.490$  And so that's probably going
- NOTE Confidence: 0.3960918375
- $00{:}49{:}33{.}490 \dashrightarrow 00{:}49{:}34{.}378$  to be context dependent.
- NOTE Confidence: 0.46254796
- 00:49:38.660 --> 00:49:38.900 Oh
- NOTE Confidence: 0.46254796

- $00:49:41.580 \longrightarrow 00:49:42.300$  go go ahead I'll,
- NOTE Confidence: 0.46254796
- $00:49:42.300 \longrightarrow 00:49:43.780$  I'll get the Mario and I'll get this.
- NOTE Confidence: 0.46254796
- 00:49:43.780 --> 00:49:48.195 In the meantime are are there about
- NOTE Confidence: 0.46254796
- $00{:}49{:}48.195 \dashrightarrow 00{:}49{:}50.732$  cell lines that are HID deficient
- NOTE Confidence: 0.46254796
- $00{:}49{:}50{.}732 \dashrightarrow 00{:}49{:}54{.}110$  where you could look at a lab rib
- NOTE Confidence: 0.46254796
- $00:49:54.110 \longrightarrow 00:49:56.450$  in one of these cell lines and
- NOTE Confidence: 0.46254796
- $00{:}49{:}56{.}450 \dashrightarrow 00{:}50{:}01{.}665$  compromisers whether there's a role for
- NOTE Confidence: 0.46254796
- $00{:}50{:}01{.}665 \dashrightarrow 00{:}50{:}04{.}590$  the sting activation in the anti
- NOTE Confidence: 0.46254796
- 00:50:04.590 --> 00:50:06.290 tumor activity of bilateral because
- NOTE Confidence: 0.46254796
- $00{:}50{:}06{.}290 \dashrightarrow 00{:}50{:}08{.}723$  that that would be an easy way to
- NOTE Confidence: 0.46254796
- $00{:}50{:}08{.}723 \dashrightarrow 00{:}50{:}11.010$  determine if if the immune activation,
- NOTE Confidence: 0.46254796
- $00:50:11.010 \longrightarrow 00:50:13.538$  activation is is important
- NOTE Confidence: 0.46254796
- $00:50:13.538 \rightarrow 00:50:15.090$  or not really agree with you.
- NOTE Confidence: 0.46254796
- $00{:}50{:}15{.}090 \dashrightarrow 00{:}50{:}16{.}609$  So I think that that is an
- NOTE Confidence: 0.46254796
- $00{:}50{:}16.609 \dashrightarrow 00{:}50{:}17.043$  excellent experiment.
- NOTE Confidence: 0.46254796
- $00:50:17.050 \longrightarrow 00:50:17.956$  It is an experiment that needs

- NOTE Confidence: 0.46254796
- $00:50:17.956 \longrightarrow 00:50:19.130$  to be done and it you're right,

00:50:19.130 --> 00:50:22.268 it's it's obvious and it's achievable.

NOTE Confidence: 0.46254796

 $00{:}50{:}22{.}270 \dashrightarrow 00{:}50{:}23{.}656$  It hasn't been what our expertise

NOTE Confidence: 0.46254796

 $00:50:23.656 \rightarrow 00:50:25.430$  has been in, but I agree with you

NOTE Confidence: 0.46254796

 $00:50:25.430 \longrightarrow 00:50:26.510$  that that's exactly the right.

NOTE Confidence: 0.46254796

 $00:50:26.510 \longrightarrow 00:50:27.968$  So we really need some genetic

NOTE Confidence: 0.46254796

 $00:50:27.968 \longrightarrow 00:50:29.150$  models to be able to,

NOTE Confidence: 0.46254796

 $00:50:29.150 \longrightarrow 00:50:30.430$  to, to do that.

NOTE Confidence: 0.46254796

 $00{:}50{:}30{.}430 \dashrightarrow 00{:}50{:}33{.}082$  So I I completely agree Jeff has

NOTE Confidence: 0.46254796

 $00:50:33.082 \rightarrow 00:50:35.186$  asked wholexome sequencing is

NOTE Confidence: 0.46254796

00:50:35.186 --> 00:50:37.950 not as commonly performed as H&E,

NOTE Confidence: 0.46254796

00:50:37.950 --> 00:50:39.774 but he's curious which degree of

NOTE Confidence: 0.46254796

 $00{:}50{:}39{.}774 \dashrightarrow 00{:}50{:}40{.}990$  mutational signature derived from

NOTE Confidence: 0.46254796

 $00{:}50{:}41.042 \dashrightarrow 00{:}50{:}42.534$  whole xome sequencing indicates the

NOTE Confidence: 0.46254796

 $00:50:42.534 \rightarrow 00:50:43.653$  effective homologous recombination

 $00:50:43.653 \rightarrow 00:50:45.747$  or is being used as a biomarker.

NOTE Confidence: 0.46254796

00:50:45.750 --> 00:50:46.990 So to Jeff's point, yes,

NOTE Confidence: 0.46254796

 $00:50:46.990 \rightarrow 00:50:49.167$  this is the only biomarker there is,

NOTE Confidence: 0.46254796

 $00:50:49.170 \rightarrow 00:50:52.124$  is a kind of scoring genomic scarring.

NOTE Confidence: 0.46254796

 $00{:}50{:}52{.}130 \dashrightarrow 00{:}50{:}54{.}125$  But the challenge I would say is,

NOTE Confidence: 0.46254796

 $00:50:54.130 \rightarrow 00:50:55.649$  and I think Jeff will appreciate this,

NOTE Confidence: 0.46254796

 $00:50:55.650 \rightarrow 00:50:58.683$  is that the cell may be HR defective now,

NOTE Confidence: 0.46254796

 $00{:}50{:}58{.}690 \dashrightarrow 00{:}51{:}00{.}804$  but then it may become a resistant

NOTE Confidence: 0.46254796

 $00{:}51{:}00{.}804 \dashrightarrow 00{:}51{:}02{.}376$  to PARP inhibitors because it's

NOTE Confidence: 0.46254796

 $00{:}51{:}02{.}376 \dashrightarrow 00{:}51{:}04{.}490$  now HR proficient and it will still

NOTE Confidence: 0.46254796

 $00{:}51{:}04{.}490 \dashrightarrow 00{:}51{:}06{.}249$  have the scarring left from the

NOTE Confidence: 0.46254796

 $00:51:06.249 \rightarrow 00:51:07.992$  period where it was HR deficient.

NOTE Confidence: 0.46254796

 $00{:}51{:}07{.}992 \dashrightarrow 00{:}51{:}10{.}386$  So that may help us to understand

NOTE Confidence: 0.46254796

 $00:51:10.386 \longrightarrow 00:51:11.660$  you know context.

NOTE Confidence: 0.46254796

 $00:51:11.660 \rightarrow 00:51:13.179$  We don't have any reason to think

NOTE Confidence: 0.46254796

 $00:51:13.179 \longrightarrow 00:51:14.896$  someone has a germ on or somatic

- NOTE Confidence: 0.46254796
- $00{:}51{:}14.896 \dashrightarrow 00{:}51{:}16.420$  mutation that they could be nefit for
- NOTE Confidence: 0.46254796
- $00:51:16.469 \dashrightarrow 00:51:18.177$  a PARP inhibitor because we see that.
- NOTE Confidence: 0.46254796
- 00:51:18.180 --> 00:51:20.504 But I'm not sure we're looking for
- NOTE Confidence: 0.46254796
- $00{:}51{:}20{.}504 \dashrightarrow 00{:}51{:}22{.}522$  that signature when there's no reason
- NOTE Confidence: 0.46254796
- $00:51:22.522 \rightarrow 00:51:24.574$  to be from the genomics already.
- NOTE Confidence: 0.46254796
- $00:51:24.580 \longrightarrow 00:51:25.658$  So I don't think we're doing that.
- NOTE Confidence: 0.46254796
- $00:51:25.660 \rightarrow 00:51:27.298$  So we're not identifying those patients.
- NOTE Confidence: 0.46254796
- $00:51:27.300 \longrightarrow 00:51:29.220$  So that's an access issue.
- NOTE Confidence: 0.46254796
- $00{:}51{:}29{.}220 \dashrightarrow 00{:}51{:}31{.}194$  We absolutely are using that when
- NOTE Confidence: 0.46254796
- $00:51:31.194 \longrightarrow 00:51:33.140$  there's a reason to think that
- NOTE Confidence: 0.46254796
- $00{:}51{:}33{.}140 \dashrightarrow 00{:}51{:}34{.}820$  there is A and HR defect,
- NOTE Confidence: 0.46254796
- $00{:}51{:}34{.}820 \dashrightarrow 00{:}51{:}36{.}230$  but it can't tell us.
- NOTE Confidence: 0.46254796
- $00:51:36.230 \longrightarrow 00:51:37.430$  It only tells us the history,
- NOTE Confidence: 0.46254796
- $00{:}51{:}37{.}430 \dashrightarrow 00{:}51{:}38{.}650$  it doesn't tell us presently
- NOTE Confidence: 0.46254796
- $00{:}51{:}38.650 \dashrightarrow 00{:}51{:}39.870$  what's happening in the tumor.
- NOTE Confidence: 0.46254796

 $00{:}51{:}39{.}870 \dashrightarrow 00{:}51{:}41{.}186$  And so I think that's the limitation.

NOTE Confidence: 0.3711792

 $00:51:43.430 \longrightarrow 00:51:44.190$  Thanks for your question.

NOTE Confidence: 0.3711792

 $00{:}51{:}47{.}150 \dashrightarrow 00{:}51{:}48{.}844$  With the bridges, are those all contained NOTE Confidence: 0.3711792

 $00:51:48.844 \rightarrow 00:51:50.443$  in cytoplasm or do those potentially

NOTE Confidence: 0.3711792

 $00{:}51{:}50{.}443 \dashrightarrow 00{:}51{:}52{.}099$  contend kind of extra targets for

NOTE Confidence: 0.3711792

 $00{:}51{:}52{.}099 \dashrightarrow 00{:}51{:}53{.}525$  antibodies and cars or something like NOTE Confidence: 0.3711792

 $00{:}51{:}53{.}525 \dashrightarrow 00{:}51{:}55{.}716$  that that would be unique to I think

NOTE Confidence: 0.3711792

 $00:51:55.716 \rightarrow 00:51:57.888$  it's a great question whether you

NOTE Confidence: 0.3711792

00:51:57.888 --> 00:52:00.478 ever I I think that there's I don't

NOTE Confidence: 0.3711792

 $00{:}52{:}00{.}478 \dashrightarrow 00{:}52{:}02{.}326$  think we ever see that the plasma

NOTE Confidence: 0.3711792

00:52:02.326 --> 00:52:03.870 membrane right actually ruptures

NOTE Confidence: 0.8885353

 $00{:}52{:}06{.}080 \dashrightarrow 00{:}52{:}10{.}120$  although you know escorts also repair holes, NOTE Confidence: 0.8885353

 $00:52:10.120 \rightarrow 00:52:12.040$  temporary holes in the plasma membrane.

NOTE Confidence: 0.8885353

 $00{:}52{:}12.040 \dashrightarrow 00{:}52{:}14.144$  So I won't say that we've actually tested

NOTE Confidence: 0.8885353

 $00{:}52{:}14.144 \dashrightarrow 00{:}52{:}16.235$  that and that would be really interesting

NOTE Confidence: 0.8885353

 $00{:}52{:}16.235 \dashrightarrow 00{:}52{:}18.196$  to know whether that's the case.

 $00:52:18.196 \rightarrow 00:52:20.642$  I mean it's interesting that these same

NOTE Confidence: 0.8885353

 $00:52:20.642 \rightarrow 00:52:23.177$  factors actually man one in particular were

NOTE Confidence: 0.8885353

 $00:52:23.177 \rightarrow 00:52:25.679$  all identified as being auto antibody.

NOTE Confidence: 0.8885353

 $00:52:25.680 \rightarrow 00:52:28.095$  They are all tied to auto antibody

NOTE Confidence: 0.8885353

00:52:28.095 --> 00:52:29.903 to autoimmune diseases as common

NOTE Confidence: 0.8885353

 $00{:}52{:}29{.}903 \dashrightarrow 00{:}52{:}32{.}033$  targets of many nuclear proteins are.

NOTE Confidence: 0.8885353

 $00{:}52{:}32{.}040 \dashrightarrow 00{:}52{:}34{.}070$  But I do think that that's interesting

NOTE Confidence: 0.8885353

 $00{:}52{:}34.070 \dashrightarrow 00{:}52{:}37.083$  and there's some evidence that that

NOTE Confidence: 0.8885353

 $00:52:37.083 \longrightarrow 00:52:38.781$  the Lam 2 protein also probably

NOTE Confidence: 0.8885353

 $00:52:38.781 \rightarrow 00:52:40.639$  in the absence of functional M2,

NOTE Confidence: 0.8885353

00:52:40.640 --> 00:52:43.920 you do have kind of a prevalence of

NOTE Confidence: 0.8885353

 $00:52:43.920 \rightarrow 00:52:46.182$  autoimmunity which would be consistent

NOTE Confidence: 0.8885353

 $00{:}52{:}46{.}182 \dashrightarrow 00{:}52{:}48{.}271$  with not being able to do this normal

NOTE Confidence: 0.8885353

00:52:48.271 --> 00:52:50.080 cycle of Nuvo Con number reformation

NOTE Confidence: 0.8885353

 $00:52:50.080 \rightarrow 00:52:51.830$  does get surveilled through this

 $00{:}52{:}51{.}830 \dashrightarrow 00{:}52{:}53{.}758$  mechanism and and can be deleterious.

NOTE Confidence: 0.8885353

00:52:53.760 --> 00:52:55.356 So I think it's but yeah,

NOTE Confidence: 0.8885353

 $00:52:55.360 \longrightarrow 00:52:57.208$  we we don't really what we see is

NOTE Confidence: 0.8885353

 $00:52:57.208 \rightarrow 00:52:58.946$  that you know likely eventually most

NOTE Confidence: 0.8885353

 $00{:}52{:}58{.}946$  -->  $00{:}53{:}01{.}312$  of those cells will give up and I

NOTE Confidence: 0.8885353

 $00:53:01.312 \rightarrow 00:53:03.209$  think it's just a just a highlight.

NOTE Confidence: 0.8885353

 $00{:}53{:}03{.}210 \dashrightarrow 00{:}53{:}05{.}847$  This is why one has to be careful in

NOTE Confidence: 0.8885353

 $00{:}53{:}05{.}847 \dashrightarrow 00{:}53{:}08{.}101$  assessing in this area particularly facts,

NOTE Confidence: 0.8885353

 $00{:}53{:}08{.}101 \dashrightarrow 00{:}53{:}09{.}847$  profiles looking at cells that look

NOTE Confidence: 0.8885353

 $00{:}53{:}09{.}847 \dashrightarrow 00{:}53{:}11{.}543$  like they're G2M cells because you NOTE Confidence: 0.8885353

00:53:11.543 --> 00:53:13.335 get these cells that are G2M cells

NOTE Confidence: 0.8885353

00:53:13.394 --> 00:53:15.361 but they're actually in G1 and that's

NOTE Confidence: 0.8885353

 $00{:}53{:}15{.}361 \dashrightarrow 00{:}53{:}16{.}994$  because they failed in cytokinesis.

NOTE Confidence: 0.8885353

 $00:53:16.994 \longrightarrow 00:53:19.738$  So now they're 4 N but they're

NOTE Confidence: 0.8885353

 $00:53:19.738 \longrightarrow 00:53:21.490$  actually no longer mitotic.

NOTE Confidence: 0.8885353

 $00:53:21.490 \longrightarrow 00:53:23.002$  And so that's one of the

NOTE Confidence: 0.8885353 00:53:23.002 --> 00:53:24.370 things that we see here. NOTE Confidence: 0.8885353 00:53:24.370 --> 00:53:25.768 So it'll show up in experiments NOTE Confidence: 0.8047927 00:53:33.110 --> 00:53:35.000 all right.