

WEBVTT

NOTE duration:"00:53:35"

NOTE recognizability:0.597

NOTE language:en-us

NOTE Confidence: 0.75512505

00:00:00.000 --> 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 --> 00:00:06.396 I'm Chief of Breast surgery and newly named

NOTE Confidence: 0.75512505

00:00:06.396 --> 00:00:08.916 Co director of the SMILO Breast Program.

NOTE Confidence: 0.75512505

00:00:08.920 --> 00:00:11.800 And I have the honor today of introducing Dr.

NOTE Confidence: 0.75512505

00:00:11.800 --> 00:00:15.620 Megan King. Doctor King is an associate

NOTE Confidence: 0.75512505

00:00:15.620 --> 00:00:18.160 professor of cell biology and of molecular,

NOTE Confidence: 0.75512505

00:00:18.160 --> 00:00:19.820 cellular and development biology.

NOTE Confidence: 0.75512505

00:00:19.820 --> 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 --> 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 --> 00:00:33.276 She did undergrad at Brandeis and

NOTE Confidence: 0.75512505

00:00:33.276 --> 00:00:36.614 then went on to receive her PhD in  
NOTE Confidence: 0.75512505

00:00:36.614 --> 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 --> 00:00:43.327 under the mentorship of Doctor Mark  
NOTE Confidence: 0.75512505

00:00:43.327 --> 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 --> 00:00:54.572 the targeting and function of integral  
NOTE Confidence: 0.75512505

00:00:54.572 --> 00:00:56.620 inter nuclear membrane proteins.  
NOTE Confidence: 0.75512505

00:00:56.620 --> 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 --> 00:01:05.846 that are integrated at the nuclear  
NOTE Confidence: 0.75512505

00:01:05.846 --> 00:01:08.412 envelope from impacts on DNA repaired  
NOTE Confidence: 0.75512505

00:01:08.412 --> 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 --> 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 --> 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 --> 00:01:32.692 Thank you so much.

NOTE Confidence: 0.9675821

00:01:32.692 --> 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 --> 00:01:38.140 hearing that bio,

NOTE Confidence: 0.9675821

00:01:38.140 --> 00:01:40.396 it always reminds me of how far I've

NOTE Confidence: 0.9675821

00:01:40.396 --> 00:01:42.878 come to what I'm going to be talking

NOTE Confidence: 0.9675821

00:01:42.878 --> 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 --> 00:01:49.092 at Yale and the interactions that

NOTE Confidence: 0.9675821

00:01:49.092 --> 00:01:50.982 really have been driven initially  
NOTE Confidence: 0.9675821

00:01:50.982 --> 00:01:53.323 by joining what was on the Radio  
NOTE Confidence: 0.9675821

00:01:53.323 --> 00:01:55.627 biology and genome and radio biology  
NOTE Confidence: 0.9675821

00:01:55.627 --> 00:01:57.575 and radiotherapy 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 --> 00:02:00.976 who's no longer here.  
NOTE Confidence: 0.9675821

00:02:00.976 --> 00:02:02.770 But he kind of immediately roped  
NOTE Confidence: 0.9675821

00:02:02.829 --> 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 --> 00:02:08.816 that particularly with Joanne,  
NOTE Confidence: 0.9675821

00:02:08.816 --> 00:02:10.748 Sweezy and Pat Larusso and really  
NOTE Confidence: 0.9675821

00:02:10.748 --> 00:02:12.414 it's that transition that is  
NOTE Confidence: 0.9675821

00:02:12.414 --> 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 --> 00:02:17.673 And so I'm really appreciative of  
NOTE Confidence: 0.9675821

00:02:17.673 --> 00:02:19.731 that because I think it's really

NOTE Confidence: 0.9675821

00:02:19.731 --> 00:02:22.419 going to broaden the the scope of

NOTE Confidence: 0.9675821

00:02:22.419 --> 00:02:24.003 where this fundamental biology,

NOTE Confidence: 0.9675821

00:02:24.010 --> 00:02:26.284 which hopefully you'll see today about

NOTE Confidence: 0.9675821

00:02:26.284 --> 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 --> 00:02:31.294 a chemotherapy approach that's being

NOTE Confidence: 0.9675821

00:02:31.294 --> 00:02:33.200 broadly used in which we're hoping

NOTE Confidence: 0.9675821

00:02:33.200 --> 00:02:35.020 could be used and even more context.

NOTE Confidence: 0.9675821

00:02:35.020 --> 00:02:36.460 And so that's what I'm going

NOTE Confidence: 0.9675821

00:02:36.516 --> 00:02:37.460 to talk about today.

NOTE Confidence: 0.9675821

00:02:37.460 --> 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 --> 00:02:40.978 and innate immune signaling,

NOTE Confidence: 0.9675821

00:02:40.980 --> 00:02:43.260 which is also not our expertise.

NOTE Confidence: 0.9675821

00:02:43.260 --> 00:02:46.236 And so I really appreciate anyone

NOTE Confidence: 0.9675821

00:02:46.236 --> 00:02:48.559 here online now later thoughts  
NOTE Confidence: 0.9675821

00:02:48.559 --> 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 --> 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 --> 00:02:56.940 So just my disclosure,  
NOTE Confidence: 0.9675821

00:02:56.940 --> 00:02:59.156 some of this work is funded through the  
NOTE Confidence: 0.9675821

00:02:59.156 --> 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 --> 00:03:09.107 with PARP inhibitors are really the  
NOTE Confidence: 0.539626

00:03:09.110 --> 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

00:03:14.746 --> 00:03:17.381 it really highlights how we might use  
NOTE Confidence: 0.539626

00:03:17.381 --> 00:03:19.131 approaches that are really specific  
NOTE Confidence: 0.539626

00:03:19.131 --> 00:03:21.613 to tumor cells and otherwise do not  
NOTE Confidence: 0.539626

00:03:21.613 --> 00:03:23.854 affect all the normal cells of the body.

NOTE Confidence: 0.539626

00:03:23.854 --> 00:03:25.904 And and what is you know, fabulous approach,

NOTE Confidence: 0.539626

00:03:25.904 --> 00:03:27.789 right that that would be.

NOTE Confidence: 0.539626

00:03:27.790 --> 00:03:31.254 And so the idea is that PARP inhibitors

NOTE Confidence: 0.539626

00:03:31.260 --> 00:03:33.035 in particular cause single stranded

NOTE Confidence: 0.539626

00:03:33.035 --> 00:03:35.481 DNA damage to persist or at least

NOTE Confidence: 0.539626

00:03:35.481 --> 00:03:37.595 that's one of the mechanisms that we

NOTE Confidence: 0.539626

00:03:37.595 --> 00:03:39.736 think about as being important here.

NOTE Confidence: 0.539626

00:03:39.740 --> 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 --> 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 --> 00:03:51.161 in SNG 2 and repair these breaks.

NOTE Confidence: 0.539626

00:03:51.161 --> 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

NOTE Confidence: 0.539626

00:03:55.845 --> 00:03:57.377 defects and homologous recombination

NOTE Confidence: 0.539626

00:03:57.377 --> 00:03:59.754 and kind of the classic example of  
NOTE Confidence: 0.539626

00:03:59.754 --> 00:04:01.553 this are pathogenic mutations in the  
NOTE Confidence: 0.539626

00:04:01.553 --> 00:04:02.885 BRCA one and BRCA 2 genes.  
NOTE Confidence: 0.539626

00:04:02.890 --> 00:04:05.746 There's a defect in tolerating this damage  
NOTE Confidence: 0.539626

00:04:05.746 --> 00:04:08.646 and this will lead to to cell death,  
NOTE Confidence: 0.539626

00:04:08.650 --> 00:04:08.962 right.  
NOTE Confidence: 0.539626

00:04:08.962 --> 00:04:11.146 And so this is the mechanism where  
NOTE Confidence: 0.539626

00:04:11.146 --> 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 --> 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 --> 00:04:26.679 as an example of of our kind of  
NOTE Confidence: 0.539626

00:04:26.679 --> 00:04:28.391 framework for thinking about the story

NOTE Confidence: 0.539626

00:04:28.391 --> 00:04:30.134 that I'm going to tell the debt.

NOTE Confidence: 0.539626

00:04:30.140 --> 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 --> 00:04:37.912 there is the activation of P53 and

NOTE Confidence: 0.539626

00:04:37.912 --> 00:04:40.614 P53 is is really this decision point,

NOTE Confidence: 0.539626

00:04:40.620 --> 00:04:44.330 It's both activating mechanisms to

NOTE Confidence: 0.539626

00:04:44.330 --> 00:04:45.662 repair that damage, right.

NOTE Confidence: 0.539626

00:04:45.662 --> 00:04:48.337 So that the first response of the cell

NOTE Confidence: 0.539626

00:04:48.337 --> 00:04:50.769 is try to tolerate and repair this damage,

NOTE Confidence: 0.539626

00:04:50.770 --> 00:04:52.314 stall the cell cycle,

NOTE Confidence: 0.539626

00:04:52.314 --> 00:04:55.584 fix the genome and then go into mitosis

NOTE Confidence: 0.539626

00:04:55.584 --> 00:04:58.643 and and and have normal cell growth.

NOTE Confidence: 0.539626

00:04:58.650 --> 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 --> 00:05:04.250 if it can't be tolerated,

NOTE Confidence: 0.539626

00:05:04.250 --> 00:05:06.168 then this is going to lead to  
NOTE Confidence: 0.539626

00:05:06.170 --> 00:05:07.674 the stimulation of apoptosis.  
NOTE Confidence: 0.539626

00:05:07.674 --> 00:05:09.930 And so really this is this  
NOTE Confidence: 0.539626

00:05:09.999 --> 00:05:12.652 combination of repair and then when  
NOTE Confidence: 0.539626

00:05:12.652 --> 00:05:15.220 we can't repair driving cell death,  
NOTE Confidence: 0.539626

00:05:15.220 --> 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 --> 00:05:18.300 we know that this is a mechanism  
NOTE Confidence: 0.539626

00:05:18.367 --> 00:05:20.581 that is dysregulated in the vast  
NOTE Confidence: 0.539626

00:05:20.581 --> 00:05:22.503 majority of tumors including those  
NOTE Confidence: 0.539626

00:05:22.503 --> 00:05:24.418 that respond to PARP inhibitors.  
NOTE Confidence: 0.539626

00:05:24.420 --> 00:05:26.697 And so this is not the mechanism, right.  
NOTE Confidence: 0.539626

00:05:26.697 --> 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 --> 00:05:32.590 with HR defects even in the  
NOTE Confidence: 0.539626

00:05:32.590 --> 00:05:34.201 context of dysregulated P53.

NOTE Confidence: 0.539626

00:05:34.201 --> 00:05:35.706 So what is this mechanism

NOTE Confidence: 0.539626

00:05:35.706 --> 00:05:37.731 actually and you might think that

NOTE Confidence: 0.539626

00:05:37.731 --> 00:05:39.247 we understand this mechanism,

NOTE Confidence: 0.539626

00:05:39.250 --> 00:05:41.106 but what I'm going to tell you about

NOTE Confidence: 0.539626

00:05:41.106 --> 00:05:43.150 today is that we we don't and I'm

NOTE Confidence: 0.539626

00:05:43.150 --> 00:05:45.250 going to focus today disclaimer on

NOTE Confidence: 0.539626

00:05:45.250 --> 00:05:47.768 the tumor cell intrinsic mechanisms.

NOTE Confidence: 0.539626

00:05:47.770 --> 00:05:49.554 That is not to negate the fact that

NOTE Confidence: 0.539626

00:05:49.554 --> 00:05:51.673 there are other roles for the immune

NOTE Confidence: 0.539626

00:05:51.673 --> 00:05:53.288 system for the tumor microenvironment.

NOTE Confidence: 0.539626

00:05:53.290 --> 00:05:55.282 But what we know is that in in

NOTE Confidence: 0.539626

00:05:55.282 --> 00:05:57.405 HR deficient cells in a dish PARP

NOTE Confidence: 0.539626

00:05:57.405 --> 00:05:58.970 inhibitors can cause cell deaths.

NOTE Confidence: 0.531500307142857

00:05:58.970 --> 00:06:01.786 So we know that there is at least

NOTE Confidence: 0.531500307142857

00:06:01.786 --> 00:06:04.074 a sufficiency in in cells and

NOTE Confidence: 0.531500307142857

00:06:04.074 --> 00:06:06.324 culture for a tumor cell intrinsic  
NOTE Confidence: 0.531500307142857

00:06:06.404 --> 00:06:09.438 mechanism of cell death and IT and  
NOTE Confidence: 0.531500307142857

00:06:09.440 --> 00:06:11.896 and how do we think about what kind  
NOTE Confidence: 0.531500307142857

00:06:11.896 --> 00:06:13.548 of surveillance mechanisms might be  
NOTE Confidence: 0.531500307142857

00:06:13.548 --> 00:06:17.080 akin to P53 that that drive this.  
NOTE Confidence: 0.531500307142857

00:06:17.080 --> 00:06:18.856 So I just want to highlight a few  
NOTE Confidence: 0.531500307142857

00:06:18.856 --> 00:06:20.838 of the challenges that we face in  
NOTE Confidence: 0.531500307142857

00:06:20.838 --> 00:06:22.664 the use of HARP inhibitors because  
NOTE Confidence: 0.531500307142857

00:06:22.664 --> 00:06:24.434 really this is our motivation for  
NOTE Confidence: 0.531500307142857

00:06:24.434 --> 00:06:26.100 the kind of fundamental studies  
NOTE Confidence: 0.531500307142857

00:06:26.100 --> 00:06:28.440 that I'm going to talk about.  
NOTE Confidence: 0.531500307142857

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  
NOTE Confidence: 0.531500307142857

00:06:31.536 --> 00:06:32.958 kill HR deficient cells,  
NOTE Confidence: 0.531500307142857

00:06:32.960 --> 00:06:33.860 but we don't understand  
NOTE Confidence: 0.531500307142857

00:06:33.860 --> 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 --> 00:06:43.062 explored in preclinical models  
NOTE Confidence: 0.531500307142857  
00:06:43.062 --> 00:06:45.439 through things like CRISPR screens.  
NOTE Confidence: 0.531500307142857  
00:06:45.440 --> 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 --> 00:06:51.499 rather limited and understanding  
NOTE Confidence: 0.531500307142857  
00:06:51.499 --> 00:06:54.194 the cell death mechanism that  
NOTE Confidence: 0.531500307142857  
00:06:54.194 --> 00:06:56.350 PARP inhibitors precipitate could  
NOTE Confidence: 0.531500307142857  
00:06:56.420 --> 00:06:58.376 really help in in this area.  
NOTE Confidence: 0.531500307142857  
00:06:58.380 --> 00:07:01.609 A major challenge is that we lack a  
NOTE Confidence: 0.531500307142857  
00:07:01.609 --> 00:07:04.052 robust biomarker that can tell us that  
NOTE Confidence: 0.531500307142857  
00:07:04.052 --> 00:07:06.496 PARP inhibitors are likely to be effective.  
NOTE Confidence: 0.531500307142857  
00:07:06.500 --> 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 --> 00:07:10.412 homologous recombination or there  
NOTE Confidence: 0.531500307142857

00:07:10.412 --> 00:07:13.258 could be other contexts outside of the  
NOTE Confidence: 0.531500307142857

00:07:13.258 --> 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 --> 00:07:22.009 is an HR defect that's actionable.  
NOTE Confidence: 0.531500307142857

00:07:22.010 --> 00:07:23.991 But because we don't have a biomarker  
NOTE Confidence: 0.531500307142857

00:07:23.991 --> 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 --> 00:07:28.450 There are kind of sequencing  
NOTE Confidence: 0.531500307142857

00:07:28.450 --> 00:07:29.170 based approaches,  
NOTE Confidence: 0.531500307142857

00:07:29.170 --> 00:07:31.900 but we don't have a classic kind  
NOTE Confidence: 0.531500307142857

00:07:31.900 --> 00:07:33.070 of pathological straightforward  
NOTE Confidence: 0.531500307142857

00:07:33.134 --> 00:07:34.678 psychology kind of approach  
NOTE Confidence: 0.531500307142857

00:07:34.678 --> 00:07:36.608 and that's a real limitation.

NOTE Confidence: 0.623311

00:07:38.730 --> 00:07:41.180 And and lastly, there's a lot of

NOTE Confidence: 0.623311

00:07:41.180 --> 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 --> 00:07:46.719 blockades and indeed a number of

NOTE Confidence: 0.623311

00:07:46.719 --> 00:07:48.399 trials that are exploring this.

NOTE Confidence: 0.623311

00:07:48.400 --> 00:07:50.680 But we don't actually understand the

NOTE Confidence: 0.623311

00:07:50.680 --> 00:07:52.702 underlying mechanisms of why those

NOTE Confidence: 0.623311

00:07:52.702 --> 00:07:54.478 combinations might be effective.

NOTE Confidence: 0.623311

00:07:54.480 --> 00:07:55.640 And to really understand that,

NOTE Confidence: 0.623311

00:07:55.640 --> 00:07:57.341 we have to understand how how carpenters

NOTE Confidence: 0.623311

00:07:57.341 --> 00:07:59.360 are working and and This is why we're

NOTE Confidence: 0.623311

00:07:59.360 --> 00:08:00.600 really interested in the crosstalk.

NOTE Confidence: 0.623311

00:08:00.600 --> 00:08:02.497 I'll talk about today with the innate

NOTE Confidence: 0.623311

00:08:02.497 --> 00:08:04.198 immune system and how that might be

NOTE Confidence: 0.623311

00:08:04.200 --> 00:08:06.678 contribute to the the rationale for

NOTE Confidence: 0.623311

00:08:06.678 --> 00:08:08.760 these combinations and might point  
NOTE Confidence: 0.623311

00:08:08.760 --> 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 --> 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 --> 00:08:22.150 we've been thinking about this problem.  
NOTE Confidence: 0.623311

00:08:22.150 --> 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 --> 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 --> 00:08:40.909 and it binds to double stranded DNA.  
NOTE Confidence: 0.623311

00:08:40.910 --> 00:08:43.278 And the idea is that it can surveil  
NOTE Confidence: 0.623311

00:08:43.278 --> 00:08:45.520 4 viruses and bacterial pathogens,

NOTE Confidence: 0.623311

00:08:45.520 --> 00:08:47.600 but there's increasing evidence that

NOTE Confidence: 0.623311

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

NOTE Confidence: 0.623311

00:08:50.760 --> 00:08:53.496 self DNA that's present within cells

NOTE Confidence: 0.623311

00:08:53.496 --> 00:08:55.320 within eukaryotic cells themselves.

NOTE Confidence: 0.623311

00:08:55.320 --> 00:08:56.400 So for example,

NOTE Confidence: 0.623311

00:08:56.400 --> 00:08:58.560 a distregated mitochondria can lead to

NOTE Confidence: 0.623311

00:08:58.560 --> 00:09:00.722 leaking of mitochondrial DNA into the

NOTE Confidence: 0.623311

00:09:00.722 --> 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 --> 00:09:07.262 how actually the chromosomes or the

NOTE Confidence: 0.623311

00:09:07.262 --> 00:09:09.621 chromatin or DNA from the nucleus can

NOTE Confidence: 0.623311

00:09:09.621 --> 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 --> 00:09:16.820 Just I'm going to say very clearly,

NOTE Confidence: 0.623311

00:09:16.820 --> 00:09:18.740 when it binds to naked DNA,

NOTE Confidence: 0.623311

00:09:18.740 --> 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 --> 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 --> 00:09:35.819 I'll talk about in more detail in a moment.  
NOTE Confidence: 0.623311

00:09:35.820 --> 00:09:37.338 So just recruiting C gas somewhere  
NOTE Confidence: 0.623311

00:09:37.338 --> 00:09:39.141 does not mean that it's actually  
NOTE Confidence: 0.623311

00:09:39.141 --> 00:09:40.609 producing this second messenger,  
NOTE Confidence: 0.623311

00:09:40.610 --> 00:09:42.416 but the second messenger is thought to  
NOTE Confidence: 0.623311

00:09:42.416 --> 00:09:44.650 be key to its downstream mechanisms.  
NOTE Confidence: 0.623311

00:09:44.650 --> 00:09:48.088 The recipient of the C gamp signal is sting.  
NOTE Confidence: 0.623311

00:09:48.090 --> 00:09:50.190 Sting is a membrane protein that  
NOTE Confidence: 0.623311

00:09:50.190 --> 00:09:52.740 is key to the canonical signaling  
NOTE Confidence: 0.623311

00:09:52.740 --> 00:09:55.405 pathway that C gas activates.

NOTE Confidence: 0.623311  
00:09:55.410 --> 00:09:58.056 And that is by driving the phosphorylation  
NOTE Confidence: 0.623311  
00:09:58.056 --> 00:10:00.660 of a kinase called TBK one once  
NOTE Confidence: 0.623311  
00:10:00.660 --> 00:10:03.128 it's traffic to the Golgi and then  
NOTE Confidence: 0.623311  
00:10:03.128 --> 00:10:05.282 this phosphorylates IRF 3 which is  
NOTE Confidence: 0.623311  
00:10:05.282 --> 00:10:07.229 a transcription factor that when  
NOTE Confidence: 0.623311  
00:10:07.229 --> 00:10:09.563 phosphorylated goes into the nucleus and  
NOTE Confidence: 0.623311  
00:10:09.563 --> 00:10:12.329 drives interferon stimulated gene expression.  
NOTE Confidence: 0.623311  
00:10:12.330 --> 00:10:14.367 So that's the kind of canonical pathway.  
NOTE Confidence: 0.623311  
00:10:14.370 --> 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 --> 00:10:22.514 and any of these may in addition to  
NOTE Confidence: 0.623311  
00:10:22.514 --> 00:10:24.768 inflammatory genes cause apoptosis.  
NOTE Confidence: 0.623311  
00:10:24.770 --> 00:10:26.548 So this could be a mechanism that  
NOTE Confidence: 0.623311  
00:10:26.548 --> 00:10:27.690 can drive cell death,  
NOTE Confidence: 0.623311  
00:10:27.690 --> 00:10:30.040 although we really don't understand  
NOTE Confidence: 0.623311

00:10:30.040 --> 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 --> 00:10:33.874 sting is also involved in some  
NOTE Confidence: 0.623311

00:10:33.874 --> 00:10:35.825 other non canonical mechanisms that  
NOTE Confidence: 0.623311

00:10:35.825 --> 00:10:37.970 could also precipitate cell death,  
NOTE Confidence: 0.5575379

00:10:37.970 --> 00:10:39.858 which as I mentioned is what I'm going  
NOTE Confidence: 0.5575379

00:10:39.858 --> 00:10:42.485 to be focusing on today and part of this  
NOTE Confidence: 0.5575379

00:10:42.485 --> 00:10:44.569 actually involves the autophagy mechanisms.  
NOTE Confidence: 0.5575379

00:10:44.570 --> 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 --> 00:10:51.177 downstream of sting and this is  
NOTE Confidence: 0.5575379

00:10:51.177 --> 00:10:53.398 independent perhaps of this canonical  
NOTE Confidence: 0.5575379

00:10:53.398 --> 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 --> 00:11:00.330 of on these upstream steps today,  
NOTE Confidence: 0.5575379

00:11:00.330 --> 00:11:02.722 we really don't know what the key downstream

NOTE Confidence: 0.5575379

00:11:02.722 --> 00:11:04.819 steps are in terms of which signaling

NOTE Confidence: 0.5575379

00:11:04.819 --> 00:11:07.370 pathways are going to be most most relevant.

NOTE Confidence: 0.5575379

00:11:07.370 --> 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 --> 00:11:13.337 by highlighting that actually AC

NOTE Confidence: 0.5575379

00:11:13.337 --> 00:11:14.945 gas is a really ancient protein.

NOTE Confidence: 0.5575379

00:11:14.950 --> 00:11:16.492 It actually goes all the way

NOTE Confidence: 0.5575379

00:11:16.492 --> 00:11:17.263 back to prokaryotes.

NOTE Confidence: 0.5575379

00:11:17.270 --> 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 --> 00:11:22.949 before the innate immune system.

NOTE Confidence: 0.5575379

00:11:22.950 --> 00:11:24.028 And so that kind of makes sense,

NOTE Confidence: 0.5575379

00:11:24.030 --> 00:11:25.530 this idea that it's actually

NOTE Confidence: 0.5575379

00:11:25.530 --> 00:11:26.730 multiple signaling pathways that

NOTE Confidence: 0.5575379

00:11:26.730 --> 00:11:28.508 lie downstream of C gas activation.

NOTE Confidence: 0.5958521

00:11:30.750 --> 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 --> 00:11:40.110 literature that HR defects on this.  
NOTE Confidence: 0.5958521

00:11:40.110 --> 00:11:42.147 In this particular case on the left,  
NOTE Confidence: 0.5958521

00:11:42.150 --> 00:11:43.050 we're looking at bracket.  
NOTE Confidence: 0.5958521

00:11:43.050 --> 00:11:43.950 In both these cases,  
NOTE Confidence: 0.5958521

00:11:43.950 --> 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 --> 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 --> 00:11:55.163 that's actually further pushed by  
NOTE Confidence: 0.5958521

00:11:55.163 --> 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 --> 00:11:59.649 the example of this data.  
NOTE Confidence: 0.5958521

00:11:59.650 --> 00:12:00.274 As I mentioned,

NOTE Confidence: 0.5958521

00:12:00.274 --> 00:12:01.730 these are BRCA 2 knock down cells.

NOTE Confidence: 0.5958521

00:12:01.730 --> 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 --> 00:12:06.802 you can see that there's a gain

NOTE Confidence: 0.5958521

00:12:06.802 --> 00:12:08.796 in IRF 3 phosphorylation which is

NOTE Confidence: 0.5958521

00:12:08.796 --> 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 --> 00:12:14.600 And this also leads in this

NOTE Confidence: 0.5958521

00:12:14.682 --> 00:12:17.127 model to Stat 1 phosphorylation.

NOTE Confidence: 0.5958521

00:12:17.130 --> 00:12:19.299 And a similar thing is seen in the in

NOTE Confidence: 0.5958521

00:12:19.299 --> 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 --> 00:12:25.005 this is a artificial system of

NOTE Confidence: 0.5958521

00:12:25.005 --> 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 --> 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 --> 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 --> 00:12:42.613 this is now in a xenograft model.  
NOTE Confidence: 0.5958521

00:12:42.620 --> 00:12:44.654 So these are actually now xenographs  
NOTE Confidence: 0.5958521

00:12:44.654 --> 00:12:47.200 looking at how PARP inhibitors affect  
NOTE Confidence: 0.5958521

00:12:47.200 --> 00:12:49.460 interferon stimulated gene expression.  
NOTE Confidence: 0.5958521

00:12:49.460 --> 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 --> 00:12:55.353 gas activation are up regulated in  
NOTE Confidence: 0.5958521

00:12:55.422 --> 00:12:57.307 the with PARP inhibitor treatment  
NOTE Confidence: 0.5958521

00:12:57.307 --> 00:12:58.815 in the xenograft model.  
NOTE Confidence: 0.5958521

00:12:58.820 --> 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 --> 00:13:05.564 the context of HR deficient cells  
NOTE Confidence: 0.5958521  
00:13:05.564 --> 00:13:07.925 that's further pushed by PARP  
NOTE Confidence: 0.5958521  
00:13:07.925 --> 00:13:09.820 inhibitors in a number of cases.  
NOTE Confidence: 0.5958521  
00:13:09.820 --> 00:13:13.019 But what is the cause of this?  
NOTE Confidence: 0.5958521  
00:13:13.020 --> 00:13:13.305 Right.  
NOTE Confidence: 0.5958521  
00:13:13.305 --> 00:13:14.160 So what the,  
NOTE Confidence: 0.5958521  
00:13:14.160 --> 00:13:15.300 what the signal is,  
NOTE Confidence: 0.5958521  
00:13:15.300 --> 00:13:18.092 How we go from HR deficiency to innate  
NOTE Confidence: 0.5958521  
00:13:18.092 --> 00:13:20.380 immune signaling has been really unclear.  
NOTE Confidence: 0.5958521  
00:13:20.380 --> 00:13:22.151 One other thing that I want to  
NOTE Confidence: 0.5958521  
00:13:22.151 --> 00:13:23.872 just alert you to is that when  
NOTE Confidence: 0.5958521  
00:13:23.872 --> 00:13:25.620 there is an HR defect in cells,  
NOTE Confidence: 0.5958521  
00:13:25.620 --> 00:13:27.640 one of the consequences is  
NOTE Confidence: 0.5958521  
00:13:27.640 --> 00:13:29.256 that we accumulate cells,  
NOTE Confidence: 0.5958521

00:13:29.260 --> 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 --> 00:13:36.254 actually from more than a decade or  
NOTE Confidence: 0.5958521

00:13:36.254 --> 00:13:38.049 probably more than 15 years ago now  
NOTE Confidence: 0.5958521

00:13:38.050 --> 00:13:40.170 where it's been recognized for a long time.  
NOTE Confidence: 0.5958521

00:13:40.170 --> 00:13:42.485 If there are challenges in  
NOTE Confidence: 0.5958521

00:13:42.485 --> 00:13:44.800 maintaining integrity of the genome,  
NOTE Confidence: 0.5958521

00:13:44.800 --> 00:13:46.948 then in mitosis you have these  
NOTE Confidence: 0.5958521

00:13:46.948 --> 00:13:48.380 intermediates that lead to  
NOTE Confidence: 0.5958521

00:13:48.446 --> 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 --> 00:13:54.910 fusion breakage cycles that can  
NOTE Confidence: 0.5958521

00:13:54.910 --> 00:13:57.879 actually be precipitated by an HR defect,  
NOTE Confidence: 0.5958521

00:13:57.880 --> 00:14:00.316 by a radiation, by taxol treatments.  
NOTE Confidence: 0.5958521

00:14:00.320 --> 00:14:01.730 You can arrive at these kind

NOTE Confidence: 0.5958521

00:14:01.730 --> 00:14:02.960 of structures in many ways.

NOTE Confidence: 0.5958521

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

NOTE Confidence: 0.5958521

00:14:04.418 --> 00:14:06.406 is not the way that most people

NOTE Confidence: 0.5958521

00:14:06.406 --> 00:14:08.006 have thought about arriving at

NOTE Confidence: 0.5958521

00:14:08.006 --> 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 --> 00:14:15.410 'cause I'm a cell biologist,

NOTE Confidence: 0.7051682

00:14:15.410 --> 00:14:18.410 that actually the nuclear envelope,

NOTE Confidence: 0.7051682

00:14:18.410 --> 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

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

NOTE Confidence: 0.7051682

00:14:29.114 --> 00:14:30.822 immune surveillance protein that is

NOTE Confidence: 0.7051682

00:14:30.822 --> 00:14:32.887 looking for DNA and yet every mitosis,

NOTE Confidence: 0.7051682

00:14:32.890 --> 00:14:35.529 the chromosomes are exposed to the cytoplasm.

NOTE Confidence: 0.7051682

00:14:35.530 --> 00:14:37.970 So we we know that that's not sufficient

NOTE Confidence: 0.7051682

00:14:37.970 --> 00:14:40.258 to drive an innate immune response.

NOTE Confidence: 0.7051682

00:14:40.260 --> 00:14:42.186 So we know in mitosis there

NOTE Confidence: 0.7051682

00:14:42.186 --> 00:14:43.860 are mechanisms to down rate,

NOTE Confidence: 0.7051682

00:14:43.860 --> 00:14:45.565 down regulate this surveillance mechanisms

NOTE Confidence: 0.7051682

00:14:45.565 --> 00:14:48.215 are a way to shield these chromosomes

NOTE Confidence: 0.7051682

00:14:48.215 --> 00:14:50.420 from actually activating this pathway.

NOTE Confidence: 0.7051682

00:14:50.420 --> 00:14:52.725 And so these recombination intermediates

NOTE Confidence: 0.7051682

00:14:52.725 --> 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 --> 00:14:59.980 they persist into the following interface.

NOTE Confidence: 0.7051682

00:14:59.980 --> 00:15:01.688 And that's going to be important here

NOTE Confidence: 0.7051682

00:15:01.688 --> 00:15:03.550 because we need to get to the next

NOTE Confidence: 0.7051682

00:15:03.550 --> 00:15:05.408 interphase in order for this innate immune

NOTE Confidence: 0.7051682

00:15:05.408 --> 00:15:07.218 surveillance mechanism to be reactivated.

NOTE Confidence: 0.44108427

00:15:09.330 --> 00:15:11.556 And indeed, there is also evidence in

NOTE Confidence: 0.44108427

00:15:11.556 --> 00:15:13.621 the literature that for PARP inhibitors

NOTE Confidence: 0.44108427

00:15:13.621 --> 00:15:15.366 to actually induce cell death,

NOTE Confidence: 0.44108427

00:15:15.370 --> 00:15:17.848 cells have to transit through mitosis.

NOTE Confidence: 0.44108427

00:15:17.850 --> 00:15:19.845 This is additional evidence that you know,

NOTE Confidence: 0.44108427

00:15:19.850 --> 00:15:22.034 unlike P53, which as I mentioned

NOTE Confidence: 0.44108427

00:15:22.034 --> 00:15:23.490 is acting an interphase,

NOTE Confidence: 0.44108427

00:15:23.490 --> 00:15:25.650 that it is essential for cells to go

NOTE Confidence: 0.44108427

00:15:25.650 --> 00:15:27.168 through mitosis for PARP inhibitors

NOTE Confidence: 0.44108427

00:15:27.168 --> 00:15:29.004 to actually cause the cell death.

NOTE Confidence: 0.44108427

00:15:29.010 --> 00:15:30.714 This is actually some work again

NOTE Confidence: 0.44108427

00:15:30.714 --> 00:15:32.582 in a xenograph model and the

NOTE Confidence: 0.44108427

00:15:32.582 --> 00:15:33.938 absence of functional bracket,

NOTE Confidence: 0.44108427

00:15:33.940 --> 00:15:36.060 two and cells treated with a laparib and

NOTE Confidence: 0.44108427

00:15:36.060 --> 00:15:38.376 what you can see is kind of these events.

NOTE Confidence: 0.44108427

00:15:38.380 --> 00:15:42.133 So we have a a cell that is likely in G2,  
NOTE Confidence: 0.44108427

00:15:42.133 --> 00:15:43.777 it goes into mitosis.  
NOTE Confidence: 0.44108427

00:15:43.780 --> 00:15:45.820 You can see this is an this is an anaphase.  
NOTE Confidence: 0.44108427

00:15:45.820 --> 00:15:48.256 So there are anaphase 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 --> 00:15:55.495 that are going to be resolved dynamically.  
NOTE Confidence: 0.44108427

00:15:55.500 --> 00:15:57.738 However, if that does not happen,  
NOTE Confidence: 0.44108427

00:15:57.740 --> 00:16:00.026 if cells are unable to resolve  
NOTE Confidence: 0.44108427

00:16:00.026 --> 00:16:01.550 these entanglements of chromosomes,  
NOTE Confidence: 0.44108427

00:16:01.550 --> 00:16:03.860 So what happens is that these cells  
NOTE Confidence: 0.44108427

00:16:03.860 --> 00:16:05.750 will biochemically come out of mitosis.  
NOTE Confidence: 0.44108427

00:16:05.750 --> 00:16:07.534 So they're back in interface and you can  
NOTE Confidence: 0.44108427

00:16:07.534 --> 00:16:09.667 see that because the nucleus is intact again.  
NOTE Confidence: 0.44108427

00:16:09.670 --> 00:16:11.110 But what you can see in this cell is  
NOTE Confidence: 0.44108427

00:16:11.110 --> 00:16:12.550 you now have a doublet essentially,

NOTE Confidence: 0.44108427  
00:16:12.550 --> 00:16:12.856 right?  
NOTE Confidence: 0.44108427  
00:16:12.856 --> 00:16:14.998 You have a cell that actually failed  
NOTE Confidence: 0.44108427  
00:16:14.998 --> 00:16:16.929 in cytokinesis and it failed because  
NOTE Confidence: 0.44108427  
00:16:16.929 --> 00:16:18.509 you couldn't actually generate 2  
NOTE Confidence: 0.44108427  
00:16:18.509 --> 00:16:20.174 cells because there was bridging  
NOTE Confidence: 0.44108427  
00:16:20.174 --> 00:16:21.784 DNA between these two cells.  
NOTE Confidence: 0.44108427  
00:16:21.790 --> 00:16:23.350 But the cell has biochemically  
NOTE Confidence: 0.44108427  
00:16:23.350 --> 00:16:25.492 come back into interface and so we  
NOTE Confidence: 0.44108427  
00:16:25.492 --> 00:16:27.076 can imagine that the innate immune  
NOTE Confidence: 0.44108427  
00:16:27.076 --> 00:16:28.350 system is active again.  
NOTE Confidence: 0.44108427  
00:16:28.350 --> 00:16:29.614 And the question is,  
NOTE Confidence: 0.44108427  
00:16:29.614 --> 00:16:31.927 is this somehow aware of the fact  
NOTE Confidence: 0.44108427  
00:16:31.927 --> 00:16:34.027 that this is a defective mitosis?  
NOTE Confidence: 0.44108427  
00:16:34.030 --> 00:16:35.703 Is there some mechanism to know that  
NOTE Confidence: 0.44108427  
00:16:35.703 --> 00:16:37.429 and that this would ultimately Dr.  
NOTE Confidence: 0.44108427

00:16:37.430 --> 00:16:38.725 the cell death and that's what we  
NOTE Confidence: 0.44108427

00:16:38.725 --> 00:16:40.133 see happening on the right with  
NOTE Confidence: 0.44108427

00:16:40.133 --> 00:16:40.946 this chromosome condensation.  
NOTE Confidence: 0.9336245

00:16:43.590 --> 00:16:45.676 I just want to highlight that this  
NOTE Confidence: 0.9336245

00:16:45.676 --> 00:16:47.630 is not really new information,  
NOTE Confidence: 0.9336245

00:16:47.630 --> 00:16:48.710 so we can go back.  
NOTE Confidence: 0.9336245

00:16:48.710 --> 00:16:52.374 This is from 2001 and there has been  
NOTE Confidence: 0.9336245

00:16:52.374 --> 00:16:56.290 long been the understanding that these,  
NOTE Confidence: 0.9336245

00:16:56.290 --> 00:16:57.770 the changes in nuclear shape,  
NOTE Confidence: 0.9336245

00:16:57.770 --> 00:17:00.930 nuclear atypia which are used all the time  
NOTE Confidence: 0.9336245

00:17:00.930 --> 00:17:03.287 by pathologists to diagnose and stays,  
NOTE Confidence: 0.9336245

00:17:03.290 --> 00:17:06.510 cancers are tied to these kind of  
NOTE Confidence: 0.9336245

00:17:06.510 --> 00:17:08.810 aberrations that I've mentioned.  
NOTE Confidence: 0.9336245

00:17:08.810 --> 00:17:10.736 So I just want to you know that they've  
NOTE Confidence: 0.9336245

00:17:10.736 --> 00:17:12.409 been called many things over time.  
NOTE Confidence: 0.9336245

00:17:12.410 --> 00:17:14.480 What I want to point out is that all

NOTE Confidence: 0.9336245

00:17:14.480 --> 00:17:16.998 of these kind of mitotic errors that

NOTE Confidence: 0.9336245

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

NOTE Confidence: 0.9336245

00:17:18.963 --> 00:17:21.270 nuclear shape are all things that we're

NOTE Confidence: 0.9336245

00:17:21.270 --> 00:17:22.750 observing in interphase cells again,

NOTE Confidence: 0.9336245

00:17:22.750 --> 00:17:24.458 so not in cells just in mitosis

NOTE Confidence: 0.9336245

00:17:24.458 --> 00:17:25.910 that have an anaphase bridge

NOTE Confidence: 0.9336245

00:17:25.910 --> 00:17:27.590 but they're in in interphase.

NOTE Confidence: 0.9336245

00:17:27.590 --> 00:17:29.970 So these were called what the structures

NOTE Confidence: 0.9336245

00:17:29.970 --> 00:17:32.211 that I just described that you can

NOTE Confidence: 0.9336245

00:17:32.211 --> 00:17:34.402 have persistent DNA that then is still

NOTE Confidence: 0.9336245

00:17:34.402 --> 00:17:36.208 there as cells reform their nucleus

NOTE Confidence: 0.9336245

00:17:36.208 --> 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 --> 00:17:41.530 25 years ago were called inter

NOTE Confidence: 0.9336245

00:17:41.598 --> 00:17:42.630 nuclear strings,

NOTE Confidence: 0.9336245

00:17:42.630 --> 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 --> 00:17:51.422 inter nuclear strings are because  
NOTE Confidence: 0.9336245

00:17:51.422 --> 00:17:53.277 of an inability to segregate the  
NOTE Confidence: 0.9336245

00:17:53.277 --> 00:17:54.945 chromosomes because the chromosomes  
NOTE Confidence: 0.9336245

00:17:54.945 --> 00:17:56.613 are literally entangled and  
NOTE Confidence: 0.9336245

00:17:56.613 --> 00:17:58.500 cannot be physically segregated.  
NOTE Confidence: 0.9336245

00:17:58.500 --> 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 --> 00:18:05.405 acentrosomal chromosome fragments  
NOTE Confidence: 0.9336245

00:18:05.405 --> 00:18:07.980 and perhaps extra chromosomal DNA,  
NOTE Confidence: 0.9336245

00:18:07.980 --> 00:18:08.218 right.  
NOTE Confidence: 0.9336245

00:18:08.218 --> 00:18:09.646 So they really are a different  
NOTE Confidence: 0.9336245

00:18:09.646 --> 00:18:11.011 structure than these two structures

NOTE Confidence: 0.9336245

00:18:11.011 --> 00:18:12.215 are actually quite different.

NOTE Confidence: 0.9336245

00:18:12.220 --> 00:18:14.266 And I'll come back to that.

NOTE Confidence: 0.9336245

00:18:14.270 --> 00:18:15.470 The consequence of this can

NOTE Confidence: 0.9336245

00:18:15.470 --> 00:18:16.430 lead to BI nucleation.

NOTE Confidence: 0.9336245

00:18:16.430 --> 00:18:18.453 That's what I just showed you in

NOTE Confidence: 0.9336245

00:18:18.453 --> 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 --> 00:18:23.700 but you can also get nuclear ruptures

NOTE Confidence: 0.9336245

00:18:23.700 --> 00:18:26.189 that happen in interface due to a

NOTE Confidence: 0.9336245

00:18:26.189 --> 00:18:27.984 defect in the nuclear integrity.

NOTE Confidence: 0.9336245

00:18:27.990 --> 00:18:29.334 But that is not an event that's

NOTE Confidence: 0.9336245

00:18:29.334 --> 00:18:29.910 tied to mitosis.

NOTE Confidence: 0.9336245

00:18:29.910 --> 00:18:31.350 So I'm not going to talk

NOTE Confidence: 0.9336245

00:18:31.350 --> 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 --> 00:18:35.040 So let me just show you kind of  
NOTE Confidence: 0.9336245

00:18:35.113 --> 00:18:37.128 the amazing cell biology that  
NOTE Confidence: 0.9336245

00:18:37.128 --> 00:18:39.143 is tied and specifically to  
NOTE Confidence: 0.9336245

00:18:39.218 --> 00:18:41.270 these persistent DNA bridges.  
NOTE Confidence: 0.9336245

00:18:41.270 --> 00:18:43.790 So here I'm showing you a movie.  
NOTE Confidence: 0.9336245

00:18:43.790 --> 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 --> 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 --> 00:18:52.150 And we're going to look at this cell  
NOTE Confidence: 0.9336245

00:18:52.150 --> 00:18:54.050 that is just going through mitosis,  
NOTE Confidence: 0.9336245

00:18:54.050 --> 00:18:55.190 if it will.  
NOTE Confidence: 0.9209971

00:18:57.830 --> 00:18:59.478 Maybe I'm not allowed to do that while  
NOTE Confidence: 0.9209971

00:18:59.478 --> 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 --> 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 --> 00:19:14.020 These cells are still linked by

NOTE Confidence: 0.9209971

00:19:14.020 --> 00:19:15.649 one of these DNA bridges and you

NOTE Confidence: 0.9209971

00:19:15.649 --> 00:19:17.083 can see there are these flashes,

NOTE Confidence: 0.9209971

00:19:17.090 --> 00:19:18.460 there are these transient ruptures

NOTE Confidence: 0.9209971

00:19:18.460 --> 00:19:20.473 of the nucleus and all the nuclear

NOTE Confidence: 0.9209971

00:19:20.473 --> 00:19:21.943 localization signal will spill out

NOTE Confidence: 0.9209971

00:19:21.943 --> 00:19:23.978 and then there seems to be some repair

NOTE Confidence: 0.9209971

00:19:23.978 --> 00:19:25.822 of that event and then the the the

NOTE Confidence: 0.9209971

00:19:25.822 --> 00:19:27.286 protein can start to accumulate again.

NOTE Confidence: 0.9209971

00:19:27.290 --> 00:19:30.076 So it's kind of these cycles of

NOTE Confidence: 0.9209971

00:19:30.076 --> 00:19:32.490 ruptures and then repair events.

NOTE Confidence: 0.9209971

00:19:32.490 --> 00:19:34.290 So this is just looking in this case,

NOTE Confidence: 0.9209971

00:19:34.290 --> 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 --> 00:19:41.451 So one of the questions is what's  
NOTE Confidence: 0.9209971

00:19:41.451 --> 00:19:43.561 the consequence of this innate  
NOTE Confidence: 0.9209971

00:19:43.561 --> 00:19:45.293 immune surveillance mechanism when  
NOTE Confidence: 0.9209971

00:19:45.293 --> 00:19:47.587 you have one of these ruptures.  
NOTE Confidence: 0.9209971

00:19:47.590 --> 00:19:49.366 So these kind of transient ruptures  
NOTE Confidence: 0.9209971

00:19:49.366 --> 00:19:50.794 of the nuclear envelopes, right.  
NOTE Confidence: 0.9209971

00:19:50.794 --> 00:19:52.746 So the nucleus, we've come out of mitosis,  
NOTE Confidence: 0.9209971

00:19:52.750 --> 00:19:55.830 it should be intact, but it's it's unstable.  
NOTE Confidence: 0.9209971

00:19:55.830 --> 00:19:57.958 And so here I'm going to show  
NOTE Confidence: 0.9209971

00:19:57.958 --> 00:19:58.870 you similarly cells,  
NOTE Confidence: 0.9209971

00:19:58.870 --> 00:20:01.990 but these cells are actually now  
NOTE Confidence: 0.9209971

00:20:01.990 --> 00:20:03.725 expressing AC gas that's tagged and  
NOTE Confidence: 0.9209971

00:20:03.725 --> 00:20:05.840 that's going to be in this panel here.  
NOTE Confidence: 0.9209971

00:20:05.840 --> 00:20:07.149 And I just want to again point  
NOTE Confidence: 0.9209971

00:20:07.149 --> 00:20:08.558 out this is not just anaphase.

NOTE Confidence: 0.9209971

00:20:08.560 --> 00:20:10.120 This is far after anaphase.

NOTE Confidence: 0.9209971

00:20:10.120 --> 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 --> 00:20:15.554 and and and segregate it, right,

NOTE Confidence: 0.9209971

00:20:15.554 --> 00:20:16.958 Not break it, but segregate it.

NOTE Confidence: 0.9209971

00:20:16.960 --> 00:20:18.731 And what I hope you can appreciate

NOTE Confidence: 0.9209971

00:20:18.731 --> 00:20:20.344 is that late in this movie,

NOTE Confidence: 0.9209971

00:20:20.344 --> 00:20:22.727 all of a sudden what we see is

NOTE Confidence: 0.9209971

00:20:22.727 --> 00:20:24.367 that there's recruitment of sea

NOTE Confidence: 0.9209971

00:20:24.367 --> 00:20:26.637 gas all over this strand of DNA.

NOTE Confidence: 0.9209971

00:20:26.640 --> 00:20:28.632 OK. So it's not something that

NOTE Confidence: 0.9209971

00:20:28.632 --> 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 --> 00:20:33.094 There is this bridge of DNA the

NOTE Confidence: 0.9209971

00:20:33.094 --> 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 --> 00:20:40.466 recruited and this is a persistent bridge.  
NOTE Confidence: 0.9209971

00:20:40.470 --> 00:20:42.207 I just want to point out you also get  
NOTE Confidence: 0.9209971

00:20:42.207 --> 00:20:43.788 this kind of thing to Micronuclei.  
NOTE Confidence: 0.9209971

00:20:43.790 --> 00:20:46.023 Here's a micronucleus and we can actually  
NOTE Confidence: 0.9209971

00:20:46.023 --> 00:20:48.068 see that that micronucleus is intact  
NOTE Confidence: 0.9209971

00:20:48.068 --> 00:20:50.382 and then it's going to rupture and  
NOTE Confidence: 0.9209971

00:20:50.382 --> 00:20:51.954 then there's massive C gas recruitment,  
NOTE Confidence: 0.9209971

00:20:51.960 --> 00:20:52.297 OK.  
NOTE Confidence: 0.9209971

00:20:52.297 --> 00:20:54.993 So any of these losses of nuclear integrity,  
NOTE Confidence: 0.9209971

00:20:55.000 --> 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 --> 00:21:00.840 can recruit the C gas protein.  
NOTE Confidence: 0.27129424

00:21:05.240 --> 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 --> 00:21:12.319 you the rationale for why that is.

NOTE Confidence: 0.27129424

00:21:12.320 --> 00:21:16.650 Now, one of them is that actually

NOTE Confidence: 0.27129424

00:21:16.650 --> 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 --> 00:21:23.792 But there's evidence in the literature

NOTE Confidence: 0.27129424

00:21:23.792 --> 00:21:26.083 that DNA bridges are actually much more

NOTE Confidence: 0.27129424

00:21:26.083 --> 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 --> 00:21:30.911 the recruitment of of C gas is

NOTE Confidence: 0.27129424

00:21:30.911 --> 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 overreacting to its own genome is the

NOTE Confidence: 0.27129424

00:21:43.309 --> 00:21:45.463 fact that nucleosomal or chromatized DNA

NOTE Confidence: 0.27129424

00:21:45.463 --> 00:21:48.292 is a poor stimulator of Segamp production.  
NOTE Confidence: 0.27129424

00:21:48.292 --> 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 --> 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 --> 00:21:57.944 And so this would suggest that  
NOTE Confidence: 0.27129424

00:21:57.944 --> 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 --> 00:22:04.474 that actually micronuclei for the  
NOTE Confidence: 0.27129424

00:22:04.474 --> 00:22:06.309 most part are chromatized substrate.  
NOTE Confidence: 0.27129424

00:22:06.310 --> 00:22:07.810 It was a lagging chromosome  
NOTE Confidence: 0.27129424

00:22:07.810 --> 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 --> 00:22:14.766 whereas this DNA in these persistent  
NOTE Confidence: 0.27129424

00:22:14.766 --> 00:22:16.869 bridges as you saw in those movies,  
NOTE Confidence: 0.27129424

00:22:16.870 --> 00:22:18.868 the DNA is being pulled apart.

NOTE Confidence: 0.27129424

00:22:18.870 --> 00:22:20.814 And so one of the ideas is that it

NOTE Confidence: 0.27129424

00:22:20.814 --> 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 --> 00:22:30.326 the DNA that's left is naked and 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 --> 00:22:35.770 And additional evidence from that

NOTE Confidence: 0.27129424

00:22:35.770 --> 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 --> 00:22:43.950 that is present in bridges,

NOTE Confidence: 0.27129424

00:22:43.950 --> 00:22:46.113 which suggests that it can also become

NOTE Confidence: 0.27129424

00:22:46.113 --> 00:22:48.109 single stranded and acted on by APOBEC.

NOTE Confidence: 0.27129424

00:22:48.110 --> 00:22:49.845 Such as additional evidence that

NOTE Confidence: 0.27129424

00:22:49.845 --> 00:22:52.000 the structure in these in these

NOTE Confidence: 0.27129424

00:22:52.000 --> 00:22:53.795 persistent DNA bridges is different  
NOTE Confidence: 0.27129424

00:22:53.795 --> 00:22:56.190 than what might be in Micronuclei.  
NOTE Confidence: 0.27129424

00:22:56.190 --> 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 --> 00:23:01.243 I need to introduce you to is the  
NOTE Confidence: 0.27129424

00:23:01.243 --> 00:23:02.677 idea that like in that NLS movie,  
NOTE Confidence: 0.27129424

00:23:02.677 --> 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 --> 00:23:07.816 for these breaks in the nuclear  
NOTE Confidence: 0.27129424

00:23:07.816 --> 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 --> 00:23:12.986 interest to our group for a long time.  
NOTE Confidence: 0.27129424

00:23:12.990 --> 00:23:14.510 So remember as I said,  
NOTE Confidence: 0.27129424

00:23:14.510 --> 00:23:15.662 in a normal mitosis,  
NOTE Confidence: 0.27129424

00:23:15.662 --> 00:23:17.390 the nuclear envelope has broken down,

NOTE Confidence: 0.27129424

00:23:17.390 --> 00:23:18.578 the chromosomes are exposed,

NOTE Confidence: 0.27129424

00:23:18.578 --> 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 --> 00:23:23.020 Then we reform the nuclear

NOTE Confidence: 0.27129424

00:23:23.020 --> 00:23:24.580 envelope at mitotic exit.

NOTE Confidence: 0.27129424

00:23:24.580 --> 00:23:26.140 When the nuclear envelope is reformed,

NOTE Confidence: 0.27129424

00:23:26.140 --> 00:23:28.140 you have sheets of endoplasmic

NOTE Confidence: 0.27129424

00:23:28.140 --> 00:23:29.740 reticulum around the chromosomes,

NOTE Confidence: 0.27129424

00:23:29.740 --> 00:23:31.258 but it's full of holes actually.

NOTE Confidence: 0.27129424

00:23:31.260 --> 00:23:32.870 And those holes are particularly

NOTE Confidence: 0.27129424

00:23:32.870 --> 00:23:34.480 where there are still microtubules

NOTE Confidence: 0.27129424

00:23:34.537 --> 00:23:35.982 from the spindle that are

NOTE Confidence: 0.27129424

00:23:35.982 --> 00:23:37.138 attached to the chromosomes.

NOTE Confidence: 0.27129424

00:23:37.140 --> 00:23:38.890 So there is a machinery that has

NOTE Confidence: 0.27129424

00:23:38.890 --> 00:23:40.957 to come in and fix all these holes

NOTE Confidence: 0.27129424

00:23:40.957 --> 00:23:42.740 at the end of every mitosis.  
NOTE Confidence: 0.27129424

00:23:42.740 --> 00:23:45.050 And that machinery is made-up of the  
NOTE Confidence: 0.27129424

00:23:45.050 --> 00:23:46.740 components that I've shown here.  
NOTE Confidence: 0.27129424

00:23:46.740 --> 00:23:48.522 There is an abundant DNA binding  
NOTE Confidence: 0.27129424

00:23:48.522 --> 00:23:49.413 protein called bath,  
NOTE Confidence: 0.73344946

00:23:49.420 --> 00:23:52.444 not to be confused with the chromatin  
NOTE Confidence: 0.73344946

00:23:52.444 --> 00:23:54.998 remodeler bath and this brings in  
NOTE Confidence: 0.73344946

00:23:54.998 --> 00:23:57.688 a protein called LEM 2 which is  
NOTE Confidence: 0.73344946

00:23:57.688 --> 00:23:59.133 an integral membrane protein and  
NOTE Confidence: 0.73344946

00:23:59.133 --> 00:24:00.789 that's shown here in the cartoon.  
NOTE Confidence: 0.73344946

00:24:00.790 --> 00:24:02.806 So this LEM Two is recruited to these  
NOTE Confidence: 0.73344946

00:24:02.806 --> 00:24:05.478 holes in the nuclear envelope and LEM Two  
NOTE Confidence: 0.73344946

00:24:05.478 --> 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 --> 00:24:11.110 nuclear envelope specific escort.  
NOTE Confidence: 0.73344946

00:24:11.110 --> 00:24:13.483 So the escorts are a membrane remodeling

NOTE Confidence: 0.73344946

00:24:13.483 --> 00:24:15.437 machinery that basically can take a hole

NOTE Confidence: 0.73344946

00:24:15.437 --> 00:24:17.279 in a membrane and they can close it.

NOTE Confidence: 0.73344946

00:24:17.280 --> 00:24:20.040 And so this machinery is recruiting,

NOTE Confidence: 0.73344946

00:24:20.040 --> 00:24:21.858 is recruiting escorts to the nuclear

NOTE Confidence: 0.73344946

00:24:21.858 --> 00:24:23.920 envelope they form these spiral polymers,

NOTE Confidence: 0.73344946

00:24:23.920 --> 00:24:25.872 and you need this to have one nuclear

NOTE Confidence: 0.73344946

00:24:25.872 --> 00:24:27.357 envelope at the end of mitosis.

NOTE Confidence: 0.73344946

00:24:27.360 --> 00:24:28.998 So this is the normal thing

NOTE Confidence: 0.73344946

00:24:29.000 --> 00:24:30.245 that's always happening.

NOTE Confidence: 0.73344946

00:24:30.245 --> 00:24:32.735 But there's abundant evidence that this

NOTE Confidence: 0.73344946

00:24:32.735 --> 00:24:35.130 same exact machinery is recruited anytime

NOTE Confidence: 0.73344946

00:24:35.130 --> 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 --> 00:24:39.560 an example of this here.

NOTE Confidence: 0.73344946

00:24:39.560 --> 00:24:41.548 This is actually where a rupture in

NOTE Confidence: 0.73344946

00:24:41.548 --> 00:24:43.320 the nuclear envelope has been induced.  
NOTE Confidence: 0.73344946

00:24:43.320 --> 00:24:45.630 And you can see that there's recruitment  
NOTE Confidence: 0.73344946

00:24:45.630 --> 00:24:48.180 of this escort chimp 7 as well as  
NOTE Confidence: 0.73344946

00:24:48.180 --> 00:24:49.740 recruitment of sea gas, right.  
NOTE Confidence: 0.73344946

00:24:49.740 --> 00:24:52.008 So one way of thinking about this  
NOTE Confidence: 0.73344946

00:24:52.008 --> 00:24:54.262 kind of similar to the P53 story,  
NOTE Confidence: 0.73344946

00:24:54.262 --> 00:24:56.117 you know, you can repair,  
NOTE Confidence: 0.73344946

00:24:56.120 --> 00:24:58.280 you can repair DNA or the cell can  
NOTE Confidence: 0.73344946

00:24:58.280 --> 00:25:00.555 die and you can give up on things.  
NOTE Confidence: 0.73344946

00:25:00.560 --> 00:25:01.868 We have this machinery that sees  
NOTE Confidence: 0.73344946

00:25:01.868 --> 00:25:03.600 a hole in the nuclear envelope.  
NOTE Confidence: 0.73344946

00:25:03.600 --> 00:25:05.497 It can try to fix the hole,  
NOTE Confidence: 0.73344946

00:25:05.500 --> 00:25:06.697 but if it can't fix the hole,  
NOTE Confidence: 0.73344946

00:25:06.700 --> 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 --> 00:25:10.085 And so there's actually a

NOTE Confidence: 0.73344946

00:25:10.085 --> 00:25:10.820 competition potentially that's

NOTE Confidence: 0.73344946

00:25:10.820 --> 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 --> 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 --> 00:25:16.456 So here is,

NOTE Confidence: 0.73344946

00:25:16.456 --> 00:25:18.792 and I'm just going to lay out why we've

NOTE Confidence: 0.73344946

00:25:18.792 --> 00:25:20.484 done the experiments that I'm going

NOTE Confidence: 0.73344946

00:25:20.484 --> 00:25:22.618 to describe in the rest of the talk.

NOTE Confidence: 0.73344946

00:25:22.620 --> 00:25:24.732 I've already walked through

NOTE Confidence: 0.73344946

00:25:24.732 --> 00:25:27.140 Interphase and the idea, P 53.

NOTE Confidence: 0.73344946

00:25:27.140 --> 00:25:29.155 So I just want to make the argument

NOTE Confidence: 0.73344946

00:25:29.155 --> 00:25:32.300 up front for the hypothesis of a

NOTE Confidence: 0.73344946

00:25:32.300 --> 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,

NOTE Confidence: 0.73344946

00:25:36.390 --> 00:25:38.790 the integrity of the mitotic process.  
NOTE Confidence: 0.73344946

00:25:38.790 --> 00:25:41.261 So if cells go into mitosis with  
NOTE Confidence: 0.73344946

00:25:41.261 --> 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 --> 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 --> 00:25:49.458 particularly one that's been  
NOTE Confidence: 0.73344946

00:25:49.458 --> 00:25:51.443 treated with PARP inhibitors or  
NOTE Confidence: 0.73344946

00:25:51.443 --> 00:25:52.948 chromosomes that are entangled.  
NOTE Confidence: 0.73344946

00:25:52.950 --> 00:25:54.906 This will initially activate mechanisms that  
NOTE Confidence: 0.73344946

00:25:54.906 --> 00:25:57.149 try to help segregate these chromosomes.  
NOTE Confidence: 0.73344946

00:25:57.150 --> 00:25:59.598 This involves proteins like the Bloom  
NOTE Confidence: 0.73344946

00:25:59.598 --> 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 --> 00:26:06.486 mediated and joining,  
NOTE Confidence: 0.73344946

00:26:06.490 --> 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 --> 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 --> 00:26:15.691 then one of the consequences I've shown

NOTE Confidence: 0.73344946

00:26:15.691 --> 00:26:17.696 you is that you can have defects in

NOTE Confidence: 0.73344946

00:26:17.696 --> 00:26:18.910 nuclear integrity and now the cell

NOTE Confidence: 0.73344946

00:26:18.910 --> 00:26:20.249 has to kind of decide what to do.

NOTE Confidence: 0.73344946

00:26:20.250 --> 00:26:21.560 So there's a nuclear envelope

NOTE Confidence: 0.73344946

00:26:21.560 --> 00:26:23.404 repair network And so I showed you

NOTE Confidence: 0.73344946

00:26:23.404 --> 00:26:25.070 this bath LEM two chimp 7 access

NOTE Confidence: 0.73344946

00:26:25.070 --> 00:26:26.524 that as I've mentioned our group

NOTE Confidence: 0.73344946

00:26:26.524 --> 00:26:28.730 has worked on for a long time

NOTE Confidence: 0.73344946

00:26:28.730 --> 00:26:30.810 understanding the mechanisms of

NOTE Confidence: 0.29974625

00:26:30.810 --> 00:26:33.645 and that this can promote cell survival

NOTE Confidence: 0.29974625

00:26:33.650 --> 00:26:36.490 and possibly genome integrity.

NOTE Confidence: 0.29974625

00:26:36.490 --> 00:26:38.688 On the other hand if they're unable  
NOTE Confidence: 0.29974625

00:26:38.688 --> 00:26:40.677 to repair these breaks in the  
NOTE Confidence: 0.29974625

00:26:40.677 --> 00:26:42.645 nucleus then this will expose DNA.  
NOTE Confidence: 0.29974625

00:26:42.650 --> 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 --> 00:26:52.581 to these observations of innate immune  
NOTE Confidence: 0.29974625

00:26:52.581 --> 00:26:55.418 signaling that occur as a consequence of  
NOTE Confidence: 0.29974625

00:26:55.418 --> 00:26:58.359 PARP inhibitors in HR deficient cells.  
NOTE Confidence: 0.29974625

00:26:58.360 --> 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 --> 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 --> 00:27:09.600 when they have not repaired their DNA,  
NOTE Confidence: 0.29974625

00:27:09.600 --> 00:27:11.833 these are more likely to happen if  
NOTE Confidence: 0.29974625

00:27:11.833 --> 00:27:14.387 you have an HR defect and if you

NOTE Confidence: 0.29974625

00:27:14.387 --> 00:27:16.680 treat cells with a PARP inhibitor.

NOTE Confidence: 0.29974625

00:27:16.680 --> 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 --> 00:27:24.246 nuclear integrity defects as a biomarker

NOTE Confidence: 0.29974625

00:27:24.246 --> 00:27:27.655 of HR defects or of of of contacts

NOTE Confidence: 0.29974625

00:27:27.655 --> 00:27:30.439 where PARP inhibitors might be effective.

NOTE Confidence: 0.29974625

00:27:30.440 --> 00:27:32.420 So I'll come back to that at the end.

NOTE Confidence: 0.29974625

00:27:32.420 --> 00:27:34.100 And also might this nuclear envelope

NOTE Confidence: 0.29974625

00:27:34.100 --> 00:27:36.224 repair network be a new target, right.

NOTE Confidence: 0.29974625

00:27:36.224 --> 00:27:38.648 These are factors which actually limit

NOTE Confidence: 0.29974625

00:27:38.648 --> 00:27:40.572 the action potentially of agents

NOTE Confidence: 0.29974625

00:27:40.572 --> 00:27:42.708 that are driving these defects that

NOTE Confidence: 0.29974625

00:27:42.708 --> 00:27:44.180 we're using clinically.

NOTE Confidence: 0.29974625

00:27:44.180 --> 00:27:44.446 OK.

NOTE Confidence: 0.29974625

00:27:44.446 --> 00:27:46.574 So now I'm just going to show you

NOTE Confidence: 0.29974625

00:27:46.574 --> 00:27:48.617 some of the data from our group.  
NOTE Confidence: 0.29974625

00:27:48.620 --> 00:27:50.972 This initial data is using actually  
NOTE Confidence: 0.29974625

00:27:50.972 --> 00:27:52.540 an ovarian cancer model,  
NOTE Confidence: 0.29974625

00:27:52.540 --> 00:27:55.096 UWB 1280 lines which are a BRCA 1 deficient,  
NOTE Confidence: 0.29974625

00:27:55.100 --> 00:27:56.604 HR deficient cell line.  
NOTE Confidence: 0.29974625

00:27:56.604 --> 00:27:59.732 And so I'm just showing you an example  
NOTE Confidence: 0.29974625

00:27:59.732 --> 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 --> 00:28:04.228 This is.  
NOTE Confidence: 0.29974625

00:28:04.228 --> 00:28:06.220 You can think of this as very much  
NOTE Confidence: 0.29974625

00:28:06.279 --> 00:28:08.064 as the end point of that movie  
NOTE Confidence: 0.29974625

00:28:08.064 --> 00:28:10.247 that I showed you that we also see  
NOTE Confidence: 0.29974625

00:28:10.247 --> 00:28:12.342 specifically in HR in this HR deficient  
NOTE Confidence: 0.29974625

00:28:12.342 --> 00:28:14.172 line that's further precipitated by  
NOTE Confidence: 0.29974625

00:28:14.172 --> 00:28:16.249 the addition of PARP inhibitors.  
NOTE Confidence: 0.29974625

00:28:16.250 --> 00:28:18.762 And so like in that example you can

NOTE Confidence: 0.29974625

00:28:18.762 --> 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 --> 00:28:25.228 is highly enriched in C gas.

NOTE Confidence: 0.29974625

00:28:25.230 --> 00:28:27.232 And so we would speculate from this

NOTE Confidence: 0.29974625

00:28:27.232 --> 00:28:29.344 that this is the region of the

NOTE Confidence: 0.29974625

00:28:29.344 --> 00:28:31.132 nucleus where the DNA is exposed

NOTE Confidence: 0.29974625

00:28:31.192 --> 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 --> 00:28:36.980 And so this is just showing you here what

NOTE Confidence: 0.29974625

00:28:36.980 --> 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 --> 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 --> 00:28:44.140 So the on the on the left is just

NOTE Confidence: 0.29974625

00:28:44.212 --> 00:28:46.240 the UWB one, this UW one cell line.

NOTE Confidence: 0.29974625

00:28:46.240 --> 00:28:48.358 And then when we add elaporib,  
NOTE Confidence: 0.29974625

00:28:48.360 --> 00:28:50.076 interestingly one of the things that  
NOTE Confidence: 0.29974625

00:28:50.076 --> 00:28:52.033 we see is the elaporib increases  
NOTE Confidence: 0.29974625

00:28:52.033 --> 00:28:54.295 the percent of cells that have  
NOTE Confidence: 0.29974625

00:28:54.295 --> 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 --> 00:29:06.800 this is not precipitated by PARP inhibitors,  
NOTE Confidence: 0.29974625

00:29:06.800 --> 00:29:08.850 at least in this context.  
NOTE Confidence: 0.29974625

00:29:08.850 --> 00:29:10.453 And so this is another reason why  
NOTE Confidence: 0.29974625

00:29:10.453 --> 00:29:11.890 we're very interested in these bridges,  
NOTE Confidence: 0.29974625

00:29:11.890 --> 00:29:13.626 because they seem to be the structure  
NOTE Confidence: 0.29974625

00:29:13.626 --> 00:29:15.169 that's most precipitated by PARP inhibitors,  
NOTE Confidence: 0.29974625

00:29:15.170 --> 00:29:17.300 whereas there's just a high rate  
NOTE Confidence: 0.29974625

00:29:17.300 --> 00:29:18.834 of micronuclei all of the time.

NOTE Confidence: 0.29974625

00:29:18.834 --> 00:29:20.070 But that does not seem to

NOTE Confidence: 0.6971082

00:29:20.123 --> 00:29:21.448 respond to the addition of,

NOTE Confidence: 0.6971082

00:29:21.450 --> 00:29:24.408 in this case, a lab rib.

NOTE Confidence: 0.6971082

00:29:24.410 --> 00:29:26.754 So we also think that for the vast

NOTE Confidence: 0.6971082

00:29:26.754 --> 00:29:28.553 majority of these persistent bridges

NOTE Confidence: 0.6971082

00:29:28.553 --> 00:29:30.845 that we observe in response to

NOTE Confidence: 0.6971082

00:29:30.845 --> 00:29:33.207 PARP inhibitors that there is that,

NOTE Confidence: 0.6971082

00:29:33.210 --> 00:29:34.895 that there has been a

NOTE Confidence: 0.6971082

00:29:34.895 --> 00:29:36.243 loss of nuclear integrity.

NOTE Confidence: 0.6971082

00:29:36.250 --> 00:29:37.930 And so one thing I just want to

NOTE Confidence: 0.6971082

00:29:37.930 --> 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 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

NOTE Confidence: 0.6971082

00:29:48.538 --> 00:29:50.547 it's too thin essentially or there's  
NOTE Confidence: 0.6971082

00:29:50.547 --> 00:29:52.352 something about the DNA structure  
NOTE Confidence: 0.6971082

00:29:52.352 --> 00:29:54.642 that disrupts the ability of the DNA  
NOTE Confidence: 0.6971082

00:29:54.642 --> 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 --> 00:29:59.030 we don't actually know yet.  
NOTE Confidence: 0.6971082

00:29:59.030 --> 00:30:00.374 So actually in order to know  
NOTE Confidence: 0.6971082

00:30:00.374 --> 00:30:01.590 that there's a bridge there,  
NOTE Confidence: 0.6971082

00:30:01.590 --> 00:30:03.424 you need a marker for a bridge.  
NOTE Confidence: 0.6971082

00:30:03.430 --> 00:30:04.739 And actually it turns out that one  
NOTE Confidence: 0.6971082

00:30:04.739 --> 00:30:06.196 of the best markers for a bridge  
NOTE Confidence: 0.6971082

00:30:06.196 --> 00:30:07.468 is this protein called man one,  
NOTE Confidence: 0.6971082

00:30:07.470 --> 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 --> 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 --> 00:30:14.950 in the nuclear envelope of all cells,

NOTE Confidence: 0.6971082

00:30:14.950 --> 00:30:16.826 but it really nicely decorates these bridges.

NOTE Confidence: 0.6971082

00:30:16.830 --> 00:30:18.504 And so this has been a really important tool.

NOTE Confidence: 0.6971082

00:30:18.510 --> 00:30:19.386 It seems very simple,

NOTE Confidence: 0.6971082

00:30:19.386 --> 00:30:20.952 but the ability to see the things

NOTE Confidence: 0.6971082

00:30:20.952 --> 00:30:22.387 that you want to look for is,

NOTE Confidence: 0.6971082

00:30:22.390 --> 00:30:23.227 is pretty important.

NOTE Confidence: 0.6971082

00:30:23.227 --> 00:30:25.180 So we've been using this antibody to

NOTE Confidence: 0.6971082

00:30:25.234 --> 00:30:26.999 this inner nuclear membrane protein,

NOTE Confidence: 0.6971082

00:30:27.000 --> 00:30:29.359 MAN one in order to surveil this.

NOTE Confidence: 0.6971082

00:30:29.360 --> 00:30:33.336 And so we can then look at the

NOTE Confidence: 0.6971082

00:30:33.336 --> 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 --> 00:30:39.973 specifically on the other elements

NOTE Confidence: 0.6971082

00:30:39.973 --> 00:30:41.873 of that DNA repair pathway.

NOTE Confidence: 0.6971082

00:30:41.880 --> 00:30:43.736 So not only is is C gas recruited  
NOTE Confidence: 0.6971082

00:30:43.736 --> 00:30:45.823 and yet we we we interpret that  
NOTE Confidence: 0.6971082

00:30:45.823 --> 00:30:46.759 as ruptured bridges,  
NOTE Confidence: 0.6971082

00:30:46.760 --> 00:30:48.200 but there's also the recruitment  
NOTE Confidence: 0.6971082

00:30:48.200 --> 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 --> 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 --> 00:30:56.347 and so this is evidence that that  
NOTE Confidence: 0.6971082

00:30:56.347 --> 00:30:57.949 same kind of antagonism that I  
NOTE Confidence: 0.6971082

00:30:58.000 --> 00:30:59.958 showed you in a induced rupture of  
NOTE Confidence: 0.6971082

00:30:59.958 --> 00:31:02.730 the nucleus is also going on here.  
NOTE Confidence: 0.6971082

00:31:02.730 --> 00:31:04.865 If we identify bridges using this man  
NOTE Confidence: 0.6971082

00:31:04.865 --> 00:31:07.137 1 antibody what what we can see is  
NOTE Confidence: 0.6971082

00:31:07.137 --> 00:31:09.529 that all bridges have limb 2 which we expect.  
NOTE Confidence: 0.6971082

00:31:09.530 --> 00:31:11.636 Those are two different inter nuclear

NOTE Confidence: 0.6971082

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

NOTE Confidence: 0.6971082

00:31:13.120 --> 00:31:14.940 half of them have C gas recruitment

NOTE Confidence: 0.6971082

00:31:14.994 --> 00:31:16.614 and so this suggests again that

NOTE Confidence: 0.6971082

00:31:16.614 --> 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 --> 00:31:22.460 is likely exposed to the cytoplasm.

NOTE Confidence: 0.4833358

00:31:25.060 --> 00:31:26.537 I also want to point out that

NOTE Confidence: 0.4833358

00:31:26.537 --> 00:31:28.582 one of the ideas in that nuclear

NOTE Confidence: 0.4833358

00:31:28.582 --> 00:31:30.272 envelope reformation is that there's

NOTE Confidence: 0.4833358

00:31:30.272 --> 00:31:32.124 local recruitment of LEM two and

NOTE Confidence: 0.4833358

00:31:32.124 --> 00:31:34.362 these escort proteins to try to to

NOTE Confidence: 0.4833358

00:31:34.362 --> 00:31:36.317 actually seal the nuclear envelope.

NOTE Confidence: 0.4833358

00:31:36.320 --> 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 --> 00:31:41.709 you can see that there are regions where

NOTE Confidence: 0.4833358

00:31:41.709 --> 00:31:43.997 there's a really high accumulation of LEM 2.  
NOTE Confidence: 0.4833358

00:31:44.000 --> 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 --> 00:31:48.279 been a loss of integrity.  
NOTE Confidence: 0.4833358

00:31:48.280 --> 00:31:50.360 And that kind of explains why sea gas  
NOTE Confidence: 0.4833358

00:31:50.360 --> 00:31:52.530 is also seen in this patchy pattern  
NOTE Confidence: 0.4833358

00:31:52.530 --> 00:31:54.930 because there probably is a local effect.  
NOTE Confidence: 0.4833358

00:31:54.930 --> 00:31:57.290 And I'm just showing you here line profiles,  
NOTE Confidence: 0.4833358

00:31:57.290 --> 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 --> 00:32:00.518 this man one protein,  
NOTE Confidence: 0.4833358

00:32:00.518 --> 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 --> 00:32:03.595 it's kind of distributed throughout  
NOTE Confidence: 0.4833358

00:32:03.595 --> 00:32:05.694 the bridge and that it's not part of  
NOTE Confidence: 0.4833358

00:32:05.694 --> 00:32:07.241 the same repair network as LEM twos.

NOTE Confidence: 0.4833358

00:32:07.250 --> 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 --> 00:32:18.642 UDO in the lab has also been looking

NOTE Confidence: 0.36765093

00:32:18.642 --> 00:32:21.394 at a model of BRCA 1 deficient

NOTE Confidence: 0.36765093

00:32:21.394 --> 00:32:23.010 triple negative breast cancer.

NOTE Confidence: 0.36765093

00:32:23.010 --> 00:32:24.258 And so these again are cells

NOTE Confidence: 0.36765093

00:32:24.258 --> 00:32:25.090 treated with a laparib.

NOTE Confidence: 0.36765093

00:32:25.090 --> 00:32:27.250 This is just showing you the Dappy staining.

NOTE Confidence: 0.36765093

00:32:27.250 --> 00:32:29.383 I just want to this I think is a

NOTE Confidence: 0.36765093

00:32:29.383 --> 00:32:31.204 beautiful example of pointing out that

NOTE Confidence: 0.36765093

00:32:31.204 --> 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 --> 00:32:36.168 these ones are a little bit earlier.

NOTE Confidence: 0.36765093

00:32:36.170 --> 00:32:37.843 So you can still kind of see

NOTE Confidence: 0.36765093

00:32:37.843 --> 00:32:39.250 faintly that there's DNA staining.  
NOTE Confidence: 0.36765093

00:32:39.250 --> 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 --> 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 --> 00:32:48.448 with the nuclear localization signal.  
NOTE Confidence: 0.36765093

00:32:48.450 --> 00:32:50.320 So there's there's actually 2  
NOTE Confidence: 0.36765093

00:32:50.320 --> 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 --> 00:32:56.530 the presence of these bridges.  
NOTE Confidence: 0.36765093

00:32:56.530 --> 00:32:58.469 One of them is the kind of  
NOTE Confidence: 0.36765093

00:32:58.469 --> 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 --> 00:33:03.122 classic changes in nuclear shape that  
NOTE Confidence: 0.36765093

00:33:03.122 --> 00:33:04.690 we see that are coincident with this.  
NOTE Confidence: 0.36765093

00:33:04.690 --> 00:33:06.184 And this may become relevant if

NOTE Confidence: 0.36765093

00:33:06.184 --> 00:33:07.924 we think about whether we can use

NOTE Confidence: 0.36765093

00:33:07.924 --> 00:33:09.079 the prevalence of these structures

NOTE Confidence: 0.36765093

00:33:09.079 --> 00:33:10.050 as a biomarker,

NOTE Confidence: 0.36765093

00:33:10.050 --> 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 --> 00:33:15.300 This is just showing you that

NOTE Confidence: 0.36765093

00:33:15.300 --> 00:33:16.750 in this MDA 436 line,

NOTE Confidence: 0.36765093

00:33:16.750 --> 00:33:18.490 preliminarily what we see is that

NOTE Confidence: 0.36765093

00:33:18.490 --> 00:33:19.962 there's a dose dependent increase

NOTE Confidence: 0.36765093

00:33:19.962 --> 00:33:21.991 in the number of cells with these

NOTE Confidence: 0.36765093

00:33:21.991 --> 00:33:23.755 bridges in response to a laparib,

NOTE Confidence: 0.36765093

00:33:23.760 --> 00:33:25.923 whereas we don't see this in a

NOTE Confidence: 0.36765093

00:33:25.923 --> 00:33:27.571 different triple negative line that's

NOTE Confidence: 0.36765093

00:33:27.571 --> 00:33:29.557 BRCA 1 proficient and HR proficient.

NOTE Confidence: 0.5707516

00:33:32.040 --> 00:33:34.744 So I've shown you this that we likely

NOTE Confidence: 0.5707516

00:33:34.744 --> 00:33:36.839 have these persistent bridges,  
NOTE Confidence: 0.5707516

00:33:36.840 --> 00:33:38.960 they accumulate in the context of a laparib,  
NOTE Confidence: 0.5707516

00:33:38.960 --> 00:33:40.104 they recruit C gas.  
NOTE Confidence: 0.5707516

00:33:40.104 --> 00:33:41.534 But is there actually activation  
NOTE Confidence: 0.5707516

00:33:41.534 --> 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 --> 00:33:49.302 C gamp which activates sting  
NOTE Confidence: 0.5707516

00:33:49.302 --> 00:33:51.006 which phosphorylates TDK one and  
NOTE Confidence: 0.5707516

00:33:51.006 --> 00:33:52.806 IRF 3 and leads to interferon  
NOTE Confidence: 0.5707516

00:33:52.806 --> 00:33:55.310 stimulated gene expression.  
NOTE Confidence: 0.5707516

00:33:55.310 --> 00:33:57.515 So if we look at the GWB one cells  
NOTE Confidence: 0.5707516

00:33:57.515 --> 00:33:59.772 in the presence of a lab rib  
NOTE Confidence: 0.5707516

00:33:59.772 --> 00:34:01.670 compared to the vehicle control,  
NOTE Confidence: 0.5707516

00:34:01.670 --> 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 --> 00:34:05.870 much of an effect.

NOTE Confidence: 0.5707516

00:34:05.870 --> 00:34:08.349 But if we look at IRF 3 phosphorylation,

NOTE Confidence: 0.5707516

00:34:08.350 --> 00:34:11.724 we see that there is a stimulation

NOTE Confidence: 0.5707516

00:34:11.724 --> 00:34:14.020 of the phosphorylation of IRF 3.

NOTE Confidence: 0.5707516

00:34:14.020 --> 00:34:15.940 And if we look at the downstream consequence,

NOTE Confidence: 0.5707516

00:34:15.940 --> 00:34:18.005 which is interferon stimulated gene

NOTE Confidence: 0.5707516

00:34:18.005 --> 00:34:20.058 expression, just picking two of those genes,

NOTE Confidence: 0.5707516

00:34:20.060 --> 00:34:21.775 we do see that we can stimulate.

NOTE Confidence: 0.5707516

00:34:21.780 --> 00:34:23.664 We can see stimulation of interferon

NOTE Confidence: 0.5707516

00:34:23.664 --> 00:34:25.297 stimulated genes with the addition

NOTE Confidence: 0.5707516

00:34:25.297 --> 00:34:27.268 of ELABORA in this cell line.

NOTE Confidence: 0.5707516

00:34:27.268 --> 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 --> 00:34:34.699 on how intact the C gasting pathway is.

NOTE Confidence: 0.5707516

00:34:34.700 --> 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 --> 00:34:40.578 there is selection against the  
NOTE Confidence: 0.5707516

00:34:40.578 --> 00:34:42.560 pathway that I'm talking about.  
NOTE Confidence: 0.5707516

00:34:42.560 --> 00:34:44.315 But these cells do as you can see here,  
NOTE Confidence: 0.5707516

00:34:44.320 --> 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 --> 00:34:50.868 as we can probably get in this  
NOTE Confidence: 0.5707516

00:34:50.868 --> 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 --> 00:34:56.047 to drive an innate immune response.  
NOTE Confidence: 0.5707516

00:34:56.047 --> 00:34:57.776 This is the two people using this  
NOTE Confidence: 0.5707516

00:34:57.776 --> 00:34:59.239 in this field all the time.  
NOTE Confidence: 0.5707516

00:34:59.240 --> 00:35:01.116 And we get a pretty similar degree  
NOTE Confidence: 0.5707516

00:35:01.116 --> 00:35:02.909 of stimulation as we get with  
NOTE Confidence: 0.5707516

00:35:02.909 --> 00:35:03.839 the elaborate treatment.  
NOTE Confidence: 0.5707516

00:35:03.840 --> 00:35:05.870 So that may be kind of the top of what

NOTE Confidence: 0.5707516

00:35:05.928 --> 00:35:08.056 we can get in this particular cell line.

NOTE Confidence: 0.5707516

00:35:08.056 --> 00:35:10.360 So we do think although this is only

NOTE Confidence: 0.5707516

00:35:10.360 --> 00:35:12.265 about four fold increase longitude

NOTE Confidence: 0.5707516

00:35:12.265 --> 00:35:15.209 full change of two that this is that

NOTE Confidence: 0.5707516

00:35:15.209 --> 00:35:17.141 this is a pretty strong response

NOTE Confidence: 0.5707516

00:35:17.141 --> 00:35:18.520 for this cell type.

NOTE Confidence: 0.5707516

00:35:18.520 --> 00:35:22.152 So does the you know does this the

NOTE Confidence: 0.5707516

00:35:22.152 --> 00:35:24.825 response actually require C gas that

NOTE Confidence: 0.5707516

00:35:24.825 --> 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 --> 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 --> 00:35:34.783 and you can see the knock down by

NOTE Confidence: 0.5707516

00:35:34.783 --> 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.

NOTE Confidence: 0.5707516

00:35:37.340 --> 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 --> 00:35:42.377 the addition of a lab rib.  
NOTE Confidence: 0.5707516

00:35:42.380 --> 00:35:45.138 If we now knock down C gas,  
NOTE Confidence: 0.5707516

00:35:45.140 --> 00:35:47.606 what we can see is that this does to  
NOTE Confidence: 0.5707516

00:35:47.606 --> 00:35:49.820 some extent limit the activation.  
NOTE Confidence: 0.5707516

00:35:49.820 --> 00:35:52.020 But to what extent that is we're not,  
NOTE Confidence: 0.5707516

00:35:52.020 --> 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 --> 00:35:56.660 gas is completely responsible.  
NOTE Confidence: 0.5707516

00:35:56.660 --> 00:35:58.428 We're trying to be kind of very agnostic  
NOTE Confidence: 0.5707516

00:35:58.428 --> 00:35:59.780 about what is lying downstream.  
NOTE Confidence: 0.5707516

00:35:59.780 --> 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 knockout  
NOTE Confidence: 0.5707516

00:36:03.269 --> 00:36:04.925 Isagenix of these cell lines to  
NOTE Confidence: 0.5707516

00:36:04.925 --> 00:36:06.699 really look at how much sea gas

NOTE Confidence: 0.5707516

00:36:06.699 --> 00:36:07.659 is important for this

NOTE Confidence: 0.531161

00:36:07.660 --> 00:36:09.740 response and also of course

NOTE Confidence: 0.531161

00:36:09.740 --> 00:36:11.820 for the cell death mechanism.

NOTE Confidence: 0.531161

00:36:11.820 --> 00:36:13.720 One of the ideas that I set up was that

NOTE Confidence: 0.531161

00:36:13.768 --> 00:36:15.568 this nuclear envelope repair network

NOTE Confidence: 0.531161

00:36:15.568 --> 00:36:17.368 could be antagonizing surveillance by

NOTE Confidence: 0.531161

00:36:17.421 --> 00:36:19.290 the innate immune system and we have

NOTE Confidence: 0.531161

00:36:19.290 --> 00:36:20.970 some evidence that that's the case.

NOTE Confidence: 0.531161

00:36:20.970 --> 00:36:22.420 So just to remind you,

NOTE Confidence: 0.531161

00:36:22.420 --> 00:36:24.093 the idea is that Bath and this

NOTE Confidence: 0.531161

00:36:24.093 --> 00:36:25.905 LEM two protein come in to recruit

NOTE Confidence: 0.531161

00:36:25.905 --> 00:36:27.805 escorts to seal these breaks in the

NOTE Confidence: 0.531161

00:36:27.805 --> 00:36:29.235 nuclear envelope and this limits

NOTE Confidence: 0.531161

00:36:29.235 --> 00:36:30.966 sea gas access and activation.

NOTE Confidence: 0.531161

00:36:30.966 --> 00:36:34.482 So here is an experiment where

NOTE Confidence: 0.531161

00:36:34.482 --> 00:36:37.488 we have used siRNA to knock down  
NOTE Confidence: 0.531161

00:36:37.488 --> 00:36:39.360 the bath protein to test this.  
NOTE Confidence: 0.531161

00:36:39.360 --> 00:36:41.684 So again here you can see the  
NOTE Confidence: 0.531161

00:36:41.684 --> 00:36:43.057 interferon stimulated gene expression  
NOTE Confidence: 0.531161

00:36:43.057 --> 00:36:45.319 in a lab with elaborative treatment.  
NOTE Confidence: 0.531161

00:36:45.320 --> 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 --> 00:36:50.176 and consistent with another study  
NOTE Confidence: 0.531161

00:36:50.176 --> 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 --> 00:36:55.432 you also get a stimulation of  
NOTE Confidence: 0.531161

00:36:55.432 --> 00:36:56.563 an immune signaling,  
NOTE Confidence: 0.531161

00:36:56.570 --> 00:36:58.100 which suggests that just knocking  
NOTE Confidence: 0.531161

00:36:58.100 --> 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 --> 00:37:03.858 And that may be as cells are reforming

NOTE Confidence: 0.531161

00:37:03.858 --> 00:37:05.919 their nuclear envelope or some other

NOTE Confidence: 0.531161

00:37:05.919 --> 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 --> 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 --> 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 --> 00:37:18.510 down Bath and adding a lab rib,

NOTE Confidence: 0.531161

00:37:18.510 --> 00:37:20.883 which suggests that a lab rib actually

NOTE Confidence: 0.531161

00:37:20.883 --> 00:37:22.612 precipitates these kind of breaks

NOTE Confidence: 0.531161

00:37:22.612 --> 00:37:24.252 in the nuclear envelope because

NOTE Confidence: 0.531161

00:37:24.252 --> 00:37:25.950 of these entangled chromosomes.

NOTE Confidence: 0.531161

00:37:25.950 --> 00:37:27.390 And then normally Bath would

NOTE Confidence: 0.531161

00:37:27.390 --> 00:37:28.542 be suppressing the signaling

NOTE Confidence: 0.531161

00:37:28.542 --> 00:37:29.470 downstream of that event.

NOTE Confidence: 0.531161

00:37:29.470 --> 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 --> 00:37:34.110 So this is consistent with  
NOTE Confidence: 0.531161

00:37:34.110 --> 00:37:35.422 that kind of antagonism.  
NOTE Confidence: 0.633801

00:37:37.470 --> 00:37:40.364 So I just want to show you just briefly  
NOTE Confidence: 0.633801

00:37:40.364 --> 00:37:41.860 I because it's just you know we're cell  
NOTE Confidence: 0.633801

00:37:41.905 --> 00:37:43.345 biologists so we love to look at things.  
NOTE Confidence: 0.633801

00:37:43.350 --> 00:37:44.745 This is this really cool  
NOTE Confidence: 0.633801

00:37:44.745 --> 00:37:46.140 reconstruction of what one of  
NOTE Confidence: 0.633801

00:37:46.193 --> 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 --> 00:37:52.456 man one which is in yellow is actually  
NOTE Confidence: 0.633801

00:37:52.456 --> 00:37:54.778 localized to the mid body and the protein  
NOTE Confidence: 0.633801

00:37:54.778 --> 00:37:56.710 LEM 2 which is that nuclear repair  
NOTE Confidence: 0.633801

00:37:56.769 --> 00:37:58.869 protein you can see along this bridge.  
NOTE Confidence: 0.633801

00:37:58.870 --> 00:38:00.290 But you can see they're

NOTE Confidence: 0.633801

00:38:00.290 --> 00:38:01.426 actually in distinct regions.

NOTE Confidence: 0.633801

00:38:01.430 --> 00:38:04.014 As I mentioned LEM two is likely to

NOTE Confidence: 0.633801

00:38:04.014 --> 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 --> 00:38:11.739 man one is sitting on the mid body.

NOTE Confidence: 0.633801

00:38:11.740 --> 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 --> 00:38:18.827 there is a known checkpoint that

NOTE Confidence: 0.633801

00:38:18.827 --> 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 --> 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 --> 00:38:28.249 this is regulated by Aurora B,

NOTE Confidence: 0.633801

00:38:28.250 --> 00:38:29.458 which is interesting because

NOTE Confidence: 0.633801

00:38:29.458 --> 00:38:30.968 the Aurora kinases have also

NOTE Confidence: 0.633801

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 --> 00:38:37.810 really terribly successful clinically.  
NOTE Confidence: 0.633801

00:38:37.810 --> 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 --> 00:38:46.849 involved would be very interesting.  
NOTE Confidence: 0.633801

00:38:46.850 --> 00:38:49.685 So that and that is a reason why you  
NOTE Confidence: 0.633801

00:38:49.685 --> 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 --> 00:38:55.669 an obscision failure downstream of  
NOTE Confidence: 0.633801

00:38:55.669 --> 00:38:57.709 the failure to segregate chromosomes.  
NOTE Confidence: 0.633801

00:38:57.710 --> 00:38:59.730 And so that's something that  
NOTE Confidence: 0.633801

00:38:59.730 --> 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 --> 00:39:08.422 idea that these nuclear integrity defects

NOTE Confidence: 0.633801

00:39:08.422 --> 00:39:11.031 are the OR and these mitotic errors

NOTE Confidence: 0.633801

00:39:11.031 --> 00:39:12.901 and then nuclear integrity defects.

NOTE Confidence: 0.633801

00:39:12.910 --> 00:39:13.514 Could this,

NOTE Confidence: 0.633801

00:39:13.514 --> 00:39:15.628 could this be something that we actually

NOTE Confidence: 0.633801

00:39:15.628 --> 00:39:17.656 take advantage of as a biomarker?

NOTE Confidence: 0.633801

00:39:17.656 --> 00:39:19.366 This is something that we're

NOTE Confidence: 0.633801

00:39:19.366 --> 00:39:21.199 really is very preliminary,

NOTE Confidence: 0.633801

00:39:21.200 --> 00:39:23.200 but we're very interested in.

NOTE Confidence: 0.633801

00:39:23.200 --> 00:39:24.880 So you know as I've already pointed out,

NOTE Confidence: 0.633801

00:39:24.880 --> 00:39:26.840 when you have these persistent DNA bridges,

NOTE Confidence: 0.633801

00:39:26.840 --> 00:39:28.160 there is this relationship

NOTE Confidence: 0.633801

00:39:28.160 --> 00:39:29.480 between the two nuclei,

NOTE Confidence: 0.633801

00:39:29.480 --> 00:39:32.189 the result from that mitosis and there

NOTE Confidence: 0.633801

00:39:32.189 --> 00:39:34.600 are these changes in nuclear shape.

NOTE Confidence: 0.633801

00:39:34.600 --> 00:39:39.160 These are actually H&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 --> 00:39:44.990 and as well as Kurt Shopper.  
NOTE Confidence: 0.633801

00:39:44.990 --> 00:39:46.908 And one of the things we've been  
NOTE Confidence: 0.633801

00:39:46.908 --> 00:39:49.196 looking at is if we look at these  
NOTE Confidence: 0.633801

00:39:49.196 --> 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 --> 00:39:55.110 can we see these structures.  
NOTE Confidence: 0.633801

00:39:55.110 --> 00:39:57.030 And I think what we've been,  
NOTE Confidence: 0.633801

00:39:57.030 --> 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&E just to be honest.  
NOTE Confidence: 0.633801

00:40:01.190 --> 00:40:04.435 But but we're kind of excited that we  
NOTE Confidence: 0.633801

00:40:04.435 --> 00:40:06.654 think that we can see these kind of  
NOTE Confidence: 0.633801

00:40:06.654 --> 00:40:08.109 arrangements that are between cells.  
NOTE Confidence: 0.633801

00:40:08.110 --> 00:40:08.458 You know,  
NOTE Confidence: 0.633801

00:40:08.458 --> 00:40:09.502 they were not the first people  
NOTE Confidence: 0.633801

00:40:09.502 --> 00:40:10.468 to ever comment on this,  
NOTE Confidence: 0.633801

00:40:10.470 --> 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 --> 00:40:16.387 mechanism that may highlight why we  
NOTE Confidence: 0.633801

00:40:16.387 --> 00:40:18.625 should be paying more attention to  
NOTE Confidence: 0.633801

00:40:18.625 --> 00:40:20.670 the prevalence of these structures.  
NOTE Confidence: 0.633801

00:40:20.670 --> 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 --> 00:40:27.054 this may be a mitotic error  
NOTE Confidence: 0.633801

00:40:27.054 --> 00:40:28.110 that's much more  
NOTE Confidence: 0.74551356

00:40:28.193 --> 00:40:30.068 easy to perceive in the  
NOTE Confidence: 0.74551356

00:40:30.068 --> 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 --> 00:40:35.849 part of this to me is that you  
NOTE Confidence: 0.74551356

00:40:35.849 --> 00:40:37.279 know these there's already an

NOTE Confidence: 0.74551356

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 --> 00:40:42.668 push further with PARP inhibitors.

NOTE Confidence: 0.74551356

00:40:42.670 --> 00:40:44.518 But this could be a kind of non

NOTE Confidence: 0.74551356

00:40:44.518 --> 00:40:46.260 genomic way of assessing is there

NOTE Confidence: 0.74551356

00:40:46.260 --> 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 --> 00:40:51.498 line Because I see these mitotic

NOTE Confidence: 0.74551356

00:40:51.498 --> 00:40:53.268 errors that actually are such,

NOTE Confidence: 0.74551356

00:40:53.270 --> 00:40:55.286 so large that they can be

NOTE Confidence: 0.74551356

00:40:55.286 --> 00:40:56.630 perceived even in HNA.

NOTE Confidence: 0.74551356

00:40:56.630 --> 00:40:58.835 To really validate that we

NOTE Confidence: 0.74551356

00:40:58.835 --> 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 --> 00:41:03.704 convince ourselves that these

NOTE Confidence: 0.74551356

00:41:03.704 --> 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 --> 00:41:07.669 see in tissue culture cells.  
NOTE Confidence: 0.74551356

00:41:07.670 --> 00:41:09.030 And so to be able to do that,  
NOTE Confidence: 0.74551356

00:41:09.030 --> 00:41:10.927 we are working on validating some of  
NOTE Confidence: 0.74551356

00:41:10.927 --> 00:41:12.825 the antibodies that we've raised to  
NOTE Confidence: 0.74551356

00:41:12.825 --> 00:41:14.550 these specific nuclear envelope proteins.  
NOTE Confidence: 0.74551356

00:41:14.550 --> 00:41:16.083 I mentioned it's really hard to see  
NOTE Confidence: 0.74551356

00:41:16.083 --> 00:41:17.390 these bridges even with DNA stain.  
NOTE Confidence: 0.74551356

00:41:17.390 --> 00:41:19.126 You really have to have the right  
NOTE Confidence: 0.74551356

00:41:19.126 --> 00:41:20.642 molecule that you're looking for and  
NOTE Confidence: 0.74551356

00:41:20.642 --> 00:41:22.126 we think that these integral and a  
NOTE Confidence: 0.74551356

00:41:22.126 --> 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 --> 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 --> 00:41:33.146 bridges because we can specifically

NOTE Confidence: 0.74551356

00:41:33.146 --> 00:41:35.105 identify them with these antibodies.

NOTE Confidence: 0.74551356

00:41:35.105 --> 00:41:36.565 And then in addition,

NOTE Confidence: 0.74551356

00:41:36.570 --> 00:41:38.163 I think just to be a bit agnostic also,

NOTE Confidence: 0.74551356

00:41:38.170 --> 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 --> 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 --> 00:41:57.330 of micronuclei and chemical samples,

NOTE Confidence: 0.74551356

00:41:57.330 --> 00:41:58.650 which would be fantastic.

NOTE Confidence: 0.5170579

00:42:01.290 --> 00:42:03.058 And you know why I think that's so

NOTE Confidence: 0.5170579

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 --> 00:42:09.198 them is that there of course is an

NOTE Confidence: 0.5170579

00:42:09.198 --> 00:42:10.888 interest in expanding PARP inhibitors

NOTE Confidence: 0.5170579

00:42:10.945 --> 00:42:12.949 beyond you know breast and ovarian,

NOTE Confidence: 0.5170579

00:42:12.950 --> 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 --> 00:42:18.213 out one of these examples of the

NOTE Confidence: 0.5170579

00:42:18.213 --> 00:42:19.707 fact that there really are some

NOTE Confidence: 0.5170579

00:42:19.754 --> 00:42:21.068 amazing clinical responders.

NOTE Confidence: 0.5170579

00:42:21.070 --> 00:42:23.778 This is in pancreatic cancer here.

NOTE Confidence: 0.5170579

00:42:23.778 --> 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 --> 00:42:28.870 but I think anecdotally,

NOTE Confidence: 0.5170579

00:42:28.870 --> 00:42:31.089 we know there are triple negative breast

NOTE Confidence: 0.5170579

00:42:31.089 --> 00:42:32.913 cancers that respond to PARP inhibitors

NOTE Confidence: 0.5170579

00:42:32.913 --> 00:42:35.009 even if we don't understand why.

NOTE Confidence: 0.5170579

00:42:35.010 --> 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 --> 00:42:40.354 A subset of which respond to PARP inhibitors

NOTE Confidence: 0.5170579

00:42:40.354 --> 00:42:42.290 even though we don't understand why.

NOTE Confidence: 0.5170579

00:42:42.290 --> 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 --> 00:42:47.894 indicate where PARP inhibitors might

NOTE Confidence: 0.5170579

00:42:47.894 --> 00:42:50.416 be effective even when the molecular

NOTE Confidence: 0.5170579

00:42:50.416 --> 00:42:52.526 or genetic signature isn't understood.

NOTE Confidence: 0.7353201

00:42:54.610 --> 00:42:57.816 OK. So just to just to restate

NOTE Confidence: 0.7353201

00:42:57.816 --> 00:43:00.310 what I've told you today,

NOTE Confidence: 0.7353201

00:43:00.310 --> 00:43:01.890 while Laparov enhances the prevalence

NOTE Confidence: 0.7353201

00:43:01.890 --> 00:43:03.470 of these persistent DNA bridges,

NOTE Confidence: 0.7353201

00:43:03.470 --> 00:43:04.710 there's already more in

NOTE Confidence: 0.7353201

00:43:04.710 --> 00:43:05.950 an HR deficient context.  
NOTE Confidence: 0.7353201

00:43:05.950 --> 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 --> 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 --> 00:43:19.218 but both are seem to be recruited  
NOTE Confidence: 0.7353201

00:43:19.218 --> 00:43:20.190 to these bridges.  
NOTE Confidence: 0.7353201

00:43:20.190 --> 00:43:21.910 So that suggests that there  
NOTE Confidence: 0.7353201

00:43:21.910 --> 00:43:23.630 many of them are ruptured.  
NOTE Confidence: 0.7353201

00:43:23.630 --> 00:43:25.574 We're interested in whether  
NOTE Confidence: 0.7353201

00:43:25.574 --> 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 --> 00:43:31.441 could actually further stimulate  
NOTE Confidence: 0.7353201

00:43:31.441 --> 00:43:33.361 the innate immune signaling  
NOTE Confidence: 0.7353201

00:43:33.429 --> 00:43:35.669 downstream of these mitotic errors.

NOTE Confidence: 0.7353201

00:43:35.670 --> 00:43:37.952 And we're excited about the idea of

NOTE Confidence: 0.7353201

00:43:37.952 --> 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 --> 00:43:42.266 which as I said,

NOTE Confidence: 0.7353201

00:43:42.270 --> 00:43:45.922 we poorly need in terms of what

NOTE Confidence: 0.7353201

00:43:45.922 --> 00:43:47.666 our next steps are and what

NOTE Confidence: 0.7353201

00:43:47.666 --> 00:43:49.340 we're focusing on at the moment,

NOTE Confidence: 0.7353201

00:43:49.340 --> 00:43:51.074 where we really need to understand

NOTE Confidence: 0.7353201

00:43:51.074 --> 00:43:53.019 if this is really the canonical

NOTE Confidence: 0.7353201

00:43:53.020 --> 00:43:55.174 ISG expression is relevant here or

NOTE Confidence: 0.7353201

00:43:55.174 --> 00:43:57.092 perhaps there's some other downstream

NOTE Confidence: 0.7353201

00:43:57.092 --> 00:43:58.784 consequence that's running in

NOTE Confidence: 0.7353201

00:43:58.784 --> 00:44:01.260 parallel with the production of Isgs.

NOTE Confidence: 0.7353201

00:44:01.260 --> 00:44:01.822 That's important.

NOTE Confidence: 0.7353201

00:44:01.822 --> 00:44:02.103 Again,

NOTE Confidence: 0.7353201

00:44:02.103 --> 00:44:04.070 you get cell killing in a tumor  
NOTE Confidence: 0.7353201

00:44:04.123 --> 00:44:05.575 cell intrinsic way in a dish.  
NOTE Confidence: 0.7353201

00:44:05.580 --> 00:44:07.869 So we don't know if that's really  
NOTE Confidence: 0.7353201

00:44:07.869 --> 00:44:09.550 a consequence directly of anything  
NOTE Confidence: 0.7353201

00:44:09.550 --> 00:44:11.135 to do with ISG expression.  
NOTE Confidence: 0.7353201

00:44:11.140 --> 00:44:13.926 And so that's something that we're exploring.  
NOTE Confidence: 0.7353201

00:44:13.930 --> 00:44:16.110 We're also taking both candidate  
NOTE Confidence: 0.7353201

00:44:16.110 --> 00:44:18.290 approaches and unbiased screens to  
NOTE Confidence: 0.7353201

00:44:18.357 --> 00:44:20.583 identify what are the factors required  
NOTE Confidence: 0.7353201

00:44:20.583 --> 00:44:22.850 for the cell death in culture.  
NOTE Confidence: 0.7353201

00:44:22.850 --> 00:44:24.383 You in some ways you would have  
NOTE Confidence: 0.7353201

00:44:24.383 --> 00:44:26.014 thought this would have come out of  
NOTE Confidence: 0.7353201

00:44:26.014 --> 00:44:27.406 CRISPR screens which have been done.  
NOTE Confidence: 0.7353201

00:44:27.410 --> 00:44:28.538 But actually I think there are  
NOTE Confidence: 0.7353201

00:44:28.538 --> 00:44:29.954 a lot of reasons to think that  
NOTE Confidence: 0.7353201

00:44:29.954 --> 00:44:30.994 those screens weren't really set

NOTE Confidence: 0.7353201

00:44:30.994 --> 00:44:32.410 up to identify this mechanism.

NOTE Confidence: 0.7353201

00:44:32.410 --> 00:44:34.842 And so that's one of the things that

NOTE Confidence: 0.7353201

00:44:34.842 --> 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 --> 00:44:39.898 so we're using correlative light

NOTE Confidence: 0.7353201

00:44:39.898 --> 00:44:41.702 and electron microscopy to really

NOTE Confidence: 0.7353201

00:44:41.702 --> 00:44:43.467 understand what's happening in these

NOTE Confidence: 0.7353201

00:44:43.467 --> 00:44:45.686 DNA bridges and also to and get

NOTE Confidence: 0.7353201

00:44:45.686 --> 00:44:47.826 information about the DNA structure.

NOTE Confidence: 0.7353201

00:44:47.830 --> 00:44:49.998 We can do that by looking at accessibility

NOTE Confidence: 0.7353201

00:44:49.998 --> 00:44:52.428 to the TN 5 transpose ACE as an example,

NOTE Confidence: 0.7353201

00:44:52.430 --> 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 --> 00:44:58.579 based experiment as well.

NOTE Confidence: 0.7353201

00:44:58.580 --> 00:45:01.058 And then we're working with our

NOTE Confidence: 0.7353201

00:45:01.058 --> 00:45:03.022 partners at AstraZeneca to really  
NOTE Confidence: 0.7353201

00:45:03.022 --> 00:45:05.549 try to test whether we can use  
NOTE Confidence: 0.7353201

00:45:05.549 --> 00:45:08.152 these bridges as a as a biomarker,  
NOTE Confidence: 0.7353201

00:45:08.152 --> 00:45:10.980 you know at the very initial stages  
NOTE Confidence: 0.7353201

00:45:10.980 --> 00:45:12.258 in a really well controlled system.  
NOTE Confidence: 0.7353201

00:45:12.260 --> 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 --> 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 --> 00:45:26.106 you know,  
NOTE Confidence: 0.7353201

00:45:26.106 --> 00:45:28.044 with and without treatment with a  
NOTE Confidence: 0.7353201

00:45:28.044 --> 00:45:29.394 laparib or other PARP inhibitors.  
NOTE Confidence: 0.7353201

00:45:29.394 --> 00:45:31.662 And so looking at the H and AE of

NOTE Confidence: 0.7353201

00:45:31.662 --> 00:45:33.578 those data sets and doing that in a

NOTE Confidence: 0.7353201

00:45:33.578 --> 00:45:35.587 blinded way will really help us to

NOTE Confidence: 0.7353201

00:45:35.587 --> 00:45:36.809 understand whether this is something

NOTE Confidence: 0.7353201

00:45:36.809 --> 00:45:38.087 that's going to be worth pursuing.

NOTE Confidence: 0.3837364

00:45:40.210 --> 00:45:42.314 All right. So I just like to thank

NOTE Confidence: 0.3837364

00:45:42.314 --> 00:45:44.405 the people who did the work and then

NOTE Confidence: 0.3837364

00:45:44.405 --> 00:45:46.290 I'm happy to take any questions.

NOTE Confidence: 0.3837364

00:45:46.290 --> 00:45:48.593 We have a really great group working

NOTE Confidence: 0.3837364

00:45:48.593 --> 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 --> 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 --> 00:45:59.985 Carrie recently joined the team

NOTE Confidence: 0.3837364

00:45:59.985 --> 00:46:02.005 and she's going to be working on

NOTE Confidence: 0.3837364

00:46:02.005 --> 00:46:03.485 these screens for DNA repair.

NOTE Confidence: 0.3837364

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 --> 00:46:08.489 not DNA repair screens to identify the

NOTE Confidence: 0.3837364

00:46:08.490 --> 00:46:10.494 the mechanisms of cell death downstream

NOTE Confidence: 0.3837364

00:46:10.494 --> 00:46:12.768 of PARP inhibitors in the cell models.

NOTE Confidence: 0.3837364

00:46:12.770 --> 00:46:14.754 And I'll say just joined the lab and

NOTE Confidence: 0.3837364

00:46:14.754 --> 00:46:16.601 he's going to try to get our our

NOTE Confidence: 0.3837364

00:46:16.601 --> 00:46:18.210 tissue part of this up and going.

NOTE Confidence: 0.3837364

00:46:18.210 --> 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 --> 00:46:24.784 essential and in all aspects of

NOTE Confidence: 0.3837364

00:46:24.784 --> 00:46:26.752 getting us involved in this direction.

NOTE Confidence: 0.3837364

00:46:26.760 --> 00:46:29.315 It would not have happened without her

NOTE Confidence: 0.3837364

00:46:29.320 --> 00:46:31.357 and I'm happy to take any questions.

NOTE Confidence: 0.3837364

00:46:31.360 --> 00:46:31.960 Thanks.

NOTE Confidence: 0.26034585

00:46:38.460 --> 00:46:42.252 Yeah. Have you seen this

NOTE Confidence: 0.26034585

00:46:42.252 --> 00:46:44.899 type outside of other HRD

NOTE Confidence: 0.26034585

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 --> 00:47:00.412 you from the literature is strongly

NOTE Confidence: 0.3960918375

00:47:00.412 --> 00:47:02.433 suggestive that also in the contents of

NOTE Confidence: 0.3960918375

00:47:02.433 --> 00:47:04.554 bracket two we need mitosis to get cell

NOTE Confidence: 0.3960918375

00:47:04.554 --> 00:47:06.610 death you get innate immune signaling.

NOTE Confidence: 0.3960918375

00:47:06.610 --> 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 --> 00:47:12.060 I don't even think Connor we haven't

NOTE Confidence: 0.3960918375

00:47:12.060 --> 00:47:13.730 stained bracket 2 deficient cells.

NOTE Confidence: 0.3960918375

00:47:13.730 --> 00:47:15.464 So I don't think we've explicitly

NOTE Confidence: 0.3960918375

00:47:15.464 --> 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

NOTE Confidence: 0.3960918375

00:47:21.708 --> 00:47:23.823 it wasn't the same in a probably  
NOTE Confidence: 0.3960918375

00:47:23.823 --> 00:47:25.870 2 or a BRCA 2 deficient line.  
NOTE Confidence: 0.3960918375

00:47:25.870 --> 00:47:28.190 And and just to make the point you  
NOTE Confidence: 0.3960918375

00:47:28.190 --> 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 --> 00:47:37.390 you know tumor cells that respond  
NOTE Confidence: 0.3960918375

00:47:37.390 --> 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 --> 00:47:44.780 So that I think that if this is not going  
NOTE Confidence: 0.3960918375

00:47:44.842 --> 00:47:47.286 to be even limited just to HR deficiency,  
NOTE Confidence: 0.3960918375

00:47:47.286 --> 00:47:50.135 it's just one of the ways that honestly  
NOTE Confidence: 0.3960918375

00:47:50.135 --> 00:47:52.685 TAXOL HR deficiencies of HARP inhibitors  
NOTE Confidence: 0.3960918375

00:47:52.685 --> 00:47:55.680 and and even a radiation probably could  
NOTE Confidence: 0.3960918375

00:47:55.680 --> 00:47:58.350 all be stimulating the same pathway.  
NOTE Confidence: 0.3960918375

00:47:58.350 --> 00:48:00.694 Yeah, as a fault.

NOTE Confidence: 0.3960918375

00:48:00.694 --> 00:48:03.141 So I mean if if you're having an

NOTE Confidence: 0.3960918375

00:48:03.141 --> 00:48:04.955 inhibition of the main signaling,

NOTE Confidence: 0.3960918375

00:48:04.955 --> 00:48:07.385 would these cancers be potentially more

NOTE Confidence: 0.3960918375

00:48:07.385 --> 00:48:09.350 sensitive to alcoholic viruses or kind

NOTE Confidence: 0.3960918375

00:48:09.350 --> 00:48:11.593 of a you know alternative fall strategy?

NOTE Confidence: 0.3960918375

00:48:11.593 --> 00:48:14.239 I think that's a great question.

NOTE Confidence: 0.3960918375

00:48:14.240 --> 00:48:15.829 And I think that as you can

NOTE Confidence: 0.3960918375

00:48:15.829 --> 00:48:16.840 see what we've done,

NOTE Confidence: 0.3960918375

00:48:16.840 --> 00:48:19.376 we've completely ignored right,

NOTE Confidence: 0.3960918375

00:48:19.376 --> 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 --> 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 --> 00:48:32.616 the depth of what you just asked.

NOTE Confidence: 0.3960918375

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 --> 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 --> 00:48:43.818 Because inflammation driven by sting  
NOTE Confidence: 0.3960918375

00:48:43.818 --> 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 --> 00:48:49.680 Is, is actually a tumor driver C gas I think.  
NOTE Confidence: 0.3960918375

00:48:49.680 --> 00:48:52.980 And actually if you look at the number  
NOTE Confidence: 0.3960918375

00:48:52.980 --> 00:48:54.880 of tumors that have inactivated  
NOTE Confidence: 0.3960918375

00:48:54.880 --> 00:48:56.400 C gas versus sting,  
NOTE Confidence: 0.3960918375

00:48:56.400 --> 00:48:57.992 very few inactivate sting,  
NOTE Confidence: 0.3960918375

00:48:57.992 --> 00:49:00.740 the vast majority have inactivated C gas  
NOTE Confidence: 0.3960918375

00:49:00.740 --> 00:49:03.359 if you just look across you know that map.  
NOTE Confidence: 0.3960918375

00:49:03.360 --> 00:49:05.889 And so I do wonder if some of the  
NOTE Confidence: 0.3960918375

00:49:05.889 --> 00:49:08.337 signaling we're seeing is C gas dependent,

NOTE Confidence: 0.3960918375

00:49:08.340 --> 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 --> 00:49:13.590 because it's multiple roles and I

NOTE Confidence: 0.3960918375

00:49:13.590 --> 00:49:15.477 think that might be important to

NOTE Confidence: 0.3960918375

00:49:15.477 --> 00:49:16.857 tease out to think about.

NOTE Confidence: 0.3960918375

00:49:16.860 --> 00:49:19.940 Then how is this going to intersect

NOTE Confidence: 0.3960918375

00:49:19.940 --> 00:49:22.460 with approaches like oncolytic viruses.

NOTE Confidence: 0.3960918375

00:49:22.460 --> 00:49:24.628 So I think that's still one of the

NOTE Confidence: 0.3960918375

00:49:24.628 --> 00:49:26.365 confusions at the moment because

NOTE Confidence: 0.3960918375

00:49:26.365 --> 00:49:28.633 honestly there's very high profile papers

NOTE Confidence: 0.3960918375

00:49:28.633 --> 00:49:30.634 saying you know sting agonists would be

NOTE Confidence: 0.3960918375

00:49:30.634 --> 00:49:32.379 great and sting agonists are terrible.

NOTE Confidence: 0.3960918375

00:49:32.380 --> 00:49:33.490 And so that's probably going

NOTE Confidence: 0.3960918375

00:49:33.490 --> 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 --> 00:49:42.300 go go ahead I'll,  
NOTE Confidence: 0.46254796

00:49:42.300 --> 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 --> 00:49:50.732 cell lines that are HID deficient  
NOTE Confidence: 0.46254796

00:49:50.732 --> 00:49:54.110 where you could look at a lab rib  
NOTE Confidence: 0.46254796

00:49:54.110 --> 00:49:56.450 in one of these cell lines and  
NOTE Confidence: 0.46254796

00:49:56.450 --> 00:50:01.665 compromisers whether there's a role for  
NOTE Confidence: 0.46254796

00:50:01.665 --> 00:50:04.590 the sting activation in 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 --> 00:50:08.723 that that would be an easy way to  
NOTE Confidence: 0.46254796

00:50:08.723 --> 00:50:11.010 determine if if the immune activation,  
NOTE Confidence: 0.46254796

00:50:11.010 --> 00:50:13.538 activation is is important  
NOTE Confidence: 0.46254796

00:50:13.538 --> 00:50:15.090 or not really agree with you.  
NOTE Confidence: 0.46254796

00:50:15.090 --> 00:50:16.609 So I think that that is an  
NOTE Confidence: 0.46254796

00:50:16.609 --> 00:50:17.043 excellent experiment.  
NOTE Confidence: 0.46254796

00:50:17.050 --> 00:50:17.956 It is an experiment that needs

NOTE Confidence: 0.46254796

00:50:17.956 --> 00:50:19.130 to be done and it you're right,

NOTE Confidence: 0.46254796

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 --> 00:50:23.656 It hasn't been what our expertise

NOTE Confidence: 0.46254796

00:50:23.656 --> 00:50:25.430 has been in, but I agree with you

NOTE Confidence: 0.46254796

00:50:25.430 --> 00:50:26.510 that that's exactly the right.

NOTE Confidence: 0.46254796

00:50:26.510 --> 00:50:27.968 So we really need some genetic

NOTE Confidence: 0.46254796

00:50:27.968 --> 00:50:29.150 models to be able to,

NOTE Confidence: 0.46254796

00:50:29.150 --> 00:50:30.430 to, to do that.

NOTE Confidence: 0.46254796

00:50:30.430 --> 00:50:33.082 So I I completely agree Jeff has

NOTE Confidence: 0.46254796

00:50:33.082 --> 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 --> 00:50:40.990 mutational signature derived from

NOTE Confidence: 0.46254796

00:50:41.042 --> 00:50:42.534 wholexome sequencing indicates the

NOTE Confidence: 0.46254796

00:50:42.534 --> 00:50:43.653 effective homologous recombination

NOTE Confidence: 0.46254796

00:50:43.653 --> 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 --> 00:50:49.167 this is the only biomarker there is,

NOTE Confidence: 0.46254796

00:50:49.170 --> 00:50:52.124 is a kind of scoring genomic scarring.

NOTE Confidence: 0.46254796

00:50:52.130 --> 00:50:54.125 But the challenge I would say is,

NOTE Confidence: 0.46254796

00:50:54.130 --> 00:50:55.649 and I think Jeff will appreciate this,

NOTE Confidence: 0.46254796

00:50:55.650 --> 00:50:58.683 is that the cell may be HR defective now,

NOTE Confidence: 0.46254796

00:50:58.690 --> 00:51:00.804 but then it may become a resistant

NOTE Confidence: 0.46254796

00:51:00.804 --> 00:51:02.376 to PARP inhibitors because it's

NOTE Confidence: 0.46254796

00:51:02.376 --> 00:51:04.490 now HR proficient and it will still

NOTE Confidence: 0.46254796

00:51:04.490 --> 00:51:06.249 have the scarring left from the

NOTE Confidence: 0.46254796

00:51:06.249 --> 00:51:07.992 period where it was HR deficient.

NOTE Confidence: 0.46254796

00:51:07.992 --> 00:51:10.386 So that may help us to understand

NOTE Confidence: 0.46254796

00:51:10.386 --> 00:51:11.660 you know context.

NOTE Confidence: 0.46254796

00:51:11.660 --> 00:51:13.179 We don't have any reason to think

NOTE Confidence: 0.46254796

00:51:13.179 --> 00:51:14.896 someone has a germ on or somatic

NOTE Confidence: 0.46254796

00:51:14.896 --> 00:51:16.420 mutation that they could benefit for

NOTE Confidence: 0.46254796

00:51:16.469 --> 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 --> 00:51:22.522 that signature when there's no reason

NOTE Confidence: 0.46254796

00:51:22.522 --> 00:51:24.574 to be from the genomics already.

NOTE Confidence: 0.46254796

00:51:24.580 --> 00:51:25.658 So I don't think we're doing that.

NOTE Confidence: 0.46254796

00:51:25.660 --> 00:51:27.298 So we're not identifying those patients.

NOTE Confidence: 0.46254796

00:51:27.300 --> 00:51:29.220 So that's an access issue.

NOTE Confidence: 0.46254796

00:51:29.220 --> 00:51:31.194 We absolutely are using that when

NOTE Confidence: 0.46254796

00:51:31.194 --> 00:51:33.140 there's a reason to think that

NOTE Confidence: 0.46254796

00:51:33.140 --> 00:51:34.820 there is A and HR defect,

NOTE Confidence: 0.46254796

00:51:34.820 --> 00:51:36.230 but it can't tell us.

NOTE Confidence: 0.46254796

00:51:36.230 --> 00:51:37.430 It only tells us the history,

NOTE Confidence: 0.46254796

00:51:37.430 --> 00:51:38.650 it doesn't tell us presently

NOTE Confidence: 0.46254796

00:51:38.650 --> 00:51:39.870 what's happening in the tumor.

NOTE Confidence: 0.46254796

00:51:39.870 --> 00:51:41.186 And so I think that's the limitation.  
NOTE Confidence: 0.3711792

00:51:43.430 --> 00:51:44.190 Thanks for your question.  
NOTE Confidence: 0.3711792

00:51:47.150 --> 00:51:48.844 With the bridges, are those all contained  
NOTE Confidence: 0.3711792

00:51:48.844 --> 00:51:50.443 in cytoplasm or do those potentially  
NOTE Confidence: 0.3711792

00:51:50.443 --> 00:51:52.099 contend kind of extra targets for  
NOTE Confidence: 0.3711792

00:51:52.099 --> 00:51:53.525 antibodies and cars or something like  
NOTE Confidence: 0.3711792

00:51:53.525 --> 00:51:55.716 that that would be unique to I think  
NOTE Confidence: 0.3711792

00:51:55.716 --> 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 --> 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 --> 00:52:10.120 although you know escorts also repair holes,  
NOTE Confidence: 0.8885353

00:52:10.120 --> 00:52:12.040 temporary holes in the plasma membrane.  
NOTE Confidence: 0.8885353

00:52:12.040 --> 00:52:14.144 So I won't say that we've actually tested  
NOTE Confidence: 0.8885353

00:52:14.144 --> 00:52:16.235 that and that would be really interesting  
NOTE Confidence: 0.8885353

00:52:16.235 --> 00:52:18.196 to know whether that's the case.

NOTE Confidence: 0.8885353

00:52:18.196 --> 00:52:20.642 I mean it's interesting that these same

NOTE Confidence: 0.8885353

00:52:20.642 --> 00:52:23.177 factors actually man one in particular were

NOTE Confidence: 0.8885353

00:52:23.177 --> 00:52:25.679 all identified as being auto antibody.

NOTE Confidence: 0.8885353

00:52:25.680 --> 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 --> 00:52:32.033 targets of many nuclear proteins are.

NOTE Confidence: 0.8885353

00:52:32.040 --> 00:52:34.070 But I do think that that's interesting

NOTE Confidence: 0.8885353

00:52:34.070 --> 00:52:37.083 and there's some evidence that that

NOTE Confidence: 0.8885353

00:52:37.083 --> 00:52:38.781 the Lam 2 protein also probably

NOTE Confidence: 0.8885353

00:52:38.781 --> 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 --> 00:52:46.182 autoimmunity which would be consistent

NOTE Confidence: 0.8885353

00:52:46.182 --> 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 --> 00:52:51.830 does get surveilled through this

NOTE Confidence: 0.8885353

00:52:51.830 --> 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 --> 00:52:57.208 we we don't really what we see is

NOTE Confidence: 0.8885353

00:52:57.208 --> 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 --> 00:53:03.209 think it's just a just a highlight.

NOTE Confidence: 0.8885353

00:53:03.210 --> 00:53:05.847 This is why one has to be careful in

NOTE Confidence: 0.8885353

00:53:05.847 --> 00:53:08.101 assessing in this area particularly facts,

NOTE Confidence: 0.8885353

00:53:08.101 --> 00:53:09.847 profiles looking at cells that look

NOTE Confidence: 0.8885353

00:53:09.847 --> 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 --> 00:53:16.994 because they failed in cytokinesis.

NOTE Confidence: 0.8885353

00:53:16.994 --> 00:53:19.738 So now they're 4 N but they're

NOTE Confidence: 0.8885353

00:53:19.738 --> 00:53:21.490 actually no longer mitotic.

NOTE Confidence: 0.8885353

00:53:21.490 --> 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.