WEBVTT

00:00:00.000 --> 00:00:04.518 Just a minute after noon, so I'd like to.

00:00:04.520 --> 00:00:06.428 A few people are still arriving,

00:00:06.430 --> 00:00:10.083 but I'd like to to welcome everybody today

00:00:10.083 --> 00:00:12.834 to the Cancer Center ground grand Rounds.

00:00:12.840 --> 00:00:14.810 And for those of you who who don't know me,

00:00:14.810 --> 00:00:16.181 I'm Mark Lemmon.

00:00:16.181 --> 00:00:19.600 I'm stepping in for Eric Weiner today

00:00:19.600 --> 00:00:22.950 because Eric is otherwise engaged.

00:00:22.950 --> 00:00:25.440 I'm mark them and I'm deputy

00:00:25.440 --> 00:00:28.429 director of of the Cancer Centre.

00:00:28.430 --> 00:00:33.042 And so I'm I'm I'm channeling.

00:00:33.042 --> 00:00:36.210 Actually, which is why I won't do it so.

00:00:36.210 --> 00:00:37.137 But the great,

00:00:37.137 --> 00:00:40.339 great to have you all here and great to have.

NOTE Confidence: 0.780325306666667

00:00:40.340 --> 00:00:43.874 Louise Escobar Hoyos and rose and

NOTE Confidence: 0.780325306666667

00:00:43.874 --> 00:00:47.803 we know Zikula to talk with us

NOTE Confidence: 0.780325306666667

00:00:47.803 --> 00:00:51.753 today and we so we begin with with

NOTE Confidence: 0.780325306666667

00:00:51.753 --> 00:00:54.518 Doctor Louisa has Escobar holes.

NOTE Confidence: 0.780325306666667

00:00:54.520 --> 00:00:57.005 Who is an assistant professor

NOTE Confidence: 0.780325306666667

00:00:57.005 --> 00:00:58.496 of therapeutic radiology.

NOTE Confidence: 0.780325306666667

00:00:58.500 --> 00:01:00.642 She received her Masters degree in

NOTE Confidence: 0.780325306666667

00:01:00.642 --> 00:01:02.462 Biomedical Sciences at the University

NOTE Confidence: 0.780325306666667

00:01:02.462 --> 00:01:04.765 at Del Valley in Cali in Colombia.

NOTE Confidence: 0.780325306666667

00:01:04.770 --> 00:01:06.438 And then as a Fulbright Scholarship,

NOTE Confidence: 0.780325306666667

00:01:06.440 --> 00:01:08.690 pursued a cache in in cancer,

NOTE Confidence: 0.780325306666667

00:01:08.690 --> 00:01:10.038 molecular and cellular pharmacology

NOTE Confidence: 0.780325306666667

00:01:10.038 --> 00:01:11.386 at Stony Brook University,

NOTE Confidence: 0.780325306666667

00:01:11.390 --> 00:01:13.390 where she was mentored by

NOTE Confidence: 0.780325306666667

00:01:13.390 --> 00:01:14.590 Doctor Kenneth Schroyer,

NOTE Confidence: 0.780325306666667

00:01:14.590 --> 00:01:16.225 then completed her postdoctoral training

NOTE Confidence: 0.780325306666667

00:01:16.225 --> 00:01:18.210 at Memorial Sloan Kettering Cancer Center.

NOTE Confidence: 0.780325306666667

00:01:18.210 --> 00:01:20.800 Commented by Doctor Stephen Stephen

NOTE Confidence: 0.780325306666667

00:01:20.800 --> 00:01:23.390 Leach and Omar Abdel Wahab,

NOTE Confidence: 0.780325306666667

00:01:23.390 --> 00:01:26.946 and the overarching goal of Doctor Escobar.

NOTE Confidence: 0.780325306666667

00:01:26.950 --> 00:01:29.710 Hoyos's lab is to develop new

NOTE Confidence: 0.780325306666667

00:01:29.710 --> 00:01:31.589 approaches to tackling pancreatic

NOTE Confidence: 0.780325306666667

00:01:31.589 --> 00:01:34.427 and lung cancers with lots of.

NOTE Confidence: 0.780325306666667

00:01:34.430 --> 00:01:36.006 Really very exciting work.

NOTE Confidence: 0.780325306666667

00:01:36.006 --> 00:01:38.888 Exciting new work going on and lots

NOTE Confidence: 0.780325306666667

00:01:38.888 --> 00:01:41.103 of innovation and specifically her

NOTE Confidence: 0.780325306666667

00:01:41.103 --> 00:01:43.898 team is currently trying to seeking

NOTE Confidence: 0.780325306666667

00:01:43.898 --> 00:01:46.283 to understand and target somatic

NOTE Confidence: 0.780325306666667

00:01:46.283 --> 00:01:48.089 mutations and importantly aberrant

NOTE Confidence: 0.780325306666667

00:01:48.089 --> 00:01:50.303 RNA processing in these tumors in

NOTE Confidence: 0.780325306666667

00:01:50.303 --> 00:01:53.130 order to to develop novel therapies.

NOTE Confidence: 0.780325306666667

00:01:53.130 --> 00:01:55.398 So it's a great pleasure to have

NOTE Confidence: 0.780325306666667

00:01:55.398 --> 00:01:56.730 you start us off.

NOTE Confidence: 0.780325306666667

00:01:56.730 --> 00:01:58.508 Louisa and I look forward very much

NOTE Confidence: 0.780325306666667

00:01:58.508 --> 00:02:01.020 to your talk, so please take it away.

NOTE Confidence: 0.882051635384615

00:02:02.630 --> 00:02:05.892 Wonderful thank you Mark. Let me just

NOTE Confidence: 0.882051635384615

00:02:05.892 --> 00:02:08.928 can everyone see my presenter mode.

NOTE Confidence: 0.882051635384615

00:02:08.930 --> 00:02:10.995 Sorry not my presenter. My full slide

NOTE Confidence: 0.592765046166667

00:02:11.670 --> 00:02:14.120 slide that's all very good perfect. So

NOTE Confidence: 0.885106782105263

00:02:14.130 --> 00:02:16.447 thank you Mark again for that Nice

NOTE Confidence: 0.885106782105263

00:02:16.447 --> 00:02:18.189 introduction and thank you everyone

NOTE Confidence: 0.885106782105263

00:02:18.189 --> 00:02:20.241 for participating today in in the

NOTE Confidence: 0.885106782105263

00:02:20.241 --> 00:02:21.950 Cancer Center grand rounds and I'm

NOTE Confidence: 0.885106782105263

00:02:21.950 --> 00:02:24.136 excited to share with you a little bit

NOTE Confidence: 0.885106782105263

00:02:24.136 --> 00:02:25.935 of the research that we've been doing

NOTE Confidence: 0.885106782105263

00:02:25.986 --> 00:02:27.874 in our lab in terms of finding how

00:02:27.874 --> 00:02:30.540 altered our release by splicing is a

00:02:30.540 --> 00:02:32.730 driver event for pancreatic cancer.

00:02:32.730 --> 00:02:35.906 So if your disclosures I'm part of the

00:02:35.906 --> 00:02:38.488 Scientific Advisory Board of QDX Diagnostics,

00:02:38.490 --> 00:02:40.062 I won't be presenting the work

00:02:40.062 --> 00:02:41.789 that I have with them today.

00:02:41.790 --> 00:02:43.326 I'll be talking about this compound.

00:02:43.330 --> 00:02:45.195 This small molecule inhibitor of

00:02:45.195 --> 00:02:47.403 splicing that has been provided to

00:02:47.403 --> 00:02:49.398 us by age 3 biomedicine and currently

00:02:49.398 --> 00:02:51.560 we're in discussions to launch a

00:02:51.560 --> 00:02:53.470 clinical trial using this compound.

00:02:53.470 --> 00:02:54.970 Based on the research that I'm

00:02:54.970 --> 00:02:56.340 going to show you today.

00:02:56.340 --> 00:02:59.080 So for many of you,

00:02:59.080 --> 00:03:01.450 it's not unheard of that pancreatic

00:03:01.450 --> 00:03:04.479 cancer is a very lethal malignancy,

00:03:04.480 --> 00:03:07.420 and in here is just plotting

00:03:07.420 --> 00:03:09.380 the survival over time.

00:03:09.380 --> 00:03:10.969 For the major cancers and what we

00:03:10.969 --> 00:03:12.931 can see in this evidence is that

00:03:12.931 --> 00:03:14.761 unfortunately we haven't been able to

00:03:14.818 --> 00:03:16.883 make that much improvement in the five

00:03:16.883 --> 00:03:18.781 year survival rate of pancreatic cancer,

00:03:18.781 --> 00:03:21.478 and this could be attributed to many reasons.

00:03:21.478 --> 00:03:23.764 It's it's a. It's a disease that

00:03:23.764 --> 00:03:25.690 is diagnosed once it has been.

00:03:25.690 --> 00:03:26.710 It's already systemic.

00:03:26.710 --> 00:03:27.730 The first line,

00:03:27.730 --> 00:03:29.842 chemotherapy and immunotherapies,

00:03:29.842 --> 00:03:31.250 are ineffective,

NOTE Confidence: 0.885106782105263

00:03:31.250 --> 00:03:33.185 and the available targeted therapies

NOTE Confidence: 0.885106782105263

00:03:33.185 --> 00:03:35.385 are only available to 1% of

NOTE Confidence: 0.885106782105263

00:03:35.385 --> 00:03:36.710 the cases that have actionable,

NOTE Confidence: 0.885106782105263

00:03:36.710 --> 00:03:37.564 actionable mutations.

NOTE Confidence: 0.885106782105263

00:03:37.564 --> 00:03:39.699 So there is a really.

NOTE Confidence: 0.885106782105263

00:03:39.700 --> 00:03:42.108 Strong clinical need to understand more of

NOTE Confidence: 0.885106782105263

00:03:42.108 --> 00:03:44.540 these tumors and develop new treatments.

NOTE Confidence: 0.885106782105263

00:03:44.540 --> 00:03:46.367 So just to introduce a little bit

NOTE Confidence: 0.885106782105263

00:03:46.367 --> 00:03:47.849 of the mutational landscape for

NOTE Confidence: 0.885106782105263

00:03:47.849 --> 00:03:49.459 these tumors and mainly today,

NOTE Confidence: 0.885106782105263

00:03:49.460 --> 00:03:50.936 I'm talking about pancreatic

NOTE Confidence: 0.885106782105263

00:03:50.936 --> 00:03:53.150 ductal at no carcinomas or petax,

NOTE Confidence: 0.885106782105263

00:03:53.150 --> 00:03:55.684 the most common form of pancreatic cancer,

NOTE Confidence: 0.885106782105263

00:03:55.690 --> 00:03:57.922 so we know that there are driven by a

NOTE Confidence: 0.885106782105263

00:03:57.922 --> 00:03:59.944 first mutation, first hit mutation,

NOTE Confidence: 0.885106782105263

00:03:59.944 --> 00:04:01.536 activating mutations in cameras,

NOTE Confidence: 0.885106782105263

00:04:01.540 --> 00:04:04.109 and also is very common to find

NOTE Confidence: 0.885106782105263

00:04:04.110 --> 00:04:04.638 T53 mutations,

NOTE Confidence: 0.885106782105263

00:04:04.638 --> 00:04:06.222 so we'll talk about a little

NOTE Confidence: 0.885106782105263

00:04:06.222 --> 00:04:07.770 bit more of these mutations.

NOTE Confidence: 0.885106782105263

00:04:07.770 --> 00:04:10.227 There is also sometimes it appears that

NOTE Confidence: 0.885106782105263

00:04:10.227 --> 00:04:12.009 other tumor suppressors are mutated,

NOTE Confidence: 0.885106782105263

00:04:12.010 --> 00:04:14.516 and then after these four top genes.

NOTE Confidence: 0.885106782105263

00:04:14.520 --> 00:04:16.386 There's really a sea of mutations

NOTE Confidence: 0.885106782105263

00:04:16.386 --> 00:04:18.879 that appear at a very low frequency,

NOTE Confidence: 0.885106782105263

00:04:18.880 --> 00:04:22.000 so using mouse models over the

NOTE Confidence: 0.885106782105263

00:04:22.000 --> 00:04:24.095 last 1520 years or so we have been

NOTE Confidence: 0.885106782105263

00:04:24.095 --> 00:04:25.963 able to kind of dissect a little

NOTE Confidence: 0.885106782105263

00:04:25.963 --> 00:04:27.667 bit the genetics of this disease.

NOTE Confidence: 0.885106782105263

00:04:27.670 --> 00:04:29.836 We know that the normal pancreas,

NOTE Confidence: 0.885106782105263

00:04:29.840 --> 00:04:31.484 if we engineer key rest mutations

NOTE Confidence: 0.885106782105263

00:04:31.484 --> 00:04:33.200 into the US and ourselves,

NOTE Confidence: 0.885106782105263

00:04:33.200 --> 00:04:35.040 these mice will start develop,

NOTE Confidence: 0.885106782105263

00:04:35.040 --> 00:04:37.568 panning or pancreatic intraepithelial

NOTE Confidence: 0.885106782105263

00:04:37.568 --> 00:04:40.573 lesions that will progress into

NOTE Confidence: 0.885106782105263

00:04:40.573 --> 00:04:42.938 pancreatic cancer if we add

NOTE Confidence: 0.885106782105263

00:04:42.938 --> 00:04:45.240 an additional mutation in P50.

NOTE Confidence: 0.885106782105263

00:04:45.240 --> 00:04:46.488 And so basically,

NOTE Confidence: 0.885106782105263

00:04:46.488 --> 00:04:49.877 this is this tumor follows kind of a

NOTE Confidence: 0.885106782105263

00:04:49.877 --> 00:04:52.229 two hit hypothesis notes and model

NOTE Confidence: 0.885106782105263

00:04:52.229 --> 00:04:55.378 and all with the with you know to

NOTE Confidence: 0.885106782105263

00:04:55.378 --> 00:04:58.790 enhance the activity of kieras over the time.

NOTE Confidence: 0.885106782105263

00:04:58.790 --> 00:05:00.575 Now for many years we've known about

NOTE Confidence: 0.885106782105263

00:05:00.575 --> 00:05:02.349 these two mutations driving this disease,

NOTE Confidence: 0.885106782105263

00:05:02.350 --> 00:05:04.744 but really we haven't made much effort

NOTE Confidence: 0.885106782105263

00:05:04.744 --> 00:05:06.672 to understand how these oncoproteins

NOTE Confidence: 0.885106782105263

00:05:06.672 --> 00:05:09.612 cooperate in the case of pancreatic cancer,

NOTE Confidence: 0.885106782105263

00:05:09.620 --> 00:05:10.844 and even other tumors.

NOTE Confidence: 0.885106782105263

00:05:10.844 --> 00:05:12.680 So a few years ago when

NOTE Confidence: 0.827377530526316

00:05:12.750 --> 00:05:15.279 I was gonna start as a postdoc at MSK,

NOTE Confidence: 0.827377530526316

00:05:15.280 --> 00:05:18.458 these studies came out in the molecular

NOTE Confidence: 0.827377530526316

00:05:18.458 --> 00:05:21.148 subtypes of pancreatic cancer with the

NOTE Confidence: 0.827377530526316

00:05:21.148 --> 00:05:23.650 squamous and basal subtype being the

NOTE Confidence: 0.827377530526316

00:05:23.650 --> 00:05:25.538 most aggressive molecular subtypes.

NOTE Confidence: 0.827377530526316

00:05:25.538 --> 00:05:28.170 And when you look into what genes are

NOTE Confidence: 0.827377530526316

00:05:28.232 --> 00:05:30.657 differentially expressed into the subtype,

NOTE Confidence: 0.827377530526316

00:05:30.660 --> 00:05:33.909 there is a small subset of genes that it's

NOTE Confidence: 0.827377530526316

00:05:33.909 --> 00:05:36.017 overexpressed in this molecular subtype.

NOTE Confidence: 0.827377530526316

00:05:36.020 --> 00:05:38.044 And when you look into their mutation status,

NOTE Confidence: 0.827377530526316

00:05:38.050 --> 00:05:39.402 they're highly associated with

NOTE Confidence: 0.827377530526316

00:05:39.402 --> 00:05:41.476 gain of function mutant, P. 53.

NOTE Confidence: 0.827377530526316

00:05:41.476 --> 00:05:43.624 And these genes that are being

NOTE Confidence: 0.827377530526316

00:05:43.624 --> 00:05:46.490 enriched are the majority are codeine

NOTE Confidence: 0.827377530526316

00:05:46.490 --> 00:05:48.566 for splicing regulatory proteins.

NOTE Confidence: 0.827377530526316

00:05:48.570 --> 00:05:50.594 So after I read these reports I kind

NOTE Confidence: 0.827377530526316

00:05:50.594 --> 00:05:52.400 of got interested on understanding

NOTE Confidence: 0.827377530526316

00:05:52.400 --> 00:05:54.872 a little bit more alternative RNA

NOTE Confidence: 0.827377530526316

00:05:54.872 --> 00:05:57.409 splicing and just to remind everyone

NOTE Confidence: 0.827377530526316

00:05:57.409 --> 00:05:58.645 during alternative splicing.

NOTE Confidence: 0.827377530526316

00:05:58.650 --> 00:06:01.258 Not only we remove the introns of genes

NOTE Confidence: 0.827377530526316

00:06:01.258 --> 00:06:03.747 but also there could be a selective

NOTE Confidence: 0.827377530526316

00:06:03.750 --> 00:06:06.172 retention or skipping of exons and this

NOTE Confidence: 0.827377530526316

00:06:06.172 --> 00:06:09.018 can lead to proteins that had opposite

NOTE Confidence: 0.827377530526316

00:06:09.018 --> 00:06:11.622 functions or no protein being formed.

NOTE Confidence: 0.827377530526316

00:06:11.630 --> 00:06:13.415 And we all have our favorite gene,

NOTE Confidence: 0.827377530526316

00:06:13.420 --> 00:06:15.586 and sometimes we don't study the

NOTE Confidence: 0.827377530526316

00:06:15.586 --> 00:06:17.377 alternative splicing of these gene

NOTE Confidence: 0.827377530526316

00:06:17.377 --> 00:06:19.372 and this pathway in general is a

NOTE Confidence: 0.827377530526316

00:06:19.372 --> 00:06:21.170 very potent and plastic that can

NOTE Confidence: 0.827377530526316

00:06:21.170 --> 00:06:23.340 actually explain a lot of the features

NOTE Confidence: 0.827377530526316

00:06:23.340 --> 00:06:25.440 that happen in cancer cells.

NOTE Confidence: 0.827377530526316

00:06:25.440 --> 00:06:28.694 So based on those reports I

NOTE Confidence: 0.827377530526316

00:06:28.694 --> 00:06:29.576 asked the question,

NOTE Confidence: 0.827377530526316

00:06:29.576 --> 00:06:31.340 is there a connection between mutations

NOTE Confidence: 0.827377530526316

00:06:31.395 --> 00:06:33.466 and P53 and alterations in RNA splicing

NOTE Confidence: 0.827377530526316

00:06:33.466 --> 00:06:36.245 and so first we took the RNA sequencing

NOTE Confidence: 0.827377530526316

00:06:36.245 --> 00:06:38.393 from many patients and we divided

NOTE Confidence: 0.827377530526316

00:06:38.463 --> 00:06:40.538 them into three different groups,

NOTE Confidence: 0.827377530526316

00:06:40.540 --> 00:06:42.180 either if they had truncating.

NOTE Confidence: 0.827377530526316

00:06:42.180 --> 00:06:44.450 Mutations in P53 meaning loss

NOTE Confidence: 0.827377530526316

00:06:44.450 --> 00:06:46.653 of function mutations of P53,

NOTE Confidence: 0.827377530526316

00:06:46.653 --> 00:06:48.568 gain of function mutations or

NOTE Confidence: 0.827377530526316

00:06:48.568 --> 00:06:50.543 mutations that make the protein

00:06:50.543 --> 00:06:52.799 going from a tumor suppressor to

00:06:52.799 --> 00:06:55.151 an uncle protein or wild type P53.

00:06:55.151 --> 00:06:56.956 And we compared this glycine.

00:06:56.960 --> 00:06:58.840 Differences between these tumors and

00:06:58.840 --> 00:07:01.210 in the case of pancreatic cancer,

00:07:01.210 --> 00:07:03.610 the most common hotspot missense

00:07:03.610 --> 00:07:06.470 mutations are these four listed here.

00:07:06.470 --> 00:07:08.210 So here are the 1st results.

00:07:08.210 --> 00:07:10.706 So in in the X axis you have

00:07:10.706 --> 00:07:12.519 a measurement of alternative.

00:07:12.520 --> 00:07:15.229 Slicing of axons and the different tumors,

00:07:15.230 --> 00:07:17.606 and here is each one of the mutations.

00:07:17.610 --> 00:07:20.410 53 compared to the wild type P53 tumors,

00:07:20.410 --> 00:07:22.930 and each one of the hotspot mutations

00:07:22.930 --> 00:07:25.166 compared to truncated P53 and what you

13

00:07:25.166 --> 00:07:27.404 are can appreciate is that all these

NOTE Confidence: 0.827377530526316

00:07:27.404 --> 00:07:29.614 hotspot gain of function mutations

NOTE Confidence: 0.827377530526316

00:07:29.614 --> 00:07:31.698 change alternative splicing and the

NOTE Confidence: 0.827377530526316

00:07:31.698 --> 00:07:33.230 R175 one of the most common ones,

NOTE Confidence: 0.827377530526316

00:07:33.230 --> 00:07:34.594 actually changes the most.

NOTE Confidence: 0.827377530526316

00:07:34.594 --> 00:07:36.299 So based on those correlation

NOTE Confidence: 0.827377530526316

00:07:36.299 --> 00:07:37.930 studies we started asking well.

NOTE Confidence: 0.827377530526316

00:07:37.930 --> 00:07:40.090 Is P53 changing splicing

NOTE Confidence: 0.827377530526316

00:07:40.090 --> 00:07:41.710 and pancreatic cancer?

NOTE Confidence: 0.827377530526316

00:07:41.710 --> 00:07:43.360 So we went ahead and developed.

NOTE Confidence: 0.827377530526316

00:07:43.360 --> 00:07:45.240 Three different model system patient

NOTE Confidence: 0.827377530526316

00:07:45.240 --> 00:07:47.120 derived organoids where we can

NOTE Confidence: 0.827377530526316

00:07:47.184 --> 00:07:48.900 actually shut off the expression of

NOTE Confidence: 0.827377530526316

00:07:48.900 --> 00:07:51.556 the mutant P 53 and after doing deep

NOTE Confidence: 0.827377530526316

00:07:51.556 --> 00:07:53.366 RNA sequencing and splicing analysis,

NOTE Confidence: 0.827377530526316

00:07:53.370 --> 00:07:56.282 we can see that there are these different

14

NOTE Confidence: 0.827377530526316

00:07:56.282 --> 00:07:58.218 exons that are either preferentially

NOTE Confidence: 0.827377530526316

00:07:58.218 --> 00:08:00.513 retained in red or preferentially

NOTE Confidence: 0.827377530526316

00:08:00.513 --> 00:08:03.337 spliced out in the context of mutant

NOTE Confidence: 0.827377530526316

00:08:03.340 --> 00:08:05.728 P53 in complex to complement this

NOTE Confidence: 0.827377530526316

00:08:05.728 --> 00:08:08.650 model we generated a murine cell line,

NOTE Confidence: 0.827377530526316

00:08:08.650 --> 00:08:10.895 also with the same capacity

NOTE Confidence: 0.827377530526316

00:08:10.895 --> 00:08:13.510 to shut down mutant P 53.

NOTE Confidence: 0.827377530526316

00:08:13.510 --> 00:08:14.142 And again,

NOTE Confidence: 0.827377530526316

00:08:14.142 --> 00:08:15.722 we were seeing these changes

NOTE Confidence: 0.827377530526316

00:08:15.722 --> 00:08:17.080 or swapping of axons.

NOTE Confidence: 0.698071543428571

00:08:17.080 --> 00:08:20.380 And lastly, we took a

NOTE Confidence: 0.698071543428571

00:08:20.380 --> 00:08:22.172 pancreatic precancer mouse,

NOTE Confidence: 0.698071543428571

00:08:22.172 --> 00:08:24.532 panning organoids where we knocking

NOTE Confidence: 0.698071543428571

00:08:24.532 --> 00:08:27.536 the mutation of our 175 and again we

NOTE Confidence: 0.698071543428571

00:08:27.536 --> 00:08:29.581 were seeing that even in early stages

NOTE Confidence: 0.698071543428571

00:08:29.581 --> 00:08:32.053 after early 19 of the mutation we were

NOTE Confidence: 0.698071543428571

00:08:32.053 --> 00:08:34.556 seeing this differential splicing of exons,

NOTE Confidence: 0.698071543428571

00:08:34.560 --> 00:08:35.630 so we wanted to ask,

NOTE Confidence: 0.698071543428571

00:08:35.630 --> 00:08:37.520 what are the specific features

NOTE Confidence: 0.698071543428571

00:08:37.520 --> 00:08:39.608 of these exons that are being

NOTE Confidence: 0.698071543428571

00:08:39.608 --> 00:08:40.936 either retained or skipped?

NOTE Confidence: 0.698071543428571

00:08:40.940 --> 00:08:43.622 And we found that there is this this that.

NOTE Confidence: 0.698071543428571

00:08:43.630 --> 00:08:46.766 The retention of these axles is not random.

NOTE Confidence: 0.698071543428571

00:08:46.770 --> 00:08:48.714 All the promoted axons after splicing

NOTE Confidence: 0.698071543428571

00:08:48.714 --> 00:08:50.824 those ones that are going to be

NOTE Confidence: 0.698071543428571

00:08:50.824 --> 00:08:53.036 retained in the mature M RNA are highly

NOTE Confidence: 0.698071543428571

00:08:53.036 --> 00:08:55.424 enriched for seas while they're repressed,

NOTE Confidence: 0.698071543428571

00:08:55.430 --> 00:08:57.950 exiles were highly enriched in a S&amp;G's,

NOTE Confidence: 0.698071543428571

00:08:57.950 --> 00:09:00.656 suggesting that this was pretty much

NOTE Confidence: 0.698071543428571

00:09:00.656 --> 00:09:03.429 a program established in these cells,

NOTE Confidence: 0.698071543428571

00:09:03.430 --> 00:09:05.854 so we wanted to focus on what were

00:09:05.854 --> 00:09:08.302 the MRE's that were being coded by

00:09:08.302 --> 00:09:11.333 these gain of of policy axons and so

00:09:11.333 --> 00:09:14.150 here we're summing into one of these.

00:09:14.150 --> 00:09:15.578 Barneys Gap 17.

00:09:15.578 --> 00:09:17.958 We're in mice and human.

00:09:17.960 --> 00:09:19.010 This Exxon 17,

00:09:19.010 --> 00:09:20.760 which is a policy Axon,

00:09:20.760 --> 00:09:22.563 is alternatively spliced,

00:09:22.563 --> 00:09:26.770 and here are the raw sequencing of

00:09:26.879 --> 00:09:28.678 the of the reeds of this Axon and

00:09:28.678 --> 00:09:30.214 what you can appreciate is that

00:09:30.214 --> 00:09:32.174 whenever the mutant P 53 is present,

00:09:32.180 --> 00:09:33.815 there is higher rates versus

00:09:33.815 --> 00:09:35.450 when you knock it down.

00:09:35.450 --> 00:09:37.124 There is a decrease on the

00:09:37.124 --> 00:09:38.240 retention of these Axon,

NOTE Confidence: 0.698071543428571

00:09:38.240 --> 00:09:40.120 but not the neighboring axons,

NOTE Confidence: 0.698071543428571

00:09:40.120 --> 00:09:41.674 and we saw this pattern across

NOTE Confidence: 0.698071543428571

00:09:41.674 --> 00:09:43.644 the marine cell line that we had

NOTE Confidence: 0.698071543428571

00:09:43.644 --> 00:09:45.104 engineer in the panning organized.

NOTE Confidence: 0.698071543428571

00:09:45.110 --> 00:09:47.590 That we had also crisped.

NOTE Confidence: 0.698071543428571

00:09:47.590 --> 00:09:50.310 So from here we actually went and said,

NOTE Confidence: 0.698071543428571

00:09:50.310 --> 00:09:50.644 well,

NOTE Confidence: 0.698071543428571

00:09:50.644 --> 00:09:52.648 let's go back to patient derived

NOTE Confidence: 0.698071543428571

00:09:52.648 --> 00:09:55.001 samples and let's see if the retention

NOTE Confidence: 0.698071543428571

00:09:55.001 --> 00:09:57.271 of these policy accounting gap 17 is

NOTE Confidence: 0.698071543428571

00:09:57.271 --> 00:09:58.896 it exclusive for the R175 mutation,

NOTE Confidence: 0.698071543428571

00:09:58.896 --> 00:10:00.737 or is it also found in other

NOTE Confidence: 0.698071543428571

00:10:00.737 --> 00:10:02.640 gain of function mutants of P53?

NOTE Confidence: 0.698071543428571

00:10:02.640 --> 00:10:04.490 And the answer was yes,

NOTE Confidence: 0.698071543428571

00:10:04.490 --> 00:10:07.392 it's actually retained and not only are 175,

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NOTE Confidence: 0.698071543428571

00:10:07.392 --> 00:10:09.862 but other gain of function mutant P53.

NOTE Confidence: 0.698071543428571

00:10:09.862 --> 00:10:12.746 As you can appreciate here from this

NOTE Confidence: 0.698071543428571

00:10:12.746 --> 00:10:15.120 targeted PCR. So then the question what?

NOTE Confidence: 0.698071543428571

00:10:15.120 --> 00:10:16.476 It was well,

NOTE Confidence: 0.698071543428571

00:10:16.476 --> 00:10:19.188 what is the consequence of incorporating

NOTE Confidence: 0.698071543428571

00:10:19.188 --> 00:10:21.899 policy exons into M RNA's over time,

NOTE Confidence: 0.698071543428571

00:10:21.900 --> 00:10:23.820 and so when we started looking at all

NOTE Confidence: 0.698071543428571

00:10:23.820 --> 00:10:26.004 of the M RNA's that were incorporating

NOTE Confidence: 0.698071543428571

00:10:26.004 --> 00:10:28.360 policy axons in the presence of mutant P.

NOTE Confidence: 0.698071543428571

00:10:28.360 --> 00:10:28.744 53,

NOTE Confidence: 0.698071543428571

00:10:28.744 --> 00:10:31.432 we found that a family of proteins

NOTE Confidence: 0.698071543428571

00:10:31.432 --> 00:10:32.600 called the GPA,

NOTE Confidence: 0.698071543428571

00:10:32.600 --> 00:10:35.528 the GPA's activating proteins or gaps

NOTE Confidence: 0.698071543428571

00:10:35.528 --> 00:10:38.460 were actually gaining these policy Axon.

NOTE Confidence: 0.698071543428571

00:10:38.460 --> 00:10:41.004 In fact 25% of total gaps encoded by

NOTE Confidence: 0.698071543428571

00:10:41.004 --> 00:10:43.395 the human genome were gaining policy

NOTE Confidence: 0.698071543428571

00:10:43.395 --> 00:10:45.921 exons and just to remind everyone.

NOTE Confidence: 0.698071543428571

00:10:45.930 --> 00:10:47.184 The gaps do.

NOTE Confidence: 0.698071543428571

00:10:47.184 --> 00:10:49.274 They actually accelerate the GTP

NOTE Confidence: 0.698071543428571

00:10:49.274 --> 00:10:51.206 hydrolysis of Ras proteins so

NOTE Confidence: 0.698071543428571

00:10:51.206 --> 00:10:53.586 they bring it from the on state,

NOTE Confidence: 0.698071543428571

00:10:53.590 --> 00:10:56.950 which is bound to GTP to the

NOTE Confidence: 0.698071543428571

00:10:56.950 --> 00:10:59.269 off state bound to GDP.

NOTE Confidence: 0.698071543428571

00:10:59.270 --> 00:11:01.205 And just to give you a sense of what,

NOTE Confidence: 0.698071543428571

00:11:01.210 --> 00:11:03.520 how was this exon impacting the

NOTE Confidence: 0.698071543428571

00:11:03.520 --> 00:11:05.941 protein we were seeing that these

NOTE Confidence: 0.698071543428571

00:11:05.941 --> 00:11:08.341 policy actions were inframe and when

NOTE Confidence: 0.698071543428571

00:11:08.341 --> 00:11:10.928 they got translated they encoded.

NOTE Confidence: 0.698071543428571

00:11:10.930 --> 00:11:12.156 For prolines,

NOTE Confidence: 0.698071543428571

00:11:12.156 --> 00:11:15.328 highly rich proline tails in the

NOTE Confidence: 0.698071543428571

00:11:15.328 --> 00:11:17.482 sea terminus of the parties and

NOTE Confidence: 0.698071543428571

00:11:17.482 --> 00:11:20.274 here is just an example to show

NOTE Confidence: 0.698071543428571

00:11:20.274 --> 00:11:22.264 you that actually these are

NOTE Confidence: 0.900612551666667

00:11:22.270 --> 00:11:24.520 different molecular weights of the protein.

NOTE Confidence: 0.900612551666667

00:11:24.520 --> 00:11:26.290 Here is the promoted by

NOTE Confidence: 0.900612551666667

00:11:26.290 --> 00:11:28.070 P53 with the policy Exxon.

NOTE Confidence: 0.900612551666667

00:11:28.070 --> 00:11:29.774 And here's the repressed

NOTE Confidence: 0.900612551666667

00:11:29.774 --> 00:11:31.904 P53 isoform of gap 17.

NOTE Confidence: 0.900612551666667

00:11:31.910 --> 00:11:33.378 Without the policy Axon,

NOTE Confidence: 0.900612551666667

00:11:33.378 --> 00:11:35.580 so both can be produced and

NOTE Confidence: 0.900612551666667

00:11:35.654 --> 00:11:37.489 translated in in the self.

NOTE Confidence: 0.900612551666667

00:11:37.490 --> 00:11:39.332 So at this point we were

NOTE Confidence: 0.900612551666667

00:11:39.332 --> 00:11:40.950 faced with the question well.

NOTE Confidence: 0.900612551666667

00:11:40.950 --> 00:11:45.644 What happens with the CARAS state of either

NOTE Confidence: 0.900612551666667

00:11:45.644 --> 00:11:48.830 GTP bound state or GDP bound bound state?

NOTE Confidence: 0.900612551666667

00:11:48.830 --> 00:11:51.236 Whenever you have a plus policy

NOTE Confidence: 0.900612551666667

00:11:51.236 --> 00:11:54.809 gap 17 or a minus policy gap 17,

NOTE Confidence: 0.900612551666667

00:11:54.810 --> 00:11:57.750 and so we did this in cell experiments

NOTE Confidence: 0.900612551666667

00:11:57.750 --> 00:12:00.650 where we actually first overexpress

NOTE Confidence: 0.900612551666667

00:12:00.650 --> 00:12:04.575 either the policy gap 17 or the minus

NOTE Confidence: 0.900612551666667

00:12:04.575 --> 00:12:07.676 policy gap 17 and we actually did a

NOTE Confidence: 0.900612551666667

00:12:07.676 --> 00:12:10.636 pull down to capture GTP bound K rest.

NOTE Confidence: 0.900612551666667

00:12:10.640 --> 00:12:11.848 And then we did.

NOTE Confidence: 0.900612551666667

00:12:11.848 --> 00:12:14.111 We used an antibody that it's only

NOTE Confidence: 0.900612551666667

00:12:14.111 --> 00:12:16.415 recognizing the mutant form of kiras

NOTE Confidence: 0.900612551666667

00:12:16.420 --> 00:12:20.144 to determine the the the levels of

NOTE Confidence: 0.900612551666667

00:12:20.144 --> 00:12:23.443 active cares in these cells and

NOTE Confidence: 0.900612551666667

00:12:23.443 --> 00:12:25.558 what we found was interesting,

NOTE Confidence: 0.900612551666667

00:12:25.560 --> 00:12:28.800 which is in the presence of policy gap 17.

NOTE Confidence: 0.900612551666667

00:12:28.800 --> 00:12:30.960 The isoform promoted by mutant P.

NOTE Confidence: 0.900612551666667

00:12:30.960 --> 00:12:31.470 53.

NOTE Confidence: 0.900612551666667

00:12:31.470 --> 00:12:35.040 The levels of active care as were

00:12:35.040 --> 00:12:36.060 actually maintained.

00:12:36.060 --> 00:12:38.508 However, as soon as we overexpress

00:12:38.508 --> 00:12:40.810 the minus policy gap 17 that.

00:12:40.810 --> 00:12:43.730 Isoform that is repressed by mutant P 53.

00:12:43.730 --> 00:12:45.907 We saw that the levels of active

00:12:45.907 --> 00:12:47.873 care has decreased and also the

00:12:47.873 --> 00:12:49.811 active levels of Arc which is

00:12:49.811 --> 00:12:51.872 downstream of of cameras were

00:12:51.872 --> 00:12:53.126 also significantly decreased,

00:12:53.130 --> 00:12:55.906 and so it was interesting to see kind

00:12:55.906 --> 00:12:58.684 of like the different effects on the

00:12:58.684 --> 00:13:01.589 active form of Keras in the presence

00:13:01.589 --> 00:13:04.466 or absence of this gap 17 isoforms.

00:13:04.470 --> 00:13:06.927 So then we went and did a

00:13:06.927 --> 00:13:09.190 self free essay where we took

00:13:09.190 --> 00:13:11.030 while type carrots or mutant.

NOTE Confidence: 0.900612551666667

00:13:11.030 --> 00:13:11.818 The arrest,

NOTE Confidence: 0.900612551666667

00:13:11.818 --> 00:13:14.576 and we incubated it with either the

NOTE Confidence: 0.900612551666667

00:13:14.576 --> 00:13:17.192 policy gap 17 or the minus policy gap

NOTE Confidence: 0.900612551666667

00:13:17.192 --> 00:13:20.292 17 and what you can see is that there

NOTE Confidence: 0.900612551666667

00:13:20.292 --> 00:13:22.828 was no much difference in the cell.

NOTE Confidence: 0.900612551666667

00:13:22.828 --> 00:13:25.460 Free assays in terms of their capacity

NOTE Confidence: 0.900612551666667

00:13:25.534 --> 00:13:27.819 to hydrolyze GTP bound cameras,

NOTE Confidence: 0.900612551666667

00:13:27.820 --> 00:13:30.277 and this was very odd and surprising

NOTE Confidence: 0.900612551666667

00:13:30.277 --> 00:13:33.173 to us because actually in the cells

NOTE Confidence: 0.900612551666667

00:13:33.173 --> 00:13:34.941 they were maintaining different

NOTE Confidence: 0.900612551666667

00:13:34.941 --> 00:13:37.240 levels of Keras bound to GTP.

NOTE Confidence: 0.900612551666667

00:13:37.240 --> 00:13:39.400 So this made us go back to the drawing

NOTE Confidence: 0.900612551666667

00:13:39.400 --> 00:13:41.060 board and start thinking about.

NOTE Confidence: 0.900612551666667

00:13:41.060 --> 00:13:43.550 What happens in the context of

NOTE Confidence: 0.900612551666667

00:13:43.550 --> 00:13:45.929 cells in the activity of gaps?

NOTE Confidence: 0.900612551666667

00:13:45.930 --> 00:13:48.372 It turns out that gaps are

NOTE Confidence: 0.900612551666667

00:13:48.372 --> 00:13:50.000 usually cytoplasmic proteins that

NOTE Confidence: 0.900612551666667

00:13:50.067 --> 00:13:52.167 when calls to deactivate Keras,

NOTE Confidence: 0.900612551666667

00:13:52.170 --> 00:13:54.300 they go to the membrane and

NOTE Confidence: 0.900612551666667

00:13:54.300 --> 00:13:56.170 that's when they actually promote

NOTE Confidence: 0.900612551666667

00:13:56.170 --> 00:13:58.070 the hydrolysis of the GTP.

NOTE Confidence: 0.900612551666667

00:13:58.070 --> 00:14:00.296 What we were seeing was the following

NOTE Confidence: 0.900612551666667

00:14:00.296 --> 00:14:02.262 and the presence of mutant P53.

NOTE Confidence: 0.900612551666667

00:14:02.262 --> 00:14:04.734 When you have the policy gap

NOTE Confidence: 0.900612551666667

00:14:04.734 --> 00:14:05.970 17 being expressed,

NOTE Confidence: 0.900612551666667

00:14:05.970 --> 00:14:07.965 the gap mainly localizes into

NOTE Confidence: 0.900612551666667

00:14:07.965 --> 00:14:10.430 the title plasm of the cell.

NOTE Confidence: 0.900612551666667

00:14:10.430 --> 00:14:12.074 Even when we gave it signals

NOTE Confidence: 0.900612551666667

00:14:12.074 --> 00:14:13.850 to go to the membrane.

NOTE Confidence: 0.900612551666667

00:14:13.850 --> 00:14:15.926 However, when you knock down P.

NOTE Confidence: 0.900612551666667

00:14:15.930 --> 00:14:17.950 53 out of the cells,

NOTE Confidence: 0.900612551666667

00:14:17.950 --> 00:14:21.145 you can see that there is this the the

NOTE Confidence: 0.900612551666667

00:14:21.145 --> 00:14:24.730 gap 17 that is now not expressing policy.

NOTE Confidence: 0.900612551666667

00:14:24.730 --> 00:14:27.736 Exxon now can more likely reach

NOTE Confidence: 0.900612551666667

00:14:27.736 --> 00:14:30.376 the membrane and promote the

NOTE Confidence: 0.900612551666667

00:14:30.376 --> 00:14:31.987 hydrolysis of Keras.

NOTE Confidence: 0.900612551666667

00:14:31.990 --> 00:14:34.048 And so we were excited to find

NOTE Confidence: 0.900612551666667

00:14:34.048 --> 00:14:35.681 these because that led us to

NOTE Confidence: 0.900612551666667

00:14:35.681 --> 00:14:37.277 a model where we had for the

NOTE Confidence: 0.8646090091

00:14:37.342 --> 00:14:39.052 first time kind of discover

NOTE Confidence: 0.8646090091

00:14:39.052 --> 00:14:40.762 how these two owner proteins,

NOTE Confidence: 0.8646090091

00:14:40.770 --> 00:14:42.760 mutant cares and mutant 53

NOTE Confidence: 0.8646090091

00:14:42.760 --> 00:14:44.352 synergizes in the following.

NOTE Confidence: 0.8646090091

00:14:44.360 --> 00:14:46.920 OK, our model suggests that in the presence

NOTE Confidence: 0.8646090091

00:14:46.920 --> 00:14:50.115 of a wild type B 53 or the loss of P53,

NOTE Confidence: 0.8646090091

00:14:50.115 --> 00:14:52.840 the cells actually lose policy

NOTE Confidence: 0.8646090091

00:14:52.840 --> 00:14:55.670 axons across multiple M RNA's,

NOTE Confidence: 0.8646090091

00:14:55.670 --> 00:14:58.974 mainly the gap in RNA's and after

NOTE Confidence: 0.8646090091

00:14:58.974 --> 00:15:01.082 this M RNA gets translated.

NOTE Confidence: 0.8646090091

00:15:01.082 --> 00:15:03.530 It encodes gaps that actually are

NOTE Confidence: 0.8646090091

00:15:03.610 --> 00:15:06.322 efficient at reaching the membrane and

NOTE Confidence: 0.8646090091

00:15:06.322 --> 00:15:09.505 being more efficient at hydrolyzing GTP

NOTE Confidence: 0.8646090091

00:15:09.505 --> 00:15:12.475 bound cameras and promoting tumor growth,

NOTE Confidence: 0.8646090091

00:15:12.480 --> 00:15:14.430 but not as much as.

NOTE Confidence: 0.8646090091

00:15:14.430 --> 00:15:16.128 When you have the hotspot mutant,

NOTE Confidence: 0.8646090091

00:15:16.130 --> 00:15:18.398 because now this time you are

NOTE Confidence: 0.8646090091

00:15:18.398 --> 00:15:21.126 gaining a policy Axon and when that

NOTE Confidence: 0.8646090091

00:15:21.126 --> 00:15:23.394 mRNA gets translated it has now

NOTE Confidence: 0.8646090091

00:15:23.394 --> 00:15:26.339 these reach domain of prolines that

NOTE Confidence: 0.8646090091

00:15:26.339 --> 00:15:28.824 prevented from reaching the membrane.

NOTE Confidence: 0.8646090091

00:15:28.830 --> 00:15:30.618 Maintaining an active care

NOTE Confidence: 0.8646090091

00:15:30.618 --> 00:15:32.853 estate and more tumor growth.

NOTE Confidence: 0.8646090091

00:15:32.860 --> 00:15:35.191 So just to go back to our model and

NOTE Confidence: 0.8646090091

00:15:35.191 --> 00:15:37.519 the genetics of pancreatic cancer.

NOTE Confidence: 0.8646090091

00:15:37.520 --> 00:15:39.606 So I've told you before that you

NOTE Confidence: 0.8646090091

00:15:39.606 --> 00:15:41.761 needed Karras and mutant P 53 and

NOTE Confidence: 0.8646090091

00:15:41.761 --> 00:15:43.549 what our findings had suggested is

NOTE Confidence: 0.8646090091

00:15:43.618 --> 00:15:45.767 that in the presence of just mutant.

NOTE Confidence: 0.8646090091

00:15:45.770 --> 00:15:48.146 The rest you still have the active rest,

NOTE Confidence: 0.8646090091

00:15:48.150 --> 00:15:50.910 but then when mutant P 53 comes specifically,

NOTE Confidence: 0.8646090091

00:15:50.910 --> 00:15:53.314 the gain of function mutant of P53,

NOTE Confidence: 0.8646090091

00:15:53.314 --> 00:15:56.702 you Now have an altered RNA splicing

NOTE Confidence: 0.8646090091

00:15:56.702 --> 00:15:58.996 and and a feedback loop that now

NOTE Confidence: 0.8646090091

00:15:58.996 --> 00:16:01.030 prevents the gaps from being active.

NOTE Confidence: 0.8646090091

00:16:01.030 --> 00:16:04.009 And then in this way you can enhance the

NOTE Confidence: 0.8646090091

00:16:04.009 --> 00:16:06.091 oncogenic signaling and activity of key

NOTE Confidence: 0.8646090091

00:16:06.091 --> 00:16:09.369 areas and this is our model system currently.

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NOTE Confidence: 0.8646090091

00:16:09.370 --> 00:16:11.176 So that was great and we published

NOTE Confidence: 0.8646090091

00:16:11.176 --> 00:16:12.709 this a couple of years ago.

NOTE Confidence: 0.8646090091

00:16:12.710 --> 00:16:14.222 So then we came back into the

NOTE Confidence: 0.8646090091

00:16:14.222 --> 00:16:15.850 lab and we started thinking,

NOTE Confidence: 0.8646090091

00:16:15.850 --> 00:16:16.276 well,

NOTE Confidence: 0.8646090091

00:16:16.276 --> 00:16:18.832 how can we target RNA splicing

NOTE Confidence: 0.8646090091

00:16:18.832 --> 00:16:20.630 and pancreatic cancer cells?

NOTE Confidence: 0.8646090091

00:16:20.630 --> 00:16:22.874 And so recently,

NOTE Confidence: 0.8646090091

00:16:22.874 --> 00:16:25.866 this small molecule compound,

NOTE Confidence: 0.8646090091

00:16:25.870 --> 00:16:28.607 H3 B 8800 it started being tested

NOTE Confidence: 0.8646090091

00:16:28.607 --> 00:16:31.229 in phase one clinical trials,

NOTE Confidence: 0.8646090091

00:16:31.230 --> 00:16:34.541 and they got interested in our research

NOTE Confidence: 0.8646090091

00:16:34.541 --> 00:16:37.160 with pancreatic cancer and mutant 53.

NOTE Confidence: 0.8646090091

00:16:37.160 --> 00:16:39.610 So basically what H3 B 8800 does.

NOTE Confidence: 0.8646090091

00:16:39.610 --> 00:16:41.140 It binds to one of the.

NOTE Confidence: 0.8646090091

00:16:41.140 --> 00:16:44.020 Course splicing proteins as F3V1 and

00:16:44.020 --> 00:16:46.428 prevents this whole machinery the

00:16:46.428 --> 00:16:48.463 spliceosome to bind and recognize

00:16:48.463 --> 00:16:51.160 fully the M RNA's, and so we were.

00:16:51.160 --> 00:16:52.220 Our hypothesis was well,

00:16:52.220 --> 00:16:54.280 if mutant P53 tumors really

00:16:54.280 --> 00:16:56.340 depend on ultra RNA splicing,

00:16:56.340 --> 00:16:58.476 they'd be more sensitive to toddler.

00:16:58.480 --> 00:17:00.930 They would be more sensitive

00:17:00.930 --> 00:17:03.380 to any perturbation into the

00:17:03.471 --> 00:17:06.472 splicing machinery with the AD 800,

00:17:06.472 --> 00:17:09.130 so we launched what we call a

00:17:09.130 --> 00:17:11.464 mouse trial where we took mice.

00:17:11.470 --> 00:17:14.458 That either had tumors that had

00:17:14.458 --> 00:17:16.958 mutant P53 in them, so that's red,

00:17:16.960 --> 00:17:19.528 or that lacked mutant 53 inone

NOTE Confidence: 0.8646090091

00:17:19.528 --> 00:17:20.812 which are blue.

NOTE Confidence: 0.8646090091

00:17:20.820 --> 00:17:23.442 And then we randomize these animals

NOTE Confidence: 0.8646090091

00:17:23.442 --> 00:17:25.939 to either receive 8800 or vehicle.

NOTE Confidence: 0.8646090091

00:17:25.939 --> 00:17:28.297 And what you can appreciate is

NOTE Confidence: 0.8646090091

00:17:28.297 --> 00:17:29.979 that the solid lines,

NOTE Confidence: 0.8646090091

00:17:29.980 --> 00:17:32.256 which are the animals that receive 8800,

NOTE Confidence: 0.8646090091

00:17:32.256 --> 00:17:34.536 they all benefited from having

NOTE Confidence: 0.8646090091

00:17:34.536 --> 00:17:36.360 from receiving the compound.

NOTE Confidence: 0.8646090091

00:17:36.360 --> 00:17:36.753 However,

NOTE Confidence: 0.8646090091

00:17:36.753 --> 00:17:38.718 the animals that survive and

NOTE Confidence: 0.8646090091

00:17:38.718 --> 00:17:40.697 benefited the most were those

NOTE Confidence: 0.8646090091

00:17:40.697 --> 00:17:43.174 ones that had mutant P53 in them,

NOTE Confidence: 0.8646090091

00:17:43.174 --> 00:17:44.686 suggesting that these mutations

NOTE Confidence: 0.8646090091

00:17:44.686 --> 00:17:45.820 sensitizes these tumors.

NOTE Confidence: 0.8646090091

00:17:45.820 --> 00:17:48.480 To this lysine modulator.

NOTE Confidence: 0.8646090091

00:17:48.480 --> 00:17:51.600 And when we did RNA splicing

NOTE Confidence: 0.8646090091

00:17:51.600 --> 00:17:53.606 analysis and after we treated

NOTE Confidence: 0.8646090091

00:17:53.606 --> 00:17:55.420 these tumors with the 8800,

NOTE Confidence: 0.8646090091

00:17:55.420 --> 00:17:58.020 we can nicely see how.

NOTE Confidence: 0.832197701666667

00:17:58.020 --> 00:18:00.174 H3 B 8800 was repressing the

NOTE Confidence: 0.832197701666667

00:18:00.174 --> 00:18:02.600 retention of that policy Axon in the

NOTE Confidence: 0.832197701666667

00:18:02.600 --> 00:18:04.735 cells in a function as a function

NOTE Confidence: 0.832197701666667

00:18:04.806 --> 00:18:06.910 depending on the concentration.

NOTE Confidence: 0.832197701666667

00:18:06.910 --> 00:18:08.590 So you know other words.

NOTE Confidence: 0.832197701666667

00:18:08.590 --> 00:18:10.822 This compound was reversing the key

NOTE Confidence: 0.832197701666667

00:18:10.822 --> 00:18:12.966 splicing events that we had seen

NOTE Confidence: 0.832197701666667

00:18:12.966 --> 00:18:15.094 in the presence of mutant P. 53.

NOTE Confidence: 0.832197701666667

00:18:15.094 --> 00:18:17.712 Lastly, we have now established a human

NOTE Confidence: 0.832197701666667

00:18:17.712 --> 00:18:20.608 model where we have isogenix cells that

NOTE Confidence: 0.832197701666667

00:18:20.608 --> 00:18:22.890 express different forms of mutant P.

NOTE Confidence: 0.832197701666667

00:18:22.890 --> 00:18:24.766 53 and we know that when we

32

00:18:24.766 --> 00:18:26.510 treat them with this compound,

00:18:26.510 --> 00:18:28.900 the mutants and particularly are

00:18:28.900 --> 00:18:31.290 more sensitive to these compounds

00:18:31.290 --> 00:18:33.084 when you compare them to the

00:18:33.084 --> 00:18:34.802 counterparts when they don't have P53

00:18:34.802 --> 00:18:36.877 or when they have a wild type P53.

00:18:36.877 --> 00:18:38.719 So based on these results we

00:18:38.719 --> 00:18:41.108 are now in discussions with HB,

00:18:41.110 --> 00:18:44.430 biomedicine and row Invad sciences,

00:18:44.430 --> 00:18:46.350 who recently bought the 88.

00:18:46.350 --> 00:18:47.685 100 compound because we would

00:18:47.685 --> 00:18:49.020 like to start a phase.

00:18:49.020 --> 00:18:50.580 Two clinical trial where

00:18:50.580 --> 00:18:52.140 we combine Gemma Broxton,

00:18:52.140 --> 00:18:53.568 which is one of the first

00:18:53.568 --> 00:18:54.520 gamma standard of care,

NOTE Confidence: 0.832197701666667

00:18:54.520 --> 00:18:56.660 chemotherapeutic lines for pancreatic

NOTE Confidence: 0.832197701666667

00:18:56.660 --> 00:18:59.335 cancer patients and start escalating

NOTE Confidence: 0.832197701666667

00:18:59.335 --> 00:19:01.696 doses of 8800 for patients whose

NOTE Confidence: 0.832197701666667

00:19:01.696 --> 00:19:03.716 tumors have gained a function.

NOTE Confidence: 0.832197701666667

00:19:03.720 --> 00:19:06.168 Mutant of P 53 so hopefully

NOTE Confidence: 0.832197701666667

00:19:06.168 --> 00:19:08.340 we can launch this soon.

NOTE Confidence: 0.832197701666667

00:19:08.340 --> 00:19:09.270 So let's back.

NOTE Confidence: 0.832197701666667

00:19:09.270 --> 00:19:11.942 Let's go back to you know what are

NOTE Confidence: 0.832197701666667

00:19:11.942 --> 00:19:14.540 the mutations that Dr pancreatic cancer?

NOTE Confidence: 0.832197701666667

00:19:14.540 --> 00:19:15.748 What have we understood

NOTE Confidence: 0.832197701666667

00:19:15.748 --> 00:19:17.258 and how can we target?

NOTE Confidence: 0.832197701666667

00:19:17.260 --> 00:19:19.508 To drive personalized medicine,

NOTE Confidence: 0.832197701666667

00:19:19.508 --> 00:19:20.070 so,

NOTE Confidence: 0.832197701666667

00:19:20.070 --> 00:19:21.622 as I mentioned before,

NOTE Confidence: 0.832197701666667

00:19:21.622 --> 00:19:23.562 we now understand that KIERAS

NOTE Confidence: 0.832197701666667

00:19:23.562 --> 00:19:25.393 mutations are the most common

NOTE Confidence: 0.832197701666667

00:19:25.393 --> 00:19:27.113 mutations and they are required

NOTE Confidence: 0.832197701666667

00:19:27.113 --> 00:19:29.030 hit mutation to form tumors.

NOTE Confidence: 0.832197701666667

00:19:29.030 --> 00:19:31.918 We know that 10% of the cases have

NOTE Confidence: 0.832197701666667

00:19:31.918 --> 00:19:33.368 familiar pancreatic cancer and

NOTE Confidence: 0.832197701666667

00:19:33.368 --> 00:19:35.664 most of them have mutations in ATM

NOTE Confidence: 0.832197701666667

00:19:35.664 --> 00:19:38.134 and when they have these mutations

NOTE Confidence: 0.832197701666667

00:19:38.134 --> 00:19:40.209 they are giving PARP inhibitors

NOTE Confidence: 0.832197701666667

00:19:40.210 --> 00:19:43.126 and that's why we do molecular

NOTE Confidence: 0.832197701666667

00:19:43.130 --> 00:19:44.790 molecular profiling industry rumors

NOTE Confidence: 0.832197701666667

00:19:44.790 --> 00:19:47.280 to identify this cohort of patients.

NOTE Confidence: 0.832197701666667

00:19:47.280 --> 00:19:49.624 To have actionable mutations.

NOTE Confidence: 0.832197701666667

00:19:49.624 --> 00:19:51.968 We also know that,

NOTE Confidence: 0.832197701666667

00:19:51.970 --> 00:19:53.394 as I mentioned before,

NOTE Confidence: 0.832197701666667

00:19:53.394 --> 00:19:56.110 that 30% of the sporadic pancreatic tumors,

NOTE Confidence: 0.832197701666667

00:19:56.110 --> 00:19:58.448 which are the most common ones are

NOTE Confidence: 0.832197701666667

00:19:58.448 --> 00:20:00.673 driven by gain of function 53.

NOTE Confidence: 0.832197701666667

00:20:00.673 --> 00:20:02.688 And as I mentioned before,

NOTE Confidence: 0.832197701666667

00:20:02.690 --> 00:20:05.012 we're hoping to start a clinical

NOTE Confidence: 0.832197701666667

00:20:05.012 --> 00:20:06.218 trial using 8800.

NOTE Confidence: 0.832197701666667

00:20:06.218 --> 00:20:08.786 These glycine inhibitors to see if

NOTE Confidence: 0.832197701666667

00:20:08.786 --> 00:20:11.711 we can bring a targeted therapy

NOTE Confidence: 0.832197701666667

00:20:11.711 --> 00:20:13.787 for these sporadic tumors.

NOTE Confidence: 0.832197701666667

00:20:13.790 --> 00:20:15.974 Now we're still facing the challenge

NOTE Confidence: 0.832197701666667

00:20:15.974 --> 00:20:18.210 that we still don't understand.

NOTE Confidence: 0.832197701666667

00:20:18.210 --> 00:20:20.320 30. What is the mutation?

NOTE Confidence: 0.832197701666667

00:20:20.320 --> 00:20:23.035 That drives the other 30% of

NOTE Confidence: 0.832197701666667

00:20:23.035 --> 00:20:25.610 pancreatic tumors because we also,

NOTE Confidence: 0.832197701666667

00:20:25.610 --> 00:20:27.591 because we already know that the other

NOTE Confidence: 0.832197701666667

00:20:27.591 --> 00:20:30.015 30% is driven by loss of function P.

NOTE Confidence: 0.832197701666667

00:20:30.020 --> 00:20:30.311 53.

NOTE Confidence: 0.832197701666667

00:20:30.311 --> 00:20:32.057 So for these two last groups.

NOTE Confidence: 0.832197701666667

00:20:32.060 --> 00:20:32.457 Unfortunately,

NOTE Confidence: 0.832197701666667

00:20:32.457 --> 00:20:35.633 right now we don't have any targeted therapy

NOTE Confidence: 0.832197701666667

00:20:35.633 --> 00:20:38.718 or any trials that are going to launch here,

NOTE Confidence: 0.832197701666667

00:20:38.720 --> 00:20:40.496 so we were curious to know

NOTE Confidence: 0.832197701666667

00:20:40.496 --> 00:20:41.680 well what is sporadic,

NOTE Confidence: 0.832197701666667

00:20:41.680 --> 00:20:44.068 what other mutations, Dr,

NOTE Confidence: 0.832197701666667

00:20:44.068 --> 00:20:47.053 sporadic tumors of pancreatic cancer,

NOTE Confidence: 0.832197701666667

00:20:47.060 --> 00:20:49.022 and so to answer that question

NOTE Confidence: 0.832197701666667

00:20:49.022 --> 00:20:50.330 I mentioned before that.

NOTE Confidence: 0.832197701666667

00:20:50.330 --> 00:20:52.946 You know there is a such a a

NOTE Confidence: 0.832197701666667

00:20:52.946 --> 00:20:55.026 large number of mutations that

NOTE Confidence: 0.832197701666667

00:20:55.026 --> 00:20:57.750 appear in very low frequencies,

NOTE Confidence: 0.832197701666667

00:20:57.750 --> 00:20:59.798 but it's hard to study each one of

NOTE Confidence: 0.832197701666667

00:20:59.798 --> 00:21:01.338 these mutations to understand well.

NOTE Confidence: 0.832197701666667

00:21:01.340 --> 00:21:03.355 Are they driver mutations or

NOTE Confidence: 0.832197701666667

00:21:03.355 --> 00:21:04.967 are they passenger mutations?

NOTE Confidence: 0.832197701666667

00:21:04.970 --> 00:21:06.854 And so we took an inform

NOTE Confidence: 0.832197701666667

00:21:06.854 --> 00:21:08.110 approach where we went

NOTE Confidence: 0.8599037

00:21:08.178 --> 00:21:10.446 back to the basic contact concept.

NOTE Confidence: 0.8599037

00:21:10.450 --> 00:21:11.962 Sorry of mutual esclusiva,

NOTE Confidence: 0.8599037

00:21:11.962 --> 00:21:15.190 so just to remind everyone we know that

NOTE Confidence: 0.8599037

00:21:15.190 --> 00:21:17.410 mutations may be mutually exclusive,

NOTE Confidence: 0.8599037

00:21:17.410 --> 00:21:20.338 meaning that if P53 is present.

NOTE Confidence: 0.8599037

00:21:20.340 --> 00:21:22.398 The mutation in P53 is present,

NOTE Confidence: 0.8599037

00:21:22.400 --> 00:21:25.433 then it would turn into a viable tumor cell.

NOTE Confidence: 0.8599037

00:21:25.440 --> 00:21:28.420 If other mutation is present but not P53,

NOTE Confidence: 0.8599037

00:21:28.420 --> 00:21:29.460 it could be viable,

NOTE Confidence: 0.8599037

00:21:29.460 --> 00:21:31.116 but if both mutations are present,

NOTE Confidence: 0.8599037

00:21:31.120 --> 00:21:32.860 it could be synthetic, lethal,

NOTE Confidence: 0.8599037

00:21:32.860 --> 00:21:35.182 and the mutual exclusivity of these

NOTE Confidence: 0.8599037

00:21:35.182 --> 00:21:37.550 mutations is because sometimes these mutual

NOTE Confidence: 0.8599037

00:21:37.550 --> 00:21:39.836 exclusive mutations either have the same

NOTE Confidence: 0.8599037

00:21:39.836 --> 00:21:42.328 function or impact the same pathway and

NOTE Confidence: 0.8599037

00:21:42.328 --> 00:21:44.460 that's what makes them driver mutations.

NOTE Confidence: 0.8599037

00:21:44.460 --> 00:21:47.680 So we started conducting a mutual exclusivity

NOTE Confidence: 0.8599037

00:21:47.680 --> 00:21:50.159 analysis by taking advantage of C.

NOTE Confidence: 0.8599037

00:21:50.160 --> 00:21:50.910 Bioportal.

NOTE Confidence: 0.8599037

00:21:50.910 --> 00:21:53.160 Which has the.

NOTE Confidence: 0.8599037

00:21:53.160 --> 00:21:56.100 Mutation signatures of over 3000

NOTE Confidence: 0.8599037

00:21:56.100 --> 00:21:59.040 patient samples of pancreatic cancer,

NOTE Confidence: 0.8599037

00:21:59.040 --> 00:22:01.084 and so the 1st results that we

NOTE Confidence: 0.8599037

00:22:01.084 --> 00:22:03.046 derive from this analysis are are

NOTE Confidence: 0.8599037

00:22:03.046 --> 00:22:05.080 shown here in this volcano plot.

NOTE Confidence: 0.8599037

00:22:05.080 --> 00:22:07.555 So on the right hand side we have the

NOTE Confidence: 0.8599037

00:22:07.555 --> 00:22:09.535 mutations that Co occur with mutant P.

NOTE Confidence: 0.8599037

00:22:09.540 --> 00:22:11.380 53 and in the left hand side we

NOTE Confidence: 0.8599037

00:22:11.380 --> 00:22:13.481 have the mutations that are mutually

NOTE Confidence: 0.8599037

00:22:13.481 --> 00:22:15.605 exclusive for P53 and this was the

NOTE Confidence: 0.8599037

00:22:15.605 --> 00:22:17.714 side of the volcano that we were

NOTE Confidence: 0.8599037

00:22:17.714 --> 00:22:19.494 interested in because this potentially

NOTE Confidence: 0.8599037

00:22:19.494 --> 00:22:21.793 could tell us what mutations were

NOTE Confidence: 0.8599037

00:22:21.793 --> 00:22:24.127 driving this disease aside from mutant.

NOTE Confidence: 0.8599037

00:22:24.130 --> 00:22:27.208 53 so as a as a proof of concept,

NOTE Confidence: 0.8599037

00:22:27.210 --> 00:22:28.794 key results in the middle is

NOTE Confidence: 0.8599037

00:22:28.794 --> 00:22:29.586 the first mutation.

NOTE Confidence: 0.8599037

00:22:29.590 --> 00:22:31.508 It appears for all of the tumors,

NOTE Confidence: 0.8599037

00:22:31.510 --> 00:22:34.046 but here's where it got surprising to us.

NOTE Confidence: 0.8599037

00:22:34.050 --> 00:22:36.120 One of the most mutually exclusive

NOTE Confidence: 0.8599037

00:22:36.120 --> 00:22:39.450 mutations to P53 was mutation in SF3B1.

NOTE Confidence: 0.8599037

00:22:39.450 --> 00:22:42.310 It's a score splicing protein.

NOTE Confidence: 0.8599037

00:22:42.310 --> 00:22:44.907 Then it on this same side we

40

NOTE Confidence: 0.8599037

00:22:44.907 --> 00:22:46.669 have mutations in RBM 10,

NOTE Confidence: 0.8599037

00:22:46.670 --> 00:22:49.210 which is another splicing factor.

NOTE Confidence: 0.8599037

00:22:49.210 --> 00:22:50.935 But on the core occurring

NOTE Confidence: 0.8599037

00:22:50.935 --> 00:22:52.610 side we had a U2AF1,

NOTE Confidence: 0.8599037

00:22:52.610 --> 00:22:54.060 again another mutation in another.

NOTE Confidence: 0.8599037

00:22:54.060 --> 00:22:54.850 License factor,

NOTE Confidence: 0.8599037

00:22:54.850 --> 00:22:57.220 so if our hypothesis was true,

NOTE Confidence: 0.8599037

00:22:57.220 --> 00:22:58.999 it's potentially that

NOTE Confidence: 0.8599037

00:22:58.999 --> 00:23:00.778 mutually exclusive mutations,

NOTE Confidence: 0.8599037

00:23:00.780 --> 00:23:03.972 meaning S3B1 and RBM 10 could be

NOTE Confidence: 0.8599037

00:23:03.972 --> 00:23:06.918 drivers of pancreatic cancer and just

NOTE Confidence: 0.8599037

00:23:06.918 --> 00:23:09.906 assuming what type of mutations are

NOTE Confidence: 0.8599037

00:23:09.906 --> 00:23:12.520 present in S4B1S4B1 in pancreatic

NOTE Confidence: 0.8599037

00:23:12.520 --> 00:23:15.620 cancer has a driver mutation.

NOTE Confidence: 0.8599037

00:23:15.620 --> 00:23:17.804 Very hot spot mutation in case 700.

NOTE Confidence: 0.8599037

00:23:17.810 --> 00:23:21.464 E RBM 10 is mainly truncating mutation.

NOTE Confidence: 0.8599037

00:23:21.470 --> 00:23:23.690 So basically you're losing the

NOTE Confidence: 0.8599037

00:23:23.690 --> 00:23:26.982 function of RBM 10 and U2AF1 has

NOTE Confidence: 0.8599037

00:23:26.982 --> 00:23:29.566 a hotspot mutation in S34F.

NOTE Confidence: 0.8599037

00:23:29.566 --> 00:23:31.746 So we our question was,

NOTE Confidence: 0.8599037

00:23:31.750 --> 00:23:34.216 are any of these three mutations

NOTE Confidence: 0.8599037

00:23:34.216 --> 00:23:35.449 driving pancreatic cancer?

NOTE Confidence: 0.8599037

00:23:35.450 --> 00:23:38.201 And so we took advantage and we

NOTE Confidence: 0.8599037

00:23:38.201 --> 00:23:39.380 started generating genetically

NOTE Confidence: 0.8599037

00:23:39.447 --> 00:23:40.968 engineered mouse models.

NOTE Confidence: 0.8599037

00:23:40.970 --> 00:23:42.430 So here's the case.

NOTE Confidence: 0.8599037

00:23:42.430 --> 00:23:44.620 C model system where it's only

NOTE Confidence: 0.8599037

00:23:44.699 --> 00:23:46.599 driven by ACARAS mutation.

NOTE Confidence: 0.8599037

00:23:46.600 --> 00:23:48.532 And what we found and what we

NOTE Confidence: 0.8599037

00:23:48.532 --> 00:23:50.215 expected was that these animals

NOTE Confidence: 0.8599037

00:23:50.215 --> 00:23:52.185 should only form pannings or

00:23:52.185 --> 00:23:54.080 pancreatic and triphenyl neoplasias,

00:23:54.080 --> 00:23:55.724 those precancer states.

00:23:55.724 --> 00:24:00.260 So then we cross this KC animal with a

00:24:00.260 --> 00:24:03.530 U2AF1 mutant animal for the S34F mutation.

00:24:03.530 --> 00:24:05.600 And what we found is that

00:24:05.600 --> 00:24:07.180 actually there are pannings,

00:24:07.180 --> 00:24:09.196 but not as much as we expected.

00:24:09.200 --> 00:24:10.349 And most importantly,

00:24:10.349 --> 00:24:13.030 there was no Peacock in these animals.

00:24:13.030 --> 00:24:13.932 But surprisingly,

00:24:13.932 --> 00:24:16.187 the animals that had them,

00:24:16.190 --> 00:24:19.446 the Keras mutation and the SFRB 1 mutation,

00:24:19.450 --> 00:24:21.046 foreign pancreatic tumors,

00:24:21.046 --> 00:24:25.748 same as the animals that we cross to have K,

00:24:25.750 --> 00:24:26.266 res,

00:24:26.266 --> 00:24:28.330 and RBM ten loss.

NOTE Confidence: 0.765729881111111

00:24:28.330 --> 00:24:30.320 So here's just the quantification

NOTE Confidence: 0.765729881111111

00:24:30.320 --> 00:24:31.912 done by our pathologist,

NOTE Confidence: 0.765729881111111

00:24:31.920 --> 00:24:34.269 who you can see that there is only pdac

NOTE Confidence: 0.765729881111111

00:24:34.269 --> 00:24:36.578 and the animals that have the nutrition

NOTE Confidence: 0.765729881111111

00:24:36.578 --> 00:24:38.527 in S4B1 and the nutrition in our BM.

NOTE Confidence: 0.765729881111111

00:24:38.530 --> 00:24:41.034 10 There is more pannings also in these

NOTE Confidence: 0.765729881111111

00:24:41.034 --> 00:24:43.448 animals and they succumb to the disease.

NOTE Confidence: 0.765729881111111

00:24:43.450 --> 00:24:44.677 Very early on,

NOTE Confidence: 0.765729881111111

00:24:44.677 --> 00:24:47.540 so we are now in this hypothesis

NOTE Confidence: 0.765729881111111

00:24:47.633 --> 00:24:51.377 that we're trying to further test which is.

NOTE Confidence: 0.765729881111111

00:24:51.380 --> 00:24:54.092 We believe now that pancreatic cancer

NOTE Confidence: 0.765729881111111

00:24:54.092 --> 00:24:56.980 cells that have a mutant carras

NOTE Confidence: 0.765729881111111

00:24:56.980 --> 00:24:59.450 actually require a splicing switch

NOTE Confidence: 0.765729881111111

00:24:59.450 --> 00:25:02.578 in order to become tumor cells,

NOTE Confidence: 0.765729881111111

00:25:02.580 --> 00:25:04.515 and most likely the majority

00:25:04.515 --> 00:25:06.946 of these of these tumors will

00:25:06.946 --> 00:25:08.992 develop through a mutant P53,

00:25:08.992 --> 00:25:11.456 which I showed you before how it

00:25:11.456 --> 00:25:13.039 drives alternative RNA splicing,

00:25:13.040 --> 00:25:15.600 but we're now fathering.

00:25:15.600 --> 00:25:19.681 Starting how these SF 3B1 mutation,

00:25:19.681 --> 00:25:23.069 and RBM ten loss also drive the the

00:25:23.069 --> 00:25:26.254 the disease based on a splicing change,

00:25:26.260 --> 00:25:29.266 and these animals are now being

00:25:29.266 --> 00:25:31.865 characterized by a couple of

00:25:31.865 --> 00:25:34.355 postdoctoral fellows in my lab,

00:25:34.360 --> 00:25:36.584 and so I just want to quickly mention

00:25:36.584 --> 00:25:38.289 that they have obtained really

00:25:38.289 --> 00:25:40.094 interesting results in terms of

00:25:40.094 --> 00:25:42.350 what are the splicing defects that

00:25:42.350 --> 00:25:44.220 these proteins mutated proteins.

NOTE Confidence: 0.765729881111111

00:25:44.220 --> 00:25:45.720 Are leading to.

NOTE Confidence: 0.765729881111111

00:25:45.720 --> 00:25:48.420 They are very similar to the

NOTE Confidence: 0.765729881111111

00:25:48.420 --> 00:25:49.722 P53 splicing changes.

NOTE Confidence: 0.765729881111111

00:25:49.722 --> 00:25:52.760 We do tons of deep RNA sequencing

NOTE Confidence: 0.765729881111111

00:25:52.844 --> 00:25:54.740 into this model systems.

NOTE Confidence: 0.765729881111111

00:25:54.740 --> 00:25:56.051 We do several.

NOTE Confidence: 0.765729881111111

00:25:56.051 --> 00:25:58.236 We run several algorithms to

NOTE Confidence: 0.765729881111111

00:25:58.236 --> 00:26:00.618 determine the splicing changes into

NOTE Confidence: 0.765729881111111

00:26:00.618 --> 00:26:03.480 not only the marine model systems,

NOTE Confidence: 0.765729881111111

00:26:03.480 --> 00:26:06.620 but also patient derived samples.

NOTE Confidence: 0.765729881111111

00:26:06.620 --> 00:26:08.804 I just want to skip quickly through

NOTE Confidence: 0.765729881111111

00:26:08.804 --> 00:26:10.966 this just so I can get here to

NOTE Confidence: 0.765729881111111

00:26:10.966 --> 00:26:12.947 how are we going to target these

NOTE Confidence: 0.765729881111111

00:26:12.947 --> 00:26:14.809 mutant splicing factor proteins.

NOTE Confidence: 0.765729881111111

00:26:14.810 --> 00:26:15.626 So similarly,

NOTE Confidence: 0.765729881111111

00:26:15.626 --> 00:26:18.730 we use the 8800 compound and we are

NOTE Confidence: 0.765729881111111

00:26:18.730 --> 00:26:21.128 now finding that also these mutant

NOTE Confidence: 0.765729881111111

00:26:21.128 --> 00:26:24.229 cells are very sensitive to this compound.

NOTE Confidence: 0.765729881111111

00:26:24.230 --> 00:26:27.392 We are also finding that these

NOTE Confidence: 0.765729881111111

00:26:27.392 --> 00:26:30.402 mutations confer sensitivity to certain

NOTE Confidence: 0.765729881111111

00:26:30.402 --> 00:26:32.570 chemotherapeutic agents. In this case.

NOTE Confidence: 0.765729881111111

00:26:32.570 --> 00:26:34.546 In particular, the case 700 E.

NOTE Confidence: 0.765729881111111

00:26:34.546 --> 00:26:35.548 As of Feb,

NOTE Confidence: 0.765729881111111

00:26:35.550 --> 00:26:37.160 one is more sensitive to

NOTE Confidence: 0.765729881111111

00:26:37.160 --> 00:26:39.349 gemcitabine than it is to five FU.

NOTE Confidence: 0.765729881111111

00:26:39.350 --> 00:26:41.516 So this is important because these

NOTE Confidence: 0.765729881111111

00:26:41.516 --> 00:26:43.294 mutation profiling can also help

NOTE Confidence: 0.765729881111111

00:26:43.294 --> 00:26:45.226 to decide what would be the best.

NOTE Confidence: 0.765729881111111

00:26:45.230 --> 00:26:47.242 Chemotherapeutic agent who assigned

NOTE Confidence: 0.765729881111111

00:26:47.242 --> 00:26:50.260 to a particular patient and when

NOTE Confidence: 0.765729881111111

00:26:50.335 --> 00:26:52.480 we did combination studies on

NOTE Confidence: 0.765729881111111

00:26:52.480 --> 00:26:55.535 mixing gemcitabine with 8800 in

NOTE Confidence: 0.765729881111111

00:26:55.535 --> 00:26:57.979 mutant versus wildtype cells,

NOTE Confidence: 0.765729881111111

00:26:57.980 --> 00:27:00.804 we can see that the mutant cells are

NOTE Confidence: 0.765729881111111

00:27:00.804 --> 00:27:02.593 more sensitive to the combination

NOTE Confidence: 0.765729881111111

00:27:02.593 --> 00:27:05.555 of jam and 8800 more so than the

NOTE Confidence: 0.765729881111111

00:27:05.555 --> 00:27:08.049 wild type cells suggesting that this

NOTE Confidence: 0.765729881111111

00:27:08.049 --> 00:27:10.339 combination of therapy could be

NOTE Confidence: 0.765729881111111

00:27:10.339 --> 00:27:12.634 important to treating the patients

NOTE Confidence: 0.765729881111111

00:27:12.634 --> 00:27:15.350 that have these K 700 E mutation.

NOTE Confidence: 0.765729881111111

00:27:15.350 --> 00:27:16.622 That's up 31,

NOTE Confidence: 0.765729881111111

00:27:16.622 --> 00:27:19.590 so I just want to finalize by

NOTE Confidence: 0.765729881111111

00:27:19.697 --> 00:27:21.674 saying that I'm currently based

NOTE Confidence: 0.765729881111111

00:27:21.674 --> 00:27:23.750 on our findings on Mutant P.

NOTE Confidence: 0.765729881111111

00:27:23.750 --> 00:27:25.170 53 and mutant SFB.

NOTE Confidence: 0.765729881111111

00:27:25.170 --> 00:27:28.430 One and RBM 10 laws as the drivers,

NOTE Confidence: 0.765729881111111

00:27:28.430 --> 00:27:29.615 as pancreatic cancer.

NOTE Confidence: 0.765729881111111

00:27:29.615 --> 00:27:31.985 All of these mutations leading to

NOTE Confidence: 0.765729881111111

00:27:31.985 --> 00:27:33.948 changes in alternative splicing.

NOTE Confidence: 0.765729881111111

00:27:33.950 --> 00:27:37.359 We're hoping to also bring into the

NOTE Confidence: 0.765729881111111

00:27:37.359 --> 00:27:39.303 trial patients eligible patients

NOTE Confidence: 0.765729881111111

00:27:39.303 --> 00:27:42.471 that are case 100 mutant or have RBM

NOTE Confidence: 0.765729881111111

00:27:42.471 --> 00:27:45.348 10 lost to be eligible for this.

NOTE Confidence: 0.765729881111111

00:27:45.350 --> 00:27:47.345 Glycine anti silicene therapy that

NOTE Confidence: 0.765729881111111

00:27:47.345 --> 00:27:49.340 we wanna lounge in combination

NOTE Confidence: 0.765729881111111

00:27:49.407 --> 00:27:51.252 with Gemini and Gemini 8800 and

NOTE Confidence: 0.765729881111111

00:27:51.252 --> 00:27:53.220 so with that I wanna wrap up by

NOTE Confidence: 0.875053478

00:27:53.283 --> 00:27:55.461 saying thank you to everyone here

NOTE Confidence: 0.875053478

00:27:55.461 --> 00:27:57.766 for your attendance today to all the

NOTE Confidence: 0.875053478

00:27:57.766 --> 00:27:59.614 people in my lab who are leading

NOTE Confidence: 0.875053478

00:27:59.620 --> 00:28:02.068 this effort to all our collaborators

NOTE Confidence: 0.875053478

00:28:02.068 --> 00:28:05.039 and also to our funding sources.

NOTE Confidence: 0.875053478

00:28:05.040 --> 00:28:06.732 Thank you very much and I'll

NOTE Confidence: 0.875053478

00:28:06.732 --> 00:28:08.120 take any questions. Thank you.

NOTE Confidence: 0.810624796

00:28:09.060 --> 00:28:10.400 Thank you so much Teresa,

NOTE Confidence: 0.810624796

00:28:10.400 --> 00:28:12.520 that was really fascinating

NOTE Confidence: 0.810624796

00:28:12.520 --> 00:28:16.160 work at great, excellent stuff.

NOTE Confidence: 0.810624796

00:28:16.160 --> 00:28:19.843 If people have questions for Louisa,

NOTE Confidence: 0.810624796

00:28:19.843 --> 00:28:23.014 please put them in the chat and

NOTE Confidence: 0.810624796

00:28:23.014 --> 00:28:25.930 I can read them to her and she

NOTE Confidence: 0.810624796

00:28:25.930 --> 00:28:28.340 can go ahead and answer them.

NOTE Confidence: 0.810624796

00:28:28.340 --> 00:28:30.510 I had one quick question.

NOTE Confidence: 0.810624796

00:28:30.510 --> 00:28:32.970 While people are formulating their thoughts,

NOTE Confidence: 0.810624796

00:28:32.970 --> 00:28:36.708 which is it is intriguing that

NOTE Confidence: 0.810624796

00:28:36.710 --> 00:28:38.348 the mutations and the and effects,

NOTE Confidence: 0.810624796

00:28:38.350 --> 00:28:43.200 and indeed the the the.

NOTE Confidence: 0.810624796

00:28:43.200 --> 00:28:46.084 8800 are all focusing on you two.

NOTE Confidence: 0.810624796

00:28:46.090 --> 00:28:50.790 Do you have some? He's out.

NOTE Confidence: 0.810624796

00:28:50.790 --> 00:28:51.870 It may be migraines,

NOTE Confidence: 0.810624796

00:28:51.870 --> 00:28:54.010 but what does that mean, mechanistically?

NOTE Confidence: 0.884566718333333

00:28:55.130 --> 00:28:57.490 Yeah, thank you Mark.

NOTE Confidence: 0.884566718333333

00:28:57.490 --> 00:29:00.320 So basically the compound targets

NOTE Confidence: 0.884566718333333

00:29:00.320 --> 00:29:03.226 mutant SF 3B1 and so it's the

NOTE Confidence: 0.884566718333333

00:29:03.226 --> 00:29:05.970 tumors have mutant SF 3B1.

NOTE Confidence: 0.884566718333333

00:29:05.970 --> 00:29:08.168 They are more sensitive to this compound,

NOTE Confidence: 0.884566718333333

00:29:08.170 --> 00:29:10.144 so that's the case for S3 one.

NOTE Confidence: 0.884566718333333

00:29:10.150 --> 00:29:12.774 But we also know that the if if

NOTE Confidence: 0.884566718333333

00:29:12.774 --> 00:29:14.890 tumors highly depend on splicing.

NOTE Confidence: 0.884566718333333

00:29:14.890 --> 00:29:17.992 There there are more sensitive to

NOTE Confidence: 0.884566718333333

00:29:17.992 --> 00:29:20.335 this compound because they cannot

NOTE Confidence: 0.884566718333333

00:29:20.335 --> 00:29:22.945 tolerate a double perturbation of the

NOTE Confidence: 0.884566718333333

00:29:22.945 --> 00:29:25.099 splicing changes and the splicing.

NOTE Confidence: 0.884566718333333

51

00:29:25.100 --> 00:29:29.293 Machinery and so that's how we are

NOTE Confidence: 0.884566718333333

00:29:29.293 --> 00:29:31.928 attributing the sensitivity of of

NOTE Confidence: 0.884566718333333

00:29:31.928 --> 00:29:35.363 mutant P 53 and mutant RBM 10 to 8800,

NOTE Confidence: 0.884566718333333

00:29:35.363 --> 00:29:38.814 and I think more dissection of the

NOTE Confidence: 0.884566718333333

00:29:38.814 --> 00:29:42.038 mechanism of of the drug within you.

NOTE Confidence: 0.884566718333333

00:29:42.040 --> 00:29:45.008 Know RBM 10 and P53 can further elucidate

NOTE Confidence: 0.884566718333333

00:29:45.008 --> 00:29:48.486 why are they so sensitive to this compound,

NOTE Confidence: 0.884566718333333

00:29:48.490 --> 00:29:49.722 at least for P53.

NOTE Confidence: 0.884566718333333

00:29:49.722 --> 00:29:51.570 We know that in certain cases

NOTE Confidence: 0.884566718333333

00:29:51.637 --> 00:29:53.209 it reverses the effects.

NOTE Confidence: 0.884566718333333

00:29:53.210 --> 00:29:55.590 The splicing changes that mutant P 53.

NOTE Confidence: 0.884566718333333

00:29:55.590 --> 00:29:56.410 Is promoting.

NOTE Confidence: 0.786254627222222

00:29:58.590 --> 00:30:00.594 Make makes sense and the other

NOTE Confidence: 0.786254627222222

00:30:00.594 --> 00:30:02.896 question I had was that we're going

NOTE Confidence: 0.786254627222222

00:30:02.896 --> 00:30:06.090 back to the gap 17 story. Do you see?

NOTE Confidence: 0.786254627222222

00:30:06.090 --> 00:30:09.196 In other circumstances the if you look

NOTE Confidence: 0.786254627222222

00:30:09.196 --> 00:30:12.040 through other cells and and indeed

NOTE Confidence: 0.786254627222222

00:30:12.040 --> 00:30:14.906 tumors that aren't don't have the

NOTE Confidence: 0.786254627222222

00:30:14.906 --> 00:30:17.630 the gain of function P53 mutations.

NOTE Confidence: 0.786254627222222

00:30:17.630 --> 00:30:21.678 Do you see the the gap 17 with

NOTE Confidence: 0.786254627222222

00:30:21.678 --> 00:30:24.438 the policy Exxon in other places?

NOTE Confidence: 0.81168588

00:30:25.030 --> 00:30:26.788 Yeah, so that's a good question.

NOTE Confidence: 0.81168588

00:30:26.790 --> 00:30:27.870 So for example.

NOTE Confidence: 0.81168588

00:30:27.870 --> 00:30:29.670 We've looked into other cancers

NOTE Confidence: 0.81168588

00:30:29.670 --> 00:30:31.660 that are not key, rest driven,

NOTE Confidence: 0.81168588

00:30:31.660 --> 00:30:34.172 but have this mutant form of P53,

NOTE Confidence: 0.81168588

00:30:34.172 --> 00:30:36.824 and we see that indeed the

NOTE Confidence: 0.81168588

00:30:36.824 --> 00:30:39.070 splicing changing gap 17 occurs.

NOTE Confidence: 0.81168588

00:30:39.070 --> 00:30:42.198 Now we have also seen some other tumors

NOTE Confidence: 0.81168588

00:30:42.198 --> 00:30:44.865 where mutant P 53 is not present and

NOTE Confidence: 0.81168588

00:30:44.865 --> 00:30:47.350 we still see the splicing change,

NOTE Confidence: 0.81168588

00:30:47.350 --> 00:30:49.954 and we think that this is attributed

NOTE Confidence: 0.81168588

00:30:49.954 --> 00:30:52.175 to the overexpression of a splicing

NOTE Confidence: 0.81168588

00:30:52.175 --> 00:30:54.170 factor called H&amp;R AMPK that today

NOTE Confidence: 0.81168588

00:30:54.170 --> 00:30:56.570 I didn't have time to go into,

NOTE Confidence: 0.81168588

00:30:56.570 --> 00:30:58.628 but we think that this splicing.

NOTE Confidence: 0.81168588

00:30:58.630 --> 00:31:03.260 Regulator also promotes the policy.

NOTE Confidence: 0.81168588

00:31:03.260 --> 00:31:06.113 The the policy acts on inclusion in M RNA,

NOTE Confidence: 0.81168588

00:31:06.120 --> 00:31:08.171 so we think that there is not

NOTE Confidence: 0.81168588

00:31:08.171 --> 00:31:10.376 a single pathway to to promote.

NOTE Confidence: 0.81168588

00:31:10.376 --> 00:31:13.470 The policy acts on retention in gaps.

NOTE Confidence: 0.735722408789474

00:31:15.000 --> 00:31:17.653 This is fascinating and I have a

NOTE Confidence: 0.735722408789474

00:31:17.653 --> 00:31:20.239 question in the chat from from

NOTE Confidence: 0.735722408789474

00:31:20.239 --> 00:31:22.975 Timothy Robinson who says great talk.

NOTE Confidence: 0.735722408789474

00:31:22.980 --> 00:31:25.528 I agree with the way you described

NOTE Confidence: 0.735722408789474

00:31:25.528 --> 00:31:27.433 using mutually exclusive analysis to

NOTE Confidence: 0.735722408789474

00:31:27.433 --> 00:31:29.659 find events within the same pathway.

NOTE Confidence: 0.735722408789474

00:31:29.660 --> 00:31:31.568 Did you look at Gap 17?

NOTE Confidence: 0.735722408789474

00:31:31.570 --> 00:31:34.625 Aberrant splicing based on mRNA

NOTE Confidence: 0.735722408789474

00:31:34.625 --> 00:31:36.828 directly to identify other drivers?

NOTE Confidence: 0.880845552222222

00:31:38.870 --> 00:31:40.118 So I'm not sure if I'm

NOTE Confidence: 0.880845552222222

00:31:40.118 --> 00:31:40.742 understanding the question.

NOTE Confidence: 0.880845552222222

00:31:40.750 --> 00:31:43.943 If I if we looked into into

NOTE Confidence: 0.880845552222222

00:31:43.943 --> 00:31:46.566 other pathways that are not

NOTE Confidence: 0.880845552222222

00:31:46.566 --> 00:31:49.014 linked to to the cares pathway.

NOTE Confidence: 0.777251266666667

00:31:49.110 --> 00:31:50.340 I think the question is

NOTE Confidence: 0.777251266666667

00:31:50.340 --> 00:31:51.324 actually did you look?

NOTE Confidence: 0.777251266666667

00:31:51.330 --> 00:31:52.675 Did you look at aberrant

NOTE Confidence: 0.777251266666667

00:31:52.675 --> 00:31:54.380 splicing based on M RNA to

NOTE Confidence: 0.777251266666667

00:31:54.380 --> 00:31:55.588 identify other drivers that

NOTE Confidence: 0.777251266666667

00:31:55.588 --> 00:31:57.330 might be other than gap 17?

NOTE Confidence: 0.777251266666667

00:31:57.330 --> 00:31:57.939 I think that's

NOTE Confidence: 0.754027668045454

55

00:31:58.660 --> 00:32:01.012 yeah. So all the splicing changes

00:32:01.012 --> 00:32:03.910 that we identified are based on mRNA

00:32:03.910 --> 00:32:06.010 sequencing and based on splicing

00:32:06.010 --> 00:32:08.776 analysis that we conduct. But if I.

00:32:08.776 --> 00:32:12.111 But I can also mention that the gaps are

00:32:12.111 --> 00:32:14.738 only 5% of the events that mutant be 50,

00:32:14.740 --> 00:32:17.169 three, 5% of the event is splicing

00:32:17.169 --> 00:32:19.520 events that mutant P 53 is triggering.

00:32:19.520 --> 00:32:22.296 So there are other M RNA's that affect

00:32:22.296 --> 00:32:24.961 other pathways that are being impacted by

00:32:24.961 --> 00:32:27.334 the aberrant splicing by mutant P. 53.

00:32:27.334 --> 00:32:29.800 So we just went with the gaps to start

00:32:29.873 --> 00:32:32.253 with because of course of the relevance

00:32:32.253 --> 00:32:34.777 and the path and the Keras pathway.

00:32:34.780 --> 00:32:37.130 But we are there is a student in the lab

00:32:37.192 --> 00:32:39.307 who's actually trying to understand.

NOTE Confidence: 0.754027668045454

00:32:39.310 --> 00:32:39.625 What?

NOTE Confidence: 0.754027668045454

00:32:39.625 --> 00:32:42.145 What is the role of the other splicing

NOTE Confidence: 0.754027668045454

00:32:42.145 --> 00:32:44.640 changes in other M RNA's that are not gaps?

NOTE Confidence: 0.806719478

00:32:46.690 --> 00:32:48.850 And presumably, in that context,

NOTE Confidence: 0.806719478

00:32:48.850 --> 00:32:50.368 I mean, it's kind of interesting

NOTE Confidence: 0.806719478

00:32:50.368 --> 00:32:52.674 that the gap 17 effect is so

NOTE Confidence: 0.806719478

00:32:52.674 --> 00:32:54.990 kind of singular in a sense,

NOTE Confidence: 0.806719478

00:32:54.990 --> 00:32:56.740 and you presumably in the other cases

NOTE Confidence: 0.806719478

00:32:56.740 --> 00:32:58.551 it's really going to be a combination

NOTE Confidence: 0.806719478

00:32:58.551 --> 00:33:00.075 that's going to be the constellation

NOTE Confidence: 0.806719478

00:33:00.126 --> 00:33:01.488 of those changes that are key,

NOTE Confidence: 0.806719478

00:33:01.490 --> 00:33:02.882 which is going to be interesting

NOTE Confidence: 0.806719478

00:33:02.882 --> 00:33:04.000 but tough to tease out

NOTE Confidence: 0.880829711666667

00:33:04.110 --> 00:33:06.360 exactly. So, as I mentioned before,

NOTE Confidence: 0.880829711666667

00:33:06.360 --> 00:33:09.909 we are seeing that 32 gaps encoded

NOTE Confidence: 0.880829711666667

00:33:09.909 --> 00:33:13.459 by the genome of of 120 dots that

NOTE Confidence: 0.880829711666667

00:33:13.459 --> 00:33:15.774 are encoded are being differentially

NOTE Confidence: 0.880829711666667

00:33:15.774 --> 00:33:17.178 spliced, we manipulated.

NOTE Confidence: 0.880829711666667

00:33:17.178 --> 00:33:19.992 One, but if you imagine manipulating

NOTE Confidence: 0.880829711666667

00:33:19.992 --> 00:33:22.265 several of them and forcing

NOTE Confidence: 0.880829711666667

00:33:22.265 --> 00:33:24.360 policy axons to be excluded,

NOTE Confidence: 0.880829711666667

00:33:24.360 --> 00:33:26.352 the the effect might be synergistic

NOTE Confidence: 0.880829711666667

00:33:26.352 --> 00:33:28.915 in terms of the the the cell

NOTE Confidence: 0.880829711666667

00:33:28.915 --> 00:33:30.865 proliferation and the tumor growth.

NOTE Confidence: 0.7890346

00:33:33.000 --> 00:33:35.958 Sure. Any other questions in the chat?

NOTE Confidence: 0.725700857857143

00:33:38.690 --> 00:33:39.901 So we don't seem to have at

NOTE Confidence: 0.725700857857143

00:33:39.901 --> 00:33:41.190 the moment of so that we could,

NOTE Confidence: 0.725700857857143

00:33:41.190 --> 00:33:43.990 and we we we should probably move on.

NOTE Confidence: 0.725700857857143

00:33:43.990 --> 00:33:45.892 So thank you very much, Lisa.

NOTE Confidence: 0.725700857857143

00:33:45.892 --> 00:33:47.584 That was a fascinating stuff with

NOTE Confidence: 0.725700857857143

00:33:47.584 --> 00:33:49.370 the enormous about everyone.

NOTE Confidence: 0.725700857857143

00:33:49.370 --> 00:33:52.078 And to think about it. Thank you.

NOTE Confidence: 0.725700857857143

00:33:52.078 --> 00:33:57.345 So, so let's move on for the second

NOTE Confidence: 0.725700857857143

00:33:57.345 --> 00:34:01.360 half to Doctor Rosa Vinod Zikula.

NOTE Confidence: 0.725700857857143

00:34:01.360 --> 00:34:03.614 So Doctor Zickler is an assistant professor

NOTE Confidence: 0.725700857857143

00:34:03.614 --> 00:34:05.679 of medicine and digestive diseases.

NOTE Confidence: 0.725700857857143

00:34:05.680 --> 00:34:08.224 She received her PhD from the

NOTE Confidence: 0.725700857857143

00:34:08.224 --> 00:34:10.760 university app Autonomo de Barcelona.

NOTE Confidence: 0.725700857857143

00:34:10.760 --> 00:34:12.535 I apologize for my pronunciation

NOTE Confidence: 0.725700857857143

00:34:12.535 --> 00:34:14.310 and oncology and her postdoctoral

NOTE Confidence: 0.725700857857143

00:34:14.366 --> 00:34:16.364 training at the Institute of Cancer

NOTE Confidence: 0.725700857857143

00:34:16.364 --> 00:34:18.070 Research at the University of

NOTE Confidence: 0.725700857857143

00:34:18.070 --> 00:34:19.640 Illinois and at Yale University.

NOTE Confidence: 0.725700857857143

00:34:19.640 --> 00:34:22.056 Dr Zickler's long term goal is to decipher.

NOTE Confidence: 0.725700857857143

00:34:22.060 --> 00:34:24.172 Known genetic alterations that

NOTE Confidence: 0.725700857857143

00:34:24.172 --> 00:34:26.284 predispose to colorectal cancer

NOTE Confidence: 0.725700857857143

00:34:26.284 --> 00:34:28.758 development and her research focus

NOTE Confidence: 0.725700857857143

00:34:28.758 --> 00:34:31.440 is on understanding molecular and the

NOTE Confidence: 0.725700857857143

00:34:31.440 --> 00:34:33.545 molecular characterization of sporadic

NOTE Confidence: 0.725700857857143

00:34:33.545 --> 00:34:35.657 and hereditary colorectal cancer

NOTE Confidence: 0.725700857857143

00:34:35.657 --> 00:34:38.224 with an interest in understanding

NOTE Confidence: 0.725700857857143

00:34:38.224 --> 00:34:40.172 the biological differences among

NOTE Confidence: 0.725700857857143

00:34:40.172 --> 00:34:42.230 racial groups to develop her

NOTE Confidence: 0.725700857857143

00:34:42.230 --> 00:34:43.310 translational research doctors.

NOTE Confidence: 0.725700857857143

00:34:43.310 --> 00:34:47.339 Zigler is a key player in several

NOTE Confidence: 0.725700857857143

00:34:47.339 --> 00:34:49.135 repositories and consortia that

NOTE Confidence: 0.725700857857143

00:34:49.135 --> 00:34:50.931 recruit cancer patients and

NOTE Confidence: 0.725700857857143

00:34:50.931 --> 00:34:52.939 then collecting biospecimens.

NOTE Confidence: 0.725700857857143

00:34:52.940 --> 00:34:55.406 And and clinical data and Doctor

NOTE Confidence: 0.725700857857143

00:34:55.406 --> 00:34:58.608 Nikola will will tell us about defining

NOTE Confidence: 0.725700857857143

00:34:58.608 --> 00:35:01.078 new pathways in colorectal tumors

NOTE Confidence: 0.725700857857143

00:35:01.078 --> 00:35:03.520 with mismatch repair deficiency.

NOTE Confidence: 0.725700857857143

00:35:03.520 --> 00:35:05.000 So thanks so much Rosa for doing this.

NOTE Confidence: 0.725700857857143

00:35:05.000 --> 00:35:06.540 I really look forward to your talk.

NOTE Confidence: 0.914238268

00:35:07.590 --> 00:35:09.680 Thank you, let me share.

NOTE Confidence: 0.9334385475

00:35:14.750 --> 00:35:17.610 Can you see properly?

NOTE Confidence: 0.9334385475

00:35:17.610 --> 00:35:19.890 OK, so thank you so much for giving

NOTE Confidence: 0.9334385475

00:35:19.890 --> 00:35:22.491 me the priority to show you all our

NOTE Confidence: 0.9334385475

00:35:22.491 --> 00:35:25.050 most recent data on the topic of

NOTE Confidence: 0.9334385475

00:35:25.050 --> 00:35:26.556 mismatch repair, deficient tools.

NOTE Confidence: 0.9334385475

00:35:26.556 --> 00:35:29.700 So the outline of the talk is going to.

NOTE Confidence: 0.9334385475

00:35:29.700 --> 00:35:31.748 I'm going to explain you give you an

NOTE Confidence: 0.9334385475

00:35:31.748 --> 00:35:34.328 overview of the mismatch repair and the

NOTE Confidence: 0.9334385475

00:35:34.328 --> 00:35:35.940 phenomena of microsatellite instability.

NOTE Confidence: 0.9334385475

00:35:35.940 --> 00:35:38.432 And then I will explain you the

NOTE Confidence: 0.9334385475

00:35:38.432 --> 00:35:40.318 clinical phenotypes and challenges in

NOTE Confidence: 0.9334385475

00:35:40.318 --> 00:35:42.943 the molecular that I diagnosis of the

NOTE Confidence: 0.9334385475

00:35:42.943 --> 00:35:45.399 tumors that have mismatched efficient.

NOTE Confidence: 0.9334385475

00:35:45.400 --> 00:35:48.627 Then I will explain you the association.

NOTE Confidence: 0.9334385475

00:35:48.630 --> 00:35:50.870 That we are describing between

NOTE Confidence: 0.9334385475

00:35:50.870 --> 00:35:53.695 deficiency of RAQUE and DNA helicases

NOTE Confidence: 0.9334385475

00:35:53.695 --> 00:35:56.205 in Lynch like syndrome cases.

NOTE Confidence: 0.9334385475

00:35:56.210 --> 00:35:58.744 And then I will show our most

NOTE Confidence: 0.9334385475

00:35:58.750 --> 00:36:00.362 recent publication that describes

NOTE Confidence: 0.9334385475

00:36:00.362 --> 00:36:02.377 the identification of tumors with

NOTE Confidence: 0.9334385475

00:36:02.377 --> 00:36:04.871 a high likelihood development and

NOTE Confidence: 0.9334385475

00:36:04.871 --> 00:36:06.903 immune response through mutational

NOTE Confidence: 0.9334385475

00:36:06.903 --> 00:36:07.919 signature profiling.

NOTE Confidence: 0.729921572

00:36:10.100 --> 00:36:12.476 So here in the left you can see that

NOTE Confidence: 0.729921572

00:36:12.476 --> 00:36:15.205 it's a cartoon that shows the the mosque

NOTE Confidence: 0.729921572

00:36:15.205 --> 00:36:17.897 important for the main proteins that are

NOTE Confidence: 0.729921572

00:36:17.897 --> 00:36:20.297 involved in the mismatch repair system.

NOTE Confidence: 0.729921572

00:36:20.300 --> 00:36:23.037 The mismatch repair system is the inner

NOTE Confidence: 0.729921572

00:36:23.037 --> 00:36:25.932 repair system that identifies mismatches like

NOTE Confidence: 0.729921572

00:36:25.932 --> 00:36:29.334 single base base or like larger mismatches.

NOTE Confidence: 0.729921572

00:36:29.340 --> 00:36:31.000 And there's two main complexes,

NOTE Confidence: 0.729921572

00:36:31.000 --> 00:36:34.132 the mute test that it's formed by message 6

NOTE Confidence: 0.729921572

00:36:34.132 --> 00:36:37.517 and Message 2 and Message 3 and a message 2.

NOTE Confidence: 0.729921572

00:36:37.520 --> 00:36:38.990 So these proteins are the

NOTE Confidence: 0.729921572

00:36:38.990 --> 00:36:40.460 first ones to recognize them.

NOTE Confidence: 0.729921572

00:36:40.460 --> 00:36:43.930 As my tools and then the mute L complexes

NOTE Confidence: 0.729921572

00:36:43.930 --> 00:36:47.570 recruited to help fix the the mismatches

NOTE Confidence: 0.729921572

00:36:47.570 --> 00:36:51.433 and mutl is formed by PMS two and MLH 1.

NOTE Confidence: 0.729921572

00:36:51.440 --> 00:36:53.792 So in the genome there are these

NOTE Confidence: 0.729921572

00:36:53.792 --> 00:36:55.775 sequences that are called microsatellites

NOTE Confidence: 0.729921572

00:36:55.775 --> 00:36:58.499 that are prone to acquire alterations

NOTE Confidence: 0.729921572

00:36:58.499 --> 00:37:01.344 when any of the proteins of the

NOTE Confidence: 0.729921572

00:37:01.344 --> 00:37:02.836 mismatch repair not working.

NOTE Confidence: 0.729921572

00:37:02.840 --> 00:37:06.520 So here you can see here you can

NOTE Confidence: 0.729921572

00:37:06.520 --> 00:37:08.838 see sorry this is on the way.

NOTE Confidence: 0.729921572

00:37:08.840 --> 00:37:11.054 Here you can see a microsatellite

NOTE Confidence: 0.729921572

00:37:11.054 --> 00:37:12.963 microsatellites are short and repetitive

NOTE Confidence: 0.729921572

00:37:12.963 --> 00:37:14.833 sequences present in coding and

NOTE Confidence: 0.729921572

00:37:14.833 --> 00:37:17.040 non coding regions of the genome.

NOTE Confidence: 0.729921572

00:37:17.040 --> 00:37:20.260 And when the any of them is not

NOTE Confidence: 0.729921572

00:37:20.260 --> 00:37:21.640 working this Microsoft.

NOTE Confidence: 0.729921572

00:37:21.640 --> 00:37:24.260 That's accumulate deletions or insertions.

NOTE Confidence: 0.729921572

00:37:24.260 --> 00:37:27.074 So when the size of the microsatellite

NOTE Confidence: 0.729921572

00:37:27.074 --> 00:37:29.208 cannot be properly kept during

NOTE Confidence: 0.729921572

00:37:29.208 --> 00:37:32.151 replication of DNA in the cells,

NOTE Confidence: 0.729921572

00:37:32.151 --> 00:37:34.379 the phenomenon of microsatellite

NOTE Confidence: 0.729921572

00:37:34.379 --> 00:37:36.869 instability isn't identified in tumors.

NOTE Confidence: 0.807376979090909

00:37:39.920 --> 00:37:41.732 So I MSI can be identified

NOTE Confidence: 0.807376979090909

00:37:41.732 --> 00:37:43.520 in a variety of tumors,

64

NOTE Confidence: 0.807376979090909

00:37:43.520 --> 00:37:45.734 but as you can see here on the table

NOTE Confidence: 0.807376979090909

00:37:45.734 --> 00:37:48.256 and in the graph in the material tumors,

NOTE Confidence: 0.807376979090909

00:37:48.260 --> 00:37:50.505 colorectal and stomach are the

NOTE Confidence: 0.807376979090909

00:37:50.505 --> 00:37:53.641 tumors that have a higher incidence

NOTE Confidence: 0.807376979090909

00:37:53.641 --> 00:37:56.050 of microsatellite instability.

NOTE Confidence: 0.807376979090909

00:37:56.050 --> 00:37:57.794 So, in colorectal tumors,

NOTE Confidence: 0.807376979090909

00:37:57.794 --> 00:38:00.715 about 10% of a sporadic tumors have

NOTE Confidence: 0.807376979090909

00:38:00.715 --> 00:38:02.760 mismatch repair deficiency and these

NOTE Confidence: 0.807376979090909

00:38:02.831 --> 00:38:05.327 deficiencies due to CPG island promoter

NOTE Confidence: 0.807376979090909

00:38:05.327 --> 00:38:07.849 musculation of the gene mileage one,

NOTE Confidence: 0.807376979090909

00:38:07.850 --> 00:38:10.104 which I show you that it's a.

NOTE Confidence: 0.807376979090909

00:38:10.110 --> 00:38:12.006 It's one of the two proteins

NOTE Confidence: 0.807376979090909

00:38:12.006 --> 00:38:13.870 that form the metal complex,

NOTE Confidence: 0.807376979090909

00:38:13.870 --> 00:38:17.109 so when there's a promoter methylation,

NOTE Confidence: 0.807376979090909

00:38:17.109 --> 00:38:19.104 there's an addition of transcription

NOTE Confidence: 0.807376979090909

00:38:19.104 --> 00:38:21.970 of the gene and it and resulting in

NOTE Confidence: 0.807376979090909

00:38:21.970 --> 00:38:24.330 the loss of expression of the protein.

NOTE Confidence: 0.807376979090909

00:38:24.330 --> 00:38:26.297 So here you can see the difference.

NOTE Confidence: 0.807376979090909

00:38:26.300 --> 00:38:28.308 Between normal expression by

NOTE Confidence: 0.807376979090909

00:38:28.308 --> 00:38:29.814 immunohistochemistry and loss

NOTE Confidence: 0.807376979090909

00:38:29.814 --> 00:38:32.488 of expression and a significant

NOTE Confidence: 0.807376979090909

00:38:32.488 --> 00:38:34.525 number of these tumors,

NOTE Confidence: 0.807376979090909

00:38:34.525 --> 00:38:36.715 they also present this hot spot

NOTE Confidence: 0.807376979090909

00:38:36.715 --> 00:38:38.879 mutation in the Bureau of Gene.

NOTE Confidence: 0.807376979090909

00:38:38.880 --> 00:38:41.568 Here you have the mutation and these

NOTE Confidence: 0.807376979090909

00:38:41.568 --> 00:38:44.168 two are molecular events are used

NOTE Confidence: 0.807376979090909

00:38:44.168 --> 00:38:46.940 to differentiate and tumors that

NOTE Confidence: 0.807376979090909

00:38:46.940 --> 00:38:49.848 develop through a sporadic events.

NOTE Confidence: 0.807376979090909

00:38:49.848 --> 00:38:52.416 Then the tumors that develop MSI

NOTE Confidence: 0.807376979090909

00:38:52.416 --> 00:38:55.444 but they are developing in the

NOTE Confidence: 0.807376979090909

00:38:55.444 --> 00:38:57.660 setting of hereditary disease.

NOTE Confidence: 0.807376979090909

00:38:57.660 --> 00:39:02.259 So Vince Syndrome is the the tumor.

NOTE Confidence: 0.807376979090909

00:39:02.260 --> 00:39:03.409 It's cancer syndrome.

NOTE Confidence: 0.807376979090909

00:39:03.409 --> 00:39:05.707 There is due to germline mutations

NOTE Confidence: 0.807376979090909

00:39:05.707 --> 00:39:07.919 in this mismatch repair genes.

NOTE Confidence: 0.807376979090909

00:39:07.920 --> 00:39:09.540 It's actually the most common

NOTE Confidence: 0.807376979090909

00:39:09.540 --> 00:39:11.680 cancer syndrome of all it's present.

NOTE Confidence: 0.807376979090909

00:39:11.680 --> 00:39:14.188 It's estimated that one in 270 people

NOTE Confidence: 0.807376979090909

00:39:14.188 --> 00:39:16.860 in the US carry one of the mutation

NOTE Confidence: 0.807376979090909

00:39:16.934 --> 00:39:19.764 in one of these genes and these

NOTE Confidence: 0.807376979090909

00:39:19.764 --> 00:39:22.590 individuals have present this syndrome

NOTE Confidence: 0.807376979090909

00:39:22.590 --> 00:39:25.635 presents as penetrance about 70 to 80%,

NOTE Confidence: 0.807376979090909

00:39:25.640 --> 00:39:26.756 which means that.

NOTE Confidence: 0.807376979090909

00:39:26.756 --> 00:39:29.989 That in in 70 to 80% of the cases

NOTE Confidence: 0.807376979090909

00:39:29.989 --> 00:39:31.654 individuals that carry a mutation,

NOTE Confidence: 0.807376979090909

00:39:31.660 --> 00:39:32.900 they end up developing

NOTE Confidence: 0.807376979090909

00:39:32.900 --> 00:39:34.450 cancer and when they develop,

NOTE Confidence: 0.807376979090909

00:39:34.450 --> 00:39:36.050 cancer is usually associated

NOTE Confidence: 0.807376979090909

00:39:36.050 --> 00:39:38.450 with an early age of onset.

NOTE Confidence: 0.807376979090909

00:39:38.450 --> 00:39:39.376 So clinically,

NOTE Confidence: 0.807376979090909

00:39:39.376 --> 00:39:41.691 Lynch syndrome patients present with

NOTE Confidence: 0.807376979090909

00:39:41.691 --> 00:39:44.336 fewer polyps than other colorectal

NOTE Confidence: 0.807376979090909

00:39:44.336 --> 00:39:46.109 cancer inherited syndromes,

NOTE Confidence: 0.807376979090909

00:39:46.110 --> 00:39:47.700 and the tumors localized in

NOTE Confidence: 0.807376979090909

00:39:47.700 --> 00:39:49.810 the right side of the column.

NOTE Confidence: 0.807376979090909

00:39:49.810 --> 00:39:51.030 And this lynch patients.

NOTE Confidence: 0.807376979090909

00:39:51.030 --> 00:39:52.860 They have a high risk of

NOTE Confidence: 0.807376979090909

00:39:52.925 --> 00:39:54.668 developing multiple cancers.

NOTE Confidence: 0.807376979090909

00:39:54.670 --> 00:39:55.972 Colorectal cancers are

NOTE Confidence: 0.807376979090909

00:39:55.972 --> 00:39:57.708 diagnosis or over time.

NOTE Confidence: 0.807376979090909

00:39:57.710 --> 00:39:59.594 And another clinical feature

NOTE Confidence: 0.807376979090909

00:39:59.594 --> 00:40:01.949 that it's important to remember.

NOTE Confidence: 0.807376979090909

00:40:01.950 --> 00:40:02.372 Sorry,

NOTE Confidence: 0.807376979090909

00:40:02.372 --> 00:40:04.482 remember from these patients is

NOTE Confidence: 0.807376979090909

00:40:04.482 --> 00:40:07.119 that the Lynch syndrome is actually

NOTE Confidence: 0.807376979090909

00:40:07.119 --> 00:40:09.309 a multi cancer syndrome affecting

NOTE Confidence: 0.807376979090909

00:40:09.310 --> 00:40:10.948 different organs and here you can

NOTE Confidence: 0.807376979090909

00:40:10.948 --> 00:40:12.924 see the list and it's significantly

NOTE Confidence: 0.807376979090909

00:40:12.924 --> 00:40:14.974 important to remember that because

NOTE Confidence: 0.807376979090909

00:40:14.974 --> 00:40:16.961 actually female lynch patients they

NOTE Confidence: 0.807376979090909

00:40:16.961 --> 00:40:19.390 developed for example like in the material,

NOTE Confidence: 0.807376979090909

00:40:19.390 --> 00:40:21.045 they have a higher incidence

NOTE Confidence: 0.807376979090909

00:40:21.045 --> 00:40:22.369 of developing endometrial than

NOTE Confidence: 0.807376979090909

00:40:22.369 --> 00:40:23.080 colorectal cancer.

NOTE Confidence: 0.77898428696

00:40:25.090 --> 00:40:27.178 So because I explained you that

NOTE Confidence: 0.77898428696

00:40:27.178 --> 00:40:29.449 Link syndrome is the most common

NOTE Confidence: 0.77898428696

00:40:29.449 --> 00:40:31.459 cancer syndrome and because of

NOTE Confidence: 0.77898428696

00:40:31.459 --> 00:40:33.621 all this clinical features that

NOTE Confidence: 0.77898428696

00:40:33.621 --> 00:40:35.365 these patients have nowadays,

NOTE Confidence: 0.77898428696

00:40:35.365 --> 00:40:37.855 all in the midfield and Jay

NOTE Confidence: 0.77898428696

00:40:37.855 --> 00:40:40.439 cancers are are supposed to be

NOTE Confidence: 0.77898428696

00:40:40.439 --> 00:40:42.947 tested for the for Lynn syndrome.

NOTE Confidence: 0.77898428696

00:40:42.950 --> 00:40:46.333 So how this works is all these cancers.

NOTE Confidence: 0.77898428696

00:40:46.333 --> 00:40:48.638 They are tested with immunohistochemistry

NOTE Confidence: 0.77898428696

00:40:48.638 --> 00:40:51.629 for the expression of the four main

NOTE Confidence: 0.77898428696

00:40:51.629 --> 00:40:54.067 proteins of the mismatch repair if.

NOTE Confidence: 0.77898428696

00:40:54.067 --> 00:40:56.689 Because of the expression in MSH

NOTE Confidence: 0.77898428696

00:40:56.689 --> 00:40:59.581 2 MSH 6 or PS2 is identified,

NOTE Confidence: 0.77898428696

00:40:59.581 --> 00:41:02.143 then the patient should be referred

NOTE Confidence: 0.77898428696

00:41:02.143 --> 00:41:04.974 to cancer genetics for testing and

NOTE Confidence: 0.77898428696

00:41:04.974 --> 00:41:06.798 contrary if the loss of emulate

NOTE Confidence: 0.77898428696

00:41:06.798 --> 00:41:08.716 one or PMS or the conduction

NOTE Confidence: 0.77898428696

00:41:08.716 --> 00:41:10.893 of emulate one and PMS two is

NOTE Confidence: 0.77898428696

00:41:10.962 --> 00:41:13.278 identified by immunohistochemistry,

NOTE Confidence: 0.77898428696

00:41:13.280 --> 00:41:15.400 then there is the one.

NOTE Confidence: 0.77898428696

00:41:15.400 --> 00:41:17.120 Methylation should be tested and

NOTE Confidence: 0.77898428696

00:41:17.120 --> 00:41:19.239 if there is no methylation then

NOTE Confidence: 0.77898428696

00:41:19.239 --> 00:41:20.929 the patient should be referred

NOTE Confidence: 0.77898428696

00:41:20.929 --> 00:41:22.912 to cancer genetics and in any

NOTE Confidence: 0.77898428696

00:41:22.912 --> 00:41:24.616 way if anyone in the identifies.

NOTE Confidence: 0.77898428696

00:41:24.620 --> 00:41:28.046 MSI case, but there was no.

NOTE Confidence: 0.77898428696

00:41:28.050 --> 00:41:29.958 I'm even Histochemistry tested,

NOTE Confidence: 0.77898428696

00:41:29.958 --> 00:41:33.470 but the physicians have a clinical concern.

NOTE Confidence: 0.77898428696

00:41:33.470 --> 00:41:35.195 Then these patients should be

NOTE Confidence: 0.77898428696

00:41:35.195 --> 00:41:36.575 preferred to cancer genetics.

NOTE Confidence: 0.682636668333333

00:41:38.730 --> 00:41:41.054 So in general, in the cancer genetics

NOTE Confidence: 0.682636668333333

00:41:41.054 --> 00:41:42.850 clinic was we've been facing,

NOTE Confidence: 0.682636668333333

00:41:42.850 --> 00:41:46.066 is that about 50% of the suspected link

NOTE Confidence: 0.682636668333333

00:41:46.066 --> 00:41:48.210 syndrome patients that are referred.

NOTE Confidence: 0.682636668333333

00:41:48.210 --> 00:41:51.633 They actually test negative for Jim for

NOTE Confidence: 0.682636668333333

00:41:51.633 --> 00:41:53.943 having germline mutations in the genes.

NOTE Confidence: 0.682636668333333

00:41:53.943 --> 00:41:56.447 And this case is where name as Lynch

NOTE Confidence: 0.682636668333333

00:41:56.447 --> 00:41:58.752 like syndrome because they are similar

NOTE Confidence: 0.682636668333333

00:41:58.752 --> 00:42:01.590 to lynch like but there's no mutations.

NOTE Confidence: 0.682636668333333

00:42:01.590 --> 00:42:04.229 So as as a definition these lines

NOTE Confidence: 0.682636668333333

00:42:04.229 --> 00:42:06.050 like syndrome patient patients,

NOTE Confidence: 0.682636668333333

00:42:06.050 --> 00:42:08.606 they develop tumors at the MSI.

NOTE Confidence: 0.682636668333333

00:42:08.610 --> 00:42:10.647 They don't have resolution of image one.

NOTE Confidence: 0.682636668333333

00:42:10.650 --> 00:42:12.870 They don't have the hotspot be

NOTE Confidence: 0.682636668333333

00:42:12.870 --> 00:42:14.863 600 imitations and they don't

NOTE Confidence: 0.682636668333333

00:42:14.863 --> 00:42:17.088 have a germline mutations either.

NOTE Confidence: 0.682636668333333

00:42:17.090 --> 00:42:20.346 So what are these things like cases they

NOTE Confidence: 0.682636668333333

00:42:20.346 --> 00:42:23.010 actually could be Lynch syndrome cases,

NOTE Confidence: 0.682636668333333

00:42:23.010 --> 00:42:25.050 but that due to difficulty on

00:42:25.050 --> 00:42:26.882 identifying mutations or because they

00:42:26.882 --> 00:42:28.546 have like encrypting mitigations.

00:42:28.550 --> 00:42:30.468 Maybe we have not been able to

00:42:30.468 --> 00:42:31.290 then defy them,

00:42:31.290 --> 00:42:33.900 or they could actually be heritary

00:42:33.900 --> 00:42:36.790 cases that they might be due to general

00:42:36.790 --> 00:42:38.740 mutations in other genes and that.

00:42:38.740 --> 00:42:43.556 They end up developing MSI as a driver

00:42:43.556 --> 00:42:48.738 effect, not as a cancer driver effect,

00:42:48.740 --> 00:42:51.090 sorry.

00:42:51.090 --> 00:42:53.800 Sorry that they developed because

00:42:53.800 --> 00:42:56.510 other germline mutations but they

00:42:56.595 --> 00:42:59.535 actually the MSI was an effect of

00:42:59.535 --> 00:43:02.310 the development of cancer but they

00:43:02.310 --> 00:43:04.685 could just be sporadic cancers.

00:43:04.690 --> 00:43:07.930 So to address these these challenges,

00:43:07.930 --> 00:43:10.888 we have developed 2 main projects,

00:43:10.890 --> 00:43:12.882 one and the general level and

00:43:12.882 --> 00:43:15.320 another one at the semantic level.

00:43:15.320 --> 00:43:17.413 The general level with our aim was

00:43:17.413 --> 00:43:19.200 to identify the current deficient

00:43:19.200 --> 00:43:21.678 DNA repair genes and the cellular

00:43:21.678 --> 00:43:23.716 consequences that contribute to the

00:43:23.716 --> 00:43:25.631 development of colorectal cancer in

00:43:25.631 --> 00:43:28.860 lines like patients and at the somatic level,

00:43:28.860 --> 00:43:31.356 we aim to define molecular factors

00:43:31.356 --> 00:43:34.050 in the three types of mismatch.

00:43:34.050 --> 00:43:36.402 Deficient tumors the lynch lynch like

00:43:36.402 --> 00:43:39.321 and the viraf methylated ones which will

00:43:39.321 --> 00:43:41.456 contribute to diagnosis and treatment.

00:43:43.550 --> 00:43:46.646 So so our collaborations with the

00:43:46.646 --> 00:43:49.610 correct with the current concerns,

00:43:49.610 --> 00:43:52.298 we were able to describe the patients have

00:43:52.298 --> 00:43:55.314 a higher frequency of family history of

00:43:55.314 --> 00:43:57.589 colorectal cancer than sporadic cases,

00:43:57.590 --> 00:44:00.894 and you can see here how the standardized

00:44:00.894 --> 00:44:03.930 incidence ratio was 2.2 for the links in

00:44:03.930 --> 00:44:07.664 comparison to 0.48 for sporadic individuals,

00:44:07.664 --> 00:44:11.072 and and and these incidents

00:44:11.072 --> 00:44:12.840 of family history was.

00:44:12.840 --> 00:44:14.308 Actually lower than lead,

00:44:14.308 --> 00:44:16.143 so this kind of foods.

00:44:16.150 --> 00:44:19.080 The Linge like phenotype and

00:44:19.080 --> 00:44:20.838 in between between.

00:44:20.840 --> 00:44:22.622 Lynch and Sprite.

00:44:22.622 --> 00:44:27.216 We're also able to to show that the

00:44:27.216 --> 00:44:30.704 average age of diagnosis for Lynch like is

NOTE Confidence: 0.523577779909091

00:44:30.704 --> 00:44:33.250 significantly younger than sporadic cases.

NOTE Confidence: 0.523577779909091

00:44:33.250 --> 00:44:35.746 So these two features are suggest

NOTE Confidence: 0.523577779909091

00:44:35.746 --> 00:44:37.889 that a potential unidentified genetic

NOTE Confidence: 0.523577779909091

00:44:37.889 --> 00:44:40.773 predisposition induced in this in a group,

NOTE Confidence: 0.523577779909091

00:44:40.780 --> 00:44:43.828 at least in Group of Lynch

NOTE Confidence: 0.523577779909091

00:44:43.828 --> 00:44:45.352 like syndrome patients.

NOTE Confidence: 0.523577779909091

00:44:45.360 --> 00:44:46.504 So to address this,

NOTE Confidence: 0.523577779909091

00:44:46.504 --> 00:44:48.939 and because we believe that that is the case,

NOTE Confidence: 0.523577779909091

00:44:48.940 --> 00:44:54.886 we develop a a study including 654

NOTE Confidence: 0.523577779909091

00:44:54.886 --> 00:44:57.516 individuals from our Chicago Colorectal

NOTE Confidence: 0.523577779909091

00:44:57.516 --> 00:44:59.620 Cancer Center consortium cohort,

NOTE Confidence: 0.523577779909091

00:44:59.620 --> 00:45:02.698 and we performed that link screening

NOTE Confidence: 0.523577779909091

00:45:02.700 --> 00:45:05.680 testing that I mentioned before

NOTE Confidence: 0.523577779909091

00:45:05.680 --> 00:45:08.620 we identified 23 suspected links.

NOTE Confidence: 0.523577779909091

00:45:08.620 --> 00:45:09.730 Lynn syndrome.

NOTE Confidence: 0.865651094285714

00:45:11.770 --> 00:45:15.567 So from those we were able to have

NOTE Confidence: 0.865651094285714

00:45:15.567 --> 00:45:17.926 germline DNA from 15 of them and

NOTE Confidence: 0.865651094285714

00:45:17.926 --> 00:45:20.194 we perform XM sequencing and we

NOTE Confidence: 0.865651094285714

00:45:20.194 --> 00:45:22.468 identified that four of them were

NOTE Confidence: 0.865651094285714

00:45:22.548 --> 00:45:25.164 actually engaged and eleven were links

NOTE Confidence: 0.865651094285714

00:45:25.164 --> 00:45:27.912 like were classified as Lynch like

NOTE Confidence: 0.865651094285714

00:45:27.912 --> 00:45:30.417 because we didn't find limitations.

NOTE Confidence: 0.865651094285714

00:45:30.420 --> 00:45:33.156 So then we take it one step further

NOTE Confidence: 0.865651094285714

00:45:33.156 --> 00:45:36.212 and we wanted to identify if if

NOTE Confidence: 0.865651094285714

00:45:36.212 --> 00:45:38.730 any of these links, like patients,

NOTE Confidence: 0.865651094285714

00:45:38.730 --> 00:45:41.775 had mutations in other DNA repair genes.

NOTE Confidence: 0.865651094285714

00:45:41.780 --> 00:45:45.630 So we analyze 162 DNA repair genes and

NOTE Confidence: 0.865651094285714

00:45:45.630 --> 00:45:48.668 we were able to see that this links,

NOTE Confidence: 0.865651094285714

00:45:48.668 --> 00:45:49.620 like patients.

NOTE Confidence: 0.865651094285714

00:45:49.620 --> 00:45:51.996 They had the higher mutational burden

NOTE Confidence: 0.865651094285714

00:45:52.000 --> 00:45:54.576 and comparison to lynch to the TCG,

NOTE Confidence: 0.865651094285714

00:45:54.580 --> 00:45:56.868 a colorectal cancer cohort,

NOTE Confidence: 0.865651094285714

00:45:56.868 --> 00:45:59.728 and to control without cancer.

NOTE Confidence: 0.865651094285714

00:45:59.730 --> 00:46:00.514 So specifically,

NOTE Confidence: 0.865651094285714

00:46:00.514 --> 00:46:03.258 we identified four loss of function variants,

NOTE Confidence: 0.865651094285714

00:46:03.260 --> 00:46:06.004 one in body, one one in Werner,

NOTE Confidence: 0.865651094285714

00:46:06.010 --> 00:46:10.717 one in MCPH one and one in Rev 3.

NOTE Confidence: 0.865651094285714

00:46:10.720 --> 00:46:12.754 So then after this first study

NOTE Confidence: 0.865651094285714

00:46:12.754 --> 00:46:14.507 that we identified that links

NOTE Confidence: 0.865651094285714

00:46:14.507 --> 00:46:16.499 like were in bridge with mutations

NOTE Confidence: 0.865651094285714

00:46:16.499 --> 00:46:18.320 in the inner river jeans,

NOTE Confidence: 0.865651094285714

00:46:18.320 --> 00:46:20.756 we include decided to include two

NOTE Confidence: 0.865651094285714

00:46:20.756 --> 00:46:22.820 different independent series of lines,

NOTE Confidence: 0.865651094285714

00:46:22.820 --> 00:46:25.448 like patients to try to identify

NOTE Confidence: 0.865651094285714

00:46:25.448 --> 00:46:28.243 genes that maybe would be recurrently

NOTE Confidence: 0.865651094285714

00:46:28.243 --> 00:46:30.787 mutated in this in this phenotype.

NOTE Confidence: 0.865651094285714

00:46:30.787 --> 00:46:33.904 So when we did that in the first

NOTE Confidence: 0.865651094285714

00:46:33.904 --> 00:46:36.487 series with unified 6 genes that

NOTE Confidence: 0.865651094285714

00:46:36.487 --> 00:46:38.449 were mutated and had lots of

NOTE Confidence: 0.865651094285714

00:46:38.449 --> 00:46:40.330 function variants and interestingly.

NOTE Confidence: 0.865651094285714

00:46:40.330 --> 00:46:42.988 We found the same splicing variant

NOTE Confidence: 0.865651094285714

00:46:42.988 --> 00:46:45.458 in two different patients in the

NOTE Confidence: 0.865651094285714

00:46:45.458 --> 00:46:47.665 regular 5 gene and we actually

NOTE Confidence: 0.865651094285714

00:46:47.665 --> 00:46:50.215 perform a kinship analysis to show

NOTE Confidence: 0.865651094285714

00:46:50.215 --> 00:46:53.406 that and to prove that these two

NOTE Confidence: 0.865651094285714

00:46:53.406 --> 00:46:55.198 patients were not genetically.

NOTE Confidence: 0.865651094285714

00:46:55.200 --> 00:46:56.860 And they were not genetically.

NOTE Confidence: 0.651248294

00:47:02.480 --> 00:47:04.520 There were no this related.

NOTE Confidence: 0.651248294

00:47:04.520 --> 00:47:06.640 Sorry, because these patients were

NOTE Confidence: 0.651248294

00:47:06.640 --> 00:47:09.774 both coming from from Spain and we just

NOTE Confidence: 0.651248294

00:47:09.774 --> 00:47:12.254 wanted to make sure that there was no

NOTE Confidence: 0.651248294

00:47:12.254 --> 00:47:15.976 any family relation that we don't know.

NOTE Confidence: 0.651248294

00:47:15.980 --> 00:47:18.059 And then when we developed the analysis

NOTE Confidence: 0.651248294

00:47:18.059 --> 00:47:20.099 of the other series of patients,

NOTE Confidence: 0.651248294

00:47:20.100 --> 00:47:22.945 we again identified another loss

NOTE Confidence: 0.651248294

00:47:22.945 --> 00:47:26.070 of function variant in regular 5.

NOTE Confidence: 0.651248294

00:47:26.070 --> 00:47:28.303 So with that, if you've been able

NOTE Confidence: 0.651248294

00:47:28.303 --> 00:47:31.138 to follow my my talk and the the

NOTE Confidence: 0.651248294

00:47:31.138 --> 00:47:32.582 the notification of mutations

NOTE Confidence: 0.651248294

00:47:32.582 --> 00:47:34.470 in our original serious,

NOTE Confidence: 0.651248294

00:47:34.470 --> 00:47:37.155 we have identified 4 different

NOTE Confidence: 0.651248294

00:47:37.155 --> 00:47:40.442 mutations in genes that belong to

NOTE Confidence: 0.651248294

00:47:40.442 --> 00:47:43.007 the Dracula DNA helicase family.

NOTE Confidence: 0.651248294

00:47:43.010 --> 00:47:46.645 So here you can see the five the

NOTE Confidence: 0.651248294

00:47:46.645 --> 00:47:49.135 five proteins that are in this

NOTE Confidence: 0.651248294

00:47:49.135 --> 00:47:51.243 family regular one bloom Werner

NOTE Confidence: 0.651248294

00:47:51.243 --> 00:47:53.980 regular four and regular 5 and all

NOTE Confidence: 0.651248294

00:47:53.980 --> 00:47:56.790 of them share the same helicase.

NOTE Confidence: 0.651248294

00:47:56.790 --> 00:47:57.800 I mean.

NOTE Confidence: 0.651248294

00:47:57.800 --> 00:47:59.295 So these are the individuals

NOTE Confidence: 0.651248294

00:47:59.295 --> 00:48:01.200 that we have identified the two

NOTE Confidence: 0.651248294

00:48:01.200 --> 00:48:02.940 individuals with the same splicing,

NOTE Confidence: 0.651248294

00:48:02.940 --> 00:48:04.875 one with the insertion and

NOTE Confidence: 0.651248294

00:48:04.875 --> 00:48:06.423 from the original cohort.

NOTE Confidence: 0.651248294

00:48:06.430 --> 00:48:08.970 We also identified this individual

NOTE Confidence: 0.651248294

00:48:08.970 --> 00:48:10.494 with a mutation.

NOTE Confidence: 0.651248294

00:48:10.500 --> 00:48:13.230 So after that we were interested in

NOTE Confidence: 0.651248294

00:48:13.230 --> 00:48:15.600 knowing if maybe the mutations in

NOTE Confidence: 0.651248294

00:48:15.600 --> 00:48:18.600 this in this family of genes were also

NOTE Confidence: 0.651248294

00:48:18.600 --> 00:48:21.280 recurring in other cancer friendships.

NOTE Confidence: 0.651248294

00:48:21.280 --> 00:48:22.788 So to do that?

NOTE Confidence: 0.651248294

00:48:22.788 --> 00:48:24.673 First took individuals that were

NOTE Confidence: 0.651248294

00:48:24.673 --> 00:48:26.769 referred to the Smilo Cancer

NOTE Confidence: 0.651248294

00:48:26.769 --> 00:48:28.413 Genetics and Prevention program

NOTE Confidence: 0.651248294

00:48:28.413 --> 00:48:30.589 that when they were referred,

NOTE Confidence: 0.651248294

00:48:30.590 --> 00:48:32.450 they and they were tested

NOTE Confidence: 0.651248294

00:48:32.450 --> 00:48:34.310 and we in the clinic.

NOTE Confidence: 0.651248294

00:48:34.310 --> 00:48:35.780 They didn't find any mutations,

NOTE Confidence: 0.651248294

00:48:35.780 --> 00:48:39.446 say many known cancer predisposition genes.

NOTE Confidence: 0.651248294

00:48:39.450 --> 00:48:43.018 So we perform XM sequencing in 156

NOTE Confidence: 0.651248294

00:48:43.018 --> 00:48:46.184 breast cancer patients in 75 individuals

NOTE Confidence: 0.651248294

00:48:46.184 --> 00:48:49.346 that had different types of tumors

NOTE Confidence: 0.651248294

00:48:49.346 --> 00:48:52.342 that were not breast breast tumors.

NOTE Confidence: 0.651248294

00:48:52.342 --> 00:48:53.770 We'll sync clouded,

NOTE Confidence: 0.651248294

00:48:53.770 --> 00:48:55.015 MSH and PC.

NOTE Confidence: 0.651248294

00:48:55.015 --> 00:48:58.873 These are very rare type of familial

NOTE Confidence: 0.651248294

00:48:58.873 --> 00:49:02.172 colorectal cancer that affects individuals

NOTE Confidence: 0.651248294

00:49:02.172 --> 00:49:04.032 in different generations and that

00:49:04.032 --> 00:49:06.339 they develop cancer at the young age.

00:49:06.340 --> 00:49:09.658 But these individuals don't have MSI RMS.

00:49:09.660 --> 00:49:10.536 And lastly,

00:49:10.536 --> 00:49:14.040 we also identify mutations in the DC G.

00:49:14.040 --> 00:49:15.930 So with this analysis we were

00:49:15.930 --> 00:49:17.880 able to see that actually,

00:49:17.880 --> 00:49:20.456 like the higher a little frequency variants

00:49:20.456 --> 00:49:23.110 in DNA repair genes that are not the.

00:49:23.110 --> 00:49:26.225 Compare and then they are not know

00:49:26.225 --> 00:49:28.286 well established cancer predisposing

00:49:28.286 --> 00:49:31.784 genes and we all the identified

00:49:31.784 --> 00:49:35.067 mutations in the REQ DNA helicases

00:49:35.067 --> 00:49:37.597 in the lynch like phenotype.

00:49:37.600 --> 00:49:41.580 So then we went back to the

00:49:41.580 --> 00:49:44.379 families that we were able to.

00:49:44.380 --> 00:49:46.588 Contact again to in the defy

NOTE Confidence: 0.651248294

00:49:46.588 --> 00:49:48.650 if the mutations were shared.

NOTE Confidence: 0.651248294

00:49:48.650 --> 00:49:50.375 If these mutations with shared

NOTE Confidence: 0.651248294

00:49:50.375 --> 00:49:51.755 with other family members,

NOTE Confidence: 0.651248294

00:49:51.760 --> 00:49:53.928 so here these are the three families that

NOTE Confidence: 0.651248294

00:49:53.928 --> 00:49:56.167 will have with mutations in the right QL.

NOTE Confidence: 0.651248294

00:49:56.170 --> 00:49:59.058 So family A&amp;B are the the ones that

NOTE Confidence: 0.651248294

00:49:59.058 --> 00:50:00.858 share the same splicing variant,

NOTE Confidence: 0.651248294

00:50:00.858 --> 00:50:03.196 so here this is the program that

NOTE Confidence: 0.651248294

00:50:03.196 --> 00:50:05.121 developed for family aid that

NOTE Confidence: 0.651248294

00:50:05.121 --> 00:50:06.267 developed colorectal cancer.

NOTE Confidence: 0.651248294

00:50:06.270 --> 00:50:06.928 At 63.

NOTE Confidence: 0.651248294

00:50:06.928 --> 00:50:08.902 We were also able to sequence

NOTE Confidence: 0.651248294

00:50:08.902 --> 00:50:11.215 the tumor of this individual and

NOTE Confidence: 0.651248294

00:50:11.215 --> 00:50:13.579 we also found a missense variant

NOTE Confidence: 0.651248294

00:50:13.653 --> 00:50:15.655 in the in the tumor of this.

NOTE Confidence: 0.651248294

00:50:15.660 --> 00:50:16.809 Of this patient,

NOTE Confidence: 0.651248294

00:50:16.809 --> 00:50:19.490 and then the brother of this program

NOTE Confidence: 0.651248294

00:50:19.569 --> 00:50:22.001 had a small bowel cancer and he was

NOTE Confidence: 0.651248294

00:50:22.001 --> 00:50:24.418 also a carrier of the mutation.

NOTE Confidence: 0.651248294

00:50:24.420 --> 00:50:25.636 The family we we.

NOTE Confidence: 0.651248294

00:50:25.636 --> 00:50:27.460 This was the program that they

NOTE Confidence: 0.651248294

00:50:27.530 --> 00:50:29.180 are of collector cancer at

NOTE Confidence: 0.815990964416667

00:50:29.180 --> 00:50:31.755 64 very strong family history

NOTE Confidence: 0.815990964416667

00:50:31.755 --> 00:50:35.319 and then we tested the two sons.

NOTE Confidence: 0.815990964416667

00:50:35.320 --> 00:50:37.259 That one was a carrier and the

NOTE Confidence: 0.815990964416667

00:50:37.259 --> 00:50:39.696 other one was not a carrier and the

NOTE Confidence: 0.815990964416667

00:50:39.696 --> 00:50:41.560 rate of diagnosis was under 40s.

NOTE Confidence: 0.815990964416667

00:50:41.560 --> 00:50:44.176 And lastly this last one we.

NOTE Confidence: 0.815990964416667

00:50:44.180 --> 00:50:46.790 This was the program developed

NOTE Confidence: 0.815990964416667

00:50:46.790 --> 00:50:49.913 colorectal cancer at 66 and we

NOTE Confidence: 0.815990964416667

00:50:49.913 --> 00:50:52.451 tested this son that also had

NOTE Confidence: 0.815990964416667

00:50:52.451 --> 00:50:54.792 sorry also had the mutation.

NOTE Confidence: 0.815990964416667

00:50:54.792 --> 00:50:56.936 But however, these individuals

NOTE Confidence: 0.815990964416667

00:50:56.936 --> 00:50:59.080 in the second generation,

NOTE Confidence: 0.815990964416667

00:50:59.080 --> 00:51:00.736 because they are in their 40s,

NOTE Confidence: 0.815990964416667

00:51:00.740 --> 00:51:02.570 they might have not been able

NOTE Confidence: 0.815990964416667

00:51:02.570 --> 00:51:03.974 to develop cancer yet.

NOTE Confidence: 0.815990964416667

00:51:03.974 --> 00:51:05.959 So this this course aggregation

NOTE Confidence: 0.815990964416667

00:51:05.959 --> 00:51:07.990 study was not definitive.

NOTE Confidence: 0.759642116333333

00:51:10.030 --> 00:51:12.811 So then we wanted to to test what was

NOTE Confidence: 0.759642116333333

00:51:12.811 --> 00:51:15.417 the effect of having a heterozygous

NOTE Confidence: 0.759642116333333

00:51:15.417 --> 00:51:18.550 loss of function barrier in intestines.

NOTE Confidence: 0.759642116333333

00:51:18.550 --> 00:51:21.820 So to do that we went back to to our

NOTE Confidence: 0.759642116333333

00:51:21.918 --> 00:51:25.649 contacts in Spain and we extracted cells,

NOTE Confidence: 0.759642116333333

00:51:25.650 --> 00:51:28.884 extracted blood samples from the two of

NOTE Confidence: 0.759642116333333

00:51:28.884 --> 00:51:32.086 these songs that I show you in family.

00:51:32.090 --> 00:51:33.458 That one was a carrier and

00:51:33.458 --> 00:51:34.630 the other one was not.

00:51:34.630 --> 00:51:36.700 And we extracted that RNA.

00:51:36.700 --> 00:51:39.794 We did the red transcription and qPCR.

00:51:39.800 --> 00:51:43.458 To show that actually the the level of gene

00:51:43.458 --> 00:51:46.160 expression was significantly lower in the in,

00:51:46.160 --> 00:51:50.059 in the brother that had the mutation.

00:51:50.060 --> 00:51:53.100 And to test the effect in the Warner,

00:51:53.100 --> 00:51:55.755 we had to use a different approach because we

00:51:55.755 --> 00:51:58.097 didn't have access to that family anymore.

00:51:58.100 --> 00:52:01.118 But we were likely to acquire

00:52:01.120 --> 00:52:04.192 Lymphoblastoid cell line from family that

00:52:04.192 --> 00:52:07.875 had there were these one mutation and

00:52:07.875 --> 00:52:10.706 heterozygosity and from a control also.

00:52:10.706 --> 00:52:12.182 And this mutation is the one

00:52:12.182 --> 00:52:13.539 that the cell lines have.

NOTE Confidence: 0.759642116333333

00:52:13.540 --> 00:52:15.988 And it's just like a loss of function

NOTE Confidence: 0.759642116333333

00:52:15.988 --> 00:52:17.841 mutation just for an amino acids

NOTE Confidence: 0.759642116333333

00:52:17.841 --> 00:52:19.605 down the line from the actual.

NOTE Confidence: 0.759642116333333

00:52:19.610 --> 00:52:20.810 Colorectal cancer mutation that

NOTE Confidence: 0.759642116333333

00:52:20.810 --> 00:52:23.170 we found in one of the patients.

NOTE Confidence: 0.759642116333333

00:52:23.170 --> 00:52:23.986 So we extracted.

NOTE Confidence: 0.759642116333333

00:52:23.986 --> 00:52:25.074 We grow the cells.

NOTE Confidence: 0.759642116333333

00:52:25.080 --> 00:52:28.455 We extracted proteins and we show that

NOTE Confidence: 0.759642116333333

00:52:28.455 --> 00:52:31.407 again that there is an effect on the

NOTE Confidence: 0.759642116333333

00:52:31.407 --> 00:52:33.607 heterozygous and the protein expression.

NOTE Confidence: 0.759642116333333

00:52:33.610 --> 00:52:35.549 So with these we show that when

NOTE Confidence: 0.759642116333333

00:52:35.549 --> 00:52:37.661 there is a when these individuals

NOTE Confidence: 0.759642116333333

00:52:37.661 --> 00:52:40.079 have a heterozygous well as a

NOTE Confidence: 0.759642116333333

00:52:40.079 --> 00:52:41.539 function in these genes,

NOTE Confidence: 0.759642116333333

00:52:41.540 --> 00:52:44.075 they actually have a downregulation

NOTE Confidence: 0.759642116333333

00:52:44.075 --> 00:52:46.610 of the gene and protein.

NOTE Confidence: 0.759642116333333

00:52:46.610 --> 00:52:48.787 So then we were interested in knowing

NOTE Confidence: 0.759642116333333

00:52:48.787 --> 00:52:51.009 well if there is a downregulation,

NOTE Confidence: 0.759642116333333

00:52:51.010 --> 00:52:53.030 what's happening with the activity

NOTE Confidence: 0.759642116333333

00:52:53.030 --> 00:52:55.550 on the activity of the genes,

NOTE Confidence: 0.759642116333333

00:52:55.550 --> 00:52:56.966 and how is that?

NOTE Confidence: 0.759642116333333

00:52:56.966 --> 00:52:59.670 How are these sales managing DNA damage?

NOTE Confidence: 0.759642116333333

00:52:59.670 --> 00:53:00.460 Because again,

NOTE Confidence: 0.759642116333333

00:53:00.460 --> 00:53:03.225 remember that these are DNA repair genes.

NOTE Confidence: 0.759642116333333

00:53:03.230 --> 00:53:05.552 So to do that we grow the cells and

NOTE Confidence: 0.759642116333333

00:53:05.552 --> 00:53:08.129 we perform a flow cytometry analysis

NOTE Confidence: 0.759642116333333

00:53:08.130 --> 00:53:10.695 that was actually testing the

NOTE Confidence: 0.759642116333333

00:53:10.695 --> 00:53:13.756 quantity of forceful relation of the

NOTE Confidence: 0.759642116333333

00:53:13.756 --> 00:53:15.990 serene 139 residue of the history.

NOTE Confidence: 0.759642116333333

00:53:15.990 --> 00:53:19.270 Age to ax as an indicator of the

NOTE Confidence: 0.759642116333333

00:53:19.270 --> 00:53:22.580 damage and DNA double strand breaks.

NOTE Confidence: 0.759642116333333

00:53:22.580 --> 00:53:24.180 So when we did that,

NOTE Confidence: 0.759642116333333

00:53:24.180 --> 00:53:25.884 we determined the phosphorylation

NOTE Confidence: 0.759642116333333

00:53:25.884 --> 00:53:28.440 at different time points and the

NOTE Confidence: 0.759642116333333

00:53:28.512 --> 00:53:30.542 black are the wild type cells and

NOTE Confidence: 0.759642116333333

00:53:30.542 --> 00:53:32.905 the and the and Gray are the the

NOTE Confidence: 0.759642116333333

00:53:32.905 --> 00:53:34.783 ones with the headers I use,

NOTE Confidence: 0.759642116333333

00:53:34.783 --> 00:53:38.306 so it's true that that the first time

NOTE Confidence: 0.759642116333333

00:53:38.306 --> 00:53:41.074 the first time point might be a delay

NOTE Confidence: 0.759642116333333

00:53:41.074 --> 00:53:44.089 on the on on the phosphorylation we see

NOTE Confidence: 0.759642116333333

00:53:44.089 --> 00:53:46.822 that on the other time points there

NOTE Confidence: 0.759642116333333

00:53:46.822 --> 00:53:49.780 is a higher dose of the frustration and

NOTE Confidence: 0.759642116333333

00:53:49.780 --> 00:53:52.289 therefore an indicator that these cells have.

NOTE Confidence: 0.759642116333333

00:53:52.290 --> 00:53:55.074 The higher DNA damage

NOTE Confidence: 0.759642116333333

00:53:55.074 --> 00:53:57.080 and here as you can see,

NOTE Confidence: 0.759642116333333

00:53:57.080 --> 00:53:58.788 this is the difference

NOTE Confidence: 0.759642116333333

00:53:58.788 --> 00:54:00.069 between the heterozygote,

NOTE Confidence: 0.759642116333333

00:54:00.070 --> 00:54:02.080 the the heterozygous that has

NOTE Confidence: 0.759642116333333

00:54:02.080 --> 00:54:07.010 like a higher phosphorylation so.

NOTE Confidence: 0.759642116333333

00:54:07.010 --> 00:54:09.770 So right now we are also doing more

NOTE Confidence: 0.759642116333333

00:54:09.770 --> 00:54:12.758 analysis and we are testing for for example,

NOTE Confidence: 0.759642116333333

00:54:12.760 --> 00:54:15.124 for the effect of these variants

NOTE Confidence: 0.759642116333333

00:54:15.124 --> 00:54:18.065 in cell cycle because some of our

NOTE Confidence: 0.759642116333333

00:54:18.065 --> 00:54:20.215 preliminary data showing that maybe

NOTE Confidence: 0.759642116333333

00:54:20.215 --> 00:54:23.196 these cells are actually arrested in G1,

NOTE Confidence: 0.759642116333333

00:54:23.200 --> 00:54:27.136 but we have not had this data yet.

NOTE Confidence: 0.759642116333333

00:54:27.140 --> 00:54:29.084 So in conclusion from this aim

NOTE Confidence: 0.759642116333333

00:54:29.084 --> 00:54:30.380 I we believe that

NOTE Confidence: 0.69297737452

00:54:30.451 --> 00:54:32.151 heterozygous loss of function

NOTE Confidence: 0.69297737452

00:54:32.151 --> 00:54:34.276 variants in DNA repair genes

NOTE Confidence: 0.69297737452

00:54:34.276 --> 00:54:36.596 such as Warner and regular five,

NOTE Confidence: 0.69297737452

00:54:36.600 --> 00:54:38.840 could predispose to tumor development

NOTE Confidence: 0.69297737452

00:54:38.840 --> 00:54:41.080 because they are enriched among

NOTE Confidence: 0.69297737452

00:54:41.150 --> 00:54:43.230 the lines like cancer phenotype.

NOTE Confidence: 0.69297737452

00:54:43.230 --> 00:54:46.302 They lead to gene down regulation

NOTE Confidence: 0.69297737452

00:54:46.302 --> 00:54:49.100 and they increase DNA damage.

NOTE Confidence: 0.69297737452

00:54:49.100 --> 00:54:51.102 So now turning it to the end

NOTE Confidence: 0.69297737452

00:54:51.102 --> 00:54:53.069 two at the somatic level.

NOTE Confidence: 0.69297737452

00:54:53.070 --> 00:54:55.068 Had to do develop these aim.

NOTE Confidence: 0.69297737452

00:54:55.070 --> 00:54:56.920 We also included two different

NOTE Confidence: 0.69297737452

00:54:56.920 --> 00:54:58.770 independent series of tumors that

NOTE Confidence: 0.69297737452

00:54:58.829 --> 00:55:00.473 mismatch repair deficient tumors

NOTE Confidence: 0.69297737452

00:55:00.473 --> 00:55:02.528 from the three different types,

NOTE Confidence: 0.69297737452

00:55:02.530 --> 00:55:05.450 and we develop exam sequencing

NOTE Confidence: 0.69297737452

00:55:05.450 --> 00:55:07.786 to identify somatic variants

NOTE Confidence: 0.69297737452

00:55:07.786 --> 00:55:10.779 and loss of hydrazoic events.

NOTE Confidence: 0.69297737452

00:55:10.780 --> 00:55:12.260 And with with this data,

NOTE Confidence: 0.69297737452

00:55:12.260 --> 00:55:14.096 with this excellent data,

NOTE Confidence: 0.69297737452

00:55:14.096 --> 00:55:16.850 we also were interested in defying

NOTE Confidence: 0.69297737452

00:55:16.935 --> 00:55:19.155 the contribution of mutational

NOTE Confidence: 0.69297737452

00:55:19.155 --> 00:55:21.375 signatures to these tumors.

NOTE Confidence: 0.69297737452

00:55:21.380 --> 00:55:23.715 So mutational signatures are like

NOTE Confidence: 0.69297737452

00:55:23.715 --> 00:55:26.617 a fingerprint of of the portrait

NOTE Confidence: 0.69297737452

00:55:26.617 --> 00:55:29.949 of the mutations that the tumor has

NOTE Confidence: 0.69297737452

00:55:29.949 --> 00:55:32.715 acquired over the development of the

NOTE Confidence: 0.69297737452

00:55:32.715 --> 00:55:35.625 tumor and they some of them are well

NOTE Confidence: 0.69297737452

00:55:35.625 --> 00:55:37.460 established and they are associated to,

NOTE Confidence: 0.69297737452

00:55:37.460 --> 00:55:38.246 for example,

NOTE Confidence: 0.69297737452

00:55:38.246 --> 00:55:40.604 exposure to carcinogens and other ones.

NOTE Confidence: 0.69297737452

00:55:40.610 --> 00:55:43.306 Associated like in the case of the mismatch,

NOTE Confidence: 0.69297737452

00:55:43.310 --> 00:55:46.684 repair to deficiency on DNA repair pathways.

NOTE Confidence: 0.69297737452

00:55:46.690 --> 00:55:50.547 So they the these are the six

NOTE Confidence: 0.69297737452

93

00:55:50.550 --> 00:55:51.806 current well established signatures

NOTE Confidence: 0.69297737452

00:55:51.806 --> 00:55:53.376 that are associated with deficiency

NOTE Confidence: 0.69297737452

00:55:53.376 --> 00:55:54.588 of the mismatch repair.

NOTE Confidence: 0.69297737452

00:55:54.590 --> 00:55:56.570 So when these tumors have,

NOTE Confidence: 0.69297737452

00:55:56.570 --> 00:55:58.572 when the tumors have deficiency and you

NOTE Confidence: 0.69297737452

00:55:58.572 --> 00:56:00.629 analyze the the mutational signatures,

NOTE Confidence: 0.69297737452

00:56:00.630 --> 00:56:02.990 you can see this one so so we

NOTE Confidence: 0.69297737452

00:56:02.990 --> 00:56:04.819 were interested in knowing what

NOTE Confidence: 0.69297737452

00:56:04.819 --> 00:56:06.759 was the contribution of these

NOTE Confidence: 0.69297737452

00:56:06.759 --> 00:56:08.849 signatures to each of the tumors.

NOTE Confidence: 0.69297737452

00:56:08.850 --> 00:56:10.634 So let me explain.

NOTE Confidence: 0.69297737452

00:56:10.634 --> 00:56:12.864 So this colorful graph here.

NOTE Confidence: 0.69297737452

00:56:12.870 --> 00:56:15.042 So we first read identified what

NOTE Confidence: 0.69297737452

00:56:15.042 --> 00:56:16.850 were the mutational signatures that

NOTE Confidence: 0.69297737452

00:56:16.850 --> 00:56:18.644 were contributing the most to each

NOTE Confidence: 0.69297737452

00:56:18.644 --> 00:56:20.887 of the tumor and then we perform

NOTE Confidence: 0.69297737452

00:56:20.887 --> 00:56:22.819 clustering to see whether the groups

NOTE Confidence: 0.69297737452

00:56:22.820 --> 00:56:26.270 of whether the tumors that have

NOTE Confidence: 0.69297737452

00:56:26.270 --> 00:56:29.280 a similar contribution of those.

NOTE Confidence: 0.69297737452

00:56:29.280 --> 00:56:33.016 So here each each row is 1 tumor

NOTE Confidence: 0.69297737452

00:56:33.016 --> 00:56:35.174 and each column is rotational.

NOTE Confidence: 0.69297737452

00:56:35.174 --> 00:56:37.214 It's a contribution of to

NOTE Confidence: 0.69297737452

00:56:37.214 --> 00:56:38.820 the mutational signatures,

NOTE Confidence: 0.69297737452

00:56:38.820 --> 00:56:42.036 and here we are also having the phenotypes.

NOTE Confidence: 0.69297737452

00:56:42.040 --> 00:56:44.936 So in here you can see the tumor

NOTE Confidence: 0.69297737452

00:56:44.936 --> 00:56:47.790 is linch light lynch or the MSI?

NOTE Confidence: 0.69297737452

00:56:47.790 --> 00:56:48.131 Isolated.

NOTE Confidence: 0.69297737452

00:56:48.131 --> 00:56:50.859 And then in the last column here we

NOTE Confidence: 0.69297737452

00:56:50.859 --> 00:56:53.445 are showing that which is the protein

NOTE Confidence: 0.69297737452

00:56:53.445 --> 00:56:55.800 that each of these tumors have.

NOTE Confidence: 0.69297737452

00:56:55.800 --> 00:56:57.436 Most of the expression.

NOTE Confidence: 0.69297737452

00:56:57.436 --> 00:56:59.890 So when we perform this analysis,

NOTE Confidence: 0.69297737452

00:56:59.890 --> 00:57:02.634 you can see with identified 2 of the

NOTE Confidence: 0.69297737452

00:57:02.640 --> 00:57:05.390 that mutational signatures based on

NOTE Confidence: 0.69297737452

00:57:05.390 --> 00:57:09.684 the the contribution of SBS 26 and 15,

NOTE Confidence: 0.69297737452

00:57:09.684 --> 00:57:11.539 which are very well established.

NOTE Confidence: 0.69297737452

00:57:11.540 --> 00:57:13.284 Mutational signatures associated with

NOTE Confidence: 0.69297737452

00:57:13.284 --> 00:57:15.464 deficiency of the mismatch repair

NOTE Confidence: 0.69297737452

00:57:15.470 --> 00:57:17.100 identified first the two clusters

NOTE Confidence: 0.69297737452

00:57:17.100 --> 00:57:19.370 that are in breach with the Lynch.

NOTE Confidence: 0.69297737452

00:57:19.370 --> 00:57:20.381 And the lynch,

NOTE Confidence: 0.69297737452

00:57:20.381 --> 00:57:22.740 like and then we then defied this

NOTE Confidence: 0.69297737452

00:57:22.812 --> 00:57:25.212 cluster that has a higher contribution

NOTE Confidence: 0.69297737452

00:57:25.212 --> 00:57:27.729 of the tumors that are missing.

NOTE Confidence: 0.69297737452

00:57:27.730 --> 00:57:29.240 MSI,

NOTE Confidence: 0.69297737452

00:57:29.240 --> 00:57:32.260 MSI dated.

NOTE Confidence: 0.69297737452

00:57:32.260 --> 00:57:35.270 So here I'm I'm showing you the

NOTE Confidence: 0.69297737452

00:57:35.270 --> 00:57:36.500 different features associated

NOTE Confidence: 0.69297737452

00:57:36.500 --> 00:57:38.900 with each of the the clusters,

NOTE Confidence: 0.69297737452

00:57:38.900 --> 00:57:40.276 and as I mentioned,

NOTE Confidence: 0.69297737452

00:57:40.276 --> 00:57:42.873 cluster two is enriched with MSI dated

NOTE Confidence: 0.69297737452

00:57:42.873 --> 00:57:46.031 and also this cluster has specific

NOTE Confidence: 0.69297737452

00:57:46.031 --> 00:57:48.486 clinical features that are well

NOTE Confidence: 0.69297737452

00:57:48.486 --> 00:57:51.259 established with this type of tumors,

NOTE Confidence: 0.69297737452

00:57:51.260 --> 00:57:53.672 which are that they develop preliminarily

NOTE Confidence: 0.69297737452

00:57:53.672 --> 00:57:55.973 and female patients at an older

NOTE Confidence: 0.69297737452

00:57:55.973 --> 00:57:57.857 age and that they are associated

NOTE Confidence: 0.69297737452

00:57:57.857 --> 00:57:59.870 with the bright side location.

NOTE Confidence: 0.764589175

00:58:01.910 --> 00:58:03.198 So as a molecularly,

NOTE Confidence: 0.764589175

00:58:03.198 --> 00:58:05.130 as I as I explained you,

NOTE Confidence: 0.764589175

00:58:05.130 --> 00:58:07.435 this cluster is associated with

NOTE Confidence: 0.764589175

00:58:07.435 --> 00:58:10.212 thousand expression of mutl and mainly

NOTE Confidence: 0.764589175

00:58:10.212 --> 00:58:12.570 due to the manipulation of image

NOTE Confidence: 0.764589175

00:58:12.570 --> 00:58:15.790 one and and then there's tumors.

NOTE Confidence: 0.764589175

00:58:15.790 --> 00:58:17.560 They also have the higher

NOTE Confidence: 0.764589175

00:58:17.560 --> 00:58:19.330 number of frames if mutations,

NOTE Confidence: 0.764589175

00:58:19.330 --> 00:58:22.095 even though there is no difference in

NOTE Confidence: 0.764589175

00:58:22.095 --> 00:58:24.230 tumor purity that could be affecting this.

NOTE Confidence: 0.764589175

00:58:24.230 --> 00:58:25.658 But we didn't see that there

NOTE Confidence: 0.764589175

00:58:25.658 --> 00:58:26.610 was a significant difference,

NOTE Confidence: 0.764589175

00:58:26.610 --> 00:58:28.164 and they don't have a significant

NOTE Confidence: 0.764589175

00:58:28.164 --> 00:58:29.430 difference in their own TMB.

NOTE Confidence: 0.764589175

00:58:29.430 --> 00:58:31.350 So to like two more.

NOTE Confidence: 0.764589175

00:58:31.350 --> 00:58:32.100 Additional burden,

NOTE Confidence: 0.764589175

00:58:32.100 --> 00:58:34.350 so it's specifically to the friendships

NOTE Confidence: 0.764589175

00:58:34.350 --> 00:58:36.498 and what this suggests is that the

NOTE Confidence: 0.764589175

00:58:36.498 --> 00:58:38.350 the the tumors in this cluster.

NOTE Confidence: 0.764589175

00:58:38.350 --> 00:58:40.140 They actually have the higher

00:58:40.140 --> 00:58:41.930 level of Microsoft the instability.

00:58:43.970 --> 00:58:46.007 So one of the results of having

00:58:46.007 --> 00:58:47.745 a higher level of microsatellite

00:58:47.745 --> 00:58:50.139 instability could be that these tumors

00:58:50.139 --> 00:58:52.708 have a different new antigen load,

00:58:52.710 --> 00:58:55.560 so new antigens are these peptides

00:58:55.560 --> 00:58:57.846 that are generated after somatic

00:58:57.846 --> 00:58:59.986 mutations arise in the tumor.

00:58:59.990 --> 00:59:01.190 And as you can see here,

00:59:01.190 --> 00:59:02.966 you can see that the normal protein and

00:59:02.966 --> 00:59:05.020 this is a missense mutation in the tumor,

00:59:05.020 --> 00:59:07.236 so this is going to be 1 amino

00:59:07.236 --> 00:59:08.718 acid different from the self.

00:59:08.720 --> 00:59:10.616 The regular normal protein,

00:59:10.616 --> 00:59:14.564 but no antigens that are that are there.

00:59:14.564 --> 00:59:16.220 Develop from frame.

NOTE Confidence: 0.84446865875

00:59:16.220 --> 00:59:18.540 Frameshift mutations are significantly

NOTE Confidence: 0.84446865875

00:59:18.540 --> 00:59:21.440 different from the normal because

NOTE Confidence: 0.84446865875

00:59:21.440 --> 00:59:25.340 they introduce a lot of well.

NOTE Confidence: 0.84446865875

00:59:25.340 --> 00:59:26.990 Insertions and deletions.

NOTE Confidence: 0.84446865875

00:59:26.990 --> 00:59:28.640 So these proteins.

NOTE Confidence: 0.84446865875

00:59:28.640 --> 00:59:30.580 These peptides are significantly

NOTE Confidence: 0.84446865875

00:59:30.580 --> 00:59:32.035 different from cells,

NOTE Confidence: 0.84446865875

00:59:32.040 --> 00:59:34.830 and these new antigens which represented

NOTE Confidence: 0.84446865875

00:59:34.830 --> 00:59:38.460 here by this dot are presented from

NOTE Confidence: 0.84446865875

00:59:38.460 --> 00:59:43.420 through the HLA 1 receptor to the TCR.

NOTE Confidence: 0.84446865875

00:59:43.420 --> 00:59:45.100 To the T cell receptors,

NOTE Confidence: 0.84446865875

00:59:45.100 --> 00:59:47.340 and this is obviously a very simplified

NOTE Confidence: 0.84446865875

00:59:47.340 --> 00:59:48.920 version of what's happening,

NOTE Confidence: 0.84446865875

00:59:48.920 --> 00:59:52.359 but then when this is when when this

NOTE Confidence: 0.84446865875

00:59:52.359 --> 00:59:55.740 is happening then the T cells identify

100

NOTE Confidence: 0.84446865875

00:59:55.740 --> 00:59:59.577 the tumor cells as as non self,

NOTE Confidence: 0.84446865875

00:59:59.577 --> 01:00:02.372 and then they're going to

NOTE Confidence: 0.84446865875

01:00:02.372 --> 01:00:05.480 start the immune response.

NOTE Confidence: 0.84446865875

01:00:05.480 --> 01:00:08.664 So we wanted to see how these new

NOTE Confidence: 0.84446865875

01:00:08.664 --> 01:00:11.707 antigens and the direction of the HLA.

NOTE Confidence: 0.84446865875

01:00:11.710 --> 01:00:13.380 Image of the patient were

NOTE Confidence: 0.84446865875

01:00:13.380 --> 01:00:15.050 occurring based on the different

NOTE Confidence: 0.84446865875

01:00:15.109 --> 01:00:16.779 clusters that we are defined.

NOTE Confidence: 0.84446865875

01:00:16.780 --> 01:00:20.924 So to do that we use several

NOTE Confidence: 0.84446865875

01:00:20.924 --> 01:00:21.978 bioinformatics pipelines.

NOTE Confidence: 0.84446865875

01:00:21.978 --> 01:00:24.726 We use Poly solver to predict

NOTE Confidence: 0.84446865875

01:00:24.726 --> 01:00:28.061 the HLA one alleles that we know

NOTE Confidence: 0.84446865875

01:00:28.061 --> 01:00:30.863 that there's three of them using

NOTE Confidence: 0.84446865875

01:00:30.955 --> 01:00:33.600 the germline XM sequence data.

NOTE Confidence: 0.84446865875

01:00:33.600 --> 01:00:36.301 Then we use unaware tool to

NOTE Confidence: 0.84446865875

01:00:36.301 --> 01:00:38.706 annotate all the mutations that

NOTE Confidence: 0.84446865875

01:00:38.706 --> 01:00:41.678 we had identified in the in the.

NOTE Confidence: 0.84446865875

01:00:41.680 --> 01:00:43.300 More excellent sequencing and

NOTE Confidence: 0.84446865875

01:00:43.300 --> 01:00:44.920 then we use net,

NOTE Confidence: 0.84446865875

01:00:44.920 --> 01:00:45.621 MCA,

NOTE Confidence: 0.84446865875

01:00:45.621 --> 01:00:49.126 MHC pan that actually identifies

NOTE Confidence: 0.84446865875

01:00:49.130 --> 01:00:50.609 what are what.

NOTE Confidence: 0.84446865875

01:00:50.609 --> 01:00:53.074 What are the interactions between

NOTE Confidence: 0.84446865875

01:00:53.074 --> 01:00:56.610 the HLA's and the new antigens?

NOTE Confidence: 0.84446865875

01:00:56.610 --> 01:00:57.982 And then we took it one step

NOTE Confidence: 0.84446865875

01:00:57.982 --> 01:00:59.348 further and we use narrow pred.

NOTE Confidence: 0.84446865875

01:00:59.350 --> 01:01:02.890 5 that actually this algorithm

NOTE Confidence: 0.84446865875

01:01:02.890 --> 01:01:04.610 computes the recognition potential.

NOTE Confidence: 0.84446865875

01:01:04.610 --> 01:01:08.678 So what it does is it provides a likelihood

NOTE Confidence: 0.84446865875

01:01:08.678 --> 01:01:11.954 that this interaction is going to occur.

NOTE Confidence: 0.84446865875

01:01:11.960 --> 01:01:14.976 And it's based on on the immune epitope.

NOTE Confidence: 0.84446865875

01:01:14.980 --> 01:01:16.460 It's it's.

NOTE Confidence: 0.84446865875

01:01:16.460 --> 01:01:18.880 It's this prediction is based

NOTE Confidence: 0.84446865875

01:01:18.880 --> 01:01:20.980 on the TCR receptor rapporteur,

NOTE Confidence: 0.84446865875

01:01:20.980 --> 01:01:24.828 that it's that it's.

NOTE Confidence: 0.84446865875

01:01:24.830 --> 01:01:27.305 That he's present in the

NOTE Confidence: 0.84446865875

01:01:27.305 --> 01:01:28.790 immune epitope database.

NOTE Confidence: 0.84446865875

01:01:28.790 --> 01:01:33.870 So with that we took this likelihood

NOTE Confidence: 0.84446865875

01:01:33.870 --> 01:01:36.470 and this recognition potential,

NOTE Confidence: 0.84446865875

01:01:36.470 --> 01:01:37.858 and we score them,

NOTE Confidence: 0.84446865875

01:01:37.858 --> 01:01:39.940 and we identified the ones that

NOTE Confidence: 0.84446865875

01:01:40.012 --> 01:01:42.250 were at the highest 10% tile and

NOTE Confidence: 0.84446865875

01:01:42.250 --> 01:01:44.810 the ones that were at the lower 10%.

NOTE Confidence: 0.84446865875

01:01:44.810 --> 01:01:48.743 So we assume that if there is no selection,

NOTE Confidence: 0.84446865875

01:01:48.750 --> 01:01:51.070 then the these interactions in

NOTE Confidence: 0.84446865875

01:01:51.070 --> 01:01:54.470 the temple in the top percentile.

NOTE Confidence: 0.84446865875

01:01:54.470 --> 01:01:57.116 Between the new antigens and the HLA,

NOTE Confidence: 0.84446865875

01:01:57.120 --> 01:01:59.490 one should be the distribution of

NOTE Confidence: 0.84446865875

01:01:59.490 --> 01:02:01.998 these alleles should be similar to

NOTE Confidence: 0.84446865875

01:02:01.998 --> 01:02:04.128 the distribution of the patients

NOTE Confidence: 0.84446865875

01:02:04.130 --> 01:02:06.488 and the little frequency in the

NOTE Confidence: 0.84446865875

01:02:06.488 --> 01:02:07.274 patient population.

NOTE Confidence: 0.84446865875

01:02:07.280 --> 01:02:11.102 So to test this hypothesis we we

NOTE Confidence: 0.84446865875

01:02:11.102 --> 01:02:13.886 compare the actual frequency of the

NOTE Confidence: 0.84446865875

01:02:13.886 --> 01:02:16.178 alleles in the patient population for

NOTE Confidence: 0.84446865875

01:02:16.178 --> 01:02:18.708 each of the different clusters and

NOTE Confidence: 0.84446865875

01:02:18.708 --> 01:02:20.783 the frequency and the distribution

NOTE Confidence: 0.84446865875

01:02:20.850 --> 01:02:22.985 of the alleles in the ones that

NOTE Confidence: 0.84446865875

01:02:22.985 --> 01:02:25.199 are selected as having the higher.

NOTE Confidence: 0.84446865875

01:02:25.199 --> 01:02:27.364 Likely for the recognition and

NOTE Confidence: 0.84446865875

01:02:27.364 --> 01:02:28.230 what we

NOTE Confidence: 0.796941060842105

01:02:28.313 --> 01:02:31.199 identified is that actually there was

01:02:31.199 --> 01:02:33.931 one specific allele B702 that were

01:02:33.931 --> 01:02:36.806 significantly in breach in this in

01:02:36.806 --> 01:02:40.486 the top 10% recognition potential,

01:02:40.490 --> 01:02:43.058 which that was not happening in

01:02:43.058 --> 01:02:46.290 the lower set of of interactions.

01:02:46.290 --> 01:02:49.594 So we think that the specific actually

01:02:49.594 --> 01:02:52.961 wanna leaves like the B702 could promote

01:02:52.961 --> 01:02:55.109 stronger immune immune response.

01:02:55.110 --> 01:02:57.646 And these tumors that are the ones with

01:02:57.646 --> 01:03:00.059 the higher microsatellite instability.

01:03:00.060 --> 01:03:02.348 And we believe that these down the line

01:03:02.348 --> 01:03:05.808 could be affecting the immune response

01:03:05.808 --> 01:03:10.790 of these tumors to and and how to

01:03:10.790 --> 01:03:13.038 immune immune checkpoint inhibitors.

01:03:13.040 --> 01:03:16.407 So obviously this is the the beginning

01:03:16.407 --> 01:03:19.146 of like expanding this work in

NOTE Confidence: 0.796941060842105

01:03:19.146 --> 01:03:21.967 the area of immune response by the

NOTE Confidence: 0.796941060842105

01:03:22.061 --> 01:03:25.237 immune checkpoint inhibitor response.

NOTE Confidence: 0.796941060842105

01:03:25.240 --> 01:03:26.317 So in conclusion,

NOTE Confidence: 0.796941060842105

01:03:26.317 --> 01:03:28.471 for him two molecular differences between

NOTE Confidence: 0.796941060842105

01:03:28.471 --> 01:03:31.225 the three different types of mismatch repair,

NOTE Confidence: 0.796941060842105

01:03:31.230 --> 01:03:34.482 deficient tumors could have a direct

NOTE Confidence: 0.796941060842105

01:03:34.482 --> 01:03:37.450 implication and immune response specific.

NOTE Confidence: 0.796941060842105

01:03:37.450 --> 01:03:39.956 One else could be driving the presentation

NOTE Confidence: 0.796941060842105

01:03:39.956 --> 01:03:41.919 of neoantigens among mismatch repair

NOTE Confidence: 0.796941060842105

01:03:41.919 --> 01:03:43.994 deficient tumors with the highest

NOTE Confidence: 0.796941060842105

01:03:43.994 --> 01:03:45.980 level of microsatellite instability.

NOTE Confidence: 0.796941060842105

01:03:45.980 --> 01:03:48.320 We probably specially this work,

NOTE Confidence: 0.796941060842105

01:03:48.320 --> 01:03:50.816 so overall the take home message is that

NOTE Confidence: 0.796941060842105

01:03:50.816 --> 01:03:53.313 our studies show that there's novel

NOTE Confidence: 0.796941060842105

01:03:53.313 --> 01:03:55.117 molecular heterogeneity among these.

01:03:55.120 --> 01:03:57.410 Under the efficient tumors and

01:03:57.410 --> 01:03:59.242 that understanding the clinical

01:03:59.242 --> 01:04:01.268 pathological features associated with

01:04:01.268 --> 01:04:03.272 this heterogeneous heterogeneity is

01:04:03.272 --> 01:04:05.620 essential to accurate diagnosis and

01:04:05.620 --> 01:04:07.575 prediction of treatment response in

01:04:07.575 --> 01:04:10.050 the setting of personalized medicine.

01:04:10.050 --> 01:04:12.650 And our future directions.

01:04:12.650 --> 01:04:14.785 It's to understand the molecular

01:04:14.785 --> 01:04:16.920 mechanism that associate trequel 5

01:04:16.987 --> 01:04:19.357 and Warner deficiency with this type

01:04:19.357 --> 01:04:21.419 of tumors identify immune regulators

01:04:21.419 --> 01:04:23.903 that determine response based on the

01:04:23.903 --> 01:04:26.602 type the specific type of mismatch

01:04:26.602 --> 01:04:27.570 repair deficiency,

01:04:27.570 --> 01:04:29.975 and investigate also the treatment

NOTE Confidence: 0.796941060842105

01:04:29.975 --> 01:04:31.899 response to immune checkpoint

NOTE Confidence: 0.796941060842105

01:04:31.899 --> 01:04:34.411 inhibitors based on this type of

NOTE Confidence: 0.796941060842105

01:04:34.411 --> 01:04:35.590 mismatch repair deficiency.

NOTE Confidence: 0.796941060842105

01:04:35.590 --> 01:04:37.015 So with that,

NOTE Confidence: 0.796941060842105

01:04:37.015 --> 01:04:39.390 just acknowledge our funding sources

NOTE Confidence: 0.796941060842105

01:04:39.390 --> 01:04:41.856 Martinek Albuch that is the the first

NOTE Confidence: 0.796941060842105

01:04:41.856 --> 01:04:44.809 dog in my lab that has one done most

NOTE Confidence: 0.796941060842105

01:04:44.809 --> 01:04:46.969 of the work and my collaborators

NOTE Confidence: 0.796941060842105

01:04:46.970 --> 01:04:49.287 in the US and also in Spain.

NOTE Confidence: 0.796941060842105

01:04:49.290 --> 01:04:51.874 And I'll be happy to take any questions.

NOTE Confidence: 0.869126174

01:04:52.850 --> 01:04:55.170 Thank you very much Rosa.

NOTE Confidence: 0.869126174

01:04:55.170 --> 01:04:57.242 A terrific work that's very interesting and

NOTE Confidence: 0.869126174

01:04:57.242 --> 01:05:00.048 we do have a couple of questions in the chat,

NOTE Confidence: 0.869126174

01:05:00.050 --> 01:05:05.056 so which hopefully I can read properly.

NOTE Confidence: 0.869126174

01:05:05.056 --> 01:05:08.014 So the first is from Jeffrey

NOTE Confidence: 0.869126174

01:05:08.014 --> 01:05:09.969 Townsend and Jeff asks,

NOTE Confidence: 0.869126174

01:05:09.970 --> 01:05:13.590 is the association of BRAF V600E

NOTE Confidence: 0.869126174

01:05:13.590 --> 01:05:16.990 with MSH mutation purely mutational?

NOTE Confidence: 0.869126174

01:05:16.990 --> 01:05:19.517 Or is there some more complex biology

NOTE Confidence: 0.869126174

01:05:19.517 --> 01:05:22.322 to the association and he asks because

NOTE Confidence: 0.869126174

01:05:22.322 --> 01:05:23.970 the trinucleotide signature in.

NOTE Confidence: 0.869126174

01:05:23.970 --> 01:05:26.658 Used by MSH is especially likely to

NOTE Confidence: 0.869126174

01:05:26.658 --> 01:05:30.050 make the B Rav 600 to E mutation. Yeah

NOTE Confidence: 0.64577244225

01:05:30.060 --> 01:05:33.300 so so. The BRAF mutation in colon cancer

NOTE Confidence: 0.64577244225

01:05:33.300 --> 01:05:36.140 is associated with the serrated pathway,

NOTE Confidence: 0.64577244225

01:05:36.140 --> 01:05:38.216 so that's like the more biological.

NOTE Confidence: 0.64577244225

01:05:38.220 --> 01:05:39.948 It's not this type of tumors,

NOTE Confidence: 0.64577244225

01:05:39.950 --> 01:05:42.056 but for the for the Ms,

NOTE Confidence: 0.64577244225

01:05:42.060 --> 01:05:44.280 I believe it's more like a

NOTE Confidence: 0.64577244225

01:05:44.280 --> 01:05:45.314 motivational association,

NOTE Confidence: 0.64577244225

109

01:05:45.314 --> 01:05:48.933 but the one that has been more

NOTE Confidence: 0.64577244225

01:05:48.933 --> 01:05:51.349 described biologically is the one

NOTE Confidence: 0.64577244225

01:05:51.349 --> 01:05:54.073 that the the the serrated pathway.

NOTE Confidence: 0.64577244225

01:05:54.080 --> 01:05:56.211 Had tumors that they were writing.

NOTE Confidence: 0.64577244225

01:05:56.211 --> 01:05:57.864 Passwords are developing,

NOTE Confidence: 0.64577244225

01:05:57.864 --> 01:06:01.170 but this is like more like.

NOTE Confidence: 0.64577244225

01:06:01.170 --> 01:06:03.475 Mutational that we used to

NOTE Confidence: 0.64577244225

01:06:03.475 --> 01:06:05.319 mainly separate the sporadic

NOTE Confidence: 0.64577244225

01:06:05.319 --> 01:06:07.398 from the hereditary ones.

NOTE Confidence: 0.831493464

01:06:09.130 --> 01:06:10.444 OK great thanks.

NOTE Confidence: 0.831493464

01:06:10.444 --> 01:06:13.072 And then the next question is

NOTE Confidence: 0.831493464

01:06:13.072 --> 01:06:15.827 from Ryan Jensen and Ryan asks.

NOTE Confidence: 0.831493464

01:06:15.830 --> 01:06:18.623 And one of the potential roles of

NOTE Confidence: 0.831493464

01:06:18.623 --> 01:06:21.918 of REC QL 5 is to prevent aberrant

NOTE Confidence: 0.831493464

01:06:21.918 --> 01:06:24.350 homologous recombination by displacing

NOTE Confidence: 0.831493464

01:06:24.350 --> 01:06:26.726 RAD 51 off single stranded DNA.

NOTE Confidence: 0.831493464

01:06:26.726 --> 01:06:28.858 And he wonders if in tumors from

NOTE Confidence: 0.831493464

01:06:28.858 --> 01:06:30.528 patients with loss of function,

NOTE Confidence: 0.831493464

01:06:30.530 --> 01:06:33.750 mutations in REC queue do you see

NOTE Confidence: 0.831493464

01:06:33.750 --> 01:06:35.514 increased chromosomal aberrations?

NOTE Confidence: 0.831493464

01:06:35.514 --> 01:06:37.470 Sister chromatid exchanges,

NOTE Confidence: 0.831493464

01:06:37.470 --> 01:06:40.480 or perhaps increases in microsatellite

NOTE Confidence: 0.831493464

01:06:40.480 --> 01:06:42.286 contraction or expansion.

NOTE Confidence: 0.865207728333333

01:06:43.010 --> 01:06:45.702 So all of these we have, we.

NOTE Confidence: 0.865207728333333

01:06:45.702 --> 01:06:50.420 There's so the the work done in Q L5

NOTE Confidence: 0.865207728333333

01:06:50.420 --> 01:06:53.280 and colorectal cancer is not very vast.

NOTE Confidence: 0.865207728333333

01:06:53.280 --> 01:06:56.508 So so right now what I can say is that

NOTE Confidence: 0.865207728333333

01:06:56.508 --> 01:06:59.721 we we just engineer a cell line that is,

NOTE Confidence: 0.865207728333333

01:06:59.730 --> 01:07:00.838 that has these mutations,

NOTE Confidence: 0.865207728333333

01:07:00.838 --> 01:07:03.058 which rupees per so we are going to

NOTE Confidence: 0.865207728333333

01:07:03.058 --> 01:07:05.058 have the cell lines that have like the

NOTE Confidence: 0.865207728333333

01:07:05.119 --> 01:07:07.357 heterozygous and homozygous and Val types.

NOTE Confidence: 0.865207728333333

01:07:07.360 --> 01:07:10.024 So we are going to be testing these

NOTE Confidence: 0.865207728333333

01:07:10.024 --> 01:07:13.256 kind of events that Brian is suggesting.

NOTE Confidence: 0.865207728333333

01:07:13.260 --> 01:07:14.886 So I don't have that information

NOTE Confidence: 0.865207728333333

01:07:14.886 --> 01:07:16.920 yet where I know that, for example,

NOTE Confidence: 0.865207728333333

01:07:16.920 --> 01:07:19.660 for Frank L5 is that there there's been one.

NOTE Confidence: 0.865207728333333

01:07:19.660 --> 01:07:22.292 There was one old paper that was

NOTE Confidence: 0.865207728333333

01:07:22.292 --> 01:07:25.798 showing that interestingly regular 5

NOTE Confidence: 0.865207728333333

01:07:25.798 --> 01:07:29.230 downregulation was identified in MSI tumors,

NOTE Confidence: 0.865207728333333

01:07:29.230 --> 01:07:32.438 and so I think that there is more

NOTE Confidence: 0.865207728333333

01:07:32.438 --> 01:07:34.965 than we can be learning about this

NOTE Confidence: 0.865207728333333

01:07:34.965 --> 01:07:36.458 and and I think that that's going

NOTE Confidence: 0.865207728333333

01:07:36.458 --> 01:07:38.147 to be one of our like next steps.

NOTE Confidence: 0.729372912222222

01:07:39.670 --> 01:07:43.189 Great thank you and I had one quick question.

NOTE Confidence: 0.729372912222222

01:07:43.190 --> 01:07:44.594 When you were going

NOTE Confidence: 0.729372912222222

01:07:44.594 --> 01:07:46.349 through and looking at the.

NOTE Confidence: 0.729372912222222

01:07:46.350 --> 01:07:48.546 The the red queue and other

NOTE Confidence: 0.729372912222222

01:07:48.546 --> 01:07:51.109 mutations in the Lynch like syndrome.

NOTE Confidence: 0.729372912222222

01:07:51.110 --> 01:07:53.789 I didn't have a sense for for whether

NOTE Confidence: 0.729372912222222

01:07:53.789 --> 01:07:55.103 it was clear whether that they're

NOTE Confidence: 0.729372912222222

01:07:55.103 --> 01:07:56.590 all loss of function mutations,

NOTE Confidence: 0.729372912222222

01:07:56.590 --> 01:07:59.518 like for example the T31K in that one

NOTE Confidence: 0.729372912222222

01:07:59.518 --> 01:08:02.668 family is that is that some is that a is

NOTE Confidence: 0.790083059375

01:08:02.680 --> 01:08:05.200 that one so that one was mutation that

NOTE Confidence: 0.790083059375

01:08:05.200 --> 01:08:07.847 we found in the tumor of that patient.

NOTE Confidence: 0.790083059375

01:08:07.850 --> 01:08:09.782 We have not been able to

NOTE Confidence: 0.790083059375

01:08:09.782 --> 01:08:11.070 test the other individual.

NOTE Confidence: 0.790083059375

01:08:11.070 --> 01:08:12.775 So the germline variants that

NOTE Confidence: 0.790083059375

01:08:12.775 --> 01:08:14.900 we are even defining in the

NOTE Confidence: 0.790083059375

01:08:14.900 --> 01:08:16.994 germline are all loss of function.

NOTE Confidence: 0.790083059375

01:08:17.000 --> 01:08:19.920 But we only have been able to test

NOTE Confidence: 0.790083059375

01:08:19.920 --> 01:08:22.738 1 tumor from these individuals.

NOTE Confidence: 0.790083059375

01:08:22.740 --> 01:08:24.525 I can tell you, not for AQL.

NOTE Confidence: 0.790083059375

01:08:24.530 --> 01:08:26.922 I know a lot of the data for

NOTE Confidence: 0.790083059375

01:08:26.922 --> 01:08:30.107 one not a lot few data from

NOTE Confidence: 0.790083059375

01:08:30.107 --> 01:08:31.604 Warner mutation somatically.

NOTE Confidence: 0.790083059375

01:08:31.610 --> 01:08:34.646 There is the there identifying loss

NOTE Confidence: 0.790083059375

01:08:34.646 --> 01:08:37.266 of function mutations and actually

NOTE Confidence: 0.790083059375

01:08:37.266 --> 01:08:40.302 these tumors that have loss of

NOTE Confidence: 0.790083059375

01:08:40.302 --> 01:08:42.990 function mutations in Werner they

NOTE Confidence: 0.790083059375

01:08:42.990 --> 01:08:45.453 have a significantly higher number

NOTE Confidence: 0.790083059375

01:08:45.453 --> 01:08:47.574 of them in comparison to the ones

NOTE Confidence: 0.790083059375

01:08:47.574 --> 01:08:49.490 that don't have mutations there.

NOTE Confidence: 0.790083059375

01:08:49.490 --> 01:08:52.808 MSI. So again another kind of.

NOTE Confidence: 0.790083059375

01:08:52.810 --> 01:08:55.342 Another clue that there have there

NOTE Confidence: 0.790083059375

01:08:55.342 --> 01:08:58.191 might be some some association between

NOTE Confidence: 0.790083059375

01:08:58.191 --> 01:09:01.419 deficiency in these genes and MSI.

NOTE Confidence: 0.790083059375

01:09:01.420 --> 01:09:03.940 However, association doesn't mean causality,

NOTE Confidence: 0.790083059375

01:09:03.940 --> 01:09:05.536 so this is what I think that

NOTE Confidence: 0.790083059375

01:09:05.536 --> 01:09:07.459 is what we actually need to do.

NOTE Confidence: 0.790083059375

01:09:07.460 --> 01:09:08.970 More research to figure out

NOTE Confidence: 0.790083059375

01:09:08.970 --> 01:09:10.910 these needs one or the other.

NOTE Confidence: 0.804723313333333

01:09:12.290 --> 01:09:17.726 Good, well I think it's been a great session.

NOTE Confidence: 0.804723313333333

01:09:17.730 --> 01:09:19.155 And lots of good questions

NOTE Confidence: 0.804723313333333

01:09:19.155 --> 01:09:20.580 and and two fantastic talks.

NOTE Confidence: 0.804723313333333

01:09:20.580 --> 01:09:22.645 So I'd like to just to finish

NOTE Confidence: 0.804723313333333

01:09:22.645 --> 01:09:24.608 by by thanking Luisa and Rosa.

NOTE Confidence: 0.804723313333333

01:09:24.610 --> 01:09:26.500 Very much for really giving very

NOTE Confidence: 0.804723313333333

01:09:26.500 --> 01:09:27.760 stimulating and exciting talks,

NOTE Confidence: 0.804723313333333

01:09:27.760 --> 01:09:30.250 great grand rounds and thank

NOTE Confidence: 0.804723313333333

01:09:30.250 --> 01:09:32.242 you very much everybody.

NOTE Confidence: 0.804723313333333

01:09:32.250 --> 01:09:34.828 Thank you. Bye bye bye.