WEBVTT

00:00:00.000 --> 00:00:03.760 All right, everyone, welcome,

00:00:03.760 --> 00:00:06.316 although he really needs no introduction.

00:00:06.320 --> 00:00:10.400 It is my honor, on behalf of the Pathology

00:00:10.400 --> 00:00:12.800 Department Grand Rounds Committee,

00:00:12.800 --> 00:00:14.676 to welcome our Grand Round speaker today,

00:00:14.680 --> 00:00:16.440 Doctor Ranjit Bindra.

00:00:16.440 --> 00:00:19.360 He is the Henry and Kate Cushing

00:00:19.360 --> 00:00:21.080 Professor of Therapeutic Radiology

00:00:21.080 --> 00:00:24.016 and of course professor of

00:00:24.016 --> 00:00:25.840 Pathology and also neurosurgery.

00:00:25.840 --> 00:00:28.840 He's also well known in our

00:00:28.840 --> 00:00:31.732 department as he's a graduate of

00:00:31.732 --> 00:00:33.828 our experimental pathology PhD

00:00:33.828 --> 00:00:36.600 program and Yale's MDPHD program.

NOTE Confidence: 0.849264795

00:00:36.600 --> 00:00:40.700 He's obviously everyone is aware that

NOTE Confidence: 0.849264795

00:00:40.700 --> 00:00:42.692 he's nationally and internationally

NOTE Confidence: 0.849264795

00:00:42.692 --> 00:00:45.080 recognized for his discoveries on onco

NOTE Confidence: 0.849264795

00:00:45.080 --> 00:00:47.205 metabolite induced dysregulation of

NOTE Confidence: 0.849264795

00:00:47.205 --> 00:00:50.355 DNA damage response and repair and

NOTE Confidence: 0.849264795

00:00:50.355 --> 00:00:54.600 how he's been able to exploit those

NOTE Confidence: 0.849264795

00:00:54.600 --> 00:00:57.320 defects to for therapeutic gain.

NOTE Confidence: 0.849264795

00:00:57.320 --> 00:01:02.280 And so maybe lesser known fact I have

NOTE Confidence: 0.849264795

00:01:02.280 --> 00:01:04.942 on good authority that Ranjit is

NOTE Confidence: 0.849264795

00:01:04.942 --> 00:01:06.994 actually an accomplished drummer as well.

NOTE Confidence: 0.849264795

00:01:07.000 --> 00:01:11.110 He also won the the the Bio CT

NOTE Confidence: 0.849264795

00:01:11.110 --> 00:01:12.833 award for Entrepreneur of the the

NOTE Confidence: 0.849264795

00:01:12.833 --> 00:01:14.398 Year a few years back.

NOTE Confidence: 0.849264795

00:01:14.400 --> 00:01:16.280 And so without further ado,

NOTE Confidence: 0.849264795

00:01:16.280 --> 00:01:17.560 I'd like to welcome

NOTE Confidence: 0.63401803

00:01:17.560 --> 00:01:19.280 Ranjit. Great, thank you.

NOTE Confidence: 0.933675728333333

00:01:22.760 --> 00:01:24.518 OK, great. Well, thanks so much.

NOTE Confidence: 0.933675728333333

00:01:24.520 --> 00:01:25.880 I'm really excited to be

NOTE Confidence: 0.933675728333333

00:01:25.880 --> 00:01:27.240 speaking in a live audience,

NOTE Confidence: 0.933675728333333

00:01:27.240 --> 00:01:28.640 not just a zoom meeting.

NOTE Confidence: 0.933675728333333

00:01:28.640 --> 00:01:30.440 So this is great to hear.

NOTE Confidence: 0.933675728333333

00:01:30.440 --> 00:01:31.920 My disclosures only be focusing

NOTE Confidence: 0.933675728333333

00:01:31.920 --> 00:01:33.718 on the last company that modified

NOTE Confidence: 0.933675728333333

00:01:33.718 --> 00:01:35.560 bio just at the very, very end.

NOTE Confidence: 0.933675728333333

00:01:35.560 --> 00:01:37.120 But we're going to make this

NOTE Confidence: 0.933675728333333

00:01:37.120 --> 00:01:38.400 very academic and obviously,

NOTE Confidence: 0.933675728333333

00:01:38.400 --> 00:01:41.040 so topics that we'll cover today,

NOTE Confidence: 0.933675728333333

00:01:41.040 --> 00:01:43.088 we'll start off sort of our quest to

NOTE Confidence: 0.933675728333333

00:01:43.088 --> 00:01:44.958 translate work from bench to the bedside.

NOTE Confidence: 0.933675728333333

00:01:44.960 --> 00:01:45.803 Some key concepts,

NOTE Confidence: 0.933675728333333

00:01:45.803 --> 00:01:47.489 progress and learnings for those who've

NOTE Confidence: 0.933675728333333

00:01:47.489 --> 00:01:49.480 seen these intro slides have changed them.

NOTE Confidence: 0.933675728333333

00:01:49.480 --> 00:01:51.800 So they're updated this year.

NOTE Confidence: 0.933675728333333

00:01:51.800 --> 00:01:54.040 And then we'll move on to our recent

NOTE Confidence: 0.933675728333333

00:01:54.040 --> 00:01:55.865 discovery of DNA modifiers and how

NOTE Confidence: 0.933675728333333

00:01:55.865 --> 00:01:57.677 we're trying to exploit loss of

NOTE Confidence: 0.933675728333333

00:01:57.743 --> 00:01:59.712 MGMT and glioma and then sort of

NOTE Confidence: 0.933675728333333

00:01:59.712 --> 00:02:01.380 deviate a little bit further into

NOTE Confidence: 0.933675728333333

00:02:01.444 --> 00:02:03.226 the horizon and what we're actually

NOTE Confidence: 0.933675728333333

00:02:03.226 --> 00:02:04.876 trying to do outside of glioma.

NOTE Confidence: 0.933675728333333

00:02:04.876 --> 00:02:06.640 And sort of in a bigger picture,

NOTE Confidence: 0.933675728333333

00:02:06.640 --> 00:02:07.760 what directions were going on?

NOTE Confidence: 0.933675728333333

00:02:07.760 --> 00:02:09.596 And then we'll sort of have an epilogue of,

NOTE Confidence: 0.933675728333333

00:02:09.600 --> 00:02:11.960 you know where do we go from here.

NOTE Confidence: 0.933675728333333

00:02:11.960 --> 00:02:13.560 So just to get started,

NOTE Confidence: 0.933675728333333

00:02:13.560 --> 00:02:15.520 So synthetic lethality therapeutic index,

NOTE Confidence: 0.933675728333333

00:02:15.520 --> 00:02:16.530 I think this audience doesn't

NOTE Confidence: 0.933675728333333

00:02:16.530 --> 00:02:17.879 need much of a background on that.

NOTE Confidence: 0.933675728333333

00:02:17.880 --> 00:02:20.211 You have two pathways A&amp;B that are

NOTE Confidence: 0.933675728333333

00:02:20.211 --> 00:02:22.360 somewhat relevant or parallel pathways.

NOTE Confidence: 0.933675728333333

00:02:22.360 --> 00:02:23.746 You knock one out and the other

NOTE Confidence: 0.933675728333333

00:02:23.746 --> 00:02:25.078 ones out in the tumor cell,

NOTE Confidence: 0.933675728333333

00:02:25.080 --> 00:02:27.380 then you have a selective targeting

NOTE Confidence: 0.933675728333333

00:02:27.380 --> 00:02:30.040 of the tumor over the normal tissue.

NOTE Confidence: 0.933675728333333

00:02:30.040 --> 00:02:31.120 And I've always been fascinated.

NOTE Confidence: 0.933675728333333

00:02:31.120 --> 00:02:32.272 I always give credit to David

NOTE Confidence: 0.933675728333333

00:02:32.272 --> 00:02:33.160 Stern because he and I,

NOTE Confidence: 0.933675728333333

00:02:33.160 --> 00:02:34.240 when I was a graduate student,

NOTE Confidence: 0.933675728333333

00:02:34.240 --> 00:02:35.955 asked to ask him the question said,

NOTE Confidence: 0.933675728333333

00:02:35.960 --> 00:02:36.216 well,

NOTE Confidence: 0.933675728333333

00:02:36.216 --> 00:02:37.752 let's let's talk about the history

NOTE Confidence: 0.933675728333333

00:02:37.752 --> 00:02:39.598 and maybe look up this old paper from

NOTE Confidence: 0.933675728333333

00:02:39.600 --> 00:02:41.685 1945 where the original Drosophila

NOTE Confidence: 0.933675728333333

00:02:41.685 --> 00:02:43.353 work were synthetically valid,

NOTE Confidence: 0.933675728333333

00:02:43.360 --> 00:02:45.216 meant you could never see it in a

NOTE Confidence: 0.933675728333333

00:02:45.216 --> 00:02:46.605 screen because you both knocking

NOTE Confidence: 0.933675728333333

00:02:46.605 --> 00:02:47.475 out both pathways,

NOTE Confidence: 0.933675728333333

00:02:47.480 --> 00:02:49.034 you wouldn't actually see it pop up.

NOTE Confidence: 0.933675728333333

00:02:49.040 --> 00:02:51.794 You'd have to engineer it for it to happen.

NOTE Confidence: 0.933675728333333

00:02:51.800 --> 00:02:54.800 And it wasn't until 1997 that Lee Hartwell,

NOTE Confidence: 0.933675728333333

00:02:54.800 --> 00:02:56.300 Steve Friend and colleagues

NOTE Confidence: 0.933675728333333

00:02:56.300 --> 00:02:58.090 published the SEMOL paper 1997,

NOTE Confidence: 0.933675728333333

00:02:58.090 --> 00:03:00.120 which are in the late 90s rather

NOTE Confidence: 0.933675728333333

00:03:00.120 --> 00:03:01.480 where they actually talked about

NOTE Confidence: 0.933675728333333

00:03:01.480 --> 00:03:02.840 this concept of synthetic lethality.

NOTE Confidence: 0.933675728333333

00:03:02.840 --> 00:03:04.215 It was fascinating because at

NOTE Confidence: 0.933675728333333

00:03:04.215 --> 00:03:05.959 that time they didn't really know

00:03:05.959 --> 00:03:06.919 about BRACA mutations.

00:03:06.920 --> 00:03:09.034 They had not been fully discovered and

00:03:09.034 --> 00:03:11.238 they thought this could have a potential.

00:03:11.240 --> 00:03:14.070 But soon after it was in 2005 that we

00:03:14.070 --> 00:03:15.520 had the back-to-back Nature papers

00:03:15.520 --> 00:03:17.720 when I was a graduate student in the

00:03:17.720 --> 00:03:20.720 Xpath program showing that Olaparib

00:03:20.720 --> 00:03:23.720 was active against Braca mutant

00:03:23.813 --> 00:03:26.360 cancers and that really opened up a

00:03:26.360 --> 00:03:28.279 PARP inhibitor bracket synthetic without it,

00:03:28.280 --> 00:03:30.723 which became the first sort of case

00:03:30.723 --> 00:03:33.079 or poster child for this approach.

00:03:33.080 --> 00:03:34.420 I still remember this.

00:03:34.420 --> 00:03:36.880 This is back in 2005 or so when I

00:03:36.880 --> 00:03:38.560 actually got a vial of the drug.

00:03:38.560 --> 00:03:39.988 I'd met one of the lead authors

NOTE Confidence: 0.933675728333333

00:03:39.988 --> 00:03:41.637 on a plane to a Gordon conference

NOTE Confidence: 0.933675728333333

00:03:41.637 --> 00:03:43.380 and he actually mailed it to me

NOTE Confidence: 0.933675728333333

00:03:43.380 --> 00:03:44.831 without an MTA and actually tested

NOTE Confidence: 0.933675728333333

00:03:44.831 --> 00:03:46.770 it in VCA Braca wall type mutants

NOTE Confidence: 0.933675728333333

00:03:46.832 --> 00:03:48.624 in Peter Glaser's lab and you can

NOTE Confidence: 0.933675728333333

00:03:48.624 --> 00:03:49.392 see the effects

NOTE Confidence: 0.655826725

00:03:49.453 --> 00:03:51.360 quite striking. And now we have

NOTE Confidence: 0.655826725

00:03:51.360 --> 00:03:52.760 4 FDA approved PARP inhibitors.

NOTE Confidence: 0.655826725

00:03:52.760 --> 00:03:54.194 So we've been making a lot

NOTE Confidence: 0.655826725

00:03:54.194 --> 00:03:55.520 of progress in this space.

NOTE Confidence: 0.655826725

00:03:55.520 --> 00:03:56.600 What I think is fascinating is,

NOTE Confidence: 0.655826725

00:03:56.600 --> 00:03:58.480 you know, monotherapy PARP inhibitors,

NOTE Confidence: 0.655826725

00:03:58.480 --> 00:03:59.548 obviously, FDA approved,

NOTE Confidence: 0.655826725

00:03:59.548 --> 00:04:02.040 It's a synthetic without a success story.

NOTE Confidence: 0.655826725

00:04:02.040 --> 00:04:04.256 But we see this both in the academic

NOTE Confidence: 0.655826725

00:04:04.256 --> 00:04:06.318 realm and in the biotech VC realm.

NOTE Confidence: 0.655826725

00:04:06.320 --> 00:04:08.312 This is really only successful example

NOTE Confidence: 0.655826725

00:04:08.312 --> 00:04:10.519 that we've seen of this approach.

NOTE Confidence: 0.655826725

00:04:10.520 --> 00:04:11.840 There's a lot being tested,

NOTE Confidence: 0.655826725

00:04:11.840 --> 00:04:14.960 but we haven't seen this fully bear fruit.

NOTE Confidence: 0.655826725

00:04:14.960 --> 00:04:16.115 And so just some thoughts on this.

NOTE Confidence: 0.655826725

00:04:16.120 --> 00:04:16.870 And so why,

NOTE Confidence: 0.655826725

00:04:16.870 --> 00:04:18.816 you know why is that we come back

NOTE Confidence: 0.655826725

00:04:18.816 --> 00:04:19.976 to our therapeutic index curves

NOTE Confidence: 0.655826725

00:04:19.976 --> 00:04:21.479 that know those who know me well,

NOTE Confidence: 0.655826725

00:04:21.480 --> 00:04:22.888 we present this a lot of, you know,

NOTE Confidence: 0.655826725

00:04:22.888 --> 00:04:23.440 it's very simple.

NOTE Confidence: 0.655826725

00:04:23.440 --> 00:04:24.688 We need to separate the red

NOTE Confidence: 0.655826725

00:04:24.688 --> 00:04:25.520 and the green curves.

NOTE Confidence: 0.655826725

00:04:25.520 --> 00:04:27.501 You need a therapy that's going to

NOTE Confidence: 0.655826725

00:04:27.501 --> 00:04:29.318 selectively target tumor over normal tissue.

NOTE Confidence: 0.655826725

00:04:29.320 --> 00:04:30.657 I always go back to my other

NOTE Confidence: 0.655826725

00:04:30.657 --> 00:04:31.560 mentors like Simon Powell,

NOTE Confidence: 0.655826725

00:04:31.560 --> 00:04:33.438 Chair of Radiation Oncology and Sloan.

NOTE Confidence: 0.655826725

00:04:33.440 --> 00:04:34.904 During my residency you said you

NOTE Confidence: 0.655826725

00:04:34.904 --> 00:04:35.880 know without tumor selectivity,

NOTE Confidence: 0.655826725

00:04:35.880 --> 00:04:37.655 if you're trying to develop

NOTE Confidence: 0.655826725

00:04:37.655 --> 00:04:38.720 a radio sensitizer,

NOTE Confidence: 0.655826725

00:04:38.720 --> 00:04:40.115 you might as well just give 10 more Gray,

NOTE Confidence: 0.655826725

00:04:40.120 --> 00:04:41.632 add that to your prescription and

NOTE Confidence: 0.655826725

00:04:41.632 --> 00:04:43.229 that's always sort of resonated with

NOTE Confidence: 0.655826725

00:04:43.229 --> 00:04:45.119 me when I first started my laboratory.

NOTE Confidence: 0.655826725

00:04:45.120 --> 00:04:46.848 And so a couple of reasons I think

NOTE Confidence: 0.655826725

00:04:46.848 --> 00:04:48.265 we're we're stumbling a little bit

NOTE Confidence: 0.655826725

00:04:48.265 --> 00:04:50.155 and we still have more work to do is

NOTE Confidence: 0.655826725

00:04:50.155 --> 00:04:51.520 I think even though this is obvious,

NOTE Confidence: 0.655826725

00:04:51.520 --> 00:04:54.635 we need a molecular tumor specific biomarker,

NOTE Confidence: 0.655826725

00:04:54.640 --> 00:04:56.004 something that's homogeneously expressed

NOTE Confidence: 0.655826725

00:04:56.004 --> 00:04:58.688 in the tumor cells and not in the

NOTE Confidence: 0.655826725

00:04:58.688 --> 00:05:00.428 normal tissues and something we can

NOTE Confidence: 0.655826725

00:05:00.428 --> 00:05:02.239 readily detect and that's that's real.

NOTE Confidence: 0.655826725

00:05:02.240 --> 00:05:03.962 This is something that Mark O'Connor

NOTE Confidence: 0.655826725

00:05:03.962 --> 00:05:05.600 who discovered elaporib a good friend

NOTE Confidence: 0.655826725

00:05:05.600 --> 00:05:07.852 of mine who noticed who notes that you

NOTE Confidence: 0.655826725

00:05:07.852 --> 00:05:10.200 need to have well separated curves.

NOTE Confidence: 0.655826725

00:05:10.200 --> 00:05:12.475 You need to have on a clonogenic

NOTE Confidence: 0.655826725

00:05:12.475 --> 00:05:14.600 survival assay log skill differences

NOTE Confidence: 0.655826725

00:05:14.600 --> 00:05:17.496 to see to see this translate into a

NOTE Confidence: 0.655826725

00:05:17.496 --> 00:05:19.502 heavily appreciated population in a

NOTE Confidence: 0.655826725

00:05:19.502 --> 00:05:21.920 phase one clinic clinical trial setting

NOTE Confidence: 0.655826725

00:05:21.920 --> 00:05:23.012 2nd 1/3 which something we've been

NOTE Confidence: 0.655826725

00:05:23.012 --> 00:05:24.519 doing a lot is combination therapy.

NOTE Confidence: 0.655826725

00:05:24.520 --> 00:05:26.900 Often monotherapy is not enough and so

NOTE Confidence: 0.655826725

00:05:26.900 --> 00:05:29.474 you need to add another drug but you

NOTE Confidence: 0.655826725

00:05:29.474 --> 00:05:30.853 have to be very careful because you

NOTE Confidence: 0.655826725

00:05:30.853 --> 00:05:32.276 shift that red curve over but you're

NOTE Confidence: 0.655826725

00:05:32.276 --> 00:05:33.674 going to drive the green curve over

NOTE Confidence: 0.655826725

00:05:33.674 --> 00:05:35.305 and you need to make sure that you

NOTE Confidence: 0.655826725

00:05:35.305 --> 00:05:37.135 don't equally shift them because you're

NOTE Confidence: 0.655826725

00:05:37.135 --> 00:05:39.238 doing no better than the single agent.

NOTE Confidence: 0.655826725

00:05:39.240 --> 00:05:40.179 And then finally,

NOTE Confidence: 0.655826725

00:05:40.179 --> 00:05:41.118 I would also,

NOTE Confidence: 0.655826725

00:05:41.120 --> 00:05:42.640 we don't have time to go too much into this,

NOTE Confidence: 0.655826725

00:05:42.640 --> 00:05:44.435 but you need model systems

NOTE Confidence: 0.655826725

00:05:44.435 --> 00:05:46.230 that will accurately model the

NOTE Confidence: 0.655826725

00:05:46.302 --> 00:05:47.880 normal tissue toxicities.

NOTE Confidence: 0.655826725

00:05:47.880 --> 00:05:50.015 The best example is looking at things

NOTE Confidence: 0.655826725

00:05:50.015 --> 00:05:51.902 like PARP inhibitors combined with

NOTE Confidence: 0.655826725

00:05:51.902 --> 00:05:53.508 chemotherapy in that heme toxicity.

NOTE Confidence: 0.655826725

00:05:53.508 --> 00:05:55.709 You don't see that in a mouse

NOTE Confidence: 0.655826725

00:05:55.709 --> 00:05:57.936 because mice actually don't use HR,

NOTE Confidence: 0.655826725

00:05:57.936 --> 00:05:59.015 believe it or not,

NOTE Confidence: 0.655826725

00:05:59.015 --> 00:06:00.305 they use anonymous end jointing in

NOTE Confidence: 0.655826725

00:06:00.305 --> 00:06:01.883 their bone marrow and you have to

NOTE Confidence: 0.655826725

00:06:01.883 --> 00:06:02.993 actually do rat tolerability studies.

NOTE Confidence: 0.655826725

00:06:03.000 --> 00:06:04.372 So you actually get fooled that you

NOTE Confidence: 0.655826725

00:06:04.372 --> 00:06:05.962 can do a combination therapy that

NOTE Confidence: 0.655826725

00:06:05.962 --> 00:06:08.376 you can't actually get to the doses

NOTE Confidence: 0.655826725

00:06:08.376 --> 00:06:10.560 you need to in clinical trials.

NOTE Confidence: 0.833701692

00:06:10.560 --> 00:06:11.808 So those are just some of the the

NOTE Confidence: 0.833701692

00:06:11.808 --> 00:06:13.080 quick learnings. As a background,

NOTE Confidence: 0.833701692

00:06:13.080 --> 00:06:15.000 obviously some of our earlier work

NOTE Confidence: 0.833701692

00:06:15.000 --> 00:06:17.497 in 2017 was focused on a very unique

00:06:17.497 --> 00:06:18.944 discovery of synthetic lethality

00:06:18.944 --> 00:06:20.768 of Brachanus phenotype between

00:06:20.768 --> 00:06:22.592 onca metabolite producing tumors.

00:06:22.600 --> 00:06:25.444 Those are tumors that have IDH one and IDH

00:06:25.444 --> 00:06:27.837 mutations interaction with PARP inhibitors,

00:06:27.840 --> 00:06:30.283 lot like the Bracha story for breast

00:06:30.283 --> 00:06:32.160 and ovarian cancer in elaporim.

00:06:32.160 --> 00:06:33.840 We published that story a while back.

00:06:33.840 --> 00:06:35.768 We moved that on about a year later

00:06:35.768 --> 00:06:37.319 into other ONCA metabolites in

00:06:37.319 --> 00:06:39.335 the citric acid cycle like femuric

00:06:39.335 --> 00:06:41.198 hydratase and succinate dehydrogenase.

00:06:41.200 --> 00:06:42.919 And then we actually spent a lot of time,

00:06:42.920 --> 00:06:44.796 this is work with Peter Glazer's lab,

00:06:44.800 --> 00:06:46.060 which is great to sort of join

NOTE Confidence: 0.833701692

00:06:46.060 --> 00:06:46.600 forces with him.

NOTE Confidence: 0.833701692

00:06:46.600 --> 00:06:48.994 Again in 2020, we broke the mechanism.

NOTE Confidence: 0.833701692

00:06:49.000 --> 00:06:51.124 We were able to show exactly

NOTE Confidence: 0.833701692

00:06:51.124 --> 00:06:52.503 how that interaction occurred.

NOTE Confidence: 0.833701692

00:06:52.503 --> 00:06:55.120 And then in in the years following we,

NOTE Confidence: 0.833701692

00:06:55.120 --> 00:06:56.814 we tested a lot of interesting ideas

NOTE Confidence: 0.833701692

00:06:56.814 --> 00:06:58.257 of looking at combination therapies

NOTE Confidence: 0.833701692

00:06:58.257 --> 00:07:00.616 as I've alluded to earlier that may be

NOTE Confidence: 0.833701692

00:07:00.616 --> 00:07:02.240 the key for some of these interactions,

NOTE Confidence: 0.833701692

00:07:02.240 --> 00:07:03.575 PARP inhibitors and ATR inhibitors

NOTE Confidence: 0.833701692

00:07:03.575 --> 00:07:05.719 and then looking at a lot of different

NOTE Confidence: 0.833701692

00:07:05.720 --> 00:07:07.598 tumor types like AML for instance,

NOTE Confidence: 0.833701692

00:07:07.600 --> 00:07:10.640 which we reported on 20/22.

NOTE Confidence: 0.833701692

00:07:10.640 --> 00:07:11.822 But then we wanted to really

NOTE Confidence: 0.833701692

00:07:11.822 --> 00:07:12.920 translate this into the clinic.

NOTE Confidence: 0.833701692

00:07:12.920 --> 00:07:14.520 And before I get to our main story,

NOTE Confidence: 0.833701692

00:07:14.520 --> 00:07:15.915 kind of want to give you an update on

NOTE Confidence: 0.833701692

00:07:15.915 --> 00:07:17.496 where we are since we made that discovery

NOTE Confidence: 0.833701692

00:07:17.496 --> 00:07:18.998 because we've still been working hard at it,

NOTE Confidence: 0.833701692

00:07:19.000 --> 00:07:21.600 but it's been a long slog what

NOTE Confidence: 0.833701692

00:07:21.600 --> 00:07:22.800 we what we thought is,

NOTE Confidence: 0.833701692

00:07:22.800 --> 00:07:23.096 well,

NOTE Confidence: 0.833701692

00:07:23.096 --> 00:07:24.872 there's a number of different tumor

NOTE Confidence: 0.833701692

00:07:24.872 --> 00:07:27.047 types here that we go after with

NOTE Confidence: 0.833701692

00:07:27.047 --> 00:07:28.275 Alka metabolite producing phenotypes

NOTE Confidence: 0.833701692

00:07:28.275 --> 00:07:30.398 or or citric acid cycle mutations.

NOTE Confidence: 0.833701692

00:07:30.400 --> 00:07:32.199 We spent a fair amount of time.

NOTE Confidence: 0.833701692

00:07:32.200 --> 00:07:34.630 We wrote about 7 clinical trials

NOTE Confidence: 0.833701692

00:07:34.630 --> 00:07:36.832 from about 2018 to about 2022.

NOTE Confidence: 0.833701692

00:07:36.832 --> 00:07:39.791 I served as either Co I or Co

NOTE Confidence: 0.833701692

00:07:39.791 --> 00:07:41.756 Pi or collaborator on these.

00:07:41.760 --> 00:07:43.776 And we obviously won't go into all these

00:07:43.776 --> 00:07:45.527 studies but I want to tell you that

00:07:45.527 --> 00:07:47.440 we are learning a lot from these trials.

00:07:47.440 --> 00:07:48.920 Paul Leader and colleagues,

00:07:48.920 --> 00:07:51.140 we we published an initial case

00:07:51.209 --> 00:07:53.219 series looking at IDH mutant

00:07:53.219 --> 00:07:55.229 ZINCOMAL sarcomas where we actually

00:07:55.292 --> 00:07:56.765 saw about three or four patients

00:07:56.765 --> 00:07:57.793 that were exceptional responders.

00:07:57.800 --> 00:07:59.990 We amended an existing protocol that

00:07:59.990 --> 00:08:02.700 he had to use Olaprip for BRAC and

00:08:02.700 --> 00:08:05.000 his tumors without BRAC and mutations.

00:08:05.000 --> 00:08:07.160 And as you can see here a very

00:08:07.160 --> 00:08:09.590 nice we had a a 14 month sustained

00:08:09.590 --> 00:08:11.352 near PR for this patient.

00:08:11.352 --> 00:08:13.272 And actually when this patient

NOTE Confidence: 0.833701692

00:08:13.272 --> 00:08:15.079 progress we're able then amend,

NOTE Confidence: 0.833701692

00:08:15.080 --> 00:08:16.280 amend another protocol to

NOTE Confidence: 0.833701692

00:08:16.280 --> 00:08:18.080 put them on a PARP ATR,

NOTE Confidence: 0.833701692

00:08:18.080 --> 00:08:19.100 inhibit accommodation based on some

NOTE Confidence: 0.833701692

00:08:19.100 --> 00:08:20.560 of the work from our laboratory.

NOTE Confidence: 0.833701692

00:08:20.560 --> 00:08:22.401 And that patient actually had a pretty

NOTE Confidence: 0.833701692

00:08:22.401 --> 00:08:23.958 durable response for quite some time.

NOTE Confidence: 0.833701692

00:08:23.960 --> 00:08:25.880 We published that in 2021.

NOTE Confidence: 0.833701692

00:08:25.880 --> 00:08:28.505 We then continued to try to find

NOTE Confidence: 0.833701692

00:08:28.505 --> 00:08:30.239 off label opportunities to chest

NOTE Confidence: 0.833701692

00:08:30.240 --> 00:08:32.105 PARP inhibitors in these onco

NOTE Confidence: 0.833701692

00:08:32.105 --> 00:08:33.102 metabolite producing tumors.

NOTE Confidence: 0.833701692

00:08:33.102 --> 00:08:35.590 This is an example of an SDH deficient

NOTE Confidence: 0.833701692

00:08:35.648 --> 00:08:37.760 gist that we saw in Pete's tumor board

NOTE Confidence: 0.833701692

00:08:37.760 --> 00:08:39.488 and Charles Singh and Juan Vasquez

00:08:39.488 --> 00:08:40.966 and actually Forzano Prezankar should

00:08:40.966 --> 00:08:42.634 also mentions the senior author here.

00:08:42.640 --> 00:08:45.517 We actually had a pretty remarkable response

00:08:45.517 --> 00:08:47.600 looking at temozolomide combined with

00:08:47.600 --> 00:08:51.596 olaparib in this particular case here.

00:08:51.600 --> 00:08:52.797 More recently though,

00:08:52.797 --> 00:08:54.792 we've now really embraced this

00:08:54.792 --> 00:08:56.445 combination approach looking at

00:08:56.445 --> 00:08:58.041 alkylator combinations like TMZ

00:08:58.041 --> 00:08:59.637 combined with PARP inhibitors.

00:08:59.640 --> 00:09:01.952 And this is a trial we started a

00:09:01.952 --> 00:09:03.903 few years back called ABC 18 O1.

00:09:03.903 --> 00:09:05.641 And I just want to give you a little

00:09:05.641 --> 00:09:07.321 update on where we are with this as

00:09:07.369 --> 00:09:08.743 well because it kind of gives you a

00:09:08.743 --> 00:09:10.229 sense of what it's like when you try

NOTE Confidence: 0.790096674166667

00:09:10.229 --> 00:09:11.440 to translate work from the bench,

NOTE Confidence: 0.790096674166667

00:09:11.440 --> 00:09:12.271 the bed size.

NOTE Confidence: 0.790096674166667

00:09:12.271 --> 00:09:13.933 So many people are involved in

NOTE Confidence: 0.790096674166667

00:09:13.933 --> 00:09:16.254 this type of work on this trial is

NOTE Confidence: 0.790096674166667

00:09:16.254 --> 00:09:17.828 recurrent IDH mutant gliomas adult

NOTE Confidence: 0.790096674166667

00:09:17.828 --> 00:09:19.704 and we also have a pediatric version

NOTE Confidence: 0.790096674166667

00:09:19.704 --> 00:09:21.856 of this with Asher marks looking at

NOTE Confidence: 0.790096674166667

00:09:21.856 --> 00:09:23.902 the PARP trapping PARP inhibitor BGB

NOTE Confidence: 0.790096674166667

00:09:23.902 --> 00:09:26.599 290 and using a full dose of the BGB

NOTE Confidence: 0.790096674166667

00:09:26.599 --> 00:09:28.831 290 with a very low dose of Tamizola

NOTE Confidence: 0.790096674166667

00:09:28.831 --> 00:09:31.226 and almost as a sensitizer to BGB 290.

NOTE Confidence: 0.790096674166667

00:09:31.226 --> 00:09:33.477 And this is a was a phase one two

NOTE Confidence: 0.790096674166667

00:09:33.477 --> 00:09:35.391 trial that broke out into three

NOTE Confidence: 0.790096674166667

00:09:35.391 --> 00:09:37.706 cohorts of which should find as

NOTE Confidence: 0.790096674166667

00:09:37.706 --> 00:09:39.856 porous patients that are alkylated

NOTE Confidence: 0.790096674166667

00:09:39.856 --> 00:09:41.690 refractory alkylator naive patients,

NOTE Confidence: 0.790096674166667

00:09:41.690 --> 00:09:44.115 R&amp;B and the exploratory GBM.

NOTE Confidence: 0.790096674166667

00:09:44.120 --> 00:09:47.198 All these are IDH Newton gliomas.

NOTE Confidence: 0.790096674166667

00:09:47.200 --> 00:09:49.848 We built a lot of exciting sort of

NOTE Confidence: 0.790096674166667

00:09:49.848 --> 00:09:51.719 correlates correlatives and oratory studies.

NOTE Confidence: 0.790096674166667

00:09:51.720 --> 00:09:52.242 For instance,

NOTE Confidence: 0.790096674166667

00:09:52.242 --> 00:09:54.330 we built a phase zero trial here we're

NOTE Confidence: 0.790096674166667

00:09:54.383 --> 00:09:56.009 able to actually biopsy patients and

NOTE Confidence: 0.790096674166667

00:09:56.009 --> 00:09:58.049 and look for drug levels and enhancing

NOTE Confidence: 0.790096674166667

00:09:58.049 --> 00:09:59.855 and non enhancing disease and also

NOTE Confidence: 0.790096674166667

00:09:59.855 --> 00:10:01.721 show you some some cool stuff we did

NOTE Confidence: 0.790096674166667

00:10:01.721 --> 00:10:03.278 looking at MRI velocity studies to

NOTE Confidence: 0.790096674166667

00:10:03.278 --> 00:10:04.940 track tumor growth because as some

NOTE Confidence: 0.790096674166667

00:10:04.940 --> 00:10:06.788 of you know these IDH mean tumors

NOTE Confidence: 0.790096674166667

00:10:06.788 --> 00:10:08.826 grow rather slowly in in patients and

NOTE Confidence: 0.790096674166667

00:10:08.826 --> 00:10:10.878 can be difficult to track responses.

NOTE Confidence: 0.790096674166667

00:10:10.880 --> 00:10:12.563 So just share a little bit of an update

NOTE Confidence: 0.790096674166667

00:10:12.563 --> 00:10:14.040 just because of time but I want to

NOTE Confidence: 0.790096674166667

00:10:14.040 --> 00:10:15.428 kind of give you a flavor of where

NOTE Confidence: 0.790096674166667

00:10:15.428 --> 00:10:17.800 we are on on for this stage of the project.

NOTE Confidence: 0.790096674166667

00:10:17.800 --> 00:10:19.896 So this is the the phase zero trial

NOTE Confidence: 0.790096674166667

00:10:19.896 --> 00:10:21.696 we we we wrote it was really exciting

NOTE Confidence: 0.790096674166667

00:10:21.696 --> 00:10:23.199 to sort of get this off the ground.

NOTE Confidence: 0.790096674166667

00:10:23.200 --> 00:10:24.873 It's one of our first phase zeros

NOTE Confidence: 0.790096674166667

00:10:24.873 --> 00:10:26.422 we've done and as you can see

NOTE Confidence: 0.790096674166667

00:10:26.422 --> 00:10:28.099 we were able to give the drug at

NOTE Confidence: 0.790096674166667

00:10:28.099 --> 00:10:29.559 a full dose 60 milligram BBID,

NOTE Confidence: 0.790096674166667

00:10:29.559 --> 00:10:31.154 the PARP inhibitor without the

NOTE Confidence: 0.790096674166667

00:10:31.154 --> 00:10:33.079 tamizole mod for seven to 10 days.

NOTE Confidence: 0.790096674166667

00:10:33.080 --> 00:10:34.711 And then we're able to take the

NOTE Confidence: 0.790096674166667

00:10:34.711 --> 00:10:36.226 patients to the OR and essentially

NOTE Confidence: 0.790096674166667

00:10:36.226 --> 00:10:37.891 biopsy not not only enhancing

NOTE Confidence: 0.790096674166667

00:10:37.891 --> 00:10:39.549 disease but non enhancing disease

NOTE Confidence: 0.790096674166667

00:10:39.549 --> 00:10:41.649 to look at whether we truly had

NOTE Confidence: 0.790096674166667

00:10:41.649 --> 00:10:43.363 blood brain barrier penetration of

NOTE Confidence: 0.790096674166667

00:10:43.363 --> 00:10:45.391 our drug and then obviously blood

NOTE Confidence: 0.790096674166667

00:10:45.400 --> 00:10:47.372 for normalization or comparison.

NOTE Confidence: 0.790096674166667

00:10:47.372 --> 00:10:49.837 We developed a protocol to

NOTE Confidence: 0.790096674166667

00:10:49.837 --> 00:10:51.944 develop BGB to detect BGB 290.

NOTE Confidence: 0.790096674166667

00:10:51.944 --> 00:10:54.280 This was Jing Lee's group at Wayne State,

NOTE Confidence: 0.790096674166667

00:10:54.280 --> 00:10:55.860 the Carmanos Cancer Institute

NOTE Confidence: 0.790096674166667

00:10:55.860 --> 00:10:57.874 to to detect the BGB 290.

NOTE Confidence: 0.790096674166667

00:10:57.874 --> 00:10:59.393 And I'll just show you some of

NOTE Confidence: 0.790096674166667

00:10:59.393 --> 00:11:01.072 the report results that we just

NOTE Confidence: 0.790096674166667

00:11:01.072 --> 00:11:03.376 reported at Snow an updated version

NOTE Confidence: 0.790096674166667

00:11:03.376 --> 00:11:04.678 and published recently.

NOTE Confidence: 0.790096674166667

00:11:04.680 --> 00:11:06.040 We can see here it was quite nice.

NOTE Confidence: 0.790096674166667

00:11:06.040 --> 00:11:08.056 We could see that we could detect high

NOTE Confidence: 0.790096674166667

00:11:08.056 --> 00:11:10.374 levels of total pimiprid that's BGB 290.

NOTE Confidence: 0.790096674166667

00:11:10.374 --> 00:11:12.009 The green circles are in

NOTE Confidence: 0.790096674166667

00:11:12.009 --> 00:11:12.990 non enhancing disease

NOTE Confidence: 0.81359031173913

00:11:13.052 --> 00:11:15.047 and then the red is the enhancing

NOTE Confidence: 0.81359031173913

00:11:15.047 --> 00:11:16.798 tumor and then we can detect,

NOTE Confidence: 0.81359031173913

00:11:16.800 --> 00:11:19.410 detect substantial levels

NOTE Confidence: 0.81359031173913

00:11:19.410 --> 00:11:21.435 of unbound drug shown here.

NOTE Confidence: 0.81359031173913

00:11:21.440 --> 00:11:23.138 And when we calculate KPUU we

NOTE Confidence: 0.81359031173913

00:11:23.138 --> 00:11:24.600 get these numbers shown here.

NOTE Confidence: 0.81359031173913

00:11:24.600 --> 00:11:26.200 It's a little skewed because

NOTE Confidence: 0.81359031173913

00:11:26.200 --> 00:11:27.396 of the plasma numbers.

NOTE Confidence: 0.81359031173913

00:11:27.396 --> 00:11:29.520 So we sort of normalize in the far right,

NOTE Confidence: 0.81359031173913

00:11:29.520 --> 00:11:31.396 but this is actually the first study

NOTE Confidence: 0.81359031173913

00:11:31.396 --> 00:11:33.460 to show that both enhancing and on

NOTE Confidence: 0.81359031173913

00:11:33.460 --> 00:11:35.266 enhancing tumor we can detect the

NOTE Confidence: 0.81359031173913

00:11:35.320 --> 00:11:37.158 part where neighbor BGB 290 which

NOTE Confidence: 0.81359031173913

00:11:37.158 --> 00:11:39.020 is thought to be seen as penetrant

NOTE Confidence: 0.81359031173913

00:11:39.085 --> 00:11:40.919 but was not known as only project

NOTE Confidence: 0.81359031173913

00:11:40.920 --> 00:11:42.852 modeled in the animals to to

NOTE Confidence: 0.81359031173913

00:11:42.852 --> 00:11:44.680 penetrate the blood brain barrier.

NOTE Confidence: 0.81359031173913

00:11:44.680 --> 00:11:45.836 Another flavor of this,

NOTE Confidence: 0.81359031173913

00:11:45.836 --> 00:11:46.992 because we're still continuing

NOTE Confidence: 0.81359031173913

00:11:46.992 --> 00:11:48.480 to now look at responses,

NOTE Confidence: 0.81359031173913

00:11:48.480 --> 00:11:50.208 I can tell you today is we don't

NOTE Confidence: 0.81359031173913

00:11:50.208 --> 00:11:51.985 have you know overwhelming responses

NOTE Confidence: 0.81359031173913

00:11:51.985 --> 00:11:53.632 with this combination therapy,

NOTE Confidence: 0.81359031173913

00:11:53.632 --> 00:11:56.096 but we do have outliers that are

NOTE Confidence: 0.81359031173913

00:11:56.096 --> 00:11:57.926 actually seeming to have some response.

NOTE Confidence: 0.81359031173913

00:11:57.926 --> 00:11:59.556 And as I mentioned earlier,

NOTE Confidence: 0.81359031173913

00:11:59.560 --> 00:12:01.380 IDH main tumors are fascinating

NOTE Confidence: 0.81359031173913

00:12:01.380 --> 00:12:03.200 because they grow incredibly slow.

NOTE Confidence: 0.81359031173913

00:12:03.200 --> 00:12:05.524 And as if anyone knows from the

NOTE Confidence: 0.81359031173913

00:12:05.524 --> 00:12:07.742 audios trials that recently are now

NOTE Confidence: 0.81359031173913

00:12:07.742 --> 00:12:09.919 an NDA filed for the IDH inhibitors,

NOTE Confidence: 0.81359031173913

00:12:09.920 --> 00:12:11.240 these tumors actually have to be

NOTE Confidence: 0.81359031173913

00:12:11.240 --> 00:12:12.394 tracked over time because they

NOTE Confidence: 0.81359031173913

00:12:12.394 --> 00:12:13.078 often don't shrink.

NOTE Confidence: 0.81359031173913

00:12:13.080 --> 00:12:14.280 It's more disease stability

NOTE Confidence: 0.81359031173913

00:12:14.280 --> 00:12:15.480 that you're looking for.

NOTE Confidence: 0.81359031173913

00:12:15.480 --> 00:12:16.998 So we worked with Ben Ellenson

NOTE Confidence: 0.81359031173913

00:12:16.998 --> 00:12:18.383 who's developed an MRI velocity

NOTE Confidence: 0.81359031173913

00:12:18.383 --> 00:12:19.963 protocol working in the company

NOTE Confidence: 0.81359031173913

00:12:19.963 --> 00:12:21.594 called Neosoma where they can

NOTE Confidence: 0.81359031173913

00:12:21.594 --> 00:12:22.858 automatically segment the enhancing

NOTE Confidence: 0.81359031173913

00:12:22.858 --> 00:12:24.922 and non enhancing areas of disease.

NOTE Confidence: 0.81359031173913

00:12:24.922 --> 00:12:27.332 Then volumetrically average and you

NOTE Confidence: 0.81359031173913

00:12:27.332 --> 00:12:29.680 can essentially get three prior

NOTE Confidence: 0.81359031173913

00:12:29.680 --> 00:12:31.702 Mris and then three Mris after

NOTE Confidence: 0.81359031173913

00:12:31.702 --> 00:12:34.047 treatment and then get a a sense

NOTE Confidence: 0.81359031173913

00:12:34.047 --> 00:12:35.597 of disease of velocity again.

NOTE Confidence: 0.81359031173913

00:12:35.600 --> 00:12:37.511 We just reported these results at Snow

NOTE Confidence: 0.81359031173913

00:12:37.511 --> 00:12:39.998 at the Neuro Oncology Conference last year.

NOTE Confidence: 0.81359031173913

00:12:40.000 --> 00:12:40.960 And what you can see here,

NOTE Confidence: 0.81359031173913

00:12:40.960 --> 00:12:42.008 looking in arm A,

NOTE Confidence: 0.81359031173913

00:12:42.008 --> 00:12:43.706 this is the alculator refractory patients.

NOTE Confidence: 0.81359031173913

00:12:43.706 --> 00:12:46.120 I know it's a little bit small here,

NOTE Confidence: 0.81359031173913

00:12:46.120 --> 00:12:47.998 but you can see three patients,

NOTE Confidence: 0.81359031173913

00:12:48.000 --> 00:12:48.480 an example.

NOTE Confidence: 0.81359031173913

00:12:48.480 --> 00:12:50.720 It's pretty clear that you had progression

NOTE Confidence: 0.81359031173913

00:12:50.720 --> 00:12:52.700 and then either disease stabilization or

NOTE Confidence: 0.81359031173913

00:12:52.700 --> 00:12:55.280 arguably some amount of disease reduction.

NOTE Confidence: 0.81359031173913

00:12:55.280 --> 00:12:57.400 And we saw this in the Arm B,

NOTE Confidence: 0.81359031173913

00:12:57.400 --> 00:12:59.758 the the arm B as well.

NOTE Confidence: 0.81359031173913

00:12:59.760 --> 00:13:00.157 Again,

NOTE Confidence: 0.81359031173913

00:13:00.157 --> 00:13:02.936 6 cases here were other disease stability

NOTE Confidence: 0.81359031173913

00:13:02.936 --> 00:13:05.960 or disease regression and also in the

NOTE Confidence: 0.81359031173913

00:13:05.960 --> 00:13:08.115 exploratory cohort of recurrent GBMS.

NOTE Confidence: 0.81359031173913

00:13:08.120 --> 00:13:10.600 Again, so this is A work in progress,

NOTE Confidence: 0.81359031173913

00:13:10.600 --> 00:13:12.200 but was real, real fun to work with.

NOTE Confidence: 0.81359031173913

00:13:12.200 --> 00:13:14.513 Ben and his group at UCLA just sort of

NOTE Confidence: 0.81359031173913

00:13:14.513 --> 00:13:16.094 track some of these tumor responses.

NOTE Confidence: 0.81359031173913

00:13:16.094 --> 00:13:18.326 So just wanted to kind of give you sort

NOTE Confidence: 0.81359031173913

00:13:18.326 --> 00:13:20.153 of a sense of where we are with that,

NOTE Confidence: 0.81359031173913

00:13:20.160 --> 00:13:20.865 with that work,

NOTE Confidence: 0.81359031173913

00:13:20.865 --> 00:13:23.359 as it's been a labor of love for us in

NOTE Confidence: 0.81359031173913

00:13:23.359 --> 00:13:25.193 terms of trying to translate that work.

NOTE Confidence: 0.81359031173913

00:13:25.200 --> 00:13:27.198 But I really want to focus on more of

NOTE Confidence: 0.81359031173913

00:13:27.198 --> 00:13:29.480 our recent discoveries in the laboratory,

NOTE Confidence: 0.81359031173913

00:13:29.480 --> 00:13:30.520 which is we've been really,

NOTE Confidence: 0.81359031173913

00:13:30.520 --> 00:13:32.716 really excited about South for this.

NOTE Confidence: 0.81359031173913

00:13:32.720 --> 00:13:34.274 We need a little bit of background.

NOTE Confidence: 0.81359031173913

00:13:34.280 --> 00:13:36.639 So I'm a GB M radiation oncologist

NOTE Confidence: 0.81359031173913

00:13:36.639 --> 00:13:37.313 by training.

NOTE Confidence: 0.81359031173913

00:13:37.320 --> 00:13:39.520 I went into CNS because there's only CNS,

NOTE Confidence: 0.81359031173913

00:13:39.520 --> 00:13:39.777 right.

NOTE Confidence: 0.81359031173913

00:13:39.777 --> 00:13:41.319 So only three trials to know

NOTE Confidence: 0.81359031173913

00:13:41.319 --> 00:13:42.759 for gliomyemics in clinic today.

NOTE Confidence: 0.81359031173913

00:13:42.760 --> 00:13:43.738 And it's very,

NOTE Confidence: 0.81359031173913

00:13:43.738 --> 00:13:44.716 it's always nice,

NOTE Confidence: 0.81359031173913

00:13:44.720 --> 00:13:46.000 not like pathology where you

NOTE Confidence: 0.81359031173913

00:13:46.000 --> 00:13:47.280 have like hundreds of papers

NOTE Confidence: 0.700767125714286

00:13:47.334 --> 00:13:48.278 you have to memorize.

NOTE Confidence: 0.700767125714286

00:13:48.280 --> 00:13:51.019 But you can see here there's 333 key trials.

NOTE Confidence: 0.700767125714286

00:13:51.019 --> 00:13:54.743 The main one here is the Walker trial 1978.

NOTE Confidence: 0.700767125714286

00:13:54.743 --> 00:13:57.521 The Walker, Walker and colleagues actually

NOTE Confidence: 0.700767125714286

00:13:57.521 --> 00:13:59.973 randomized patients to surgical resection

NOTE Confidence: 0.700767125714286

00:13:59.973 --> 00:14:02.955 for GBM followed by adjuvant chemotherapy,

NOTE Confidence: 0.700767125714286

00:14:02.960 --> 00:14:05.744 sorry followed by adjuvant radiation or

NOTE Confidence: 0.700767125714286

00:14:05.744 --> 00:14:07.600 adjuvant alkylator chemotherapy BCNU,

NOTE Confidence: 0.700767125714286

00:14:07.600 --> 00:14:09.511 the structure shown there which will be

NOTE Confidence: 0.700767125714286

00:14:09.511 --> 00:14:11.358 important or the combination of both.

NOTE Confidence: 0.700767125714286

00:14:11.360 --> 00:14:12.540 This trial put radiation oncology

NOTE Confidence: 0.700767125714286

00:14:12.540 --> 00:14:14.239 in the map in the CNS space.

NOTE Confidence: 0.700767125714286

00:14:14.240 --> 00:14:16.970 Essentially all patients now from then

NOTE Confidence: 0.700767125714286

00:14:16.970 --> 00:14:19.858 on received post OP radiation therapy

NOTE Confidence: 0.700767125714286

00:14:19.858 --> 00:14:22.569 for GBM and then we had about a million

NOTE Confidence: 0.700767125714286

00:14:22.569 --> 00:14:23.855 negative trials until about 2005.

NOTE Confidence: 0.700767125714286

00:14:23.855 --> 00:14:25.640 And then we had the pivotal trial.

NOTE Confidence: 0.700767125714286

00:14:25.640 --> 00:14:28.125 This was the STOOP trial which essentially

NOTE Confidence: 0.700767125714286

00:14:28.125 --> 00:14:30.252 tested a different alkylator, A,

NOTE Confidence: 0.700767125714286

00:14:30.252 --> 00:14:32.724 a, a more selective mono functional

NOTE Confidence: 0.700767125714286

00:14:32.724 --> 00:14:34.437 alkylator called temazolamide and

NOTE Confidence: 0.700767125714286

00:14:34.437 --> 00:14:37.299 looked at whether adding it concurrent

NOTE Confidence: 0.700767125714286

00:14:37.299 --> 00:14:39.373 with temazolamide with radiation

NOTE Confidence: 0.700767125714286

00:14:39.373 --> 00:14:41.866 rather and adjuvantly Temazoma would

NOTE Confidence: 0.700767125714286

00:14:41.866 --> 00:14:43.438 have a survival benefit.

NOTE Confidence: 0.700767125714286

00:14:43.440 --> 00:14:44.995 And they're even though this

NOTE Confidence: 0.700767125714286

00:14:44.995 --> 00:14:46.239 doesn't look very impressive,

NOTE Confidence: 0.700767125714286

00:14:46.240 --> 00:14:48.440 this is actually a was a pretty pretty

NOTE Confidence: 0.700767125714286

00:14:48.440 --> 00:14:50.599 big result for the glioma field because

NOTE Confidence: 0.700767125714286

00:14:50.599 --> 00:14:52.880 we've had so many failures in the past.

NOTE Confidence: 0.700767125714286

00:14:52.880 --> 00:14:54.896 A follow up study based on this

NOTE Confidence: 0.700767125714286

00:14:54.896 --> 00:14:56.880 trial though made a key distinction.

NOTE Confidence: 0.700767125714286

00:14:56.880 --> 00:14:58.987 It was the patients that had tumors

NOTE Confidence: 0.700767125714286

00:14:58.987 --> 00:15:00.531 with silenced methylone E methyl

NOTE Confidence: 0.700767125714286

00:15:00.531 --> 00:15:02.277 transferase and this is ADNA repair

NOTE Confidence: 0.700767125714286

00:15:02.277 --> 00:15:04.398 protein that we'll talk about in a moment.

NOTE Confidence: 0.700767125714286

00:15:04.400 --> 00:15:06.880 When you're stratified by that you get

NOTE Confidence: 0.700767125714286

00:15:06.880 --> 00:15:09.040 a huge difference in overall survival.

NOTE Confidence: 0.700767125714286

00:15:09.040 --> 00:15:09.570 So this,

NOTE Confidence: 0.700767125714286

00:15:09.570 --> 00:15:10.100 this real,

NOTE Confidence: 0.700767125714286

00:15:10.100 --> 00:15:12.676 this paper from Hagee ET all that that did

NOTE Confidence: 0.700767125714286

00:15:12.676 --> 00:15:14.839 the analysis from Roger Stoops data really

NOTE Confidence: 0.700767125714286

00:15:14.899 --> 00:15:16.999 established that MGMT was a biomarker.

NOTE Confidence: 0.700767125714286

00:15:17.000 --> 00:15:18.272 I would actually argue if you

NOTE Confidence: 0.700767125714286

00:15:18.272 --> 00:15:19.120 talk about synthetically valid,

NOTE Confidence: 0.700767125714286

00:15:19.120 --> 00:15:21.458 this is one of the first synthetic

NOTE Confidence: 0.700767125714286

00:15:21.458 --> 00:15:23.200 lethal interactions that had clinical

00:15:23.200 --> 00:15:24.310 significance where tamazolmide

00:15:24.310 --> 00:15:26.160 works in MGMT silence tumors.

00:15:26.160 --> 00:15:28.960 But we could argue that for for hours.

00:15:28.960 --> 00:15:30.490 So now delving a little bit

00:15:30.490 --> 00:15:31.800 deeper into the laboratory side.

00:15:31.800 --> 00:15:34.600 So why? Why is this the case?

00:15:34.600 --> 00:15:36.652 So I've been fascinated ever since I was a

00:15:36.652 --> 00:15:38.356 graduate student here in the early 2000s.

00:15:38.360 --> 00:15:38.809 Molecularly,

00:15:38.809 --> 00:15:41.952 what we understand is that temozolomide opens

00:15:41.952 --> 00:15:45.435 up into this methyl diazonium ion shown here,

00:15:45.440 --> 00:15:47.198 and it methylates the O six

00:15:47.198 --> 00:15:48.077 position of guanine.

00:15:48.080 --> 00:15:49.977 Now only about 5% of the damage

00:15:49.977 --> 00:15:52.238 from TMZ is actually at the O six.

00:15:52.240 --> 00:15:53.440 It's actually all over the bases,

NOTE Confidence: 0.700767125714286

00:15:53.440 --> 00:15:55.477 but this is the important one for

NOTE Confidence: 0.700767125714286

00:15:55.477 --> 00:15:56.992 the cytotoxicity that you see

NOTE Confidence: 0.700767125714286

00:15:56.992 --> 00:15:58.156 with MGMT SCIENCE TUMORS.

NOTE Confidence: 0.700767125714286

00:15:58.160 --> 00:15:58.684 So first,

NOTE Confidence: 0.700767125714286

00:15:58.684 --> 00:15:59.994 normal cells express high levels

NOTE Confidence: 0.700767125714286

00:15:59.994 --> 00:16:01.586 of this enzyme called methyl

NOTE Confidence: 0.700767125714286

00:16:01.586 --> 00:16:02.717 guanine methyl transferase.

NOTE Confidence: 0.700767125714286

00:16:02.720 --> 00:16:03.952 It's a suicide enzyme.

NOTE Confidence: 0.700767125714286

00:16:03.952 --> 00:16:07.010 It plucks that O 6 methyl off and

NOTE Confidence: 0.700767125714286

00:16:07.010 --> 00:16:08.664 other potential lesions as well.

NOTE Confidence: 0.700767125714286

00:16:08.664 --> 00:16:10.880 But if you don't have MGMT what

NOTE Confidence: 0.700767125714286

00:16:10.880 --> 00:16:12.455 you get is during replication

NOTE Confidence: 0.700767125714286

00:16:12.455 --> 00:16:14.056 with about 90% bypass efficiency,

NOTE Confidence: 0.700767125714286

00:16:14.056 --> 00:16:15.696 the polymerase will drive across

NOTE Confidence: 0.700767125714286

00:16:15.696 --> 00:16:17.899 that O 6 methyl guanine and it

NOTE Confidence: 0.700767125714286

00:16:17.899 --> 00:16:19.354 will miss pair with thyme.

NOTE Confidence: 0.700767125714286

00:16:19.360 --> 00:16:20.308 This activates mismatch repair

NOTE Confidence: 0.700767125714286

00:16:20.308 --> 00:16:21.493 which basically says you've made

NOTE Confidence: 0.700767125714286

00:16:21.493 --> 00:16:22.639 an error to the polymerase.

NOTE Confidence: 0.700767125714286

00:16:22.640 --> 00:16:24.248 Polymerase does the same thing over

NOTE Confidence: 0.700767125714286

00:16:24.248 --> 00:16:26.222 and over again and you get this

NOTE Confidence: 0.700767125714286

00:16:26.222 --> 00:16:27.944 thing called futile cycling which is

NOTE Confidence: 0.700767125714286

00:16:27.944 --> 00:16:29.112 very fascinating because essentially

NOTE Confidence: 0.700767125714286

00:16:29.112 --> 00:16:31.458 the the at at one point mismatch

NOTE Confidence: 0.700767125714286

00:16:31.458 --> 00:16:32.958 repair essentially realizes cannot

NOTE Confidence: 0.551995579166667

00:16:32.960 --> 00:16:35.064 actually, you know change

NOTE Confidence: 0.551995579166667

00:16:35.064 --> 00:16:36.116 polymerase's errors.

NOTE Confidence: 0.551995579166667

00:16:36.120 --> 00:16:37.961 I'm sure it doesn't actually do it

NOTE Confidence: 0.551995579166667

00:16:37.961 --> 00:16:39.519 that dramatically but it stimulates

NOTE Confidence: 0.551995579166667

00:16:39.519 --> 00:16:41.100 apoptosis and this actually accounts

NOTE Confidence: 0.551995579166667

00:16:41.100 --> 00:16:42.930 for the cytotoxicity even though it's

NOTE Confidence: 0.551995579166667

00:16:42.979 --> 00:16:44.596 a very small amount of the damage.

NOTE Confidence: 0.551995579166667

00:16:44.600 --> 00:16:47.197 And what we now understand is that

NOTE Confidence: 0.551995579166667

00:16:47.200 --> 00:16:49.321 over the last three or four years

NOTE Confidence: 0.551995579166667

00:16:49.321 --> 00:16:50.875 quantitatively we can say that

NOTE Confidence: 0.551995579166667

00:16:50.875 --> 00:16:52.627 large fractions of of tumors that

NOTE Confidence: 0.551995579166667

00:16:52.627 --> 00:16:54.319 respond to TMZ that have MGMT.

NOTE Confidence: 0.551995579166667

00:16:54.320 --> 00:16:55.610 Silence promoters.

NOTE Confidence: 0.551995579166667

00:16:55.610 --> 00:16:58.190 They simply just knockout

NOTE Confidence: 0.551995579166667

00:16:58.190 --> 00:16:59.712 mismatch repair again.

NOTE Confidence: 0.551995579166667

00:16:59.712 --> 00:17:01.104 We knew about this in the

NOTE Confidence: 0.551995579166667

00:17:01.104 --> 00:17:02.256 90s and the early 2000s,

NOTE Confidence: 0.551995579166667

00:17:02.256 --> 00:17:03.852 but it was really these two papers

NOTE Confidence: 0.551995579166667

00:17:03.852 --> 00:17:05.691 I'm presenting here in the last few

NOTE Confidence: 0.551995579166667

00:17:05.691 --> 00:17:07.000 years that have quantified this.

NOTE Confidence: 0.551995579166667

00:17:07.000 --> 00:17:08.548 And so just to show exactly

NOTE Confidence: 0.551995579166667

00:17:08.548 --> 00:17:09.580 what's happening is you're

NOTE Confidence: 0.551995579166667

00:17:09.630 --> 00:17:11.160 simply turning off the firewall.

NOTE Confidence: 0.551995579166667

00:17:11.160 --> 00:17:12.714 So now you're knocking out mismatch repair.

NOTE Confidence: 0.551995579166667

00:17:12.720 --> 00:17:14.176 You're actually creating mismatches,

NOTE Confidence: 0.551995579166667

00:17:14.176 --> 00:17:16.360 all of the genome genetic instability,

NOTE Confidence: 0.551995579166667

00:17:16.360 --> 00:17:18.607 but there's no fire alarm to to

NOTE Confidence: 0.551995579166667

00:17:18.607 --> 00:17:20.560 trigger apoptosis or futile cycling.

NOTE Confidence: 0.551995579166667

00:17:20.560 --> 00:17:21.598 Sort of like a tree following

NOTE Confidence: 0.551995579166667

00:17:21.598 --> 00:17:22.840 the woods if no one's around.

NOTE Confidence: 0.551995579166667

00:17:22.840 --> 00:17:25.156 Does it really make a sound?

NOTE Confidence: 0.551995579166667

00:17:25.160 --> 00:17:27.600 So if you're sort of just checking e-mail,

NOTE Confidence: 0.551995579166667

00:17:27.600 --> 00:17:29.357 just the the take home message here.

NOTE Confidence: 0.551995579166667

00:17:29.360 --> 00:17:31.040 TMZ works well on MGMC.

NOTE Confidence: 0.551995579166667

00:17:31.040 --> 00:17:32.216 Silence, tumors OK,

NOTE Confidence: 0.551995579166667

00:17:32.216 --> 00:17:34.960 but resistance emerges and I'd say in

NOTE Confidence: 0.551995579166667

00:17:35.036 --> 00:17:37.976 in half of all gliomas it's actually

NOTE Confidence: 0.551995579166667

00:17:37.976 --> 00:17:40.479 clonally driven mismatch repair mutations.

NOTE Confidence: 0.551995579166667

00:17:40.480 --> 00:17:42.316 So for us this was a sort of multi

NOTE Confidence: 0.551995579166667

00:17:42.316 --> 00:17:44.007 forks in the road where when we saw

NOTE Confidence: 0.551995579166667

00:17:44.007 --> 00:17:46.237 this in in the clinic this is actually

NOTE Confidence: 0.551995579166667

00:17:46.237 --> 00:17:47.797 an example we're seeing patients,

NOTE Confidence: 0.551995579166667

00:17:47.800 --> 00:17:49.276 we said well this is fascinating,

NOTE Confidence: 0.551995579166667

00:17:49.280 --> 00:17:52.080 these patients still have silence

NOTE Confidence: 0.551995579166667

00:17:52.080 --> 00:17:54.020 MGMT and they've acquired A mismatch

NOTE Confidence: 0.551995579166667

00:17:54.020 --> 00:17:55.400 permutation TMZ is not working.

NOTE Confidence: 0.551995579166667

00:17:55.400 --> 00:17:56.918 So how could we fix this?

NOTE Confidence: 0.551995579166667

00:17:56.920 --> 00:17:58.927 Can we come up with a new therapy that

NOTE Confidence: 0.551995579166667

00:17:58.927 --> 00:18:00.498 still exploited the MGMT biomarker

NOTE Confidence: 0.551995579166667

00:18:00.498 --> 00:18:02.766 and we first thought about creating

NOTE Confidence: 0.551995579166667

00:18:02.766 --> 00:18:05.040 alkylators that could be MMR independent.

NOTE Confidence: 0.551995579166667

00:18:05.040 --> 00:18:06.924 So just let's just make superpotent

NOTE Confidence: 0.551995579166667

00:18:06.924 --> 00:18:08.900 alkylators that would just crush anything

NOTE Confidence: 0.551995579166667

00:18:08.900 --> 00:18:11.720 that walked and well we've done that before.

NOTE Confidence: 0.551995579166667

00:18:11.720 --> 00:18:12.628 So the Walker trial,

NOTE Confidence: 0.551995579166667

00:18:12.628 --> 00:18:14.440 I showed you BCNU back in the day,

NOTE Confidence: 0.551995579166667

00:18:14.440 --> 00:18:15.852 non selective alkylator, Kintara,

NOTE Confidence: 0.551995579166667

00:18:15.852 --> 00:18:18.325 this is a drug called VALO A3

NOTE Confidence: 0.551995579166667

00:18:18.325 --> 00:18:20.677 reformulation of an old drug from the 70s,

NOTE Confidence: 0.551995579166667

00:18:20.680 --> 00:18:21.784 non selective alkylator.

NOTE Confidence: 0.551995579166667

00:18:21.784 --> 00:18:24.360 Again this actually just failed in the

NOTE Confidence: 0.551995579166667

00:18:24.422 --> 00:18:26.684 GBM agile phase three trial and a drug.

NOTE Confidence: 0.551995579166667

00:18:26.684 --> 00:18:28.280 We'll talk about Azelastone in a moment.

NOTE Confidence: 0.551995579166667

00:18:28.280 --> 00:18:30.476 These are effectively steamrolling the DNA.

NOTE Confidence: 0.551995579166667

00:18:30.480 --> 00:18:33.378 This is my 4 year old's steamroller

NOTE Confidence: 0.551995579166667

00:18:33.378 --> 00:18:35.669 to be dramatic there we also thought,

NOTE Confidence: 0.551995579166667

00:18:35.669 --> 00:18:35.852 OK,

NOTE Confidence: 0.551995579166667

00:18:35.852 --> 00:18:37.205 so we're not going to do that

NOTE Confidence: 0.551995579166667

00:18:37.205 --> 00:18:38.453 because that's going to not going

NOTE Confidence: 0.551995579166667

00:18:38.453 --> 00:18:39.713 to have that therapeutic index

NOTE Confidence: 0.551995579166667

00:18:39.713 --> 00:18:41.198 constraint that we really wanted.

NOTE Confidence: 0.551995579166667

00:18:41.200 --> 00:18:42.840 So what about reactivating MMR?

NOTE Confidence: 0.551995579166667

00:18:42.840 --> 00:18:43.840 That could be cool.

NOTE Confidence: 0.551995579166667

00:18:43.840 --> 00:18:45.995 We actually had a a pitch competition

NOTE Confidence: 0.551995579166667

00:18:45.995 --> 00:18:47.920 maybe Demetrius remembers the pitch

NOTE Confidence: 0.551995579166667

00:18:47.920 --> 00:18:49.534 competitions back in several years

NOTE Confidence: 0.551995579166667

00:18:49.534 --> 00:18:51.256 ago to to start a company around this

NOTE Confidence: 0.551995579166667

00:18:51.256 --> 00:18:52.961 and and this got shut down because

NOTE Confidence: 0.551995579166667

00:18:52.961 --> 00:18:54.509 there's too many mutations that you

NOTE Confidence: 0.551995579166667

00:18:54.555 --> 00:18:56.115 can't you know custom reactivate

NOTE Confidence: 0.551995579166667

00:18:56.115 --> 00:18:57.675 mismatch repair if there's mutations

NOTE Confidence: 0.551995579166667

00:18:57.680 --> 00:19:00.278 all across the open reading frame.

NOTE Confidence: 0.551995579166667

00:19:00.280 --> 00:19:02.576 But we landed on this idea of creating

NOTE Confidence: 0.551995579166667

00:19:02.576 --> 00:19:04.200 alkylators which are MMR independent

NOTE Confidence: 0.551995579166667

00:19:04.200 --> 00:19:06.756 but would retain the MGMT dependence.

NOTE Confidence: 0.551995579166667

00:19:06.760 --> 00:19:07.925 So harkening back to this

NOTE Confidence: 0.551995579166667

00:19:07.925 --> 00:19:09.090 therapeutic index curves that I

NOTE Confidence: 0.705756121538461

00:19:09.139 --> 00:19:10.000 talked about earlier.

NOTE Confidence: 0.705756121538461

00:19:10.000 --> 00:19:11.764 So the red and the green curves

NOTE Confidence: 0.705756121538461

00:19:11.764 --> 00:19:13.456 because we know these tumors still

NOTE Confidence: 0.705756121538461

00:19:13.456 --> 00:19:15.514 have silenced MGMT in the cases that

NOTE Confidence: 0.705756121538461

00:19:15.576 --> 00:19:17.556 acquire the mismatch repair mutation.

NOTE Confidence: 0.705756121538461

00:19:17.560 --> 00:19:19.240 So with that we turn to Seth Herzan.

NOTE Confidence: 0.705756121538461

00:19:19.240 --> 00:19:21.480 We had been working together in the

NOTE Confidence: 0.705756121538461

00:19:21.480 --> 00:19:24.357 past and we got our band back together.

NOTE Confidence: 0.705756121538461

00:19:24.360 --> 00:19:25.760 Seth is actually a really good guitarist

NOTE Confidence: 0.705756121538461

00:19:25.760 --> 00:19:27.238 and we haven't played a show together,

NOTE Confidence: 0.705756121538461

00:19:27.240 --> 00:19:28.952 but I'm still playing drums trying to quit

NOTE Confidence: 0.705756121538461

00:19:28.952 --> 00:19:30.998 my day job, which I because I'm here today.

NOTE Confidence: 0.705756121538461

00:19:31.000 --> 00:19:33.040 I haven't been able to do it yet.

NOTE Confidence: 0.705756121538461

00:19:33.040 --> 00:19:35.960 But so in 2018 came to Seth and I said,

NOTE Confidence: 0.705756121538461

00:19:35.960 --> 00:19:37.423 listen, you know, we've been working on

NOTE Confidence: 0.705756121538461

00:19:37.423 --> 00:19:39.000 some DNA repair inhibitors a while back.

NOTE Confidence: 0.705756121538461

00:19:39.000 --> 00:19:40.304 So let's let's figure out a way to

NOTE Confidence: 0.705756121538461

00:19:40.304 --> 00:19:41.637 come up with these new molecules.

NOTE Confidence: 0.705756121538461

00:19:41.640 --> 00:19:43.320 We called it Secret name with

NOTE Confidence: 0.705756121538461

00:19:43.320 --> 00:19:45.612 Crowbar into O 6, the CEO 6 project.

NOTE Confidence: 0.705756121538461

00:19:45.612 --> 00:19:46.198 You know,

NOTE Confidence: 0.705756121538461

00:19:46.200 --> 00:19:48.080 at the time I was doing the IDH parp story,

NOTE Confidence: 0.705756121538461

00:19:48.080 --> 00:19:50.248 he was working on all his crazy antibiotics

NOTE Confidence: 0.705756121538461

00:19:50.248 --> 00:19:52.759 that he makes and publishes in big journals.

NOTE Confidence: 0.705756121538461

00:19:52.760 --> 00:19:55.160 And it all centered around a simple question,

NOTE Confidence: 0.705756121538461

00:19:55.160 --> 00:19:58.877 which is, can we change the R group here?

NOTE Confidence: 0.705756121538461

00:19:58.880 --> 00:19:59.840 And again, I'm not a chemist,

NOTE Confidence: 0.705756121538461

00:19:59.840 --> 00:20:01.028 my dad's a chemist.

NOTE Confidence: 0.705756121538461

00:20:01.028 --> 00:20:03.160 I did not inherit his chemistry gene.

NOTE Confidence: 0.705756121538461

00:20:03.160 --> 00:20:04.280 But it certainly was very

NOTE Confidence: 0.705756121538461

00:20:04.280 --> 00:20:05.715 interesting in the idea of, like,

NOTE Confidence: 0.705756121538461

00:20:05.715 --> 00:20:08.235 there's got to be something that we could

NOTE Confidence: 0.705756121538461

00:20:08.235 --> 00:20:10.956 put on here that could be removed by MGMT,

NOTE Confidence: 0.705756121538461

00:20:10.960 --> 00:20:11.351 right?

NOTE Confidence: 0.705756121538461

00:20:11.351 --> 00:20:11.742 But.

NOTE Confidence: 0.705756121538461

00:20:11.742 --> 00:20:13.306 But independent of mismatch

NOTE Confidence: 0.705756121538461

00:20:13.306 --> 00:20:15.440 repair status for cell killing.

NOTE Confidence: 0.705756121538461

00:20:15.440 --> 00:20:15.816 OK.

NOTE Confidence: 0.705756121538461

00:20:15.816 --> 00:20:17.920 So at that point, I'm very,

NOTE Confidence: 0.705756121538461

00:20:17.920 --> 00:20:19.420 very grateful to have talented

NOTE Confidence: 0.705756121538461

00:20:19.420 --> 00:20:20.800 trainees come in the lab.

NOTE Confidence: 0.705756121538461

00:20:20.800 --> 00:20:21.960 Kingston Lynn who's here today.

NOTE Confidence: 0.705756121538461

00:20:21.960 --> 00:20:24.440 Susan Gable at Thinkston Clinic

00:20:24.440 --> 00:20:25.882 in a cycle of life because Susan

00:20:25.882 --> 00:20:27.358 Gable did her PhD in Peter Glazer's

00:20:27.358 --> 00:20:28.840 lab and then came to my labs.

00:20:28.840 --> 00:20:31.128 And so these two folks came in and

00:20:31.128 --> 00:20:33.797 we had a a mission for both of them,

00:20:33.800 --> 00:20:35.280 which is essentially, you know,

00:20:35.280 --> 00:20:36.200 put in our group.

00:20:36.200 --> 00:20:37.120 That's not a methyl,

00:20:37.120 --> 00:20:38.895 that's more complex that can

00:20:38.895 --> 00:20:40.315 be removed by MGMT.

00:20:40.320 --> 00:20:43.158 But kill cells independent our status

00:20:43.160 --> 00:20:46.037 and semi jokingly told them you know

00:20:46.040 --> 00:20:47.433 let's look at this plot and sort

00:20:47.433 --> 00:20:49.091 of walk them through it and said OK

00:20:49.091 --> 00:20:51.065 look at the green curve you get MGMT

NOTE Confidence: 0.705756121538461

00:20:51.065 --> 00:20:52.277 silence mismatch repair proficient.

NOTE Confidence: 0.705756121538461

00:20:52.280 --> 00:20:54.436 Very nice to sell killing with TMZ.

NOTE Confidence: 0.705756121538461

00:20:54.440 --> 00:20:55.987 OK yellow line is when you knock

NOTE Confidence: 0.705756121538461

00:20:55.987 --> 00:20:57.305 out mismatch repair you see the

NOTE Confidence: 0.705756121538461

00:20:57.305 --> 00:20:58.529 drug now looks invisible and then

NOTE Confidence: 0.705756121538461

00:20:58.529 --> 00:21:00.005 if you have MGMT doesn't matter

NOTE Confidence: 0.705756121538461

00:21:00.005 --> 00:21:01.468 because the methyl group gets ******

NOTE Confidence: 0.705756121538461

00:21:01.468 --> 00:21:03.292 ** and we sort of semi joking and

NOTE Confidence: 0.705756121538461

00:21:03.292 --> 00:21:04.814 said make some molecules and do

NOTE Confidence: 0.705756121538461

00:21:04.814 --> 00:21:06.662 not call us back until the yellow

NOTE Confidence: 0.705756121538461

00:21:06.662 --> 00:21:08.037 line drops below the green.

NOTE Confidence: 0.705756121538461

00:21:08.040 --> 00:21:10.800 Do not bring the black or the blue line down.

NOTE Confidence: 0.705756121538461

00:21:10.800 --> 00:21:12.820 Obviously we Kingston knows we're

NOTE Confidence: 0.705756121538461

00:21:12.820 --> 00:21:15.016 always available as mentors but they

NOTE Confidence: 0.705756121538461

00:21:15.016 --> 00:21:17.032 made about 100 molecules and one of

NOTE Confidence: 0.705756121538461

00:21:17.032 --> 00:21:19.360 the molecules fulfilled the criteria.

NOTE Confidence: 0.705756121538461

00:21:19.360 --> 00:21:21.222 I still remember and I'm sure Kingston

NOTE Confidence: 0.705756121538461

00:21:21.222 --> 00:21:22.832 and Cesar remember the day that

NOTE Confidence: 0.705756121538461

00:21:22.832 --> 00:21:24.356 they emailed us about this molecule.

NOTE Confidence: 0.705756121538461

00:21:24.360 --> 00:21:26.508 Literally isogenic cell lines

NOTE Confidence: 0.705756121538461

00:21:26.508 --> 00:21:28.656 selectively killing cells based

NOTE Confidence: 0.705756121538461

00:21:28.656 --> 00:21:31.092 on MGMT status but independent

NOTE Confidence: 0.705756121538461

00:21:31.092 --> 00:21:32.716 of mismatch repair status.

NOTE Confidence: 0.93402193

00:21:32.720 --> 00:21:35.030 Really, really nice sort of

NOTE Confidence: 0.93402193

00:21:35.030 --> 00:21:36.878 potential therapeutic index here.

NOTE Confidence: 0.93402193

00:21:36.880 --> 00:21:38.400 And so just to dive into some of the data,

NOTE Confidence: 0.93402193

00:21:38.400 --> 00:21:40.182 we spent a lot of time where we had

NOTE Confidence: 0.93402193

00:21:40.182 --> 00:21:42.116 that phenotype and we didn't really

NOTE Confidence: 0.93402193

00:21:42.116 --> 00:21:43.801 understand exactly what the mechanism

NOTE Confidence: 0.93402193

00:21:43.850 --> 00:21:45.634 was and we're going to get to the

NOTE Confidence: 0.93402193

00:21:45.634 --> 00:21:48.320 chemistry a little bit towards the end.

NOTE Confidence: 0.93402193

00:21:48.320 --> 00:21:50.416 And so Susan came in and started doing

NOTE Confidence: 0.93402193

00:21:50.416 --> 00:21:52.918 a lot of DNA repair functional assays.

NOTE Confidence: 0.93402193

00:21:52.920 --> 00:21:54.776 And what you can see here she did

NOTE Confidence: 0.93402193

00:21:54.776 --> 00:21:56.438 the neutral comment simply asking,

NOTE Confidence: 0.93402193

00:21:56.440 --> 00:21:58.090 you know, are there an increase

NOTE Confidence: 0.93402193

00:21:58.090 --> 00:22:00.200 in DNA double strand breaks in the

NOTE Confidence: 0.93402193

00:22:00.200 --> 00:22:02.120 background of the double negative cells.

NOTE Confidence: 0.93402193

00:22:02.120 --> 00:22:03.992 And so first I'll just walk you through

NOTE Confidence: 0.93402193

00:22:03.992 --> 00:22:05.637 here's TMZ and then you know it's a

NOTE Confidence: 0.93402193

00:22:05.637 --> 00:22:07.520 little bit of a good figure minus plus,

NOTE Confidence: 0.93402193

00:22:07.520 --> 00:22:09.828 that's MGMT minus miss,

NOTE Confidence: 0.93402193

00:22:09.828 --> 00:22:11.559 mismatch appear proficient,

NOTE Confidence: 0.93402193

00:22:11.560 --> 00:22:12.276 you can see that.

NOTE Confidence: 0.93402193

00:22:12.276 --> 00:22:13.589 So you get you get double strim

NOTE Confidence: 0.93402193

00:22:13.589 --> 00:22:14.954 breaks and we had published on this

NOTE Confidence: 0.93402193

47

00:22:14.954 --> 00:22:16.520 a few years back that made sense.

NOTE Confidence: 0.93402193

00:22:16.520 --> 00:22:18.200 But with the KO50 molecule,

NOTE Confidence: 0.93402193

00:22:18.200 --> 00:22:19.782 the minus plus and the minus minus

NOTE Confidence: 0.93402193

00:22:19.782 --> 00:22:21.439 you don't really get a a huge

NOTE Confidence: 0.93402193

00:22:21.439 --> 00:22:22.599 difference in double strim breaks.

NOTE Confidence: 0.93402193

00:22:22.600 --> 00:22:25.054 And note that when you knockout MGMT

NOTE Confidence: 0.93402193

00:22:25.054 --> 00:22:27.298 and mismatch repair here with TMZ

NOTE Confidence: 0.93402193

00:22:27.298 --> 00:22:29.773 the drugs invisible in terms of the

NOTE Confidence: 0.93402193

00:22:29.773 --> 00:22:31.705 damage and that's a futile cycling

NOTE Confidence: 0.93402193

00:22:31.774 --> 00:22:34.159 inducing strand breaks and apoptosis.

NOTE Confidence: 0.93402193

00:22:34.160 --> 00:22:36.015 But here clearly not double

NOTE Confidence: 0.93402193

00:22:36.015 --> 00:22:37.514 strand break clear mechanism.

NOTE Confidence: 0.93402193

00:22:37.514 --> 00:22:39.776 She then actually pulled the paper

NOTE Confidence: 0.93402193

00:22:39.776 --> 00:22:41.836 from the mid 90s and this is what

NOTE Confidence: 0.93402193

00:22:41.836 --> 00:22:43.030 I love about trainees working with

NOTE Confidence: 0.93402193

00:22:43.074 --> 00:22:44.382 trainees has pulled this out herself

NOTE Confidence: 0.93402193

00:22:44.382 --> 00:22:48.200 in an old cross linking comet assay

NOTE Confidence: 0.93402193

00:22:48.200 --> 00:22:50.160 and this is how this assay works.

NOTE Confidence: 0.93402193

00:22:50.160 --> 00:22:52.197 So here's some of you don't know.

NOTE Confidence: 0.93402193

00:22:52.200 --> 00:22:52.878 You take nuclei,

NOTE Confidence: 0.93402193

00:22:52.878 --> 00:22:54.788 you put it in agros gel and you

NOTE Confidence: 0.93402193

00:22:54.788 --> 00:22:56.158 run it across electric field

NOTE Confidence: 0.93402193

00:22:56.160 --> 00:22:57.240 and if there's DNA breaks,

NOTE Confidence: 0.93402193

00:22:57.240 --> 00:22:59.832 they'll sort of fade behind it like a comet.

NOTE Confidence: 0.93402193

00:22:59.840 --> 00:23:01.082 And so in this assay drug

NOTE Confidence: 0.93402193

00:23:01.082 --> 00:23:02.240 induced DNA double strand breaks,

NOTE Confidence: 0.93402193

00:23:02.240 --> 00:23:04.200 single strand breaks will induce a comet.

NOTE Confidence: 0.93402193

00:23:04.200 --> 00:23:06.110 IR induced breaks will induce

NOTE Confidence: 0.93402193

00:23:06.110 --> 00:23:07.638 an even bigger comment.

NOTE Confidence: 0.93402193

00:23:07.640 --> 00:23:09.496 But if you have a drug that has

NOTE Confidence: 0.93402193

00:23:09.496 --> 00:23:11.185 a cross linking effect, OK,

NOTE Confidence: 0.93402193

00:23:11.185 --> 00:23:13.546 it and you, the way we add, you know,

NOTE Confidence: 0.93402193

00:23:13.546 --> 00:23:15.317 we add these drugs and then treat,

NOTE Confidence: 0.93402193

00:23:15.320 --> 00:23:16.718 it'll actually stitch the DNA up,

NOTE Confidence: 0.93402193

00:23:16.720 --> 00:23:18.640 it'll prevent that comment from forming.

NOTE Confidence: 0.93402193

00:23:18.640 --> 00:23:18.996 OK.

NOTE Confidence: 0.93402193

00:23:18.996 --> 00:23:21.488 And this was used in the Fanconi

NOTE Confidence: 0.93402193

00:23:21.488 --> 00:23:22.200 anaemia days.

NOTE Confidence: 0.93402193

00:23:22.200 --> 00:23:22.668 So very,

NOTE Confidence: 0.93402193

00:23:22.668 --> 00:23:23.838 very nice assay to consider.

NOTE Confidence: 0.93402193

00:23:23.840 --> 00:23:25.464 So I'm going to walk you through

NOTE Confidence: 0.93402193

00:23:25.464 --> 00:23:27.024 what she found because this basically

NOTE Confidence: 0.93402193

00:23:27.024 --> 00:23:29.040 gave us our first clue on exactly

NOTE Confidence: 0.93402193

00:23:29.100 --> 00:23:30.078 what was happening.

NOTE Confidence: 0.93402193

00:23:30.080 --> 00:23:31.304 So let's just walk through the

NOTE Confidence: 0.93402193

00:23:31.304 --> 00:23:32.120 0 Gray shown here.

NOTE Confidence: 0.93402193

00:23:32.120 --> 00:23:34.920 So DMSO no, no Comet Tail Mitomycin.

NOTE Confidence: 0.93402193

00:23:34.920 --> 00:23:37.250 See, that's a cross linking agents, you know.

NOTE Confidence: 0.93402193

00:23:37.250 --> 00:23:39.075 So no, no effect there.

NOTE Confidence: 0.93402193

00:23:39.080 --> 00:23:40.620 TMZ induces single tram breaks

NOTE Confidence: 0.93402193

00:23:40.620 --> 00:23:42.160 and some double tram breaks.

NOTE Confidence: 0.93402193

00:23:42.160 --> 00:23:44.834 You can see a significant effect there.

NOTE Confidence: 0.93402193

00:23:44.840 --> 00:23:47.000 And then KL50 some damage but

NOTE Confidence: 0.93402193

00:23:47.000 --> 00:23:48.440 but not as significant.

NOTE Confidence: 0.93402193

00:23:48.440 --> 00:23:51.896 Now when you add the the radiation sort of

NOTE Confidence: 0.93402193

00:23:51.896 --> 00:23:54.236 probe for the potential crossing in activity,

NOTE Confidence: 0.93402193

00:23:54.240 --> 00:23:55.848 you can see here that when

NOTE Confidence: 0.93402193

00:23:55.848 --> 00:23:56.920 you add mitomycin C,

NOTE Confidence: 0.93402193

00:23:56.920 --> 00:23:58.294 when you go to high doses

NOTE Confidence: 0.93402193

00:23:58.294 --> 00:23:59.440 you're stitching the DNA out,

NOTE Confidence: 0.888377290909091

00:23:59.440 --> 00:24:02.080 OK. And so now you're unable to create

NOTE Confidence: 0.888377290909091

00:24:02.080 --> 00:24:04.600 that common tail and then TMZ as expected,

NOTE Confidence: 0.888377290909091

00:24:04.600 --> 00:24:07.358 no cross linking activity. But then KL50,

NOTE Confidence: 0.888377290909091

00:24:07.360 --> 00:24:09.370 we started to notice an appreciable

NOTE Confidence: 0.888377290909091

00:24:09.370 --> 00:24:11.519 sort of restriction of that comment.

NOTE Confidence: 0.888377290909091

00:24:11.520 --> 00:24:12.720 The pictures are there, shown on the right.

NOTE Confidence: 0.888377290909091

00:24:12.720 --> 00:24:15.826 So this is the first realization that this

NOTE Confidence: 0.888377290909091

00:24:15.826 --> 00:24:18.358 is probably a cross linking mechanism,

NOTE Confidence: 0.888377290909091

00:24:18.360 --> 00:24:21.978 but selected to the MGMT minus background.

NOTE Confidence: 0.888377290909091

00:24:21.978 --> 00:24:25.920 She then went on and did some DDR foci assays

NOTE Confidence: 0.888377290909091

00:24:25.920 --> 00:24:28.452 and I'll just sort of gloss over because the

NOTE Confidence: 0.888377290909091

00:24:28.452 --> 00:24:30.358 time won't be able to go through all this.

NOTE Confidence: 0.888377290909091

00:24:30.360 --> 00:24:32.748 But look at the red shaded box here again.

NOTE Confidence: 0.888377290909091

00:24:32.748 --> 00:24:34.836 What was great about doing this

NOTE Confidence: 0.888377290909091

00:24:34.836 --> 00:24:36.376 isogenically modeling each MGMT

NOTE Confidence: 0.888377290909091

00:24:36.376 --> 00:24:38.360 versus mismatch repair status.

NOTE Confidence: 0.888377290909091

00:24:38.360 --> 00:24:40.440 You know the red shaded box here you

NOTE Confidence: 0.888377290909091

00:24:40.440 --> 00:24:43.040 can see basically DMSO versus TMZ.

NOTE Confidence: 0.888377290909091

00:24:43.040 --> 00:24:44.600 Again, the drug is invisible,

NOTE Confidence: 0.888377290909091

00:24:44.600 --> 00:24:45.640 damage is being induced,

NOTE Confidence: 0.888377290909091

00:24:45.640 --> 00:24:47.360 but it's not being detected.

NOTE Confidence: 0.888377290909091

00:24:47.360 --> 00:24:48.480 We can see KL50,

NOTE Confidence: 0.888377290909091

00:24:48.480 --> 00:24:50.160 now we're getting induction DNA damage.

NOTE Confidence: 0.888377290909091

00:24:50.160 --> 00:24:52.274 You can follow that kinetically over time.

NOTE Confidence: 0.888377290909091

00:24:52.280 --> 00:24:55.640 You can see or by 96 hours TMZ versus KL50.

NOTE Confidence: 0.888377290909091

00:24:55.640 --> 00:24:56.840 The yellow line,

NOTE Confidence: 0.888377290909091

00:24:56.840 --> 00:24:58.280 that's the MGMT deficient,

NOTE Confidence: 0.888377290909091

00:24:58.280 --> 00:25:00.080 double negative mismatch for deficient.

NOTE Confidence: 0.888377290909091

00:25:00.080 --> 00:25:01.634 You can see that that in the

NOTE Confidence: 0.888377290909091

00:25:01.634 --> 00:25:02.680 KL50 get induction damage.

NOTE Confidence: 0.888377290909091

00:25:02.680 --> 00:25:05.340 And then what I think is really cool is we

NOTE Confidence: 0.888377290909091

00:25:05.403 --> 00:25:08.000 then segmented the nuclei by DNA content,

NOTE Confidence: 0.888377290909091

00:25:08.000 --> 00:25:11.160 just geometric averaging and segmentation.

NOTE Confidence: 0.888377290909091

00:25:11.160 --> 00:25:13.208 You can see here this is done actually

NOTE Confidence: 0.888377290909091

00:25:13.208 --> 00:25:15.520 with the CMD when you look at G1S and G2.

NOTE Confidence: 0.888377290909091

00:25:15.520 --> 00:25:17.552 What was really cool here is you actually

NOTE Confidence: 0.888377290909091

00:25:17.552 --> 00:25:19.718 get damage in every phase in the cell cycle.

NOTE Confidence: 0.888377290909091

00:25:19.720 --> 00:25:21.911 So this actually suggests that the the

NOTE Confidence: 0.888377290909091

00:25:21.911 --> 00:25:23.766 cross linking activity that we think is

NOTE Confidence: 0.888377290909091

00:25:23.766 --> 00:25:25.679 there based on the on the comet assay

NOTE Confidence: 0.888377290909091

00:25:25.680 --> 00:25:27.360 and then the cell cycle profile suggests

NOTE Confidence: 0.888377290909091

00:25:27.360 --> 00:25:28.600 that doesn't require replication.

NOTE Confidence: 0.888377290909091

00:25:28.600 --> 00:25:30.672 Even so this is not a futile cycling

NOTE Confidence: 0.888377290909091

00:25:30.672 --> 00:25:32.438 mechanism unlike TMZ for the real DNA

NOTE Confidence: 0.888377290909091

00:25:32.438 --> 00:25:34.013 repair efficient out this is actually

NOTE Confidence: 0.888377290909091

00:25:34.013 --> 00:25:35.628 phosphor RPA which is interesting

NOTE Confidence: 0.888377290909091

00:25:35.628 --> 00:25:37.799 because our patient not be loading in

NOTE Confidence: 0.888377290909091

00:25:37.799 --> 00:25:40.321 G1 or G0 just at a conference over

NOTE Confidence: 0.888377290909091

00:25:40.321 --> 00:25:42.685 the weekend in Cancun DNA repair

NOTE Confidence: 0.888377290909091

00:25:42.685 --> 00:25:44.720 conference and someone had to do it

NOTE Confidence: 0.888377290909091

00:25:44.720 --> 00:25:46.766 and went there and actually spoke

NOTE Confidence: 0.888377290909091

00:25:46.766 --> 00:25:49.337 to some people about RPA can form at

NOTE Confidence: 0.888377290909091

00:25:49.337 --> 00:25:51.725 single strand DNA in G0G1 cells and

NOTE Confidence: 0.888377290909091

00:25:51.725 --> 00:25:53.800 so mechanistically really cool stuff.

NOTE Confidence: 0.888377290909091

00:25:53.800 --> 00:25:55.120 So now what about the chemistry.

NOTE Confidence: 0.888377290909091

00:25:55.120 --> 00:25:57.528 So going to gloss over a fair amount

NOTE Confidence: 0.888377290909091

00:25:57.528 --> 00:25:59.316 of Kingston's thesis just because of

NOTE Confidence: 0.888377290909091

00:25:59.316 --> 00:26:01.080 time today and I know it presented

NOTE Confidence: 0.888377290909091

00:26:01.136 --> 00:26:02.596 elements of the story before,

NOTE Confidence: 0.888377290909091

00:26:02.600 --> 00:26:05.504 but Kingston and Seth Herzan really

NOTE Confidence: 0.888377290909091

00:26:05.504 --> 00:26:08.596 dove in the chemistry up on sign sale

NOTE Confidence: 0.888377290909091

00:26:08.596 --> 00:26:10.772 with Susan sort of back stopping on

NOTE Confidence: 0.888377290909091

00:26:10.772 --> 00:26:12.677 the DNA repair mechanistic studies.

NOTE Confidence: 0.888377290909091

00:26:12.680 --> 00:26:14.510 And this is basically what they

NOTE Confidence: 0.888377290909091

00:26:14.510 --> 00:26:16.000 figured out and they taught me to

NOTE Confidence: 0.888377290909091

00:26:16.000 --> 00:26:17.320 say when you talk about chemistry,

NOTE Confidence: 0.888377290909091

00:26:17.320 --> 00:26:19.798 say things like 4A4B and 4C,

NOTE Confidence: 0.888377290909091

00:26:19.800 --> 00:26:21.495 very chemistry savvy.

NOTE Confidence: 0.888377290909091

00:26:21.495 --> 00:26:23.755 SO4A is the molecule.

NOTE Confidence: 0.888377290909091

00:26:23.760 --> 00:26:25.839 So Kale 50 is a fluoro ethyl

NOTE Confidence: 0.888377290909091

00:26:25.839 --> 00:26:27.864 instead of a methyl and so Team

NOTE Confidence: 0.888377290909091

00:26:27.864 --> 00:26:29.112 Z would have the methyl here.

NOTE Confidence: 0.888377290909091

00:26:29.120 --> 00:26:31.535 Very simple but elegant change

NOTE Confidence: 0.888377290909091

00:26:31.535 --> 00:26:32.984 that fundamentally changes

NOTE Confidence: 0.888377290909091

00:26:32.984 --> 00:26:35.440 the way this molecule acts.

NOTE Confidence: 0.888377290909091

00:26:35.440 --> 00:26:37.491 You get a ring opening which then

NOTE Confidence: 0.888377290909091

00:26:37.491 --> 00:26:38.817 creates this fluoroethyl diazonium

NOTE Confidence: 0.888377290909091

00:26:38.817 --> 00:26:40.757 which is this reactive intermediate.

NOTE Confidence: 0.846847728214286

00:26:40.760 --> 00:26:42.385 This fluoroethyl diazonium then attaches

NOTE Confidence: 0.846847728214286

00:26:42.385 --> 00:26:44.881 to the O six position of guanine and

00:26:44.881 --> 00:26:46.785 what Kingston and and Seth and others

00:26:46.846 --> 00:26:48.838 have shown is that MGMT can remove it.

00:26:48.840 --> 00:26:51.129 So the old name for MGMT is

00:26:51.129 --> 00:26:52.440 alkyl guanine transfer AGT.

00:26:52.440 --> 00:26:54.360 So it's not just a methyl

00:26:54.360 --> 00:26:55.320 guanine methyl transferase,

00:26:55.320 --> 00:26:57.880 even though we think of it just as

00:26:57.880 --> 00:27:00.280 MGMTMGMT can remove this pretty readily.

00:27:00.280 --> 00:27:01.780 But what what's fascinating is

00:27:01.780 --> 00:27:03.280 Kingston pulled out some belief

00:27:03.332 --> 00:27:04.640 papers from the 80s or 90s.

00:27:04.640 --> 00:27:06.495 If I remember where he found some

00:27:06.495 --> 00:27:08.078 oligo studies where they looked at

00:27:08.078 --> 00:27:09.793 fluoro ethyl addicts of the O 6:00

00:27:09.846 --> 00:27:11.421 and had some literature precedents

00:27:11.421 --> 00:27:12.996 that it was actually forming

NOTE Confidence: 0.846847728214286

00:27:13.000 --> 00:27:14.384 an ethanol guanine intermediate

NOTE Confidence: 0.846847728214286

00:27:14.384 --> 00:27:16.114 which would be highly unstable,

NOTE Confidence: 0.846847728214286

00:27:16.120 --> 00:27:17.628 could possibly cross link.

NOTE Confidence: 0.846847728214286

00:27:17.628 --> 00:27:18.759 And that's exactly,

NOTE Confidence: 0.846847728214286

00:27:18.760 --> 00:27:20.223 you know you know blowing past a

NOTE Confidence: 0.846847728214286

00:27:20.223 --> 00:27:22.380 lot of the work that that he and the

NOTE Confidence: 0.846847728214286

00:27:22.380 --> 00:27:23.959 Horizon Laboratory did to prove this,

NOTE Confidence: 0.846847728214286

00:27:23.960 --> 00:27:25.796 but essentially show with a very

NOTE Confidence: 0.846847728214286

00:27:25.796 --> 00:27:27.989 slow T 1/2 this actually forms

NOTE Confidence: 0.846847728214286

00:27:27.989 --> 00:27:29.258 ethanoguanine intermediate molecule

NOTE Confidence: 0.846847728214286

00:27:29.258 --> 00:27:32.181 6 and then cross links with this

NOTE Confidence: 0.846847728214286

00:27:32.181 --> 00:27:34.168 adjacent cytosine as you can imagine.

NOTE Confidence: 0.846847728214286

00:27:34.168 --> 00:27:35.678 Now this is MGMT dependence.

NOTE Confidence: 0.846847728214286

00:27:35.680 --> 00:27:37.367 So if you don't have MGMT you

NOTE Confidence: 0.846847728214286

00:27:37.367 --> 00:27:38.440 you have the slow,

NOTE Confidence: 0.846847728214286

00:27:38.440 --> 00:27:42.745 slow reactive process but not

NOTE Confidence: 0.846847728214286

00:27:42.745 --> 00:27:45.120 dependent on mismatch repair activity.

NOTE Confidence: 0.846847728214286

00:27:45.120 --> 00:27:48.277 So very, very nice mechanistic studies there.

NOTE Confidence: 0.846847728214286

00:27:48.280 --> 00:27:49.435 But now I sort of want to,

NOTE Confidence: 0.846847728214286

00:27:49.440 --> 00:27:50.042 you know,

NOTE Confidence: 0.846847728214286

00:27:50.042 --> 00:27:52.149 step back to the clinical data because

NOTE Confidence: 0.846847728214286

00:27:52.149 --> 00:27:54.184 this is something that had always

NOTE Confidence: 0.846847728214286

00:27:54.184 --> 00:27:56.460 vexed me even during residency and as

NOTE Confidence: 0.846847728214286

00:27:56.460 --> 00:27:58.518 an attending is as I showed you earlier,

NOTE Confidence: 0.846847728214286

00:27:58.520 --> 00:28:00.424 if you look at the Walker trial in 1978,

NOTE Confidence: 0.846847728214286

00:28:00.424 --> 00:28:01.320 well they, you know,

NOTE Confidence: 0.846847728214286

00:28:01.320 --> 00:28:04.274 they did an alculator, they used BCNU.

NOTE Confidence: 0.846847728214286

00:28:04.280 --> 00:28:05.918 And so why didn't a cross

NOTE Confidence: 0.846847728214286

00:28:05.918 --> 00:28:07.320 linking Alculator work back then?

NOTE Confidence: 0.846847728214286

00:28:07.320 --> 00:28:08.400 You know, could it be,

NOTE Confidence: 0.846847728214286

00:28:08.400 --> 00:28:09.516 you know, you know what what,

NOTE Confidence: 0.846847728214286

00:28:09.520 --> 00:28:11.400 what are the factors that the trial was

NOTE Confidence: 0.846847728214286

00:28:11.400 --> 00:28:12.756 negative because the Stoop trial in

NOTE Confidence: 0.846847728214286

00:28:12.756 --> 00:28:14.480 the far right was positive with Alculator.

NOTE Confidence: 0.846847728214286

00:28:14.480 --> 00:28:16.720 But I told you it's a mono functional

NOTE Confidence: 0.846847728214286

00:28:16.720 --> 00:28:19.000 alculator that doesn't cross link.

NOTE Confidence: 0.846847728214286

00:28:19.000 --> 00:28:20.620 And we actually spent a lot of time I

NOTE Confidence: 0.846847728214286

00:28:20.620 --> 00:28:22.237 think my first five years in attending,

NOTE Confidence: 0.846847728214286

00:28:22.240 --> 00:28:24.200 I was delving the literature.

NOTE Confidence: 0.846847728214286

00:28:24.200 --> 00:28:25.845 I was obsessed with the idea that

NOTE Confidence: 0.846847728214286

00:28:25.845 --> 00:28:27.601 Oh well it's because BCNU is given

NOTE Confidence: 0.846847728214286

00:28:27.601 --> 00:28:29.564 every six weeks and so it's not

NOTE Confidence: 0.846847728214286

00:28:29.564 --> 00:28:31.196 given during fractionated radiation.

NOTE Confidence: 0.846847728214286

00:28:31.200 --> 00:28:33.375 So they missed the opportunity

NOTE Confidence: 0.846847728214286

00:28:33.375 --> 00:28:34.680 for radio sensitization.

NOTE Confidence: 0.846847728214286

00:28:34.680 --> 00:28:36.075 We spend a lot of grant money on that,

00:28:36.080 --> 00:28:37.184 not true,

00:28:37.184 --> 00:28:39.097 doesn't really matter and

00:28:39.097 --> 00:28:40.639 so we'll we'll go into that.

00:28:40.640 --> 00:28:42.103 But if you actually look at the

00:28:42.103 --> 00:28:43.549 chemistry and I really you know

00:28:43.549 --> 00:28:45.097 thank the trainees for teaching Seth

00:28:45.097 --> 00:28:46.599 Roson for teaching me this stuff.

00:28:46.600 --> 00:28:48.462 But if you look at the these

00:28:48.462 --> 00:28:50.584 reactive chlorine, these are very,

00:28:50.584 --> 00:28:53.224 very efficient non selective cross

00:28:53.224 --> 00:28:55.517 linking sort of payloads as we'll call them.

00:28:55.520 --> 00:28:57.200 Compare that with this methyl here,

00:28:57.200 --> 00:28:59.500 which is essentially non cross

00:28:59.500 --> 00:29:00.954 linking MGMT dependent.

00:29:00.954 --> 00:29:03.439 Futile cycling is the mechanism.

00:29:03.440 --> 00:29:05.240 And actually as I we started to dive

NOTE Confidence: 0.846847728214286

00:29:05.240 --> 00:29:06.641 into this literature around the

NOTE Confidence: 0.846847728214286

00:29:06.641 --> 00:29:08.435 time that we started this project

NOTE Confidence: 0.846847728214286

00:29:08.440 --> 00:29:09.640 started going deeper

NOTE Confidence: 0.86257736

00:29:10.400 --> 00:29:11.720 and it turns out between

NOTE Confidence: 0.69353630375

00:29:11.720 --> 00:29:13.911 and actually became friends with Rose Stoop

NOTE Confidence: 0.69353630375

00:29:13.911 --> 00:29:16.398 who's now a mentor and A and a friend.

NOTE Confidence: 0.69353630375

00:29:16.400 --> 00:29:17.945 And actually he talked to

NOTE Confidence: 0.69353630375

00:29:17.945 --> 00:29:19.880 to Roger about this as well.

NOTE Confidence: 0.69353630375

00:29:19.880 --> 00:29:21.784 There was a in between around the time

NOTE Confidence: 0.69353630375

00:29:21.784 --> 00:29:24.294 of BC and U and before the Stoop trial

NOTE Confidence: 0.69353630375

00:29:24.294 --> 00:29:25.899 there were actually other tamizolamide

NOTE Confidence: 0.69353630375

00:29:25.899 --> 00:29:28.011 precursors that were tested in the

NOTE Confidence: 0.69353630375

00:29:28.011 --> 00:29:30.202 clinic that kind of give a little bit

NOTE Confidence: 0.69353630375

00:29:30.202 --> 00:29:32.200 of sense of what likely happened.

NOTE Confidence: 0.69353630375

00:29:32.200 --> 00:29:34.513 So DTICI think many of you may know is

NOTE Confidence: 0.69353630375

00:29:34.513 --> 00:29:36.918 the carbazine we use this in Melanoma,

NOTE Confidence: 0.69353630375

00:29:36.920 --> 00:29:39.244 but there's actually a drug called azolastone

NOTE Confidence: 0.69353630375

00:29:39.244 --> 00:29:40.984 that was developed before tamizolamide.

NOTE Confidence: 0.69353630375

00:29:40.984 --> 00:29:43.960 And I'll just have you note there the,

NOTE Confidence: 0.69353630375

00:29:43.960 --> 00:29:44.700 the chlorine,

NOTE Confidence: 0.69353630375

00:29:44.700 --> 00:29:46.550 the similarity here very reactive

NOTE Confidence: 0.69353630375

00:29:46.550 --> 00:29:48.666 drug and this was actually brought

NOTE Confidence: 0.69353630375

00:29:48.666 --> 00:29:50.871 into the into phase one and two

NOTE Confidence: 0.69353630375

00:29:50.937 --> 00:29:52.513 clinical trials before temozoline

NOTE Confidence: 0.69353630375

00:29:52.513 --> 00:29:54.877 made its debut into the clinic.

NOTE Confidence: 0.69353630375

00:29:54.880 --> 00:29:56.077 And actually just to sort of get,

NOTE Confidence: 0.69353630375

00:29:56.080 --> 00:29:57.158 you know, going to the rabbit hole,

NOTE Confidence: 0.69353630375

00:29:57.160 --> 00:30:00.600 please not TMI or too much information here,

NOTE Confidence: 0.69353630375

00:30:00.600 --> 00:30:02.769 but this drug was made by actually a post

NOTE Confidence: 0.69353630375

00:30:02.769 --> 00:30:05.157 grad named Robert Stone and Aston University,

NOTE Confidence: 0.69353630375

00:30:05.160 --> 00:30:07.836 Aston University and in the UK,

NOTE Confidence: 0.69353630375

00:30:07.840 --> 00:30:08.928 hence the name Azelastone.

NOTE Confidence: 0.69353630375

00:30:08.928 --> 00:30:11.033 And it has this sort of chlorine

NOTE Confidence: 0.69353630375

00:30:11.033 --> 00:30:13.078 reactivity that I mentioned earlier.

NOTE Confidence: 0.69353630375

00:30:13.080 --> 00:30:14.340 And again, very interesting

NOTE Confidence: 0.69353630375

00:30:14.340 --> 00:30:15.915 because the molecule at Kingston,

NOTE Confidence: 0.69353630375

00:30:15.920 --> 00:30:17.915 it actually looks quite similar to this,

NOTE Confidence: 0.69353630375

00:30:17.920 --> 00:30:18.150 right,

NOTE Confidence: 0.69353630375

00:30:18.150 --> 00:30:19.760 But it only only differs by flooring.

NOTE Confidence: 0.69353630375

00:30:19.760 --> 00:30:20.976 The chemist will say,

NOTE Confidence: 0.69353630375

00:30:20.976 --> 00:30:22.800 well this is important because flooring

NOTE Confidence: 0.69353630375

00:30:22.852 --> 00:30:25.120 is actually a very poor leaving group

NOTE Confidence: 0.69353630375

00:30:25.120 --> 00:30:27.846 and some of us remember that from

NOTE Confidence: 0.69353630375

00:30:27.846 --> 00:30:29.802 college level chemistry and when

NOTE Confidence: 0.69353630375

00:30:29.802 --> 00:30:31.488 Robert Stone made this molecule they

NOTE Confidence: 0.69353630375

00:30:31.488 --> 00:30:32.840 actually tested this in animals.

NOTE Confidence: 0.69353630375

00:30:32.840 --> 00:30:35.180 They actually flatlined a number

NOTE Confidence: 0.69353630375

00:30:35.180 --> 00:30:36.716 of different tumor models.

NOTE Confidence: 0.69353630375

00:30:36.716 --> 00:30:38.504 And actually this book that that

NOTE Confidence: 0.69353630375

00:30:38.504 --> 00:30:40.120 Kings and I read about this,

NOTE Confidence: 0.69353630375

00:30:40.120 --> 00:30:41.974 they actually made a poster called

NOTE Confidence: 0.69353630375

00:30:41.974 --> 00:30:43.808 Azolastone the movie because they were

NOTE Confidence: 0.69353630375

00:30:43.808 --> 00:30:45.712 going to cure cancer with this molecule.

NOTE Confidence: 0.69353630375

00:30:45.720 --> 00:30:48.100 This was going to be the alkylator

NOTE Confidence: 0.69353630375

00:30:48.100 --> 00:30:49.120 of all alkylators.

NOTE Confidence: 0.69353630375

00:30:49.120 --> 00:30:50.608 But alas it went into multiple

NOTE Confidence: 0.69353630375

00:30:50.608 --> 00:30:51.352 phase one trials.

NOTE Confidence: 0.69353630375

00:30:51.360 --> 00:30:52.932 The drug was also called Monozola

NOTE Confidence: 0.69353630375

00:30:52.932 --> 00:30:54.740 line and actually failed in the mid

NOTE Confidence: 0.69353630375

00:30:54.740 --> 00:30:56.156 80s because of dose living toxicity.

NOTE Confidence: 0.69353630375

00:30:56.160 --> 00:30:57.952 They tried multiple scheduling

NOTE Confidence: 0.69353630375

00:30:57.952 --> 00:30:59.635 regimens and and and then soon

NOTE Confidence: 0.69353630375

00:30:59.635 --> 00:31:01.240 after Roger Stoop came on board,

NOTE Confidence: 0.69353630375

00:31:01.240 --> 00:31:02.842 picked up TMZ and then ran

NOTE Confidence: 0.69353630375

00:31:02.842 --> 00:31:04.320 that into the stoop trial.

NOTE Confidence: 0.69353630375

00:31:04.320 --> 00:31:06.016 And so it's fascinating for me when we

NOTE Confidence: 0.69353630375

00:31:06.016 --> 00:31:07.501 think about this and this competitors

NOTE Confidence: 0.69353630375

00:31:07.501 --> 00:31:09.235 made this this really funny poster to

NOTE Confidence: 0.69353630375

00:31:09.235 --> 00:31:10.976 make fun of them for failing I guess

NOTE Confidence: 0.69353630375

00:31:10.976 --> 00:31:13.598 back in the day it was a lot more fun

NOTE Confidence: 0.69353630375

00:31:13.600 --> 00:31:15.119 And if you think about it clinically,

NOTE Confidence: 0.69353630375

00:31:15.120 --> 00:31:17.213 so in the clinic we use lomastine

NOTE Confidence: 0.69353630375

00:31:17.213 --> 00:31:19.219 to salvage patients when they failed

NOTE Confidence: 0.69353630375

00:31:19.219 --> 00:31:21.405 team azolamide or if they just you

NOTE Confidence: 0.69353630375

00:31:21.405 --> 00:31:22.811 know recurrent glioma patients and

NOTE Confidence: 0.69353630375

00:31:22.811 --> 00:31:24.499 again not a chemist but the red shaded

NOTE Confidence: 0.69353630375

00:31:24.499 --> 00:31:25.999 box will show you the chlorine.

NOTE Confidence: 0.69353630375

00:31:26.000 --> 00:31:28.640 Again similar warhead here,

NOTE Confidence: 0.69353630375

00:31:28.640 --> 00:31:30.878 highly reactive and interestingly even

NOTE Confidence: 0.69353630375

00:31:30.878 --> 00:31:32.714 though we salvage patients with Lumosity,

NOTE Confidence: 0.69353630375

00:31:32.720 --> 00:31:34.120 it really has no survival

NOTE Confidence: 0.69353630375

00:31:34.120 --> 00:31:35.240 benefit in recurrent glioma.

NOTE Confidence: 0.69353630375

00:31:35.240 --> 00:31:36.580 This is something that we

NOTE Confidence: 0.69353630375

00:31:36.580 --> 00:31:37.920 struggled with for a while.

NOTE Confidence: 0.69353630375

00:31:37.920 --> 00:31:39.816 And so I would argue that or we

NOTE Confidence: 0.69353630375

00:31:39.816 --> 00:31:41.595 would argue rather that this is

NOTE Confidence: 0.69353630375

00:31:41.595 --> 00:31:43.155 again a therapeutic index play.

NOTE Confidence: 0.763178658

00:31:43.160 --> 00:31:46.280 The slow cross linking activity of

NOTE Confidence: 0.763178658

00:31:46.280 --> 00:31:48.926 KL50 with the MGMT dependency sort

NOTE Confidence: 0.763178658

00:31:48.926 --> 00:31:50.894 of possibly makes it the the best of

NOTE Confidence: 0.763178658

00:31:50.894 --> 00:31:53.016 both worlds in terms of having more

NOTE Confidence: 0.763178658

00:31:53.016 --> 00:31:55.156 DNA damage that's MMR independence.

NOTE Confidence: 0.763178658

00:31:55.160 --> 00:31:58.030 It doesn't fall prey to a mismatch

NOTE Confidence: 0.763178658

00:31:58.030 --> 00:32:00.276 permutation which I think is the key.

NOTE Confidence: 0.763178658

00:32:00.280 --> 00:32:01.837 So to get at this we looked at this,

NOTE Confidence: 0.763178658

00:32:01.840 --> 00:32:03.424 we went back from serve clinical

NOTE Confidence: 0.763178658

00:32:03.424 --> 00:32:05.277 observations and went back to the Herzon

NOTE Confidence: 0.763178658

00:32:05.277 --> 00:32:06.527 laboratory and also our laboratory

NOTE Confidence: 0.763178658

00:32:06.527 --> 00:32:08.200 to look at this little more deep

NOTE Confidence: 0.763178658

00:32:08.200 --> 00:32:10.778 because again this is all just sort of

NOTE Confidence: 0.763178658

00:32:10.778 --> 00:32:12.906 hearsay without some preclinical data.

NOTE Confidence: 0.763178658

00:32:12.906 --> 00:32:15.237 And so Eric Kuzman and and Kingston

NOTE Confidence: 0.763178658

00:32:15.237 --> 00:32:17.206 and folks in Herzon lab actually

NOTE Confidence: 0.763178658

00:32:17.206 --> 00:32:19.080 then measured the rate of ICO.

NOTE Confidence: 0.763178658

00:32:19.080 --> 00:32:21.800 Interesting cross link formation

NOTE Confidence: 0.763178658

00:32:21.800 --> 00:32:23.348 using a very nice elegant technique

NOTE Confidence: 0.763178658

00:32:23.348 --> 00:32:25.405 which I I won't go into because I

NOTE Confidence: 0.763178658

00:32:25.405 --> 00:32:27.117 couldn't do justice to us this was

68

NOTE Confidence: 0.763178658

00:32:27.117 --> 00:32:28.838 just is it hopefully about to be

NOTE Confidence: 0.763178658

00:32:28.838 --> 00:32:30.320 published and deposited in chem RVX.

NOTE Confidence: 0.763178658

00:32:30.320 --> 00:32:31.928 We can see here looking at the floor

NOTE Confidence: 0.763178658

00:32:31.928 --> 00:32:33.437 out the with this cross linking

NOTE Confidence: 0.763178658

00:32:33.440 --> 00:32:35.484 assay in vitro you can see indeed

NOTE Confidence: 0.763178658

00:32:35.484 --> 00:32:37.439 very slow cross linking activity.

NOTE Confidence: 0.763178658

00:32:37.440 --> 00:32:40.080 OK, so if you have MGMT,

NOTE Confidence: 0.763178658

00:32:40.080 --> 00:32:42.600 arguably if a normal solo has MGMT,

NOTE Confidence: 0.763178658

00:32:42.600 --> 00:32:45.040 there will be time for it to pluck that off.

NOTE Confidence: 0.763178658

00:32:45.040 --> 00:32:47.720 By contrast, if you look at the chloroethyl,

NOTE Confidence: 0.763178658

00:32:47.720 --> 00:32:50.424 that's the mitozole, my version, or the CCNU.

NOTE Confidence: 0.763178658

00:32:50.424 --> 00:32:53.346 Arguably you can see very rapid cross

NOTE Confidence: 0.763178658

00:32:53.346 --> 00:32:56.192 linking activities T 1/2 of 6.3 hours.

NOTE Confidence: 0.763178658

00:32:56.192 --> 00:32:58.240 So this likely is consistent with the idea

NOTE Confidence: 0.763178658

00:32:58.295 --> 00:33:00.276 that if you're cross linking too quickly,

NOTE Confidence: 0.763178658

00:33:00.280 --> 00:33:01.440 you're not going to have.

NOTE Confidence: 0.763178658

00:33:01.440 --> 00:33:02.958 Even if MGMT can get to

NOTE Confidence: 0.763178658

00:33:02.958 --> 00:33:04.200 that lesion and remove it,

NOTE Confidence: 0.763178658

00:33:04.200 --> 00:33:05.929 it's unlikely to have as much of

NOTE Confidence: 0.763178658

00:33:05.929 --> 00:33:07.225 A therapeutic index as something

NOTE Confidence: 0.763178658

00:33:07.225 --> 00:33:08.996 like a fluoroethyl that has a very,

NOTE Confidence: 0.763178658

00:33:09.000 --> 00:33:10.600 very slow T 1/2.

NOTE Confidence: 0.763178658

00:33:10.600 --> 00:33:11.400 And again,

NOTE Confidence: 0.763178658

00:33:11.400 --> 00:33:13.185 I'll I'll note that this is really

NOTE Confidence: 0.763178658

00:33:13.185 --> 00:33:14.560 the 1st for this KL50.

NOTE Confidence: 0.763178658

00:33:14.560 --> 00:33:16.832 It's the first time this molecule has really

NOTE Confidence: 0.763178658

00:33:16.832 --> 00:33:20.160 ever been described by Kingston and Susan.

NOTE Confidence: 0.763178658

00:33:20.160 --> 00:33:21.899 So then we brought that chemistry

NOTE Confidence: 0.763178658

00:33:21.899 --> 00:33:23.693 observation back to our laboratory and

NOTE Confidence: 0.763178658

00:33:23.693 --> 00:33:25.715 we just like to do the thing we do,

NOTE Confidence: 0.763178658

00:33:25.720 --> 00:33:27.142 which is cloning survival assays over

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NOTE Confidence: 0.763178658

00:33:27.142 --> 00:33:28.998 and over again in Isagenix cell lines.

NOTE Confidence: 0.763178658

00:33:29.000 --> 00:33:30.280 Some people hate us when we do this,

NOTE Confidence: 0.763178658

00:33:30.280 --> 00:33:32.480 but we think it's important.

NOTE Confidence: 0.763178658

00:33:32.480 --> 00:33:33.180 So look at TMZ.

NOTE Confidence: 0.763178658

00:33:33.180 --> 00:33:34.480 I've walked you through that date again.

NOTE Confidence: 0.763178658

00:33:34.480 --> 00:33:36.328 The methyl group futile cycling, right?

NOTE Confidence: 0.763178658

00:33:36.328 --> 00:33:38.168 The green line becomes invisible

NOTE Confidence: 0.763178658

00:33:38.168 --> 00:33:39.640 with the yellow line.

NOTE Confidence: 0.763178658

00:33:39.640 --> 00:33:40.918 Then look at kale 50 again,

NOTE Confidence: 0.763178658

00:33:40.920 --> 00:33:42.360 very nice therapeutic index here.

NOTE Confidence: 0.763178658

00:33:42.360 --> 00:33:43.920 You're going to very high doses,

NOTE Confidence: 0.763178658

00:33:43.920 --> 00:33:46.678 200 micromolar kale 50 and you're not

NOTE Confidence: 0.763178658

00:33:46.678 --> 00:33:48.999 killing anything that has MGMT intact.

NOTE Confidence: 0.763178658

00:33:49.000 --> 00:33:51.450 Now let's compare CC and U and

NOTE Confidence: 0.763178658

00:33:51.450 --> 00:33:53.184 mitozolamide and indeed you can

NOTE Confidence: 0.763178658

00:33:53.184 --> 00:33:55.548 look at azolastone and you you do

NOTE Confidence: 0.763178658

00:33:55.548 --> 00:33:57.624 get MMR independent cell killing.

NOTE Confidence: 0.763178658

00:33:57.624 --> 00:33:59.954 But it's that therapeutic index.

NOTE Confidence: 0.763178658

00:33:59.960 --> 00:34:01.983 We would argue it's it's with both

NOTE Confidence: 0.763178658

00:34:01.983 --> 00:34:04.357 myzolamide and CC and U very potent alkalis.

NOTE Confidence: 0.763178658

00:34:04.360 --> 00:34:05.608 But that window is narrow and

NOTE Confidence: 0.763178658

00:34:05.608 --> 00:34:06.232 some people say,

NOTE Confidence: 0.763178658

00:34:06.240 --> 00:34:08.165 well then why don't you just dose

NOTE Confidence: 0.763178658

00:34:08.165 --> 00:34:10.019 the patients 150 micromolar 100.

NOTE Confidence: 0.763178658

00:34:10.019 --> 00:34:11.318 It's not easy.

NOTE Confidence: 0.763178658

00:34:11.320 --> 00:34:13.399 As many of you know in a clinical trial

NOTE Confidence: 0.763178658

00:34:13.399 --> 00:34:15.261 getting those doses right across a

NOTE Confidence: 0.763178658

00:34:15.261 --> 00:34:16.836 very heterogeneous group of patients,

NOTE Confidence: 0.90533006125

00:34:16.840 --> 00:34:18.165 you're going to need this

NOTE Confidence: 0.90533006125

00:34:18.165 --> 00:34:18.960 wider therapeutic index.

NOTE Confidence: 0.90533006125

00:34:18.960 --> 00:34:19.716 So it's red in the green.

NOTE Confidence: 0.90533006125

00:34:19.720 --> 00:34:22.600 Curves need to be far apart.

NOTE Confidence: 0.90533006125

00:34:22.600 --> 00:34:24.220 So just to summarize for

NOTE Confidence: 0.90533006125

00:34:24.220 --> 00:34:25.840 this part of the talk,

NOTE Confidence: 0.90533006125

00:34:25.840 --> 00:34:27.317 you know what we believe is happening.

NOTE Confidence: 0.90533006125

00:34:27.320 --> 00:34:29.385 This is actually a slide summary from

NOTE Confidence: 0.90533006125

00:34:29.385 --> 00:34:31.449 Susan Gable who now has her own lab

NOTE Confidence: 0.90533006125

00:34:31.449 --> 00:34:33.479 here at Yale looking at tamozolamide.

NOTE Confidence: 0.90533006125

00:34:33.479 --> 00:34:34.838 Again, futile cycling,

NOTE Confidence: 0.90533006125

00:34:34.840 --> 00:34:36.770 removed by A rapidly removed

NOTE Confidence: 0.90533006125

00:34:36.770 --> 00:34:38.314 by MGMT expressing cells.

NOTE Confidence: 0.90533006125

00:34:38.320 --> 00:34:42.340 Futile cycling then induces tumor

NOTE Confidence: 0.90533006125

00:34:42.340 --> 00:34:44.720 cell death in the absence of MGMT,

NOTE Confidence: 0.90533006125

00:34:44.720 --> 00:34:46.500 but requires MMR proficiency

NOTE Confidence: 0.90533006125

00:34:46.500 --> 00:34:48.280 when you knockout MMR.

NOTE Confidence: 0.90533006125

00:34:48.280 --> 00:34:49.576 The lesion,

NOTE Confidence: 0.90533006125

00:34:49.576 --> 00:34:51.520 essentially invisible mitazolamide,

NOTE Confidence: 0.90533006125

00:34:51.520 --> 00:34:52.312 the chloroethyl,

NOTE Confidence: 0.90533006125

00:34:52.312 --> 00:34:55.480 So very fast acting forms at Athena Guanine.

NOTE Confidence: 0.90533006125

00:34:55.480 --> 00:34:59.020 OK and is MMR independent but

NOTE Confidence: 0.90533006125

00:34:59.020 --> 00:35:02.937 has an MGM is is less dependent

NOTE Confidence: 0.90533006125

00:35:02.937 --> 00:35:05.679 on MGMT status and then KL50,

NOTE Confidence: 0.90533006125

00:35:05.680 --> 00:35:07.824 which we would say is sort of the

NOTE Confidence: 0.90533006125

00:35:07.824 --> 00:35:09.394 possibly the Goldilocks phenomenon

NOTE Confidence: 0.90533006125

00:35:09.394 --> 00:35:11.637 but has has the best of both worlds.

NOTE Confidence: 0.90533006125

00:35:11.640 --> 00:35:14.556 OK and I'll just show you one example.

NOTE Confidence: 0.90533006125

00:35:14.560 --> 00:35:15.718 Because this date has been published,

NOTE Confidence: 0.90533006125

00:35:15.720 --> 00:35:17.484 I'd like to move on to sort of some

NOTE Confidence: 0.90533006125

00:35:17.484 --> 00:35:19.440 of our more recent unpublished work.

NOTE Confidence: 0.90533006125

00:35:19.440 --> 00:35:20.608 This works incredibly well.

NOTE Confidence: 0.90533006125

00:35:20.608 --> 00:35:22.758 We sent this date we sent these

NOTE Confidence: 0.90533006125

00:35:22.758 --> 00:35:25.145 molecules to Jan Sarcoria the at the

NOTE Confidence: 0.90533006125

00:35:25.145 --> 00:35:27.027 translational brain tumor Center at the

NOTE Confidence: 0.90533006125

00:35:27.027 --> 00:35:28.880 Mayo Clinic and asked them to compare.

NOTE Confidence: 0.90533006125

00:35:28.880 --> 00:35:30.836 Let's look at TMZ lomastine and

NOTE Confidence: 0.90533006125

00:35:30.836 --> 00:35:33.109 KL50 and let's look at intracranial

NOTE Confidence: 0.90533006125

00:35:33.109 --> 00:35:35.349 GBM xenographs that have acquired

NOTE Confidence: 0.90533006125

00:35:35.349 --> 00:35:37.788 this this aggressive phenotype MGMT

NOTE Confidence: 0.90533006125

00:35:37.788 --> 00:35:39.836 science mismatch period efficient

NOTE Confidence: 0.90533006125

00:35:39.840 --> 00:35:41.885 and you can see here on the left as

NOTE Confidence: 0.90533006125

00:35:41.885 --> 00:35:43.355 expected and this is aggressive model.

NOTE Confidence: 0.90533006125

00:35:43.360 --> 00:35:45.440 All the animals 30 days the vehicle

NOTE Confidence: 0.90533006125

00:35:45.440 --> 00:35:47.240 are are dead Temazolamide is invisible

NOTE Confidence: 0.90533006125

00:35:47.240 --> 00:35:48.738 under these conditions lomusting we

NOTE Confidence: 0.90533006125

00:35:48.738 --> 00:35:50.705 wouldn't expect it to work as that

NOTE Confidence: 0.90533006125

00:35:50.755 --> 00:35:52.837 therapeutic index issue in this experiment,

NOTE Confidence: 0.90533006125

00:35:52.840 --> 00:35:54.800 no efficacy here on the right though.

NOTE Confidence: 0.90533006125

00:35:54.800 --> 00:35:56.408 You know we've been doing these

NOTE Confidence: 0.90533006125

00:35:56.408 --> 00:35:57.927 types of experiments for about 12

NOTE Confidence: 0.90533006125

00:35:57.927 --> 00:35:59.864 years in our own lab and pretty

NOTE Confidence: 0.90533006125

00:35:59.864 --> 00:36:01.280 remarkable efficacy here.

NOTE Confidence: 0.90533006125

00:36:01.280 --> 00:36:03.555 This is an 8 fold improvement in

NOTE Confidence: 0.90533006125

00:36:03.555 --> 00:36:05.235 overall survival as a monotherapy

NOTE Confidence: 0.90533006125

00:36:05.235 --> 00:36:07.155 or again TMZ has no effect.

NOTE Confidence: 0.90533006125

00:36:07.160 --> 00:36:07.710 So really,

NOTE Confidence: 0.90533006125

00:36:07.710 --> 00:36:09.910 really excited about the in vivo data that

NOTE Confidence: 0.90533006125

00:36:09.963 --> 00:36:12.035 really is building the story of of this,

NOTE Confidence: 0.90533006125

00:36:12.040 --> 00:36:14.752 this MGMT dependency and the mismatch

NOTE Confidence: 0.90533006125

00:36:14.752 --> 00:36:16.560 repair independence could have

NOTE Confidence: 0.90533006125

00:36:16.632 --> 00:36:18.972 some some potential therapeutic

NOTE Confidence: 0.90533006125

00:36:18.972 --> 00:36:20.424 implications because that's sort of

NOTE Confidence: 0.90533006125

00:36:20.424 --> 00:36:21.720 a summary of the initial discovery.

NOTE Confidence: 0.90533006125

00:36:21.720 --> 00:36:24.079 So where are we going from here.

NOTE Confidence: 0.90533006125

00:36:24.080 --> 00:36:25.578 So one of the things that we're

NOTE Confidence: 0.90533006125

00:36:25.578 --> 00:36:27.115 interested in is it turns out

NOTE Confidence: 0.90533006125

00:36:27.115 --> 00:36:28.239 that MGMT promoter methylation,

NOTE Confidence: 0.90533006125

00:36:28.240 --> 00:36:29.680 we only talk about that in

NOTE Confidence: 0.90533006125

00:36:29.680 --> 00:36:30.640 like CNS tumor board.

NOTE Confidence: 0.90533006125

00:36:30.640 --> 00:36:32.400 We never like to think about this that

NOTE Confidence: 0.90533006125

00:36:32.400 --> 00:36:34.198 MGMT could be silenced in other cancers.

NOTE Confidence: 0.90533006125

00:36:34.200 --> 00:36:37.755 It turns out that subsets of all cancers AML,

NOTE Confidence: 0.90533006125

00:36:37.760 --> 00:36:38.107 colon,

NOTE Confidence: 0.90533006125

00:36:38.107 --> 00:36:39.148 sarcoma and lung,

NOTE Confidence: 0.90533006125

00:36:39.148 --> 00:36:41.230 they all actually have silence for

NOTE Confidence: 0.90533006125

00:36:41.292 --> 00:36:43.142 whatever reason have have subsets

NOTE Confidence: 0.90533006125

00:36:43.142 --> 00:36:44.992 of cancers have silence MGMT.

NOTE Confidence: 0.90533006125

00:36:45.000 --> 00:36:45.840 And so get at this.

NOTE Confidence: 0.90533006125

00:36:45.840 --> 00:36:48.157 The team did a use the Prism

NOTE Confidence: 0.90533006125

00:36:48.157 --> 00:36:50.080 screening platform up at the broad.

NOTE Confidence: 0.90533006125

00:36:50.080 --> 00:36:51.056 I'd encourage anyone who's

NOTE Confidence: 0.90533006125

00:36:51.056 --> 00:36:52.276 interested in using this platform.

NOTE Confidence: 0.90533006125

00:36:52.280 --> 00:36:55.717 It's a really cool pooled bar coded

NOTE Confidence: 0.90533006125

00:36:55.720 --> 00:36:58.692 drug screen $10,000 a molecule and

NOTE Confidence: 0.90533006125

00:36:58.692 --> 00:37:00.741 you actually compared to some of their

NOTE Confidence: 0.90533006125

00:37:00.741 --> 00:37:02.785 existing data and what not and it's

NOTE Confidence: 0.90533006125

00:37:02.785 --> 00:37:05.360 basically 930 cell lines across 45

NOTE Confidence: 0.755507468571428

00:37:05.360 --> 00:37:07.562 lineages. You essentially send your drug

NOTE Confidence: 0.755507468571428

00:37:07.562 --> 00:37:10.239 up there and what they'd said is OK,

NOTE Confidence: 0.755507468571428

00:37:10.240 --> 00:37:11.878 let's ask, let's look at KL50 and

NOTE Confidence: 0.755507468571428

00:37:11.878 --> 00:37:13.454 look and they've got all the genomic

NOTE Confidence: 0.755507468571428

00:37:13.454 --> 00:37:15.196 data or a seat data that you can

NOTE Confidence: 0.755507468571428

00:37:15.196 --> 00:37:16.799 correlate with it and say are there.

NOTE Confidence: 0.755507468571428

00:37:16.800 --> 00:37:17.880 When we treat with KL50,

NOTE Confidence: 0.755507468571428

00:37:17.880 --> 00:37:20.530 are there any specific genomic

NOTE Confidence: 0.755507468571428

00:37:20.530 --> 00:37:22.496 biomarkers that correlate with

NOTE Confidence: 0.755507468571428

00:37:22.496 --> 00:37:24.376 sensitivity or resistance and MGMT

NOTE Confidence: 0.755507468571428

00:37:24.376 --> 00:37:26.795 was the true correlate was the

NOTE Confidence: 0.755507468571428

00:37:26.795 --> 00:37:28.920 reproducible correlate for KL50 activity.

NOTE Confidence: 0.755507468571428

00:37:28.920 --> 00:37:30.832 And when you break it out by different

NOTE Confidence: 0.755507468571428

00:37:30.832 --> 00:37:33.039 cell of origin types for the cell lines,

NOTE Confidence: 0.755507468571428

00:37:33.040 --> 00:37:35.760 you can see MGMT low is in the

NOTE Confidence: 0.755507468571428

00:37:35.760 --> 00:37:38.000 orange and MGMT high is in the green.

NOTE Confidence: 0.755507468571428

00:37:38.000 --> 00:37:40.373 You could see across the board all

NOTE Confidence: 0.755507468571428

00:37:40.373 --> 00:37:42.479 different tumor types when you have low

NOTE Confidence: 0.755507468571428

00:37:42.480 --> 00:37:45.636 MGMTKL 50 is significantly more active.

NOTE Confidence: 0.755507468571428

00:37:45.640 --> 00:37:47.503 So this prompted us to move on and this

NOTE Confidence: 0.755507468571428

00:37:47.503 --> 00:37:49.635 is work that as Susan finished up her MD,

NOTE Confidence: 0.755507468571428

00:37:49.640 --> 00:37:51.509 PhD in our laboratory or sorry her

NOTE Confidence: 0.755507468571428

00:37:51.509 --> 00:37:53.108 sorry her residency in our laboratory

NOTE Confidence: 0.755507468571428

00:37:53.108 --> 00:37:55.198 and then went on and started her own

NOTE Confidence: 0.755507468571428

00:37:55.198 --> 00:37:57.312 lab and we're now our two laboratories

NOTE Confidence: 0.755507468571428

00:37:57.312 --> 00:37:57.916 are collaborating.

NOTE Confidence: 0.755507468571428

00:37:57.920 --> 00:38:01.640 She went and started sampling PDX

NOTE Confidence: 0.755507468571428

00:38:01.640 --> 00:38:04.640 libraries across a number of CROs

NOTE Confidence: 0.755507468571428

00:38:04.640 --> 00:38:05.154 and academically.

NOTE Confidence: 0.755507468571428

00:38:05.154 --> 00:38:06.953 We were able to find a number

NOTE Confidence: 0.755507468571428

00:38:06.953 --> 00:38:08.038 of of models here.

NOTE Confidence: 0.755507468571428

00:38:08.040 --> 00:38:09.876 These are all different tumor types,

NOTE Confidence: 0.755507468571428

00:38:09.880 --> 00:38:11.800 some that have lost mismatch repair,

NOTE Confidence: 0.755507468571428

00:38:11.800 --> 00:38:14.194 some that have lost MGMT or both.

NOTE Confidence: 0.755507468571428

00:38:14.200 --> 00:38:17.070 Focusing in on 2 examples here shown

NOTE Confidence: 0.755507468571428

00:38:17.070 --> 00:38:20.291 here and you can see in this case

NOTE Confidence: 0.755507468571428

00:38:20.291 --> 00:38:22.072 this these two models both silence

NOTE Confidence: 0.755507468571428

00:38:22.072 --> 00:38:25.080 MGMT one loss MLH one and one loss

NOTE Confidence: 0.755507468571428

00:38:25.160 --> 00:38:27.420 MSH 2 and again pretty remarkable

NOTE Confidence: 0.755507468571428

00:38:27.420 --> 00:38:29.280 data for monotherapy efficacy.

NOTE Confidence: 0.755507468571428

00:38:29.280 --> 00:38:30.568 Getting back to the the idea of

NOTE Confidence: 0.755507468571428

00:38:30.568 --> 00:38:31.920 like if you've got data like this,

NOTE Confidence: 0.755507468571428

00:38:31.920 --> 00:38:33.590 this is the type of stuff you want to try

NOTE Confidence: 0.755507468571428

00:38:33.634 --> 00:38:35.034 to move in the clinic because there's

NOTE Confidence: 0.755507468571428

00:38:35.034 --> 00:38:37.019 a chance we could see an efficacy in a

NOTE Confidence: 0.755507468571428

00:38:37.019 --> 00:38:38.291 heavily pretreated phase one population.

NOTE Confidence: 0.755507468571428

00:38:38.291 --> 00:38:41.320 You can see here this is looking at

NOTE Confidence: 0.755507468571428

00:38:41.320 --> 00:38:43.720 Melanoma model and a lung model.

NOTE Confidence: 0.755507468571428

00:38:43.720 --> 00:38:45.688 Again TMZ versus KL50.

NOTE Confidence: 0.755507468571428

00:38:45.688 --> 00:38:48.148 TMZ as expected invisible under

NOTE Confidence: 0.755507468571428

00:38:48.148 --> 00:38:49.812 these in this tumor genotype,

NOTE Confidence: 0.755507468571428

00:38:49.812 --> 00:38:51.570 very nice tumor growth delay with

NOTE Confidence: 0.755507468571428

00:38:51.630 --> 00:38:53.398 KL50 and and I'll just know this is

NOTE Confidence: 0.755507468571428

00:38:53.398 --> 00:38:55.349 3 doses times 3 cycles and then we

NOTE Confidence: 0.755507468571428

00:38:55.349 --> 00:38:57.192 stop dosing and then you go out to

NOTE Confidence: 0.755507468571428

00:38:57.192 --> 00:38:58.500 day 80 and we've got essentially

NOTE Confidence: 0.755507468571428

00:38:58.556 --> 00:39:00.635 sustained tumor regressions and we see

NOTE Confidence: 0.755507468571428

00:39:00.635 --> 00:39:02.574 this also for lung cancer as well.

NOTE Confidence: 0.755507468571428

00:39:02.574 --> 00:39:04.416 We've since been now moving on

NOTE Confidence: 0.755507468571428

00:39:04.416 --> 00:39:05.799 to different tumor types.

NOTE Confidence: 0.755507468571428

00:39:05.800 --> 00:39:07.662 I talked to you about our interest

NOTE Confidence: 0.755507468571428

00:39:07.662 --> 00:39:09.671 in AML and started a collaboration

NOTE Confidence: 0.755507468571428

00:39:09.671 --> 00:39:11.975 with Stephanie Helene and what you'll

NOTE Confidence: 0.755507468571428

00:39:11.975 --> 00:39:14.472 see here is in is a petite in our

NOTE Confidence: 0.755507468571428

00:39:14.472 --> 00:39:16.102 laboratory post doc started modeling

NOTE Confidence: 0.755507468571428

00:39:16.102 --> 00:39:18.440 this in a number of different AML cell lines.

NOTE Confidence: 0.755507468571428

00:39:18.440 --> 00:39:20.302 Pulled some of that data from the

NOTE Confidence: 0.755507468571428

00:39:20.302 --> 00:39:22.560 PRISM screen, the 930 cell line data.

NOTE Confidence: 0.755507468571428

00:39:22.560 --> 00:39:25.520 And you can see that when you look at

NOTE Confidence: 0.755507468571428

00:39:25.520 --> 00:39:28.348 TMZ and KL FIT MGMT low versus high

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NOTE Confidence: 0.755507468571428

00:39:28.348 --> 00:39:31.680 you can see largely very nice correlation.

NOTE Confidence: 0.755507468571428

00:39:31.680 --> 00:39:33.283 And he's now what he's been doing

NOTE Confidence: 0.755507468571428

00:39:33.283 --> 00:39:35.023 is doing the same thing we did

NOTE Confidence: 0.755507468571428

00:39:35.023 --> 00:39:36.517 earlier with the other models is

NOTE Confidence: 0.755507468571428

00:39:36.573 --> 00:39:38.163 doing isogenic knockouts now asking

NOTE Confidence: 0.755507468571428

00:39:38.163 --> 00:39:40.620 the question of you know MGMT status

NOTE Confidence: 0.755507468571428

00:39:40.620 --> 00:39:42.120 versus mismatch repair status.

NOTE Confidence: 0.942712165

00:39:42.120 --> 00:39:44.430 And you can see here in these

NOTE Confidence: 0.942712165

00:39:44.430 --> 00:39:45.960 models now you get a very nice,

NOTE Confidence: 0.942712165

00:39:45.960 --> 00:39:48.220 this is KL50 in a in a molem 13 AML

NOTE Confidence: 0.942712165

00:39:48.294 --> 00:39:50.109 model where we knockout mismatch

NOTE Confidence: 0.942712165

00:39:50.109 --> 00:39:52.326 repair and then in MGMT deficient

NOTE Confidence: 0.942712165

00:39:52.326 --> 00:39:55.022 that's the red and the blue shown here

NOTE Confidence: 0.942712165

00:39:55.022 --> 00:39:57.358 and you see very nice activity here.

NOTE Confidence: 0.942712165

00:39:57.360 --> 00:39:58.440 We're now working with Stephanie,

NOTE Confidence: 0.942712165

00:39:58.440 --> 00:40:00.638 don't have the data to show today

NOTE Confidence: 0.942712165

00:40:00.640 --> 00:40:02.188 looking at her PDX models because

NOTE Confidence: 0.942712165

00:40:02.188 --> 00:40:03.726 we actually think there could be

NOTE Confidence: 0.942712165

00:40:03.726 --> 00:40:05.336 a potential to use some of these

NOTE Confidence: 0.942712165

00:40:05.336 --> 00:40:06.480 molecules in the AML setting,

NOTE Confidence: 0.942712165

00:40:06.480 --> 00:40:08.760 the subsets that have silenced MGMT.

NOTE Confidence: 0.868727302307692

00:40:11.120 --> 00:40:13.976 So really in the last you know five

NOTE Confidence: 0.868727302307692

00:40:13.976 --> 00:40:16.864 about 10-10 minutes or so sort of talk

NOTE Confidence: 0.868727302307692

00:40:16.864 --> 00:40:19.072 about where we're going from here.

NOTE Confidence: 0.868727302307692

00:40:19.080 --> 00:40:21.075 So the first thing which is really

NOTE Confidence: 0.868727302307692

00:40:21.075 --> 00:40:23.199 interesting is we had this molecule KL50

NOTE Confidence: 0.868727302307692

00:40:23.200 --> 00:40:25.560 never really been described before.

NOTE Confidence: 0.868727302307692

00:40:25.560 --> 00:40:26.944 We want to translate this in the clinic

NOTE Confidence: 0.868727302307692

00:40:26.944 --> 00:40:28.460 and we had you know gotten really lucky

NOTE Confidence: 0.868727302307692

00:40:28.460 --> 00:40:29.921 with the IDH PARP story because there

NOTE Confidence: 0.868727302307692

00:40:29.921 --> 00:40:31.475 was FDA approved PARP and intervals and

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NOTE Confidence: 0.868727302307692

00:40:31.480 --> 00:40:33.076 we just needed to call those companies,

NOTE Confidence: 0.868727302307692

00:40:33.080 --> 00:40:35.048 write the trials and then and

NOTE Confidence: 0.868727302307692

00:40:35.048 --> 00:40:36.360 then run them here.

NOTE Confidence: 0.868727302307692

00:40:36.360 --> 00:40:39.185 There's really no source of KL50 and

NOTE Confidence: 0.868727302307692

00:40:39.185 --> 00:40:40.775 we've started a few companies before

NOTE Confidence: 0.868727302307692

00:40:40.775 --> 00:40:43.080 this so we sort of knew how to do this.

NOTE Confidence: 0.868727302307692

00:40:43.080 --> 00:40:44.998 But ultimately to to cut to the

NOTE Confidence: 0.868727302307692

00:40:44.998 --> 00:40:47.158 chase here we ended up just spinning

NOTE Confidence: 0.868727302307692

00:40:47.158 --> 00:40:49.253 out our own company and this was

NOTE Confidence: 0.868727302307692

00:40:49.253 --> 00:40:51.150 great to work with Kingston who as

NOTE Confidence: 0.868727302307692

00:40:51.213 --> 00:40:53.320 a as a MDPHD student and then Seth

NOTE Confidence: 0.868727302307692

00:40:53.320 --> 00:40:55.600 Herzan's Co Pi and then my long time

NOTE Confidence: 0.868727302307692

00:40:55.600 --> 00:40:56.879 business partner Kevin Ragan.

NOTE Confidence: 0.868727302307692

00:40:56.880 --> 00:40:59.148 We had a nice write up and end points

NOTE Confidence: 0.868727302307692

00:40:59.148 --> 00:41:01.200 about two years back and this is just a

NOTE Confidence: 0.868727302307692

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00:41:01.200 --> 00:41:02.620 glimpse of the founding team and right

NOTE Confidence: 0.868727302307692

00:41:02.620 --> 00:41:04.000 around that time Kingston very proud.

NOTE Confidence: 0.868727302307692

00:41:04.000 --> 00:41:06.840 It's Forbes 30 under 30.

NOTE Confidence: 0.868727302307692

00:41:06.840 --> 00:41:08.156 I'm still waiting for 50 under 50,

NOTE Confidence: 0.868727302307692

00:41:08.160 --> 00:41:09.564 but I don't think they're going

NOTE Confidence: 0.868727302307692

00:41:09.564 --> 00:41:12.896 to have one it's too but so,

NOTE Confidence: 0.868727302307692

00:41:12.896 --> 00:41:14.036 so what's the company doing.

NOTE Confidence: 0.868727302307692

00:41:14.040 --> 00:41:15.520 So it's been really great.

NOTE Confidence: 0.868727302307692

00:41:15.520 --> 00:41:15.814 So,

NOTE Confidence: 0.868727302307692

00:41:15.814 --> 00:41:17.578 so really the company is now

NOTE Confidence: 0.868727302307692

00:41:17.578 --> 00:41:19.670 taking that tool compound KO 50

NOTE Confidence: 0.868727302307692

00:41:19.670 --> 00:41:21.680 and really now engineering it for

NOTE Confidence: 0.868727302307692

00:41:21.680 --> 00:41:24.000 ready for prime time so to speak.

NOTE Confidence: 0.868727302307692

00:41:24.000 --> 00:41:25.150 Turning that into what we

NOTE Confidence: 0.868727302307692

00:41:25.150 --> 00:41:25.840 call development candidate,

NOTE Confidence: 0.868727302307692

00:41:25.840 --> 00:41:27.597 some of you know what that means,

NOTE Confidence: 0.868727302307692

00:41:27.600 --> 00:41:29.108 but essentially suitable for

NOTE Confidence: 0.868727302307692

00:41:29.108 --> 00:41:30.239 Ind enabling studies.

NOTE Confidence: 0.868727302307692

00:41:30.240 --> 00:41:31.584 Didn't want to focus too much on

NOTE Confidence: 0.868727302307692

00:41:31.584 --> 00:41:32.902 this because of you know it's

NOTE Confidence: 0.868727302307692

00:41:32.902 --> 00:41:33.838 more company related stuff,

NOTE Confidence: 0.868727302307692

00:41:33.840 --> 00:41:35.958 but it has the original molecules,

NOTE Confidence: 0.868727302307692

00:41:35.960 --> 00:41:37.208 metabolic liabilities that preclude

NOTE Confidence: 0.868727302307692

00:41:37.208 --> 00:41:39.080 it from going to the clinic.

NOTE Confidence: 0.868727302307692

00:41:39.080 --> 00:41:39.985 We welcome anyone who reads

NOTE Confidence: 0.868727302307692

00:41:39.985 --> 00:41:41.239 the paper to try to do that.

NOTE Confidence: 0.868727302307692

00:41:41.240 --> 00:41:41.903 It's not possible.

NOTE Confidence: 0.868727302307692

00:41:41.903 --> 00:41:43.229 So we've been able to engineer

NOTE Confidence: 0.868727302307692

00:41:43.229 --> 00:41:44.559 that molecule and we have that.

NOTE Confidence: 0.868727302307692

00:41:44.560 --> 00:41:46.696 We have a new version of KL50 that

NOTE Confidence: 0.868727302307692

00:41:46.696 --> 00:41:48.668 has very good PKPD properties

NOTE Confidence: 0.868727302307692

00:41:48.668 --> 00:41:50.958 enhancing its penetration and whatnot.

NOTE Confidence: 0.868727302307692

00:41:50.960 --> 00:41:52.836 And the company hopes to over the

NOTE Confidence: 0.868727302307692

00:41:52.836 --> 00:41:54.395 next year perform the necessary

NOTE Confidence: 0.868727302307692

00:41:54.395 --> 00:41:56.079 ID enabling studies to drive this

NOTE Confidence: 0.868727302307692

00:41:56.079 --> 00:41:56.718 into the clinic.

NOTE Confidence: 0.868727302307692

00:41:56.720 --> 00:41:58.400 And we hope if all goes according to

NOTE Confidence: 0.868727302307692

00:41:58.400 --> 00:42:00.079 plan that we can actually bring this

NOTE Confidence: 0.868727302307692

00:42:00.079 --> 00:42:01.839 into patients about a year from April,

NOTE Confidence: 0.868727302307692

00:42:01.840 --> 00:42:03.718 which would be really, really exciting.

NOTE Confidence: 0.868727302307692

00:42:03.720 --> 00:42:05.277 But we have to close our Series A first,

NOTE Confidence: 0.868727302307692

00:42:05.280 --> 00:42:09.120 which is going to be still a bit of a path.

NOTE Confidence: 0.868727302307692

00:42:09.120 --> 00:42:10.445 And what's really exciting is

NOTE Confidence: 0.868727302307692

00:42:10.445 --> 00:42:12.359 we think that we can use these,

NOTE Confidence: 0.868727302307692

00:42:12.360 --> 00:42:14.825 this molecule KL50 for tumors

NOTE Confidence: 0.868727302307692

00:42:14.825 --> 00:42:16.797 outside of the brain.

NOTE Confidence: 0.868727302307692

00:42:16.800 --> 00:42:18.480 We really think there's a potential

NOTE Confidence: 0.868727302307692

00:42:18.480 --> 00:42:20.450 here to move this into things like

NOTE Confidence: 0.868727302307692

00:42:20.450 --> 00:42:22.840 colon cancer where 30 to 40% of tumors

NOTE Confidence: 0.868727302307692

00:42:22.840 --> 00:42:25.300 are MGMT silence and we've modeled this,

NOTE Confidence: 0.868727302307692

00:42:25.300 --> 00:42:27.440 this is just an example mod 16,

NOTE Confidence: 0.868727302307692

00:42:27.440 --> 00:42:29.512 this is sort of a a next generation

NOTE Confidence: 0.868727302307692

00:42:29.512 --> 00:42:31.666 kill 50 before our our development

NOTE Confidence: 0.868727302307692

00:42:31.666 --> 00:42:33.234 candidate called mod 246.

NOTE Confidence: 0.868727302307692

00:42:33.240 --> 00:42:35.190 But you can see here mod 16 in a colon

NOTE Confidence: 0.8227583925

00:42:35.250 --> 00:42:38.236 cancer model, a flank model MGMT science Mr.

NOTE Confidence: 0.8227583925

00:42:38.240 --> 00:42:40.838 prepared efficient very nice dose dependent

NOTE Confidence: 0.8227583925

00:42:40.840 --> 00:42:44.560 activity 10 Meg per keg treatment regimen

NOTE Confidence: 0.8227583925

00:42:44.560 --> 00:42:47.160 here inducing A tumor regressions.

NOTE Confidence: 0.8227583925

00:42:47.160 --> 00:42:48.864 And we're excited about this because

NOTE Confidence: 0.8227583925

00:42:48.864 --> 00:42:50.585 we've been working with folks that

NOTE Confidence: 0.8227583925

00:42:50.585 --> 00:42:52.199 you know well like Kirk Schopper

NOTE Confidence: 0.8227583925

00:42:52.199 --> 00:42:53.680 pathology and Mike Tuccini already

NOTE Confidence: 0.8227583925

00:42:53.680 --> 00:42:55.920 looking at whether we can do alkylator

NOTE Confidence: 0.8227583925

00:42:55.920 --> 00:42:57.919 DNA repair inhibitor combinations.

NOTE Confidence: 0.8227583925

00:42:57.920 --> 00:43:01.154 For example in MGMT silence colon cancer.

NOTE Confidence: 0.8227583925

00:43:01.160 --> 00:43:02.882 And this is this is Mike Tuccini

NOTE Confidence: 0.8227583925

00:43:02.882 --> 00:43:05.046 study that he ran recently with Kirk

NOTE Confidence: 0.8227583925

00:43:05.046 --> 00:43:06.756 Chopper developed some really cool

NOTE Confidence: 0.8227583925

00:43:06.756 --> 00:43:08.740 assays detect MGMT expression on this

NOTE Confidence: 0.8227583925

00:43:08.740 --> 00:43:10.714 case using temazolomide in a Labra.

NOTE Confidence: 0.8227583925

00:43:10.714 --> 00:43:13.431 This is before we discovered KL50 and

NOTE Confidence: 0.8227583925

00:43:13.431 --> 00:43:15.888 now Mike's actually moved on to looking

NOTE Confidence: 0.8227583925

00:43:15.888 --> 00:43:17.838 at Temazolomide in an ATR inhibitor.

NOTE Confidence: 0.8227583925

00:43:17.840 --> 00:43:19.674 And so we're really excited for this

NOTE Confidence: 0.8227583925

00:43:19.674 --> 00:43:21.762 because what we believe is not only can we

NOTE Confidence: 0.8227583925

00:43:21.762 --> 00:43:24.028 test KL50 as a monotherapy in these cancers,

NOTE Confidence: 0.8227583925

00:43:24.028 --> 00:43:25.960 we could actually probably combine this with

00:43:26.014 --> 00:43:27.796 other agents like DNA repair inhibitors,

00:43:27.800 --> 00:43:30.724 PARP inhibitors and ATR

00:43:30.724 --> 00:43:32.917 inhibitors for example.

00:43:32.920 --> 00:43:34.864 And then in the last sort of few slides

00:43:34.864 --> 00:43:36.678 just kind of talk about sort of some

00:43:36.678 --> 00:43:38.518 of the Wilder stuff that we're doing.

00:43:38.520 --> 00:43:40.120 And so I showed you that mechanism earlier,

00:43:40.120 --> 00:43:42.264 right, with all the, you know, 4A4B4C.

00:43:42.264 --> 00:43:45.720 So when you focus on the blue box area,

00:43:45.720 --> 00:43:47.120 we've got this kind of crazy idea.

00:43:47.120 --> 00:43:49.000 I know our lab can sometimes be a

00:43:49.000 --> 00:43:51.000 little going off the beaten path,

00:43:51.000 --> 00:43:53.072 but we call this project breaking DDR

00:43:53.072 --> 00:43:55.477 if you guys ever see a Breaking Bad.

00:43:55.480 --> 00:43:57.160 So it's just sort of a little wild,

00:43:57.160 --> 00:43:59.372 but but I promise you there there's

NOTE Confidence: 0.8227583925

00:43:59.372 --> 00:44:00.320 some sanity here.

NOTE Confidence: 0.8227583925

00:44:00.320 --> 00:44:01.838 So if you think about it,

NOTE Confidence: 0.8227583925

00:44:01.840 --> 00:44:04.024 we're creating cross links that are

NOTE Confidence: 0.8227583925

00:44:04.024 --> 00:44:06.000 specifically active in MGMT silence,

NOTE Confidence: 0.8227583925

00:44:06.000 --> 00:44:08.598 misreactor deficient cells and arguably MGMT.

NOTE Confidence: 0.8227583925

00:44:08.600 --> 00:44:11.300 Science misreproficient we are now

NOTE Confidence: 0.8227583925

00:44:11.300 --> 00:44:14.000 by making this simple fluoroethyl

NOTE Confidence: 0.8227583925

00:44:14.086 --> 00:44:16.780 substitution for the for the methyl

NOTE Confidence: 0.8227583925

00:44:16.780 --> 00:44:19.079 group here we're actually now making

NOTE Confidence: 0.8227583925

00:44:19.079 --> 00:44:21.524 the futile cycling pathway that

NOTE Confidence: 0.8227583925

00:44:21.524 --> 00:44:23.480 Tamizoli works totally irrelevant.

NOTE Confidence: 0.8227583925

00:44:23.480 --> 00:44:25.692 So now the cell is actually being

NOTE Confidence: 0.8227583925

00:44:25.692 --> 00:44:27.455 forced because of its genomic

NOTE Confidence: 0.8227583925

00:44:27.455 --> 00:44:29.315 biomorg because it lacks MGMT.

NOTE Confidence: 0.8227583925

00:44:29.320 --> 00:44:31.693 It's now being driven into a cross

00:44:31.693 --> 00:44:33.719 link repair pathway probably right.

00:44:33.720 --> 00:44:35.624 So the question is are we now able

00:44:35.624 --> 00:44:38.119 to at a bigger picture create DNA

00:44:38.119 --> 00:44:40.079 modifiers right create novel analogues

00:44:40.146 --> 00:44:42.309 that for instance here create a cross

00:44:42.309 --> 00:44:44.248 link or create a double strand break.

00:44:44.248 --> 00:44:45.760 So we're making new analog sets

00:44:45.807 --> 00:44:47.157 sets lab and we've got James,

00:44:47.160 --> 00:44:49.312 Ilia here and others that are grad student

00:44:49.312 --> 00:44:50.968 that are working on other analogues

00:44:50.968 --> 00:44:52.998 and and different DNA repair defects.

00:44:53.000 --> 00:44:55.232 But we could actually force a cell to

00:44:55.232 --> 00:44:57.560 switch from one repair pathway to another.

00:44:57.560 --> 00:44:57.857 OK.

00:44:57.857 --> 00:44:59.936 And so this could be an enormous

00:44:59.936 --> 00:45:01.327 opportunity for novel combinations

NOTE Confidence: 0.8227583925

00:45:01.327 --> 00:45:03.523 of KL50 with DNA repair enhibbers

NOTE Confidence: 0.8227583925

00:45:03.523 --> 00:45:05.806 that either you wouldn't think were

NOTE Confidence: 0.8227583925

00:45:05.806 --> 00:45:07.666 possible or targeting DNA repair

NOTE Confidence: 0.8227583925

00:45:07.666 --> 00:45:09.800 proteins that are not, you know,

NOTE Confidence: 0.8227583925

00:45:09.800 --> 00:45:10.960 really thought to be relevant,

NOTE Confidence: 0.8227583925

00:45:10.960 --> 00:45:12.100 but they become relevant.

NOTE Confidence: 0.8227583925

00:45:12.100 --> 00:45:12.955 So for this,

NOTE Confidence: 0.8227583925

00:45:12.960 --> 00:45:14.717 I'll just show you a little bit

NOTE Confidence: 0.8227583925

00:45:14.720 --> 00:45:15.758 of some of our prelim data.

NOTE Confidence: 0.8227583925

00:45:15.760 --> 00:45:17.496 And this is Colin a post doc

NOTE Confidence: 0.8227583925

00:45:17.496 --> 00:45:18.240 in our laboratory.

NOTE Confidence: 0.8227583925

00:45:18.240 --> 00:45:20.880 So he's been addressing this

NOTE Confidence: 0.9259897225

00:45:20.880 --> 00:45:22.920 and also James and others in our laboratory,

NOTE Confidence: 0.9259897225

00:45:22.920 --> 00:45:24.782 but he's been leading the efforts of

NOTE Confidence: 0.9259897225

00:45:24.782 --> 00:45:26.800 creating a focused DNA repair gene library.

NOTE Confidence: 0.9259897225

00:45:26.800 --> 00:45:28.534 And we're always excited about potential

NOTE Confidence: 0.9259897225

00:45:28.534 --> 00:45:29.939 collaborations in this space because

NOTE Confidence: 0.9259897225

00:45:29.939 --> 00:45:31.547 he's really spent a lot of time the

NOTE Confidence: 0.9259897225

00:45:31.547 --> 00:45:32.851 last year building this platform

NOTE Confidence: 0.9259897225

00:45:32.851 --> 00:45:35.100 working with Select and Agilent and the

NOTE Confidence: 0.9259897225

00:45:35.100 --> 00:45:37.740 Agilent sequencing profile platform

NOTE Confidence: 0.9259897225

00:45:37.740 --> 00:45:40.430 about 335 DNA repair and response

NOTE Confidence: 0.9259897225

00:45:40.430 --> 00:45:43.585 genes targeting 6 guide RN as per gene

NOTE Confidence: 0.9259897225

00:45:43.585 --> 00:45:45.678 standard sort of protocol shown here.

NOTE Confidence: 0.9259897225

00:45:45.678 --> 00:45:47.408 And essentially looking at what

NOTE Confidence: 0.9259897225

00:45:47.408 --> 00:45:49.561 are the nodes of sensitivity and

NOTE Confidence: 0.9259897225

00:45:49.561 --> 00:45:51.667 resistance for your drug of interest

NOTE Confidence: 0.9259897225

00:45:51.732 --> 00:45:53.520 that are related to DNA repair.

NOTE Confidence: 0.9259897225

00:45:53.520 --> 00:45:54.864 Obviously you can do a whole

NOTE Confidence: 0.9259897225

00:45:54.864 --> 00:45:56.342 genome crisper screen and we have

NOTE Confidence: 0.9259897225

00:45:56.342 --> 00:45:57.677 aspirations of doing that eventually.

NOTE Confidence: 0.9259897225

00:45:57.680 --> 00:45:59.450 But these are giant experiments by

NOTE Confidence: 0.9259897225

00:45:59.450 --> 00:46:01.280 doing a focus screen you can do,

NOTE Confidence: 0.9259897225

00:46:01.280 --> 00:46:03.128 you know, you know,

NOTE Confidence: 0.9259897225

00:46:03.128 --> 00:46:05.975 2015 centimeter dishes and and you'll

NOTE Confidence: 0.9259897225

00:46:05.975 --> 00:46:08.400 be and it's relatively tractable.

NOTE Confidence: 0.9259897225

00:46:08.400 --> 00:46:10.808 And so I'll just give you just a

NOTE Confidence: 0.9259897225

00:46:10.808 --> 00:46:12.754 little smattering of some of the

NOTE Confidence: 0.9259897225

00:46:12.754 --> 00:46:14.359 data that he's produced recently.

NOTE Confidence: 0.9259897225

00:46:14.360 --> 00:46:16.248 So the first thing he did is started

NOTE Confidence: 0.9259897225

00:46:16.248 --> 00:46:18.429 looking at KL50 and TMZ and ran it

NOTE Confidence: 0.9259897225

00:46:18.429 --> 00:46:20.040 through his Christmas screening platform.

NOTE Confidence: 0.9259897225

00:46:20.040 --> 00:46:21.188 And I should have been remiss of

NOTE Confidence: 0.9259897225

00:46:21.188 --> 00:46:22.159 it and mentioned Sam Friedman,

NOTE Confidence: 0.9259897225

00:46:22.160 --> 00:46:23.600 the bioinformaticist in our lab

NOTE Confidence: 0.9259897225

00:46:23.600 --> 00:46:25.344 that built the platform for the

NOTE Confidence: 0.9259897225

00:46:25.344 --> 00:46:26.360 analysis of this data.

NOTE Confidence: 0.9259897225

00:46:26.360 --> 00:46:27.840 And what you can see here just as a glimpse,

NOTE Confidence: 0.9259897225

00:46:27.840 --> 00:46:30.605 you can see very nice in terms of

NOTE Confidence: 0.9259897225

00:46:30.605 --> 00:46:32.948 everything here is sensitive knockout of

NOTE Confidence: 0.9259897225

00:46:32.948 --> 00:46:35.072 that gene induces sensitivity and then

NOTE Confidence: 0.9259897225

00:46:35.072 --> 00:46:37.440 everything on the right induces resistance.

NOTE Confidence: 0.9259897225

00:46:37.440 --> 00:46:38.400 TP 53 comes out,

NOTE Confidence: 0.9259897225

00:46:38.400 --> 00:46:40.294 but it's at a pretty low magnitude

NOTE Confidence: 0.9259897225

00:46:40.294 --> 00:46:41.479 of effects there.

NOTE Confidence: 0.9259897225

00:46:41.480 --> 00:46:43.456 But you can actually see if you notice

NOTE Confidence: 0.9259897225

00:46:43.456 --> 00:46:45.422 there's a lot of Fanconi genes and

NOTE Confidence: 0.9259897225

00:46:45.422 --> 00:46:47.360 interesting genes that are are involved.

NOTE Confidence: 0.9259897225

00:46:47.360 --> 00:46:49.118 When you overlay this with TMZ,

NOTE Confidence: 0.9259897225

00:46:49.120 --> 00:46:50.336 it gets really interesting.

NOTE Confidence: 0.9259897225

00:46:50.336 --> 00:46:52.799 And so I'll show you this data here.

NOTE Confidence: 0.9259897225

00:46:52.800 --> 00:46:54.456 He's doing a lot of work here but I'm

NOTE Confidence: 0.9259897225

00:46:54.456 --> 00:46:55.918 just summarizing because of time.

NOTE Confidence: 0.9259897225

00:46:55.920 --> 00:46:58.592 You can see here now in these different

NOTE Confidence: 0.9259897225

00:46:58.592 --> 00:47:00.633 quadrants you've got when you compare

NOTE Confidence: 0.9259897225

00:47:00.633 --> 00:47:02.601 KL50 versus control and TMZ versus

NOTE Confidence: 0.9259897225

00:47:02.662 --> 00:47:04.280 control what you can see are the

NOTE Confidence: 0.9259897225

00:47:04.280 --> 00:47:05.786 genes that are whose knockout not

NOTE Confidence: 0.9259897225

00:47:05.786 --> 00:47:07.598 when knocked out and do sensitivity.

NOTE Confidence: 0.9259897225

00:47:07.600 --> 00:47:10.390 TMZ only versus resistance to TMZ

NOTE Confidence: 0.9259897225

00:47:10.390 --> 00:47:13.320 only and then sensitive to KL50 only

NOTE Confidence: 0.9259897225

00:47:13.320 --> 00:47:14.832 And you can see some interesting like

NOTE Confidence: 0.9259897225

00:47:14.832 --> 00:47:16.871 one sort of knew that but you know

NOTE Confidence: 0.9259897225

00:47:16.871 --> 00:47:17.947 arguably still pretty interesting

NOTE Confidence: 0.9259897225

00:47:17.947 --> 00:47:19.893 then one on the right here this was

NOTE Confidence: 0.9259897225

00:47:19.893 --> 00:47:21.144 actually great because you could

NOTE Confidence: 0.9259897225

00:47:21.144 --> 00:47:22.776 see the mismatch repaired genes all

NOTE Confidence: 0.9259897225

00:47:22.776 --> 00:47:24.686 come out when you knock them out

NOTE Confidence: 0.9259897225

00:47:24.686 --> 00:47:25.996 and become resistant to TMZ.

NOTE Confidence: 0.9259897225

00:47:26.000 --> 00:47:27.476 And you'll notice actually for the

NOTE Confidence: 0.9259897225

00:47:27.476 --> 00:47:28.940 again the DNA repair official is

NOTE Confidence: 0.9259897225

00:47:28.940 --> 00:47:30.438 the missing gene here is MSH 3.

NOTE Confidence: 0.9259897225

00:47:30.440 --> 00:47:32.764 So the two three complex which repairs

NOTE Confidence: 0.9259897225

00:47:32.764 --> 00:47:35.240 loops and not insert mismatches was

NOTE Confidence: 0.9259897225

00:47:35.240 --> 00:47:37.160 not a determinant of of resistance.

NOTE Confidence: 0.9259897225

00:47:37.160 --> 00:47:38.670 So then functionally validating the

NOTE Confidence: 0.9259897225

00:47:38.670 --> 00:47:41.458 screen as a as a really great way

NOTE Confidence: 0.9259897225

00:47:41.458 --> 00:47:42.676 to fingerprint molecules.

NOTE Confidence: 0.9259897225

00:47:42.680 --> 00:47:44.766 But we can see one gene actually

NOTE Confidence: 0.9259897225

00:47:44.766 --> 00:47:46.672 popped out that was really interesting

NOTE Confidence: 0.9259897225

00:47:46.672 --> 00:47:49.229 and this is called B Rip One which

NOTE Confidence: 0.9259897225

00:47:49.229 --> 00:47:50.879 is also known as Frank J.

NOTE Confidence: 0.9259897225

00:47:50.880 --> 00:47:53.244 And so we've been interested in

NOTE Confidence: 0.9259897225

00:47:53.244 --> 00:47:54.820 understanding this further and

NOTE Confidence: 0.76271804125

00:47:54.888 --> 00:47:56.841 to to get at this we reached out to

NOTE Confidence: 0.76271804125

00:47:56.841 --> 00:47:58.691 Sharon Kanter who's done a lot of work

NOTE Confidence: 0.76271804125

00:47:58.691 --> 00:48:00.278 in the Fang Jay space and Colin reached

NOTE Confidence: 0.76271804125

00:48:00.278 --> 00:48:02.159 out to her to see if we could validate

NOTE Confidence: 0.76271804125

00:48:02.159 --> 00:48:03.755 this in some Fang Jay knockouts.

NOTE Confidence: 0.76271804125

00:48:03.760 --> 00:48:05.468 All lines and here's 3 knockouts all

NOTE Confidence: 0.76271804125

00:48:05.468 --> 00:48:07.480 lines that we got you can see her MGMT.

NOTE Confidence: 0.76271804125

00:48:07.480 --> 00:48:10.150 Science. Mr. repair proficient it's a

NOTE Confidence: 0.76271804125

00:48:10.150 --> 00:48:14.080 double negative and then MGMT proficient

NOTE Confidence: 0.76271804125

00:48:14.080 --> 00:48:16.845 but knockout sorry knockout MGMT.

NOTE Confidence: 0.76271804125

00:48:16.845 --> 00:48:18.505 Chemically those expensive guanine

NOTE Confidence: 0.76271804125

00:48:18.505 --> 00:48:20.997 and you can see there's no real

NOTE Confidence: 0.76271804125

00:48:21.000 --> 00:48:24.438 effects of knocking out, thank Jay

NOTE Confidence: 0.76271804125

00:48:24.440 --> 00:48:26.120 in terms of tamzolamide sensitivity.

NOTE Confidence: 0.76271804125

00:48:26.120 --> 00:48:27.488 And again we would not expect

NOTE Confidence: 0.76271804125

00:48:27.488 --> 00:48:28.760 that from the crisper screen,

NOTE Confidence: 0.76271804125

00:48:28.760 --> 00:48:29.924 but you can see some this

NOTE Confidence: 0.76271804125

00:48:29.924 --> 00:48:31.000 is short term growth delay.

NOTE Confidence: 0.76271804125

00:48:31.000 --> 00:48:32.872 So we still have some clonogenics to do here.

NOTE Confidence: 0.76271804125

00:48:32.880 --> 00:48:34.308 But just you can see in the

NOTE Confidence: 0.76271804125

00:48:34.308 --> 00:48:35.979 middle here that in this HEK,

NOTE Confidence: 0.76271804125

00:48:35.979 --> 00:48:37.038 this hex align,

NOTE Confidence: 0.76271804125

00:48:37.040 --> 00:48:39.320 MGC science mismatch very deficient,

NOTE Confidence: 0.76271804125

00:48:39.320 --> 00:48:40.200 you can see a very,

NOTE Confidence: 0.76271804125

00:48:40.200 --> 00:48:42.972 very nice effect of a Fank

NOTE Confidence: 0.76271804125

00:48:42.972 --> 00:48:44.358 Jay inducing sensitivity.

NOTE Confidence: 0.76271804125

00:48:44.360 --> 00:48:46.292 So this platform is exciting because

NOTE Confidence: 0.76271804125

00:48:46.292 --> 00:48:48.758 just sort of going the previous slide,

NOTE Confidence: 0.76271804125

00:48:48.760 --> 00:48:50.360 what we're trying to do,

NOTE Confidence: 0.76271804125

00:48:50.360 --> 00:48:51.984 what we're now going to be looking

NOTE Confidence: 0.76271804125

00:48:51.984 --> 00:48:54.170 at is actually using this platform to

NOTE Confidence: 0.76271804125

00:48:54.170 --> 00:48:55.610 actually start fingerprinting different

NOTE Confidence: 0.76271804125

00:48:55.610 --> 00:48:57.189 alkylators as we make different

NOTE Confidence: 0.76271804125

00:48:57.189 --> 00:48:58.809 model modifiers and warheads to sort

NOTE Confidence: 0.76271804125

00:48:58.809 --> 00:49:00.640 of see how the landscape shifts.

NOTE Confidence: 0.76271804125

00:49:00.640 --> 00:49:02.380 And actually we're always open

NOTE Confidence: 0.76271804125

00:49:02.380 --> 00:49:03.076 to collaborations,

NOTE Confidence: 0.76271804125

00:49:03.080 --> 00:49:04.620 you know shoot calling or or mean

NOTE Confidence: 0.76271804125

00:49:04.620 --> 00:49:05.802 e-mail if you're interested in

NOTE Confidence: 0.76271804125

00:49:05.802 --> 00:49:07.475 testing a drug out in our platform.

NOTE Confidence: 0.76271804125

00:49:07.480 --> 00:49:09.520 And depending on the interest in the fit,

NOTE Confidence: 0.76271804125

00:49:09.520 --> 00:49:11.476 we could, we could certainly collaborate,

NOTE Confidence: 0.76271804125

00:49:11.480 --> 00:49:14.040 we have this kind of running pretty well.

NOTE Confidence: 0.76271804125

00:49:14.040 --> 00:49:16.105 So with that sort of just conclusions

NOTE Confidence: 0.76271804125

00:49:16.105 --> 00:49:17.643 and future directions hopefully I've

NOTE Confidence: 0.76271804125

00:49:17.643 --> 00:49:19.443 shown you that we've identified the

NOTE Confidence: 0.76271804125

00:49:19.443 --> 00:49:21.206 first MGT dependent mismatch repair

NOTE Confidence: 0.76271804125

00:49:21.206 --> 00:49:23.056 independent alculator which has a

NOTE Confidence: 0.76271804125

00:49:23.056 --> 00:49:24.976 very favorable TI which I believe

NOTE Confidence: 0.76271804125

00:49:24.976 --> 00:49:26.152 potentially meets the constraints

NOTE Confidence: 0.76271804125

00:49:26.152 --> 00:49:28.775 of of what could be successful as a

NOTE Confidence: 0.76271804125

00:49:28.775 --> 00:49:30.095 synthetic lethal targeting strategy

NOTE Confidence: 0.76271804125

00:49:30.146 --> 00:49:31.714 that can make it in the clinic.

NOTE Confidence: 0.76271804125

00:49:31.720 --> 00:49:33.771 We've spent a lot of time loosening

NOTE Confidence: 0.76271804125

00:49:33.771 --> 00:49:35.704 the mechanism of activity then a

NOTE Confidence: 0.76271804125

00:49:35.704 --> 00:49:37.064 lot of validation experiments that

NOTE Confidence: 0.76271804125

00:49:37.064 --> 00:49:38.200 are presented here today.

NOTE Confidence: 0.76271804125

00:49:38.200 --> 00:49:40.146 We'd argue this is a whole new

NOTE Confidence: 0.76271804125

00:49:40.146 --> 00:49:42.159 way to exploit DNA repair defects

NOTE Confidence: 0.76271804125

00:49:42.160 --> 00:49:44.160 and hopefully you'll see James

NOTE Confidence: 0.76271804125

00:49:44.160 --> 00:49:45.199 Elias upcoming RIP talk.

NOTE Confidence: 0.76271804125

00:49:45.199 --> 00:49:46.960 I don't know if it's coming up soon,

NOTE Confidence: 0.76271804125

00:49:46.960 --> 00:49:48.820 but sometimes doing this for

NOTE Confidence: 0.76271804125

00:49:48.820 --> 00:49:50.680 HRD or brach immune cancers,

NOTE Confidence: 0.76271804125

00:49:50.680 --> 00:49:52.728 we can do this for IDH immune cancers

NOTE Confidence: 0.76271804125

00:49:52.728 --> 00:49:54.239 with actually inhibit out BH.

NOTE Confidence: 0.76271804125

00:49:54.239 --> 00:49:56.237 There's a lot of different pathways

NOTE Confidence: 0.76271804125

00:49:56.237 --> 00:49:58.452 we can go here and I think we

NOTE Confidence: 0.76271804125

00:49:58.452 --> 00:49:59.867 can actually do really novel

NOTE Confidence: 0.76271804125

00:49:59.867 --> 00:50:01.618 combinations here looking at DNA

NOTE Confidence: 0.76271804125

00:50:01.618 --> 00:50:02.680 preparing hip accommodations.

NOTE Confidence: 0.76271804125

00:50:02.680 --> 00:50:04.759 What I haven't shown you Juan Vasquez,

NOTE Confidence: 0.76271804125

00:50:04.760 --> 00:50:06.866 postdoc in our lab and now has his own

NOTE Confidence: 0.76271804125

00:50:06.866 --> 00:50:09.259 lab here is looking at immunotherapy

NOTE Confidence: 0.76271804125

00:50:09.259 --> 00:50:11.048 combinations again because of immunogenic

NOTE Confidence: 0.76271804125

00:50:11.048 --> 00:50:12.758 cell death from cross linking.

NOTE Confidence: 0.76271804125

00:50:12.760 --> 00:50:14.074 And of course very exciting to

NOTE Confidence: 0.76271804125

00:50:14.074 --> 00:50:15.360 launch this into a company.

NOTE Confidence: 0.76271804125

00:50:15.360 --> 00:50:16.236 We just shared a little bit.

NOTE Confidence: 0.76271804125

00:50:16.240 --> 00:50:17.759 There's a lot going on with modify

NOTE Confidence: 0.76271804125

00:50:17.759 --> 00:50:19.226 but didn't want to focus on on

NOTE Confidence: 0.76271804125

00:50:19.226 --> 00:50:20.771 that today which we hope will be in

NOTE Confidence: 0.76271804125

00:50:20.771 --> 00:50:23.436 the clinic in about a year or so.

NOTE Confidence: 0.790767504545455

00:50:23.440 --> 00:50:24.472 So of course as always I

NOTE Confidence: 0.790767504545455

00:50:24.472 --> 00:50:25.400 just make the slides here.

NOTE Confidence: 0.790767504545455

00:50:25.400 --> 00:50:27.024 So I got to thank the people

NOTE Confidence: 0.790767504545455

00:50:27.024 --> 00:50:28.437 actually do the the work and

NOTE Confidence: 0.790767504545455

00:50:28.437 --> 00:50:29.859 folks that I'll mention here run

NOTE Confidence: 0.790767504545455

00:50:29.859 --> 00:50:31.779 to me or long time lab manager

NOTE Confidence: 0.790767504545455

00:50:31.779 --> 00:50:33.513 Colin who did the crisper screen.

NOTE Confidence: 0.790767504545455

00:50:33.520 --> 00:50:35.570 Kingston Lynn and the PhD

NOTE Confidence: 0.790767504545455

00:50:35.570 --> 00:50:36.800 student graduating soon.

NOTE Confidence: 0.790767504545455

00:50:36.800 --> 00:50:38.576 Pratik who did the post doc

NOTE Confidence: 0.790767504545455

00:50:38.576 --> 00:50:39.760 doing the AML work.

NOTE Confidence: 0.790767504545455

00:50:39.760 --> 00:50:41.699 And I've eluded some of the other

NOTE Confidence: 0.790767504545455

00:50:41.699 --> 00:50:43.384 folks like James and and others

NOTE Confidence: 0.790767504545455

00:50:43.384 --> 00:50:45.246 and then Susan Gable who now just

NOTE Confidence: 0.790767504545455

00:50:45.301 --> 00:50:47.166 started her laboratory and Juan

NOTE Confidence: 0.790767504545455

00:50:47.166 --> 00:50:49.104 Vasquez and of course the Herzog

NOTE Confidence: 0.790767504545455

00:50:49.104 --> 00:50:51.017 Laboratory who's been really a joint

NOTE Confidence: 0.790767504545455

00:50:51.017 --> 00:50:52.695 project through and through and then

NOTE Confidence: 0.790767504545455

00:50:52.695 --> 00:50:54.335 finally thank all the folks that

NOTE Confidence: 0.790767504545455

00:50:54.335 --> 00:50:56.160 fund our work and got ended on time.

NOTE Confidence: 0.790767504545455

00:50:56.160 --> 00:50:56.880 This is great.

NOTE Confidence: 0.790767504545455

00:50:56.880 --> 00:50:57.120 All right.

NOTE Confidence: 0.76173267625

00:51:04.440 --> 00:51:08.160 So we have time for questions or yeah, sorry

NOTE Confidence: 0.521108948666667

00:51:08.840 --> 00:51:11.153 the one you like your second or less of

NOTE Confidence: 0.521108948666667

00:51:11.153 --> 00:51:13.797 a second talk about immune interactions

NOTE Confidence: 0.521108948666667

00:51:13.800 --> 00:51:15.224 they've done about lung cancer,

NOTE Confidence: 0.521108948666667

00:51:15.224 --> 00:51:18.336 colon cancer and the DNA response problems.

NOTE Confidence: 0.521108948666667

00:51:18.336 --> 00:51:21.200 We know those are very sensitive in

NOTE Confidence: 0.521108948666667

00:51:21.200 --> 00:51:23.339 the but I wonder if the but how much

NOTE Confidence: 0.521108948666667

00:51:23.339 --> 00:51:25.290 are you pushing on the idea that you're

NOTE Confidence: 0.521108948666667

00:51:25.290 --> 00:51:27.458 going to be enhancing the effectiveness

NOTE Confidence: 0.521108948666667

00:51:27.458 --> 00:51:29.410 by also enhancing that pathway.

NOTE Confidence: 0.521108948666667

00:51:29.410 --> 00:51:30.635 We already know it was

NOTE Confidence: 0.366382148

00:51:33.440 --> 00:51:35.607 important that the so of of mismatch repair

NOTE Confidence: 0.366382148

00:51:35.607 --> 00:51:37.490 loss or yeah so it's interesting because

NOTE Confidence: 0.366382148

00:51:37.536 --> 00:51:39.360 you know there's been a lot of interest.

NOTE Confidence: 0.366382148

00:51:39.360 --> 00:51:41.346 I think this may diagonally answer

NOTE Confidence: 0.366382148

00:51:41.346 --> 00:51:43.619 your question and tell me if it doesn't

NOTE Confidence: 0.366382148

00:51:43.619 --> 00:51:46.352 is a lot of people are now trying to

NOTE Confidence: 0.366382148

00:51:46.352 --> 00:51:48.136 give tamazolamide to induce Microsoft

NOTE Confidence: 0.366382148

00:51:48.136 --> 00:51:50.280 instability and mismatch repair.

NOTE Confidence: 0.366382148

00:51:50.280 --> 00:51:52.009 And there's AGI trial of the air

NOTE Confidence: 0.366382148

00:51:52.009 --> 00:51:53.745 through the trial where they actually

NOTE Confidence: 0.366382148

00:51:53.745 --> 00:51:55.320 took MGMT silence colon cancer.

NOTE Confidence: 0.366382148

00:51:55.320 --> 00:51:56.544 And they found that when you

NOTE Confidence: 0.366382148

00:51:56.544 --> 00:51:58.080 give them TMZ the tumors respond,

NOTE Confidence: 0.366382148

00:51:58.080 --> 00:51:59.064 they become resistant,

NOTE Confidence: 0.366382148

00:51:59.064 --> 00:52:01.360 60% of them get mismatched pair mutations.

NOTE Confidence: 0.366382148

00:52:01.360 --> 00:52:03.475 And then they went on to get immunotherapy

NOTE Confidence: 0.366382148

00:52:03.475 --> 00:52:05.680 and they thought that they would respond

NOTE Confidence: 0.366382148

00:52:05.680 --> 00:52:07.837 but the responses were quite limited.

NOTE Confidence: 0.366382148

00:52:07.840 --> 00:52:10.560 And this is Keith Liggin up at up in

NOTE Confidence: 0.366382148

00:52:10.560 --> 00:52:12.410 Boston pathologist who would has shown

NOTE Confidence: 0.366382148

00:52:12.410 --> 00:52:14.405 that it's likely that there's just not

NOTE Confidence: 0.366382148

00:52:14.405 --> 00:52:16.359 enough time for NEO antigen formation.

NOTE Confidence: 0.366382148

00:52:16.360 --> 00:52:19.615 So I think acquired mismatch of pair

NOTE Confidence: 0.366382148

00:52:19.615 --> 00:52:21.428 mutations after TMZ for instance

NOTE Confidence: 0.366382148

00:52:21.428 --> 00:52:23.113 will not respond to immunotherapy

NOTE Confidence: 0.366382148

00:52:23.113 --> 00:52:24.398 like we think we did.

NOTE Confidence: 0.366382148

00:52:24.400 --> 00:52:26.297 We do think though the KL50 induced

NOTE Confidence: 0.366382148

00:52:26.297 --> 00:52:27.744 cross linking could be immunogenic

NOTE Confidence: 0.366382148

00:52:27.744 --> 00:52:29.199 cell death could sensitize that

NOTE Confidence: 0.366382148

00:52:29.199 --> 00:52:30.959 sort of gets at your question.

NOTE Confidence: 0.366382148

00:52:30.960 --> 00:52:31.200 But

NOTE Confidence: 0.18066235

00:52:33.240 --> 00:52:36.595 yeah it's beautiful work and I think

NOTE Confidence: 0.18066235

00:52:36.595 --> 00:52:38.360 you know your work illustrates to

NOTE Confidence: 0.694995168

00:52:38.360 --> 00:52:41.600 training is the power of having you

NOTE Confidence: 0.694995168

00:52:41.600 --> 00:52:43.900 know a broad perspective historically

NOTE Confidence: 0.694995168

00:52:43.900 --> 00:52:47.055 what what what didn't mean why and

NOTE Confidence: 0.694995168

00:52:47.055 --> 00:52:49.599 then the focus on individual residues,

NOTE Confidence: 0.694995168

00:52:49.600 --> 00:52:52.960 the obsession that you've shown in your work,

NOTE Confidence: 0.694995168

00:52:52.960 --> 00:52:56.024 you know the details of all of this work.

NOTE Confidence: 0.694995168

00:52:56.024 --> 00:52:57.572 So Congrats. Thank you.

NOTE Confidence: 0.694995168

00:52:57.572 --> 00:53:01.648 I I have a basic question.

NOTE Confidence: 0.694995168

00:53:01.648 --> 00:53:06.400 The MGMT dependency, this is related

NOTE Confidence: 0.694995168

00:53:06.400 --> 00:53:08.985 to the the tumor lacking that enzyme,

NOTE Confidence: 0.694995168

00:53:08.985 --> 00:53:10.635 but the wild type cells have

NOTE Confidence: 0.694995168

00:53:10.635 --> 00:53:12.237 that enzyme as you understand.

NOTE Confidence: 0.694995168

00:53:12.240 --> 00:53:14.438 Yeah. So that's in part a great

NOTE Confidence: 0.486917185

00:53:16.840 --> 00:53:19.640 tolman of specificity there. Yes. And

NOTE Confidence: 0.516340701666667

00:53:21.920 --> 00:53:24.280 I was a question. The question is,

NOTE Confidence: 0.25214335

00:53:28.520 --> 00:53:33.079 yeah, it's a tough crowd, tough crowd.

NOTE Confidence: 0.25214335

00:53:33.080 --> 00:53:34.720 Demetrius always asking questions. The

NOTE Confidence: 0.778426584285714

00:53:35.480 --> 00:53:36.368 question is, you know,

NOTE Confidence: 0.778426584285714

00:53:36.368 --> 00:53:37.502 I was thinking, you know,

NOTE Confidence: 0.778426584285714

00:53:37.502 --> 00:53:38.888 would it be useful to wash

110

NOTE Confidence: 0.778426584285714

00:53:38.888 --> 00:53:40.318 it out because you have,

NOTE Confidence: 0.778426584285714

00:53:40.320 --> 00:53:41.432 it's so sensitive. Right.

NOTE Confidence: 0.778426584285714

00:53:41.432 --> 00:53:42.822 So you could add back

NOTE Confidence: 0.778426584285714

00:53:42.822 --> 00:53:43.800 that enzyme essentially.

NOTE Confidence: 0.5585509425

00:53:44.560 --> 00:53:46.280 So. Oh, yeah. Yeah.

NOTE Confidence: 0.674997036153846

00:53:46.280 --> 00:53:47.864 Oh, interesting. And I don't know

NOTE Confidence: 0.674997036153846

00:53:47.864 --> 00:53:49.800 if that's if that would be useful,

NOTE Confidence: 0.674997036153846

00:53:49.800 --> 00:53:51.312 but it seems like your wild

NOTE Confidence: 0.674997036153846

00:53:51.312 --> 00:53:52.760 type does have that enzyme.

NOTE Confidence: 0.674997036153846

00:53:52.760 --> 00:53:54.195 So you're really not washing out there.

NOTE Confidence: 0.674997036153846

00:53:54.200 --> 00:53:56.475 I was thinking in terms of toxicity,

NOTE Confidence: 0.674997036153846

00:53:56.475 --> 00:53:59.520 but it will give you even greater.

NOTE Confidence: 0.674997036153846

00:53:59.520 --> 00:54:00.879 Yeah even wider

NOTE Confidence: 0.77165078

00:54:01.520 --> 00:54:02.192 dose. Yeah. Yeah.

NOTE Confidence: 0.77165078

00:54:02.192 --> 00:54:04.070 No, no, it's it's actually we're we

NOTE Confidence: 0.77165078

00:54:04.070 --> 00:54:06.599 have a it's kind of a secret project.

NOTE Confidence: 0.77165078

00:54:06.600 --> 00:54:09.040 Some grads didn't get mad if I talk about it.

NOTE Confidence: 0.77165078

00:54:09.040 --> 00:54:11.040 But we're trying to go the other way

NOTE Confidence: 0.77165078

00:54:11.040 --> 00:54:13.272 which is trying to like a radiation

NOTE Confidence: 0.77165078

00:54:13.272 --> 00:54:15.312 activated version where where you knock

NOTE Confidence: 0.77165078

00:54:15.312 --> 00:54:17.184 out MGMT like because MGT unmethylated

NOTE Confidence: 0.77165078

00:54:17.184 --> 00:54:19.344 tumors is a huge unmet need there

NOTE Confidence: 0.77165078

00:54:19.344 --> 00:54:20.874 because then the therapeutic index.

NOTE Confidence: 0.77165078

00:54:20.880 --> 00:54:21.864 So again this is a diagonal

NOTE Confidence: 0.77165078

00:54:21.864 --> 00:54:22.520 answer to your question,

NOTE Confidence: 0.77165078

00:54:22.520 --> 00:54:24.805 but where we could actually

NOTE Confidence: 0.77165078

00:54:24.805 --> 00:54:26.063 have MGMT inhibition,

NOTE Confidence: 0.77165078

00:54:26.063 --> 00:54:28.121 so O 6 pencil guanine that's

NOTE Confidence: 0.77165078

00:54:28.121 --> 00:54:30.400 activated only in the radiation field.

NOTE Confidence: 0.77165078

00:54:30.400 --> 00:54:31.744 So that's kind of one way

NOTE Confidence: 0.77165078

00:54:31.744 --> 00:54:32.640 we're getting at that.

00:54:32.640 --> 00:54:34.656 But to your point of some people have tried

00:54:34.656 --> 00:54:36.837 to do like rescue experiments and whatnot,

00:54:36.840 --> 00:54:38.240 I think it's it's hard,

00:54:38.240 --> 00:54:39.800 I think it would come down to to

00:54:39.800 --> 00:54:41.024 timing and sequencing just to

00:54:41.024 --> 00:54:42.596 try to magnify the therapy index.

00:54:42.600 --> 00:54:42.786 Yeah.

00:54:42.786 --> 00:54:43.158 In the

00:54:43.640 --> 00:54:46.356 animal studies that fail, do they fail

00:54:46.356 --> 00:54:49.960 because of progression? They fail, yeah,

00:54:51.680 --> 00:54:52.796 yeah. Yeah. I think,

00:54:52.796 --> 00:54:55.018 I think the therapeutic index is the issue

00:54:55.018 --> 00:54:56.994 with the mouse studies we show is is,

00:54:57.000 --> 00:54:59.344 is and we didn't show this because the

00:54:59.344 --> 00:55:01.212 companies mainly working on this is the

00:55:01.212 --> 00:55:03.239 Heen tox is is severely dose limiting.

NOTE Confidence: 0.7920387015

00:55:03.240 --> 00:55:06.440 And and actually even with KL50 the the,

NOTE Confidence: 0.7920387015

00:55:06.440 --> 00:55:08.197 the, the therapeutic index that we get

NOTE Confidence: 0.7920387015

00:55:08.197 --> 00:55:10.110 if you do a rat tolerability study

NOTE Confidence: 0.7920387015

00:55:10.110 --> 00:55:12.087 which is a better which I've been

NOTE Confidence: 0.7920387015

00:55:12.087 --> 00:55:14.175 taught is the is a better surrogate for

NOTE Confidence: 0.7920387015

00:55:14.175 --> 00:55:16.554 human Heen tox and like an actual rat.

NOTE Confidence: 0.7920387015

00:55:16.560 --> 00:55:18.078 Straight up you know, 30 day,

NOTE Confidence: 0.7920387015

00:55:18.080 --> 00:55:19.648 five day on observation.

NOTE Confidence: 0.7920387015

00:55:19.648 --> 00:55:22.000 The Heen tox is dose limiting.

NOTE Confidence: 0.7920387015

00:55:22.000 --> 00:55:23.480 And so that is probably the biggest issue.

NOTE Confidence: 0.7920387015

00:55:23.480 --> 00:55:24.480 That's interesting.

NOTE Confidence: 0.5216595525

00:55:26.520 --> 00:55:28.570 Think about dosing the blood

NOTE Confidence: 0.5216595525

00:55:28.570 --> 00:55:30.120 based enzyme like that. That's

NOTE Confidence: 0.793485329285714

00:55:30.120 --> 00:55:31.244 interesting. Oh yeah. Yeah.

NOTE Confidence: 0.793485329285714

00:55:31.244 --> 00:55:33.301 And they could be taken up in

NOTE Confidence: 0.793485329285714

00:55:33.301 --> 00:55:34.380 the Heen compartment. Yeah.

NOTE Confidence: 0.793485329285714

00:55:34.380 --> 00:55:35.264 We should talk actually.

NOTE Confidence: 0.793485329285714

00:55:35.264 --> 00:55:36.040 Yeah. Yeah. Yeah.

NOTE Confidence: 0.754584102

00:55:36.680 --> 00:55:37.704 It's something to consider.

NOTE Confidence: 0.754584102

00:55:37.704 --> 00:55:39.144 Yeah. Because if you're getting

NOTE Confidence: 0.754584102

00:55:39.144 --> 00:55:40.688 dose limiting tox. Yeah.

NOTE Confidence: 0.754584102

00:55:40.688 --> 00:55:42.648 You have this enzyme dependent,

NOTE Confidence: 0.754584102

00:55:42.648 --> 00:55:44.406 you know, to leave. Yeah. Yeah.

NOTE Confidence: 0.754584102

00:55:44.406 --> 00:55:45.200 There's a you might be able

NOTE Confidence: 0.754584102

00:55:45.200 --> 00:55:46.000 to take advantage of that,

NOTE Confidence: 0.754584102

00:55:46.000 --> 00:55:47.600 especially if it's Heen related.

NOTE Confidence: 0.531490425

00:55:48.080 --> 00:55:48.940 Yeah. We should talk later

NOTE Confidence: 0.531490425

00:55:48.940 --> 00:55:49.800 if there'd be an interesting

NOTE Confidence: 0.531490425

00:55:49.840 --> 00:55:50.720 way to selectively delivery.

NOTE Confidence: 0.531490425

00:55:50.720 --> 00:55:53.720 That's cool. Yeah. Yeah. Like,

NOTE Confidence: 0.6358923

00:55:55.760 --> 00:55:56.759 yeah, we'll see.

NOTE Confidence: 0.63761854

00:56:06.520 --> 00:56:07.000 Yeah.

NOTE Confidence: 0.5259187

00:56:14.120 --> 00:56:14.560 Yeah,

NOTE Confidence: 0.70450163

00:56:17.560 --> 00:56:18.560 100%, Yeah.

NOTE Confidence: 0.5181751

00:56:21.040 --> 00:56:23.852 Yeah, it's very, no,

NOTE Confidence: 0.5181751

00:56:23.852 --> 00:56:25.076 it's very stressful actually.

NOTE Confidence: 0.5181751

00:56:25.080 --> 00:56:27.036 We're thinking about this a lot

NOTE Confidence: 0.5181751

00:56:27.040 --> 00:56:28.590 both academically and then obviously

NOTE Confidence: 0.5181751

00:56:28.590 --> 00:56:30.140 the company but academically and

NOTE Confidence: 0.5181751

00:56:30.187 --> 00:56:31.903 actually been relying a lot of

NOTE Confidence: 0.5181751

00:56:31.903 --> 00:56:33.006 pathology colleagues here for

NOTE Confidence: 0.5181751

00:56:33.006 --> 00:56:34.584 for input because one thing I've

NOTE Confidence: 0.5181751

00:56:34.584 --> 00:56:36.038 been digging in the literature,

NOTE Confidence: 0.5181751

00:56:36.040 --> 00:56:37.465 it's like so MGMT promoter

NOTE Confidence: 0.5181751

00:56:37.465 --> 00:56:39.235 methylation as many people in this

NOTE Confidence: 0.5181751

00:56:39.235 --> 00:56:40.680 audience know better than me.

00:56:40.680 --> 00:56:42.264 You know it's sort of a cut off

00:56:42.264 --> 00:56:43.827 and sort of arbitrary and so but

00:56:43.827 --> 00:56:45.420 then on the same side we've been

00:56:45.420 --> 00:56:46.756 trying to do an MGMTIHC essay,

00:56:46.756 --> 00:56:48.184 we've been doing some TM as

00:56:48.184 --> 00:56:49.679 right now we're working on this

00:56:49.680 --> 00:56:52.560 working with Kurt and then others.

00:56:52.560 --> 00:56:55.213 And the issue with the MGMTIHC is it

00:56:55.213 --> 00:56:57.880 it seems to not be as the threshold,

00:56:57.880 --> 00:56:59.386 the dynamic range where even if

00:56:59.386 --> 00:57:01.196 it's out on IHC there's still

00:57:01.196 --> 00:57:02.318 low level expression.

00:57:02.320 --> 00:57:02.924 Craig Orbinski,

00:57:02.924 --> 00:57:05.038 I don't know if he's a neuropathologist

00:57:05.040 --> 00:57:06.395 at Northwestern talks about this

00:57:06.395 --> 00:57:08.312 all the time and the other elephant
NOTE Confidence: 0.5181751

00:57:08.312 --> 00:57:10.352 in his room is the IHC is negative.
NOTE Confidence: 0.5181751

00:57:10.360 --> 00:57:12.383 When you treat the TMZ there is
NOTE Confidence: 0.5181751

00:57:12.383 --> 00:57:14.670 some data that MGMT can be re
NOTE Confidence: 0.5181751

00:57:14.670 --> 00:57:16.365 expressed and depending on the
NOTE Confidence: 0.5181751

00:57:16.365 --> 00:57:18.316 promoter methylation sites and so.
NOTE Confidence: 0.5181751

00:57:18.316 --> 00:57:20.220 So what I think is going to be
NOTE Confidence: 0.5181751

00:57:20.285 --> 00:57:22.040 the answer is a combination.
NOTE Confidence: 0.5181751

00:57:22.040 --> 00:57:24.302 So in the colon cancer literature
NOTE Confidence: 0.5181751

00:57:24.302 --> 00:57:26.000 recently what they're doing is
NOTE Confidence: 0.5181751

00:57:26.000 --> 00:57:28.880 both IHC for MGMT and promoter
NOTE Confidence: 0.5181751

00:57:28.880 --> 00:57:30.348 methylation and they're actually
NOTE Confidence: 0.5181751

00:57:30.348 --> 00:57:31.872 doing this thing called the methyl
NOTE Confidence: 0.5181751

00:57:31.872 --> 00:57:33.264 beam assay which you guys probably
NOTE Confidence: 0.5181751

00:57:33.264 --> 00:57:34.912 know more than meets like a digital
NOTE Confidence: 0.5181751

00:57:34.912 --> 00:57:35.959 MGMT promoter methylation.

NOTE Confidence: 0.5181751

00:57:35.960 --> 00:57:37.556 So Long story short is I think

NOTE Confidence: 0.5181751

00:57:37.560 --> 00:57:39.732 trying to have a double selection

NOTE Confidence: 0.5181751

00:57:39.732 --> 00:57:41.582 for homogeneously silenced by IHC

NOTE Confidence: 0.5181751

00:57:41.582 --> 00:57:43.616 and meets the criteria for promoter

NOTE Confidence: 0.5181751

00:57:43.616 --> 00:57:45.781 methylation will be key because there

NOTE Confidence: 0.5181751

00:57:45.781 --> 00:57:47.591 are partially methylated cases that

NOTE Confidence: 0.5181751

00:57:47.591 --> 00:57:49.160 are going to totally screw this up.

NOTE Confidence: 0.5181751

00:57:49.160 --> 00:57:49.960 It's related

NOTE Confidence: 0.65060273

00:57:51.360 --> 00:57:51.640 but I

NOTE Confidence: 0.6487414

00:57:54.400 --> 00:57:55.560 don't know, I don't want

NOTE Confidence: 0.446819254

00:57:58.440 --> 00:58:01.040 that. Oh yeah, because they are, yeah,

NOTE Confidence: 0.446819254

00:58:01.360 --> 00:58:03.079 100% yeah, so so TET is some of the,

NOTE Confidence: 0.446819254

00:58:03.080 --> 00:58:05.005 you know as question was

NOTE Confidence: 0.446819254

00:58:05.005 --> 00:58:06.160 about TET expression.

NOTE Confidence: 0.446819254

00:58:06.160 --> 00:58:10.176 So mutations in the 10/10/11 trans low case,

NOTE Confidence: 0.446819254

00:58:10.176 --> 00:58:12.396 which is hydroxy methyl cytosine

NOTE Confidence: 0.446819254

00:58:12.396 --> 00:58:13.434 maintenance in AML.

NOTE Confidence: 0.446819254

00:58:13.434 --> 00:58:15.216 We're doing this with Stephanie Helene's

NOTE Confidence: 0.446819254

00:58:15.216 --> 00:58:17.440 lab where TET mutations are common.

NOTE Confidence: 0.446819254

00:58:17.440 --> 00:58:19.552 We're trying to see if TET will be

NOTE Confidence: 0.446819254

00:58:19.552 --> 00:58:21.476 a predictor for MGMT expression and

NOTE Confidence: 0.446819254

00:58:21.476 --> 00:58:23.474 IDH mutations as many people know,

NOTE Confidence: 0.446819254

00:58:23.480 --> 00:58:24.580 inhibit TET as well.

NOTE Confidence: 0.446819254

00:58:24.580 --> 00:58:25.955 That's another project that we're

NOTE Confidence: 0.446819254

00:58:25.955 --> 00:58:27.463 trying to get that which has been

NOTE Confidence: 0.446819254

00:58:27.463 --> 00:58:28.800 harder to do than we thought.

NOTE Confidence: 0.446819254

00:58:28.800 --> 00:58:29.958 But yeah, it's a great question.

NOTE Confidence: 0.446819254

00:58:29.960 --> 00:58:31.200 Yeah, I have a question.

NOTE Confidence: 0.603680027777778

00:58:31.320 --> 00:58:33.696 One of the sort of tumor you showed

NOTE Confidence: 0.603680027777778

00:58:33.696 --> 00:58:36.520 with MGMT insulation is breast cancer,

NOTE Confidence: 0.603680027777778

00:58:36.520 --> 00:58:38.171 breast cancer with the DRC one

NOTE Confidence: 0.603680027777778

00:58:38.171 --> 00:58:39.359 deficiency in general line,

NOTE Confidence: 0.603680027777778

00:58:39.360 --> 00:58:41.120 the bottom is really nice.

NOTE Confidence: 0.603680027777778

00:58:41.120 --> 00:58:42.944 And the other showroom MIC mutation.

NOTE Confidence: 0.603680027777778

00:58:42.944 --> 00:58:45.248 But when they used it in

NOTE Confidence: 0.603680027777778

00:58:45.248 --> 00:58:46.400 the semantic mutation,

NOTE Confidence: 0.603680027777778

00:58:46.400 --> 00:58:48.815 the trial team made it and they

NOTE Confidence: 0.603680027777778

00:58:48.815 --> 00:58:51.920 did the HR score and they should

NOTE Confidence: 0.603680027777778

00:58:51.920 --> 00:58:53.760 benefit from Barbara negative.

NOTE Confidence: 0.603680027777778

00:58:53.760 --> 00:58:54.796 They only have semantic.

NOTE Confidence: 0.603680027777778

00:58:54.796 --> 00:58:56.840 So what's your thought the HR revealed?

NOTE Confidence: 0.603680027777778

00:58:56.840 --> 00:58:58.178 Mm hmm. Mm

NOTE Confidence: 0.788802108

00:58:58.180 --> 00:59:01.040 hmm. Yeah. I mean for you know,

NOTE Confidence: 0.788802108

00:59:01.040 --> 00:59:02.120 for that, that's a great question.

NOTE Confidence: 0.788802108

00:59:02.120 --> 00:59:03.255 I mean, there's even questions

NOTE Confidence: 0.788802108

00:59:03.255 --> 00:59:04.720 about loss of the second allele.

NOTE Confidence: 0.788802108

00:59:04.720 --> 00:59:06.540 Susan, Don check at Pennis

NOTE Confidence: 0.788802108

00:59:06.540 --> 00:59:08.360 asked that question as well.

NOTE Confidence: 0.788802108

00:59:08.360 --> 00:59:09.860 It's confounded though because I think

NOTE Confidence: 0.788802108

00:59:09.860 --> 00:59:11.637 the new PARP one selective PARP numbers

NOTE Confidence: 0.788802108

00:59:11.637 --> 00:59:13.560 that you like like AZD 5 three O 5,

NOTE Confidence: 0.788802108

00:59:13.560 --> 00:59:15.824 I think they may be able to get

NOTE Confidence: 0.788802108

00:59:15.824 --> 00:59:18.110 enough PARP inhibition to hit even

NOTE Confidence: 0.788802108

00:59:18.110 --> 00:59:19.760 if it's a happenence efficiency.

NOTE Confidence: 0.788802108

00:59:19.760 --> 00:59:22.077 But you know, on a side note,

NOTE Confidence: 0.788802108

00:59:22.080 --> 00:59:24.360 we're also looking at MGMT loss and HRD,

NOTE Confidence: 0.788802108

00:59:24.360 --> 00:59:26.475 this is Susan Gables Labs doing that as well.

NOTE Confidence: 0.788802108

00:59:26.480 --> 00:59:27.320 I don't know if I have a

NOTE Confidence: 0.788802108

00:59:27.320 --> 00:59:28.040 full answer for you though.

NOTE Confidence: 0.788802108

00:59:28.040 --> 00:59:28.760 Yeah, good, great.

NOTE Confidence: 0.788802108

00:59:28.760 --> 00:59:29.720 So I just wanted

NOTE Confidence: 0.721014983333333

00:59:31.440 --> 00:59:36.280 to know how how much question.

00:59:41.840 --> 00:59:43.440 Yeah, it's it's it's we're

00:59:43.440 --> 00:59:44.400 alluding this earlier.

00:59:44.400 --> 00:59:46.860 I think the correlation between

00:59:46.860 --> 00:59:48.828 MGMT promoter silencing and

00:59:48.828 --> 00:59:50.331 and MMGMT protein expression,

00:59:50.331 --> 00:59:52.353 it's quite variable and that's it's

00:59:52.353 --> 00:59:55.180 a little bit in the glioma world if

00:59:55.180 --> 00:59:57.172 you're promoter methylated MGM TS out.

00:59:57.172 --> 00:59:58.876 But in other cancers they're finding

00:59:58.876 --> 01:00:01.047 that you can be promoter methylated but

01:00:01.047 --> 01:00:03.079 still express MGMT the protein level.

01:00:03.080 --> 01:00:04.440 So I think there's a lot of variability,

01:00:04.440 --> 01:00:05.344 which is I think.

01:00:05.344 --> 01:00:07.002 Going to be important especially for this

01:00:07.002 --> 01:00:08.794 because the MGMT dependency is so exquisite.

01:00:08.800 --> 01:00:12.512 So great. Cool.

NOTE Confidence: 0.61136632625

01:00:12.512 --> 01:00:13.880 I think we're at the top of the hour.

NOTE Confidence: 0.61136632625

01:00:13.880 --> 01:00:16.000 Thank you.