WEBVTT

00:00:00.000 --> 00:00:02.015 Everyone for attending this week's

00:00:02.015 --> 00:00:04.540 grant Yo Council Center grand rounds.

00:00:04.540 --> 00:00:08.236 It's my privilege and pleasure to introduce

00:00:08.236 --> 00:00:12.069 Dr Juan Vasquez for this this week talk.

00:00:12.070 --> 00:00:14.005 Dr Vasquez is an assistant

00:00:14.005 --> 00:00:15.166 professor of Pediatrics.

00:00:15.170 --> 00:00:16.470 He received his medical degree

00:00:16.470 --> 00:00:18.080 from Brown University and a Master

00:00:18.080 --> 00:00:19.385 of Health Science from Yale,

00:00:19.390 --> 00:00:21.814 where he also completed his fellowship

00:00:21.814 --> 00:00:23.430 in Pediatric Hematology Oncology.

00:00:23.430 --> 00:00:24.800 His clinical focus on the

00:00:24.800 --> 00:00:26.170 care of children with cancer,

00:00:26.170 --> 00:00:27.775 particularly solid tumors,

NOTE Confidence: 0.776826744545455

00:00:27.775 --> 00:00:29.380 as reachers research,

NOTE Confidence: 0.776826744545455

00:00:29.380 --> 00:00:30.965 is focused on the development

NOTE Confidence: 0.776826744545455

00:00:30.965 --> 00:00:31.599 of immunotherapy.

NOTE Confidence: 0.776826744545455

00:00:31.600 --> 00:00:33.073 For pediatric tumors,

NOTE Confidence: 0.776826744545455

00:00:33.073 --> 00:00:35.037 particularly malignant brain tumors,

NOTE Confidence: 0.776826744545455

00:00:35.040 --> 00:00:36.424 he's interested in characterizing

NOTE Confidence: 0.776826744545455

00:00:36.424 --> 00:00:38.154 the immune landscape of pediatric

NOTE Confidence: 0.776826744545455

00:00:38.154 --> 00:00:39.488 brain tumors and understanding

NOTE Confidence: 0.776826744545455

00:00:39.488 --> 00:00:41.053 the interplay between DNA repair

NOTE Confidence: 0.776826744545455

00:00:41.053 --> 00:00:42.768 and anti tumor immune response.

NOTE Confidence: 0.776826744545455

00:00:42.770 --> 00:00:44.960 One is been an embedded assistant

NOTE Confidence: 0.776826744545455

00:00:44.960 --> 00:00:47.024 professor in our laboratory for a

NOTE Confidence: 0.776826744545455

00:00:47.024 --> 00:00:48.907 little over two years now and is

NOTE Confidence: 0.776826744545455

00:00:48.907 --> 00:00:51.454 really hit the ground running as

NOTE Confidence: 0.776826744545455

00:00:51.454 --> 00:00:52.780 rapidly approaching independence.

NOTE Confidence: 0.776826744545455

00:00:52.780 --> 00:00:55.138 On that note, he did recently receive his KO,

NOTE Confidence: 0.776826744545455

00:00:55.140 --> 00:00:56.640 a career development grant to

NOTE Confidence: 0.776826744545455

00:00:56.640 --> 00:00:57.540 fund this project,

NOTE Confidence: 0.776826744545455

00:00:57.540 --> 00:00:59.118 which will be talking about today.

NOTE Confidence: 0.776826744545455

00:00:59.120 --> 00:01:01.920 So with that I will let one take.

NOTE Confidence: 0.776826744545455

00:01:01.920 --> 00:01:03.388 Take the show away.

NOTE Confidence: 0.77283492

00:01:08.390 --> 00:01:10.060 Great thank you Ranjit Saunders

NOTE Confidence: 0.77283492

00:01:10.060 --> 00:01:11.396 Commissioner my screen here.

NOTE Confidence: 0.90387700375

00:01:28.610 --> 00:01:31.234 All right? Can you see my screen OK?

NOTE Confidence: 0.951264578333333

00:01:33.720 --> 00:01:36.360 Great. Alright, so thank you again.

NOTE Confidence: 0.951264578333333

00:01:36.360 --> 00:01:37.795 It's a real honor to be able

NOTE Confidence: 0.951264578333333

00:01:37.795 --> 00:01:38.940 to present for you today.

NOTE Confidence: 0.951264578333333

00:01:38.940 --> 00:01:40.980 An uncle metabolite induced

NOTE Confidence: 0.951264578333333

00:01:40.980 --> 00:01:43.020 repair DNA repair defects.

NOTE Confidence: 0.951264578333333

00:01:43.020 --> 00:01:47.330 Uhm? I've got no disclosures.

NOTE Confidence: 0.951264578333333

00:01:47.330 --> 00:01:50.282 So today I'll briefly review some

NOTE Confidence: 0.951264578333333

00:01:50.282 --> 00:01:52.250 background on Uncle Metabolite

NOTE Confidence: 0.951264578333333

00:01:52.332 --> 00:01:54.408 induced DNA repair defects,

NOTE Confidence: 0.951264578333333

00:01:54.410 --> 00:01:56.198 which really was established by the

NOTE Confidence: 0.951264578333333

00:01:56.198 --> 00:01:58.329 seminal work of my research mentor.

NOTE Confidence: 0.951264578333333

00:01:58.330 --> 00:02:00.826 Doctor Ben drove heard from as well as

NOTE Confidence: 0.951264578333333

00:02:00.826 --> 00:02:03.600 Doctor Peter Glaser here at Yale and in

NOTE Confidence: 0.951264578333333

00:02:03.600 --> 00:02:05.549 collaboration with Brian Shuck at UCLA.

NOTE Confidence: 0.951264578333333

00:02:05.550 --> 00:02:07.916 Also present some of our work on

NOTE Confidence: 0.951264578333333

00:02:07.916 --> 00:02:10.016 targeting DNA damage response pathways

NOTE Confidence: 0.951264578333333

00:02:10.016 --> 00:02:12.566 and uncle metabolite producing tumors.

NOTE Confidence: 0.951264578333333

00:02:12.570 --> 00:02:13.278 And then lastly,

NOTE Confidence: 0.951264578333333

00:02:13.278 --> 00:02:14.930 I'll touch a bit on the potential

NOTE Confidence: 0.951264578333333

00:02:14.979 --> 00:02:16.327 for exploiting these uncle

NOTE Confidence: 0.951264578333333

00:02:16.327 --> 00:02:17.338 metabolite induced DNA.

NOTE Confidence: 0.951264578333333

00:02:17.340 --> 00:02:20.154 Repair defects in order to promote an

NOTE Confidence: 0.951264578333333

00:02:20.154 --> 00:02:21.360 inflammatory tumor microenvironment

NOTE Confidence: 0.951264578333333

00:02:21.418 --> 00:02:23.274 and potentially synergized with

NOTE Confidence: 0.951264578333333

00:02:23.274 --> 00:02:24.666 immune checkpoint blockade.

NOTE Confidence: 0.824376642857143

00:02:29.320 --> 00:02:31.518 So just as a very brief reminder,

NOTE Confidence: 0.824376642857143

00:02:31.520 --> 00:02:34.012 the Krebs cycle is very important in

NOTE Confidence: 0.824376642857143

00:02:34.012 --> 00:02:35.742 cellular energy production and alpha

NOTE Confidence: 0.824376642857143

00:02:35.742 --> 00:02:37.842 ketoglutarate is a is a key intermediate

NOTE Confidence: 0.824376642857143

00:02:37.842 --> 00:02:40.676 in the Krebs cycle and Alpha Ketoglutarate

NOTE Confidence: 0.824376642857143

00:02:40.676 --> 00:02:42.823 dependent dioxygenase is regulate a

NOTE Confidence: 0.824376642857143

00:02:42.823 --> 00:02:45.288 number of key cellular processes.

NOTE Confidence: 0.824376642857143

00:02:45.290 --> 00:02:47.432 Mutations in enzymes of the Krebs cycle

NOTE Confidence: 0.824376642857143

00:02:47.432 --> 00:02:50.193 result in an excess accumulation of two

NOTE Confidence: 0.824376642857143

00:02:50.193 --> 00:02:52.418 hydroxy glutarate succinate and fumarate,

NOTE Confidence: 0.824376642857143

00:02:52.420 --> 00:02:53.866 and I'll go through these in

NOTE Confidence: 0.824376642857143

00:02:53.866 --> 00:02:55.610 more detail in the coming slides.

NOTE Confidence: 0.824376642857143

00:02:55.610 --> 00:02:57.146 But in general,

NOTE Confidence: 0.824376642857143

00:02:57.146 --> 00:02:59.194 these uncle metabolites competitively

NOTE Confidence: 0.824376642857143

00:02:59.194 --> 00:03:01.254 inhibit alpha ketoglutarate dependent

NOTE Confidence: 0.824376642857143

00:03:01.254 --> 00:03:04.446 dioxygenase is by virtue of their structural

NOTE Confidence: 0.824376642857143

00:03:04.446 --> 00:03:06.622 similarity there by dysregulating AKI,

NOTE Confidence: 0.824376642857143

00:03:06.622 --> 00:03:09.190 variety of downstream cellular processes and

NOTE Confidence: 0.824376642857143

00:03:09.252 --> 00:03:11.747 resulting in prolonged congenic signaling,

NOTE Confidence: 0.824376642857143

00:03:11.750 --> 00:03:14.424 and this is really why there are

NOTE Confidence: 0.824376642857143

00:03:14.424 --> 00:03:17.029 classified now is uncle metabolites.

NOTE Confidence: 0.824376642857143

00:03:17.030 --> 00:03:20.252 So focusing first on IDH mutations

NOTE Confidence: 0.824376642857143

00:03:20.252 --> 00:03:23.024 or isocitrate dehydrogenase so IDH

NOTE Confidence: 0.824376642857143

00:03:23.024 --> 00:03:25.332 catalyzes the oxidation oxidative

NOTE Confidence: 0.824376642857143

00:03:25.332 --> 00:03:27.063 decarboxylation of isocitrate

NOTE Confidence: 0.824376642857143

00:03:27.063 --> 00:03:29.230 producing alpha keto glutarate.

NOTE Confidence: 0.824376642857143

00:03:29.230 --> 00:03:31.115 Uhm, and these heterozygous IDH

NOTE Confidence: 0.824376642857143

00:03:31.115 --> 00:03:33.524 mutations result in a new amorphic

NOTE Confidence: 0.824376642857143

00:03:33.524 --> 00:03:35.774 activity of that enzyme whereby

NOTE Confidence: 0.824376642857143

00:03:35.774 --> 00:03:38.144 alpha ketoglutarate is then further

NOTE Confidence: 0.824376642857143

00:03:38.144 --> 00:03:40.629 converted into two hydroxy glutarate.

NOTE Confidence: 0.824376642857143

00:03:40.630 --> 00:03:43.850 And most commonly are missense

NOTE Confidence: 0.824376642857143

00:03:43.850 --> 00:03:46.426 arginine to histidine mutations.

NOTE Confidence: 0.824376642857143

00:03:46.430 --> 00:03:48.208 Make up about 70% of all these

NOTE Confidence: 0.824376642857143

00:03:48.208 --> 00:03:49.826 mutations and you can see IDH

NOTE Confidence: 0.824376642857143

00:03:49.826 --> 00:03:51.416 mutations in a variety of tumors.

NOTE Confidence: 0.824376642857143

00:03:51.420 --> 00:03:54.171 Most most commonly in low grade gliomas

NOTE Confidence: 0.824376642857143

00:03:54.171 --> 00:03:57.510 and secondary GBM's as well as AML and

NOTE Confidence: 0.824376642857143

00:03:57.510 --> 00:03:59.210 chondrosarcoma and cholangio carcinoma.

NOTE Confidence: 0.877308717142857

00:04:01.610 --> 00:04:03.647 Further on down to the Krebs cycle

NOTE Confidence: 0.877308717142857

00:04:03.650 --> 00:04:05.458 succinate dehydrogenase catalyzes the

NOTE Confidence: 0.877308717142857

00:04:05.458 --> 00:04:07.718 oxidation of succinate to fumarate

NOTE Confidence: 0.877308717142857

00:04:07.718 --> 00:04:09.501 and fumarate hydratase catalyzes

NOTE Confidence: 0.877308717142857

00:04:09.501 --> 00:04:12.039 the hydration of fumarate to malate

NOTE Confidence: 0.877308717142857

00:04:12.040 --> 00:04:13.584 germline heterozygotes loss of

NOTE Confidence: 0.877308717142857

00:04:13.584 --> 00:04:15.514 function mutations in these genes

NOTE Confidence: 0.877308717142857

00:04:15.514 --> 00:04:17.489 are associated with a predisposition

NOTE Confidence: 0.877308717142857

00:04:17.489 --> 00:04:19.775 to cancer formation thought to act

NOTE Confidence: 0.877308717142857

00:04:19.834 --> 00:04:21.742 through a two hit hypothesis whereby

NOTE Confidence: 0.877308717142857

00:04:21.742 --> 00:04:23.562 tumors have loss of heterozygosity,

NOTE Confidence: 0.877308717142857

00:04:23.562 --> 00:04:25.730 leading to excess accumulation

NOTE Confidence: 0.877308717142857

00:04:25.730 --> 00:04:27.898 of femur and succinate.

NOTE Confidence: 0.877308717142857

00:04:27.900 --> 00:04:29.552 Germline FH mutations predispose

NOTE Confidence: 0.877308717142857

00:04:29.552 --> 00:04:31.204 to hereditary leiomyoma ptosis

NOTE Confidence: 0.877308717142857

00:04:31.204 --> 00:04:32.999 and renal cancer syndrome.

NOTE Confidence: 0.877308717142857

00:04:33.000 --> 00:04:36.288 And germline SDH mutations predispose to

NOTE Confidence: 0.877308717142857

00:04:36.288 --> 00:04:38.480 succinate dehydrogenase related hereditary

NOTE Confidence: 0.877308717142857

00:04:38.552 --> 00:04:40.028 paraganglioma and pheochromocytoma

NOTE Confidence: 0.877308717142857

00:04:40.028 --> 00:04:42.980 as well as renal cell carcinoma.

NOTE Confidence: 0.877308717142857

00:04:42.980 --> 00:04:43.530 And, importantly,

NOTE Confidence: 0.877308717142857

00:04:43.530 --> 00:04:45.180 renal cell carcinoma in the setting

NOTE Confidence: 0.877308717142857

00:04:45.180 --> 00:04:46.955 of both these syndromes is typically

NOTE Confidence: 0.877308717142857

00:04:46.955 --> 00:04:48.713 aggressive with a high propensity to

NOTE Confidence: 0.877308717142857

00:04:48.767 --> 00:04:50.501 present with metastases early in disease

NOTE Confidence: 0.877308717142857

00:04:50.501 --> 00:04:52.465 and once these patients metastasize,

NOTE Confidence: 0.877308717142857

00:04:52.465 --> 00:04:56.490 very limited treatment options exist.

NOTE Confidence: 0.877308717142857

00:04:56.490 --> 00:04:57.840 So, as I mentioned before,

NOTE Confidence: 0.877308717142857

00:04:57.840 --> 00:04:59.556 this is a field really pioneered

NOTE Confidence: 0.877308717142857

00:04:59.556 --> 00:05:00.866 by Doctor Benjamin, Dr.

NOTE Confidence: 0.877308717142857

00:05:00.866 --> 00:05:02.650 Glaser and former grad

NOTE Confidence: 0.877308717142857

00:05:02.650 --> 00:05:03.988 student portal Cylkowski,

NOTE Confidence: 0.877308717142857

00:05:03.990 --> 00:05:06.888 and a series of high impact publications

NOTE Confidence: 0.877308717142857

00:05:06.888 --> 00:05:09.092 where uncle Metabolites were found

NOTE Confidence: 0.877308717142857

00:05:09.092 --> 00:05:10.876 to inhibit homologous recombination

NOTE Confidence: 0.877308717142857

00:05:10.876 --> 00:05:13.510 and confer prohibit or sensitivity.

NOTE Confidence: 0.877308717142857

00:05:13.510 --> 00:05:15.466 So I'm just going to very

NOTE Confidence: 0.877308717142857

00:05:15.466 --> 00:05:16.770 briefly summarize this work,

NOTE Confidence: 0.877308717142857

00:05:16.770 --> 00:05:19.482 but what they found is uncle

NOTE Confidence: 0.877308717142857

00:05:19.482 --> 00:05:21.290 metabolites inhibit alpha ketoglutarate

NOTE Confidence: 0.877308717142857

00:05:21.366 --> 00:05:22.998 dependent histone lysine demethylase

NOTE Confidence: 0.877308717142857

00:05:22.998 --> 00:05:26.198 is KTM 4 AMB leading to a Baron

NOTE Confidence: 0.877308717142857

00:05:26.198 --> 00:05:27.766 hypermethylation of histone 3,

NOTE Confidence: 0.877308717142857

00:05:27.770 --> 00:05:32.270 lysine 9 or HK H3K9 at loci

NOTE Confidence: 0.877308717142857

00:05:32.270 --> 00:05:33.770 surrounding DNA breaks.

NOTE Confidence: 0.877308717142857

00:05:33.770 --> 00:05:36.220 So they used a really elegant double

NOTE Confidence: 0.877308717142857

00:05:36.220 --> 00:05:38.049 strand break chip seek assay,

NOTE Confidence: 0.877308717142857

00:05:38.050 --> 00:05:41.386 in which you can see that control cells

NOTE Confidence: 0.877308717142857

00:05:41.390 --> 00:05:44.150 there's a spike of H3K9 trimethylation.

NOTE Confidence: 0.877308717142857

00:05:44.150 --> 00:05:45.995 That induced double strand breaks

NOTE Confidence: 0.877308717142857

00:05:45.995 --> 00:05:47.840 followed by a coordinated recruitment

NOTE Confidence: 0.877308717142857

00:05:47.894 --> 00:05:49.868 of double strand break repair factors.

NOTE Confidence: 0.877308717142857

00:05:49.870 --> 00:05:50.340 However,

NOTE Confidence: 0.877308717142857

00:05:50.340 --> 00:05:53.160 in cells with an uncle metabolite

NOTE Confidence: 0.877308717142857

00:05:53.160 --> 00:05:55.150 succinate fumarate and two HG,

NOTE Confidence: 0.877308717142857

00:05:55.150 --> 00:05:56.602 there is H3K9 trimethylation

NOTE Confidence: 0.877308717142857

00:05:56.602 --> 00:05:58.780 already present at the site before

NOTE Confidence: 0.877308717142857

00:05:58.840 --> 00:06:00.800 induction of double strand breaks,

NOTE Confidence: 0.877308717142857

00:06:00.800 --> 00:06:02.828 and this really serves to mask

NOTE Confidence: 0.877308717142857

00:06:02.828 --> 00:06:04.180 that local trimethylation signal

NOTE Confidence: 0.877308717142857

00:06:04.240 --> 00:06:06.132 that's important for triggering

NOTE Confidence: 0.877308717142857

00:06:06.132 --> 00:06:08.024 proper recruitment of homologous

NOTE Confidence: 0.877308717142857

00:06:08.024 --> 00:06:08.970 recombination proteins,

NOTE Confidence: 0.877308717142857

00:06:08.970 --> 00:06:10.382 essentially leading to defective

NOTE Confidence: 0.877308717142857

00:06:10.382 --> 00:06:12.500 HR and a bracken NIST phenotype.

NOTE Confidence: 0.87331146

00:06:14.510 --> 00:06:17.198 So now just to very briefly and generally

NOTE Confidence: 0.87331146

00:06:17.198 --> 00:06:19.708 introduce the topic of synthetic lethality.

NOTE Confidence: 0.87331146

00:06:19.710 --> 00:06:21.447 So as you can see here from this figure,

NOTE Confidence: 0.87331146

00:06:21.450 --> 00:06:24.715 part is really an important enzyme

NOTE Confidence: 0.87331146

00:06:24.715 --> 00:06:27.060 involved in the repair of single strand

NOTE Confidence: 0.87331146

00:06:27.060 --> 00:06:29.020 breaks during basic scission repair.

NOTE Confidence: 0.87331146

00:06:29.020 --> 00:06:31.588 Pop inhibition and results in impaired

NOTE Confidence: 0.87331146

00:06:31.588 --> 00:06:33.910 based excision repair and converts

NOTE Confidence: 0.87331146

00:06:33.910 --> 00:06:35.535 single strand then single strand

NOTE Confidence: 0.87331146

00:06:35.535 --> 00:06:37.518 breaks are converted to double strand

NOTE Confidence: 0.87331146

00:06:37.518 --> 00:06:39.646 breaks in the in the process of

NOTE Confidence: 0.87331146

00:06:39.646 --> 00:06:41.493 cellular replication in cells with

NOTE Confidence: 0.87331146

00:06:41.493 --> 00:06:43.137 an intact homologous recombination.

NOTE Confidence: 0.87331146

00:06:43.140 --> 00:06:44.450 This DNA damage is effectively

NOTE Confidence: 0.87331146

00:06:44.450 --> 00:06:46.220 repaired and you have cell survival.

NOTE Confidence: 0.87331146

00:06:46.220 --> 00:06:48.660 However, in the setting of an HR deficiency,

NOTE Confidence: 0.87331146

00:06:48.660 --> 00:06:50.280 there's a buildup or accumulation

NOTE Confidence: 0.87331146

00:06:50.280 --> 00:06:51.576 of unrepaired DNA damage,

NOTE Confidence: 0.87331146

00:06:51.580 --> 00:06:53.190 ultimately leading to cell death and this

NOTE Confidence: 0.87331146

00:06:53.190 --> 00:06:54.909 is this idea of synthetic lethality.

NOTE Confidence: 0.780967909444445

00:06:57.090 --> 00:06:58.878 So this same synthetic lethality was

NOTE Confidence: 0.780967909444445

00:06:58.878 --> 00:07:01.262 found also in the setting of uncle

NOTE Confidence: 0.780967909444445

00:07:01.262 --> 00:07:03.157 metabolite induced DNA repair defects.

NOTE Confidence: 0.780967909444445

00:07:03.160 --> 00:07:05.148 So just looking at just a snippet

NOTE Confidence: 0.780967909444445

00:07:05.148 --> 00:07:07.737 of that data you can see here in the

NOTE Confidence: 0.780967909444445

00:07:07.737 --> 00:07:10.028 isagenix model and he LA cells with IDH,

NOTE Confidence: 0.780967909444445

00:07:10.030 --> 00:07:14.506 wildtype and I DH R132H mutant.

NOTE Confidence: 0.780967909444445

00:07:14.510 --> 00:07:16.245 There's an increased amount of

NOTE Confidence: 0.780967909444445

00:07:16.245 --> 00:07:17.633 baseline unrepaired DNA damage,

NOTE Confidence: 0.780967909444445

00:07:17.640 --> 00:07:20.440 and this is as measured through a

NOTE Confidence: 0.780967909444445

00:07:20.440 --> 00:07:23.128 common tale essay where damaged DNA.

NOTE Confidence: 0.780967909444445

00:07:23.130 --> 00:07:25.086 As its nucleus informs US, Comet tail,

NOTE Confidence: 0.780967909444445

00:07:25.086 --> 00:07:27.026 which is his representative unrepaired

00:07:27.026 --> 00:07:29.707 DNA damage and you can see that IDH

00:07:29.707 --> 00:07:31.544 mutant Tumors Harbor an increased

00:07:31.544 --> 00:07:33.634 amount of damage at baseline.

00:07:33.640 --> 00:07:35.240 Uh, additionally looking here

00:07:35.240 --> 00:07:37.240 at a clonogenic survival assay,

00:07:37.240 --> 00:07:39.568 you can see that these cells,

00:07:39.570 --> 00:07:41.826 these IDH mutant cells have more

00:07:41.826 --> 00:07:43.330 sensitivity to irreparably than

00:07:43.394 --> 00:07:45.098 their wild type counterparts,

00:07:45.100 --> 00:07:48.180 and the same was seen in in vivo.

00:07:48.180 --> 00:07:50.292 A study using HTTR human cancer

00:07:50.292 --> 00:07:52.514 colon cancer cell line with an

00:07:52.514 --> 00:07:54.374 IDH mutation where these tumors

00:07:54.374 --> 00:07:56.600 were sensitive to PARP inhibition,

00:07:56.600 --> 00:07:58.290 leading to delayed tumor growth.

NOTE Confidence: 0.944530772

00:08:01.750 --> 00:08:03.750 Similarly, in a subsequent study,

NOTE Confidence: 0.944530772

00:08:03.750 --> 00:08:06.456 a similar DNA repair defects and

NOTE Confidence: 0.944530772

00:08:06.456 --> 00:08:08.260 corporate hipper sensitivity were

NOTE Confidence: 0.944530772

00:08:08.330 --> 00:08:10.857 shown in FH and SDH deficient models.

NOTE Confidence: 0.944530772

00:08:10.860 --> 00:08:15.207 So looking here now at a collection of human.

NOTE Confidence: 0.944530772

00:08:15.210 --> 00:08:18.300 Tissues, let's see.

NOTE Confidence: 0.944530772

00:08:18.300 --> 00:08:20.910 You can see that again compared

NOTE Confidence: 0.944530772

00:08:20.910 --> 00:08:22.215 to normal tissues.

NOTE Confidence: 0.944530772

00:08:22.220 --> 00:08:24.146 Those with SDHB mutations in FH

NOTE Confidence: 0.944530772

00:08:24.146 --> 00:08:25.828 mutations have an increased amount

NOTE Confidence: 0.944530772

00:08:25.828 --> 00:08:27.508 of baseline DNA repair damage.

NOTE Confidence: 0.944530772

00:08:27.510 --> 00:08:29.352 I mean sorry baseline DNA damage

NOTE Confidence: 0.944530772

00:08:29.352 --> 00:08:31.353 and then here looking at a FH

NOTE Confidence: 0.944530772

00:08:31.353 --> 00:08:33.019 deficient PDX model you can see in

NOTE Confidence: 0.944530772

00:08:33.085 --> 00:08:34.960 vivo there's delayed tumor growth

NOTE Confidence: 0.944530772

00:08:34.960 --> 00:08:36.835 with a different park inhibitor.

00:08:36.840 --> 00:08:38.589 Here bnes 673.

00:08:43.800 --> 00:08:45.340 Based on these findings,

00:08:45.340 --> 00:08:47.265 clinical trials have been started,

00:08:47.270 --> 00:08:48.242 including here at Yale,

00:08:48.242 --> 00:08:50.010 so this is just a report from

00:08:50.010 --> 00:08:51.275 our Phase one group here,

00:08:51.280 --> 00:08:52.918 showing that there's a subset of

00:08:52.918 --> 00:08:54.680 patients with IDH mutated solid tumors.

00:08:54.680 --> 00:08:56.486 In this case, chondrosarcoma is that

00:08:56.486 --> 00:08:58.200 derives clinical benefit from elaborate,

00:08:58.200 --> 00:09:00.220 cheap, elaborate treatment with some

00:09:00.220 --> 00:09:02.240 patients showing either stable disease,

00:09:02.240 --> 00:09:04.820 or in this case, highlighted here,

00:09:04.820 --> 00:09:08.570 partial remission of their tumor burden.

00:09:08.570 --> 00:09:10.916 And obviously these trials are continuing

NOTE Confidence: 0.941766565555556

00:09:10.916 --> 00:09:12.920 to recruit patients in our ongoing.

NOTE Confidence: 0.78691315

00:09:16.150 --> 00:09:19.262 Switching now to to our work looking at

NOTE Confidence: 0.78691315

00:09:19.262 --> 00:09:21.853 targeting DNA damage response pathways

NOTE Confidence: 0.78691315

00:09:21.853 --> 00:09:24.743 and uncle metabolite producing tumors,

NOTE Confidence: 0.78691315

00:09:24.750 --> 00:09:26.784 we turned our attention here so we so we

NOTE Confidence: 0.78691315

00:09:26.784 --> 00:09:28.687 know that monotherapy is unlikely to be

NOTE Confidence: 0.78691315

00:09:28.687 --> 00:09:30.878 curative and in the majority of patients.

NOTE Confidence: 0.78691315

00:09:30.880 --> 00:09:33.183 So we set avenues for exploring other

NOTE Confidence: 0.78691315

00:09:33.183 --> 00:09:35.319 DNA repair pathways that could be

NOTE Confidence: 0.78691315

00:09:35.319 --> 00:09:37.124 targeted in a combinatorial fashion.

NOTE Confidence: 0.78691315

00:09:37.130 --> 00:09:40.412 So we turn to the ATR pathway shown here.

NOTE Confidence: 0.78691315

00:09:40.412 --> 00:09:42.519 So in the setting of DNA damage

NOTE Confidence: 0.78691315

00:09:42.519 --> 00:09:44.492 ATR phosphorylates, check one.

NOTE Confidence: 0.78691315

00:09:44.492 --> 00:09:47.060 Which intense intern sets off a cascade to

NOTE Confidence: 0.78691315

00:09:47.123 --> 00:09:49.788 coordinate several important cell functions,

NOTE Confidence: 0.78691315

00:09:49.790 --> 00:09:52.569 including the arrest of cell cycle by

NOTE Confidence: 0.78691315

00:09:52.569 --> 00:09:55.367 activation of intra S and G2M checkpoints.

NOTE Confidence: 0.78691315

00:09:55.370 --> 00:09:57.939 This allows DNA repair to occur effectively,

NOTE Confidence: 0.78691315

00:09:57.940 --> 00:10:00.470 and prevents premature mitotic entry

NOTE Confidence: 0.78691315

00:10:00.470 --> 00:10:02.006 in the setting of ATR inhibition.

NOTE Confidence: 0.78691315

00:10:02.010 --> 00:10:03.425 Damaged cells are allowed to

NOTE Confidence: 0.78691315

00:10:03.425 --> 00:10:05.490 proceed past the S phase checkpoint,

NOTE Confidence: 0.78691315

00:10:05.490 --> 00:10:07.542 thereby promoting the induction of double

NOTE Confidence: 0.78691315

00:10:07.542 --> 00:10:09.550 strand breaks, premature mitotic entry,

NOTE Confidence: 0.78691315

00:10:09.550 --> 00:10:12.540 and ultimately, cell death.

NOTE Confidence: 0.78691315

00:10:12.540 --> 00:10:15.570 As you can see here.

NOTE Confidence: 0.78691315

00:10:15.570 --> 00:10:18.074 So this is a work led by an

NOTE Confidence: 0.78691315

00:10:18.074 --> 00:10:19.400 excellent postdoctoral associate,

NOTE Confidence: 0.78691315

00:10:19.400 --> 00:10:20.297 that term retool,

NOTE Confidence: 0.78691315

00:10:20.297 --> 00:10:22.390 and as you can see from the

NOTE Confidence: 0.78691315

00:10:22.465 --> 00:10:24.529 clonogenic survival graph here,

NOTE Confidence: 0.78691315

00:10:24.530 --> 00:10:26.894 IDH mutant cells were more sensitive

NOTE Confidence: 0.78691315

00:10:26.894 --> 00:10:29.249 to a combination of a leopard

NOTE Confidence: 0.78691315

00:10:29.249 --> 00:10:31.630 and the ATR inhibitor Azd 6738.

NOTE Confidence: 0.78691315

00:10:31.630 --> 00:10:35.350 Compared to the wild type counterparts.

NOTE Confidence: 0.78691315

00:10:35.350 --> 00:10:37.550 And similarly, in vivo,

NOTE Confidence: 0.78691315

00:10:37.550 --> 00:10:40.242 using again HCT xenograft flank model,

NOTE Confidence: 0.78691315

00:10:40.242 --> 00:10:42.630 you can see that the combination

NOTE Confidence: 0.78691315

00:10:42.700 --> 00:10:44.590 of of a Labrador department,

NOTE Confidence: 0.78691315

00:10:44.590 --> 00:10:47.366 her elaborate and ATR inhibition resulted

NOTE Confidence: 0.78691315

00:10:47.366 --> 00:10:49.596 in significantly delayed tumor growth.

NOTE Confidence: 0.909161469230769

00:10:51.760 --> 00:10:53.712 Just to get an idea of what mechanisms

NOTE Confidence: 0.909161469230769

00:10:53.712 --> 00:10:55.719 might be underlying decided toxicity.

NOTE Confidence: 0.909161469230769

00:10:55.720 --> 00:10:58.359 We then assessed for DNA damage as

NOTE Confidence: 0.909161469230769

00:10:58.359 --> 00:11:00.988 measured by gamma H2X flow side in

NOTE Confidence: 0.909161469230769

00:11:00.988 --> 00:11:03.706 these wild type and mutant cells after

NOTE Confidence: 0.909161469230769

19

00:11:03.706 --> 00:11:06.754 treatment with elaborate is ATR inhibitor

NOTE Confidence: 0.909161469230769

00:11:06.754 --> 00:11:08.896 or combination therapy and what you see

NOTE Confidence: 0.909161469230769

00:11:08.896 --> 00:11:10.230 is that after 24 hours of treatment,

NOTE Confidence: 0.909161469230769

00:11:10.230 --> 00:11:12.425 IDH mutant cells had significantly

NOTE Confidence: 0.909161469230769

00:11:12.425 --> 00:11:15.430 increased proportion of damage to X foci

NOTE Confidence: 0.909161469230769

00:11:15.430 --> 00:11:17.656 relative to the wild type counterparts,

NOTE Confidence: 0.909161469230769

00:11:17.660 --> 00:11:20.220 suggesting increased level of unrepaired

NOTE Confidence: 0.909161469230769

00:11:20.220 --> 00:11:22.780 DNA damage after drug treatment.

NOTE Confidence: 0.909161469230769

00:11:22.780 --> 00:11:24.100 As I mentioned before,

NOTE Confidence: 0.909161469230769

00:11:24.100 --> 00:11:26.507 ATR also plays an important role in

NOTE Confidence: 0.909161469230769

00:11:26.507 --> 00:11:27.861 regulating cell cycle progression

NOTE Confidence: 0.909161469230769

00:11:27.861 --> 00:11:29.487 in the setting of DNA damage.

NOTE Confidence: 0.909161469230769

00:11:29.490 --> 00:11:31.793 So we assessed for the mitotic cell

NOTE Confidence: 0.909161469230769

00:11:31.793 --> 00:11:33.326 population looking at phosphorylated

NOTE Confidence: 0.909161469230769

00:11:33.326 --> 00:11:36.030 histone 3, which is a marker of mitosis,

NOTE Confidence: 0.909161469230769

00:11:36.030 --> 00:11:38.654 and you can see again that with the

NOTE Confidence: 0.909161469230769

00:11:38.654 --> 00:11:40.642 combination treatment you see an increase

NOTE Confidence: 0.909161469230769

00:11:40.642 --> 00:11:42.165 amount of cells entering mitosis.

NOTE Confidence: 0.909161469230769

00:11:42.165 --> 00:11:44.859 So the the idea here is that in the setting

NOTE Confidence: 0.909161469230769

00:11:44.859 --> 00:11:47.587 of increased DNA damage and IDH mutant cells,

NOTE Confidence: 0.909161469230769

00:11:47.590 --> 00:11:48.910 when you add ATR inhibition,

NOTE Confidence: 0.909161469230769

00:11:48.910 --> 00:11:49.672 these cells progressed

NOTE Confidence: 0.909161469230769

00:11:49.672 --> 00:11:50.688 through their cell cycle,

NOTE Confidence: 0.909161469230769

00:11:50.690 --> 00:11:51.704 enter enter mitosis.

NOTE Confidence: 0.909161469230769

00:11:51.704 --> 00:11:53.732 Prematurely and leading to cell death.

NOTE Confidence: 0.925392715

00:11:57.280 --> 00:11:59.128 Again, turning out to the clinic,

NOTE Confidence: 0.925392715

00:11:59.130 --> 00:12:00.394 there's actually trials now

NOTE Confidence: 0.925392715

00:12:00.394 --> 00:12:01.658 ongoing of this combination,

NOTE Confidence: 0.925392715

00:12:01.660 --> 00:12:02.692 including here at Yale,

NOTE Confidence: 0.925392715

00:12:02.692 --> 00:12:04.240 where there's a phase two trial,

NOTE Confidence: 0.925392715

00:12:04.240 --> 00:12:07.324 looking at elaborate and ATR inhibitor

NOTE Confidence: 0.925392715

00:12:07.324 --> 00:12:10.120 Azd 6738 in the setting of IDH,

NOTE Confidence: 0.925392715

00:12:10.120 --> 00:12:11.101 even solid tumors.

NOTE Confidence: 0.925392715

00:12:11.101 --> 00:12:13.390 So we're looking forward to seeing the

NOTE Confidence: 0.925392715

00:12:13.449 --> 00:12:15.190 results of this in the coming years.

NOTE Confidence: 0.897393076666667

00:12:17.820 --> 00:12:20.020 So turning now to the other Krebs cycle

NOTE Confidence: 0.897393076666667

00:12:20.020 --> 00:12:22.220 mutations I mentioned before, succinate

NOTE Confidence: 0.897393076666667

00:12:22.220 --> 00:12:24.940 dehydrogenase and fumarate hydratase.

NOTE Confidence: 0.897393076666667

00:12:24.940 --> 00:12:27.145 So in this study done in collaboration

NOTE Confidence: 0.897393076666667

00:12:27.145 --> 00:12:29.270 with Doctor Shep, who's now at UCLA,

NOTE Confidence: 0.897393076666667

00:12:29.270 --> 00:12:30.745 he's a urologic cancer surgeon.

NOTE Confidence: 0.897393076666667

00:12:30.750 --> 00:12:33.382 We wanted to identify other potential novel

NOTE Confidence: 0.897393076666667

00:12:33.382 --> 00:12:35.893 treatment approaches that exploit this uncle

NOTE Confidence: 0.897393076666667

00:12:35.893 --> 00:12:37.665 metabolite induced genomic instability

NOTE Confidence: 0.897393076666667

00:12:37.670 --> 00:12:40.220 using renal cell carcinoma models.

NOTE Confidence: 0.897393076666667

00:12:40.220 --> 00:12:44.616 So here we turned our attention to.

NOTE Confidence: 0.897393076666667

00:12:44.620 --> 00:12:46.750 Missoula made, which is an alkylating

NOTE Confidence: 0.897393076666667

00:12:46.750 --> 00:12:48.978 agent that mediates its cytotoxic effects

NOTE Confidence: 0.897393076666667

00:12:48.978 --> 00:12:51.481 by attaching methyl groups to DNA and

NOTE Confidence: 0.897393076666667

00:12:51.481 --> 00:12:53.649 the repair of the N7 methyl guanine adduct.

NOTE Confidence: 0.897393076666667

00:12:53.650 --> 00:12:55.816 In particular is needed by mediated

NOTE Confidence: 0.897393076666667

00:12:55.816 --> 00:12:58.229 by the base excision repair pathway

NOTE Confidence: 0.897393076666667

00:12:58.230 --> 00:13:00.048 in a process that involves park.

NOTE Confidence: 0.897393076666667

00:13:00.050 --> 00:13:00.491 Therefore,

NOTE Confidence: 0.897393076666667

00:13:00.491 --> 00:13:02.696 we hypothesize that apartment habisch

NOTE Confidence: 0.897393076666667

00:13:02.696 --> 00:13:04.926 and will enhance Tim Assamite

NOTE Confidence: 0.897393076666667

00:13:04.926 --> 00:13:07.338 induced city toxicity and FHN SDH

NOTE Confidence: 0.897393076666667

00:13:07.338 --> 00:13:09.700 deficient renal cell carcinoma models.

NOTE Confidence: 0.938353535

00:13:14.160 --> 00:13:18.340 To investigate this, we engineered

NOTE Confidence: 0.938353535

00:13:18.340 --> 00:13:21.360 isagenix FH1 and SDHB knockout cells,

NOTE Confidence: 0.938353535

00:13:21.360 --> 00:13:23.925 and for this we use the rank a cell

NOTE Confidence: 0.938353535

00:13:23.925 --> 00:13:27.269 line rank is a pretty well established

NOTE Confidence: 0.938353535

00:13:27.269 --> 00:13:29.261 mirroring renal adenocarcinoma model

NOTE Confidence: 0.938353535

00:13:29.340 --> 00:13:31.620 that's derived from balb C mice.

NOTE Confidence: 0.938353535

00:13:31.620 --> 00:13:34.182 So first by Western blot we

NOTE Confidence: 0.938353535

00:13:34.182 --> 00:13:36.930 confirmed FH1 and SDHB knockout.

NOTE Confidence: 0.938353535

00:13:36.930 --> 00:13:39.090 We then also further functionally

NOTE Confidence: 0.938353535

00:13:39.090 --> 00:13:40.852 validated this knockout using

NOTE Confidence: 0.938353535

00:13:40.852 --> 00:13:42.700 LCMS or liquid chromatography.

NOTE Confidence: 0.938353535

00:13:42.700 --> 00:13:44.295 Mass spectrometry to look for

NOTE Confidence: 0.938353535

00:13:44.295 --> 00:13:45.890 buildup of these uncle metabolites

NOTE Confidence: 0.938353535

00:13:45.943 --> 00:13:47.038 succinate in fumarate,

NOTE Confidence: 0.938353535

00:13:47.040 --> 00:13:49.280 respectively, and found that indeed,

NOTE Confidence: 0.938353535

00:13:49.280 --> 00:13:51.068 our CRISPR mediated knockout does lead

NOTE Confidence: 0.938353535

00:13:51.068 --> 00:13:53.669 to build up of these uncle metabolites,

NOTE Confidence: 0.938353535

00:13:53.670 --> 00:13:55.870 as one would expect.

NOTE Confidence: 0.938353535

00:13:55.870 --> 00:13:58.276 We next performed a seahorse assay

NOTE Confidence: 0.938353535

00:13:58.276 --> 00:13:59.880 to measure oxidative phosphorylation

00:13:59.942 --> 00:14:01.836 and found that again, as expected,

00:14:01.836 --> 00:14:04.660 SDHB and FH1 loss of function and the

00:14:04.740 --> 00:14:06.552 subsequent Krebs cycle dysfunction

00:14:06.552 --> 00:14:09.270 that comes from that leads to

00:14:09.342 --> 00:14:11.889 decreased oxidative phosphorylation.

00:14:11.890 --> 00:14:14.730 So this helps sort of validate our model.

00:14:14.730 --> 00:14:15.121 Next,

00:14:15.121 --> 00:14:17.467 we sought to assess the intrinsic

00:14:17.467 --> 00:14:19.474 DNA repair capability of Krebs

00:14:19.474 --> 00:14:21.629 cycle deficient cells by looking at

00:14:21.629 --> 00:14:23.627 markers of DNA damage at baseline.

00:14:23.630 --> 00:14:26.220 So here again we turn to phosphorylated

00:14:26.220 --> 00:14:28.576 gamma HTX as well as 53 BP,

00:14:28.576 --> 00:14:30.574 one which are markers of unrepaired

00:14:30.574 --> 00:14:33.195 DNA damage and the cellular response to

00:14:33.195 --> 00:14:35.310 DNA double strand breaks, respectively.

00:14:35.310 --> 00:14:38.910 We found that similar to our

00:14:38.910 --> 00:14:42.260 previous work looking at.

00:14:42.260 --> 00:14:45.660 C and A's deficient human tissues we see

00:14:45.660 --> 00:14:48.998 an increased amount of baseline DNA repair,

00:14:49.000 --> 00:14:51.289 unrepaired DNA damage in the knockout cells

00:14:51.289 --> 00:14:53.600 compared to the wild type counterparts,

00:14:53.600 --> 00:14:55.637 and as measured by the full site.

00:14:55.640 --> 00:14:55.898 Here,

00:14:55.898 --> 00:14:57.704 you can see these are the damage

00:14:57.704 --> 00:14:59.381 to expose and read and hear the

00:14:59.381 --> 00:15:00.481 53 BP one in green.

00:15:02.780 --> 00:15:05.349 Next we tested for the ability of

00:15:05.349 --> 00:15:07.314 the chemical might of tomorrow

00:15:07.314 --> 00:15:09.684 night to potentiate the in vitro

00:15:09.684 --> 00:15:13.180 activity of PARP inhibitor BGB 290.

NOTE Confidence: 0.736748746818182

00:15:13.180 --> 00:15:15.320 So in this clonogenic survival

NOTE Confidence: 0.736748746818182

00:15:15.320 --> 00:15:17.819 assay here cells were treated with

NOTE Confidence: 0.736748746818182

00:15:17.819 --> 00:15:20.099 a dose of B GB 290 ranging from

NOTE Confidence: 0.736748746818182

00:15:20.099 --> 00:15:22.457 one micromolar to 10 micromolar.

NOTE Confidence: 0.736748746818182

00:15:22.460 --> 00:15:24.679 In this, in the presence or absence

NOTE Confidence: 0.736748746818182

00:15:24.679 --> 00:15:27.327 of 15 micro molars at Tim's Olamide,

NOTE Confidence: 0.736748746818182

00:15:27.330 --> 00:15:28.740 so appear. These two lines.

NOTE Confidence: 0.736748746818182

00:15:28.740 --> 00:15:31.444 Here BG be alone and here is with

NOTE Confidence: 0.736748746818182

00:15:31.444 --> 00:15:33.928 combined to Missoula might as well.

NOTE Confidence: 0.736748746818182

00:15:33.930 --> 00:15:36.198 And what you can see again is that both

NOTE Confidence: 0.736748746818182

00:15:36.198 --> 00:15:39.030 in SDHB knockout cells and FH knockout cells,

NOTE Confidence: 0.736748746818182

00:15:39.030 --> 00:15:41.170 there's an increased cytotoxicity

NOTE Confidence: 0.736748746818182

00:15:41.170 --> 00:15:43.240 with combination and Tim is Olumide.

NOTE Confidence: 0.852406293636364

00:15:49.620 --> 00:15:52.189 Lastly, we tested for the in vivo

NOTE Confidence: 0.852406293636364

00:15:52.189 --> 00:15:54.000 efficacy of combination treatment,

NOTE Confidence: 0.852406293636364

00:15:54.000 --> 00:15:56.600 and these SDH be deficient

NOTE Confidence: 0.852406293636364

00:15:56.600 --> 00:15:58.680 rank of flank models.

NOTE Confidence: 0.852406293636364

00:15:58.680 --> 00:16:00.198 Of note, one thing that's interesting

NOTE Confidence: 0.852406293636364

00:16:00.198 --> 00:16:02.230 here is that in terms of clinical

NOTE Confidence: 0.852406293636364

00:16:02.230 --> 00:16:03.850 experience with the combinations of

NOTE Confidence: 0.852406293636364

00:16:03.850 --> 00:16:05.459 PARP inhibitor and Thomas Olumide,

NOTE Confidence: 0.852406293636364

00:16:05.460 --> 00:16:07.095 which has been tried and

NOTE Confidence: 0.852406293636364

00:16:07.095 --> 00:16:08.730 not setting up other tumors,

NOTE Confidence: 0.852406293636364

00:16:08.730 --> 00:16:10.872 one of the the limitations of

NOTE Confidence: 0.852406293636364

00:16:10.872 --> 00:16:12.743 these trials has been increased.

NOTE Confidence: 0.852406293636364

00:16:12.743 --> 00:16:15.401 Set of toxicity with full dose

NOTE Confidence: 0.852406293636364

00:16:15.401 --> 00:16:17.460 combination of both of those.

NOTE Confidence: 0.852406293636364

00:16:17.460 --> 00:16:19.574 And so typically for in vivo studies.

NOTE Confidence: 0.852406293636364

00:16:19.580 --> 00:16:21.631 That is, all my dose is anywhere

NOTE Confidence: 0.852406293636364

00:16:21.631 --> 00:16:23.183 between 25 milligrams per kilogram

NOTE Confidence: 0.852406293636364

00:16:23.183 --> 00:16:24.718 to 50 milligrams per kilogram

NOTE Confidence: 0.852406293636364

00:16:24.718 --> 00:16:26.948 per dose which translate to human

NOTE Confidence: 0.852406293636364

00:16:26.948 --> 00:16:29.510 equivalent dose of about 75 to

NOTE Confidence: 0.852406293636364

00:16:29.510 --> 00:16:31.885 150 milligrams per meter squared.

NOTE Confidence: 0.852406293636364

00:16:31.890 --> 00:16:34.258 So here we were interested to see if

NOTE Confidence: 0.852406293636364

00:16:34.258 --> 00:16:36.594 we could find some anti tumor effect

NOTE Confidence: 0.852406293636364

00:16:36.594 --> 00:16:38.870 at lower doses of Tim's Olumide.

NOTE Confidence: 0.852406293636364

00:16:38.870 --> 00:16:40.646 Which might limit some of those

NOTE Confidence: 0.852406293636364

00:16:40.646 --> 00:16:42.529 toxicities so for this study we

NOTE Confidence: 0.852406293636364

00:16:42.529 --> 00:16:44.437 used Tim Alumite at three milligrams

NOTE Confidence: 0.852406293636364

00:16:44.437 --> 00:16:45.629 per kilogram per dose,

NOTE Confidence: 0.852406293636364

00:16:45.630 --> 00:16:47.933 and and did indeed find that even

NOTE Confidence: 0.852406293636364

00:16:47.933 --> 00:16:50.472 at such lower doses of temozolomide

NOTE Confidence: 0.852406293636364

00:16:50.472 --> 00:16:52.927 we find delayed tumor progression.

NOTE Confidence: 0.852406293636364

00:16:52.930 --> 00:16:55.060 And importantly, there were no.

NOTE Confidence: 0.852406293636364

00:16:55.060 --> 00:16:56.670 There was no increased toxicity

NOTE Confidence: 0.852406293636364

00:16:56.670 --> 00:16:57.958 with the combination treatment,

NOTE Confidence: 0.852406293636364

00:16:57.960 --> 00:17:00.528 at least as measured by animal body weight.

NOTE Confidence: 0.943057265555555

00:17:04.440 --> 00:17:06.631 So based on this we can say

NOTE Confidence: 0.943057265555555

00:17:06.631 --> 00:17:08.872 that the band FH1 knockout Cells

NOTE Confidence: 0.943057265555555

00:17:08.872 --> 00:17:10.887 Harbor and increased levels of

NOTE Confidence: 0.943057265555555

00:17:10.887 --> 00:17:12.777 unrepaired DNA damage at baseline,

NOTE Confidence: 0.943057265555555

00:17:12.780 --> 00:17:14.754 and that the combination of pop

NOTE Confidence: 0.943057265555555

00:17:14.754 --> 00:17:16.373 inhibitor Intimes Olamide enhances set

NOTE Confidence: 0.943057265555555

00:17:16.373 --> 00:17:18.116 of toxicity in these cells in vitro,

NOTE Confidence: 0.943057265555555

00:17:18.120 --> 00:17:19.974 and that the combination with low

NOTE Confidence: 0.943057265555555

00:17:19.974 --> 00:17:21.555 dose temozolomide led to delayed

NOTE Confidence: 0.943057265555555

00:17:21.555 --> 00:17:23.247 tumor growth in vivo as well.

NOTE Confidence: 0.93221934

00:17:26.020 --> 00:17:27.755 And turning now to the

NOTE Confidence: 0.93221934

00:17:27.755 --> 00:17:28.796 clinical setting again.

NOTE Confidence: 0.93221934

00:17:28.800 --> 00:17:31.110 We recently had an interesting case within

NOTE Confidence: 0.93221934

00:17:31.110 --> 00:17:33.399 our own department within our own section.

NOTE Confidence: 0.93221934

00:17:33.400 --> 00:17:35.144 This is a patient cared for by one

NOTE Confidence: 0.93221934

00:17:35.144 --> 00:17:37.000 of my colleagues Dr pushing car

NOTE Confidence: 0.93221934

00:17:37.000 --> 00:17:39.989 and this is a patient with GIST

NOTE Confidence: 0.93221934

00:17:39.989 --> 00:17:42.274 and PARAGANGLIOMAS in the setting

NOTE Confidence: 0.93221934

00:17:42.274 --> 00:17:44.574 of a germline SDHB mutation.

NOTE Confidence: 0.93221934

00:17:44.580 --> 00:17:45.972 This is a patient that progressed

NOTE Confidence: 0.93221934

00:17:45.972 --> 00:17:47.340 through multiple lines of treatment,

NOTE Confidence: 0.93221934

00:17:47.340 --> 00:17:49.874 including imatinib than that in as well

NOTE Confidence: 0.93221934

00:17:49.874 --> 00:17:53.249 as a heat shock protein phase one trial.

NOTE Confidence: 0.93221934

00:17:53.250 --> 00:17:55.280 And so at this point,

NOTE Confidence: 0.93221934

00:17:55.280 --> 00:17:57.480 having progressive multiple lines of

NOTE Confidence: 0.93221934

00:17:57.480 --> 00:18:00.329 treatment doctor pushing car up to trial.

NOTE Confidence: 0.93221934

00:18:00.330 --> 00:18:03.420 Cycles of elaborate with Tim's Olumide.

NOTE Confidence: 0.93221934

00:18:03.420 --> 00:18:05.576 And this is off any clinical trial.

NOTE Confidence: 0.93221934

00:18:05.580 --> 00:18:07.776 As you can see here from the pet images.

NOTE Confidence: 0.93221934

00:18:07.780 --> 00:18:11.146 These are the pretreatment images showing

NOTE Confidence: 0.93221934

00:18:11.146 --> 00:18:13.847 multiple liver metastatic nodules as

NOTE Confidence: 0.93221934

00:18:13.847 --> 00:18:16.465 well as Bony lesions along the spine.

NOTE Confidence: 0.93221934

00:18:16.470 --> 00:18:18.898 And after six cycles,

NOTE Confidence: 0.93221934

00:18:18.898 --> 00:18:21.326 this patient had a.

NOTE Confidence: 0.93221934

00:18:21.330 --> 00:18:23.766 Partial remission in remission of all the

NOTE Confidence: 0.93221934

00:18:23.766 --> 00:18:26.467 Bony lesions as well as partial remission,

NOTE Confidence: 0.93221934

00:18:26.470 --> 00:18:30.090 multiple liver nodules as well.

NOTE Confidence: 0.93221934

00:18:30.090 --> 00:18:32.886 Of course this is just anecdotal.

NOTE Confidence: 0.93221934

00:18:32.890 --> 00:18:34.140 This is an anecdotal case,

NOTE Confidence: 0.93221934

00:18:34.140 --> 00:18:36.225 so there are trails about

NOTE Confidence: 0.93221934

00:18:36.225 --> 00:18:37.893 clinical trials currently ongoing,

NOTE Confidence: 0.93221934

00:18:37.900 --> 00:18:40.306 including a phase two trial that's

NOTE Confidence: 0.93221934

00:18:40.306 --> 00:18:42.809 currently in development and soon to open,

NOTE Confidence: 0.93221934

00:18:42.810 --> 00:18:44.390 led by our collaborator Dr.

NOTE Confidence: 0.93221934

00:18:44.390 --> 00:18:45.734 Shuck at UCLA,

NOTE Confidence: 0.93221934

00:18:45.734 --> 00:18:48.898 and in this trial they'll be testing

NOTE Confidence: 0.93221934

00:18:48.898 --> 00:18:51.530 combinations of 290 and low dose

NOTE Confidence: 0.93221934

00:18:51.530 --> 00:18:54.110 temozolomide in the setting of patients

NOTE Confidence: 0.93221934

00:18:54.189 --> 00:18:56.795 with refractory or recurrent renal

NOTE Confidence: 0.93221934

00:18:56.795 --> 00:18:59.980 cell carcinoma that is at FH deficient.

NOTE Confidence: 0.903934720833333

00:19:04.560 --> 00:19:06.120 Lastly, I just wanted to touch

NOTE Confidence: 0.903934720833333

00:19:06.120 --> 00:19:07.670 a little bit on my work,

NOTE Confidence: 0.903934720833333

00:19:07.670 --> 00:19:09.578 focused more on the immune aspects

NOTE Confidence: 0.903934720833333

00:19:09.578 --> 00:19:11.614 of Uncle metabolite and DNA repair

NOTE Confidence: 0.903934720833333

00:19:11.614 --> 00:19:13.369 defects and potential for leveraging

NOTE Confidence: 0.903934720833333

00:19:13.369 --> 00:19:16.152 these defects in order to promote an

NOTE Confidence: 0.903934720833333

00:19:16.152 --> 00:19:17.403 inflammatory tumor microenvironment

NOTE Confidence: 0.903934720833333

00:19:17.403 --> 00:19:19.084 and even potentially desensitized

NOTE Confidence: 0.903934720833333

00:19:19.084 --> 00:19:20.780 to mean checkpoint blockade,

NOTE Confidence: 0.903934720833333

00:19:20.780 --> 00:19:24.495 which I know is a topic near and dear to

NOTE Confidence: 0.903934720833333

00:19:24.495 --> 00:19:27.160 the heart of many folks on this call.

NOTE Confidence: 0.903934720833333

00:19:27.160 --> 00:19:28.780 So as folks on this audience,

NOTE Confidence: 0.903934720833333

00:19:28.780 --> 00:19:30.551 I'm sure already acutely aware of only

NOTE Confidence: 0.903934720833333

00:19:30.551 --> 00:19:32.390 a subset of patients really benefit

NOTE Confidence: 0.903934720833333

00:19:32.390 --> 00:19:34.090 from immune checkpoint blockade and

NOTE Confidence: 0.903934720833333

00:19:34.090 --> 00:19:36.039 some of the markers of response

NOTE Confidence: 0.903934720833333

00:19:36.039 --> 00:19:37.863 that have been described relate both

NOTE Confidence: 0.903934720833333

00:19:37.870 --> 00:19:40.714 to tumor increase amount of tumor

NOTE Confidence: 0.903934720833333

00:19:40.714 --> 00:19:42.610 associated mutations and subsequent

NOTE Confidence: 0.903934720833333

00:19:42.685 --> 00:19:46.052 neoantigen load as well as a more

NOTE Confidence: 0.903934720833333

00:19:46.052 --> 00:19:47.495 inflammatory tumor microenvironment.

NOTE Confidence: 0.957039336

00:19:49.790 --> 00:19:50.790 So with this in mind,

NOTE Confidence: 0.957039336

00:19:50.790 --> 00:19:52.510 a lot of attention has really been paid

NOTE Confidence: 0.957039336

00:19:52.510 --> 00:19:54.389 lately to the role of DNA damage response,

NOTE Confidence: 0.957039336

00:19:54.390 --> 00:19:56.150 and specifically DNA repair defects

NOTE Confidence: 0.957039336

00:19:56.150 --> 00:19:57.910 and mediating the tumor immune

NOTE Confidence: 0.957039336

00:19:57.967 --> 00:19:59.887 microenvironment in response to

NOTE Confidence: 0.957039336

00:19:59.887 --> 00:20:01.362 immunotherapy and the general idea.

NOTE Confidence: 0.957039336

00:20:01.362 --> 00:20:02.970 Again, just very generally speaking,

NOTE Confidence: 0.957039336

00:20:02.970 --> 00:20:05.353 is that the there's a potential in

NOTE Confidence: 0.957039336

00:20:05.353 --> 00:20:07.057 the setting of DNA repair defects

NOTE Confidence: 0.957039336

00:20:07.057 --> 00:20:08.928 when you treat these these tumors

NOTE Confidence: 0.957039336

00:20:08.928 --> 00:20:10.623 with additional DNA damaging agents

NOTE Confidence: 0.957039336

00:20:10.623 --> 00:20:12.827 that you have an increased number

NOTE Confidence: 0.957039336

00:20:12.827 --> 00:20:14.335 of mutations and subsequently

NOTE Confidence: 0.957039336

00:20:14.335 --> 00:20:15.838 increased number of neoantigens

NOTE Confidence: 0.957039336

00:20:15.838 --> 00:20:18.036 that can be recognized by T cells.

NOTE Confidence: 0.957039336

00:20:18.040 --> 00:20:21.280 The other sort of a main train of thought

NOTE Confidence: 0.957039336

00:20:21.280 --> 00:20:24.509 is that these DNA damaged DNA repair.

NOTE Confidence: 0.957039336

00:20:24.510 --> 00:20:26.535 Defects can also serve to

NOTE Confidence: 0.957039336

00:20:26.535 --> 00:20:28.560 activate the innate immune system,

NOTE Confidence: 0.957039336

00:20:28.560 --> 00:20:29.904 for example through activation

NOTE Confidence: 0.957039336

00:20:29.904 --> 00:20:31.920 of the C gas sting pathway,

NOTE Confidence: 0.957039336

00:20:31.920 --> 00:20:34.180 which is a double stranded

NOTE Confidence: 0.957039336

00:20:34.180 --> 00:20:35.536 DNA sensing pathway.

NOTE Confidence: 0.957039336

00:20:35.540 --> 00:20:37.130 Of course there are now multiple

NOTE Confidence: 0.957039336

00:20:37.130 --> 00:20:38.514 pathways that are described in

NOTE Confidence: 0.957039336

00:20:38.514 --> 00:20:39.879 terms of innate immune activation,

NOTE Confidence: 0.957039336

00:20:39.880 --> 00:20:41.233 including recognition of

NOTE Confidence: 0.957039336

00:20:41.233 --> 00:20:43.037 double stranded RNA sensing,

NOTE Confidence: 0.957039336

00:20:43.040 --> 00:20:44.312 which a lot of folks here at Yale

NOTE Confidence: 0.957039336

00:20:44.312 --> 00:20:45.378 have been working on as well.

NOTE Confidence: 0.957039336

00:20:45.380 --> 00:20:48.062 But since we're working talking mainly

NOTE Confidence: 0.957039336

00:20:48.062 --> 00:20:50.410 about double stranded DNA damage,

NOTE Confidence: 0.957039336

00:20:50.410 --> 00:20:51.754 our focus has mainly been on

NOTE Confidence: 0.957039336

00:20:51.754 --> 00:20:52.650 the C guesting pathway.

NOTE Confidence: 0.813189323333333

00:20:55.180 --> 00:20:57.112 So, as I mentioned before for for

36

NOTE Confidence: 0.813189323333333

00:20:57.112 --> 00:20:59.272 this study we utilized the SYNGENEIC

NOTE Confidence: 0.813189323333333

00:20:59.272 --> 00:21:01.775 ranking model and this is a model

NOTE Confidence: 0.813189323333333

00:21:01.775 --> 00:21:03.430 that has been characterized before

NOTE Confidence: 0.813189323333333

00:21:03.499 --> 00:21:04.836 as being minimally responsive

NOTE Confidence: 0.813189323333333

00:21:04.836 --> 00:21:06.528 to immune checkpoint blockade,

NOTE Confidence: 0.813189323333333

00:21:06.530 --> 00:21:07.720 and this is our own experiment here,

NOTE Confidence: 0.813189323333333

00:21:07.720 --> 00:21:09.075 confirming that at least the

NOTE Confidence: 0.813189323333333

00:21:09.075 --> 00:21:10.781 wild type version of this cell

NOTE Confidence: 0.813189323333333

00:21:10.781 --> 00:21:12.246 is pretty unresponsive to PD1,

NOTE Confidence: 0.813189323333333

00:21:12.250 --> 00:21:14.788 which allows us to to sort of use this

NOTE Confidence: 0.813189323333333

00:21:14.788 --> 00:21:17.795 as a model to see if we can increase

NOTE Confidence: 0.813189323333333

00:21:17.795 --> 00:21:20.390 sensitivity to immune checkpoint blockade.

NOTE Confidence: 0.813189323333333

00:21:20.390 --> 00:21:22.644 And again, this is a very preliminary,

NOTE Confidence: 0.813189323333333

00:21:22.650 --> 00:21:24.228 but we've we've been starting to

NOTE Confidence: 0.813189323333333

00:21:24.228 --> 00:21:25.613 really explore the immune effects

NOTE Confidence: 0.813189323333333

00:21:25.613 --> 00:21:27.048 of these crab cycle mutations,

NOTE Confidence: 0.813189323333333

00:21:27.050 --> 00:21:29.178 so this is again a an early experiment

NOTE Confidence: 0.813189323333333

00:21:29.178 --> 00:21:30.807 where we performed bulk sequencing

NOTE Confidence: 0.813189323333333

00:21:30.807 --> 00:21:33.529 just in the cells looking at wild

NOTE Confidence: 0.813189323333333

00:21:33.529 --> 00:21:35.744 type versus knockout cell models.

NOTE Confidence: 0.813189323333333

00:21:35.750 --> 00:21:37.320 And there's definitely a differential

NOTE Confidence: 0.813189323333333

00:21:37.320 --> 00:21:37.948 gene expression.

NOTE Confidence: 0.813189323333333

00:21:37.950 --> 00:21:39.833 But one thing I just want to

NOTE Confidence: 0.813189323333333

00:21:39.833 --> 00:21:41.419 characterize a point out here in

NOTE Confidence: 0.813189323333333

00:21:41.419 --> 00:21:43.106 terms of a related to the immune

NOTE Confidence: 0.813189323333333

00:21:43.167 --> 00:21:44.647 effects of these mutations.

NOTE Confidence: 0.813189323333333

00:21:44.650 --> 00:21:46.546 As you can see that one of the

NOTE Confidence: 0.813189323333333

00:21:46.546 --> 00:21:48.722 top hits for both of these in the

NOTE Confidence: 0.813189323333333

00:21:48.722 --> 00:21:50.430 knockout cells is an increased

NOTE Confidence: 0.813189323333333

00:21:50.430 --> 00:21:52.938 expression or upregulation of

NOTE Confidence: 0.813189323333333

00:21:52.938 --> 00:21:55.446 the antigen presenting pathways.

NOTE Confidence: 0.813189323333333

00:21:55.450 --> 00:21:57.328 We've followed this up with a

NOTE Confidence: 0.813189323333333

00:21:57.328 --> 00:21:58.580 separate study looking actually

NOTE Confidence: 0.813189323333333

00:21:58.633 --> 00:21:59.888 now at single cell sequencing

NOTE Confidence: 0.813189323333333

00:21:59.888 --> 00:22:01.968 and this is just so far had been

NOTE Confidence: 0.813189323333333

00:22:01.968 --> 00:22:03.504 done in our SDHP knockout cells,

NOTE Confidence: 0.813189323333333

00:22:03.510 --> 00:22:05.665 and thankfully we confirmed SDHP

NOTE Confidence: 0.813189323333333

00:22:05.665 --> 00:22:09.180 knockout as we we already did using other

NOTE Confidence: 0.813189323333333

00:22:09.180 --> 00:22:11.580 methods and again we see differential

NOTE Confidence: 0.813189323333333

00:22:11.580 --> 00:22:13.156 gene expression patterns between

NOTE Confidence: 0.813189323333333

00:22:13.156 --> 00:22:15.318 well tape and SDHP knockout cells.

NOTE Confidence: 0.813189323333333

00:22:15.320 --> 00:22:17.616 And again this is with work that's been

NOTE Confidence: 0.813189323333333

00:22:17.616 --> 00:22:21.380 done and help with help from Doctor Sule.

NOTE Confidence: 0.813189323333333

00:22:21.380 --> 00:22:21.800 Interestingly,

NOTE Confidence: 0.813189323333333

00:22:21.800 --> 00:22:25.580 we see here as well that the knockout cells

NOTE Confidence: 0.813189323333333

00:22:25.659 --> 00:22:28.557 seem to upregulate beta 2 microglobulin,

NOTE Confidence: 0.813189323333333

00:22:28.560 --> 00:22:30.387 which I'm sure folks or where is

00:22:30.387 --> 00:22:31.833 an important component will is is

00:22:31.833 --> 00:22:33.261 a component of the MHC class one

00:22:33.312 --> 00:22:35.002 molecule and is really required

00:22:35.002 --> 00:22:36.016 for antigen presentation,

00:22:36.020 --> 00:22:37.588 and there's been a lot of great

00:22:37.588 --> 00:22:39.271 work from folks here at Yale to

00:22:39.271 --> 00:22:40.705 show that made it two microalbumin

00:22:40.753 --> 00:22:42.790 losses is one of the markers of

00:22:42.790 --> 00:22:43.663 immune checkpoint resistance.

00:22:45.800 --> 00:22:47.501 We also then went on to look

00:22:47.501 --> 00:22:48.673 at differential gene expression

00:22:48.673 --> 00:22:50.748 with PARP inhibition and and so

00:22:50.748 --> 00:22:52.584 we looked at treatment after we

00:22:52.584 --> 00:22:54.579 looked at single cell sequencing.

00:22:54.580 --> 00:22:56.540 After 24 hours of treatment

NOTE Confidence: 0.896956759285715

00:22:56.540 --> 00:22:58.157 and and what we found so far.

NOTE Confidence: 0.896956759285715

00:22:58.160 --> 00:22:59.712 And this is still work in progress and

NOTE Confidence: 0.896956759285715

00:22:59.712 --> 00:23:01.159 we're still looking through this data,

NOTE Confidence: 0.896956759285715

00:23:01.160 --> 00:23:02.798 but one of the things we've seen

NOTE Confidence: 0.896956759285715

00:23:02.798 --> 00:23:04.157 is an increased expression after

NOTE Confidence: 0.896956759285715

00:23:04.157 --> 00:23:05.657 24 hours of the labyrinth,

NOTE Confidence: 0.896956759285715

00:23:05.660 --> 00:23:08.200 specifically in the knockout cells

NOTE Confidence: 0.896956759285715

00:23:08.200 --> 00:23:10.232 with upregulation of interferon

NOTE Confidence: 0.896956759285715

00:23:10.232 --> 00:23:12.119 induced protein protein 44,

NOTE Confidence: 0.896956759285715

00:23:12.120 --> 00:23:13.961 which is one of the interferon stimulated

NOTE Confidence: 0.896956759285715

00:23:13.961 --> 00:23:15.929 genes that has been associated with an.

NOTE Confidence: 0.896956759285715

00:23:15.930 --> 00:23:19.100 Interferon related DNA damage signature.

NOTE Confidence: 0.896956759285715

00:23:19.100 --> 00:23:21.823 We also saw upregulation of stat one

NOTE Confidence: 0.896956759285715

00:23:21.823 --> 00:23:23.798 with elaborate treatment and those

NOTE Confidence: 0.896956759285715

00:23:23.798 --> 00:23:26.200 SDHB knockout cells and stat one.

NOTE Confidence: 0.896956759285715

00:23:26.200 --> 00:23:27.490 The Jack stat.

00:23:27.490 --> 00:23:30.297 One pathway has been shown to be

00:23:30.297 --> 00:23:31.963 important for interferon stimulated

00:23:31.963 --> 00:23:33.898 gene expression and has been

00:23:33.898 --> 00:23:36.964 shown to play a role in mediating

00:23:36.964 --> 00:23:38.407 amino therapy response.

00:23:38.410 --> 00:23:40.030 So these are interesting.

00:23:40.030 --> 00:23:42.055 Sort of very preliminary data

00:23:42.055 --> 00:23:44.264 and and gives us a direction to

00:23:44.264 --> 00:23:46.250 look for as we go forward.

00:23:46.250 --> 00:23:49.090 I also again performed.

00:23:49.090 --> 00:23:50.068 Some flow cytometry,

00:23:50.068 --> 00:23:52.610 and this is now just looking at the

00:23:52.610 --> 00:23:54.440 tumor cells after implantation and

00:23:54.440 --> 00:23:58.053 what we see here is that in the SDHB

00:23:58.053 --> 00:24:00.188 knockout cells there's an increased

NOTE Confidence: 0.896956759285715

00:24:00.188 --> 00:24:02.352 proportion in terms of the percentage

NOTE Confidence: 0.896956759285715

00:24:02.352 --> 00:24:04.632 of live cells that are CD3 positive

NOTE Confidence: 0.896956759285715

00:24:04.632 --> 00:24:06.774 and of those CD 3 positive cells.

NOTE Confidence: 0.896956759285715

00:24:06.780 --> 00:24:08.802 There's an increased proportion that have

NOTE Confidence: 0.896956759285715

00:24:08.802 --> 00:24:11.130 PD one expression within the SDHP knockout,

NOTE Confidence: 0.896956759285715

00:24:11.130 --> 00:24:13.002 so again very preliminary.

NOTE Confidence: 0.896956759285715

00:24:13.002 --> 00:24:15.810 But this is sort of exciting

NOTE Confidence: 0.896956759285715

00:24:15.810 --> 00:24:20.045 data to follow up on for us.

NOTE Confidence: 0.896956759285715

00:24:20.050 --> 00:24:20.386 Uhm?

NOTE Confidence: 0.896956759285715

00:24:20.386 --> 00:24:23.410 Now I will turn to the other part of

NOTE Confidence: 0.896956759285715

00:24:23.498 --> 00:24:26.697 our talk from earlier the IDH mutations

NOTE Confidence: 0.896956759285715

00:24:26.700 --> 00:24:28.695 because this is also an area that

NOTE Confidence: 0.896956759285715

00:24:28.695 --> 00:24:30.613 I'm interested in is not to mention

NOTE Confidence: 0.896956759285715

00:24:30.613 --> 00:24:33.118 that have an interest in in the glioma,

NOTE Confidence: 0.896956759285715

00:24:33.120 --> 00:24:34.203 tumor immune microenvironment

NOTE Confidence: 0.896956759285715

00:24:34.203 --> 00:24:36.008 and have performed some studies

NOTE Confidence: 0.896956759285715

00:24:36.008 --> 00:24:37.139 previously looking at that.

NOTE Confidence: 0.896956759285715

00:24:37.140 --> 00:24:38.195 So I was really interested

NOTE Confidence: 0.896956759285715

00:24:38.195 --> 00:24:39.039 to develop an idea.

NOTE Confidence: 0.896956759285715

00:24:39.040 --> 00:24:42.113 Each mutant syngeneic model to allow us

NOTE Confidence: 0.896956759285715

00:24:42.113 --> 00:24:45.677 to to explore this a little bit further.

NOTE Confidence: 0.896956759285715

00:24:45.680 --> 00:24:47.630 So traditionally the the main

NOTE Confidence: 0.896956759285715

00:24:47.630 --> 00:24:50.204 model that's been used for the main

NOTE Confidence: 0.896956759285715

00:24:50.204 --> 00:24:51.764 syngeneic model that's been used

NOTE Confidence: 0.896956759285715

00:24:51.764 --> 00:24:53.831 for looking at glioma response to

NOTE Confidence: 0.896956759285715

00:24:53.831 --> 00:24:55.259 immune checkpoint blockade has

NOTE Confidence: 0.896956759285715

00:24:55.259 --> 00:24:57.762 been the steel 261 model which is

NOTE Confidence: 0.896956759285715

00:24:57.762 --> 00:24:59.443 chemically induced line with a

NOTE Confidence: 0.896956759285715

00:24:59.443 --> 00:25:00.767 moderate degree of immunogenicity

NOTE Confidence: 0.896956759285715

00:25:00.767 --> 00:25:02.640 at baseline and as you can see,

NOTE Confidence: 0.896956759285715

00:25:02.640 --> 00:25:04.558 this is our own experiment in our

NOTE Confidence: 0.896956759285715

00:25:04.558 --> 00:25:07.019 own hands and it goes in line with

NOTE Confidence: 0.896956759285715

00:25:07.019 --> 00:25:08.948 previous research that shows that this

NOTE Confidence: 0.896956759285715

00:25:08.948 --> 00:25:10.997 about 50% of mice with field to six.

NOTE Confidence: 0.896956759285715

00:25:11.000 --> 00:25:12.554 One tumors will respond to anti PD,

NOTE Confidence: 0.896956759285715

00:25:12.560 --> 00:25:13.932 one blockade and as a lot of

NOTE Confidence: 0.896956759285715

00:25:13.932 --> 00:25:14.810 folks here on this.

NOTE Confidence: 0.896956759285715

00:25:14.810 --> 00:25:16.602 So I will know that really doesn't

NOTE Confidence: 0.896956759285715

00:25:16.602 --> 00:25:18.190 recapitulate the human experience where,

NOTE Confidence: 0.896956759285715

00:25:18.190 --> 00:25:19.774 unfortunately so far clinical

NOTE Confidence: 0.896956759285715

00:25:19.774 --> 00:25:22.150 trials looking at I mean checkpoint

NOTE Confidence: 0.896956759285715

00:25:22.212 --> 00:25:24.108 blockade in GBM have been have

NOTE Confidence: 0.896956759285715

00:25:24.108 --> 00:25:25.930 not shown really much benefit.

NOTE Confidence: 0.896956759285715

00:25:25.930 --> 00:25:27.226 So we were hoping to find a model

NOTE Confidence: 0.896956759285715

00:25:27.226 --> 00:25:28.607 that maybe might be a little

NOTE Confidence: 0.896956759285715

00:25:28.607 --> 00:25:29.366 more translationally relevant,

NOTE Confidence: 0.896956759285715

00:25:29.370 --> 00:25:30.602 understanding the limitations that

NOTE Confidence: 0.896956759285715

00:25:30.602 --> 00:25:33.003 we're working with that we have to sort

NOTE Confidence: 0.896956759285715

00:25:33.003 --> 00:25:34.509 of rely on these syngenetic models.

NOTE Confidence: 0.896956759285715

00:25:34.510 --> 00:25:36.310 So we turned to our collaborator

NOTE Confidence: 0.896956759285715

00:25:36.310 --> 00:25:37.510 Dale Carter at UCSF,

NOTE Confidence: 0.90662077625

00:25:37.510 --> 00:25:40.606 and his group developed this SB 28 line,

NOTE Confidence: 0.90662077625

00:25:40.610 --> 00:25:44.173 which is a genetically engineered line that.

NOTE Confidence: 0.90662077625

00:25:44.173 --> 00:25:45.322 They've already characterized,

NOTE Confidence: 0.90662077625

00:25:45.322 --> 00:25:48.112 and they found that more more closely

NOTE Confidence: 0.90662077625

00:25:48.112 --> 00:25:50.698 mimics the poorly immunogenic human gliomas,

NOTE Confidence: 0.90662077625

00:25:50.700 --> 00:25:53.108 and so this is a line that.

NOTE Confidence: 0.90662077625

00:25:53.110 --> 00:25:55.546 Intends to have low T cell infiltration,

NOTE Confidence: 0.90662077625

00:25:55.550 --> 00:25:58.345 high number of tumor associated

NOTE Confidence: 0.90662077625

00:25:58.345 --> 00:26:00.581 macrophages and more immunosuppressive

NOTE Confidence: 0.90662077625

00:26:00.581 --> 00:26:03.130 micro micro environment and these

NOTE Confidence: 0.90662077625

00:26:03.130 --> 00:26:05.440 tumors do not really respond to even

46

00:26:05.440 --> 00:26:07.963 dual blockade with PD one and C TL A4.

00:26:07.970 --> 00:26:09.360 They've also characterized this line

00:26:09.360 --> 00:26:11.110 in terms of the mutational burden.

00:26:11.110 --> 00:26:13.801 Showed that again SB 28 cells have a much

00:26:13.801 --> 00:26:16.140 lower mutational burden these GL261 line.

00:26:16.140 --> 00:26:17.925 So we hope that perhaps this is

00:26:17.925 --> 00:26:20.363 this will be a little more of a

00:26:20.363 --> 00:26:22.168 translationally relevant model as we go

00:26:22.168 --> 00:26:23.836 forward looking at the immune effects.

00:26:23.840 --> 00:26:25.674 So in terms of developing this as

00:26:25.674 --> 00:26:27.294 an IDH mutant model, specifically,

00:26:27.294 --> 00:26:29.898 we've we've used a stable transfection

00:26:29.898 --> 00:26:32.126 with an R132H open reading frame,

00:26:32.126 --> 00:26:33.821 and again characterized that there

00:26:33.821 --> 00:26:35.668 is an expression of the R 138,

00:26:35.670 --> 00:26:38.365 two H mutation as well as accumulation

NOTE Confidence: 0.90662077625

00:26:38.365 --> 00:26:40.320 of two hydroxy glutarate.

NOTE Confidence: 0.90662077625

00:26:40.320 --> 00:26:44.598 We've also characterized the in vivo

NOTE Confidence: 0.90662077625

00:26:44.600 --> 00:26:47.210 intracranial growth kinetics of this

NOTE Confidence: 0.90662077625

00:26:47.210 --> 00:26:51.009 model and shown that these IDH mutant

NOTE Confidence: 0.90662077625

00:26:51.009 --> 00:26:53.595 cells form tumors effectively and

NOTE Confidence: 0.90662077625

00:26:53.595 --> 00:26:55.470 characterize the survival with the

NOTE Confidence: 0.90662077625

00:26:55.470 --> 00:26:58.730 IDH mutation. In these in this model.

NOTE Confidence: 0.90662077625

00:26:58.730 --> 00:26:59.050 Again,

NOTE Confidence: 0.90662077625

00:26:59.050 --> 00:27:01.290 we further characterized in vivo as well,

NOTE Confidence: 0.90662077625

00:27:01.290 --> 00:27:03.330 and not just in vitro that in vivo.

NOTE Confidence: 0.90662077625

00:27:03.330 --> 00:27:05.070 These tumors maintain their expression

NOTE Confidence: 0.90662077625

00:27:05.070 --> 00:27:08.342 of the art 132 H mutation seen here

NOTE Confidence: 0.90662077625

00:27:08.342 --> 00:27:10.294 is through the immunohistochemistry

NOTE Confidence: 0.90662077625

00:27:10.300 --> 00:27:11.866 with this rust brown stain here,

NOTE Confidence: 0.90662077625

00:27:11.870 --> 00:27:14.446 as well as again through LCMS looking

NOTE Confidence: 0.90662077625

00:27:14.446 --> 00:27:16.799 for accumulation of two hydroxy glutarate

NOTE Confidence: 0.90662077625

00:27:16.799 --> 00:27:19.557 and tumor tissue and seeing an increase

NOTE Confidence: 0.90662077625

00:27:19.623 --> 00:27:21.620 accumulation in the R132H tumors.

NOTE Confidence: 0.885832098571429

00:27:23.880 --> 00:27:25.112 So I really want to take this as

NOTE Confidence: 0.885832098571429

00:27:25.112 --> 00:27:26.598 a in terms of future directions.

NOTE Confidence: 0.885832098571429

00:27:26.600 --> 00:27:29.074 This is really the the the main project

NOTE Confidence: 0.885832098571429

00:27:29.074 --> 00:27:31.521 that my K8 was funded for and I want

NOTE Confidence: 0.885832098571429

00:27:31.521 --> 00:27:33.465 to really investigate the impact of

NOTE Confidence: 0.885832098571429

00:27:33.465 --> 00:27:35.332 uncle metabolites on both cancer cell

NOTE Confidence: 0.885832098571429

00:27:35.332 --> 00:27:36.847 intrinsic immune signaling as well

NOTE Confidence: 0.885832098571429

00:27:36.847 --> 00:27:39.017 as the tumor immune microenvironment.

NOTE Confidence: 0.885832098571429

00:27:39.020 --> 00:27:41.085 And I want to explore the immunomodulatory

NOTE Confidence: 0.885832098571429

00:27:41.085 --> 00:27:43.420 effects of DNA damage response inhibitors,

NOTE Confidence: 0.885832098571429

00:27:43.420 --> 00:27:45.513 such as ATR inhibitors in the setting

NOTE Confidence: 0.885832098571429

00:27:45.513 --> 00:27:47.164 of uncle metabolite producing tumors

NOTE Confidence: 0.885832098571429

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00:27:47.164 --> 00:27:49.270 or really extending the findings we've

NOTE Confidence: 0.885832098571429

00:27:49.270 --> 00:27:51.463 already had in our flank models to see

NOTE Confidence: 0.885832098571429

00:27:51.463 --> 00:27:54.628 how this works in the tumor microenvironment.

NOTE Confidence: 0.885832098571429

00:27:54.630 --> 00:27:56.298 I also want to investigate synergistic

NOTE Confidence: 0.885832098571429

00:27:56.298 --> 00:27:57.772 interactions between the mean checkpoint

NOTE Confidence: 0.885832098571429

00:27:57.772 --> 00:27:59.698 blockade and DNA damage response inhibitors,

NOTE Confidence: 0.885832098571429

00:27:59.700 --> 00:28:01.125 and these uncle metabolite producing

NOTE Confidence: 0.885832098571429

00:28:01.125 --> 00:28:03.130 tumors and hope to get started on

NOTE Confidence: 0.885832098571429

00:28:03.130 --> 00:28:04.455 these preclinical studies in the

NOTE Confidence: 0.885832098571429

00:28:04.455 --> 00:28:06.079 next in the upcoming months.

NOTE Confidence: 0.747156045333333

00:28:08.320 --> 00:28:10.210 So with that I'll end up and I want

NOTE Confidence: 0.747156045333333

00:28:10.210 --> 00:28:12.197 to just thank Doctor Bindra again,

NOTE Confidence: 0.747156045333333

00:28:12.200 --> 00:28:14.096 who's my primary mentor and has

NOTE Confidence: 0.747156045333333

00:28:14.096 --> 00:28:15.740 really been instrumental in in me,

NOTE Confidence: 0.747156045333333

00:28:15.740 --> 00:28:17.964 sort of advancing and receiving my K-8 as

NOTE Confidence: 0.747156045333333

00:28:17.964 --> 00:28:20.397 I build my pathway towards independence,

NOTE Confidence: 0.747156045333333

00:28:20.400 --> 00:28:22.408 as well as all the members of the

NOTE Confidence: 0.747156045333333

00:28:22.408 --> 00:28:24.001 Bingil lab have been instrumental

NOTE Confidence: 0.747156045333333

00:28:24.001 --> 00:28:25.963 in helping me sort of progress,

NOTE Confidence: 0.747156045333333

00:28:25.963 --> 00:28:28.140 as well as all those folks specifically

NOTE Confidence: 0.747156045333333

00:28:28.196 --> 00:28:30.380 who helped with the projects I outlined.

NOTE Confidence: 0.747156045333333

00:28:30.380 --> 00:28:32.782 I also want to thank Dr Shuck and his

NOTE Confidence: 0.747156045333333

00:28:32.782 --> 00:28:35.900 lab at UCLA, and my many advisors here.

NOTE Confidence: 0.747156045333333

00:28:35.900 --> 00:28:37.678 You know, only a few of which.

NOTE Confidence: 0.747156045333333

00:28:37.680 --> 00:28:39.430 They're listed here as well as to

NOTE Confidence: 0.747156045333333

00:28:39.430 --> 00:28:41.000 all my funders, so thank you again.

NOTE Confidence: 0.826594380833333

00:28:42.850 --> 00:28:43.894 Thanks so much. One,

NOTE Confidence: 0.826594380833333

00:28:43.894 --> 00:28:45.738 that was a wonderful talk and I

NOTE Confidence: 0.826594380833333

00:28:45.738 --> 00:28:47.530 know we're a little bit over but we

NOTE Confidence: 0.826594380833333

00:28:47.530 --> 00:28:49.484 don't have a second speaker so if

NOTE Confidence: 0.826594380833333

00:28:49.484 --> 00:28:50.919 there are any burning questions,

NOTE Confidence: 0.826594380833333

00:28:50.920 --> 00:28:54.056 feel free to put them in the chat.

NOTE Confidence: 0.853936105

00:29:11.460 --> 00:29:14.380 Crystal clear. You know,

NOTE Confidence: 0.853936105

00:29:14.380 --> 00:29:16.550 I'll start with one question I might

NOTE Confidence: 0.853936105

00:29:16.550 --> 00:29:18.976 have missed this of the DDR inhibitors

NOTE Confidence: 0.853936105

00:29:18.976 --> 00:29:21.939 that you want to look at to combine,

NOTE Confidence: 0.853936105

00:29:21.940 --> 00:29:24.215 possibly with PD one in the setting

NOTE Confidence: 0.853936105

00:29:24.215 --> 00:29:26.457 of IDH mutants are is there a

NOTE Confidence: 0.853936105

00:29:26.457 --> 00:29:28.251 wish list of the DDR inhibitors

NOTE Confidence: 0.853936105

00:29:28.322 --> 00:29:30.077 they would want to combine?

NOTE Confidence: 0.853936105

00:29:30.080 --> 00:29:32.453 Maybe you could put one of them

NOTE Confidence: 0.853936105

00:29:32.453 --> 00:29:33.897 in particular synergized in the

NOTE Confidence: 0.853936105

00:29:33.897 --> 00:29:35.310 in tablet producing backgrounds.

NOTE Confidence: 0.837334244545454

00:29:35.840 --> 00:29:37.800 I mean I think the ATR inhibitors

NOTE Confidence: 0.837334244545454

00:29:37.800 --> 00:29:39.806 are really an interesting area to

NOTE Confidence: 0.837334244545454

00:29:39.806 --> 00:29:41.144 explore and one that really hasn't

NOTE Confidence: 0.837334244545454

00:29:41.144 --> 00:29:42.564 been looked at too much in terms

NOTE Confidence: 0.837334244545454

00:29:42.564 --> 00:29:43.950 of the immune effects of these and.

NOTE Confidence: 0.837334244545454

00:29:43.950 --> 00:29:45.528 It sort of makes sense conceptually,

NOTE Confidence: 0.837334244545454

00:29:45.530 --> 00:29:47.812 that in the setting of these cells

NOTE Confidence: 0.837334244545454

00:29:47.812 --> 00:29:50.010 entering sort of premature mitosis,

NOTE Confidence: 0.837334244545454

00:29:50.010 --> 00:29:51.780 you'd have a lot of formation

NOTE Confidence: 0.837334244545454

00:29:51.780 --> 00:29:53.344 of these micronuclei that could

NOTE Confidence: 0.837334244545454

00:29:53.344 --> 00:29:55.246 activate the CSC gas sting pathway.

NOTE Confidence: 0.837334244545454

00:29:55.246 --> 00:29:57.404 So certainly I think again, you know,

NOTE Confidence: 0.837334244545454

00:29:57.404 --> 00:29:59.448 based on our initial work with Rita

NOTE Confidence: 0.837334244545454

00:29:59.448 --> 00:30:01.825 and her findings in the flank model I,

NOTE Confidence: 0.837334244545454

00:30:01.830 --> 00:30:03.426 I really want to pursue this more

NOTE Confidence: 0.837334244545454

00:30:03.426 --> 00:30:05.886 and see if we can see signs of immune

NOTE Confidence: 0.837334244545454

00:30:05.886 --> 00:30:07.839 activation and synergy with PD1 blockade.

NOTE Confidence: 0.820368816666667

00:30:10.210 --> 00:30:11.446 Where to ask one more question.

NOTE Confidence: 0.820368816666667

00:30:11.450 --> 00:30:13.298 Then we will close up if no others.

NOTE Confidence: 0.820368816666667

00:30:13.300 --> 00:30:14.752 Any plans to write up that

NOTE Confidence: 0.820368816666667

00:30:14.752 --> 00:30:16.190 wonderful case study with Farzaneh.

NOTE Confidence: 0.948000931666667

00:30:17.610 --> 00:30:18.648 We've talked about it and yes,

NOTE Confidence: 0.948000931666667

00:30:18.650 --> 00:30:20.190 I would love to know,

NOTE Confidence: 0.948000931666667

00:30:20.190 --> 00:30:21.884 so I definitely want to check more

NOTE Confidence: 0.948000931666667

00:30:21.884 --> 00:30:23.477 about that because I think that would

NOTE Confidence: 0.948000931666667

00:30:23.477 --> 00:30:25.169 be a nice corollary to the you know,

NOTE Confidence: 0.948000931666667

00:30:25.170 --> 00:30:27.032 as you know, the aranka work we're

NOTE Confidence: 0.948000931666667

00:30:27.032 --> 00:30:28.949 hoping to write that up soon and

NOTE Confidence: 0.948000931666667

00:30:28.949 --> 00:30:30.279 submit that as a manuscript.

NOTE Confidence: 0.948000931666667

00:30:30.280 --> 00:30:31.533 So I think it would be a

NOTE Confidence: 0.948000931666667

00:30:31.533 --> 00:30:32.330 great corollary to that.

NOTE Confidence: 0.948000931666667

00:30:32.330 --> 00:30:34.746 So I definitely hope to write that up.

NOTE Confidence: 0.948000931666667

00:30:34.750 --> 00:30:35.520 Wonderful,

NOTE Confidence: 0.911709772727273

00:30:35.750 --> 00:30:36.406 well this is great.

NOTE Confidence: 0.911709772727273

00:30:36.406 --> 00:30:38.124 We had a great turn out today and I

NOTE Confidence: 0.911709772727273

00:30:38.124 --> 00:30:39.284 think you just answered everyone's

NOTE Confidence: 0.911709772727273

00:30:39.284 --> 00:30:40.250 questions with your slides.

NOTE Confidence: 0.911709772727273

00:30:40.250 --> 00:30:41.855 So thanks everyone for joining

NOTE Confidence: 0.911709772727273

00:30:41.855 --> 00:30:43.980 us and have a great rest of

NOTE Confidence: 0.86915465

00:30:43.990 --> 00:30:45.920 your Tuesday thank you room.

NOTE Confidence: 0.9110548025

00:30:46.560 --> 00:30:47.680 Take care bye bye.