WEBVTT

NOTE duration:"00:30:50"

NOTE recognizability:0.872

NOTE language:en-us

NOTE Confidence: 0.776826744545455

 $00:00:00.000 \rightarrow 00:00:02.015$  Everyone for attending this week's

NOTE Confidence: 0.776826744545455

 $00:00:02.015 \rightarrow 00:00:04.540$  grant Yo Council Center grand rounds.

NOTE Confidence: 0.776826744545455

 $00:00:04.540 \rightarrow 00:00:08.236$  It's my privilege and pleasure to introduce

NOTE Confidence: 0.776826744545455

 $00:00:08.236 \rightarrow 00:00:12.069$  Dr Juan Vasquez for this this week talk.

NOTE Confidence: 0.776826744545455

 $00:00:12.070 \longrightarrow 00:00:14.005$  Dr Vasquez is an assistant

NOTE Confidence: 0.776826744545455

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

NOTE Confidence: 0.776826744545455

 $00:00:15.170 \longrightarrow 00:00:16.470$  He received his medical degree

NOTE Confidence: 0.776826744545455

 $00{:}00{:}16{.}470 \dashrightarrow 00{:}00{:}18{.}080$  from Brown University and a Master

NOTE Confidence: 0.776826744545455

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

NOTE Confidence: 0.776826744545455

 $00:00:19.390 \longrightarrow 00:00:21.814$  where he also completed his fellowship

NOTE Confidence: 0.776826744545455

 $00:00:21.814 \dashrightarrow 00:00:23.430$  in Pediatric Hematology Oncology.

NOTE Confidence: 0.776826744545455

 $00{:}00{:}23.430 \dashrightarrow 00{:}00{:}24.800$  H is clinical focus on the

NOTE Confidence: 0.776826744545455

 $00:00:24.800 \longrightarrow 00:00:26.170$  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

 $00:00:29.380 \dashrightarrow 00:00:30.965$  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

 $00:00:33.073 \rightarrow 00:00:35.037$  particularly malignant brain tumors,

NOTE Confidence: 0.776826744545455

 $00:00:35.040 \rightarrow 00:00:36.424$  he's interested in characterizing

NOTE Confidence: 0.776826744545455

 $00{:}00{:}36{.}424 \dashrightarrow 00{:}00{:}38{.}154$  the immune landscape of pediatric

NOTE Confidence: 0.776826744545455

 $00:00:38.154 \rightarrow 00:00:39.488$  brain tumors and understanding

NOTE Confidence: 0.776826744545455

 $00{:}00{:}39{.}488 \dashrightarrow 00{:}00{:}41{.}053$  the interplay between DNA repair

NOTE Confidence: 0.776826744545455

 $00{:}00{:}41.053 \dashrightarrow 00{:}00{:}42.768$  and anti tumor immune response.

NOTE Confidence: 0.776826744545455

 $00{:}00{:}42.770 \dashrightarrow 00{:}00{:}44.960$  One is been an embedded assistant

NOTE Confidence: 0.776826744545455

 $00:00:44.960 \rightarrow 00:00:47.024$  professor in our laboratory for a

NOTE Confidence: 0.776826744545455

 $00:00:47.024 \rightarrow 00:00:48.907$  little over two years now and is

NOTE Confidence: 0.776826744545455

 $00{:}00{:}48{.}907 \dashrightarrow 00{:}00{:}51{.}454$  really hit the ground running as

NOTE Confidence: 0.776826744545455

 $00:00:51.454 \rightarrow 00:00:52.780$  rapidly approaching independence.

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

NOTE Confidence: 0.776826744545455

 $00:00:55.140 \longrightarrow 00:00:56.640$  a career development grant to

NOTE Confidence: 0.776826744545455

 $00:00:56.640 \longrightarrow 00:00:57.540$  fund this project,

NOTE Confidence: 0.776826744545455

 $00:00:57.540 \rightarrow 00:00:59.118$  which will be talking about today.

NOTE Confidence: 0.776826744545455

 $00:00:59.120 \longrightarrow 00:01:01.920$  So with that I will let one take.

NOTE Confidence: 0.776826744545455

 $00:01:01.920 \longrightarrow 00:01:03.388$  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

 $00:01:36.360 \longrightarrow 00:01:37.795$  It's a real honor to be able

NOTE Confidence: 0.951264578333333

 $00:01:37.795 \longrightarrow 00:01:38.940$  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

 $00{:}01{:}43.020 \dashrightarrow 00{:}01{:}47.330$  Uhm? I've got no disclosures.

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

 $00{:}01{:}54{.}410 \dashrightarrow 00{:}01{:}56{.}198$  which really was established by the

NOTE Confidence: 0.951264578333333

 $00:01:56.198 \longrightarrow 00:01:58.329$  seminal work of my research mentor.

NOTE Confidence: 0.951264578333333

 $00:01:58.330 \longrightarrow 00:02:00.826$  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

 $00:02:03.600 \dashrightarrow 00:02:05.549$  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

 $00:02:07.916 \dashrightarrow 00:02:10.016$  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

 $00:02:12.570 \longrightarrow 00:02:13.278$  And then lastly,

NOTE Confidence: 0.951264578333333

 $00:02:13.278 \longrightarrow 00:02:14.930$  I'll touch a bit on the potential

NOTE Confidence: 0.951264578333333

 $00:02:14.979 \longrightarrow 00:02:16.327$  for exploiting these uncle

NOTE Confidence: 0.951264578333333

 $00:02:16.327 \longrightarrow 00:02:17.338$  metabolite induced DNA.

NOTE Confidence: 0.951264578333333

 $00:02:17.340 \longrightarrow 00:02:20.154$  Repair defects in order to promote an

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

NOTE Confidence: 0.951264578333333

 $00:02:21.418 \rightarrow 00:02:23.274$  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

 $00{:}02{:}31{.}520 \dashrightarrow 00{:}02{:}34{.}012$  the Krebs cycle is very important in

NOTE Confidence: 0.824376642857143

 $00{:}02{:}34.012 \dashrightarrow 00{:}02{:}35.742$  cellular energy production and alpha

NOTE Confidence: 0.824376642857143

 $00:02:35.742 \longrightarrow 00:02:37.842$  ketoglutarate is a is a key intermediate

NOTE Confidence: 0.824376642857143

 $00:02:37.842 \rightarrow 00:02:40.676$  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

 $00:02:42.823 \rightarrow 00:02:45.288$  number of key cellular processes.

NOTE Confidence: 0.824376642857143

 $00:02:45.290 \rightarrow 00:02:47.432$  Mutations in enzymes of the Krebs cycle

NOTE Confidence: 0.824376642857143

 $00{:}02{:}47{.}432 \dashrightarrow 00{:}02{:}50{.}193$  result in an excess accumulation of two

NOTE Confidence: 0.824376642857143

 $00:02:50.193 \rightarrow 00:02:52.418$  hydroxy glutarate succinate and fumarate,

NOTE Confidence: 0.824376642857143

 $00{:}02{:}52{.}420 \dashrightarrow 00{:}02{:}53{.}866$  and I'll go through these in

NOTE Confidence: 0.824376642857143

 $00{:}02{:}53.866 \dashrightarrow 00{:}02{:}55.610$  more detail in the coming slides.

 $00:02:55.610 \rightarrow 00:02:57.146$  But in general,

NOTE Confidence: 0.824376642857143

 $00:02:57.146 \rightarrow 00:02:59.194$  these uncle metabolites competitively

NOTE Confidence: 0.824376642857143

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

NOTE Confidence: 0.824376642857143

 $00:03:01.254 \rightarrow 00:03:04.446$  dioxygenase is by virtue of their structural

NOTE Confidence: 0.824376642857143

 $00:03:04.446 \rightarrow 00:03:06.622$  similarity there by dysregulating AKI,

NOTE Confidence: 0.824376642857143

 $00:03:06.622 \dashrightarrow 00:03:09.190$  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

 $00:03:11.750 \longrightarrow 00:03:14.424$  and this is really why there are

NOTE Confidence: 0.824376642857143

 $00:03:14.424 \dashrightarrow 00:03:17.029$  classified now is uncle metabolites.

NOTE Confidence: 0.824376642857143

 $00{:}03{:}17.030 \dashrightarrow 00{:}03{:}20.252$  So focusing first on IDH mutations

NOTE Confidence: 0.824376642857143

 $00{:}03{:}20{.}252 \dashrightarrow 00{:}03{:}23{.}024$  or isocitrate dehydrogenase so IDH

NOTE Confidence: 0.824376642857143

 $00:03:23.024 \rightarrow 00:03:25.332$  catalyzes the oxidation oxidative

NOTE Confidence: 0.824376642857143

 $00{:}03{:}25{.}332 \dashrightarrow 00{:}03{:}27{.}063$  decarboxylation of isocitrate

NOTE Confidence: 0.824376642857143

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

NOTE Confidence: 0.824376642857143

 $00:03:29.230 \rightarrow 00:03:31.115$  Uhm, and these heterozygous IDH

NOTE Confidence: 0.824376642857143

 $00:03:31.115 \rightarrow 00:03:33.524$  mutations result in a new amorphic

 $00:03:33.524 \rightarrow 00:03:35.774$  activity of that enzyme whereby

NOTE Confidence: 0.824376642857143

 $00:03:35.774 \longrightarrow 00:03:38.144$  alpha ketoglutarate is then further

NOTE Confidence: 0.824376642857143

 $00:03:38.144 \rightarrow 00:03:40.629$  converted into two hydroxy glutarate.

NOTE Confidence: 0.824376642857143

 $00:03:40.630 \rightarrow 00:03:43.850$  And most commonly are missense

NOTE Confidence: 0.824376642857143

 $00:03:43.850 \rightarrow 00:03:46.426$  arginine to histidine mutations.

NOTE Confidence: 0.824376642857143

 $00:03:46.430 \longrightarrow 00:03:48.208$  Make up about 70% of all these

NOTE Confidence: 0.824376642857143

 $00{:}03{:}48{.}208 \dashrightarrow 00{:}03{:}49{.}826$  mutations and you can see IDH

NOTE Confidence: 0.824376642857143

 $00:03:49.826 \dashrightarrow 00:03:51.416$  mutations in a variety of tumors.

NOTE Confidence: 0.824376642857143

 $00{:}03{:}51{.}420 \dashrightarrow 00{:}03{:}54{.}171$  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

 $00:03:57.510 \rightarrow 00:03:59.210$  chondrosarcoma and cholangio carcinoma.

NOTE Confidence: 0.877308717142857

 $00:04:01.610 \dashrightarrow 00:04:03.647$  Further on down to the Krebs cycle

NOTE Confidence: 0.877308717142857

 $00:04:03.650 \rightarrow 00:04:05.458$  succinate dehydrogenase catalyzes the

NOTE Confidence: 0.877308717142857

 $00{:}04{:}05{.}458 \dashrightarrow 00{:}04{:}07{.}718$  oxidation of succinate to fumarate

NOTE Confidence: 0.877308717142857

 $00:04:07.718 \rightarrow 00:04:09.501$  and fumarate hydratase catalyzes

 $00:04:09.501 \rightarrow 00:04:12.039$  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

 $00:04:13.584 \rightarrow 00:04:15.514$  function mutations in these genes

NOTE Confidence: 0.877308717142857

 $00:04:15.514 \rightarrow 00:04:17.489$  are associated with a predisposition

NOTE Confidence: 0.877308717142857

 $00{:}04{:}17{.}489 \dashrightarrow 00{:}04{:}19{.}775$  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

 $00{:}04{:}23.562 \dashrightarrow 00{:}04{:}25.730$  leading to excess accumulation

NOTE Confidence: 0.877308717142857

 $00:04:25.730 \longrightarrow 00:04:27.898$  of femur and succinate.

NOTE Confidence: 0.877308717142857

 $00:04:27.900 \rightarrow 00:04:29.552$  Germline FH mutations predispose

NOTE Confidence: 0.877308717142857

 $00{:}04{:}29{.}552 \dashrightarrow 00{:}04{:}31{.}204$  to hereditary leiomyoma ptosis

NOTE Confidence: 0.877308717142857

 $00:04:31.204 \rightarrow 00:04:32.999$  and renal cancer syndrome.

NOTE Confidence: 0.877308717142857

 $00:04:33.000 \rightarrow 00:04:36.288$  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

 $00{:}04{:}38.552 \dashrightarrow 00{:}04{:}40.028$  paraganglioma and pheochromocytoma

NOTE Confidence: 0.877308717142857

 $00:04:40.028 \dashrightarrow 00:04:42.980$  as well as renal cell carcinoma.

- NOTE Confidence: 0.877308717142857
- 00:04:42.980 --> 00:04:43.530 And, importantly,
- NOTE Confidence: 0.877308717142857
- $00:04:43.530 \rightarrow 00:04:45.180$  renal cell carcinoma in the setting
- NOTE Confidence: 0.877308717142857
- $00:04:45.180 \rightarrow 00:04:46.955$  of both these syndromes is typically
- NOTE Confidence: 0.877308717142857
- $00:04:46.955 \rightarrow 00:04:48.713$  aggressive with a high propensity to
- NOTE Confidence: 0.877308717142857
- $00{:}04{:}48.767 \dashrightarrow 00{:}04{:}50.501$  present with metastases early in disease
- NOTE Confidence: 0.877308717142857
- $00{:}04{:}50{.}501 \dashrightarrow 00{:}04{:}52{.}465$  and once these patients metastasize,
- NOTE Confidence: 0.877308717142857
- $00:04:52.465 \longrightarrow 00:04:56.490$  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
- $00:04:57.840 \longrightarrow 00:04:59.556$  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
- $00:05:03.990 \longrightarrow 00:05:06.888$  and a series of high impact publications
- NOTE Confidence: 0.877308717142857
- $00{:}05{:}06.888 \dashrightarrow 00{:}05{:}09.092$  where uncle Metabolites were found
- NOTE Confidence: 0.877308717142857
- $00:05:09.092 \rightarrow 00:05:10.876$  to inhibit homologous recombination
- NOTE Confidence: 0.877308717142857

 $00:05:10.876 \rightarrow 00:05:13.510$  and confer prohibit or sensitivity.

NOTE Confidence: 0.877308717142857

 $00{:}05{:}13.510 \dashrightarrow 00{:}05{:}15.466$  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

 $00:05:16.770 \longrightarrow 00:05:19.482$  but what they found is uncle

NOTE Confidence: 0.877308717142857

 $00{:}05{:}19.482 \dashrightarrow 00{:}05{:}21.290$  metabolites inhibit alpha ketoglutarate

NOTE Confidence: 0.877308717142857

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

NOTE Confidence: 0.877308717142857

 $00{:}05{:}22.998 \dashrightarrow 00{:}05{:}26.198$  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

 $00:05:32.270 \longrightarrow 00:05:33.770$  surrounding DNA breaks.

NOTE Confidence: 0.877308717142857

 $00{:}05{:}33.770 \dashrightarrow 00{:}05{:}36.220$  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

 $00:05:38.050 \rightarrow 00:05:41.386$  in which you can see that control cells

NOTE Confidence: 0.877308717142857

 $00{:}05{:}41.390 \dashrightarrow 00{:}05{:}44.150$  there's a spike of H3K9 trimethylation.

NOTE Confidence: 0.877308717142857

 $00{:}05{:}44{.}150 \dashrightarrow 00{:}05{:}45{.}995$  That induced double strand breaks

NOTE Confidence: 0.877308717142857

 $00:05:45.995 \rightarrow 00:05:47.840$  followed by a coordinated recruitment

 $00:05:47.894 \rightarrow 00:05:49.868$  of double strand break repair factors.

NOTE Confidence: 0.877308717142857

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

NOTE Confidence: 0.877308717142857

 $00{:}05{:}50{.}340 \dashrightarrow 00{:}05{:}53{.}160$  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

 $00:05:55.150 \longrightarrow 00:05:56.602$  there is H3K9 trimethylation

NOTE Confidence: 0.877308717142857

 $00:05:56.602 \rightarrow 00:05:58.780$  already present at the site before

NOTE Confidence: 0.877308717142857

 $00:05:58.840 \rightarrow 00:06:00.800$  induction of double strand breaks,

NOTE Confidence: 0.877308717142857

 $00:06:00.800 \dashrightarrow 00:06:02.828$  and this really serves to mask

NOTE Confidence: 0.877308717142857

 $00:06:02.828 \longrightarrow 00:06:04.180$  that local trimethylation signal

NOTE Confidence: 0.877308717142857

 $00:06:04.240 \rightarrow 00:06:06.132$  that's important for triggering

NOTE Confidence: 0.877308717142857

 $00:06:06.132 \rightarrow 00:06:08.024$  proper recruitment of homologous

NOTE Confidence: 0.877308717142857

 $00:06:08.024 \longrightarrow 00:06:08.970$  recombination proteins,

NOTE Confidence: 0.877308717142857

 $00{:}06{:}08{.}970 \dashrightarrow 00{:}06{:}10{.}382$  essentially leading to defective

NOTE Confidence: 0.877308717142857

 $00{:}06{:}10.382 \dashrightarrow 00{:}06{:}12.500$  HR and a bracken NIST phenotype.

NOTE Confidence: 0.87331146

 $00:06:14.510 \rightarrow 00:06:17.198$  So now just to very briefly and generally

 $00:06:17.198 \dashrightarrow 00:06:19.708$  introduce the topic of synthetic lethality.

NOTE Confidence: 0.87331146

 $00:06:19.710 \longrightarrow 00:06:21.447$  So as you can see here from this figure,

NOTE Confidence: 0.87331146

 $00{:}06{:}21.450 \dashrightarrow 00{:}06{:}24.715$  part is really an important enzyme

NOTE Confidence: 0.87331146

 $00{:}06{:}24.715 \dashrightarrow 00{:}06{:}27.060$  involved in the repair of single strand

NOTE Confidence: 0.87331146

 $00{:}06{:}27.060 \dashrightarrow 00{:}06{:}29.020$  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

 $00{:}06{:}31.588 \dashrightarrow 00{:}06{:}33.910$  based excision repair and converts

NOTE Confidence: 0.87331146

 $00:06:33.910 \rightarrow 00:06:35.535$  single strand then single strand

NOTE Confidence: 0.87331146

 $00{:}06{:}35{.}535 \dashrightarrow 00{:}06{:}37{.}518$  breaks are converted to double strand

NOTE Confidence: 0.87331146

 $00{:}06{:}37{.}518 \dashrightarrow 00{:}06{:}39{.}646$  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

 $00:06:41.493 \longrightarrow 00:06:43.137$  an intact homologous recombination.

NOTE Confidence: 0.87331146

 $00:06:43.140 \longrightarrow 00:06:44.450$  This DNA damage is effectively

NOTE Confidence: 0.87331146

 $00:06:44.450 \longrightarrow 00:06:46.220$  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

 $00{:}06{:}48.660 \dashrightarrow 00{:}06{:}50.280$  there's a buildup or accumulation

- NOTE Confidence: 0.87331146
- 00:06:50.280 --> 00:06:51.576 of unrepaired DNA damage,

 $00:06:51.580 \rightarrow 00:06:53.190$  ultimately leading to cell death and this

NOTE Confidence: 0.87331146

 $00:06:53.190 \rightarrow 00:06:54.909$  is this idea of synthetic lethality.

NOTE Confidence: 0.780967909444445

 $00:06:57.090 \rightarrow 00:06:58.878$  So this same synthetic lethality was

NOTE Confidence: 0.780967909444445

 $00:06:58.878 \rightarrow 00:07:01.262$  found also in the setting of uncle

NOTE Confidence: 0.780967909444445

 $00:07:01.262 \rightarrow 00:07:03.157$  metabolite induced DNA repair defects.

NOTE Confidence: 0.780967909444445

 $00:07:03.160 \longrightarrow 00:07:05.148$  So just looking at just a snippet

NOTE Confidence: 0.780967909444445

 $00:07:05.148 \longrightarrow 00:07:07.737$  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: 0.78096790944445

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

NOTE Confidence: 0.780967909444445

 $00{:}07{:}14.510 \dashrightarrow 00{:}07{:}16.245$  There's an increased amount of

NOTE Confidence: 0.780967909444445

 $00:07:16.245 \dashrightarrow 00:07:17.633$  baseline unrepaired DNA damage,

NOTE Confidence: 0.78096790944445

 $00{:}07{:}17.640 \dashrightarrow 00{:}07{:}20.440$  and this is as measured through a

NOTE Confidence: 0.780967909444445

 $00:07:20.440 \rightarrow 00:07:23.128$  common tale essay where damaged DNA.

NOTE Confidence: 0.78096790944445

 $00:07:23.130 \dashrightarrow 00:07:25.086$  As its nucleus informs US, Comet tail,

 $00:07:25.086 \rightarrow 00:07:27.026$  which is his representative unrepaired

NOTE Confidence: 0.780967909444445

 $00{:}07{:}27.026 \dashrightarrow 00{:}07{:}29.707$  DNA damage and you can see that IDH

NOTE Confidence: 0.780967909444445

 $00{:}07{:}29{.}707 \dashrightarrow 00{:}07{:}31{.}544$  mutant Tumors Harbor an increased

NOTE Confidence: 0.780967909444445

 $00:07:31.544 \rightarrow 00:07:33.634$  amount of damage at baseline.

NOTE Confidence: 0.780967909444445

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

NOTE Confidence: 0.780967909444445

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

NOTE Confidence: 0.78096790944445

 $00:07:37.240 \longrightarrow 00:07:39.568$  you can see that these cells,

NOTE Confidence: 0.780967909444445

 $00{:}07{:}39{.}570 \dashrightarrow 00{:}07{:}41{.}826$  these IDH mutant cells have more

NOTE Confidence: 0.780967909444445

 $00{:}07{:}41.826 \dashrightarrow 00{:}07{:}43.330$  sensitivity to irreparably than

NOTE Confidence: 0.780967909444445

 $00:07:43.394 \rightarrow 00:07:45.098$  their wild type counterparts,

NOTE Confidence: 0.780967909444445

 $00{:}07{:}45.100 \dashrightarrow 00{:}07{:}48.180$  and the same was seen in in vivo.

NOTE Confidence: 0.780967909444445

 $00:07:48.180 \dashrightarrow 00:07:50.292$  A study using HTTR human cancer

NOTE Confidence: 0.78096790944445

 $00{:}07{:}50.292 \dashrightarrow 00{:}07{:}52.514$  colon cancer cell line with an

NOTE Confidence: 0.780967909444445

 $00{:}07{:}52.514 \dashrightarrow 00{:}07{:}54.374$  IDH mutation where these tumors

NOTE Confidence: 0.780967909444445

 $00:07:54.374 \rightarrow 00:07:56.600$  were sensitive to PARP inhibition,

NOTE Confidence: 0.780967909444445

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

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

 $00:08:06.456 \rightarrow 00:08:08.260$  corporate hipper sensitivity were

NOTE Confidence: 0.944530772

 $00:08:08.330 \longrightarrow 00:08:10.857$  shown in FH and SDH deficient models.

NOTE Confidence: 0.944530772

 $00:08:10.860 \longrightarrow 00:08:15.207$  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

 $00:08:18.300 \dashrightarrow 00:08:20.910$  You can see that again compared

NOTE Confidence: 0.944530772

 $00:08:20.910 \longrightarrow 00:08:22.215$  to normal tissues.

NOTE Confidence: 0.944530772

 $00{:}08{:}22{.}220 \dashrightarrow 00{:}08{:}24{.}146$  Those with SDHB mutations in FH

NOTE Confidence: 0.944530772

 $00{:}08{:}24.146 \dashrightarrow 00{:}08{:}25.828$  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

 $00:08:29.352 \longrightarrow 00:08:31.353$  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

 $00{:}08{:}33{.}085 \dashrightarrow 00{:}08{:}34{.}960$  vivo there's delayed tumor growth

 $00{:}08{:}34{.}960 \dashrightarrow 00{:}08{:}36{.}835$  with a different park inhibitor.

NOTE Confidence: 0.944530772

 $00:08:36.840 \longrightarrow 00:08:38.589$  Here bnes 673.

NOTE Confidence: 0.94176656555556

 $00:08:43.800 \longrightarrow 00:08:45.340$  Based on these findings,

NOTE Confidence: 0.94176656555556

 $00:08:45.340 \longrightarrow 00:08:47.265$  clinical trials have been started,

NOTE Confidence: 0.941766565555556

 $00:08:47.270 \longrightarrow 00:08:48.242$  including here at Yale,

NOTE Confidence: 0.94176656555556

 $00:08:48.242 \longrightarrow 00:08:50.010$  so this is just a report from

NOTE Confidence: 0.94176656555556

 $00:08:50.010 \rightarrow 00:08:51.275$  our Phase one group here,

NOTE Confidence: 0.94176656555556

 $00:08:51.280 \rightarrow 00:08:52.918$  showing that there's a subset of

NOTE Confidence: 0.94176656555556

 $00:08:52.918 \rightarrow 00:08:54.680$  patients with IDH mutated solid tumors.

NOTE Confidence: 0.94176656555556

 $00:08:54.680 \dashrightarrow 00:08:56.486$  In this case, chondrosarcoma is that

NOTE Confidence: 0.94176656555556

 $00:08:56.486 \rightarrow 00:08:58.200$  derives clinical benefit from elaborate,

NOTE Confidence: 0.94176656555556

 $00:08:58.200 \rightarrow 00:09:00.220$  cheap, elaborate treatment with some

NOTE Confidence: 0.94176656555556

 $00:09:00.220 \rightarrow 00:09:02.240$  patients showing either stable disease,

NOTE Confidence: 0.94176656555556

 $00:09:02.240 \longrightarrow 00:09:04.820$  or in this case, highlighted here,

NOTE Confidence: 0.941766565555556

 $00:09:04.820 \longrightarrow 00:09:08.570$  partial remission of their tumor burden.

NOTE Confidence: 0.94176656555556

 $00:09:08.570 \dashrightarrow 00:09:10.916$  And obviously these trials are continuing

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

 $00:09:21.853 \rightarrow 00:09:24.743$  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

 $00:09:28.687 \rightarrow 00:09:30.878$  curative and in the majority of patients.

NOTE Confidence: 0.78691315

 $00:09:30.880 \longrightarrow 00:09:33.183$  So we set avenues for exploring other

NOTE Confidence: 0.78691315

 $00{:}09{:}33.183 \dashrightarrow 00{:}09{:}35.319$  DNA repair pathways that could be

NOTE Confidence: 0.78691315

 $00:09:35.319 \longrightarrow 00:09:37.124$  targeted in a combinatorial fashion.

NOTE Confidence: 0.78691315

 $00{:}09{:}37.130 \dashrightarrow 00{:}09{:}40.412$  So we turn to the ATR pathway shown here.

NOTE Confidence: 0.78691315

 $00:09:40.412 \rightarrow 00:09:42.519$  So in the setting of DNA damage

NOTE Confidence: 0.78691315

 $00:09:42.519 \dashrightarrow 00:09:44.492$  ATR phosphorylates, check one.

NOTE Confidence: 0.78691315

 $00{:}09{:}44.492 \dashrightarrow 00{:}09{:}47.060$  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,

 $00:09:49.790 \rightarrow 00:09:52.569$  including the arrest of cell cycle by

NOTE Confidence: 0.78691315

 $00:09:52.569 \dashrightarrow 00:09:55.367$  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

 $00:09:57.940 \dashrightarrow 00:10:00.470$  and prevents premature mitotic entry

NOTE Confidence: 0.78691315

 $00{:}10{:}00{.}470 \dashrightarrow 00{:}10{:}02{.}006$  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

 $00:10:03.425 \rightarrow 00:10:05.490$  proceed past the S phase checkpoint,

NOTE Confidence: 0.78691315

 $00:10:05.490 \rightarrow 00:10:07.542$  thereby promoting the induction of double

NOTE Confidence: 0.78691315

 $00{:}10{:}07{.}542 \dashrightarrow 00{:}10{:}09{.}550$  strand breaks, premature mitotic entry,

NOTE Confidence: 0.78691315

 $00:10:09.550 \longrightarrow 00:10:12.540$  and ultimately, cell death.

NOTE Confidence: 0.78691315

 $00{:}10{:}12{.}540 \dashrightarrow 00{:}10{:}15{.}570$  As you can see here.

NOTE Confidence: 0.78691315

 $00:10:15.570 \longrightarrow 00:10:18.074$  So this is a work led by an

NOTE Confidence: 0.78691315

 $00{:}10{:}18.074 \dashrightarrow 00{:}10{:}19.400$  excellent postdoctoral associate,

NOTE Confidence: 0.78691315

 $00:10:19.400 \longrightarrow 00:10:20.297$  that term retool,

NOTE Confidence: 0.78691315

 $00{:}10{:}20.297 \dashrightarrow 00{:}10{:}22.390$  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
- $00:10:24.530 \rightarrow 00:10:26.894$  IDH mutant cells were more sensitive

 $00:10:26.894 \longrightarrow 00:10:29.249$  to a combination of a leopard

NOTE Confidence: 0.78691315

 $00:10:29.249 \longrightarrow 00:10:31.630$  and the ATR inhibitor Azd 6738.

NOTE Confidence: 0.78691315

 $00:10:31.630 \rightarrow 00:10:35.350$  Compared to the wild type counterparts.

NOTE Confidence: 0.78691315

 $00{:}10{:}35{.}350 \dashrightarrow 00{:}10{:}37{.}550$  And similarly, in vivo,

NOTE Confidence: 0.78691315

 $00{:}10{:}37{.}550 \dashrightarrow 00{:}10{:}40{.}242$  using again HCT xenograft flank model,

NOTE Confidence: 0.78691315

 $00{:}10{:}40{.}242 \dashrightarrow 00{:}10{:}42{.}630$  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

 $00{:}10{:}44.590 \dashrightarrow 00{:}10{:}47.366$  her elaborate and ATR inhibition resulted

NOTE Confidence: 0.78691315

 $00:10:47.366 \rightarrow 00:10:49.596$  in significantly delayed tumor growth.

NOTE Confidence: 0.909161469230769

 $00:10:51.760 \rightarrow 00:10:53.712$  Just to get an idea of what mechanisms

NOTE Confidence: 0.909161469230769

 $00{:}10{:}53.712 \dashrightarrow 00{:}10{:}55.719$  might be underlying decided toxicity.

NOTE Confidence: 0.909161469230769

 $00:10:55.720 \longrightarrow 00:10:58.359$  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

 $00:11:00.988 \rightarrow 00:11:03.706$  these wild type and mutant cells after NOTE Confidence: 0.909161469230769

 $00:11:03.706 \rightarrow 00:11:06.754$  treatment with elaborate is ATR inhibitor

NOTE Confidence: 0.909161469230769

 $00:11:06.754 \rightarrow 00:11:08.896$  or combination therapy and what you see

NOTE Confidence: 0.909161469230769

 $00:11:08.896 \rightarrow 00:11:10.230$  is that after 24 hours of treatment,

NOTE Confidence: 0.909161469230769

 $00:11:10.230 \rightarrow 00:11:12.425$  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

 $00:11:15.430 \rightarrow 00:11:17.656$  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

 $00{:}11{:}22.780 \dashrightarrow 00{:}11{:}24.100$  As I mentioned before,

NOTE Confidence: 0.909161469230769

 $00{:}11{:}24{.}100 \dashrightarrow 00{:}11{:}26{.}507$  ATR also plays an important role in

NOTE Confidence: 0.909161469230769

 $00{:}11{:}26{.}507 \dashrightarrow 00{:}11{:}27{.}861$  regulating cell cycle progression

NOTE Confidence: 0.909161469230769

 $00:11:27.861 \rightarrow 00:11:29.487$  in the setting of DNA damage.

NOTE Confidence: 0.909161469230769

 $00{:}11{:}29{.}490 \dashrightarrow 00{:}11{:}31{.}793$  So we assessed for the mitotic cell

NOTE Confidence: 0.909161469230769

 $00:11:31.793 \longrightarrow 00:11:33.326$  population looking at phosphorylated

NOTE Confidence: 0.909161469230769

 $00:11:33.326 \rightarrow 00:11:36.030$  histone 3, which is a marker of mitosis,

NOTE Confidence: 0.909161469230769

 $00:11:36.030 \rightarrow 00:11:38.654$  and you can see again that with the

- NOTE Confidence: 0.909161469230769
- $00:11:38.654 \rightarrow 00:11:40.642$  combination treatment you see an increase
- NOTE Confidence: 0.909161469230769
- $00:11:40.642 \longrightarrow 00:11:42.165$  amount of cells entering mitosis.
- NOTE Confidence: 0.909161469230769
- $00{:}11{:}42.165 \dashrightarrow 00{:}11{:}44.859$  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
- $00:11:48.910 \longrightarrow 00:11:49.672$  these cells progressed
- NOTE Confidence: 0.909161469230769
- $00:11:49.672 \rightarrow 00:11:50.688$  through their cell cycle,
- NOTE Confidence: 0.909161469230769
- $00{:}11{:}50.690 \dashrightarrow 00{:}11{:}51.704$  enter enter mitosis.
- NOTE Confidence: 0.909161469230769
- $00{:}11{:}51{.}704 \dashrightarrow 00{:}11{:}53{.}732$  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
- $00:11:59.130 \longrightarrow 00:12:00.394$  there's actually trials now
- NOTE Confidence: 0.925392715
- $00:12:00.394 \longrightarrow 00:12:01.658$  ongoing of this combination,
- NOTE Confidence: 0.925392715
- $00:12:01.660 \rightarrow 00:12:02.692$  including here at Yale,
- NOTE Confidence: 0.925392715
- $00:12:02.692 \longrightarrow 00:12:04.240$  where there's a phase two trial,
- NOTE Confidence: 0.925392715
- $00{:}12{:}04{.}240 \dashrightarrow 00{:}12{:}07{.}324$  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

 $00:12:10.120 \longrightarrow 00:12:11.101$  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

 $00:12:13.449 \rightarrow 00:12:15.190$  results of this in the coming years.

NOTE Confidence: 0.8973930766666667

 $00{:}12{:}17{.}820 \dashrightarrow 00{:}12{:}20{.}020$  So turning now to the other Krebs cycle

NOTE Confidence: 0.8973930766666667

 $00{:}12{:}20.020$  -->  $00{:}12{:}22.220$  mutations I mentioned before, succinate NOTE Confidence: 0.8973930766666667

 $00:12:22.220 \rightarrow 00:12:24.940$  dehydrogenase and fumarate hydratase.

NOTE Confidence: 0.8973930766666667

 $00{:}12{:}24{.}940 \dashrightarrow 00{:}12{:}27{.}145$  So in this study done in collaboration

NOTE Confidence: 0.8973930766666667

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

NOTE Confidence: 0.8973930766666667

 $00:12:29.270 \longrightarrow 00:12:30.745$  he's a urologic cancer surgeon.

NOTE Confidence: 0.8973930766666667

 $00{:}12{:}30{.}750 \dashrightarrow 00{:}12{:}33{.}382$  We wanted to identify other potential novel

NOTE Confidence: 0.8973930766666667

 $00{:}12{:}33{.}382 \dashrightarrow 00{:}12{:}35{.}893$  treatment approaches that exploit this uncle

NOTE Confidence: 0.8973930766666667

 $00:12:35.893 \rightarrow 00:12:37.665$  metabolite induced genomic instability

NOTE Confidence: 0.8973930766666667

 $00{:}12{:}37.670 \dashrightarrow 00{:}12{:}40.220$  using renal cell carcinoma models.

NOTE Confidence: 0.8973930766666667

 $00{:}12{:}40{.}220 \dashrightarrow 00{:}12{:}44{.}616$  So here we turned our attention to.

NOTE Confidence: 0.8973930766666667

 $00:12:44.620 \rightarrow 00:12:46.750$  Missoula made, which is an alkylating

- NOTE Confidence: 0.8973930766666667
- $00:12:46.750 \longrightarrow 00:12:48.978$  agent that mediates its cytotoxic effects
- NOTE Confidence: 0.8973930766666667
- $00{:}12{:}48{.}978$  -->  $00{:}12{:}51{.}481$  by attaching methyl groups to DNA and
- NOTE Confidence: 0.8973930766666667
- $00{:}12{:}51{.}481 \dashrightarrow 00{:}12{:}53{.}649$  the repair of the N7 methyl guanine adduct.
- NOTE Confidence: 0.8973930766666667
- $00{:}12{:}53.650 \dashrightarrow 00{:}12{:}55.816$  In particular is needed by mediated
- NOTE Confidence: 0.8973930766666667
- $00:12:55.816 \rightarrow 00:12:58.229$  by the base excision repair pathway
- NOTE Confidence: 0.8973930766666667
- $00{:}12{:}58{.}230 \dashrightarrow 00{:}13{:}00{.}048$  in a process that involves park.
- NOTE Confidence: 0.8973930766666667
- 00:13:00.050 --> 00:13:00.491 Therefore,
- NOTE Confidence: 0.897393076666667
- $00:13:00.491 \rightarrow 00:13:02.696$  we hypothesize that apartment habisch
- NOTE Confidence: 0.8973930766666667
- $00{:}13{:}02.696 \dashrightarrow 00{:}13{:}04.926$  and will enhance Tim Assamite
- NOTE Confidence: 0.8973930766666667
- 00:13:04.926 --> 00:13:07.338 induced city toxicity and FHN SDH
- NOTE Confidence: 0.8973930766666667
- $00{:}13{:}07{.}338 \dashrightarrow 00{:}13{:}09{.}700$  deficient renal cell carcinoma models.
- NOTE Confidence: 0.938353535
- $00{:}13{:}14{.}160 \dashrightarrow 00{:}13{:}18{.}340$  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
- $00{:}13{:}21{.}360 \dashrightarrow 00{:}13{:}23{.}925$  and for this we use the rank a cell
- NOTE Confidence: 0.938353535
- $00:13:23.925 \rightarrow 00:13:27.269$  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

 $00{:}13{:}29{.}340 \dashrightarrow 00{:}13{:}31{.}620$  that's derived from balb C mice.

NOTE Confidence: 0.938353535

 $00:13:31.620 \longrightarrow 00:13:34.182$  So first by Western blot we

NOTE Confidence: 0.938353535

 $00{:}13{:}34{.}182 \dashrightarrow 00{:}13{:}36{.}930$  confirmed FH1 and SDHB knockout.

NOTE Confidence: 0.938353535

 $00:13:36.930 \longrightarrow 00:13:39.090$  We then also further functionally

NOTE Confidence: 0.938353535

 $00{:}13{:}39{.}090 \dashrightarrow 00{:}13{:}40{.}852$  validated this knock out using

NOTE Confidence: 0.938353535

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

NOTE Confidence: 0.938353535

 $00:13:42.700 \longrightarrow 00:13:44.295$  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

 $00:13:45.943 \longrightarrow 00:13:47.038$  succinate in fumarate,

NOTE Confidence: 0.938353535

 $00{:}13{:}47.040 \dashrightarrow 00{:}13{:}49.280$  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

 $00{:}13{:}51.068 \dashrightarrow 00{:}13{:}53.669$  to build up of these uncle metabolites,

NOTE Confidence: 0.938353535

 $00:13:53.670 \longrightarrow 00:13:55.870$  as one would expect.

NOTE Confidence: 0.938353535

 $00{:}13{:}55.870 \dashrightarrow 00{:}13{:}58.276$  We next performed a seahorse as say

NOTE Confidence: 0.938353535

 $00:13:58.276 \rightarrow 00:13:59.880$  to measure oxidative phosphorylation

- NOTE Confidence: 0.938353535
- 00:13:59.942 --> 00:14:01.836 and found that again, as expected,
- NOTE Confidence: 0.938353535
- $00{:}14{:}01{.}836 \dashrightarrow 00{:}14{:}04{.}660$  SDHB and FH1 loss of function and the
- NOTE Confidence: 0.938353535
- $00:14:04.740 \rightarrow 00:14:06.552$  subsequent Krebs cycle dysfunction
- NOTE Confidence: 0.938353535
- $00:14:06.552 \longrightarrow 00:14:09.270$  that comes from that leads to
- NOTE Confidence: 0.938353535
- $00:14:09.342 \rightarrow 00:14:11.889$  decreased oxidative phosphorylation.
- NOTE Confidence: 0.938353535
- $00{:}14{:}11{.}890 \dashrightarrow 00{:}14{:}14{.}730$  So this helps sort of validate our model.
- NOTE Confidence: 0.938353535
- 00:14:14.730 --> 00:14:15.121 Next,
- NOTE Confidence: 0.938353535
- $00:14:15.121 \rightarrow 00:14:17.467$  we sought to assess the intrinsic
- NOTE Confidence: 0.938353535
- 00:14:17.467 --> 00:14:19.474 DNA repair capability of Krebs
- NOTE Confidence: 0.938353535
- $00:14:19.474 \rightarrow 00:14:21.629$  cycle deficient cells by looking at
- NOTE Confidence: 0.938353535
- 00:14:21.629 --> 00:14:23.627 markers of DNA damage at baseline.
- NOTE Confidence: 0.938353535
- $00{:}14{:}23.630 \dashrightarrow 00{:}14{:}26.220$  So here again we turn to phosphorylated
- NOTE Confidence: 0.938353535
- 00:14:26.220 --> 00:14:28.576 gamma HTX as well as 53 BP,
- NOTE Confidence: 0.938353535
- $00{:}14{:}28{.}576$  -->  $00{:}14{:}30{.}574$  one which are markers of unrepaired
- NOTE Confidence: 0.938353535
- $00{:}14{:}30{.}574 \dashrightarrow 00{:}14{:}33{.}195$  DNA damage and the cellular response to
- NOTE Confidence: 0.938353535

 $00:14:33.195 \rightarrow 00:14:35.310$  DNA double strand breaks, respectively.

NOTE Confidence: 0.938353535

 $00{:}14{:}35{.}310 \dashrightarrow 00{:}14{:}38{.}910$  We found that similar to our

NOTE Confidence: 0.938353535

 $00:14:38.910 \longrightarrow 00:14:42.260$  previous work looking at.

NOTE Confidence: 0.938353535

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

NOTE Confidence: 0.938353535

 $00{:}14{:}45{.}660 \dashrightarrow 00{:}14{:}48{.}998$  an increased amount of baseline DNA repair,

NOTE Confidence: 0.938353535

 $00{:}14{:}49{.}000 \dashrightarrow 00{:}14{:}51{.}289$  unrepaired DNA damage in the knockout cells NOTE Confidence: 0.938353535

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 $00{:}14{:}51.289 \dashrightarrow 00{:}14{:}53.600$  compared to the wild type counterparts,

NOTE Confidence: 0.938353535

 $00:14:53.600 \rightarrow 00:14:55.637$  and as measured by the full site.

NOTE Confidence: 0.938353535

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

NOTE Confidence: 0.938353535

 $00{:}14{:}55{.}898 \dashrightarrow 00{:}14{:}57{.}704$  you can see these are the damage

NOTE Confidence: 0.938353535

 $00{:}14{:}57{.}704 \dashrightarrow 00{:}14{:}59{.}381$  to expose and read and hear the

NOTE Confidence: 0.938353535

 $00{:}14{:}59{.}381 \dashrightarrow 00{:}15{:}00{.}481$ 53 BP one in green.

NOTE Confidence: 0.736748746818182

 $00{:}15{:}02.780 \dashrightarrow 00{:}15{:}05{.}349$  Next we tested for the ability of

NOTE Confidence: 0.736748746818182

 $00{:}15{:}05{.}349 \dashrightarrow 00{:}15{:}07{.}314$  the chemical might of tomorrow

NOTE Confidence: 0.736748746818182

 $00:15:07.314 \rightarrow 00:15:09.684$  night to potentiate the in vitro

NOTE Confidence: 0.736748746818182

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

 $00{:}15{:}13.180 \dashrightarrow 00{:}15{:}15.320$  So in this clonogenic survival

NOTE Confidence: 0.736748746818182

 $00:15:15.320 \rightarrow 00:15:17.819$  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

 $00:15:20.099 \rightarrow 00:15:22.457$  one micromolar to 10 micromolar.

NOTE Confidence: 0.736748746818182

 $00{:}15{:}22{.}460 \dashrightarrow 00{:}15{:}24{.}679$  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

 $00:15:27.330 \longrightarrow 00:15:28.740$  so appear. These two lines.

NOTE Confidence: 0.736748746818182

 $00{:}15{:}28{.}740 \dashrightarrow 00{:}15{:}31{.}444$  Here BG be alone and here is with

NOTE Confidence: 0.736748746818182

 $00{:}15{:}31{.}444 \dashrightarrow 00{:}15{:}33{.}928$  combined to Missoula might as well.

NOTE Confidence: 0.736748746818182

 $00:15:33.930 \rightarrow 00:15:36.198$  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

 $00{:}15{:}39{.}030 \dashrightarrow 00{:}15{:}41{.}170$  there's an increased cytotoxicity

NOTE Confidence: 0.736748746818182

 $00{:}15{:}41{.}170 \dashrightarrow 00{:}15{:}43{.}240$  with combination and Tim is Olumide.

NOTE Confidence: 0.852406293636364

 $00{:}15{:}49{.}620 \dashrightarrow 00{:}15{:}52{.}189$  Lastly, we tested for the in vivo

NOTE Confidence: 0.852406293636364

 $00{:}15{:}52{.}189 \dashrightarrow 00{:}15{:}54{.}000$  efficacy of combination treatment,

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

NOTE Confidence: 0.852406293636364

 $00{:}15{:}56{.}600 \dashrightarrow 00{:}15{:}58{.}680$  rank of flank models.

NOTE Confidence: 0.852406293636364

 $00:15:58.680 \rightarrow 00:16:00.198$  Of note, one thing that's interesting

NOTE Confidence: 0.852406293636364

 $00:16:00.198 \longrightarrow 00:16:02.230$  here is that in terms of clinical

NOTE Confidence: 0.852406293636364

 $00{:}16{:}02{.}230 \dashrightarrow 00{:}16{:}03{.}850$  experience with the combinations of

NOTE Confidence: 0.852406293636364

 $00:16:03.850 \dashrightarrow 00:16:05.459$  PARP inhibitor and Thomas Olumide,

NOTE Confidence: 0.852406293636364

 $00{:}16{:}05{.}460 \dashrightarrow 00{:}16{:}07{.}095$  which has been tried and

NOTE Confidence: 0.852406293636364

 $00:16:07.095 \rightarrow 00:16:08.730$  not setting up other tumors,

NOTE Confidence: 0.852406293636364

 $00{:}16{:}08{.}730 \dashrightarrow 00{:}16{:}10{.}872$  one of the the limitations of

NOTE Confidence: 0.852406293636364

 $00:16:10.872 \longrightarrow 00:16:12.743$  these trials has been increased.

NOTE Confidence: 0.852406293636364

 $00{:}16{:}12.743 \dashrightarrow 00{:}16{:}15.401$  Set of toxicity with full dose

NOTE Confidence: 0.852406293636364

 $00:16:15.401 \longrightarrow 00:16:17.460$  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

 $00:16:19.580 \rightarrow 00:16:21.631$  That is, all my dose is anywhere

NOTE Confidence: 0.852406293636364

 $00{:}16{:}21.631 \dashrightarrow 00{:}16{:}23.183$  between 25 milligrams per kilogram

NOTE Confidence: 0.852406293636364

 $00:16:23.183 \longrightarrow 00:16:24.718$  to 50 milligrams per kilogram

- NOTE Confidence: 0.852406293636364
- $00:16:24.718 \longrightarrow 00:16:26.948$  per dose which translate to human
- NOTE Confidence: 0.852406293636364
- $00:16:26.948 \longrightarrow 00:16:29.510$  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
- $00:16:31.890 \longrightarrow 00:16:34.258$  So here we were interested to see if
- NOTE Confidence: 0.852406293636364
- $00{:}16{:}34.258 \dashrightarrow 00{:}16{:}36.594$  we could find some anti tumor effect
- NOTE Confidence: 0.852406293636364
- $00:16:36.594 \dashrightarrow 00:16:38.870$  at lower doses of Tim's Olumide.
- NOTE Confidence: 0.852406293636364
- $00:16:38.870 \rightarrow 00:16:40.646$  Which might limit some of those
- NOTE Confidence: 0.852406293636364
- $00:16:40.646 \longrightarrow 00:16:42.529$  toxicities so for this study we
- NOTE Confidence: 0.852406293636364
- $00{:}16{:}42.529 \dashrightarrow 00{:}16{:}44.437$  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
- $00:16:45.630 \longrightarrow 00:16:47.933$  and and did indeed find that even
- NOTE Confidence: 0.852406293636364
- $00:16:47.933 \rightarrow 00:16:50.472$  at such lower doses of temozolomide
- NOTE Confidence: 0.852406293636364
- $00:16:50.472 \longrightarrow 00:16:52.927$  we find delayed tumor progression.
- NOTE Confidence: 0.852406293636364
- $00:16:52.930 \longrightarrow 00:16:55.060$  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

 $00:16:57.960 \rightarrow 00:17:00.528$  at least as measured by animal body weight.

NOTE Confidence: 0.94305726555555

 $00:17:04.440 \longrightarrow 00:17:06.631$  So based on this we can say

NOTE Confidence: 0.94305726555555

 $00:17:06.631 \longrightarrow 00:17:08.872$  that the band FH1 knockout Cells

NOTE Confidence: 0.94305726555555

 $00{:}17{:}08.872 \dashrightarrow 00{:}17{:}10.887$  Harbor and increased levels of

NOTE Confidence: 0.94305726555555

 $00{:}17{:}10.887 \dashrightarrow 00{:}17{:}12.777$  unrepaired DNA damage at baseline,

NOTE Confidence: 0.94305726555555

 $00:17:12.780 \longrightarrow 00:17:14.754$  and that the combination of pop

NOTE Confidence: 0.94305726555555

 $00{:}17{:}14.754 \dashrightarrow 00{:}17{:}16.373$  inhibitor Intimes Olamide enhances set

NOTE Confidence: 0.94305726555555

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

NOTE Confidence: 0.94305726555555

 $00{:}17{:}18{.}120 \dashrightarrow 00{:}17{:}19{.}974$  and that the combination with low

NOTE Confidence: 0.94305726555555

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

NOTE Confidence: 0.94305726555555

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

NOTE Confidence: 0.93221934

 $00:17:26.020 \longrightarrow 00:17:27.755$  And turning now to the

NOTE Confidence: 0.93221934

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

NOTE Confidence: 0.93221934

 $00:17:28.800 \rightarrow 00:17:31.110$  We recently had an interesting case within

NOTE Confidence: 0.93221934

 $00:17:31.110 \rightarrow 00:17:33.399$  our own department within our own section.

 $00:17:33.400 \rightarrow 00:17:35.144$  This is a patient cared for by one

NOTE Confidence: 0.93221934

 $00{:}17{:}35{.}144 \dashrightarrow 00{:}17{:}37{.}000$  of my colleagues Dr pushing car

NOTE Confidence: 0.93221934

 $00{:}17{:}37{.}000 \dashrightarrow 00{:}17{:}39{.}989$  and this is a patient with GIST

NOTE Confidence: 0.93221934

 $00:17:39.989 \rightarrow 00:17:42.274$  and PARAGANGLIOMAS in the setting

NOTE Confidence: 0.93221934

 $00:17:42.274 \longrightarrow 00:17:44.574$  of a germline SDHB mutation.

NOTE Confidence: 0.93221934

 $00:17:44.580 \rightarrow 00:17:45.972$  This is a patient that progressed

NOTE Confidence: 0.93221934

 $00:17:45.972 \rightarrow 00:17:47.340$  through multiple lines of treatment,

NOTE Confidence: 0.93221934

 $00:17:47.340 \longrightarrow 00:17:49.874$  including imatinib than that in as well

NOTE Confidence: 0.93221934

 $00{:}17{:}49{.}874 \dashrightarrow 00{:}17{:}53{.}249$  as a heat shock protein phase one trial.

NOTE Confidence: 0.93221934

 $00:17:53.250 \longrightarrow 00:17:55.280$  And so at this point,

NOTE Confidence: 0.93221934

 $00:17:55.280 \rightarrow 00:17:57.480$  having progressive multiple lines of

NOTE Confidence: 0.93221934

 $00{:}17{:}57{.}480 \dashrightarrow 00{:}18{:}00{.}329$  treatment doctor pushing car up to trial.

NOTE Confidence: 0.93221934

 $00{:}18{:}00{.}330 \dashrightarrow 00{:}18{:}03{.}420$  Cycles of elaborate with Tim's Olumide.

NOTE Confidence: 0.93221934

 $00{:}18{:}03{.}420 \dashrightarrow 00{:}18{:}05{.}576$  And this is off any clinical trial.

NOTE Confidence: 0.93221934

 $00{:}18{:}05{.}580 \dashrightarrow 00{:}18{:}07{.}776$  As you can see here from the pet images.

 $00:18:07.780 \rightarrow 00:18:11.146$  These are the pretreatment images showing

NOTE Confidence: 0.93221934

 $00:18:11.146 \rightarrow 00:18:13.847$  multiple liver metastatic nodules as

NOTE Confidence: 0.93221934

 $00:18:13.847 \rightarrow 00:18:16.465$  well as Bony lesions along the spine.

NOTE Confidence: 0.93221934

 $00:18:16.470 \longrightarrow 00:18:18.898$  And after six cycles,

NOTE Confidence: 0.93221934

 $00{:}18{:}18{.}898 \dashrightarrow 00{:}18{:}21{.}326$  this patient had a.

NOTE Confidence: 0.93221934

 $00{:}18{:}21{.}330 \dashrightarrow 00{:}18{:}23{.}766$  Partial remission in remission of all the

NOTE Confidence: 0.93221934

 $00:18:23.766 \rightarrow 00:18:26.467$  Bony lesions as well as partial remission,

NOTE Confidence: 0.93221934

 $00:18:26.470 \rightarrow 00:18:30.090$  multiple liver nodules as well.

NOTE Confidence: 0.93221934

 $00:18:30.090 \longrightarrow 00:18:32.886$  Of course this is just an ecdotal.

NOTE Confidence: 0.93221934

 $00:18:32.890 \rightarrow 00:18:34.140$  This is an anecdotal case,

NOTE Confidence: 0.93221934

 $00{:}18{:}34{.}140 \dashrightarrow 00{:}18{:}36{.}225$  so there are trails about

NOTE Confidence: 0.93221934

 $00{:}18{:}36.225 \dashrightarrow 00{:}18{:}37.893$  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

 $00{:}18{:}40.306 \dashrightarrow 00{:}18{:}42.809$  currently in development and soon to open,

NOTE Confidence: 0.93221934

 $00:18:42.810 \longrightarrow 00:18:44.390$  led by our collaborator Dr.

NOTE Confidence: 0.93221934

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

- NOTE Confidence: 0.93221934
- $00:18:45.734 \rightarrow 00:18:48.898$  and in this trial they'll be testing
- NOTE Confidence: 0.93221934
- $00{:}18{:}48{.}898 \dashrightarrow 00{:}18{:}51{.}530$  combinations of 290 and low dose
- NOTE Confidence: 0.93221934
- $00:18:51.530 \rightarrow 00:18:54.110$  temozolomide in the setting of patients
- NOTE Confidence: 0.93221934
- $00:18:54.189 \rightarrow 00:18:56.795$  with refractory or recurrent renal
- NOTE Confidence: 0.93221934
- $00{:}18{:}56{.}795 \dashrightarrow 00{:}18{:}59{.}980$  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
- $00:19:06.120 \longrightarrow 00:19:07.670$  a little bit on my work,
- NOTE Confidence: 0.903934720833333
- $00{:}19{:}07.670 \dashrightarrow 00{:}19{:}09.578$  focused more on the immune aspects
- NOTE Confidence: 0.903934720833333
- $00{:}19{:}09{.}578 \dashrightarrow 00{:}19{:}11{.}614$  of Uncle metabolite and DNA repair
- NOTE Confidence: 0.903934720833333
- $00:19:11.614 \rightarrow 00:19:13.369$  defects and potential for leveraging
- NOTE Confidence: 0.903934720833333
- $00:19:13.369 \rightarrow 00:19:16.152$  these defects in order to promote an
- NOTE Confidence: 0.903934720833333
- $00:19:16.152 \rightarrow 00:19:17.403$  inflammatory tumor microenvironment
- NOTE Confidence: 0.903934720833333
- $00:19:17.403 \rightarrow 00:19:19.084$  and even potentially desensitized
- NOTE Confidence: 0.903934720833333
- $00{:}19{:}19{.}084 \dashrightarrow 00{:}19{:}20{.}780$  to mean checkpoint blockade,
- NOTE Confidence: 0.903934720833333
- $00{:}19{:}20.780 \dashrightarrow 00{:}19{:}24.495$  which I know is a topic near and dear to
- NOTE Confidence: 0.903934720833333

 $00:19:24.495 \rightarrow 00:19:27.160$  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

 $00:19:30.551 \rightarrow 00:19:32.390$  a subset of patients really benefit

NOTE Confidence: 0.903934720833333

 $00{:}19{:}32{.}390 \dashrightarrow 00{:}19{:}34{.}090$  from immune checkpoint blockade and

NOTE Confidence: 0.903934720833333

 $00{:}19{:}34.090 \dashrightarrow 00{:}19{:}36.039$  some of the markers of response

NOTE Confidence: 0.903934720833333

 $00{:}19{:}36.039 \dashrightarrow 00{:}19{:}37.863$  that have been described relate both

NOTE Confidence: 0.903934720833333

 $00:19:37.870 \longrightarrow 00:19:40.714$  to tumor increase amount of tumor

NOTE Confidence: 0.903934720833333

 $00{:}19{:}40{.}714 \dashrightarrow 00{:}19{:}42{.}610$  associated mutations and subsequent

NOTE Confidence: 0.903934720833333

 $00{:}19{:}42.685 \dashrightarrow 00{:}19{:}46.052$  neoantigen load as well as a more

NOTE Confidence: 0.903934720833333

 $00{:}19{:}46.052 \dashrightarrow 00{:}19{:}47.495$  inflammatory tumor microenvironment.

NOTE Confidence: 0.957039336

 $00:19:49.790 \longrightarrow 00:19:50.790$  So with this in mind,

NOTE Confidence: 0.957039336

 $00{:}19{:}50{.}790 \dashrightarrow 00{:}19{:}52{.}510$  a lot of attention has really been paid

NOTE Confidence: 0.957039336

 $00:19:52.510 \rightarrow 00:19:54.389$  lately to the role of DNA damage response,

NOTE Confidence: 0.957039336

 $00{:}19{:}54{.}390 \dashrightarrow 00{:}19{:}56{.}150$  and specifically DNA repair defects

NOTE Confidence: 0.957039336

 $00{:}19{:}56{.}150 \dashrightarrow 00{:}19{:}57{.}910$  and mediating the tumor immune

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

NOTE Confidence: 0.957039336

 $00{:}19{:}59{.}887 \dashrightarrow 00{:}20{:}01{.}362$  immuno therapy 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

 $00:20:02.970 \longrightarrow 00:20:05.353$  is that the there's a potential in

NOTE Confidence: 0.957039336

 $00{:}20{:}05{.}353 \dashrightarrow 00{:}20{:}07{.}057$  the setting of DNA repair defects

NOTE Confidence: 0.957039336

 $00{:}20{:}07{.}057 \dashrightarrow 00{:}20{:}08{.}928$  when you treat these these tumors

NOTE Confidence: 0.957039336

 $00:20:08.928 \longrightarrow 00:20:10.623$  with additional DNA damaging agents

NOTE Confidence: 0.957039336

 $00:20:10.623 \rightarrow 00:20:12.827$  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

 $00:20:15.838 \rightarrow 00:20:18.036$  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

 $00{:}20{:}21{.}280 \dashrightarrow 00{:}20{:}24{.}509$  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

 $00{:}20{:}26.535 \dashrightarrow 00{:}20{:}28.560$  activate the innate immune system,

 $00:20:28.560 \rightarrow 00:20:29.904$  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

 $00:20:31.920 \longrightarrow 00:20:34.180$  which is a double stranded

NOTE Confidence: 0.957039336

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

NOTE Confidence: 0.957039336

 $00{:}20{:}35{.}540 \dashrightarrow 00{:}20{:}37{.}130$  Of course there are now multiple

NOTE Confidence: 0.957039336

 $00{:}20{:}37.130 \dashrightarrow 00{:}20{:}38.514$  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

 $00:20:39.880 \longrightarrow 00:20:41.233$  including recognition of

NOTE Confidence: 0.957039336

 $00{:}20{:}41{.}233 \dashrightarrow 00{:}20{:}43{.}037$  double stranded RNA sensing,

NOTE Confidence: 0.957039336

 $00:20:43.040 \longrightarrow 00:20:44.312$  which a lot of folks here at Yale

NOTE Confidence: 0.957039336

 $00:20:44.312 \longrightarrow 00:20:45.378$  have been working on as well.

NOTE Confidence: 0.957039336

 $00:20:45.380 \rightarrow 00:20:48.062$  But since we're working talking mainly

NOTE Confidence: 0.957039336

 $00{:}20{:}48.062 \dashrightarrow 00{:}20{:}50.410$  about double stranded DNA damage,

NOTE Confidence: 0.957039336

 $00:20:50.410 \longrightarrow 00:20:51.754$  our focus has mainly been on

NOTE Confidence: 0.957039336

 $00:20:51.754 \rightarrow 00:20:52.650$  the C guesting pathway.

NOTE Confidence: 0.813189323333333

 $00{:}20{:}55{.}180 \dashrightarrow 00{:}20{:}57{.}112$  So, as I mentioned before for for

- NOTE Confidence: 0.813189323333333
- $00:20:57.112 \rightarrow 00:20:59.272$  this study we utilized the SYNGENEIC
- NOTE Confidence: 0.813189323333333
- $00{:}20{:}59{.}272 \dashrightarrow 00{:}21{:}01{.}775$  ranking model and this is a model
- NOTE Confidence: 0.813189323333333
- $00{:}21{:}01.775 \dashrightarrow 00{:}21{:}03.430$  that has been characterized before
- NOTE Confidence: 0.813189323333333
- $00:21:03.499 \rightarrow 00:21:04.836$  as being minimally responsive
- NOTE Confidence: 0.813189323333333
- $00:21:04.836 \rightarrow 00:21:06.528$  to immune checkpoint blockade,
- NOTE Confidence: 0.813189323333333
- $00:21:06.530 \longrightarrow 00:21:07.720$  and this is our own experiment here,
- NOTE Confidence: 0.813189323333333
- $00:21:07.720 \longrightarrow 00:21:09.075$  confirming that at least the
- NOTE Confidence: 0.813189323333333
- $00:21:09.075 \rightarrow 00:21:10.781$  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
- $00:21:12.250 \longrightarrow 00:21:14.788$  which allows us to to sort of use this
- NOTE Confidence: 0.813189323333333
- $00:21:14.788 \longrightarrow 00:21:17.795$  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
- $00{:}21{:}22.650 \dashrightarrow 00{:}21{:}24.228$  but we've we've been starting to
- NOTE Confidence: 0.813189323333333
- $00:21:24.228 \rightarrow 00:21:25.613$  really explore the immune effects
- NOTE Confidence: 0.813189323333333

 $00:21:25.613 \rightarrow 00:21:27.048$  of these crab cycle mutations,

NOTE Confidence: 0.813189323333333

 $00{:}21{:}27.050 \dashrightarrow 00{:}21{:}29.178$  so this is again a an early experiment

NOTE Confidence: 0.813189323333333

 $00{:}21{:}29{.}178 \dashrightarrow 00{:}21{:}30{.}807$  where we performed bulk sequencing

NOTE Confidence: 0.813189323333333

 $00{:}21{:}30{.}807 \dashrightarrow 00{:}21{:}33{.}529$  just in the cells looking at wild

NOTE Confidence: 0.813189323333333

 $00:21:33.529 \rightarrow 00:21:35.744$  type versus knockout cell models.

NOTE Confidence: 0.813189323333333

 $00{:}21{:}35{.}750 \dashrightarrow 00{:}21{:}37{.}320$  And there's definitely a differential

NOTE Confidence: 0.813189323333333

 $00:21:37.320 \longrightarrow 00:21:37.948$  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

 $00:21:41.419 \rightarrow 00:21:43.106$  terms of a related to the immune

NOTE Confidence: 0.813189323333333

 $00:21:43.167 \longrightarrow 00:21:44.647$  effects of these mutations.

NOTE Confidence: 0.813189323333333

 $00:21:44.650 \longrightarrow 00:21:46.546$  As you can see that one of the

NOTE Confidence: 0.813189323333333

 $00:21:46.546 \longrightarrow 00:21:48.722$  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

 $00:21:50.430 \longrightarrow 00:21:52.938$  expression or upregulation of

NOTE Confidence: 0.813189323333333

 $00:21:52.938 \rightarrow 00:21:55.446$  the antigen presenting pathways.

 $00:21:55.450 \longrightarrow 00:21:57.328$  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

 $00:21:58.633 \rightarrow 00:21:59.888$  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

 $00:22:03.510 \longrightarrow 00:22:05.665$  and thankfully we confirmed SDHP

NOTE Confidence: 0.813189323333333

 $00:22:05.665 \rightarrow 00:22:09.180$  knockout as we we already did using other

NOTE Confidence: 0.813189323333333

 $00:22:09.180 \longrightarrow 00:22:11.580$  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

 $00:22:15.320 \longrightarrow 00:22:17.616$  And again this is with work that's been

NOTE Confidence: 0.813189323333333

 $00{:}22{:}17.616 \dashrightarrow 00{:}22{:}21.380$  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

 $00{:}22{:}21.800 \dashrightarrow 00{:}22{:}25.580$  we see here as well that the knock out cells

NOTE Confidence: 0.813189323333333

 $00{:}22{:}25.659 \dashrightarrow 00{:}22{:}28.557$  seem to up regulate beta 2 microglobulin,

 $00:22:28.560 \longrightarrow 00:22:30.387$  which I'm sure folks or where is

NOTE Confidence: 0.813189323333333

 $00{:}22{:}30{.}387 \dashrightarrow 00{:}22{:}31{.}833$  an important component will is is

NOTE Confidence: 0.813189323333333

 $00{:}22{:}31{.}833 \dashrightarrow 00{:}22{:}33{.}261$  a component of the MHC class one

NOTE Confidence: 0.813189323333333

 $00:22:33.312 \rightarrow 00:22:35.002$  molecule and is really required

NOTE Confidence: 0.813189323333333

 $00:22:35.002 \longrightarrow 00:22:36.016$  for antigen presentation,

NOTE Confidence: 0.813189323333333

 $00:22:36.020 \longrightarrow 00:22:37.588$  and there's been a lot of great

NOTE Confidence: 0.813189323333333

 $00{:}22{:}37{.}588 \dashrightarrow 00{:}22{:}39{.}271$  work from folks here at Yale to

NOTE Confidence: 0.813189323333333

 $00{:}22{:}39{.}271 \dashrightarrow 00{:}22{:}40{.}705$  show that made it two microal bumin

NOTE Confidence: 0.813189323333333

 $00{:}22{:}40.753 \dashrightarrow 00{:}22{:}42.790$  losses is one of the markers of

NOTE Confidence: 0.813189323333333

 $00:22:42.790 \rightarrow 00:22:43.663$  immune checkpoint resistance.

NOTE Confidence: 0.896956759285715

 $00{:}22{:}45{.}800 \dashrightarrow 00{:}22{:}47{.}501$  We also then went on to look

NOTE Confidence: 0.896956759285715

 $00{:}22{:}47.501 \dashrightarrow 00{:}22{:}48.673$  at differential gene expression

NOTE Confidence: 0.896956759285715

 $00{:}22{:}48.673 \dashrightarrow 00{:}22{:}50.748$  with PARP inhibition and and so

NOTE Confidence: 0.896956759285715

 $00{:}22{:}50.748 \dashrightarrow 00{:}22{:}52.584$  we looked at treatment after we

NOTE Confidence: 0.896956759285715

 $00:22:52.584 \rightarrow 00:22:54.579$  looked at single cell sequencing.

NOTE Confidence: 0.896956759285715

 $00:22:54.580 \longrightarrow 00:22:56.540$  After 24 hours of treatment

- NOTE Confidence: 0.896956759285715
- $00:22:56.540 \longrightarrow 00:22:58.157$  and and what we found so far.
- NOTE Confidence: 0.896956759285715
- $00{:}22{:}58{.}160 \dashrightarrow 00{:}22{:}59{.}712$  And this is still work in progress and
- NOTE Confidence: 0.896956759285715
- $00:22:59.712 \rightarrow 00:23:01.159$  we're still looking through this data,
- NOTE Confidence: 0.896956759285715
- $00:23:01.160 \longrightarrow 00:23:02.798$  but one of the things we've seen
- NOTE Confidence: 0.896956759285715
- $00{:}23{:}02{.}798 \dashrightarrow 00{:}23{:}04{.}157$  is an increased expression after
- NOTE Confidence: 0.896956759285715
- $00:23:04.157 \longrightarrow 00:23:05.657$  24 hours of the labyrinth,
- NOTE Confidence: 0.896956759285715
- $00:23:05.660 \rightarrow 00:23:08.200$  specifically in the knockout cells
- NOTE Confidence: 0.896956759285715
- $00:23:08.200 \rightarrow 00:23:10.232$  with upregulation of interferon
- NOTE Confidence: 0.896956759285715
- 00:23:10.232 --> 00:23:12.119 induced protein protein 44,
- NOTE Confidence: 0.896956759285715
- $00{:}23{:}12{.}120 \dashrightarrow 00{:}23{:}13{.}961$  which is one of the interferon stimulated
- NOTE Confidence: 0.896956759285715
- $00:23:13.961 \longrightarrow 00:23:15.929$  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 up regulation of stat one
- NOTE Confidence: 0.896956759285715
- $00{:}23{:}21{.}823 \dashrightarrow 00{:}23{:}23{.}798$  with elaborate treatment and those
- NOTE Confidence: 0.896956759285715
- $00{:}23{:}23{.}798 \dashrightarrow 00{:}23{:}26{.}200$  SDHB knockout cells and stat one.
- NOTE Confidence: 0.896956759285715

 $00{:}23{:}26{.}200 \dashrightarrow 00{:}23{:}27{.}490$  The Jack stat.

NOTE Confidence: 0.896956759285715

 $00{:}23{:}27{.}490 \dashrightarrow 00{:}23{:}30{.}297$  One pathway has been shown to be

NOTE Confidence: 0.896956759285715

 $00:23:30.297 \longrightarrow 00:23:31.963$  important for interferon stimulated

NOTE Confidence: 0.896956759285715

 $00:23:31.963 \longrightarrow 00:23:33.898$  gene expression and has been

NOTE Confidence: 0.896956759285715

 $00:23:33.898 \rightarrow 00:23:36.964$  shown to play a role in mediating

NOTE Confidence: 0.896956759285715

 $00:23:36.964 \rightarrow 00:23:38.407$  amino therapy response.

NOTE Confidence: 0.896956759285715

 $00{:}23{:}38{.}410 \dashrightarrow 00{:}23{:}40{.}030$  So these are interesting.

NOTE Confidence: 0.896956759285715

 $00:23:40.030 \longrightarrow 00:23:42.055$  Sort of very preliminary data

NOTE Confidence: 0.896956759285715

 $00{:}23{:}42.055 \dashrightarrow 00{:}23{:}44.264$  and and gives us a direction to

NOTE Confidence: 0.896956759285715

 $00:23:44.264 \rightarrow 00:23:46.250$  look for as we go forward.

NOTE Confidence: 0.896956759285715

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

NOTE Confidence: 0.896956759285715

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

NOTE Confidence: 0.896956759285715

 $00{:}23{:}50{.}068 \dashrightarrow 00{:}23{:}52{.}610$  and this is now just looking at the

NOTE Confidence: 0.896956759285715

 $00:23:52.610 \rightarrow 00:23:54.440$  tumor cells after implantation and

NOTE Confidence: 0.896956759285715

 $00:23:54.440 \rightarrow 00:23:58.053$  what we see here is that in the SDHB

NOTE Confidence: 0.896956759285715

 $00:23:58.053 \rightarrow 00:24:00.188$  knockout cells there's an increased

- NOTE Confidence: 0.896956759285715
- $00{:}24{:}00{.}188 \dashrightarrow 00{:}24{:}02{.}352$  proportion in terms of the percentage
- NOTE Confidence: 0.896956759285715
- $00{:}24{:}02{.}352 \dashrightarrow 00{:}24{:}04{.}632$  of live cells that are CD3 positive
- NOTE Confidence: 0.896956759285715
- $00:24:04.632 \rightarrow 00:24:06.774$  and of those CD 3 positive cells.
- NOTE Confidence: 0.896956759285715
- $00{:}24{:}06{.}780 \dashrightarrow 00{:}24{:}08{.}802$  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
- $00:24:11.130 \longrightarrow 00:24:13.002$  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
- $00:24:15.810 \longrightarrow 00:24:20.045$  data to follow up on for us.
- NOTE Confidence: 0.896956759285715
- $00:24:20.050 \rightarrow 00:24:20.386$  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
- $00{:}24{:}23{.}498 \dashrightarrow 00{:}24{:}26{.}697$  our talk from earlier the IDH mutations
- NOTE Confidence: 0.896956759285715
- $00{:}24{:}26.700 \dashrightarrow 00{:}24{:}28.695$  because this is also an area that
- NOTE Confidence: 0.896956759285715
- $00{:}24{:}28.695 \dashrightarrow 00{:}24{:}30.613$  I'm interested in is not to mention
- NOTE Confidence: 0.896956759285715
- $00{:}24{:}30{.}613 \dashrightarrow 00{:}24{:}33{.}118$  that have an interest in in the glioma,
- NOTE Confidence: 0.896956759285715
- $00{:}24{:}33.120 \dashrightarrow 00{:}24{:}34.203$  tumor immune microenvironment
- NOTE Confidence: 0.896956759285715

 $00:24:34.203 \rightarrow 00:24:36.008$  and have performed some studies

NOTE Confidence: 0.896956759285715

 $00:24:36.008 \longrightarrow 00:24:37.139$  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

 $00:24:38.195 \longrightarrow 00:24:39.039$  to develop an idea.

NOTE Confidence: 0.896956759285715

 $00:24:39.040 \rightarrow 00:24:42.113$  Each mutant syngeneic model to allow us

NOTE Confidence: 0.896956759285715

 $00:24:42.113 \rightarrow 00:24:45.677$  to to explore this a little bit further.

NOTE Confidence: 0.896956759285715

 $00:24:45.680 \longrightarrow 00:24:47.630$  So traditionally the the main

NOTE Confidence: 0.896956759285715

 $00{:}24{:}47.630 \dashrightarrow 00{:}24{:}50.204$  model that's been used for the main

NOTE Confidence: 0.896956759285715

 $00{:}24{:}50{.}204 \dashrightarrow 00{:}24{:}51{.}764$  syngeneic model that's been used

NOTE Confidence: 0.896956759285715

 $00{:}24{:}51{.}764 \dashrightarrow 00{:}24{:}53{.}831$  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

 $00:24:55.259 \longrightarrow 00:24:57.762$  been the steel 261 model which is

NOTE Confidence: 0.896956759285715

 $00{:}24{:}57{.}762 \dashrightarrow 00{:}24{:}59{.}443$  chemically induced line with a

NOTE Confidence: 0.896956759285715

 $00:24:59.443 \rightarrow 00:25:00.767$  moderate degree of immunogenicity

NOTE Confidence: 0.896956759285715

 $00{:}25{:}00{.}767 \dashrightarrow 00{:}25{:}02{.}640$  at baseline and as you can see,

NOTE Confidence: 0.896956759285715

 $00:25:02.640 \rightarrow 00:25:04.558$  this is our own experiment in our

- NOTE Confidence: 0.896956759285715
- $00{:}25{:}04{.}558 \dashrightarrow 00{:}25{:}07{.}019$  own hands and it goes in line with
- NOTE Confidence: 0.896956759285715
- $00:25:07.019 \longrightarrow 00:25:08.948$  previous research that shows that this
- NOTE Confidence: 0.896956759285715
- $00{:}25{:}08{.}948 \dashrightarrow 00{:}25{:}10{.}997$  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
- $00{:}25{:}12.560 \dashrightarrow 00{:}25{:}13.932$  one blockade and as a lot of
- NOTE Confidence: 0.896956759285715
- $00:25:13.932 \longrightarrow 00:25:14.810$  folks here on this.
- NOTE Confidence: 0.896956759285715
- $00:25:14.810 \longrightarrow 00:25:16.602$  So I will know that really doesn't
- NOTE Confidence: 0.896956759285715
- $00:25:16.602 \rightarrow 00:25:18.190$  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
- $00:25:22.212 \rightarrow 00:25:24.108$  blockade in GBM have been have
- NOTE Confidence: 0.896956759285715
- $00{:}25{:}24.108 \dashrightarrow 00{:}25{:}25.930$  not shown really much benefit.
- NOTE Confidence: 0.896956759285715
- $00{:}25{:}25{.}930 \dashrightarrow 00{:}25{:}27{.}226$  So we were hoping to find a model
- NOTE Confidence: 0.896956759285715
- $00{:}25{:}27{.}226 \dashrightarrow 00{:}25{:}28{.}607$  that may be might be a little
- NOTE Confidence: 0.896956759285715
- $00:25:28.607 \rightarrow 00:25:29.366$  more translationally relevant,
- NOTE Confidence: 0.896956759285715

 $00:25:29.370 \rightarrow 00:25:30.602$  understanding the limitations that

NOTE Confidence: 0.896956759285715

 $00{:}25{:}30{.}602 \dashrightarrow 00{:}25{:}33{.}003$  we're working with that we have to sort

NOTE Confidence: 0.896956759285715

 $00:25:33.003 \rightarrow 00:25:34.509$  of rely on these syngenetic models.

NOTE Confidence: 0.896956759285715

 $00:25:34.510 \longrightarrow 00:25:36.310$  So we turned to our collaborator

NOTE Confidence: 0.896956759285715

 $00:25:36.310 \longrightarrow 00:25:37.510$  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

 $00:25:40.610 \rightarrow 00:25:44.173$  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

 $00{:}25{:}45{.}322 \dashrightarrow 00{:}25{:}48{.}112$  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

 $00:25:50.700 \longrightarrow 00:25:53.108$  and so this is a line that.

NOTE Confidence: 0.90662077625

 $00:25:53.110 \rightarrow 00:25:55.546$  Intends to have low T cell infiltration,

NOTE Confidence: 0.90662077625

 $00:25:55.550 \rightarrow 00:25:58.345$  high number of tumor associated

NOTE Confidence: 0.90662077625

 $00{:}25{:}58{.}345 \dashrightarrow 00{:}26{:}00{.}581$  macrophages and more immunosuppressive

NOTE Confidence: 0.90662077625

 $00{:}26{:}00{.}581 \dashrightarrow 00{:}26{:}03{.}130$  micro micro environment and these

NOTE Confidence: 0.90662077625

 $00:26:03.130 \rightarrow 00:26:05.440$  tumors do not really respond to even

 $00{:}26{:}05{.}440 \dashrightarrow 00{:}26{:}07{.}963$  dual blockade with PD one and C TL A4.

NOTE Confidence: 0.90662077625

 $00:26:07.970 \rightarrow 00:26:09.360$  They've also characterized this line

NOTE Confidence: 0.90662077625

 $00:26:09.360 \longrightarrow 00:26:11.110$  in terms of the mutational burden.

NOTE Confidence: 0.90662077625

 $00{:}26{:}11.110 \dashrightarrow 00{:}26{:}13.801$  Showed that again SB 28 cells have a much

NOTE Confidence: 0.90662077625

 $00:26:13.801 \rightarrow 00:26:16.140$  lower mutational burden these GL261 line.

NOTE Confidence: 0.90662077625

 $00:26:16.140 \longrightarrow 00:26:17.925$  So we hope that perhaps this is

NOTE Confidence: 0.90662077625

 $00:26:17.925 \longrightarrow 00:26:20.363$  this will be a little more of a

NOTE Confidence: 0.90662077625

 $00:26:20.363 \rightarrow 00:26:22.168$  translationally relevant model as we go

NOTE Confidence: 0.90662077625

 $00{:}26{:}22.168 \dashrightarrow 00{:}26{:}23.836$  forward looking at the immune effects.

NOTE Confidence: 0.90662077625

 $00:26:23.840 \rightarrow 00:26:25.674$  So in terms of developing this as

NOTE Confidence: 0.90662077625

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

NOTE Confidence: 0.90662077625

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

NOTE Confidence: 0.90662077625

 $00:26:29.898 \longrightarrow 00:26:32.126$  with an R132H open reading frame,

NOTE Confidence: 0.90662077625

 $00{:}26{:}32.126 \dashrightarrow 00{:}26{:}33.821$  and again characterized that there

NOTE Confidence: 0.90662077625

 $00:26:33.821 \longrightarrow 00:26:35.668$  is an expression of the R 138,

 $00:26:35.670 \longrightarrow 00:26:38.365$  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

 $00{:}26{:}40{.}320 \dashrightarrow 00{:}26{:}44{.}598$  We've also characterized the in vivo

NOTE Confidence: 0.90662077625

 $00:26:44.600 \rightarrow 00:26:47.210$  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

 $00:26:51.009 \rightarrow 00:26:53.595$  cells form tumors effectively and

NOTE Confidence: 0.90662077625

 $00{:}26{:}53.595 \dashrightarrow 00{:}26{:}55.470$  characterize the survival with the

NOTE Confidence: 0.90662077625

 $00:26:55.470 \rightarrow 00:26:58.730$  IDH mutation. In these in this model.

NOTE Confidence: 0.90662077625

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

NOTE Confidence: 0.90662077625

 $00:26:59.050 \rightarrow 00:27:01.290$  we further characterized in vivo as well,

NOTE Confidence: 0.90662077625

 $00:27:01.290 \rightarrow 00:27:03.330$  and not just in vitro that in vivo.

NOTE Confidence: 0.90662077625

 $00{:}27{:}03{.}330 \dashrightarrow 00{:}27{:}05{.}070$  These tumors maintain their expression

NOTE Confidence: 0.90662077625

 $00{:}27{:}05{.}070 \dashrightarrow 00{:}27{:}08{.}342$  of the art 132 H mutation seen here

NOTE Confidence: 0.90662077625

 $00{:}27{:}08{.}342 \dashrightarrow 00{:}27{:}10{.}294$  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

 $00{:}27{:}11.870 \dashrightarrow 00{:}27{:}14.446$  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
- $00{:}27{:}16.799 \dashrightarrow 00{:}27{:}19.557$  and tumor tissue and seeing an increase
- NOTE Confidence: 0.90662077625
- $00:27:19.623 \rightarrow 00:27:21.620$  accumulation in the R132H tumors.
- NOTE Confidence: 0.885832098571429
- $00:27:23.880 \longrightarrow 00:27:25.112$  So I really want to take this as
- NOTE Confidence: 0.885832098571429
- $00{:}27{:}25.112 \dashrightarrow 00{:}27{:}26.598$  a in terms of future directions.
- NOTE Confidence: 0.885832098571429
- $00{:}27{:}26.600 \dashrightarrow 00{:}27{:}29.074$  This is really 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
- $00:27:31.521 \rightarrow 00:27:33.465$  to really investigate the impact of
- NOTE Confidence: 0.885832098571429
- $00{:}27{:}33.465 \dashrightarrow 00{:}27{:}35.332$  uncle metabolites on both cancer cell
- NOTE Confidence: 0.885832098571429
- $00:27:35.332 \rightarrow 00:27:36.847$  intrinsic immune signaling as well
- NOTE Confidence: 0.885832098571429
- $00:27:36.847 \rightarrow 00:27:39.017$  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
- $00{:}27{:}43.420 \dashrightarrow 00{:}27{:}45.513$  such as ATR inhibitors in the setting
- NOTE Confidence: 0.885832098571429
- $00{:}27{:}45{.}513 \dashrightarrow 00{:}27{:}47{.}164$  of uncle metabolite producing tumors
- NOTE Confidence: 0.885832098571429

 $00:27:47.164 \rightarrow 00:27:49.270$  or really extending the findings we've

NOTE Confidence: 0.885832098571429

 $00{:}27{:}49{.}270 \dashrightarrow 00{:}27{:}51{.}463$  already had in our flank models to see

NOTE Confidence: 0.885832098571429

 $00:27:51.463 \rightarrow 00:27:54.628$  how this works in the tumor microenvironment.

NOTE Confidence: 0.885832098571429

 $00:27:54.630 \rightarrow 00:27:56.298$  I also want to investigate synergistic

NOTE Confidence: 0.885832098571429

 $00{:}27{:}56.298 \dashrightarrow 00{:}27{:}57.772$  interactions between the mean checkpoint

NOTE Confidence: 0.885832098571429

 $00{:}27{:}57{.}772 \dashrightarrow 00{:}27{:}59{.}698$  blockade and DNA damage response inhibitors,

NOTE Confidence: 0.885832098571429

 $00:27:59.700 \rightarrow 00:28:01.125$  and these uncle metabolite producing

NOTE Confidence: 0.885832098571429

 $00{:}28{:}01{.}125 \dashrightarrow 00{:}28{:}03{.}130$  tumors and hope to get started on

NOTE Confidence: 0.885832098571429

 $00{:}28{:}03{.}130 \dashrightarrow 00{:}28{:}04{.}455$  these preclinical studies in the

NOTE Confidence: 0.885832098571429

 $00:28:04.455 \longrightarrow 00:28:06.079$  next in the upcoming months.

NOTE Confidence: 0.747156045333333

 $00{:}28{:}08{.}320 \dashrightarrow 00{:}28{:}10{.}210$  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

 $00:28:14.096 \rightarrow 00:28:15.740$  really been instrumental in in me,

NOTE Confidence: 0.747156045333333

 $00:28:15.740 \rightarrow 00:28:17.964$  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,

 $00:28:20.400 \longrightarrow 00:28:22.408$  as well as all the members of the

NOTE Confidence: 0.747156045333333

 $00{:}28{:}22{.}408 \dashrightarrow 00{:}28{:}24{.}001$ 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

 $00:28:25.963 \rightarrow 00:28:28.140$  as well as all those folks specifically

NOTE Confidence: 0.747156045333333

 $00:28:28.196 \rightarrow 00:28:30.380$  who helped with the projects I outlined.

NOTE Confidence: 0.747156045333333

 $00{:}28{:}30{.}380 \dashrightarrow 00{:}28{:}32{.}782$  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

 $00:28:37.680 \longrightarrow 00:28:39.430$  They're listed here as well as to

NOTE Confidence: 0.747156045333333

 $00:28:39.430 \longrightarrow 00:28:41.000$  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

 $00{:}28{:}43{.}894 \dashrightarrow 00{:}28{:}45{.}738$  that was a wonderful talk and I

NOTE Confidence: 0.826594380833333

 $00{:}28{:}45.738 \dashrightarrow 00{:}28{:}47.530$  know we're a little bit over but we

NOTE Confidence: 0.826594380833333

 $00{:}28{:}47{.}530 \dashrightarrow 00{:}28{:}49{.}484$  don't have a second speaker so if

NOTE Confidence: 0.826594380833333

 $00{:}28{:}49{.}484 \dashrightarrow 00{:}28{:}50{.}919$  there are any burning questions,

 $00:28:50.920 \longrightarrow 00:28:54.056$  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

 $00{:}29{:}14.380 \dashrightarrow 00{:}29{:}16.550$  I'll start with one question I might

NOTE Confidence: 0.853936105

 $00{:}29{:}16.550 \dashrightarrow 00{:}29{:}18.976$  have missed this of the DDR inhibitors

NOTE Confidence: 0.853936105

 $00{:}29{:}18.976 \dashrightarrow 00{:}29{:}21.939$  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

 $00{:}29{:}24{.}215 \dashrightarrow 00{:}29{:}26{.}457$  of IDH mutants are is there a

NOTE Confidence: 0.853936105

 $00{:}29{:}26.457 \dashrightarrow 00{:}29{:}28.251$  wish list of the DDR inhibitors

NOTE Confidence: 0.853936105

 $00:29:28.322 \longrightarrow 00:29:30.077$  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

 $00{:}29{:}32{.}453 \dashrightarrow 00{:}29{:}33{.}897$  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

 $00{:}29{:}35{.}840 \dashrightarrow 00{:}29{:}37{.}800$  I mean I think the ATR inhibitors

NOTE Confidence: 0.837334244545454

 $00{:}29{:}37{.}800 \dashrightarrow 00{:}29{:}39{.}806$  are really an interesting area to

NOTE Confidence: 0.837334244545454

 $00{:}29{:}39{.}806 \dashrightarrow 00{:}29{:}41{.}144$  explore and one that really hasn't

NOTE Confidence: 0.837334244545454

 $00:29:41.144 \longrightarrow 00:29:42.564$  been looked at too much in terms

- NOTE Confidence: 0.837334244545454
- $00:29:42.564 \rightarrow 00:29:43.950$  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
- $00:29:45.530 \longrightarrow 00:29:47.812$  that in the setting of these cells
- NOTE Confidence: 0.837334244545454
- $00:29:47.812 \rightarrow 00:29:50.010$  entering sort of premature mitosis,
- NOTE Confidence: 0.837334244545454
- $00:29:50.010 \longrightarrow 00:29:51.780$  you'd have a lot of formation
- NOTE Confidence: 0.837334244545454
- $00{:}29{:}51.780 \dashrightarrow 00{:}29{:}53.344$  of these micronuclei that could
- NOTE Confidence: 0.837334244545454
- $00:29:53.344 \rightarrow 00:29:55.246$  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
- $00{:}29{:}57{.}404 \dashrightarrow 00{:}29{:}59{.}448$  based on our initial work with Rita
- NOTE Confidence: 0.837334244545454
- $00:29:59.448 \rightarrow 00:30:01.825$  and her findings in the flank model I,
- NOTE Confidence: 0.837334244545454
- $00:30:01.830 \longrightarrow 00:30:03.426$  I really want to pursue this more
- NOTE Confidence: 0.837334244545454
- $00{:}30{:}03{.}426 \dashrightarrow 00{:}30{:}05{.}886$  and see if we can see signs of immune
- NOTE Confidence: 0.837334244545454
- $00:30:05.886 \rightarrow 00:30:07.839$  activation and synergy with PD1 blockade.
- NOTE Confidence: 0.8203688166666667
- $00{:}30{:}10{.}210 \dashrightarrow 00{:}30{:}11{.}446$  Where to ask one more question.
- NOTE Confidence: 0.8203688166666667
- $00:30:11.450 \longrightarrow 00:30:13.298$  Then we will close up if no others.
- NOTE Confidence: 0.820368816666667

 $00:30:13.300 \longrightarrow 00:30:14.752$  Any plans to write up that

NOTE Confidence: 0.8203688166666667

 $00:30:14.752 \dashrightarrow 00:30:16.190$  wonderful case study with Farzaneh.

NOTE Confidence: 0.948000931666667

 $00:30:17.610 \longrightarrow 00:30:18.648$  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

 $00:30:20.190 \longrightarrow 00:30:21.884$  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: 0.9480009316666667

00:30:23.477 -> 00:30:25.169 be a nice corollary to the you know,

NOTE Confidence: 0.948000931666667

 $00:30:25.170 \longrightarrow 00:30:27.032$  as you know, the aranka work we're

NOTE Confidence: 0.948000931666667

 $00{:}30{:}27.032 \dashrightarrow 00{:}30{:}28.949$  hoping to write that up soon and

NOTE Confidence: 0.948000931666667

 $00:30:28.949 \longrightarrow 00:30:30.279$  submit that as a manuscript.

NOTE Confidence: 0.948000931666667

 $00{:}30{:}30{.}280 \dashrightarrow 00{:}30{:}31{.}533$  So I think it would be a

NOTE Confidence: 0.9480009316666667

 $00:30:31.533 \longrightarrow 00:30:32.330$  great corollary to that.

NOTE Confidence: 0.948000931666667

 $00:30:32.330 \longrightarrow 00:30:34.746$  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

 $00:30:35.750 \longrightarrow 00:30:36.406$  well this is great.

NOTE Confidence: 0.911709772727273

 $00:30:36.406 \dashrightarrow 00:30:38.124$  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
- $00:30:39.284 \longrightarrow 00:30:40.250$  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
- $00{:}30{:}41.855 \dashrightarrow 00{:}30{:}43.980$  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
- $00:30:46.560 \longrightarrow 00:30:47.680$  Take care by by.