WEBVTT

NOTE duration:"00:47:22.1600000"

NOTE recognizability:0.788

NOTE language:en-us

NOTE Confidence: 0.759128495384615

00:00:00.000 --> 00:00:02.527 Friday, and thank you so much Harriet

NOTE Confidence: 0.759128495384615

00:00:02.527 --> 00:00:05.139 and Marcus for your kind invitation.

NOTE Confidence: 0.759128495384615

00:00:05.140 --> 00:00:08.156 I promise I'll go back in person and

NOTE Confidence: 0.759128495384615

00:00:08.156 --> 00:00:10.620 hopefully with less technical issues.

NOTE Confidence: 0.759128495384615

00:00:10.620 --> 00:00:13.218 So as all of you know,

NOTE Confidence: 0.759128495384615

00:00:13.220 --> 00:00:15.140 probably even better than me,

NOTE Confidence: 0.759128495384615

00:00:15.140 --> 00:00:16.862 Melanoma is the fifth most common

NOTE Confidence: 0.759128495384615

00:00:16.862 --> 00:00:18.859 cancer in men and sixteen women.

NOTE Confidence: 0.759128495384615

00:00:18.860 --> 00:00:21.350 And can you please keep clicking?

NOTE Confidence: 0.759128495384615

00:00:21.350 --> 00:00:23.070 I'm going to go fast through this first

NOTE Confidence: 0.759128495384615

00:00:23.070 --> 00:00:24.380 slides because it's just background.

NOTE Confidence: 0.759128495384615

00:00:24.380 --> 00:00:26.036 As you know, the incidence of

NOTE Confidence: 0.759128495384615

00:00:26.036 --> 00:00:27.140 Melanoma continues to increase.

NOTE Confidence: 0.759128495384615

00:00:27.140 --> 00:00:29.018 It double s every 20 years

NOTE Confidence: 0.759128495384615

00:00:29.018 --> 00:00:30.680 and luckily this is like.

NOTE Confidence: 0.759128495384615

00:00:30.680 --> 00:00:31.218 Unfortunately,

NOTE Confidence: 0.759128495384615

00:00:31.218 --> 00:00:34.446 it's not a updated the mortality

NOTE Confidence: 0.759128495384615

00:00:34.446 --> 00:00:37.234 associated with Melanoma is starting to

NOTE Confidence: 0.759128495384615

00:00:37.234 --> 00:00:40.214 decrease and this is you definitely to

NOTE Confidence: 0.759128495384615

00:00:40.214 --> 00:00:43.099 the development of better therapies.

NOTE Confidence: 0.759128495384615

00:00:43.100 --> 00:00:45.680 For the past 15 years,

NOTE Confidence: 0.759128495384615

00:00:45.680 --> 00:00:47.930 Melanoma has become the poster

NOTE Confidence: 0.759128495384615

00:00:47.930 --> 00:00:50.180 child for many targeted therapies

NOTE Confidence: 0.759128495384615

00:00:50.257 --> 00:00:52.437 as well as immunotherapy space.

NOTE Confidence: 0.759128495384615

00:00:52.440 --> 00:00:53.649 Please keep clicking,

NOTE Confidence: 0.759128495384615

00:00:53.649 --> 00:00:56.960 but all of you know there is still

NOTE Confidence: 0.759128495384615

00:00:56.960 --> 00:01:00.570 despite the success of this.

NOTE Confidence: 0.759128495384615

00:01:00.570 --> 00:01:01.170 Uh,

NOTE Confidence: 0.759128495384615

00:01:01.170 --> 00:01:03.570 we're developing immunotherapy treatments.

NOTE Confidence: 0.759128495384615

00:01:03.570 --> 00:01:05.730 We still can keep clicking.

NOTE Confidence: 0.759128495384615

00:01:05.730 --> 00:01:11.382 We are still facing significant resistance

NOTE Confidence: 0.759128495384615

00:01:11.382 --> 00:01:17.870 to some of these treatments or a.

NOTE Confidence: 0.759128495384615

00:01:17.870 --> 00:01:20.330 Year um side effects.

NOTE Confidence: 0.759128495384615

00:01:20.330 --> 00:01:22.910 So approximately 40% of the

NOTE Confidence: 0.759128495384615

00:01:22.910 --> 00:01:24.370 metastatic Melanoma patients have

NOTE Confidence: 0.759128495384615

00:01:24.370 --> 00:01:26.189 not benefited from the advances

NOTE Confidence: 0.759128495384615

00:01:26.189 --> 00:01:28.254 that have been done over the past

NOTE Confidence: 0.759128495384615

00:01:28.254 --> 00:01:30.419 years in the treatment of Melanoma.

NOTE Confidence: 0.759128495384615

00:01:30.420 --> 00:01:34.857 So this takes me, can you please go on to my,

NOTE Confidence: 0.759128495384615

00:01:34.857 --> 00:01:37.479 the, the focus of my lab.

NOTE Confidence: 0.759128495384615

00:01:37.480 --> 00:01:38.840 Can you go back?

NOTE Confidence: 0.759128495384615

00:01:38.840 --> 00:01:39.180 Yeah,

NOTE Confidence: 0.759128495384615

00:01:39.180 --> 00:01:43.220 which evolves around these questions,

NOTE Confidence: 0.759128495384615

00:01:43.220 --> 00:01:45.320 right, the fact that we still need

NOTE Confidence: 0.759128495384615

00:01:45.320 --> 00:01:47.300 better markers for patient selection,

NOTE Confidence: 0.759128495384615

00:01:47.300 --> 00:01:47.603 understand.

NOTE Confidence: 0.759128495384615

00:01:47.603 --> 00:01:49.724 Where we check the patients that are

NOTE Confidence: 0.759128495384615

00:01:49.724 --> 00:01:52.170 going to uh go on to recur after the

NOTE Confidence: 0.759128495384615

00:01:52.170 --> 00:01:53.630 initial resection of their tumor,

NOTE Confidence: 0.759128495384615

00:01:53.630 --> 00:01:57.116 which ones are going to metastasize.

NOTE Confidence: 0.759128495384615

00:01:57.120 --> 00:01:58.780 And also in particular,

NOTE Confidence: 0.759128495384615

00:01:58.780 --> 00:02:00.025 as Harriet mentioned,

NOTE Confidence: 0.759128495384615

00:02:00.030 --> 00:02:01.910 we've developed an interest in

NOTE Confidence: 0.759128495384615

00:02:01.910 --> 00:02:04.510 understanding the biology of CNS metastases,

NOTE Confidence: 0.759128495384615

00:02:04.510 --> 00:02:06.574 particularly of brain metastasis

NOTE Confidence: 0.759128495384615

00:02:06.574 --> 00:02:09.670 because they show less level responses

NOTE Confidence: 0.759128495384615

00:02:09.750 --> 00:02:12.075 to immunotherapy and the incidence

NOTE Confidence: 0.759128495384615

00:02:12.075 --> 00:02:14.968 is increasing as patients are living

NOTE Confidence: 0.759128495384615

00:02:14.968 --> 00:02:17.896 longer and surviving from other systems.

NOTE Confidence: 0.759128495384615

00:02:17.900 --> 00:02:20.684 Astasis, so my lab is focused

NOTE Confidence: 0.759128495384615

00:02:20.684 --> 00:02:22.540 into aspects of metastasis,

NOTE Confidence: 0.759128495384615

00:02:22.540 --> 00:02:25.198 the initial steps of early dissemination,

NOTE Confidence: 0.759128495384615

00:02:25.200 --> 00:02:27.750 we now know that primary tumors,

NOTE Confidence: 0.759128495384615

00:02:27.750 --> 00:02:29.364 especially in Melanoma.

NOTE Confidence: 0.759128495384615

00:02:29.364 --> 00:02:30.978 Is that uh,

NOTE Confidence: 0.759128495384615

00:02:30.980 --> 00:02:33.260 disseminating start sharing cells that

NOTE Confidence: 0.759128495384615

00:02:33.260 --> 00:02:35.540 go into circulation and metastasize

NOTE Confidence: 0.759128495384615

00:02:35.607 --> 00:02:37.515 really early on in the process.

NOTE Confidence: 0.759128495384615

00:02:37.520 --> 00:02:38.960 So we want to understand,

NOTE Confidence: 0.759128495384615

00:02:38.960 --> 00:02:40.409 please click uh,

NOTE Confidence: 0.759128495384615

00:02:40.409 --> 00:02:42.824 which are the mechanisms that

NOTE Confidence: 0.759128495384615

00:02:42.824 --> 00:02:45.695 drive the metastatic behavior of

NOTE Confidence: 0.759128495384615

00:02:45.695 --> 00:02:48.715 certain melanomas and not others.

NOTE Confidence: 0.759128495384615

00:02:48.720 --> 00:02:50.705 We know that unity alterations

NOTE Confidence: 0.759128495384615

00:02:50.705 --> 00:02:52.690 don't explain this behavior because

NOTE Confidence: 0.759128495384615

00:02:52.751 --> 00:02:54.706 none of the well characterized

NOTE Confidence: 0.759128495384615

00:02:54.706 --> 00:02:56.270 genetic alterations of Melanoma

NOTE Confidence: 0.759128495384615

00:02:56.270 --> 00:02:58.465 or combinations of those genetic

NOTE Confidence: 0.759128495384615

00:02:58.465 --> 00:03:00.209 alterations can explain why.

NOTE Confidence: 0.759128495384615

00:03:00.210 --> 00:03:02.190 And primary tumors recurred,

NOTE Confidence: 0.759128495384615

00:03:02.190 --> 00:03:04.665 metastasized and some others don't.

NOTE Confidence: 0.759128495384615

00:03:04.670 --> 00:03:06.800 And also we want to understand

NOTE Confidence: 0.759128495384615

00:03:06.800 --> 00:03:08.936 what is the contribution of

NOTE Confidence: 0.759128495384615

00:03:08.936 --> 00:03:10.228 intratumoral heterogeneity.

NOTE Confidence: 0.759128495384615

00:03:10.230 --> 00:03:12.624 So we know now that despite the

NOTE Confidence: 0.759128495384615

00:03:12.624 --> 00:03:15.172 fact that primary tumors can have

NOTE Confidence: 0.759128495384615

00:03:15.172 --> 00:03:17.100 a relatively homogeneous genetic

NOTE Confidence: 0.759128495384615

00:03:17.100 --> 00:03:19.110 profile inside those tumors,

NOTE Confidence: 0.759128495384615

00:03:19.110 --> 00:03:22.120 we can recognize groups of cells with

NOTE Confidence: 0.759128495384615

00:03:22.120 --> 00:03:23.410 different transcriptional programs,

NOTE Confidence: 0.759128495384615

00:03:23.410 --> 00:03:25.290 what we call transcriptional states.

NOTE Confidence: 0.759128495384615

00:03:25.290 --> 00:03:27.762 And there is a recent search for what

NOTE Confidence: 0.759128495384615

00:03:27.762 --> 00:03:30.240 are the programs for their states.

NOTE Confidence: 0.759128495384615

00:03:30.240 --> 00:03:32.130 That drive these metastatic behavior

NOTE Confidence: 0.759128495384615

00:03:32.130 --> 00:03:34.644 and people have pointed to the neural

NOTE Confidence: 0.759128495384615

00:03:34.644 --> 00:03:36.900 Crest like or the EMT program on the

NOTE Confidence: 0.8062973056

00:03:36.960 --> 00:03:38.580 other side of the equation.

NOTE Confidence: 0.8062973056

00:03:38.580 --> 00:03:40.332 We are also trying to understand

NOTE Confidence: 0.8062973056

00:03:40.332 --> 00:03:42.418 what happens at the end of the

NOTE Confidence: 0.8062973056

00:03:42.418 --> 00:03:43.853 process once the cancer cells,

NOTE Confidence: 0.8062973056

00:03:43.860 --> 00:03:46.226 in this case Melanoma cells have already

NOTE Confidence: 0.8062973056

00:03:46.226 --> 00:03:48.039 extravasated into those distal organs.

NOTE Confidence: 0.8062973056

00:03:48.040 --> 00:03:50.231 As you know Melanoma metastasis to the

NOTE Confidence: 0.8062973056

00:03:50.231 --> 00:03:52.827 lung delivered in the brain and we are

NOTE Confidence: 0.8062973056

00:03:52.827 --> 00:03:54.840 interested in understanding what are the

NOTE Confidence: 0.8062973056

00:03:54.840 --> 00:03:57.000 site specific adaptations in those sites,

NOTE Confidence: 0.8062973056

00:03:57.000 --> 00:04:00.829 where are the type of metabolic changes.

NOTE Confidence: 0.8062973056

00:04:00.830 --> 00:04:02.882 The cell types of the cancer

NOTE Confidence: 0.8062973056

00:04:02.882 --> 00:04:03.908 cells are interacting.

NOTE Confidence: 0.8062973056

00:04:03.910 --> 00:04:05.625 And what is this crosstalk between the

NOTE Confidence: 0.8062973056

00:04:05.625 --> 00:04:07.209 cancer cells and their environment?

NOTE Confidence: 0.8062973056

00:04:07.210 --> 00:04:09.426 How is shaping the ability of animal cells

NOTE Confidence: 0.8062973056

00:04:09.426 --> 00:04:11.727 to adapt and grow in those environments?

NOTE Confidence: 0.8062973056

00:04:11.730 --> 00:04:14.550 And I will have to stories

NOTE Confidence: 0.8062973056

00:04:14.550 --> 00:04:17.270 presenting today if time permits,

NOTE Confidence: 0.8062973056

00:04:17.270 --> 00:04:19.622 one that focuses more in just the

NOTE Confidence: 0.8062973056

00:04:19.622 --> 00:04:21.609 metastatic potential in general and how

NOTE Confidence: 0.8062973056

00:04:21.609 --> 00:04:24.147 muscles cops some of the programs of the

NOTE Confidence: 0.8062973056

00:04:24.147 --> 00:04:26.464 neural Crest cells from which they arise.

NOTE Confidence: 0.8062973056

00:04:26.470 --> 00:04:29.530 And also in the second part of the talk,

NOTE Confidence: 0.8062973056

00:04:29.530 --> 00:04:30.840 I will talk more specifically.

NOTE Confidence: 0.8062973056

00:04:30.840 --> 00:04:34.774 About to bring metastasis and how Melanoma

NOTE Confidence: 0.8062973056

00:04:34.774 --> 00:04:37.714 cells mimic some of the processes

NOTE Confidence: 0.8062973056

00:04:37.714 --> 00:04:40.050 that happen during neurodegeneration,

NOTE Confidence: 0.8062973056

00:04:40.050 --> 00:04:41.860 particularly to suppress new inflammation

NOTE Confidence: 0.8062973056

00:04:41.860 --> 00:04:44.739 and be able to grow within the brain.

NOTE Confidence: 0.8062973056

00:04:44.740 --> 00:04:47.218 So diving into the first story,

NOTE Confidence: 0.8062973056

00:04:47.220 --> 00:04:49.460 these are the four areas in which my

NOTE Confidence: 0.8062973056

00:04:49.460 --> 00:04:51.940 lab has been focused in recent years,

NOTE Confidence: 0.8062973056

00:04:51.940 --> 00:04:53.581 epigenetic alterations, noncollinear,

NOTE Confidence: 0.8062973056

00:04:53.581 --> 00:04:55.769 a post translational modifications

NOTE Confidence: 0.8062973056

00:04:55.769 --> 00:04:57.410 particularly like oscillation

NOTE Confidence: 0.8062973056

00:04:57.469 --> 00:04:59.077 and site specific adaptations.

NOTE Confidence: 0.8062973056

00:04:59.080 --> 00:05:00.514 So moving on,

NOTE Confidence: 0.8062973056

00:05:00.514 --> 00:05:04.160 can you please move these slides one more,

NOTE Confidence: 0.8062973056

00:05:04.160 --> 00:05:07.292 the first story that has been

NOTE Confidence: 0.8062973056

00:05:07.292 --> 00:05:09.160 recently accepted for publication

NOTE Confidence: 0.8062973056

00:05:09.160 --> 00:05:11.620 is the work of three people.

NOTE Confidence: 0.8062973056

00:05:11.620 --> 00:05:14.868 It evolve over time and we have.

NOTE Confidence: 0.8062973056

00:05:14.870 --> 00:05:15.223 Uh,

NOTE Confidence: 0.8062973056

00:05:15.223 --> 00:05:17.694 tightly muscles invoke and you like clear

NOTE Confidence: 0.8062973056

00:05:17.694 --> 00:05:19.990 sticky genetic program during metastasis.

NOTE Confidence: 0.8062973056

00:05:19.990 --> 00:05:24.058 So the genesis for this project was a very

NOTE Confidence: 0.8062973056

00:05:24.058 --> 00:05:26.328 simple premise and it's the fact that,

NOTE Confidence: 0.8062973056

00:05:26.330 --> 00:05:26.580 well,

NOTE Confidence: 0.8062973056

00:05:26.580 --> 00:05:28.580 we all know that neural Crest cells are

NOTE Confidence: 0.8062973056

00:05:28.580 --> 00:05:30.466 the cells of origin of melanocytes.

NOTE Confidence: 0.8062973056

00:05:30.470 --> 00:05:33.333 And these are among the most totipotent

NOTE Confidence: 0.8062973056

00:05:33.333 --> 00:05:36.247 and among the most invasive and migratory

NOTE Confidence: 0.8062973056

00:05:36.247 --> 00:05:39.511 cells of our body and is well known

NOTE Confidence: 0.8062973056

00:05:39.511 --> 00:05:42.490 now if you keep clicking that Melanoma

NOTE Confidence: 0.8062973056

00:05:42.490 --> 00:05:45.130 cells adopt programs characteristic.

NOTE Confidence: 0.8062973056

00:05:45.130 --> 00:05:47.538 You address the cells during the progression

NOTE Confidence: 0.8062973056

00:05:47.538 --> 00:05:49.670 from primary to metastatic cancer.

NOTE Confidence: 0.8062973056

00:05:49.670 --> 00:05:52.028 So we wanted to investigate which

NOTE Confidence: 0.8062973056

00:05:52.028 --> 00:05:53.600 epigenetic changes happen during

NOTE Confidence: 0.8062973056

00:05:53.663 --> 00:05:55.355 melanocyte differentiation from the

NOTE Confidence: 0.8062973056

00:05:55.355 --> 00:05:57.893 neural Crest to the melanocyte that

NOTE Confidence: 0.8062973056

00:05:57.955 --> 00:06:00.205 potentially could be reversed in the

NOTE Confidence: 0.8062973056

00:06:00.205 --> 00:06:02.116 transition from primary to metastasis.

NOTE Confidence: 0.8062973056

00:06:02.116 --> 00:06:04.552 And we did this by looking

NOTE Confidence: 0.8062973056

00:06:04.552 --> 00:06:06.690 specifically at DNA methylation.

NOTE Confidence: 0.8062973056

00:06:06.690 --> 00:06:08.838 There are of course many other

NOTE Confidence: 0.8062973056

00:06:08.838 --> 00:06:10.270 mechanisms of epigenetic regulation

NOTE Confidence: 0.8062973056

00:06:10.325 --> 00:06:12.167 being the enumeration one of them.

NOTE Confidence: 0.8062973056

00:06:12.170 --> 00:06:15.514 So if you move to the next slide.

NOTE Confidence: 0.8062973056

00:06:15.520 --> 00:06:17.466 This is what we did basically was

NOTE Confidence: 0.8062973056

00:06:17.466 --> 00:06:19.218 a comparison of four data sets.

NOTE Confidence: 0.8062973056

00:06:19.220 --> 00:06:22.379 So in one hand I cannot use my pointer,

NOTE Confidence: 0.8062973056

00:06:22.380 --> 00:06:24.738 but you can see that we have 4 columns.

NOTE Confidence: 0.8062973056

00:06:24.740 --> 00:06:27.008 We have neural Crest cells that were

NOTE Confidence: 0.8062973056

00:06:27.008 --> 00:06:29.480 obtained from a collaborator in France.

NOTE Confidence: 0.8062973056

00:06:29.480 --> 00:06:30.908 These are human cells.

NOTE Confidence: 0.8062973056

00:06:30.908 --> 00:06:33.050 We also had the human melanocytes

NOTE Confidence: 0.8062973056

00:06:33.116 --> 00:06:34.520 from different donors.

NOTE Confidence: 0.8062973056

00:06:34.520 --> 00:06:36.144 And as you can see there is

NOTE Confidence: 0.8062973056

00:06:36.144 --> 00:06:38.039 kind of a mirroring pattern.

NOTE Confidence: 0.8062973056

00:06:38.040 --> 00:06:41.162 We were looking for CPG islands that

NOTE Confidence: 0.8062973056

00:06:41.162 --> 00:06:43.424 were either hypomethylated in the

NOTE Confidence: 0.8062973056

00:06:43.424 --> 00:06:45.549 conversion from neural Crest cells.

NOTE Confidence: 0.8062973056

00:06:45.550 --> 00:06:48.232 To Milano sites that were progressively

NOTE Confidence: 0.8062973056

00:06:48.232 --> 00:06:50.020 hypermethylated from primary to

NOTE Confidence: 0.769571231333333

00:06:50.083 --> 00:06:52.348 metastatic Melanoma or the converse,

NOTE Confidence: 0.769571231333333

00:06:52.350 --> 00:06:53.706 if you see at the bottom,

NOTE Confidence: 0.769571231333333

00:06:53.710 --> 00:06:56.700 we have some CPG islands.

NOTE Confidence: 0.769571231333333

00:06:56.700 --> 00:06:58.210 If you can click again,

NOTE Confidence: 0.769571231333333

00:06:58.210 --> 00:07:00.352 you will see there are some CPG

NOTE Confidence: 0.769571231333333

00:07:00.352 --> 00:07:02.349 islands around the gene called NR

NOTE Confidence: 0.769571231333333

00:07:02.349 --> 00:07:04.371 22 that are hypomethylated in the

NOTE Confidence: 0.769571231333333

00:07:04.371 --> 00:07:06.905 neural grass cells that become

NOTE Confidence: 0.769571231333333

00:07:06.905 --> 00:07:09.037 hypermethylated in melanocytes and

NOTE Confidence: 0.769571231333333

00:07:09.037 --> 00:07:10.562 progressively hypomethylated from

NOTE Confidence: 0.769571231333333

00:07:10.562 --> 00:07:12.370 primary to metastatic Melanoma.

NOTE Confidence: 0.769571231333333

00:07:12.370 --> 00:07:14.602 And this really call our attention

NOTE Confidence: 0.769571231333333

00:07:14.602 --> 00:07:16.090 because it really represented.

NOTE Confidence: 0.769571231333333

00:07:16.090 --> 00:07:19.205 Example of a potential gene or or

NOTE Confidence: 0.769571231333333

00:07:19.205 --> 00:07:21.820 candidate program to be modulated

NOTE Confidence: 0.769571231333333

00:07:21.820 --> 00:07:24.196 during neural Crest differentiation

NOTE Confidence: 0.769571231333333

00:07:24.196 --> 00:07:27.320 to melanocytes that was reversed

NOTE Confidence: 0.769571231333333

00:07:27.320 --> 00:07:29.260 during the progression from primary

NOTE Confidence: 0.769571231333333

00:07:29.260 --> 00:07:31.200 to metastatic Melanoma and what

NOTE Confidence: 0.769571231333333

00:07:31.260 --> 00:07:32.940 is first of all an R2 of two,

NOTE Confidence: 0.769571231333333

00:07:32.940 --> 00:07:35.380 so it's a nuclear receptor

NOTE Confidence: 0.769571231333333

00:07:35.380 --> 00:07:36.796 is also called cooked.

NOTE Confidence: 0.769571231333333

00:07:36.796 --> 00:07:38.920 TF2 is an orphan nuclear receptor.

NOTE Confidence: 0.769571231333333

00:07:38.920 --> 00:07:40.260 We don't know still what

NOTE Confidence: 0.769571231333333

00:07:40.260 --> 00:07:41.332 is the natural ligand,

NOTE Confidence: 0.769571231333333

00:07:41.340 --> 00:07:43.990 although retinoic acid can bind

NOTE Confidence: 0.769571231333333

00:07:43.990 --> 00:07:46.110 it at high concentrations.

NOTE Confidence: 0.769571231333333

00:07:46.110 --> 00:07:47.405 This is the motif that it binds,

NOTE Confidence: 0.769571231333333

00:07:47.410 --> 00:07:50.850 and as you can see the NRF 2 full

NOTE Confidence: 0.769571231333333

00:07:50.850 --> 00:07:53.970 isoform has a DNA binding domain.

NOTE Confidence: 0.769571231333333

00:07:53.970 --> 00:07:55.490 It has a ligand domain.

NOTE Confidence: 0.769571231333333

00:07:55.490 --> 00:07:57.668 So it's a conventional nuclear receptor

NOTE Confidence: 0.769571231333333

00:07:57.668 --> 00:08:00.794 that can form a **** or heterodimers.

NOTE Confidence: 0.769571231333333

00:08:00.794 --> 00:08:04.154 It is essential if you,

NOTE Confidence: 0.769571231333333

00:08:04.160 --> 00:08:04.626 yeah,

NOTE Confidence: 0.769571231333333

00:08:04.626 --> 00:08:06.956 it's essential for development and

NOTE Confidence: 0.769571231333333

00:08:06.956 --> 00:08:09.464 particularly for the formation of blood

NOTE Confidence: 0.769571231333333

00:08:09.464 --> 00:08:11.768 vessels and it has been shown to be

NOTE Confidence: 0.769571231333333

00:08:11.842 --> 00:08:14.597 important for neural test differentiation.

NOTE Confidence: 0.769571231333333

00:08:14.600 --> 00:08:17.365 Now there have been already some studies

NOTE Confidence: 0.769571231333333

00:08:17.365 --> 00:08:20.338 showing the role of NRF 2IN cancer,

NOTE Confidence: 0.769571231333333

00:08:20.338 --> 00:08:21.916 particularly pancreatic and

NOTE Confidence: 0.769571231333333

00:08:21.916 --> 00:08:23.494 prostate cancer metastasis,

NOTE Confidence: 0.769571231333333

00:08:23.500 --> 00:08:25.365 whereas in breast cancer it

NOTE Confidence: 0.769571231333333

00:08:25.365 --> 00:08:26.857 had a controversial effects.

NOTE Confidence: 0.769571231333333

00:08:26.860 --> 00:08:28.940 So you can say well you know this,

NOTE Confidence: 0.769571231333333

00:08:28.940 --> 00:08:30.220 this may already be known

NOTE Confidence: 0.769571231333333

00:08:30.220 --> 00:08:31.500 that this factor is important.

NOTE Confidence: 0.769571231333333

00:08:31.500 --> 00:08:32.354 Cancer, however,

NOTE Confidence: 0.769571231333333

00:08:32.354 --> 00:08:34.916 if you click one more slide,

NOTE Confidence: 0.769571231333333

00:08:34.920 --> 00:08:37.230 what really cool our attention is

NOTE Confidence: 0.769571231333333

00:08:37.230 --> 00:08:40.300 that the CPG islands that we found

NOTE Confidence: 0.769571231333333

00:08:40.300 --> 00:08:42.240 to be differential differentially

NOTE Confidence: 0.769571231333333

00:08:42.240 --> 00:08:44.611 methylated in neural Crest cells

NOTE Confidence: 0.769571231333333

00:08:44.611 --> 00:08:46.716 versus melanocytes and then later

NOTE Confidence: 0.769571231333333

00:08:46.716 --> 00:08:49.394 on in primary versus Melanoma,

NOTE Confidence: 0.769571231333333

00:08:49.394 --> 00:08:52.929 we're actually affecting exactly that

NOTE Confidence: 0.769571231333333

00:08:52.929 --> 00:08:55.728 region in the transcription start

NOTE Confidence: 0.769571231333333

00:08:55.728 --> 00:08:58.338 site that controls the expression

NOTE Confidence: 0.769571231333333

00:08:58.338 --> 00:09:01.680 of an alternative isoform isoform 2.

NOTE Confidence: 0.769571231333333

00:09:01.680 --> 00:09:03.850 Which is not the one that has

NOTE Confidence: 0.769571231333333

00:09:03.850 --> 00:09:04.780 been commonly characterized.

NOTE Confidence: 0.769571231333333

00:09:04.780 --> 00:09:06.328 So most studies have focused on

NOTE Confidence: 0.769571231333333

00:09:06.328 --> 00:09:07.766 the full length isoform, isoform,

NOTE Confidence: 0.769571231333333

00:09:07.766 --> 00:09:10.608 one that has the DNA binding domain,

NOTE Confidence: 0.769571231333333

00:09:10.610 --> 00:09:12.574 the like minded domain.

NOTE Confidence: 0.769571231333333

00:09:12.574 --> 00:09:15.692 But this methylated region or the

NOTE Confidence: 0.769571231333333

00:09:15.692 --> 00:09:17.956 methylated region is in atss that

NOTE Confidence: 0.769571231333333

00:09:17.956 --> 00:09:19.750 gives rise to a truncated isoform

NOTE Confidence: 0.769571231333333

00:09:19.820 --> 00:09:21.896 that lacks the DNA binding domain.

NOTE Confidence: 0.769571231333333

00:09:21.900 --> 00:09:25.356 So on the right you can see that as

NOTE Confidence: 0.769571231333333

00:09:25.356 --> 00:09:29.558 we had shown before the CPG islands

NOTE Confidence: 0.769571231333333

00:09:29.558 --> 00:09:32.393 controlling this this nuclear receptor.

NOTE Confidence: 0.769571231333333

00:09:32.393 --> 00:09:36.110 Networks to ISO two are hypomethylated and

NOTE Confidence: 0.769571231333333

00:09:36.193 --> 00:09:39.798 they appear in green in cells and stem cells,

NOTE Confidence: 0.769571231333333

00:09:39.798 --> 00:09:41.160 but completely hypermethylated

NOTE Confidence: 0.769571231333333

00:09:41.160 --> 00:09:42.068 in melanocytes,

NOTE Confidence: 0.769571231333333

00:09:42.070 --> 00:09:44.790 and this is also described here at the

NOTE Confidence: 0.769571231333333

00:09:44.790 --> 00:09:47.345 bottom where you can see the beta value.

NOTE Confidence: 0.769571231333333

00:09:47.350 --> 00:09:49.996 The beta value of 1 means completely

NOTE Confidence: 0.769571231333333

00:09:49.996 --> 00:09:53.007 methylated and a better value close to

NOTE Confidence: 0.769571231333333

00:09:53.007 --> 00:09:55.262 0 represents a hypomethylated gene.

NOTE Confidence: 0.769571231333333

00:09:55.270 --> 00:09:57.305 This completely corresponds to gene

NOTE Confidence: 0.769571231333333

00:09:57.305 --> 00:09:59.757 expression because you can see that

NOTE Confidence: 0.769571231333333

00:09:59.757 --> 00:10:02.186 whereas isoform one is expressed in ESL.

NOTE Confidence: 0.769571231333333

00:10:02.190 --> 00:10:04.134 1000 monocytes isoform 2 is expressed

NOTE Confidence: 0.769571231333333

00:10:04.134 --> 00:10:06.620 in your cells and neural Crest cells,

NOTE Confidence: 0.769571231333333

00:10:06.620 --> 00:10:09.770 but not expressed at all in melanocytes.

NOTE Confidence: 0.769571231333333

00:10:09.770 --> 00:10:10.058 OK.

NOTE Confidence: 0.769571231333333

00:10:10.058 --> 00:10:12.650 So in when you look at the human samples,

NOTE Confidence: 0.769571231333333

00:10:12.650 --> 00:10:14.778 you can see and that even though

NOTE Confidence: 0.769571231333333

00:10:14.778 --> 00:10:15.690 it's not completely

NOTE Confidence: 0.880226573846154

00:10:15.753 --> 00:10:18.415 black and white, what we see is that

NOTE Confidence: 0.880226573846154

00:10:18.415 --> 00:10:20.641 there is an increased percentage of

NOTE Confidence: 0.880226573846154

00:10:20.641 --> 00:10:23.227 hypomethylation of isotope in the metastatic

NOTE Confidence: 0.880226573846154

00:10:23.227 --> 00:10:25.788 cases compared to the primary cases.

NOTE Confidence: 0.880226573846154

00:10:25.790 --> 00:10:29.356 You can see there is from 30% approximately

NOTE Confidence: 0.880226573846154

00:10:29.356 --> 00:10:33.034 to more than 50% of the samples have

NOTE Confidence: 0.880226573846154

00:10:33.034 --> 00:10:35.414 hypomethylation for NR2ISO2 and if you

NOTE Confidence: 0.880226573846154

00:10:35.414 --> 00:10:38.195 keep clicking you will see that you can

NOTE Confidence: 0.880226573846154

00:10:38.195 --> 00:10:40.379 see there is a progressive increase.

NOTE Confidence: 0.880226573846154

00:10:40.380 --> 00:10:42.924 In the better value from Levi

NOTE Confidence: 0.880226573846154

00:10:42.924 --> 00:10:44.620 to primary and metastasis,

NOTE Confidence: 0.880226573846154

00:10:44.620 --> 00:10:47.155 so more hypomethylated and conversely

NOTE Confidence: 0.880226573846154

00:10:47.155 --> 00:10:49.690 increase expression from primary to

NOTE Confidence: 0.880226573846154

00:10:49.762 --> 00:10:52.426 metastasis with a very nice correlation

NOTE Confidence: 0.880226573846154

00:10:52.426 --> 00:10:55.390 between M RNA expression and methylation.

NOTE Confidence: 0.880226573846154

00:10:55.390 --> 00:10:57.382 Is exactly, if you look at

NOTE Confidence: 0.880226573846154

00:10:57.382 --> 00:10:58.378 the protein levels,

NOTE Confidence: 0.880226573846154

00:10:58.380 --> 00:11:00.368 we were able to develop actually an

NOTE Confidence: 0.880226573846154

00:11:00.368 --> 00:11:01.769 antibody specific for isoform 2,

NOTE Confidence: 0.880226573846154

00:11:01.770 --> 00:11:02.786 which was challenging because

NOTE Confidence: 0.880226573846154

00:11:02.786 --> 00:11:04.660 there are only 15 amino acid symbol

NOTE Confidence: 0.880226573846154

00:11:04.660 --> 00:11:06.160 amino terminal that that specific.

NOTE Confidence: 0.880226573846154

00:11:06.160 --> 00:11:08.270 But also two you can see that there is an

NOTE Confidence: 0.880226573846154

00:11:08.327 --> 00:11:10.385 increase in the expression of isoform 2.

NOTE Confidence: 0.880226573846154

00:11:10.390 --> 00:11:12.812 There are few cells that are positive

NOTE Confidence: 0.880226573846154

00:11:12.812 --> 00:11:15.214 in the primary cases and this

NOTE Confidence: 0.880226573846154

00:11:15.214 --> 00:11:17.374 population expands in the metastasis.

NOTE Confidence: 0.880226573846154

00:11:17.380 --> 00:11:20.173 This is something that we are actually

NOTE Confidence: 0.880226573846154

00:11:20.173 --> 00:11:22.154 trying to understand now whether

NOTE Confidence: 0.880226573846154

00:11:22.154 --> 00:11:24.660 there is a selection for those cells

NOTE Confidence: 0.880226573846154

00:11:24.660 --> 00:11:27.116 that expressed isoform 2 over time.

NOTE Confidence: 0.880226573846154

00:11:27.120 --> 00:11:29.780 And again this is this is something

NOTE Confidence: 0.880226573846154

00:11:29.780 --> 00:11:31.858 we're coming time to investigate but

NOTE Confidence: 0.880226573846154

00:11:31.858 --> 00:11:34.886 if we can go on we we can see that

NOTE Confidence: 0.880226573846154

00:11:34.886 --> 00:11:37.529 isoform one the one that is the full

NOTE Confidence: 0.880226573846154

00:11:37.529 --> 00:11:40.103 length isoform is not modulated by

NOTE Confidence: 0.880226573846154

00:11:40.103 --> 00:11:41.870 methylation is completely hypomethylated

NOTE Confidence: 0.880226573846154

00:11:41.870 --> 00:11:44.733 in ES cells you know cells melanocytes

NOTE Confidence: 0.880226573846154

00:11:44.733 --> 00:11:47.419 and both in primary and metastatic

NOTE Confidence: 0.880226573846154

00:11:47.419 --> 00:11:50.260 Melanoma and there is no correlation

NOTE Confidence: 0.880226573846154

00:11:50.260 --> 00:11:52.172 between expression and methylation.

NOTE Confidence: 0.880226573846154

00:11:52.180 --> 00:11:54.238 So isoform one is always there,

NOTE Confidence: 0.880226573846154

00:11:54.240 --> 00:11:56.277 but is isoform 2 the one that.

NOTE Confidence: 0.880226573846154

00:11:56.280 --> 00:11:58.386 Is normally not expressed in melanocytes,

NOTE Confidence: 0.880226573846154

00:11:58.390 --> 00:12:00.582 but is increasingly demethylated

NOTE Confidence: 0.880226573846154

00:12:00.582 --> 00:12:03.322 and expressed from primary to

NOTE Confidence: 0.880226573846154

00:12:03.322 --> 00:12:04.630 metastatic Melanoma.

NOTE Confidence: 0.880226573846154

00:12:04.630 --> 00:12:06.280 Now of course the question is,

NOTE Confidence: 0.880226573846154

00:12:06.280 --> 00:12:08.255 is this isoform tool doing

NOTE Confidence: 0.880226573846154

00:12:08.255 --> 00:12:09.835 anything in Melanoma metastasis?

NOTE Confidence: 0.880226573846154

00:12:09.840 --> 00:12:12.571 And for that we had to move to cell

NOTE Confidence: 0.880226573846154

00:12:12.571 --> 00:12:14.650 lines and again we found this pattern

NOTE Confidence: 0.880226573846154

00:12:14.713 --> 00:12:17.425 in which melanocytes and some melanomas

NOTE Confidence: 0.880226573846154

00:12:17.425 --> 00:12:19.233 aliens had complete hypermethylation

NOTE Confidence: 0.880226573846154

00:12:19.293 --> 00:12:21.429 and lack of expression as you can see

NOTE Confidence: 0.880226573846154

00:12:21.429 --> 00:12:26.975 here on the right and you can also see.

NOTE Confidence: 0.880226573846154

00:12:26.980 --> 00:12:29.095 Hypomethylation in some of the

NOTE Confidence: 0.880226573846154

00:12:29.095 --> 00:12:31.210 cell lines and this corresponds

NOTE Confidence: 0.880226573846154

00:12:31.280 --> 00:12:33.429 to expression and the same can be

NOTE Confidence: 0.880226573846154

00:12:33.429 --> 00:12:35.578 seen at the level of protein.

NOTE Confidence: 0.880226573846154

00:12:35.580 --> 00:12:37.476 You can see isoform 2 expressed only in

NOTE Confidence: 0.880226573846154

00:12:37.476 --> 00:12:39.209 those cells that have hypomethylation.

NOTE Confidence: 0.880226573846154

00:12:39.210 --> 00:12:41.266 So this represents a good model to study

NOTE Confidence: 0.880226573846154

00:12:41.266 --> 00:12:43.448 loss of function and general function.

NOTE Confidence: 0.880226573846154

00:12:43.450 --> 00:12:49.470 But before I go into that you can see that.

NOTE Confidence: 0.880226573846154

00:12:49.470 --> 00:12:51.546 The methylation uh status can also

NOTE Confidence: 0.880226573846154

00:12:51.546 --> 00:12:53.880 be seen in short term culture.

NOTE Confidence: 0.880226573846154

00:12:53.880 --> 00:12:56.255 These are cells isolated from

NOTE Confidence: 0.880226573846154

00:12:56.255 --> 00:12:59.130 patients and again you have some,

NOTE Confidence: 0.880226573846154

00:12:59.130 --> 00:13:01.265 some of these short-term cultures

NOTE Confidence: 0.880226573846154

00:13:01.265 --> 00:13:02.973 have hypomethylation and some

NOTE Confidence: 0.880226573846154

00:13:02.973 --> 00:13:05.220 of them have hypermethylation.

NOTE Confidence: 0.880226573846154

00:13:05.220 --> 00:13:08.244 So this is not an artifact of invitro

NOTE Confidence: 0.880226573846154

00:13:08.250 --> 00:13:13.080 culture and it happens in cells derive

NOTE Confidence: 0.880226573846154

00:13:13.080 --> 00:13:15.786 very shortly from from patients.

NOTE Confidence: 0.880226573846154

00:13:15.786 --> 00:13:19.658 So if now we move into cells that.

NOTE Confidence: 0.880226573846154

00:13:19.658 --> 00:13:21.778 Have hypermethylation like mayor cells.

NOTE Confidence: 0.880226573846154

00:13:21.780 --> 00:13:24.510 If we treat them with editing agent

NOTE Confidence: 0.880226573846154

00:13:24.510 --> 00:13:28.266 like 5 ASA you can see that there is

NOTE Confidence: 0.880226573846154

00:13:28.266 --> 00:13:31.185 an induction of isoform 2 and this

NOTE Confidence: 0.880226573846154

00:13:31.185 --> 00:13:33.915 is seen also in short term cultures

NOTE Confidence: 0.675399618333333

00:13:33.920 --> 00:13:36.762 in which treatment with FAFSA results in

NOTE Confidence: 0.675399618333333

00:13:36.762 --> 00:13:38.745 induction of isophorone to expression

NOTE Confidence: 0.675399618333333

00:13:38.745 --> 00:13:40.839 with no change in isoform one.

NOTE Confidence: 0.675399618333333

00:13:40.840 --> 00:13:43.102 Now when we silence isoform to

NOTE Confidence: 0.675399618333333

00:13:43.102 --> 00:13:45.061 using the specific srnas against

NOTE Confidence: 0.675399618333333

00:13:45.061 --> 00:13:46.946 these isoform that don't have

NOTE Confidence: 0.675399618333333

00:13:46.946 --> 00:13:49.489 any impact on the other isoform.

NOTE Confidence: 0.675399618333333

00:13:49.490 --> 00:13:51.962 Initially we did not see any

NOTE Confidence: 0.675399618333333

00:13:51.962 --> 00:13:53.610 effect onto the proliferation,

NOTE Confidence: 0.675399618333333

00:13:53.610 --> 00:13:56.100 but we observed a clear decrease

NOTE Confidence: 0.675399618333333

00:13:56.100 --> 00:13:58.612 in the ability to form colonies

NOTE Confidence: 0.675399618333333

00:13:58.612 --> 00:14:01.668 in soft Agar or to form a sphere

NOTE Confidence: 0.675399618333333

00:14:01.670 --> 00:14:03.170 spheres upon single cells.

NOTE Confidence: 0.675399618333333

00:14:03.170 --> 00:14:05.045 So these are properties that

NOTE Confidence: 0.675399618333333

00:14:05.045 --> 00:14:07.107 are characteristic of metastatic

NOTE Confidence: 0.675399618333333

00:14:07.107 --> 00:14:08.982 cells and basically measure the

NOTE Confidence: 0.675399618333333

00:14:08.982 --> 00:14:11.545 ability of the cells to grow under

NOTE Confidence: 0.675399618333333

00:14:11.545 --> 00:14:13.027 very stressful conditions.

NOTE Confidence: 0.675399618333333

00:14:13.030 --> 00:14:14.290 Now if we overexpressed,

NOTE Confidence: 0.675399618333333

00:14:14.290 --> 00:14:16.890 sorry before we go into their expression.

NOTE Confidence: 0.675399618333333

00:14:16.890 --> 00:14:19.610 This is the experiment in in this case.

NOTE Confidence: 0.675399618333333

00:14:19.610 --> 00:14:21.932 We injected on the cancer cells

NOTE Confidence: 0.675399618333333

00:14:21.932 --> 00:14:23.480 intracardiac in a conventional

NOTE Confidence: 0.675399618333333

00:14:23.545 --> 00:14:25.303 in a model of metastasis that

NOTE Confidence: 0.675399618333333

00:14:25.303 --> 00:14:27.230 we use very often in the lab.

NOTE Confidence: 0.675399618333333

00:14:27.230 --> 00:14:29.710 And you can see that the silencing of

NOTE Confidence: 0.675399618333333

00:14:29.710 --> 00:14:31.985 isoform 2 between independent HR and

NOTE Confidence: 0.675399618333333

00:14:31.985 --> 00:14:34.848 I had a very significant decrease in

NOTE Confidence: 0.675399618333333

00:14:34.848 --> 00:14:36.938 metastatic potential in this model,

NOTE Confidence: 0.675399618333333

00:14:36.940 --> 00:14:39.136 which is quantified here on the

NOTE Confidence: 0.675399618333333

00:14:39.136 --> 00:14:40.882 right by bioluminescence as well

NOTE Confidence: 0.675399618333333

00:14:40.882 --> 00:14:42.522 as fluorescence intensity when

NOTE Confidence: 0.675399618333333

00:14:42.522 --> 00:14:44.418 we extract the organs.

NOTE Confidence: 0.675399618333333

00:14:44.420 --> 00:14:47.864 So it seems like isoform 2 silencing

NOTE Confidence: 0.675399618333333

00:14:47.864 --> 00:14:49.910 suppresses metastasis in these.

NOTE Confidence: 0.675399618333333

00:14:49.910 --> 00:14:52.444 A model and now we move into

NOTE Confidence: 0.675399618333333

00:14:52.444 --> 00:14:54.079 overexpression systems in which

NOTE Confidence: 0.675399618333333

00:14:54.079 --> 00:14:56.489 ectopic expression of isoform 2IN

NOTE Confidence: 0.675399618333333

00:14:56.489 --> 00:14:58.844 cells that have hypermethylation has

NOTE Confidence: 0.675399618333333

00:14:58.844 --> 00:15:00.968 no effect again into the culture,

NOTE Confidence: 0.675399618333333

00:15:00.970 --> 00:15:03.553 but it has a significant ability to

NOTE Confidence: 0.675399618333333

00:15:03.553 --> 00:15:05.841 increase the number of colonies and

NOTE Confidence: 0.675399618333333

00:15:05.841 --> 00:15:08.424 soft tagar as well as sphere formation.

NOTE Confidence: 0.675399618333333

00:15:08.430 --> 00:15:10.164 In vivo we injected these cells

NOTE Confidence: 0.675399618333333

00:15:10.164 --> 00:15:12.677 in the flank of the mice and then

NOTE Confidence: 0.675399618333333

00:15:12.677 --> 00:15:13.969 we did survival surgery.

NOTE Confidence: 0.675399618333333

00:15:13.970 --> 00:15:15.826 You can see that we cover two more

NOTE Confidence: 0.675399618333333

00:15:15.826 --> 00:15:17.506 area because there is always a lot

NOTE Confidence: 0.675399618333333

00:15:17.506 --> 00:15:19.019 of signal that comes even after

NOTE Confidence: 0.675399618333333

00:15:19.019 --> 00:15:19.910 you have resected.

NOTE Confidence: 0.675399618333333

00:15:19.910 --> 00:15:22.788 The majority of the tumor is the

NOTE Confidence: 0.675399618333333

00:15:22.788 --> 00:15:25.212 subcutaneous tumor and you can see

NOTE Confidence: 0.675399618333333

00:15:25.212 --> 00:15:27.565 that isotonic expression enhances

NOTE Confidence: 0.675399618333333

00:15:27.565 --> 00:15:29.605 metastasis both by bioluminescence

NOTE Confidence: 0.675399618333333

00:15:29.605 --> 00:15:32.215 as well as by histological analysis.

NOTE Confidence: 0.675399618333333

00:15:32.220 --> 00:15:34.182 We did this also by intracardiac

NOTE Confidence: 0.675399618333333

00:15:34.182 --> 00:15:35.932 injection and again we observed

NOTE Confidence: 0.675399618333333

00:15:35.932 --> 00:15:38.212 the same effect with an increase

NOTE Confidence: 0.675399618333333

00:15:38.212 --> 00:15:39.352 in metastasis overall.

NOTE Confidence: 0.675399618333333

00:15:39.360 --> 00:15:41.496 So it seems like ISO two,

NOTE Confidence: 0.675399618333333

00:15:41.500 --> 00:15:43.770 this particular truncated isoform of

NOTE Confidence: 0.675399618333333

00:15:43.770 --> 00:15:46.558 the orphan nuclear receptor and R2F2

NOTE Confidence: 0.675399618333333

00:15:46.558 --> 00:15:50.184 is able to promote metastasis and is.

NOTE Confidence: 0.675399618333333

00:15:50.190 --> 00:15:51.726 There's to be required in some

NOTE Confidence: 0.675399618333333

00:15:51.726 --> 00:15:53.477 models to in most of the models

NOTE Confidence: 0.675399618333333

00:15:53.477 --> 00:15:55.420 that we tried in lab and the paper,

NOTE Confidence: 0.675399618333333

00:15:55.420 --> 00:15:57.716 we have three or four different models.

NOTE Confidence: 0.675399618333333

00:15:57.720 --> 00:16:00.552 You can see a decrease in metastasis when

NOTE Confidence: 0.675399618333333

00:16:00.552 --> 00:16:02.839 you're silence or knockout this change.

NOTE Confidence: 0.675399618333333

00:16:02.840 --> 00:16:04.802 So now what are the programs

NOTE Confidence: 0.675399618333333

00:16:04.802 --> 00:16:06.840 that are modulated by isoform 2?

NOTE Confidence: 0.675399618333333

00:16:06.840 --> 00:16:09.536 We did RNA sequencing to get to this

NOTE Confidence: 0.675399618333333

00:16:09.536 --> 00:16:11.928 question and one of the pathways

NOTE Confidence: 0.675399618333333

00:16:11.928 --> 00:16:13.988 that was significantly modulated was

NOTE Confidence: 0.675399618333333

00:16:13.988 --> 00:16:16.540 EMT DPL to mesenchymal transition.

NOTE Confidence: 0.675399618333333

00:16:16.540 --> 00:16:18.794 Now we went on to demonstrate that

NOTE Confidence: 0.675399618333333

00:16:18.794 --> 00:16:21.724 a lot of the typical genes involved

NOTE Confidence: 0.675399618333333

00:16:21.724 --> 00:16:24.092 in the epithelial transition where

NOTE Confidence: 0.675399618333333

00:16:24.092 --> 00:16:26.472 silence in different cell lines

NOTE Confidence: 0.675399618333333

00:16:26.472 --> 00:16:28.852 when we deplete isoform 2.

NOTE Confidence: 0.675399618333333

00:16:28.852 --> 00:16:32.170 And here you can see a validation

NOTE Confidence: 0.675399618333333

00:16:32.268 --> 00:16:34.766 for snail which is reduced both

NOTE Confidence: 0.675399618333333

00:16:34.766 --> 00:16:36.861 transcriptionally and at the protein

NOTE Confidence: 0.675399618333333

00:16:36.861 --> 00:16:39.120 level when we silence ice form 2.

NOTE Confidence: 0.791361322727273

00:16:41.430 --> 00:16:43.040 Importantly, I as I mentioned

NOTE Confidence: 0.791361322727273

00:16:43.040 --> 00:16:45.030 at the beginning of my talk,

NOTE Confidence: 0.791361322727273

00:16:45.030 --> 00:16:47.658 now we have an understanding of

NOTE Confidence: 0.791361322727273

00:16:47.658 --> 00:16:48.972 intratumoral heterogeneity Melanoma

NOTE Confidence: 0.791361322727273

00:16:48.972 --> 00:16:51.326 and we have seen that most melanomas

NOTE Confidence: 0.791361322727273

00:16:51.326 --> 00:16:53.575 both in mouse and human display

NOTE Confidence: 0.791361322727273

00:16:53.575 --> 00:16:55.416 different transcriptional states,

NOTE Confidence: 0.791361322727273

00:16:55.416 --> 00:16:57.465 intermediate neural Crest

NOTE Confidence: 0.791361322727273

00:16:57.465 --> 00:17:00.880 like proliferation EMT or more

NOTE Confidence: 0.791361322727273

00:17:00.968 --> 00:17:03.530 melanocytic or differentiated.

NOTE Confidence: 0.791361322727273

00:17:03.530 --> 00:17:05.644 So we were curious to see whether

NOTE Confidence: 0.791361322727273

00:17:05.644 --> 00:17:08.204 NRF 2 and particularly the signature

NOTE Confidence: 0.791361322727273

00:17:08.204 --> 00:17:10.839 of genes modulated by isophorone.

NOTE Confidence: 0.791361322727273

00:17:10.840 --> 00:17:13.336 Who were particularly enriched in any

NOTE Confidence: 0.791361322727273

00:17:13.336 --> 00:17:15.542 of these transcriptional States and as

NOTE Confidence: 0.791361322727273

00:17:15.542 --> 00:17:18.252 you can see in this heat map, the EMT,

NOTE Confidence: 0.791361322727273

00:17:18.252 --> 00:17:20.296 in particular the transcriptional

NOTE Confidence: 0.791361322727273

00:17:20.296 --> 00:17:23.022 state that corresponds to an

NOTE Confidence: 0.791361322727273

00:17:23.022 --> 00:17:25.234 epithelial to mesenchymal transition

NOTE Confidence: 0.791361322727273

00:17:25.234 --> 00:17:28.553 seems to be the one that is more

NOTE Confidence: 0.791361322727273

00:17:28.553 --> 00:17:30.734 enriched in these two signature

NOTE Confidence: 0.791361322727273

00:17:30.734 --> 00:17:33.174 together with the neural signature.

NOTE Confidence: 0.791361322727273

00:17:33.180 --> 00:17:36.099 So this goes together with our findings

NOTE Confidence: 0.791361322727273

00:17:36.099 --> 00:17:40.762 that if two could be regulating the EMT.

NOTE Confidence: 0.791361322727273

00:17:40.762 --> 00:17:43.198 Um estate and in this additional

NOTE Confidence: 0.791361322727273

00:17:43.198 --> 00:17:46.267 analysis in which we we used scenic

NOTE Confidence: 0.791361322727273

00:17:46.267 --> 00:17:48.447 to understand the regulations the

NOTE Confidence: 0.791361322727273

00:17:48.531 --> 00:17:51.361 the basically the epigenetic and

NOTE Confidence: 0.791361322727273

00:17:51.361 --> 00:17:54.191 transcriptional factors that control each

NOTE Confidence: 0.791361322727273

00:17:54.200 --> 00:17:56.475 of these states melanocytic intermediate

NOTE Confidence: 0.791361322727273

00:17:56.475 --> 00:17:59.060 proliferative neural Crest like an EMT.

NOTE Confidence: 0.791361322727273

00:17:59.060 --> 00:18:01.388 You can see an I think it's more

NOTE Confidence: 0.791361322727273

00:18:01.388 --> 00:18:03.970 visible in the next slide that the

NOTE Confidence: 0.791361322727273

00:18:03.970 --> 00:18:05.900 top regulon controlling the event

NOTE Confidence: 0.791361322727273

00:18:05.968 --> 00:18:08.446 signature and this is a completely

NOTE Confidence: 0.791361322727273

00:18:08.446 --> 00:18:11.024 different analysis done in our mouse.

NOTE Confidence: 0.791361322727273

00:18:11.024 --> 00:18:14.258 Levels of Melanoma you can see that

NOTE Confidence: 0.791361322727273

00:18:14.258 --> 00:18:17.915 inner 2F2 is at the top is a top regulon.

NOTE Confidence: 0.791361322727273

00:18:17.920 --> 00:18:19.784 Controlling the EMT signature.

NOTE Confidence: 0.791361322727273

00:18:19.784 --> 00:18:23.086 So it seems like these transcriptional state

NOTE Confidence: 0.791361322727273

00:18:23.086 --> 00:18:25.246 of epithelium to mesenchymal transition

NOTE Confidence: 0.791361322727273

00:18:25.246 --> 00:18:29.186 seems to be mostly controlled by NF2 now.

NOTE Confidence: 0.791361322727273

00:18:29.186 --> 00:18:31.070 How this happens?

NOTE Confidence: 0.791361322727273

00:18:31.070 --> 00:18:34.141 Like I told you at the beginning that N2I2,

NOTE Confidence: 0.791361322727273

00:18:34.141 --> 00:18:38.069 another two ISO two is a truncated isoform.

NOTE Confidence: 0.791361322727273

00:18:38.070 --> 00:18:40.326 It lacks the DNA binding domain.

NOTE Confidence: 0.791361322727273

00:18:40.330 --> 00:18:43.147 So how is it possible that it has this

NOTE Confidence: 0.791361322727273

00:18:43.147 --> 00:18:45.330 capacity to control gene expression?

NOTE Confidence: 0.791361322727273

00:18:45.330 --> 00:18:47.913 Now when we started to work in this isoform,

NOTE Confidence: 0.791361322727273

00:18:47.920 --> 00:18:51.928 there were only two other papers that were

NOTE Confidence: 0.791361322727273

00:18:51.928 --> 00:18:54.288 studying alternative isoforms of two,

NOTE Confidence: 0.791361322727273

00:18:54.290 --> 00:18:58.124 all the papers that have been put out there.

NOTE Confidence: 0.791361322727273

00:18:58.130 --> 00:19:00.559 And study only the full length isoform.

NOTE Confidence: 0.791361322727273

00:19:00.560 --> 00:19:02.900 So there were two papers.

NOTE Confidence: 0.791361322727273

00:19:02.900 --> 00:19:06.740 One was suggesting that I2 acted as a

NOTE Confidence: 0.791361322727273

00:19:06.740 --> 00:19:09.957 dominant negative and was not removing

NOTE Confidence: 0.791361322727273

00:19:09.957 --> 00:19:13.203 or displacing isoform one from chromatin.

NOTE Confidence: 0.791361322727273

00:19:13.210 --> 00:19:15.317 With us another paper suggested the opposite

NOTE Confidence: 0.791361322727273

00:19:15.317 --> 00:19:17.818 that I saw two contributed to bind ISO,

NOTE Confidence: 0.791361322727273

00:19:17.820 --> 00:19:20.466 one to the chromatin and also what

NOTE Confidence: 0.791361322727273

00:19:20.466 --> 00:19:22.059 complicates more this interpretation

NOTE Confidence: 0.791361322727273

00:19:22.059 --> 00:19:24.796 of the results is the fact that

NOTE Confidence: 0.791361322727273

00:19:24.796 --> 00:19:27.594 isoform one has been or inner 2F2 has

NOTE Confidence: 0.791361322727273

00:19:27.594 --> 00:19:29.576 been described both as a receptor

NOTE Confidence: 0.791361322727273

00:19:29.576 --> 00:19:31.634 as a repressor of transcription as

NOTE Confidence: 0.791361322727273

00:19:31.634 --> 00:19:33.230 well as an activator.

NOTE Confidence: 0.791361322727273

00:19:33.230 --> 00:19:36.110 So we.

NOTE Confidence: 0.791361322727273

00:19:36.110 --> 00:19:37.976 It tested and the possibility that

NOTE Confidence: 0.791361322727273

00:19:37.976 --> 00:19:40.591 NRF 2 ISO two was interacting with

NOTE Confidence: 0.791361322727273

00:19:40.591 --> 00:19:42.761 isoform one and somehow modulating

NOTE Confidence: 0.791361322727273

00:19:42.761 --> 00:19:45.681 the ability of an artist to to bind

NOTE Confidence: 0.791361322727273

00:19:45.681 --> 00:19:47.359 chromatin and regulate gene expression.

NOTE Confidence: 0.791361322727273

00:19:47.359 --> 00:19:50.151 But for this to be true also from

NOTE Confidence: 0.791361322727273

00:19:50.151 --> 00:19:52.586 two had to have the capacity to

NOTE Confidence: 0.791361322727273

00:19:52.586 --> 00:19:55.068 bind to isoform one in the nucleus,

NOTE Confidence: 0.791361322727273

00:19:55.070 --> 00:19:59.370 and isoform 2 lacks the nuclear

NOTE Confidence: 0.791361322727273

00:19:59.370 --> 00:20:01.770 localization signal present in isoform one.

NOTE Confidence: 0.791361322727273

00:20:01.770 --> 00:20:03.918 It has an alternative nuclear localization

NOTE Confidence: 0.791361322727273

00:20:03.918 --> 00:20:06.110 signal that is much less potent.

NOTE Confidence: 0.791361322727273

00:20:06.110 --> 00:20:11.297 Thought we first show in a A

NOTE Confidence: 0.791361322727273

00:20:11.300 --> 00:20:13.180 fragmentation analysis that isoform

NOTE Confidence: 0.791361322727273

00:20:13.180 --> 00:20:16.000 2 is able to reach the

NOTE Confidence: 0.803509978181818

00:20:16.082 --> 00:20:18.635 nucleus. You can see there not

NOTE Confidence: 0.803509978181818

00:20:18.635 --> 00:20:20.266 only the cytoplasm, right?

NOTE Confidence: 0.803509978181818

00:20:20.266 --> 00:20:23.182 So this suggests the possibility that

NOTE Confidence: 0.803509978181818

00:20:23.182 --> 00:20:26.019 it can interact with iPhone one.

NOTE Confidence: 0.803509978181818

00:20:26.020 --> 00:20:27.754 Then we also did IP analysis

NOTE Confidence: 0.803509978181818

00:20:27.754 --> 00:20:29.692 where we show that isoform one

NOTE Confidence: 0.803509978181818

00:20:29.692 --> 00:20:32.191 can pull down isoform two with two

NOTE Confidence: 0.803509978181818

00:20:32.191 --> 00:20:33.694 independent antibodies and the

NOTE Confidence: 0.803509978181818

00:20:33.694 --> 00:20:36.295 opposite is also true, we can use.

NOTE Confidence: 0.803509978181818

00:20:36.295 --> 00:20:38.605 Mile a GFP pulled down because

NOTE Confidence: 0.803509978181818

00:20:38.605 --> 00:20:40.633 they unfortunately the endogenous

NOTE Confidence: 0.803509978181818

00:20:40.633 --> 00:20:43.747 IP for I2 doesn't work well.

NOTE Confidence: 0.803509978181818

00:20:43.750 --> 00:20:45.760 So we use the exogenous construct

NOTE Confidence: 0.803509978181818

00:20:45.760 --> 00:20:48.547 that has a GP fusion and so we

NOTE Confidence: 0.803509978181818

00:20:48.547 --> 00:20:50.599 can pull down again isoform too

NOTE Confidence: 0.803509978181818

00:20:50.679 --> 00:20:52.594 with the isoform 1 suggesting

NOTE Confidence: 0.803509978181818

00:20:52.594 --> 00:20:54.740 that it's two isoforms interact.

NOTE Confidence: 0.803509978181818

00:20:54.740 --> 00:20:58.700 And when we look now at Chief of

NOTE Confidence: 0.803509978181818

00:20:58.801 --> 00:21:02.588 isoform or chromatin IP of isoform one,

NOTE Confidence: 0.803509978181818

00:21:02.590 --> 00:21:05.014 we can see that indeed when we silence

NOTE Confidence: 0.803509978181818

00:21:05.014 --> 00:21:07.325 isoform 2 there is a group of peaks.

NOTE Confidence: 0.803509978181818

00:21:07.330 --> 00:21:09.640 Of isoform one that now lose

NOTE Confidence: 0.803509978181818

00:21:09.640 --> 00:21:11.180 binding of isoform one,

NOTE Confidence: 0.803509978181818

00:21:11.180 --> 00:21:13.791 and this is more dramatic in this

NOTE Confidence: 0.803509978181818

00:21:13.791 --> 00:21:16.179 group of targets is a little bit

NOTE Confidence: 0.803509978181818

00:21:16.179 --> 00:21:18.898 less prevalent in this subset of of

NOTE Confidence: 0.803509978181818

00:21:18.898 --> 00:21:21.800 pigs that are bound by isoform one.

NOTE Confidence: 0.803509978181818

00:21:21.800 --> 00:21:23.620 But we can also observe the opposite.

NOTE Confidence: 0.803509978181818

00:21:23.620 --> 00:21:26.020 We can see that in a group of peaks there

NOTE Confidence: 0.803509978181818

00:21:26.088 --> 00:21:28.377 is an increased binding of isoform one.

NOTE Confidence: 0.803509978181818

00:21:28.380 --> 00:21:29.840 When I do is gone.

NOTE Confidence: 0.803509978181818

00:21:29.840 --> 00:21:32.130 So definitely the interaction between

NOTE Confidence: 0.803509978181818

00:21:32.130 --> 00:21:34.420 these two isoforms is complex.

NOTE Confidence: 0.803509978181818

00:21:34.420 --> 00:21:37.759 We know that the chip works because.

NOTE Confidence: 0.803509978181818

00:21:37.760 --> 00:21:40.952 Um and active two is their most

NOTE Confidence: 0.803509978181818

00:21:40.952 --> 00:21:42.320 significantly enriched transcription

NOTE Confidence: 0.803509978181818

00:21:42.397 --> 00:21:45.097 factor in these pics together with

NOTE Confidence: 0.803509978181818

00:21:45.097 --> 00:21:46.897 some other transcription factors

NOTE Confidence: 0.803509978181818

00:21:46.966 --> 00:21:48.711 which are we're also interested

NOTE Confidence: 0.803509978181818

00:21:48.711 --> 00:21:50.830 in in looking at the potential

NOTE Confidence: 0.803509978181818

00:21:50.830 --> 00:21:52.680 interaction of MR2 with those.

NOTE Confidence: 0.803509978181818

00:21:52.680 --> 00:21:56.632 So we can see that N22ISO2 modulates

NOTE Confidence: 0.803509978181818

00:21:56.632 --> 00:21:59.302 the binding capacity of the chromatin,

NOTE Confidence: 0.803509978181818

00:21:59.302 --> 00:22:02.675 but it not only in a way seems to be

NOTE Confidence: 0.803509978181818

00:22:02.675 --> 00:22:05.212 in a in a gene specific manner and

NOTE Confidence: 0.803509978181818

00:22:05.212 --> 00:22:07.810 when we integrate the cheap data.

NOTE Confidence: 0.803509978181818

00:22:07.810 --> 00:22:10.510 Our transcriptomic sequencing of cells

NOTE Confidence: 0.803509978181818

00:22:10.510 --> 00:22:13.969 in which we have depleted ISO two,

NOTE Confidence: 0.803509978181818

00:22:13.970 --> 00:22:16.904 we found that the majority of the genes are.

NOTE Confidence: 0.803509978181818

00:22:16.910 --> 00:22:19.150 A significant portion of the genes that

NOTE Confidence: 0.803509978181818

00:22:19.150 --> 00:22:20.988 are downregulated when we sell in size.

NOTE Confidence: 0.803509978181818

00:22:20.990 --> 00:22:24.094 Or two that are targets for an R2F2

NOTE Confidence: 0.803509978181818

00:22:24.094 --> 00:22:27.466 are genes that are involved in the EMT,

NOTE Confidence: 0.803509978181818

00:22:27.470 --> 00:22:30.410 snail, twist, Peter two, etc.

NOTE Confidence: 0.803509978181818

00:22:30.410 --> 00:22:34.478 So it seems like a lot of the NR2ISO1

NOTE Confidence: 0.803509978181818

00:22:34.478 --> 00:22:37.766 targets are actually in the direct.

NOTE Confidence: 0.803509978181818

00:22:37.770 --> 00:22:38.626 Same teachings.

NOTE Confidence: 0.803509978181818

00:22:38.626 --> 00:22:41.622 The opposite is that when we see

NOTE Confidence: 0.803509978181818

00:22:41.622 --> 00:22:44.608 look at the genes that are now

NOTE Confidence: 0.803509978181818

00:22:44.608 --> 00:22:46.256 upregulated by isoform 2,

NOTE Confidence: 0.803509978181818

00:22:46.260 --> 00:22:48.774 the majority of those genes are

NOTE Confidence: 0.803509978181818

00:22:48.774 --> 00:22:50.031 involving differentiation and

NOTE Confidence: 0.803509978181818

00:22:50.031 --> 00:22:51.590 pigmentation such as tyrosinase,

NOTE Confidence: 0.803509978181818

00:22:51.590 --> 00:22:52.646 DCT, etcetera.

NOTE Confidence: 0.803509978181818

00:22:52.646 --> 00:22:55.286 So with all of these,

NOTE Confidence: 0.803509978181818

00:22:55.290 --> 00:22:57.558 and still with many questions still open,

NOTE Confidence: 0.803509978181818

00:22:57.560 --> 00:22:59.590 we propose this modeling which

NOTE Confidence: 0.803509978181818

00:22:59.590 --> 00:23:02.232 in primary tumors isoform 2 is

NOTE Confidence: 0.803509978181818

00:23:02.232 --> 00:23:03.858 hypermethylated and silence.

NOTE Confidence: 0.803509978181818

00:23:03.860 --> 00:23:07.124 So the dimers of isoform 1 prevail over

NOTE Confidence: 0.803509978181818

00:23:07.124 --> 00:23:09.975 the heterodimers of isoform 2 and isoform 1,

NOTE Confidence: 0.803509978181818

00:23:09.980 --> 00:23:13.179 whereas in metastasis we see a displacement

NOTE Confidence: 0.803509978181818

00:23:13.179 --> 00:23:15.880 of the equilibrium towards the home,

NOTE Confidence: 0.803509978181818

00:23:15.880 --> 00:23:16.602 the heterodimer.

NOTE Confidence: 0.803509978181818

00:23:16.602 --> 00:23:16.963 Sorry,

NOTE Confidence: 0.803509978181818

00:23:16.963 --> 00:23:19.129 because now isoform 2 is present

NOTE Confidence: 0.803509978181818

00:23:19.129 --> 00:23:21.424 and is this heterodimer that allows

NOTE Confidence: 0.803509978181818

00:23:21.424 --> 00:23:23.600 the expression of neural Crest and.

NOTE Confidence: 0.803509978181818

00:23:23.600 --> 00:23:26.680 Empty genes such as twisted slag etcetera.

NOTE Confidence: 0.803509978181818

00:23:26.680 --> 00:23:29.808 So what we are now in the process

NOTE Confidence: 0.803509978181818

00:23:29.808 --> 00:23:31.913 of understanding is how these

NOTE Confidence: 0.803509978181818

00:23:31.913 --> 00:23:33.983 heterodimer is able to activate

NOTE Confidence: 0.803509978181818

00:23:33.983 --> 00:23:36.617 this EMT genes and we think that

NOTE Confidence: 0.803509978181818

00:23:36.617 --> 00:23:38.337 in part could be due

NOTE Confidence: 0.78339154368421

00:23:38.340 --> 00:23:41.220 to the interaction with third parties

NOTE Confidence: 0.78339154368421

00:23:41.220 --> 00:23:43.140 like additional transcription factors

NOTE Confidence: 0.78339154368421

00:23:43.207 --> 00:23:44.915 that are specifically attracted

NOTE Confidence: 0.78339154368421

00:23:44.915 --> 00:23:47.050 to the complex like isoform.

NOTE Confidence: 0.78339154368421

00:23:47.050 --> 00:23:49.466 So we are doing our time and other

NOTE Confidence: 0.78339154368421

00:23:49.466 --> 00:23:51.793 techniques to understand what are the

NOTE Confidence: 0.78339154368421

00:23:51.793 --> 00:23:53.840 complexes that are attracted in bound

NOTE Confidence: 0.78339154368421

00:23:53.840 --> 00:23:56.442 to the chromatin where we have the

NOTE Confidence: 0.78339154368421

00:23:56.442 --> 00:23:58.250 homodimers versus the heterodimers.

NOTE Confidence: 0.78339154368421

00:23:58.250 --> 00:24:00.638 Now moving on into the second

NOTE Confidence: 0.78339154368421

00:24:00.638 --> 00:24:02.230 part of my talk,

NOTE Confidence: 0.78339154368421

00:24:02.230 --> 00:24:04.478 I don't think I have to repeat the

NOTE Confidence: 0.78339154368421

00:24:04.478 --> 00:24:05.736 conclusions because that's basically

NOTE Confidence: 0.78339154368421

00:24:05.736 --> 00:24:07.962 the summary that I just have provided.

NOTE Confidence: 0.78339154368421

00:24:07.970 --> 00:24:09.950 So in the interest of time,

NOTE Confidence: 0.78339154368421

00:24:09.950 --> 00:24:12.620 I will move to the second part of the story

NOTE Confidence: 0.78339154368421

00:24:12.689 --> 00:24:15.572 in which we have focused on brain metastasis.

NOTE Confidence: 0.78339154368421

00:24:15.572 --> 00:24:19.779 This was the work mostly done by.

NOTE Confidence: 0.78339154368421

00:24:19.780 --> 00:24:21.475 I actually incorrectly stated PhD

NOTE Confidence: 0.78339154368421

00:24:21.475 --> 00:24:24.239 is an MD PhD from our laboratory,

NOTE Confidence: 0.78339154368421

00:24:24.240 --> 00:24:28.140 Kevin Kleffman that is now a.

NOTE Confidence: 0.78339154368421

00:24:28.140 --> 00:24:31.332 Accident at mass general.

NOTE Confidence: 0.78339154368421

00:24:31.332 --> 00:24:34.218 So we of course are interested in

NOTE Confidence: 0.78339154368421

00:24:34.218 --> 00:24:36.007 brain metastasis because it's an

NOTE Confidence: 0.78339154368421

00:24:36.007 --> 00:24:37.697 important and met clinical need.

NOTE Confidence: 0.78339154368421

00:24:37.700 --> 00:24:40.715 And although these tumors can

NOTE Confidence: 0.78339154368421

00:24:40.715 --> 00:24:42.524 respond to immunotherapy,

NOTE Confidence: 0.78339154368421

00:24:42.530 --> 00:24:44.714 we know that these responses are mostly

NOTE Confidence: 0.78339154368421

00:24:44.714 --> 00:24:46.828 seen in patients that are asymptomatic

NOTE Confidence: 0.78339154368421

00:24:46.828 --> 00:24:49.066 and in the symptomatic patients the

NOTE Confidence: 0.78339154368421

00:24:49.066 --> 00:24:51.086 responses are much poorer and these

NOTE Confidence: 0.78339154368421

00:24:51.086 --> 00:24:53.236 patients have overall very poor survival.

NOTE Confidence: 0.78339154368421

00:24:53.236 --> 00:24:56.016 So this remains very important

NOTE Confidence: 0.78339154368421

00:24:56.016 --> 00:24:58.240 clinical question and definitely.

NOTE Confidence: 0.78339154368421

00:24:58.240 --> 00:25:00.100 Fascinating biological, um.

NOTE Confidence: 0.78339154368421

00:25:00.100 --> 00:25:00.720 Uh,

NOTE Confidence: 0.78339154368421

00:25:00.720 --> 00:25:01.340 question.

NOTE Confidence: 0.78339154368421

00:25:01.340 --> 00:25:03.746 How Melanoma cells adapt to the

NOTE Confidence: 0.78339154368421

00:25:03.746 --> 00:25:05.350 brain microenvironment and why

NOTE Confidence: 0.78339154368421

00:25:05.420 --> 00:25:07.358 they have such a profound tropism

NOTE Confidence: 0.78339154368421

00:25:07.358 --> 00:25:09.646 for the brain is still something

NOTE Confidence: 0.78339154368421

00:25:09.646 --> 00:25:11.956 that we don't entirely understand.

NOTE Confidence: 0.78339154368421

00:25:11.960 --> 00:25:14.634 So uh in collaboration with the management,

NOTE Confidence: 0.78339154368421

00:25:14.640 --> 00:25:17.160 the director of the Melanoma program at NYU,

NOTE Confidence: 0.78339154368421

00:25:17.160 --> 00:25:19.448 we develop Melanoma short-term

NOTE Confidence: 0.78339154368421

00:25:19.448 --> 00:25:21.580 cultures that in some cases are

NOTE Confidence: 0.78339154368421

00:25:21.580 --> 00:25:23.140 derived from the same patients.

NOTE Confidence: 0.78339154368421

00:25:23.140 --> 00:25:25.327 So we can in some of the cases we

NOTE Confidence: 0.78339154368421

00:25:25.327 --> 00:25:27.463 were able to obtain a short-term

NOTE Confidence: 0.78339154368421

00:25:27.463 --> 00:25:29.288 cultures derived from a brain

NOTE Confidence: 0.78339154368421

00:25:29.353 --> 00:25:31.305 metastasis and extracranial metastasis

NOTE Confidence: 0.78339154368421

00:25:31.305 --> 00:25:33.257 from the same patient.

NOTE Confidence: 0.78339154368421

00:25:33.260 --> 00:25:35.294 And again this is a very

NOTE Confidence: 0.78339154368421

00:25:35.294 --> 00:25:36.650 difficult comparison to make,

NOTE Confidence: 0.78339154368421

00:25:36.650 --> 00:25:38.690 but we think it's very useful

NOTE Confidence: 0.78339154368421

00:25:38.690 --> 00:25:41.019 because it reduces some of the

NOTE Confidence: 0.78339154368421

00:25:41.019 --> 00:25:42.366 inter tumoral heterogeneity.

NOTE Confidence: 0.78339154368421

00:25:42.370 --> 00:25:44.465 As we observe what genetically

NOTE Confidence: 0.78339154368421

00:25:44.465 --> 00:25:46.560 and transcriptionally and what was

NOTE Confidence: 0.78339154368421

00:25:46.630 --> 00:25:48.933 really exciting to us is that when

NOTE Confidence: 0.78339154368421

00:25:48.933 --> 00:25:51.069 we labeled these cells with GFP

NOTE Confidence: 0.78339154368421

00:25:51.069 --> 00:25:53.235 luciferase and inject them back into

NOTE Confidence: 0.78339154368421

00:25:53.235 --> 00:25:55.445 mice with intracardiac injections,

NOTE Confidence: 0.78339154368421

00:25:55.445 --> 00:25:58.902 we observed that that metastatic the

NOTE Confidence: 0.78339154368421

00:25:58.902 --> 00:26:01.194 the the short-term culture that has

NOTE Confidence: 0.78339154368421

00:26:01.194 --> 00:26:04.652 been derived from the brain has in

NOTE Confidence: 0.78339154368421

00:26:04.652 --> 00:26:06.700 general more metastatic potential

NOTE Confidence: 0.78339154368421

00:26:06.700 --> 00:26:08.488 than the one that was derived

NOTE Confidence: 0.78339154368421

00:26:08.488 --> 00:26:09.680 from an extracranial metastasis.

NOTE Confidence: 0.78339154368421

00:26:09.680 --> 00:26:11.619 This is represented here on the right,

NOTE Confidence: 0.78339154368421

00:26:11.620 --> 00:26:12.829 but more specifically.

NOTE Confidence: 0.78339154368421

00:26:12.829 --> 00:26:15.650 The one that derives from the brain

NOTE Confidence: 0.78339154368421

00:26:15.727 --> 00:26:18.310 has more ability to metastasize to the

NOTE Confidence: 0.78339154368421

00:26:18.310 --> 00:26:21.017 brain and this is measured here as a

NOTE Confidence: 0.78339154368421

00:26:21.017 --> 00:26:22.834 ratio of brain to body luminescence.

NOTE Confidence: 0.78339154368421

00:26:22.834 --> 00:26:25.390 So it seems like this is a short term.

NOTE Confidence: 0.78339154368421

00:26:25.390 --> 00:26:28.570 Cultures retain some of the properties,

NOTE Confidence: 0.78339154368421

00:26:28.570 --> 00:26:30.970 some of the ability that they

NOTE Confidence: 0.78339154368421

00:26:30.970 --> 00:26:33.270 had gained in in people,

NOTE Confidence: 0.78339154368421

00:26:33.270 --> 00:26:35.979 in the patients of colonizing the brain

NOTE Confidence: 0.78339154368421

00:26:35.979 --> 00:26:38.261 and therefore could be a good model

NOTE Confidence: 0.78339154368421

00:26:38.261 --> 00:26:40.482 to study brain specific adaptations.

NOTE Confidence: 0.78339154368421

00:26:40.482 --> 00:26:43.866 So we went on to conduct.

NOTE Confidence: 0.78339154368421

00:26:43.870 --> 00:26:46.922 For the Omega analysis of these short-term

NOTE Confidence: 0.78339154368421

00:26:46.922 --> 00:26:49.490 cultures, in total we profile 25,

NOTE Confidence: 0.78339154368421

00:26:49.490 --> 00:26:52.080 approximately 12 and 13 brain

NOTE Confidence: 0.78339154368421

00:26:52.080 --> 00:26:54.152 metastasis versus second metastasis.

NOTE Confidence: 0.78339154368421

00:26:54.160 --> 00:26:55.700 Only a few of them, of course,

NOTE Confidence: 0.78339154368421

00:26:55.700 --> 00:26:56.200 were pair,

NOTE Confidence: 0.78339154368421

00:26:56.200 --> 00:26:57.700 the rest were unfair and the

NOTE Confidence: 0.752316441666667

00:26:57.754 --> 00:27:00.194 idea was to try to identify proteins that

NOTE Confidence: 0.752316441666667

00:27:00.194 --> 00:27:02.010 were differentially expressed in the brain.

NOTE Confidence: 0.752316441666667

00:27:02.010 --> 00:27:04.615 Metastasis input could be potential

NOTE Confidence: 0.752316441666667

00:27:04.615 --> 00:27:06.699 drivers of the adaptation.

NOTE Confidence: 0.752316441666667

00:27:06.700 --> 00:27:08.796 The first reply is that we found when

NOTE Confidence: 0.752316441666667

00:27:08.796 --> 00:27:10.963 analyzing the data is that the majority

NOTE Confidence: 0.752316441666667

00:27:10.963 --> 00:27:12.553 of the proteins found differentially

NOTE Confidence: 0.752316441666667

00:27:12.612 --> 00:27:14.360 expressed where proteins involved.

NOTE Confidence: 0.752316441666667

00:27:14.360 --> 00:27:15.770 Being neurodegenerative disorders

NOTE Confidence: 0.752316441666667

00:27:15.770 --> 00:27:17.811 such as Parkinson's, Alzheimer's,

NOTE Confidence: 0.752316441666667

00:27:17.811 --> 00:27:21.597 Oxfords and this was rewarding because

NOTE Confidence: 0.752316441666667

00:27:21.597 --> 00:27:25.269 our collaborator in at in the Anderson,

NOTE Confidence: 0.752316441666667

00:27:25.270 --> 00:27:27.496 Mike Davis had previously found that

NOTE Confidence: 0.752316441666667

00:27:27.496 --> 00:27:30.924 a lot of the proteins involved in

NOTE Confidence: 0.752316441666667

00:27:30.924 --> 00:27:33.408 different study transcript transcriptional

NOTE Confidence: 0.752316441666667

00:27:33.408 --> 00:27:36.308 profiling of brain metastases wouldn't

NOTE Confidence: 0.752316441666667

00:27:36.308 --> 00:27:39.170 reach in Oxford or proteins involved

NOTE Confidence: 0.752316441666667

00:27:39.170 --> 00:27:41.447 in the respiratory chain mitochondria

NOTE Confidence: 0.752316441666667

00:27:41.447 --> 00:27:44.520 and so this was confirmed in our.

NOTE Confidence: 0.752316441666667

00:27:44.520 --> 00:27:44.958 Plans.

NOTE Confidence: 0.752316441666667

00:27:44.958 --> 00:27:47.586 We found that short-term cultures of

NOTE Confidence: 0.752316441666667

00:27:47.586 --> 00:27:50.550 brain metastasis had elongated mitochondria,

NOTE Confidence: 0.752316441666667

00:27:50.550 --> 00:27:53.532 and they also had increased oxygen

NOTE Confidence: 0.752316441666667

00:27:53.532 --> 00:27:57.130 consumption rate in this seahorse analysis.

NOTE Confidence: 0.752316441666667

00:27:57.130 --> 00:28:00.433 But what we focus on was in the differential

NOTE Confidence: 0.752316441666667

00:28:00.433 --> 00:28:02.880 expression of proteins involved in

NOTE Confidence: 0.752316441666667

00:28:02.880 --> 00:28:04.884 Alzheimer's and Parkinson's disease.

NOTE Confidence: 0.752316441666667

00:28:04.890 --> 00:28:05.716 In particular,

NOTE Confidence: 0.752316441666667

00:28:05.716 --> 00:28:08.607 we landed for this study on AP.

NOTE Confidence: 0.752316441666667

00:28:08.610 --> 00:28:11.315 The amyloid processing protein there

NOTE Confidence: 0.752316441666667

00:28:11.315 --> 00:28:14.540 is a precursor for amyloid beta.

NOTE Confidence: 0.752316441666667

00:28:14.540 --> 00:28:17.012 It was induced in pre metastasis

NOTE Confidence: 0.752316441666667

00:28:17.012 --> 00:28:18.246 compared to metastasis,

NOTE Confidence: 0.752316441666667

00:28:18.246 --> 00:28:20.276 but not only AP itself,

NOTE Confidence: 0.752316441666667

00:28:20.280 --> 00:28:23.262 but the proteins that leave AP into

NOTE Confidence: 0.752316441666667

00:28:23.262 --> 00:28:25.782 amyloid beta like beta secretase

NOTE Confidence: 0.752316441666667

00:28:25.782 --> 00:28:27.519 or present presently.

NOTE Confidence: 0.752316441666667

00:28:27.520 --> 00:28:29.389 So we decided to modulate the loss

NOTE Confidence: 0.752316441666667

00:28:29.389 --> 00:28:32.404 of a P to see if it had an effect

NOTE Confidence: 0.752316441666667

00:28:32.404 --> 00:28:33.322 on brain metastasis.

NOTE Confidence: 0.752316441666667

00:28:33.330 --> 00:28:36.700 And initially we found that

NOTE Confidence: 0.752316441666667

00:28:36.700 --> 00:28:39.064 sorry went too fast.

NOTE Confidence: 0.752316441666667

00:28:39.064 --> 00:28:41.388 We found that supernatants

NOTE Confidence: 0.752316441666667

00:28:41.388 --> 00:28:43.580 of brain metastasis, Dr.

NOTE Confidence: 0.752316441666667

00:28:43.580 --> 00:28:44.400 short-term cultures,

NOTE Confidence: 0.752316441666667

00:28:44.400 --> 00:28:46.860 had higher secretion of family beta

NOTE Confidence: 0.752316441666667

00:28:46.860 --> 00:28:48.824 compared to the extracranial brain

NOTE Confidence: 0.752316441666667

00:28:48.824 --> 00:28:51.351 metastasis not only in our own hands,

NOTE Confidence: 0.752316441666667

00:28:51.360 --> 00:28:54.587 but also in short term cultures obtained

NOTE Confidence: 0.752316441666667

00:28:54.587 --> 00:28:57.410 from collaborators that we study institute.

NOTE Confidence: 0.752316441666667

00:28:57.410 --> 00:28:57.803 Silence.

NOTE Confidence: 0.752316441666667

00:28:57.803 --> 00:29:00.161 AP Again, we found no effect

NOTE Confidence: 0.752316441666667

00:29:00.161 --> 00:29:01.960 in proliferation in culture,

NOTE Confidence: 0.752316441666667

00:29:01.960 --> 00:29:04.678 but when we inject these cells

NOTE Confidence: 0.752316441666667

00:29:04.678 --> 00:29:06.490 intracardiac in immunodeficient mice,

NOTE Confidence: 0.752316441666667

00:29:06.490 --> 00:29:08.520 we observed this reduction of

NOTE Confidence: 0.752316441666667

00:29:08.520 --> 00:29:10.550 the brain to body ratio,

NOTE Confidence: 0.752316441666667

00:29:10.550 --> 00:29:13.042 suggesting that the loss of AP was

NOTE Confidence: 0.752316441666667

00:29:13.042 --> 00:29:14.790 particularly affecting brain metastasis.

NOTE Confidence: 0.752316441666667

00:29:14.790 --> 00:29:17.610 This was confirmed by histological analysis.

NOTE Confidence: 0.752316441666667

00:29:17.610 --> 00:29:19.810 This is entertaining of NUMA,

NOTE Confidence: 0.752316441666667

00:29:19.810 --> 00:29:21.520 which is a human marker,

NOTE Confidence: 0.752316441666667

00:29:21.520 --> 00:29:24.650 and therefore it can perfectly

NOTE Confidence: 0.752316441666667

00:29:24.650 --> 00:29:27.420 mark the cells that are.

NOTE Confidence: 0.752316441666667

00:29:27.420 --> 00:29:29.534 The deriving from the from the scenography,

NOTE Confidence: 0.752316441666667

00:29:29.540 --> 00:29:32.396 from the implant and you can see that

NOTE Confidence: 0.752316441666667

00:29:32.396 --> 00:29:35.016 there was a very significant reduction

NOTE Confidence: 0.752316441666667

00:29:35.016 --> 00:29:38.669 of brain and one positive cells but no

NOTE Confidence: 0.752316441666667

00:29:38.669 --> 00:29:41.177 effect on kidney or liver metastasis.

NOTE Confidence: 0.752316441666667

00:29:41.180 --> 00:29:45.948 We did ex vivo imaging MRI to conduct

NOTE Confidence: 0.752316441666667

00:29:45.948 --> 00:29:49.163 volumetric analysis that show us that

NOTE Confidence: 0.752316441666667

00:29:49.163 --> 00:29:51.950 we're not only less perimeter studies

NOTE Confidence: 0.752316441666667

00:29:51.950 --> 00:29:54.650 but also smaller brain metastasis and

NOTE Confidence: 0.752316441666667

00:29:54.650 --> 00:29:57.459 of course we show that this effect.

NOTE Confidence: 0.752316441666667

00:29:57.460 --> 00:29:58.570 Happens, you know other models,

NOTE Confidence: 0.752316441666667

00:29:58.570 --> 00:30:01.146 this is not a brain Tropic Melanoma cell

NOTE Confidence: 0.752316441666667

00:30:01.146 --> 00:30:03.985 line type one and we use national approach,

NOTE Confidence: 0.752316441666667

00:30:03.990 --> 00:30:06.125 in this case a crisper cast 9,

NOTE Confidence: 0.752316441666667

00:30:06.130 --> 00:30:08.890 to show again a reduction in

NOTE Confidence: 0.752316441666667

00:30:08.890 --> 00:30:09.810 brain metastasis.

NOTE Confidence: 0.752316441666667

00:30:09.810 --> 00:30:12.294 But this of course open a lot of questions.

NOTE Confidence: 0.752316441666667

00:30:12.300 --> 00:30:15.807 The first one is which step offering

NOTE Confidence: 0.752316441666667

00:30:15.807 --> 00:30:17.680 metastasis is the one in which

NOTE Confidence: 0.752316441666667

00:30:17.680 --> 00:30:19.775 is particularly required for the

NOTE Confidence: 0.752316441666667

00:30:19.775 --> 00:30:21.870 adaptation and the the arrival

NOTE Confidence: 0.752316441666667

00:30:21.944 --> 00:30:24.008 of Melanoma cells to the brain.

NOTE Confidence: 0.752316441666667

00:30:24.010 --> 00:30:26.439 So as you know brain metas is

NOTE Confidence: 0.752316441666667

00:30:26.439 --> 00:30:27.480 a complex process.

NOTE Confidence: 0.752316441666667

00:30:27.480 --> 00:30:30.704 It involves multiple steps,

NOTE Confidence: 0.752316441666667

00:30:30.704 --> 00:30:33.460 the intravasation from the tumor

NOTE Confidence: 0.752316441666667

00:30:33.460 --> 00:30:35.740 into the first into the stroma,

NOTE Confidence: 0.679529493333333

00:30:35.740 --> 00:30:37.960 then the intravasation into the vasculature,

NOTE Confidence: 0.679529493333333

00:30:37.960 --> 00:30:38.782 survival in circulation,

NOTE Confidence: 0.679529493333333

00:30:38.782 --> 00:30:41.330 and when the cells arrive to the distal site,

NOTE Confidence: 0.679529493333333

00:30:41.330 --> 00:30:42.480 in this case the brain,

NOTE Confidence: 0.679529493333333

00:30:42.480 --> 00:30:44.340 they have to again extravasate.

NOTE Confidence: 0.679529493333333

00:30:44.340 --> 00:30:46.182 Many of these cells will undergo

NOTE Confidence: 0.679529493333333

00:30:46.182 --> 00:30:47.940 cell death or become dormant,

NOTE Confidence: 0.679529493333333

00:30:47.940 --> 00:30:51.425 but those that are able to proliferate

NOTE Confidence: 0.679529493333333

00:30:51.425 --> 00:30:53.340 and survive in this environment will

NOTE Confidence: 0.679529493333333

00:30:53.340 --> 00:30:54.925 form micro and macro metastasis.

NOTE Confidence: 0.679529493333333

00:30:54.930 --> 00:30:58.276 So when was abeta required for this?

NOTE Confidence: 0.679529493333333

00:30:58.280 --> 00:31:00.098 For this process,

NOTE Confidence: 0.679529493333333

00:31:00.098 --> 00:31:03.046 so Kevin embark himself in really

NOTE Confidence: 0.679529493333333

00:31:03.046 --> 00:31:05.650 a difficult task of monitoring the

NOTE Confidence: 0.679529493333333

00:31:05.723 --> 00:31:08.213 kinetics of cancer cells injected

NOTE Confidence: 0.679529493333333

00:31:08.213 --> 00:31:10.205 intracardiac in these mice.

NOTE Confidence: 0.679529493333333

00:31:10.210 --> 00:31:13.318 So he did brain slice immunofluorescence

NOTE Confidence: 0.679529493333333

00:31:13.320 --> 00:31:15.480 and a lot of confocal microscopy

NOTE Confidence: 0.679529493333333

00:31:15.480 --> 00:31:17.689 and was tracking this GFP positive

NOTE Confidence: 0.679529493333333

00:31:17.689 --> 00:31:19.789 cells in the brain over days.

NOTE Confidence: 0.679529493333333

00:31:19.790 --> 00:31:24.155 So you can see that just one day after.

NOTE Confidence: 0.679529493333333

00:31:24.160 --> 00:31:25.184 In the cardiac injection,

NOTE Confidence: 0.679529493333333

00:31:25.184 --> 00:31:27.340 these cells are stuck in the vasculature.

NOTE Confidence: 0.679529493333333

00:31:27.340 --> 00:31:28.395 They even have the shape

NOTE Confidence: 0.679529493333333

00:31:28.395 --> 00:31:29.239 of the blood vessels.

NOTE Confidence: 0.679529493333333

00:31:29.240 --> 00:31:30.940 This is a tomato, tomato,

NOTE Confidence: 0.679529493333333

00:31:30.940 --> 00:31:33.210 lectin marking the the blood

NOTE Confidence: 0.679529493333333

00:31:33.210 --> 00:31:35.480 vessels you can see there.

NOTE Confidence: 0.679529493333333

00:31:35.480 --> 00:31:38.360 At day three they start extravasation,

NOTE Confidence: 0.679529493333333

00:31:38.360 --> 00:31:41.258 they start getting out of the vasculature.

NOTE Confidence: 0.679529493333333

00:31:41.260 --> 00:31:42.500 Some of these cells die.

NOTE Confidence: 0.679529493333333

00:31:42.500 --> 00:31:44.844 A lot of these cells die in the

NOTE Confidence: 0.679529493333333

00:31:44.844 --> 00:31:46.983 blood vessels or outside when they

NOTE Confidence: 0.679529493333333

00:31:46.983 --> 00:31:49.209 are able to extravasate as sustained

NOTE Confidence: 0.679529493333333

00:31:49.280 --> 00:31:51.268 by Clifton Space Stream and you

NOTE Confidence: 0.679529493333333

00:31:51.268 --> 00:31:52.976 can see that later on they start

NOTE Confidence: 0.679529493333333

00:31:52.976 --> 00:31:54.569 crawling through the blood vessels.

NOTE Confidence: 0.679529493333333

00:31:54.570 --> 00:31:57.510 In these process called Vascular Co option,

NOTE Confidence: 0.679529493333333

00:31:57.510 --> 00:31:59.856 they can later on form micrometastasis

NOTE Confidence: 0.679529493333333

00:31:59.856 --> 00:32:03.230 that day 14 and finally micrometastasis.

NOTE Confidence: 0.679529493333333

00:32:03.230 --> 00:32:05.660 So when you compare the kinetics

NOTE Confidence: 0.679529493333333

00:32:05.660 --> 00:32:08.045 of control cells here in the

NOTE Confidence: 0.679529493333333

00:32:08.045 --> 00:32:10.439 black line to those that lack app,

NOTE Confidence: 0.679529493333333

00:32:10.440 --> 00:32:12.526 you can see that the first steps

NOTE Confidence: 0.679529493333333

00:32:12.526 --> 00:32:14.670 of the kinetics are really similar.

NOTE Confidence: 0.679529493333333

00:32:14.670 --> 00:32:17.310 There is this big crisis where most of

NOTE Confidence: 0.679529493333333

00:32:17.310 --> 00:32:19.898 the cells that are able to extravasate

NOTE Confidence: 0.679529493333333

00:32:19.898 --> 00:32:22.609 die either in the vessels or right

NOTE Confidence: 0.679529493333333

00:32:22.609 --> 00:32:25.339 after extravasation but then after they 7.

NOTE Confidence: 0.679529493333333

00:32:25.340 --> 00:32:27.828 When the control cells are able to start

NOTE Confidence: 0.679529493333333

00:32:27.828 --> 00:32:29.763 expanding and proliferating happily,

NOTE Confidence: 0.679529493333333

00:32:29.763 --> 00:32:33.516 the ones that lack APP can no longer

NOTE Confidence: 0.679529493333333

00:32:33.516 --> 00:32:36.400 grow after the first or second division

NOTE Confidence: 0.679529493333333

00:32:36.482 --> 00:32:38.413 and they eventually disappear.

NOTE Confidence: 0.679529493333333

00:32:38.413 --> 00:32:40.678 They are they are dead.

NOTE Confidence: 0.679529493333333

00:32:40.680 --> 00:32:44.558 So we wonder which effects were required

NOTE Confidence: 0.679529493333333

00:32:44.558 --> 00:32:49.159 for for this role of ebata in the brain.

NOTE Confidence: 0.679529493333333

00:32:49.160 --> 00:32:51.379 And remember that this is a very

NOTE Confidence: 0.679529493333333

00:32:51.379 --> 00:32:52.940 complex environment where there are,

NOTE Confidence: 0.679529493333333

00:32:52.940 --> 00:32:54.638 you know, the resident myeloid cells,

NOTE Confidence: 0.679529493333333

00:32:54.640 --> 00:32:55.410 the microglia.

NOTE Confidence: 0.679529493333333

00:32:55.410 --> 00:32:57.335 Macrophages in some cases will

NOTE Confidence: 0.679529493333333

00:32:57.335 --> 00:32:58.854 matter derived macrophages that

NOTE Confidence: 0.679529493333333

00:32:58.854 --> 00:33:00.989 attracted to the tumor and it excels

NOTE Confidence: 0.679529493333333

00:33:00.989 --> 00:33:02.780 interfiling for sites and astrocytes.

NOTE Confidence: 0.679529493333333

00:33:02.780 --> 00:33:05.060 So we first look at astrocytes

NOTE Confidence: 0.679529493333333

00:33:05.060 --> 00:33:06.200 as a potential.

NOTE Confidence: 0.833985785833333

00:33:08.620 --> 00:33:11.290 Still of interest, because of the

NOTE Confidence: 0.833985785833333

00:33:11.290 --> 00:33:13.714 literature that had shown previously

NOTE Confidence: 0.833985785833333

00:33:13.714 --> 00:33:15.835 that activated astrocytes can be Co

NOTE Confidence: 0.833985785833333

00:33:15.835 --> 00:33:18.100 opted by the cancer cells to support

NOTE Confidence: 0.833985785833333

00:33:18.100 --> 00:33:20.056 the growth in the brain environment.

NOTE Confidence: 0.833985785833333

00:33:20.060 --> 00:33:21.740 And this is indeed the case.

NOTE Confidence: 0.833985785833333

00:33:21.740 --> 00:33:24.420 Also in our models where we see that

NOTE Confidence: 0.833985785833333

00:33:24.420 --> 00:33:27.039 if you look at the left panels,

NOTE Confidence: 0.833985785833333

00:33:27.040 --> 00:33:28.816 you can see that over time,

NOTE Confidence: 0.833985785833333

00:33:28.820 --> 00:33:30.549 as the muscles arrive to the brain,

NOTE Confidence: 0.833985785833333

00:33:30.550 --> 00:33:32.040 these are the control cells,

NOTE Confidence: 0.833985785833333

00:33:32.040 --> 00:33:34.674 you can see an increased presence

NOTE Confidence: 0.833985785833333

00:33:34.674 --> 00:33:36.430 of GFP positive astrocytes.

NOTE Confidence: 0.833985785833333

00:33:36.430 --> 00:33:37.690 So there is.

NOTE Confidence: 0.833985785833333

00:33:37.690 --> 00:33:39.790 Some equipment of activated astrocytes

NOTE Confidence: 0.833985785833333

00:33:39.790 --> 00:33:42.337 we cannot distinguish if it's

NOTE Confidence: 0.833985785833333

00:33:42.337 --> 00:33:44.513 recruitment versus activation of

NOTE Confidence: 0.833985785833333

00:33:44.513 --> 00:33:46.910 the surrounding astrocytes to the

NOTE Confidence: 0.833985785833333

00:33:46.910 --> 00:33:48.974 point that they form this network

NOTE Confidence: 0.833985785833333

00:33:48.974 --> 00:33:52.982 of active astrocytes that is called

NOTE Confidence: 0.833985785833333

00:33:52.982 --> 00:33:56.819 active Astro cytosis supporting

NOTE Confidence: 0.833985785833333

00:33:56.819 --> 00:33:59.828 the Melanoma micrometastasis.

NOTE Confidence: 0.833985785833333

00:33:59.830 --> 00:34:02.686 So what we observe is that cells

NOTE Confidence: 0.833985785833333

00:34:02.686 --> 00:34:05.639 that lack APP are unable to

NOTE Confidence: 0.833985785833333

00:34:05.639 --> 00:34:07.280 trigger these reactive.

NOTE Confidence: 0.833985785833333

00:34:07.280 --> 00:34:08.360 Cytosis around them.

NOTE Confidence: 0.833985785833333

00:34:08.360 --> 00:34:10.520 When they arrive to the brain,

NOTE Confidence: 0.833985785833333

00:34:10.520 --> 00:34:13.185 there is a significant reduction

NOTE Confidence: 0.833985785833333

00:34:13.185 --> 00:34:15.600 of positive cells of GFP.

NOTE Confidence: 0.833985785833333

00:34:15.600 --> 00:34:17.950 Positive cells around the cells

NOTE Confidence: 0.833985785833333

00:34:17.950 --> 00:34:20.199 demand muscles that lack APP,

NOTE Confidence: 0.833985785833333

00:34:20.200 --> 00:34:23.329 suggesting that perhaps a beta is important

NOTE Confidence: 0.833985785833333

00:34:23.329 --> 00:34:25.740 in triggering these Astro cytosis.

NOTE Confidence: 0.833985785833333

00:34:25.740 --> 00:34:27.624 Now, in data that I don't

NOTE Confidence: 0.833985785833333

00:34:27.624 --> 00:34:29.560 have the time to explain,

NOTE Confidence: 0.833985785833333

00:34:29.560 --> 00:34:33.070 we also show that Amelia better not only has

NOTE Confidence: 0.833985785833333

00:34:33.070 --> 00:34:36.479 the capacity to activate the astrocytes,

NOTE Confidence: 0.833985785833333

00:34:36.480 --> 00:34:37.528 but also.

NOTE Confidence: 0.833985785833333

00:34:37.528 --> 00:34:39.624 Can suppress the phagocytosis

NOTE Confidence: 0.833985785833333

00:34:39.624 --> 00:34:41.720 coming from the microglia.

NOTE Confidence: 0.833985785833333

00:34:41.720 --> 00:34:43.864 So we can see that there is a

NOTE Confidence: 0.833985785833333

00:34:43.864 --> 00:34:45.283 reduction of neural inflammation

NOTE Confidence: 0.833985785833333

00:34:45.283 --> 00:34:47.725 in the presence of family beta.

NOTE Confidence: 0.833985785833333

00:34:47.730 --> 00:34:49.767 So we think that Ali beta secreted

NOTE Confidence: 0.833985785833333

00:34:49.767 --> 00:34:51.788 by cancer cells can have multiple

NOTE Confidence: 0.833985785833333

00:34:51.788 --> 00:34:53.603 effects in the brain metastasis,

NOTE Confidence: 0.833985785833333

00:34:53.610 --> 00:34:55.910 macular vironment, particularly on

NOTE Confidence: 0.833985785833333

00:34:55.910 --> 00:34:58.785 the astrocytes and the microglia,

NOTE Confidence: 0.833985785833333

00:34:58.790 --> 00:35:01.070 but also it can influence,

NOTE Confidence: 0.833985785833333

00:35:01.070 --> 00:35:03.464 as it has been reported in Alzheimer's,

NOTE Confidence: 0.833985785833333

00:35:03.470 --> 00:35:06.428 the interaction with the endothelial cells.

NOTE Confidence: 0.833985785833333

00:35:06.430 --> 00:35:08.650 So of course these open,

NOTE Confidence: 0.833985785833333

00:35:08.650 --> 00:35:11.406 these findings open some

NOTE Confidence: 0.833985785833333

00:35:11.406 --> 00:35:13.473 possibilities and therapeutic

NOTE Confidence: 0.833985785833333

00:35:13.473 --> 00:35:16.330 opportunities because of all the.

NOTE Confidence: 0.833985785833333

00:35:16.330 --> 00:35:19.570 Armamentarium of drugs that have

NOTE Confidence: 0.833985785833333

00:35:19.570 --> 00:35:22.426 been developed against America beta,

NOTE Confidence: 0.833985785833333

00:35:22.426 --> 00:35:25.597 some of them beta secretase inhibitors and

NOTE Confidence: 0.833985785833333

00:35:25.597 --> 00:35:28.649 more recently anti American antibodies,

NOTE Confidence: 0.833985785833333

00:35:28.650 --> 00:35:30.996 some of which have been developed

NOTE Confidence: 0.833985785833333

00:35:30.996 --> 00:35:33.346 for clinical use and in some

NOTE Confidence: 0.833985785833333

00:35:33.346 --> 00:35:35.464 cases even approved by the FDA.

NOTE Confidence: 0.833985785833333

00:35:35.470 --> 00:35:37.564 So these open the possibility of

NOTE Confidence: 0.833985785833333

00:35:37.564 --> 00:35:39.733 repurposing some of these drugs which

NOTE Confidence: 0.833985785833333

00:35:39.733 --> 00:35:41.863 are generally safe for brain metastasis

NOTE Confidence: 0.833985785833333

00:35:41.863 --> 00:35:44.128 and for proof of principle we've

NOTE Confidence: 0.833985785833333

00:35:44.128 --> 00:35:46.366 been testing some of these compounds.

NOTE Confidence: 0.833985785833333

00:35:46.370 --> 00:35:48.400 In collaboration with Eli Lilly,

NOTE Confidence: 0.833985785833333

00:35:48.400 --> 00:35:50.985 so we obtain beta secretase

NOTE Confidence: 0.833985785833333

00:35:50.985 --> 00:35:54.088 inhibitors in the diet of the mice.

NOTE Confidence: 0.833985785833333

00:35:54.088 --> 00:35:56.868 So initially we injected a cancer cells

NOTE Confidence: 0.833985785833333

00:35:56.868 --> 00:35:59.521 Melanoma cells in these mice and gave

NOTE Confidence: 0.833985785833333

00:35:59.521 --> 00:36:02.183 them a better second base inhibitor

NOTE Confidence: 0.833985785833333

00:36:02.183 --> 00:36:04.913 in the food or controlled diet.

NOTE Confidence: 0.833985785833333

00:36:04.920 --> 00:36:07.448 And you can see how this reduces the

NOTE Confidence: 0.833985785833333

00:36:07.448 --> 00:36:10.286 number of brain metastasis in this model.

NOTE Confidence: 0.833985785833333

00:36:10.290 --> 00:36:12.355 This is a short term culture but

NOTE Confidence: 0.833985785833333

00:36:12.355 --> 00:36:14.918 also in the five one Melanoma cells.

NOTE Confidence: 0.833985785833333

00:36:14.920 --> 00:36:16.736 Now of course this is more a prophylactic.

NOTE Confidence: 0.833985785833333

00:36:16.740 --> 00:36:18.092 Model because treatment starts

NOTE Confidence: 0.833985785833333

00:36:18.092 --> 00:36:19.782 at the time of injection,

NOTE Confidence: 0.833985785833333

00:36:19.790 --> 00:36:22.510 so we raise the bar a little bit

NOTE Confidence: 0.833985785833333

00:36:22.510 --> 00:36:25.040 by allowing the cells to establish

NOTE Confidence: 0.833985785833333

00:36:25.040 --> 00:36:27.686 metastasis first and then after 21

NOTE Confidence: 0.833985785833333

00:36:27.769 --> 00:36:30.480 days we gave doxycycline to the food

NOTE Confidence: 0.833985785833333

00:36:30.480 --> 00:36:32.960 and the in the water of the mice

NOTE Confidence: 0.833985785833333

00:36:32.960 --> 00:36:35.747 to activate docs inducible SH RNA.

NOTE Confidence: 0.833985785833333

00:36:35.750 --> 00:36:37.726 And again we saw that in this context,

NOTE Confidence: 0.894519268333333

00:36:37.730 --> 00:36:39.446 even when the treatment is initiated,

NOTE Confidence: 0.894519268333333

00:36:39.450 --> 00:36:41.370 once metastasis have been formed,

NOTE Confidence: 0.894519268333333

00:36:41.370 --> 00:36:43.330 we can see a reduction in the number

NOTE Confidence: 0.894519268333333

00:36:43.330 --> 00:36:45.158 of brain metastases and if we do

NOTE Confidence: 0.894519268333333

00:36:45.158 --> 00:36:47.040 the same thing with the Secretary.

NOTE Confidence: 0.894519268333333

00:36:47.040 --> 00:36:50.480 Keep in touch. We can also see again

NOTE Confidence: 0.894519268333333

00:36:50.480 --> 00:36:52.008 after initiating the treatment.

NOTE Confidence: 0.894519268333333

00:36:52.008 --> 00:36:54.570 Once the micrometer studies have been formed,

NOTE Confidence: 0.894519268333333

00:36:54.570 --> 00:36:57.020 we can see a reduction in brain

NOTE Confidence: 0.894519268333333

00:36:57.020 --> 00:36:59.580 metastasis we are currently trying to.

NOTE Confidence: 0.780478655

00:37:01.720 --> 00:37:05.200 Moving to well before I go into that,

NOTE Confidence: 0.780478655

00:37:05.200 --> 00:37:09.770 we are now testing the antibodies against

NOTE Confidence: 0.780478655

00:37:09.770 --> 00:37:12.140 Emily Beta either as a monotherapy

NOTE Confidence: 0.780478655

00:37:12.140 --> 00:37:14.292 or in combination with immunotherapy

NOTE Confidence: 0.780478655

00:37:14.292 --> 00:37:16.866 to see if we can recapitulate

NOTE Confidence: 0.780478655

00:37:16.866 --> 00:37:19.106 the same effects of surf here.

NOTE Confidence: 0.780478655

00:37:19.110 --> 00:37:21.190 So to summarize this part of the talk,

NOTE Confidence: 0.780478655

00:37:21.190 --> 00:37:24.004 we have shown the proteomic studies

NOTE Confidence: 0.780478655

00:37:24.004 --> 00:37:26.708 have revealed a novel connection

NOTE Confidence: 0.780478655

00:37:26.708 --> 00:37:29.010 between brain metastasis and

NOTE Confidence: 0.780478655

00:37:29.010 --> 00:37:30.050 neurodegenerative pathologies.

NOTE Confidence: 0.780478655

00:37:30.050 --> 00:37:32.234 This has now been confirmed by other studies.

NOTE Confidence: 0.780478655

00:37:32.240 --> 00:37:33.724 We collaborated with a group of men,

NOTE Confidence: 0.780478655

00:37:33.730 --> 00:37:35.239 iser, last year.

NOTE Confidence: 0.780478655

00:37:35.239 --> 00:37:39.290 We got a study done in single cell

NOTE Confidence: 0.780478655

00:37:39.290 --> 00:37:42.642 analysis of primate testis that also

NOTE Confidence: 0.780478655

00:37:42.642 --> 00:37:45.276 recapitulated these these finding

NOTE Confidence: 0.780478655

00:37:45.276 --> 00:37:49.026 that Melanoma cells mimic the.

NOTE Confidence: 0.780478655

00:37:49.026 --> 00:37:53.085 A neuronal pathways in another of the

NOTE Confidence: 0.780478655

00:37:53.085 --> 00:37:54.980 alterations that are seen in you know,

NOTE Confidence: 0.780478655

00:37:54.980 --> 00:37:56.435 degenerative disorders once

NOTE Confidence: 0.780478655

00:37:56.435 --> 00:37:58.375 they reach the brain.

NOTE Confidence: 0.780478655

00:37:58.380 --> 00:38:00.865 We see that Amelia Beta is particularly

NOTE Confidence: 0.780478655

00:38:00.865 --> 00:38:02.758 required for pre metastasis and

NOTE Confidence: 0.780478655

00:38:02.758 --> 00:38:05.038 not other sites of metastasis is

NOTE Confidence: 0.780478655

00:38:05.038 --> 00:38:07.467 acquired for steps that happen after

NOTE Confidence: 0.780478655

00:38:07.467 --> 00:38:09.063 extravasation and early survival

NOTE Confidence: 0.780478655

00:38:09.063 --> 00:38:11.766 in the brain parenchyma and among

NOTE Confidence: 0.780478655

00:38:11.766 --> 00:38:14.136 the multiple functions of family.

NOTE Confidence: 0.780478655

00:38:14.140 --> 00:38:16.363 But in this context we have seen that it

NOTE Confidence: 0.780478655

00:38:16.363 --> 00:38:17.853 triggers an anti-inflammatory response

NOTE Confidence: 0.780478655

00:38:17.853 --> 00:38:19.838 in the astrocytes and suppresses.

NOTE Confidence: 0.780478655

00:38:19.840 --> 00:38:22.800 Your inflammation, as I mentioned,

NOTE Confidence: 0.780478655

00:38:22.800 --> 00:38:25.884 we are also studying now whether

NOTE Confidence: 0.780478655

00:38:25.884 --> 00:38:27.675 these effects of family beta can

NOTE Confidence: 0.780478655

00:38:27.675 --> 00:38:29.380 be seen also in other models.

NOTE Confidence: 0.780478655

00:38:29.380 --> 00:38:31.102 So we have done a spatial

NOTE Confidence: 0.780478655

00:38:31.102 --> 00:38:31.676 transcriptomic analysis.

NOTE Confidence: 0.780478655

00:38:31.680 --> 00:38:32.505 In this case,

NOTE Confidence: 0.780478655

00:38:32.505 --> 00:38:33.880 it's not a Melanoma model,

NOTE Confidence: 0.780478655

00:38:33.880 --> 00:38:36.656 is the 41 model which is a breast

NOTE Confidence: 0.780478655

00:38:36.656 --> 00:38:38.523 cancer triple negative model

NOTE Confidence: 0.780478655

00:38:38.523 --> 00:38:41.258 that also colonizes the brain

NOTE Confidence: 0.780478655

00:38:41.258 --> 00:38:42.899 after intracardiac injection.

NOTE Confidence: 0.780478655

00:38:42.900 --> 00:38:46.640 These are on the top is a is a brain,

NOTE Confidence: 0.780478655

00:38:46.640 --> 00:38:48.928 is half of a brain of a sham

NOTE Confidence: 0.780478655

00:38:48.928 --> 00:38:50.479 mouse and this is the.

NOTE Confidence: 0.780478655

00:38:50.480 --> 00:38:50.802 Mouse,

NOTE Confidence: 0.780478655

00:38:50.802 --> 00:38:53.056 this is a mouse that was injected

NOTE Confidence: 0.780478655

00:38:53.056 --> 00:38:55.394 with the 41 cells and what I want

NOTE Confidence: 0.780478655

00:38:55.394 --> 00:38:57.659 to bring to your attention is that

NOTE Confidence: 0.780478655

00:38:57.660 --> 00:39:01.286 in this the next vision analysis we

NOTE Confidence: 0.780478655

00:39:01.286 --> 00:39:04.212 can see that the gfap positive cells

NOTE Confidence: 0.780478655

00:39:04.212 --> 00:39:06.580 around the areas where the tumors are,

NOTE Confidence: 0.780478655

00:39:06.580 --> 00:39:08.924 you have to probably take me you know

NOTE Confidence: 0.780478655

00:39:08.924 --> 00:39:11.459 take my my word these are the areas

NOTE Confidence: 0.780478655

00:39:11.459 --> 00:39:13.507 where the tumors are circle here

NOTE Confidence: 0.780478655

00:39:13.507 --> 00:39:16.062 and we see a special expression or

NOTE Confidence: 0.780478655

00:39:16.062 --> 00:39:17.882 increased expression of GFP around

NOTE Confidence: 0.780478655

00:39:17.882 --> 00:39:20.060 those tumor cells we also see.

NOTE Confidence: 0.780478655

00:39:20.060 --> 00:39:22.388 This one is 100 which has been seen

NOTE Confidence: 0.780478655

00:39:22.388 --> 00:39:25.283 it used in tumor cells in the brain

NOTE Confidence: 0.780478655

00:39:25.283 --> 00:39:27.250 environment in other cancer types.

NOTE Confidence: 0.780478655

00:39:27.250 --> 00:39:29.440 And interestingly we find these

NOTE Confidence: 0.780478655

00:39:29.440 --> 00:39:32.231 signature that we have that has

NOTE Confidence: 0.780478655

00:39:32.231 --> 00:39:35.393 been previously reported as the an

NOTE Confidence: 0.780478655

00:39:35.393 --> 00:39:36.974 Alzheimer's associated microglia

NOTE Confidence: 0.780478655

00:39:37.050 --> 00:39:38.980 signature that is a combination

NOTE Confidence: 0.780478655

00:39:38.980 --> 00:39:42.616 of 10 markers and is again seen

NOTE Confidence: 0.780478655

00:39:42.616 --> 00:39:46.028 particularly activated around the

NOTE Confidence: 0.780478655

00:39:46.030 --> 00:39:48.740 brain metastasis here in here.

NOTE Confidence: 0.780478655

00:39:48.740 --> 00:39:51.547 So it seems like perhaps these Alzheimer

NOTE Confidence: 0.780478655

00:39:51.547 --> 00:39:54.092 like response in the microglia genes

NOTE Confidence: 0.780478655

00:39:54.092 --> 00:39:55.771 around the brain metastasis cells

NOTE Confidence: 0.780478655

00:39:55.771 --> 00:39:57.710 could be a more general finding and

NOTE Confidence: 0.780478655

00:39:57.760 --> 00:39:59.480 not only characteristic of Melanoma.

NOTE Confidence: 0.780478655

00:39:59.480 --> 00:40:00.419 As I mentioned,

NOTE Confidence: 0.780478655

00:40:00.419 --> 00:40:02.898 we are now very excited by studying

NOTE Confidence: 0.780478655

00:40:02.898 --> 00:40:05.888 whether app genetic and pharmacological

NOTE Confidence: 0.780478655

00:40:05.888 --> 00:40:08.905 inhibition extends to other cancer

NOTE Confidence: 0.780478655

00:40:08.905 --> 00:40:12.163 types and whether the combination of

NOTE Confidence: 0.780478655

00:40:12.163 --> 00:40:14.491 beta secretase inhibitors or antibodies

NOTE Confidence: 0.780478655

00:40:14.491 --> 00:40:17.257 can work alone or in combination

NOTE Confidence: 0.780478655

00:40:17.257 --> 00:40:19.170 with checkpoint checkpoint locate.

NOTE Confidence: 0.780478655

00:40:19.170 --> 00:40:20.484 In immunocompetent models,

NOTE Confidence: 0.780478655

00:40:20.484 --> 00:40:24.028 I was hoping to tell you about a

NOTE Confidence: 0.780478655

00:40:24.028 --> 00:40:26.786 another very exciting story in the lab,

NOTE Confidence: 0.780478655

00:40:26.790 --> 00:40:29.220 but I I see the clock and we are reaching

NOTE Confidence: 0.831005876153846

00:40:29.279 --> 00:40:34.748 the 1:00 PM. So I will stop here and.

NOTE Confidence: 0.831005876153846

00:40:34.750 --> 00:40:37.654 This is this data I wanted to present

NOTE Confidence: 0.831005876153846

00:40:37.654 --> 00:40:39.982 but perhaps at the second occasion

NOTE Confidence: 0.831005876153846

00:40:39.982 --> 00:40:42.850 and just wanna thank all the members

NOTE Confidence: 0.831005876153846

00:40:42.850 --> 00:40:46.270 of the lab for their contributions.

NOTE Confidence: 0.831005876153846

00:40:46.270 --> 00:40:48.112 This work that I presented was

NOTE Confidence: 0.831005876153846

00:40:48.112 --> 00:40:50.099 mostly done by the first part,

NOTE Confidence: 0.831005876153846

00:40:50.100 --> 00:40:52.962 which are Veronica and Claudia in

NOTE Confidence: 0.831005876153846

00:40:52.962 --> 00:40:57.008 NRF 2 and Ali and Maya in CDP one.

NOTE Confidence: 0.831005876153846

00:40:57.010 --> 00:41:01.564 And Kevin Kleffman led the I'm a

NOTE Confidence: 0.831005876153846

00:41:01.564 --> 00:41:03.860 little better story and I want to thank

NOTE Confidence: 0.831005876153846

00:41:03.928 --> 00:41:06.100 of course all our funding sources.

NOTE Confidence: 0.831005876153846

00:41:06.100 --> 00:41:08.858 And thank you all for your attention

NOTE Confidence: 0.831005876153846

00:41:08.858 --> 00:41:11.036 and your patience with the technical

NOTE Confidence: 0.831005876153846

00:41:11.036 --> 00:41:12.380 issues at the beginning.

NOTE Confidence: 0.831005876153846

00:41:12.380 --> 00:41:13.815 I'll stop here and take any questions.

NOTE Confidence: 0.831005876153846

00:41:13.820 --> 00:41:14.180 Thank you.

NOTE Confidence: 0.821179502

00:41:16.510 --> 00:41:18.593 Alright, thank you so much, Eva.

NOTE Confidence: 0.821179502

00:41:18.593 --> 00:41:20.651 I'm going to ask folks to

NOTE Confidence: 0.821179502

00:41:20.651 --> 00:41:22.409 put questions in the chat.

NOTE Confidence: 0.821179502

00:41:22.410 --> 00:41:24.370 We only got a couple of minutes,

NOTE Confidence: 0.821179502

00:41:24.370 --> 00:41:26.225 but while people type in the questions,

NOTE Confidence: 0.821179502

00:41:26.230 --> 00:41:27.742 maybe I don't know if Marcus

NOTE Confidence: 0.821179502

00:41:27.742 --> 00:41:29.550 has any or I can ask one.

NOTE Confidence: 0.821179502

00:41:29.550 --> 00:41:33.600 Go ahead Marcus, I've got plenty.

NOTE Confidence: 0.821179502

00:41:33.600 --> 00:41:36.869 So either really Congrats also on the,

NOTE Confidence: 0.821179502

00:41:36.870 --> 00:41:39.240 you know the nature communications paper.

NOTE Confidence: 0.821179502

00:41:39.240 --> 00:41:42.140 And I was wondering with the NR2F2 story,

NOTE Confidence: 0.821179502

00:41:42.140 --> 00:41:44.265 you're probably aware of Chris,

NOTE Confidence: 0.821179502

00:41:44.270 --> 00:41:49.184 Marines work in Nature last fall on TCF 4.

NOTE Confidence: 0.821179502

00:41:49.190 --> 00:41:52.598 And I'm kind of wondering if you think

NOTE Confidence: 0.821179502

00:41:52.598 --> 00:41:55.102 your NR 2F2 is upstream of TCF four if

NOTE Confidence: 0.821179502

00:41:55.102 --> 00:41:57.102 you've seen any role there and there's

NOTE Confidence: 0.821179502

00:41:57.102 --> 00:41:59.027 probably going to be a subsequent

NOTE Confidence: 0.821179502

00:41:59.027 --> 00:42:01.287 story about resistance to therapies,

NOTE Confidence: 0.821179502

00:42:01.290 --> 00:42:02.230 so there's.

NOTE Confidence: 0.821179502

00:42:02.230 --> 00:42:04.580 Multiple parts to this question.

NOTE Confidence: 0.821179502

00:42:04.580 --> 00:42:06.260 A, the upstream downstream part,

NOTE Confidence: 0.821179502

00:42:06.260 --> 00:42:08.055 but then also the heterogeneity

NOTE Confidence: 0.821179502

00:42:08.055 --> 00:42:09.850 because you're talking about these

NOTE Confidence: 0.821179502

00:42:09.906 --> 00:42:11.806 things happening sort of uniformly.

NOTE Confidence: 0.821179502

00:42:11.810 --> 00:42:13.670 But I'm imagining that the epigenetic

NOTE Confidence: 0.821179502

00:42:13.670 --> 00:42:15.648 regulation is kind of cell by cell

NOTE Confidence: 0.821179502

00:42:15.648 --> 00:42:17.230 and that there's going to be a

NOTE Confidence: 0.821179502

00:42:17.287 --> 00:42:18.865 population of cells that have more

NOTE Confidence: 0.821179502

00:42:18.865 --> 00:42:22.458 or less of that along the way.

NOTE Confidence: 0.821179502

00:42:22.460 --> 00:42:23.540 All excellent questions and and

NOTE Confidence: 0.821179502

00:42:23.540 --> 00:42:24.840 these are all the questions that

NOTE Confidence: 0.821179502

00:42:24.840 --> 00:42:25.908 we are trying to address now.

NOTE Confidence: 0.821179502

00:42:25.910 --> 00:42:26.346 So,

NOTE Confidence: 0.821179502

00:42:26.346 --> 00:42:29.398 so we didn't see a total overlap

NOTE Confidence: 0.821179502

00:42:29.398 --> 00:42:32.290 between our population of N2F2

NOTE Confidence: 0.821179502

00:42:32.290 --> 00:42:35.250 with Chris Marines population.

NOTE Confidence: 0.821179502

00:42:35.250 --> 00:42:38.694 It seems like his population is smaller

NOTE Confidence: 0.821179502

00:42:38.694 --> 00:42:42.767 one inner two seems to be more broadly.

NOTE Confidence: 0.821179502

00:42:42.770 --> 00:42:47.190 I expressed in both EMT and also partially

NOTE Confidence: 0.821179502

00:42:47.190 --> 00:42:49.020 in the neural Crest like population.

NOTE Confidence: 0.821179502

00:42:49.020 --> 00:42:51.180 So his population seems to be a more,

NOTE Confidence: 0.821179502

00:42:51.180 --> 00:42:52.436 I wouldn't say minority,

NOTE Confidence: 0.821179502

00:42:52.436 --> 00:42:54.006 but it's a smaller population

NOTE Confidence: 0.821179502

00:42:54.006 --> 00:42:55.739 and not not directly overlap.

NOTE Confidence: 0.840730844782609

00:42:58.330 --> 00:43:00.563 You also ask the other challenge that

NOTE Confidence: 0.840730844782609

00:43:00.563 --> 00:43:03.503 we have is that a lot of the single

NOTE Confidence: 0.840730844782609

00:43:03.503 --> 00:43:05.779 cell analysis that have allowed us to.

NOTE Confidence: 0.840730844782609

00:43:05.780 --> 00:43:07.110 Distinguish this.

NOTE Confidence: 0.840730844782609

00:43:07.110 --> 00:43:09.770 Transcriptionist states don't have,

NOTE Confidence: 0.840730844782609

00:43:09.770 --> 00:43:11.877 don't allow us, don't don't have the

NOTE Confidence: 0.840730844782609

00:43:11.877 --> 00:43:14.058 death to look into isoforms, right?

NOTE Confidence: 0.840730844782609

00:43:14.058 --> 00:43:17.002 So you really have to have a different

NOTE Confidence: 0.840730844782609

00:43:17.002 --> 00:43:19.275 library preparation and pipeline to

NOTE Confidence: 0.840730844782609

00:43:19.275 --> 00:43:22.023 identify the different types of forms.

NOTE Confidence: 0.840730844782609

00:43:22.030 --> 00:43:23.836 So when people look at R2,

NOTE Confidence: 0.840730844782609

00:43:23.840 --> 00:43:26.808 they are just examining an R2 ISO one,

NOTE Confidence: 0.840730844782609

00:43:26.810 --> 00:43:29.477 the full length and the one that

NOTE Confidence: 0.840730844782609

00:43:29.477 --> 00:43:31.509 is really switching from the

NOTE Confidence: 0.840730844782609

00:43:31.509 --> 00:43:33.549 the primary to the metastatic,

NOTE Confidence: 0.840730844782609

00:43:33.550 --> 00:43:36.054 the one that is really triggering the EMT.

NOTE Confidence: 0.840730844782609

00:43:36.060 --> 00:43:38.610 Like program is only isoform

NOTE Confidence: 0.840730844782609

00:43:38.610 --> 00:43:40.650 2 because of this.

NOTE Confidence: 0.840730844782609

00:43:40.650 --> 00:43:42.450 Balance between home and headliners.

NOTE Confidence: 0.793306258125

00:43:44.690 --> 00:43:46.060 Yeah. So we we're definitely

NOTE Confidence: 0.793306258125

00:43:46.060 --> 00:43:47.783 trying to understand what is the

NOTE Confidence: 0.793306258125

00:43:47.783 --> 00:43:49.268 error key between these pathways,

NOTE Confidence: 0.793306258125

00:43:49.270 --> 00:43:51.377 where is upstream, it seems to be

NOTE Confidence: 0.793306258125

00:43:51.377 --> 00:43:53.730 one of the critical regulators.

NOTE Confidence: 0.793306258125

00:43:53.730 --> 00:43:56.856 So again when we do this.

NOTE Confidence: 0.793306258125

00:43:56.860 --> 00:43:59.040 Um, analysis is sending analysis,

NOTE Confidence: 0.793306258125

00:43:59.040 --> 00:44:00.336 but still we don't know which

NOTE Confidence: 0.793306258125

00:44:00.336 --> 00:44:01.822 one is upstream of which, right?

NOTE Confidence: 0.793306258125

00:44:01.822 --> 00:44:03.634 Yeah, that's a very good question.

NOTE Confidence: 0.793306258125

00:44:03.640 --> 00:44:05.068 And then you ask.

NOTE Confidence: 0.793306258125

00:44:05.068 --> 00:44:06.853 The dynamics right of this

NOTE Confidence: 0.793306258125

00:44:06.853 --> 00:44:08.510 of this population.

NOTE Confidence: 0.793306258125

00:44:08.510 --> 00:44:10.792 So we are now in the process

NOTE Confidence: 0.793306258125

00:44:10.792 --> 00:44:12.124 of labeling endogenously this

NOTE Confidence: 0.793306258125

00:44:12.124 --> 00:44:14.168 isoform to be able to trace them.

NOTE Confidence: 0.793306258125

00:44:14.170 --> 00:44:17.195 We want to understand whether

NOTE Confidence: 0.793306258125

00:44:17.195 --> 00:44:19.787 these isoforms are, you know,

NOTE Confidence: 0.793306258125

00:44:19.787 --> 00:44:21.623 dynamically regulated during the

NOTE Confidence: 0.793306258125

00:44:21.623 --> 00:44:23.795 metastatic process and we have

NOTE Confidence: 0.793306258125

00:44:23.795 --> 00:44:25.239 different labeling systems now

NOTE Confidence: 0.793306258125

00:44:25.239 --> 00:44:27.682 that allow us to sell to monitor

NOTE Confidence: 0.793306258125

00:44:27.682 --> 00:44:29.570 single cells during metastasis.

NOTE Confidence: 0.793306258125

00:44:29.570 --> 00:44:31.282 So I hope we will have soon an

NOTE Confidence: 0.793306258125

00:44:31.282 --> 00:44:33.134 answer for that, but we don't know.

NOTE Confidence: 0.793306258125

00:44:33.134 --> 00:44:35.650 I I also dissipate that it would change.

NOTE Confidence: 0.793306258125

00:44:35.650 --> 00:44:37.846 From the primary tumor as the

NOTE Confidence: 0.793306258125

00:44:37.850 --> 00:44:39.685 cells switch from the more

NOTE Confidence: 0.793306258125

00:44:39.685 --> 00:44:41.520 proliferative to the more invasive,

NOTE Confidence: 0.793306258125

00:44:41.520 --> 00:44:43.122 and then back when they arrive

NOTE Confidence: 0.793306258125

00:44:43.122 --> 00:44:44.970 to them at the static side.

NOTE Confidence: 0.793306258125

00:44:44.970 --> 00:44:46.385 But still we don't have

NOTE Confidence: 0.793306258125

00:44:46.385 --> 00:44:47.517 full evidence for that.

NOTE Confidence: 0.854771814210526

00:44:50.660 --> 00:44:52.697 So, but there were a couple of

NOTE Confidence: 0.854771814210526

00:44:52.697 --> 00:44:55.367 questions in the chat both relating to

NOTE Confidence: 0.854771814210526

00:44:55.367 --> 00:44:57.532 Alzheimer's disease and brain metastases.

NOTE Confidence: 0.854771814210526

00:44:57.540 --> 00:45:00.144 One is there an increased incidence

NOTE Confidence: 0.854771814210526

00:45:00.144 --> 00:45:02.370 in brain metastases amount Alzheimer's

NOTE Confidence: 0.854771814210526

00:45:02.370 --> 00:45:05.310 disease patients and the other one was

NOTE Confidence: 0.854771814210526

00:45:05.310 --> 00:45:08.208 whether a postmortem you see Alzheimer's

NOTE Confidence: 0.854771814210526

00:45:08.208 --> 00:45:11.190 clogs in patients with brain metastases.

NOTE Confidence: 0.854771814210526

00:45:11.190 --> 00:45:12.254 Good questions.

NOTE Confidence: 0.854771814210526

00:45:12.254 --> 00:45:15.446 So we haven't seen brain metastasis,

NOTE Confidence: 0.854771814210526

00:45:15.450 --> 00:45:17.788 we haven't seen plaques in brain metastasis.

NOTE Confidence: 0.854771814210526

00:45:17.790 --> 00:45:19.410 We look for for them,

NOTE Confidence: 0.854771814210526

00:45:19.410 --> 00:45:22.170 we don't think that they get to accumulate,

NOTE Confidence: 0.854771814210526

00:45:22.170 --> 00:45:25.082 so we don't, we don't think that the

NOTE Confidence: 0.854771814210526

00:45:25.082 --> 00:45:27.860 processing is wrong is to simply induced.

NOTE Confidence: 0.854771814210526

00:45:27.860 --> 00:45:30.708 So we see more soluble abeta being produced,

NOTE Confidence: 0.854771814210526

00:45:30.710 --> 00:45:32.742 but we don't see oligomers and we don't

NOTE Confidence: 0.854771814210526

00:45:32.742 --> 00:45:34.586 see plaques. We did that staining.

NOTE Confidence: 0.854771814210526

00:45:34.586 --> 00:45:36.590 That conversion is done by pathologists

NOTE Confidence: 0.854771814210526

00:45:36.647 --> 00:45:38.861 to to look at the plaques and we couldn't

NOTE Confidence: 0.854771814210526

00:45:38.861 --> 00:45:41.029 see either in our models nor in human.

NOTE Confidence: 0.854771814210526

00:45:41.030 --> 00:45:44.556 Examples and that's the reason why we

NOTE Confidence: 0.854771814210526

00:45:44.556 --> 00:45:46.724 think that the antibodies that we wanna

NOTE Confidence: 0.854771814210526

00:45:46.724 --> 00:45:48.566 try are antibodies that design against

NOTE Confidence: 0.854771814210526

00:45:48.566 --> 00:45:50.815 the soluble and libetta and not against

NOTE Confidence: 0.854771814210526

00:45:50.815 --> 00:45:52.913 the plaques which are the ones that

NOTE Confidence: 0.854771814210526

00:45:52.913 --> 00:45:54.880 have been now or the oligomers which

NOTE Confidence: 0.854771814210526

00:45:54.944 --> 00:45:56.855 have been now approved by the FDA.

NOTE Confidence: 0.854771814210526

00:45:56.860 --> 00:45:59.278 Now you ask the other question,

NOTE Confidence: 0.854771814210526

00:45:59.280 --> 00:46:01.350 the incidence in in Alzheimer's.

NOTE Confidence: 0.854771814210526

00:46:01.350 --> 00:46:05.855 So we'll look into that and we didn't see

NOTE Confidence: 0.854771814210526

00:46:05.855 --> 00:46:09.380 a epidemiological studies and association

NOTE Confidence: 0.854771814210526

00:46:09.380 --> 00:46:12.870 between Alzheimer's and brain metastasis.

NOTE Confidence: 0.854771814210526

00:46:12.870 --> 00:46:15.040 But normally remember that in the majority

NOTE Confidence: 0.854771814210526

00:46:15.040 --> 00:46:16.490 of the neurodegenerative disorders,

NOTE Confidence: 0.854771814210526

00:46:16.490 --> 00:46:19.000 there is an inverse correlation

NOTE Confidence: 0.854771814210526

00:46:19.000 --> 00:46:21.008 between cancer incidence and

NOTE Confidence: 0.854771814210526

00:46:21.010 --> 00:46:22.316 neurodegenerative disorders,

NOTE Confidence: 0.854771814210526

00:46:22.316 --> 00:46:24.928 particularly Alzheimer's and Parkinson's.

NOTE Confidence: 0.854771814210526

00:46:24.930 --> 00:46:26.155 And even though there is

NOTE Confidence: 0.854771814210526

00:46:26.155 --> 00:46:27.135 not a positive correlation,

NOTE Confidence: 0.854771814210526

00:46:27.140 --> 00:46:29.430 there is no negative association.

NOTE Confidence: 0.854771814210526

00:46:29.430 --> 00:46:32.328 Now there is a reported association

NOTE Confidence: 0.854771814210526

00:46:32.328 --> 00:46:34.260 between Parkinson's and and

NOTE Confidence: 0.854771814210526

00:46:34.337 --> 00:46:36.329 Melanoma brain metastases.

NOTE Confidence: 0.854771814210526

00:46:36.330 --> 00:46:39.266 And I mean I think Harry,

NOTE Confidence: 0.854771814210526

00:46:39.266 --> 00:46:42.653 this is skeptical or not, I see you.

NOTE Confidence: 0.854771814210526

00:46:42.653 --> 00:46:44.658 No, there's a slight increase,

NOTE Confidence: 0.854771814210526

00:46:44.660 --> 00:46:47.316 but anyway, I don't know that it's brain

NOTE Confidence: 0.854771814210526

00:46:47.316 --> 00:46:49.820 metastases specifically, it's just.

NOTE Confidence: 0.854771814210526

00:46:49.820 --> 00:46:50.660 Come on. I'm sorry. Sorry.

NOTE Confidence: 0.854771814210526

00:46:50.660 --> 00:46:51.850 Yeah, yeah, yeah. I misspoke.

NOTE Confidence: 0.854771814210526

00:46:51.850 --> 00:46:53.266 I I meant that. I know my kid.

NOTE Confidence: 0.854771814210526

00:46:53.270 --> 00:46:54.120 Right.

NOTE Confidence: 0.854771814210526

00:46:54.120 --> 00:46:54.970 Yeah.

NOTE Confidence: 0.854771814210526

00:46:54.970 --> 00:46:55.820 Yeah.

NOTE Confidence: 0.854771814210526

00:46:55.820 --> 00:46:56.195 No,

NOTE Confidence: 0.854771814210526

00:46:56.195 --> 00:46:58.070 but there's a really interesting

NOTE Confidence: 0.854771814210526

00:46:58.070 --> 00:46:58.820 observation there.

NOTE Confidence: 0.854771814210526

00:46:58.820 --> 00:47:00.636 So thank you and thank you so much

NOTE Confidence: 0.854771814210526

00:47:00.636 --> 00:47:02.259 for this amazing presentation.

NOTE Confidence: 0.854771814210526

00:47:02.260 --> 00:47:03.500 I have more questions,

NOTE Confidence: 0.854771814210526

00:47:03.500 --> 00:47:05.850 but I'm going to e-mail them to you.

NOTE Confidence: 0.854771814210526

00:47:05.850 --> 00:47:07.570 I don't believe there anymore in the chat.

NOTE Confidence: 0.854771814210526

00:47:07.570 --> 00:47:09.340 We appreciate your patience with all

NOTE Confidence: 0.854771814210526

00:47:09.340 --> 00:47:10.874 the technical challenges and thanks

NOTE Confidence: 0.854771814210526

00:47:10.874 --> 00:47:12.389 for virtually visiting next time.

NOTE Confidence: 0.854771814210526

00:47:12.390 --> 00:47:13.902 It'll be in person.

NOTE Confidence: 0.854771814210526

00:47:13.902 --> 00:47:15.792 Thanks for wonderful talk to

NOTE Confidence: 0.854771814210526

00:47:15.792 --> 00:47:17.409 really fascinating work.

NOTE Confidence: 0.854771814210526

00:47:17.410 --> 00:47:18.058 Thank you,

NOTE Confidence: 0.854771814210526

00:47:18.058 --> 00:47:18.382 Harriet.

NOTE Confidence: 0.854771814210526

00:47:18.382 --> 00:47:20.002 Looking forward to see you

NOTE Confidence: 0.854771814210526

00:47:20.002 --> 00:47:21.709 soon and thanks everybody.

NOTE Confidence: 0.854771814210526

00:47:21.710 --> 00:47:22.160 Bye.