WEBVTT

NOTE duration:"01:03:36"

NOTE recognizability:0.809

NOTE language:en-us

NOTE Confidence: 0.81217790625

00:00:00.000 --> 00:00:01.515 Was a grand drones today.

NOTE Confidence: 0.81217790625

00:00:01.515 --> 00:00:04.622 It is my honor and great pleasure to

NOTE Confidence: 0.81217790625

00:00:04.622 --> 00:00:08.480 introduce today's speaker, Bob Coffey.

NOTE Confidence: 0.81217790625

00:00:08.480 --> 00:00:10.820 Doctor Coffey wears many hats.

NOTE Confidence: 0.81217790625

00:00:10.820 --> 00:00:12.940 Professor of Medicine and settle

NOTE Confidence: 0.81217790625

00:00:12.940 --> 00:00:14.636 in developmental biology at

NOTE Confidence: 0.81217790625

00:00:14.636 --> 00:00:16.679 Vanderbilt University Medical Center.

NOTE Confidence: 0.81217790625

00:00:16.680 --> 00:00:19.530 And he's Co director of the

NOTE Confidence: 0.81217790625

00:00:19.530 --> 00:00:22.000 Epithelial Biology Center and Ingram

NOTE Confidence: 0.81217790625

00:00:22.000 --> 00:00:24.080 Professor of Cancer Research.

NOTE Confidence: 0.81217790625

00:00:24.080 --> 00:00:26.768 And he's also the principal investigator

NOTE Confidence: 0.81217790625

00:00:26.768 --> 00:00:30.340 of the GI GI Spore at Vanderbilt.

NOTE Confidence: 0.81217790625

00:00:30.340 --> 00:00:33.095 He went to Princeton University

NOTE Confidence: 0.81217790625

00:00:33.095 --> 00:00:35.299 for majoring in politics,

NOTE Confidence: 0.81217790625

00:00:35.300 --> 00:00:37.600 not in biology or chemistry.

NOTE Confidence: 0.81217790625

00:00:37.600 --> 00:00:38.330 And then.

NOTE Confidence: 0.81217790625

00:00:38.330 --> 00:00:41.533 Went to law school at at Georgetown

NOTE Confidence: 0.81217790625

00:00:41.533 --> 00:00:43.577 after graduating from Princeton

NOTE Confidence: 0.81217790625

00:00:43.577 --> 00:00:47.169 and but they dropped off on three

NOTE Confidence: 0.81217790625

00:00:47.169 --> 00:00:49.634 weeks after entering law school.

NOTE Confidence: 0.81217790625

00:00:49.640 --> 00:00:52.460 Then prepare to enter the medical

NOTE Confidence: 0.81217790625

00:00:52.460 --> 00:00:55.300 school and enter the Georgetown

NOTE Confidence: 0.81217790625

00:00:55.300 --> 00:00:58.220 Medical School and then politics

NOTE Confidence: 0.81217790625

00:00:58.220 --> 00:01:01.020 is internal medicine residency at

NOTE Confidence: 0.81217790625

00:01:01.020 --> 00:01:03.820 Emory and then Medical Oncology

NOTE Confidence: 0.81217790625

00:01:03.820 --> 00:01:06.620 Fellowship at Georgetown and then

NOTE Confidence: 0.81217790625

00:01:06.620 --> 00:01:08.580 gastroenterology fellowship double.

NOTE Confidence: 0.81217790625

00:01:08.580 --> 00:01:11.250 Fellowship and at Mayo Clinic,

NOTE Confidence: 0.81217790625

00:01:11.250 --> 00:01:14.826 and stayed there as an assistant

NOTE Confidence: 0.81217790625

00:01:14.826 --> 00:01:18.452 professor for a foreign year before

NOTE Confidence: 0.81217790625

00:01:18.452 --> 00:01:21.626 he moved to Vanderbilt in 1986,

NOTE Confidence: 0.81217790625

00:01:21.626 --> 00:01:24.474 and he has stayed at Vanderbilt since then.

NOTE Confidence: 0.66733843

00:01:26.530 --> 00:01:32.606 He. Is the most hardworking person

NOTE Confidence: 0.66733843

00:01:32.606 --> 00:01:34.712 I've I've ever met, actually.

NOTE Confidence: 0.66733843

00:01:34.712 --> 00:01:38.400 So he's a really successful,

NOTE Confidence: 0.66733843

00:01:38.400 --> 00:01:40.800 exemplary physician and scientist.

NOTE Confidence: 0.66733843

00:01:40.800 --> 00:01:44.248 I really admire and.

NOTE Confidence: 0.66733843

00:01:44.250 --> 00:01:47.655 So his, you know, work day and

NOTE Confidence: 0.66733843

00:01:47.655 --> 00:01:49.470 during the week is like Monday,

NOTE Confidence: 0.66733843

00:01:49.470 --> 00:01:51.042 Tuesday, Wednesday, Thursday,

NOTE Confidence: 0.66733843

00:01:51.042 --> 00:01:54.460 Friday, Friday, Friday.

NOTE Confidence: 0.66733843

00:01:54.460 --> 00:01:58.780 That's done. And when I try to

NOTE Confidence: 0.66733843

00:01:58.780 --> 00:02:01.880 join his laboratory as a postdoc.

NOTE Confidence: 0.66733843

00:02:01.880 --> 00:02:04.694 That he set up our first meeting

NOTE Confidence: 0.66733843

00:02:04.694 --> 00:02:07.213 on Thursday at 8:00 in the

NOTE Confidence: 0.66733843

00:02:07.213 --> 00:02:10.619 morning and he always comes in,

NOTE Confidence: 0.66733843

00:02:10.619 --> 00:02:12.977 you know during the weekend holidays

NOTE Confidence: 0.66733843

00:02:12.977 --> 00:02:15.771 and then comes in the oldest among

NOTE Confidence: 0.66733843

00:02:15.771 --> 00:02:19.655 the all the land members and leave the

NOTE Confidence: 0.66733843

00:02:19.655 --> 00:02:22.763 last yeah in the laboratory I and.

NOTE Confidence: 0.66733843

00:02:22.770 --> 00:02:24.910 This is Eugene Cliffy.

NOTE Confidence: 0.66733843

00:02:24.910 --> 00:02:27.350 So after he moved to Vanderbilt

NOTE Confidence: 0.66733843

00:02:27.350 --> 00:02:29.414 within a year, I just looked at.

NOTE Confidence: 0.66733843

00:02:29.414 --> 00:02:30.167 I didn't know.

NOTE Confidence: 0.66733843

00:02:30.170 --> 00:02:32.949 I just realized that he published 5

NOTE Confidence: 0.66733843

00:02:32.949 --> 00:02:35.229 first author papers within a year,

NOTE Confidence: 0.66733843

00:02:35.230 --> 00:02:40.660 including Nature, Cancer Research and ACI.

NOTE Confidence: 0.66733843

00:02:40.660 --> 00:02:43.677 Clearly shows how you know the he's

NOTE Confidence: 0.66733843

00:02:43.677 --> 00:02:45.840 a really successful physician,

NOTE Confidence: 0.66733843

00:02:45.840 --> 00:02:47.168 physician, scientist.

NOTE Confidence: 0.66733843

00:02:47.168 --> 00:02:53.390 And he has also one thing I also admire.

NOTE Confidence: 0.66733843

00:02:53.390 --> 00:02:55.754 Respect him as though he always

NOTE Confidence: 0.66733843

00:02:55.754 --> 00:02:57.960 tried to learn new things.

NOTE Confidence: 0.66733843

00:02:57.960 --> 00:03:01.256 He tried to keep learning at

NOTE Confidence: 0.66733843

00:03:01.256 --> 00:03:03.470 least one new thing every day,

NOTE Confidence: 0.66733843

00:03:03.470 --> 00:03:06.620 so he may take notes in every

NOTE Confidence: 0.66733843

00:03:06.620 --> 00:03:09.579 seminars and conferences and on.

NOTE Confidence: 0.66733843

00:03:09.579 --> 00:03:13.916 Read the papers every day has

NOTE Confidence: 0.66733843

00:03:13.916 --> 00:03:19.300 practicing that over 30 years so.

NOTE Confidence: 0.66733843

00:03:19.300 --> 00:03:22.744 And he has published more than 300

NOTE Confidence: 0.66733843

00:03:22.744 --> 00:03:27.140 papers so far and I had this many

NOTE Confidence: 0.66733843

00:03:27.140 --> 00:03:29.204 seminal discoveries including the,

NOTE Confidence: 0.66733843

00:03:29.204 --> 00:03:31.840 you know, TGF alpha is the,

NOTE Confidence: 0.66733843

00:03:31.840 --> 00:03:33.180 you know,

NOTE Confidence: 0.66733843

00:03:33.180 --> 00:03:35.440 pathogenesis for the mandatory disease.

NOTE Confidence: 0.66733843

00:03:35.440 --> 00:03:39.740 Also performed the clinical trial

NOTE Confidence: 0.66733843

00:03:39.740 --> 00:03:41.840 treating the military disease patient

NOTE Confidence: 0.66733843

00:03:41.840 --> 00:03:43.940 with the cetuximab treatment and

NOTE Confidence: 0.66733843

00:03:44.000 --> 00:03:46.340 also found the Elic wine is a,

NOTE Confidence: 0.66733843

00:03:46.340 --> 00:03:47.232 you know,

NOTE Confidence: 0.66733843

00:03:47.232 --> 00:03:49.908 quiescent stem cell marker in intestine.

NOTE Confidence: 0.66733843

00:03:49.910 --> 00:03:51.830 And also showed that you know,

NOTE Confidence: 0.66733843

00:03:51.830 --> 00:03:56.588 long non coding RNA's near 100 HD is

NOTE Confidence: 0.66733843

00:03:56.588 --> 00:03:59.696 the reason why the colorectal cancer.

NOTE Confidence: 0.66733843

00:03:59.700 --> 00:04:02.232 Shows the resistance to the setup

NOTE Confidence: 0.66733843

00:04:02.232 --> 00:04:05.261 symmetry kment via the wind better

NOTE Confidence: 0.66733843

00:04:05.261 --> 00:04:07.160 containing signaling pathways.

NOTE Confidence: 0.66733843

00:04:07.160 --> 00:04:10.719 And recently he also showed that EGFR

NOTE Confidence: 0.66733843

00:04:10.719 --> 00:04:14.352 is secreted in within the oxygen from

NOTE Confidence: 0.66733843

00:04:14.352 --> 00:04:18.520 the colorectal cancer and also showed that.

NOTE Confidence: 0.66733843

00:04:18.520 --> 00:04:22.517 In the contrary to the fields belief,

NOTE Confidence: 0.66733843

00:04:22.520 --> 00:04:25.558 RNA's are not included in the EXOGEN,

NOTE Confidence: 0.66733843

00:04:25.560 --> 00:04:28.668 but it's mainly secreted from the,

NOTE Confidence: 0.66733843

00:04:28.670 --> 00:04:28.960 you know,

NOTE Confidence: 0.66733843

00:04:28.960 --> 00:04:33.032 smaller compartment secreted from the cells,

NOTE Confidence: 0.66733843

00:04:33.032 --> 00:04:35.404 different from the exogen

NOTE Confidence: 0.66733843

00:04:35.404 --> 00:04:37.720 and recently discovered.

NOTE Confidence: 0.66733843

00:04:37.720 --> 00:04:39.286 Smaller nano nanoparticles,

NOTE Confidence: 0.66733843

00:04:39.286 --> 00:04:41.374 smaller than the exosome.

NOTE Confidence: 0.66733843

00:04:41.380 --> 00:04:44.439 And he named it Super Mere and

NOTE Confidence: 0.66733843

00:04:44.440 --> 00:04:46.384 showed that it's functionally

NOTE Confidence: 0.66733843

00:04:46.384 --> 00:04:48.460 important in biology.

NOTE Confidence: 0.66733843

00:04:48.460 --> 00:04:49.220 So.

NOTE Confidence: 0.5320036

00:04:51.480 --> 00:04:53.020 Ohh, sorry again.

NOTE Confidence: 0.5320036

00:04:53.020 --> 00:04:54.193 Maybe that was too much.

NOTE Confidence: 0.5320036

00:04:54.193 --> 00:04:55.858 OK, so without further ado,

NOTE Confidence: 0.5320036

00:04:55.860 --> 00:04:57.498 his title on the talk of

NOTE Confidence: 0.5320036

00:04:57.498 --> 00:04:59.726 his title is the update on

NOTE Confidence: 0.5320036

00:04:59.726 --> 00:05:01.325 extracellular vesicles and

NOTE Confidence: 0.5320036

00:05:01.325 --> 00:05:03.457 nanoparticles in colorectal cancer.

NOTE Confidence: 0.5320036

00:05:03.460 --> 00:05:04.810 Please join me in welcoming

NOTE Confidence: 0.890958998333333

00:05:04.820 --> 00:05:06.716 Doctor Patrick. Thank you so much.

NOTE Confidence: 0.8199451575

00:05:09.760 --> 00:05:14.002 So it reminding me that I started

NOTE Confidence: 0.8199451575

00:05:14.002 --> 00:05:17.058 in 1986 at Vanderbilt and I remember

NOTE Confidence: 0.8199451575

00:05:17.058 --> 00:05:20.721 I trained in as an MD and I I met

NOTE Confidence: 0.8199451575

00:05:20.721 --> 00:05:23.230 Stanley Cohen at that time who I

NOTE Confidence: 0.8199451575

00:05:23.230 --> 00:05:25.996 hadn't known before and you know I

NOTE Confidence: 0.8199451575

00:05:25.996 --> 00:05:28.880 said to him can somebody like myself

NOTE Confidence: 0.8199451575

00:05:28.880 --> 00:05:31.763 trained and in medicine do anything

NOTE Confidence: 0.8199451575

00:05:31.763 --> 00:05:34.148 worthwhile and and research and

NOTE Confidence: 0.8199451575

00:05:34.150 --> 00:05:37.167 Stanley used to walk around the 6th

NOTE Confidence: 0.8199451575

00:05:37.167 --> 00:05:39.648 floor the biochemistry with a corncob.

NOTE Confidence: 0.8199451575

00:05:39.650 --> 00:05:42.062 Type and just thinking of the

NOTE Confidence: 0.8199451575

00:05:42.062 --> 00:05:43.670 simplest experiment that would

NOTE Confidence: 0.8199451575

00:05:43.741 --> 00:05:45.349 be the most informative.

NOTE Confidence: 0.8199451575

00:05:45.350 --> 00:05:48.168 And he said to me, yes, it can do two things.

NOTE Confidence: 0.8199451575

00:05:48.170 --> 00:05:50.303 He and he would usually cut his hands over

NOTE Confidence: 0.8199451575

00:05:50.303 --> 00:05:52.598 his eyes when he was going to make a point.

NOTE Confidence: 0.8199451575

00:05:52.600 --> 00:05:55.148 And he said if you pay careful

NOTE Confidence: 0.8199451575

00:05:55.148 --> 00:05:57.730 attention to your data and you're lucky.

NOTE Confidence: 0.8199451575

00:05:57.730 --> 00:05:59.950 And I thought that was some

NOTE Confidence: 0.8199451575

00:05:59.950 --> 00:06:02.480 of the best advice I ever got.

NOTE Confidence: 0.8199451575

00:06:02.480 --> 00:06:05.833 So it's great to be here and

NOTE Confidence: 0.8199451575

00:06:05.833 --> 00:06:08.650 it's nice to see how well.

NOTE Confidence: 0.8199451575

00:06:08.650 --> 00:06:12.290 That one Jay is settling in and how

NOTE Confidence: 0.8199451575

00:06:12.401 --> 00:06:16.300 welcoming everyone has been and that he

NOTE Confidence: 0.8199451575

00:06:16.300 --> 00:06:20.809 has such superb mentors and Katie and Fred.

NOTE Confidence: 0.8199451575

00:06:20.810 --> 00:06:24.790 And So what I'm going to try to do is,

NOTE Confidence: 0.8199451575

00:06:24.790 --> 00:06:26.974 is sort of give you an overview

NOTE Confidence: 0.8199451575

00:06:26.974 --> 00:06:29.209 about some of the things that

NOTE Confidence: 0.8199451575

00:06:29.209 --> 00:06:31.249 we've been doing more recently.

NOTE Confidence: 0.8199451575

00:06:31.250 --> 00:06:33.128 I'd like to keep it informal,

NOTE Confidence: 0.8199451575

00:06:33.130 --> 00:06:34.410 so if you have questions,

NOTE Confidence: 0.8199451575

00:06:34.410 --> 00:06:37.735 don't hesitate to stop and

NOTE Confidence: 0.8199451575

00:06:37.735 --> 00:06:40.272 ask me and I'm also.

NOTE Confidence: 0.8199451575

00:06:40.272 --> 00:06:41.898 I want to present a fair

NOTE Confidence: 0.8199451575

00:06:41.898 --> 00:06:43.549 amount of unpublished data.

NOTE Confidence: 0.8199451575

00:06:43.550 --> 00:06:44.050 So.

NOTE Confidence: 0.736038506666667

00:06:52.210 --> 00:06:54.256 Was told if I press that.

NOTE Confidence: 0.927748111666667

00:06:56.320 --> 00:06:59.020 It would work. But maybe not.

NOTE Confidence: 0.85166

00:07:02.180 --> 00:07:02.640 This one.

NOTE Confidence: 0.84061304

00:07:05.840 --> 00:07:08.720 OK, let's see it. Yep.

NOTE Confidence: 0.84061304

00:07:08.720 --> 00:07:13.760 OK, so I wanted to give first.

NOTE Confidence: 0.84061304

00:07:13.760 --> 00:07:16.184 A little bit of background and

NOTE Confidence: 0.84061304

00:07:16.184 --> 00:07:19.089 and I wanna tell you about this

NOTE Confidence: 0.84061304

00:07:19.090 --> 00:07:21.166 overarching 3 pronged approach.

NOTE Confidence: 0.84061304

00:07:21.166 --> 00:07:23.761 We start taken to study

NOTE Confidence: 0.84061304

00:07:23.761 --> 00:07:26.019 colorectal cancer at Vanderbilt.

NOTE Confidence: 0.84061304

00:07:26.020 --> 00:07:28.210 And I think this could be

NOTE Confidence: 0.84061304

00:07:28.210 --> 00:07:30.230 applied to any solid tumor.

NOTE Confidence: 0.84061304

00:07:30.230 --> 00:07:33.002 And so we start with polarized

NOTE Confidence: 0.84061304

00:07:33.002 --> 00:07:36.070 epithelial cells and we're interested in,

NOTE Confidence: 0.84061304

00:07:36.070 --> 00:07:38.386 in various acts, aspects that I'll,

NOTE Confidence: 0.84061304

00:07:38.390 --> 00:07:40.406 I'll tell you about in just a moment.

NOTE Confidence: 0.84061304

00:07:40.410 --> 00:07:44.414 And then we moved from in vitro.

NOTE Confidence: 0.84061304

00:07:44.420 --> 00:07:48.470 To mouse models of colon cancer and then to

NOTE Confidence: 0.84061304

00:07:48.470 --> 00:07:52.325 human colorectal cancer and each of these.

NOTE Confidence: 0.84061304

00:07:52.330 --> 00:07:55.312 These approaches are are going by

NOTE Confidence: 0.84061304

00:07:55.312 --> 00:07:59.076 directionally and we can in an iterative

NOTE Confidence: 0.84061304

00:07:59.076 --> 00:08:02.448 way to hopefully make significant advances.

NOTE Confidence: 0.84061304

00:08:02.450 --> 00:08:04.946 And so as Juan J mentioned,

NOTE Confidence: 0.84061304

00:08:04.950 --> 00:08:07.182 in 2010 I started the epithelial

NOTE Confidence: 0.84061304

00:08:07.182 --> 00:08:09.070 Biology Center and that's something

NOTE Confidence: 0.84061304

00:08:09.070 --> 00:08:11.750 that Jim Golden Ring and I Co direct.

NOTE Confidence: 0.84061304

00:08:11.750 --> 00:08:14.348 Now we have over 40 members.

NOTE Confidence: 0.84061304

00:08:14.350 --> 00:08:16.590 Areas of interest include

NOTE Confidence: 0.84061304

00:08:16.590 --> 00:08:17.710 epithelial polarity,

NOTE Confidence: 0.84061304

00:08:17.710 --> 00:08:19.130 vesicle trafficking,

NOTE Confidence: 0.84061304

00:08:19.130 --> 00:08:22.680 stem cells and extracellular vesicles.

NOTE Confidence: 0.84061304

00:08:22.680 --> 00:08:25.123 And and the center tries to bring

NOTE Confidence: 0.84061304

00:08:25.123 --> 00:08:27.773 forward new tools that can be used

NOTE Confidence: 0.84061304

00:08:27.773 --> 00:08:29.688 throughout their the university we

NOTE Confidence: 0.84061304

00:08:29.688 --> 00:08:32.195 have a pipeline for single cell RNA

NOTE Confidence: 0.84061304

00:08:32.195 --> 00:08:33.698 seek Multiplex immunofluorescence

NOTE Confidence: 0.84061304

00:08:33.698 --> 00:08:37.751 that David Rim gave us some good

NOTE Confidence: 0.84061304

00:08:37.751 --> 00:08:40.286 advice about a few years ago.

NOTE Confidence: 0.84061304

00:08:40.290 --> 00:08:40.891 And.

NOTE Confidence: 0.84061304

00:08:40.891 --> 00:08:44.497 Isolation of the ebbs and nanoparticles,

NOTE Confidence: 0.84061304

00:08:44.500 --> 00:08:46.908 which I'll be telling you about today

NOTE Confidence: 0.84061304

00:08:46.908 --> 00:08:50.077 and we have a symposium that alternates

NOTE Confidence: 0.84061304

00:08:50.077 --> 00:08:52.652 with an epithelial pathobiology class.

NOTE Confidence: 0.84061304

00:08:52.660 --> 00:08:55.020 This year is the symposium

NOTE Confidence: 0.84061304

00:08:55.020 --> 00:08:57.380 in and on April 3rd.

NOTE Confidence: 0.84061304

00:08:57.380 --> 00:09:00.362 The theme this year is a basic

NOTE Confidence: 0.84061304

00:09:00.362 --> 00:09:02.177 biology that therapeutic intervention

NOTE Confidence: 0.84061304

00:09:02.177 --> 00:09:05.376 and we have Carl Sawyers and Health

NOTE Confidence: 0.84061304

00:09:05.376 --> 00:09:08.230 Chapman as as our keynote speakers.

NOTE Confidence: 0.84061304

00:09:08.230 --> 00:09:11.464 And then as far as mouse modeling,

NOTE Confidence: 0.84061304

00:09:11.470 --> 00:09:14.039 we've been working on trying to determine

NOTE Confidence: 0.84061304

00:09:14.039 --> 00:09:16.709 the cell of origin and colonic neoplasia

NOTE Confidence: 0.84061304

00:09:16.709 --> 00:09:19.510 use this elry one pre jot driver.

NOTE Confidence: 0.84061304

00:09:19.510 --> 00:09:22.348 This panel will be negative regulator

NOTE Confidence: 0.84061304

00:09:22.350 --> 00:09:24.762 that won Jay mentioned and then

NOTE Confidence: 0.84061304

00:09:24.762 --> 00:09:26.883 we've made a useful reporter

NOTE Confidence: 0.84061304

00:09:26.883 --> 00:09:29.488 mouse that I think monitors EGFR

NOTE Confidence: 0.84061304

00:09:29.488 --> 00:09:32.631 visually and and Juan Jay I think

NOTE Confidence: 0.84061304

00:09:32.631 --> 00:09:35.570 is going to take really effective

NOTE Confidence: 0.84061304

00:09:35.570 --> 00:09:38.186 use of that model and then.

NOTE Confidence: 0.84061304

00:09:38.186 --> 00:09:40.970 We've had our GI Sport since 2002 and.

NOTE Confidence: 0.918880293636364

00:09:44.220 --> 00:09:48.028 Presently we have the three projects that

NOTE Confidence: 0.918880293636364

00:09:48.028 --> 00:09:51.502 are are listed here and we're facing as

NOTE Confidence: 0.918880293636364

00:09:51.502 --> 00:09:54.309 I was telling Katie a little while ago,

NOTE Confidence: 0.918880293636364

00:09:54.310 --> 00:09:56.806 we're facing our competitive renewal in

NOTE Confidence: 0.918880293636364

00:09:56.806 --> 00:09:59.963 September and one of the projects and I'm

NOTE Confidence: 0.918880293636364

00:09:59.963 --> 00:10:02.931 going to be talking about this as I go

NOTE Confidence: 0.918880293636364

00:10:02.931 --> 00:10:05.506 through the talk is to try to overcome

NOTE Confidence: 0.918880293636364

00:10:05.506 --> 00:10:09.386 immune exclusion and microsatellite stable,

NOTE Confidence: 0.918880293636364

00:10:09.390 --> 00:10:13.658 chromosomally unstable colorectal cancer.

NOTE Confidence: 0.79412067

00:10:15.740 --> 00:10:22.180 So about. Couple years ago now.

NOTE Confidence: 0.79412067

00:10:22.180 --> 00:10:26.212 We have been involved in human

NOTE Confidence: 0.79412067

00:10:26.212 --> 00:10:30.332 tumor Atlas network and our project

NOTE Confidence: 0.79412067

00:10:30.332 --> 00:10:33.155 which was headed by myself,

NOTE Confidence: 0.79412067

00:10:33.155 --> 00:10:35.970 Ken Lau and Martha Shrubsole was

NOTE Confidence: 0.79412067

00:10:35.970 --> 00:10:38.290 to do a single cell Atlas of the

NOTE Confidence: 0.79412067

00:10:38.290 --> 00:10:40.166 two most common pre malignant

NOTE Confidence: 0.79412067

00:10:40.166 --> 00:10:42.979 tumors of the of the colon and

NOTE Confidence: 0.79412067

00:10:42.979 --> 00:10:45.339 those are the conventional adenoma.

NOTE Confidence: 0.79412067

00:10:45.340 --> 00:10:50.010 And and sessile serrated lesions

NOTE Confidence: 0.79412067

00:10:50.010 --> 00:10:54.274 this is going to be about 85% of pre

NOTE Confidence: 0.79412067

00:10:54.274 --> 00:10:57.314 malignant tumors these are 15% and

NOTE Confidence: 0.79412067

00:10:57.314 --> 00:11:00.706 these were really pretty well uncertain

NOTE Confidence: 0.79412067

00:11:00.706 --> 00:11:06.094 in terms of their origin and what

NOTE Confidence: 0.79412067

00:11:06.094 --> 00:11:08.604 we found perhaps not unexpectedly

NOTE Confidence: 0.79412067

00:11:08.604 --> 00:11:10.687 was that the conventional abnormal

NOTE Confidence: 0.79412067

00:11:10.687 --> 00:11:13.200 was a wind driven expansion of stem

NOTE Confidence: 0.79412067

00:11:13.263 --> 00:11:15.752 progenitor cells that grip base but.

NOTE Confidence: 0.79412067

00:11:15.752 --> 00:11:17.076 Very unexpectedly,

NOTE Confidence: 0.79412067

00:11:17.076 --> 00:11:20.386 the sessile serrated lesions which

NOTE Confidence: 0.79412067

00:11:20.386 --> 00:11:23.894 are occurring in in a background

NOTE Confidence: 0.79412067

00:11:23.894 --> 00:11:25.392 of inflammation predominantly

NOTE Confidence: 0.79412067

00:11:25.392 --> 00:11:28.556 on the right side of the colon,

NOTE Confidence: 0.79412067

00:11:28.560 --> 00:11:31.670 we're due to gastric metaplasia and and

NOTE Confidence: 0.79412067

00:11:31.670 --> 00:11:35.400 we think it's driven by a loss of CD,

NOTE Confidence: 0.79412067

00:11:35.400 --> 00:11:39.840 A CD X2 which is a fine gut fate determinant.

NOTE Confidence: 0.79412067

00:11:39.840 --> 00:11:43.280 And when that happens you revert to a

NOTE Confidence: 0.79412067

00:11:43.280 --> 00:11:46.129 more rostral fate and in this case.

NOTE Confidence: 0.79412067

00:11:46.130 --> 00:11:48.538 Have histologic elements that

NOTE Confidence: 0.79412067

00:11:48.538 --> 00:11:51.548 are seen in the stomach.

NOTE Confidence: 0.79412067

00:11:51.550 --> 00:11:53.930 So we were able to provide now

NOTE Confidence: 0.79412067

00:11:53.930 --> 00:11:56.824 a tool for pathologists to make

NOTE Confidence: 0.79412067

00:11:56.824 --> 00:11:59.809 this diagnosis because it's a

NOTE Confidence: 0.79412067

00:11:59.809 --> 00:12:01.749 challenging diagnosis to make.

NOTE Confidence: 0.79412067

00:12:01.750 --> 00:12:04.598 But now you have a number of markers

NOTE Confidence: 0.79412067

00:12:04.598 --> 00:12:07.252 that you can do that you can use

NOTE Confidence: 0.79412067

00:12:07.252 --> 00:12:09.760 to to help make that diagnosis.

NOTE Confidence: 0.79412067

00:12:09.760 --> 00:12:12.170 And.

NOTE Confidence: 0.79412067

00:12:12.170 --> 00:12:15.635 What we've done more recently and we've

NOTE Confidence: 0.79412067

00:12:15.635 --> 00:12:19.426 just submitted a paper is to now advance.

NOTE Confidence: 0.79412067

00:12:19.426 --> 00:12:22.810 So conventional adenomas are going to be

NOTE Confidence: 0.79412067

00:12:22.810 --> 00:12:25.350 moving towards microsatellite stable,

NOTE Confidence: 0.79412067

00:12:25.350 --> 00:12:28.526 chromosomal unstable cancer whereas

NOTE Confidence: 0.79412067

00:12:28.526 --> 00:12:30.908 the microsatellite unstable.

NOTE Confidence: 0.79412067

00:12:30.910 --> 00:12:34.648 Or the gastric metaplasia tend to

NOTE Confidence: 0.79412067

00:12:34.648 --> 00:12:38.006 evolve to a microsatellite unstable

NOTE Confidence: 0.79412067

00:12:38.006 --> 00:12:42.106 hyper mutated tumor and and these

NOTE Confidence: 0.79412067

00:12:42.106 --> 00:12:45.417 tumors we see a lot of immune cells,

NOTE Confidence: 0.79412067

00:12:45.420 --> 00:12:51.148 CDA T cells but but by and large.

NOTE Confidence: 0.79412067

00:12:51.150 --> 00:12:55.432 CDA T cells are not there in the

NOTE Confidence: 0.79412067

00:12:55.432 --> 00:12:57.516 microsatellite stable colon cancers.

NOTE Confidence: 0.79412067

00:12:57.520 --> 00:12:59.338 There are nuances that I don't

NOTE Confidence: 0.79412067

00:12:59.338 --> 00:13:01.390 have a chance to go in today,

NOTE Confidence: 0.79412067

00:13:01.390 --> 00:13:03.710 but as a generalization that

NOTE Confidence: 0.79412067

00:13:03.710 --> 00:13:06.030 appears to be the case.

NOTE Confidence: 0.79412067

00:13:06.030 --> 00:13:08.646 And So what we've just submitted

NOTE Confidence: 0.79412067

00:13:08.646 --> 00:13:12.608 now is a four gene Abune exclusion

NOTE Confidence: 0.79412067

00:13:12.608 --> 00:13:15.924 signature that we've identified in

NOTE Confidence: 0.79412067

00:13:15.924 --> 00:13:18.888 these cancers and I'll be telling

NOTE Confidence: 0.79412067

00:13:18.888 --> 00:13:21.924 you more about these proteins as

NOTE Confidence: 0.79412067

00:13:21.924 --> 00:13:24.344 I go along and that's.

NOTE Confidence: 0.79412067

00:13:24.350 --> 00:13:28.130 Dipeptidase one TGF beta induced,

NOTE Confidence: 0.79412067

00:13:28.130 --> 00:13:31.010 not to be confused, which it always is,

NOTE Confidence: 0.79412067

00:13:31.010 --> 00:13:35.870 with TGF beta 1DR1 and then pack four.

NOTE Confidence: 0.79412067

00:13:35.870 --> 00:13:39.334 So these are all membrane or

NOTE Confidence: 0.79412067

00:13:39.334 --> 00:13:40.378 secreted proteins.

NOTE Confidence: 0.79412067

00:13:40.378 --> 00:13:43.446 This is a cytosolic protein that

NOTE Confidence: 0.79412067

00:13:43.446 --> 00:13:45.398 in microsatellite stable colon

NOTE Confidence: 0.79412067

00:13:45.398 --> 00:13:48.060 cancer appears to be associated

NOTE Confidence: 0.79412067

00:13:48.060 --> 00:13:49.947 with immune exclusion.

NOTE Confidence: 0.79412067

00:13:49.950 --> 00:13:52.358 So that what I am hoping to

NOTE Confidence: 0.79412067

00:13:52.358 --> 00:13:54.460 cover today is to tell you.

NOTE Confidence: 0.79412067

00:13:54.460 --> 00:13:57.617 About work and we've in our isolation

NOTE Confidence: 0.79412067

00:13:57.617 --> 00:13:59.519 of extracellular vesicles and

NOTE Confidence: 0.79412067

00:13:59.519 --> 00:14:01.884 examiners are discovery of super

NOTE Confidence: 0.79412067

00:14:01.884 --> 00:14:04.334 meres and then identification of

NOTE Confidence: 0.79412067

00:14:04.334 --> 00:14:06.769 these ECM related clinically relevant

NOTE Confidence: 0.79412067

00:14:06.769 --> 00:14:09.380 cargo and colorectal cancer that

NOTE Confidence: 0.79412067

00:14:09.380 --> 00:14:12.680 may contribute to immune exclusion

NOTE Confidence: 0.79412067

00:14:12.680 --> 00:14:14.660 as I've indicated.

NOTE Confidence: 0.79412067

00:14:14.660 --> 00:14:17.782 So how I got involved in extracellular

NOTE Confidence: 0.79412067

00:14:17.782 --> 00:14:19.928 vesicles was really an outgrowth

NOTE Confidence: 0.79412067

00:14:19.928 --> 00:14:22.824 of the basic work in the lab which

NOTE Confidence: 0.79412067

00:14:22.901 --> 00:14:24.749 is really to understand.

NOTE Confidence: 0.79412067

00:14:24.750 --> 00:14:27.228 The trafficking of the EGF receptor

NOTE Confidence: 0.79412067

00:14:27.228 --> 00:14:30.070 ligands and the context of a polarized

NOTE Confidence: 0.79412067

00:14:30.070 --> 00:14:32.667 epithelial cell and by and large we've

NOTE Confidence: 0.832465664

00:14:32.742 --> 00:14:35.682 used polarized MDCK cells which we

NOTE Confidence: 0.832465664

00:14:35.682 --> 00:14:37.642 overexpressed the different ligands

NOTE Confidence: 0.832465664

00:14:37.650 --> 00:14:41.094 and they have 20 to 40,000 basolateral

NOTE Confidence: 0.832465664

00:14:41.094 --> 00:14:44.562 egbdf receptors as what we think is a

NOTE Confidence: 0.832465664

00:14:44.562 --> 00:14:48.019 complement of of a normal epithelial cells.

NOTE Confidence: 0.832465664

00:14:48.020 --> 00:14:49.840 And So what we've systematically

NOTE Confidence: 0.832465664

00:14:49.840 --> 00:14:53.025 done over the years is to look at the

NOTE Confidence: 0.832465664

00:14:53.025 --> 00:14:55.570 trafficking of the ligands in that setting.

NOTE Confidence: 0.832465664

00:14:55.570 --> 00:14:57.834 And it's really been what I would say,

NOTE Confidence: 0.832465664

00:14:57.840 --> 00:15:00.199 a mother lode of good cell biology

NOTE Confidence: 0.832465664

00:15:00.199 --> 00:15:02.457 in terms of each ligand having

NOTE Confidence: 0.832465664

00:15:02.457 --> 00:15:05.180 nuances in terms of where it goes.

NOTE Confidence: 0.763065059411765

00:15:07.190 --> 00:15:10.732 Which surface, who cleaves it and then

NOTE Confidence: 0.763065059411765

00:15:10.732 --> 00:15:14.725 how actively it engages the receptor

NOTE Confidence: 0.763065059411765

00:15:14.725 --> 00:15:17.889 with different signaling consequences.

NOTE Confidence: 0.763065059411765

00:15:17.890 --> 00:15:22.130 And so when we were studying HB EGF,

NOTE Confidence: 0.763065059411765

00:15:22.130 --> 00:15:24.671 we were surprised to see that there

NOTE Confidence: 0.763065059411765

00:15:24.671 --> 00:15:27.286 was full length HB EGF in the apical

NOTE Confidence: 0.763065059411765

00:15:27.286 --> 00:15:30.029 media but but not at the cell surface.

NOTE Confidence: 0.763065059411765

00:15:30.030 --> 00:15:33.174 So one formal possibility was that it was

NOTE Confidence: 0.763065059411765

00:15:33.174 --> 00:15:37.880 being released and an exosome and so in fact.

NOTE Confidence: 0.763065059411765

00:15:37.880 --> 00:15:39.844 By combining sequential ultracentrifugation

NOTE Confidence: 0.763065059411765

00:15:39.844 --> 00:15:43.378 and and a technique that we developed

NOTE Confidence: 0.763065059411765

00:15:43.378 --> 00:15:45.953 in the lab called fluorescence

NOTE Confidence: 0.763065059411765

00:15:45.953 --> 00:15:47.498 activated vesicle sorting,

NOTE Confidence: 0.763065059411765

00:15:47.500 --> 00:15:49.816 which I'll mention in a minute,

NOTE Confidence: 0.763065059411765

00:15:49.820 --> 00:15:53.556 we were able to show that in fact

NOTE Confidence: 0.763065059411765

00:15:53.560 --> 00:15:55.888 these different live bands were present

NOTE Confidence: 0.763065059411765

00:15:55.888 --> 00:15:57.887 in individual exosomes from breast

NOTE Confidence: 0.763065059411765

00:15:57.887 --> 00:15:59.817 and colorectal cancer cell lines,

NOTE Confidence: 0.763065059411765

00:15:59.820 --> 00:16:03.110 but they differ and a rag exosomes

NOTE Confidence: 0.763065059411765

00:16:03.110 --> 00:16:05.100 enhanced invasiveness of recipient

NOTE Confidence: 0.763065059411765

00:16:05.100 --> 00:16:07.560 cancer cells more than TDF.

NOTE Confidence: 0.763065059411765

00:16:07.560 --> 00:16:10.577 Often HEEF exosomes and this was in

NOTE Confidence: 0.763065059411765

00:16:10.577 --> 00:16:13.196 the setting of overexpressing these

NOTE Confidence: 0.763065059411765

00:16:13.196 --> 00:16:16.886 different ligands in the MDCK cells.

NOTE Confidence: 0.763065059411765

00:16:16.890 --> 00:16:18.100 And we were able to.

NOTE Confidence: 0.694047500375

00:16:20.580 --> 00:16:22.570 Identified that there were 24

NOTE Confidence: 0.694047500375

00:16:22.570 --> 00:16:25.035 molecules of amperage on that were

NOTE Confidence: 0.694047500375

00:16:25.035 --> 00:16:27.060 packaged in individual axes on.

NOTE Confidence: 0.694047500375

00:16:27.060 --> 00:16:31.440 So these are like signaling payloads.

NOTE Confidence: 0.694047500375

00:16:31.440 --> 00:16:35.224 And we coined the term that a

NOTE Confidence: 0.694047500375

00:16:35.224 --> 00:16:38.026 Reg was in part working through

NOTE Confidence: 0.694047500375

00:16:38.026 --> 00:16:40.630 EGFR receptor to introduce the

NOTE Confidence: 0.694047500375

00:16:40.630 --> 00:16:43.265 idea of extra print signaling,

NOTE Confidence: 0.694047500375

00:16:43.270 --> 00:16:46.318 which has not become a household

NOTE Confidence: 0.694047500375

00:16:46.318 --> 00:16:48.350 term by any means.

NOTE Confidence: 0.694047500375

00:16:48.350 --> 00:16:51.959 And we were also able to show that EGF

NOTE Confidence: 0.694047500375

00:16:51.959 --> 00:16:54.706 receptor itself was packaged in EB's

NOTE Confidence: 0.694047500375

00:16:54.706 --> 00:16:58.090 and and this is an example of a line

NOTE Confidence: 0.694047500375

00:16:58.187 --> 00:17:01.309 that we frequently use in the lab.

NOTE Confidence: 0.694047500375

00:17:01.310 --> 00:17:02.729 So this is.

NOTE Confidence: 0.694047500375

00:17:02.729 --> 00:17:06.040 50, which is a polar rectal cancer

NOTE Confidence: 0.694047500375

00:17:06.147 --> 00:17:08.456 cell line that has 5,000,000

NOTE Confidence: 0.694047500375

00:17:08.456 --> 00:17:10.280 EGF receptors per cell.

NOTE Confidence: 0.694047500375

00:17:10.280 --> 00:17:12.926 So it's sort of the granddaddy

NOTE Confidence: 0.694047500375

00:17:12.926 --> 00:17:15.522 of an EGF receptor overexpressing

NOTE Confidence: 0.694047500375

00:17:15.522 --> 00:17:17.748 cancer cell lines.

NOTE Confidence: 0.694047500375

00:17:17.750 --> 00:17:21.313 And so Jim Higginbotham in the lab

NOTE Confidence: 0.694047500375

00:17:21.313 --> 00:17:25.840 was able to flow sort with directly

NOTE Confidence: 0.694047500375

00:17:25.840 --> 00:17:29.910 labeled antibodies to either.

NOTE Confidence: 0.694047500375

00:17:29.910 --> 00:17:30.605 Cetuximab,

NOTE Confidence: 0.694047500375

00:17:30.605 --> 00:17:34.080 or a tetraspanin that's commonly

NOTE Confidence: 0.694047500375

00:17:34.080 --> 00:17:36.165 used to mark.

NOTE Confidence: 0.694047500375

00:17:36.170 --> 00:17:40.358 Exosomes and was able to flow

NOTE Confidence: 0.694047500375

00:17:40.358 --> 00:17:42.452 short double positive,

NOTE Confidence: 0.694047500375

00:17:42.460 --> 00:17:46.032 double negative further enriching

NOTE Confidence: 0.694047500375

00:17:46.032 --> 00:17:49.900 for those EB's and then we could

NOTE Confidence: 0.694047500375

00:17:49.900 --> 00:17:52.460 do Western blotting and show in

NOTE Confidence: 0.694047500375

00:17:52.460 --> 00:17:54.812 fact in the double positive we

NOTE Confidence: 0.694047500375

00:17:54.812 --> 00:17:57.514 could see EGFR and Centennial and

NOTE Confidence: 0.694047500375

00:17:57.514 --> 00:18:00.400 other exosome marker and you hear,

NOTE Confidence: 0.694047500375

00:18:00.400 --> 00:18:00.821 see,

NOTE Confidence: 0.694047500375

00:18:00.821 --> 00:18:03.768 hear that CD 81 was present in

NOTE Confidence: 0.694047500375

00:18:03.768 --> 00:18:06.289 both although enriched in the

NOTE Confidence: 0.694047500375

00:18:06.289 --> 00:18:07.879 EGFR double positive.

NOTE Confidence: 0.694047500375

00:18:07.880 --> 00:18:10.267 And then Jeff Franklin in the lab

NOTE Confidence: 0.694047500375

00:18:10.267 --> 00:18:12.854 was able to take a drop and and

NOTE Confidence: 0.694047500375

00:18:12.854 --> 00:18:15.460 put that on a cover slip and then

NOTE Confidence: 0.694047500375

00:18:15.460 --> 00:18:18.272 use storm with antibodies to EGFR

NOTE Confidence: 0.694047500375

00:18:18.272 --> 00:18:21.038 and CD9 and showing that they were

NOTE Confidence: 0.694047500375

00:18:21.040 --> 00:18:24.792 single particle that were of the

NOTE Confidence: 0.694047500375

00:18:24.792 --> 00:18:27.200 right size for an exosome that

NOTE Confidence: 0.694047500375

00:18:27.200 --> 00:18:29.780 were positive for EGFR and CD9.

NOTE Confidence: 0.89549243

00:18:32.520 --> 00:18:33.110 And.

NOTE Confidence: 0.742612754

00:18:35.370 --> 00:18:39.416 How we've taken this forward clinically is

NOTE Confidence: 0.742612754

00:18:39.416 --> 00:18:44.240 in Leo Blastoma where we know in some cases

NOTE Confidence: 0.742612754

00:18:44.240 --> 00:18:47.438 there's more overexpression of EGF receptor,

NOTE Confidence: 0.742612754

00:18:47.438 --> 00:18:50.148 there's going to be amplification.

NOTE Confidence: 0.742612754

00:18:50.150 --> 00:18:51.650 And in this particular case,

NOTE Confidence: 0.742612754

00:18:51.650 --> 00:18:53.726 we were looking at at patients

NOTE Confidence: 0.742612754

00:18:53.726 --> 00:18:55.696 that had the V3 mutation,

NOTE Confidence: 0.742612754

00:18:55.696 --> 00:18:59.400 so they have a chunk of the actual

NOTE Confidence: 0.742612754

00:18:59.498 --> 00:19:02.376 domain removed and. In this.

NOTE Confidence: 0.742612754

00:19:02.376 --> 00:19:07.668 We were able to show that we're now using.

NOTE Confidence: 0.742612754

00:19:07.670 --> 00:19:09.250 Not only she talks about,

NOTE Confidence: 0.742612754

00:19:09.250 --> 00:19:12.304 but we're also using monoclonal antibody

NOTE Confidence: 0.742612754

00:19:12.304 --> 00:19:16.486 8O6 which was generated to a by a group

NOTE Confidence: 0.742612754

00:19:16.486 --> 00:19:18.551 in Australia to the Conformationally

NOTE Confidence: 0.742612754

00:19:18.638 --> 00:19:20.516 active Ectodomain conformationally

NOTE Confidence: 0.742612754

00:19:20.516 --> 00:19:23.646 active form of EGF receptor.

NOTE Confidence: 0.742612754

00:19:23.650 --> 00:19:27.440 And so there we could see in the normal

NOTE Confidence: 0.742612754

00:19:27.440 --> 00:19:30.310 control we we didn't see a signal,

NOTE Confidence: 0.742612754

00:19:30.310 --> 00:19:33.595 whereas these four patients were

NOTE Confidence: 0.742612754

00:19:33.595 --> 00:19:36.223 positive although at differing

NOTE Confidence: 0.742612754

00:19:36.223 --> 00:19:38.898 percentages for double positivity.

NOTE Confidence: 0.742612754

00:19:38.900 --> 00:19:42.500 4806 and setup samap and so.

NOTE Confidence: 0.742612754

00:19:42.500 --> 00:19:45.120 We could then perform Westerns

NOTE Confidence: 0.742612754

00:19:45.120 --> 00:19:49.292 and here the lower band the faster

NOTE Confidence: 0.742612754

00:19:49.292 --> 00:19:52.599 migrating ban is is spurious.

NOTE Confidence: 0.742612754

00:19:52.600 --> 00:19:56.456 But we can see that the receptor is

NOTE Confidence: 0.742612754

00:19:56.456 --> 00:19:59.909 present in the normal at the right

NOTE Confidence: 0.742612754

00:19:59.909 --> 00:20:03.280 size and these B3 individuals are

NOTE Confidence: 0.742612754

00:20:03.280 --> 00:20:08.390 cancers were were had a a smaller

NOTE Confidence: 0.742612754

00:20:08.390 --> 00:20:10.368 band appropriate loading control

NOTE Confidence: 0.742612754

00:20:10.368 --> 00:20:12.864 and then we can see that.

NOTE Confidence: 0.742612754

00:20:12.870 --> 00:20:15.866 All three of the GBM patients appear

NOTE Confidence: 0.742612754

00:20:15.866 --> 00:20:19.454 to have active ETF receptor in their

NOTE Confidence: 0.742612754

00:20:19.454 --> 00:20:21.698 circulating EV's that have clearly

NOTE Confidence: 0.742612754

00:20:21.698 --> 00:20:23.808 crossed the blood brain barrier.

NOTE Confidence: 0.93552761

00:20:27.130 --> 00:20:29.650 So I've been fortunate to be

NOTE Confidence: 0.93552761

00:20:29.650 --> 00:20:33.030 involved in two rounds now of the

NOTE Confidence: 0.93552761

00:20:33.030 --> 00:20:36.183 extracellular RNA Community consortium,

NOTE Confidence: 0.93552761

00:20:36.183 --> 00:20:42.165 and this now will just give you a

NOTE Confidence: 0.93552761

00:20:42.165 --> 00:20:45.474 sense of the complexity of what

NOTE Confidence: 0.93552761

00:20:45.474 --> 00:20:49.086 one can detect in the circulation.

NOTE Confidence: 0.93552761

00:20:49.090 --> 00:20:52.366 So here's a cell for or size,

NOTE Confidence: 0.93552761

00:20:52.370 --> 00:20:54.710 here's some viruses and what

NOTE Confidence: 0.93552761

00:20:54.710 --> 00:20:57.680 I'm going to be talking about.

NOTE Confidence: 0.93552761

00:20:57.680 --> 00:21:00.142 Is that there are large EB's

NOTE Confidence: 0.93552761

00:21:00.142 --> 00:21:01.590 that are thought to.

NOTE Confidence: 0.93552761

00:21:01.590 --> 00:21:04.026 That are often called micro vesicles.

NOTE Confidence: 0.93552761

00:21:04.030 --> 00:21:06.406 They're budding from the cell surface

NOTE Confidence: 0.93552761

00:21:06.406 --> 00:21:08.520 and then they're small eddies,

NOTE Confidence: 0.93552761

00:21:08.520 --> 00:21:12.290 some of which are exosomes,

NOTE Confidence: 0.93552761

00:21:12.290 --> 00:21:18.086 and that is if they have the Tetra spaniens.

NOTE Confidence: 0.93552761

00:21:18.090 --> 00:21:20.660 And uh.

NOTE Confidence: 0.93552761

00:21:20.660 --> 00:21:25.215 The exosome is rather it's also

NOTE Confidence: 0.93552761

00:21:25.215 --> 00:21:28.306 starting at the plasma membrane but

NOTE Confidence: 0.93552761

00:21:28.306 --> 00:21:30.841 then it's endocytosed and during

NOTE Confidence: 0.93552761

00:21:30.841 --> 00:21:34.079 its late endosomes they pinch off

NOTE Confidence: 0.93552761

00:21:34.079 --> 00:21:36.311 and forward inward vaccinations

NOTE Confidence: 0.93552761

00:21:36.311 --> 00:21:38.980 within a multi vesicular body.

NOTE Confidence: 0.93552761

00:21:38.980 --> 00:21:42.420 So which is really a bag of intraluminal

NOTE Confidence: 0.93552761

00:21:42.420 --> 00:21:45.516 vesicles in which the topology is changed.

NOTE Confidence: 0.93552761

00:21:45.520 --> 00:21:47.784 So the transmembrane protein

NOTE Confidence: 0.93552761

00:21:47.784 --> 00:21:50.614 now has its ectodomain facing.

NOTE Confidence: 0.93552761

00:21:50.620 --> 00:21:53.848 Outward and the cytoplasmic tail inward.

NOTE Confidence: 0.93552761

00:21:53.850 --> 00:21:56.590 So when these multi vasectomy

NOTE Confidence: 0.93552761

00:21:56.590 --> 00:21:59.250 particular bodies choose to budget

NOTE Confidence: 0.93552761

00:21:59.250 --> 00:22:02.370 the plasma membrane rather than going

NOTE Confidence: 0.93552761

00:22:02.370 --> 00:22:05.539 to the lysosome that they will.

NOTE Confidence: 0.93552761

00:22:05.540 --> 00:22:10.760 Release their signaling competent material.

NOTE Confidence: 0.93552761

00:22:10.760 --> 00:22:14.027 And I'm going to tell you a little bit

NOTE Confidence: 0.93552761

00:22:14.027 --> 00:22:17.776 more about these a membranous nanoparticles,

NOTE Confidence: 0.93552761

00:22:17.780 --> 00:22:22.898 which are examiners and super meres.

NOTE Confidence: 0.93552761

00:22:22.900 --> 00:22:26.444 And and so we've been able to publish

NOTE Confidence: 0.93552761

00:22:26.444 --> 00:22:30.956 a number of papers in this space most

NOTE Confidence: 0.93552761

00:22:30.956 --> 00:22:33.298 recently for those of us that are interested,

NOTE Confidence: 0.93552761

00:22:33.300 --> 00:22:37.020 we have a comprehensive protocol for

NOTE Confidence: 0.93552761

00:22:37.020 --> 00:22:39.587 isolating extracellular vesicles and

NOTE Confidence: 0.93552761

00:22:39.587 --> 00:22:42.832 nanoparticles from the same starting

NOTE Confidence: 0.93552761

00:22:42.832 --> 00:22:46.180 material and then two recent reviews

NOTE Confidence: 0.93552761

00:22:46.180 --> 00:22:49.336 that for those that are interested.

NOTE Confidence: 0.93552761

00:22:49.340 --> 00:22:52.950 So the first important paper

NOTE Confidence: 0.93552761

00:22:52.950 --> 00:22:56.004 we published was by Dennis,

NOTE Confidence: 0.93552761

00:22:56.004 --> 00:22:56.446 Yep,

NOTE Confidence: 0.93552761

00:22:56.446 --> 00:23:00.753 Person in the lab who published

NOTE Confidence: 0.93552761

00:23:00.753 --> 00:23:04.537 this paper and sell and we got a

NOTE Confidence: 0.93552761

00:23:04.537 --> 00:23:07.908 lot of nice PR in terms of that.

NOTE Confidence: 0.93552761

00:23:07.908 --> 00:23:11.076 We provided a much needed reappraisal

NOTE Confidence: 0.93552761

00:23:11.076 --> 00:23:14.157 of what constitutes a bona fide

NOTE Confidence: 0.93552761

00:23:14.157 --> 00:23:16.502 exosome through a highly stringent

NOTE Confidence: 0.93552761

00:23:16.502 --> 00:23:18.540 and novel methodology.

NOTE Confidence: 0.93552761

00:23:18.540 --> 00:23:22.404 And So what Dennis did was he used

NOTE Confidence: 0.93552761

00:23:22.404 --> 00:23:25.416 the conventional way of of a series

NOTE Confidence: 0.93552761

00:23:25.416 --> 00:23:27.696 of low speed spans passing through

NOTE Confidence: 0.93552761

00:23:27.696 --> 00:23:30.202 a filter and then a high speed

NOTE Confidence: 0.93552761

00:23:30.202 --> 00:23:33.940 spin to get his SB pellet.

NOTE Confidence: 0.93552761

00:23:33.940 --> 00:23:37.900 Now until somewhat recently that was

NOTE Confidence: 0.93552761

00:23:37.900 --> 00:23:42.140 considered enough to call it an exosome,

NOTE Confidence: 0.93552761

00:23:42.140 --> 00:23:45.668 but clearly there's a lot more

NOTE Confidence: 0.93552761

00:23:45.668 --> 00:23:48.510 there in this evening pellet than.

NOTE Confidence: 0.93552761

00:23:48.510 --> 00:23:49.719 Just an exosome.

NOTE Confidence: 0.93552761

00:23:49.719 --> 00:23:53.054 So what Dennis did was he then took

NOTE Confidence: 0.93552761

00:23:53.054 --> 00:23:56.435 that pellet and then bottom loaded it,

NOTE Confidence: 0.93552761

00:23:56.435 --> 00:23:59.765 which is very important and then

NOTE Confidence: 0.93552761

00:23:59.770 --> 00:24:05.270 spun that over this discontinuous

NOTE Confidence: 0.93552761

00:24:05.270 --> 00:24:09.695 gradient at 120,000 G in this

NOTE Confidence: 0.93552761

00:24:09.695 --> 00:24:12.382 case overnight and what he was

NOTE Confidence: 0.93552761

00:24:12.382 --> 00:24:15.110 and and we did this not only in

NOTE Confidence: 0.93552761

00:24:15.110 --> 00:24:18.500 colorectal cancer cells and breast.

NOTE Confidence: 0.93552761

00:24:18.500 --> 00:24:21.155 BM primary human renal epithelial

NOTE Confidence: 0.93552761

00:24:21.155 --> 00:24:24.540 cells in human even human plasma.

NOTE Confidence: 0.93552761

00:24:24.540 --> 00:24:28.327 And and So what Dennis was able

NOTE Confidence: 0.93552761

00:24:28.327 --> 00:24:31.822 to show was that when he looked

NOTE Confidence: 0.93552761

00:24:31.822 --> 00:24:35.342 at at the proteins now both in a

NOTE Confidence: 0.93552761

00:24:35.342 --> 00:24:38.492 colorectal cancer cell line and a

NOTE Confidence: 0.93552761

00:24:38.492 --> 00:24:41.678 glioblastoma he could see that in

NOTE Confidence: 0.93552761

00:24:41.678 --> 00:24:44.390 the lighter fractions was where

NOTE Confidence: 0.93552761

00:24:44.390 --> 00:24:49.520 he was able to to detect what we.

NOTE Confidence: 0.93552761

00:24:49.520 --> 00:24:51.080 We consider.

NOTE Confidence: 0.93552761

00:24:51.080 --> 00:24:53.020 Bicycle exosome markers whereas

NOTE Confidence: 0.93552761

00:24:53.020 --> 00:24:56.398 in the non vesicular there were a

NOTE Confidence: 0.93552761

00:24:56.398 --> 00:24:58.708 number of proteins that have been

NOTE Confidence: 0.764581394375

00:24:58.710 --> 00:25:02.550 outed to be in in exosomes but clearly

NOTE Confidence: 0.764581394375

00:25:02.550 --> 00:25:06.406 aren't in in both of these cell lines.

NOTE Confidence: 0.764581394375

00:25:06.410 --> 00:25:08.706 And but he went one step further,

NOTE Confidence: 0.764581394375

00:25:08.710 --> 00:25:12.287 so there's been concern that maybe damaged.

NOTE Confidence: 0.764581394375

00:25:12.290 --> 00:25:14.509 These EB's with a high speed spin.

NOTE Confidence: 0.764581394375

00:25:14.510 --> 00:25:19.534 So what he did was he then within

NOTE Confidence: 0.764581394375

00:25:19.534 --> 00:25:21.276 individual immunity Immunoaffinity

NOTE Confidence: 0.764581394375

00:25:21.276 --> 00:25:23.706 captured with the different Tetris.

NOTE Confidence: 0.764581394375

00:25:23.710 --> 00:25:29.277 Spaniens was able to then prior to the

NOTE Confidence: 0.764581394375

00:25:29.277 --> 00:25:31.797 high speed ultracentrifugation place beads

NOTE Confidence: 0.764581394375

00:25:31.797 --> 00:25:35.066 with these antibodies and then pull down

NOTE Confidence: 0.764581394375

00:25:35.066 --> 00:25:38.584 and then was able to validate that much

NOTE Confidence: 0.764581394375

00:25:38.584 --> 00:25:42.374 of the material that he identified in the.

NOTE Confidence: 0.764581394375

00:25:42.374 --> 00:25:45.496 High speed span was was was shown

NOTE Confidence: 0.764581394375

00:25:45.496 --> 00:25:49.132 to be the same and so at the end of

NOTE Confidence: 0.764581394375

00:25:49.132 --> 00:25:51.352 the day Dennis could say OK,

NOTE Confidence: 0.764581394375

00:25:51.360 --> 00:25:54.328 what's in classical exosomes.

NOTE Confidence: 0.764581394375

00:25:54.328 --> 00:25:57.296 What's weakly associated with

NOTE Confidence: 0.764581394375

00:25:57.296 --> 00:25:58.780 classical exosome?

NOTE Confidence: 0.764581394375

00:25:58.780 --> 00:26:02.680 Absent from classical exosomes and then

NOTE Confidence: 0.764581394375

00:26:02.680 --> 00:26:07.920 completely absent from any type of small EV.

NOTE Confidence: 0.764581394375

00:26:07.920 --> 00:26:09.996 So I think this was an

NOTE Confidence: 0.764581394375

00:26:09.996 --> 00:26:11.900 important advance in the field.

NOTE Confidence: 0.764581394375

00:26:11.900 --> 00:26:15.666 A few of the other highlights of

NOTE Confidence: 0.764581394375

00:26:15.666 --> 00:26:21.256 of that work was is depicted here.

NOTE Confidence: 0.764581394375

00:26:21.256 --> 00:26:25.798 And. About that same time.

NOTE Confidence: 0.764581394375

00:26:25.800 --> 00:26:27.549 A little before,

NOTE Confidence: 0.764581394375

00:26:27.549 --> 00:26:31.047 David Lyden's group had identified examiners,

NOTE Confidence: 0.764581394375

00:26:31.050 --> 00:26:34.221 and he did that by using asymmetric

NOTE Confidence: 0.764581394375

00:26:34.221 --> 00:26:36.920 flow field flow fractionation.

NOTE Confidence: 0.764581394375

00:26:36.920 --> 00:26:40.586 So this required about a $300,000

NOTE Confidence: 0.764581394375

00:26:40.586 --> 00:26:44.766 instrument and it's low yield.

NOTE Confidence: 0.764581394375

00:26:44.770 --> 00:26:46.510 And at Vanderbilt,

NOTE Confidence: 0.764581394375

00:26:46.510 --> 00:26:49.698 we couldn't afford that piece of equipment.

NOTE Confidence: 0.764581394375

00:26:49.698 --> 00:26:53.045 So Kinzang and the lab had the idea, OK,

NOTE Confidence: 0.764581394375

00:26:53.045 --> 00:26:55.775 well, let's just take the supernatant.

NOTE Confidence: 0.764581394375

00:26:55.780 --> 00:26:58.874 From that EV pellet and let's spend

NOTE Confidence: 0.764581394375

00:26:58.874 --> 00:27:01.424 that harder and and then let's

NOTE Confidence: 0.764581394375

00:27:01.424 --> 00:27:03.319 see what we we find.

NOTE Confidence: 0.764581394375

00:27:03.320 --> 00:27:06.160 And so she did that and she was

NOTE Confidence: 0.764581394375

00:27:06.160 --> 00:27:09.704 able to show that I'm using this

NOTE Confidence: 0.764581394375

00:27:09.704 --> 00:27:13.405 simplified method that we were able to

NOTE Confidence: 0.764581394375

00:27:13.405 --> 00:27:16.740 identify pretty much the same cargo,

NOTE Confidence: 0.764581394375

00:27:16.740 --> 00:27:19.694 many of the same cargo that David

NOTE Confidence: 0.764581394375

00:27:19.694 --> 00:27:20.960 had had seen,

NOTE Confidence: 0.764581394375

00:27:20.960 --> 00:27:22.510 although we were using different

NOTE Confidence: 0.764581394375

00:27:22.510 --> 00:27:24.060 cell lines in this case,

NOTE Confidence: 0.764581394375

00:27:24.060 --> 00:27:26.346 but an awful lot of overlap.

NOTE Confidence: 0.764581394375

00:27:26.350 --> 00:27:30.422 And we were able to identify 2 functional

NOTE Confidence: 0.764581394375

00:27:30.422 --> 00:27:33.114 properties of these examiners and

NOTE Confidence: 0.764581394375

00:27:33.114 --> 00:27:37.050 that there was ST6 gal one and examiners.

NOTE Confidence: 0.764581394375

00:27:37.050 --> 00:27:40.186 And it was able to simulate recipient

NOTE Confidence: 0.764581394375

00:27:40.186 --> 00:27:42.868 cell surface targets including beta 1

NOTE Confidence: 0.764581394375

00:27:42.868 --> 00:27:45.787 integrins and EGFR not shown here and

NOTE Confidence: 0.764581394375

00:27:45.874 --> 00:27:48.970 increase the activity of those proteins.

NOTE Confidence: 0.764581394375

00:27:48.970 --> 00:27:51.832 And then we could show that a Reg and

NOTE Confidence: 0.764581394375

00:27:51.832 --> 00:27:54.046 examiners were able to modulate EGFR,

NOTE Confidence: 0.764581394375

00:27:54.050 --> 00:27:57.346 separate tracking, trafficking and.

NOTE Confidence: 0.764581394375

00:27:57.346 --> 00:27:58.170 Increase.

NOTE Confidence: 0.764581394375

00:27:58.170 --> 00:28:02.153 Whom organoid an order of magnitude more

NOTE Confidence: 0.764581394375

00:28:02.153 --> 00:28:05.979 equivalent amounts of recombinant camparada.

NOTE Confidence: 0.764581394375

00:28:05.980 --> 00:28:08.804 So then that set the stage for the

NOTE Confidence: 0.764581394375

00:28:08.804 --> 00:28:11.518 paper I'm about to tell you about,

NOTE Confidence: 0.764581394375

00:28:11.520 --> 00:28:14.490 which was published.

NOTE Confidence: 0.764581394375

00:28:14.490 --> 00:28:18.132 In December of 2021 and that's

NOTE Confidence: 0.764581394375

00:28:18.132 --> 00:28:19.953 identifying super mirrors.

NOTE Confidence: 0.764581394375

00:28:19.960 --> 00:28:22.704 But we did more than just show the

NOTE Confidence: 0.764581394375

00:28:22.704 --> 00:28:25.219 discovery of superiors in this paper.

NOTE Confidence: 0.764581394375

00:28:25.220 --> 00:28:27.645 We did a comprehensive classification

NOTE Confidence: 0.764581394375

00:28:27.645 --> 00:28:30.914 or analysis both at the M RNA

NOTE Confidence: 0.764581394375

00:28:30.914 --> 00:28:33.200 and protein level of of cargo

NOTE Confidence: 0.764581394375

00:28:33.200 --> 00:28:35.639 within these different fractions.

NOTE Confidence: 0.764581394375

00:28:35.640 --> 00:28:38.080 And so that I'm going to tell you

NOTE Confidence: 0.764581394375

00:28:38.080 --> 00:28:40.144 about that work that was carried

NOTE Confidence: 0.764581394375

00:28:40.144 --> 00:28:41.874 out by Dennis and Chin.

NOTE Confidence: 0.764581394375

00:28:41.880 --> 00:28:44.799 So Chen figured out if this trick

NOTE Confidence: 0.764581394375

00:28:44.799 --> 00:28:47.530 worked once, maybe it would work again.

NOTE Confidence: 0.764581394375

00:28:47.530 --> 00:28:50.141 So all she did was take the

NOTE Confidence: 0.764581394375

00:28:50.141 --> 00:28:52.659 supernatant from the examiner palette.

NOTE Confidence: 0.764581394375

00:28:52.660 --> 00:28:57.353 And now she's spun that even harder than

NOTE Confidence: 0.764581394375

00:28:57.353 --> 00:29:01.217 we had spawned things before for 16 hours.

NOTE Confidence: 0.764581394375

00:29:01.220 --> 00:29:03.710 And so we coined the term

NOTE Confidence: 0.764581394375

00:29:03.710 --> 00:29:05.370 super mere because it's

NOTE Confidence: 0.775794291

00:29:05.458 --> 00:29:08.839 the supernatant of examiners and it also

NOTE Confidence: 0.775794291

00:29:08.839 --> 00:29:11.900 has really super interesting cargo.

NOTE Confidence: 0.775794291

00:29:11.900 --> 00:29:15.064 Which. I'm going to tell you about.

NOTE Confidence: 0.775794291

00:29:15.070 --> 00:29:19.326 So this is just a fluid phase atomic

NOTE Confidence: 0.775794291

00:29:19.326 --> 00:29:22.309 force microscopy showing that there

NOTE Confidence: 0.775794291

00:29:22.310 --> 00:29:25.346 were some differences we could detect

NOTE Confidence: 0.775794291

00:29:25.350 --> 00:29:27.630 between examiners and super meres.

NOTE Confidence: 0.775794291

00:29:27.630 --> 00:29:30.168 We're in the process of doing

NOTE Confidence: 0.775794291

00:29:30.168 --> 00:29:34.215 prior OEM of of these a membranous

NOTE Confidence: 0.775794291

00:29:34.215 --> 00:29:37.010 nanoparticles and that work is underway,

NOTE Confidence: 0.775794291

00:29:37.010 --> 00:29:40.042 but we were able to show that the

NOTE Confidence: 0.775794291

00:29:40.042 --> 00:29:42.345 Super mirrors were shorter and

NOTE Confidence: 0.775794291

00:29:42.345 --> 00:29:44.994 smaller than the examiners and.

NOTE Confidence: 0.775794291

00:29:44.994 --> 00:29:48.240 Interesting when we took the different

NOTE Confidence: 0.775794291

00:29:48.330 --> 00:29:52.973 fractions and labeled them IR 800 labeled

NOTE Confidence: 0.775794291

00:29:52.973 --> 00:29:57.602 and then injected them IP200 micrograms.

NOTE Confidence: 0.775794291

00:29:57.602 --> 00:30:01.988 IP. And then look 24 hour

NOTE Confidence: 0.775794291

00:30:01.990 --> 00:30:04.270 later at the biodistribution,

NOTE Confidence: 0.775794291

00:30:04.270 --> 00:30:09.349 we were able to show that the Super meres

NOTE Confidence: 0.775794291

00:30:09.350 --> 00:30:13.700 were more enriched in the different

NOTE Confidence: 0.775794291

00:30:13.700 --> 00:30:17.655 organs and perhaps most notably in

NOTE Confidence: 0.775794291

00:30:17.655 --> 00:30:21.238 the brain than the other fractions.

NOTE Confidence: 0.775794291

00:30:21.238 --> 00:30:24.090 And examiners are about 35 nanometers

NOTE Confidence: 0.775794291

00:30:24.090 --> 00:30:26.970 and super meres are about 25 nanometers.

NOTE Confidence: 0.775794291

00:30:26.970 --> 00:30:28.170 So I don't think.

NOTE Confidence: 0.775794291

00:30:28.170 --> 00:30:31.800 That small size is enough to.

NOTE Confidence: 0.889699062777778

00:30:33.820 --> 00:30:37.026 To allow for this marked difference in

NOTE Confidence: 0.889699062777778

00:30:37.026 --> 00:30:40.284 ability to cross the blood brain barrier

NOTE Confidence: 0.889699062777778

00:30:40.284 --> 00:30:43.370 and we've now shown these particles are

NOTE Confidence: 0.889699062777778

00:30:43.370 --> 00:30:46.940 taken up in different cells in the brain.

NOTE Confidence: 0.889699062777778

00:30:46.940 --> 00:30:51.196 And this is just a quantifying those results.

NOTE Confidence: 0.889699062777778

00:30:51.200 --> 00:30:53.170 The other thing that was

NOTE Confidence: 0.889699062777778

00:30:53.170 --> 00:30:54.746 really interesting to us?

NOTE Confidence: 0.889699062777778

00:30:54.750 --> 00:30:55.978 Was that, you know,

NOTE Confidence: 0.889699062777778

00:30:55.978 --> 00:30:57.820 a lot of people are studying

NOTE Confidence: 0.889699062777778

00:30:57.890 --> 00:31:00.660 micro RNA's in EB's and there's

NOTE Confidence: 0.889699062777778

00:31:00.660 --> 00:31:04.010 a lot of people working on that.

NOTE Confidence: 0.889699062777778

00:31:04.010 --> 00:31:06.014 Some people including ourselves

NOTE Confidence: 0.889699062777778

00:31:06.014 --> 00:31:09.020 don't think there's all that much

NOTE Confidence: 0.889699062777778

00:31:09.099 --> 00:31:12.190 RNA and EB's and access zones.

NOTE Confidence: 0.889699062777778

00:31:12.190 --> 00:31:15.259 And what we were able to show in this

NOTE Confidence: 0.889699062777778

00:31:15.259 --> 00:31:18.060 study was when we look at total RNA.

NOTE Confidence: 0.889699062777778

00:31:18.060 --> 00:31:20.994 We were able to see that most of the

NOTE Confidence: 0.889699062777778

00:31:20.994 --> 00:31:23.260 total RNA that was being released

NOTE Confidence: 0.889699062777778

00:31:23.260 --> 00:31:26.060 from the cell was in super meres

NOTE Confidence: 0.889699062777778

00:31:26.060 --> 00:31:29.246 rather than these two other fraction.

NOTE Confidence: 0.889699062777778

00:31:29.250 --> 00:31:31.946 And this just goes to show you that

NOTE Confidence: 0.889699062777778

00:31:31.946 --> 00:31:34.910 the small nuclear RNA seemed to be

NOTE Confidence: 0.889699062777778

00:31:34.910 --> 00:31:37.650 particularly enriched in the Super meres.

NOTE Confidence: 0.889699062777778

00:31:37.650 --> 00:31:38.990 And then in this case,

NOTE Confidence: 0.889699062777778

00:31:38.990 --> 00:31:43.127 we did the comprehensive small RNA analysis

NOTE Confidence: 0.889699062777778

00:31:43.127 --> 00:31:46.580 and mere 1246 was the most upregulated.

NOTE Confidence: 0.803967858666667

00:31:48.660 --> 00:31:52.340 Micro RNA in the Super Myers I should

NOTE Confidence: 0.803967858666667

00:31:52.340 --> 00:31:56.000 say that we are 1246 is not a micro RNA.

NOTE Confidence: 0.803967858666667

00:31:56.000 --> 00:31:59.960 It's actually processed from

NOTE Confidence: 0.803967858666667

00:31:59.960 --> 00:32:02.850 splicing factors R&U 2.1,

NOTE Confidence: 0.803967858666667

00:32:02.850 --> 00:32:05.125 but it doesn't mean it

NOTE Confidence: 0.803967858666667

00:32:05.125 --> 00:32:08.320 couldn't be a useful biomarker.

NOTE Confidence: 0.803967858666667

00:32:08.320 --> 00:32:10.434 And so there was a very nice

NOTE Confidence: 0.803967858666667

00:32:10.434 --> 00:32:11.800 editorial in that issue,

NOTE Confidence: 0.803967858666667

00:32:11.800 --> 00:32:15.640 nature cell biology trying to now

NOTE Confidence: 0.803967858666667

00:32:15.640 --> 00:32:18.512 classify extracellular vesicles with

NOTE Confidence: 0.803967858666667

00:32:18.512 --> 00:32:22.232 the lipid bilayer and extracellular

NOTE Confidence: 0.803967858666667

00:32:22.232 --> 00:32:25.014 and nanoparticles that include

NOTE Confidence: 0.803967858666667

00:32:25.014 --> 00:32:27.999 now super mirrors and examiners

NOTE Confidence: 0.803967858666667

00:32:27.999 --> 00:32:30.440 and their associated Carta.

NOTE Confidence: 0.803967858666667

00:32:30.440 --> 00:32:32.888 So now I want to delve into some of

NOTE Confidence: 0.803967858666667

00:32:32.888 --> 00:32:35.532 the more interesting cargo that we

NOTE Confidence: 0.803967858666667

00:32:35.532 --> 00:32:37.832 found in these different fractions.

NOTE Confidence: 0.803967858666667

00:32:37.840 --> 00:32:40.633 And remember I tried to set the

NOTE Confidence: 0.803967858666667

00:32:40.633 --> 00:32:43.593 stage to tell you that we've

NOTE Confidence: 0.803967858666667

00:32:43.593 --> 00:32:46.514 identified in immune exclusion

NOTE Confidence: 0.803967858666667

00:32:46.514 --> 00:32:49.754 signature that included deep one,

NOTE Confidence: 0.803967858666667

00:32:49.754 --> 00:32:52.938 TGF, beta I and and Dr. one.

NOTE Confidence: 0.803967858666667

00:32:52.938 --> 00:32:57.402 And so we could see by principal component

NOTE Confidence: 0.803967858666667

00:32:57.402 --> 00:33:00.658 analysis that the and in this case.

NOTE Confidence: 0.803967858666667

00:33:00.660 --> 00:33:02.790 We're using Diffie cells again,

NOTE Confidence: 0.803967858666667

00:33:02.790 --> 00:33:04.812 but we've done this in other

NOTE Confidence: 0.803967858666667

00:33:04.812 --> 00:33:06.160 cell lines as well.

NOTE Confidence: 0.803967858666667

00:33:06.160 --> 00:33:10.462 We can see that the small

NOTE Confidence: 0.803967858666667

00:33:10.462 --> 00:33:13.630 extracellular vesicles live here.

NOTE Confidence: 0.803967858666667

00:33:13.630 --> 00:33:14.996 Not surprising,

NOTE Confidence: 0.803967858666667

00:33:14.996 --> 00:33:19.094 the examiners and the non vesicular

NOTE Confidence: 0.803967858666667

00:33:19.094 --> 00:33:21.745 material are clustered here

NOTE Confidence: 0.803967858666667

00:33:21.745 --> 00:33:25.267 and the Super meres are here.

NOTE Confidence: 0.803967858666667

00:33:25.270 --> 00:33:30.608 And what we found was that the

NOTE Confidence: 0.803967858666667

00:33:30.608 --> 00:33:35.396 most abundant protein in the small

NOTE Confidence: 0.803967858666667

00:33:35.396 --> 00:33:38.490 extracellular vesicles was deep one.

NOTE Confidence: 0.803967858666667

00:33:38.490 --> 00:33:41.407 And the work I'm going to tell you

NOTE Confidence: 0.803967858666667

00:33:41.407 --> 00:33:44.845 about now is the work of a graduate student,

NOTE Confidence: 0.803967858666667

00:33:44.850 --> 00:33:45.860 Sarah Glass.

NOTE Confidence: 0.934209522857143

00:33:48.890 --> 00:33:52.166 And this is just to remind you,

NOTE Confidence: 0.934209522857143

00:33:52.170 --> 00:33:55.411 this is a vocal logogram and we're

NOTE Confidence: 0.934209522857143

00:33:55.411 --> 00:33:59.290 talking now about the sequence of events

NOTE Confidence: 0.934209522857143

00:33:59.290 --> 00:34:04.480 in microsatellite stable and positive.

NOTE Confidence: 0.934209522857143

00:34:04.480 --> 00:34:09.232 Colon cancer. As contrasted to

NOTE Confidence: 0.934209522857143

00:34:09.232 --> 00:34:12.048 microsatellite unstable colon cancer.

NOTE Confidence: 0.934209522857143

00:34:12.050 --> 00:34:14.954 And and it was very interesting

NOTE Confidence: 0.934209522857143

00:34:14.954 --> 00:34:17.940 to us that when Bert Vogelstein,

NOTE Confidence: 0.934209522857143

00:34:17.940 --> 00:34:21.510 some 11 years after that first paper,

NOTE Confidence: 0.934209522857143

00:34:21.510 --> 00:34:24.750 he now had all this sage data and he said OK,

NOTE Confidence: 0.934209522857143

00:34:24.750 --> 00:34:27.132 how do we decide what genes

NOTE Confidence: 0.934209522857143

00:34:27.132 --> 00:34:29.650 are we going to go after?

NOTE Confidence: 0.934209522857143

00:34:29.650 --> 00:34:31.568 And so they sat down and said,

NOTE Confidence: 0.934209522857143

00:34:31.570 --> 00:34:34.624 OK, gene has to encode either

NOTE Confidence: 0.934209522857143

00:34:34.624 --> 00:34:37.550 a membrane or secreted protein.

NOTE Confidence: 0.934209522857143

00:34:37.550 --> 00:34:40.529 So it's got to be a target or a

NOTE Confidence: 0.934209522857143

00:34:40.529 --> 00:34:43.124 biomarker and it's got to be 20 fold.

NOTE Confidence: 0.934209522857143

00:34:43.130 --> 00:34:47.930 Greater in both adenomas and cancers.

NOTE Confidence: 0.934209522857143

00:34:47.930 --> 00:34:50.275 And when he did that there were

NOTE Confidence: 0.934209522857143

00:34:50.275 --> 00:34:53.142 only 6 genes that they identified.

NOTE Confidence: 0.934209522857143

00:34:53.142 --> 00:34:55.882 One was dipeptidase one and

NOTE Confidence: 0.934209522857143

00:34:55.882 --> 00:34:58.566 one was a TDF beta induce,

NOTE Confidence: 0.934209522857143

00:34:58.570 --> 00:35:00.882 which I'm going to tell you a little

NOTE Confidence: 0.934209522857143

00:35:00.882 --> 00:35:03.934 bit more about now, so deep one.

NOTE Confidence: 0.934209522857143

00:35:03.934 --> 00:35:09.427 For a long time had thought of being to

NOTE Confidence: 0.934209522857143

00:35:09.427 --> 00:35:13.294 be merely an extracellular dipeptidase,

NOTE Confidence: 0.934209522857143

00:35:13.294 --> 00:35:16.806 and it's GPI linked.

NOTE Confidence: 0.934209522857143

00:35:16.810 --> 00:35:19.228 So it's at the April membrane

NOTE Confidence: 0.934209522857143

00:35:19.228 --> 00:35:21.280 of a polarized epithelial cell.

NOTE Confidence: 0.892050113333333

00:35:23.440 --> 00:35:25.700 More recently has been found

NOTE Confidence: 0.892050113333333

00:35:25.700 --> 00:35:27.960 to have non enzymatic activity

NOTE Confidence: 0.892050113333333

00:35:28.040 --> 00:35:30.340 as well as enzymatic activity.

NOTE Confidence: 0.892050113333333

00:35:30.340 --> 00:35:32.320 It is expressed in normal kidney,

NOTE Confidence: 0.892050113333333

00:35:32.320 --> 00:35:33.896 pancreas and small intestine,

NOTE Confidence: 0.892050113333333

00:35:33.896 --> 00:35:35.078 but it's overexpressed

NOTE Confidence: 0.892050113333333

00:35:35.078 --> 00:35:36.999 in a number of cancers.

NOTE Confidence: 0.892050113333333

00:35:37.000 --> 00:35:39.107 And I'm just going to summarize a

NOTE Confidence: 0.892050113333333

00:35:39.107 --> 00:35:41.604 body of work that we've carried out

NOTE Confidence: 0.892050113333333

00:35:41.604 --> 00:35:43.884 but haven't published yet and which

NOTE Confidence: 0.892050113333333

00:35:43.955 --> 00:35:46.235 we could show that there's increased

NOTE Confidence: 0.892050113333333

00:35:46.235 --> 00:35:50.546 standing for deep one and 2527% of

NOTE Confidence: 0.892050113333333

00:35:50.546 --> 00:35:53.864 adenomas and that increases to 70.

NOTE Confidence: 0.892050113333333

00:35:53.864 --> 00:35:58.320 1% in in colorectal cancer and diffuse

NOTE Confidence: 0.892050113333333

00:35:58.320 --> 00:36:00.300 staining and colorectal cancer

NOTE Confidence: 0.892050113333333

00:36:00.300 --> 00:36:03.260 correlates with a worse performance,

NOTE Confidence: 0.892050113333333

00:36:03.260 --> 00:36:06.570 progression free and overall survival.

NOTE Confidence: 0.892050113333333

00:36:06.570 --> 00:36:08.966 And importantly it's overexpressed

NOTE Confidence: 0.892050113333333

00:36:08.966 --> 00:36:11.961 in microsatellite stable but not

NOTE Confidence: 0.892050113333333

00:36:11.961 --> 00:36:15.050 as contrasted to microsatellite

NOTE Confidence: 0.892050113333333

00:36:15.050 --> 00:36:17.447 unstable colorectal cancer.

NOTE Confidence: 0.892050113333333

00:36:17.450 --> 00:36:21.576 And using fabs we can show that EB's

NOTE Confidence: 0.892050113333333

00:36:21.576 --> 00:36:23.928 isolated from the blood of colorectal cancer.

NOTE Confidence: 0.892050113333333

00:36:23.930 --> 00:36:30.426 Patients have increased deep one CEA Cam 5.

NOTE Confidence: 0.892050113333333

00:36:30.430 --> 00:36:34.286 Compared to healthy individuals and

NOTE Confidence: 0.892050113333333

00:36:34.286 --> 00:36:37.617 and this just depicts the enzymatic

NOTE Confidence: 0.892050113333333

00:36:37.617 --> 00:36:41.096 activity of of deep one which is

NOTE Confidence: 0.892050113333333

00:36:41.096 --> 00:36:43.912 so it's acting extracellularly

NOTE Confidence: 0.892050113333333

00:36:43.912 --> 00:36:47.356 and breakdown of glutathione.

NOTE Confidence: 0.892050113333333

00:36:47.360 --> 00:36:50.045 So glutathione then is converted

NOTE Confidence: 0.892050113333333

00:36:50.045 --> 00:36:52.193 to cysteinyl lysine dipeptide.

NOTE Confidence: 0.892050113333333

00:36:52.200 --> 00:36:54.510 Pep one will convert it to cysteine

NOTE Confidence: 0.892050113333333

00:36:54.510 --> 00:36:56.344 and glycine which is then thought

NOTE Confidence: 0.892050113333333

00:36:56.344 --> 00:36:59.288 to be able to taken up by the

NOTE Confidence: 0.892050113333333

00:36:59.288 --> 00:37:01.196 cells and replenish intracellular.

NOTE Confidence: 0.892050113333333

00:37:01.200 --> 00:37:04.399 Do the style and it converts Ltd

NOTE Confidence: 0.892050113333333

00:37:04.399 --> 00:37:09.227 or to LTE four and this increases

NOTE Confidence: 0.892050113333333

00:37:09.227 --> 00:37:10.897 vascular permeability.

NOTE Confidence: 0.892050113333333

00:37:10.900 --> 00:37:13.144 And then several years ago it

NOTE Confidence: 0.892050113333333

00:37:13.144 --> 00:37:15.120 was shown that in mice,

NOTE Confidence: 0.892050113333333

00:37:15.120 --> 00:37:18.492 if they were given LPSS to

NOTE Confidence: 0.892050113333333

00:37:18.492 --> 00:37:20.746 activate endothelial cells in

NOTE Confidence: 0.892050113333333

00:37:20.746 --> 00:37:23.556 liver and lung endothelial cells,

NOTE Confidence: 0.892050113333333

00:37:23.560 --> 00:37:27.241 there is now an increase in deep one and

NOTE Confidence: 0.892050113333333

00:37:27.241 --> 00:37:31.747 it was serving as a receptor for neutrophils.

NOTE Confidence: 0.892050113333333

00:37:31.750 --> 00:37:35.758 And that really caught our attention

NOTE Confidence: 0.892050113333333

00:37:35.760 --> 00:37:40.212 because of a link now between neutrophils

NOTE Confidence: 0.892050113333333

00:37:40.212 --> 00:37:46.190 and possibly tumor progression and so.

NOTE Confidence: 0.892050113333333

00:37:46.190 --> 00:37:50.430 There is evidence that neutrophils

NOTE Confidence: 0.892050113333333

00:37:50.430 --> 00:37:54.790 can also result in immune evasion,

NOTE Confidence: 0.892050113333333

00:37:54.790 --> 00:37:58.150 and this is 1 paper where that's

NOTE Confidence: 0.892050113333333

00:37:58.150 --> 00:38:01.002 shown where neutrophils are producing

NOTE Confidence: 0.892050113333333

00:38:01.002 --> 00:38:04.416 MP nine that's going to activate

NOTE Confidence: 0.892050113333333

00:38:04.512 --> 00:38:07.809 latent TGF beta and TGF beta will

NOTE Confidence: 0.892050113333333

00:38:07.809 --> 00:38:11.806 impair the activity of CDA T cells

NOTE Confidence: 0.892050113333333

00:38:11.806 --> 00:38:16.390 and increase the activity of T Rex.

NOTE Confidence: 0.892050113333333

00:38:16.390 --> 00:38:18.562 And and they're actually in the

NOTE Confidence: 0.892050113333333

00:38:18.562 --> 00:38:20.882 clinic now drugs that will block

NOTE Confidence: 0.892050113333333

00:38:20.882 --> 00:38:23.294 both the enzymatic and non enzymatic

NOTE Confidence: 0.892050113333333

00:38:23.294 --> 00:38:24.789 activity of dpep one.

NOTE Confidence: 0.892050113333333

00:38:24.790 --> 00:38:28.996 So it's if you have beta lactam

NOTE Confidence: 0.892050113333333

00:38:28.996 --> 00:38:31.573 antibodies it turns out deep one

NOTE Confidence: 0.892050113333333

00:38:31.573 --> 00:38:34.003 will cleave them and they're half

NOTE Confidence: 0.892050113333333

00:38:34.003 --> 00:38:36.190 life is very very short.

NOTE Confidence: 0.892050113333333

00:38:36.190 --> 00:38:38.948 So what's done is you give cellar

NOTE Confidence: 0.892050113333333

00:38:38.948 --> 00:38:42.078 statin which is a deep one enzymatic

NOTE Confidence: 0.892050113333333

00:38:42.078 --> 00:38:44.874 activity inhibitor and then that will

NOTE Confidence: 0.892050113333333

00:38:44.962 --> 00:38:48.014 prolong the half life of the antibody.

NOTE Confidence: 0.892050113333333

00:38:48.020 --> 00:38:50.176 So it's been used just you know

NOTE Confidence: 0.892050113333333

00:38:50.176 --> 00:38:52.490 week 10 days not longer but it's

NOTE Confidence: 0.892050113333333

00:38:52.490 --> 00:38:55.044 used and then El Sol peptide which

NOTE Confidence: 0.892050113333333

00:38:55.044 --> 00:38:56.217 is actually there's,

NOTE Confidence: 0.892050113333333

00:38:56.220 --> 00:38:59.620 it's a 16 amino acid peptide that's

NOTE Confidence: 0.892050113333333

00:38:59.620 --> 00:39:03.460 been grown to be able to block the

NOTE Confidence: 0.892050113333333

00:39:03.559 --> 00:39:07.374 ability of neutrophils to bind to deep.

NOTE Confidence: 0.892050113333333

00:39:07.380 --> 00:39:10.250 And I should say that we don't

NOTE Confidence: 0.892050113333333

00:39:10.250 --> 00:39:12.726 know the Libyan in neutrophils

NOTE Confidence: 0.892050113333333

00:39:12.726 --> 00:39:16.084 bind that binds to deep one,

NOTE Confidence: 0.892050113333333

00:39:16.084 --> 00:39:18.676 but we know that neutrophils bind.

NOTE Confidence: 0.892050113333333

00:39:18.680 --> 00:39:21.304 And so this now is used in the

NOTE Confidence: 0.892050113333333

00:39:21.304 --> 00:39:23.684 clinic and COVID patients that are

NOTE Confidence: 0.892050113333333

00:39:23.684 --> 00:39:26.459 at high risk for either having

NOTE Confidence: 0.892050113333333

00:39:26.459 --> 00:39:29.024 lung or kidney problems because

NOTE Confidence: 0.892050113333333

00:39:29.024 --> 00:39:31.920 it's going to block the ability

NOTE Confidence: 0.892050113333333

00:39:31.920 --> 00:39:34.590 of neutrophils to get there and

NOTE Confidence: 0.871791943461538

00:39:34.676 --> 00:39:37.496 it appears to have some efficacy.

NOTE Confidence: 0.871791943461538

00:39:37.500 --> 00:39:40.268 So this is just showing now by single

NOTE Confidence: 0.871791943461538

00:39:40.268 --> 00:39:44.844 cell RNA seek that we can see that deep

NOTE Confidence: 0.871791943461538

00:39:44.844 --> 00:39:49.424 one is relatively up in microsatellite

NOTE Confidence: 0.871791943461538

00:39:49.424 --> 00:39:55.034 stable colon cancer and are.

NOTE Confidence: 0.871791943461538

00:39:55.040 --> 00:39:59.842 Are adenoma stem cell like cells?

NOTE Confidence: 0.871791943461538

00:39:59.842 --> 00:40:03.250 Compared to SSL and

NOTE Confidence: 0.871791943461538

00:40:03.250 --> 00:40:04.954 microsatellite instability.

NOTE Confidence: 0.871791943461538

00:40:04.960 --> 00:40:07.879 And this is just showing staining now.

NOTE Confidence: 0.871791943461538

00:40:07.880 --> 00:40:10.409 So we can see in the normal colon that

NOTE Confidence: 0.871791943461538

00:40:10.409 --> 00:40:12.680 there is staining more towards the base

NOTE Confidence: 0.871791943461538

00:40:12.680 --> 00:40:15.545 of the **** down in the progenitor zone

NOTE Confidence: 0.871791943461538

00:40:15.545 --> 00:40:18.870 and you can see nice staining as you

NOTE Confidence: 0.871791943461538

00:40:18.870 --> 00:40:23.460 might expect for this GPI linked protein.

NOTE Confidence: 0.871791943461538

00:40:23.460 --> 00:40:26.020 We think it may be a wink targeting,

NOTE Confidence: 0.871791943461538

00:40:26.020 --> 00:40:28.438 but we haven't shown that conclusively.

NOTE Confidence: 0.871791943461538

00:40:28.440 --> 00:40:31.116 We can see that in adenomas

NOTE Confidence: 0.871791943461538

00:40:31.120 --> 00:40:32.964 we see increased standing.

NOTE Confidence: 0.871791943461538

00:40:32.964 --> 00:40:35.269 It seems to be restricted.

NOTE Confidence: 0.871791943461538

00:40:35.270 --> 00:40:36.830 To the room,

NOTE Confidence: 0.871791943461538

00:40:36.830 --> 00:40:38.910 to the apical domain.

NOTE Confidence: 0.871791943461538

00:40:38.910 --> 00:40:41.248 And then when we moved to cancer,

NOTE Confidence: 0.871791943461538

00:40:41.250 --> 00:40:45.118 we can see either further increase and

NOTE Confidence: 0.871791943461538

00:40:45.118 --> 00:40:48.622 then in some cancers we see this I

NOTE Confidence: 0.871791943461538

00:40:48.622 --> 00:40:52.578 think what appears to be more diffuse

NOTE Confidence: 0.871791943461538

00:40:52.578 --> 00:40:55.090 staining and that's the staining

NOTE Confidence: 0.871791943461538

00:40:55.090 --> 00:40:58.143 that when we have K Washington,

NOTE Confidence: 0.871791943461538

00:40:58.143 --> 00:41:00.798 our GI pathologist of clinically

NOTE Confidence: 0.871791943461538

00:41:00.798 --> 00:41:04.172 well and annotated TMA can show

NOTE Confidence: 0.871791943461538

00:41:04.172 --> 00:41:06.296 that that's associated with.

NOTE Confidence: 0.871791943461538

00:41:06.300 --> 00:41:11.540 A worse survival, and that's just shown here.

NOTE Confidence: 0.86718601375

00:41:13.640 --> 00:41:15.632 Now we're in a position where

NOTE Confidence: 0.86718601375

00:41:15.632 --> 00:41:17.490 we take abnormal organoids.

NOTE Confidence: 0.86718601375

00:41:17.490 --> 00:41:22.860 And we can show that in this particular case,

NOTE Confidence: 0.86718601375

00:41:22.860 --> 00:41:25.779 we're seeing an adenoma that has deep

NOTE Confidence: 0.86718601375

00:41:25.779 --> 00:41:29.335 1 restricted to the apical domain

NOTE Confidence: 0.86718601375

00:41:29.335 --> 00:41:33.500 where it's in this particular organoid.

NOTE Confidence: 0.86718601375

00:41:33.500 --> 00:41:36.986 It looks like there's more diffuse

NOTE Confidence: 0.86718601375

00:41:36.986 --> 00:41:39.844 stain even though this is an abnormal

NOTE Confidence: 0.86718601375

00:41:39.844 --> 00:41:43.363 and and now we have the ability of

NOTE Confidence: 0.86718601375

00:41:43.363 --> 00:41:45.753 placing these organoids on trans

NOTE Confidence: 0.86718601375

00:41:45.753 --> 00:41:49.060 wells and now we'll have a bully.

NOTE Confidence: 0.86718601375

00:41:49.060 --> 00:41:52.388 Polarized. Ordinarily that allows

NOTE Confidence: 0.86718601375

00:41:52.388 --> 00:41:56.858 us the opportunity to now place,

NOTE Confidence: 0.86718601375

00:41:56.858 --> 00:42:00.558 in this case, neutrophils at at the

NOTE Confidence: 0.86718601375

00:42:00.558 --> 00:42:03.150 at the bottom of the transplant.

NOTE Confidence: 0.86718601375

00:42:03.150 --> 00:42:07.567 And now we can look at neutrophil

NOTE Confidence: 0.86718601375

00:42:07.567 --> 00:42:10.222 adenoma interactions and see if

NOTE Confidence: 0.86718601375

00:42:10.222 --> 00:42:13.470 they are any change in the behavior.

NOTE Confidence: 0.86718601375

00:42:13.470 --> 00:42:16.875 These have to be fractionally

NOTE Confidence: 0.86718601375

00:42:16.875 --> 00:42:18.237 isolated neutrophils.

NOTE Confidence: 0.86718601375

00:42:18.240 --> 00:42:21.450 Have a half life of about.

NOTE Confidence: 0.86718601375

00:42:21.450 --> 00:42:25.216 6 to 10 hours and they're all

NOTE Confidence: 0.86718601375

00:42:25.216 --> 00:42:26.830 varieties of neutrophils.

NOTE Confidence: 0.86718601375

00:42:26.830 --> 00:42:28.789 As I'm learning.

NOTE Confidence: 0.86718601375

00:42:28.789 --> 00:42:30.748 There's net posis.

NOTE Confidence: 0.86718601375

00:42:30.750 --> 00:42:33.642 They make their own set of

NOTE Confidence: 0.86718601375

00:42:33.642 --> 00:42:34.606 extracellular vesicles.

NOTE Confidence: 0.86718601375

00:42:34.610 --> 00:42:37.874 And then we have our adenomas

NOTE Confidence: 0.86718601375

00:42:37.874 --> 00:42:40.204 with or without deep one,

NOTE Confidence: 0.86718601375

00:42:40.204 --> 00:42:42.980 and we can begin and their vesicles and

NOTE Confidence: 0.86718601375

00:42:43.054 --> 00:42:45.630 we can begin to look at combinations

NOTE Confidence: 0.86718601375

00:42:45.630 --> 00:42:48.114 of of different articles and and look

NOTE Confidence: 0.86718601375

00:42:48.114 --> 00:42:51.702 at some of the genes and biology that.

NOTE Confidence: 0.86718601375

00:42:51.702 --> 00:42:54.150 That are unearthed.

NOTE Confidence: 0.86718601375

00:42:54.150 --> 00:42:57.934 So that's where we stand with the pep

NOTE Confidence: 0.86718601375

00:42:57.934 --> 00:43:02.386 one work in in the extracellular vesicles.

NOTE Confidence: 0.86718601375

00:43:02.390 --> 00:43:05.400 The most abundant protein that we found

NOTE Confidence: 0.86718601375

00:43:05.400 --> 00:43:08.750 in the Super meres was TGF beta I.

NOTE Confidence: 0.86718601375

00:43:08.750 --> 00:43:12.134 And so obviously now we've got two of

NOTE Confidence: 0.86718601375

00:43:12.134 --> 00:43:14.519 the three proteins we're interested

NOTE Confidence: 0.86718601375

00:43:14.519 --> 00:43:17.590 in and that was a interest to us.

NOTE Confidence: 0.86718601375

00:43:17.590 --> 00:43:19.138 So TGF beta I,

NOTE Confidence: 0.86718601375

00:43:19.138 --> 00:43:22.558 it was actually it goes by a number

NOTE Confidence: 0.86718601375

00:43:22.558 --> 00:43:25.558 of different names and Greg Plowman

NOTE Confidence: 0.86718601375

00:43:25.558 --> 00:43:28.615 about 20 years ago added TGF beta

NOTE Confidence: 0.86718601375

00:43:28.615 --> 00:43:32.580 to a 549 lung cancer cells cloned.

NOTE Confidence: 0.86718601375

00:43:32.580 --> 00:43:35.917 Has Gene which he called TGF beta I,

NOTE Confidence: 0.86718601375

00:43:35.917 --> 00:43:37.926 but it probably has little if anything

NOTE Confidence: 0.86718601375

00:43:37.926 --> 00:43:40.027 to do with TGF beta signaling,

NOTE Confidence: 0.86718601375

00:43:40.030 --> 00:43:42.750 at least as far as we can understand

NOTE Confidence: 0.86718601375

00:43:42.750 --> 00:43:43.430 thus far.

NOTE Confidence: 0.86718601375

00:43:43.430 --> 00:43:45.570 It's expressed by epithelial cells

NOTE Confidence: 0.86718601375

00:43:45.570 --> 00:43:48.410 and macrophages and loss of function,

NOTE Confidence: 0.86718601375

00:43:48.410 --> 00:43:51.932 germline loss of function mutations are

NOTE Confidence: 0.86718601375

00:43:51.932 --> 00:43:54.280 associated with corneal dystrophies.

NOTE Confidence: 0.86718601375

00:43:54.280 --> 00:43:57.205 And it's been implicated in

NOTE Confidence: 0.86718601375

00:43:57.205 --> 00:43:58.960 glycolysis past thesis.

NOTE Confidence: 0.86718601375

00:43:58.960 --> 00:44:02.158 Migration and angiogenesis.

NOTE Confidence: 0.86718601375

00:44:02.160 --> 00:44:03.699 We do staining.

NOTE Confidence: 0.86718601375

00:44:03.699 --> 00:44:07.207 We can see that it really it,

NOTE Confidence: 0.86718601375

00:44:07.207 --> 00:44:10.623 it's got a signal peptide and we can

NOTE Confidence: 0.86718601375

00:44:10.623 --> 00:44:14.487 see that it really is enriched in the

NOTE Confidence: 0.86718601375

00:44:14.487 --> 00:44:18.348 stroma of these colorectal cancer cells.

NOTE Confidence: 0.86718601375

00:44:18.350 --> 00:44:20.986 In in vivo and.

NOTE Confidence: 0.86718601375

00:44:20.986 --> 00:44:25.936 When once again Kay store scores the

NOTE Confidence: 0.86718601375

00:44:25.936 --> 00:44:30.914 colorectal cancer TMI I TTF beta I

NOTE Confidence: 0.86718601375

00:44:30.914 --> 00:44:33.919 is associated with worse survival

NOTE Confidence: 0.86718601375

00:44:33.919 --> 00:44:38.070 and we actually now have an ELISA

NOTE Confidence: 0.86718601375

00:44:38.070 --> 00:44:42.116 for TGF beta I and taking plasma and

NOTE Confidence: 0.86718601375

00:44:42.116 --> 00:44:44.244 and this was our first attempts at this.

NOTE Confidence: 0.86718601375

00:44:44.250 --> 00:44:46.394 So I think we can do a better

NOTE Confidence: 0.86718601375

00:44:46.394 --> 00:44:48.914 job of separating the different

NOTE Confidence: 0.86718601375

00:44:48.914 --> 00:44:52.980 fractions but you can see that.

NOTE Confidence: 0.86718601375

00:44:52.980 --> 00:44:56.068 There is a mark enrichment of TGF beta

NOTE Confidence: 0.86718601375

00:44:56.068 --> 00:44:59.589 I in these three colorectal cancer

NOTE Confidence: 0.86718601375

00:44:59.589 --> 00:45:03.573 patients compared to three healthy controls.

NOTE Confidence: 0.84045345

00:45:05.690 --> 00:45:10.030 So. Now we've accounted for two

NOTE Confidence: 0.84045345

00:45:10.030 --> 00:45:13.490 of them. And so now we're very

NOTE Confidence: 0.84045345

00:45:13.490 --> 00:45:16.090 interested in and DDR1 and.

NOTE Confidence: 0.846718211666667

00:45:18.720 --> 00:45:21.696 DDR1 is actually a tyrosine kinase.

NOTE Confidence: 0.846718211666667

00:45:21.700 --> 00:45:24.418 But rather than having a growth

NOTE Confidence: 0.846718211666667

00:45:24.418 --> 00:45:28.238 factor bind, it's activated by column.

NOTE Confidence: 0.846718211666667

00:45:28.238 --> 00:45:31.146 So collagen will activate.

NOTE Confidence: 0.820981882857143

00:45:33.710 --> 00:45:39.100 DDR1 it's got a PDZ binding motif.

NOTE Confidence: 0.820981882857143

00:45:39.100 --> 00:45:42.194 And it's been studied quite a bit

NOTE Confidence: 0.820981882857143

00:45:42.194 --> 00:45:44.252 by Ambra Posey at Vanderbilt,

NOTE Confidence: 0.820981882857143

00:45:44.252 --> 00:45:46.964 who's found that it plays a

NOTE Confidence: 0.820981882857143

00:45:46.964 --> 00:45:51.990 role in kidney fibrosis. Show.

NOTE Confidence: 0.847840461666667

00:45:54.230 --> 00:45:58.010 There were two recent nature papers

NOTE Confidence: 0.847840461666667

00:45:58.010 --> 00:46:02.120 which found different roles by which

NOTE Confidence: 0.847840461666667

00:46:02.120 --> 00:46:06.429 they thought DDR one was working.

NOTE Confidence: 0.847840461666667

00:46:06.430 --> 00:46:09.238 The first is from Ron Lee,

NOTE Confidence: 0.847840461666667

00:46:09.240 --> 00:46:14.637 an investigator at GW who found that

NOTE Confidence: 0.847840461666667

00:46:14.637 --> 00:46:19.958 the shed ectodomain of DDR1 is able

NOTE Confidence: 0.847840461666667

00:46:19.958 --> 00:46:23.718 to alter the alignment collagen.

NOTE Confidence: 0.847840461666667

00:46:23.720 --> 00:46:26.540 In a way that he's arguing

NOTE Confidence: 0.847840461666667

00:46:26.540 --> 00:46:29.040 he's cells we don't know.

NOTE Confidence: 0.847840461666667

00:46:29.040 --> 00:46:31.994 Other immune cells are affected as well,

NOTE Confidence: 0.847840461666667

00:46:32.000 --> 00:46:34.150 don't get to the action.

NOTE Confidence: 0.847840461666667

00:46:34.150 --> 00:46:36.642 And this is in the setting of

NOTE Confidence: 0.847840461666667

00:46:36.642 --> 00:46:38.260 triple negative breast cancer.

NOTE Confidence: 0.847840461666667

00:46:38.260 --> 00:46:40.472 So that's his model.

NOTE Confidence: 0.847840461666667

00:46:40.472 --> 00:46:43.790 And then Michael Karen Year later

NOTE Confidence: 0.847840461666667

00:46:43.899 --> 00:46:46.769 comes up with another story.

NOTE Confidence: 0.847840461666667

00:46:46.770 --> 00:46:48.580 Which I think is experimentally

NOTE Confidence: 0.847840461666667

00:46:48.580 --> 00:46:50.753 flawed but I don't really have

NOTE Confidence: 0.847840461666667

00:46:50.753 --> 00:46:52.547 time to go into the reasons.

NOTE Confidence: 0.847840461666667

00:46:52.550 --> 00:46:56.090 But he and pancreatic cancer

NOTE Confidence: 0.847840461666667

00:46:56.090 --> 00:46:59.630 said that the ectodomain of Dr.

NOTE Confidence: 0.847840461666667

00:46:59.630 --> 00:47:02.550 One is not checked in pancreatic cancer.

NOTE Confidence: 0.847840461666667

00:47:02.550 --> 00:47:06.169 So now what we're left with OK

NOTE Confidence: 0.847840461666667

00:47:06.169 --> 00:47:09.480 is there release of of soluble

NOTE Confidence: 0.847840461666667

00:47:09.480 --> 00:47:12.626 ectodomain of of DR1 and so this

NOTE Confidence: 0.847840461666667

00:47:12.626 --> 00:47:14.496 is very preliminary data but

NOTE Confidence: 0.847840461666667

00:47:14.496 --> 00:47:17.096 we now took our our fractions.

NOTE Confidence: 0.847840461666667

00:47:17.100 --> 00:47:19.916 Once again from Diffie cells and

NOTE Confidence: 0.847840461666667

00:47:19.916 --> 00:47:23.120 this is overexpression of DDR1 and

NOTE Confidence: 0.847840461666667

00:47:23.120 --> 00:47:25.570 Heck 293 cells and then this is

NOTE Confidence: 0.847840461666667

00:47:25.570 --> 00:47:28.098 Super Myers isolated from our Diffie

NOTE Confidence: 0.847840461666667

00:47:28.098 --> 00:47:31.236 cells and I think you're going to

NOTE Confidence: 0.847840461666667

00:47:31.236 --> 00:47:35.140 appreciate there's a large band Dr.

NOTE Confidence: 0.847840461666667

00:47:35.140 --> 00:47:38.500 One is glycosylated so but it's

NOTE Confidence: 0.847840461666667

00:47:38.500 --> 00:47:43.610 a large band for DR1 in in super.

NOTE Confidence: 0.847840461666667

00:47:43.610 --> 00:47:47.702 So that's really what I wanted

NOTE Confidence: 0.847840461666667

00:47:47.702 --> 00:47:50.430 to tell you about.

NOTE Confidence: 0.847840461666667

00:47:50.430 --> 00:47:54.560 I'm going forward like many in the

NOTE Confidence: 0.847840461666667

00:47:54.560 --> 00:47:57.434 field were interested in overcoming

NOTE Confidence: 0.847840461666667

00:47:57.434 --> 00:48:00.860 immune exclusion in this case and

NOTE Confidence: 0.847840461666667

00:48:00.959 --> 00:48:04.587 microsatellite stable colorectal cancer.

NOTE Confidence: 0.847840461666667

00:48:04.590 --> 00:48:07.809 And so we think that DDR1,

NOTE Confidence: 0.847840461666667

00:48:07.809 --> 00:48:09.167 TGF data,

NOTE Confidence: 0.847840461666667

00:48:09.167 --> 00:48:13.920 ID PEP one are all therapeutic targets.

NOTE Confidence: 0.847840461666667

00:48:13.920 --> 00:48:16.804 And our first approach is going to

NOTE Confidence: 0.847840461666667

00:48:16.804 --> 00:48:20.063 be to conduct a clinical trial with

NOTE Confidence: 0.847840461666667

00:48:20.063 --> 00:48:22.315 a company Parthenon Therapeutics

NOTE Confidence: 0.847840461666667

00:48:22.315 --> 00:48:24.567 that is in Boston.

NOTE Confidence: 0.847840461666667

00:48:24.570 --> 00:48:27.498 The founders were trained at Vanderbilt,

NOTE Confidence: 0.847840461666667

00:48:27.500 --> 00:48:29.545 hence the named Parthenon for

NOTE Confidence: 0.847840461666667

00:48:29.545 --> 00:48:31.590 those not interested we have.

NOTE Confidence: 0.847840461666667

00:48:31.590 --> 00:48:35.140 A replica of the Parthenon in Nashville,

NOTE Confidence: 0.847840461666667

00:48:35.140 --> 00:48:37.165 across the street from Vanderbilt,

NOTE Confidence: 0.847840461666667

00:48:37.170 --> 00:48:39.696 so they were favorably disposed from

NOTE Confidence: 0.847840461666667

00:48:39.696 --> 00:48:42.451 their experience in at Vanderbilt and

NOTE Confidence: 0.847840461666667

00:48:42.451 --> 00:48:44.946 have called the company Parthenon.

NOTE Confidence: 0.847840461666667

00:48:44.950 --> 00:48:47.175 And the medical oncologist overlap

NOTE Confidence: 0.847840461666667

00:48:47.175 --> 00:48:50.069 with me during my medical oncology

NOTE Confidence: 0.847840461666667

00:48:50.069 --> 00:48:51.848 training at Vanderbilt.

NOTE Confidence: 0.847840461666667

00:48:51.850 --> 00:48:55.136 So everything's kind of fitting

NOTE Confidence: 0.847840461666667

00:48:55.136 --> 00:48:58.011 together here and we're going to try

NOTE Confidence: 0.847840461666667

00:48:58.011 --> 00:49:00.315 this neutralizing antibody to see if

NOTE Confidence: 0.847840461666667

00:49:00.315 --> 00:49:03.024 it permits return of cytotoxic T cells.

NOTE Confidence: 0.847840461666667

00:49:03.024 --> 00:49:05.453 The plan is to do the phase

NOTE Confidence: 0.847840461666667

00:49:05.453 --> 00:49:07.562 one and then introduce Contrada

NOTE Confidence: 0.847840461666667

00:49:07.562 --> 00:49:10.850 to see if in fact we can get.

NOTE Confidence: 0.847840461666667

00:49:10.850 --> 00:49:15.800 T cells to get back to where they need to be.

NOTE Confidence: 0.847840461666667

00:49:15.800 --> 00:49:21.110 All three. We have biomarkers 4.

NOTE Confidence: 0.847840461666667

00:49:21.110 --> 00:49:25.686 And we can monitor plasma DR1 and TGF beta

NOTE Confidence: 0.847840461666667

00:49:25.686 --> 00:49:29.630 and Super mares and deep pep one and EB.

NOTE Confidence: 0.847840461666667

00:49:29.630 --> 00:49:32.108 So even though this is an

NOTE Confidence: 0.847840461666667

00:49:32.108 --> 00:49:33.347 investigator initiated trial,

NOTE Confidence: 0.847840461666667

00:49:33.350 --> 00:49:35.900 we have correlated biomarkers which

NOTE Confidence: 0.847840461666667

00:49:35.900 --> 00:49:39.209 will meet the standard of of what

NOTE Confidence: 0.847840461666667

00:49:39.209 --> 00:49:42.455 you need for reading or reaching a

NOTE Confidence: 0.847840461666667

00:49:42.455 --> 00:49:45.266 translational goal in a sport trial.

NOTE Confidence: 0.847840461666667

00:49:45.266 --> 00:49:48.580 And So what I've tried to tell

NOTE Confidence: 0.847840461666667

00:49:48.580 --> 00:49:51.820 you about and and very rapid

NOTE Confidence: 0.847840461666667

00:49:51.820 --> 00:49:55.428 fashion today is our isolation of

NOTE Confidence: 0.847840461666667

00:49:55.428 --> 00:49:57.956 extracellular vesicles and examiners

NOTE Confidence: 0.847840461666667

00:49:57.956 --> 00:50:01.294 are discovery of super meres and

NOTE Confidence: 0.847840461666667

00:50:01.294 --> 00:50:04.270 and then identification all of these

NOTE Confidence: 0.847840461666667

00:50:04.366 --> 00:50:08.290 three proteins that are part of this

NOTE Confidence: 0.847840461666667

00:50:08.290 --> 00:50:10.950 gene exclusion signature that that

NOTE Confidence: 0.847840461666667

00:50:11.051 --> 00:50:14.189 paper has been submitted to cell.

NOTE Confidence: 0.814797744166667

00:50:14.190 --> 00:50:18.594 And we think that we've identified

NOTE Confidence: 0.814797744166667

00:50:18.594 --> 00:50:21.530 some tractable targets and

NOTE Confidence: 0.814797744166667

00:50:21.654 --> 00:50:25.025 and correlative biomarker.

NOTE Confidence: 0.814797744166667

00:50:25.025 --> 00:50:28.942 So obviously this this work.

NOTE Confidence: 0.814797744166667

00:50:28.942 --> 00:50:32.092 Couldn't have taken place with with

NOTE Confidence: 0.814797744166667

00:50:32.092 --> 00:50:35.260 help from a lot of people I've tried

NOTE Confidence: 0.814797744166667

00:50:35.349 --> 00:50:38.019 to highlight Sarah Dennis Chin,

NOTE Confidence: 0.814797744166667

00:50:38.020 --> 00:50:39.064 Jim Higginbotham,

NOTE Confidence: 0.814797744166667

00:50:39.064 --> 00:50:42.718 Jeff Franklin's a senior member of the

NOTE Confidence: 0.814797744166667

00:50:42.718 --> 00:50:46.196 lab Oleg 2 Tonov joined from Siberia.

NOTE Confidence: 0.814797744166667

00:50:46.200 --> 00:50:49.926 He left Russia the day after

NOTE Confidence: 0.814797744166667

00:50:49.930 --> 00:50:53.510 the exercise in Ukraine.

NOTE Confidence: 0.814797744166667

00:50:53.510 --> 00:50:56.807 You know, he's happy to be he

NOTE Confidence: 0.814797744166667

00:50:56.807 --> 00:51:00.238 and his wife and in Nashville.

NOTE Confidence: 0.814797744166667

00:51:00.240 --> 00:51:02.664 We have both this human tumor

NOTE Confidence: 0.814797744166667

00:51:02.664 --> 00:51:05.451 Atlas network and we recently were

NOTE Confidence: 0.814797744166667

00:51:05.451 --> 00:51:08.161 awarded a translational and basic

NOTE Confidence: 0.814797744166667

00:51:08.161 --> 00:51:10.775 science research in early lesions

NOTE Confidence: 0.814797744166667

00:51:10.775 --> 00:51:13.946 and and our project within that is

NOTE Confidence: 0.814797744166667

00:51:13.946 --> 00:51:18.584 related to D PEP one and both in the

NOTE Confidence: 0.814797744166667

00:51:18.584 --> 00:51:22.234 H10 and T valve can allow Martha

NOTE Confidence: 0.814797744166667

00:51:22.234 --> 00:51:25.102 Shrubsole and and Cindy Sears who's

NOTE Confidence: 0.814797744166667

00:51:25.102 --> 00:51:28.617 an expert on the microbiome and

NOTE Confidence: 0.814797744166667

00:51:28.617 --> 00:51:30.973 colorectal neoplasia at Hopkins.

NOTE Confidence: 0.814797744166667

00:51:30.980 --> 00:51:33.444 Are all part of our team and we

NOTE Confidence: 0.814797744166667

00:51:33.444 --> 00:51:36.304 have you know tremendous support at

NOTE Confidence: 0.814797744166667

00:51:36.304 --> 00:51:39.316 Vanderbilt and and as well elsewhere

NOTE Confidence: 0.814797744166667

00:51:39.316 --> 00:51:42.656 and I've been fortunate for the well

NOTE Confidence: 0.814797744166667

00:51:42.656 --> 00:51:45.979 funded for the for the time being.

NOTE Confidence: 0.814797744166667

00:51:45.980 --> 00:51:49.060 So I'll be happy to answer any questions.

NOTE Confidence: 0.81440246

00:51:57.290 --> 00:51:57.700 David.

NOTE Confidence: 0.843164694761905

00:52:19.330 --> 00:52:23.110 No, really the that that's been done

NOTE Confidence: 0.843164694761905

00:52:23.110 --> 00:52:25.705 at Parthenon Therapeutics and it

NOTE Confidence: 0.843164694761905

00:52:25.705 --> 00:52:28.369 was only when we recently acquired

NOTE Confidence: 0.843164694761905

00:52:28.369 --> 00:52:31.850 this gene exclusion signature

NOTE Confidence: 0.843164694761905

00:52:31.850 --> 00:52:33.590 that we were thinking about OK,

NOTE Confidence: 0.843164694761905

00:52:33.590 --> 00:52:36.116 which of these proteins do we

NOTE Confidence: 0.843164694761905

00:52:36.116 --> 00:52:39.029 want to target and then realized

NOTE Confidence: 0.843164694761905

00:52:39.030 --> 00:52:44.808 that actually over a drink with a

NOTE Confidence: 0.843164694761905

00:52:44.808 --> 00:52:47.084 colleague that Parthenon Therapeutics

NOTE Confidence: 0.843164694761905

00:52:47.084 --> 00:52:49.360 had this neutralizing antibody.

NOTE Confidence: 0.843164694761905

00:52:49.360 --> 00:52:51.586 To DDR1 and decided to then

NOTE Confidence: 0.843164694761905

00:52:51.586 --> 00:52:54.089 focus on that to start with.

NOTE Confidence: 0.7746998

00:52:58.230 --> 00:53:04.060 Pardon me? So, so they have data. Right.

NOTE Confidence: 0.7746998

00:53:04.060 --> 00:53:07.765 That they have data that they think the

NOTE Confidence: 0.7746998

00:53:07.765 --> 00:53:11.086 effects that they get are independent

NOTE Confidence: 0.7746998

00:53:11.086 --> 00:53:14.526 of the tyrosine kinase activity,

NOTE Confidence: 0.7746998

00:53:14.530 --> 00:53:16.728 but that you know, that's their data.

NOTE Confidence: 0.7746998

00:53:16.730 --> 00:53:19.943 We we haven't repeated that with kinase

NOTE Confidence: 0.7746998

00:53:19.943 --> 00:53:22.859 dead constructs and and that work is

NOTE Confidence: 0.7746998

00:53:22.859 --> 00:53:24.920 just really beginning to be carried out

NOTE Confidence: 0.7746998

00:53:24.920 --> 00:53:26.759 by a graduate student and all that.

NOTE Confidence: 0.810510912

00:53:32.080 --> 00:53:35.440 How do you get here? These years.

NOTE Confidence: 0.700067353333333

00:53:37.760 --> 00:53:40.052 Great question.

NOTE Confidence: 0.700067353333333

00:53:40.052 --> 00:53:43.522 Clueless. So these are.

NOTE Confidence: 0.700067353333333

00:53:43.522 --> 00:53:45.844 A membranous nanoparticles

NOTE Confidence: 0.700067353333333

00:53:45.844 --> 00:53:49.480 they've got a lot of.

NOTE Confidence: 0.700067353333333

00:53:49.480 --> 00:53:50.350 Ribosomal components,

NOTE Confidence: 0.700067353333333

00:53:50.350 --> 00:53:52.960 they've got a lot of RNA,

NOTE Confidence: 0.700067353333333

00:53:52.960 --> 00:53:57.624 they have a lot of RNA binding proteins.

NOTE Confidence: 0.700067353333333

00:53:57.630 --> 00:54:04.455 And. I had a a talk today with

NOTE Confidence: 0.700067353333333

00:54:04.460 --> 00:54:09.550 somebody who's still awake.

NOTE Confidence: 0.700067353333333

00:54:09.550 --> 00:54:12.728 Who just submitted his first R1 after

NOTE Confidence: 0.700067353333333

00:54:12.728 --> 00:54:16.636 being up for four days and he gave

NOTE Confidence: 0.700067353333333

00:54:16.636 --> 00:54:19.086 me some really great suggestions

NOTE Confidence: 0.700067353333333

00:54:19.185 --> 00:54:21.730 for proceeding in that area.

NOTE Confidence: 0.700067353333333

00:54:21.730 --> 00:54:24.562 So I'm hoping that we'll be able to

NOTE Confidence: 0.700067353333333

00:54:24.562 --> 00:54:26.909 collaborate on on that going forward,

NOTE Confidence: 0.700067353333333

00:54:26.910 --> 00:54:29.770 whether it's related to stress,

NOTE Confidence: 0.700067353333333

00:54:29.770 --> 00:54:32.960 stress, granules.

NOTE Confidence: 0.700067353333333

00:54:32.960 --> 00:54:34.996 Either base separation components

NOTE Confidence: 0.700067353333333

00:54:34.996 --> 00:54:39.041 of this with all the RNA there and

NOTE Confidence: 0.700067353333333

00:54:39.041 --> 00:54:41.281 some of the positively charged

NOTE Confidence: 0.700067353333333

00:54:41.281 --> 00:54:44.118 Eno one is one of the most.

NOTE Confidence: 0.700067353333333

00:54:44.120 --> 00:54:46.450 Upregulated proteins we find in

NOTE Confidence: 0.700067353333333

00:54:46.450 --> 00:54:49.676 in super mirrors and and that has

NOTE Confidence: 0.700067353333333

00:54:49.676 --> 00:54:52.140 a positive charge for him just

NOTE Confidence: 0.700067353333333

00:54:52.140 --> 00:54:54.340 hand waving explanations but so

NOTE Confidence: 0.700067353333333

00:54:54.340 --> 00:54:57.365 we we really don't know the the

NOTE Confidence: 0.700067353333333

00:54:57.365 --> 00:54:59.717 Biogenesis but as some people in

NOTE Confidence: 0.700067353333333

00:54:59.717 --> 00:55:02.196 the field have said you know.

NOTE Confidence: 0.700067353333333

00:55:02.200 --> 00:55:05.850 One persons, one cells track.

NOTE Confidence: 0.700067353333333

00:55:05.850 --> 00:55:09.050 Maybe another sells treasure,

NOTE Confidence: 0.700067353333333

00:55:09.050 --> 00:55:13.518 so you know whether this is just junk

NOTE Confidence: 0.700067353333333

00:55:13.518 --> 00:55:17.340 being thrown out or whether it has some.

NOTE Confidence: 0.813436262

00:55:19.590 --> 00:55:23.852 Impact on on recipient sales, we don't.

NOTE Confidence: 0.813436262

00:55:23.852 --> 00:55:27.444 But we try to proceed, you know,

NOTE Confidence: 0.813436262

00:55:27.444 --> 00:55:30.529 cautiously and rigorously as we

NOTE Confidence: 0.813436262

00:55:30.529 --> 00:55:34.780 go forward. Gave. Patrick. So.

NOTE Confidence: 0.660928

00:55:53.750 --> 00:55:54.100 Got it.

NOTE Confidence: 0.898635282

00:55:56.980 --> 00:55:58.820 No, no, that's exactly right.

NOTE Confidence: 0.898635282

00:55:58.820 --> 00:56:01.620 So and and at the level of light

NOTE Confidence: 0.898635282

00:56:01.620 --> 00:56:03.619 microscopy we can't see these,

NOTE Confidence: 0.898635282

00:56:03.620 --> 00:56:07.120 you know that X the Super mirrors

NOTE Confidence: 0.898635282

00:56:07.120 --> 00:56:09.844 are 25 nanometer examiners are 35

NOTE Confidence: 0.898635282

00:56:09.844 --> 00:56:13.060 that LED's are you know 80 to 120.

NOTE Confidence: 0.424134945

00:56:17.110 --> 00:56:20.270 Yeah, distracted.

NOTE Confidence: 0.424134945

00:56:20.270 --> 00:56:22.961 I don't know, but we're, we're,

NOTE Confidence: 0.424134945

00:56:22.961 --> 00:56:25.316 we're we're unable to detect

NOTE Confidence: 0.424134945

00:56:25.316 --> 00:56:27.870 them what with our immuno stain.

NOTE Confidence: 0.424134945

00:56:27.870 --> 00:56:30.240 Clearly if you have cultured cells

NOTE Confidence: 0.424134945

00:56:30.240 --> 00:56:33.269 and you have high enough resolution.

NOTE Confidence: 0.424134945

00:56:33.270 --> 00:56:35.290 You can see these.

NOTE Confidence: 0.424134945

00:56:35.290 --> 00:56:36.670 And and there are tricks,

NOTE Confidence: 0.424134945

00:56:36.670 --> 00:56:38.501 you know that you can pH,

NOTE Confidence: 0.424134945

00:56:38.501 --> 00:56:40.556 Lauren, so it'll light up.

NOTE Confidence: 0.611031804444444

00:56:43.160 --> 00:56:45.325 Certain pH. You can just

NOTE Confidence: 0.611031804444444

00:56:45.325 --> 00:56:47.057 see things being released.

NOTE Confidence: 0.5979428

00:56:50.410 --> 00:56:50.560 Yeah.

NOTE Confidence: 0.864542141428571

00:56:54.830 --> 00:56:56.475 Right. So that's what we've been doing.

NOTE Confidence: 0.864542141428571

00:56:56.480 --> 00:56:59.830 We have very good antibodies.

NOTE Confidence: 0.864542141428571

00:56:59.830 --> 00:57:04.120 For. To work carefully with self

NOTE Confidence: 0.864542141428571

00:57:04.120 --> 00:57:07.748 taking 94 not one antibody.

NOTE Confidence: 0.864542141428571

00:57:07.750 --> 00:57:09.920 And actually. There anybody that

NOTE Confidence: 0.864542141428571

00:57:09.920 --> 00:57:12.674 can work very well overtime another.

NOTE Confidence: 0.864542141428571

00:57:12.674 --> 00:57:16.730 Yeah and you know less than 12 says

NOTE Confidence: 0.864542141428571

00:57:16.829 --> 00:57:20.364 that antibodies PSA I think you're OK

NOTE Confidence: 0.864542141428571

00:57:20.370 --> 00:57:23.990 and ER one well once again that cells.

NOTE Confidence: 0.53792086

00:57:26.480 --> 00:57:27.420 OK, great.

NOTE Confidence: 0.57114482

00:57:29.650 --> 00:57:34.350 Question about. Yeah. In those.

NOTE Confidence: 0.650054758333333

00:57:40.090 --> 00:57:44.650 Yeah. We get. Would go in.

NOTE Confidence: 0.650054758333333

00:57:44.650 --> 00:57:46.850 Target Fairmount go now is

NOTE Confidence: 0.650054758333333

00:57:46.850 --> 00:57:48.170 what's really interesting.

NOTE Confidence: 0.650054758333333

00:57:48.170 --> 00:57:53.560 So we can now we flow sort. You've got.

NOTE Confidence: 0.650054758333333

00:57:53.560 --> 00:57:58.096 Now we're close sort, EGFR and TECHSPAN.

NOTE Confidence: 0.650054758333333

00:57:58.100 --> 00:58:00.112 And DDR1 by itself,

NOTE Confidence: 0.650054758333333

00:58:00.112 --> 00:58:04.830 but a number of other. April.

NOTE Confidence: 0.650054758333333

00:58:04.830 --> 00:58:08.070 GPI links like those proteins.

NOTE Confidence: 0.650054758333333

00:58:08.070 --> 00:58:10.334 And including CD 73.

NOTE Confidence: 0.650054758333333

00:58:10.334 --> 00:58:13.164 So we think that's interesting.

NOTE Confidence: 0.650054758333333

00:58:13.170 --> 00:58:15.648 I mean, this is very speculative,

NOTE Confidence: 0.650054758333333

00:58:15.650 --> 00:58:18.436 but you might have a dual warhead.

NOTE Confidence: 0.650054758333333

00:58:18.440 --> 00:58:21.272 That in that they're being released by a

NOTE Confidence: 0.650054758333333

00:58:21.272 --> 00:58:23.897 cancer cell and that local environment.

NOTE Confidence: 0.650054758333333

00:58:23.900 --> 00:58:25.355 So you've got.

NOTE Confidence: 0.650054758333333

00:58:25.355 --> 00:58:27.780 Now keep one that's gonna.

NOTE Confidence: 0.650054758333333

00:58:27.780 --> 00:58:31.074 It's a team and it can be a chemoattractant

NOTE Confidence: 0.650054758333333

00:58:31.074 --> 00:58:34.164 and all this after for neutrophils and

NOTE Confidence: 0.650054758333333

00:58:34.164 --> 00:58:37.249 mild mild cycle now more recently.

NOTE Confidence: 0.650054758333333

00:58:37.250 --> 00:58:38.948 OK, going to bring those in,

NOTE Confidence: 0.650054758333333

00:58:38.950 --> 00:58:42.330 but that doesn't exclude detail.

NOTE Confidence: 0.650054758333333

00:58:42.330 --> 00:58:45.521 We've got CD73 making Dennis,

NOTE Confidence: 0.650054758333333

00:58:45.521 --> 00:58:48.023 which was going to begin suppressive.

NOTE Confidence: 0.650054758333333

00:58:48.030 --> 00:58:50.550 So you know churning out studying.

NOTE Confidence: 0.650054758333333

00:58:50.550 --> 00:58:53.412 Now we're looking to see if

NOTE Confidence: 0.650054758333333

00:58:53.412 --> 00:58:57.058 they can see that predicted.

NOTE Confidence: 0.650054758333333

00:58:57.060 --> 00:58:59.915 Presence of neutrophils in the

NOTE Confidence: 0.650054758333333

00:58:59.915 --> 00:59:02.880 absence of of CDA sets and there

NOTE Confidence: 0.650054758333333

00:59:02.880 --> 00:59:04.700 is a correlation we think,

NOTE Confidence: 0.650054758333333

00:59:04.700 --> 00:59:08.130 between deep 1 staining and

NOTE Confidence: 0.650054758333333

00:59:08.130 --> 00:59:10.874 we use neutrophil elastase.

NOTE Confidence: 0.650054758333333

00:59:10.880 --> 00:59:11.394 Now,

NOTE Confidence: 0.650054758333333

00:59:11.394 --> 00:59:13.964 probably HNE probably is is

NOTE Confidence: 0.650054758333333

00:59:13.964 --> 00:59:16.560 probably even better than that,

NOTE Confidence: 0.650054758333333

00:59:16.560 --> 00:59:18.012 because mutual elastase can

NOTE Confidence: 0.650054758333333

00:59:18.012 --> 00:59:19.464 be produced by others.

NOTE Confidence: 0.824575513333333

00:59:21.860 --> 00:59:27.780 Yeah, V6. Yeah. But even better,

NOTE Confidence: 0.824575513333333

00:59:27.780 --> 00:59:29.768 maybe just. With the ballot.

NOTE Confidence: 0.79161274

00:59:34.600 --> 00:59:35.030 Yeah.

NOTE Confidence: 0.24867126

00:59:38.040 --> 00:59:38.360 Question.

NOTE Confidence: 0.5227354

00:59:42.630 --> 00:59:43.220 Other than.

NOTE Confidence: 0.710167833333333

00:59:47.740 --> 00:59:48.388 What I'm thinking?

NOTE Confidence: 0.77461085

00:59:51.540 --> 00:59:54.160 Face. Face. Here.

NOTE Confidence: 0.639147223333333

00:59:58.890 --> 01:00:00.696 So I showed the data for.

NOTE Confidence: 0.596572304

01:00:03.530 --> 01:00:05.340 So we we can exercise.

NOTE Confidence: 0.30914773

01:00:08.220 --> 01:00:13.290 Cancel pensions. You don't like.

NOTE Confidence: 0.30914773

01:00:13.290 --> 01:00:18.368 Detective and all of it. It it is.

NOTE Confidence: 0.6696537

01:00:21.010 --> 01:00:28.410 Thank you. We need to refine our plasma.

NOTE Confidence: 0.6696537

01:00:28.410 --> 01:00:33.972 So yeah, you can measure a cargo in superior.

NOTE Confidence: 0.579514135

01:00:42.670 --> 01:00:43.978 Good question, you mentioned.

NOTE Confidence: 0.64464223

01:00:50.060 --> 01:00:50.300 This.

NOTE Confidence: 0.945145433333333

01:00:55.470 --> 01:00:58.830 You know, people are starting

NOTE Confidence: 0.945145433333333

01:00:58.830 --> 01:01:04.700 to use these for drug delivery.

NOTE Confidence: 0.945145433333333

01:01:04.700 --> 01:01:07.564 And but we and there's a lot of

NOTE Confidence: 0.945145433333333

01:01:07.564 --> 01:01:09.622 activity in that space right

NOTE Confidence: 0.945145433333333

01:01:09.622 --> 01:01:13.481 now we really haven't undertaken

NOTE Confidence: 0.945145433333333

01:01:13.481 --> 01:01:15.645 those experiments we're we're

NOTE Confidence: 0.945145433333333

01:01:15.645 --> 01:01:18.350 we're more inclined towards you

NOTE Confidence: 0.945145433333333

01:01:18.429 --> 01:01:20.934 know looking them as biomarkers

NOTE Confidence: 0.945145433333333

01:01:20.934 --> 01:01:22.938 and therapeutic targets and.

NOTE Confidence: 0.795876265882353

01:01:25.700 --> 01:01:27.745 Not so much that therapeutic

NOTE Confidence: 0.795876265882353

01:01:27.745 --> 01:01:30.233 opportunities I think it's it would

NOTE Confidence: 0.795876265882353

01:01:30.233 --> 01:01:32.465 be it's still a real challenge.

NOTE Confidence: 0.795876265882353

01:01:32.470 --> 01:01:36.385 You know what cell is gonna be your producer

NOTE Confidence: 0.795876265882353

01:01:36.385 --> 01:01:40.754 cell and what other cargo might be there.

NOTE Confidence: 0.795876265882353

01:01:40.760 --> 01:01:43.064 And you know, this field has been tarnished,

NOTE Confidence: 0.795876265882353

01:01:43.070 --> 01:01:46.016 I think, by a lot of.

NOTE Confidence: 0.795876265882353

01:01:46.020 --> 01:01:48.144 Extravagant claims that then

NOTE Confidence: 0.795876265882353

01:01:48.144 --> 01:01:51.330 haven't been able to be reproduced

NOTE Confidence: 0.795876265882353

01:01:51.419 --> 01:01:53.946 and and we're also as a field,

NOTE Confidence: 0.795876265882353

01:01:53.950 --> 01:01:56.299 have been giving.

NOTE Confidence: 0.795876265882353

01:01:56.300 --> 01:01:58.868 Pharmacological industrial doses

NOTE Confidence: 0.795876265882353

01:01:58.868 --> 01:02:04.304 of of these EB's into into mice

NOTE Confidence: 0.795876265882353

01:02:04.304 --> 01:02:07.440 and claiming we're seeing a real

NOTE Confidence: 0.795876265882353

01:02:07.440 --> 01:02:10.698 biological effect so you know it's

NOTE Confidence: 0.795876265882353

01:02:10.698 --> 01:02:14.339 there's a note of caution here.

NOTE Confidence: 0.795876265882353

01:02:14.340 --> 01:02:15.670 As the field moves forward.

NOTE Confidence: 0.680040615

01:02:22.070 --> 01:02:25.570 On red cells and. It doesn't.

NOTE Confidence: 0.8002267495

01:02:28.880 --> 01:02:32.184 I mean you know platelets are huge

NOTE Confidence: 0.8002267495

01:02:32.184 --> 01:02:35.005 producer of abuse and so we're

NOTE Confidence: 0.8002267495

01:02:35.005 --> 01:02:38.057 very careful in all of our studies.

NOTE Confidence: 0.8002267495

01:02:38.060 --> 01:02:40.220 We're dumbing it down you know,

NOTE Confidence: 0.8002267495

01:02:40.220 --> 01:02:43.258 so I can hope to understand what's

NOTE Confidence: 0.8002267495

01:02:43.258 --> 01:02:46.738 going on but we our extraction

NOTE Confidence: 0.8002267495

01:02:46.738 --> 01:02:48.817 process excludes platelets,

NOTE Confidence: 0.8002267495

01:02:48.820 --> 01:02:52.744 but that's that's a another area

NOTE Confidence: 0.8002267495

01:02:52.744 --> 01:02:57.138 everybody makes every cell it's making EB.

NOTE Confidence: 0.8002267495

01:02:57.140 --> 01:03:00.434 Grapefruit, there are people in the

NOTE Confidence: 0.8002267495

01:03:00.434 --> 01:03:03.488 consortium that are studying the the

NOTE Confidence: 0.8002267495

01:03:03.488 --> 01:03:06.745 release of EV's from grapefruit and the

NOTE Confidence: 0.8002267495

01:03:06.745 --> 01:03:09.640 biological effects that that that has.

NOTE Confidence: 0.8002267495

01:03:09.640 --> 01:03:12.992 So in the next time you know you're

NOTE Confidence: 0.8002267495

01:03:12.992 --> 01:03:16.209 eating a grapefruit or an orange.

NOTE Confidence: 0.8002267495

01:03:16.210 --> 01:03:20.213 Think about all those EV's that are

NOTE Confidence: 0.8002267495

01:03:20.213 --> 01:03:22.318 being released and thinking about,

NOTE Confidence: 0.8002267495

01:03:22.320 --> 01:03:24.688 you know, what is the consequence of that.