WEBVTT

NOTE duration:"01:06:07.3600000"

NOTE recognizability:0.808

NOTE language:en-us

NOTE Confidence: 0.919102911111111

00:00:00.000 --> 00:00:02.970 Thank you everyone for joining

NOTE Confidence: 0.919102911111111

00:00:02.970 --> 00:00:05.346 our grand rounds today.

NOTE Confidence: 0.919102911111111

00:00:05.350 --> 00:00:08.941 It is my honor and great pleasure

NOTE Confidence: 0.919102911111111

00:00:08.941 --> 00:00:11.740 to introduce Doctor Jason Mills.

NOTE Confidence: 0.919102911111111

00:00:11.740 --> 00:00:14.953 He is a Herman Brown endowed professor

NOTE Confidence: 0.919102911111111

00:00:14.953 --> 00:00:17.400 at Baylor College of Medicine,

NOTE Confidence: 0.919102911111111

00:00:17.400 --> 00:00:20.172 Chief of Research in the section

NOTE Confidence: 0.919102911111111

00:00:20.172 --> 00:00:22.020 of gastroenterology and Hepatology,

NOTE Confidence: 0.919102911111111

00:00:22.020 --> 00:00:24.515 and the Co director of Digestive Disease

NOTE Confidence: 0.919102911111111

00:00:24.515 --> 00:00:27.500 Center at the Texas Medical Center.

NOTE Confidence: 0.919102911111111

00:00:27.500 --> 00:00:31.066 So he graduated summa *** laude from

NOTE Confidence: 0.919102911111111

00:00:31.066 --> 00:00:33.460 Washington University in Saint Louis with

NOTE Confidence: 0.919102911111111

00:00:33.460 --> 00:00:38.140 double major in Russian and biology, right?

NOTE Confidence: 0.919102911111111

00:00:38.140 --> 00:00:41.339 Then he received the MD and PhD

NOTE Confidence: 0.919102911111111

00:00:41.340 --> 00:00:43.365 from University of Pennsylvania and

NOTE Confidence: 0.919102911111111

00:00:43.365 --> 00:00:45.990 went back to Washu for his anatomic

NOTE Confidence: 0.919102911111111

00:00:46.068 --> 00:00:49.990 pathology residency and postdoctoral.

NOTE Confidence: 0.919102911111111

00:00:49.990 --> 00:00:50.994 Fellowship there.

NOTE Confidence: 0.919102911111111

00:00:50.994 --> 00:00:54.508 And he mentioned that he had a

NOTE Confidence: 0.919102911111111

00:00:54.508 --> 00:00:56.921 traumatizing experience with Doctor

NOTE Confidence: 0.919102911111111

00:00:56.921 --> 00:01:00.840 Peter Humphrey as pathologist here at Yale.

NOTE Confidence: 0.919102911111111

00:01:00.840 --> 00:01:03.000 Now when they were, you know,

NOTE Confidence: 0.919102911111111

00:01:03.000 --> 00:01:05.499 signing out a big stack of the

NOTE Confidence: 0.919102911111111

00:01:05.499 --> 00:01:07.618 Hershey Springs case in the middle,

NOTE Confidence: 0.919102911111111

00:01:07.620 --> 00:01:08.860 they had a, you know,

NOTE Confidence: 0.919102911111111

00:01:08.860 --> 00:01:10.696 frozen section and had to leave.

NOTE Confidence: 0.919102911111111

00:01:10.700 --> 00:01:12.988 And then when they came back and they

NOTE Confidence: 0.919102911111111

00:01:12.988 --> 00:01:15.040 didn't remember which stack half stack

NOTE Confidence: 0.919102911111111

00:01:15.040 --> 00:01:17.497 they have reviewed versus they have not.

NOTE Confidence: 0.919102911111111

00:01:17.500 --> 00:01:20.236 So they had to go over again the.

NOTE Confidence: 0.919102911111111

00:01:20.240 --> 00:01:23.126 Except that's the entire case again.

NOTE Confidence: 0.919102911111111

00:01:23.130 --> 00:01:25.482 So they will have a reunion

NOTE Confidence: 0.919102911111111

00:01:25.482 --> 00:01:27.050 in the afternoon today.

NOTE Confidence: 0.919102911111111

00:01:27.050 --> 00:01:30.336 So you can have some conversation on that,

NOTE Confidence: 0.919102911111111

00:01:30.336 --> 00:01:31.069 right?

NOTE Confidence: 0.919102911111111

00:01:31.070 --> 00:01:34.325 And actually Jason was my PhD thesis

NOTE Confidence: 0.919102911111111

00:01:34.325 --> 00:01:36.920 mentor at Washu and so I have known

NOTE Confidence: 0.919102911111111

00:01:36.920 --> 00:01:39.962 him for 18 years now and all my

NOTE Confidence: 0.919102911111111

00:01:39.962 --> 00:01:42.170 interest in the GI research came

NOTE Confidence: 0.919102911111111

00:01:42.170 --> 00:01:46.408 from him and and he was a positive

NOTE Confidence: 0.919102911111111

00:01:46.410 --> 00:01:48.881 influence for me to pursue my career

NOTE Confidence: 0.919102911111111

00:01:48.881 --> 00:01:50.960 in pathology on the first day.

NOTE Confidence: 0.919102911111111

00:01:50.960 --> 00:01:53.350 When I joined this laboratory,

NOTE Confidence: 0.919102911111111

00:01:53.350 --> 00:01:55.870 we sit down on the double headed

NOTE Confidence: 0.919102911111111

00:01:55.870 --> 00:01:58.352 microscope and he went over mouse

NOTE Confidence: 0.919102911111111

00:01:58.352 --> 00:02:00.552 and human stomach Histology and

NOTE Confidence: 0.919102911111111

00:02:00.552 --> 00:02:03.239 encouraged me to become a pathologist.

NOTE Confidence: 0.919102911111111

00:02:03.240 --> 00:02:06.768 And at that time I was very negative

NOTE Confidence: 0.919102911111111

00:02:06.770 --> 00:02:09.605 because I never thought about becoming a

NOTE Confidence: 0.919102911111111

00:02:09.605 --> 00:02:12.328 pathologist during my entire medical school.

NOTE Confidence: 0.919102911111111

00:02:12.330 --> 00:02:15.710 But see now I'm a I became a pathologist.

NOTE Confidence: 0.919102911111111

00:02:15.710 --> 00:02:17.850 That's how influence influential

NOTE Confidence: 0.919102911111111

00:02:17.850 --> 00:02:20.980 he is and as pathologists.

NOTE Confidence: 0.919102911111111

00:02:20.980 --> 00:02:22.940 And some researchers here,

NOTE Confidence: 0.919102911111111

00:02:22.940 --> 00:02:26.572 we know well what metaplasia looks like,

NOTE Confidence: 0.919102911111111

00:02:26.572 --> 00:02:28.148 but we do not know.

NOTE Confidence: 0.919102911111111

00:02:28.148 --> 00:02:29.560 Well, you know, how it happens.

NOTE Confidence: 0.919102911111111

00:02:29.560 --> 00:02:32.759 What's the process mechanism on the line?

NOTE Confidence: 0.919102911111111

00:02:32.760 --> 00:02:34.766 So Doctor Miller says,

NOTE Confidence: 0.919102911111111

00:02:34.766 --> 00:02:37.574 focused on his research in the

NOTE Confidence: 0.919102911111111

00:02:37.574 --> 00:02:40.020 cellular and molecular process

NOTE Confidence: 0.919102911111111

00:02:40.020 --> 00:02:42.048 changes during the metaplasia.

NOTE Confidence: 0.919102911111111

00:02:42.048 --> 00:02:44.076 And published more than,

NOTE Confidence: 0.919102911111111

00:02:44.080 --> 00:02:45.024 you know,

NOTE Confidence: 0.919102911111111

00:02:45.024 --> 00:02:48.593 hundred papers on the metaplasia and in

NOTE Confidence: 0.919102911111111

00:02:48.593 --> 00:02:51.560 addition to the seminal scientific works,

NOTE Confidence: 0.919102911111111

00:02:51.560 --> 00:02:53.630 he is very talented as he told

NOTE Confidence: 0.919102911111111

00:02:53.630 --> 00:02:55.240 you that he majored in Russian,

NOTE Confidence: 0.919102911111111

00:02:55.240 --> 00:02:58.872 he is very fluent in Russian and French

NOTE Confidence: 0.919102911111111

00:02:58.872 --> 00:03:01.770 and also he can speak some Chinese

NOTE Confidence: 0.919102911111111

00:03:01.770 --> 00:03:04.395 and he knows many words in Korean.

NOTE Confidence: 0.919102911111111

00:03:04.400 --> 00:03:08.978 So with his talents in language,

NOTE Confidence: 0.919102911111111

00:03:08.980 --> 00:03:13.830 he recently coined terminology collagenosis.

NOTE Confidence: 0.919102911111111

00:03:13.830 --> 00:03:16.826 Which describes a universal program

NOTE Confidence: 0.919102911111111

00:03:16.826 --> 00:03:20.510 how mature cells reenter and change

NOTE Confidence: 0.919102911111111

00:03:20.604 --> 00:03:23.655 their subcellular structure and

NOTE Confidence: 0.919102911111111

00:03:23.655 --> 00:03:28.005 re-enter cell cycle and becoming a.

NOTE Confidence: 0.919102911111111

00:03:28.010 --> 00:03:31.170 The regenerative cells which

NOTE Confidence: 0.919102911111111

00:03:31.170 --> 00:03:32.830 happens during the metaplasia,

NOTE Confidence: 0.919102911111111

00:03:32.830 --> 00:03:36.225 so he's on the title of his talk today

NOTE Confidence: 0.919102911111111

00:03:36.225 --> 00:03:38.835 is the common features of metaplasia

NOTE Confidence: 0.919102911111111

00:03:38.835 --> 00:03:41.708 and tumorigenesis in the GI track which

NOTE Confidence: 0.919102911111111

00:03:41.710 --> 00:03:43.850 implies the polygenesis basically.

NOTE Confidence: 0.919102911111111

00:03:43.850 --> 00:03:46.740 So please join me in welcoming Dr.

NOTE Confidence: 0.919102911111111

00:03:46.750 --> 00:03:47.060 Mills.

NOTE Confidence: 0.35584447

00:03:50.230 --> 00:03:50.510 That's.

NOTE Confidence: 0.805820654166667

00:03:53.460 --> 00:03:55.350 Thanks. Thanks so much for the

NOTE Confidence: 0.805820654166667

00:03:55.350 --> 00:03:57.190 invitation and thanks to Juan Jay.

NOTE Confidence: 0.805820654166667

00:03:57.190 --> 00:03:59.068 I mean it's it's fantastic growth

NOTE Confidence: 0.805820654166667

00:03:59.068 --> 00:04:01.148 obviously to come here and and see

NOTE Confidence: 0.805820654166667

00:04:01.148 --> 00:04:02.690 people again and meet and meet

NOTE Confidence: 0.805820654166667

00:04:02.690 --> 00:04:04.679 new people and but it it's really

NOTE Confidence: 0.805820654166667

00:04:04.679 --> 00:04:06.576 fantastic to see you know somebody

NOTE Confidence: 0.805820654166667

00:04:06.576 --> 00:04:09.292 that you saw kind of come immediately

NOTE Confidence: 0.805820654166667

00:04:09.292 --> 00:04:11.712 can just over from in fact I picked

NOTE Confidence: 0.805820654166667

00:04:11.712 --> 00:04:13.119 you up at the airport I think

NOTE Confidence: 0.805820654166667

00:04:13.119 --> 00:04:15.310 when you were interviewing for a

NOTE Confidence: 0.805820654166667

00:04:15.310 --> 00:04:17.685 Graduate School at Washington St.

NOTE Confidence: 0.805820654166667

00:04:17.690 --> 00:04:19.104 Louis and then to have him come

NOTE Confidence: 0.805820654166667

00:04:19.104 --> 00:04:21.127 to my lab and then not even be

NOTE Confidence: 0.805820654166667

00:04:21.127 --> 00:04:22.487 interested in pathology and coming

NOTE Confidence: 0.805820654166667

00:04:22.537 --> 00:04:24.112 to do a PhD and then to wind up.

NOTE Confidence: 0.805820654166667

00:04:24.120 --> 00:04:26.262 A pathologist and then here is an

NOTE Confidence: 0.805820654166667

00:04:26.262 --> 00:04:27.670 assistant professor and Andre is

NOTE Confidence: 0.805820654166667

00:04:27.670 --> 00:04:29.390 the first out of my group to to

NOTE Confidence: 0.805820654166667

00:04:29.446 --> 00:04:31.058 become an assistant professor.

NOTE Confidence: 0.805820654166667

00:04:31.060 --> 00:04:33.664 So it's just you know it's fantastic

NOTE Confidence: 0.805820654166667

00:04:33.664 --> 00:04:36.094 honor and and fun to see see how

NOTE Confidence: 0.805820654166667

00:04:36.094 --> 00:04:37.576 things are things grow and and

NOTE Confidence: 0.805820654166667

00:04:37.576 --> 00:04:39.200 it was a fantastic introduction

NOTE Confidence: 0.805820654166667

00:04:39.200 --> 00:04:41.342 because you know essentially I just

NOTE Confidence: 0.805820654166667

00:04:41.342 --> 00:04:43.590 want to I usually don't do a lot

NOTE Confidence: 0.805820654166667

00:04:43.590 --> 00:04:45.188 of introduction for how I organize

NOTE Confidence: 0.805820654166667

00:04:45.188 --> 00:04:47.425 the talk but because you know I am

NOTE Confidence: 0.805820654166667

00:04:47.425 --> 00:04:49.448 a pathologist but also a cell and

NOTE Confidence: 0.805820654166667

00:04:49.448 --> 00:04:50.546 developmental biologist my talk

NOTE Confidence: 0.805820654166667

00:04:50.546 --> 00:04:52.500 kind of it will go back and forth.

NOTE Confidence: 0.805820654166667

00:04:52.500 --> 00:04:54.300 The first part is all going to be sort

NOTE Confidence: 0.805820654166667

00:04:54.349 --> 00:04:55.966 of human. Well, it's your background.

NOTE Confidence: 0.805820654166667

00:04:55.966 --> 00:04:58.401 And then the middle part is gonna go

NOTE Confidence: 0.805820654166667

00:04:58.401 --> 00:05:00.333 all the way down into ribosomes and,

NOTE Confidence: 0.805820654166667

00:05:00.340 --> 00:05:02.560 you know, very cell biological.

NOTE Confidence: 0.805820654166667

00:05:02.560 --> 00:05:04.604 But if you're interested in human pathology,

NOTE Confidence: 0.805820654166667

00:05:04.610 --> 00:05:06.416 don't give up there because it'll

NOTE Confidence: 0.805820654166667

00:05:06.416 --> 00:05:07.923 come back also to human pathology.

NOTE Confidence: 0.805820654166667

00:05:07.923 --> 00:05:09.910 So that's on the sort of that organization.

NOTE Confidence: 0.805820654166667

00:05:09.910 --> 00:05:11.954 And then just as one day said,

NOTE Confidence: 0.805820654166667

00:05:11.960 --> 00:05:13.541 as a resident,

NOTE Confidence: 0.805820654166667

00:05:13.541 --> 00:05:16.176 I became fascinated with metaplasia.

NOTE Confidence: 0.805820654166667

00:05:16.180 --> 00:05:17.128 And, you know,

NOTE Confidence: 0.805820654166667

00:05:17.128 --> 00:05:19.500 how do these cells that are sort of

NOTE Confidence: 0.805820654166667

00:05:19.500 --> 00:05:21.536 normal cells show up in the wrong

NOTE Confidence: 0.805820654166667

00:05:21.536 --> 00:05:23.198 place and how does that happen

NOTE Confidence: 0.805820654166667

00:05:23.198 --> 00:05:24.810 at a cell biological?

NOTE Confidence: 0.805820654166667

00:05:24.810 --> 00:05:25.593 Point of view,

NOTE Confidence: 0.805820654166667

00:05:25.593 --> 00:05:26.898 so that's my clinical interest.

NOTE Confidence: 0.805820654166667

00:05:26.900 --> 00:05:29.252 So we we're always doing sort of

NOTE Confidence: 0.805820654166667

00:05:29.252 --> 00:05:30.949 translational work on that side,

NOTE Confidence: 0.805820654166667

00:05:30.950 --> 00:05:32.588 but then on the research side,

NOTE Confidence: 0.805820654166667

00:05:32.590 --> 00:05:38.170 my cell biologist always side says.

NOTE Confidence: 0.805820654166667

00:05:38.170 --> 00:05:40.249 You know what what how does cells do that?

NOTE Confidence: 0.805820654166667

00:05:40.250 --> 00:05:42.049 How can cells like make this happen?

NOTE Confidence: 0.805820654166667

00:05:42.050 --> 00:05:43.210 So what are the mechanisms?

NOTE Confidence: 0.805820654166667

00:05:43.210 --> 00:05:44.449 So that's what the talk is about.

NOTE Confidence: 0.805820654166667

00:05:44.450 --> 00:05:47.060 So yes the cell biological

NOTE Confidence: 0.805820654166667

00:05:47.060 --> 00:05:48.964 changes are the cell,

NOTE Confidence: 0.805820654166667

00:05:48.964 --> 00:05:50.672 biological processes polygenesis and

NOTE Confidence: 0.805820654166667

00:05:50.672 --> 00:05:55.998 then you know the the context for the.

NOTE Confidence: 0.805820654166667

00:05:56.000 --> 00:05:58.469 Pathology is metaplasia.

NOTE Confidence: 0.805820654166667

00:05:58.470 --> 00:06:01.320 So.

NOTE Confidence: 0.805820654166667

00:06:01.320 --> 00:06:02.958 One just said why don't you put

NOTE Confidence: 0.805820654166667

00:06:02.958 --> 00:06:04.283 prognosis in your title so I

NOTE Confidence: 0.805820654166667

00:06:04.283 --> 00:06:05.429 I added it last night so.

NOTE Confidence: 0.859913548333333

00:06:07.800 --> 00:06:09.156 OK. So you know as far

NOTE Confidence: 0.859913548333333

00:06:09.156 --> 00:06:10.679 as I said it's like the,

NOTE Confidence: 0.859913548333333

00:06:10.680 --> 00:06:12.402 the clinical drive for this is

NOTE Confidence: 0.859913548333333

00:06:12.402 --> 00:06:13.980 how do these metaplasia happen,

NOTE Confidence: 0.859913548333333

00:06:13.980 --> 00:06:15.500 how do precancerous lesions arise

NOTE Confidence: 0.859913548333333

00:06:15.500 --> 00:06:17.620 along the GI tract and and how

NOTE Confidence: 0.859913548333333

00:06:17.620 --> 00:06:18.975 do they progress to tumors.

NOTE Confidence: 0.859913548333333

00:06:18.980 --> 00:06:22.172 So that's kind of what drives and

NOTE Confidence: 0.859913548333333

00:06:22.172 --> 00:06:25.024 funds our work and lately you know

NOTE Confidence: 0.859913548333333

00:06:25.024 --> 00:06:28.084 it's not just us but with the advent

NOTE Confidence: 0.859913548333333

00:06:28.084 --> 00:06:31.228 of of single cell RNA seek in in

NOTE Confidence: 0.859913548333333

00:06:31.228 --> 00:06:33.436 multiple organs I think you know

NOTE Confidence: 0.859913548333333

00:06:33.436 --> 00:06:34.981 we're beginning to realize that

NOTE Confidence: 0.859913548333333

00:06:34.981 --> 00:06:36.815 there's a lot more commonality

NOTE Confidence: 0.859913548333333

00:06:36.815 --> 00:06:38.279 in metaplasia across multiple.

NOTE Confidence: 0.859913548333333

00:06:38.280 --> 00:06:38.930 The Oregon.

NOTE Confidence: 0.859913548333333

00:06:38.930 --> 00:06:41.205 So there might be commonality in in

NOTE Confidence: 0.859913548333333

00:06:41.205 --> 00:06:43.013 these precancerous lesions that that

NOTE Confidence: 0.859913548333333

00:06:43.013 --> 00:06:46.040 you know I was trained when I was an,

NOTE Confidence: 0.859913548333333

00:06:46.040 --> 00:06:50.720 you know an AP resident to think it was.

NOTE Confidence: 0.859913548333333

00:06:50.720 --> 00:06:51.686 Sort of process.

NOTE Confidence: 0.859913548333333

00:06:51.686 --> 00:06:53.618 Interest on metaplasia in the stomach

NOTE Confidence: 0.859913548333333

00:06:53.618 --> 00:06:55.470 and and certainly has nothing to

NOTE Confidence: 0.859913548333333

00:06:55.470 --> 00:06:57.363 do with how colon cancer starts

NOTE Confidence: 0.859913548333333

00:06:57.363 --> 00:06:59.168 or how pancreatic cancer starts.

NOTE Confidence: 0.859913548333333

00:06:59.170 --> 00:07:01.159 On the other hand it's kind of like you

NOTE Confidence: 0.859913548333333

00:07:01.159 --> 00:07:02.968 know it's kind of becoming clear that

NOTE Confidence: 0.859913548333333

00:07:02.968 --> 00:07:04.850 that there's a lot of similarities.

NOTE Confidence: 0.859913548333333

00:07:04.850 --> 00:07:06.570 So let's talk about that.

NOTE Confidence: 0.859913548333333

00:07:06.570 --> 00:07:08.190 So you know with with Jim

NOTE Confidence: 0.859913548333333

00:07:08.190 --> 00:07:09.270 Golden Ring at Vanderbilt,

NOTE Confidence: 0.859913548333333

00:07:09.270 --> 00:07:11.455 we had this review recently

NOTE Confidence: 0.859913548333333

00:07:11.455 --> 00:07:12.766 in gastroenterology talking

NOTE Confidence: 0.859913548333333

00:07:12.766 --> 00:07:14.910 about some of these concepts.

NOTE Confidence: 0.859913548333333

00:07:14.910 --> 00:07:17.046 In this one in particular we

NOTE Confidence: 0.859913548333333

00:07:17.046 --> 00:07:18.470 focused on the similarities

NOTE Confidence: 0.859913548333333

00:07:18.537 --> 00:07:20.665 between Barrett's metaplasia and

NOTE Confidence: 0.859913548333333

00:07:20.665 --> 00:07:22.793 gastric and intestinal metaplasia.

NOTE Confidence: 0.859913548333333

00:07:22.800 --> 00:07:23.696 And basically you know,

NOTE Confidence: 0.859913548333333

00:07:23.696 --> 00:07:24.816 if you think of Barretts,

NOTE Confidence: 0.859913548333333

00:07:24.820 --> 00:07:26.820 the ideology there is obviously

NOTE Confidence: 0.859913548333333

00:07:26.820 --> 00:07:29.284 quite different from the way you

NOTE Confidence: 0.859913548333333

00:07:29.284 --> 00:07:31.249 get intestinal metaplasia in the

NOTE Confidence: 0.859913548333333

00:07:31.249 --> 00:07:33.430 stomach and and that's because,

NOTE Confidence: 0.859913548333333

00:07:33.430 --> 00:07:34.950 you know, we know that.

NOTE Confidence: 0.859913548333333

00:07:34.950 --> 00:07:37.560 Had a thing of of reflux of acid and

NOTE Confidence: 0.859913548333333

00:07:37.560 --> 00:07:40.748 and probably also importantly bile as well.

NOTE Confidence: 0.859913548333333

00:07:40.750 --> 00:07:42.742 And then that takes your squamous

NOTE Confidence: 0.859913548333333

00:07:42.742 --> 00:07:44.568 epithelium right and turns it into

NOTE Confidence: 0.859913548333333

00:07:44.568 --> 00:07:46.950 this what in Barretts is called,

NOTE Confidence: 0.859913548333333

00:07:46.950 --> 00:07:47.926 you know,

NOTE Confidence: 0.859913548333333

00:07:47.926 --> 00:07:51.342 a columnar mucosa at least at first,

NOTE Confidence: 0.859913548333333

00:07:51.350 --> 00:07:53.270 which is basically organized

NOTE Confidence: 0.859913548333333

00:07:53.270 --> 00:07:55.670 a pyloric gastric unit is.

NOTE Confidence: 0.859913548333333

00:07:55.670 --> 00:07:56.975 So it's essentially just a

NOTE Confidence: 0.859913548333333

00:07:56.975 --> 00:07:58.280 pyloric metaplasia or a pseudo

NOTE Confidence: 0.859913548333333

00:07:58.334 --> 00:07:59.850 pyloric metaplasia from squamous,

NOTE Confidence: 0.859913548333333

00:07:59.850 --> 00:08:01.450 although nobody ever calls it

NOTE Confidence: 0.859913548333333

00:08:01.450 --> 00:08:02.610 that in the esophagus,

NOTE Confidence: 0.859913548333333

00:08:02.610 --> 00:08:05.380 I want to point out that to researchers.

NOTE Confidence: 0.859913548333333

00:08:05.380 --> 00:08:07.916 Jim being the one on golden Ring that

NOTE Confidence: 0.859913548333333

00:08:07.916 --> 00:08:10.092 coined this term at Vanderbilt that

NOTE Confidence: 0.859913548333333

00:08:10.092 --> 00:08:12.276 that that what that means is that

NOTE Confidence: 0.859913548333333

00:08:12.276 --> 00:08:15.296 that the cells at the bottom are stem cells,

NOTE Confidence: 0.859913548333333

00:08:15.300 --> 00:08:16.074 spasmolytic polypeptide

NOTE Confidence: 0.859913548333333

00:08:16.074 --> 00:08:16.848 expressing metaplasia.

NOTE Confidence: 0.859913548333333

00:08:16.848 --> 00:08:19.980 And so that's a term that was coined in,

NOTE Confidence: 0.859913548333333

00:08:19.980 --> 00:08:22.758 in the stomach actually originally in

NOTE Confidence: 0.859913548333333

00:08:22.758 --> 00:08:24.610 humans because spasmolytic polypeptide

NOTE Confidence: 0.859913548333333

00:08:24.671 --> 00:08:26.589 is trefoil factor 2 and that shows

NOTE Confidence: 0.859913548333333

00:08:26.589 --> 00:08:28.885 up only in these pyloric sort of

NOTE Confidence: 0.859913548333333

00:08:28.885 --> 00:08:30.698 lesions in the body of the stomach.

NOTE Confidence: 0.859913548333333

00:08:30.700 --> 00:08:33.316 So a lot of what we'll talk about

NOTE Confidence: 0.859913548333333

00:08:33.316 --> 00:08:35.500 involves this transition into this.

NOTE Confidence: 0.859913548333333

00:08:35.500 --> 00:08:38.332 Mucus secreting deep, antral,

NOTE Confidence: 0.859913548333333

00:08:38.332 --> 00:08:40.590 deep pyloric TF2 positive

NOTE Confidence: 0.859913548333333

00:08:40.590 --> 00:08:42.270 muck 6 positive lineage.

NOTE Confidence: 0.859913548333333

00:08:42.270 --> 00:08:42.574 OK,

NOTE Confidence: 0.859913548333333

00:08:42.574 --> 00:08:43.790 so in the stomach,

NOTE Confidence: 0.859913548333333

00:08:43.790 --> 00:08:45.323 when H pylori get tired of being

NOTE Confidence: 0.859913548333333

00:08:45.323 --> 00:08:45.980 in the Antrim,

NOTE Confidence: 0.859913548333333

00:08:45.980 --> 00:08:47.564 they want to expand their knee and they

NOTE Confidence: 0.859913548333333

00:08:47.564 --> 00:08:49.346 want to go into the body of the stomach.

NOTE Confidence: 0.859913548333333

00:08:49.350 --> 00:08:51.390 And it turns out that the way they do this,

NOTE Confidence: 0.859913548333333

00:08:51.390 --> 00:08:54.034 or we can model this with drugs.

NOTE Confidence: 0.859913548333333

00:08:54.034 --> 00:08:56.008 And in fact Juan Jade pioneered this.

NOTE Confidence: 0.859913548333333

00:08:56.010 --> 00:08:57.599 And there are hundreds of papers now

NOTE Confidence: 0.859913548333333

00:08:57.599 --> 00:08:59.309 in the world using this technique,

NOTE Confidence: 0.891849746666667

00:08:59.310 --> 00:09:03.078 which is using high doses of tamoxifen can

NOTE Confidence: 0.891849746666667

00:09:03.078 --> 00:09:05.819 completely reprogram the stomach of a mouse.

NOTE Confidence: 0.891849746666667

00:09:05.820 --> 00:09:07.844 The same way that H pylori can in

NOTE Confidence: 0.891849746666667

00:09:07.844 --> 00:09:09.938 humans and actually H pylori and mouse

NOTE Confidence: 0.891849746666667

00:09:09.938 --> 00:09:12.273 over a longer time course and what

NOTE Confidence: 0.891849746666667

00:09:12.273 --> 00:09:14.143 happens during that reprogramming is

NOTE Confidence: 0.891849746666667

00:09:14.143 --> 00:09:16.641 essentially what we talk about as

NOTE Confidence: 0.891849746666667

00:09:16.641 --> 00:09:18.926 pathologist as chronic atrophic gastritis,

NOTE Confidence: 0.891849746666667

00:09:18.930 --> 00:09:21.198 but is actually also a metaplasia

NOTE Confidence: 0.891849746666667

00:09:21.198 --> 00:09:23.964 because it turns the corpus units away

NOTE Confidence: 0.891849746666667

00:09:23.964 --> 00:09:26.708 from being oxyntic units with gas with

NOTE Confidence: 0.891849746666667

00:09:26.785 --> 00:09:29.496 the parietal cells and chief cells into

NOTE Confidence: 0.891849746666667

00:09:29.496 --> 00:09:31.126 basically a pyloric like structure

NOTE Confidence: 0.891849746666667

00:09:31.126 --> 00:09:33.969 with MUC 5 AC positive foveolar cells,

NOTE Confidence: 0.891849746666667

00:09:33.970 --> 00:09:35.446 a lower ismal.

NOTE Confidence: 0.891849746666667

00:09:35.446 --> 00:09:37.906 Proliferative center and again these

NOTE Confidence: 0.891849746666667

00:09:37.906 --> 00:09:40.814 deep antral like cells which are

NOTE Confidence: 0.891849746666667

00:09:40.814 --> 00:09:43.784 characterized in the stomach as

NOTE Confidence: 0.891849746666667

00:09:43.784 --> 00:09:45.566 spasmolytic polypeptide expressing

NOTE Confidence: 0.891849746666667

00:09:45.566 --> 00:09:46.463 metaplasia. So.

NOTE Confidence: 0.891849746666667

00:09:46.463 --> 00:09:47.069 You know,

NOTE Confidence: 0.891849746666667

00:09:47.069 --> 00:09:49.190 the first step basically of H pylori

NOTE Confidence: 0.891849746666667

00:09:49.256 --> 00:09:51.720 is to turn normal oxyntic glands into

NOTE Confidence: 0.891849746666667

00:09:51.720 --> 00:09:53.929 these pseudo pyloric metaplasia glands,

NOTE Confidence: 0.891849746666667

00:09:53.930 --> 00:09:55.256 which is much more what they're

NOTE Confidence: 0.891849746666667

00:09:55.256 --> 00:09:56.480 accustomed to in the antrum,

NOTE Confidence: 0.891849746666667

00:09:56.480 --> 00:09:59.864 and that's how they spread from the stomach.

NOTE Confidence: 0.891849746666667

00:09:59.870 --> 00:10:01.562 So basically what that means is

NOTE Confidence: 0.891849746666667

00:10:01.562 --> 00:10:03.833 that that you know as we kind of

NOTE Confidence: 0.891849746666667

00:10:03.833 --> 00:10:05.459 learn more and more about Barretts

NOTE Confidence: 0.891849746666667

00:10:05.515 --> 00:10:07.363 and we do the single cell RNA seek

NOTE Confidence: 0.891849746666667

00:10:07.363 --> 00:10:09.450 and we do the genome studies and we

NOTE Confidence: 0.891849746666667

00:10:09.450 --> 00:10:11.729 try to look at the clonal origin,

NOTE Confidence: 0.891849746666667

00:10:11.730 --> 00:10:13.690 origin of the Barrett's lesions.

NOTE Confidence: 0.891849746666667

00:10:13.690 --> 00:10:16.570 And you know the best consensus

NOTE Confidence: 0.891849746666667

00:10:16.570 --> 00:10:19.649 is that these kind of columnar

NOTE Confidence: 0.891849746666667

00:10:19.650 --> 00:10:21.378 lesions that look gastric are the

NOTE Confidence: 0.891849746666667

00:10:21.378 --> 00:10:23.199 first ones that appear in Barretts.

NOTE Confidence: 0.891849746666667

00:10:23.200 --> 00:10:25.958 But even these can be traced back

NOTE Confidence: 0.891849746666667

00:10:25.958 --> 00:10:27.970 to roots in in oxyntic mucosa,

NOTE Confidence: 0.891849746666667

00:10:27.970 --> 00:10:30.714 in other words, if you do clonal.

NOTE Confidence: 0.891849746666667

00:10:30.714 --> 00:10:31.626 Genomic analysis,

NOTE Confidence: 0.891849746666667

00:10:31.630 --> 00:10:34.303 you see that these often can be found in

NOTE Confidence: 0.891849746666667

00:10:34.303 --> 00:10:37.388 a patient near where they're you know,

NOTE Confidence: 0.891849746666667

00:10:37.388 --> 00:10:39.558 most proximal eccentric glands are.

NOTE Confidence: 0.891849746666667

00:10:39.560 --> 00:10:41.696 So the idea then is that bile or

NOTE Confidence: 0.891849746666667

00:10:41.696 --> 00:10:43.999 acid can turn these oxyntic glands

NOTE Confidence: 0.891849746666667

00:10:43.999 --> 00:10:45.695 into these pyloric glands.

NOTE Confidence: 0.891849746666667

00:10:45.700 --> 00:10:47.806 And then pretty clearly what happens

NOTE Confidence: 0.891849746666667

00:10:47.806 --> 00:10:50.280 then is they become intestinal used.

NOTE Confidence: 0.891849746666667

00:10:50.280 --> 00:10:51.496 And why do I say it's pretty clear?

NOTE Confidence: 0.891849746666667

00:10:51.500 --> 00:10:53.908 It's because if you look at all Barrett

NOTE Confidence: 0.891849746666667

00:10:53.908 --> 00:10:55.030 specimens, especially if you have,

NOTE Confidence: 0.891849746666667

00:10:55.030 --> 00:10:56.150 you know, full thickness,

NOTE Confidence: 0.891849746666667

00:10:56.150 --> 00:10:58.280 they almost always have bases that

NOTE Confidence: 0.891849746666667

00:10:58.280 --> 00:11:00.379 are muck 6 positive or trefoil.

NOTE Confidence: 0.891849746666667

00:11:00.380 --> 00:11:02.580 Factor 2 positive or look just like these,

NOTE Confidence: 0.891849746666667

00:11:02.580 --> 00:11:04.184 you know spasmolytic polypeptide

NOTE Confidence: 0.891849746666667

00:11:04.184 --> 00:11:06.189 expressing metaplasia cells and it's

NOTE Confidence: 0.891849746666667

00:11:06.189 --> 00:11:08.182 only the surface at least until you

NOTE Confidence: 0.891849746666667

00:11:08.182 --> 00:11:09.844 get a high grade dysplasia that

NOTE Confidence: 0.891849746666667

00:11:09.844 --> 00:11:11.602 has a lot of intestinal lization

NOTE Confidence: 0.891849746666667

00:11:11.602 --> 00:11:13.782 and of course then the progression

NOTE Confidence: 0.891849746666667

00:11:13.782 --> 00:11:16.170 progression from here is into dysplasia.

NOTE Confidence: 0.891849746666667

00:11:16.170 --> 00:11:19.586 So our research really is into you know,

NOTE Confidence: 0.891849746666667

00:11:19.590 --> 00:11:21.014 how do you get from here to here,

NOTE Confidence: 0.891849746666667

00:11:21.020 --> 00:11:22.436 how do you get from here to here

NOTE Confidence: 0.891849746666667

00:11:22.436 --> 00:11:24.034 and how do you get from here to

NOTE Confidence: 0.891849746666667

00:11:24.034 --> 00:11:25.370 here from a pathology standpoint,

NOTE Confidence: 0.891849746666667

00:11:25.370 --> 00:11:27.470 you know then that gives you cancer.

NOTE Confidence: 0.891849746666667

00:11:27.470 --> 00:11:29.297 One thing just as a take home

NOTE Confidence: 0.891849746666667

00:11:29.297 --> 00:11:30.540 is that we think.

NOTE Confidence: 0.891849746666667

00:11:30.540 --> 00:11:32.622 Critical event in all of these

NOTE Confidence: 0.891849746666667

00:11:32.622 --> 00:11:34.670 transitions very early on is 53

NOTE Confidence: 0.891849746666667

00:11:34.670 --> 00:11:36.749 mutation and we're going to dig right

NOTE Confidence: 0.891849746666667

00:11:36.749 --> 00:11:38.894 into the cell biology as we we you

NOTE Confidence: 0.891849746666667

00:11:38.894 --> 00:11:41.240 know why we think that now clinically

NOTE Confidence: 0.891849746666667

00:11:41.240 --> 00:11:43.215 and Barretts and molecularly we're

NOTE Confidence: 0.891849746666667

00:11:43.215 --> 00:11:45.274 finding that that basically as soon as

NOTE Confidence: 0.891849746666667

00:11:45.274 --> 00:11:47.398 you have a loss of heterozygosity for

NOTE Confidence: 0.891849746666667

00:11:47.398 --> 00:11:49.715 people 53 and and and patients have

NOTE Confidence: 0.695209716363636

00:11:49.720 --> 00:11:52.576 loss of function for PD3 then those

NOTE Confidence: 0.695209716363636

00:11:52.576 --> 00:11:54.700 Barretts lesions behave differently.

NOTE Confidence: 0.695209716363636

00:11:54.700 --> 00:11:56.324 They're almost always become

NOTE Confidence: 0.695209716363636

00:11:56.324 --> 00:11:58.760 dysplastic and the rate of conversion

NOTE Confidence: 0.695209716363636

00:11:58.822 --> 00:12:02.440 to neoplasms much higher. So.

NOTE Confidence: 0.695209716363636

00:12:02.440 --> 00:12:04.358 What I'm saying is that I think,

NOTE Confidence: 0.695209716363636

00:12:04.360 --> 00:12:05.660 you know, basically based on

NOTE Confidence: 0.695209716363636

00:12:05.660 --> 00:12:07.271 the the lineage tracing and all

NOTE Confidence: 0.695209716363636

00:12:07.271 --> 00:12:08.807 these sort of parallels and the

NOTE Confidence: 0.695209716363636

00:12:08.807 --> 00:12:10.112 molecular work that we're doing

NOTE Confidence: 0.695209716363636

00:12:10.112 --> 00:12:11.576 that what we think happens is,

NOTE Confidence: 0.695209716363636

00:12:11.580 --> 00:12:13.278 you know, violent acid comes in,

NOTE Confidence: 0.695209716363636

00:12:13.280 --> 00:12:14.975 Barretts and it.

NOTE Confidence: 0.695209716363636

00:12:14.975 --> 00:12:17.800 Takes out the squamous epithelium

NOTE Confidence: 0.695209716363636

00:12:17.800 --> 00:12:21.709 and then in the in the that sort

NOTE Confidence: 0.695209716363636

00:12:21.709 --> 00:12:24.331 of damaged bedding and in that

NOTE Confidence: 0.695209716363636

00:12:24.331 --> 00:12:26.466 reflex setting you get migration

NOTE Confidence: 0.695209716363636

00:12:26.466 --> 00:12:29.629 of this kind of gastric epithelium.

NOTE Confidence: 0.695209716363636

00:12:29.630 --> 00:12:32.780 And then the gastric epithelium

NOTE Confidence: 0.695209716363636

00:12:32.780 --> 00:12:34.040 becomes intestinalis.

NOTE Confidence: 0.695209716363636

00:12:34.040 --> 00:12:35.606 And so you can kind of see some of

NOTE Confidence: 0.695209716363636

00:12:35.606 --> 00:12:36.930 these examples from and a lot of

NOTE Confidence: 0.695209716363636

00:12:36.930 --> 00:12:38.410 the work that I was telling you,

NOTE Confidence: 0.695209716363636

00:12:38.410 --> 00:12:40.786 the molecular work showing the origins

NOTE Confidence: 0.695209716363636

00:12:40.786 --> 00:12:43.420 of the Barretts lesions in in,

NOTE Confidence: 0.695209716363636

00:12:43.420 --> 00:12:44.340 you know,

NOTE Confidence: 0.695209716363636

00:12:44.340 --> 00:12:46.404 way back at some point in a patient

NOTE Confidence: 0.695209716363636

00:12:46.404 --> 00:12:48.278 in oxyntic mucosa is from Stuart

NOTE Confidence: 0.695209716363636

00:12:48.278 --> 00:12:49.903 McDonald and Marnick Sanson and

NOTE Confidence: 0.695209716363636

00:12:49.903 --> 00:12:51.665 Nick Wright who've been doing this

NOTE Confidence: 0.695209716363636

00:12:51.665 --> 00:12:54.378 for a decade or two in in London.

NOTE Confidence: 0.695209716363636

00:12:54.378 --> 00:12:57.366 So you can see like these oxyntic

NOTE Confidence: 0.695209716363636

00:12:57.366 --> 00:12:58.896 lesions in in sometimes distal

NOTE Confidence: 0.695209716363636

00:12:58.896 --> 00:13:00.945 Barretts and then you can see this

NOTE Confidence: 0.695209716363636

00:13:00.945 --> 00:13:02.475 is just from their paper actually

NOTE Confidence: 0.695209716363636

00:13:02.475 --> 00:13:04.169 and you see these more pyloric.

NOTE Confidence: 0.695209716363636

00:13:04.170 --> 00:13:05.958 Regions where you have the spam

NOTE Confidence: 0.695209716363636

00:13:05.958 --> 00:13:08.050 mucous cells at the bottom and then

NOTE Confidence: 0.695209716363636

00:13:08.050 --> 00:13:10.010 you see spam mucous cells at the

NOTE Confidence: 0.695209716363636

00:13:10.075 --> 00:13:12.247 bottom as the tops become intestinalis

NOTE Confidence: 0.695209716363636

00:13:12.247 --> 00:13:15.930 used with goblet cells, so.

NOTE Confidence: 0.695209716363636

00:13:15.930 --> 00:13:17.158 So we've been working,

NOTE Confidence: 0.695209716363636

00:13:17.158 --> 00:13:19.000 we started working on Barretts five

NOTE Confidence: 0.695209716363636

00:13:19.061 --> 00:13:21.098 or six years ago and started seeing

NOTE Confidence: 0.695209716363636

00:13:21.098 --> 00:13:24.290 that all come together with our stomach work.

NOTE Confidence: 0.695209716363636

00:13:24.290 --> 00:13:25.738 And then you know when you kind of

NOTE Confidence: 0.695209716363636

00:13:25.738 --> 00:13:27.316 do this sort of thing then you go

NOTE Confidence: 0.695209716363636

00:13:27.316 --> 00:13:29.008 back to the stomach and you think again,

NOTE Confidence: 0.695209716363636

00:13:29.010 --> 00:13:31.392 well do we really understand how

NOTE Confidence: 0.695209716363636

00:13:31.392 --> 00:13:32.980 the stomach metaplasia happens.

NOTE Confidence: 0.695209716363636

00:13:32.980 --> 00:13:35.248 And so we started really kind of

NOTE Confidence: 0.695209716363636

00:13:35.248 --> 00:13:37.298 digging into the different types

NOTE Confidence: 0.695209716363636

00:13:37.298 --> 00:13:38.807 of stomach metaplasia.

NOTE Confidence: 0.695209716363636

00:13:38.810 --> 00:13:40.637 You know that from a research side

NOTE Confidence: 0.695209716363636

00:13:40.637 --> 00:13:42.782 and and actually in in Asia it's a

NOTE Confidence: 0.695209716363636

00:13:42.782 --> 00:13:44.087 diagnostic thing where you really

NOTE Confidence: 0.695209716363636

00:13:44.145 --> 00:13:45.529 make a distinction between.

NOTE Confidence: 0.695209716363636

00:13:45.530 --> 00:13:47.156 Incomplete and test on that ablation,

NOTE Confidence: 0.695209716363636

00:13:47.160 --> 00:13:49.070 complete and test on metaplasia.

NOTE Confidence: 0.695209716363636

00:13:49.070 --> 00:13:49.630 In fact,

NOTE Confidence: 0.695209716363636

00:13:49.630 --> 00:13:51.590 you know they're type ones and type

NOTE Confidence: 0.695209716363636

00:13:51.590 --> 00:13:53.417 twos based on use and patterns.

NOTE Confidence: 0.695209716363636

00:13:53.420 --> 00:13:55.298 But what does all that mean?

NOTE Confidence: 0.695209716363636

00:13:55.300 --> 00:13:55.529 Well,

NOTE Confidence: 0.695209716363636

00:13:55.529 --> 00:13:57.132 it turns out that really if you

NOTE Confidence: 0.695209716363636

00:13:57.132 --> 00:13:59.120 go back in the in the stomach and

NOTE Confidence: 0.695209716363636

00:13:59.120 --> 00:14:00.901 especially look at the borders of

NOTE Confidence: 0.695209716363636

00:14:00.901 --> 00:14:02.397 patches of intestinal metaplasia,

NOTE Confidence: 0.695209716363636

00:14:02.400 --> 00:14:04.472 a lot of the times they're they're

NOTE Confidence: 0.695209716363636

00:14:04.472 --> 00:14:06.419 incomplete and they have the same

NOTE Confidence: 0.695209716363636

00:14:06.419 --> 00:14:08.094 kind of organizations Barretts with

NOTE Confidence: 0.695209716363636

00:14:08.100 --> 00:14:09.462 spasmolytic polypeptide expressing

NOTE Confidence: 0.695209716363636

00:14:09.462 --> 00:14:12.186 metaplasia type deep pyloric cells at

NOTE Confidence: 0.695209716363636

00:14:12.186 --> 00:14:14.226 the bottom and then internalization

NOTE Confidence: 0.695209716363636

00:14:14.226 --> 00:14:15.750 of of goblet cells.

NOTE Confidence: 0.695209716363636

00:14:15.750 --> 00:14:17.773 At the top and during COVID when

NOTE Confidence: 0.695209716363636

00:14:17.773 --> 00:14:20.219 I had more time to kind of mess

NOTE Confidence: 0.695209716363636

00:14:20.219 --> 00:14:22.391 around and and look into history of

NOTE Confidence: 0.695209716363636

00:14:22.391 --> 00:14:24.751 stuff and I was trying to go back

NOTE Confidence: 0.695209716363636

00:14:24.760 --> 00:14:27.329 and and try to figure out where

NOTE Confidence: 0.695209716363636

00:14:27.329 --> 00:14:29.710 it was that everybody in the in

NOTE Confidence: 0.695209716363636

00:14:29.710 --> 00:14:31.310 the stomach became obsessed with

NOTE Confidence: 0.695209716363636

00:14:31.310 --> 00:14:32.240 intestinal metaplasia.

NOTE Confidence: 0.695209716363636

00:14:32.240 --> 00:14:34.160 You know is this something that's

NOTE Confidence: 0.695209716363636

00:14:34.160 --> 00:14:35.440 always happened because pretty

NOTE Confidence: 0.695209716363636

00:14:35.490 --> 00:14:36.865 clearly the first thing that

NOTE Confidence: 0.695209716363636

00:14:36.865 --> 00:14:38.240 happens in atrophy is this

NOTE Confidence: 0.807014336521739

00:14:38.290 --> 00:14:39.490 more pyloric metaplasia.

NOTE Confidence: 0.807014336521739

00:14:39.490 --> 00:14:40.726 Yet we never signed that out.

NOTE Confidence: 0.807014336521739

00:14:40.730 --> 00:14:42.010 We never diagnosed that.

NOTE Confidence: 0.807014336521739

00:14:42.010 --> 00:14:44.266 I started going back in history and

NOTE Confidence: 0.807014336521739

00:14:44.266 --> 00:14:46.170 and you find that people you know.

NOTE Confidence: 0.807014336521739

00:14:46.170 --> 00:14:48.395 Have been talking about pyloric

NOTE Confidence: 0.807014336521739

00:14:48.395 --> 00:14:50.620 metaplasia actually since like the

NOTE Confidence: 0.807014336521739

00:14:50.692 --> 00:14:53.239 1890s and it was only in the sort of

NOTE Confidence: 0.807014336521739

00:14:53.239 --> 00:14:56.221 1960s or 70s that people became so

NOTE Confidence: 0.807014336521739

00:14:56.221 --> 00:14:57.973 interested in intestinal medication.

NOTE Confidence: 0.807014336521739

00:14:57.980 --> 00:15:00.206 It was about the time that endoscopic

NOTE Confidence: 0.807014336521739

00:15:00.206 --> 00:15:01.937 biopsies came around and and

NOTE Confidence: 0.807014336521739

00:15:01.937 --> 00:15:03.737 pathologists got only little snippets.

NOTE Confidence: 0.807014336521739

00:15:03.740 --> 00:15:05.658 And you couldn't sort of tell the

NOTE Confidence: 0.807014336521739

00:15:05.658 --> 00:15:07.777 orientation to tell whether there was basil,

NOTE Confidence: 0.807014336521739

00:15:07.780 --> 00:15:10.420 you know, pyloric glands or not.

NOTE Confidence: 0.807014336521739

00:15:10.420 --> 00:15:12.142 But even, you know in the 1890s

NOTE Confidence: 0.807014336521739

00:15:12.142 --> 00:15:14.141 they kind of had this concept that

NOTE Confidence: 0.807014336521739

00:15:14.141 --> 00:15:16.180 there were these sort of pyloric or.

NOTE Confidence: 0.807014336521739

00:15:16.180 --> 00:15:18.007 Or acid or mucin cell like glance

NOTE Confidence: 0.807014336521739

00:15:18.007 --> 00:15:20.053 at the bottom that these then might

NOTE Confidence: 0.807014336521739

00:15:20.053 --> 00:15:22.416 have might be feeding these kind of

NOTE Confidence: 0.807014336521739

00:15:22.416 --> 00:15:23.919 incomplete intestinal metaplasia.

NOTE Confidence: 0.807014336521739

00:15:23.920 --> 00:15:27.441 This is from a textbook on gastric

NOTE Confidence: 0.807014336521739

00:15:27.441 --> 00:15:29.838 pathology in 1897 just to kind

NOTE Confidence: 0.807014336521739

00:15:29.838 --> 00:15:32.430 of show this diagram with sort of

NOTE Confidence: 0.807014336521739

00:15:32.430 --> 00:15:35.034 spam metaplasia on the bottom and

NOTE Confidence: 0.807014336521739

00:15:35.034 --> 00:15:36.989 then internalization on the top.

NOTE Confidence: 0.807014336521739

00:15:36.990 --> 00:15:38.300 And then just you know,

NOTE Confidence: 0.807014336521739

00:15:38.300 --> 00:15:40.370 I as I do a lot of sort of translational

NOTE Confidence: 0.807014336521739

00:15:40.428 --> 00:15:41.989 work and I have slides about my

NOTE Confidence: 0.807014336521739

00:15:41.989 --> 00:15:43.902 desk that I look at all the time

NOTE Confidence: 0.807014336521739

00:15:43.902 --> 00:15:45.514 and you know bring people in like

NOTE Confidence: 0.807014336521739

00:15:45.514 --> 00:15:46.963 Juan J and and sit and look.

NOTE Confidence: 0.807014336521739

00:15:46.970 --> 00:15:48.842 You can actually see this pretty

NOTE Confidence: 0.807014336521739

00:15:48.842 --> 00:15:50.888 frequently if you look for it where

NOTE Confidence: 0.807014336521739

00:15:50.888 --> 00:15:52.596 you can see these kind of deep

NOTE Confidence: 0.807014336521739

00:15:52.660 --> 00:15:54.765 pyloric glands erupting into more

NOTE Confidence: 0.807014336521739

00:15:54.765 --> 00:15:56.449 superficial transitioning into this

NOTE Confidence: 0.807014336521739

00:15:56.449 --> 00:15:58.742 kind of incomplete metaplasia.

NOTE Confidence: 0.807014336521739

00:15:58.742 --> 00:16:02.486 OK, so that's stomach and esophagus.

NOTE Confidence: 0.807014336521739

00:16:02.490 --> 00:16:04.394 But it turns out now with single

NOTE Confidence: 0.807014336521739

00:16:04.394 --> 00:16:06.638 cell or in a site where you can

NOTE Confidence: 0.807014336521739

00:16:06.638 --> 00:16:08.799 take apart each one of these cells

NOTE Confidence: 0.807014336521739

00:16:08.799 --> 00:16:11.001 during progression to pan in lesions

NOTE Confidence: 0.807014336521739

00:16:11.001 --> 00:16:12.905 again for some reason in you know

NOTE Confidence: 0.807014336521739

00:16:12.905 --> 00:16:14.480 pathology we only talk about panning,

NOTE Confidence: 0.807014336521739

00:16:14.480 --> 00:16:16.314 but in in the mouse where we

NOTE Confidence: 0.807014336521739

00:16:16.314 --> 00:16:18.349 can sort of look at each step,

NOTE Confidence: 0.807014336521739

00:16:18.350 --> 00:16:21.115 there's an intermediate step called

NOTE Confidence: 0.807014336521739

00:16:21.115 --> 00:16:23.327 acinar ductal metaplasia where

NOTE Confidence: 0.807014336521739

00:16:23.330 --> 00:16:26.084 the acinar cells shrink and become

NOTE Confidence: 0.807014336521739

00:16:26.084 --> 00:16:28.530 more cuboidal columnar cells and

NOTE Confidence: 0.807014336521739

00:16:28.530 --> 00:16:29.598 and proliferative.

NOTE Confidence: 0.807014336521739

00:16:29.600 --> 00:16:31.622 In an acute or chronic pancreatitis

NOTE Confidence: 0.807014336521739

00:16:31.622 --> 00:16:33.663 setting and when you start to

NOTE Confidence: 0.807014336521739

00:16:33.663 --> 00:16:35.541 profile those cells by single cell

NOTE Confidence: 0.807014336521739

00:16:35.541 --> 00:16:37.358 RNA seek what's interesting and

NOTE Confidence: 0.807014336521739

00:16:37.358 --> 00:16:39.608 this was work done at Vanderbilt.

NOTE Confidence: 0.807014336521739

00:16:39.610 --> 00:16:41.938 With a from Kathy Delgiorno's group

NOTE Confidence: 0.807014336521739

00:16:41.938 --> 00:16:44.619 and and a number of collaborators

NOTE Confidence: 0.807014336521739

00:16:44.619 --> 00:16:46.188 including Ken Lau.

NOTE Confidence: 0.807014336521739

00:16:46.190 --> 00:16:47.534 I don't think you were on this paper

NOTE Confidence: 0.807014336521739

00:16:47.534 --> 00:16:50.580 though on J while you were there, but.

NOTE Confidence: 0.807014336521739

00:16:50.580 --> 00:16:53.788 But what you see in these early pancreatic

NOTE Confidence: 0.807014336521739

00:16:53.788 --> 00:16:57.098 lesions is the same sorts of gastric cells.

NOTE Confidence: 0.807014336521739

00:16:57.100 --> 00:16:57.799 Now of course,

NOTE Confidence: 0.807014336521739

00:16:57.799 --> 00:16:59.197 they're not organized into a gland,

NOTE Confidence: 0.807014336521739

00:16:59.200 --> 00:17:00.726 you know, they're all on these asinine.

NOTE Confidence: 0.807014336521739

00:17:00.730 --> 00:17:02.470 But by single cell RNA seek,

NOTE Confidence: 0.807014336521739

00:17:02.470 --> 00:17:03.860 you see cells that look

NOTE Confidence: 0.807014336521739

00:17:03.860 --> 00:17:04.972 like foveolar pit cells.

NOTE Confidence: 0.807014336521739

00:17:04.980 --> 00:17:07.902 You see cells that look like

NOTE Confidence: 0.807014336521739

00:17:07.902 --> 00:17:09.363 these spasmolytic polypeptide

NOTE Confidence: 0.807014336521739

00:17:09.363 --> 00:17:11.189 pyloric metaplasia cells.

NOTE Confidence: 0.807014336521739

00:17:11.190 --> 00:17:12.905 So and you see the same kinds

NOTE Confidence: 0.807014336521739

00:17:12.905 --> 00:17:14.323 of cytokines that are starting

NOTE Confidence: 0.807014336521739

00:17:14.323 --> 00:17:15.888 to emerge as being universal.

NOTE Confidence: 0.807014336521739

00:17:15.890 --> 00:17:17.626 So I'm not going to talk about this,

NOTE Confidence: 0.807014336521739

00:17:17.630 --> 00:17:19.694 but aisle 13,

NOTE Confidence: 0.807014336521739

00:17:19.694 --> 00:17:22.982 aisle 33 shows up as mediating

NOTE Confidence: 0.807014336521739

00:17:22.982 --> 00:17:25.850 these metaplasia as in the esophagus

NOTE Confidence: 0.807014336521739

00:17:25.932 --> 00:17:28.434 and the stomach and even as we're

NOTE Confidence: 0.807014336521739

00:17:28.434 --> 00:17:30.268 going to say now in the intestines.

NOTE Confidence: 0.842524026842105

00:17:30.270 --> 00:17:32.286 And so the other thing I think

NOTE Confidence: 0.842524026842105

00:17:32.286 --> 00:17:34.201 it's been really kind of exploding

NOTE Confidence: 0.842524026842105

00:17:34.201 --> 00:17:36.163 in in from the pathology side.

NOTE Confidence: 0.842524026842105

00:17:36.170 --> 00:17:38.070 Is that the right sided,

NOTE Confidence: 0.842524026842105

00:17:38.070 --> 00:17:40.274 you know serrated sessile.

NOTE Confidence: 0.842524026842105

00:17:40.274 --> 00:17:41.786 You know, polyps,

NOTE Confidence: 0.842524026842105

00:17:41.786 --> 00:17:44.222 we used to call them serrated

NOTE Confidence: 0.842524026842105

00:17:44.222 --> 00:17:46.195 sessile lesions also had this

NOTE Confidence: 0.842524026842105

00:17:46.195 --> 00:17:48.120 same kind of basic format.

NOTE Confidence: 0.842524026842105

00:17:48.120 --> 00:17:50.004 So in this case you're taking

NOTE Confidence: 0.842524026842105

00:17:50.004 --> 00:17:51.563 things that were 100% intestinal

NOTE Confidence: 0.842524026842105

00:17:51.563 --> 00:17:53.381 and then now they're moving towards

NOTE Confidence: 0.842524026842105

00:17:53.381 --> 00:17:55.302 the gastric side and they wind up

NOTE Confidence: 0.842524026842105

00:17:55.302 --> 00:17:57.083 somewhere in the middle with this kind

NOTE Confidence: 0.842524026842105

00:17:57.083 --> 00:17:58.503 of pyloric morphology where again

NOTE Confidence: 0.842524026842105

00:17:58.503 --> 00:18:00.080 single cell RNA seek shows that.

NOTE Confidence: 0.842524026842105

00:18:00.080 --> 00:18:00.960 But then you know,

NOTE Confidence: 0.842524026842105

00:18:00.960 --> 00:18:03.576 as I've been collecting these lesions

NOTE Confidence: 0.842524026842105

00:18:03.576 --> 00:18:06.856 and we've been looking at them

NOTE Confidence: 0.842524026842105

00:18:06.856 --> 00:18:09.040 morphologically and immunohistochemically,

NOTE Confidence: 0.842524026842105

00:18:09.040 --> 00:18:10.816 you again see you know and.

NOTE Confidence: 0.842524026842105

00:18:10.820 --> 00:18:13.004 And it's been described before too by

NOTE Confidence: 0.842524026842105

00:18:13.004 --> 00:18:14.878 others that there's muck 6 positive,

NOTE Confidence: 0.842524026842105

00:18:14.880 --> 00:18:16.794 which is exactly the same expression

NOTE Confidence: 0.842524026842105

00:18:16.794 --> 00:18:18.444 pattern as spam cells that

NOTE Confidence: 0.842524026842105

00:18:18.444 --> 00:18:19.720 emerge that are gastric,

NOTE Confidence: 0.842524026842105

00:18:19.720 --> 00:18:20.538 you know,

NOTE Confidence: 0.842524026842105

00:18:20.538 --> 00:18:22.583 that are characteristic deep sort

NOTE Confidence: 0.842524026842105

00:18:22.583 --> 00:18:25.019 of acinar lesions within these SSL.

NOTE Confidence: 0.842524026842105

00:18:25.020 --> 00:18:27.204 And then there's an ad mix sort

NOTE Confidence: 0.842524026842105

00:18:27.204 --> 00:18:29.578 of muck 5 AC full Viola and

NOTE Confidence: 0.842524026842105

00:18:29.578 --> 00:18:31.050 goblet cell surface lesions.

NOTE Confidence: 0.842524026842105

00:18:31.050 --> 00:18:34.886 So at least on the right sided.

NOTE Confidence: 0.842524026842105

00:18:34.890 --> 00:18:36.954 SSL type of lesion there seems to be

NOTE Confidence: 0.842524026842105

00:18:36.954 --> 00:18:39.483 the same kind of metaplasia but sort of

NOTE Confidence: 0.842524026842105

00:18:39.483 --> 00:18:41.769 coming from intestine back towards gastric.

NOTE Confidence: 0.842524026842105

00:18:41.770 --> 00:18:43.300 Now that polyps and tubular adenoma

NOTE Confidence: 0.842524026842105

00:18:43.300 --> 00:18:45.380 seem to take a different course that's

NOTE Confidence: 0.842524026842105

00:18:45.380 --> 00:18:47.396 kind of more traditionally stem cell

NOTE Confidence: 0.842524026842105

00:18:47.396 --> 00:18:49.729 based and doesn't fall within that category.

NOTE Confidence: 0.842524026842105

00:18:49.730 --> 00:18:53.010 But still now we got four different organs

NOTE Confidence: 0.842524026842105

00:18:53.010 --> 00:18:55.419 all converging towards this sort of,

NOTE Confidence: 0.842524026842105

00:18:55.420 --> 00:18:57.919 you know pyloric like which is actually

NOTE Confidence: 0.842524026842105

00:18:57.919 --> 00:19:00.162 probably maybe one of the primordial

NOTE Confidence: 0.842524026842105

00:19:00.162 --> 00:19:02.376 embryonic states of the stomach and

NOTE Confidence: 0.842524026842105

00:19:02.376 --> 00:19:04.812 that's probably why and repair the stomach.

NOTE Confidence: 0.842524026842105

00:19:04.812 --> 00:19:06.558 Kind of chooses to go back

NOTE Confidence: 0.842524026842105

00:19:06.558 --> 00:19:08.070 to this sort of lesion.

NOTE Confidence: 0.842524026842105

00:19:08.070 --> 00:19:10.650 But once you have an established

NOTE Confidence: 0.842524026842105

00:19:10.650 --> 00:19:13.379 lesion that's mixed lineage where it's,

NOTE Confidence: 0.842524026842105

00:19:13.380 --> 00:19:14.670 you know, making both intestinal

NOTE Confidence: 0.842524026842105

00:19:14.670 --> 00:19:16.459 and gastric cells at the same time,

NOTE Confidence: 0.842524026842105

00:19:16.460 --> 00:19:18.294 you could see at least you know,

NOTE Confidence: 0.842524026842105

00:19:18.300 --> 00:19:21.002 reason why that might be a risk

NOTE Confidence: 0.842524026842105

00:19:21.002 --> 00:19:22.780 for progressing to cancer.

NOTE Confidence: 0.842524026842105

00:19:22.780 --> 00:19:23.720 And so part of that,

NOTE Confidence: 0.842524026842105

00:19:23.720 --> 00:19:24.522 you know,

NOTE Confidence: 0.842524026842105

00:19:24.522 --> 00:19:26.857 manifest itself when you do genome

NOTE Confidence: 0.842524026842105

00:19:26.857 --> 00:19:28.819 sequencing and you look for mutations.

NOTE Confidence: 0.842524026842105

00:19:28.820 --> 00:19:30.220 And that's why this is kind of

NOTE Confidence: 0.842524026842105

00:19:30.220 --> 00:19:31.963 some of the clinical data for why

NOTE Confidence: 0.842524026842105

00:19:31.963 --> 00:19:33.595 people do 3 mutations so important,

NOTE Confidence: 0.842524026842105

00:19:33.600 --> 00:19:34.110 which is that,

NOTE Confidence: 0.842524026842105

00:19:34.110 --> 00:19:34.450 you know,

NOTE Confidence: 0.842524026842105

00:19:34.450 --> 00:19:35.974 in these Barretts glands as they

NOTE Confidence: 0.842524026842105

00:19:35.974 --> 00:19:37.268 start to progress and clones

NOTE Confidence: 0.842524026842105

00:19:37.268 --> 00:19:38.878 emerge and they start to get the

NOTE Confidence: 0.842524026842105

00:19:38.878 --> 00:19:40.379 ones that are mixed intestinal,

NOTE Confidence: 0.842524026842105

00:19:40.380 --> 00:19:42.396 it seems like those are the ones that

NOTE Confidence: 0.842524026842105

00:19:42.396 --> 00:19:44.348 are prone to developing P53 mutation.

NOTE Confidence: 0.842524026842105

00:19:44.348 --> 00:19:46.756 It's those clones that then very rapidly,

NOTE Confidence: 0.842524026842105

00:19:46.760 --> 00:19:48.200 you know, from a heterozygote,

NOTE Confidence: 0.842524026842105

00:19:48.200 --> 00:19:50.186 once there's a loss of heterozygosity,

NOTE Confidence: 0.842524026842105

00:19:50.190 --> 00:19:52.830 they almost immediately go into dysplasia.

NOTE Confidence: 0.842524026842105

00:19:52.830 --> 00:19:56.148 And and neoplasia and then and

NOTE Confidence: 0.842524026842105

00:19:56.148 --> 00:19:57.807 metastatic and metastasis.

NOTE Confidence: 0.842524026842105

00:19:57.810 --> 00:19:58.177 OK.

NOTE Confidence: 0.842524026842105

00:19:58.177 --> 00:20:01.480 So that's the like if my talks at sandwich,

NOTE Confidence: 0.842524026842105

00:20:01.480 --> 00:20:02.914 that's this is the path introduction

NOTE Confidence: 0.842524026842105

00:20:02.914 --> 00:20:04.574 that we're going to delve into what

NOTE Confidence: 0.842524026842105

00:20:04.574 --> 00:20:06.100 we think some of the mechanisms are

NOTE Confidence: 0.842524026842105

00:20:06.147 --> 00:20:07.673 for how we get these metaplasia and

NOTE Confidence: 0.842524026842105

00:20:07.673 --> 00:20:09.350 then we'll come back out again to

NOTE Confidence: 0.842524026842105

00:20:09.350 --> 00:20:11.194 see some of the clinical trial work

NOTE Confidence: 0.842524026842105

00:20:11.194 --> 00:20:13.226 that we're doing to try to address it.

NOTE Confidence: 0.842524026842105

00:20:13.230 --> 00:20:18.027 So the question is to where are all these?

NOTE Confidence: 0.747923522

00:20:18.030 --> 00:20:19.470 Lesions coming from, you know,

NOTE Confidence: 0.747923522

00:20:19.470 --> 00:20:21.222 in these four different organs and

NOTE Confidence: 0.747923522

00:20:21.222 --> 00:20:23.573 you know the knee jerk response that I

NOTE Confidence: 0.747923522

00:20:23.573 --> 00:20:25.831 would have given you 15 years ago when

NOTE Confidence: 0.747923522

00:20:25.831 --> 00:20:27.895 Juan Jason the lab was the stem cell.

NOTE Confidence: 0.747923522

00:20:27.900 --> 00:20:29.305 Everybody thinks stem cells are

NOTE Confidence: 0.747923522

00:20:29.305 --> 00:20:31.046 what gives rise to, you know,

NOTE Confidence: 0.747923522

00:20:31.046 --> 00:20:32.894 lesions and and that are proliferative

NOTE Confidence: 0.747923522

00:20:32.894 --> 00:20:34.369 and gives rise to cancer.

NOTE Confidence: 0.747923522

00:20:34.370 --> 00:20:35.916 Well, but it turns out, you know,

NOTE Confidence: 0.747923522

00:20:35.916 --> 00:20:38.020 the stem cells are kind of tricky and

NOTE Confidence: 0.747923522

00:20:38.084 --> 00:20:40.160 in the pyloric versus oxyntic mucosa.

NOTE Confidence: 0.747923522

00:20:40.160 --> 00:20:41.840 So the, the professional stem cells

NOTE Confidence: 0.747923522

00:20:41.840 --> 00:20:43.679 and the oxyntic costs are way up

NOTE Confidence: 0.747923522

00:20:43.679 --> 00:20:45.005 here close to the surface and

NOTE Confidence: 0.747923522

00:20:45.005 --> 00:20:46.607 then when you get this you know,

NOTE Confidence: 0.747923522

00:20:46.610 --> 00:20:48.170 change into this more pyloric.

NOTE Confidence: 0.747923522

00:20:48.170 --> 00:20:50.480 They're kind of down here.

NOTE Confidence: 0.747923522

00:20:50.480 --> 00:20:52.345 So there's a change there

NOTE Confidence: 0.747923522

00:20:52.345 --> 00:20:53.968 already work towards the base.

NOTE Confidence: 0.747923522

00:20:53.968 --> 00:20:56.060 But then there's another thing that we,

NOTE Confidence: 0.747923522

00:20:56.060 --> 00:20:56.440 you know,

NOTE Confidence: 0.747923522

00:20:56.440 --> 00:20:57.580 have to think about which is

NOTE Confidence: 0.747923522

00:20:57.580 --> 00:20:58.837 that say in the pancreas there

NOTE Confidence: 0.747923522

00:20:58.837 --> 00:21:00.079 aren't any stem cells at all.

NOTE Confidence: 0.747923522

00:21:00.080 --> 00:21:01.710 So where are those proliferative

NOTE Confidence: 0.747923522

00:21:01.710 --> 00:21:02.688 cells coming from?

NOTE Confidence: 0.747923522

00:21:02.690 --> 00:21:04.839 And and there's been a long strain,

NOTE Confidence: 0.747923522

00:21:04.840 --> 00:21:06.778 relatively long for this kind of

NOTE Confidence: 0.747923522

00:21:06.778 --> 00:21:08.803 cell plasticity field of maybe 10-15

NOTE Confidence: 0.747923522

00:21:08.803 --> 00:21:11.148 years of good mouse work with human

NOTE Confidence: 0.747923522

00:21:11.148 --> 00:21:13.836 correlation showing that most of the

NOTE Confidence: 0.747923522

00:21:13.836 --> 00:21:15.213 reparative metaplastic proliferating

NOTE Confidence: 0.747923522

00:21:15.213 --> 00:21:17.184 proliferating cells in the pancreas

NOTE Confidence: 0.747923522

00:21:17.184 --> 00:21:18.924 that come about during pancreatitis.

NOTE Confidence: 0.747923522

00:21:18.930 --> 00:21:20.130 And pancreatic injuries actually

NOTE Confidence: 0.747923522

00:21:20.130 --> 00:21:22.309 all come from the acinar cells that

NOTE Confidence: 0.747923522

00:21:22.309 --> 00:21:23.929 are doing their digestive enzyme

NOTE Confidence: 0.747923522

00:21:23.929 --> 00:21:25.225 secretion that that reprogram.

NOTE Confidence: 0.747923522

00:21:25.230 --> 00:21:25.454 Well,

NOTE Confidence: 0.747923522

00:21:25.454 --> 00:21:27.470 it turns out we have a ton of evidence

NOTE Confidence: 0.747923522

00:21:27.521 --> 00:21:28.996 now that actually similar things

NOTE Confidence: 0.747923522

00:21:28.996 --> 00:21:30.780 are happening down at the base.

NOTE Confidence: 0.747923522

00:21:30.780 --> 00:21:32.964 And the reason probably why you get

NOTE Confidence: 0.747923522

00:21:32.964 --> 00:21:35.040 this change from an oxyntic mucosa,

NOTE Confidence: 0.747923522

00:21:35.040 --> 00:21:36.905 this kind of organization with

NOTE Confidence: 0.747923522

00:21:36.905 --> 00:21:38.770 proliferative cells at the base

NOTE Confidence: 0.747923522

00:21:38.836 --> 00:21:39.739 is because the,

NOTE Confidence: 0.747923522

00:21:39.740 --> 00:21:41.707 the fuel for these changes in in

NOTE Confidence: 0.747923522

00:21:41.707 --> 00:21:43.595 these lesions is actually at the

NOTE Confidence: 0.747923522

00:21:43.595 --> 00:21:45.230 base and the differentiated cells

NOTE Confidence: 0.747923522

00:21:45.230 --> 00:21:47.498 just as it happens in the pancreas,

NOTE Confidence: 0.747923522

00:21:47.500 --> 00:21:48.664 in the acinar cells,

NOTE Confidence: 0.747923522

00:21:48.664 --> 00:21:50.119 it's in the digestive enzymes.

NOTE Confidence: 0.747923522

00:21:50.120 --> 00:21:52.286 Recruiting chief cells at the base.

NOTE Confidence: 0.747923522

00:21:52.290 --> 00:21:54.924 So that brings up this concept

NOTE Confidence: 0.747923522

00:21:54.924 --> 00:21:57.829 that how do you get from a,

NOTE Confidence: 0.747923522

00:21:57.830 --> 00:21:59.626 a, a differentiated cell,

NOTE Confidence: 0.747923522

00:21:59.626 --> 00:22:01.871 massive secretory cell like the

NOTE Confidence: 0.747923522

00:22:01.871 --> 00:22:04.007 pancreatic acinar solar chief cell

NOTE Confidence: 0.747923522

00:22:04.007 --> 00:22:06.425 to a much smaller proliferating cell.

NOTE Confidence: 0.747923522

00:22:06.430 --> 00:22:08.370 And you know that actually,

NOTE Confidence: 0.747923522

00:22:08.370 --> 00:22:10.218 you know stirred us to begin to

NOTE Confidence: 0.747923522

00:22:10.218 --> 00:22:12.119 explore the idea of cell plasticity,

NOTE Confidence: 0.747923522

00:22:12.120 --> 00:22:13.730 which is where this fits.

NOTE Confidence: 0.747923522

00:22:13.730 --> 00:22:15.122 And you know this,

NOTE Confidence: 0.747923522

00:22:15.122 --> 00:22:17.582 this concept has exploded in the last

NOTE Confidence: 0.747923522

00:22:17.582 --> 00:22:20.228 five to 10 years and we had the first,

NOTE Confidence: 0.747923522

00:22:20.230 --> 00:22:22.534 I think the first ever meeting that I helped.

NOTE Confidence: 0.747923522

00:22:22.540 --> 00:22:22.939 Organized,

NOTE Confidence: 0.747923522

00:22:22.939 --> 00:22:26.530 which is a keystone meeting in 2019 on it,

NOTE Confidence: 0.747923522

00:22:26.530 --> 00:22:27.853 but then there was a follow up

NOTE Confidence: 0.747923522

00:22:27.853 --> 00:22:29.420 and now there are a number of

NOTE Confidence: 0.747923522

00:22:29.420 --> 00:22:30.368 meetings that are scheduled.

NOTE Confidence: 0.747923522

00:22:30.370 --> 00:22:32.056 We had a paper on nomenclature,

NOTE Confidence: 0.747923522

00:22:32.060 --> 00:22:34.020 but just to kind of put us all in the

NOTE Confidence: 0.747923522

00:22:34.077 --> 00:22:35.802 same cell and developmental biology

NOTE Confidence: 0.747923522

00:22:35.802 --> 00:22:38.270 page when we're talking about this lesions,

NOTE Confidence: 0.747923522

00:22:38.270 --> 00:22:39.955 you know the canonical stem

NOTE Confidence: 0.747923522

00:22:39.955 --> 00:22:42.000 cell idea of how you get.

NOTE Confidence: 0.747923522

00:22:42.000 --> 00:22:43.730 Differentiation in a tissue is

NOTE Confidence: 0.747923522

00:22:43.730 --> 00:22:45.907 that you have these stem cells

NOTE Confidence: 0.747923522

00:22:45.907 --> 00:22:47.764 that make faith choices, right.

NOTE Confidence: 0.747923522

00:22:47.764 --> 00:22:49.484 And as they differentiate and

NOTE Confidence: 0.747923522

00:22:49.484 --> 00:22:50.860 they're basically like marbles

NOTE Confidence: 0.747923522

00:22:50.918 --> 00:22:52.410 rolling down this Waddington,

NOTE Confidence: 0.747923522

00:22:52.410 --> 00:22:53.786 this Conrad Waddington was

NOTE Confidence: 0.747923522

00:22:53.786 --> 00:22:55.850 the person who came up with

NOTE Confidence: 0.825815031333333

00:22:55.918 --> 00:22:58.683 this concept of a landscape of sort

NOTE Confidence: 0.825815031333333

00:22:58.683 --> 00:23:00.522 of differentiation choices and then

NOTE Confidence: 0.825815031333333

00:23:00.522 --> 00:23:02.573 the ball sort of slowly roll down

NOTE Confidence: 0.825815031333333

00:23:02.573 --> 00:23:04.214 and then you get your chief cells and

NOTE Confidence: 0.825815031333333

00:23:04.214 --> 00:23:05.519 parietal cells and acinar cells at the

NOTE Confidence: 0.825815031333333

00:23:05.519 --> 00:23:06.820 base and then they just sit there.

NOTE Confidence: 0.825815031333333

00:23:06.820 --> 00:23:08.514 You know, the idea inherent to this

NOTE Confidence: 0.825815031333333

00:23:08.514 --> 00:23:10.050 concept is that it's a unidirectional

NOTE Confidence: 0.825815031333333

00:23:10.050 --> 00:23:12.100 flow of the balls roll down the hill.

NOTE Confidence: 0.825815031333333

00:23:12.100 --> 00:23:13.837 And so then if you need to get repair,

NOTE Confidence: 0.825815031333333

00:23:13.840 --> 00:23:14.760 any kind of repair done,

NOTE Confidence: 0.825815031333333

00:23:14.760 --> 00:23:16.335 then you need to take one of

NOTE Confidence: 0.825815031333333

00:23:16.335 --> 00:23:17.380 these progenitors to repair.

NOTE Confidence: 0.825815031333333

00:23:17.380 --> 00:23:19.306 But it's pretty clearly not the

NOTE Confidence: 0.825815031333333

00:23:19.306 --> 00:23:21.540 case because now we all know that.

NOTE Confidence: 0.825815031333333

00:23:21.540 --> 00:23:23.164 The balls can kind of go back up

NOTE Confidence: 0.825815031333333

00:23:23.164 --> 00:23:24.662 the hill and you can get just

NOTE Confidence: 0.825815031333333

00:23:24.662 --> 00:23:26.200 in the setting like I told you.

NOTE Confidence: 0.825815031333333

00:23:26.200 --> 00:23:28.310 If acinar cells they can

NOTE Confidence: 0.825815031333333

00:23:28.310 --> 00:23:29.154 become proliferative.

NOTE Confidence: 0.825815031333333

00:23:29.160 --> 00:23:30.960 You can get sort of the balls going

NOTE Confidence: 0.825815031333333

00:23:30.960 --> 00:23:32.717 over the grooves and being becoming

NOTE Confidence: 0.825815031333333

00:23:32.717 --> 00:23:34.744 other cells like beta cells in the

NOTE Confidence: 0.825815031333333

00:23:34.744 --> 00:23:36.370 pancreatic islets can become alpha cells.

NOTE Confidence: 0.825815031333333

00:23:36.370 --> 00:23:39.070 So these are trans differentiation

NOTE Confidence: 0.825815031333333

00:23:39.070 --> 00:23:40.690 and dedifferentiation events.

NOTE Confidence: 0.825815031333333

00:23:40.690 --> 00:23:42.748 And in fact when you really think

NOTE Confidence: 0.825815031333333

00:23:42.748 --> 00:23:44.943 where we care is pathologists and

NOTE Confidence: 0.825815031333333

00:23:44.943 --> 00:23:47.013 and pathology researchers about the

NOTE Confidence: 0.825815031333333

00:23:47.013 --> 00:23:49.410 injury and inflammation standpoint.

NOTE Confidence: 0.825815031333333

00:23:49.410 --> 00:23:50.838 You know it's quite possible that

NOTE Confidence: 0.825815031333333

00:23:50.838 --> 00:23:52.610 none of these grooves even stay the

NOTE Confidence: 0.825815031333333

00:23:52.610 --> 00:23:53.890 same during inflammation in the

NOTE Confidence: 0.825815031333333

00:23:53.890 --> 00:23:55.472 entire niches changing and all the

NOTE Confidence: 0.825815031333333

00:23:55.472 --> 00:23:56.752 groups are changing the identities

NOTE Confidence: 0.825815031333333

00:23:56.752 --> 00:23:58.781 may change you know and as we do

NOTE Confidence: 0.825815031333333

00:23:58.781 --> 00:24:00.929 more single cell RNA seek we see that

NOTE Confidence: 0.825815031333333

00:24:00.929 --> 00:24:02.873 you know I cell identities are all

NOTE Confidence: 0.825815031333333

00:24:02.873 --> 00:24:04.840 kind of overlapping you know and and

NOTE Confidence: 0.825815031333333

00:24:04.840 --> 00:24:09.176 these groups may not be so so clear.

NOTE Confidence: 0.825815031333333

00:24:09.180 --> 00:24:11.630 So there's a lot of interest in

NOTE Confidence: 0.825815031333333

00:24:11.630 --> 00:24:14.346 collagenosis and or in itself by in

NOTE Confidence: 0.825815031333333

00:24:14.346 --> 00:24:16.336 plasticity and differentiation and in

NOTE Confidence: 0.825815031333333

00:24:16.336 --> 00:24:18.560 fact that kind of got I was tickled

NOTE Confidence: 0.825815031333333

00:24:18.560 --> 00:24:20.480 to see that there was a last month

NOTE Confidence: 0.825815031333333

00:24:20.480 --> 00:24:22.295 the call for in scientific reports

NOTE Confidence: 0.825815031333333

00:24:22.295 --> 00:24:24.431 for papers on on plasticity and

NOTE Confidence: 0.825815031333333

00:24:24.431 --> 00:24:26.117 specifically specifically pathogenesis.

NOTE Confidence: 0.825815031333333

00:24:26.120 --> 00:24:26.502 OK.

NOTE Confidence: 0.825815031333333

00:24:26.502 --> 00:24:29.558 So the why do we have this term

NOTE Confidence: 0.825815031333333

00:24:29.558 --> 00:24:31.933 pathogenesis and the reason is because

NOTE Confidence: 0.825815031333333

00:24:31.933 --> 00:24:34.723 all of those balls are rolling around

NOTE Confidence: 0.825815031333333

00:24:34.723 --> 00:24:37.907 on the hill that that I was showing

NOTE Confidence: 0.825815031333333

00:24:37.910 --> 00:24:39.494 you had to do sort of with the.

NOTE Confidence: 0.825815031333333

00:24:39.500 --> 00:24:42.746 That, that tissue and developmental biology,

NOTE Confidence: 0.825815031333333

00:24:42.750 --> 00:24:45.830 the idea that every cell has got its

NOTE Confidence: 0.825815031333333

00:24:45.830 --> 00:24:47.982 own identity and that in plasticity

NOTE Confidence: 0.825815031333333

00:24:47.982 --> 00:24:49.448 events the cells, you know,

NOTE Confidence: 0.825815031333333

00:24:49.448 --> 00:24:50.822 change identity and it matters if

NOTE Confidence: 0.825815031333333

00:24:50.822 --> 00:24:51.943 they become less differentiated

NOTE Confidence: 0.825815031333333

00:24:51.943 --> 00:24:53.167 than they're rolling up.

NOTE Confidence: 0.825815031333333

00:24:53.170 --> 00:24:54.580 And if they're trans differentiated,

NOTE Confidence: 0.825815031333333

00:24:54.580 --> 00:24:55.690 they're, you know,

NOTE Confidence: 0.825815031333333

00:24:55.690 --> 00:24:57.170 becoming another cell type.

NOTE Confidence: 0.825815031333333

00:24:57.170 --> 00:24:59.096 But what if we're actually interested

NOTE Confidence: 0.825815031333333

00:24:59.096 --> 00:25:01.660 in the process of how you take a

NOTE Confidence: 0.825815031333333

00:25:01.660 --> 00:25:02.876 differentiated cell and convert

NOTE Confidence: 0.825815031333333

00:25:02.876 --> 00:25:04.769 it to a proliferating cell?

NOTE Confidence: 0.825815031333333

00:25:04.770 --> 00:25:05.406 You know,

NOTE Confidence: 0.825815031333333

00:25:05.406 --> 00:25:07.632 that is not likely to be different

NOTE Confidence: 0.825815031333333

00:25:07.632 --> 00:25:09.874 in every single organ, just like.

NOTE Confidence: 0.825815031333333

00:25:09.874 --> 00:25:11.848 If you need a program cell death,

NOTE Confidence: 0.825815031333333

00:25:11.850 --> 00:25:13.656 you have the apoptotic program and you

NOTE Confidence: 0.825815031333333

00:25:13.656 --> 00:25:15.199 have apoptosis and that's the same.

NOTE Confidence: 0.825815031333333

00:25:15.200 --> 00:25:17.230 And nobody thinks that apoptosis

NOTE Confidence: 0.825815031333333

00:25:17.230 --> 00:25:19.680 is different in every cell type.

NOTE Confidence: 0.825815031333333

00:25:19.680 --> 00:25:21.820 So this change in identity,

NOTE Confidence: 0.825815031333333

00:25:21.820 --> 00:25:23.476 these dedifferentiation events are

NOTE Confidence: 0.825815031333333

00:25:23.476 --> 00:25:26.380 likely to be similar across tissue types.

NOTE Confidence: 0.825815031333333

00:25:26.380 --> 00:25:29.212 So there must be a cell biological process

NOTE Confidence: 0.825815031333333

00:25:29.212 --> 00:25:32.358 or an osis that dictates these events.

NOTE Confidence: 0.825815031333333

00:25:32.360 --> 00:25:35.070 And so we came up with this idea that if

NOTE Confidence: 0.909255652083333

00:25:35.143 --> 00:25:37.527 we wanted to look at the cell biology

NOTE Confidence: 0.909255652083333

00:25:37.527 --> 00:25:40.029 of how these cells rearrange then.

NOTE Confidence: 0.909255652083333

00:25:40.030 --> 00:25:40.885 We should have a term

NOTE Confidence: 0.909255652083333

00:25:40.885 --> 00:25:41.910 so we can talk about it.

NOTE Confidence: 0.909255652083333

00:25:41.910 --> 00:25:43.866 And Paola is the Greek return,

NOTE Confidence: 0.909255652083333

00:25:43.870 --> 00:25:45.290 like in palindromes, you know,

NOTE Confidence: 0.909255652083333

00:25:45.290 --> 00:25:49.820 a site that goes back and forth.

NOTE Confidence: 0.909255652083333

00:25:49.820 --> 00:25:51.878 Can be read both ways right.

NOTE Confidence: 0.909255652083333

00:25:51.880 --> 00:25:54.645 And and and Jen is the general,

NOTE Confidence: 0.909255652083333

00:25:54.650 --> 00:25:55.634 you know, generative.

NOTE Confidence: 0.909255652083333

00:25:55.634 --> 00:25:57.930 So Palingenesis is the return to the

NOTE Confidence: 0.909255652083333

00:25:57.996 --> 00:25:59.694 generative state, regenerative state.

NOTE Confidence: 0.909255652083333

00:25:59.694 --> 00:26:02.630 So but when we're talking about this then

NOTE Confidence: 0.909255652083333

00:26:02.692 --> 00:26:04.978 what we're talking about is basically.

NOTE Confidence: 0.909255652083333

00:26:04.980 --> 00:26:07.176 How do you take these chief cells and make

NOTE Confidence: 0.909255652083333

00:26:07.176 --> 00:26:09.098 these metaplastic proliferative cells?

NOTE Confidence: 0.909255652083333

00:26:09.100 --> 00:26:11.002 So these are very Long live

NOTE Confidence: 0.909255652083333

00:26:11.002 --> 00:26:12.400 cells that don't proliferate.

NOTE Confidence: 0.909255652083333

00:26:12.400 --> 00:26:14.600 How do they become proliferative?

NOTE Confidence: 0.909255652083333

00:26:14.600 --> 00:26:17.694 So the take home is that it?

NOTE Confidence: 0.909255652083333

00:26:17.700 --> 00:26:19.110 It's a the.

NOTE Confidence: 0.909255652083333

00:26:19.110 --> 00:26:19.580 Basic.

NOTE Confidence: 0.909255652083333

00:26:19.580 --> 00:26:21.930 Like so biological change that

NOTE Confidence: 0.909255652083333

00:26:21.930 --> 00:26:24.671 has to happen here is a change

NOTE Confidence: 0.909255652083333

00:26:24.671 --> 00:26:27.730 in the way the cell uses energy.

NOTE Confidence: 0.909255652083333

00:26:27.730 --> 00:26:30.264 When the cell is in the base

NOTE Confidence: 0.909255652083333

00:26:30.264 --> 00:26:31.890 of a gastric unit,

NOTE Confidence: 0.909255652083333

00:26:31.890 --> 00:26:33.846 then it uses energy to produce

NOTE Confidence: 0.909255652083333

00:26:33.846 --> 00:26:35.150 digestive enzymes and secrete.

NOTE Confidence: 0.909255652083333

00:26:35.150 --> 00:26:37.142 When it's in the base of a of

NOTE Confidence: 0.909255652083333

00:26:37.142 --> 00:26:38.709 a reparative metaplastic unit,

NOTE Confidence: 0.909255652083333

00:26:38.710 --> 00:26:41.308 then it uses energy to divide.

NOTE Confidence: 0.909255652083333

00:26:41.310 --> 00:26:43.008 So all of the in between.

NOTE Confidence: 0.909255652083333

00:26:43.010 --> 00:26:45.602 The Collagenosis part is how the

NOTE Confidence: 0.909255652083333

00:26:45.602 --> 00:26:48.310 cell adapts itself to go from

NOTE Confidence: 0.909255652083333

00:26:48.310 --> 00:26:50.102 a digestive enzyme secreting

NOTE Confidence: 0.909255652083333

00:26:50.102 --> 00:26:53.100 energetic cell to a proliferating.

NOTE Confidence: 0.909255652083333

00:26:53.100 --> 00:26:56.856 Non energetic but but non secretory.

NOTE Confidence: 0.909255652083333

00:26:56.860 --> 00:26:59.247 So and basically this is the basic

NOTE Confidence: 0.909255652083333

00:26:59.247 --> 00:27:01.818 scheme which seems to be conserved across,

NOTE Confidence: 0.909255652083333

00:27:01.820 --> 00:27:04.676 you know, from fly guts to, you know,

NOTE Confidence: 0.909255652083333

00:27:04.676 --> 00:27:06.416 pancreas to stomach to lung.

NOTE Confidence: 0.909255652083333

00:27:06.420 --> 00:27:08.065 Every time you are calling

NOTE Confidence: 0.909255652083333

00:27:08.065 --> 00:27:09.381 differentiated cells back into

NOTE Confidence: 0.909255652083333

00:27:09.381 --> 00:27:11.650 the cell cycle and that is that

NOTE Confidence: 0.909255652083333

00:27:11.650 --> 00:27:13.291 there's a massive upregulation of

NOTE Confidence: 0.909255652083333

00:27:13.291 --> 00:27:15.265 autophagy and lysosome as the cell

NOTE Confidence: 0.909255652083333

00:27:15.265 --> 00:27:16.694 reprograms its internal organs.

NOTE Confidence: 0.909255652083333

00:27:16.694 --> 00:27:19.298 Followed by a second stage where

NOTE Confidence: 0.909255652083333

00:27:19.298 --> 00:27:22.138 the genes that we recognize it

NOTE Confidence: 0.909255652083333

00:27:22.138 --> 00:27:23.596 as being metaplastic.

NOTE Confidence: 0.909255652083333

00:27:23.600 --> 00:27:25.679 And those are a lot of different

NOTE Confidence: 0.909255652083333

00:27:25.679 --> 00:27:27.336 genes like trefoil factor or

NOTE Confidence: 0.909255652083333

00:27:27.336 --> 00:27:28.736 spasmolytic polypeptide or some

NOTE Confidence: 0.909255652083333

00:27:28.736 --> 00:27:30.840 of the socks genes like Sox 9.

NOTE Confidence: 0.909255652083333

00:27:30.840 --> 00:27:33.378 Followed by this very important one,

NOTE Confidence: 0.909255652083333

00:27:33.380 --> 00:27:35.095 which is the stage when the cell

NOTE Confidence: 0.909255652083333

00:27:35.095 --> 00:27:36.135 decides whether to actually

NOTE Confidence: 0.909255652083333

00:27:36.135 --> 00:27:37.659 enter the cell cycle or not.

NOTE Confidence: 0.909255652083333

00:27:37.660 --> 00:27:39.788 And this is the key stage for cancer

NOTE Confidence: 0.909255652083333

00:27:39.788 --> 00:27:41.288 because you're taking these old

NOTE Confidence: 0.909255652083333

00:27:41.288 --> 00:27:43.106 long lived cells and you're bringing

NOTE Confidence: 0.909255652083333

00:27:43.106 --> 00:27:44.768 them back into the cell cycle.

NOTE Confidence: 0.909255652083333

00:27:44.770 --> 00:27:46.569 And so this is a checkpoint that

NOTE Confidence: 0.909255652083333

00:27:46.569 --> 00:27:48.389 we'll talk about as being important.

NOTE Confidence: 0.909255652083333

00:27:48.390 --> 00:27:50.094 And just to kind of put us on

NOTE Confidence: 0.909255652083333

00:27:50.094 --> 00:27:50.920 an ultrastructural footing,

NOTE Confidence: 0.909255652083333

00:27:50.920 --> 00:27:53.104 what we're talking about is a very

NOTE Confidence: 0.909255652083333

00:27:53.104 --> 00:27:54.759 large pancreatic acinar cell or

NOTE Confidence: 0.909255652083333

00:27:54.759 --> 00:27:56.424 digestive enzyme secreting chief cell

NOTE Confidence: 0.909255652083333

00:27:56.424 --> 00:27:58.450 with layer after layer of rough ER,

NOTE Confidence: 0.909255652083333

00:27:58.450 --> 00:28:00.860 all these secretory granules becoming

NOTE Confidence: 0.909255652083333

00:28:00.860 --> 00:28:02.788 this much smaller proliferative

NOTE Confidence: 0.909255652083333

00:28:02.788 --> 00:28:03.990 stem like cell.

NOTE Confidence: 0.909255652083333

00:28:03.990 --> 00:28:06.302 And this can happen in the mouse and

NOTE Confidence: 0.909255652083333

00:28:06.302 --> 00:28:09.940 you know about 42 hours basically.

NOTE Confidence: 0.909255652083333

00:28:09.940 --> 00:28:11.613 So the kinds of things that are

NOTE Confidence: 0.909255652083333

00:28:11.613 --> 00:28:13.132 going to happen and we're going

NOTE Confidence: 0.909255652083333

00:28:13.132 --> 00:28:14.875 to talk about are modeled in this

NOTE Confidence: 0.909255652083333

00:28:14.880 --> 00:28:17.750 little video that Jeff Brown is a

NOTE Confidence: 0.909255652083333

00:28:17.750 --> 00:28:18.980 gastroenterologist and assistant

NOTE Confidence: 0.909255652083333

00:28:19.042 --> 00:28:20.659 professor at Washu now.

NOTE Confidence: 0.909255652083333

00:28:20.659 --> 00:28:21.158 Um,

NOTE Confidence: 0.909255652083333

00:28:21.158 --> 00:28:24.152 basically all this rough ER turns

NOTE Confidence: 0.909255652083333

00:28:24.152 --> 00:28:26.616 into autophagosomes and then starts

NOTE Confidence: 0.909255652083333

00:28:26.616 --> 00:28:28.911 to digest all the secretory

NOTE Confidence: 0.909255652083333

00:28:28.911 --> 00:28:31.794 apparatus and also gets rid of all

NOTE Confidence: 0.909255652083333

00:28:31.794 --> 00:28:33.298 that extra ER itself.

NOTE Confidence: 0.909255652083333

00:28:33.300 --> 00:28:34.772 The cell reshapes like

NOTE Confidence: 0.909255652083333

00:28:34.772 --> 00:28:36.980 this and then the next step

NOTE Confidence: 0.837158596315789

00:28:37.058 --> 00:28:40.298 is that's going to enter the the cell cycle.

NOTE Confidence: 0.837158596315789

00:28:40.300 --> 00:28:43.090 So how do we study this?

NOTE Confidence: 0.837158596315789

00:28:43.090 --> 00:28:46.114 So what we've taken to do doing is to

NOTE Confidence: 0.837158596315789

00:28:46.114 --> 00:28:48.540 looking at these metaplasia models,

NOTE Confidence: 0.837158596315789

00:28:48.540 --> 00:28:50.420 both of which involve collagenosis,

NOTE Confidence: 0.837158596315789

00:28:50.420 --> 00:28:53.290 both of which are drug induced and

NOTE Confidence: 0.837158596315789

00:28:53.290 --> 00:28:55.130 relatively short term like within days

NOTE Confidence: 0.837158596315789

00:28:55.130 --> 00:28:57.414 we can get these changes in both the

NOTE Confidence: 0.837158596315789

00:28:57.414 --> 00:28:59.600 stomach and the pancreas at the same time.

NOTE Confidence: 0.837158596315789

00:28:59.600 --> 00:29:00.867 That way we can look at all

NOTE Confidence: 0.837158596315789

00:29:00.867 --> 00:29:01.410 the conserved features,

NOTE Confidence: 0.837158596315789

00:29:01.410 --> 00:29:03.776 not just what happens in the stomach.

NOTE Confidence: 0.837158596315789

00:29:03.780 --> 00:29:06.130 And so we use two systems for the most part,

NOTE Confidence: 0.837158596315789

00:29:06.130 --> 00:29:08.290 one of which.

NOTE Confidence: 0.837158596315789

00:29:08.290 --> 00:29:10.922 Juan Jay invented which is our discovery,

NOTE Confidence: 0.837158596315789

00:29:10.922 --> 00:29:12.504 which is that if you treat mice

NOTE Confidence: 0.837158596315789

00:29:12.504 --> 00:29:13.847 with high doses of tamoxifen,

NOTE Confidence: 0.837158596315789

00:29:13.850 --> 00:29:16.524 it has an estrogen and sex independent

NOTE Confidence: 0.837158596315789

00:29:16.524 --> 00:29:18.550 toxicity effect on the stomach,

NOTE Confidence: 0.837158596315789

00:29:18.550 --> 00:29:20.512 which kills all the parietal cells

NOTE Confidence: 0.837158596315789

00:29:20.512 --> 00:29:22.810 within a couple of days basically,

NOTE Confidence: 0.837158596315789

00:29:22.810 --> 00:29:24.905 and reprograms the chief cells

NOTE Confidence: 0.837158596315789

00:29:24.905 --> 00:29:27.000 and the entire oxyntic mucosa

NOTE Confidence: 0.837158596315789

00:29:27.073 --> 00:29:29.168 into this pyloric like mucosa.

NOTE Confidence: 0.837158596315789

00:29:29.170 --> 00:29:31.354 And the other is an established

NOTE Confidence: 0.837158596315789

00:29:31.354 --> 00:29:32.810 model of of Cerulean,

NOTE Confidence: 0.837158596315789

00:29:32.810 --> 00:29:35.673 which is a CCK hormone analog treatment

NOTE Confidence: 0.837158596315789

00:29:35.673 --> 00:29:38.338 that turns the pancreas into this.

NOTE Confidence: 0.837158596315789

00:29:38.338 --> 00:29:39.810 Kind of duck like,

NOTE Confidence: 0.837158596315789

00:29:39.810 --> 00:29:43.170 but it's really just more again

NOTE Confidence: 0.837158596315789

00:29:43.170 --> 00:29:44.850 metaplastic proliferative phenotype.

NOTE Confidence: 0.837158596315789

00:29:44.850 --> 00:29:46.824 So this is the dosing scheme for

NOTE Confidence: 0.837158596315789

00:29:46.824 --> 00:29:48.666 high dose tamoxifen and this is

NOTE Confidence: 0.837158596315789

00:29:48.666 --> 00:29:50.226 what it looks like pathologically.

NOTE Confidence: 0.837158596315789

00:29:50.230 --> 00:29:51.445 Here's a normal mouse stomach

NOTE Confidence: 0.837158596315789

00:29:51.445 --> 00:29:52.660 with parietal cells up here,

NOTE Confidence: 0.837158596315789

00:29:52.660 --> 00:29:54.048 digestive enzyme secreting chief

NOTE Confidence: 0.837158596315789

00:29:54.048 --> 00:29:56.546 cells here and within three days of

NOTE Confidence: 0.837158596315789

00:29:56.546 --> 00:29:58.326 those tamoxifen injections the cells,

NOTE Confidence: 0.837158596315789

00:29:58.330 --> 00:30:00.004 the units become like tubes with

NOTE Confidence: 0.837158596315789

00:30:00.004 --> 00:30:01.792 just mucus cells on top and

NOTE Confidence: 0.837158596315789

00:30:01.792 --> 00:30:03.628 mucous cells in the bottom and

NOTE Confidence: 0.837158596315789

00:30:03.628 --> 00:30:04.890 then proliferation throughout,

NOTE Confidence: 0.837158596315789

00:30:04.890 --> 00:30:06.135 whereas normally proliferation

NOTE Confidence: 0.837158596315789

00:30:06.135 --> 00:30:09.040 is confined to this top area in.

NOTE Confidence: 0.837158596315789

00:30:09.040 --> 00:30:12.120 The normal stomach and pancreas,

NOTE Confidence: 0.837158596315789

00:30:12.120 --> 00:30:14.430 all of these acinar acini open up

NOTE Confidence: 0.837158596315789

00:30:14.430 --> 00:30:17.057 and you get these kind of cuboidal

NOTE Confidence: 0.837158596315789

00:30:17.057 --> 00:30:19.301 cyst like proliferative cells also

NOTE Confidence: 0.837158596315789

00:30:19.301 --> 00:30:22.223 if we do the cerulean treatment

NOTE Confidence: 0.837158596315789

00:30:22.223 --> 00:30:24.677 there just to give him a plug.

NOTE Confidence: 0.837158596315789

00:30:24.680 --> 00:30:27.740 To embarrass him a little bit.

NOTE Confidence: 0.837158596315789

00:30:27.740 --> 00:30:29.532 So with this system then we've been

NOTE Confidence: 0.837158596315789

00:30:29.532 --> 00:30:31.727 able to and I'm just going to show

NOTE Confidence: 0.837158596315789

00:30:31.727 --> 00:30:33.421 you some highlights but you know

NOTE Confidence: 0.837158596315789

00:30:33.421 --> 00:30:35.332 because a lot of this is published

NOTE Confidence: 0.837158596315789

00:30:35.332 --> 00:30:37.404 because it the the stomach system

NOTE Confidence: 0.837158596315789

00:30:37.404 --> 00:30:40.240 is so synchronous and then we can

NOTE Confidence: 0.837158596315789

00:30:40.240 --> 00:30:42.472 transmit translate that into lesions

NOTE Confidence: 0.837158596315789

00:30:42.472 --> 00:30:44.936 in humans and and and then confirm

NOTE Confidence: 0.837158596315789

00:30:44.936 --> 00:30:47.225 with the the pancreatic system we've

NOTE Confidence: 0.837158596315789

00:30:47.225 --> 00:30:50.057 been really able to kind of pretty

NOTE Confidence: 0.837158596315789

00:30:50.057 --> 00:30:52.256 quickly delineate us and others

NOTE Confidence: 0.837158596315789

00:30:52.256 --> 00:30:55.363 the the the program that happens in

NOTE Confidence: 0.837158596315789

00:30:55.363 --> 00:30:58.057 polygenesis and basically you take an.

NOTE Confidence: 0.837158596315789

00:30:58.060 --> 00:30:59.944 A uninjured secretory cell and you

NOTE Confidence: 0.837158596315789

00:30:59.944 --> 00:31:02.048 cause some kind of injury that's

NOTE Confidence: 0.837158596315789

00:31:02.048 --> 00:31:03.998 going to induce some metaplasia.

NOTE Confidence: 0.837158596315789

00:31:04.000 --> 00:31:05.568 And of course you know as we know

NOTE Confidence: 0.837158596315789

00:31:05.568 --> 00:31:07.401 the whole point of that is to induce

NOTE Confidence: 0.837158596315789

00:31:07.401 --> 00:31:09.250 proliferation so that it repairs the damage.

NOTE Confidence: 0.837158596315789

00:31:09.250 --> 00:31:10.774 But the other thing that happens

NOTE Confidence: 0.837158596315789

00:31:10.774 --> 00:31:12.678 is about this kind of time course

NOTE Confidence: 0.837158596315789

00:31:12.678 --> 00:31:14.073 all the different the organelles

NOTE Confidence: 0.837158596315789

00:31:14.073 --> 00:31:16.249 that are specifically tied to the

NOTE Confidence: 0.837158596315789

00:31:16.249 --> 00:31:17.817 differentiated function are decreased.

NOTE Confidence: 0.837158596315789

00:31:17.820 --> 00:31:18.256 You know,

NOTE Confidence: 0.837158596315789

00:31:18.256 --> 00:31:20.000 so things like the rough ER and and

NOTE Confidence: 0.837158596315789

00:31:20.050 --> 00:31:21.938 and and this is focused on the stomach,

NOTE Confidence: 0.837158596315789

00:31:21.940 --> 00:31:23.905 but they're equivalents in in

NOTE Confidence: 0.837158596315789

00:31:23.905 --> 00:31:25.477 pancreas and other organs,

NOTE Confidence: 0.837158596315789

00:31:25.480 --> 00:31:29.048 but things like pepsinogen and and so on.

NOTE Confidence: 0.837158596315789

00:31:29.050 --> 00:31:32.060 And that occurs across these three stages.

NOTE Confidence: 0.837158596315789

00:31:32.060 --> 00:31:34.454 The first stage is this massive autophagy,

NOTE Confidence: 0.855814773846154

00:31:34.460 --> 00:31:35.902 which is of course what's helping to

NOTE Confidence: 0.855814773846154

00:31:35.902 --> 00:31:37.799 get rid of these differentiated organs.

NOTE Confidence: 0.855814773846154

00:31:37.800 --> 00:31:40.146 The second stage is that METAPLASTIC

NOTE Confidence: 0.855814773846154

00:31:40.146 --> 00:31:42.783 gene expression where you start to see

NOTE Confidence: 0.855814773846154

00:31:42.783 --> 00:31:45.121 that the cells have rearranged how they.

NOTE Confidence: 0.855814773846154

00:31:45.130 --> 00:31:47.510 Actually Mark and label and

NOTE Confidence: 0.855814773846154

00:31:47.510 --> 00:31:50.450 then the final stage is this.

NOTE Confidence: 0.855814773846154

00:31:50.450 --> 00:31:53.390 Mtorc increase, which is critical for

NOTE Confidence: 0.855814773846154

00:31:53.390 --> 00:31:57.336 entering into the cell cycle and that is

NOTE Confidence: 0.855814773846154

00:31:57.336 --> 00:31:59.522 immediately after a stage of induction

NOTE Confidence: 0.855814773846154

00:31:59.522 --> 00:32:01.370 and then suppression of people 53.

NOTE Confidence: 0.855814773846154

00:32:01.370 --> 00:32:03.498 So this crossing point is very important

NOTE Confidence: 0.855814773846154

00:32:03.498 --> 00:32:05.489 because the main thing that P53 does

NOTE Confidence: 0.855814773846154

00:32:05.489 --> 00:32:07.400 is I'll show you is suppress mtorc.

NOTE Confidence: 0.855814773846154

00:32:07.400 --> 00:32:10.154 So CP3 has to decrease for these cells to

NOTE Confidence: 0.855814773846154

00:32:10.154 --> 00:32:13.110 be licensed to read into the cell cycle.

NOTE Confidence: 0.855814773846154

00:32:13.110 --> 00:32:14.265 So you know we're going to head

NOTE Confidence: 0.855814773846154

00:32:14.265 --> 00:32:15.309 on this theme several times,

NOTE Confidence: 0.855814773846154

00:32:15.310 --> 00:32:17.137 but I already hinted at it from

NOTE Confidence: 0.855814773846154

00:32:17.137 --> 00:32:19.099 what we know about Barretts and

NOTE Confidence: 0.855814773846154

00:32:19.099 --> 00:32:20.954 why this kind of reprogramming.

NOTE Confidence: 0.855814773846154

00:32:20.960 --> 00:32:22.420 Is so important in NYPD.

NOTE Confidence: 0.855814773846154

00:32:22.420 --> 00:32:23.599 Three is important.

NOTE Confidence: 0.855814773846154

00:32:23.599 --> 00:32:25.957 It's important for this licensing step.

NOTE Confidence: 0.855814773846154

00:32:25.960 --> 00:32:28.010 You don't let differentiated cells

NOTE Confidence: 0.855814773846154

00:32:28.010 --> 00:32:30.600 back into the cell cycle unless

NOTE Confidence: 0.855814773846154

00:32:30.600 --> 00:32:32.920 they've cleared up 53 checkpoint.

NOTE Confidence: 0.855814773846154

00:32:32.920 --> 00:32:34.580 So thinking about mtorc one,

NOTE Confidence: 0.855814773846154

00:32:34.580 --> 00:32:36.092 it's the central energy regulator and

NOTE Confidence: 0.855814773846154

00:32:36.092 --> 00:32:38.338 this is a super simplistic version of it.

NOTE Confidence: 0.855814773846154

00:32:38.340 --> 00:32:40.599 But just so that we're on the same page,

NOTE Confidence: 0.855814773846154

00:32:40.600 --> 00:32:42.772 you know it's pretty much integrates

NOTE Confidence: 0.855814773846154

00:32:42.772 --> 00:32:44.996 the vast majority of the cells

NOTE Confidence: 0.855814773846154

00:32:44.996 --> 00:32:46.771 energetic inputs and outputs with

NOTE Confidence: 0.855814773846154

00:32:46.771 --> 00:32:49.178 the two main wings being related,

NOTE Confidence: 0.855814773846154

00:32:49.180 --> 00:32:50.820 wings being protein translation

NOTE Confidence: 0.855814773846154

00:32:50.820 --> 00:32:53.280 and of course driving the cell

NOTE Confidence: 0.855814773846154

00:32:53.347 --> 00:32:55.437 cycle via phosphorylation of the

NOTE Confidence: 0.855814773846154

00:32:55.437 --> 00:32:56.805 small ribosomal subunit 6.

NOTE Confidence: 0.855814773846154

00:32:56.805 --> 00:32:59.010 So this is going to be important

NOTE Confidence: 0.855814773846154

00:32:59.073 --> 00:33:01.236 because this is a great marker for

NOTE Confidence: 0.855814773846154

00:33:01.236 --> 00:33:03.120 Mturk activity by immunostaining.

NOTE Confidence: 0.855814773846154

00:33:03.120 --> 00:33:04.968 Works great or an IF you can tell

NOTE Confidence: 0.855814773846154

00:33:04.968 --> 00:33:07.009 how much import there is by how

NOTE Confidence: 0.855814773846154

00:33:07.009 --> 00:33:08.524 much phosphorylated S6 there is,

NOTE Confidence: 0.855814773846154

00:33:08.530 --> 00:33:09.781 so Amtrak increases.

NOTE Confidence: 0.855814773846154

00:33:09.781 --> 00:33:12.283 This in itself is stimulated by

NOTE Confidence: 0.855814773846154

00:33:12.283 --> 00:33:14.904 low energy and by autophagy and

NOTE Confidence: 0.855814773846154

00:33:14.904 --> 00:33:17.029 all of the breakdown products

NOTE Confidence: 0.855814773846154

00:33:17.103 --> 00:33:19.336 in in the lysosomes and a key.

NOTE Confidence: 0.855814773846154

00:33:19.340 --> 00:33:21.948 Inhibitor of mtorc is this gene called before

NOTE Confidence: 0.855814773846154

00:33:21.948 --> 00:33:24.667 or red one which we'll talk about also.

NOTE Confidence: 0.855814773846154

00:33:24.670 --> 00:33:27.393 So let's look at some of how

NOTE Confidence: 0.855814773846154

00:33:27.393 --> 00:33:29.704 what this looks like in actual

NOTE Confidence: 0.855814773846154

00:33:29.704 --> 00:33:31.439 ultrastructure and you can see

NOTE Confidence: 0.855814773846154

00:33:31.439 --> 00:33:33.834 that within 24 hours down now we're

NOTE Confidence: 0.855814773846154

00:33:33.834 --> 00:33:36.310 looking in chief cells that we have

NOTE Confidence: 0.855814773846154

00:33:36.310 --> 00:33:38.230 all these massive autophagosomes,

NOTE Confidence: 0.855814773846154

00:33:38.230 --> 00:33:39.004 auto lysosomes,

NOTE Confidence: 0.855814773846154

00:33:39.004 --> 00:33:40.939 all this auto degraded machinery

NOTE Confidence: 0.855814773846154

00:33:40.939 --> 00:33:43.268 that these cells start to rearrange

NOTE Confidence: 0.855814773846154

00:33:43.268 --> 00:33:44.744 their their entire architecture

NOTE Confidence: 0.855814773846154

00:33:44.744 --> 00:33:47.519 and you can see just here this is

NOTE Confidence: 0.855814773846154

00:33:47.519 --> 00:33:49.528 quantified by how much lysosomes there.

NOTE Confidence: 0.855814773846154

00:33:49.528 --> 00:33:52.722 And then we use this 3D electron

NOTE Confidence: 0.855814773846154

00:33:52.722 --> 00:33:55.126 microscopic tactic called focused

NOTE Confidence: 0.855814773846154

00:33:55.126 --> 00:33:57.530 IMDb scanning electron microscopy

NOTE Confidence: 0.855814773846154

00:33:57.611 --> 00:34:00.195 to kind of look at it more detail.

NOTE Confidence: 0.855814773846154

00:34:00.200 --> 00:34:02.336 And you can see as we kind of

NOTE Confidence: 0.855814773846154

00:34:02.340 --> 00:34:03.039 spin this around,

NOTE Confidence: 0.855814773846154

00:34:03.039 --> 00:34:05.107 this is a single chief cell as this

NOTE Confidence: 0.855814773846154

00:34:05.107 --> 00:34:07.047 polygenesis process that's happening early.

NOTE Confidence: 0.855814773846154

00:34:07.050 --> 00:34:08.808 This is a capillary loop and

NOTE Confidence: 0.855814773846154

00:34:08.808 --> 00:34:10.550 these are the secretory granules,

NOTE Confidence: 0.855814773846154

00:34:10.550 --> 00:34:11.999 this is the nucleus and these are

NOTE Confidence: 0.855814773846154

00:34:11.999 --> 00:34:13.280 all lysosomes and autophagosomes.

NOTE Confidence: 0.855814773846154

00:34:13.280 --> 00:34:15.680 So like half the cell becomes

NOTE Confidence: 0.855814773846154

00:34:15.680 --> 00:34:19.260 auto degradative as the.

NOTE Confidence: 0.855814773846154

00:34:19.260 --> 00:34:23.054 As this early stage in Polygenesis happens,

NOTE Confidence: 0.855814773846154

00:34:23.060 --> 00:34:26.520 so that's what's happening to

NOTE Confidence: 0.855814773846154

00:34:26.520 --> 00:34:29.288 autophagosomes and and lysosomes.

NOTE Confidence: 0.855814773846154

00:34:29.290 --> 00:34:31.298 For that to happen Mturk has to decrease

NOTE Confidence: 0.855814773846154

00:34:31.298 --> 00:34:33.072 and here we're looking at mtorc

NOTE Confidence: 0.855814773846154

00:34:33.072 --> 00:34:34.890 activity using this phosphorus 6 and

NOTE Confidence: 0.796392662222222

00:34:34.944 --> 00:34:36.638 here we focus on the chief cells.

NOTE Confidence: 0.796392662222222

00:34:36.640 --> 00:34:39.529 And here within 12 hours all all of this

NOTE Confidence: 0.796392662222222

00:34:39.529 --> 00:34:41.728 phosphorus 6 or M torc activity is lost

NOTE Confidence: 0.796392662222222

00:34:41.728 --> 00:34:44.272 in the chief cells and then by maximum

NOTE Confidence: 0.796392662222222

00:34:44.272 --> 00:34:46.251 metaplasia it all comes back again.

NOTE Confidence: 0.796392662222222

00:34:46.251 --> 00:34:47.877 So here it's working for secretion

NOTE Confidence: 0.796392662222222

00:34:47.877 --> 00:34:49.460 and not for proliferation,

NOTE Confidence: 0.796392662222222

00:34:49.460 --> 00:34:51.120 here it's working for proliferation.

NOTE Confidence: 0.796392662222222

00:34:51.120 --> 00:34:53.464 And in between is when all that autophagy

NOTE Confidence: 0.796392662222222

00:34:53.464 --> 00:34:55.611 is happening and you can see even on

NOTE Confidence: 0.796392662222222

00:34:55.611 --> 00:34:57.498 Western blots of mouse stomach you can

NOTE Confidence: 0.796392662222222

00:34:57.498 --> 00:34:59.437 see it happening on the other hand.

NOTE Confidence: 0.796392662222222

00:34:59.440 --> 00:35:01.876 We knock out this suppressive ddit 4,

NOTE Confidence: 0.796392662222222

00:35:01.880 --> 00:35:04.200 which I showed you in that cartoon with

NOTE Confidence: 0.796392662222222

00:35:04.200 --> 00:35:06.937 it gets induced early to suppress network.

NOTE Confidence: 0.796392662222222

00:35:06.940 --> 00:35:10.246 You don't have the same decrease

NOTE Confidence: 0.796392662222222

00:35:10.246 --> 00:35:12.740 in mtorc activity and you don't

NOTE Confidence: 0.796392662222222

00:35:12.740 --> 00:35:13.860 have the same autophagy.

NOTE Confidence: 0.796392662222222

00:35:13.860 --> 00:35:14.838 So if you look at mtorc,

NOTE Confidence: 0.796392662222222

00:35:14.840 --> 00:35:17.400 basically it's much, you know.

NOTE Confidence: 0.796392662222222

00:35:17.400 --> 00:35:19.086 Normally it's like that and in

NOTE Confidence: 0.796392662222222

00:35:19.086 --> 00:35:20.799 the four knockout it's like that.

NOTE Confidence: 0.796392662222222

00:35:20.800 --> 00:35:23.500 So that leads to actually more,

NOTE Confidence: 0.796392662222222

00:35:23.500 --> 00:35:24.972 more proliferation,

NOTE Confidence: 0.796392662222222

00:35:24.972 --> 00:35:27.180 more metaplasia downstream.

NOTE Confidence: 0.796392662222222

00:35:27.180 --> 00:35:28.736 And conversely,

NOTE Confidence: 0.796392662222222

00:35:28.736 --> 00:35:31.848 when you inhibit mtorc.

NOTE Confidence: 0.796392662222222

00:35:31.850 --> 00:35:34.682 That's how we know that the cell cycle

NOTE Confidence: 0.796392662222222

00:35:34.682 --> 00:35:37.919 reentry is critical because taking rapamycin,

NOTE Confidence: 0.796392662222222

00:35:37.920 --> 00:35:39.488 an M TORC inhibitor,

NOTE Confidence: 0.796392662222222

00:35:39.488 --> 00:35:42.377 and treating mice with it does not block

NOTE Confidence: 0.796392662222222

00:35:42.377 --> 00:35:44.231 the the metaplasia or the autophagy

NOTE Confidence: 0.796392662222222

00:35:44.231 --> 00:35:46.228 or those first couple of steps,

NOTE Confidence: 0.796392662222222

00:35:46.230 --> 00:35:49.440 but it it blocks the

NOTE Confidence: 0.796392662222222

00:35:49.440 --> 00:35:50.724 proliferation completely.

NOTE Confidence: 0.796392662222222

00:35:50.730 --> 00:35:53.634 So early on did it 4 suppresses mtorc.

NOTE Confidence: 0.796392662222222

00:35:53.640 --> 00:35:56.268 We have all that autophagy but on

NOTE Confidence: 0.796392662222222

00:35:56.268 --> 00:35:58.081 that last slide we also see that

NOTE Confidence: 0.796392662222222

00:35:58.081 --> 00:36:00.244 did it four goes away within the

NOTE Confidence: 0.796392662222222

00:36:00.244 --> 00:36:02.115 first couple of stages and that's

NOTE Confidence: 0.796392662222222

00:36:02.115 --> 00:36:04.138 when 53 comes on and P53 continues

NOTE Confidence: 0.796392662222222

00:36:04.138 --> 00:36:06.185 to suppress M torque until or

NOTE Confidence: 0.796392662222222

00:36:06.185 --> 00:36:08.298 unless the cell then decides to

NOTE Confidence: 0.796392662222222

00:36:08.298 --> 00:36:10.050 come back and the cell cycle.

NOTE Confidence: 0.796392662222222

00:36:10.050 --> 00:36:12.498 So that part of the way we know that

NOTE Confidence: 0.796392662222222

00:36:12.498 --> 00:36:15.327 is that in P53 knockouts we also don't

NOTE Confidence: 0.796392662222222

00:36:15.327 --> 00:36:17.947 have this mtorc loss early on we

NOTE Confidence: 0.796392662222222

00:36:17.947 --> 00:36:20.161 have more proliferation both in the.

NOTE Confidence: 0.796392662222222

00:36:20.170 --> 00:36:22.414 The stomach and the pancreas and

NOTE Confidence: 0.796392662222222

00:36:22.414 --> 00:36:25.339 then what we know that the critical

NOTE Confidence: 0.796392662222222

00:36:25.339 --> 00:36:28.140 regulator of P53 that tells the cell

NOTE Confidence: 0.796392662222222

00:36:28.140 --> 00:36:30.040 whether the cell should increase

NOTE Confidence: 0.796392662222222

00:36:30.116 --> 00:36:32.412 M Turk and go back into the cell

NOTE Confidence: 0.796392662222222

00:36:32.412 --> 00:36:34.356 cycle is a protein called ifrd one.

NOTE Confidence: 0.796392662222222

00:36:34.360 --> 00:36:36.404 And we'll show you how that works

NOTE Confidence: 0.796392662222222

00:36:36.404 --> 00:36:38.688 and how that P3 I 41 access works.

NOTE Confidence: 0.796392662222222

00:36:38.690 --> 00:36:41.522 But you can see it's massively

NOTE Confidence: 0.796392662222222

00:36:41.522 --> 00:36:42.642 upregulated during collagenosis

NOTE Confidence: 0.796392662222222

00:36:42.642 --> 00:36:44.889 and then as the cells we enter

NOTE Confidence: 0.796392662222222

00:36:44.889 --> 00:36:46.697 the cell cycle it goes away.

NOTE Confidence: 0.796392662222222

00:36:46.700 --> 00:36:48.891 And in the absence of in the

NOTE Confidence: 0.796392662222222

00:36:48.891 --> 00:36:50.112 absence of ID 11,

NOTE Confidence: 0.796392662222222

00:36:50.112 --> 00:36:52.184 all the cells wind up dying and

NOTE Confidence: 0.796392662222222

00:36:52.184 --> 00:36:54.179 not completing the process.

NOTE Confidence: 0.796392662222222

00:36:54.180 --> 00:36:56.035 But if you knock out paid 53,

NOTE Confidence: 0.796392662222222

00:36:56.040 --> 00:36:57.192 then they're rescued and

NOTE Confidence: 0.796392662222222

00:36:57.192 --> 00:36:58.632 they reenter the cell cycle.

NOTE Confidence: 0.796392662222222

00:36:58.640 --> 00:37:00.033 So that's how we know I pretty

NOTE Confidence: 0.796392662222222

00:37:00.033 --> 00:37:00.920 when it's upstream of 53.

NOTE Confidence: 0.796392662222222

00:37:00.920 --> 00:37:02.696 So we'll talk about how RD1

NOTE Confidence: 0.796392662222222

00:37:02.696 --> 00:37:05.069 dictates to P3 to dictate M torque.

NOTE Confidence: 0.796392662222222

00:37:05.070 --> 00:37:07.920 A lot of this work was done by Max Yao,

NOTE Confidence: 0.796392662222222

00:37:07.920 --> 00:37:12.480 who's in China now as an assistant professor.

NOTE Confidence: 0.796392662222222

00:37:12.480 --> 00:37:15.104 So let's talk now about some of the

NOTE Confidence: 0.796392662222222

00:37:15.104 --> 00:37:16.911 machinery that executes this process

NOTE Confidence: 0.796392662222222

00:37:16.911 --> 00:37:20.029 and the way that we've started to do this.

NOTE Confidence: 0.796392662222222

00:37:20.030 --> 00:37:20.788 Stepping back,

NOTE Confidence: 0.796392662222222

00:37:20.788 --> 00:37:21.167 right,

NOTE Confidence: 0.796392662222222

00:37:21.167 --> 00:37:23.441 like if this process of taking

NOTE Confidence: 0.796392662222222

00:37:23.441 --> 00:37:25.490 a differentiated cell and bring

NOTE Confidence: 0.796392662222222

00:37:25.490 --> 00:37:28.323 it back into the cell cycle is,

NOTE Confidence: 0.796392662222222

00:37:28.323 --> 00:37:29.189 you know,

NOTE Confidence: 0.796392662222222

00:37:29.189 --> 00:37:30.921 a conserve process across

NOTE Confidence: 0.796392662222222

00:37:30.921 --> 00:37:32.220 multiple tissues just

NOTE Confidence: 0.774541726666667

00:37:32.294 --> 00:37:34.460 like apoptosis, then there should be

NOTE Confidence: 0.774541726666667

00:37:34.460 --> 00:37:36.590 genes that are dedicated to the process,

NOTE Confidence: 0.774541726666667

00:37:36.590 --> 00:37:39.306 just as there are genes dedicated to

NOTE Confidence: 0.774541726666667

00:37:39.306 --> 00:37:41.410 apoptosis like BCL's and caspases and so on.

NOTE Confidence: 0.774541726666667

00:37:41.410 --> 00:37:45.322 So we started doing screens in

NOTE Confidence: 0.774541726666667

00:37:45.322 --> 00:37:47.278 these regenerative metaplastic.

NOTE Confidence: 0.774541726666667

00:37:47.280 --> 00:37:51.092 Organs after after you know during

NOTE Confidence: 0.774541726666667

00:37:51.092 --> 00:37:52.670 the regenerative phase and look for

NOTE Confidence: 0.774541726666667

00:37:52.722 --> 00:37:54.241 genes that are all ex Co expressed

NOTE Confidence: 0.774541726666667

00:37:54.241 --> 00:37:56.130 and and from these I FD one indeed it

NOTE Confidence: 0.774541726666667

00:37:56.130 --> 00:37:57.848 four came out I've already told you

NOTE Confidence: 0.774541726666667

00:37:57.848 --> 00:37:59.684 about them need it for suppressing

NOTE Confidence: 0.774541726666667

00:37:59.684 --> 00:38:01.881 mtorc I-41 suppressing P53 but we have

NOTE Confidence: 0.774541726666667

00:38:01.881 --> 00:38:03.740 other targets that we've been working

NOTE Confidence: 0.774541726666667

00:38:03.740 --> 00:38:05.770 on another really strong one is ATF

NOTE Confidence: 0.774541726666667

00:38:05.770 --> 00:38:07.740 three which I want to talk about and

NOTE Confidence: 0.774541726666667

00:38:07.740 --> 00:38:09.416 we're starting to piece together then

NOTE Confidence: 0.774541726666667

00:38:09.416 --> 00:38:11.216 this architecture but this is what

NOTE Confidence: 0.774541726666667

00:38:11.216 --> 00:38:13.114 we've learned so far in in this talk

NOTE Confidence: 0.774541726666667

00:38:13.114 --> 00:38:15.140 do you injury happens the cell starts

NOTE Confidence: 0.774541726666667

00:38:15.140 --> 00:38:17.510 to undergo a topology did it for.

NOTE Confidence: 0.774541726666667

00:38:17.510 --> 00:38:19.250 Suppresses mtorc to turn it off

NOTE Confidence: 0.774541726666667

00:38:19.250 --> 00:38:21.010 to allow the autophagy to happen.

NOTE Confidence: 0.774541726666667

00:38:21.010 --> 00:38:23.593 I have heard one is induced that

NOTE Confidence: 0.774541726666667

00:38:23.593 --> 00:38:25.390 eventually accumulates and suppresses

NOTE Confidence: 0.774541726666667

00:38:25.390 --> 00:38:29.656 P53 which allows cell cycle entry.

NOTE Confidence: 0.774541726666667

00:38:29.660 --> 00:38:33.258 So. Why then is mtorc so important?

NOTE Confidence: 0.774541726666667

00:38:33.260 --> 00:38:34.130 Because, you know,

NOTE Confidence: 0.774541726666667

00:38:34.130 --> 00:38:35.870 when we think about why Barretts

NOTE Confidence: 0.774541726666667

00:38:35.870 --> 00:38:36.560 becomes cancer,

NOTE Confidence: 0.774541726666667

00:38:36.560 --> 00:38:38.380 why gastric intestinal metaplasia

NOTE Confidence: 0.774541726666667

00:38:38.380 --> 00:38:39.745 or you know,

NOTE Confidence: 0.774541726666667

00:38:39.750 --> 00:38:41.630 pseudo pyloric metaplasia gives

NOTE Confidence: 0.774541726666667

00:38:41.630 --> 00:38:44.660 rise to cancer and we think about

NOTE Confidence: 0.774541726666667

00:38:44.660 --> 00:38:45.875 this pathogenesis process,

NOTE Confidence: 0.774541726666667

00:38:45.880 --> 00:38:46.556 this conversion,

NOTE Confidence: 0.774541726666667

00:38:46.556 --> 00:38:47.232 you know,

NOTE Confidence: 0.774541726666667

00:38:47.232 --> 00:38:49.669 being critical for that and mtorc being

NOTE Confidence: 0.774541726666667

00:38:49.669 --> 00:38:51.763 critical for that cell cycle reentry

NOTE Confidence: 0.774541726666667

00:38:51.763 --> 00:38:54.000 because that's what you need for cancer.

NOTE Confidence: 0.774541726666667

00:38:54.000 --> 00:38:55.360 Why is it so important?

NOTE Confidence: 0.774541726666667

00:38:55.360 --> 00:38:55.619 Well,

NOTE Confidence: 0.774541726666667

00:38:55.619 --> 00:38:57.432 here's what we delve like the deepest

NOTE Confidence: 0.774541726666667

00:38:57.432 --> 00:38:58.842 into the structure and organelles

NOTE Confidence: 0.774541726666667

00:38:58.842 --> 00:39:01.150 before we kind of come back out again.

NOTE Confidence: 0.774541726666667

00:39:01.150 --> 00:39:04.734 Our thinking now is that it's all about

NOTE Confidence: 0.774541726666667

00:39:04.734 --> 00:39:06.190 ribosomes when you're a chief cell.

NOTE Confidence: 0.774541726666667

00:39:06.190 --> 00:39:08.662 I showed you that electron microscope

NOTE Confidence: 0.774541726666667

00:39:08.662 --> 00:39:11.007 micrograph where it's just layer after

NOTE Confidence: 0.774541726666667

00:39:11.007 --> 00:39:13.527 layer after layer of rough ER and all

NOTE Confidence: 0.774541726666667

00:39:13.597 --> 00:39:17.098 that roughly RISER line by ribosomes.

NOTE Confidence: 0.774541726666667

00:39:17.100 --> 00:39:19.916 That are making digestive enzymes to go into,

NOTE Confidence: 0.774541726666667

00:39:19.920 --> 00:39:20.386 you know,

NOTE Confidence: 0.774541726666667

00:39:20.386 --> 00:39:23.010 the lumen of the R and then to be secreted.

NOTE Confidence: 0.774541726666667

00:39:23.010 --> 00:39:24.666 When you become a proliferative cell,

NOTE Confidence: 0.774541726666667

00:39:24.670 --> 00:39:26.272 you don't need all that secretory

NOTE Confidence: 0.774541726666667

00:39:26.272 --> 00:39:28.370 roufi R you need ribosomes in the

NOTE Confidence: 0.774541726666667

00:39:28.370 --> 00:39:30.320 cytosol to make more ribosomes than

NOTE Confidence: 0.774541726666667

00:39:30.320 --> 00:39:32.149 histones to make a copy of the cell.

NOTE Confidence: 0.774541726666667

00:39:32.150 --> 00:39:35.174 And the key driver for ribosome

NOTE Confidence: 0.774541726666667

00:39:35.174 --> 00:39:37.570 Biogenesis is M torque OK,

NOTE Confidence: 0.774541726666667

00:39:37.570 --> 00:39:39.838 and the reason why ribosome Biogenesis

NOTE Confidence: 0.774541726666667

00:39:39.838 --> 00:39:42.629 needs so much energy is because it's

NOTE Confidence: 0.774541726666667

00:39:42.629 --> 00:39:44.649 an incredibly complex process of

NOTE Confidence: 0.774541726666667

00:39:44.649 --> 00:39:46.835 assembling all of these ribosomal

NOTE Confidence: 0.774541726666667

00:39:46.835 --> 00:39:49.112 proteins and ribosomal RNA's that

NOTE Confidence: 0.774541726666667

00:39:49.112 --> 00:39:51.517 require all three RNA polymerases

NOTE Confidence: 0.774541726666667

00:39:51.517 --> 00:39:53.480 and translation into these.

NOTE Confidence: 0.774541726666667

00:39:53.480 --> 00:39:57.158 Large and small 1640 subunits which

NOTE Confidence: 0.774541726666667

00:39:57.158 --> 00:39:59.594 come together as a single subunit,

NOTE Confidence: 0.774541726666667

00:39:59.600 --> 00:40:01.075 multiple modifications happen and all

NOTE Confidence: 0.774541726666667

00:40:01.075 --> 00:40:03.449 of its sort of starts in the nucleolus.

NOTE Confidence: 0.774541726666667

00:40:03.450 --> 00:40:05.880 So that's our basic ribosome review.

NOTE Confidence: 0.774541726666667

00:40:05.880 --> 00:40:06.978 And then as I talked about,

NOTE Confidence: 0.774541726666667

00:40:06.980 --> 00:40:08.738 there's a big difference between this

NOTE Confidence: 0.774541726666667

00:40:08.738 --> 00:40:10.698 pool and this side of solid pool,

NOTE Confidence: 0.774541726666667

00:40:10.700 --> 00:40:11.040 right,

NOTE Confidence: 0.774541726666667

00:40:11.040 --> 00:40:13.420 because this is for secretion and this

NOTE Confidence: 0.774541726666667

00:40:13.420 --> 00:40:16.089 is more for division and housekeeping.

NOTE Confidence: 0.774541726666667

00:40:16.090 --> 00:40:20.274 So to get from the ribosome to translation,

NOTE Confidence: 0.774541726666667

00:40:20.280 --> 00:40:21.946 we have to realize that the M

NOTE Confidence: 0.774541726666667

00:40:21.946 --> 00:40:24.146 RNA is going to be loaded up

NOTE Confidence: 0.774541726666667

00:40:24.146 --> 00:40:25.214 the preinitiation complexes.

NOTE Confidence: 0.774541726666667

00:40:25.220 --> 00:40:26.822 That's going to bring the two

NOTE Confidence: 0.774541726666667

00:40:26.822 --> 00:40:27.356 subunits together.

NOTE Confidence: 0.774541726666667

00:40:27.360 --> 00:40:28.685 So the two subunits only

NOTE Confidence: 0.774541726666667

00:40:28.685 --> 00:40:30.010 come together with M RNA

NOTE Confidence: 0.763685607272727

00:40:30.072 --> 00:40:32.950 normally, OK. So they're kept together

NOTE Confidence: 0.763685607272727

00:40:32.950 --> 00:40:34.960 with M RNA as they translate.

NOTE Confidence: 0.763685607272727

00:40:34.960 --> 00:40:36.864 And then the way most of our

NOTE Confidence: 0.763685607272727

00:40:36.864 --> 00:40:38.356 translation happens is not with

NOTE Confidence: 0.763685607272727

00:40:38.356 --> 00:40:39.901 single ribosomes but multiple ones

NOTE Confidence: 0.763685607272727

00:40:39.901 --> 00:40:41.874 like pearls on a string, line up,

NOTE Confidence: 0.763685607272727

00:40:41.874 --> 00:40:43.638 line up and those are called polysomes.

NOTE Confidence: 0.763685607272727

00:40:43.640 --> 00:40:44.954 We're not going to go too much into this,

NOTE Confidence: 0.763685607272727

00:40:44.960 --> 00:40:46.640 but you can tell the difference.

NOTE Confidence: 0.763685607272727

00:40:46.640 --> 00:40:48.215 Between Monisms and polysomes by

NOTE Confidence: 0.763685607272727

00:40:48.215 --> 00:40:50.128 spinning them down and the longer

NOTE Confidence: 0.763685607272727

00:40:50.128 --> 00:40:52.074 you know ones or polysomes so they

NOTE Confidence: 0.763685607272727

00:40:52.074 --> 00:40:53.966 take lower longer to spin spin out.

NOTE Confidence: 0.763685607272727

00:40:53.970 --> 00:40:57.106 So the last review slide here on ribosomes.

NOTE Confidence: 0.763685607272727

00:40:57.110 --> 00:40:59.406 The reason why they require so much,

NOTE Confidence: 0.763685607272727

00:40:59.410 --> 00:41:01.664 they require 80% of the cells energy.

NOTE Confidence: 0.763685607272727

00:41:01.670 --> 00:41:03.366 So that's why it's so important how you,

NOTE Confidence: 0.763685607272727

00:41:03.370 --> 00:41:05.956 you know, regulate ribosome Biogenesis and

NOTE Confidence: 0.763685607272727

00:41:05.956 --> 00:41:09.966 60% of your RNA in each cell is ribosomes.

NOTE Confidence: 0.763685607272727

00:41:09.970 --> 00:41:12.088 So there's huge proportions of the

NOTE Confidence: 0.763685607272727

00:41:12.088 --> 00:41:13.500 transcription and translation that

NOTE Confidence: 0.763685607272727

00:41:13.554 --> 00:41:15.090 goes into ribosome Biogenesis.

NOTE Confidence: 0.763685607272727

00:41:15.090 --> 00:41:17.430 So what happens to ribosomes

NOTE Confidence: 0.763685607272727

00:41:17.430 --> 00:41:18.024 during palingenesis?

NOTE Confidence: 0.763685607272727

00:41:18.024 --> 00:41:20.400 So we knew already that they had to

NOTE Confidence: 0.763685607272727

00:41:20.462 --> 00:41:22.568 be coming off the rough ER and we saw

NOTE Confidence: 0.763685607272727

00:41:22.568 --> 00:41:24.607 that's what all the autophagy was doing.

NOTE Confidence: 0.763685607272727

00:41:24.610 --> 00:41:26.045 But you can also just document it,

NOTE Confidence: 0.763685607272727

00:41:26.050 --> 00:41:27.151 there's many ways.

NOTE Confidence: 0.763685607272727

00:41:27.151 --> 00:41:29.353 To to show that you're losing

NOTE Confidence: 0.763685607272727

00:41:29.353 --> 00:41:30.898 both large and small.

NOTE Confidence: 0.763685607272727

00:41:30.900 --> 00:41:32.706 Subunits of ribosomes are just Western

NOTE Confidence: 0.763685607272727

00:41:32.706 --> 00:41:34.788 blots early on in the process and

NOTE Confidence: 0.763685607272727

00:41:34.788 --> 00:41:36.706 then they come back on again later.

NOTE Confidence: 0.763685607272727

00:41:36.710 --> 00:41:38.648 So there's a loss and then

NOTE Confidence: 0.763685607272727

00:41:38.648 --> 00:41:39.294 regeneration process.

NOTE Confidence: 0.763685607272727

00:41:39.300 --> 00:41:42.475 But you can also see some of the

NOTE Confidence: 0.763685607272727

00:41:42.475 --> 00:41:43.800 ribosomes getting taken up into

NOTE Confidence: 0.763685607272727

00:41:43.800 --> 00:41:45.697 the the rough ER and you can also

NOTE Confidence: 0.763685607272727

00:41:45.697 --> 00:41:47.470 see them kind of spinning off the

NOTE Confidence: 0.763685607272727

00:41:47.470 --> 00:41:48.870 ER here into the sideshow.

NOTE Confidence: 0.763685607272727

00:41:48.870 --> 00:41:51.020 And in fact Juan J was one of the first

NOTE Confidence: 0.763685607272727

00:41:51.085 --> 00:41:53.077 to show this by knocking out a gene

NOTE Confidence: 0.763685607272727

00:41:53.077 --> 00:41:54.736 that that regulates all that rough

NOTE Confidence: 0.763685607272727

00:41:54.736 --> 00:41:56.627 ER when he was a graduate student.

NOTE Confidence: 0.763685607272727

00:41:56.627 --> 00:41:58.443 So this is kind of what we think

NOTE Confidence: 0.763685607272727

00:41:58.443 --> 00:41:59.240 is happening.

NOTE Confidence: 0.763685607272727

00:41:59.240 --> 00:42:01.858 In terms of stages of of pathogenesis,

NOTE Confidence: 0.763685607272727

00:42:01.860 --> 00:42:05.528 normally you have all these rough ER.

NOTE Confidence: 0.763685607272727

00:42:05.530 --> 00:42:08.170 Ribosomes making peptides and then,

NOTE Confidence: 0.763685607272727

00:42:08.170 --> 00:42:08.812 you know,

NOTE Confidence: 0.763685607272727

00:42:08.812 --> 00:42:10.738 there's an injury and these autophagosomes

NOTE Confidence: 0.763685607272727

00:42:10.738 --> 00:42:12.975 start to take up the raffia and the

NOTE Confidence: 0.763685607272727

00:42:12.975 --> 00:42:14.642 ribosomes all come off OK what's the

NOTE Confidence: 0.763685607272727

00:42:14.642 --> 00:42:16.058 problem with the ribosomes coming off?

NOTE Confidence: 0.763685607272727

00:42:16.060 --> 00:42:17.329 As soon as they come off the M RNA,

NOTE Confidence: 0.763685607272727

00:42:17.330 --> 00:42:19.574 then they fall apart into their

NOTE Confidence: 0.763685607272727

00:42:19.574 --> 00:42:21.710 subunits and into ribosomal proteins,

NOTE Confidence: 0.763685607272727

00:42:21.710 --> 00:42:23.920 and those can stimulate P53.

NOTE Confidence: 0.763685607272727

00:42:23.920 --> 00:42:25.033 I'm going to show you that again

NOTE Confidence: 0.763685607272727

00:42:25.033 --> 00:42:26.130 a couple of different times,

NOTE Confidence: 0.763685607272727

00:42:26.130 --> 00:42:28.629 but that's probably why this whole ribosome

NOTE Confidence: 0.763685607272727

00:42:28.629 --> 00:42:31.208 is the center of this mtorc P53 axis.

NOTE Confidence: 0.763685607272727

00:42:31.210 --> 00:42:32.983 But this is just to show you that we

NOTE Confidence: 0.763685607272727

00:42:32.983 --> 00:42:34.827 also get a lot of ribosome Biogenesis,

NOTE Confidence: 0.763685607272727

00:42:34.830 --> 00:42:35.664 so we're losing.

NOTE Confidence: 0.763685607272727

00:42:35.664 --> 00:42:37.610 Have some and then later we see

NOTE Confidence: 0.763685607272727

00:42:37.668 --> 00:42:39.578 huge increases in nucleolar size,

NOTE Confidence: 0.763685607272727

00:42:39.580 --> 00:42:41.596 which you can see here in quantify

NOTE Confidence: 0.763685607272727

00:42:41.596 --> 00:42:44.099 in both the stomach and the pancreas.

NOTE Confidence: 0.763685607272727

00:42:44.100 --> 00:42:46.284 So what that means is we're losing

NOTE Confidence: 0.763685607272727

00:42:46.284 --> 00:42:48.230 ribosomes here and then the nucleoli

NOTE Confidence: 0.763685607272727

00:42:48.230 --> 00:42:50.132 are getting turned on or making

NOTE Confidence: 0.763685607272727

00:42:50.132 --> 00:42:51.399 more ribosomes here.

NOTE Confidence: 0.763685607272727

00:42:51.400 --> 00:42:54.484 But that's not the entire story as we see,

NOTE Confidence: 0.763685607272727

00:42:54.484 --> 00:42:56.474 because I 41's going to play an important

NOTE Confidence: 0.763685607272727

00:42:56.474 --> 00:42:58.478 part in between those two things.

NOTE Confidence: 0.763685607272727

00:42:58.480 --> 00:43:00.160 So to be able to study these things,

NOTE Confidence: 0.763685607272727

00:43:00.160 --> 00:43:01.714 we already have one tool which

NOTE Confidence: 0.763685607272727

00:43:01.714 --> 00:43:02.750 is the ID one

NOTE Confidence: 0.789456304545455

00:43:02.810 --> 00:43:05.560 knockout. But Charles Chow in the lab,

NOTE Confidence: 0.789456304545455

00:43:05.560 --> 00:43:09.296 who's an instructor looking for a job soon,

NOTE Confidence: 0.789456304545455

00:43:09.300 --> 00:43:10.980 also made a knockout of ribosome

NOTE Confidence: 0.789456304545455

00:43:10.980 --> 00:43:12.400 Biogenesis for the first time,

NOTE Confidence: 0.789456304545455

00:43:12.400 --> 00:43:14.008 surprisingly that he can.

NOTE Confidence: 0.789456304545455

00:43:14.008 --> 00:43:16.018 Reduced ribosome Biogenesis knockout by

NOTE Confidence: 0.789456304545455

00:43:16.018 --> 00:43:18.074 knocking out this key modifier that's

NOTE Confidence: 0.789456304545455

00:43:18.074 --> 00:43:20.440 critical for the small subunit of ribosomes.

NOTE Confidence: 0.789456304545455

00:43:20.440 --> 00:43:22.400 And when he does that you that you

NOTE Confidence: 0.789456304545455

00:43:22.400 --> 00:43:24.153 can no longer make ribosomes and

NOTE Confidence: 0.789456304545455

00:43:24.153 --> 00:43:26.355 when you do that and you induce

NOTE Confidence: 0.789456304545455

00:43:26.355 --> 00:43:28.401 collagenosis all the cells die unless

NOTE Confidence: 0.789456304545455

00:43:28.401 --> 00:43:30.740 you also put them on a P53 knockout.

NOTE Confidence: 0.789456304545455

00:43:30.740 --> 00:43:33.434 So again PD3 knockout is critical

NOTE Confidence: 0.789456304545455

00:43:33.434 --> 00:43:36.649 that's sensing the death of of cells

NOTE Confidence: 0.789456304545455

00:43:36.649 --> 00:43:38.874 that don't make ribosomes anymore.

NOTE Confidence: 0.789456304545455

00:43:38.880 --> 00:43:41.220 So this particular gene which is

NOTE Confidence: 0.789456304545455

00:43:41.220 --> 00:43:43.610 involved in the ribosome Biogenesis.

NOTE Confidence: 0.789456304545455

00:43:43.610 --> 00:43:45.522 Suppresses P53 presumably because

NOTE Confidence: 0.789456304545455

00:43:45.522 --> 00:43:47.434 it makes both subunits.

NOTE Confidence: 0.789456304545455

00:43:47.440 --> 00:43:48.736 So they're both subunits are there.

NOTE Confidence: 0.789456304545455

00:43:48.740 --> 00:43:50.420 It stops the people to three

NOTE Confidence: 0.789456304545455

00:43:50.420 --> 00:43:51.540 induction that happens with

NOTE Confidence: 0.789456304545455

00:43:51.596 --> 00:43:53.248 ribosome will breakdown products,

NOTE Confidence: 0.789456304545455

00:43:53.250 --> 00:43:56.256 but I have 41 is occurring here

NOTE Confidence: 0.789456304545455

00:43:56.256 --> 00:43:58.678 earlier I showed you and it's also

NOTE Confidence: 0.789456304545455

00:43:58.678 --> 00:44:00.449 responsible for suppressing P53.

NOTE Confidence: 0.789456304545455

00:44:00.450 --> 00:44:01.714 How does that work?

NOTE Confidence: 0.789456304545455

00:44:01.714 --> 00:44:03.710 Well, it turns out that it's in between.

NOTE Confidence: 0.789456304545455

00:44:03.710 --> 00:44:05.138 That's just to remind you of

NOTE Confidence: 0.789456304545455

00:44:05.138 --> 00:44:06.769 that and that NAP 10 is there,

NOTE Confidence: 0.789456304545455

00:44:06.770 --> 00:44:08.121 but I heard you once turning on

NOTE Confidence: 0.789456304545455

00:44:08.121 --> 00:44:09.370 earlier and doing the suppression.

NOTE Confidence: 0.789456304545455

00:44:09.370 --> 00:44:11.570 So how does it work?

NOTE Confidence: 0.789456304545455

00:44:11.570 --> 00:44:13.250 So it turns on it, you know,

NOTE Confidence: 0.789456304545455

00:44:13.250 --> 00:44:14.250 it turns on here.

NOTE Confidence: 0.789456304545455

00:44:14.250 --> 00:44:15.974 And what it does,

NOTE Confidence: 0.789456304545455

00:44:15.974 --> 00:44:17.267 it turns out.

NOTE Confidence: 0.789456304545455

00:44:17.270 --> 00:44:20.050 Is that I 41 fits right here right where the

NOTE Confidence: 0.789456304545455

00:44:20.113 --> 00:44:22.633 M RNA would go between the two subunits.

NOTE Confidence: 0.789456304545455

00:44:22.640 --> 00:44:24.344 So when I offered you one

NOTE Confidence: 0.789456304545455

00:44:24.344 --> 00:44:25.790 attaches just like M RNA,

NOTE Confidence: 0.789456304545455

00:44:25.790 --> 00:44:27.428 it can keep the two ribosomal

NOTE Confidence: 0.789456304545455

00:44:27.428 --> 00:44:28.890 subunits together as a whole.

NOTE Confidence: 0.789456304545455

00:44:28.890 --> 00:44:30.786 So instead of having this happen

NOTE Confidence: 0.789456304545455

00:44:30.786 --> 00:44:32.050 during those early stages,

NOTE Confidence: 0.789456304545455

00:44:32.050 --> 00:44:33.665 which then leads to breakdown

NOTE Confidence: 0.789456304545455

00:44:33.665 --> 00:44:34.958 in P53 activation,

NOTE Confidence: 0.789456304545455

00:44:34.958 --> 00:44:39.630 I 41 can come right there in that pocket.

NOTE Confidence: 0.789456304545455

00:44:39.630 --> 00:44:41.275 And as they come off the ribosomes,

NOTE Confidence: 0.789456304545455

00:44:41.280 --> 00:44:42.080 they're preserved.

NOTE Confidence: 0.789456304545455

00:44:42.080 --> 00:44:44.480 So essentially 53 is blocked because

NOTE Confidence: 0.789456304545455

00:44:44.480 --> 00:44:47.131 you don't get breakdown of all the

NOTE Confidence: 0.789456304545455

00:44:47.131 --> 00:44:48.916 ribosomes during the first stage.

NOTE Confidence: 0.789456304545455

00:44:48.920 --> 00:44:51.674 So on the one hand you could have this,

NOTE Confidence: 0.789456304545455

00:44:51.680 --> 00:44:53.894 but when you have ribosome Biogenesis

NOTE Confidence: 0.789456304545455

00:44:53.894 --> 00:44:57.079 you can stop P53 by making new ribosomes,

NOTE Confidence: 0.789456304545455

00:44:57.080 --> 00:44:59.152 and if you have 41 then you salvage

NOTE Confidence: 0.789456304545455

00:44:59.152 --> 00:45:00.605 the existing ribosomes so both

NOTE Confidence: 0.789456304545455

00:45:00.605 --> 00:45:02.690 of those then converge on P53.

NOTE Confidence: 0.789456304545455

00:45:02.690 --> 00:45:06.470 OK, so that is the ********.

NOTE Confidence: 0.789456304545455

00:45:06.470 --> 00:45:07.730 Organellar and molecular stuff.

NOTE Confidence: 0.789456304545455

00:45:07.730 --> 00:45:10.411 So now let's come kind of back out to

NOTE Confidence: 0.789456304545455

00:45:10.411 --> 00:45:12.478 how this all comes out in tumors and

NOTE Confidence: 0.789456304545455

00:45:12.478 --> 00:45:14.606 and come back out towards the pathology.

NOTE Confidence: 0.789456304545455

00:45:14.610 --> 00:45:16.465 So with all this background

NOTE Confidence: 0.789456304545455

00:45:16.465 --> 00:45:17.949 then it's pretty clear,

NOTE Confidence: 0.789456304545455

00:45:17.950 --> 00:45:19.942 you know that the cells spent a lot

NOTE Confidence: 0.789456304545455

00:45:19.942 --> 00:45:21.864 of time trying to regulate them to

NOTE Confidence: 0.789456304545455

00:45:21.864 --> 00:45:24.091 work via PD3 and via this protein deed

NOTE Confidence: 0.789456304545455

00:45:24.091 --> 00:45:26.211 at 4:00 to be able to ensure that

NOTE Confidence: 0.789456304545455

00:45:26.211 --> 00:45:27.968 the there's no tumors that come out

NOTE Confidence: 0.789456304545455

00:45:27.968 --> 00:45:29.911 of this taking these old cells and

NOTE Confidence: 0.789456304545455

00:45:29.911 --> 00:45:31.930 driving them back into the cell cycle.

NOTE Confidence: 0.789456304545455

00:45:31.930 --> 00:45:34.720 So what if we get rid of the ability to

NOTE Confidence: 0.789456304545455

00:45:34.795 --> 00:45:37.658 stop mtorc and regulate this process so.

NOTE Confidence: 0.789456304545455

00:45:37.660 --> 00:45:40.132 You know what if we take out them

NOTE Confidence: 0.789456304545455

00:45:40.132 --> 00:45:41.599 torque regulation and then in

NOTE Confidence: 0.789456304545455

00:45:41.599 --> 00:45:43.426 in a system where we can induce

NOTE Confidence: 0.789456304545455

00:45:43.487 --> 00:45:45.337 metaplasia multiple times and the

NOTE Confidence: 0.789456304545455

00:45:45.337 --> 00:45:47.453 thinking would be then that what's

NOTE Confidence: 0.789456304545455

00:45:47.453 --> 00:45:49.294 going to happen is we kind of

NOTE Confidence: 0.839834078

00:45:49.300 --> 00:45:50.836 injure each time and we don't

NOTE Confidence: 0.839834078

00:45:50.836 --> 00:45:51.860 have much error checking.

NOTE Confidence: 0.839834078

00:45:51.860 --> 00:45:53.680 Then you go through collagenosis,

NOTE Confidence: 0.839834078

00:45:53.680 --> 00:45:55.192 then you heal, then you go through

NOTE Confidence: 0.839834078

00:45:55.192 --> 00:45:56.080 pathogenesis and you heal.

NOTE Confidence: 0.839834078

00:45:56.080 --> 00:45:58.264 But each time you can accumulate

NOTE Confidence: 0.839834078

00:45:58.264 --> 00:46:00.442 mutations until finally you get to

NOTE Confidence: 0.839834078

00:46:00.442 --> 00:46:02.410 the mutations like Karas or something

NOTE Confidence: 0.839834078

00:46:02.410 --> 00:46:04.462 like that that drives a tumor and

NOTE Confidence: 0.839834078

00:46:04.462 --> 00:46:06.268 then you know you no longer go

NOTE Confidence: 0.839834078

00:46:06.268 --> 00:46:07.906 back to being a chief seller and.

NOTE Confidence: 0.839834078

00:46:07.910 --> 00:46:08.750 Lesson or so.

NOTE Confidence: 0.839834078

00:46:08.750 --> 00:46:11.068 So I already showed you how we kind

NOTE Confidence: 0.839834078

00:46:11.068 --> 00:46:13.112 of we do these screens and coming

NOTE Confidence: 0.839834078

00:46:13.112 --> 00:46:15.596 back to dead at 4 so that you know

NOTE Confidence: 0.839834078

00:46:15.596 --> 00:46:17.380 knocks out the ability of the cell

NOTE Confidence: 0.839834078

00:46:17.380 --> 00:46:19.177 to decrease M torque and it knocks

NOTE Confidence: 0.839834078

00:46:19.177 --> 00:46:20.885 out its ability to be able to

NOTE Confidence: 0.839834078

00:46:20.885 --> 00:46:22.922 sense the P53 damage and to be able

NOTE Confidence: 0.839834078

00:46:22.922 --> 00:46:24.719 to stop cells from coming back.

NOTE Confidence: 0.839834078

00:46:24.720 --> 00:46:26.645 And cell cycle basically just kind of

NOTE Confidence: 0.839834078

00:46:26.645 --> 00:46:28.636 skips past all this error checking

NOTE Confidence: 0.839834078

00:46:28.636 --> 00:46:30.116 right into the proliferation.

NOTE Confidence: 0.839834078

00:46:30.120 --> 00:46:31.758 So you see a lot more proliferation

NOTE Confidence: 0.839834078

00:46:31.758 --> 00:46:33.258 when you knock out deed it for.

NOTE Confidence: 0.839834078

00:46:33.260 --> 00:46:35.006 And So what happens is essentially

NOTE Confidence: 0.839834078

00:46:35.006 --> 00:46:36.849 you can take mutations and carry

NOTE Confidence: 0.839834078

00:46:36.849 --> 00:46:38.414 them right into these dysplasias.

NOTE Confidence: 0.839834078

00:46:38.420 --> 00:46:40.298 And so functionally what Max did

NOTE Confidence: 0.839834078

00:46:40.298 --> 00:46:42.896 in the lab was do multiple rounds

NOTE Confidence: 0.839834078

00:46:42.896 --> 00:46:45.026 of Immunogen which causes gastric

NOTE Confidence: 0.839834078

00:46:45.026 --> 00:46:47.614 tumors kind of slowly in the stomach

NOTE Confidence: 0.839834078

00:46:47.614 --> 00:46:49.876 in these cells that could no longer

NOTE Confidence: 0.839834078

00:46:49.876 --> 00:46:51.962 in these mice that could no longer

NOTE Confidence: 0.839834078

00:46:51.962 --> 00:46:53.805 regulate the the collagenosis and

NOTE Confidence: 0.839834078

00:46:53.805 --> 00:46:55.660 that mtor checkpoint versus control

NOTE Confidence: 0.839834078

00:46:55.660 --> 00:46:57.638 cells that could still did multiple

NOTE Confidence: 0.839834078

00:46:57.638 --> 00:46:59.540 rounds of tamoxifen to do multiple

NOTE Confidence: 0.839834078

00:46:59.540 --> 00:47:01.290 rounds of metaplasia and repair.

NOTE Confidence: 0.839834078

00:47:01.290 --> 00:47:03.330 And what he saw as we predicted was

NOTE Confidence: 0.839834078

00:47:03.330 --> 00:47:05.827 a lot more tumors in the deed at 4

NOTE Confidence: 0.839834078

00:47:05.827 --> 00:47:07.732 knockouts and a lot bigger tumors

NOTE Confidence: 0.839834078

00:47:07.732 --> 00:47:09.766 in fact just for the pathology.

NOTE Confidence: 0.839834078

00:47:09.770 --> 00:47:11.810 This is one that arose as a huge

NOTE Confidence: 0.839834078

00:47:11.810 --> 00:47:13.999 sort of polypoid tumor that was

NOTE Confidence: 0.839834078

00:47:13.999 --> 00:47:16.009 more intestinal type between the

NOTE Confidence: 0.839834078

00:47:16.009 --> 00:47:17.438 Antrim and the corpus,

NOTE Confidence: 0.839834078

00:47:17.440 --> 00:47:20.450 but then had a had a focus of the diffuse

NOTE Confidence: 0.839834078

00:47:20.527 --> 00:47:23.096 signet ring cells that you can see.

NOTE Confidence: 0.839834078

00:47:23.100 --> 00:47:24.668 And it's rare in the mouse to get

NOTE Confidence: 0.839834078

00:47:24.668 --> 00:47:26.399 such an obviously metastatic tumor.

NOTE Confidence: 0.839834078

00:47:26.400 --> 00:47:28.368 You can see them kind of in this

NOTE Confidence: 0.839834078

00:47:28.368 --> 00:47:30.261 PAS stain going right through the

NOTE Confidence: 0.839834078

00:47:30.261 --> 00:47:32.265 muscle area and into this aerosan

NOTE Confidence: 0.839834078

00:47:32.331 --> 00:47:33.738 intelink vascular space.

NOTE Confidence: 0.839834078

00:47:33.740 --> 00:47:36.440 So in other words, if you can't do this,

NOTE Confidence: 0.839834078

00:47:36.440 --> 00:47:38.114 check here to make sure these

NOTE Confidence: 0.839834078

00:47:38.114 --> 00:47:40.199 cells are OK and send them back,

NOTE Confidence: 0.839834078

00:47:40.200 --> 00:47:41.310 you know, to repair them.

NOTE Confidence: 0.839834078

00:47:41.310 --> 00:47:43.746 They come back to repair with mutations

NOTE Confidence: 0.839834078

00:47:43.746 --> 00:47:45.860 and then eventually they form tumors.

NOTE Confidence: 0.839834078

00:47:45.860 --> 00:47:50.256 OK, so last thing, the human thing.

NOTE Confidence: 0.839834078

00:47:50.260 --> 00:47:53.140 You coming back all the way back to human,

NOTE Confidence: 0.839834078

00:47:53.140 --> 00:47:56.020 the human part of the talk.

NOTE Confidence: 0.839834078

00:47:56.020 --> 00:47:56.447 Again,

NOTE Confidence: 0.839834078

00:47:56.447 --> 00:47:59.009 we've been again going back to

NOTE Confidence: 0.839834078

00:47:59.009 --> 00:48:01.420 Barretts and trying to study this,

NOTE Confidence: 0.839834078

00:48:01.420 --> 00:48:03.250 how these processes happen and how

NOTE Confidence: 0.839834078

00:48:03.250 --> 00:48:05.060 people heal from these processes.

NOTE Confidence: 0.839834078

00:48:05.060 --> 00:48:05.363 Unfortunately,

NOTE Confidence: 0.839834078

00:48:05.363 --> 00:48:07.181 this great mouse models that we

NOTE Confidence: 0.839834078

00:48:07.181 --> 00:48:08.891 can use for tumorigenesis and

NOTE Confidence: 0.839834078

00:48:08.891 --> 00:48:10.746 metaplasia and stomach don't apply

NOTE Confidence: 0.839834078

00:48:10.746 --> 00:48:12.599 because mice don't get variants,

NOTE Confidence: 0.839834078

00:48:12.600 --> 00:48:13.800 they don't reflux at all,

NOTE Confidence: 0.839834078

00:48:13.800 --> 00:48:15.204 they don't have any bile or

NOTE Confidence: 0.839834078

00:48:15.204 --> 00:48:16.700 acid ever in their esophagus.

NOTE Confidence: 0.839834078

00:48:16.700 --> 00:48:18.806 So there's no really good rodent

NOTE Confidence: 0.839834078

00:48:18.806 --> 00:48:19.859 models for this.

NOTE Confidence: 0.839834078

00:48:19.860 --> 00:48:21.606 So you know, you have to study the human.

NOTE Confidence: 0.839834078

00:48:21.610 --> 00:48:24.208 And so I've been collaborating in

NOTE Confidence: 0.839834078

00:48:24.208 --> 00:48:25.940 this amazing collaboration with.

NOTE Confidence: 0.839834078

00:48:25.940 --> 00:48:28.175 Rhonda Souza and Stu Spechler's

NOTE Confidence: 0.839834078

00:48:28.175 --> 00:48:29.963 group and Rob odds.

NOTE Confidence: 0.702047116

00:48:29.970 --> 00:48:31.242 Also, you know, pathologist,

NOTE Confidence: 0.702047116

00:48:31.242 --> 00:48:31.885 yeah, pathologist.

NOTE Confidence: 0.702047116

00:48:31.885 --> 00:48:34.160 To look at, at their models of

NOTE Confidence: 0.702047116

00:48:34.160 --> 00:48:36.088 Barretts and some clinical trials,

NOTE Confidence: 0.702047116

00:48:36.090 --> 00:48:36.834 I'll just show you.

NOTE Confidence: 0.702047116

00:48:36.834 --> 00:48:38.419 Here's where I had them down to Houston.

NOTE Confidence: 0.702047116

00:48:38.420 --> 00:48:40.990 There's Rob and and me.

NOTE Confidence: 0.702047116

00:48:40.990 --> 00:48:42.310 And there's actually, there's my.

NOTE Confidence: 0.702047116

00:48:42.310 --> 00:48:44.542 There's the same microscope that Wanj

NOTE Confidence: 0.702047116

00:48:44.542 --> 00:48:48.470 learned on, taken down to down to Houston.

NOTE Confidence: 0.702047116

00:48:48.470 --> 00:48:50.171 And Rhonda like is fond of saying

NOTE Confidence: 0.702047116

00:48:50.171 --> 00:48:52.048 that humans are the best model system.

NOTE Confidence: 0.702047116

00:48:52.050 --> 00:48:53.607 So it with Barretts we have to do that.

NOTE Confidence: 0.702047116

00:48:53.610 --> 00:48:56.965 So, So what in this model what

NOTE Confidence: 0.702047116

00:48:56.965 --> 00:48:59.590 they've done is they you know with

NOTE Confidence: 0.702047116

00:48:59.590 --> 00:49:02.005 the dysplastic Barretts you can treat

NOTE Confidence: 0.702047116

00:49:02.005 --> 00:49:04.401 it by radiofrequency ablation just to

NOTE Confidence: 0.702047116

00:49:04.401 --> 00:49:06.195 basically take out all the Barretts

NOTE Confidence: 0.702047116

00:49:06.195 --> 00:49:09.058 and take it down to the ulcer bed and

NOTE Confidence: 0.702047116

00:49:09.058 --> 00:49:10.894 granulation tissue and then for some

NOTE Confidence: 0.702047116

00:49:10.894 --> 00:49:12.586 reason it heals back as squamous.

NOTE Confidence: 0.702047116

00:49:12.590 --> 00:49:14.220 So basically what you're doing

NOTE Confidence: 0.702047116

00:49:14.220 --> 00:49:15.198 is radiofrequency ablation,

NOTE Confidence: 0.702047116

00:49:15.200 --> 00:49:15.730 the Barretts,

NOTE Confidence: 0.702047116

00:49:15.730 --> 00:49:18.460 and it goes to this just ulcer bed basically.

NOTE Confidence: 0.702047116

00:49:18.460 --> 00:49:20.910 What's leftover?

NOTE Confidence: 0.702047116

00:49:20.910 --> 00:49:23.465 And then you know what happens though,

NOTE Confidence: 0.702047116

00:49:23.470 --> 00:49:25.066 you know after this ulceration is it

NOTE Confidence: 0.702047116

00:49:25.066 --> 00:49:26.655 comes back as a squamous and what

NOTE Confidence: 0.702047116

00:49:26.655 --> 00:49:28.474 they did was they they took a bunch

NOTE Confidence: 0.702047116

00:49:28.474 --> 00:49:29.926 of patients and enrolled them should

NOTE Confidence: 0.702047116

00:49:29.926 --> 00:49:31.565 also say for the this study and

NOTE Confidence: 0.702047116

00:49:31.565 --> 00:49:33.530 then did the pre and then one week,

NOTE Confidence: 0.702047116

00:49:33.530 --> 00:49:35.246 two week and four week biopsies

NOTE Confidence: 0.702047116

00:49:35.246 --> 00:49:36.953 all the way proximal to distal

NOTE Confidence: 0.702047116

00:49:36.953 --> 00:49:38.724 from before the margin of RFA to

NOTE Confidence: 0.702047116

00:49:38.724 --> 00:49:40.629 the gastric margin after the RFA.

NOTE Confidence: 0.702047116

00:49:40.630 --> 00:49:42.454 And you know try to look at how

NOTE Confidence: 0.702047116

00:49:42.454 --> 00:49:44.665 the healing process, how all this,

NOTE Confidence: 0.702047116

00:49:44.665 --> 00:49:47.215 you know mucosa became squamous again.

NOTE Confidence: 0.92109934625

00:49:49.370 --> 00:49:51.546 So that's kind of what it looks like.

NOTE Confidence: 0.92109934625

00:49:51.550 --> 00:49:52.792 You know, the question is where

NOTE Confidence: 0.92109934625

00:49:52.792 --> 00:49:54.049 does all that squamous come from?

NOTE Confidence: 0.92109934625

00:49:54.050 --> 00:49:55.874 And the only source of squamous or even

NOTE Confidence: 0.92109934625

00:49:55.874 --> 00:49:57.380 epithelial cells that you could think of

NOTE Confidence: 0.92109934625

00:49:57.380 --> 00:49:58.968 would be at this proximal margin, right.

NOTE Confidence: 0.92109934625

00:49:58.968 --> 00:50:00.258 But it turns out that's

NOTE Confidence: 0.92109934625

00:50:00.258 --> 00:50:01.290 actually not what happens.

NOTE Confidence: 0.92109934625

00:50:01.290 --> 00:50:03.125 What happens is it comes

NOTE Confidence: 0.92109934625

00:50:03.125 --> 00:50:04.593 back as squamous throughout.

NOTE Confidence: 0.92109934625

00:50:04.600 --> 00:50:07.132 So there's some source of squamous

NOTE Confidence: 0.92109934625

00:50:07.132 --> 00:50:09.874 epithelium that's obviously trans or D or

NOTE Confidence: 0.92109934625

00:50:09.874 --> 00:50:12.132 some kind of differentiating, you know,

NOTE Confidence: 0.92109934625

00:50:12.132 --> 00:50:14.487 that's that's feeding the squamous.

NOTE Confidence: 0.92109934625

00:50:14.490 --> 00:50:17.190 And you know we have a couple of clues,

NOTE Confidence: 0.92109934625

00:50:17.190 --> 00:50:19.626 one of which well we talked about.

NOTE Confidence: 0.92109934625

00:50:19.630 --> 00:50:21.597 But one of which I'll show you

NOTE Confidence: 0.92109934625

00:50:21.597 --> 00:50:22.784 evidence for here, you know,

NOTE Confidence: 0.92109934625

00:50:22.784 --> 00:50:23.988 so the idea is that coming from

NOTE Confidence: 0.92109934625

00:50:23.988 --> 00:50:25.322 the proximal squamous, you know,

NOTE Confidence: 0.92109934625

00:50:25.322 --> 00:50:26.834 there's a come from the distal gastric,

NOTE Confidence: 0.92109934625

00:50:26.840 --> 00:50:28.436 but then why would that be squamous?

NOTE Confidence: 0.92109934625

00:50:28.440 --> 00:50:29.800 But it turns out it just comes in

NOTE Confidence: 0.92109934625

00:50:29.800 --> 00:50:31.169 all these little islands like this.

NOTE Confidence: 0.92109934625

00:50:31.170 --> 00:50:32.060 And so if you focus,

NOTE Confidence: 0.92109934625

00:50:32.060 --> 00:50:35.021 here's one of these islands of this

NOTE Confidence: 0.92109934625

00:50:35.021 --> 00:50:37.200 NEO squamous healing epithelium.

NOTE Confidence: 0.92109934625

00:50:37.200 --> 00:50:37.905 And, you know,

NOTE Confidence: 0.92109934625

00:50:37.905 --> 00:50:39.840 where does this come from on either side?

NOTE Confidence: 0.92109934625

00:50:39.840 --> 00:50:41.280 Basically it's going to go down

NOTE Confidence: 0.92109934625

00:50:41.280 --> 00:50:42.540 to like a single cell.

NOTE Confidence: 0.92109934625

00:50:42.540 --> 00:50:45.123 It turns out that there's pretty good

NOTE Confidence: 0.92109934625

00:50:45.123 --> 00:50:46.900 evidence both morphologically and also

NOTE Confidence: 0.92109934625

00:50:46.900 --> 00:50:48.415 with their advanced endoscopy that

NOTE Confidence: 0.92109934625

00:50:48.415 --> 00:50:50.710 if you look under each of these new.

NOTE Confidence: 0.92109934625

00:50:50.710 --> 00:50:52.642 Kind of ulcerated surface as a single

NOTE Confidence: 0.92109934625

00:50:52.642 --> 00:50:54.610 cell layer of squamous is forming.

NOTE Confidence: 0.92109934625

00:50:54.610 --> 00:50:57.010 They're all underneath ducts

NOTE Confidence: 0.92109934625

00:50:57.010 --> 00:50:58.507 from submucosal glands.

NOTE Confidence: 0.92109934625

00:50:58.507 --> 00:50:59.398 So you know,

NOTE Confidence: 0.92109934625

00:50:59.398 --> 00:51:01.745 just for those of you don't remember

NOTE Confidence: 0.92109934625

00:51:01.745 --> 00:51:03.729 your human esophageal theology.

NOTE Confidence: 0.92109934625

00:51:03.730 --> 00:51:05.008 These are the 70 coastal glands,

NOTE Confidence: 0.92109934625

00:51:05.010 --> 00:51:07.122 and they have ducts that reach

NOTE Confidence: 0.92109934625

00:51:07.122 --> 00:51:08.796 up to the squamous epithelium.

NOTE Confidence: 0.92109934625

00:51:08.796 --> 00:51:10.392 And normally like if you blade

NOTE Confidence: 0.92109934625

00:51:10.392 --> 00:51:11.430 all this with RFA,

NOTE Confidence: 0.92109934625

00:51:11.430 --> 00:51:13.019 then there's still a source of epithelium.

NOTE Confidence: 0.92109934625

00:51:13.020 --> 00:51:15.330 At least you know distally for

NOTE Confidence: 0.92109934625

00:51:15.330 --> 00:51:17.530 some of these squamous islands.

NOTE Confidence: 0.92109934625

00:51:17.530 --> 00:51:19.378 But the other source is probably some of

NOTE Confidence: 0.92109934625

00:51:19.378 --> 00:51:21.028 these deeper Barretts that escapes the.

NOTE Confidence: 0.92109934625

00:51:21.030 --> 00:51:23.370 RFA as we have a lot of work showing

NOTE Confidence: 0.92109934625

00:51:23.370 --> 00:51:25.538 that there's transitions in there.

NOTE Confidence: 0.92109934625

00:51:25.540 --> 00:51:27.187 So like in fact that's what we're doing now.

NOTE Confidence: 0.92109934625

00:51:27.190 --> 00:51:28.850 We're doing spatial transcriptomics,

NOTE Confidence: 0.92109934625

00:51:28.850 --> 00:51:31.340 we're growing organoids and we're doing

NOTE Confidence: 0.92109934625

00:51:31.402 --> 00:51:33.418 a lot of IHC and Multiplex IFF to kind

NOTE Confidence: 0.92109934625

00:51:33.418 --> 00:51:35.560 of show how these transitions happen.

NOTE Confidence: 0.92109934625

00:51:35.560 --> 00:51:38.930 So that's that. So summarizing.

NOTE Confidence: 0.92109934625

00:51:38.930 --> 00:51:41.360 Take homes.

NOTE Confidence: 0.92109934625

00:51:41.360 --> 00:51:42.925 This kind of pyloric metaplasia

NOTE Confidence: 0.92109934625

00:51:42.925 --> 00:51:44.883 is some kind of like maybe

NOTE Confidence: 0.92109934625

00:51:44.883 --> 00:51:46.538 or metaplasia that you see,

NOTE Confidence: 0.92109934625

00:51:46.540 --> 00:51:47.330 you know,

NOTE Confidence: 0.92109934625

00:51:47.330 --> 00:51:50.095 intestine in the cases of SL going

NOTE Confidence: 0.92109934625

00:51:50.095 --> 00:51:52.465 towards that you see the body of.

NOTE Confidence: 0.92109934625

00:51:52.470 --> 00:51:55.428 I don't mean gastritis and H

NOTE Confidence: 0.92109934625

00:51:55.428 --> 00:51:57.400 pylori induced atrophic gastritis,

NOTE Confidence: 0.92109934625

00:51:57.400 --> 00:52:00.382 it's the what seems to be

NOTE Confidence: 0.92109934625

00:52:00.382 --> 00:52:01.873 happening in Barretts.

NOTE Confidence: 0.92109934625

00:52:01.880 --> 00:52:04.240 And the root of this and although we

NOTE Confidence: 0.92109934625

00:52:04.240 --> 00:52:06.507 don't know this yet in the SL how

NOTE Confidence: 0.92109934625

00:52:06.507 --> 00:52:08.882 that happens but but at least in the

NOTE Confidence: 0.92109934625

00:52:08.882 --> 00:52:10.724 pancreas and the stomach for sure

NOTE Confidence: 0.92109934625

00:52:10.730 --> 00:52:13.187 and probably in Barretts is the cell

NOTE Confidence: 0.92109934625

00:52:13.187 --> 00:52:15.039 biological process that's driving this,

NOTE Confidence: 0.92109934625

00:52:15.040 --> 00:52:16.285 the palingenesis process.

NOTE Confidence: 0.92109934625

00:52:16.285 --> 00:52:19.190 And that basically is about cells converting

NOTE Confidence: 0.92109934625

00:52:19.253 --> 00:52:21.325 energy from one state to the other.

NOTE Confidence: 0.92109934625

00:52:21.330 --> 00:52:23.594 Now you know this is a pathology grand

NOTE Confidence: 0.92109934625

00:52:23.594 --> 00:52:25.538 rounds and I'll tell you that when

NOTE Confidence: 0.92109934625

00:52:25.538 --> 00:52:27.682 I was doing a lot of this looking

NOTE Confidence: 0.92109934625

00:52:27.682 --> 00:52:29.741 at where this metaplasia happened

NOTE Confidence: 0.92109934625

00:52:29.741 --> 00:52:32.327 and where what people thought about

NOTE Confidence: 0.84734664

00:52:32.398 --> 00:52:33.510 it 100 years ago.

NOTE Confidence: 0.84734664

00:52:33.510 --> 00:52:34.810 Well, over 100 years ago,

NOTE Confidence: 0.84734664

00:52:34.810 --> 00:52:36.694 George Adami was a famous pathologist

NOTE Confidence: 0.84734664

00:52:36.694 --> 00:52:39.076 who at the time was at McGill said,

NOTE Confidence: 0.84734664

00:52:39.076 --> 00:52:41.078 you know, it looks like in tissues

NOTE Confidence: 0.84734664

00:52:41.078 --> 00:52:43.227 that are going to become cancerous,

NOTE Confidence: 0.84734664

00:52:43.230 --> 00:52:45.030 there's all this reprogram,

NOTE Confidence: 0.84734664

00:52:45.030 --> 00:52:48.230 you didn't use that term of cells

NOTE Confidence: 0.84734664

00:52:48.230 --> 00:52:50.930 from mature cells to dividing cells,

NOTE Confidence: 0.84734664

00:52:50.930 --> 00:52:52.204 and that seems to fuel the cancer.

NOTE Confidence: 0.84734664

00:52:52.210 --> 00:52:54.106 So he kind of anticipated all of this.

NOTE Confidence: 0.84734664

00:52:54.110 --> 00:52:56.112 And he said that what must happen

NOTE Confidence: 0.84734664

00:52:56.112 --> 00:52:58.259 is the cell converts its energy

NOTE Confidence: 0.84734664

00:52:58.259 --> 00:53:00.289 use from secretion to division.

NOTE Confidence: 0.84734664

00:53:00.290 --> 00:53:01.606 So, you know, it's kind of funny.

NOTE Confidence: 0.84734664

00:53:01.610 --> 00:53:03.461 Then we forgot that for like 9000.

NOTE Confidence: 0.84734664

00:53:03.461 --> 00:53:03.672 Years.

NOTE Confidence: 0.84734664

00:53:03.672 --> 00:53:04.516 And then, you know,

NOTE Confidence: 0.84734664

00:53:04.520 --> 00:53:06.236 we've come back to that old

NOTE Confidence: 0.84734664

00:53:06.236 --> 00:53:07.708 pathologists who just by looking

NOTE Confidence: 0.84734664

00:53:07.708 --> 00:53:09.556 at a bunch of tissues made the

NOTE Confidence: 0.84734664

00:53:09.556 --> 00:53:11.314 same kind of analysis that it

NOTE Confidence: 0.84734664

00:53:11.314 --> 00:53:13.066 was the same in multiple tissues,

NOTE Confidence: 0.84734664

00:53:13.070 --> 00:53:13.506 you know,

NOTE Confidence: 0.84734664

00:53:13.506 --> 00:53:15.576 even as a picture of a liver cell with

NOTE Confidence: 0.84734664

00:53:15.576 --> 00:53:17.190 its kind of autophagy before they

NOTE Confidence: 0.84734664

00:53:17.190 --> 00:53:19.070 even knew what the organelles were.

NOTE Confidence: 0.84734664

00:53:19.070 --> 00:53:21.102 So a lot of that depends on ribosomes

NOTE Confidence: 0.84734664

00:53:21.102 --> 00:53:23.452 and and so the metaplasia depends on

NOTE Confidence: 0.84734664

00:53:23.452 --> 00:53:25.800 this collagenosis which depends on ribosome.

NOTE Confidence: 0.84734664

00:53:25.800 --> 00:53:28.047 So these are all areas where you

NOTE Confidence: 0.84734664

00:53:28.047 --> 00:53:29.922 could target potentially both to.

NOTE Confidence: 0.84734664

00:53:29.922 --> 00:53:30.834 First metaplasia,

NOTE Confidence: 0.84734664

00:53:30.834 --> 00:53:33.570 but also if cancers emerge from

NOTE Confidence: 0.84734664

00:53:33.656 --> 00:53:35.700 those this aberrant checking

NOTE Confidence: 0.84734664

00:53:35.700 --> 00:53:37.744 of pathogenesis or P53,

NOTE Confidence: 0.84734664

00:53:37.750 --> 00:53:39.140 then maybe with they proliferate

NOTE Confidence: 0.84734664

00:53:39.140 --> 00:53:40.252 by going through that.

NOTE Confidence: 0.74812823

00:53:48.360 --> 00:53:52.950 The city. Ohh, it's all the eye.

NOTE Confidence: 0.74812823

00:53:52.950 --> 00:53:55.267 And where we got some of the

NOTE Confidence: 0.74812823

00:53:55.267 --> 00:53:57.704 mice and this is our group down

NOTE Confidence: 0.74812823

00:53:57.704 --> 00:53:59.806 in Texas with my wife's lab,

NOTE Confidence: 0.74812823

00:53:59.806 --> 00:54:01.930 she's mysorekar and on the mills,

NOTE Confidence: 0.74812823

00:54:01.930 --> 00:54:04.210 so we're the M&M labs together, so.

NOTE Confidence: 0.87300657

00:54:10.950 --> 00:54:11.920 Yes, you know. And then.

NOTE Confidence: 0.852713134

00:54:14.080 --> 00:54:16.220 So, so I don't know,

NOTE Confidence: 0.852713134

00:54:16.220 --> 00:54:18.636 but I think there are papers already too.

NOTE Confidence: 0.852713134

00:54:18.640 --> 00:54:21.220 But I'm, I I bet you it's the same aisle 13,

NOTE Confidence: 0.852713134

00:54:21.220 --> 00:54:24.244 aisle 33 access which drives it

NOTE Confidence: 0.852713134

00:54:24.244 --> 00:54:26.777 seemingly in in Barretts and

NOTE Confidence: 0.852713134

00:54:26.777 --> 00:54:30.460 in pancreas and and in stomach.

NOTE Confidence: 0.852713134

00:54:30.460 --> 00:54:32.770 The, the very idea Polygenist

NOTE Confidence: 0.852713134

00:54:32.770 --> 00:54:34.156 is absolutely reversible.

NOTE Confidence: 0.852713134

00:54:34.160 --> 00:54:35.189 Yeah, 100% it's,

NOTE Confidence: 0.852713134

00:54:35.189 --> 00:54:38.070 it's a normal way to recruit stem cells,

NOTE Confidence: 0.852713134

00:54:38.070 --> 00:54:39.200 especially for organs that don't

NOTE Confidence: 0.852713134

00:54:39.200 --> 00:54:40.730 have stem cells like the pancreas.

NOTE Confidence: 0.852713134

00:54:40.730 --> 00:54:42.158 That's the only way the pancreas

NOTE Confidence: 0.852713134

00:54:42.158 --> 00:54:43.976 can kind of repair itself is by

NOTE Confidence: 0.852713134

00:54:43.976 --> 00:54:45.068 recruiting the acinar cells.

NOTE Confidence: 0.852713134

00:54:45.070 --> 00:54:46.988 And then normally they come right back.

NOTE Confidence: 0.852713134

00:54:46.990 --> 00:54:49.090 It's only when you know they acquire

NOTE Confidence: 0.852713134

00:54:49.090 --> 00:54:50.870 enough mutations that they don't read,

NOTE Confidence: 0.852713134

00:54:50.870 --> 00:54:51.822 differentiate and they think

NOTE Confidence: 0.852713134

00:54:51.822 --> 00:54:53.250 it's an idea to keep growing.

NOTE Confidence: 0.852713134

00:54:53.250 --> 00:54:55.308 You know, that it becomes irreversible.

NOTE Confidence: 0.852713134

00:54:55.310 --> 00:54:56.520 And that's why we think,

NOTE Confidence: 0.852713134

00:54:56.520 --> 00:54:57.656 you know, chronic inflammation,

NOTE Confidence: 0.852713134

00:54:57.656 --> 00:54:59.590 which is the first question you had,

NOTE Confidence: 0.852713134

00:54:59.590 --> 00:55:00.946 is so important.

NOTE Confidence: 0.852713134

00:55:00.946 --> 00:55:02.754 Because it keeps stimulating

NOTE Confidence: 0.852713134

00:55:02.754 --> 00:55:04.770 this collagenosis until of these

NOTE Confidence: 0.852713134

00:55:04.770 --> 00:55:05.950 kind of old cells.

NOTE Confidence: 0.852713134

00:55:05.950 --> 00:55:07.056 You know, if you think about it,

NOTE Confidence: 0.852713134

00:55:07.060 --> 00:55:08.782 they don't really do much error

NOTE Confidence: 0.852713134

00:55:08.782 --> 00:55:10.316 checking of their chromatin under

NOTE Confidence: 0.852713134

00:55:10.316 --> 00:55:11.309 normal circumstances because

NOTE Confidence: 0.852713134

00:55:11.309 --> 00:55:13.295 they're just making a handful of,

NOTE Confidence: 0.852713134

00:55:13.300 --> 00:55:13.820 you know,

NOTE Confidence: 0.852713134

00:55:13.820 --> 00:55:15.380 digestive enzymes over and over again.

NOTE Confidence: 0.852713134

00:55:15.380 --> 00:55:16.700 And most of their ribosomes

NOTE Confidence: 0.852713134

00:55:16.700 --> 00:55:18.020 are already taken care of,

NOTE Confidence: 0.852713134

00:55:18.020 --> 00:55:20.020 so they're most of their chromatin is inert.

NOTE Confidence: 0.852713134

00:55:20.020 --> 00:55:22.036 So then you ask them to rearrange everything,

NOTE Confidence: 0.852713134

00:55:22.040 --> 00:55:23.444 come back into cell cycle and

NOTE Confidence: 0.852713134

00:55:23.444 --> 00:55:25.279 expose a bunch of cell cycle genes,

NOTE Confidence: 0.852713134

00:55:25.280 --> 00:55:26.420 which is very dangerous.

NOTE Confidence: 0.852713134

00:55:26.420 --> 00:55:28.690 So they need this error checking and it

NOTE Confidence: 0.852713134

00:55:28.690 --> 00:55:30.475 just seems like we've evolved only one.

NOTE Confidence: 0.852713134

00:55:30.480 --> 00:55:32.195 Protein which is P53 to do all

NOTE Confidence: 0.852713134

00:55:32.195 --> 00:55:32.930 that error checking.

NOTE Confidence: 0.852713134

00:55:32.930 --> 00:55:36.017 So each time you go through that cycle of

NOTE Confidence: 0.852713134

00:55:36.017 --> 00:55:38.648 you're asking people to three to work.

NOTE Confidence: 0.852713134

00:55:38.650 --> 00:55:40.432 And the more you do it the more chances

NOTE Confidence: 0.852713134

00:55:40.432 --> 00:55:41.978 you're taking until you get a you

NOTE Confidence: 0.852713134

00:55:41.978 --> 00:55:43.449 know clone that doesn't have it work.

NOTE Confidence: 0.852713134

00:55:43.450 --> 00:55:45.538 And then you start having more

NOTE Confidence: 0.852713134

00:55:45.538 --> 00:55:46.930 errors in each replication.

NOTE Confidence: 0.852713134

00:55:46.930 --> 00:55:48.772 And then when that happens then

NOTE Confidence: 0.852713134

00:55:48.772 --> 00:55:50.578 eventually you'll get a make or

NOTE Confidence: 0.852713134

00:55:50.578 --> 00:55:52.377 a rass or you know something else

NOTE Confidence: 0.852713134

00:55:52.377 --> 00:55:54.430 that drives it outside the geotrack.

NOTE Confidence: 0.852713134

00:55:54.430 --> 00:55:54.701 Yeah.

NOTE Confidence: 0.852713134

00:55:54.701 --> 00:55:56.598 Actually you know I 41 is conserved

NOTE Confidence: 0.852713134

00:55:56.598 --> 00:55:58.248 all the way through plants.

NOTE Confidence: 0.852713134

00:55:58.250 --> 00:56:00.590 It's the the the the it's.

NOTE Confidence: 0.852713134

00:56:00.590 --> 00:56:01.202 Amazing protein.

NOTE Confidence: 0.852713134

00:56:01.202 --> 00:56:03.038 It goes right between the ribosomes.

NOTE Confidence: 0.852713134

00:56:03.040 --> 00:56:04.380 That's why it's so conserved.

NOTE Confidence: 0.852713134

00:56:04.380 --> 00:56:07.476 And it has 0 phenotype in any Organism,

NOTE Confidence: 0.852713134

00:56:07.480 --> 00:56:11.698 from plants to flies to yeast.

NOTE Confidence: 0.852713134

00:56:11.700 --> 00:56:13.135 Even if it's not in all yeast.

NOTE Confidence: 0.852713134

00:56:13.140 --> 00:56:15.384 Because I think it's more multicellular

NOTE Confidence: 0.852713134

00:56:15.384 --> 00:56:17.314 thing when you knock it out until

NOTE Confidence: 0.852713134

00:56:17.314 --> 00:56:19.612 you injure and ask them to kind of

NOTE Confidence: 0.852713134

00:56:19.612 --> 00:56:21.112 reprogram and respond to injury.

NOTE Confidence: 0.852713134

00:56:21.120 --> 00:56:22.912 So there's flying effort you want and

NOTE Confidence: 0.852713134

00:56:22.912 --> 00:56:24.971 if you knock it out then you can't

NOTE Confidence: 0.852713134

00:56:24.971 --> 00:56:26.669 recruit stem cells and the fly gut.

NOTE Confidence: 0.567696278571429

00:56:28.760 --> 00:56:30.940 Deliver after partial hepatectomy

NOTE Confidence: 0.567696278571429

00:56:30.940 --> 00:56:33.980 of you knockout I31 you screw up

NOTE Confidence: 0.567696278571429

00:56:33.980 --> 00:56:37.144 the ability to to get all that GI

NOTE Confidence: 0.567696278571429

00:56:37.144 --> 00:56:39.584 tract again and parasites kidney.

NOTE Confidence: 0.567696278571429

00:56:39.590 --> 00:56:41.590 That's a non GI Oregon also and in

NOTE Confidence: 0.567696278571429

00:56:41.590 --> 00:56:43.612 fact all this is tied to aging in

NOTE Confidence: 0.567696278571429

00:56:43.612 --> 00:56:45.380 the sense that as you get older

NOTE Confidence: 0.567696278571429

00:56:45.380 --> 00:56:47.088 you seem to be able to lose.

NOTE Confidence: 0.567696278571429

00:56:47.090 --> 00:56:48.446 You lose these markers in these

NOTE Confidence: 0.567696278571429

00:56:48.446 --> 00:56:50.167 genes and in in the bladder we

NOTE Confidence: 0.567696278571429

00:56:50.167 --> 00:56:51.697 know that actually where each time

NOTE Confidence: 0.567696278571429

00:56:51.697 --> 00:56:53.442 you go through UTI of shedding you

NOTE Confidence: 0.567696278571429

00:56:53.442 --> 00:56:55.280 need to recruit new stem cells.

NOTE Confidence: 0.567696278571429

00:56:55.280 --> 00:56:58.587 As you age you lose I 41 and

NOTE Confidence: 0.567696278571429

00:56:58.587 --> 00:57:00.129 you're less able to do this.

NOTE Confidence: 0.567696278571429

00:57:00.130 --> 00:57:02.994 That's work from the My wife side actually

NOTE Confidence: 0.567696278571429

00:57:02.994 --> 00:57:04.987 because she's a a bladder expert.

NOTE Confidence: 0.808378845625

00:57:14.930 --> 00:57:15.978 Yeah, right. So, yeah,

NOTE Confidence: 0.808378845625

00:57:15.978 --> 00:57:17.923 the question is why are some metaplasia

NOTE Confidence: 0.808378845625

00:57:17.923 --> 00:57:19.838 is dangerous and some not, right?

NOTE Confidence: 0.808378845625

00:57:19.838 --> 00:57:22.462 You know, I have no idea because that's

NOTE Confidence: 0.808378845625

00:57:22.462 --> 00:57:24.783 the same thing with stomach, right?

NOTE Confidence: 0.808378845625

00:57:24.783 --> 00:57:26.195 I mean, autoimmune gastritis

NOTE Confidence: 0.808378845625

00:57:26.195 --> 00:57:27.254 causes massive metaplasia.

NOTE Confidence: 0.808378845625

00:57:27.260 --> 00:57:29.549 And you know, there's a huge controversy

NOTE Confidence: 0.808378845625

00:57:29.549 --> 00:57:31.520 about whether it increases risk of

NOTE Confidence: 0.808378845625

00:57:31.520 --> 00:57:33.690 gastric cancer or not in the absence

NOTE Confidence: 0.808378845625

00:57:33.748 --> 00:57:35.470 of Co infection with H pylori.

NOTE Confidence: 0.808378845625

00:57:35.470 --> 00:57:36.890 And I think probably the

NOTE Confidence: 0.808378845625

00:57:36.890 --> 00:57:38.026 consensus is it doesn't.

NOTE Confidence: 0.808378845625

00:57:38.030 --> 00:57:40.352 So even the very same metaplasia

NOTE Confidence: 0.808378845625

00:57:40.352 --> 00:57:41.900 and H pylori context.

NOTE Confidence: 0.808378845625

00:57:41.900 --> 00:57:44.258 You know it's risky, but but it's not in

NOTE Confidence: 0.808378845625

00:57:44.258 --> 00:57:48.720 the autoimmune gastritis context, so.

NOTE Confidence: 0.808378845625

00:57:48.720 --> 00:57:51.936 I, I, I don't know, uh, I, you know,

NOTE Confidence: 0.808378845625

00:57:51.936 --> 00:57:54.209 I think 1 aspect would be the

NOTE Confidence: 0.808378845625

00:57:54.209 --> 00:57:56.559 repetitive nature and the chronicity.

NOTE Confidence: 0.808378845625

00:57:56.560 --> 00:57:58.324 Another aspect, you know,

NOTE Confidence: 0.808378845625

00:57:58.324 --> 00:57:59.647 in the stomach,

NOTE Confidence: 0.808378845625

00:57:59.650 --> 00:58:01.338 I've always thought of that H pylori is

NOTE Confidence: 0.808378845625

00:58:01.338 --> 00:58:03.240 also got oncogenes that it, you know,

NOTE Confidence: 0.808378845625

00:58:03.240 --> 00:58:04.840 pretty much injects into cells.

NOTE Confidence: 0.808378845625

00:58:04.840 --> 00:58:08.557 And also there's this sense of kind

NOTE Confidence: 0.808378845625

00:58:08.557 --> 00:58:11.764 of progression and that that that

NOTE Confidence: 0.808378845625

00:58:11.764 --> 00:58:13.605 that glands on the border between

NOTE Confidence: 0.808378845625

00:58:13.605 --> 00:58:15.644 the Antrim and the corpus going to go

NOTE Confidence: 0.808378845625

00:58:15.644 --> 00:58:17.233 through this more and more and more

NOTE Confidence: 0.808378845625

00:58:17.288 --> 00:58:19.096 as autoimmune gastritis, I think.

NOTE Confidence: 0.808378845625

00:58:19.096 --> 00:58:19.742 You know,

NOTE Confidence: 0.808378845625

00:58:19.742 --> 00:58:21.034 kind of happens sporadically,

NOTE Confidence: 0.808378845625

00:58:21.040 --> 00:58:21.670 hits an area,

NOTE Confidence: 0.808378845625

00:58:21.670 --> 00:58:23.658 then comes back and it's kind of back and

NOTE Confidence: 0.808378845625

00:58:23.658 --> 00:58:25.289 forth in different areas as opposed to

NOTE Confidence: 0.808378845625

00:58:25.289 --> 00:58:27.217 the same area going over and over again,

NOTE Confidence: 0.808378845625

00:58:27.220 --> 00:58:29.090 but.

NOTE Confidence: 0.808378845625

00:58:29.090 --> 00:58:30.308 I've never been asked that question.

NOTE Confidence: 0.808378845625

00:58:30.310 --> 00:58:31.626 It's a really good about the cervix,

NOTE Confidence: 0.808378845625

00:58:31.630 --> 00:58:33.898 you know like in areas where you

NOTE Confidence: 0.808378845625

00:58:33.898 --> 00:58:35.602 get metaplasia that don't that

NOTE Confidence: 0.808378845625

00:58:35.602 --> 00:58:37.010 may even be protective.

NOTE Confidence: 0.808378845625

00:58:37.010 --> 00:58:39.034 I mean you know in the stomach a

NOTE Confidence: 0.808378845625

00:58:39.034 --> 00:58:40.394 complete intestinal metaplasia seems

NOTE Confidence: 0.808378845625

00:58:40.394 --> 00:58:42.409 almost protective against gastric cancer.

NOTE Confidence: 0.808378845625

00:58:42.410 --> 00:58:45.690 So that's another interesting fact.

NOTE Confidence: 0.808378845625

00:58:45.690 --> 00:58:48.108 And and I think in autoimmune

NOTE Confidence: 0.808378845625

00:58:48.108 --> 00:58:49.720 gastritis there's more complete

NOTE Confidence: 0.808378845625

00:58:49.795 --> 00:58:51.447 than there is incomplete.

NOTE Confidence: 0.808378845625

00:58:51.450 --> 00:58:53.112 But I think it's definitely risky

NOTE Confidence: 0.808378845625

00:58:53.112 --> 00:58:55.128 to have the kind of metaplasia where

NOTE Confidence: 0.808378845625

00:58:55.128 --> 00:58:57.326 you have a mixed phenotype where it's

NOTE Confidence: 0.808378845625

00:58:57.326 --> 00:58:59.790 both gastric and intestinal and it keeps.

NOTE Confidence: 0.808378845625

00:58:59.790 --> 00:59:02.090 Happening it almost, you know,

NOTE Confidence: 0.808378845625

00:59:02.090 --> 00:59:03.410 is asking for trouble.

NOTE Confidence: 0.808378845625

00:59:03.410 --> 00:59:05.390 So maybe pure metaplasia are better.

NOTE Confidence: 0.808378845625

00:59:05.390 --> 00:59:06.446 I don't know.

NOTE Confidence: 0.808378845625

00:59:06.446 --> 00:59:07.854 It's a good question.

NOTE Confidence: 0.808378845625

00:59:07.860 --> 00:59:08.240 Haven't.

NOTE Confidence: 0.559212765

00:59:10.510 --> 00:59:11.160 Haven't asked.

NOTE Confidence: 0.70453817

00:59:13.220 --> 00:59:15.690 OK. Question on the.

NOTE Confidence: 0.25466174

00:59:18.090 --> 00:59:22.780 Building. And you describe.

NOTE Confidence: 0.25466174

00:59:22.780 --> 00:59:23.780 But when you look at.

NOTE Confidence: 0.56233963

00:59:26.390 --> 00:59:27.749 Or the before.

NOTE Confidence: 0.9236553

00:59:30.990 --> 00:59:33.800 Yeah, yeah. He.

NOTE Confidence: 0.56206702125

00:59:36.560 --> 00:59:40.172 Your life experiences that are known

NOTE Confidence: 0.56206702125

00:59:40.172 --> 00:59:42.680 to alters. So the question is, drew,

NOTE Confidence: 0.56206702125

00:59:42.680 --> 00:59:44.948 are there germline variants of genes

NOTE Confidence: 0.56206702125

00:59:44.948 --> 00:59:49.040 like D at 4 the AG is the autophagy

NOTE Confidence: 0.56206702125

00:59:49.040 --> 00:59:51.036 genes that affect susceptibility?

NOTE Confidence: 0.56206702125

00:59:51.040 --> 00:59:53.620 I. That's a good question.

NOTE Confidence: 0.56206702125

00:59:53.620 --> 00:59:54.890 I don't know did it.

NOTE Confidence: 0.56206702125

00:59:54.890 --> 00:59:56.725 Four is very controversial also

NOTE Confidence: 0.56206702125

00:59:56.725 --> 00:59:58.193 from the cancer standpoint,

NOTE Confidence: 0.56206702125

00:59:58.200 --> 00:59:59.994 it seems like half the literature

NOTE Confidence: 0.56206702125

00:59:59.994 --> 01:00:01.855 says that mutations are variants or

NOTE Confidence: 0.56206702125

01:00:01.855 --> 01:00:03.667 pro tumorigenic and half are anti.

NOTE Confidence: 0.56206702125

01:00:03.670 --> 01:00:05.930 But the issue with pathogenesis

NOTE Confidence: 0.56206702125

01:00:05.930 --> 01:00:08.618 and tumorigenesis is you know it's

NOTE Confidence: 0.56206702125

01:00:08.618 --> 01:00:10.880 a cycle normally so umm and it's

NOTE Confidence: 0.56206702125

01:00:10.880 --> 01:00:12.470 sort of aberration in the cycling

NOTE Confidence: 0.56206702125

01:00:12.470 --> 01:00:14.487 that we think is giving the tumors.

NOTE Confidence: 0.56206702125

01:00:14.490 --> 01:00:17.010 So just kind of completely knocking

NOTE Confidence: 0.56206702125

01:00:17.010 --> 01:00:19.140 it down might not would probably

NOTE Confidence: 0.56206702125

01:00:19.140 --> 01:00:20.490 give you a premature aging thing

NOTE Confidence: 0.56206702125

01:00:20.490 --> 01:00:22.008 if in fact that's what I said,

NOTE Confidence: 0.56206702125

01:00:22.010 --> 01:00:23.132 I pretty one has no phenotype

NOTE Confidence: 0.56206702125

01:00:23.132 --> 01:00:24.269 but actually it has an aging.

NOTE Confidence: 0.56206702125

01:00:24.270 --> 01:00:27.721 Genotype so as you age then and

NOTE Confidence: 0.56206702125

01:00:27.721 --> 01:00:30.449 you get inability to regenerate

NOTE Confidence: 0.56206702125

01:00:30.449 --> 01:00:33.360 the that tends to be where you

NOTE Confidence: 0.56206702125

01:00:33.360 --> 01:00:34.920 manifest your pathogenesis defects

NOTE Confidence: 0.56206702125

01:00:34.987 --> 01:00:37.062 because you probably wouldn't be

NOTE Confidence: 0.56206702125

01:00:37.062 --> 01:00:39.137 able to necessarily you've never

NOTE Confidence: 0.56206702125

01:00:39.209 --> 01:00:41.243 traced people that don't get tumors

NOTE Confidence: 0.56206702125

01:00:41.243 --> 01:00:43.497 based on you know lacking that but

NOTE Confidence: 0.56206702125

01:00:43.497 --> 01:00:45.590 obviously people do three is a key

NOTE Confidence: 0.56206702125

01:00:45.652 --> 01:00:47.948 checkpoint and that is the you know

NOTE Confidence: 0.56206702125

01:00:47.948 --> 01:00:49.759 incredibly tight the tumor genesis

NOTE Confidence: 0.56206702125

01:00:49.760 --> 01:00:52.520 the in terms I'll be a little bit

NOTE Confidence: 0.56206702125

01:00:52.520 --> 01:00:54.978 more specific though about autophagy.

NOTE Confidence: 0.56206702125

01:00:54.980 --> 01:00:58.326 Which is that we have tried with a

NOTE Confidence: 0.56206702125

01:00:58.326 --> 01:01:00.902 G57 and 1601 variant to show effects

NOTE Confidence: 0.56206702125

01:01:00.902 --> 01:01:03.789 and haven't really been successful.

NOTE Confidence: 0.56206702125

01:01:03.790 --> 01:01:05.698 Where we have genetically been able

NOTE Confidence: 0.56206702125

01:01:05.698 --> 01:01:06.970 to completely shut palingenesis

NOTE Confidence: 0.56206702125

01:01:07.020 --> 01:01:08.581 down both in the pancreas and the

NOTE Confidence: 0.56206702125

01:01:08.581 --> 01:01:10.250 stomach is by affecting lysosomes.

NOTE Confidence: 0.56206702125

01:01:10.250 --> 01:01:11.858 So if you want to really get dive

NOTE Confidence: 0.56206702125

01:01:11.858 --> 01:01:13.409 into the autophagy aspect of it,

NOTE Confidence: 0.56206702125

01:01:13.410 --> 01:01:14.370 we actually think it.

NOTE Confidence: 0.56206702125

01:01:14.370 --> 01:01:16.490 It's from the EPG 5 which is the

NOTE Confidence: 0.56206702125

01:01:16.490 --> 01:01:17.738 fusion of autophagosomes and

NOTE Confidence: 0.56206702125

01:01:17.738 --> 01:01:19.489 lysosome steps down there are the

NOTE Confidence: 0.56206702125

01:01:19.489 --> 01:01:21.064 most important and a lot of it

NOTE Confidence: 0.56206702125

01:01:21.064 --> 01:01:22.460 maybe non canonical autophagy.

NOTE Confidence: 0.56206702125

01:01:22.460 --> 01:01:25.190 So a knockout the the best knockout.

NOTE Confidence: 0.56206702125

01:01:25.190 --> 01:01:26.382 They had to stop.

NOTE Confidence: 0.56206702125

01:01:26.382 --> 01:01:28.766 The whole process is as in the

NOTE Confidence: 0.56206702125

01:01:28.766 --> 01:01:31.406 phosphorylation that phosphorylase that puts

NOTE Confidence: 0.56206702125

01:01:31.406 --> 01:01:34.200 phosphate phosphate groups on Mano six,

NOTE Confidence: 0.56206702125

01:01:34.200 --> 01:01:35.635 you know to make Manor 6 phosphate.

NOTE Confidence: 0.56206702125

01:01:35.640 --> 01:01:37.120 So none of the digestive,

NOTE Confidence: 0.56206702125

01:01:37.120 --> 01:01:39.360 the license only enzymes go to the lysosome.

NOTE Confidence: 0.56206702125

01:01:39.360 --> 01:01:40.785 Those mice are completely resistant

NOTE Confidence: 0.56206702125

01:01:40.785 --> 01:01:42.834 to you know which is not necessarily

NOTE Confidence: 0.56206702125

01:01:42.834 --> 01:01:44.544 a good thing because it means

NOTE Confidence: 0.56206702125

01:01:44.544 --> 01:01:46.084 they can't repair in the pancreas

NOTE Confidence: 0.56206702125

01:01:46.084 --> 01:01:47.891 is kind of if you keep forcing

NOTE Confidence: 0.56206702125

01:01:47.891 --> 01:01:50.046 pancreatitis or pancreas is turned

NOTE Confidence: 0.56206702125

01:01:50.046 --> 01:01:52.504 to snot basically because they can't

NOTE Confidence: 0.56206702125

01:01:52.504 --> 01:01:54.575 you know repair the damage so.

NOTE Confidence: 0.56206702125

01:01:54.575 --> 01:01:55.760 In our experience,

NOTE Confidence: 0.56206702125

01:01:55.760 --> 01:01:58.130 it's really lysosomes I you know,

NOTE Confidence: 0.56206702125

01:01:58.130 --> 01:01:59.294 it's massive autophagy.

NOTE Confidence: 0.56206702125

01:01:59.294 --> 01:02:00.070 Clearly LC3,

NOTE Confidence: 0.56206702125

01:02:00.070 --> 01:02:02.870 it's all the classic but the the main.

NOTE Confidence: 0.56206702125

01:02:02.870 --> 01:02:04.641 The thing seems to be required is

NOTE Confidence: 0.56206702125

01:02:04.641 --> 01:02:06.169 the flux through the lysosomes.

NOTE Confidence: 0.480954455

01:02:08.800 --> 01:02:09.470 Short question.

NOTE Confidence: 0.6431545

01:02:11.550 --> 01:02:11.850 Cheap.

NOTE Confidence: 0.823314832142857

01:02:17.630 --> 01:02:19.674 Yeah. So, so the question is whether

NOTE Confidence: 0.823314832142857

01:02:19.674 --> 01:02:21.568 parietal cells can do the same thing.

NOTE Confidence: 0.823314832142857

01:02:21.570 --> 01:02:23.793 And in fact, as part of the more general

NOTE Confidence: 0.823314832142857

01:02:23.793 --> 01:02:25.609 question of is it like universal and

NOTE Confidence: 0.823314832142857

01:02:25.609 --> 01:02:27.415 the parietal cells are great test case

NOTE Confidence: 0.823314832142857

01:02:27.415 --> 01:02:29.570 of the only cell that we've never seen

NOTE Confidence: 0.823314832142857

01:02:29.570 --> 01:02:32.090 couldn't do any kind of plasticity.

NOTE Confidence: 0.823314832142857

01:02:32.090 --> 01:02:33.674 And actually Juan Jay also did

NOTE Confidence: 0.823314832142857

01:02:33.674 --> 01:02:35.230 the that the experiment early on.

NOTE Confidence: 0.823314832142857

01:02:35.230 --> 01:02:37.374 So if he did when he was doing

NOTE Confidence: 0.823314832142857

01:02:37.374 --> 01:02:39.609 the the tamoxifen to be marked,

NOTE Confidence: 0.823314832142857

01:02:39.610 --> 01:02:41.418 all the parietal cells,

NOTE Confidence: 0.823314832142857

01:02:41.418 --> 01:02:45.179 they all died basically and they they didn't,

NOTE Confidence: 0.823314832142857

01:02:45.180 --> 01:02:47.916 they never seem to. D differentiate.

NOTE Confidence: 0.823314832142857

01:02:47.920 --> 01:02:49.397 Actually we have a pretty good idea

NOTE Confidence: 0.823314832142857

01:02:49.397 --> 01:02:51.362 because some of our work is just on

NOTE Confidence: 0.823314832142857

01:02:51.362 --> 01:02:52.390 the regular differentiation parietal

NOTE Confidence: 0.823314832142857

01:02:52.390 --> 01:02:54.208 cells and there seems to be a

NOTE Confidence: 0.823314832142857

01:02:54.208 --> 01:02:55.220 checkpoint and their differentiation,

NOTE Confidence: 0.823314832142857

01:02:55.220 --> 01:02:57.056 after which they are no longer

NOTE Confidence: 0.823314832142857

01:02:57.056 --> 01:02:59.188 plastic at all, but up to about

NOTE Confidence: 0.823314832142857

01:02:59.188 --> 01:03:00.698 halfway into becoming a parietal,

NOTE Confidence: 0.823314832142857

01:03:00.700 --> 01:03:03.040 so then they can take detours.

NOTE Confidence: 0.823314832142857

01:03:03.040 --> 01:03:04.660 And in fact,

NOTE Confidence: 0.823314832142857

01:03:04.660 --> 01:03:07.900 working with Shilpa Jane at Baylor,

NOTE Confidence: 0.823314832142857

01:03:07.900 --> 01:03:09.442 we've been collecting some of the

NOTE Confidence: 0.823314832142857

01:03:09.442 --> 01:03:10.803 interesting sort of parietal hyperplasia

NOTE Confidence: 0.823314832142857

01:03:10.803 --> 01:03:12.495 that happen in a neuroendocrine setting

NOTE Confidence: 0.823314832142857

01:03:12.495 --> 01:03:14.139 or an autoimmune gastritis setting,

NOTE Confidence: 0.823314832142857

01:03:14.140 --> 01:03:16.030 and you can definitely see some pretty

NOTE Confidence: 0.823314832142857

01:03:16.030 --> 01:03:17.660 odd using markers that we know of.

NOTE Confidence: 0.823314832142857

01:03:17.660 --> 01:03:19.495 Pre parietal cells some odd

NOTE Confidence: 0.823314832142857

01:03:19.495 --> 01:03:21.330 sort of parietal cell variance,

NOTE Confidence: 0.823314832142857

01:03:21.330 --> 01:03:23.010 but I don't think those are coming backwards.

NOTE Confidence: 0.823314832142857

01:03:23.010 --> 01:03:24.702 I think those are actually coming

NOTE Confidence: 0.823314832142857

01:03:24.702 --> 01:03:26.808 from the stem cell and then in

NOTE Confidence: 0.823314832142857

01:03:26.808 --> 01:03:28.333 the setting bottom you gastritis.

NOTE Confidence: 0.823314832142857

01:03:28.340 --> 01:03:30.224 They take a detour because they're

NOTE Confidence: 0.823314832142857

01:03:30.224 --> 01:03:32.295 going to be destroyed basically by

NOTE Confidence: 0.823314832142857

01:03:32.295 --> 01:03:34.180 the anti parietal cell antibodies.

NOTE Confidence: 0.823314832142857

01:03:34.180 --> 01:03:36.244 So yeah, not all cells can do it.

NOTE Confidence: 0.823314832142857

01:03:36.250 --> 01:03:39.538 Seems like protocells are quite resistant.

NOTE Confidence: 0.823314832142857

01:03:39.540 --> 01:03:40.368 A lot of questions.

NOTE Confidence: 0.8811298

01:03:45.310 --> 01:03:45.890 Yeah.

NOTE Confidence: 0.72511107

01:03:51.070 --> 01:03:53.520 He said great. It's great to like,

NOTE Confidence: 0.72511107

01:03:53.520 --> 01:03:56.340 you know, don't present that often,

NOTE Confidence: 0.72511107

01:03:56.340 --> 01:04:01.020 but before a bunch of pathologists, so.

NOTE Confidence: 0.72511107

01:04:01.020 --> 01:04:04.240 Yeah, is the neuroendocrine proliferation,

NOTE Confidence: 0.72511107

01:04:04.240 --> 01:04:05.997 you know those little tumors or little

NOTE Confidence: 0.72511107

01:04:05.997 --> 01:04:07.991 growths or you know that you get with

NOTE Confidence: 0.72511107

01:04:07.991 --> 01:04:09.610 chronic bridal cell loss or chronic,

NOTE Confidence: 0.72511107

01:04:09.610 --> 01:04:11.054 you know, PPI's and.

NOTE Confidence: 0.72511107

01:04:11.054 --> 01:04:13.308 You know, is are those metaplastic?

NOTE Confidence: 0.72511107

01:04:13.308 --> 01:04:15.034 They sure look funny, right?

NOTE Confidence: 0.72511107

01:04:15.034 --> 01:04:15.810 I mean, you know,

NOTE Confidence: 0.72511107

01:04:15.810 --> 01:04:18.612 they don't look like they're normal

NOTE Confidence: 0.72511107

01:04:18.612 --> 01:04:20.820 endocrine cells sitting lining up

NOTE Confidence: 0.72511107

01:04:20.820 --> 01:04:23.432 with the rest of the epithelium,

NOTE Confidence: 0.72511107

01:04:23.432 --> 01:04:25.001 because normally integrins

NOTE Confidence: 0.72511107

01:04:25.001 --> 01:04:27.750 cells are always surrounded by.

NOTE Confidence: 0.72511107

01:04:27.750 --> 01:04:28.990 Other non neuroendocrine epithelial

NOTE Confidence: 0.72511107

01:04:28.990 --> 01:04:31.191 cells and then you know in these

NOTE Confidence: 0.72511107

01:04:31.191 --> 01:04:32.646 lesions you get these little,

NOTE Confidence: 0.72511107

01:04:32.650 --> 01:04:36.049 you know, expansions.

NOTE Confidence: 0.72511107

01:04:36.050 --> 01:04:39.566 And I yeah great great question.

NOTE Confidence: 0.72511107

01:04:39.570 --> 01:04:41.481 How would they you know the the

NOTE Confidence: 0.72511107

01:04:41.481 --> 01:04:43.491 only the one thing that that might

NOTE Confidence: 0.72511107

01:04:43.491 --> 01:04:45.880 speak to that is one of the detours

NOTE Confidence: 0.72511107

01:04:45.880 --> 01:04:47.818 it seems like those riddles can

NOTE Confidence: 0.72511107

01:04:47.818 --> 01:04:49.695 make but I just said is towards

NOTE Confidence: 0.72511107

01:04:49.695 --> 01:04:50.920 more of an endocrine lineage.

NOTE Confidence: 0.72511107

01:04:50.920 --> 01:04:53.412 So you know maybe maybe that's why

NOTE Confidence: 0.72511107

01:04:53.412 --> 01:04:55.790 I never really thought about it.

NOTE Confidence: 0.72511107

01:04:55.790 --> 01:04:57.742 We had a mouse model where we drove

NOTE Confidence: 0.72511107

01:04:57.742 --> 01:04:59.730 large tea energen you know to drive

NOTE Confidence: 0.72511107

01:04:59.730 --> 01:05:01.712 proliferation and to to try to get

NOTE Confidence: 0.72511107

01:05:01.712 --> 01:05:03.420 a bunch of pre parietal cells but

NOTE Confidence: 0.72511107

01:05:03.420 --> 01:05:04.685 what happened with time this is

NOTE Confidence: 0.72511107

01:05:04.685 --> 01:05:06.340 when I was in Jeff Gordon's lab.

NOTE Confidence: 0.72511107

01:05:06.340 --> 01:05:08.884 What happened with time was they all

NOTE Confidence: 0.72511107

01:05:08.884 --> 01:05:10.858 turned into endocrine tumors in the stomach.

NOTE Confidence: 0.72511107

01:05:10.860 --> 01:05:12.610 So they actually went through.

NOTE Confidence: 0.72511107

01:05:12.610 --> 01:05:15.090 So it's like they hit a certain wall

NOTE Confidence: 0.72511107

01:05:15.090 --> 01:05:17.110 of parietal cell differentiation and

NOTE Confidence: 0.72511107

01:05:17.110 --> 01:05:19.780 then took a detour towards endocrine.

NOTE Confidence: 0.72511107

01:05:19.780 --> 01:05:21.360 Then it became endocrine proliferations,

NOTE Confidence: 0.72511107

01:05:21.360 --> 01:05:23.520 and then they became metastatic

NOTE Confidence: 0.72511107

01:05:23.520 --> 01:05:24.306 neuroendocrine tumors.

NOTE Confidence: 0.72511107

01:05:24.306 --> 01:05:25.878 So I don't know,

NOTE Confidence: 0.72511107

01:05:25.880 --> 01:05:27.800 maybe we just solved a mystery.

NOTE Confidence: 0.72511107

01:05:27.800 --> 01:05:29.928 Maybe it's because the reason why they

NOTE Confidence: 0.72511107

01:05:29.928 --> 01:05:32.456 happen so much is not just because of

NOTE Confidence: 0.72511107

01:05:32.456 --> 01:05:34.760 hypergastrinemia and the G cell stimulation,

NOTE Confidence: 0.72511107

01:05:34.760 --> 01:05:36.146 but also because.

NOTE Confidence: 0.72511107

01:05:36.146 --> 01:05:38.918 The pre parietal cells themselves can

NOTE Confidence: 0.72511107

01:05:38.918 --> 01:05:41.928 fuel endocrine cells in that setting.

NOTE Confidence: 0.72511107

01:05:41.930 --> 01:05:43.530 Yeah, and take a detour.

NOTE Confidence: 0.72511107

01:05:43.530 --> 01:05:46.032 They clearly can in the mouse we showed.

NOTE Confidence: 0.72511107

01:05:46.032 --> 01:05:46.796 That means it's hard,

NOTE Confidence: 0.72511107

01:05:46.800 --> 01:05:48.104 it's artificial because we're

NOTE Confidence: 0.72511107

01:05:48.104 --> 01:05:50.060 expressing large T but but still,

NOTE Confidence: 0.72511107

01:05:50.060 --> 01:05:51.716 they start off as pre parietal cells and

NOTE Confidence: 0.72511107

01:05:51.716 --> 01:05:53.410 then you could watch them even become,

NOTE Confidence: 0.72511107

01:05:53.410 --> 01:05:54.156 you know,

NOTE Confidence: 0.72511107

01:05:54.156 --> 01:05:56.767 through EM and and staining become endocrine.

NOTE Confidence: 0.72511107

01:05:56.770 --> 01:05:57.460 So yeah,

NOTE Confidence: 0.72511107

01:05:57.460 --> 01:05:57.805 maybe,

NOTE Confidence: 0.72511107

01:05:57.805 --> 01:05:59.530 maybe that's maybe your two

NOTE Confidence: 0.72511107

01:05:59.530 --> 01:06:00.710 questions are linked.

NOTE Confidence: 0.890194292

01:06:06.090 --> 01:06:07.360 All right. Thank you, everybody. Yeah.