WEBVTT

NOTE duration:"01:06:07.3600000"

NOTE recognizability:0.808

NOTE language:en-us

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.91910291111111

 $00:00:02.970 \longrightarrow 00:00:05.346$  our grand rounds today.

NOTE Confidence: 0.91910291111111

 $00{:}00{:}05{.}350 \dashrightarrow 00{:}00{:}08{.}941$  It is my honor and great pleasure

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.91910291111111

 $00{:}00{:}11.740 \dashrightarrow 00{:}00{:}14.953$  He is a Herman Brown endowed professor

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.91910291111111

 $00{:}00{:}17{.}400 \dashrightarrow 00{:}00{:}20{.}172$  Chief of Research in the section

NOTE Confidence: 0.91910291111111

 $00:00:20.172 \rightarrow 00:00:22.020$  of gastroenterology and Hepatology,

NOTE Confidence: 0.91910291111111

 $00:00:22.020 \rightarrow 00:00:24.515$  and the Co director of Digestive Disease

NOTE Confidence: 0.91910291111111

 $00{:}00{:}24.515 \dashrightarrow 00{:}00{:}27.500$  Center at the Texas Medical Center.

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.91910291111111

00:00:31.066 --> 00:00:33.460 Washington University in Saint Louis with NOTE Confidence: 0.91910291111111

 $00:00:33.460 \rightarrow 00:00:38.140$  double major in Russian and biology, right? NOTE Confidence: 0.91910291111111

 $00:00:38.140 \dashrightarrow 00:00:41.339$  Then he received the MD and PhD

NOTE Confidence: 0.91910291111111

 $00{:}00{:}41.340 \dashrightarrow 00{:}00{:}43.365$  from University of Pennsylvania and

NOTE Confidence: 0.91910291111111

 $00{:}00{:}43.365 \dashrightarrow 00{:}00{:}45.990$  went back to Washu for his anatomic

NOTE Confidence: 0.91910291111111

 $00:00:46.068 \rightarrow 00:00:49.990$  pathology residency and postdoctoral.

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 $00{:}00{:}49{.}990 \dashrightarrow 00{:}00{:}50{.}994$  Fellowship there.

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 $00{:}00{:}50{.}994 \dashrightarrow 00{:}00{:}54{.}508$  And he mentioned that he had a

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 $00:00:54.508 \rightarrow 00:00:56.921$  traumatizing experience with Doctor

NOTE Confidence: 0.91910291111111

 $00:00:56.921 \rightarrow 00:01:00.840$  Peter Humphrey as pathologist here at Yale.

NOTE Confidence: 0.91910291111111

 $00:01:00.840 \longrightarrow 00:01:03.000$  Now when they were, you know,

NOTE Confidence: 0.91910291111111

 $00:01:03.000 \rightarrow 00:01:05.499$  signing out a big stack of the

NOTE Confidence: 0.91910291111111

 $00:01:05.499 \dashrightarrow 00:01:07.618$  Hershey Springs case in the middle,

NOTE Confidence: 0.91910291111111

 $00:01:07.620 \longrightarrow 00:01:08.860$  they had a, you know,

NOTE Confidence: 0.91910291111111

 $00:01:08.860 \dashrightarrow 00:01:10.696$  frozen section and had to leave.

NOTE Confidence: 0.91910291111111

 $00:01:10.700 \rightarrow 00:01:12.988$  And then when they came back and they

NOTE Confidence: 0.91910291111111

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

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 $00:01:15.040 \rightarrow 00:01:17.497$  they have reviewed versus they have not.

 $00{:}01{:}17.500 \dashrightarrow 00{:}01{:}20.236$  So they had to go over again the.

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 $00:01:20.240 \longrightarrow 00:01:23.126$  Except that's the entire case again.

NOTE Confidence: 0.91910291111111

 $00:01:23.130 \longrightarrow 00:01:25.482$  So they will have a reunion

NOTE Confidence: 0.91910291111111

 $00:01:25.482 \longrightarrow 00:01:27.050$  in the afternoon today.

NOTE Confidence: 0.91910291111111

 $00:01:27.050 \rightarrow 00:01:30.336$  So you can have some conversation on that,

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.91910291111111

 $00:01:31.070 \longrightarrow 00:01:34.325$  And actually Jason was my PhD thesis

NOTE Confidence: 0.91910291111111

 $00{:}01{:}34{.}325 \dashrightarrow 00{:}01{:}36{.}920$  mentor at Washu and so I have known

NOTE Confidence: 0.91910291111111

 $00:01:36.920 \longrightarrow 00:01:39.962$  him for 18 years now and all my

NOTE Confidence: 0.91910291111111

 $00{:}01{:}39{.}962 \dashrightarrow 00{:}01{:}42{.}170$  interest in the GI research came

NOTE Confidence: 0.91910291111111

 $00{:}01{:}42.170 \dashrightarrow 00{:}01{:}46.408$  from him and he was a positive

NOTE Confidence: 0.91910291111111

 $00{:}01{:}46.410 \dashrightarrow 00{:}01{:}48.881$  influence for me to pursue my career

NOTE Confidence: 0.91910291111111

 $00{:}01{:}48.881 \dashrightarrow 00{:}01{:}50.960$  in pathology on the first day.

NOTE Confidence: 0.91910291111111

 $00{:}01{:}50{.}960 \dashrightarrow 00{:}01{:}53{.}350$  When I joined this laboratory,

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 $00{:}01{:}53{.}350 \dashrightarrow 00{:}01{:}55{.}870$  we sit down on the double headed

 $00:01:55.870 \rightarrow 00:01:58.352$  microscope and he went over mouse

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 $00{:}01{:}58.352 \dashrightarrow 00{:}02{:}00.552$  and human stomach Histology and

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 $00:02:00.552 \rightarrow 00:02:03.239$  encouraged me to become a pathologist.

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 $00:02:03.240 \dashrightarrow 00:02:06.768$  And at that time I was very negative

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 $00{:}02{:}06.770 \dashrightarrow 00{:}02{:}09.605$  because I never thought about becoming a

NOTE Confidence: 0.91910291111111

 $00{:}02{:}09{.}605 \dashrightarrow 00{:}02{:}12{.}328$  pathologist during my entire medical school.

NOTE Confidence: 0.91910291111111

 $00:02:12.330 \rightarrow 00:02:15.710$  But see now I'm a I became a pathologist.

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 $00{:}02{:}15.710 \dashrightarrow 00{:}02{:}17.850$  That's how influence influential

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 $00{:}02{:}17.850 \dashrightarrow 00{:}02{:}20.980$  he is and as pathologists.

NOTE Confidence: 0.91910291111111

 $00:02:20.980 \rightarrow 00:02:22.940$  And some researchers here,

NOTE Confidence: 0.91910291111111

 $00{:}02{:}22{.}940 \dashrightarrow 00{:}02{:}26{.}572$  we know well what metaplasia looks like,

NOTE Confidence: 0.91910291111111

 $00:02:26.572 \longrightarrow 00:02:28.148$  but we do not know.

NOTE Confidence: 0.91910291111111

 $00:02:28.148 \rightarrow 00:02:29.560$  Well, you know, how it happens.

NOTE Confidence: 0.91910291111111

 $00:02:29.560 \rightarrow 00:02:32.759$  What's the process mechanism on the line?

NOTE Confidence: 0.91910291111111

 $00:02:32.760 \longrightarrow 00:02:34.766$  So Doctor Miller says,

NOTE Confidence: 0.91910291111111

 $00:02:34.766 \longrightarrow 00:02:37.574$  focused on his research in the

 $00{:}02{:}37{.}574 \dashrightarrow 00{:}02{:}40{.}020$  cellular and molecular process

NOTE Confidence: 0.91910291111111

 $00:02:40.020 \rightarrow 00:02:42.048$  changes during the metaplasia.

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.91910291111111

 $00:02:44.080 \longrightarrow 00:02:45.024$  you know,

NOTE Confidence: 0.91910291111111

 $00{:}02{:}45{.}024 \dashrightarrow 00{:}02{:}48{.}593$  hundred papers on the metaplasia and in

NOTE Confidence: 0.91910291111111

 $00:02:48.593 \rightarrow 00:02:51.560$  addition to the seminal scientific works,

NOTE Confidence: 0.91910291111111

 $00:02:51.560 \longrightarrow 00:02:53.630$  he is very talented as he told

NOTE Confidence: 0.91910291111111

 $00:02:53.630 \longrightarrow 00:02:55.240$  you that he majored in Russian,

NOTE Confidence: 0.91910291111111

 $00:02:55.240 \longrightarrow 00:02:58.872$  he is very fluent in Russian and French

NOTE Confidence: 0.91910291111111

 $00:02:58.872 \rightarrow 00:03:01.770$  and also he can speak some Chinese

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.91910291111111

 $00{:}03{:}04{.}400 \dashrightarrow 00{:}03{:}08{.}978$  So with his talents in language,

NOTE Confidence: 0.91910291111111

 $00:03:08.980 \rightarrow 00:03:13.830$  he recently coined terminology collagenosis.

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 $00{:}03{:}13.830 \dashrightarrow 00{:}03{:}16.826$  Which describes a universal program

NOTE Confidence: 0.91910291111111

 $00:03:16.826 \rightarrow 00:03:20.510$  how mature cells reenter and change

 $00:03:20.604 \rightarrow 00:03:23.655$  their subcellular structure and

NOTE Confidence: 0.91910291111111

 $00:03:23.655 \dashrightarrow 00:03:28.005$  re-enter cell cycle and becoming a.

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.91910291111111

 $00:03:31.170 \rightarrow 00:03:32.830$  happens during the metaplasia,

NOTE Confidence: 0.91910291111111

 $00:03:32.830 \longrightarrow 00:03:36.225$  so he's on the title of his talk today

NOTE Confidence: 0.91910291111111

 $00{:}03{:}36{.}225 \dashrightarrow 00{:}03{:}38{.}835$  is the common features of metaplasia

NOTE Confidence: 0.91910291111111

 $00{:}03{:}38.835 \dashrightarrow 00{:}03{:}41.708$  and tumorigenesis in the GI track which

NOTE Confidence: 0.91910291111111

 $00:03:41.710 \longrightarrow 00:03:43.850$  implies the polygenesis basically.

NOTE Confidence: 0.91910291111111

 $00{:}03{:}43.850 \dashrightarrow 00{:}03{:}46.740$  So please join me in welcoming Dr.

NOTE Confidence: 0.91910291111111

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

NOTE Confidence: 0.35584447

 $00:03:50.230 \longrightarrow 00:03:50.510$  That's.

NOTE Confidence: 0.805820654166667

 $00:03:53.460 \longrightarrow 00:03:55.350$  Thanks. Thanks so much for the

NOTE Confidence: 0.805820654166667

 $00{:}03{:}55{.}350 \dashrightarrow 00{:}03{:}57{.}190$  invitation and thanks to Juan Jay.

NOTE Confidence: 0.805820654166667

 $00{:}03{:}57{.}190 \dashrightarrow 00{:}03{:}59{.}068$  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
- $00:04:02.690 \rightarrow 00:04:04.679$  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
- $00:04:06.576 \rightarrow 00:04:09.292$  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
- $00:04:11.712 \longrightarrow 00:04:13.119$  you up at the airport I think
- NOTE Confidence: 0.805820654166667
- $00{:}04{:}13.119 \dashrightarrow 00{:}04{:}15.310$  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
- $00:04:17.690 \longrightarrow 00:04:19.104$  Louis and then to have him come
- NOTE Confidence: 0.805820654166667
- $00:04:19.104 \longrightarrow 00:04:21.127$  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
- $00:04:22.537 \rightarrow 00:04:24.112$  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
- $00{:}04{:}26.262 \dashrightarrow 00{:}04{:}27.670$  assistant professor and Andre is
- NOTE Confidence: 0.805820654166667
- $00:04:27.670 \longrightarrow 00:04:29.390$  the first out of my group to to
- NOTE Confidence: 0.805820654166667
- $00:04:29.446 \longrightarrow 00:04:31.058$  become an assistant professor.
- NOTE Confidence: 0.805820654166667

 $00{:}04{:}31{.}060 \dashrightarrow 00{:}04{:}33{.}664$  So it's just you know it's fantastic

NOTE Confidence: 0.805820654166667

 $00{:}04{:}33{.}664 \dashrightarrow 00{:}04{:}36{.}094$  honor and fun to see see how

NOTE Confidence: 0.805820654166667

 $00:04:36.094 \dashrightarrow 00:04:37.576$  things are things grow and and

NOTE Confidence: 0.805820654166667

 $00{:}04{:}37.576 \dashrightarrow 00{:}04{:}39.200$  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

 $00:04:41.342 \longrightarrow 00:04:43.590$  want to I usually don't do a lot

NOTE Confidence: 0.805820654166667

 $00:04:43.590 \dashrightarrow 00:04:45.188$  of introduction for how I organize

NOTE Confidence: 0.805820654166667

 $00:04:45.188 \rightarrow 00:04:47.425$  the talk but because you know I am

NOTE Confidence: 0.805820654166667

 $00{:}04{:}47{.}425 \dashrightarrow 00{:}04{:}49{.}448$  a pathologist but also a cell and

NOTE Confidence: 0.805820654166667

 $00{:}04{:}49{.}448 \dashrightarrow 00{:}04{:}50{.}546$  developmental biologist my talk

NOTE Confidence: 0.805820654166667

 $00{:}04{:}50{.}546 \dashrightarrow 00{:}04{:}52{.}500$  kind of it will go back and forth.

NOTE Confidence: 0.805820654166667

 $00:04:52.500 \rightarrow 00:04:54.300$  The first part is all going to be sort

NOTE Confidence: 0.805820654166667

 $00:04:54.349 \dashrightarrow 00:04:55.966$  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

 $00:05:00.340 \rightarrow 00:05:02.560$  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
- $00:05:04.610 \longrightarrow 00:05:06.416$  don't give up there because it'll
- NOTE Confidence: 0.805820654166667
- $00:05:06.416 \dashrightarrow 00:05:07.923$  come back also to human pathology.
- NOTE Confidence: 0.805820654166667
- $00:05:07.923 \dashrightarrow 00:05:09.910$  So that's on the sort of that organization.
- NOTE Confidence: 0.805820654166667
- $00:05:09.910 \longrightarrow 00:05:11.954$  And then just as one day said,
- NOTE Confidence: 0.805820654166667
- $00:05:11.960 \longrightarrow 00:05:13.541$  as a resident,
- NOTE Confidence: 0.805820654166667
- $00:05:13.541 \dashrightarrow 00:05:16.176$  I became fascinated with metaplasia.
- NOTE Confidence: 0.805820654166667
- 00:05:16.180 --> 00:05:17.128 And, you know,
- NOTE Confidence: 0.805820654166667
- $00{:}05{:}17.128 \dashrightarrow 00{:}05{:}19.500$  how do these cells that are sort of
- NOTE Confidence: 0.805820654166667
- $00:05:19.500 \rightarrow 00:05:21.536$  normal cells show up in the wrong
- NOTE Confidence: 0.805820654166667
- $00:05:21.536 \dashrightarrow 00:05:23.198$  place and how does that happen
- NOTE Confidence: 0.805820654166667
- $00:05:23.198 \longrightarrow 00:05:24.810$  at a cell biological?
- NOTE Confidence: 0.805820654166667
- $00:05:24.810 \longrightarrow 00:05:25.593$  Point of view,
- NOTE Confidence: 0.805820654166667
- $00{:}05{:}25{.}593 \dashrightarrow 00{:}05{:}26{.}898$  so that's my clinical interest.
- NOTE Confidence: 0.805820654166667
- $00:05:26.900 \rightarrow 00:05:29.252$  So we we're always doing sort of
- NOTE Confidence: 0.805820654166667

 $00:05:29.252 \rightarrow 00:05:30.949$  translational work on that side,

NOTE Confidence: 0.805820654166667

 $00{:}05{:}30{.}950 \dashrightarrow 00{:}05{:}32{.}588$  but then on the research side,

NOTE Confidence: 0.805820654166667

 $00:05:32.590 \rightarrow 00:05:38.170$  my cell biologist always side says.

NOTE Confidence: 0.805820654166667

 $00:05:38.170 \rightarrow 00:05:40.249$  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

 $00:05:42.050 \longrightarrow 00:05:43.210$  So what are the mechanisms?

NOTE Confidence: 0.805820654166667

 $00:05:43.210 \dashrightarrow 00:05:44.449$  So that's what the talk is about.

NOTE Confidence: 0.805820654166667

 $00:05:44.450 \longrightarrow 00:05:47.060$  So yes the cell biological

NOTE Confidence: 0.805820654166667

 $00:05:47.060 \longrightarrow 00:05:48.964$  changes are the cell,

NOTE Confidence: 0.805820654166667

 $00:05:48.964 \rightarrow 00:05:50.672$  biological processes polygenesis and

NOTE Confidence: 0.805820654166667

 $00:05:50.672 \dashrightarrow 00:05:55.998$  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

 $00{:}05{:}58{.}470 \dashrightarrow 00{:}06{:}01{.}320$  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

 $00:06:04.283 \longrightarrow 00:06:05.429$  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
- $00:06:09.156 \longrightarrow 00:06:10.679$  as I said it's like the,
- NOTE Confidence: 0.859913548333333
- $00:06:10.680 \longrightarrow 00:06:12.402$  the clinical drive for this is
- NOTE Confidence: 0.859913548333333
- $00:06:12.402 \rightarrow 00:06:13.980$  how do these metaplasia happen,
- NOTE Confidence: 0.859913548333333
- $00:06:13.980 \dashrightarrow 00:06:15.500$  how do precancerous lesions arise
- NOTE Confidence: 0.859913548333333
- $00:06:15.500 \longrightarrow 00:06:17.620$  along the GI tract and how
- NOTE Confidence: 0.859913548333333
- $00:06:17.620 \longrightarrow 00:06:18.975$  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
- $00{:}06{:}22.172 \dashrightarrow 00{:}06{:}25.024$  funds our work and lately you know
- NOTE Confidence: 0.859913548333333
- $00:06:25.024 \rightarrow 00:06:28.084$  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
- $00:06:31.228 \dashrightarrow 00:06:33.436$  multiple organs I think you know
- NOTE Confidence: 0.859913548333333
- $00:06:33.436 \longrightarrow 00:06:34.981$  we're beginning to realize that
- NOTE Confidence: 0.859913548333333
- $00:06:34.981 \longrightarrow 00:06:36.815$  there's a lot more commonality
- NOTE Confidence: 0.859913548333333
- $00{:}06{:}36.815 \dashrightarrow 00{:}06{:}38.279$  in metaplasia across multiple.
- NOTE Confidence: 0.859913548333333

 $00:06:38.280 \longrightarrow 00:06:38.930$  The Oregon.

NOTE Confidence: 0.859913548333333

 $00:06:38.930 \longrightarrow 00:06:41.205$  So there might be commonality in in

NOTE Confidence: 0.859913548333333

 $00:06:41.205 \longrightarrow 00:06:43.013$  these precance rous 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

 $00:06:46.040 \dashrightarrow 00:06:50.720$  you know an AP resident to think it was.

NOTE Confidence: 0.859913548333333

 $00:06:50.720 \longrightarrow 00:06:51.686$  Sort of process.

NOTE Confidence: 0.859913548333333

 $00{:}06{:}51{.}686 \dashrightarrow 00{:}06{:}53{.}618$  Interest on metaplasia in the stomach

NOTE Confidence: 0.859913548333333

 $00:06:53.618 \dashrightarrow 00:06:55.470$  and and certainly has nothing to

NOTE Confidence: 0.859913548333333

 $00{:}06{:}55{.}470 \dashrightarrow 00{:}06{:}57{.}363$  do with how colon cancer starts

NOTE Confidence: 0.859913548333333

 $00:06:57.363 \rightarrow 00:06:59.168$  or how pancreatic cancer starts.

NOTE Confidence: 0.859913548333333

 $00{:}06{:}59{.}170 \dashrightarrow 00{:}07{:}01{.}159$  On the other hand it's kind of like you

NOTE Confidence: 0.859913548333333

 $00:07:01.159 \longrightarrow 00:07:02.968$  know it's kind of becoming clear that

NOTE Confidence: 0.859913548333333

 $00{:}07{:}02{.}968 \dashrightarrow 00{:}07{:}04{.}850$  that there's a lot of similarities.

NOTE Confidence: 0.859913548333333

 $00{:}07{:}04.850 \dashrightarrow 00{:}07{:}06.570$  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

 $00{:}07{:}08.190 \dashrightarrow 00{:}07{:}09.270$  Golden Ring at Vanderbilt,

- NOTE Confidence: 0.859913548333333
- $00:07:09.270 \longrightarrow 00:07:11.455$  we had this review recently
- NOTE Confidence: 0.859913548333333
- 00:07:11.455 --> 00:07:12.766 in gas<br/>troenterology talking
- NOTE Confidence: 0.859913548333333
- $00:07:12.766 \longrightarrow 00:07:14.910$  about some of these concepts.
- NOTE Confidence: 0.859913548333333
- $00:07:14.910 \longrightarrow 00:07:17.046$  In this one in particular we
- NOTE Confidence: 0.859913548333333
- $00{:}07{:}17.046 \dashrightarrow 00{:}07{:}18.470$  focused on the similarities
- NOTE Confidence: 0.859913548333333
- $00{:}07{:}18.537 \dashrightarrow 00{:}07{:}20.665$  between Barrett's metaplasia and
- NOTE Confidence: 0.859913548333333
- $00:07:20.665 \rightarrow 00:07:22.793$  gastric and intestinal metaplasia.
- NOTE Confidence: 0.859913548333333
- $00:07:22.800 \longrightarrow 00:07:23.696$  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
- $00:07:24.820 \longrightarrow 00:07:26.820$  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
- $00{:}07{:}29{.}284 \dashrightarrow 00{:}07{:}31{.}249$  get intestinal metaplasia in the
- NOTE Confidence: 0.859913548333333
- $00:07:31.249 \rightarrow 00:07:33.430$  stomach and that's because,
- NOTE Confidence: 0.859913548333333
- $00{:}07{:}33{.}430 \dashrightarrow 00{:}07{:}34{.}950$  you know, we know that.
- NOTE Confidence: 0.859913548333333
- $00{:}07{:}34{.}950 \dashrightarrow 00{:}07{:}37{.}560$  Had a thing of of reflux of acid and
- NOTE Confidence: 0.859913548333333

 $00:07:37.560 \rightarrow 00:07:40.748$  and probably also importantly bile as well.

NOTE Confidence: 0.859913548333333

 $00{:}07{:}40.750 \dashrightarrow 00{:}07{:}42.742$  And then that takes your squamous

NOTE Confidence: 0.859913548333333

 $00{:}07{:}42.742 \dashrightarrow 00{:}07{:}44.568$  epithelium right and turns it into

NOTE Confidence: 0.859913548333333

 $00:07:44.568 \rightarrow 00:07:46.950$  this what in Barretts is called,

NOTE Confidence: 0.859913548333333

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

NOTE Confidence: 0.859913548333333

 $00:07:47.926 \longrightarrow 00:07:51.342$  a columnar mucosa at least at first,

NOTE Confidence: 0.859913548333333

 $00:07:51.350 \longrightarrow 00:07:53.270$  which is basically organized

NOTE Confidence: 0.859913548333333

 $00:07:53.270 \longrightarrow 00:07:55.670$  a pyloric gastric unit is.

NOTE Confidence: 0.859913548333333

 $00{:}07{:}55{.}670 \dashrightarrow 00{:}07{:}56{.}975$  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

 $00:07:58.334 \dashrightarrow 00:07:59.850$  pyloric metaplasia from squamous,

NOTE Confidence: 0.859913548333333

 $00:07:59.850 \longrightarrow 00:08:01.450$  although nobody ever calls it

NOTE Confidence: 0.859913548333333

 $00:08:01.450 \longrightarrow 00:08:02.610$  that in the esophagus,

NOTE Confidence: 0.859913548333333

 $00:08:02.610 \longrightarrow 00:08:05.380$  I want to point out that to researchers.

NOTE Confidence: 0.859913548333333

 $00:08:05.380 \dashrightarrow 00:08:07.916$  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

 $00{:}08{:}10.092 \dashrightarrow 00{:}08{:}12.276$  that that what that means is that

NOTE Confidence: 0.859913548333333

 $00:08:12.276 \longrightarrow 00:08:15.296$  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

 $00:08:16.074 \longrightarrow 00:08:16.848$  expressing metaplasia.

NOTE Confidence: 0.859913548333333

 $00:08:16.848 \rightarrow 00:08:19.980$  And so that's a term that was coined in,

NOTE Confidence: 0.859913548333333

 $00:08:19.980 \rightarrow 00:08:22.758$  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

 $00{:}08{:}24.671 \dashrightarrow 00{:}08{:}26.589$  is trefoil factor 2 and that shows

NOTE Confidence: 0.859913548333333

 $00:08:26.589 \longrightarrow 00:08:28.885$  up only in these pyloric sort of

NOTE Confidence: 0.859913548333333

 $00:08:28.885 \rightarrow 00:08:30.698$  lesions in the body of the stomach.

NOTE Confidence: 0.859913548333333

 $00{:}08{:}30{.}700 \dashrightarrow 00{:}08{:}33{.}316$  So a lot of what we'll talk about

NOTE Confidence: 0.859913548333333

 $00{:}08{:}33{.}316 \dashrightarrow 00{:}08{:}35{.}500$  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

 $00{:}08{:}40.590 \dashrightarrow 00{:}08{:}42.270$  muck 6 positive lineage.

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

NOTE Confidence: 0.859913548333333

 $00:08:42.574 \longrightarrow 00:08:43.790$  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

 $00:08:45.323 \longrightarrow 00:08:45.980$  in the Antrim,

NOTE Confidence: 0.859913548333333

 $00{:}08{:}45{.}980 \dashrightarrow 00{:}08{:}47{.}564$  they want to expand their knee and they

NOTE Confidence: 0.859913548333333

 $00:08:47.564 \dashrightarrow 00:08:49.346$  want to go into the body of the stomach.

NOTE Confidence: 0.859913548333333

 $00:08:49.350 \rightarrow 00:08:51.390$  And it turns out that the way they do this,

NOTE Confidence: 0.859913548333333

 $00:08:51.390 \longrightarrow 00:08:54.034$  or we can model this with drugs.

NOTE Confidence: 0.859913548333333

 $00:08:54.034 \rightarrow 00:08:56.008$  And in fact Juan Jade pioneered this.

NOTE Confidence: 0.859913548333333

 $00{:}08{:}56{.}010 \dashrightarrow 00{:}08{:}57{.}599$  And there are hundreds of papers now

NOTE Confidence: 0.859913548333333

 $00{:}08{:}57{.}599 \dashrightarrow 00{:}08{:}59{.}309$  in the world using this technique,

NOTE Confidence: 0.8918497466666667

 $00{:}08{:}59{.}310 \dashrightarrow 00{:}09{:}03{.}078$  which is using high doses of tam oxifen can

NOTE Confidence: 0.8918497466666667

 $00:09:03.078 \rightarrow 00:09:05.819$  completely reprogram the stomach of a mouse.

NOTE Confidence: 0.8918497466666667

 $00:09:05.820 \longrightarrow 00:09:07.844$  The same way that H pylori can in

NOTE Confidence: 0.8918497466666667

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

NOTE Confidence: 0.8918497466666667

 $00:09:09.938 \rightarrow 00:09:12.273$  over a longer time course and what

- NOTE Confidence: 0.8918497466666667
- $00:09:12.273 \rightarrow 00:09:14.143$  happens during that reprogramming is
- NOTE Confidence: 0.8918497466666667
- $00:09:14.143 \rightarrow 00:09:16.641$  essentially what we talk about as
- NOTE Confidence: 0.8918497466666667
- 00:09:16.641 --> 00:09:18.926 pathologist as chronic atrophic gastritis,
- NOTE Confidence: 0.8918497466666667
- $00:09:18.930 \longrightarrow 00:09:21.198$  but is actually also a metaplasia
- NOTE Confidence: 0.8918497466666667
- 00:09:21.198 --> 00:09:23.964 because it turns the corpus units away
- NOTE Confidence: 0.8918497466666667
- $00:09:23.964 \rightarrow 00:09:26.708$  from being oxyntic units with gas with
- NOTE Confidence: 0.8918497466666667
- $00:09:26.785 \dashrightarrow 00:09:29.496$  the parietal cells and chief cells into
- NOTE Confidence: 0.8918497466666667
- 00:09:29.496 --> 00:09:31.126 basically a pyloric like structure
- NOTE Confidence: 0.8918497466666667
- $00:09:31.126 \dashrightarrow 00:09:33.969$  with MUC 5 AC positive foveolar cells,
- NOTE Confidence: 0.8918497466666667
- $00:09:33.970 \longrightarrow 00:09:35.446$  a lower ismal.
- NOTE Confidence: 0.8918497466666667
- $00:09:35.446 \rightarrow 00:09:37.906$  Proliferative center and again these
- NOTE Confidence: 0.8918497466666667
- $00:09:37.906 \longrightarrow 00:09:40.814$  deep antral like cells which are
- NOTE Confidence: 0.8918497466666667
- $00{:}09{:}40{.}814 \dashrightarrow 00{:}09{:}43{.}784$  characterized in the stomach as
- NOTE Confidence: 0.8918497466666667
- 00:09:43.784 --> 00:09:45.566 spasmolytic polypeptide expressing
- NOTE Confidence: 0.8918497466666667
- $00:09:45.566 \longrightarrow 00:09:46.463$  metaplasia. So.
- NOTE Confidence: 0.8918497466666667

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

NOTE Confidence: 0.8918497466666667

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

NOTE Confidence: 0.8918497466666667

 $00:09:49.256 \longrightarrow 00:09:51.720$  is to turn normal oxyntic glands into

NOTE Confidence: 0.8918497466666667

 $00:09:51.720 \rightarrow 00:09:53.929$  these pseudo pyloric metaplasia glands,

NOTE Confidence: 0.8918497466666667

 $00:09:53.930 \longrightarrow 00:09:55.256$  which is much more what they're

NOTE Confidence: 0.8918497466666667

 $00:09:55.256 \rightarrow 00:09:56.480$  accustomed to in the antrum,

NOTE Confidence: 0.8918497466666667

 $00:09:56.480 \longrightarrow 00:09:59.864$  and that's how they spread from the stomach.

NOTE Confidence: 0.8918497466666667

 $00:09:59.870 \longrightarrow 00:10:01.562$  So basically what that means is

NOTE Confidence: 0.8918497466666667

 $00{:}10{:}01{.}562 \dashrightarrow 00{:}10{:}03{.}833$  that that you know as we kind of

NOTE Confidence: 0.8918497466666667

 $00{:}10{:}03.833 \dashrightarrow 00{:}10{:}05.459$  learn more and more about Barretts

NOTE Confidence: 0.8918497466666667

 $00:10:05.515 \rightarrow 00:10:07.363$  and we do the single cell RNA seek

NOTE Confidence: 0.8918497466666667

 $00:10:07.363 \rightarrow 00:10:09.450$  and we do the genome studies and we

NOTE Confidence: 0.8918497466666667

 $00:10:09.450 \longrightarrow 00:10:11.729$  try to look at the clonal origin,

NOTE Confidence: 0.8918497466666667

 $00:10:11.730 \longrightarrow 00:10:13.690$  origin of the Barrett's lesions.

NOTE Confidence: 0.8918497466666667

 $00:10:13.690 \dashrightarrow 00:10:16.570$  And you know the best consensus

NOTE Confidence: 0.8918497466666667

 $00:10:16.570 \longrightarrow 00:10:19.649$  is that these kind of columnar

- NOTE Confidence: 0.8918497466666667
- $00:10:19.650 \longrightarrow 00:10:21.378$  lesions that look gastric are the
- NOTE Confidence: 0.8918497466666667
- $00:10:21.378 \longrightarrow 00:10:23.199$  first ones that appear in Barretts.
- NOTE Confidence: 0.8918497466666667
- $00{:}10{:}23.200 \dashrightarrow 00{:}10{:}25.958$  But even these can be traced back
- NOTE Confidence: 0.8918497466666667
- $00:10:25.958 \longrightarrow 00:10:27.970$  to roots in in oxyntic mucosa,
- NOTE Confidence: 0.8918497466666667
- $00:10:27.970 \longrightarrow 00:10:30.714$  in other words, if you do clonal.
- NOTE Confidence: 0.8918497466666667
- 00:10:30.714 --> 00:10:31.626 Genomic analysis,
- NOTE Confidence: 0.8918497466666667
- $00:10:31.630 \longrightarrow 00:10:34.303$  you see that these often can be found in
- NOTE Confidence: 0.8918497466666667
- 00:10:34.303 00:10:37.388 a patient near where they're you know,
- NOTE Confidence: 0.8918497466666667
- $00{:}10{:}37{.}388 \dashrightarrow 00{:}10{:}39{.}558$  most proximal eccentric glands are.
- NOTE Confidence: 0.8918497466666667
- $00:10:39.560 \longrightarrow 00:10:41.696$  So the idea then is that bile or
- NOTE Confidence: 0.8918497466666667
- $00{:}10{:}41.696 \dashrightarrow 00{:}10{:}43.999$  acid can turn these oxyntic glands
- NOTE Confidence: 0.8918497466666667
- $00{:}10{:}43.999 \dashrightarrow 00{:}10{:}45.695$  into these pyloric glands.
- NOTE Confidence: 0.8918497466666667
- $00{:}10{:}45{.}700 \dashrightarrow 00{:}10{:}47{.}806$  And then pretty clearly what happens
- NOTE Confidence: 0.8918497466666667
- $00{:}10{:}47.806 \dashrightarrow 00{:}10{:}50.280$  then is they become intestinal used.
- NOTE Confidence: 0.8918497466666667
- 00:10:50.280 --> 00:10:51.496 And why do I say it's pretty clear?
- NOTE Confidence: 0.8918497466666667

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

NOTE Confidence: 0.8918497466666667

 $00{:}10{:}53{.}908 \dashrightarrow 00{:}10{:}55{.}030$  specimens, especially if you have,

NOTE Confidence: 0.8918497466666667

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

NOTE Confidence: 0.8918497466666667

 $00:10:56.150 \longrightarrow 00:10:58.280$  they almost always have bases that

NOTE Confidence: 0.8918497466666667

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

NOTE Confidence: 0.8918497466666667

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

NOTE Confidence: 0.8918497466666667

 $00:11:02.580 \rightarrow 00:11:04.184$  you know spasmolytic polypeptide

NOTE Confidence: 0.8918497466666667

 $00:11:04.184 \rightarrow 00:11:06.189$  expressing metaplasia cells and it's

NOTE Confidence: 0.8918497466666667

00:11:06.189 $\operatorname{-->}$ 00:11:08.182 only the surface at least until you

NOTE Confidence: 0.8918497466666667

 $00:11:08.182 \longrightarrow 00:11:09.844$  get a high grade dysplasia that

NOTE Confidence: 0.8918497466666667

 $00{:}11{:}09{.}844 \dashrightarrow 00{:}11{:}11{.}602$  has a lot of intestinal lization

NOTE Confidence: 0.8918497466666667

 $00:11:11.602 \rightarrow 00:11:13.782$  and of course then the progression

NOTE Confidence: 0.8918497466666667

 $00{:}11{:}13.782 \dashrightarrow 00{:}11{:}16.170$  progression from here is into dysplasia.

NOTE Confidence: 0.8918497466666667

 $00:11:16.170 \rightarrow 00:11:19.586$  So our research really is into you know,

NOTE Confidence: 0.8918497466666667

 $00:11:19.590 \rightarrow 00:11:21.014$  how do you get from here to here,

NOTE Confidence: 0.8918497466666667

 $00:11:21.020 \longrightarrow 00:11:22.436$  how do you get from here to here

 $00:11:22.436 \longrightarrow 00:11:24.034$  and how do you get from here to

NOTE Confidence: 0.8918497466666667

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

NOTE Confidence: 0.8918497466666667

 $00:11:25.370 \longrightarrow 00:11:27.470$  you know then that gives you cancer.

NOTE Confidence: 0.8918497466666667

 $00:11:27.470 \longrightarrow 00:11:29.297$  One thing just as a take home

NOTE Confidence: 0.8918497466666667

 $00{:}11{:}29{.}297 \dashrightarrow 00{:}11{:}30{.}540$  is that we think.

NOTE Confidence: 0.8918497466666667

 $00:11:30.540 \longrightarrow 00:11:32.622$  Critical event in all of these

NOTE Confidence: 0.8918497466666667

 $00:11:32.622 \rightarrow 00:11:34.670$  transitions very early on is 53

NOTE Confidence: 0.8918497466666667

 $00:11:34.670 \rightarrow 00:11:36.749$  mutation and we're going to dig right

NOTE Confidence: 0.8918497466666667

 $00{:}11{:}36{.}749 \dashrightarrow 00{:}11{:}38{.}894$  into the cell biology as we we you

NOTE Confidence: 0.8918497466666667

 $00{:}11{:}38{.}894 \dashrightarrow 00{:}11{:}41{.}240$  know why we think that now clinically

NOTE Confidence: 0.8918497466666667

 $00{:}11{:}41{.}240 \dashrightarrow 00{:}11{:}43{.}215$  and Barretts and molecularly we're

NOTE Confidence: 0.8918497466666667

00:11:43.215 --> 00:11:45.274 finding that that basically as soon as NOTE Confidence: 0.8918497466666667

 $00:11:45.274 \rightarrow 00:11:47.398$  you have a loss of heterozygosity for NOTE Confidence: 0.8918497466666667

 $00:11:47.398 \rightarrow 00:11:49.715$  people 53 and and patients have NOTE Confidence: 0.695209716363636

 $00:11:49.720 \longrightarrow 00:11:52.576$  loss of function for PD3 then those

 $00:11:52.576 \rightarrow 00:11:54.700$  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

 $00{:}11{:}56{.}324 \dashrightarrow 00{:}11{:}58{.}760$  dysplastic and the rate of conversion

NOTE Confidence: 0.695209716363636

 $00:11:58.822 \rightarrow 00:12:02.440$  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

 $00:12:05.660 \longrightarrow 00:12:07.271$  the the lineage tracing and all

NOTE Confidence: 0.695209716363636

 $00{:}12{:}07{.}271 \dashrightarrow 00{:}12{:}08{.}807$  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

 $00:12:10.112 \longrightarrow 00:12:11.576$  that what we think happens is,

NOTE Confidence: 0.695209716363636

 $00:12:11.580 \longrightarrow 00:12:13.278$  you know, violent acid comes in,

NOTE Confidence: 0.695209716363636

 $00{:}12{:}13.280 \dashrightarrow 00{:}12{:}14.975$  Barretts and it.

NOTE Confidence: 0.695209716363636

 $00{:}12{:}14.975 \dashrightarrow 00{:}12{:}17.800$  Takes out the squamous epithelium

NOTE Confidence: 0.695209716363636

 $00{:}12{:}17.800 \dashrightarrow 00{:}12{:}21.709$  and then in the in the that sort

NOTE Confidence: 0.695209716363636

 $00:12:21.709 \longrightarrow 00:12:24.331$  of damaged bedding and in that

NOTE Confidence: 0.695209716363636

 $00:12:24.331 \rightarrow 00:12:26.466$  reflex setting you get migration

- NOTE Confidence: 0.695209716363636
- $00:12:26.466 \rightarrow 00:12:29.629$  of this kind of gastric epithelium.
- NOTE Confidence: 0.695209716363636
- $00:12:29.630 \longrightarrow 00:12:32.780$  And then the gastric epithelium
- NOTE Confidence: 0.695209716363636
- $00:12:32.780 \longrightarrow 00:12:34.040$  becomes intestinal is.
- 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
- $00{:}12{:}35{.}606 \dashrightarrow 00{:}12{:}36{.}930$  these examples from and a lot of
- NOTE Confidence: 0.695209716363636
- $00:12:36.930 \rightarrow 00:12:38.410$  the work that I was telling you,
- NOTE Confidence: 0.695209716363636
- $00:12:38.410 \longrightarrow 00:12:40.786$  the molecular work showing the origins
- NOTE Confidence: 0.695209716363636
- $00:12:40.786 \longrightarrow 00:12:43.420$  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
- $00{:}12{:}51.665 \dashrightarrow 00{:}12{:}54.378$  for a decade or two in in London.
- NOTE Confidence: 0.695209716363636
- $00{:}12{:}54{.}378 \dashrightarrow 00{:}12{:}57{.}366$  So you can see like these oxyntic
- NOTE Confidence: 0.695209716363636

 $00:12:57.366 \longrightarrow 00:12:58.896$  lesions in in sometimes distal

NOTE Confidence: 0.695209716363636

 $00{:}12{:}58.896 \dashrightarrow 00{:}13{:}00.945$  Barretts and then you can see this

NOTE Confidence: 0.695209716363636

 $00:13:00.945 \longrightarrow 00:13:02.475$  is just from their paper actually

NOTE Confidence: 0.695209716363636

 $00:13:02.475 \longrightarrow 00:13:04.169$  and you see these more pyloric.

NOTE Confidence: 0.695209716363636

00:13:04.170 $\operatorname{-->}$ 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

 $00{:}13{:}08{.}050 \dashrightarrow 00{:}13{:}10{.}010$  you see spam mucous cells at the

NOTE Confidence: 0.695209716363636

 $00{:}13{:}10.075 \dashrightarrow 00{:}13{:}12.247$  bottom as the tops become intestinal is

NOTE Confidence: 0.695209716363636

 $00{:}13{:}12{.}247 \dashrightarrow 00{:}13{:}15{.}930$  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

 $00{:}13{:}17{.}158 \dashrightarrow 00{:}13{:}19{.}000$  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

 $00:13:21.098 \rightarrow 00:13:24.290$  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

 $00:13:25.738 \rightarrow 00:13:27.316$  do this sort of thing then you go

NOTE Confidence: 0.695209716363636

 $00:13:27.316 \rightarrow 00:13:29.008$  back to the stomach and you think again,

- NOTE Confidence: 0.695209716363636
- $00:13:29.010 \rightarrow 00:13:31.392$  well do we really understand how
- NOTE Confidence: 0.695209716363636
- $00:13:31.392 \rightarrow 00:13:32.980$  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
- $00:13:35.248 \rightarrow 00:13:37.298$  digging into the different types
- NOTE Confidence: 0.695209716363636
- 00:13:37.298 --> 00:13:38.807 of stomach metaplasia.
- NOTE Confidence: 0.695209716363636
- $00{:}13{:}38{.}810 \dashrightarrow 00{:}13{:}40{.}637$  You know that from a research side
- NOTE Confidence: 0.695209716363636
- $00{:}13{:}40{.}637 \dashrightarrow 00{:}13{:}42{.}782$  and and actually in in Asia it's a
- NOTE Confidence: 0.695209716363636
- $00:13:42.782 \rightarrow 00:13:44.087$  diagnostic thing where you really
- NOTE Confidence: 0.695209716363636
- $00:13:44.145 \longrightarrow 00:13:45.529$  make a distinction between.
- NOTE Confidence: 0.695209716363636
- $00:13:45.530 \rightarrow 00:13:47.156$  Incomplete and test on that ablation,
- NOTE Confidence: 0.695209716363636
- $00:13:47.160 \dashrightarrow 00:13:49.070$  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
- $00{:}13{:}51{.}590 \dashrightarrow 00{:}13{:}53{.}417$  twos based on use and patterns.
- NOTE Confidence: 0.695209716363636
- $00:13:53.420 \longrightarrow 00:13:55.298$  But what does all that mean?
- NOTE Confidence: 0.695209716363636

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

NOTE Confidence: 0.695209716363636

 $00{:}13{:}55{.}529 \dashrightarrow 00{:}13{:}57{.}132$  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

 $00:13:59.120 \longrightarrow 00:14:00.901$  especially look at the borders of

NOTE Confidence: 0.695209716363636

 $00{:}14{:}00{.}901 \dashrightarrow 00{:}14{:}02{.}397$  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

 $00{:}14{:}04{.}472 \dashrightarrow 00{:}14{:}06{.}419$  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

 $00{:}14{:}08{.}100 \dashrightarrow 00{:}14{:}09{.}462$  spasmolytic polypeptide expressing NOTE Confidence: 0.695209716363636

 $00{:}14{:}09{.}462 \dashrightarrow 00{:}14{:}12{.}186$  metaplasia type deep pyloric cells at NOTE Confidence: 0.695209716363636

 $00{:}14{:}12{.}186 \dashrightarrow 00{:}14{:}14{.}226$  the bottom and then internalization

NOTE Confidence: 0.695209716363636

 $00:14:14.226 \longrightarrow 00:14:15.750$  of of goblet cells.

NOTE Confidence: 0.695209716363636

 $00{:}14{:}15{.}750 \dashrightarrow 00{:}14{:}17{.}773$  At the top and during COVID when

NOTE Confidence: 0.695209716363636

 $00{:}14{:}17{.}773 \dashrightarrow 00{:}14{:}20{.}219$  I had more time to kind of mess

NOTE Confidence: 0.695209716363636

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

NOTE Confidence: 0.695209716363636

 $00{:}14{:}22{.}391 \dashrightarrow 00{:}14{:}24{.}751$  stuff and I was trying to go back

 $00:14:24.760 \longrightarrow 00:14:27.329$  and and try to figure out where

NOTE Confidence: 0.695209716363636

 $00:14:27.329 \longrightarrow 00:14:29.710$  it was that everybody in the in

NOTE Confidence: 0.695209716363636

 $00{:}14{:}29{.}710 \dashrightarrow 00{:}14{:}31{.}310$  the stomach became obsessed with

NOTE Confidence: 0.695209716363636

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

NOTE Confidence: 0.695209716363636

 $00:14:32.240 \rightarrow 00:14:34.160$  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

 $00:14:35.490 \longrightarrow 00:14:36.865$  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

 $00{:}14{:}38{.}290 \dashrightarrow 00{:}14{:}39{.}490$  more pyloric metaplasia.

NOTE Confidence: 0.807014336521739

 $00:14:39.490 \longrightarrow 00:14:40.726$  Yet we never signed that out.

NOTE Confidence: 0.807014336521739

 $00:14:40.730 \longrightarrow 00:14:42.010$  We never diagnosed that.

NOTE Confidence: 0.807014336521739

 $00{:}14{:}42.010 \dashrightarrow 00{:}14{:}44.266$  I started going back in history and

NOTE Confidence: 0.807014336521739

 $00{:}14{:}44{.}266 \dashrightarrow 00{:}14{:}46{.}170$  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

 $00{:}14{:}48.395 \dashrightarrow 00{:}14{:}50.620$  metaplasia actually since like the

 $00:14:50.692 \rightarrow 00:14:53.239$  1890s and it was only in the sort of

NOTE Confidence: 0.807014336521739

 $00:14:53.239 \longrightarrow 00:14:56.221$  1960s or 70s that people became so

NOTE Confidence: 0.807014336521739

 $00{:}14{:}56{.}221 \dashrightarrow 00{:}14{:}57{.}973$  interested in intestinal medication.

NOTE Confidence: 0.807014336521739

 $00{:}14{:}57{.}980 \dashrightarrow 00{:}15{:}00{.}206$  It was about the time that endoscopic

NOTE Confidence: 0.807014336521739

 $00{:}15{:}00{.}206 \dashrightarrow 00{:}15{:}01{.}937$  biopsies came around and and

NOTE Confidence: 0.807014336521739

 $00:15:01.937 \rightarrow 00:15:03.737$  pathologists got only little snippets.

NOTE Confidence: 0.807014336521739

 $00{:}15{:}03.740 \dashrightarrow 00{:}15{:}05.658$  And you couldn't sort of tell the

NOTE Confidence: 0.807014336521739

 $00:15:05.658 \rightarrow 00:15:07.777$  orientation to tell whether there was basil,

NOTE Confidence: 0.807014336521739

 $00{:}15{:}07.780 \dashrightarrow 00{:}15{:}10.420$  you know, pyloric glands or not.

NOTE Confidence: 0.807014336521739

 $00:15:10.420 \longrightarrow 00:15:12.142$  But even, you know in the 1890s

NOTE Confidence: 0.807014336521739

 $00{:}15{:}12{.}142 \dashrightarrow 00{:}15{:}14{.}141$  they kind of had this concept that

NOTE Confidence: 0.807014336521739

00:15:14.141 $\operatorname{-->}$ 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

 $00:15:18.007 \longrightarrow 00:15:20.053$  at the bottom that these then might

NOTE Confidence: 0.807014336521739

 $00:15:20.053 \rightarrow 00:15:22.416$  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
- $00{:}15{:}23{.}920 \dashrightarrow 00{:}15{:}27{.}441$  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
- $00:15:29.838 \rightarrow 00:15:32.430$  of show this diagram with sort of
- NOTE Confidence: 0.807014336521739
- $00{:}15{:}32{.}430 \dashrightarrow 00{:}15{:}35{.}034$  spam metaplasia on the bottom and
- NOTE Confidence: 0.807014336521739
- $00:15:35.034 \rightarrow 00:15:36.989$  then internalization on the top.
- NOTE Confidence: 0.807014336521739
- $00:15:36.990 \rightarrow 00:15:38.300$  And then just you know,
- NOTE Confidence: 0.807014336521739
- $00{:}15{:}38{.}300 \dashrightarrow 00{:}15{:}40{.}370$  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
- $00:15:41.989 \longrightarrow 00:15:43.902$  desk that I look at all the time
- NOTE Confidence: 0.807014336521739
- $00:15:43.902 \rightarrow 00:15:45.514$  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
- $00:15:46.970 \longrightarrow 00:15:48.842$  You can actually see this pretty
- NOTE Confidence: 0.807014336521739
- $00:15:48.842 \rightarrow 00:15:50.888$  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
- $00:15:52.660 \rightarrow 00:15:54.765$  pyloric glands erupting into more
- NOTE Confidence: 0.807014336521739

 $00:15:54.765 \rightarrow 00:15:56.449$  superficial transitioning into this

NOTE Confidence: 0.807014336521739

 $00:15:56.449 \dashrightarrow 00:15:58.742$  kind of incomplete metaplasia.

NOTE Confidence: 0.807014336521739

 $00:15:58.742 \longrightarrow 00:16:02.486$  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

 $00:16:04.394 \longrightarrow 00:16:06.638$  cell or in a site where you can

NOTE Confidence: 0.807014336521739

 $00{:}16{:}06{.}638 \dashrightarrow 00{:}16{:}08{.}799$  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

 $00:16:12.905 \rightarrow 00:16:14.480$  pathology we only talk about panning,

NOTE Confidence: 0.807014336521739

 $00:16:14.480 \longrightarrow 00:16:16.314$  but in the mouse where we

NOTE Confidence: 0.807014336521739

 $00:16:16.314 \longrightarrow 00:16:18.349$  can sort of look at each step,

NOTE Confidence: 0.807014336521739

 $00{:}16{:}18.350 \dashrightarrow 00{:}16{:}21.115$  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

 $00{:}16{:}23{.}330 \dashrightarrow 00{:}16{:}26{.}084$  the acinar cells shrink and become

NOTE Confidence: 0.807014336521739

 $00{:}16{:}26.084 \dashrightarrow 00{:}16{:}28.530$  more cuboidal columnar cells and

NOTE Confidence: 0.807014336521739

 $00:16:28.530 \longrightarrow 00:16:29.598$  and proliferative.

- NOTE Confidence: 0.807014336521739
- $00{:}16{:}29{.}600 \dashrightarrow 00{:}16{:}31{.}622$  In an acute or chronic pancreatitis
- NOTE Confidence: 0.807014336521739
- $00:16:31.622 \longrightarrow 00:16:33.663$  setting and when you start to
- NOTE Confidence: 0.807014336521739
- $00:16:33.663 \rightarrow 00:16:35.541$  profile those cells by single cell
- NOTE Confidence: 0.807014336521739
- $00{:}16{:}35{.}541 \dashrightarrow 00{:}16{:}37{.}358$  RNA seek what's interesting and
- NOTE Confidence: 0.807014336521739
- $00{:}16{:}37{.}358 \dashrightarrow 00{:}16{:}39{.}608$  this was work done at Vanderbilt.
- NOTE Confidence: 0.807014336521739
- $00{:}16{:}39{.}610 \dashrightarrow 00{:}16{:}41{.}938$  With a from Kathy Delgiorno's group
- NOTE Confidence: 0.807014336521739
- $00{:}16{:}41.938 \dashrightarrow 00{:}16{:}44.619$  and and a number of collaborators
- NOTE Confidence: 0.807014336521739
- $00:16:44.619 \longrightarrow 00:16:46.188$  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
- $00:16:47.534 \rightarrow 00:16:50.580$  though on J while you were there, but.
- NOTE Confidence: 0.807014336521739
- $00:16:50.580 \rightarrow 00:16:53.788$  But what you see in these early pancreatic
- NOTE Confidence: 0.807014336521739
- $00:16:53.788 \rightarrow 00:16:57.098$  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
- $00{:}16{:}57{.}799 \dashrightarrow 00{:}16{:}59{.}197$  they're not organized into a gland,
- NOTE Confidence: 0.807014336521739
- $00{:}16{:}59{.}200 \dashrightarrow 00{:}17{:}00{.}726$  you know, they're all on these as inine.
- NOTE Confidence: 0.807014336521739

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

NOTE Confidence: 0.807014336521739

 $00{:}17{:}02{.}470 \dashrightarrow 00{:}17{:}03{.}860$  you see cells that look

NOTE Confidence: 0.807014336521739

 $00:17:03.860 \longrightarrow 00:17:04.972$  like fove olar pit cells.

NOTE Confidence: 0.807014336521739

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

NOTE Confidence: 0.807014336521739

 $00:17:07.902 \rightarrow 00:17:09.363$  these spasmolytic polypeptide

NOTE Confidence: 0.807014336521739

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

NOTE Confidence: 0.807014336521739

 $00:17:11.190 \longrightarrow 00:17:12.905$  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

 $00:17:14.323 \rightarrow 00:17:15.888$  to emerge as being universal.

NOTE Confidence: 0.807014336521739

 $00{:}17{:}15.890 \dashrightarrow 00{:}17{:}17.626$  So I'm not going to talk about this,

NOTE Confidence: 0.807014336521739

 $00:17:17.630 \longrightarrow 00:17:19.694$  but aisle 13,

NOTE Confidence: 0.807014336521739

 $00:17:19.694 \rightarrow 00:17:22.982$  aisle 33 shows up as mediating

NOTE Confidence: 0.807014336521739

 $00{:}17{:}22.982 \dashrightarrow 00{:}17{:}25.850$  these metaplasia as in the esophagus

NOTE Confidence: 0.807014336521739

 $00{:}17{:}25{.}932 \dashrightarrow 00{:}17{:}28{.}434$  and the stomach and even as we're

NOTE Confidence: 0.807014336521739

 $00:17:28.434 \rightarrow 00:17:30.268$  going to say now in the intestines.

NOTE Confidence: 0.842524026842105

 $00:17:30.270 \longrightarrow 00:17:32.286$  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
- $00:17:34.201 \longrightarrow 00:17:36.163$  in in from the pathology side.
- NOTE Confidence: 0.842524026842105
- $00:17:36.170 \longrightarrow 00:17:38.070$  Is that the right sided,
- NOTE Confidence: 0.842524026842105
- $00:17:38.070 \longrightarrow 00:17:40.274$  you know serrated sessile.
- NOTE Confidence: 0.842524026842105
- 00:17:40.274 --> 00:17:41.786 You know, polyps,
- NOTE Confidence: 0.842524026842105
- $00{:}17{:}41.786 \dashrightarrow 00{:}17{:}44.222$  we used to call them serrated
- NOTE Confidence: 0.842524026842105
- $00{:}17{:}44.222 \dashrightarrow 00{:}17{:}46.195$  sessile lesions also had this
- NOTE Confidence: 0.842524026842105
- $00:17:46.195 \longrightarrow 00:17:48.120$  same kind of basic format.
- NOTE Confidence: 0.842524026842105
- $00{:}17{:}48{.}120 \dashrightarrow 00{:}17{:}50{.}004$  So in this case you're taking
- NOTE Confidence: 0.842524026842105
- $00:17:50.004 \rightarrow 00:17:51.563$  things that were 100% intestinal
- NOTE Confidence: 0.842524026842105
- $00:17:51.563 \rightarrow 00:17:53.381$  and then now they're moving towards
- NOTE Confidence: 0.842524026842105
- $00{:}17{:}53{.}381 \dashrightarrow 00{:}17{:}55{.}302$  the gastric side and they wind up
- NOTE Confidence: 0.842524026842105
- $00{:}17{:}55{.}302 \dashrightarrow 00{:}17{:}57{.}083$  somewhere in the middle with this kind
- NOTE Confidence: 0.842524026842105
- $00{:}17{:}57{.}083 \dashrightarrow 00{:}17{:}58{.}503$  of pyloric morphology where again
- NOTE Confidence: 0.842524026842105
- $00:17:58.503 \dashrightarrow 00:18:00.080$  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

 $00{:}18{:}00{.}960 \dashrightarrow 00{:}18{:}03{.}576$  as I've been collecting these lesions

NOTE Confidence: 0.842524026842105

 $00:18:03.576 \longrightarrow 00:18:06.856$  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

 $00:18:09.040 \longrightarrow 00:18:10.816$  you again see you know and.

NOTE Confidence: 0.842524026842105

 $00:18:10.820 \rightarrow 00:18:13.004$  And it's been described before too by

NOTE Confidence: 0.842524026842105

 $00{:}18{:}13.004 \dashrightarrow 00{:}18{:}14.878$  others that there's muck 6 positive,

NOTE Confidence: 0.842524026842105

 $00:18:14.880 \rightarrow 00:18:16.794$  which is exactly the same expression

NOTE Confidence: 0.842524026842105

 $00:18:16.794 \longrightarrow 00:18:18.444$  pattern as spam cells that

NOTE Confidence: 0.842524026842105

 $00:18:18.444 \rightarrow 00:18:19.720$  emerge that are gastric,

NOTE Confidence: 0.842524026842105

 $00:18:19.720 \longrightarrow 00:18:20.538$  you know,

NOTE Confidence: 0.842524026842105

 $00{:}18{:}20{.}538 \dashrightarrow 00{:}18{:}22{.}583$  that are characteristic deep sort

NOTE Confidence: 0.842524026842105

 $00{:}18{:}22{.}583 \dashrightarrow 00{:}18{:}25{.}019$  of a cinar lesions within these SSL.

NOTE Confidence: 0.842524026842105

 $00{:}18{:}25{.}020 \dashrightarrow 00{:}18{:}27{.}204$  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

 $00:18:29.578 \longrightarrow 00:18:31.050$  goblet cell surface lesions.

 $00:18:31.050 \longrightarrow 00:18:34.886$  So at least on the right sided.

NOTE Confidence: 0.842524026842105

 $00:18:34.890 \longrightarrow 00:18:36.954$  SSL type of lesion there seems to be

NOTE Confidence: 0.842524026842105

 $00:18:36.954 \rightarrow 00:18:39.483$  the same kind of metaplasia but sort of

NOTE Confidence: 0.842524026842105

 $00:18:39.483 \rightarrow 00:18:41.769$  coming from intestine back towards gastric.

NOTE Confidence: 0.842524026842105

 $00{:}18{:}41.770 \dashrightarrow 00{:}18{:}43.300$  Now that polyps and tubular a denoma

NOTE Confidence: 0.842524026842105

 $00{:}18{:}43{.}300 \dashrightarrow 00{:}18{:}45{.}380$  seem to take a different course that's

NOTE Confidence: 0.842524026842105

 $00:18:45.380 \longrightarrow 00:18:47.396$  kind of more traditionally stem cell

NOTE Confidence: 0.842524026842105

 $00:18:47.396 \rightarrow 00:18:49.729$  based and doesn't fall within that category.

NOTE Confidence: 0.842524026842105

 $00{:}18{:}49{.}730 \dashrightarrow 00{:}18{:}53{.}010$  But still now we got four different organs

NOTE Confidence: 0.842524026842105

 $00:18:53.010 \rightarrow 00:18:55.419$  all converging towards this sort of,

NOTE Confidence: 0.842524026842105

 $00:18:55.420 \rightarrow 00:18:57.919$  you know pyloric like which is actually

NOTE Confidence: 0.842524026842105

 $00{:}18{:}57{.}919 \dashrightarrow 00{:}19{:}00{.}162$  probably maybe one of the primordial

NOTE Confidence: 0.842524026842105

 $00:19:00.162 \longrightarrow 00:19:02.376$  embryonic states of the stomach and

NOTE Confidence: 0.842524026842105

 $00{:}19{:}02{.}376 \dashrightarrow 00{:}19{:}04{.}812$  that's probably why and repair the stomach.

NOTE Confidence: 0.842524026842105

 $00{:}19{:}04.812 \dashrightarrow 00{:}19{:}06.558$  Kind of chooses to go back

 $00:19:06.558 \longrightarrow 00:19:08.070$  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

 $00:19:10.650 \rightarrow 00:19:13.379$  lesion that's mixed lineage where it's,

NOTE Confidence: 0.842524026842105

 $00:19:13.380 \longrightarrow 00:19:14.670$  you know, making both intestinal

NOTE Confidence: 0.842524026842105

 $00{:}19{:}14.670 \dashrightarrow 00{:}19{:}16.459$  and gastric cells at the same time,

NOTE Confidence: 0.842524026842105

 $00:19:16.460 \longrightarrow 00:19:18.294$  you could see at least you know,

NOTE Confidence: 0.842524026842105

 $00:19:18.300 \longrightarrow 00:19:21.002$  reason why that might be a risk

NOTE Confidence: 0.842524026842105

 $00:19:21.002 \longrightarrow 00:19:22.780$  for progressing to cancer.

NOTE Confidence: 0.842524026842105

 $00{:}19{:}22.780 \dashrightarrow 00{:}19{:}23.720$  And so part of that,

NOTE Confidence: 0.842524026842105

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

NOTE Confidence: 0.842524026842105

 $00{:}19{:}24{.}522 \dashrightarrow 00{:}19{:}26{.}857$  manifest itself when you do genome

NOTE Confidence: 0.842524026842105

 $00{:}19{:}26.857 \dashrightarrow 00{:}19{:}28.819$  sequencing and you look for mutations.

NOTE Confidence: 0.842524026842105

 $00:19:28.820 \longrightarrow 00:19:30.220$  And that's why this is kind of

NOTE Confidence: 0.842524026842105

 $00{:}19{:}30{.}220 \dashrightarrow 00{:}19{:}31{.}963$  some of the clinical data for why

NOTE Confidence: 0.842524026842105

 $00:19:31.963 \dashrightarrow 00:19:33.595$  people do 3 mutations so important,

NOTE Confidence: 0.842524026842105

 $00:19:33.600 \longrightarrow 00:19:34.110$  which is that,
00:19:34.110 --> 00:19:34.450 you know,

NOTE Confidence: 0.842524026842105

 $00:19:34.450 \longrightarrow 00:19:35.974$  in these Barretts glands as they

NOTE Confidence: 0.842524026842105

 $00:19:35.974 \longrightarrow 00:19:37.268$  start to progress and clones

NOTE Confidence: 0.842524026842105

 $00:19:37.268 \rightarrow 00:19:38.878$  emerge and they start to get the

NOTE Confidence: 0.842524026842105

 $00:19:38.878 \rightarrow 00:19:40.379$  ones that are mixed intestinal,

NOTE Confidence: 0.842524026842105

 $00{:}19{:}40{.}380 \dashrightarrow 00{:}19{:}42{.}396$  it seems like those are the ones that

NOTE Confidence: 0.842524026842105

 $00{:}19{:}42.396 \dashrightarrow 00{:}19{:}44.348$  are prone to developing P53 mutation.

NOTE Confidence: 0.842524026842105

 $00:19:44.348 \rightarrow 00:19:46.756$  It's those clones that then very rapidly,

NOTE Confidence: 0.842524026842105

 $00{:}19{:}46.760 \dashrightarrow 00{:}19{:}48.200$  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

 $00:19:50.190 \rightarrow 00:19:52.830$  they almost immediately go into dysplasia.

NOTE Confidence: 0.842524026842105

 $00{:}19{:}52{.}830 \dashrightarrow 00{:}19{:}56{.}148$  And and neoplasia and then and

NOTE Confidence: 0.842524026842105

 $00{:}19{:}56{.}148 \dashrightarrow 00{:}19{:}57{.}807$  metastatic and metastasis.

NOTE Confidence: 0.842524026842105

 $00{:}19{:}57{.}810 \dashrightarrow 00{:}19{:}58{.}177$  OK.

NOTE Confidence: 0.842524026842105

 $00{:}19{:}58{.}177 \dashrightarrow 00{:}20{:}01{.}480$  So that's the like if my talks at sandwich,

 $00{:}20{:}01{.}480 \dashrightarrow 00{:}20{:}02{.}914$  that's this is the path introduction

NOTE Confidence: 0.842524026842105

 $00{:}20{:}02{.}914 \dashrightarrow 00{:}20{:}04{.}574$  that we're going to delve into what

NOTE Confidence: 0.842524026842105

 $00:20:04.574 \longrightarrow 00:20:06.100$  we think some of the mechanisms are NOTE Confidence: 0.842524026842105

 $00{:}20{:}06{.}147 \dashrightarrow 00{:}20{:}07{.}673$  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

 $00{:}20{:}09{.}350 \dashrightarrow 00{:}20{:}11{.}194$  see some of the clinical trial work

NOTE Confidence: 0.842524026842105

 $00:20:11.194 \longrightarrow 00:20:13.226$  that we're doing to try to address it.

NOTE Confidence: 0.842524026842105

 $00:20:13.230 \longrightarrow 00:20:18.027$  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

 $00:20:19.470 \longrightarrow 00:20:21.222$  in these four different organs and

NOTE Confidence: 0.747923522

 $00{:}20{:}21{.}222 \dashrightarrow 00{:}20{:}23{.}573$  you know the knee jerk response that I

NOTE Confidence: 0.747923522

 $00{:}20{:}23{.}573 \dashrightarrow 00{:}20{:}25{.}831$  would have given you 15 years ago when NOTE Confidence: 0.747923522

 $00{:}20{:}25{.}831 \dashrightarrow 00{:}20{:}27{.}895$  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

 $00:20:31.046 \rightarrow 00:20:32.894$  lesions and that are proliferative

- NOTE Confidence: 0.747923522
- $00{:}20{:}32{.}894 \dashrightarrow 00{:}20{:}34{.}369$  and gives rise to cancer.

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

NOTE Confidence: 0.747923522

 $00:20:35.916 \longrightarrow 00:20:38.020$  the stem cells are kind of tricky and

NOTE Confidence: 0.747923522

 $00:20:38.084 \rightarrow 00:20:40.160$  in the pyloric versus oxyntic mucosa.

NOTE Confidence: 0.747923522

 $00{:}20{:}40.160 \dashrightarrow 00{:}20{:}41.840$  So the, the professional stem cells

NOTE Confidence: 0.747923522

 $00{:}20{:}41.840 \dashrightarrow 00{:}20{:}43.679$  and the oxyntic costs are way up

NOTE Confidence: 0.747923522

 $00{:}20{:}43.679 \dashrightarrow 00{:}20{:}45.005$  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

 $00:20:46.610 \longrightarrow 00:20:48.170$  change into this more pyloric.

NOTE Confidence: 0.747923522

 $00:20:48.170 \longrightarrow 00:20:50.480$  They're kind of down here.

NOTE Confidence: 0.747923522

 $00{:}20{:}50{.}480 \dashrightarrow 00{:}20{:}52{.}345$  So there's a change there

NOTE Confidence: 0.747923522

 $00{:}20{:}52{.}345 \dashrightarrow 00{:}20{:}53{.}968$  already work towards the base.

NOTE Confidence: 0.747923522

 $00:20:53.968 \rightarrow 00:20:56.060$  But then there's another thing that we,

NOTE Confidence: 0.747923522

 $00:20:56.060 \longrightarrow 00:20:56.440$  you know,

NOTE Confidence: 0.747923522

 $00{:}20{:}56{.}440 \dashrightarrow 00{:}20{:}57{.}580$  have to think about which is

 $00:20:57.580 \longrightarrow 00:20:58.837$  that say in the pancreas there

NOTE Confidence: 0.747923522

 $00{:}20{:}58.837 \dashrightarrow 00{:}21{:}00.079$  aren't any stem cells at all.

NOTE Confidence: 0.747923522

 $00{:}21{:}00{.}080 \dashrightarrow 00{:}21{:}01{.}710$  So where are those proliferative

NOTE Confidence: 0.747923522

 $00:21:01.710 \longrightarrow 00:21:02.688$  cells coming from?

NOTE Confidence: 0.747923522

 $00{:}21{:}02.690 \dashrightarrow 00{:}21{:}04.839$  And and there's been a long strain,

NOTE Confidence: 0.747923522

 $00{:}21{:}04{.}840 \dashrightarrow 00{:}21{:}06{.}778$  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

 $00{:}21{:}08.803 \dashrightarrow 00{:}21{:}11.148$  years of good mouse work with human

NOTE Confidence: 0.747923522

 $00{:}21{:}11{.}148 \dashrightarrow 00{:}21{:}13{.}836$  correlation showing that most of the NOTE Confidence: 0.747923522

10112 Communee. 0.111920022

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

 $00{:}21{:}17{.}184 \dashrightarrow 00{:}21{:}18{.}924$  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

 $00{:}21{:}20{.}130 \dashrightarrow 00{:}21{:}22{.}309$  all come from the acinar cells that

NOTE Confidence: 0.747923522

 $00{:}21{:}22{.}309 \dashrightarrow 00{:}21{:}23{.}929$  are doing their digestive enzyme

NOTE Confidence: 0.747923522

 $00:21:23.929 \rightarrow 00:21:25.225$  secretion that that reprogram.

- NOTE Confidence: 0.747923522
- 00:21:25.230 --> 00:21:25.454 Well,
- NOTE Confidence: 0.747923522
- $00:21:25.454 \longrightarrow 00:21:27.470$  it turns out we have a ton of evidence
- NOTE Confidence: 0.747923522
- $00:21:27.521 \rightarrow 00:21:28.996$  now that actually similar things
- NOTE Confidence: 0.747923522
- $00:21:28.996 \rightarrow 00:21:30.780$  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
- $00{:}21{:}32{.}964 \dashrightarrow 00{:}21{:}35{.}040$  this change from an oxyntic mucosa,
- NOTE Confidence: 0.747923522
- $00:21:35.040 \longrightarrow 00:21:36.905$  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
- $00:21:38.836 \longrightarrow 00:21:39.739$  is because the,
- NOTE Confidence: 0.747923522
- $00:21:39.740 \longrightarrow 00:21:41.707$  the fuel for these changes in in
- NOTE Confidence: 0.747923522
- $00:21:41.707 \longrightarrow 00:21:43.595$  these lesions is actually at the
- NOTE Confidence: 0.747923522
- $00{:}21{:}43.595 \dashrightarrow 00{:}21{:}45.230$  base and the differentiated cells
- NOTE Confidence: 0.747923522
- $00:21:45.230 \rightarrow 00:21:47.498$  just as it happens in the pancreas,
- NOTE Confidence: 0.747923522
- $00{:}21{:}47{.}500 \dashrightarrow 00{:}21{:}48{.}664$  in the acinar cells,
- NOTE Confidence: 0.747923522
- $00:21:48.664 \rightarrow 00:21:50.119$  it's in the digestive enzymes.
- NOTE Confidence: 0.747923522

 $00:21:50.120 \rightarrow 00:21:52.286$  Recruiting chief cells at the base.

NOTE Confidence: 0.747923522

 $00:21:52.290 \longrightarrow 00:21:54.924$  So that brings up this concept

NOTE Confidence: 0.747923522

 $00:21:54.924 \longrightarrow 00:21:57.829$  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

 $00{:}21{:}59.626 \dashrightarrow 00{:}22{:}01.871$  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

 $00:22:04.007 \rightarrow 00:22:06.425$  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

 $00:22:10.218 \rightarrow 00:22:12.119$  explore the idea of cell plasticity,

NOTE Confidence: 0.747923522

 $00:22:12.120 \longrightarrow 00:22:13.730$  which is where this fits.

NOTE Confidence: 0.747923522

 $00:22:13.730 \longrightarrow 00:22:15.122$  And you know this,

NOTE Confidence: 0.747923522

 $00{:}22{:}15{.}122 \dashrightarrow 00{:}22{:}17{.}582$  this concept has exploded in the last

NOTE Confidence: 0.747923522

 $00:22:17.582 \longrightarrow 00:22:20.228$  five to 10 years and we had the first,

NOTE Confidence: 0.747923522

 $00:22:20.230 \rightarrow 00:22:22.534$  I think the first ever meeting that I helped.

NOTE Confidence: 0.747923522

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

 $00:22:22.939 \rightarrow 00:22:26.530$  which is a keystone meeting in 2019 on it,

NOTE Confidence: 0.747923522

 $00:22:26.530 \longrightarrow 00:22:27.853$  but then there was a follow up

NOTE Confidence: 0.747923522

 $00:22:27.853 \longrightarrow 00:22:29.420$  and now there are a number of

NOTE Confidence: 0.747923522

 $00:22:29.420 \rightarrow 00:22:30.368$  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

 $00:22:32.060 \longrightarrow 00:22:34.020$  but just to kind of put us all in the

NOTE Confidence: 0.747923522

 $00:22:34.077 \rightarrow 00:22:35.802$  same cell and developmental biology

NOTE Confidence: 0.747923522

 $00:22:35.802 \rightarrow 00:22:38.270$  page when we're talking about this lesions,

NOTE Confidence: 0.747923522

 $00:22:38.270 \longrightarrow 00:22:39.955$  you know the canonical stem

NOTE Confidence: 0.747923522

 $00:22:39.955 \longrightarrow 00:22:42.000$  cell idea of how you get.

NOTE Confidence: 0.747923522

 $00:22:42.000 \longrightarrow 00:22:43.730$  Differentiation in a tissue is

NOTE Confidence: 0.747923522

 $00{:}22{:}43.730 \dashrightarrow 00{:}22{:}45.907$  that you have these stem cells

NOTE Confidence: 0.747923522

 $00:22:45.907 \longrightarrow 00:22:47.764$  that make faith choices, right.

NOTE Confidence: 0.747923522

 $00{:}22{:}47.764 \dashrightarrow 00{:}22{:}49.484$  And as they differentiate and

NOTE Confidence: 0.747923522

 $00{:}22{:}49{.}484 \dashrightarrow 00{:}22{:}50{.}860$  they're basically like marbles

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

 $00:22:53.786 \longrightarrow 00:22:55.850$  the person who came up with

NOTE Confidence: 0.825815031333333

 $00:22:55.918 \rightarrow 00:22:58.683$  this concept of a landscape of sort

NOTE Confidence: 0.825815031333333

 $00{:}22{:}58.683 \dashrightarrow 00{:}23{:}00.522$  of differentiation choices and then

NOTE Confidence: 0.825815031333333

 $00{:}23{:}00{.}522 \dashrightarrow 00{:}23{:}02{.}573$  the ball sort of slowly roll down

NOTE Confidence: 0.825815031333333

 $00:23:02.573 \rightarrow 00:23:04.214$  and then you get your chief cells and

NOTE Confidence: 0.825815031333333

00:23:04.214 $\operatorname{-->}$ 00:23:05.519 parietal cells and a cinar cells at the

NOTE Confidence: 0.825815031333333

 $00{:}23{:}05{.}519 \dashrightarrow 00{:}23{:}06{.}820$  base and then they just sit there.

NOTE Confidence: 0.825815031333333

 $00:23:06.820 \longrightarrow 00:23:08.514$  You know, the idea inherent to this NOTE Confidence: 0.825815031333333

 $00:23:08.514 \rightarrow 00:23:10.050$  concept is that it's a unidirectional

NOTE Confidence: 0.825815031333333

 $00:23:10.050 \longrightarrow 00:23:12.100$  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

 $00:23:13.840 \longrightarrow 00:23:14.760$  any kind of repair done,

NOTE Confidence: 0.825815031333333

 $00{:}23{:}14.760 \dashrightarrow 00{:}23{:}16.335$  then you need to take one of

NOTE Confidence: 0.825815031333333

 $00:23:16.335 \rightarrow 00:23:17.380$  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
- $00{:}23{:}19{.}306 \dashrightarrow 00{:}23{:}21{.}540$  case because now we all know that.
- NOTE Confidence: 0.825815031333333
- $00:23:21.540 \longrightarrow 00:23:23.164$  The balls can kind of go back up
- NOTE Confidence: 0.825815031333333
- $00:23:23.164 \rightarrow 00:23:24.662$  the hill and you can get just
- NOTE Confidence: 0.825815031333333
- $00:23:24.662 \rightarrow 00:23:26.200$  in the setting like I told you.
- NOTE Confidence: 0.825815031333333
- $00{:}23{:}26{.}200 \dashrightarrow 00{:}23{:}28{.}310$  If a cinar cells they can
- NOTE Confidence: 0.825815031333333
- $00:23:28.310 \longrightarrow 00:23:29.154$  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
- $00{:}23{:}30{.}960 \dashrightarrow 00{:}23{:}32{.}717$  over the grooves and being becoming
- NOTE Confidence: 0.825815031333333
- $00:23:32.717 \longrightarrow 00:23:34.744$  other cells like beta cells in the
- NOTE Confidence: 0.825815031333333
- $00:23:34.744 \rightarrow 00:23:36.370$  pancreatic islets can become alpha cells.
- NOTE Confidence: 0.825815031333333
- $00{:}23{:}36{.}370 \dashrightarrow 00{:}23{:}39{.}070$  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
- $00:23:42.748 \rightarrow 00:23:44.943$  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

 $00{:}23{:}47.013 \dashrightarrow 00{:}23{:}49.410$  in jury and inflammation standpoint.

NOTE Confidence: 0.825815031333333

 $00{:}23{:}49{.}410 \dashrightarrow 00{:}23{:}50{.}838$  You know it's quite possible that

NOTE Confidence: 0.825815031333333

 $00:23:50.838 \rightarrow 00:23:52.610$  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

 $00:23:53.890 \longrightarrow 00:23:55.472$  entire niches changing and all the NOTE Confidence: 0.825815031333333

 $00:23:55.472 \rightarrow 00:23:56.752$  groups are changing the identities

NOTE Confidence: 0.825815031333333

 $00{:}23{:}56{.}752 \dashrightarrow 00{:}23{:}58{.}781$  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

 $00:24:04.840 \longrightarrow 00:24:09.176$  these groups may not be so so clear.

NOTE Confidence: 0.825815031333333

 $00{:}24{:}09{.}180 \dashrightarrow 00{:}24{:}11.630$  So there's a lot of interest in

NOTE Confidence: 0.825815031333333

 $00{:}24{:}11.630 \dashrightarrow 00{:}24{:}14.346$  collagenosis and or in itself by in

NOTE Confidence: 0.825815031333333

 $00{:}24{:}14{.}346 \dashrightarrow 00{:}24{:}16{.}336$  plasticity and differentiation and in

NOTE Confidence: 0.825815031333333

 $00{:}24{:}16{.}336 \dashrightarrow 00{:}24{:}18{.}560$  fact that kind of got I was tickled

- NOTE Confidence: 0.825815031333333
- $00{:}24{:}18{.}560 \dashrightarrow 00{:}24{:}20{.}480$  to see that there was a last month
- NOTE Confidence: 0.825815031333333
- $00{:}24{:}20{.}480 \dashrightarrow 00{:}24{:}22{.}295$  the call for in scientific reports
- NOTE Confidence: 0.825815031333333
- $00:24:22.295 \longrightarrow 00:24:24.431$  for papers on on plasticity and
- NOTE Confidence: 0.825815031333333
- $00:24:24.431 \rightarrow 00:24:26.117$  specifically specifically pathogenesis.
- NOTE Confidence: 0.825815031333333
- $00{:}24{:}26{.}120 \dashrightarrow 00{:}24{:}26{.}502$  OK.
- NOTE Confidence: 0.825815031333333
- $00:24:26.502 \longrightarrow 00:24:29.558$  So the why do we have this term
- NOTE Confidence: 0.825815031333333
- $00:24:29.558 \rightarrow 00:24:31.933$  pathogenesis and the reason is because
- NOTE Confidence: 0.825815031333333
- $00{:}24{:}31{.}933 \dashrightarrow 00{:}24{:}34{.}723$  all of those balls are rolling around
- NOTE Confidence: 0.825815031333333
- $00{:}24{:}34{.}723 \dashrightarrow 00{:}24{:}37{.}907$  on the hill that I was showing
- NOTE Confidence: 0.825815031333333
- $00:24:37.910 \longrightarrow 00:24:39.494$  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
- $00{:}24{:}42.750 \dashrightarrow 00{:}24{:}45.830$  the idea that every cell has got its
- NOTE Confidence: 0.825815031333333
- $00{:}24{:}45{.}830 \dashrightarrow 00{:}24{:}47{.}982$  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
- $00{:}24{:}49{.}448 \dashrightarrow 00{:}24{:}50{.}822$  change identity and it matters if
- NOTE Confidence: 0.825815031333333

 $00:24:50.822 \rightarrow 00:24:51.943$  they become less differentiated

NOTE Confidence: 0.825815031333333

 $00:24:51.943 \longrightarrow 00:24:53.167$  than they're rolling up.

NOTE Confidence: 0.825815031333333

 $00:24:53.170 \longrightarrow 00:24:54.580$  And if they're trans differentiated,

NOTE Confidence: 0.825815031333333

 $00:24:54.580 \rightarrow 00:24:55.690$  they're, you know,

NOTE Confidence: 0.825815031333333

 $00:24:55.690 \longrightarrow 00:24:57.170$  becoming another cell type.

NOTE Confidence: 0.825815031333333

 $00{:}24{:}57{.}170 \dashrightarrow 00{:}24{:}59{.}096$  But what if we're actually interested

NOTE Confidence: 0.825815031333333

 $00:24:59.096 \rightarrow 00:25:01.660$  in the process of how you take a

NOTE Confidence: 0.825815031333333

 $00{:}25{:}01.660 \dashrightarrow 00{:}25{:}02.876$  differentiated cell and convert

NOTE Confidence: 0.825815031333333

 $00:25:02.876 \longrightarrow 00:25:04.769$  it to a proliferating cell?

NOTE Confidence: 0.825815031333333

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

NOTE Confidence: 0.825815031333333

 $00{:}25{:}05{.}406 \dashrightarrow 00{:}25{:}07{.}632$  that is not likely to be different

NOTE Confidence: 0.825815031333333

 $00{:}25{:}07.632 \dashrightarrow 00{:}25{:}09.874$  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

 $00:25:11.850 \rightarrow 00:25:13.656$  you have the apoptotic program and you

NOTE Confidence: 0.825815031333333

 $00:25:13.656 \rightarrow 00:25:15.199$  have apoptosis and that's the same.

NOTE Confidence: 0.825815031333333

 $00:25:15.200 \rightarrow 00:25:17.230$  And nobody thinks that apoptosis

 $00:25:17.230 \longrightarrow 00:25:19.680$  is different in every cell type.

NOTE Confidence: 0.825815031333333

 $00:25:19.680 \longrightarrow 00:25:21.820$  So this change in identity,

NOTE Confidence: 0.825815031333333

 $00:25:21.820 \longrightarrow 00:25:23.476$  these dedifferentiation events are

NOTE Confidence: 0.825815031333333

 $00:25:23.476 \rightarrow 00:25:26.380$  likely to be similar across tissue types.

NOTE Confidence: 0.825815031333333

 $00:25:26.380 \longrightarrow 00:25:29.212$  So there must be a cell biological process

NOTE Confidence: 0.825815031333333

 $00{:}25{:}29{.}212 \dashrightarrow 00{:}25{:}32{.}358$  or an osis that dictates these events.

NOTE Confidence: 0.825815031333333

 $00{:}25{:}32{.}360 \dashrightarrow 00{:}25{:}35{.}070$  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

 $00{:}25{:}37{.}527 \dashrightarrow 00{:}25{:}40{.}029$  of how these cells rearrange then.

NOTE Confidence: 0.909255652083333

 $00:25:40.030 \longrightarrow 00:25:40.885$  We should have a term

NOTE Confidence: 0.909255652083333

 $00:25:40.885 \longrightarrow 00:25:41.910$  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

 $00:25:45.290 \longrightarrow 00:25:49.820$  a site that goes back and forth.

NOTE Confidence: 0.909255652083333

 $00{:}25{:}49{.}820 \dashrightarrow 00{:}25{:}51{.}878$  Can be read both ways right.

 $00:25:51.880 \rightarrow 00:25:54.645$  And and I den is the general,

NOTE Confidence: 0.909255652083333

 $00{:}25{:}54.650 \dashrightarrow 00{:}25{:}55.634$  you know, generative.

NOTE Confidence: 0.909255652083333

 $00{:}25{:}55{.}634 \dashrightarrow 00{:}25{:}57{.}930$  So Palingenesis is the return to the

NOTE Confidence: 0.909255652083333

 $00:25:57.996 \rightarrow 00:25:59.694$  generative state, regenerative state.

NOTE Confidence: 0.909255652083333

 $00{:}25{:}59{.}694 \dashrightarrow 00{:}26{:}02{.}630$  So but when we're talking about this then

NOTE Confidence: 0.909255652083333

 $00:26:02.692 \rightarrow 00:26:04.978$  what we're talking about is basically.

NOTE Confidence: 0.909255652083333

 $00{:}26{:}04.980 \dashrightarrow 00{:}26{:}07.176$  How do you take these chief cells and make

NOTE Confidence: 0.909255652083333

 $00:26:07.176 \rightarrow 00:26:09.098$  these metaplastic proliferative cells?

NOTE Confidence: 0.909255652083333

 $00:26:09.100 \longrightarrow 00:26:11.002$  So these are very Long live

NOTE Confidence: 0.909255652083333

 $00:26:11.002 \rightarrow 00:26:12.400$  cells that don't proliferate.

NOTE Confidence: 0.909255652083333

 $00:26:12.400 \rightarrow 00:26:14.600$  How do they become proliferative?

NOTE Confidence: 0.909255652083333

 $00:26:14.600 \longrightarrow 00:26:17.694$  So the take home is that it?

NOTE Confidence: 0.909255652083333

 $00{:}26{:}17.700 \dashrightarrow 00{:}26{:}19.110$  It's a the.

NOTE Confidence: 0.909255652083333

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

NOTE Confidence: 0.909255652083333

 $00:26:19.580 \longrightarrow 00:26:21.930$  Like so biological change that

NOTE Confidence: 0.909255652083333

 $00:26:21.930 \longrightarrow 00:26:24.671$  has to happen here is a change

- NOTE Confidence: 0.909255652083333
- $00:26:24.671 \rightarrow 00:26:27.730$  in the way the cell uses energy.
- NOTE Confidence: 0.909255652083333
- $00:26:27.730 \longrightarrow 00:26:30.264$  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
- $00:26:31.890 \longrightarrow 00:26:33.846$  then it uses energy to produce
- NOTE Confidence: 0.909255652083333
- $00{:}26{:}33.846 \dashrightarrow 00{:}26{:}35.150$  digestive enzymes and secrete.
- NOTE Confidence: 0.909255652083333
- $00{:}26{:}35{.}150 \dashrightarrow 00{:}26{:}37{.}142$  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
- $00:26:38.710 \longrightarrow 00:26:41.308$  then it uses energy to divide.
- NOTE Confidence: 0.909255652083333
- $00:26:41.310 \longrightarrow 00:26:43.008$  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
- $00:26:45.602 \rightarrow 00:26:48.310$  cell adapts itself to go from
- NOTE Confidence: 0.909255652083333
- $00:26:48.310 \longrightarrow 00:26:50.102$  a digestive enzyme secreting
- NOTE Confidence: 0.909255652083333
- $00:26:50.102 \rightarrow 00:26:53.100$  energetic cell to a proliferating.
- NOTE Confidence: 0.909255652083333
- $00{:}26{:}53.100 \dashrightarrow 00{:}26{:}56.856$  Non energetic but but non secretory.
- NOTE Confidence: 0.909255652083333
- $00{:}26{:}56{.}860 \dashrightarrow 00{:}26{:}59{.}247$  So and basically this is the basic
- NOTE Confidence: 0.909255652083333

 $00:26:59.247 \rightarrow 00:27:01.818$  scheme which seems to be conserved across,

NOTE Confidence: 0.909255652083333

 $00{:}27{:}01.820 \dashrightarrow 00{:}27{:}04.676$  you know, from fly guts to, you know,

NOTE Confidence: 0.909255652083333

 $00:27:04.676 \longrightarrow 00:27:06.416$  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

 $00{:}27{:}08.065 \dashrightarrow 00{:}27{:}09.381$  differentiated cells back into

NOTE Confidence: 0.909255652083333

 $00:27:09.381 \longrightarrow 00:27:11.650$  the cell cycle and that is that

NOTE Confidence: 0.909255652083333

 $00{:}27{:}11.650 \dashrightarrow 00{:}27{:}13.291$  there's a massive up regulation of

NOTE Confidence: 0.909255652083333

 $00:27:13.291 \rightarrow 00:27:15.265$  autophagy and lysosome as the cell

NOTE Confidence: 0.909255652083333

 $00{:}27{:}15{.}265 \dashrightarrow 00{:}27{:}16{.}694$  reprograms its internal organs.

NOTE Confidence: 0.909255652083333

 $00:27:16.694 \rightarrow 00:27:19.298$  Followed by a second stage where

NOTE Confidence: 0.909255652083333

 $00{:}27{:}19{.}298 \dashrightarrow 00{:}27{:}22{.}138$  the genes that we recognize it

NOTE Confidence: 0.909255652083333

 $00{:}27{:}22.138 \dashrightarrow 00{:}27{:}23.596$  as being metaplastic.

NOTE Confidence: 0.909255652083333

 $00{:}27{:}23.600 \dashrightarrow 00{:}27{:}25.679$  And those are a lot of different

NOTE Confidence: 0.909255652083333

 $00:27:25.679 \longrightarrow 00:27:27.336$  genes like trefoil factor or

NOTE Confidence: 0.909255652083333

 $00{:}27{:}27{.}336 \dashrightarrow 00{:}27{:}28{.}736$  spasmolytic polypeptide or some

NOTE Confidence: 0.909255652083333

 $00:27:28.736 \longrightarrow 00:27:30.840$  of the socks genes like Sox 9.

- NOTE Confidence: 0.909255652083333
- $00:27:30.840 \rightarrow 00:27:33.378$  Followed by this very important one,
- NOTE Confidence: 0.909255652083333
- $00:27:33.380 \longrightarrow 00:27:35.095$  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
- $00:27:36.135 \rightarrow 00:27:37.659$  enter the cell cycle or not.
- NOTE Confidence: 0.909255652083333
- $00:27:37.660 \rightarrow 00:27:39.788$  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
- $00:27:41.288 \rightarrow 00:27:43.106$  long lived cells and you're bringing
- NOTE Confidence: 0.909255652083333
- $00:27:43.106 \longrightarrow 00:27:44.768$  them back into the cell cycle.
- NOTE Confidence: 0.909255652083333
- $00:27:44.770 \longrightarrow 00:27:46.569$  And so this is a checkpoint that
- NOTE Confidence: 0.909255652083333
- $00:27:46.569 \rightarrow 00:27:48.389$  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
- $00:27:50.094 \longrightarrow 00:27:50.920$  an ultrastructural footing,
- NOTE Confidence: 0.909255652083333
- $00{:}27{:}50{.}920 \dashrightarrow 00{:}27{:}53{.}104$  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
- $00{:}27{:}54.759 \dashrightarrow 00{:}27{:}56.424$  digestive enzyme secreting chief cell
- NOTE Confidence: 0.909255652083333

 $00:27:56.424 \rightarrow 00:27:58.450$  with layer after layer of rough ER,

NOTE Confidence: 0.909255652083333

 $00:27:58.450 \rightarrow 00:28:00.860$  all these secretory granules becoming

NOTE Confidence: 0.909255652083333

 $00{:}28{:}00{.}860 \dashrightarrow 00{:}28{:}02{.}788$  this much smaller proliferative

NOTE Confidence: 0.909255652083333

 $00:28:02.788 \longrightarrow 00:28:03.990$  stem like cell.

NOTE Confidence: 0.909255652083333

 $00{:}28{:}03{.}990 \dashrightarrow 00{:}28{:}06{.}302$  And this can happen in the mouse and

NOTE Confidence: 0.909255652083333

 $00:28:06.302 \rightarrow 00:28:09.940$  you know about 42 hours basically.

NOTE Confidence: 0.909255652083333

 $00:28:09.940 \longrightarrow 00:28:11.613$  So the kinds of things that are

NOTE Confidence: 0.909255652083333

 $00:28:11.613 \rightarrow 00:28:13.132$  going to happen and we're going

NOTE Confidence: 0.909255652083333

 $00{:}28{:}13.132 \dashrightarrow 00{:}28{:}14.875$  to talk about are modeled in this

NOTE Confidence: 0.909255652083333

 $00{:}28{:}14.880 \dashrightarrow 00{:}28{:}17.750$  little video that Jeff Brown is a

NOTE Confidence: 0.909255652083333

 $00{:}28{:}17.750 \dashrightarrow 00{:}28{:}18.980$  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

 $00{:}28{:}24.152 \dashrightarrow 00{:}28{:}26.616$  into autophagosomes and then starts

NOTE Confidence: 0.909255652083333

 $00:28:26.616 \rightarrow 00:28:28.911$  to digest all the secretory

00:28:28.911 --> 00:28:31.794 apparatus and also gets rid of all

NOTE Confidence: 0.909255652083333

 $00:28:31.794 \longrightarrow 00:28:33.298$  that extra ER itself.

NOTE Confidence: 0.909255652083333

 $00:28:33.300 \longrightarrow 00:28:34.772$  The cell reshapes like

NOTE Confidence: 0.909255652083333

 $00:28:34.772 \longrightarrow 00:28:36.980$  this and then the next step

NOTE Confidence: 0.837158596315789

 $00:28:37.058 \rightarrow 00:28:40.298$  is that's going to enter the the cell cycle.

NOTE Confidence: 0.837158596315789

 $00:28:40.300 \longrightarrow 00:28:43.090$  So how do we study this?

NOTE Confidence: 0.837158596315789

 $00{:}28{:}43.090 \dashrightarrow 00{:}28{:}46.114$  So what we've taken to do doing is to

NOTE Confidence: 0.837158596315789

 $00:28:46.114 \rightarrow 00:28:48.540$  looking at these metaplasia models,

NOTE Confidence: 0.837158596315789

 $00:28:48.540 \longrightarrow 00:28:50.420$  both of which involve collagenosis,

NOTE Confidence: 0.837158596315789

 $00:28:50.420 \longrightarrow 00:28:53.290$  both of which are drug induced and

NOTE Confidence: 0.837158596315789

 $00:28:53.290 \rightarrow 00:28:55.130$  relatively short term like within days

NOTE Confidence: 0.837158596315789

 $00{:}28{:}55{.}130 \dashrightarrow 00{:}28{:}57{.}414$  we can get these changes in both the

NOTE Confidence: 0.837158596315789

 $00{:}28{:}57{.}414 \dashrightarrow 00{:}28{:}59{.}600$  stomach and the pancreas at the same time.

NOTE Confidence: 0.837158596315789

 $00:28:59.600 \longrightarrow 00:29:00.867$  That way we can look at all

NOTE Confidence: 0.837158596315789

00:29:00.867 -> 00:29:01.410 the conserved features,

00:29:01.410 - 00:29:03.776 not just what happens in the stomach.

NOTE Confidence: 0.837158596315789

 $00{:}29{:}03{.}780 \dashrightarrow 00{:}29{:}06{.}130$  And so we use two systems for the most part,

NOTE Confidence: 0.837158596315789

 $00:29:06.130 \longrightarrow 00:29:08.290$  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

 $00:29:10.922 \longrightarrow 00:29:12.504$  which is that if you treat mice

NOTE Confidence: 0.837158596315789

 $00:29:12.504 \longrightarrow 00:29:13.847$  with high doses of tam oxifen,

NOTE Confidence: 0.837158596315789

 $00:29:13.850 \longrightarrow 00:29:16.524$  it has an estrogen and sex independent

NOTE Confidence: 0.837158596315789

 $00:29:16.524 \rightarrow 00:29:18.550$  toxicity effect on the stomach,

NOTE Confidence: 0.837158596315789

 $00{:}29{:}18.550 \dashrightarrow 00{:}29{:}20.512$  which kills all the parietal cells

NOTE Confidence: 0.837158596315789

 $00:29:20.512 \rightarrow 00:29:22.810$  within a couple of days basically,

NOTE Confidence: 0.837158596315789

 $00{:}29{:}22{.}810 \dashrightarrow 00{:}29{:}24{.}905$  and reprograms the chief cells

NOTE Confidence: 0.837158596315789

 $00{:}29{:}24.905 \dashrightarrow 00{:}29{:}27.000$  and the entire oxyntic mucosa

NOTE Confidence: 0.837158596315789

 $00{:}29{:}27.073 \dashrightarrow 00{:}29{:}29.168$  into this pyloric like mucosa.

NOTE Confidence: 0.837158596315789

 $00{:}29{:}29{.}170 \dashrightarrow 00{:}29{:}31{.}354$  And the other is an established

NOTE Confidence: 0.837158596315789

00:29:31.354 - 00:29:32.810 model of Cerulean,

NOTE Confidence: 0.837158596315789

 $00{:}29{:}32{.}810 \dashrightarrow 00{:}29{:}35{.}673$  which is a CCK hormone analog treatment

 $00:29:35.673 \rightarrow 00:29:38.338$  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

 $00:29:39.810 \longrightarrow 00:29:43.170$  but it's really just more again

NOTE Confidence: 0.837158596315789

 $00:29:43.170 \rightarrow 00:29:44.850$  metaplastic proliferative phenotype.

NOTE Confidence: 0.837158596315789

 $00:29:44.850 \longrightarrow 00:29:46.824$  So this is the dosing scheme for

NOTE Confidence: 0.837158596315789

 $00:29:46.824 \longrightarrow 00:29:48.666$  high dose tamoxifen and this is

NOTE Confidence: 0.837158596315789

 $00:29:48.666 \rightarrow 00:29:50.226$  what it looks like pathologically.

NOTE Confidence: 0.837158596315789

 $00{:}29{:}50{.}230 \dashrightarrow 00{:}29{:}51{.}445$  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

 $00:29:54.048 \rightarrow 00:29:56.546$  cells here and within three days of

NOTE Confidence: 0.837158596315789

 $00:29:56.546 \rightarrow 00:29:58.326$  those tamoxifen injections the cells,

NOTE Confidence: 0.837158596315789

 $00{:}29{:}58{.}330 \dashrightarrow 00{:}30{:}00{.}004$  the units become like tubes with

NOTE Confidence: 0.837158596315789

 $00{:}30{:}00{.}004 \dashrightarrow 00{:}30{:}01.792$  just mucus cells on top and

NOTE Confidence: 0.837158596315789

 $00:30:01.792 \longrightarrow 00:30:03.628$  mucous cells in the bottom and

 $00:30:03.628 \rightarrow 00:30:04.890$  then proliferation throughout,

NOTE Confidence: 0.837158596315789

 $00{:}30{:}04.890 \dashrightarrow 00{:}30{:}06.135$  whereas normally proliferation

NOTE Confidence: 0.837158596315789

 $00:30:06.135 \longrightarrow 00:30:09.040$  is confined to this top area in.

NOTE Confidence: 0.837158596315789

 $00:30:09.040 \rightarrow 00:30:12.120$  The normal stomach and pancreas,

NOTE Confidence: 0.837158596315789

 $00:30:12.120 \longrightarrow 00:30:14.430$  all of these acinar acini open up

NOTE Confidence: 0.837158596315789

 $00:30:14.430 \longrightarrow 00:30:17.057$  and you get these kind of cuboidal NOTE Confidence: 0.837158596315789

 $00:30:17.057 \rightarrow 00:30:19.301$  cyst like proliferative cells also

NOTE Confidence: 0.837158596315789

 $00{:}30{:}19{.}301 \dashrightarrow 00{:}30{:}22{.}223$  if we do the cerulean treatment

NOTE Confidence: 0.837158596315789

 $00{:}30{:}22{.}223 \dashrightarrow 00{:}30{:}24.677$  there just to give him a plug.

NOTE Confidence: 0.837158596315789

 $00{:}30{:}24.680 \dashrightarrow 00{:}30{:}27.740$  To embarrass him a little bit.

NOTE Confidence: 0.837158596315789

 $00{:}30{:}27.740 \dashrightarrow 00{:}30{:}29.532$  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

 $00:30:31.727 \dashrightarrow 00:30:33.421$  you some highlights but you know

NOTE Confidence: 0.837158596315789

 $00{:}30{:}33{.}421 \dashrightarrow 00{:}30{:}35{.}332$  because a lot of this is published

NOTE Confidence: 0.837158596315789

 $00:30:35.332 \dashrightarrow 00:30:37.404$  because it the the stomach system

NOTE Confidence: 0.837158596315789

 $00:30:37.404 \dashrightarrow 00:30:40.240$  is so synchronous and then we can

 $00{:}30{:}40{.}240 \dashrightarrow 00{:}30{:}42{.}472$  transmit translate that into lesions

NOTE Confidence: 0.837158596315789

 $00{:}30{:}42.472 \dashrightarrow 00{:}30{:}44.936$  in humans and and then confirm

NOTE Confidence: 0.837158596315789

 $00{:}30{:}44{.}936 \dashrightarrow 00{:}30{:}47{.}225$  with the the pancreatic system we've

NOTE Confidence: 0.837158596315789

 $00:30:47.225 \longrightarrow 00:30:50.057$  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

 $00{:}30{:}52{.}256 \dashrightarrow 00{:}30{:}55{.}363$  the the the program that happens in

NOTE Confidence: 0.837158596315789

 $00:30:55.363 \rightarrow 00:30:58.057$  polygenesis and basically you take an.

NOTE Confidence: 0.837158596315789

 $00{:}30{:}58.060 \dashrightarrow 00{:}30{:}59.944$  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

 $00:31:02.048 \rightarrow 00:31:03.998$  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

 $00:31:05.568 \dashrightarrow 00:31:07.401$  the whole point of that is to induce

NOTE Confidence: 0.837158596315789

 $00:31:07.401 \rightarrow 00:31:09.250$  proliferation so that it repairs the damage.

NOTE Confidence: 0.837158596315789

 $00{:}31{:}09{.}250 \dashrightarrow 00{:}31{:}10.774$  But the other thing that happens

NOTE Confidence: 0.837158596315789

 $00{:}31{:}10.774 \dashrightarrow 00{:}31{:}12.678$  is about this kind of time course

 $00:31:12.678 \longrightarrow 00:31:14.073$  all the different the organelles

NOTE Confidence: 0.837158596315789

 $00:31:14.073 \longrightarrow 00:31:16.249$  that are specifically tied to the

NOTE Confidence: 0.837158596315789

 $00:31:16.249 \dashrightarrow 00:31:17.817$  differentiated function are decreased.

NOTE Confidence: 0.837158596315789

00:31:17.820 --> 00:31:18.256 You know,

NOTE Confidence: 0.837158596315789

 $00{:}31{:}18.256 \dashrightarrow 00{:}31{:}20.000$  so things like the rough ER and and

NOTE Confidence: 0.837158596315789

 $00{:}31{:}20.050 \dashrightarrow 00{:}31{:}21.938$  and and this is focused on the stomach,

NOTE Confidence: 0.837158596315789

 $00:31:21.940 \longrightarrow 00:31:23.905$  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

 $00:31:25.480 \dashrightarrow 00:31:29.048$  but things like pepsinogen and and so on.

NOTE Confidence: 0.837158596315789

 $00:31:29.050 \dashrightarrow 00:31:32.060$  And that occurs across these three stages.

NOTE Confidence: 0.837158596315789

 $00:31:32.060 \rightarrow 00:31:34.454$  The first stage is this massive autophagy,

NOTE Confidence: 0.855814773846154

 $00:31:34.460 \longrightarrow 00:31:35.902$  which is of course what's helping to

NOTE Confidence: 0.855814773846154

 $00:31:35.902 \dashrightarrow 00:31:37.799$  get rid of these differentiated organs.

NOTE Confidence: 0.855814773846154

 $00:31:37.800 \rightarrow 00:31:40.146$  The second stage is that METAPLASTIC

NOTE Confidence: 0.855814773846154

 $00:31:40.146 \longrightarrow 00:31:42.783$  gene expression where you start to see

NOTE Confidence: 0.855814773846154

 $00:31:42.783 \rightarrow 00:31:45.121$  that the cells have rearranged how they.

00:31:45.130 --> 00:31:47.510 Actually Mark and label and

NOTE Confidence: 0.855814773846154

 $00:31:47.510 \longrightarrow 00:31:50.450$  then the final stage is this.

NOTE Confidence: 0.855814773846154

 $00:31:50.450 \rightarrow 00:31:53.390$  Mtorc increase, which is critical for

NOTE Confidence: 0.855814773846154

 $00:31:53.390 \rightarrow 00:31:57.336$  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

 $00:31:59.522 \rightarrow 00:32:01.370$  and then suppression of people 53.

NOTE Confidence: 0.855814773846154

 $00:32:01.370 \longrightarrow 00:32:03.498$  So this crossing point is very important

NOTE Confidence: 0.855814773846154

 $00:32:03.498 \dashrightarrow 00:32:05.489$  because the main thing that P53 does

NOTE Confidence: 0.855814773846154

 $00{:}32{:}05{.}489 \dashrightarrow 00{:}32{:}07{.}400$  is I'll show you is suppress mtorc.

NOTE Confidence: 0.855814773846154

 $00{:}32{:}07{.}400 \dashrightarrow 00{:}32{:}10{.}154$  So CP3 has to decrease for these cells to

NOTE Confidence: 0.855814773846154

 $00:32:10.154 \rightarrow 00:32:13.110$  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

 $00{:}32{:}14.265 \dashrightarrow 00{:}32{:}15.309$  on this theme several times,

NOTE Confidence: 0.855814773846154

 $00{:}32{:}15{.}310 \dashrightarrow 00{:}32{:}17{.}137$  but I already hinted at it from

NOTE Confidence: 0.855814773846154

 $00{:}32{:}17{.}137 \dashrightarrow 00{:}32{:}19{.}099$  what we know about Barretts and

 $00:32:19.099 \rightarrow 00:32:20.954$  why this kind of reprogramming.

NOTE Confidence: 0.855814773846154

 $00{:}32{:}20{.}960 \dashrightarrow 00{:}32{:}22{.}420$  Is so important in NYPD.

NOTE Confidence: 0.855814773846154

 $00:32:22.420 \longrightarrow 00:32:23.599$  Three is important.

NOTE Confidence: 0.855814773846154

 $00:32:23.599 \rightarrow 00:32:25.957$  It's important for this licensing step.

NOTE Confidence: 0.855814773846154

 $00{:}32{:}25{.}960 \dashrightarrow 00{:}32{:}28{.}010$  You don't let differentiated cells

NOTE Confidence: 0.855814773846154

 $00{:}32{:}28.010 \dashrightarrow 00{:}32{:}30.600$  back into the cell cycle unless

NOTE Confidence: 0.855814773846154

 $00:32:30.600 \rightarrow 00:32:32.920$  they've cleared up 53 checkpoint.

NOTE Confidence: 0.855814773846154

 $00:32:32.920 \longrightarrow 00:32:34.580$  So thinking about mtorc one,

NOTE Confidence: 0.855814773846154

 $00:32:34.580 \rightarrow 00:32:36.092$  it's the central energy regulator and

NOTE Confidence: 0.855814773846154

 $00:32:36.092 \rightarrow 00:32:38.338$  this is a super simplistic version of it.

NOTE Confidence: 0.855814773846154

 $00:32:38.340 \longrightarrow 00:32:40.599$  But just so that we're on the same page,

NOTE Confidence: 0.855814773846154

 $00:32:40.600 \rightarrow 00:32:42.772$  you know it's pretty much integrates

NOTE Confidence: 0.855814773846154

 $00{:}32{:}42.772 \dashrightarrow 00{:}32{:}44.996$  the vast majority of the cells

NOTE Confidence: 0.855814773846154

 $00:32:44.996 \rightarrow 00:32:46.771$  energetic inputs and outputs with

NOTE Confidence: 0.855814773846154

 $00:32:46.771 \rightarrow 00:32:49.178$  the two main wings being related,

NOTE Confidence: 0.855814773846154

 $00:32:49.180 \longrightarrow 00:32:50.820$  wings being protein translation

 $00:32:50.820 \longrightarrow 00:32:53.280$  and of course driving the cell

NOTE Confidence: 0.855814773846154

 $00:32:53.347 \longrightarrow 00:32:55.437$  cycle via phosphorylation of the

NOTE Confidence: 0.855814773846154

 $00:32:55.437 \longrightarrow 00:32:56.805$  small ribosomal subunit 6.

NOTE Confidence: 0.855814773846154

 $00{:}32{:}56{.}805 \dashrightarrow 00{:}32{:}59{.}010$  So this is going to be important

NOTE Confidence: 0.855814773846154

 $00{:}32{:}59{.}073 \dashrightarrow 00{:}33{:}01{.}236$  because this is a great marker for

NOTE Confidence: 0.855814773846154

 $00:33:01.236 \dashrightarrow 00:33:03.120$  Mturk activity by immunostaining.

NOTE Confidence: 0.855814773846154

 $00:33:03.120 \dashrightarrow 00:33:04.968$  Works great or an IF you can tell

NOTE Confidence: 0.855814773846154

 $00:33:04.968 \longrightarrow 00:33:07.009$  how much import there is by how

NOTE Confidence: 0.855814773846154

 $00{:}33{:}07{.}009 \dashrightarrow 00{:}33{:}08{.}524$  much phosphorylated S6 there is,

NOTE Confidence: 0.855814773846154

 $00:33:08.530 \longrightarrow 00:33:09.781$  so Amtrak increases.

NOTE Confidence: 0.855814773846154

 $00:33:09.781 \longrightarrow 00:33:12.283$  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

 $00{:}33{:}14{.}904 \dashrightarrow 00{:}33{:}17{.}029$  all of the breakdown products

NOTE Confidence: 0.855814773846154

 $00{:}33{:}17.103 \dashrightarrow 00{:}33{:}19.336$  in in the lysosomes and a key.

NOTE Confidence: 0.855814773846154

 $00{:}33{:}19{.}340 \dashrightarrow 00{:}33{:}21{.}948$  Inhibitor of mtorc is this gene called before

 $00:33:21.948 \longrightarrow 00:33:24.667$  or red one which we'll talk about also.

NOTE Confidence: 0.855814773846154

 $00{:}33{:}24.670 \dashrightarrow 00{:}33{:}27.393$  So let's look at some of how

NOTE Confidence: 0.855814773846154

 $00{:}33{:}27{.}393 \dashrightarrow 00{:}33{:}29{.}704$  what this looks like in actual

NOTE Confidence: 0.855814773846154

 $00:33:29.704 \rightarrow 00:33:31.439$  ultrastructure and you can see

NOTE Confidence: 0.855814773846154

 $00:33:31.439 \longrightarrow 00:33:33.834$  that within 24 hours down now we're

NOTE Confidence: 0.855814773846154

 $00:33:33.834 \rightarrow 00:33:36.310$  looking in chief cells that we have

NOTE Confidence: 0.855814773846154

 $00:33:36.310 \rightarrow 00:33:38.230$  all these massive autophagosomes,

NOTE Confidence: 0.855814773846154

00:33:38.230 --> 00:33:39.004 auto lysosomes,

NOTE Confidence: 0.855814773846154

 $00:33:39.004 \rightarrow 00:33:40.939$  all this auto degraded machinery

NOTE Confidence: 0.855814773846154

 $00:33:40.939 \rightarrow 00:33:43.268$  that these cells start to rearrange

NOTE Confidence: 0.855814773846154

 $00{:}33{:}43.268 \dashrightarrow 00{:}33{:}44.744$  their their entire architecture

NOTE Confidence: 0.855814773846154

 $00:33:44.744 \longrightarrow 00:33:47.519$  and you can see just here this is

NOTE Confidence: 0.855814773846154

 $00:33:47.519 \rightarrow 00:33:49.528$  quantified by how much lysosomes there.

NOTE Confidence: 0.855814773846154

 $00{:}33{:}49{.}528 \dashrightarrow 00{:}33{:}52{.}722$  And then we use this 3D electron

NOTE Confidence: 0.855814773846154

 $00{:}33{:}52.722 \dashrightarrow 00{:}33{:}55.126$  microscopic tactic called focused

NOTE Confidence: 0.855814773846154

 $00:33:55.126 \rightarrow 00:33:57.530$  IMDb scanning electron microscopy

 $00:33:57.611 \longrightarrow 00:34:00.195$  to kind of look at it more detail.

NOTE Confidence: 0.855814773846154

 $00:34:00.200 \longrightarrow 00:34:02.336$  And you can see as we kind of

NOTE Confidence: 0.855814773846154

 $00{:}34{:}02{.}340 \dashrightarrow 00{:}34{:}03{.}039$  spin this around,

NOTE Confidence: 0.855814773846154

 $00:34:03.039 \rightarrow 00:34:05.107$  this is a single chief cell as this

NOTE Confidence: 0.855814773846154

 $00:34:05.107 \rightarrow 00:34:07.047$  polygenesis process that's happening early.

NOTE Confidence: 0.855814773846154

 $00:34:07.050 \longrightarrow 00:34:08.808$  This is a capillary loop and

NOTE Confidence: 0.855814773846154

 $00:34:08.808 \rightarrow 00:34:10.550$  these are the secretory granules,

NOTE Confidence: 0.855814773846154

 $00{:}34{:}10{.}550 \dashrightarrow 00{:}34{:}11{.}999$  this is the nucleus and these are

NOTE Confidence: 0.855814773846154

 $00{:}34{:}11{.}999 \dashrightarrow 00{:}34{:}13{.}280$  all lysosomes and autophagosomes.

NOTE Confidence: 0.855814773846154

 $00:34:13.280 \longrightarrow 00:34:15.680$  So like half the cell becomes

NOTE Confidence: 0.855814773846154

 $00:34:15.680 \longrightarrow 00:34:19.260$  auto degradative as the.

NOTE Confidence: 0.855814773846154

 $00:34:19.260 \rightarrow 00:34:23.054$  As this early stage in Polygenesis happens,

NOTE Confidence: 0.855814773846154

 $00{:}34{:}23.060 \dashrightarrow 00{:}34{:}26.520$  so that's what's happening to

NOTE Confidence: 0.855814773846154

 $00{:}34{:}26{.}520 \dashrightarrow 00{:}34{:}29{.}288$  autophagosomes and and lysosomes.

NOTE Confidence: 0.855814773846154

 $00{:}34{:}29{.}290 \dashrightarrow 00{:}34{:}31{.}298$  For that to happen Mturk has to decrease

 $00:34:31.298 \longrightarrow 00:34:33.072$  and here we're looking at mtorc

NOTE Confidence: 0.855814773846154

 $00:34:33.072 \rightarrow 00:34:34.890$  activity using this phosphorus 6 and

NOTE Confidence: 0.796392662222222

 $00:34:34.944 \longrightarrow 00:34:36.638$  here we focus on the chief cells.

NOTE Confidence: 0.796392662222222

 $00:34:36.640 \longrightarrow 00:34:39.529$  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

 $00:34:44.272 \dashrightarrow 00:34:46.251$  metaplasia it all comes back again.

NOTE Confidence: 0.796392662222222

 $00{:}34{:}46{.}251 \dashrightarrow 00{:}34{:}47{.}877$  So here it's working for secretion

NOTE Confidence: 0.796392662222222

 $00{:}34{:}47.877 \dashrightarrow 00{:}34{:}49.460$  and not for proliferation,

NOTE Confidence: 0.796392662222222

 $00:34:49.460 \rightarrow 00:34:51.120$  here it's working for proliferation.

NOTE Confidence: 0.796392662222222

 $00{:}34{:}51{.}120 \dashrightarrow 00{:}34{:}53{.}464$  And in between is when all that autophagy

NOTE Confidence: 0.796392662222222

 $00:34:53.464 \rightarrow 00:34:55.611$  is happening and you can see even on

NOTE Confidence: 0.796392662222222

 $00{:}34{:}55{.}611 \dashrightarrow 00{:}34{:}57{.}498$  Western blots of mouse stomach you can

NOTE Confidence: 0.796392662222222

 $00:34:57.498 \rightarrow 00:34:59.437$  see it happening on the other hand.

NOTE Confidence: 0.796392662222222

 $00:34:59.440 \longrightarrow 00:35:01.876$  We knock out this suppressive ddit 4,

NOTE Confidence: 0.796392662222222

 $00:35:01.880 \longrightarrow 00:35:04.200$  which I showed you in that cartoon with

- NOTE Confidence: 0.796392662222222
- $00:35:04.200 \rightarrow 00:35:06.937$  it gets induced early to suppress network.
- NOTE Confidence: 0.796392662222222
- $00{:}35{:}06{.}940 \dashrightarrow 00{:}35{:}10{.}246$  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
- $00:35:12.740 \longrightarrow 00:35:13.860$  have the same autophagy.
- NOTE Confidence: 0.796392662222222
- $00:35:13.860 \longrightarrow 00:35:14.838$  So if you look at mtore,
- NOTE Confidence: 0.796392662222222
- 00:35:14.840 --> 00:35:17.400 basically it's much, you know.
- NOTE Confidence: 0.796392662222222
- $00:35:17.400 \longrightarrow 00:35:19.086$  Normally it's like that and in
- NOTE Confidence: 0.796392662222222
- $00:35:19.086 \longrightarrow 00:35:20.799$  the four knockout it's like that.
- NOTE Confidence: 0.796392662222222
- $00:35:20.800 \rightarrow 00:35:23.500$  So that leads to actually more,
- NOTE Confidence: 0.796392662222222
- $00:35:23.500 \rightarrow 00:35:24.972$  more proliferation,
- NOTE Confidence: 0.796392662222222
- $00:35:24.972 \dashrightarrow 00:35:27.180$  more metaplasia downstream.
- NOTE Confidence: 0.796392662222222
- 00:35:27.180 --> 00:35:28.736 And conversely,
- NOTE Confidence: 0.796392662222222
- $00{:}35{:}28.736 \dashrightarrow 00{:}35{:}31.848$  when you inhibit m torc.
- NOTE Confidence: 0.796392662222222
- $00{:}35{:}31.850 \dashrightarrow 00{:}35{:}34.682$  That's how we know that the cell cycle
- NOTE Confidence: 0.796392662222222
- $00{:}35{:}34.682 \dashrightarrow 00{:}35{:}37.919$  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

 $00{:}35{:}39{.}488 \dashrightarrow 00{:}35{:}42{.}377$  and treating mice with it does not block

NOTE Confidence: 0.796392662222222

 $00:35:42.377 \rightarrow 00:35:44.231$  the the metaplasia or the autophagy

NOTE Confidence: 0.796392662222222

 $00:35:44.231 \rightarrow 00:35:46.228$  or those first couple of steps,

NOTE Confidence: 0.796392662222222

 $00{:}35{:}46{.}230 \dashrightarrow 00{:}35{:}49{.}440$  but it it blocks the

NOTE Confidence: 0.796392662222222

 $00:35:49.440 \longrightarrow 00:35:50.724$  proliferation completely.

NOTE Confidence: 0.796392662222222

 $00:35:50.730 \longrightarrow 00:35:53.634$  So early on did it 4 suppresses mtorc.

NOTE Confidence: 0.796392662222222

 $00:35:53.640 \longrightarrow 00:35:56.268$  We have all that autophagy but on

NOTE Confidence: 0.796392662222222

 $00{:}35{:}56{.}268 \dashrightarrow 00{:}35{:}58{.}081$  that last slide we also see that

NOTE Confidence: 0.796392662222222

 $00:35:58.081 \rightarrow 00:36:00.244$  did it four goes away within the

NOTE Confidence: 0.796392662222222

 $00{:}36{:}00{.}244 \dashrightarrow 00{:}36{:}02{.}115$  first couple of stages and that's

NOTE Confidence: 0.796392662222222

 $00{:}36{:}02.115 \dashrightarrow 00{:}36{:}04.138$  when 53 comes on and P53 continues

NOTE Confidence: 0.796392662222222

 $00{:}36{:}04{.}138 \dashrightarrow 00{:}36{:}06{.}185$  to suppress M torque until or

NOTE Confidence: 0.796392662222222

 $00{:}36{:}06.185 \dashrightarrow 00{:}36{:}08.298$  unless the cell then decides to

NOTE Confidence: 0.796392662222222

 $00{:}36{:}08{.}298 \dashrightarrow 00{:}36{:}10{.}050$  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

 $00{:}36{:}12.498 \dashrightarrow 00{:}36{:}15.327$  is that in P53 knock outs we also don't

NOTE Confidence: 0.796392662222222

 $00{:}36{:}15{.}327 \dashrightarrow 00{:}36{:}17{.}947$  have this mtorc loss early on we

NOTE Confidence: 0.796392662222222

 $00:36:17.947 \rightarrow 00:36:20.161$  have more proliferation both in the.

NOTE Confidence: 0.796392662222222

 $00{:}36{:}20{.}170 \dashrightarrow 00{:}36{:}22{.}414$  The stomach and the pancreas and

NOTE Confidence: 0.796392662222222

 $00:36:22.414 \rightarrow 00:36:25.339$  then what we know that the critical

NOTE Confidence: 0.796392662222222

 $00{:}36{:}25{.}339 \dashrightarrow 00{:}36{:}28{.}140$  regulator of P53 that tells the cell

NOTE Confidence: 0.796392662222222

 $00{:}36{:}28.140 \dashrightarrow 00{:}36{:}30.040$  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

 $00{:}36{:}32{.}412 \dashrightarrow 00{:}36{:}34{.}356$  cycle is a protein called if rd one.

NOTE Confidence: 0.796392662222222

 $00{:}36{:}34{.}360 \dashrightarrow 00{:}36{:}36{.}404$  And we'll show you how that works

NOTE Confidence: 0.796392662222222

 $00:36:36.404 \rightarrow 00:36:38.688$  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

 $00:36:41.522 \rightarrow 00:36:42.642$  upregulated during collagenosis

NOTE Confidence: 0.796392662222222

 $00{:}36{:}42.642 \dashrightarrow 00{:}36{:}44.889$  and then as the cells we enter

NOTE Confidence: 0.796392662222222

 $00{:}36{:}44.889 \dashrightarrow 00{:}36{:}46.697$  the cell cycle it goes away.

 $00:36:46.700 \longrightarrow 00:36:48.891$  And in the absence of in the

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00:36:48.891 --> 00:36:50.112 absence of ID 11,

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 $00{:}36{:}50{.}112 \dashrightarrow 00{:}36{:}52{.}184$  all the cells wind up dying and

NOTE Confidence: 0.796392662222222

 $00:36:52.184 \rightarrow 00:36:54.179$  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

 $00:36:56.040 \longrightarrow 00:36:57.192$  then they're rescued and

NOTE Confidence: 0.796392662222222

 $00:36:57.192 \rightarrow 00:36:58.632$  they reenter the cell cycle.

NOTE Confidence: 0.796392662222222

 $00:36:58.640 \longrightarrow 00:37:00.033$  So that's how we know I pretty

NOTE Confidence: 0.796392662222222

 $00{:}37{:}00{.}033 \dashrightarrow 00{:}37{:}00{.}920$  when it's upstream of 53.

NOTE Confidence: 0.796392662222222

 $00{:}37{:}00{.}920 \dashrightarrow 00{:}37{:}02{.}696$  So we'll talk about how RD1

NOTE Confidence: 0.796392662222222

 $00{:}37{:}02.696 \dashrightarrow 00{:}37{:}05.069$  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

 $00{:}37{:}07{.}920 \dashrightarrow 00{:}37{:}12{.}480$  who's in China now as an assistant professor.

NOTE Confidence: 0.796392662222222

 $00{:}37{:}12.480 \dashrightarrow 00{:}37{:}15.104$  So let's talk now about some of the

NOTE Confidence: 0.796392662222222

 $00:37:15.104 \rightarrow 00:37:16.911$  machinery that executes this process

NOTE Confidence: 0.796392662222222

 $00:37:16.911 \dashrightarrow 00:37:20.029$  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
- $00{:}37{:}23.441 \dashrightarrow 00{:}37{:}25.490$  a differentiated cell and bring
- NOTE Confidence: 0.796392662222222
- $00:37:25.490 \longrightarrow 00:37:28.323$  it back into the cell cycle is,
- NOTE Confidence: 0.796392662222222
- $00:37:28.323 \longrightarrow 00:37:29.189$  you know,
- NOTE Confidence: 0.796392662222222
- 00:37:29.189 --> 00:37:30.921 a conserve process across
- NOTE Confidence: 0.796392662222222
- $00:37:30.921 \rightarrow 00:37:32.220$  multiple tissues just
- NOTE Confidence: 0.7745417266666667
- $00{:}37{:}32.294 \dashrightarrow 00{:}37{:}34.460$  like apoptosis, then there should be
- NOTE Confidence: 0.7745417266666667
- $00:37:34.460 \rightarrow 00:37:36.590$  genes that are dedicated to the process,
- NOTE Confidence: 0.7745417266666667
- $00:37:36.590 \rightarrow 00:37:39.306$  just as there are genes dedicated to
- NOTE Confidence: 0.7745417266666667
- $00:37:39.306 \dashrightarrow 00:37:41.410$  apoptosis like BCL's and caspases and so on.
- NOTE Confidence: 0.7745417266666667
- $00{:}37{:}41{.}410 \dashrightarrow 00{:}37{:}45{.}322$  So we started doing screens in
- NOTE Confidence: 0.7745417266666667
- $00{:}37{:}45{.}322 \dashrightarrow 00{:}37{:}47{.}278$  these regenerative metaplastic.
- NOTE Confidence: 0.7745417266666667
- $00{:}37{:}47{.}280 \dashrightarrow 00{:}37{:}51{.}092$  Organs after after you know during
- NOTE Confidence: 0.7745417266666667

 $00:37:51.092 \rightarrow 00:37:52.670$  the regenerative phase and look for

NOTE Confidence: 0.7745417266666667

 $00{:}37{:}52.722 \dashrightarrow 00{:}37{:}54.241$  genes that are all ex Co expressed

NOTE Confidence: 0.7745417266666667

 $00{:}37{:}54{.}241 \dashrightarrow 00{:}37{:}56{.}130$  and and from these I FD one indeed it NOTE Confidence: 0.7745417266666667

 $00:37:56.130 \longrightarrow 00:37:57.848$  four came out I've already told you

NOTE Confidence: 0.7745417266666667

 $00{:}37{:}57{.}848 \dashrightarrow 00{:}37{:}59{.}684$  about them need it for suppressing

NOTE Confidence: 0.7745417266666667

 $00:37:59.684 \rightarrow 00:38:01.881$  mtorc I-41 suppressing P53 but we have NOTE Confidence: 0.7745417266666667

00:38:01.881 --> 00:38:03.740 other targets that we've been working

NOTE Confidence: 0.7745417266666667

 $00:38:03.740 \rightarrow 00:38:05.770$  on another really strong one is ATF

NOTE Confidence: 0.7745417266666667

 $00{:}38{:}05{.}770$  -->  $00{:}38{:}07{.}740$  three which I want to talk about and NOTE Confidence: 0.774541726666667

 $00{:}38{:}07{.}740 \dashrightarrow 00{:}38{:}09{.}416$  we're starting to piece together then

NOTE Confidence: 0.7745417266666667

 $00{:}38{:}09{.}416 \dashrightarrow 00{:}38{:}11{.}216$  this architecture but this is what

NOTE Confidence: 0.7745417266666667

 $00{:}38{:}11{.}216 \dashrightarrow 00{:}38{:}13{.}114$  we've learned so far in this talk

NOTE Confidence: 0.7745417266666667

00:38:13.114 $\operatorname{-->}$ 00:38:15.140 do you injury happens the cell starts

NOTE Confidence: 0.7745417266666667

 $00:38:15.140 \longrightarrow 00:38:17.510$  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: 0.7745417266666667

 $00:38:19.250 \rightarrow 00:38:21.010$  to allow the autophagy to happen.
- NOTE Confidence: 0.7745417266666667
- 00:38:21.010 -> 00:38:23.593 I have heard one is induced that
- NOTE Confidence: 0.7745417266666667
- $00{:}38{:}23{.}593 \dashrightarrow 00{:}38{:}25{.}390$  eventually accumulates and suppresses
- NOTE Confidence: 0.7745417266666667
- $00:38:25.390 \longrightarrow 00:38:29.656$  P53 which allows cell cycle entry.
- NOTE Confidence: 0.7745417266666667
- $00:38:29.660 \rightarrow 00:38:33.258$  So. Why then is mtore so important?
- NOTE Confidence: 0.7745417266666667
- 00:38:33.260 --> 00:38:34.130 Because, you know,
- NOTE Confidence: 0.7745417266666667
- $00:38:34.130 \rightarrow 00:38:35.870$  when we think about why Barretts
- NOTE Confidence: 0.7745417266666667
- 00:38:35.870 --> 00:38:36.560 becomes cancer,
- NOTE Confidence: 0.7745417266666667
- $00:38:36.560 \rightarrow 00:38:38.380$  why gastric intestinal metaplasia
- NOTE Confidence: 0.7745417266666667
- 00:38:38.380 --> 00:38:39.745 or you know,
- NOTE Confidence: 0.7745417266666667
- 00:38:39.750 --> 00:38:41.630 pseudo pyloric metaplasia gives
- NOTE Confidence: 0.7745417266666667
- $00{:}38{:}41.630 \dashrightarrow 00{:}38{:}44.660$  rise to cancer and we think about
- NOTE Confidence: 0.774541726666667
- 00:38:44.660 --> 00:38:45.875 this pathogenesis process,
- NOTE Confidence: 0.7745417266666667
- $00{:}38{:}45{.}880 \dashrightarrow 00{:}38{:}46{.}556$  this conversion,
- NOTE Confidence: 0.7745417266666667
- 00:38:46.556 --> 00:38:47.232 you know,
- NOTE Confidence: 0.7745417266666667
- $00{:}38{:}47{.}232 \dashrightarrow 00{:}38{:}49{.}669$  being critical for that and m torc being
- NOTE Confidence: 0.7745417266666667

 $00:38:49.669 \rightarrow 00:38:51.763$  critical for that cell cycle reentry

NOTE Confidence: 0.7745417266666667

 $00:38:51.763 \dashrightarrow 00:38:54.000$  because that's what you need for cancer.

NOTE Confidence: 0.7745417266666667

 $00:38:54.000 \rightarrow 00:38:55.360$  Why is it so important?

NOTE Confidence: 0.7745417266666667

00:38:55.360 --> 00:38:55.619 Well,

NOTE Confidence: 0.7745417266666667

 $00{:}38{:}55{.}619 \dashrightarrow 00{:}38{:}57{.}432$  here's what we delve like the deepest

NOTE Confidence: 0.7745417266666667

 $00{:}38{:}57{.}432 \dashrightarrow 00{:}38{:}58{.}842$  into the structure and organelles

NOTE Confidence: 0.7745417266666667

 $00{:}38{:}58{.}842 \dashrightarrow 00{:}39{:}01{.}150$  before we kind of come back out again.

NOTE Confidence: 0.7745417266666667

 $00{:}39{:}01{.}150 \dashrightarrow 00{:}39{:}04{.}734$  Our thinking now is that it's all about

NOTE Confidence: 0.7745417266666667

 $00:39:04.734 \rightarrow 00:39:06.190$  ribosomes when you're a chief cell.

NOTE Confidence: 0.7745417266666667

00:39:06.190 --> 00:39:08.662 I showed you that electron microscope

NOTE Confidence: 0.7745417266666667

 $00{:}39{:}08.662 \dashrightarrow 00{:}39{:}11.007$  micrograph where it's just layer after

NOTE Confidence: 0.7745417266666667

 $00{:}39{:}11.007 \dashrightarrow 00{:}39{:}13.527$  layer after layer of rough ER and all

NOTE Confidence: 0.7745417266666667

 $00:39:13.597 \rightarrow 00:39:17.098$  that roughly RISER line by ribosomes.

NOTE Confidence: 0.7745417266666667

 $00{:}39{:}17{.}100 \dashrightarrow 00{:}39{:}19{.}916$  That are making digestive enzymes to go into,

NOTE Confidence: 0.7745417266666667

00:39:19.920 --> 00:39:20.386 you know,

NOTE Confidence: 0.7745417266666667

00:39:20.386 --> 00:39:23.010 the lumen of the R and then to be secreted.

 $00:39:23.010 \rightarrow 00:39:24.666$  When you become a proliferative cell,

NOTE Confidence: 0.7745417266666667

00:39:24.670 --> 00:39:26.272 you don't need all that secretory

NOTE Confidence: 0.7745417266666667

 $00:39:26.272 \rightarrow 00:39:28.370$  roufi R you need ribosomes in the

NOTE Confidence: 0.7745417266666667

 $00:39:28.370 \longrightarrow 00:39:30.320$  cytosol to make more ribosomes than

NOTE Confidence: 0.7745417266666667

 $00:39:30.320 \longrightarrow 00:39:32.149$  histores to make a copy of the cell.

NOTE Confidence: 0.7745417266666667

 $00:39:32.150 \longrightarrow 00:39:35.174$  And the key driver for ribosome

NOTE Confidence: 0.7745417266666667

00:39:35.174 --> 00:39:37.570 Biogenesis is M torque OK,

NOTE Confidence: 0.7745417266666667

 $00:39:37.570 \rightarrow 00:39:39.838$  and the reason why ribosome Biogenesis

NOTE Confidence: 0.7745417266666667

 $00:39:39.838 \rightarrow 00:39:42.629$  needs so much energy is because it's

NOTE Confidence: 0.7745417266666667

 $00:39:42.629 \rightarrow 00:39:44.649$  an incredibly complex process of

NOTE Confidence: 0.7745417266666667

 $00:39:44.649 \rightarrow 00:39:46.835$  assembling all of these ribosomal

NOTE Confidence: 0.774541726666667

 $00{:}39{:}46.835 \ldots > 00{:}39{:}49.112$  proteins and ribosomal RNA's that

NOTE Confidence: 0.7745417266666667

 $00:39:49.112 \rightarrow 00:39:51.517$  require all three RNA polymerases

NOTE Confidence: 0.7745417266666667

 $00{:}39{:}51{.}517 \dashrightarrow 00{:}39{:}53{.}480$  and translation into these.

NOTE Confidence: 0.7745417266666667

 $00:39:53.480 \longrightarrow 00:39:57.158$  Large and small 1640 subunits which

 $00:39:57.158 \rightarrow 00:39:59.594$  come together as a single subunit,

NOTE Confidence: 0.7745417266666667

 $00{:}39{:}59{.}600 \dashrightarrow 00{:}40{:}01{.}075$  multiple modifications happen and all

NOTE Confidence: 0.7745417266666667

 $00{:}40{:}01.075 \dashrightarrow 00{:}40{:}03.449$  of its sort of starts in the nucleolus.

NOTE Confidence: 0.7745417266666667

 $00:40:03.450 \rightarrow 00:40:05.880$  So that's our basic ribosome review.

NOTE Confidence: 0.7745417266666667

 $00{:}40{:}05{.}880 \dashrightarrow 00{:}40{:}06{.}978$  And then as I talked about,

NOTE Confidence: 0.7745417266666667

 $00{:}40{:}06{.}980 \dashrightarrow 00{:}40{:}08{.}738$  there's a big difference between this

NOTE Confidence: 0.774541726666667

 $00:40:08.738 \longrightarrow 00:40:10.698$  pool and this side of solid pool,

NOTE Confidence: 0.7745417266666667

00:40:10.700 --> 00:40:11.040 right,

NOTE Confidence: 0.7745417266666667

 $00{:}40{:}11.040 \dashrightarrow 00{:}40{:}13.420$  because this is for secretion and this

NOTE Confidence: 0.7745417266666667

 $00:40:13.420 \rightarrow 00:40:16.089$  is more for division and housekeeping.

NOTE Confidence: 0.7745417266666667

 $00{:}40{:}16.090 \dashrightarrow 00{:}40{:}20.274$  So to get from the ribosome to translation,

NOTE Confidence: 0.7745417266666667

 $00{:}40{:}20.280 \dashrightarrow 00{:}40{:}21.946$  we have to realize that the M

NOTE Confidence: 0.7745417266666667

 $00:40:21.946 \longrightarrow 00:40:24.146$  RNA is going to be loaded up

NOTE Confidence: 0.7745417266666667

 $00:40:24.146 \longrightarrow 00:40:25.214$  the preinitiation complexes.

NOTE Confidence: 0.774541726666667

 $00:40:25.220 \longrightarrow 00:40:26.822$  That's going to bring the two

NOTE Confidence: 0.7745417266666667

 $00:40:26.822 \rightarrow 00:40:27.356$  subunits together.

- NOTE Confidence: 0.7745417266666667
- $00:40:27.360 \longrightarrow 00:40:28.685$  So the two subunits only
- NOTE Confidence: 0.7745417266666667
- $00{:}40{:}28.685 \dashrightarrow 00{:}40{:}30.010$  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
- $00:40:32.950 \longrightarrow 00:40:34.960$  with M RNA as they translate.
- NOTE Confidence: 0.763685607272727
- $00:40:34.960 \longrightarrow 00:40:36.864$  And then the way most of our
- NOTE Confidence: 0.763685607272727
- $00:40:36.864 \rightarrow 00:40:38.356$  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
- $00{:}40{:}41.874 \dashrightarrow 00{:}40{:}43.638$  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
- $00:40:44.960 \longrightarrow 00:40:46.640$  but you can tell the difference.
- NOTE Confidence: 0.763685607272727
- $00{:}40{:}46.640 \dashrightarrow 00{:}40{:}48.215$  Between Monisms and polysomes by
- NOTE Confidence: 0.763685607272727
- $00{:}40{:}48{.}215 \dashrightarrow 00{:}40{:}50{.}128$  spinning them down and the longer
- NOTE Confidence: 0.763685607272727
- $00{:}40{:}50{.}128 \dashrightarrow 00{:}40{:}52{.}074$  you know ones or polysomes so they
- NOTE Confidence: 0.763685607272727
- $00{:}40{:}52.074 \dashrightarrow 00{:}40{:}53.966$  take lower longer to spin spin out.
- NOTE Confidence: 0.763685607272727

 $00{:}40{:}53.970 \dashrightarrow 00{:}40{:}57.106$  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

 $00:40:59.410 \longrightarrow 00:41:01.664$  they require 80% of the cells energy.

NOTE Confidence: 0.763685607272727

 $00:41:01.670 \rightarrow 00:41:03.366$  So that's why it's so important how you,

NOTE Confidence: 0.763685607272727

 $00{:}41{:}03{.}370 \dashrightarrow 00{:}41{:}05{.}956$  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

 $00{:}41{:}09{.}970 \dashrightarrow 00{:}41{:}12{.}088$  So there's huge proportions of the

NOTE Confidence: 0.763685607272727

 $00:41:12.088 \longrightarrow 00:41:13.500$  transcription and translation that

NOTE Confidence: 0.763685607272727

 $00{:}41{:}13.554 \dashrightarrow 00{:}41{:}15.090$  goes into ribosome Biogenesis.

NOTE Confidence: 0.763685607272727

 $00:41:15.090 \longrightarrow 00:41:17.430$  So what happens to ribosomes

NOTE Confidence: 0.763685607272727

 $00:41:17.430 \longrightarrow 00:41:18.024$  during palingenesis?

NOTE Confidence: 0.763685607272727

 $00{:}41{:}18.024 \dashrightarrow 00{:}41{:}20.400$  So we knew already that they had to

NOTE Confidence: 0.763685607272727

 $00{:}41{:}20{.}462 \dashrightarrow 00{:}41{:}22{.}568$  be coming off the rough ER and we saw

NOTE Confidence: 0.763685607272727

 $00{:}41{:}22{.}568 \dashrightarrow 00{:}41{:}24{.}607$  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

 $00:41:26.050 \rightarrow 00:41:27.151$  there's many ways.

 $00:41:27.151 \longrightarrow 00:41:29.353$  To to show that you're losing

NOTE Confidence: 0.763685607272727

 $00:41:29.353 \longrightarrow 00:41:30.898$  both large and small.

NOTE Confidence: 0.763685607272727

 $00{:}41{:}30{.}900 \dashrightarrow 00{:}41{:}32{.}706$  Subunits of ribosomes are just Western

NOTE Confidence: 0.763685607272727

 $00{:}41{:}32.706 \dashrightarrow 00{:}41{:}34.788$  blots early on in the process and

NOTE Confidence: 0.763685607272727

 $00{:}41{:}34.788 \dashrightarrow 00{:}41{:}36.706$  then they come back on again later.

NOTE Confidence: 0.763685607272727

 $00{:}41{:}36{.}710 \dashrightarrow 00{:}41{:}38{.}648$  So there's a loss and then

NOTE Confidence: 0.763685607272727

 $00:41:38.648 \longrightarrow 00:41:39.294$  regeneration process.

NOTE Confidence: 0.763685607272727

 $00:41:39.300 \longrightarrow 00:41:42.475$  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

 $00{:}41{:}43.800 \dashrightarrow 00{:}41{:}45.697$  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

 $00{:}41{:}47{.}470 \dashrightarrow 00{:}41{:}48.870$  ER here into the side show.

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

 $00{:}41{:}51.085 \dashrightarrow 00{:}41{:}53.077$  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

 $00{:}41{:}54{.}736 \dashrightarrow 00{:}41{:}56{.}627$  ER when he was a graduate student.

NOTE Confidence: 0.763685607272727

 $00:41:56.627 \longrightarrow 00:41:58.443$  So this is kind of what we think

NOTE Confidence: 0.763685607272727

 $00:41:58.443 \rightarrow 00:41:59.240$  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

 $00{:}42{:}01{.}860 \dashrightarrow 00{:}42{:}05{.}528$  normally you have all these rough ER.

NOTE Confidence: 0.763685607272727

 $00:42:05.530 \rightarrow 00:42:08.170$  Ribosomes making peptides and then,

NOTE Confidence: 0.763685607272727

 $00:42:08.170 \longrightarrow 00:42:08.812$  you know,

NOTE Confidence: 0.763685607272727

 $00:42:08.812 \rightarrow 00:42:10.738$  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

 $00{:}42{:}12.975 \dashrightarrow 00{:}42{:}14.642$  ribosomes all come off OK what's the

NOTE Confidence: 0.763685607272727

 $00:42:14.642 \rightarrow 00:42:16.058$  problem with the ribosomes coming off?

NOTE Confidence: 0.763685607272727

 $00{:}42{:}16.060 \dashrightarrow 00{:}42{:}17.329$  As soon as they come off the M RNA,

NOTE Confidence: 0.763685607272727

 $00:42:17.330 \longrightarrow 00:42:19.574$  then they fall apart into their

NOTE Confidence: 0.763685607272727

 $00{:}42{:}19.574 \dashrightarrow 00{:}42{:}21.710$  subunits and into ribosomal proteins,

NOTE Confidence: 0.763685607272727

 $00:42:21.710 \longrightarrow 00:42:23.920$  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
- $00:42:25.033 \rightarrow 00:42:26.130$  a couple of different times,
- NOTE Confidence: 0.763685607272727
- $00:42:26.130 \longrightarrow 00:42:28.629$  but that's probably why this whole ribosome
- NOTE Confidence: 0.763685607272727
- $00{:}42{:}28.629 \dashrightarrow 00{:}42{:}31.208$  is the center of this mtorc P53 axis.
- NOTE Confidence: 0.763685607272727
- $00:42:31.210 \rightarrow 00:42:32.983$  But this is just to show you that we
- NOTE Confidence: 0.763685607272727
- $00:42:32.983 \rightarrow 00:42:34.827$  also get a lot of ribosome Biogenesis,
- NOTE Confidence: 0.763685607272727
- $00:42:34.830 \rightarrow 00:42:35.664$  so we're losing.
- NOTE Confidence: 0.763685607272727
- $00{:}42{:}35{.}664 \dashrightarrow 00{:}42{:}37{.}610$  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
- $00:42:39.580 \longrightarrow 00:42:41.596$  which you can see here in quantify
- NOTE Confidence: 0.763685607272727
- $00:42:41.596 \rightarrow 00:42:44.099$  in both the stomach and the pancreas.
- NOTE Confidence: 0.763685607272727
- $00:42:44.100 \longrightarrow 00:42:46.284$  So what that means is we're losing
- NOTE Confidence: 0.763685607272727
- $00{:}42{:}46.284 \dashrightarrow 00{:}42{:}48.230$  ribosomes here and then the nucleoli
- NOTE Confidence: 0.763685607272727
- $00:42:48.230 \longrightarrow 00:42:50.132$  are getting turned on or making
- NOTE Confidence: 0.763685607272727
- $00{:}42{:}50{.}132 \dashrightarrow 00{:}42{:}51{.}399$  more ribosomes here.
- NOTE Confidence: 0.763685607272727
- $00{:}42{:}51{.}400 \dashrightarrow 00{:}42{:}54{.}484$  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

 $00:42:56.474 \rightarrow 00:42:58.478$  part in between those two things.

NOTE Confidence: 0.763685607272727

 $00:42:58.480 \longrightarrow 00:43:00.160$  So to be able to study these things,

NOTE Confidence: 0.763685607272727

 $00:43:00.160 \longrightarrow 00:43:01.714$  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

 $00:43:05.560 \rightarrow 00:43:09.296$  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

 $00:43:10.980 \longrightarrow 00:43:12.400$  Biogenesis for the first time,

NOTE Confidence: 0.789456304545455

 $00:43:12.400 \longrightarrow 00:43:14.008$  surprisingly that he can.

NOTE Confidence: 0.789456304545455

 $00:43:14.008 \rightarrow 00:43:16.018$  Reduced ribosome Biogenesis knockout by

NOTE Confidence: 0.789456304545455

 $00:43:16.018 \longrightarrow 00:43:18.074$  knocking out this key modifier that's

NOTE Confidence: 0.789456304545455

 $00:43:18.074 \rightarrow 00:43:20.440$  critical for the small subunit of ribosomes.

NOTE Confidence: 0.789456304545455

 $00:43:20.440 \longrightarrow 00:43:22.400$  And when he does that you that you

NOTE Confidence: 0.789456304545455

 $00{:}43{:}22{.}400 \dashrightarrow 00{:}43{:}24{.}153$  can no longer make ribosomes and

NOTE Confidence: 0.789456304545455

 $00:43:24.153 \longrightarrow 00:43:26.355$  when you do that and you induce

- NOTE Confidence: 0.789456304545455
- $00:43:26.355 \rightarrow 00:43:28.401$  collagenosis all the cells die unless
- NOTE Confidence: 0.789456304545455
- $00{:}43{:}28{.}401 \dashrightarrow 00{:}43{:}30{.}740$  you also put them on a P53 knock out.
- NOTE Confidence: 0.789456304545455
- 00:43:30.740 --> 00:43:33.434 So again PD3 knockout is critical
- NOTE Confidence: 0.789456304545455
- $00:43:33.434 \rightarrow 00:43:36.649$  that's sensing the death of of cells
- NOTE Confidence: 0.789456304545455
- $00:43:36.649 \rightarrow 00:43:38.874$  that don't make ribosomes anymore.
- NOTE Confidence: 0.789456304545455
- $00:43:38.880 \longrightarrow 00:43:41.220$  So this particular gene which is
- NOTE Confidence: 0.789456304545455
- $00:43:41.220 \rightarrow 00:43:43.610$  involved in the ribosome Biogenesis.
- NOTE Confidence: 0.789456304545455
- $00:43:43.610 \rightarrow 00:43:45.522$  Suppresses P53 presumably because
- NOTE Confidence: 0.789456304545455
- $00:43:45.522 \longrightarrow 00:43:47.434$  it makes both subunits.
- NOTE Confidence: 0.789456304545455
- $00:43:47.440 \longrightarrow 00:43:48.736$  So they're both subunits are there.
- NOTE Confidence: 0.789456304545455
- $00{:}43{:}48.740 \dashrightarrow 00{:}43{:}50.420$  It stops the people to three
- NOTE Confidence: 0.789456304545455
- $00:43:50.420 \longrightarrow 00:43:51.540$  induction that happens with
- NOTE Confidence: 0.789456304545455
- 00:43:51.596 --> 00:43:53.248 ribosome will breakdown products,
- NOTE Confidence: 0.789456304545455
- $00:43:53.250 \longrightarrow 00:43:56.256$  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

 $00:43:58.678 \rightarrow 00:44:00.449$  responsible for suppressing P53.

NOTE Confidence: 0.789456304545455

 $00:44:00.450 \longrightarrow 00:44:01.714$  How does that work?

NOTE Confidence: 0.789456304545455

 $00:44:01.714 \longrightarrow 00:44:03.710$  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

 $00:44:05.138 \rightarrow 00:44:06.769$  that and that NAP 10 is there,

NOTE Confidence: 0.789456304545455

 $00{:}44{:}06{.}770 \dashrightarrow 00{:}44{:}08{.}121$  but I heard you once turning on

NOTE Confidence: 0.789456304545455

 $00:44:08.121 \rightarrow 00:44:09.370$  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

 $00{:}44{:}13.250 \dashrightarrow 00{:}44{:}14.250$  it turns on here.

NOTE Confidence: 0.789456304545455

 $00{:}44{:}14.250 \dashrightarrow 00{:}44{:}15.974$  And what it does,

NOTE Confidence: 0.789456304545455

 $00{:}44{:}15{.}974 \dashrightarrow 00{:}44{:}17{.}267$  it turns out.

NOTE Confidence: 0.789456304545455

 $00:44:17.270 \rightarrow 00:44:20.050$  Is that I 41 fits right here right where the

NOTE Confidence: 0.789456304545455

 $00{:}44{:}20{.}113 \dashrightarrow 00{:}44{:}22{.}633$  M RNA would go between the two subunits.

NOTE Confidence: 0.789456304545455

 $00:44:22.640 \longrightarrow 00:44:24.344$  So when I offered you one

NOTE Confidence: 0.789456304545455

00:44:24.344 --> 00:44:25.790 attaches just like M RNA,

 $00:44:25.790 \longrightarrow 00:44:27.428$  it can keep the two ribosomal

NOTE Confidence: 0.789456304545455

 $00:44:27.428 \longrightarrow 00:44:28.890$  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

 $00:44:30.786 \longrightarrow 00:44:32.050$  during those early stages,

NOTE Confidence: 0.789456304545455

 $00{:}44{:}32.050 \dashrightarrow 00{:}44{:}33.665$  which then leads to breakdown

NOTE Confidence: 0.789456304545455

00:44:33.665 --> 00:44:34.958 in P53 activation,

NOTE Confidence: 0.789456304545455

 $00:44:34.958 \rightarrow 00:44:39.630$  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

 $00:44:41.280 \longrightarrow 00:44:42.080$  they're preserved.

NOTE Confidence: 0.789456304545455

 $00:44:42.080 \longrightarrow 00:44:44.480$  So essentially 53 is blocked because

NOTE Confidence: 0.789456304545455

 $00:44:44.480 \longrightarrow 00:44:47.131$  you don't get breakdown of all the

NOTE Confidence: 0.789456304545455

 $00{:}44{:}47{.}131 \dashrightarrow 00{:}44{:}48{.}916$  ribosomes during the first stage.

NOTE Confidence: 0.789456304545455

 $00:44:48.920 \longrightarrow 00:44:51.674$  So on the one hand you could have this,

NOTE Confidence: 0.789456304545455

 $00{:}44{:}51{.}680 \dashrightarrow 00{:}44{:}53{.}894$  but when you have ribosome Biogenesis

NOTE Confidence: 0.789456304545455

 $00{:}44{:}53.894 \dashrightarrow 00{:}44{:}57.079$  you can stop P53 by making new ribosomes,

 $00:44:57.080 \longrightarrow 00:44:59.152$  and if you have 41 then you salvage

NOTE Confidence: 0.789456304545455

 $00{:}44{:}59{.}152 \dashrightarrow 00{:}45{:}00{.}605$  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

 $00{:}45{:}02.690 \dashrightarrow 00{:}45{:}06.470$  OK, so that is the \*\*\*\*\*\*\*.

NOTE Confidence: 0.789456304545455

 $00{:}45{:}06{.}470 \dashrightarrow 00{:}45{:}07{.}730$  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

 $00{:}45{:}10{.}411 \dashrightarrow 00{:}45{:}12{.}478$  how this all comes out in tumors and

NOTE Confidence: 0.789456304545455

 $00:45:12.478 \rightarrow 00:45:14.606$  and come back out towards the pathology.

NOTE Confidence: 0.789456304545455

 $00{:}45{:}14.610 \dashrightarrow 00{:}45{:}16.465$  So with all this background

NOTE Confidence: 0.789456304545455

 $00:45:16.465 \longrightarrow 00:45:17.949$  then it's pretty clear,

NOTE Confidence: 0.789456304545455

 $00{:}45{:}17.950 \dashrightarrow 00{:}45{:}19.942$  you know that the cells spent a lot

NOTE Confidence: 0.789456304545455

 $00:45:19.942 \longrightarrow 00:45:21.864$  of time trying to regulate them to

NOTE Confidence: 0.789456304545455

 $00{:}45{:}21{.}864 \dashrightarrow 00{:}45{:}24{.}091$  work via PD3 and via this protein deed

NOTE Confidence: 0.789456304545455

 $00{:}45{:}24.091 \dashrightarrow 00{:}45{:}26.211$  at 4:00 to be able to ensure that

NOTE Confidence: 0.789456304545455

 $00{:}45{:}26{.}211 \dashrightarrow 00{:}45{:}27{.}968$  the there's no tumors that come out

NOTE Confidence: 0.789456304545455

 $00:45:27.968 \rightarrow 00:45:29.911$  of this taking these old cells and

- NOTE Confidence: 0.789456304545455
- $00:45:29.911 \rightarrow 00:45:31.930$  driving them back into the cell cycle.
- NOTE Confidence: 0.789456304545455
- $00{:}45{:}31{.}930 \dashrightarrow 00{:}45{:}34{.}720$  So what if we get rid of the ability to
- NOTE Confidence: 0.789456304545455
- $00:45:34.795 \rightarrow 00:45:37.658$  stop mtorc and regulate this process so.
- NOTE Confidence: 0.789456304545455
- $00:45:37.660 \longrightarrow 00:45:40.132$  You know what if we take out them
- NOTE Confidence: 0.789456304545455
- $00:45:40.132 \longrightarrow 00:45:41.599$  torque regulation and then in
- NOTE Confidence: 0.789456304545455
- $00:45:41.599 \rightarrow 00:45:43.426$  in a system where we can induce
- NOTE Confidence: 0.789456304545455
- $00{:}45{:}43{.}487 \dashrightarrow 00{:}45{:}45{.}337$  metaplasia multiple times and the
- NOTE Confidence: 0.789456304545455
- $00{:}45{:}45{.}337 \dashrightarrow 00{:}45{:}47{.}453$  thinking would be then that what's
- NOTE Confidence: 0.789456304545455
- $00{:}45{:}47{.}453 \dashrightarrow 00{:}45{:}49{.}294$  going to happen is we kind of
- NOTE Confidence: 0.839834078
- $00:45:49.300 \longrightarrow 00:45:50.836$  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
- $00{:}45{:}51{.}860 \dashrightarrow 00{:}45{:}53{.}680$  Then you go through collagenosis,
- NOTE Confidence: 0.839834078
- $00{:}45{:}53.680 \dashrightarrow 00{:}45{:}55.192$  then you heal, then you go through
- NOTE Confidence: 0.839834078
- $00{:}45{:}55{.}192 \dashrightarrow 00{:}45{:}56{.}080$  pathogenesis and you heal.
- NOTE Confidence: 0.839834078
- $00{:}45{:}56{.}080 \dashrightarrow 00{:}45{:}58{.}264$  But each time you can accumulate
- NOTE Confidence: 0.839834078

 $00:45:58.264 \rightarrow 00:46:00.442$  mutations until finally you get to

NOTE Confidence: 0.839834078

 $00:46:00.442 \longrightarrow 00:46:02.410$  the mutations like Karas or something

NOTE Confidence: 0.839834078

 $00{:}46{:}02{.}410 \dashrightarrow 00{:}46{:}04{.}462$  like that that drives a tumor and

NOTE Confidence: 0.839834078

 $00:46:04.462 \longrightarrow 00:46:06.268$  then you know you no longer go

NOTE Confidence: 0.839834078

 $00:46:06.268 \rightarrow 00:46:07.906$  back to being a chief seller and.

NOTE Confidence: 0.839834078

 $00{:}46{:}07{.}910 \dashrightarrow 00{:}46{:}08{.}750$  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

 $00:46:11.068 \rightarrow 00:46:13.112$  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

 $00{:}46{:}15.596 \dashrightarrow 00{:}46{:}17.380$  knocks out the ability of the cell

NOTE Confidence: 0.839834078

 $00{:}46{:}17{.}380 \dashrightarrow 00{:}46{:}19{.}177$  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

 $00{:}46{:}20.885 \dashrightarrow 00{:}46{:}22.922$  sense the P53 damage and to be able

NOTE Confidence: 0.839834078

 $00{:}46{:}22.922 \dashrightarrow 00{:}46{:}24.719$  to stop cells from coming back.

NOTE Confidence: 0.839834078

 $00:46:24.720 \rightarrow 00:46:26.645$  And cell cycle basically just kind of

NOTE Confidence: 0.839834078

 $00:46:26.645 \rightarrow 00:46:28.636$  skips past all this error checking

 $00:46:28.636 \longrightarrow 00:46:30.116$  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

 $00:46:31.758 \longrightarrow 00:46:33.258$  when you knock out deed it for.

NOTE Confidence: 0.839834078

 $00{:}46{:}33{.}260 \dashrightarrow 00{:}46{:}35{.}006$  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

 $00{:}46{:}36{.}849 \dashrightarrow 00{:}46{:}38{.}414$  them right into these dysplasias.

NOTE Confidence: 0.839834078

 $00{:}46{:}38{.}420 \dashrightarrow 00{:}46{:}40{.}298$  And so functionally what Max did

NOTE Confidence: 0.839834078

 $00{:}46{:}40.298 \dashrightarrow 00{:}46{:}42.896$  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

 $00{:}46{:}47.614 \dashrightarrow 00{:}46{:}49.876$  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

 $00:46:53.805 \dashrightarrow 00:46:55.660$  that mtor checkpoint versus control

NOTE Confidence: 0.839834078

 $00{:}46{:}55{.}660 \dashrightarrow 00{:}46{:}57{.}638$  cells that could still did multiple

 $00:46:57.638 \rightarrow 00:46:59.540$  rounds of tamoxifen to do multiple

NOTE Confidence: 0.839834078

 $00:46:59.540 \rightarrow 00:47:01.290$  rounds of metaplasia and repair.

NOTE Confidence: 0.839834078

 $00{:}47{:}01{.}290 \dashrightarrow 00{:}47{:}03{.}330$  And what he saw as we predicted was NOTE Confidence: 0.839834078

 $00{:}47{:}03.330 \dashrightarrow 00{:}47{:}05.827$  a lot more tumors in the deed at 4

NOTE Confidence: 0.839834078

 $00{:}47{:}05{.}827 \dashrightarrow 00{:}47{:}07{.}732$  knockouts and a lot bigger tumors

NOTE Confidence: 0.839834078

 $00:47:07.732 \longrightarrow 00:47:09.766$  in fact just for the pathology.

NOTE Confidence: 0.839834078

 $00:47:09.770 \longrightarrow 00:47:11.810$  This is one that arose as a huge

NOTE Confidence: 0.839834078

 $00:47:11.810 \longrightarrow 00:47:13.999$  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

 $00{:}47{:}17{.}440 \dashrightarrow 00{:}47{:}20{.}450$  but then had a had a focus of the diffuse

NOTE Confidence: 0.839834078

 $00:47:20.527 \rightarrow 00:47:23.096$  signet ring cells that you can see.

NOTE Confidence: 0.839834078

 $00:47:23.100 \longrightarrow 00:47:24.668$  And it's rare in the mouse to get

NOTE Confidence: 0.839834078

 $00:47:24.668 \rightarrow 00:47:26.399$  such an obviously metastatic tumor.

NOTE Confidence: 0.839834078

 $00:47:26.400 \longrightarrow 00:47:28.368$  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
- $00{:}47{:}30{.}261 \dashrightarrow 00{:}47{:}32{.}265$  muscle area and into this aerosan

 $00:47:32.331 \longrightarrow 00:47:33.738$  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

 $00:47:36.440 \longrightarrow 00:47:38.114$  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

 $00{:}47{:}40.200 \dashrightarrow 00{:}47{:}41.310$  you know, to repair them.

NOTE Confidence: 0.839834078

 $00:47:41.310 \longrightarrow 00:47:43.746$  They come back to repair with mutations

NOTE Confidence: 0.839834078

 $00:47:43.746 \rightarrow 00:47:45.860$  and then eventually they form tumors.

NOTE Confidence: 0.839834078

 $00:47:45.860 \longrightarrow 00:47:50.256$  OK, so last thing, the human thing.

NOTE Confidence: 0.839834078

 $00{:}47{:}50{.}260 \dashrightarrow 00{:}47{:}53{.}140$  You coming back all the way back to human,

NOTE Confidence: 0.839834078

 $00:47:53.140 \longrightarrow 00:47:56.020$  the human part of the talk.

NOTE Confidence: 0.839834078

00:47:56.020 --> 00:47:56.447 Again,

NOTE Confidence: 0.839834078

 $00{:}47{:}56{.}447 \dashrightarrow 00{:}47{:}59{.}009$  we've been again going back to

NOTE Confidence: 0.839834078

 $00{:}47{:}59.009 \dashrightarrow 00{:}48{:}01.420$  Barretts and trying to study this,

NOTE Confidence: 0.839834078

 $00:48:01.420 \rightarrow 00:48:03.250$  how these processes happen and how

 $00:48:03.250 \rightarrow 00:48:05.060$  people heal from these processes.

NOTE Confidence: 0.839834078

 $00:48:05.060 \dashrightarrow 00:48:05.363$  Unfortunately,

NOTE Confidence: 0.839834078

00:48:05.363 --> 00:48:07.181 this great mouse models that we

NOTE Confidence: 0.839834078

 $00:48:07.181 \longrightarrow 00:48:08.891$  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

 $00:48:12.600 \longrightarrow 00:48:13.800$  they don't reflux at all,

NOTE Confidence: 0.839834078

 $00:48:13.800 \longrightarrow 00:48:15.204$  they don't have any bile or

NOTE Confidence: 0.839834078

 $00{:}48{:}15{.}204 \dashrightarrow 00{:}48{:}16{.}700$  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

 $00{:}48{:}18.806 \dashrightarrow 00{:}48{:}19.859$  models for this.

NOTE Confidence: 0.839834078

 $00:48:19.860 \rightarrow 00:48:21.606$  So you know, you have to study the human.

NOTE Confidence: 0.839834078

 $00{:}48{:}21.610 \dashrightarrow 00{:}48{:}24.208$  And so I've been collaborating in

NOTE Confidence: 0.839834078

 $00{:}48{:}24{.}208 \dashrightarrow 00{:}48{:}25{.}940$  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

 $00:48:28.175 \rightarrow 00:48:29.963$  group and Rob odds.

- NOTE Confidence: 0.702047116
- 00:48:29.970 --> 00:48:31.242 Also, you know, pathologist,

00:48:31.242 --> 00:48:31.885 yeah, pathologist.

NOTE Confidence: 0.702047116

 $00:48:31.885 \longrightarrow 00:48:34.160$  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

 $00:48:36.090 \longrightarrow 00:48:36.834$  I'll just show you.

NOTE Confidence: 0.702047116

 $00{:}48{:}36{.}834 \dashrightarrow 00{:}48{:}38{.}419$  Here's where I had them down to Houston.

NOTE Confidence: 0.702047116

 $00:48:38.420 \longrightarrow 00:48:40.990$  There's Rob and and me.

NOTE Confidence: 0.702047116

 $00:48:40.990 \longrightarrow 00:48:42.310$  And there's actually, there's my.

NOTE Confidence: 0.702047116

 $00{:}48{:}42{.}310 \dashrightarrow 00{:}48{:}44{.}542$  There's the same microscope that Wanj

NOTE Confidence: 0.702047116

 $00{:}48{:}44{.}542 \dashrightarrow 00{:}48{:}48{.}470$  learned on, taken down to down to Houston.

NOTE Confidence: 0.702047116

 $00{:}48{:}48{.}470 \dashrightarrow 00{:}48{:}50{.}171$  And Rhonda like is fond of saying

NOTE Confidence: 0.702047116

 $00{:}48{:}50{.}171 \dashrightarrow 00{:}48{:}52{.}048$  that humans are the best model system.

NOTE Confidence: 0.702047116

 $00{:}48{:}52.050 \dashrightarrow 00{:}48{:}53.607$  So it with Barretts we have to do that.

NOTE Confidence: 0.702047116

 $00{:}48{:}53.610 \dashrightarrow 00{:}48{:}56.965$  So, So what in this model what

NOTE Confidence: 0.702047116

 $00:48:56.965 \rightarrow 00:48:59.590$  they've done is they you know with

 $00{:}48{:}59{.}590 \dashrightarrow 00{:}49{:}02{.}005$  the dysplastic Barretts you can treat

NOTE Confidence: 0.702047116

 $00:49:02.005 \rightarrow 00:49:04.401$  it by radiofrequency ablation just to

NOTE Confidence: 0.702047116

 $00:49:04.401 \longrightarrow 00:49:06.195$  basically take out all the Barretts

NOTE Confidence: 0.702047116

 $00{:}49{:}06{.}195 \dashrightarrow 00{:}49{:}09{.}058$  and take it down to the ulcer bed and

NOTE Confidence: 0.702047116

 $00{:}49{:}09{.}058 \dashrightarrow 00{:}49{:}10.894$  granulation tissue and then for some

NOTE Confidence: 0.702047116

 $00{:}49{:}10.894 \dashrightarrow 00{:}49{:}12.586$  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

 $00:49:14.220 \rightarrow 00:49:15.198$  is radiofrequency ablation,

NOTE Confidence: 0.702047116

 $00:49:15.200 \longrightarrow 00:49:15.730$  the Barretts,

NOTE Confidence: 0.702047116

 $00:49:15.730 \rightarrow 00:49:18.460$  and it goes to this just ulcer bed basically.

NOTE Confidence: 0.702047116

 $00:49:18.460 \longrightarrow 00:49:20.910$  What's leftover?

NOTE Confidence: 0.702047116

 $00:49:20.910 \rightarrow 00:49:23.465$  And then you know what happens though,

NOTE Confidence: 0.702047116

 $00{:}49{:}23{.}470 \dashrightarrow 00{:}49{:}25{.}066$  you know after this ulceration is it

NOTE Confidence: 0.702047116

 $00{:}49{:}25.066 \dashrightarrow 00{:}49{:}26.655$  comes back as a squamous and what

NOTE Confidence: 0.702047116

00:49:26.655 --> 00:49:28.474 they did was they took a bunch

NOTE Confidence: 0.702047116

 $00:49:28.474 \rightarrow 00:49:29.926$  of patients and enrolled them should

 $00:49:29.926 \longrightarrow 00:49:31.565$  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

 $00{:}49{:}33{.}530 \dashrightarrow 00{:}49{:}35{.}246$  two week and four week biopsies

NOTE Confidence: 0.702047116

 $00:49:35.246 \rightarrow 00:49:36.953$  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

 $00:49:38.724 \rightarrow 00:49:40.629$  the gastric margin after the RFA.

NOTE Confidence: 0.702047116

 $00:49:40.630 \longrightarrow 00:49:42.454$  And you know try to look at how

NOTE Confidence: 0.702047116

 $00:49:42.454 \rightarrow 00:49:44.665$  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

 $00:49:49.370 \longrightarrow 00:49:51.546$  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

 $00:49:52.792 \longrightarrow 00:49:54.049$  does all that squamous come from?

NOTE Confidence: 0.92109934625

 $00{:}49{:}54.050 \dashrightarrow 00{:}49{:}55.874$  And the only source of squamous or even

NOTE Confidence: 0.92109934625

 $00{:}49{:}55{.}874 \dashrightarrow 00{:}49{:}57{.}380$  epithelial cells that you could think of

NOTE Confidence: 0.92109934625

 $00:49:57.380 \rightarrow 00:49:58.968$  would be at this proximal margin, right.

 $00:49:58.968 \longrightarrow 00:50:00.258$  But it turns out that's

NOTE Confidence: 0.92109934625

 $00:50:00.258 \longrightarrow 00:50:01.290$  actually not what happens.

NOTE Confidence: 0.92109934625

 $00:50:01.290 \rightarrow 00:50:03.125$  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

 $00{:}50{:}04.600 \dashrightarrow 00{:}50{:}07.132$  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

 $00{:}50{:}09{.}874 \dashrightarrow 00{:}50{:}12.132$  some kind of differentiating, you know,

NOTE Confidence: 0.92109934625

 $00:50:12.132 \rightarrow 00:50:14.487$  that's that's feeding the squamous.

NOTE Confidence: 0.92109934625

 $00{:}50{:}14.490 \dashrightarrow 00{:}50{:}17.190$  And you know we have a couple of clues,

NOTE Confidence: 0.92109934625

 $00{:}50{:}17.190 \dashrightarrow 00{:}50{:}19.626$  one of which well we talked about.

NOTE Confidence: 0.92109934625

 $00:50:19.630 \longrightarrow 00:50:21.597$  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

 $00{:}50{:}22.784 \dashrightarrow 00{:}50{:}23.988$  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

 $00:50:25.322 \rightarrow 00:50:26.834$  there's a come from the distal gastric,

NOTE Confidence: 0.92109934625

 $00:50:26.840 \rightarrow 00:50:28.436$  but then why would that be squamous?

00:50:28.440 --> 00:50:29.800 But it turns out it just comes in

NOTE Confidence: 0.92109934625

 $00{:}50{:}29{.}800 \dashrightarrow 00{:}50{:}31{.}169$  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

 $00{:}50{:}35{.}021 \dashrightarrow 00{:}50{:}37{.}200$  NEO squamous healing epithelium.

NOTE Confidence: 0.92109934625

00:50:37.200 --> 00:50:37.905 And, you know,

NOTE Confidence: 0.92109934625

 $00:50:37.905 \dashrightarrow 00:50:39.840$  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

 $00:50:41.280 \longrightarrow 00:50:42.540$  to like a single cell.

NOTE Confidence: 0.92109934625

 $00{:}50{:}42.540 \dashrightarrow 00{:}50{:}45.123$  It turns out that there's pretty good

NOTE Confidence: 0.92109934625

 $00:50:45.123 \rightarrow 00:50:46.900$  evidence both morphologically and also

NOTE Confidence: 0.92109934625

 $00{:}50{:}46{.}900 \dashrightarrow 00{:}50{:}48{.}415$  with their advanced endoscopy that

NOTE Confidence: 0.92109934625

 $00{:}50{:}48{.}415 \dashrightarrow 00{:}50{.}50{.}710$  if you look under each of these new.

NOTE Confidence: 0.92109934625

 $00{:}50{:}50{.}710 \dashrightarrow 00{:}50{:}52{.}642$  Kind of ulcerated surface as a single

NOTE Confidence: 0.92109934625

 $00{:}50{:}52{.}642 \dashrightarrow 00{:}50{:}54{.}610$  cell layer of squamous is forming.

00:50:54.610 --> 00:50:57.010 They're all underneath ducts

NOTE Confidence: 0.92109934625

 $00{:}50{:}57{.}010 \dashrightarrow 00{:}50{:}58{.}507$  from submucos al glands.

NOTE Confidence: 0.92109934625

00:50:58.507 --> 00:50:59.398 So you know,

NOTE Confidence: 0.92109934625

 $00:50:59.398 \longrightarrow 00:51:01.745$  just for those of you don't remember

NOTE Confidence: 0.92109934625

 $00{:}51{:}01{.}745 \dashrightarrow 00{:}51{:}03{.}729$  your human esophageal theology.

NOTE Confidence: 0.92109934625

 $00:51:03.730 \longrightarrow 00:51:05.008$  These are the 70 coastal glands,

NOTE Confidence: 0.92109934625

 $00{:}51{:}05{.}010 \dashrightarrow 00{:}51{:}07{.}122$  and they have ducts that reach

NOTE Confidence: 0.92109934625

 $00:51:07.122 \dashrightarrow 00:51:08.796$  up to the squamous epithelium.

NOTE Confidence: 0.92109934625

00:51:08.796 $\operatorname{-->}$ 00:51:10.392 And normally like if you blade

NOTE Confidence: 0.92109934625

 $00:51:10.392 \rightarrow 00:51:11.430$  all this with RFA,

NOTE Confidence: 0.92109934625

 $00{:}51{:}11{.}430 \dashrightarrow 00{:}51{:}13{.}019$  then there's still a source of epithelium.

NOTE Confidence: 0.92109934625

 $00:51:13.020 \longrightarrow 00:51:15.330$  At least you know distally for

NOTE Confidence: 0.92109934625

 $00{:}51{:}15{.}330 \dashrightarrow 00{:}51{:}17{.}530$  some of these squamous islands.

NOTE Confidence: 0.92109934625

 $00{:}51{:}17{.}530 \dashrightarrow 00{:}51{:}19{.}378$  But the other source is probably some of

NOTE Confidence: 0.92109934625

 $00:51:19.378 \longrightarrow 00:51:21.028$  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
- $00{:}51{:}23{.}370 \dashrightarrow 00{:}51{:}25{.}538$  that there's transitions in there.
- NOTE Confidence: 0.92109934625
- $00{:}51{:}25{.}540 \dashrightarrow 00{:}51{:}27{.}187$  So like in fact that's what we're doing now.
- NOTE Confidence: 0.92109934625
- $00:51:27.190 \rightarrow 00:51:28.850$  We're doing spatial transcriptomics,
- NOTE Confidence: 0.92109934625
- $00:51:28.850 \rightarrow 00:51:31.340$  we're growing organoids and we're doing
- NOTE Confidence: 0.92109934625
- $00{:}51{:}31{.}402 \dashrightarrow 00{:}51{:}33{.}418$  a lot of IHC and Multiplex IFF to kind
- NOTE Confidence: 0.92109934625
- $00{:}51{:}33{.}418 \dashrightarrow 00{:}51{:}35{.}560$  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
- $00:51:38.930 \longrightarrow 00:51:41.360$  Take homes.
- NOTE Confidence: 0.92109934625
- $00:51:41.360 \longrightarrow 00:51:42.925$  This kind of pyloric metaplasia
- NOTE Confidence: 0.92109934625
- $00:51:42.925 \longrightarrow 00:51:44.883$  is some kind of like maybe
- NOTE Confidence: 0.92109934625
- $00:51:44.883 \rightarrow 00:51:46.538$  or metaplasia that you see,
- NOTE Confidence: 0.92109934625
- 00:51:46.540 --> 00:51:47.330 you know,
- NOTE Confidence: 0.92109934625
- $00:51:47.330 \rightarrow 00:51:50.095$  intestine in the cases of SL going
- NOTE Confidence: 0.92109934625
- $00{:}51{:}50.095 \dashrightarrow 00{:}51{:}52.465$  towards that you see the body of.
- NOTE Confidence: 0.92109934625
- 00:51:52.470 --> 00:51:55.428 I don't mean gas<br/>tritis and H
- NOTE Confidence: 0.92109934625

 $00:51:55.428 \rightarrow 00:51:57.400$  pylori induced atrophic gastritis,

NOTE Confidence: 0.92109934625

 $00{:}51{:}57{.}400 \dashrightarrow 00{:}52{:}00{.}382$  it's the what seems to be

NOTE Confidence: 0.92109934625

 $00:52:00.382 \longrightarrow 00:52:01.873$  happening in Barretts.

NOTE Confidence: 0.92109934625

 $00{:}52{:}01{.}880 \dashrightarrow 00{:}52{:}04{.}240$  And the root of this and although we

NOTE Confidence: 0.92109934625

 $00:52:04.240 \longrightarrow 00:52:06.507$  don't know this yet in the SL how

NOTE Confidence: 0.92109934625

 $00{:}52{:}06{.}507 \dashrightarrow 00{:}52{:}08{.}882$  that happens but but at least in the NOTE Confidence: 0.92109934625

 $00{:}52{:}08{.}882 \dashrightarrow 00{:}52{:}10{.}724$  pancreas and the stomach for sure

NOTE Confidence: 0.92109934625

 $00:52:10.730 \rightarrow 00:52:13.187$  and probably in Barretts is the cell

NOTE Confidence: 0.92109934625

 $00{:}52{:}13.187 \dashrightarrow 00{:}52{:}15.039$  biological process that's driving this,

NOTE Confidence: 0.92109934625

 $00:52:15.040 \longrightarrow 00:52:16.285$  the palingenesis process.

NOTE Confidence: 0.92109934625

 $00{:}52{:}16.285 \dashrightarrow 00{:}52{:}19.190$  And that basically is about cells converting

NOTE Confidence: 0.92109934625

 $00{:}52{:}19{.}253 \dashrightarrow 00{:}52{:}21{.}325$  energy from one state to the other.

NOTE Confidence: 0.92109934625

 $00:52:21.330 \rightarrow 00:52:23.594$  Now you know this is a pathology grand

NOTE Confidence: 0.92109934625

 $00:52:23.594 \rightarrow 00:52:25.538$  rounds and I'll tell you that when

NOTE Confidence: 0.92109934625

 $00:52:25.538 \rightarrow 00:52:27.682$  I was doing a lot of this looking

NOTE Confidence: 0.92109934625

 $00{:}52{:}27.682 \dashrightarrow 00{:}52{:}29.741$  at where this metaplasia happened

- NOTE Confidence: 0.92109934625
- $00:52:29.741 \longrightarrow 00:52:32.327$  and where what people thought about

 $00:52:32.398 \longrightarrow 00:52:33.510$  it 100 years ago.

NOTE Confidence: 0.84734664

 $00:52:33.510 \longrightarrow 00:52:34.810$  Well, over 100 years ago,

NOTE Confidence: 0.84734664

 $00{:}52{:}34{.}810 \dashrightarrow 00{:}52{:}36{.}694$ George Adami was a famous pathologist

NOTE Confidence: 0.84734664

 $00{:}52{:}36{.}694 \dashrightarrow 00{:}52{:}39{.}076$  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

 $00:52:41.078 \rightarrow 00:52:43.227$  that are going to become cancerous,

NOTE Confidence: 0.84734664

 $00:52:43.230 \rightarrow 00:52:45.030$  there's all this reprogram,

NOTE Confidence: 0.84734664

 $00:52:45.030 \longrightarrow 00:52:48.230$  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

 $00{:}52{:}50{.}930 \dashrightarrow 00{:}52{:}52{.}204$  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

 $00{:}52{:}54{.}110 \dashrightarrow 00{:}52{:}56{.}112$  And he said that what must happen

NOTE Confidence: 0.84734664

 $00{:}52{:}56{.}112 \dashrightarrow 00{:}52{:}58{.}259$  is the cell converts its energy

NOTE Confidence: 0.84734664

 $00{:}52{:}58{.}259 \dashrightarrow 00{:}53{:}00{.}289$  use from secretion to division.

00:53:00.290 --> 00:53:01.606 So, you know, it's kind of funny.

NOTE Confidence: 0.84734664

 $00:53:01.610 \longrightarrow 00:53:03.461$  Then we forgot that for like 9000.

NOTE Confidence: 0.84734664

 $00{:}53{:}03{.}461 \dashrightarrow 00{:}53{:}03{.}672$  Years.

NOTE Confidence: 0.84734664

 $00:53:03.672 \longrightarrow 00:53:04.516$  And then, you know,

NOTE Confidence: 0.84734664

 $00{:}53{:}04{.}520 \dashrightarrow 00{:}53{:}06{.}236$  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

 $00{:}53{:}07{.}708 \dashrightarrow 00{:}53{:}09{.}556$  at a bunch of tissues made the

NOTE Confidence: 0.84734664

 $00:53:09.556 \longrightarrow 00:53:11.314$  same kind of analysis that it

NOTE Confidence: 0.84734664

 $00{:}53{:}11{.}314 \dashrightarrow 00{:}53{:}13{.}066$  was the same in multiple tissues,

NOTE Confidence: 0.84734664

00:53:13.070 --> 00:53:13.506 you know,

NOTE Confidence: 0.84734664

 $00{:}53{:}13.506 \dashrightarrow 00{:}53{:}15.576$  even as a picture of a liver cell with

NOTE Confidence: 0.84734664

 $00:53:15.576 \rightarrow 00:53:17.190$  its kind of autophagy before they

NOTE Confidence: 0.84734664

 $00{:}53{:}17{.}190 \dashrightarrow 00{:}53{:}19{.}070$  even knew what the organelles were.

NOTE Confidence: 0.84734664

 $00{:}53{:}19{.}070 \dashrightarrow 00{:}53{:}21{.}102$  So a lot of that depends on ribosomes

NOTE Confidence: 0.84734664

 $00{:}53{:}21{.}102 \dashrightarrow 00{:}53{:}23{.}452$  and and so the metaplasia depends on

NOTE Confidence: 0.84734664

 $00:53:23.452 \rightarrow 00:53:25.800$  this collagenosis which depends on ribosome.

- NOTE Confidence: 0.84734664
- $00:53:25.800 \rightarrow 00:53:28.047$  So these are all areas where you

 $00{:}53{:}28.047 \dashrightarrow 00{:}53{:}29.922$  could target potentially both to.

NOTE Confidence: 0.84734664

00:53:29.922 --> 00:53:30.834 First metaplasia,

NOTE Confidence: 0.84734664

 $00:53:30.834 \dashrightarrow 00:53:33.570$  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

 $00:53:35.700 \longrightarrow 00:53:37.744$  of pathogenesis or P53,

NOTE Confidence: 0.84734664

 $00:53:37.750 \rightarrow 00:53:39.140$  then maybe with they proliferate

NOTE Confidence: 0.84734664

 $00:53:39.140 \longrightarrow 00:53:40.252$  by going through that.

NOTE Confidence: 0.74812823

 $00:53:48.360 \longrightarrow 00:53:52.950$  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

 $00{:}53{:}55{.}267 \dashrightarrow 00{:}53{:}57{.}704$  mice and this is our group down

NOTE Confidence: 0.74812823

 $00{:}53{:}57{.}704 \dashrightarrow 00{:}53{:}59{.}806$  in Texas with my wife's lab,

NOTE Confidence: 0.74812823

 $00:53:59.806 \rightarrow 00:54:01.930$  she's mysorekar and on the mills,

NOTE Confidence: 0.74812823

 $00:54:01.930 \dashrightarrow 00:54:04.210$  so we're the M&M labs together, so.

NOTE Confidence: 0.87300657

 $00{:}54{:}10{.}950 \dashrightarrow 00{:}54{:}11{.}920$  Yes, you know. And then.

00:54:14.080 --> 00:54:16.220 So, so I don't know,

NOTE Confidence: 0.852713134

 $00:54:16.220 \rightarrow 00:54:18.636$  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

 $00:54:21.220 \longrightarrow 00:54:24.244$  aisle 33 access which drives it

NOTE Confidence: 0.852713134

 $00:54:24.244 \rightarrow 00:54:26.777$  seemingly in in Barretts and

NOTE Confidence: 0.852713134

 $00{:}54{:}26.777 \dashrightarrow 00{:}54{:}30.460$  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

 $00:54:32.770 \longrightarrow 00:54:34.156$  is absolutely reversible.

NOTE Confidence: 0.852713134

00:54:34.160 --> 00:54:35.189 Yeah, 100% it's,

NOTE Confidence: 0.852713134

 $00:54:35.189 \rightarrow 00:54:38.070$  it's a normal way to recruit stem cells,

NOTE Confidence: 0.852713134

 $00:54:38.070 \longrightarrow 00:54:39.200$  especially for organs that don't

NOTE Confidence: 0.852713134

 $00:54:39.200 \dashrightarrow 00:54:40.730$  have stem cells like the pancreas.

NOTE Confidence: 0.852713134

 $00:54:40.730 \longrightarrow 00:54:42.158$  That's the only way the pancreas

NOTE Confidence: 0.852713134

 $00:54:42.158 \longrightarrow 00:54:43.976$  can kind of repair itself is by

NOTE Confidence: 0.852713134

 $00:54:43.976 \rightarrow 00:54:45.068$  recruiting the acinar cells.

NOTE Confidence: 0.852713134

 $00{:}54{:}45{.}070 \dashrightarrow 00{:}54{:}46{.}988$  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
- $00{:}54{:}49{.}090 \dashrightarrow 00{:}54{:}50{.}870$  enough mutations that they don't read,
- NOTE Confidence: 0.852713134
- $00:54:50.870 \longrightarrow 00:54:51.822$  differentiate and they think
- NOTE Confidence: 0.852713134
- $00:54:51.822 \rightarrow 00:54:53.250$  it's an idea to keep growing.
- NOTE Confidence: 0.852713134
- $00:54:53.250 \rightarrow 00:54:55.308$  You know, that it becomes irreversible.
- NOTE Confidence: 0.852713134
- $00:54:55.310 \longrightarrow 00:54:56.520$  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
- $00:54:57.656 \rightarrow 00:54:59.590$  which is the first question you had,
- NOTE Confidence: 0.852713134
- $00:54:59.590 \longrightarrow 00:55:00.946$  is so important.
- NOTE Confidence: 0.852713134
- 00:55:00.946 --> 00:55:02.754 Because it keeps stimulating
- NOTE Confidence: 0.852713134
- $00:55:02.754 \rightarrow 00:55:04.770$  this collagenosis until of these
- NOTE Confidence: 0.852713134
- $00{:}55{:}04{.}770 \dashrightarrow 00{:}55{:}05{.}950$  kind of old cells.
- NOTE Confidence: 0.852713134
- $00:55:05.950 \rightarrow 00:55:07.056$  You know, if you think about it,
- NOTE Confidence: 0.852713134
- $00:55:07.060 \longrightarrow 00:55:08.782$  they don't really do much error
- NOTE Confidence: 0.852713134
- $00{:}55{:}08.782 \dashrightarrow 00{:}55{:}10.316$  checking of their chromatin under
- NOTE Confidence: 0.852713134

 $00{:}55{:}10.316 \dashrightarrow 00{:}55{:}11.309$  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

 $00:55:13.820 \rightarrow 00:55:15.380$  digestive enzymes over and over again.

NOTE Confidence: 0.852713134

 $00{:}55{:}15{.}380 \dashrightarrow 00{:}55{:}16{.}700$  And most of their ribosomes

NOTE Confidence: 0.852713134

 $00:55:16.700 \longrightarrow 00:55:18.020$  are already taken care of,

NOTE Confidence: 0.852713134

 $00:55:18.020 \rightarrow 00:55:20.020$  so they're most of their chromatin is inert.

NOTE Confidence: 0.852713134

 $00:55:20.020 \rightarrow 00:55:22.036$  So then you ask them to rearrange everything,

NOTE Confidence: 0.852713134

 $00{:}55{:}22.040 \dashrightarrow 00{:}55{:}23.444$  come back into cell cycle and

NOTE Confidence: 0.852713134

 $00:55:23.444 \rightarrow 00:55:25.279$  expose a bunch of cell cycle genes,

NOTE Confidence: 0.852713134

 $00:55:25.280 \rightarrow 00:55:26.420$  which is very dangerous.

NOTE Confidence: 0.852713134

 $00:55:26.420 \longrightarrow 00:55:28.690$  So they need this error checking and it

NOTE Confidence: 0.852713134

 $00:55:28.690 \rightarrow 00:55:30.475$  just seems like we've evolved only one.

NOTE Confidence: 0.852713134

 $00:55:30.480 \longrightarrow 00:55:32.195$  Protein which is P53 to do all

NOTE Confidence: 0.852713134

 $00{:}55{:}32{.}195 \dashrightarrow 00{:}55{:}32{.}930$  that error checking.

NOTE Confidence: 0.852713134

 $00:55:32.930 \rightarrow 00:55:36.017$  So each time you go through that cycle of

 $00:55:36.017 \rightarrow 00:55:38.648$  you're asking people to three to work.

NOTE Confidence: 0.852713134

 $00:55:38.650 \rightarrow 00:55:40.432$  And the more you do it the more chances

NOTE Confidence: 0.852713134

 $00{:}55{:}40{.}432 \dashrightarrow 00{:}55{:}41{.}978$  you're taking until you get a you

NOTE Confidence: 0.852713134

 $00{:}55{:}41{.}978 \dashrightarrow 00{:}55{:}43{.}449$  know clone that doesn't have it work.

NOTE Confidence: 0.852713134

 $00:55:43.450 \rightarrow 00:55:45.538$  And then you start having more

NOTE Confidence: 0.852713134

 $00:55:45.538 \longrightarrow 00:55:46.930$  errors in each replication.

NOTE Confidence: 0.852713134

 $00{:}55{:}46{.}930 \dashrightarrow 00{:}55{:}48{.}772$  And then when that happens then

NOTE Confidence: 0.852713134

 $00:55:48.772 \longrightarrow 00:55:50.578$  eventually you'll get a make or

NOTE Confidence: 0.852713134

 $00{:}55{:}50{.}578 \dashrightarrow 00{:}55{:}52{.}377$  a rass or you know something else

NOTE Confidence: 0.852713134

 $00:55:52.377 \rightarrow 00:55:54.430$  that drives it outside the geotrack.

NOTE Confidence: 0.852713134

 $00{:}55{:}54{.}430 \dashrightarrow 00{:}55{:}54{.}701$  Yeah.

NOTE Confidence: 0.852713134

00:55:54.701 --> 00:55:56.598 Actually you know I 41 is conserved

NOTE Confidence: 0.852713134

 $00:55:56.598 \rightarrow 00:55:58.248$  all the way through plants.

NOTE Confidence: 0.852713134

 $00{:}55{:}58{.}250 \dashrightarrow 00{:}56{:}00{.}590$  It's the the the it's.

NOTE Confidence: 0.852713134

 $00:56:00.590 \rightarrow 00:56:01.202$  Amazing protein.

 $00:56:01.202 \rightarrow 00:56:03.038$  It goes right between the ribosomes.

NOTE Confidence: 0.852713134

 $00:56:03.040 \longrightarrow 00:56:04.380$  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

 $00:56:07.480 \longrightarrow 00:56:11.698$  from plants to flies to yeast.

NOTE Confidence: 0.852713134

 $00:56:11.700 \longrightarrow 00:56:13.135$  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

 $00{:}56{:}15{.}384 \dashrightarrow 00{:}56{:}17{.}314$  thing when you knock it out until

NOTE Confidence: 0.852713134

 $00{:}56{:}17.314 \dashrightarrow 00{:}56{:}19.612$  you injure and ask them to kind of

NOTE Confidence: 0.852713134

 $00{:}56{:}19.612 \dashrightarrow 00{:}56{:}21.112$  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

 $00:56:33.980 \longrightarrow 00:56:37.144$  the ability to to get all that GI

NOTE Confidence: 0.567696278571429

 $00:56:37.144 \dashrightarrow 00:56:39.584$  tract again and parasites kidney.
00:56:39.590 --> 00:56:41.590 That's a non GI Oregon also and in

NOTE Confidence: 0.567696278571429

 $00{:}56{:}41{.}590 \dashrightarrow 00{:}56{:}43{.}612$  fact all this is tied to aging in

NOTE Confidence: 0.567696278571429

 $00:56:43.612 \rightarrow 00:56:45.380$  the sense that as you get older

NOTE Confidence: 0.567696278571429

 $00:56:45.380 \longrightarrow 00:56:47.088$  you seem to be able to lose.

NOTE Confidence: 0.567696278571429

 $00{:}56{:}47.090 \dashrightarrow 00{:}56{:}48.446$  You lose these markers in these

NOTE Confidence: 0.567696278571429

 $00:56:48.446 \longrightarrow 00:56:50.167$  genes and in the bladder we

NOTE Confidence: 0.567696278571429

 $00:56:50.167 \dashrightarrow 00:56:51.697$  know that actually where each time

NOTE Confidence: 0.567696278571429

 $00{:}56{:}51{.}697 \dashrightarrow 00{:}56{:}53{.}442$  you go through UTI of shedding you

NOTE Confidence: 0.567696278571429

 $00:56:53.442 \longrightarrow 00:56:55.280$  need to recruit new stem cells.

NOTE Confidence: 0.567696278571429

 $00:56:55.280 \rightarrow 00:56:58.587$  As you age you lose I 41 and

NOTE Confidence: 0.567696278571429

 $00:56:58.587 \rightarrow 00:57:00.129$  you're less able to do this.

NOTE Confidence: 0.567696278571429

 $00:57:00.130 \rightarrow 00:57:02.994$  That's work from the My wife side actually

NOTE Confidence: 0.567696278571429

 $00{:}57{:}02.994 \dashrightarrow 00{:}57{:}04.987$  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

00:57:17.923 --> 00:57:19.838 is dangerous and some not, right?

NOTE Confidence: 0.808378845625

 $00{:}57{:}19.838 \dashrightarrow 00{:}57{:}22.462$  You know, I have no idea because that's

NOTE Confidence: 0.808378845625

 $00:57:22.462 \longrightarrow 00:57:24.783$  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

 $00:57:27.260 \rightarrow 00:57:29.549$  And you know, there's a huge controversy

NOTE Confidence: 0.808378845625

 $00{:}57{:}29{.}549 \dashrightarrow 00{:}57{:}31{.}520$  about whether it increases risk of

NOTE Confidence: 0.808378845625

 $00:57:31.520 \rightarrow 00:57:33.690$  gastric cancer or not in the absence

NOTE Confidence: 0.808378845625

 $00:57:33.748 \longrightarrow 00:57:35.470$  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

 $00{:}57{:}36{.}890 \dashrightarrow 00{:}57{:}38{.}026$  consensus is it doesn't.

NOTE Confidence: 0.808378845625

 $00:57:38.030 \dashrightarrow 00:57:40.352$  So even the very same metaplasia

NOTE Confidence: 0.808378845625

 $00{:}57{:}40{.}352 \dashrightarrow 00{:}57{:}41{.}900$  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

 $00:57:44.258 \rightarrow 00:57:48.720$  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
- $00:57:51.936 \longrightarrow 00:57:54.209$  I think 1 aspect would be the
- NOTE Confidence: 0.808378845625
- $00:57:54.209 \rightarrow 00:57:56.559$  repetitive nature and the chronicity.
- NOTE Confidence: 0.808378845625
- $00:57:56.560 \rightarrow 00:57:58.324$  Another aspect, you know,
- NOTE Confidence: 0.808378845625
- $00:57:58.324 \rightarrow 00:57:59.647$  in the stomach,
- NOTE Confidence: 0.808378845625
- $00:57:59.650 \rightarrow 00:58:01.338$  I've always thought of that H pylori is
- NOTE Confidence: 0.808378845625
- $00:58:01.338 \longrightarrow 00:58:03.240$  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
- $00{:}58{:}04{.}840 \dashrightarrow 00{:}58{:}08{.}557$  And also there's this sense of kind
- NOTE Confidence: 0.808378845625
- $00{:}58{:}08{.}557 \dashrightarrow 00{:}58{:}11{.}764$  of progression and that that
- NOTE Confidence: 0.808378845625
- $00{:}58{:}11.764 \dashrightarrow 00{:}58{:}13.605$  that glands on the border between
- NOTE Confidence: 0.808378845625
- $00{:}58{:}13.605 \dashrightarrow 00{:}58{:}15.644$  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

- $00:58:21.040 \longrightarrow 00:58:21.670$  hits an area,
- NOTE Confidence: 0.808378845625
- $00{:}58{:}21.670 \dashrightarrow 00{:}58{:}23.658$  then comes back and it's kind of back and
- NOTE Confidence: 0.808378845625
- $00{:}58{:}23.658 \dashrightarrow 00{:}58{:}25.289$  forth in different areas as opposed to
- NOTE Confidence: 0.808378845625
- $00:58:25.289 \rightarrow 00:58:27.217$  the same area going over and over again,
- NOTE Confidence: 0.808378845625
- $00{:}58{:}27{.}220 \dashrightarrow 00{:}58{:}29{.}090$  but.
- NOTE Confidence: 0.808378845625
- $00{:}58{:}29{.}090 \dashrightarrow 00{:}58{:}30{.}308$  I've never been asked that question.
- NOTE Confidence: 0.808378845625
- $00:58:30.310 \rightarrow 00:58:31.626$  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
- $00:58:35.602 \rightarrow 00:58:37.010$  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
- $00:58:39.034 \rightarrow 00:58:40.394$  complete intestinal metaplasia seems
- NOTE Confidence: 0.808378845625
- $00:58:40.394 \rightarrow 00:58:42.409$  almost protective against gastric cancer.
- NOTE Confidence: 0.808378845625
- $00:58:42.410 \dashrightarrow 00:58:45.690$  So that's another interesting fact.
- NOTE Confidence: 0.808378845625
- $00{:}58{:}45{.}690 \dashrightarrow 00{:}58{:}48{.}108$  And and I think in autoimmune
- NOTE Confidence: 0.808378845625
- $00:58:48.108 \rightarrow 00:58:49.720$  gastritis there's more complete

- NOTE Confidence: 0.808378845625
- $00:58:49.795 \longrightarrow 00:58:51.447$  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
- $00:58:53.112 \longrightarrow 00:58:55.128$  to have the kind of metaplasia where
- NOTE Confidence: 0.808378845625
- $00{:}58{:}55{.}128 \dashrightarrow 00{:}58{:}57{.}326$  you have a mixed phenotype where it's
- NOTE Confidence: 0.808378845625
- $00:58:57.326 \rightarrow 00:58:59.790$  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
- $00:59:02.090 \longrightarrow 00:59:03.410$  is asking for trouble.
- NOTE Confidence: 0.808378845625
- $00:59:03.410 \longrightarrow 00:59:05.390$  So maybe pure metaplasia are better.
- NOTE Confidence: 0.808378845625
- $00{:}59{:}05{.}390 \dashrightarrow 00{:}59{:}06{.}446$  I don't know.
- NOTE Confidence: 0.808378845625
- $00:59:06.446 \longrightarrow 00:59:07.854$  It's a good question.
- NOTE Confidence: 0.808378845625
- $00:59:07.860 \longrightarrow 00:59:08.240$  Haven't.
- NOTE Confidence: 0.559212765
- 00:59:10.510 --> 00:59:11.160 Haven't asked.
- NOTE Confidence: 0.70453817
- $00{:}59{:}13.220 \dashrightarrow 00{:}59{:}15.690$  OK. Question on the.
- NOTE Confidence: 0.25466174
- $00{:}59{:}18.090 \dashrightarrow 00{:}59{:}22.780$  Building. And you describe.
- NOTE Confidence: 0.25466174
- $00{:}59{:}22.780 \dashrightarrow 00{:}59{:}23.780$  But when you look at.
- NOTE Confidence: 0.56233963

- $00{:}59{:}26{.}390 \dashrightarrow 00{:}59{:}27{.}749$  Or the before.
- NOTE Confidence: 0.9236553
- 00:59:30.990 --> 00:59:33.800 Yeah, yeah. He.
- NOTE Confidence: 0.56206702125
- $00{:}59{:}36{.}560 \dashrightarrow 00{:}59{:}40{.}172$  Your life experiences that are known
- NOTE Confidence: 0.56206702125
- $00:59:40.172 \longrightarrow 00:59:42.680$  to alters. So the question is, drew,
- NOTE Confidence: 0.56206702125
- $00{:}59{:}42.680 \dashrightarrow 00{:}59{:}44.948$  are there germline variants of genes
- NOTE Confidence: 0.56206702125
- $00{:}59{:}44{.}948 \dashrightarrow 00{:}59{:}49{.}040$  like D at 4 the AG is the autophagy NOTE Confidence: 0.56206702125
- $00:59:49.040 \rightarrow 00:59:51.036$  genes that affect susceptibility?
- NOTE Confidence: 0.56206702125
- $00:59:51.040 \longrightarrow 00:59:53.620$  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
- $00:59:54.890 \longrightarrow 00:59:56.725$  Four is very controversial also
- NOTE Confidence: 0.56206702125
- $00:59:56.725 \longrightarrow 00:59:58.193$  from the cancer standpoint,
- NOTE Confidence: 0.56206702125
- $00{:}59{:}58{.}200 \dashrightarrow 00{:}59{:}59{.}994$  it seems like half the literature
- NOTE Confidence: 0.56206702125
- $00{:}59{:}59{.}994 \dashrightarrow 01{:}00{:}01{.}855$  says that mutations are variants or
- NOTE Confidence: 0.56206702125
- $01{:}00{:}01{.}855 \dashrightarrow 01{:}00{:}03.667$  pro tumorigenic and half are anti.
- NOTE Confidence: 0.56206702125
- $01{:}00{:}03.670 \dashrightarrow 01{:}00{:}05.930$  But the issue with pathogenesis
- NOTE Confidence: 0.56206702125
- $01:00:05.930 \rightarrow 01:00:08.618$  and tumorigenesis is you know it's

 $01{:}00{:}08.618 \dashrightarrow 01{:}00{:}10.880$  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

 $01:00:12.470 \rightarrow 01:00:14.487$  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

 $01:00:19.140 \longrightarrow 01:00:20.490$  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

 $01:00:23.132 \longrightarrow 01:00:24.269$  but actually it has an aging.

NOTE Confidence: 0.56206702125

 $01{:}00{:}24{.}270 \dashrightarrow 01{:}00{:}27{.}721$  Genotype so as you age then and

NOTE Confidence: 0.56206702125

 $01{:}00{:}27.721 \dashrightarrow 01{:}00{:}30.449$  you get inability to regenerate

NOTE Confidence: 0.56206702125

 $01{:}00{:}30{.}449 \dashrightarrow 01{:}00{:}33{.}360$  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

 $01:00:37.062 \rightarrow 01:00:39.137$  able to necessarily you've never

 $01{:}00{:}39{.}209 \dashrightarrow 01{:}00{:}41{.}243$  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

 $01{:}00{:}45.652 \dashrightarrow 01{:}00{:}47.948$  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

 $01{:}00{:}52.520 \dashrightarrow 01{:}00{:}54.978$  more specific though about autophagy.

NOTE Confidence: 0.56206702125

 $01{:}00{:}54.980 \dashrightarrow 01{:}00{:}58.326$  Which is that we have tried with a

NOTE Confidence: 0.56206702125

 $01:00:58.326 \rightarrow 01:01:00.902$  G57 and 1601 variant to show effects NOTE Confidence: 0.56206702125

 $01:01:00.902 \rightarrow 01:01:03.789$  and haven't really been successful.

NOTE Confidence: 0.56206702125

 $01{:}01{:}03.790 \dashrightarrow 01{:}01{:}05.698$  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 $\operatorname{-->}$ 01:01:08.581 down both in the pancreas and the

NOTE Confidence: 0.56206702125

 $01{:}01{:}08.581 \dashrightarrow 01{:}01{:}10.250$  stomach is by affecting lysosomes.

NOTE Confidence: 0.56206702125

 $01:01:10.250 \longrightarrow 01:01:11.858$  So if you want to really get dive

NOTE Confidence: 0.56206702125

 $01{:}01{:}11{.}858 \dashrightarrow 01{:}01{:}13{.}409$  into the autophagy aspect of it,

- NOTE Confidence: 0.56206702125
- $01:01:13.410 \longrightarrow 01:01:14.370$  we actually think it.
- NOTE Confidence: 0.56206702125
- $01:01:14.370 \longrightarrow 01:01:16.490$  It's from the EPG 5 which is the
- NOTE Confidence: 0.56206702125
- $01:01:16.490 \longrightarrow 01:01:17.738$  fusion of autophagosomes and
- NOTE Confidence: 0.56206702125
- $01:01:17.738 \rightarrow 01:01:19.489$  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
- $01:01:21.064 \rightarrow 01:01:22.460$  maybe non canonical autophagy.
- NOTE Confidence: 0.56206702125
- $01{:}01{:}22.460 \dashrightarrow 01{:}01{:}25.190$  So a knock out the the best knock out.
- NOTE Confidence: 0.56206702125
- $01:01:25.190 \longrightarrow 01:01:26.382$  They had to stop.
- NOTE Confidence: 0.56206702125
- $01:01:26.382 \longrightarrow 01:01:28.766$  The whole process is as in the
- NOTE Confidence: 0.56206702125
- $01{:}01{:}28.766 \dashrightarrow 01{:}01{:}31.406$  phosphorylation that phosphorylase that puts
- NOTE Confidence: 0.56206702125
- $01{:}01{:}31{.}406 \dashrightarrow 01{:}01{:}34{.}200$  phosphate phosphate groups on Mano six,
- NOTE Confidence: 0.56206702125
- $01{:}01{:}34.200 \dashrightarrow 01{:}01{:}35.635$  you know to make Manor 6 phosphate.
- NOTE Confidence: 0.56206702125
- $01:01:35.640 \longrightarrow 01:01:37.120$  So none of the digestive,
- NOTE Confidence: 0.56206702125
- $01{:}01{:}37{.}120 \dashrightarrow 01{:}01{:}39{.}360$  the license only enzymes go to the lysosome.
- NOTE Confidence: 0.56206702125
- $01{:}01{:}39{.}360 \dashrightarrow 01{:}01{:}40{.}785$  Those mice are completely resistant
- NOTE Confidence: 0.56206702125

 $01:01:40.785 \rightarrow 01:01:42.834$  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

 $01:01:44.544 \rightarrow 01:01:46.084$  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

 $01:01:52.504 \rightarrow 01:01:54.575$  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

 $01:01:58.130 \longrightarrow 01:01:59.294$  it's massive autophagy.

NOTE Confidence: 0.56206702125

01:01:59.294 --> 01:02:00.070 Clearly LC3,

NOTE Confidence: 0.56206702125

 $01{:}02{:}00{.}070 \dashrightarrow 01{:}02{:}02{.}870$  it's all the classic but the the main.

NOTE Confidence: 0.56206702125

 $01:02:02.870 \longrightarrow 01:02:04.641$  The thing seems to be required is

NOTE Confidence: 0.56206702125

 $01{:}02{:}04{.}641 \dashrightarrow 01{:}02{:}06{.}169$  the flux through the lysosomes.

NOTE Confidence: 0.480954455

01:02:08.800 --> 01:02:09.470 Short question.

NOTE Confidence: 0.6431545

 $01{:}02{:}11.550 \dashrightarrow 01{:}02{:}11.850$  Cheap.

 $01:02:17.630 \longrightarrow 01:02:19.674$  Yeah. So, so the question is whether

NOTE Confidence: 0.823314832142857

 $01{:}02{:}19.674 \dashrightarrow 01{:}02{:}21.568$  parietal cells can do the same thing.

NOTE Confidence: 0.823314832142857

 $01{:}02{:}21{.}570 \dashrightarrow 01{:}02{:}23{.}793$  And in fact, as part of the more general

NOTE Confidence: 0.823314832142857

 $01:02:23.793 \rightarrow 01:02:25.609$  question of is it like universal and

NOTE Confidence: 0.823314832142857

 $01{:}02{:}25{.}609 \dashrightarrow 01{:}02{:}27{.}415$  the parietal cells are great test case

NOTE Confidence: 0.823314832142857

 $01{:}02{:}27{.}415 \dashrightarrow 01{:}02{:}29{.}570$  of the only cell that we've never seen

NOTE Confidence: 0.823314832142857

 $01{:}02{:}29{.}570 \dashrightarrow 01{:}02{:}32{.}090$  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

 $01:02:33.674 \longrightarrow 01:02:35.230$  the that the experiment early on.

NOTE Confidence: 0.823314832142857

 $01:02:35.230 \longrightarrow 01:02:37.374$  So if he did when he was doing

NOTE Confidence: 0.823314832142857

 $01:02:37.374 \rightarrow 01:02:39.609$  the the tamoxifen to be marked,

NOTE Confidence: 0.823314832142857

 $01:02:39.610 \longrightarrow 01:02:41.418$  all the parietal cells,

NOTE Confidence: 0.823314832142857

 $01:02:41.418 \longrightarrow 01:02:45.179$  they all died basically and they they didn't,

NOTE Confidence: 0.823314832142857

 $01{:}02{:}45{.}180 \dashrightarrow 01{:}02{:}47{.}916$  they never seem to. D differentiate.

NOTE Confidence: 0.823314832142857

 $01{:}02{:}47{.}920 \dashrightarrow 01{:}02{:}49{.}397$  Actually we have a pretty good idea

 $01:02:49.397 \rightarrow 01:02:51.362$  because some of our work is just on

NOTE Confidence: 0.823314832142857

 $01:02:51.362 \longrightarrow 01:02:52.390$  the regular differentiation parietal

NOTE Confidence: 0.823314832142857

 $01{:}02{:}52{.}390 \dashrightarrow 01{:}02{:}54{.}208$  cells and there seems to be a

NOTE Confidence: 0.823314832142857

 $01:02:54.208 \rightarrow 01:02:55.220$  checkpoint and their differentiation,

NOTE Confidence: 0.823314832142857

 $01:02:55.220 \longrightarrow 01:02:57.056$  after which they are no longer

NOTE Confidence: 0.823314832142857

 $01:02:57.056 \longrightarrow 01:02:59.188$  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

 $01:03:00.700 \longrightarrow 01:03:03.040$  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

 $01{:}03{:}07{.}900 \dashrightarrow 01{:}03{:}09{.}442$  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

 $01{:}03{:}12.495 \dashrightarrow 01{:}03{:}14.139$  or an autoimmune gas tritis setting,

NOTE Confidence: 0.823314832142857

 $01:03:14.140 \longrightarrow 01:03:16.030$  and you can definitely see some pretty

NOTE Confidence: 0.823314832142857

 $01:03:16.030 \rightarrow 01:03:17.660$  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
- $01{:}03{:}21{.}330 \dashrightarrow 01{:}03{:}23{.}010$  but I don't think those are coming backwards.
- NOTE Confidence: 0.823314832142857
- $01:03:23.010 \rightarrow 01:03:24.702$  I think those are actually coming
- NOTE Confidence: 0.823314832142857
- $01{:}03{:}24.702 \dashrightarrow 01{:}03{:}26.808$  from the stem cell and then in
- NOTE Confidence: 0.823314832142857
- $01{:}03{:}26.808 \dashrightarrow 01{:}03{:}28.333$  the setting bottom you gas tritis.
- NOTE Confidence: 0.823314832142857
- $01{:}03{:}28{.}340 \dashrightarrow 01{:}03{:}30{.}224$  They take a detour because they're
- NOTE Confidence: 0.823314832142857
- $01:03:30.224 \rightarrow 01:03:32.295$  going to be destroyed basically by
- NOTE Confidence: 0.823314832142857
- $01{:}03{:}32{.}295 \dashrightarrow 01{:}03{:}34{.}180$  the anti parietal cell antibodies.
- NOTE Confidence: 0.823314832142857
- $01:03:34.180 \longrightarrow 01:03:36.244$  So yeah, not all cells can do it.
- NOTE Confidence: 0.823314832142857
- $01:03:36.250 \longrightarrow 01:03:39.538$  Seems like protocells are quite resistant.
- NOTE Confidence: 0.823314832142857
- $01{:}03{:}39{.}540 \dashrightarrow 01{:}03{:}40{.}368$  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
- $01:03:53.520 \rightarrow 01:03:56.340$  you know, don't present that often,
- NOTE Confidence: 0.72511107

 $01:03:56.340 \longrightarrow 01:04:01.020$  but before a bunch of pathologists, so.

NOTE Confidence: 0.72511107

 $01:04:01.020 \rightarrow 01:04:04.240$  Yeah, is the neuroendocrine proliferation,

NOTE Confidence: 0.72511107

 $01{:}04{:}04{.}240 \dashrightarrow 01{:}04{:}05{.}997$  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

 $01{:}04{:}09{.}610 \dashrightarrow 01{:}04{:}11{.}054$  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

 $01:04:15.810 \longrightarrow 01:04:18.612$  they don't look like they're normal

NOTE Confidence: 0.72511107

01:04:18.612 $\operatorname{-->}$ 01:04:20.820 endocrine cells sitting lining up

NOTE Confidence: 0.72511107

 $01:04:20.820 \longrightarrow 01:04:23.432$  with the rest of the epithelium,

NOTE Confidence: 0.72511107

 $01:04:23.432 \longrightarrow 01:04:25.001$  because normally integrins

NOTE Confidence: 0.72511107

 $01:04:25.001 \rightarrow 01:04:27.750$  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

 $01:04:28.990 \longrightarrow 01:04:31.191$  cells and then you know in these

01:04:31.191 --> 01:04:32.646 lesions you get these little,

NOTE Confidence: 0.72511107

 $01{:}04{:}32.650 \dashrightarrow 01{:}04{:}36.049$  you know, expansions.

NOTE Confidence: 0.72511107

01:04:36.050 --> 01:04:39.566 And I yeah great question.

NOTE Confidence: 0.72511107

 $01:04:39.570 \longrightarrow 01:04:41.481$  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

 $01{:}04{:}43{.}491 \dashrightarrow 01{:}04{:}45{.}880$  speak to that is one of the detours

NOTE Confidence: 0.72511107

 $01{:}04{:}45.880 \dashrightarrow 01{:}04{:}47.818$  it seems like those riddles can

NOTE Confidence: 0.72511107

 $01:04:47.818 \longrightarrow 01:04:49.695$  make but I just said is towards

NOTE Confidence: 0.72511107

 $01:04:49.695 \rightarrow 01:04:50.920$  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

 $01:04:53.412 \rightarrow 01:04:55.790$  I never really thought about it.

NOTE Confidence: 0.72511107

 $01{:}04{:}55{.}790 \dashrightarrow 01{:}04{:}57{.}742$  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

 $01{:}04{:}59{.}730 \dashrightarrow 01{:}05{:}01{.}712$  proliferation and to to try to get

NOTE Confidence: 0.72511107

 $01{:}05{:}01{.}712 \dashrightarrow 01{:}05{:}03{.}420$  a bunch of pre parietal cells but

 $01:05:03.420 \rightarrow 01:05:04.685$  what happened with time this is

NOTE Confidence: 0.72511107

 $01{:}05{:}04.685 \dashrightarrow 01{:}05{:}06.340$  when I was in Jeff Gordon's lab.

NOTE Confidence: 0.72511107

 $01:05:06.340 \longrightarrow 01:05:08.884$  What happened with time was they all

NOTE Confidence: 0.72511107

 $01:05:08.884 \rightarrow 01:05:10.858$  turned into endocrine tumors in the stomach.

NOTE Confidence: 0.72511107

 $01{:}05{:}10.860 \dashrightarrow 01{:}05{:}12.610$  So they actually went through.

NOTE Confidence: 0.72511107

 $01{:}05{:}12.610 \dashrightarrow 01{:}05{:}15.090$  So it's like they hit a certain wall

NOTE Confidence: 0.72511107

 $01{:}05{:}15{.}090 \dashrightarrow 01{:}05{:}17{.}110$  of parietal cell differentiation and

NOTE Confidence: 0.72511107

 $01{:}05{:}17{.}110 \dashrightarrow 01{:}05{:}19{.}780$  then took a detour towards endocrine.

NOTE Confidence: 0.72511107

 $01{:}05{:}19.780 \dashrightarrow 01{:}05{:}21.360$  Then it became endocrine proliferations,

NOTE Confidence: 0.72511107

 $01{:}05{:}21{.}360 \dashrightarrow 01{:}05{:}23{.}520$  and then they became metastatic

NOTE Confidence: 0.72511107

 $01:05:23.520 \longrightarrow 01:05:24.306$  neuroendocrine tumors.

NOTE Confidence: 0.72511107

01:05:24.306 --> 01:05:25.878 So I don't know,

NOTE Confidence: 0.72511107

 $01:05:25.880 \dashrightarrow 01:05:27.800$  maybe we just solved a mystery.

NOTE Confidence: 0.72511107

 $01{:}05{:}27.800 \dashrightarrow 01{:}05{:}29.928$  Maybe it's because the reason why they

NOTE Confidence: 0.72511107

 $01{:}05{:}29{.}928 \dashrightarrow 01{:}05{:}32{.}456$  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
- $01:05:34.760 \longrightarrow 01:05:36.146$  but also because.
- NOTE Confidence: 0.72511107
- $01{:}05{:}36{.}146 \dashrightarrow 01{:}05{:}38{.}918$  The pre parietal cells themselves can
- NOTE Confidence: 0.72511107
- $01:05:38.918 \longrightarrow 01:05:41.928$  fuel endocrine cells in that setting.
- NOTE Confidence: 0.72511107
- $01{:}05{:}41{.}930 \dashrightarrow 01{:}05{:}43{.}530$  Yeah, and take a detour.
- NOTE Confidence: 0.72511107
- $01:05:43.530 \longrightarrow 01:05:46.032$  They clearly can in the mouse we showed.
- NOTE Confidence: 0.72511107
- $01:05:46.032 \rightarrow 01:05:46.796$  That means it's hard,
- NOTE Confidence: 0.72511107
- $01:05:46.800 \longrightarrow 01:05:48.104$  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
- $01{:}05{:}50{.}060 \dashrightarrow 01{:}05{:}51{.}716$  they start off as pre parietal cells and
- NOTE Confidence: 0.72511107
- $01:05:51.716 \rightarrow 01:05:53.410$  then you could watch them even become,
- NOTE Confidence: 0.72511107
- $01:05:53.410 \longrightarrow 01:05:54.156$  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
- $01:05:56.770 \longrightarrow 01:05:57.460$  So yeah,
- NOTE Confidence: 0.72511107
- 01:05:57.460 --> 01:05:57.805 maybe,
- NOTE Confidence: 0.72511107
- $01:05:57.805 \longrightarrow 01:05:59.530$  maybe that's maybe your two
- NOTE Confidence: 0.72511107

 $01{:}05{:}59{.}530 \dashrightarrow 01{:}06{:}00{.}710$  questions are linked.

NOTE Confidence: 0.890194292

01:06:06.090 --> 01:06:07.360 All right. Thank you, everybody. Yeah.