WEBVTT

NOTE duration:"01:02:25"

NOTE recognizability:0.864

NOTE language:en-us

NOTE Confidence: 0.7578171925

00:00:00.000 --> 00:00:02.280 Thank you all for being here this morning.

NOTE Confidence: 0.954685983333333

00:00:04.200 --> 00:00:07.520 So today it is my pleasure to

NOTE Confidence: 0.851591256666667

00:00:07.520 --> 00:00:09.680 introduce our speaker,

NOTE Confidence: 0.851591256666667

00:00:09.680 --> 00:00:11.840 Doctor Juanita Merchant.

NOTE Confidence: 0.851591256666667

00:00:11.840 --> 00:00:14.450 Juanita joined the faculty at the

NOTE Confidence: 0.851591256666667

00:00:14.450 --> 00:00:16.692 University of Arizona College of

NOTE Confidence: 0.851591256666667

00:00:16.692 --> 00:00:20.454 Medicine in Tucson in 2018 as a

NOTE Confidence: 0.851591256666667

00:00:20.454 --> 00:00:23.633 Professor of Medicine in the UA

NOTE Confidence: 0.851591256666667

00:00:23.633 --> 00:00:26.198 Department of Medicine and Chief

NOTE Confidence: 0.851591256666667

00:00:26.198 --> 00:00:28.250 of Division of Gastroenterology

NOTE Confidence: 0.851591256666667

00:00:28.328 --> 00:00:30.393 and Hepatology and is currently

NOTE Confidence: 0.851591256666667

00:00:30.393 --> 00:00:33.063 a member of the Cancer Biology

NOTE Confidence: 0.851591256666667

00:00:33.063 --> 00:00:35.678 Research Program and is currently

NOTE Confidence: 0.851591256666667

00:00:35.680 --> 00:00:37.964 also serving as Interim Cancer

NOTE Confidence: 0.851591256666667

00:00:37.964 --> 00:00:40.440 Center Director for the Arizona

NOTE Confidence: 0.851591256666667

00:00:40.440 --> 00:00:43.440 University of Arizona Cancer Center.

NOTE Confidence: 0.851591256666667

00:00:43.440 --> 00:00:47.157 She is coming back home as she earned her

NOTE Confidence: 0.851591256666667

00:00:47.160 --> 00:00:49.880 MDPHD hair at Yale School of Medicine,

NOTE Confidence: 0.851591256666667

00:00:49.880 --> 00:00:52.905 did her internship and residency

NOTE Confidence: 0.851591256666667

00:00:52.905 --> 00:00:55.320 internal medicine at Boston,

NOTE Confidence: 0.851591256666667

00:00:55.320 --> 00:00:58.360 MA General Hospital before completing

NOTE Confidence: 0.851591256666667

00:00:58.360 --> 00:01:00.565 her Gastroenterology Fellowship

NOTE Confidence: 0.851591256666667

00:01:00.565 --> 00:01:04.240 at the University of California,

NOTE Confidence: 0.851591256666667

00:01:04.240 --> 00:01:05.892 Los Angeles.

NOTE Confidence: 0.851591256666667

00:01:05.892 --> 00:01:07.100 In 2008,

NOTE Confidence: 0.851591256666667

00:01:07.100 --> 00:01:09.170 Doctor Merchant was elected to the

NOTE Confidence: 0.851591256666667

00:01:09.170 --> 00:01:10.860 National Academy of Medicine and

NOTE Confidence: 0.851591256666667

00:01:10.917 --> 00:01:12.945 appointed a member of the National

NOTE Confidence: 0.851591256666667

00:01:12.945 --> 00:01:15.679 Institute of Health Council of Councils,

NOTE Confidence: 0.851591256666667

00:01:15.680 --> 00:01:18.130 and in 2016 she also joined the

NOTE Confidence: 0.851591256666667

00:01:18.130 --> 00:01:20.175 Board of Scientific Counselors for

NOTE Confidence: 0.851591256666667

00:01:20.175 --> 00:01:22.475 the National Institute of Diabetes

NOTE Confidence: 0.851591256666667

00:01:22.475 --> 00:01:24.959 and Digestive and Kidney Disease,

NOTE Confidence: 0.851591256666667

00:01:24.960 --> 00:01:26.840 a unit of the NIH.

NOTE Confidence: 0.851591256666667

00:01:26.840 --> 00:01:28.200 Prior to joining UA,

NOTE Confidence: 0.851591256666667

00:01:28.200 --> 00:01:30.440 she was on the faculty of

NOTE Confidence: 0.851591256666667

00:01:30.440 --> 00:01:31.640 University of Michigan.

NOTE Confidence: 0.851591256666667

00:01:31.640 --> 00:01:34.240 She's Board certified in Internal

NOTE Confidence: 0.851591256666667

00:01:34.240 --> 00:01:35.800 Medicine and Gastroenterology.

NOTE Confidence: 0.851591256666667

00:01:35.800 --> 00:01:39.640 She has written or Co written more than

NOTE Confidence: 0.851591256666667

00:01:39.640 --> 00:01:41.910 165 pair reviewed research publication

NOTE Confidence: 0.851591256666667

00:01:41.910 --> 00:01:45.279 and is editor or Co editor of two

NOTE Confidence: 0.851591256666667

00:01:45.280 --> 00:01:47.160 books and several book chapters.

NOTE Confidence: 0.851591256666667

00:01:47.160 --> 00:01:51.346 She is a Co Pi on the NAHAG Forward

NOTE Confidence: 0.851591256666667

00:01:51.346 --> 00:01:52.920 program which was developed

NOTE Confidence: 0.851591256666667

00:01:52.920 --> 00:01:55.700 to increase the number of

NOTE Confidence: 0.851591256666667

00:01:55.700 --> 00:01:56.812 academic gastroenterologists

NOTE Confidence: 0.851591256666667

00:01:56.812 --> 00:01:58.480 from underrepresented groups.

NOTE Confidence: 0.851591256666667

00:01:58.480 --> 00:02:00.500 Doctor Merchant has remained continuously

NOTE Confidence: 0.851591256666667

00:02:00.500 --> 00:02:03.473 funded by the Nah for her work in

NOTE Confidence: 0.851591256666667

00:02:03.473 --> 00:02:06.438 Gastric and newer endocrine tumors.

NOTE Confidence: 0.851591256666667

00:02:06.440 --> 00:02:08.216 Head Hodge signaling,

NOTE Confidence: 0.851591256666667

00:02:08.216 --> 00:02:09.400 gastric cancer,

NOTE Confidence: 0.851591256666667

00:02:09.400 --> 00:02:11.200 and transcriptional control

NOTE Confidence: 0.851591256666667

00:02:11.200 --> 00:02:13.600 mechanisms in colon cancer.

NOTE Confidence: 0.851591256666667

00:02:13.600 --> 00:02:16.733 Please join me in welcoming Dr.

NOTE Confidence: 0.851591256666667

00:02:16.733 --> 00:02:17.719 Monita Wharton.

NOTE Confidence: 0.46492526

00:02:21.720 --> 00:02:24.760 Great. Thank you, Doctor Rogers. Oh,

NOTE Confidence: 0.669391365

00:02:24.760 --> 00:02:25.680 here we get started.

NOTE Confidence: 0.633541566666667

00:02:26.680 --> 00:02:29.999 Well, like to present to you this plaque

NOTE Confidence: 0.8206486

00:02:30.440 --> 00:02:32.400 in honor of your presentation.

NOTE Confidence: 0.8206486

00:02:32.400 --> 00:02:35.120 PDE inhibitors, block MDSC

NOTE Confidence: 0.8206486

00:02:35.120 --> 00:02:37.840 metabolism in gastric endocarcinoma.

NOTE Confidence: 0.58184991

00:02:37.880 --> 00:02:39.960 Oh, free. Thank you. OK.

NOTE Confidence: 0.58184991

00:02:39.960 --> 00:02:41.960 So oh fixture, thank

NOTE Confidence: 0.7137229

00:02:46.040 --> 00:02:47.199 you. OK. Thank you.

NOTE Confidence: 0.880694144444444

00:02:49.240 --> 00:02:50.026 Great. Well, I'm,

NOTE Confidence: 0.880694144444444

00:02:50.026 --> 00:02:51.598 I'm really excited to be here.

NOTE Confidence: 0.880694144444444

00:02:51.600 --> 00:02:53.712 I'd probably come back

NOTE Confidence: 0.880694144444444

00:02:53.712 --> 00:02:55.260 about once or twice a year.

NOTE Confidence: 0.880694144444444

00:02:55.260 --> 00:02:57.480 I'll be back in November for the

NOTE Confidence: 0.880694144444444

00:02:57.480 --> 00:02:59.320 the Dean's Advisory Committee,

NOTE Confidence: 0.880694144444444

00:02:59.320 --> 00:03:01.224 but I'm excited to present to the

NOTE Confidence: 0.880694144444444

00:03:01.224 --> 00:03:02.559 Cancer Center today because I

NOTE Confidence: 0.880694144444444

00:03:02.560 --> 00:03:04.852 really love to get some feedback

NOTE Confidence: 0.880694144444444

00:03:04.852 --> 00:03:07.139 from the esteemed oncologists

NOTE Confidence: 0.880694144444444

00:03:07.139 --> 00:03:10.340 and faculty here at Yale.

NOTE Confidence: 0.880694144444444

00:03:10.340 --> 00:03:14.135 So that so those of us,

NOTE Confidence: 0.880694144444444

00:03:14.135 --> 00:03:14.955 so as you know,

NOTE Confidence: 0.880694144444444

00:03:14.960 --> 00:03:16.572 I'm a practicing gastroenterologist

NOTE Confidence: 0.880694144444444

00:03:16.572 --> 00:03:19.466 and for those of us on the

NOTE Confidence: 0.880694144444444

00:03:19.466 --> 00:03:21.078 more the diagnostic side,

NOTE Confidence: 0.880694144444444

00:03:21.080 --> 00:03:23.728 gastrogatinal carcinoma is primarily

NOTE Confidence: 0.880694144444444

00:03:23.728 --> 00:03:27.038 initiated by an infectious Organism

NOTE Confidence: 0.880694144444444

00:03:27.040 --> 00:03:30.211 which I'll review on the next slide

NOTE Confidence: 0.880694144444444

00:03:30.211 --> 00:03:33.400 and therefore is largely preventable.

NOTE Confidence: 0.880694144444444

00:03:33.400 --> 00:03:35.160 There obviously are some caveats

NOTE Confidence: 0.880694144444444

00:03:35.160 --> 00:03:36.920 which we can talk about,

NOTE Confidence: 0.880694144444444

00:03:36.920 --> 00:03:39.576 particularly in underrepresented minorities,

NOTE Confidence: 0.880694144444444

00:03:39.576 --> 00:03:43.560 but here is the basic summary.

NOTE Confidence: 0.880694144444444

00:03:43.560 --> 00:03:46.240 Gastric cancer worldwide has used,

NOTE Confidence: 0.880694144444444

00:03:46.240 --> 00:03:48.179 we used to say the second or

NOTE Confidence: 0.880694144444444

00:03:48.179 --> 00:03:49.480 third most frequent cancer,

NOTE Confidence: 0.880694144444444

00:03:49.480 --> 00:03:51.440 but has now dropped to about the 5th,

NOTE Confidence: 0.880694144444444

00:03:51.440 --> 00:03:52.880 probably because more intensive,

NOTE Confidence: 0.880694144444444

00:03:52.880 --> 00:03:53.960 particularly in Asia,

NOTE Confidence: 0.880694144444444

00:03:53.960 --> 00:03:56.516 in terms of screening and surveillance.

NOTE Confidence: 0.880694144444444

00:03:56.520 --> 00:03:57.496 But still,

NOTE Confidence: 0.880694144444444

00:03:57.496 --> 00:04:00.912 if that type of diagnosis is still

NOTE Confidence: 0.880694144444444

00:04:00.912 --> 00:04:03.837 associated with a high mortality rate,

NOTE Confidence: 0.880694144444444

00:04:03.840 --> 00:04:05.550 about 27,000 cases,

NOTE Confidence: 0.880694144444444

00:04:05.550 --> 00:04:09.360 new cases will be identified in the

NOTE Confidence: 0.880694144444444

00:04:09.360 --> 00:04:13.320 US and it's about 11,000 deaths.

NOTE Confidence: 0.880694144444444

00:04:13.320 --> 00:04:15.546 The important point here with respect

NOTE Confidence: 0.880694144444444

00:04:15.546 --> 00:04:17.562 to prevention is the infectious

NOTE Confidence: 0.880694144444444

00:04:17.562 --> 00:04:20.358 component that can initiate this cancer.

NOTE Confidence: 0.880694144444444

00:04:20.360 --> 00:04:22.526 And the person Barry Marshall and

NOTE Confidence: 0.880694144444444

00:04:22.526 --> 00:04:25.006 Robin Warren got the Nobel Prize

NOTE Confidence: 0.880694144444444

00:04:25.006 --> 00:04:26.934 for discovering the association

NOTE Confidence: 0.880694144444444

00:04:26.934 --> 00:04:28.862 of Helicobacter pylori first

NOTE Confidence: 0.880694144444444

00:04:28.929 --> 00:04:31.419 with ulcers but then made the

NOTE Confidence: 0.880694144444444

00:04:31.419 --> 00:04:33.079 association with gastric cancer.

NOTE Confidence: 0.880694144444444

00:04:33.080 --> 00:04:37.200 But also there we need to think about dietary

NOTE Confidence: 0.880694144444444

00:04:37.200 --> 00:04:40.560 components such as high salt nitrates.

NOTE Confidence: 0.880694144444444

00:04:40.560 --> 00:04:45.280 The other less frequent infection is a viral

NOTE Confidence: 0.880694144444444

00:04:45.280 --> 00:04:49.160 infection with Epstein Barr virus or EBV.

NOTE Confidence: 0.880694144444444

00:04:49.160 --> 00:04:54.900 So the in the US the prevalence

NOTE Confidence: 0.880694144444444

00:04:54.900 --> 00:04:57.576 of gastric cancer has declined.

NOTE Confidence: 0.880694144444444

00:04:57.576 --> 00:04:59.896 So from probably from about

NOTE Confidence: 0.880694144444444

00:04:59.896 --> 00:05:02.440 the 1920s to about the 1960s,

NOTE Confidence: 0.880694144444444

00:05:02.440 --> 00:05:05.070 gastric cancer was probably the

NOTE Confidence: 0.880694144444444

00:05:05.070 --> 00:05:06.944 second most frequent cancer,

NOTE Confidence: 0.880694144444444

00:05:06.944 --> 00:05:10.080 but then with an improvement in sanitation,

NOTE Confidence: 0.880694144444444

00:05:10.080 --> 00:05:12.236 which has not occurred in certain places.

NOTE Confidence: 0.880694144444444

00:05:12.240 --> 00:05:13.329 Being in Arizona,

NOTE Confidence: 0.880694144444444

00:05:13.329 --> 00:05:15.870 this is a big issue on the

NOTE Confidence: 0.880694144444444

00:05:15.960 --> 00:05:17.616 Native American reservations,

NOTE Confidence: 0.880694144444444

00:05:17.616 --> 00:05:20.112 but that was what was probably

NOTE Confidence: 0.880694144444444

00:05:20.112 --> 00:05:22.444 driving the decline in the US

NOTE Confidence: 0.880694144444444

00:05:22.444 --> 00:05:23.796 because Helicobacter is found

NOTE Confidence: 0.880694144444444

00:05:23.796 --> 00:05:25.919 in the water table basically.

NOTE Confidence: 0.880694144444444

00:05:25.920 --> 00:05:26.485 However,

NOTE Confidence: 0.880694144444444

00:05:26.485 --> 00:05:29.875 it is continuing to rise in

NOTE Confidence: 0.880694144444444

00:05:29.880 --> 00:05:31.720 minorities and immigrant communities.

NOTE Confidence: 0.880694144444444

00:05:31.720 --> 00:05:33.560 The other interesting issue

NOTE Confidence: 0.880694144444444

00:05:33.560 --> 00:05:35.598 with respect to gastric cancer,

NOTE Confidence: 0.880694144444444

00:05:35.600 --> 00:05:37.172 so that's really the distal cancer

NOTE Confidence: 0.880694144444444

00:05:37.172 --> 00:05:39.000 and I don't remember if I I think

NOTE Confidence: 0.880694144444444

00:05:39.000 --> 00:05:40.422 I do include a picture of the

NOTE Confidence: 0.880694144444444

00:05:40.422 --> 00:05:41.832 stomach for those not familiar

NOTE Confidence: 0.880694144444444

00:05:41.832 --> 00:05:43.328 about thinking about the different

NOTE Confidence: 0.880694144444444

00:05:43.328 --> 00:05:44.800 regions of the stomach.

NOTE Confidence: 0.880694144444444

00:05:44.800 --> 00:05:45.280 But the

NOTE Confidence: 0.937493095714286

00:05:47.400 --> 00:05:50.933 cancers that are arising in the cardia are

NOTE Confidence: 0.937493095714286

00:05:50.933 --> 00:05:55.197 rising and are thought to be more associated

NOTE Confidence: 0.937493095714286

00:05:55.200 --> 00:05:59.080 with the maybe increase in use of Ppis.

NOTE Confidence: 0.937493095714286

00:05:59.080 --> 00:06:02.280 I'll come back to that point in a little bit.

NOTE Confidence: 0.937493095714286

00:06:02.280 --> 00:06:06.388 But in general the the needle really has

NOTE Confidence: 0.937493095714286

00:06:06.388 --> 00:06:08.997 been moved more in Asia where Helicobacter

NOTE Confidence: 0.937493095714286

00:06:08.997 --> 00:06:12.154 is pretty much endemic in the population

NOTE Confidence: 0.937493095714286

00:06:12.160 --> 00:06:13.910 and certainly on the West Coast where

NOTE Confidence: 0.937493095714286

00:06:13.910 --> 00:06:15.917 you see more of the Asian immigrants.

NOTE Confidence: 0.937493095714286

00:06:15.920 --> 00:06:18.920 It's still fairly prevalent with

NOTE Confidence: 0.937493095714286

00:06:18.920 --> 00:06:21.320 the first degree relatives,

NOTE Confidence: 0.937493095714286

00:06:21.320 --> 00:06:23.690 but you can see the highest

NOTE Confidence: 0.937493095714286

00:06:23.690 --> 00:06:26.399 incidence tends to be in East Asia.

NOTE Confidence: 0.937493095714286

00:06:26.400 --> 00:06:29.112 China, Japan and Korea per capita

NOTE Confidence: 0.937493095714286

00:06:29.112 --> 00:06:31.640 is actually Korea's the highest.

NOTE Confidence: 0.937493095714286

00:06:31.640 --> 00:06:35.476 So what I'll be covering today is

NOTE Confidence: 0.937493095714286

00:06:35.476 --> 00:06:39.208 how we ended up starting to address

NOTE Confidence: 0.937493095714286

00:06:39.208 --> 00:06:42.455 this issue or why we started looking

NOTE Confidence: 0.937493095714286

00:06:42.455 --> 00:06:45.749 at this question in terms of what is

NOTE Confidence: 0.937493095714286

00:06:45.749 --> 00:06:48.830 driving the inflammation to change the

NOTE Confidence: 0.937493095714286

00:06:48.830 --> 00:06:51.540 mucosa from chronic inflammation to

NOTE Confidence: 0.937493095714286

00:06:51.632 --> 00:06:54.836 the metaplastic changes in the stomach.

NOTE Confidence: 0.937493095714286

00:06:54.840 --> 00:06:57.900 And we came at this or I came at this

NOTE Confidence: 0.937493095714286

00:06:57.989 --> 00:07:02.200 from the the Hedgehog signaling pathway

NOTE Confidence: 0.937493095714286

00:07:02.200 --> 00:07:04.477 which I'll show you why in a few minutes.

NOTE Confidence: 0.937493095714286

00:07:04.480 --> 00:07:06.868 And then we started asking questions

NOTE Confidence: 0.937493095714286

00:07:06.868 --> 00:07:09.776 in terms of translating from our mouse

NOTE Confidence: 0.937493095714286

00:07:09.776 --> 00:07:14.346 models to what can we do in in people

NOTE Confidence: 0.937493095714286

00:07:14.346 --> 00:07:18.357 and in moving from Michigan to Arizona,

NOTE Confidence: 0.937493095714286

00:07:18.360 --> 00:07:20.460 have been fortunate to start to collaborate

NOTE Confidence: 0.937493095714286

00:07:20.460 --> 00:07:22.634 with some of the oncologists there to

NOTE Confidence: 0.937493095714286

00:07:22.634 --> 00:07:24.804 begin a phase two clinical trial which

NOTE Confidence: 0.937493095714286

00:07:24.804 --> 00:07:26.502 we're very excited about based upon

NOTE Confidence: 0.937493095714286

00:07:26.502 --> 00:07:30.520 some of the findings in our mouse models.

NOTE Confidence: 0.937493095714286

00:07:30.520 --> 00:07:33.184 So again from a

NOTE Confidence: 0.937493095714286

00:07:33.184 --> 00:07:34.516 gastroenterologist perspective,

NOTE Confidence: 0.937493095714286

00:07:34.520 --> 00:07:38.076 you know what we typically are seeing

NOTE Confidence: 0.937493095714286

00:07:38.080 --> 00:07:40.155 in many instances patients really

NOTE Confidence: 0.937493095714286

00:07:40.155 --> 00:07:43.900 don't even come to be seen by the

NOTE Confidence: 0.937493095714286

00:07:43.900 --> 00:07:45.976 physician and already have metaplasia.

NOTE Confidence: 0.937493095714286

00:07:45.976 --> 00:07:48.340 So I scoped many patients that

NOTE Confidence: 0.937493095714286

00:07:48.409 --> 00:07:50.277 just have chronic gastritis,

NOTE Confidence: 0.937493095714286

00:07:50.280 --> 00:07:51.240 sometimes metaplasia,

NOTE Confidence: 0.937493095714286

00:07:51.240 --> 00:07:55.080 but no helicobacter is nowhere to be found.

NOTE Confidence: 0.937493095714286

00:07:55.080 --> 00:07:57.402 What is the connection between metaplasia

NOTE Confidence: 0.937493095714286

00:07:57.402 --> 00:07:59.919 in the stomach and the esophagus?

NOTE Confidence: 0.937493095714286

00:07:59.920 --> 00:08:01.712 And when I looked into the history

NOTE Confidence: 0.937493095714286

00:08:01.712 --> 00:08:02.880 of this term, metaplasia,

NOTE Confidence: 0.937493095714286

00:08:02.880 --> 00:08:04.480 what's interesting is that,

NOTE Confidence: 0.937493095714286

00:08:04.480 --> 00:08:05.860 so if people remember,

NOTE Confidence: 0.937493095714286

00:08:05.860 --> 00:08:07.930 you basically have that goblet cell

NOTE Confidence: 0.937493095714286

00:08:07.996 --> 00:08:10.318 that's normally in the small intestine,

NOTE Confidence: 0.937493095714286

00:08:10.320 --> 00:08:12.196 but it's showing up in the stomach

NOTE Confidence: 0.937493095714286

00:08:12.196 --> 00:08:13.680 or in the esophagus.

NOTE Confidence: 0.937493095714286

00:08:13.680 --> 00:08:15.472 So I like to the pathologist like to

NOTE Confidence: 0.937493095714286

00:08:15.472 --> 00:08:17.637 say a normal cell in the wrong place,

NOTE Confidence: 0.937493095714286

00:08:17.640 --> 00:08:20.478 but that's signifying that the mucosa

NOTE Confidence: 0.937493095714286

00:08:20.478 --> 00:08:24.039 is starting to move more toward cancer,

NOTE Confidence: 0.937493095714286

00:08:24.040 --> 00:08:27.250 we think maybe more directly in

NOTE Confidence: 0.937493095714286

00:08:27.250 --> 00:08:29.691 response to the immune microenvironment

NOTE Confidence: 0.937493095714286

00:08:29.691 --> 00:08:32.890 as opposed to the bug being there

NOTE Confidence: 0.937493095714286

00:08:32.967 --> 00:08:35.437 pushing the mucosa toward cancer.

NOTE Confidence: 0.937493095714286

00:08:35.440 --> 00:08:37.778 But this issue of metaplasia and it

NOTE Confidence: 0.937493095714286

00:08:37.778 --> 00:08:40.592 the link of metaplasia to a cancer

NOTE Confidence: 0.937493095714286

00:08:40.592 --> 00:08:43.196 was really initially identified in the

NOTE Confidence: 0.937493095714286

00:08:43.269 --> 00:08:45.757 esophagus with Barrett's esophagus.

NOTE Confidence: 0.937493095714286

00:08:45.760 --> 00:08:48.640 So that metaplastic change in the

NOTE Confidence: 0.937493095714286

00:08:48.640 --> 00:08:52.171 esophagus is a precursor lesion and we

NOTE Confidence: 0.937493095714286

00:08:52.171 --> 00:08:54.319 actually have surveillance approaches

NOTE Confidence: 0.937493095714286

00:08:54.319 --> 00:08:57.960 for patients that have Barrett's esophagus.

NOTE Confidence: 0.937493095714286

00:08:57.960 --> 00:09:01.455 So the debate in the GI field is

NOTE Confidence: 0.937493095714286

00:09:01.455 --> 00:09:04.551 you know is it going to be worth to

NOTE Confidence: 0.937493095714286

00:09:04.551 --> 00:09:06.587 actually start doing surveillance

NOTE Confidence: 0.937493095714286

00:09:06.587 --> 00:09:08.932 for gastric cancer based upon

NOTE Confidence: 0.937493095714286

00:09:08.932 --> 00:09:10.556 identification of intestinal metaplasia

NOTE Confidence: 0.937493095714286

00:09:10.556 --> 00:09:12.480 and the jury still out.

NOTE Confidence: 0.937493095714286

00:09:12.480 --> 00:09:15.000 I'm actually going to an NCI think

NOTE Confidence: 0.937493095714286

00:09:15.000 --> 00:09:18.272 tank next week we're we're going to be

NOTE Confidence: 0.937493095714286

00:09:18.272 --> 00:09:21.157 discussing this whether we can change

NOTE Confidence: 0.937493095714286

00:09:21.157 --> 00:09:23.757 the recommendations for gastric metaplasia.

NOTE Confidence: 0.850938991428571

00:09:23.760 --> 00:09:25.797 But the reason why that that is,

NOTE Confidence: 0.850938991428571

00:09:25.800 --> 00:09:27.416 is because the question

NOTE Confidence: 0.850938991428571

00:09:27.416 --> 00:09:29.436 becomes who do we survey,

NOTE Confidence: 0.850938991428571

00:09:29.440 --> 00:09:31.800 when do we survey them and how often,

NOTE Confidence: 0.850938991428571

00:09:31.800 --> 00:09:35.200 which is where the cost comes in.

NOTE Confidence: 0.850938991428571

00:09:35.200 --> 00:09:37.824 So this is a picture of for those

NOTE Confidence: 0.850938991428571

00:09:37.824 --> 00:09:40.065 not familiar with the four regions

NOTE Confidence: 0.850938991428571

00:09:40.065 --> 00:09:41.816 of the stomach, the cardia,

NOTE Confidence: 0.850938991428571

00:09:41.816 --> 00:09:43.972 which is where you see the incidence

NOTE Confidence: 0.850938991428571

00:09:43.972 --> 00:09:46.160 of this cardiac cancer is higher.

NOTE Confidence: 0.850938991428571

00:09:46.160 --> 00:09:49.156 And this was a nice review article

NOTE Confidence: 0.850938991428571

00:09:49.160 --> 00:09:51.528 by the Gastroenterology Group

NOTE Confidence: 0.850938991428571

00:09:51.528 --> 00:09:55.080 Samir Gupta leading that from UCSD,

NOTE Confidence: 0.850938991428571

00:09:55.080 --> 00:09:58.208 where cancer at the cardia tends to be

NOTE Confidence: 0.850938991428571

00:09:58.208 --> 00:10:01.600 higher in lice and less so in minorities.

NOTE Confidence: 0.850938991428571

00:10:01.600 --> 00:10:03.615 And it's more strongly associated

NOTE Confidence: 0.850938991428571

00:10:03.615 --> 00:10:06.220 with GERD and obesity and not

NOTE Confidence: 0.850938991428571

00:10:06.220 --> 00:10:07.759 with socioeconomic status.

NOTE Confidence: 0.850938991428571

00:10:07.760 --> 00:10:11.514 Whereas the traditional cancer that

NOTE Confidence: 0.850938991428571

00:10:11.514 --> 00:10:13.299 is associated with Helicobacter pylori

NOTE Confidence: 0.850938991428571

00:10:13.299 --> 00:10:15.665 infection tends to be in the body of

NOTE Confidence: 0.850938991428571

00:10:15.665 --> 00:10:17.480 the stomach where the parietal cells sit.

NOTE Confidence: 0.850938991428571

00:10:17.480 --> 00:10:18.800 And the antrum of the stomach,

NOTE Confidence: 0.850938991428571

00:10:18.800 --> 00:10:20.662 which is another name for is the

NOTE Confidence: 0.850938991428571

00:10:20.662 --> 00:10:22.160 endocrine part of the stomach,

NOTE Confidence: 0.850938991428571

00:10:22.160 --> 00:10:23.777 which is where the G cells that

NOTE Confidence: 0.850938991428571

00:10:23.777 --> 00:10:24.239 produce gastro.

NOTE Confidence: 0.850938991428571

00:10:24.240 --> 00:10:25.182 And the reason I'll be coming

NOTE Confidence: 0.850938991428571

00:10:25.182 --> 00:10:26.160 back to that in a second.

NOTE Confidence: 0.850938991428571

00:10:26.160 --> 00:10:29.120 And so it's this region here that then

NOTE Confidence: 0.850938991428571

00:10:29.120 --> 00:10:31.520 it's connected to the small intestine.

NOTE Confidence: 0.850938991428571

00:10:31.520 --> 00:10:33.685 So this is more strongly

NOTE Confidence: 0.850938991428571

00:10:33.685 --> 00:10:36.244 associated with socio increase in,

NOTE Confidence: 0.850938991428571

00:10:36.244 --> 00:10:38.899 decrease in socio economic status

NOTE Confidence: 0.850938991428571

00:10:38.899 --> 00:10:41.959 and underrepresented minorities.

NOTE Confidence: 0.850938991428571

00:10:41.960 --> 00:10:44.200 And so definitely in Arizona,

NOTE Confidence: 0.850938991428571

00:10:44.200 --> 00:10:47.350 we're seeing high incidence in Hispanics

NOTE Confidence: 0.850938991428571

00:10:47.350 --> 00:10:50.440 and the Native American population.

NOTE Confidence: 0.850938991428571

00:10:50.440 --> 00:10:53.520 So as I mentioned earlier,

NOTE Confidence: 0.850938991428571

00:10:53.520 --> 00:10:56.075 there's a increase in interest

NOTE Confidence: 0.850938991428571

00:10:56.075 --> 00:10:58.119 in the tumor microenvironment,

NOTE Confidence: 0.850938991428571

00:10:58.120 --> 00:11:00.808 which I think this is well known

NOTE Confidence: 0.850938991428571

00:11:00.808 --> 00:11:02.920 to the oncology group here,

NOTE Confidence: 0.850938991428571

00:11:02.920 --> 00:11:07.022 which is a very heterogeneous environment

NOTE Confidence: 0.850938991428571

00:11:07.022 --> 00:11:09.794 that is comprised of stromal cells,

NOTE Confidence: 0.850938991428571

00:11:09.800 --> 00:11:10.608 neuronal endothelial.

NOTE Confidence: 0.850938991428571

00:11:10.608 --> 00:11:13.840 But you know most of the work now

NOTE Confidence: 0.850938991428571

00:11:13.914 --> 00:11:16.248 is really focused on the immune

NOTE Confidence: 0.850938991428571

00:11:16.248 --> 00:11:19.234 cells because this is a the target

NOTE Confidence: 0.850938991428571

00:11:19.234 --> 00:11:21.038 for the checkpoint inhibitors.

NOTE Confidence: 0.850938991428571

00:11:21.040 --> 00:11:23.344 And so we are coming at this from the

NOTE Confidence: 0.850938991428571

00:11:23.344 --> 00:11:25.378 approach that if we can decipher a bit

NOTE Confidence: 0.850938991428571

00:11:25.378 --> 00:11:27.010 more about the tumor microenvironment

NOTE Confidence: 0.850938991428571

00:11:27.010 --> 00:11:29.100 particularly in gastric cancer where

NOTE Confidence: 0.850938991428571

00:11:29.100 --> 00:11:31.635 we already know that the initiation

NOTE Confidence: 0.850938991428571

00:11:31.635 --> 00:11:34.610 of the inflammation is from a an

NOTE Confidence: 0.850938991428571

00:11:34.693 --> 00:11:37.339 infectious agents most of the time

NOTE Confidence: 0.850938991428571

00:11:37.339 --> 00:11:40.448 that we can develop better targets

NOTE Confidence: 0.850938991428571

00:11:40.448 --> 00:11:43.520 for treatment and biomarkers.

NOTE Confidence: 0.850938991428571

00:11:43.520 --> 00:11:47.200 So this is actually an example of the

NOTE Confidence: 0.850938991428571

00:11:47.200 --> 00:11:50.952 what we call the Correa paradigm which

NOTE Confidence: 0.850938991428571

00:11:50.952 --> 00:11:53.593 Playa Correa who say epidemiologist

NOTE Confidence: 0.850938991428571

00:11:53.593 --> 00:11:56.758 who initially was in Columbia,

NOTE Confidence: 0.850938991428571

00:11:56.760 --> 00:11:59.238 South America and made the observation

NOTE Confidence: 0.850938991428571

00:11:59.238 --> 00:12:01.880 and published in The Lancet in 75.

NOTE Confidence: 0.850938991428571

00:12:01.880 --> 00:12:03.700 This observation that there was

NOTE Confidence: 0.850938991428571

00:12:03.700 --> 00:12:05.520 chronic inflammation in the stomach

NOTE Confidence: 0.850938991428571

00:12:05.520 --> 00:12:07.620 that progressed on to cancer and

NOTE Confidence: 0.850938991428571

00:12:07.620 --> 00:12:09.931 this is looking at obviously if

NOTE Confidence: 0.850938991428571

00:12:09.931 --> 00:12:12.026 this is an epidemiologic study

NOTE Confidence: 0.850938991428571

00:12:12.026 --> 00:12:14.039 looking at people over time.

NOTE Confidence: 0.850938991428571

00:12:14.040 --> 00:12:16.819 But he noticed that there was sort

NOTE Confidence: 0.850938991428571

00:12:16.819 --> 00:12:18.866 of this intermediate stage where

NOTE Confidence: 0.850938991428571

00:12:18.866 --> 00:12:21.596 some people had loss of the acid

NOTE Confidence: 0.850938991428571

00:12:21.596 --> 00:12:24.443 secreting portion of the stomach and a

NOTE Confidence: 0.850938991428571

00:12:24.443 --> 00:12:28.238 substitution of the normal epithelium of

NOTE Confidence: 0.850938991428571

00:12:28.238 --> 00:12:31.754 the stomach with this mucous phenotype,

NOTE Confidence: 0.850938991428571

00:12:31.760 --> 00:12:33.908 what we call metaplasia.

NOTE Confidence: 0.850938991428571

00:12:33.908 --> 00:12:36.230 And in the in humans,

NOTE Confidence: 0.850938991428571

00:12:36.230 --> 00:12:37.650 the pathologists will read

NOTE Confidence: 0.850938991428571

00:12:37.650 --> 00:12:38.715 out intestinal metaplasia,

NOTE Confidence: 0.850938991428571

00:12:38.720 --> 00:12:41.960 which is an example here where

NOTE Confidence: 0.850938991428571

00:12:41.960 --> 00:12:43.720 you see goblet cells,

NOTE Confidence: 0.850938991428571

00:12:43.720 --> 00:12:45.838 even panic cells in the stomach.

NOTE Confidence: 0.850938991428571

00:12:45.840 --> 00:12:47.880 This is the intestinal type.

NOTE Confidence: 0.850938991428571

00:12:47.880 --> 00:12:50.826 The colonic type is actually more

NOTE Confidence: 0.850938991428571

00:12:50.826 --> 00:12:53.218 strongly associated with gastric cancer

NOTE Confidence: 0.850938991428571

00:12:53.218 --> 00:12:55.994 and it's more of this foamy type of

NOTE Confidence: 0.83324198

00:12:56.000 --> 00:12:57.335 mucous metaplasia that

NOTE Confidence: 0.83324198

00:12:57.335 --> 00:12:59.560 one sees in the stomach.

NOTE Confidence: 0.83324198

00:12:59.560 --> 00:13:02.220 And so there's about half the world

NOTE Confidence: 0.83324198

00:13:02.220 --> 00:13:04.523 is infected with Helicobacter and

NOTE Confidence: 0.83324198

00:13:04.523 --> 00:13:07.238 may develop this chronic gastritis,

NOTE Confidence: 0.83324198

00:13:07.240 --> 00:13:10.714 but then about 10% will go on to develop

NOTE Confidence: 0.83324198

00:13:10.720 --> 00:13:15.052 metaplasia and 1 to 3% gastric carcinoma.

NOTE Confidence: 0.83324198

00:13:15.052 --> 00:13:16.756 So the thought is,

NOTE Confidence: 0.83324198

00:13:16.760 --> 00:13:21.550 is that this the tipping point in with

NOTE Confidence: 0.83324198

00:13:21.550 --> 00:13:24.000 respect to the progression toward

NOTE Confidence: 0.83324198

00:13:24.000 --> 00:13:26.400 the the likelihood of progression

NOTE Confidence: 0.83324198

00:13:26.400 --> 00:13:29.820 toward cancer is at this step where

NOTE Confidence: 0.83324198

00:13:29.820 --> 00:13:32.280 there is atrophy and metaplasia.

NOTE Confidence: 0.83324198

00:13:32.280 --> 00:13:35.196 And we started asking the question

NOTE Confidence: 0.83324198

00:13:35.196 --> 00:13:37.632 whether hedgehog signaling might be

NOTE Confidence: 0.83324198

00:13:37.632 --> 00:13:40.152 important in this transition of the

NOTE Confidence: 0.83324198

00:13:40.152 --> 00:13:42.056 mucosa from chronic inflammation

NOTE Confidence: 0.83324198

00:13:42.056 --> 00:13:44.316 to the metaplastic change.

NOTE Confidence: 0.83324198

00:13:44.320 --> 00:13:47.320 And I've added here to emphasize

NOTE Confidence: 0.83324198

00:13:47.320 --> 00:13:49.320 that the Pilea Correa,

NOTE Confidence: 0.83324198

00:13:49.320 --> 00:13:51.980 the paradigm was basically formulated

NOTE Confidence: 0.83324198

00:13:51.980 --> 00:13:55.144 before the discovery of Helicobacter and

NOTE Confidence: 0.83324198

00:13:55.144 --> 00:13:57.264 then once Helicobacter was identified

NOTE Confidence: 0.83324198

00:13:57.264 --> 00:14:00.480 that the link was then made to this

NOTE Confidence: 0.83324198

00:14:00.480 --> 00:14:02.264 chronic and then atrophic gastritis.

NOTE Confidence: 0.83324198

00:14:02.264 --> 00:14:04.400 But we asked the question about

NOTE Confidence: 0.83324198

00:14:04.468 --> 00:14:06.631 hedgehog signaling and really is it was

NOTE Confidence: 0.83324198

00:14:06.631 --> 00:14:09.592 because of a incidental finding by Andy

NOTE Confidence: 0.83324198

00:14:09.592 --> 00:14:12.640 McMahon's group at Harvard in 2000,

NOTE Confidence: 0.83324198

00:14:12.640 --> 00:14:14.914 where they published a paper saying

NOTE Confidence: 0.83324198

00:14:14.914 --> 00:14:16.949 that the Sonic Hedgehog knockout

NOTE Confidence: 0.83324198

00:14:16.949 --> 00:14:18.760 mouse resulted in gastric metaplasia.

NOTE Confidence: 0.83324198

00:14:18.760 --> 00:14:21.320 It turned out that probably wasn't accurate,

NOTE Confidence: 0.83324198

00:14:21.320 --> 00:14:24.240 it probably was more hyperproliferation,

NOTE Confidence: 0.83324198

00:14:24.240 --> 00:14:26.688 but they didn't have any GI

NOTE Confidence: 0.83324198

00:14:26.688 --> 00:14:28.320 pathologists reviewing those slides.

NOTE Confidence: 0.94402933

00:14:30.840 --> 00:14:34.828 So, but based upon that MO El Zatari

NOTE Confidence: 0.94402933

00:14:34.828 --> 00:14:36.800 at the time who was in my lab,

NOTE Confidence: 0.94402933

00:14:36.800 --> 00:14:40.916 we actually obtained the mice that

NOTE Confidence: 0.94402933

00:14:40.920 --> 00:14:43.496 are in which the Laxi reporter is

NOTE Confidence: 0.94402933

00:14:43.496 --> 00:14:46.299 knocked into the locus of the Glee

NOTE Confidence: 0.94402933

00:14:46.299 --> 00:14:48.324 one which is the transcription

NOTE Confidence: 0.94402933

00:14:48.324 --> 00:14:50.942 factor and is the transcriptional

NOTE Confidence: 0.94402933

00:14:50.942 --> 00:14:53.078 readout for Hedgehog signaling.

NOTE Confidence: 0.94402933

00:14:53.080 --> 00:14:54.520 So we obtained these mice,

NOTE Confidence: 0.94402933

00:14:54.520 --> 00:14:58.680 so the knock in of the Laxi molecule,

NOTE Confidence: 0.94402933

00:14:58.680 --> 00:15:00.500 we're able to maintain these mice in

NOTE Confidence: 0.94402933

00:15:00.500 --> 00:15:02.120 the heterozygous or homozygous state.

NOTE Confidence: 0.94402933

00:15:02.120 --> 00:15:04.652 But essentially you have a, you know,

NOTE Confidence: 0.94402933

00:15:04.652 --> 00:15:07.214 a total body knockout and he infected

NOTE Confidence: 0.94402933

00:15:07.214 --> 00:15:08.643 those mice with helicobacter.

NOTE Confidence: 0.94402933

00:15:08.643 --> 00:15:11.184 Now we typically use Feliz in the

NOTE Confidence: 0.94402933

00:15:11.184 --> 00:15:13.985 mice because you get a much more

NOTE Confidence: 0.94402933

00:15:13.985 --> 00:15:15.597 aggressive inflammatory response sooner.

NOTE Confidence: 0.94402933

00:15:15.600 --> 00:15:18.048 We were hoping to save a little bit of

NOTE Confidence: 0.94402933

00:15:18.048 --> 00:15:22.118 money and and see changes, you know,

NOTE Confidence: 0.94402933

00:15:22.120 --> 00:15:23.597 and not have to wait six months.

NOTE Confidence: 0.94402933

00:15:23.600 --> 00:15:25.525 But with pylori itself using

NOTE Confidence: 0.94402933

00:15:25.525 --> 00:15:26.680 the human pathogen,

NOTE Confidence: 0.94402933

00:15:26.680 --> 00:15:28.880 it can take a lot longer and the

NOTE Confidence: 0.94402933

00:15:28.880 --> 00:15:31.478 inflammatory response is not as robust.

NOTE Confidence: 0.94402933

00:15:31.480 --> 00:15:35.180 So he looked at the mice

NOTE Confidence: 0.94402933

00:15:35.180 --> 00:15:37.680 at the time of infection,

NOTE Confidence: 0.94402933

00:15:37.680 --> 00:15:39.480 two months after infection and

NOTE Confidence: 0.94402933

00:15:39.480 --> 00:15:41.280 then six months after infection.

NOTE Confidence: 0.94402933

00:15:41.280 --> 00:15:45.426 And so you can actually identify

NOTE Confidence: 0.94402933

00:15:45.426 --> 00:15:47.935 fluorescently using an antibody.

NOTE Confidence: 0.94402933

00:15:47.935 --> 00:15:52.025 So in the uninfected mice you see that

NOTE Confidence: 0.94402933

00:15:52.025 --> 00:15:54.155 the alpha smooth muscle positive cells,

NOTE Confidence: 0.94402933

00:15:54.160 --> 00:15:57.023 which are the mild fibroblasts in the

NOTE Confidence: 0.94402933

00:15:57.023 --> 00:15:59.238 stomach are positive for Glee one,

NOTE Confidence: 0.94402933

00:15:59.240 --> 00:16:02.264 and pretty much those were the only

NOTE Confidence: 0.94402933

00:16:02.264 --> 00:16:04.808 cells that were expressing Glee one.

NOTE Confidence: 0.94402933

00:16:04.808 --> 00:16:05.640 So again,

NOTE Confidence: 0.94402933

00:16:05.640 --> 00:16:08.616 Glee one is in the stroma and typically

NOTE Confidence: 0.94402933

00:16:08.616 --> 00:16:11.039 what happens is that the epithelial

NOTE Confidence: 0.94402933

00:16:11.039 --> 00:16:13.606 cells such as the parietal cells will

NOTE Confidence: 0.94402933

00:16:13.606 --> 00:16:15.943 make the ligand Sonic hedgehog and

NOTE Confidence: 0.94402933

00:16:15.943 --> 00:16:18.397 it's received by the stromal cells.

NOTE Confidence: 0.94402933

00:16:18.400 --> 00:16:20.520 So in the uninfected mice,

NOTE Confidence: 0.94402933

00:16:20.520 --> 00:16:24.836 it's the alpha smooth muscle positive cells.

NOTE Confidence: 0.94402933

00:16:24.836 --> 00:16:27.692 But during after two months of

NOTE Confidence: 0.94402933

00:16:27.692 --> 00:16:29.120 infection with Helicobacter,

NOTE Confidence: 0.94402933

00:16:29.120 --> 00:16:31.736 not surprisingly you have a pro

NOTE Confidence: 0.94402933

00:16:31.736 --> 00:16:33.980 inflammatory situation where you have

NOTE Confidence: 0.94402933

00:16:33.980 --> 00:16:36.095 an infiltration of inflammatory cells

NOTE Confidence: 0.94402933

00:16:36.095 --> 00:16:39.358 and those cells are positive for Glee one.

NOTE Confidence: 0.94402933

00:16:39.360 --> 00:16:41.400 And when we did flow cytometry,

NOTE Confidence: 0.94402933

00:16:41.400 --> 00:16:44.310 this is published several years

NOTE Confidence: 0.94402933

00:16:44.310 --> 00:16:46.864 ago now mostly myeloid cells but

NOTE Confidence: 0.94402933

00:16:46.864 --> 00:16:49.884 not T or B cells were the cells

NOTE Confidence: 0.94402933

00:16:49.884 --> 00:16:52.034 that were expressing Glee one.

NOTE Confidence: 0.94402933

00:16:52.040 --> 00:16:56.048 And so just to summarize that

NOTE Confidence: 0.94402933

00:16:56.048 --> 00:16:59.005 basically we then we're asking the

NOTE Confidence: 0.94402933

00:16:59.005 --> 00:17:01.883 question well what are these Glee

NOTE Confidence: 0.94402933

00:17:01.883 --> 00:17:04.398 1 positive immune cells doing.

NOTE Confidence: 0.94402933

00:17:04.400 --> 00:17:07.040 And what was interesting is that

NOTE Confidence: 0.94402933

00:17:07.040 --> 00:17:09.568 when we infected again wild type

NOTE Confidence: 0.94402933

00:17:09.568 --> 00:17:12.320 mice and now what you see here is

NOTE Confidence: 0.94402933

00:17:12.400 --> 00:17:15.196 an immunofluorescent stain for the

NOTE Confidence: 0.94402933

00:17:15.196 --> 00:17:17.176 different cell populations in the

NOTE Confidence: 0.94402933

00:17:17.176 --> 00:17:20.388 corpus of or the body of the stomach

NOTE Confidence: 0.94402933

00:17:20.388 --> 00:17:23.194 intrinsic factor in the mice mark the

NOTE Confidence: 0.94402933

00:17:23.194 --> 00:17:25.570 chief cells whereas in human it's

NOTE Confidence: 0.94402933

00:17:25.570 --> 00:17:28.959 it's normally in the parietal cells,

NOTE Confidence: 0.94402933

00:17:28.960 --> 00:17:31.354 HKTPAS marks the parietal cells and

NOTE Confidence: 0.94402933

00:17:31.354 --> 00:17:33.998 this GS2 lectin marks a mucous cell.

NOTE Confidence: 0.94402933

00:17:34.000 --> 00:17:36.432 So here in the mice that are infected

NOTE Confidence: 0.94402933

00:17:36.432 --> 00:17:39.266 for six months you see that they're

NOTE Confidence: 0.94402933

00:17:39.266 --> 00:17:41.576 developing A metaplasia and atrophy.

NOTE Confidence: 0.94402933

00:17:41.576 --> 00:17:44.116 So these this region should

NOTE Confidence: 0.94402933

00:17:44.120 --> 00:17:45.452 show parietal cells,

NOTE Confidence: 0.94402933

00:17:45.452 --> 00:17:48.116 which would be the orange stain,

NOTE Confidence: 0.94402933

00:17:48.120 --> 00:17:49.905 but you can see here they're kind

NOTE Confidence: 0.94402933

00:17:49.905 --> 00:17:52.018 of moved off to the side because

NOTE Confidence: 0.94402933

00:17:52.018 --> 00:17:53.628 they're starting to disappear and

NOTE Confidence: 0.94402933

00:17:53.628 --> 00:17:55.423 show atrophy and being replaced

NOTE Confidence: 0.94402933

00:17:55.423 --> 00:17:56.839 by this mucus phenotype.

NOTE Confidence: 0.94402933

00:17:56.840 --> 00:17:57.400 However,

NOTE Confidence: 0.94402933

00:17:57.400 --> 00:18:00.736 in the cells that or in the the

NOTE Confidence: 0.94402933

00:18:00.736 --> 00:18:02.380 mice that were heterozygous for the

NOTE Confidence: 0.817670631818182

00:18:02.440 --> 00:18:07.211 Glee, one deletion or because of the Laxi

NOTE Confidence: 0.817670631818182

00:18:07.211 --> 00:18:10.397 insertion into the locus or homozygous,

NOTE Confidence: 0.817670631818182

00:18:10.400 --> 00:18:11.840 they maintain the normal

NOTE Confidence: 0.817670631818182

00:18:11.840 --> 00:18:13.280 architecture of the stomach.

NOTE Confidence: 0.817670631818182

00:18:13.280 --> 00:18:15.443 And so we were really surprised by

NOTE Confidence: 0.817670631818182

00:18:15.443 --> 00:18:17.680 that because as I mentioned earlier,

NOTE Confidence: 0.817670631818182

00:18:17.680 --> 00:18:19.555 it's the stromal cell that's

NOTE Confidence: 0.817670631818182

00:18:19.555 --> 00:18:20.680 expressing Glee one.

NOTE Confidence: 0.817670631818182

00:18:20.680 --> 00:18:22.906 So this was telling us right there

NOTE Confidence: 0.817670631818182

00:18:22.906 --> 00:18:24.583 that there was something going

NOTE Confidence: 0.817670631818182

00:18:24.583 --> 00:18:26.804 on in the micro environment,

NOTE Confidence: 0.817670631818182

00:18:26.804 --> 00:18:29.292 in the immune environment

NOTE Confidence: 0.817670631818182

00:18:29.292 --> 00:18:33.960 that was affecting the mucosa.

NOTE Confidence: 0.817670631818182

00:18:33.960 --> 00:18:37.075 So to try to summarize this quickly,

NOTE Confidence: 0.817670631818182

00:18:37.080 --> 00:18:39.762 so we started looking at hedgehog

NOTE Confidence: 0.817670631818182

00:18:39.762 --> 00:18:41.550 signaling in this transition

NOTE Confidence: 0.817670631818182

00:18:41.627 --> 00:18:43.719 from gastritis to metaplasia.

NOTE Confidence: 0.817670631818182

00:18:43.720 --> 00:18:45.808 I should also mention one of

NOTE Confidence: 0.817670631818182

00:18:45.808 --> 00:18:47.671 the issues with working with

NOTE Confidence: 0.817670631818182

00:18:47.671 --> 00:18:50.041 the mouse models is they never

NOTE Confidence: 0.817670631818182

00:18:50.041 --> 00:18:52.040 progressed to dysplasia and cancer,

NOTE Confidence: 0.817670631818182

00:18:52.040 --> 00:18:56.238 just with an infection from Helicobacter.

NOTE Confidence: 0.817670631818182

00:18:56.240 --> 00:18:59.600 So we could only look at this step.

NOTE Confidence: 0.817670631818182

00:18:59.600 --> 00:19:01.970 So I've just shown you that

NOTE Confidence: 0.817670631818182

00:19:01.970 --> 00:19:05.680 Glee one is important in the

NOTE Confidence: 0.817670631818182

00:19:05.680 --> 00:19:07.164 meta formation of metaplasia.

NOTE Confidence: 0.817670631818182

00:19:07.164 --> 00:19:10.040 So this like I said is you know

NOTE Confidence: 0.817670631818182

00:19:10.040 --> 00:19:12.032 2015 sixteen we were doing this

NOTE Confidence: 0.817670631818182

00:19:12.032 --> 00:19:14.800 so we did microarrays and we

NOTE Confidence: 0.817670631818182

00:19:14.800 --> 00:19:18.400 identified this molecule Schlafen 4.

NOTE Confidence: 0.817670631818182

00:19:18.400 --> 00:19:21.080 There certainly were quite a few other genes,

NOTE Confidence: 0.817670631818182

00:19:21.080 --> 00:19:23.138 but this one was interesting because

NOTE Confidence: 0.817670631818182

00:19:23.138 --> 00:19:25.159 there were some papers of both

NOTE Confidence: 0.817670631818182

00:19:25.159 --> 00:19:27.196 Schlafen 2 and Four I should mention.

NOTE Confidence: 0.817670631818182

00:19:27.200 --> 00:19:29.918 But the reason why we didn't

NOTE Confidence: 0.817670631818182

00:19:29.920 --> 00:19:33.288 pursue the pathogenesis related

NOTE Confidence: 0.817670631818182

00:19:33.288 --> 00:19:36.956 to Schlafen 2 is because Two does

NOTE Confidence: 0.817670631818182

00:19:36.956 --> 00:19:39.872 not have a ortholog in in humans.

NOTE Confidence: 0.817670631818182

00:19:39.872 --> 00:19:43.559 So there is an ortholog for Schlafen 4.

NOTE Confidence: 0.817670631818182

00:19:43.560 --> 00:19:45.751 So we wanted to be eventually be

NOTE Confidence: 0.817670631818182

00:19:45.751 --> 00:19:47.654 able to translate the work that

NOTE Confidence: 0.817670631818182

00:19:47.654 --> 00:19:49.754 we were doing in mice into humans.

NOTE Confidence: 0.817670631818182

00:19:49.760 --> 00:19:52.840 So that's why we focus on Schlafen 4.

NOTE Confidence: 0.817670631818182

00:19:52.840 --> 00:19:57.572 So this was the further analysis

NOTE Confidence: 0.817670631818182

00:19:57.572 --> 00:20:00.488 of this locus which we identified

NOTE Confidence: 0.817670631818182

00:20:00.488 --> 00:20:03.077 in the array of the mice.

NOTE Confidence: 0.817670631818182

00:20:03.080 --> 00:20:04.760 Comparing wild type mice to

NOTE Confidence: 0.817670631818182

00:20:04.760 --> 00:20:06.440 the Glee One knockout mice,

NOTE Confidence: 0.817670631818182

00:20:06.440 --> 00:20:08.618 you can see here that there's

NOTE Confidence: 0.817670631818182

00:20:08.618 --> 00:20:10.280 a decrease in Schlafman 4,

NOTE Confidence: 0.817670631818182

00:20:10.280 --> 00:20:13.880 which suggested that this gene was

NOTE Confidence: 0.817670631818182

00:20:13.880 --> 00:20:17.528 regulated by hedgehog signaling.

NOTE Confidence: 0.817670631818182

00:20:17.528 --> 00:20:23.000 And so we did chromatin immunoprecipitation

NOTE Confidence: 0.817670631818182

00:20:23.120 --> 00:20:27.439 at the time to determine that indeed

NOTE Confidence: 0.817670631818182

00:20:27.440 --> 00:20:30.959 Schlafen 4 is a direct target of Glee one.

NOTE Confidence: 0.817670631818182

00:20:30.960 --> 00:20:33.056 So you can show that it does sit

NOTE Confidence: 0.817670631818182

00:20:33.056 --> 00:20:35.399 on the promoter of Schlafen Four.

NOTE Confidence: 0.817670631818182

00:20:35.400 --> 00:20:36.000 However,

NOTE Confidence: 0.779132571333333

00:20:38.480 --> 00:20:41.479 I do want to get into in a in a second

NOTE Confidence: 0.779132571333333

00:20:41.479 --> 00:20:43.706 what exactly are these Schlafen's.

NOTE Confidence: 0.779132571333333

00:20:43.706 --> 00:20:46.408 So the reason why we focused on

NOTE Confidence: 0.779132571333333

00:20:46.408 --> 00:20:49.042 them again is because there was a

NOTE Confidence: 0.779132571333333

00:20:49.042 --> 00:20:52.292 paper in immunity in 1999 that said

NOTE Confidence: 0.779132571333333

00:20:52.292 --> 00:20:55.007 that the Schlafen molecules were

NOTE Confidence: 0.779132571333333

00:20:55.007 --> 00:20:58.041 involved in both T cell and and

NOTE Confidence: 0.779132571333333

00:20:58.041 --> 00:20:59.620 and myeloid cell differentiation.

NOTE Confidence: 0.779132571333333

00:20:59.620 --> 00:21:01.894 So that's why we thought, well,

NOTE Confidence: 0.779132571333333

00:21:01.894 --> 00:21:04.512 you know if we're looking at Hedgehog

NOTE Confidence: 0.779132571333333

00:21:04.512 --> 00:21:06.343 signaling and it's rolling the

NOTE Confidence: 0.779132571333333

00:21:06.343 --> 00:21:08.860 stroma and its effect in mediating

NOTE Confidence: 0.779132571333333

00:21:08.860 --> 00:21:11.360 the this metaplast gastritis and

NOTE Confidence: 0.779132571333333

00:21:11.360 --> 00:21:13.023 metaplasic transition that that

NOTE Confidence: 0.779132571333333

00:21:13.023 --> 00:21:14.793 would be a a good target.

NOTE Confidence: 0.779132571333333

00:21:14.800 --> 00:21:16.320 So actually I'm gonna just

NOTE Confidence: 0.779132571333333

00:21:16.320 --> 00:21:17.840 give you a quick primer.

NOTE Confidence: 0.779132571333333

00:21:17.840 --> 00:21:19.540 The Schlafen locus however is

NOTE Confidence: 0.779132571333333

00:21:19.540 --> 00:21:21.240 fairly complicated and this is

NOTE Confidence: 0.779132571333333

00:21:21.299 --> 00:21:23.000 what I was kind of getting at.

NOTE Confidence: 0.779132571333333

00:21:23.000 --> 00:21:25.840 So we identified Schlafen 4.

NOTE Confidence: 0.779132571333333

00:21:25.840 --> 00:21:28.165 There's actually quite a bit

NOTE Confidence: 0.779132571333333

00:21:28.165 --> 00:21:30.096 of information from one group

NOTE Confidence: 0.779132571333333

00:21:30.096 --> 00:21:31.436 that's looking at Schlafen 2.

NOTE Confidence: 0.779132571333333

00:21:31.440 --> 00:21:33.520 We did see this go up in mice,

NOTE Confidence: 0.779132571333333

00:21:33.520 --> 00:21:35.830 but you can see that it doesn't

NOTE Confidence: 0.779132571333333

00:21:35.830 --> 00:21:38.200 have it's ortholog in humans.

NOTE Confidence: 0.779132571333333

00:21:38.200 --> 00:21:41.260 So you'll hear me talk about

NOTE Confidence: 0.779132571333333

00:21:41.358 --> 00:21:44.132 as we move to the human data,

NOTE Confidence: 0.779132571333333

00:21:44.132 --> 00:21:46.397 the ortholog for Schloffen 4,

NOTE Confidence: 0.779132571333333

00:21:46.400 --> 00:21:50.416 that's about 60% similar is Schloffen

NOTE Confidence: 0.779132571333333

00:21:50.416 --> 00:21:54.359 12 L So I'm just showing you this now.

NOTE Confidence: 0.779132571333333

00:21:54.360 --> 00:21:56.880 Just plant that seed in your brain.

NOTE Confidence: 0.779132571333333

00:21:56.880 --> 00:21:59.380 These are what are called

NOTE Confidence: 0.779132571333333

00:21:59.380 --> 00:22:00.880 the intermediate schloffens.

NOTE Confidence: 0.779132571333333

00:22:00.880 --> 00:22:03.172 And the reason why that's important

NOTE Confidence: 0.779132571333333

00:22:03.172 --> 00:22:05.440 is because the longer schloffens

NOTE Confidence: 0.779132571333333

00:22:05.440 --> 00:22:08.092 ones in green have another domain

NOTE Confidence: 0.779132571333333

00:22:08.092 --> 00:22:10.381 that's a helicase domain that's

NOTE Confidence: 0.779132571333333

00:22:10.381 --> 00:22:12.997 thought to bind to nucleic acids.

NOTE Confidence: 0.779132571333333

00:22:13.000 --> 00:22:18.280 I will be coming back to this point later,

NOTE Confidence: 0.779132571333333

00:22:18.280 --> 00:22:18.880 OK.

NOTE Confidence: 0.779132571333333

00:22:18.880 --> 00:22:23.080 So coming back to the mouse model,

NOTE Confidence: 0.779132571333333

00:22:23.080 --> 00:22:23.518 we,

NOTE Confidence: 0.779132571333333

00:22:23.518 --> 00:22:24.832 as I mentioned,

NOTE Confidence: 0.779132571333333

00:22:24.832 --> 00:22:27.022 we're interested in that gastritis

NOTE Confidence: 0.779132571333333

00:22:27.022 --> 00:22:29.648 to metaplastic change and we've

NOTE Confidence: 0.779132571333333

00:22:29.648 --> 00:22:31.104 identified these immune cells

NOTE Confidence: 0.779132571333333

00:22:31.104 --> 00:22:32.560 that are Schlafen positive.

NOTE Confidence: 0.779132571333333

00:22:32.560 --> 00:22:35.176 And so to to understand more

NOTE Confidence: 0.779132571333333

00:22:35.176 --> 00:22:36.920 of what they did,

NOTE Confidence: 0.779132571333333

00:22:36.920 --> 00:22:40.119 we created a very fancy mouse model.

NOTE Confidence: 0.779132571333333

00:22:40.120 --> 00:22:42.464 And I know some people are not as

NOTE Confidence: 0.779132571333333

00:22:42.464 --> 00:22:44.557 familiar with some of these you know,

NOTE Confidence: 0.779132571333333

00:22:44.560 --> 00:22:46.674 kind of mouse tricks that we do.

NOTE Confidence: 0.779132571333333

00:22:46.680 --> 00:22:50.880 But essentially we took the mouse promoter,

NOTE Confidence: 0.779132571333333

00:22:50.880 --> 00:22:53.358 it was a large back trans gene.

NOTE Confidence: 0.779132571333333

00:22:53.360 --> 00:22:56.880 We hook it up to inducible Cree recombinase.

NOTE Confidence: 0.779132571333333

00:22:56.880 --> 00:22:59.778 We breed this mouse line to a

NOTE Confidence: 0.779132571333333

00:22:59.778 --> 00:23:01.959 reporter mouse line TD tomato.

NOTE Confidence: 0.779132571333333

00:23:01.960 --> 00:23:07.798 So this hybrid mouse is expressing

NOTE Confidence: 0.779132571333333

00:23:07.800 --> 00:23:09.914 or can be expressed in the presence

NOTE Confidence: 0.779132571333333

00:23:09.914 --> 00:23:11.975 when we give it tamoxifen this

NOTE Confidence: 0.779132571333333

00:23:11.975 --> 00:23:14.153 reporter so turning the cells red.

NOTE Confidence: 0.779132571333333

00:23:14.160 --> 00:23:18.168 But what we also did is to do a

NOTE Confidence: 0.779132571333333

00:23:18.168 --> 00:23:20.460 bone marrow transplant and put the

NOTE Confidence: 0.779132571333333

00:23:20.547 --> 00:23:23.766 bone marrow from these mice into a

NOTE Confidence: 0.779132571333333

00:23:23.766 --> 00:23:26.081 radiated mice so that essentially

NOTE Confidence: 0.779132571333333

00:23:26.081 --> 00:23:28.795 only the immune cells are going

NOTE Confidence: 0.779132571333333

00:23:28.795 --> 00:23:31.273 to be labeled with TD tomato.

NOTE Confidence: 0.779132571333333

00:23:31.280 --> 00:23:32.760 And ask the question,

NOTE Confidence: 0.779132571333333

00:23:32.760 --> 00:23:35.280 can we lineage trace this Schlopfen

NOTE Confidence: 0.779132571333333

00:23:35.280 --> 00:23:38.400 positive cell from the bone marrow

NOTE Confidence: 0.779132571333333

00:23:38.400 --> 00:23:41.118 of these mice that have recovered

NOTE Confidence: 0.779132571333333

00:23:41.120 --> 00:23:43.265 and infected with Helicobacter in

NOTE Confidence: 0.779132571333333

00:23:43.265 --> 00:23:45.920 waiting four to six months to see

NOTE Confidence: 0.779132571333333

00:23:45.920 --> 00:23:48.120 you know how they get to the stomach.

NOTE Confidence: 0.779132571333333

00:23:48.120 --> 00:23:50.592 Again this is was published in 2016,

NOTE Confidence: 0.779132571333333

00:23:50.592 --> 00:23:53.088 but I just wanted to show you that

NOTE Confidence: 0.779132571333333

00:23:53.088 --> 00:23:55.237 it's really been a very powerful

NOTE Confidence: 0.779132571333333

00:23:55.237 --> 00:23:57.669 tool for us because you can see

NOTE Confidence: 0.779132571333333

00:23:57.669 --> 00:24:00.030 here like stars in the sky and what

NOTE Confidence: 0.779132571333333

00:24:00.030 --> 00:24:02.390 I'm showing you here is a wild type

NOTE Confidence: 0.779132571333333

00:24:02.463 --> 00:24:04.679 mouse infected with Helicobacter.

NOTE Confidence: 0.914759469523809

00:24:04.680 --> 00:24:07.837 But I'm taking we're taking these mice

NOTE Confidence: 0.914759469523809

00:24:07.837 --> 00:24:11.497 at four months before we have seen the

NOTE Confidence: 0.914759469523809

00:24:11.497 --> 00:24:14.480 cells actually arrive in the stomach.

NOTE Confidence: 0.914759469523809

00:24:14.480 --> 00:24:16.808 However, if we breed those mice

NOTE Confidence: 0.914759469523809

00:24:16.808 --> 00:24:18.896 onto a background where they're

NOTE Confidence: 0.914759469523809

00:24:18.896 --> 00:24:20.756 where the Sonic Hedgehog,

NOTE Confidence: 0.914759469523809

00:24:20.760 --> 00:24:22.998 the ligand signal is goosed up.

NOTE Confidence: 0.914759469523809

00:24:23.000 --> 00:24:24.720 So it was pretty easy.

NOTE Confidence: 0.914759469523809

00:24:24.720 --> 00:24:27.960 It was just a PCMV Sonic Hedgehog Transgene.

NOTE Confidence: 0.914759469523809

00:24:27.960 --> 00:24:30.558 We breed those mice, you know,

NOTE Confidence: 0.914759469523809

00:24:30.560 --> 00:24:32.808 with the TD tomato signal and you can

NOTE Confidence: 0.914759469523809

00:24:32.808 --> 00:24:35.097 see at four months there are these

NOTE Confidence: 0.914759469523809

00:24:35.097 --> 00:24:37.400 cells that are TD tomato positive.

NOTE Confidence: 0.914759469523809

00:24:37.400 --> 00:24:40.200 Here's a high-powered view.

NOTE Confidence: 0.914759469523809

00:24:40.200 --> 00:24:40.905 Since they're fluorescent,

NOTE Confidence: 0.914759469523809

00:24:40.905 --> 00:24:42.080 we can pull them out.

NOTE Confidence: 0.914759469523809

00:24:42.080 --> 00:24:44.950 You can see they have a granulocytic

NOTE Confidence: 0.914759469523809

00:24:44.950 --> 00:24:47.294 nucleus and they are exhibiting

NOTE Confidence: 0.914759469523809

00:24:47.294 --> 00:24:49.358 markers of a granulocyte.

NOTE Confidence: 0.914759469523809

00:24:49.360 --> 00:24:49.928 Even better.

NOTE Confidence: 0.914759469523809

00:24:49.928 --> 00:24:52.200 You can certainly do all sorts of arrays,

NOTE Confidence: 0.914759469523809

00:24:52.200 --> 00:24:54.240 which I'll get into a little bit later.

NOTE Confidence: 0.914759469523809

00:24:54.240 --> 00:24:55.548 But more importantly,

NOTE Confidence: 0.914759469523809

00:24:55.548 --> 00:24:58.164 we could actually isolate these cells

NOTE Confidence: 0.914759469523809

00:24:58.164 --> 00:25:00.721 from the infected stomach and show that

NOTE Confidence: 0.914759469523809

00:25:00.721 --> 00:25:03.519 they had T cell suppressor activity.

NOTE Confidence: 0.914759469523809

00:25:03.520 --> 00:25:06.840 So we did the Co culture and show

NOTE Confidence: 0.914759469523809

00:25:06.840 --> 00:25:08.840 that they were really functionally

NOTE Confidence: 0.914759469523809

00:25:08.840 --> 00:25:13.080 T myeloid derived suppressor cells.

NOTE Confidence: 0.914759469523809

00:25:13.080 --> 00:25:16.592 So I wanted to show you well what's

NOTE Confidence: 0.914759469523809

00:25:16.592 --> 00:25:19.320 the connection between Hedgehog and

NOTE Confidence: 0.914759469523809

00:25:19.320 --> 00:25:22.045 how this gene is regulated and and

NOTE Confidence: 0.914759469523809

00:25:22.045 --> 00:25:24.250 why I think we were I'm happy that we

NOTE Confidence: 0.914759469523809

00:25:24.313 --> 00:25:26.657 we decided to kind of stick with this

NOTE Confidence: 0.914759469523809

00:25:26.657 --> 00:25:28.917 even though nobody's heard of Stroffen.

NOTE Confidence: 0.914759469523809

00:25:28.920 --> 00:25:31.704 So what you see here is where you

NOTE Confidence: 0.914759469523809

00:25:31.704 --> 00:25:33.960 can isolate the these cells from.

NOTE Confidence: 0.914759469523809

00:25:33.960 --> 00:25:36.877 We basically you know create a a

NOTE Confidence: 0.914759469523809

00:25:36.877 --> 00:25:39.362 pus situation by injecting them

NOTE Confidence: 0.914759469523809

00:25:39.362 --> 00:25:40.356 with thioglycolate,

NOTE Confidence: 0.914759469523809

00:25:40.360 --> 00:25:42.604 take the peritoneal cells and then

NOTE Confidence: 0.914759469523809

00:25:42.604 --> 00:25:45.658 we can culture them and incubate them

NOTE Confidence: 0.914759469523809

00:25:45.658 --> 00:25:47.638 with recombinant Sonic hedgehog.

NOTE Confidence: 0.914759469523809

00:25:47.640 --> 00:25:49.840 About a fivefold induction of

NOTE Confidence: 0.914759469523809

00:25:49.840 --> 00:25:51.160 Sonic hedgehog message.

NOTE Confidence: 0.914759469523809

00:25:51.160 --> 00:25:53.324 Helicobacter alone threefold but

NOTE Confidence: 0.914759469523809

00:25:53.324 --> 00:25:56.029 the two together synergize but

NOTE Confidence: 0.914759469523809

00:25:56.029 --> 00:25:58.959 more importantly interferon alpha.

NOTE Confidence: 0.914759469523809

00:25:58.960 --> 00:26:03.320 So type 1 interferons, 800 fold induction,

NOTE Confidence: 0.914759469523809

00:26:03.320 --> 00:26:07.041 This gene is and that locus is very

NOTE Confidence: 0.914759469523809

00:26:07.041 --> 00:26:10.359 strongly induced by type 1 interferons.

NOTE Confidence: 0.914759469523809

00:26:10.360 --> 00:26:10.842 However,

NOTE Confidence: 0.914759469523809

00:26:10.842 --> 00:26:13.734 if you isolate those cells from

NOTE Confidence: 0.914759469523809

00:26:13.734 --> 00:26:16.319 a Glee One null mouse,

NOTE Confidence: 0.914759469523809

00:26:16.320 --> 00:26:19.191 you can see that This is why this locus

NOTE Confidence: 0.914759469523809

00:26:19.191 --> 00:26:21.879 is still dependent upon hedgehog.

NOTE Confidence: 0.914759469523809

00:26:21.880 --> 00:26:23.840 You can get a little bit of induction,

NOTE Confidence: 0.914759469523809

00:26:23.840 --> 00:26:25.916 but essentially it's a dead promoter.

NOTE Confidence: 0.914759469523809

00:26:25.920 --> 00:26:29.844 So it's like you need 2 keys to unlock

NOTE Confidence: 0.914759469523809

00:26:29.844 --> 00:26:35.132 this gene and follow it and we mapped the,

NOTE Confidence: 0.914759469523809

00:26:35.132 --> 00:26:37.352 so essentially the hedgehog signal

NOTE Confidence: 0.914759469523809

00:26:37.352 --> 00:26:40.239 Glee one is a constitutive signal.

NOTE Confidence: 0.914759469523809

00:26:40.240 --> 00:26:42.590 The inducible signal is through

NOTE Confidence: 0.914759469523809

00:26:42.590 --> 00:26:44.000 type 1 interferons.

NOTE Confidence: 0.914759469523809

00:26:44.000 --> 00:26:45.155 And so then we asked the question,

NOTE Confidence: 0.914759469523809

00:26:45.160 --> 00:26:49.120 well you know in the infected Mao

NOTE Confidence: 0.914759469523809

00:26:49.120 --> 00:26:52.971 stomach where is we're is type 1

NOTE Confidence: 0.914759469523809

00:26:52.971 --> 00:26:55.816 interferons coming from and it turns

NOTE Confidence: 0.914759469523809

00:26:55.816 --> 00:26:58.252 out that and we've done some later

NOTE Confidence: 0.914759469523809

00:26:58.252 --> 00:27:00.777 work that was published in 2022.

NOTE Confidence: 0.914759469523809

00:27:00.777 --> 00:27:03.662 But basically plasma cytoid dendritic

NOTE Confidence: 0.914759469523809

00:27:03.662 --> 00:27:06.080 cells are sort of resident dendritic

NOTE Confidence: 0.914759469523809

00:27:06.080 --> 00:27:09.056 cells that are the most the cell

NOTE Confidence: 0.914759469523809

00:27:09.056 --> 00:27:11.896 population that is probably sensing

NOTE Confidence: 0.914759469523809

00:27:11.896 --> 00:27:14.619 the debris field there chronically

NOTE Confidence: 0.914759469523809

00:27:14.619 --> 00:27:17.832 and why probably why it takes time

NOTE Confidence: 0.914759469523809

00:27:17.832 --> 00:27:19.759 for this to develop.

NOTE Confidence: 0.914759469523809

00:27:19.760 --> 00:27:21.425 So really putting putting this

NOTE Confidence: 0.914759469523809

00:27:21.425 --> 00:27:23.697 all together and you may want to

NOTE Confidence: 0.914759469523809

00:27:23.697 --> 00:27:25.840 look at our gastro paper in 2022,

NOTE Confidence: 0.914759469523809

00:27:25.840 --> 00:27:28.186 what we're saying is that Helicobacter

NOTE Confidence: 0.914759469523809

00:27:28.186 --> 00:27:30.916 infection is detected not only

NOTE Confidence: 0.914759469523809

00:27:30.916 --> 00:27:32.554 by the epithelium,

NOTE Confidence: 0.914759469523809

00:27:32.560 --> 00:27:34.360 so the epithelial cells will

NOTE Confidence: 0.914759469523809

00:27:34.360 --> 00:27:36.160 also produce type 1 interferon,

NOTE Confidence: 0.914759469523809

00:27:36.160 --> 00:27:40.192 but sort of PER on a per cell basis,

NOTE Confidence: 0.667306056666667

00:27:40.200 --> 00:27:42.558 it's the plasma cytoid dendritic cell.

NOTE Confidence: 0.667306056666667

00:27:42.560 --> 00:27:44.960 There's a certain pathway with activation

NOTE Confidence: 0.667306056666667

00:27:44.960 --> 00:27:47.824 of the interferon response factors,

NOTE Confidence: 0.667306056666667

00:27:47.824 --> 00:27:50.026 which are the factors,

NOTE Confidence: 0.667306056666667

00:27:50.026 --> 00:27:52.504 transcription factors that bind to the

NOTE Confidence: 0.667306056666667

00:27:52.504 --> 00:27:54.968 type 1 interferon promoters releasing

NOTE Confidence: 0.667306056666667

00:27:54.968 --> 00:27:58.608 type 1 interferons that then will polarize

NOTE Confidence: 0.667306056666667

00:27:58.686 --> 00:28:01.038 what we now think is a neutrophil

NOTE Confidence: 0.667306056666667

00:28:01.040 --> 00:28:02.954 or granulocytic cell that has been

NOTE Confidence: 0.667306056666667

00:28:02.954 --> 00:28:04.871 sitting there and had was recruited

NOTE Confidence: 0.667306056666667

00:28:04.871 --> 00:28:07.191 to the stomach at some point in time.

NOTE Confidence: 0.667306056666667

00:28:07.200 --> 00:28:09.264 But then this debris field and

NOTE Confidence: 0.667306056666667

00:28:09.264 --> 00:28:11.319 threshold must be reached over time.

NOTE Confidence: 0.667306056666667

00:28:11.320 --> 00:28:14.046 So these cells are PDL 1 positive

NOTE Confidence: 0.667306056666667

00:28:14.046 --> 00:28:17.294 and we were able to show as I

NOTE Confidence: 0.667306056666667

00:28:17.294 --> 00:28:19.783 mentioned earlier that they do

NOTE Confidence: 0.667306056666667

00:28:19.783 --> 00:28:22.273 have T cell suppressor function.

NOTE Confidence: 0.667306056666667

00:28:22.280 --> 00:28:25.178 But analysis of these cells also

NOTE Confidence: 0.667306056666667

00:28:25.178 --> 00:28:27.953 reveals that they are producing

NOTE Confidence: 0.667306056666667

00:28:27.953 --> 00:28:31.389 other cytokines not surprisingly some

NOTE Confidence: 0.667306056666667

00:28:31.389 --> 00:28:33.963 of which that were of particular

NOTE Confidence: 0.667306056666667

00:28:33.963 --> 00:28:37.159 interest to us or was IO 1A and Beta.

NOTE Confidence: 0.667306056666667

00:28:37.160 --> 00:28:39.872 And we think that and that's why we

NOTE Confidence: 0.667306056666667

00:28:39.872 --> 00:28:42.416 think that it's the immune cells that

NOTE Confidence: 0.667306056666667

00:28:42.416 --> 00:28:45.154 are really picking up the baton and

NOTE Confidence: 0.667306056666667

00:28:45.154 --> 00:28:47.638 really pushing the mucosa more toward

NOTE Confidence: 0.667306056666667

00:28:47.640 --> 00:28:51.595 cancer as opposed to the bug itself.

NOTE Confidence: 0.667306056666667

00:28:51.600 --> 00:28:54.000 And recently and I didn't put

NOTE Confidence: 0.667306056666667

00:28:54.000 --> 00:28:55.600 the reference in here,

NOTE Confidence: 0.667306056666667

00:28:55.600 --> 00:28:58.904 we we actually had for other reasons

NOTE Confidence: 0.667306056666667

00:28:58.904 --> 00:29:01.562 had generated a triple transgenic

NOTE Confidence: 0.667306056666667

00:29:01.562 --> 00:29:04.994 mouse where we can inducibly over

NOTE Confidence: 0.667306056666667

00:29:04.994 --> 00:29:07.422 express I-1 beta in the antrum.

NOTE Confidence: 0.667306056666667

00:29:07.422 --> 00:29:08.725 So you may ask, well,

NOTE Confidence: 0.667306056666667

00:29:08.725 --> 00:29:10.160 why would I bother to do that?

NOTE Confidence: 0.667306056666667

00:29:10.160 --> 00:29:12.476 And it's because the Helicobacter infection,

NOTE Confidence: 0.667306056666667

00:29:12.480 --> 00:29:15.320 whether it's Feliz or Pylori,

NOTE Confidence: 0.667306056666667

00:29:15.320 --> 00:29:16.440 when we infect the mouse,

NOTE Confidence: 0.667306056666667

00:29:16.440 --> 00:29:18.099 because the mouse stomach is actually aph

NOTE Confidence: 0.667306056666667

00:29:18.099 --> 00:29:20.197 of three or four compared to our stomachs,

NOTE Confidence: 0.667306056666667

00:29:20.200 --> 00:29:22.200 which is pH of one,

NOTE Confidence: 0.667306056666667

00:29:22.200 --> 00:29:25.740 the the Organism tends to

NOTE Confidence: 0.667306056666667

00:29:25.740 --> 00:29:27.606 only infect the corpus,

NOTE Confidence: 0.667306056666667

00:29:27.606 --> 00:29:29.636 not the antrum where traditionally

NOTE Confidence: 0.667306056666667

00:29:29.636 --> 00:29:31.840 you see it in people.

NOTE Confidence: 0.667306056666667

00:29:31.840 --> 00:29:34.829 So we really wanted to understand distal

NOTE Confidence: 0.667306056666667

00:29:34.829 --> 00:29:37.240 gastric cancer where we can drive a,

NOTE Confidence: 0.667306056666667

00:29:37.240 --> 00:29:38.104 you know,

NOTE Confidence: 0.667306056666667

00:29:38.104 --> 00:29:40.200 much more aggressive tumor in

NOTE Confidence: 0.667306056666667

00:29:40.200 --> 00:29:42.200 the antrum of the stomach.

NOTE Confidence: 0.667306056666667

00:29:42.200 --> 00:29:43.880 And so we took the gastroin,

NOTE Confidence: 0.667306056666667

00:29:43.880 --> 00:29:46.400 we made a gastroin Cree ERT two,

NOTE Confidence: 0.667306056666667

00:29:46.400 --> 00:29:50.258 crossed it to a TET activator, RTTA.

NOTE Confidence: 0.667306056666667

00:29:50.258 --> 00:29:52.592 So these are three different mice

NOTE Confidence: 0.667306056666667

00:29:52.592 --> 00:29:54.996 that have to be all bred together.

NOTE Confidence: 0.667306056666667

00:29:55.000 --> 00:29:56.240 So a lot of alleles.

NOTE Confidence: 0.667306056666667

00:29:56.240 --> 00:29:59.804 And then this mouse is then bred to a

NOTE Confidence: 0.667306056666667

00:29:59.804 --> 00:30:03.879 Tet on where we've inserted the IO1 beta,

NOTE Confidence: 0.667306056666667

00:30:03.880 --> 00:30:06.400 where it'll generate A secreted form.

NOTE Confidence: 0.667306056666667

00:30:06.400 --> 00:30:09.634 And so you give the mice tamoxifen.

NOTE Confidence: 0.667306056666667

00:30:09.640 --> 00:30:14.010 So the the TET TET activator will

NOTE Confidence: 0.667306056666667

00:30:14.010 --> 00:30:16.498 sit in the cytoplasm until we give

NOTE Confidence: 0.667306056666667

00:30:16.498 --> 00:30:18.556 the mice doxycycline in the water.

NOTE Confidence: 0.667306056666667

00:30:18.560 --> 00:30:21.528 And so we keep them on doxycycline

NOTE Confidence: 0.667306056666667

00:30:21.528 --> 00:30:24.448 and after about six months we about

NOTE Confidence: 0.667306056666667

00:30:24.448 --> 00:30:27.144 40% of the mice will develop these

NOTE Confidence: 0.667306056666667

00:30:27.144 --> 00:30:28.680 ugly dysplastic looking tumors.

NOTE Confidence: 0.667306056666667

00:30:28.680 --> 00:30:31.440 I I caution to call it cancer because

NOTE Confidence: 0.667306056666667

00:30:31.440 --> 00:30:34.040 the mouse models never metastasize.

NOTE Confidence: 0.667306056666667

00:30:34.040 --> 00:30:35.438 I have yet even the colon,

NOTE Confidence: 0.667306056666667

00:30:35.440 --> 00:30:37.834 all the models that people talk about,

NOTE Confidence: 0.667306056666667

00:30:37.840 --> 00:30:38.674 they never metastasize.

NOTE Confidence: 0.667306056666667

00:30:38.674 --> 00:30:40.960 So you know you can kind of quibble

NOTE Confidence: 0.667306056666667

00:30:40.960 --> 00:30:42.920 about what you want to call that.

NOTE Confidence: 0.667306056666667

00:30:42.920 --> 00:30:44.968 But I'll I'll just say you can see

NOTE Confidence: 0.667306056666667

00:30:44.968 --> 00:30:47.125 there is they're pretty ugly looking

NOTE Confidence: 0.667306056666667

00:30:47.125 --> 00:30:49.095 cells and more importantly these

NOTE Confidence: 0.667306056666667

00:30:49.095 --> 00:30:51.681 cells are so they do have and have

NOTE Confidence: 0.667306056666667

00:30:51.681 --> 00:30:53.695 recruited the Schlafen for positive MDS,

NOTE Confidence: 0.667306056666667

00:30:53.695 --> 00:30:55.155 CS into the tumor.

NOTE Confidence: 0.667306056666667

00:30:55.160 --> 00:30:57.700 So at least we now have a sort of a

NOTE Confidence: 0.832998670769231

00:30:57.773 --> 00:31:01.918 pre clinical model to actually study.

NOTE Confidence: 0.832998670769231

00:31:01.920 --> 00:31:04.755 So going back again in time a little bit,

NOTE Confidence: 0.832998670769231

00:31:04.760 --> 00:31:08.225 So 2020 we started to do bulk

NOTE Confidence: 0.832998670769231

00:31:08.225 --> 00:31:12.020 RNAC which we did with these mice

NOTE Confidence: 0.832998670769231

00:31:12.020 --> 00:31:14.920 that were TD Tomato positive.

NOTE Confidence: 0.832998670769231

00:31:14.920 --> 00:31:18.079 What I want to point out here that was

NOTE Confidence: 0.832998670769231

00:31:18.080 --> 00:31:20.408 quite interesting and coming back to

NOTE Confidence: 0.832998670769231

00:31:20.408 --> 00:31:23.107 the Type 1 interferon theme is that a

NOTE Confidence: 0.832998670769231

00:31:23.107 --> 00:31:25.520 lot of the genes that we identified.

NOTE Confidence: 0.832998670769231

00:31:25.520 --> 00:31:28.400 So this is the heat map happened to

NOTE Confidence: 0.832998670769231

00:31:28.400 --> 00:31:31.331 be interferon, strongly interferon

NOTE Confidence: 0.832998670769231

00:31:31.331 --> 00:31:35.240 regulated and were these guanalite

NOTE Confidence: 0.832998670769231

00:31:35.240 --> 00:31:37.640 binding proteins or GTP aces,

NOTE Confidence: 0.692170605

00:31:40.360 --> 00:31:43.748 GBP, 2G VIN and they're of the

NOTE Confidence: 0.692170605

00:31:43.748 --> 00:31:46.240 dynamin class of GTP aces.

NOTE Confidence: 0.692170605

00:31:46.240 --> 00:31:53.360 This is our the changes in the heat map,

NOTE Confidence: 0.692170605

00:31:53.360 --> 00:31:55.760 the full log pole change.

NOTE Confidence: 0.692170605

00:31:55.760 --> 00:32:00.169 But I am comparing it to a paper in

NOTE Confidence: 0.692170605

00:32:00.169 --> 00:32:04.390 2019 where it was really elegant study

NOTE Confidence: 0.692170605

00:32:04.519 --> 00:32:09.199 of both a mouse and human lung cancer.

NOTE Confidence: 0.692170605

00:32:09.200 --> 00:32:11.450 So there were seven patients with

NOTE Confidence: 0.692170605

00:32:11.450 --> 00:32:13.904 lung cancer and they had a mouse

NOTE Confidence: 0.692170605

00:32:13.904 --> 00:32:16.692 model using Ras and I want to say P53.

NOTE Confidence: 0.692170605

00:32:16.692 --> 00:32:19.164 There was another gene where they

NOTE Confidence: 0.692170605

00:32:19.164 --> 00:32:21.841 were able to generate lung cancer

NOTE Confidence: 0.692170605

00:32:21.841 --> 00:32:25.005 and they did a complete analysis by

NOTE Confidence: 0.692170605

00:32:25.095 --> 00:32:28.448 single cell sequencing of the of the

NOTE Confidence: 0.692170605

00:32:28.448 --> 00:32:30.968 tumor microenvironment what they call

NOTE Confidence: 0.692170605

00:32:30.968 --> 00:32:34.589 in two or neutrophil 2 cells which

NOTE Confidence: 0.692170605

00:32:34.589 --> 00:32:38.375 we now are thinking those are those

NOTE Confidence: 0.692170605

00:32:38.375 --> 00:32:41.715 tumor associated neutrophils or Tans.

NOTE Confidence: 0.692170605

00:32:41.720 --> 00:32:45.584 They the they had the same gene profile

NOTE Confidence: 0.692170605

00:32:45.584 --> 00:32:49.254 that we identified in our Schloffen

NOTE Confidence: 0.692170605

00:32:49.254 --> 00:32:53.142 positive MDSCS and I highlight here

NOTE Confidence: 0.692170605

00:32:53.252 --> 00:32:57.256 that their mouse into was positive for

NOTE Confidence: 0.692170605

00:32:57.256 --> 00:33:00.638 Schloffen 4 and here this is the human

NOTE Confidence: 0.911876981666667

00:33:02.680 --> 00:33:04.088 counterpart for seven patients.

NOTE Confidence: 0.911876981666667

00:33:04.088 --> 00:33:06.812 I think one of the problems they I

NOTE Confidence: 0.911876981666667

00:33:06.812 --> 00:33:08.456 didn't we didn't see Schloffen 12

NOTE Confidence: 0.911876981666667

00:33:08.456 --> 00:33:10.752 L but again when you move to human

NOTE Confidence: 0.911876981666667

00:33:10.752 --> 00:33:14.460 you've got a whole variety of stages,

NOTE Confidence: 0.911876981666667

00:33:14.460 --> 00:33:17.040 tumor types etcetera.

NOTE Confidence: 0.911876981666667

00:33:17.040 --> 00:33:21.528 And so we we they did not observe it in

NOTE Confidence: 0.911876981666667

00:33:21.528 --> 00:33:24.316 that but all the other genes were similar.

NOTE Confidence: 0.911876981666667

00:33:24.320 --> 00:33:28.717 We've also gone on to show that using

NOTE Confidence: 0.911876981666667

00:33:28.717 --> 00:33:31.312 proteomic analysis and using the

NOTE Confidence: 0.911876981666667

00:33:31.312 --> 00:33:34.738 Schloffen 4 antibody that we can actually

NOTE Confidence: 0.911876981666667

00:33:34.738 --> 00:33:38.159 pull down and show that Schloffen 4,

NOTE Confidence: 0.911876981666667

00:33:38.160 --> 00:33:40.690 which I didn't mention is

NOTE Confidence: 0.911876981666667

00:33:40.690 --> 00:33:42.418 actually a cytoplasmic.

NOTE Confidence: 0.911876981666667

00:33:42.418 --> 00:33:45.463 It's actually an ER membrane

NOTE Confidence: 0.911876981666667

00:33:45.463 --> 00:33:48.040 endoplasmic reticular membrane protein.

NOTE Confidence: 0.911876981666667

00:33:48.040 --> 00:33:49.396 So I'll come back to that.

NOTE Confidence: 0.911876981666667

00:33:49.400 --> 00:33:52.244 So that even adds to the complexity

NOTE Confidence: 0.911876981666667

00:33:52.244 --> 00:33:53.954 what are we dealing with.

NOTE Confidence: 0.911876981666667

00:33:53.960 --> 00:33:56.930 But interestingly it forms a complex

NOTE Confidence: 0.911876981666667

00:33:56.930 --> 00:34:00.220 with at least when we pull down

NOTE Confidence: 0.911876981666667

00:34:00.220 --> 00:34:03.055 with many of these genes that we

NOTE Confidence: 0.911876981666667

00:34:03.149 --> 00:34:07.080 identified in the bulk RNA seq.

NOTE Confidence: 0.911876981666667

00:34:07.080 --> 00:34:09.144 A little bit of a complicated

NOTE Confidence: 0.911876981666667

00:34:09.144 --> 00:34:11.200 slide here again it's published

NOTE Confidence: 0.911876981666667

00:34:11.200 --> 00:34:13.080 for those that are interested.

NOTE Confidence: 0.911876981666667

00:34:13.080 --> 00:34:18.232 So if we take that pull down using

NOTE Confidence: 0.911876981666667

00:34:18.232 --> 00:34:22.152 Schlafen for antibody and we wanted

NOTE Confidence: 0.911876981666667

00:34:22.152 --> 00:34:25.400 to know whether it had Gtpas activity.

NOTE Confidence: 0.911876981666667

00:34:25.400 --> 00:34:28.984 So we take that complex where we

NOTE Confidence: 0.911876981666667

00:34:28.984 --> 00:34:32.388 pulled it down and actually show

NOTE Confidence: 0.911876981666667

00:34:32.388 --> 00:34:36.414 that it can hydrolyze GTP and so

NOTE Confidence: 0.911876981666667

00:34:36.414 --> 00:34:40.243 shown here and it does that here

NOTE Confidence: 0.911876981666667

00:34:40.243 --> 00:34:44.279 higher levels in blue of GTP bold

NOTE Confidence: 0.911876981666667

00:34:44.279 --> 00:34:46.928 change and the interferon treated

NOTE Confidence: 0.911876981666667

00:34:46.928 --> 00:34:50.560 cells where we do the pull down

NOTE Confidence: 0.911876981666667

00:34:50.560 --> 00:34:54.700 versus we have also made recently a

NOTE Confidence: 0.911876981666667

00:34:54.700 --> 00:34:56.800 Schlafmann for knockout mouse model.

NOTE Confidence: 0.911876981666667

00:34:56.800 --> 00:35:00.586 So if we isolate cells from

NOTE Confidence: 0.911876981666667

00:35:00.586 --> 00:35:02.479 those versus sildenafil,

NOTE Confidence: 0.911876981666667

00:35:02.480 --> 00:35:03.800 now why did I use sildenafil?

NOTE Confidence: 0.911876981666667

00:35:03.800 --> 00:35:06.817 I kind of skipped over that and

NOTE Confidence: 0.911876981666667

00:35:06.817 --> 00:35:09.688 that's because some of the genes

NOTE Confidence: 0.911876981666667

00:35:09.688 --> 00:35:14.776 also were these G cyclic GMP

NOTE Confidence: 0.911876981666667

00:35:14.776 --> 00:35:17.160 related phosphodiesterases.

NOTE Confidence: 0.911876981666667

00:35:17.160 --> 00:35:20.198 So we already were starting to think,

NOTE Confidence: 0.911876981666667

00:35:20.200 --> 00:35:22.756 well, you know, maybe, you know,

NOTE Confidence: 0.911876981666667

00:35:22.760 --> 00:35:25.076 there's already an off the shelf.

NOTE Confidence: 0.911876981666667

00:35:25.080 --> 00:35:27.720 Oh, did I do that?

NOTE Confidence: 0.911876981666667

00:35:27.720 --> 00:35:29.760 There's already an off the shelf

NOTE Confidence: 0.911876981666667

00:35:29.760 --> 00:35:31.305 inhibitor of phosphodiesterases,

NOTE Confidence: 0.911876981666667

00:35:31.305 --> 00:35:33.880 plus I'm sure the oncologists

NOTE Confidence: 0.911876981666667

00:35:33.880 --> 00:35:36.000 are very familiar with,

NOTE Confidence: 0.911876981666667

00:35:36.000 --> 00:35:38.336 particularly from the multiple

NOTE Confidence: 0.911876981666667

00:35:38.336 --> 00:35:42.576 myeloma field where you can use these

NOTE Confidence: 0.911876981666667

00:35:42.576 --> 00:35:44.784 phosphodiesterase 5-6 inhibitors

NOTE Confidence: 0.911876981666667

00:35:44.784 --> 00:35:46.532 as a sort of neoadjuvant.

NOTE Confidence: 0.911876981666667

00:35:46.532 --> 00:35:48.430 So that was one of the reasons

NOTE Confidence: 0.911876981666667

00:35:48.430 --> 00:35:49.806 why we thought, oh,

NOTE Confidence: 0.911876981666667

00:35:49.806 --> 00:35:51.836 let's see whether this works.

NOTE Confidence: 0.911876981666667

00:35:51.840 --> 00:35:56.035 And indeed it also knocks down the

NOTE Confidence: 0.911876981666667

00:35:56.035 --> 00:36:00.155 ability of the this complex to form GTP.

NOTE Confidence: 0.911876981666667

00:36:00.160 --> 00:36:04.222 So we put together this model which I'm

NOTE Confidence: 0.911876981666667

00:36:04.222 --> 00:36:07.776 showing you here that interferon will induce.

NOTE Confidence: 0.911876981666667

00:36:07.776 --> 00:36:10.016 Because remember it's a very

NOTE Confidence: 0.911876981666667

00:36:10.016 --> 00:36:12.200 strong inducer of Schlopfen,

NOTE Confidence: 0.911876981666667

00:36:12.200 --> 00:36:14.984 so we can mark these cells but along

NOTE Confidence: 0.911876981666667

00:36:14.984 --> 00:36:16.978 with Schlopfen there are other

NOTE Confidence: 0.911876981666667

00:36:16.978 --> 00:36:19.564 very important type 1 interferon

NOTE Confidence: 0.911876981666667

00:36:19.564 --> 00:36:22.504 regulated genes that appear to

NOTE Confidence: 0.911876981666667

00:36:22.504 --> 00:36:25.319 be somewhere in this pathway.

NOTE Confidence: 0.911876981666667

00:36:25.320 --> 00:36:28.632 And I try you know this is this kind

NOTE Confidence: 0.911876981666667

00:36:28.632 --> 00:36:31.317 of a model because essentially what

NOTE Confidence: 0.911876981666667

00:36:31.317 --> 00:36:33.393 these myeloid derived suppressor

NOTE Confidence: 0.911876981666667

00:36:33.393 --> 00:36:35.995 cells their their ability to inhibit

NOTE Confidence: 0.911876981666667

00:36:35.995 --> 00:36:38.665 T cells has to do with their them

NOTE Confidence: 0.911876981666667

00:36:38.665 --> 00:36:41.102 being able to gobble up L arginine

NOTE Confidence: 0.911876981666667

00:36:41.102 --> 00:36:44.080 out of the the the environment so

NOTE Confidence: 0.911876981666667

00:36:44.080 --> 00:36:46.840 that the T cells can't proliferate.

NOTE Confidence: 0.911876981666667

00:36:46.840 --> 00:36:49.360 But what are these myeloid derived

NOTE Confidence: 0.911876981666667

00:36:49.360 --> 00:36:51.040 suppressor cells are actually

NOTE Confidence: 0.911876981666667

00:36:51.114 --> 00:36:53.322 using that L arginine themselves to

NOTE Confidence: 0.911876981666667

00:36:53.322 --> 00:36:55.860 what I'm not showing here generate

NOTE Confidence: 0.911876981666667

00:36:55.860 --> 00:36:57.357 reactive oxygen species.

NOTE Confidence: 0.911876981666667

00:36:57.360 --> 00:36:58.840 Here are some of the

NOTE Confidence: 0.85330483

00:36:58.840 --> 00:37:02.210 pathways. So arginase making nitric

NOTE Confidence: 0.85330483

00:37:02.210 --> 00:37:07.120 oxide or No2 make making nitric oxide,

NOTE Confidence: 0.85330483

00:37:07.120 --> 00:37:10.600 which happens to be a cofactor

NOTE Confidence: 0.85330483

00:37:10.600 --> 00:37:15.480 for soluble guanillate cyclase.

NOTE Confidence: 0.85330483

00:37:15.480 --> 00:37:22.158 So guanalase cyclase generates cyclic GMP.

NOTE Confidence: 0.85330483

00:37:22.160 --> 00:37:26.131 Cyclic GMP, if it hangs around is

NOTE Confidence: 0.85330483

00:37:26.131 --> 00:37:29.317 a cofactor for protein kinase G,

NOTE Confidence: 0.85330483

00:37:29.320 --> 00:37:32.800 which can in some cell populations

NOTE Confidence: 0.85330483

00:37:32.800 --> 00:37:35.957 trigger the cells to undergo cell death.

NOTE Confidence: 0.85330483

00:37:35.960 --> 00:37:39.776 So if you have high levels of something

NOTE Confidence: 0.85330483

00:37:39.776 --> 00:37:43.120 that's going to break down cyclic GMP,

NOTE Confidence: 0.85330483

00:37:43.120 --> 00:37:45.650 you're going to move the

NOTE Confidence: 0.85330483

00:37:45.650 --> 00:37:47.674 cells away from apoptosis,

NOTE Confidence: 0.85330483

00:37:47.680 --> 00:37:50.810 regenerate this the sort of

NOTE Confidence: 0.85330483

00:37:50.810 --> 00:37:53.314 backbone for regenerating GTP.

NOTE Confidence: 0.85330483

00:37:53.320 --> 00:37:56.160 And so that's why we think and I've

NOTE Confidence: 0.85330483

00:37:56.160 --> 00:37:59.087 shown you that Schlafen 4 is at least

NOTE Confidence: 0.85330483

00:37:59.087 --> 00:38:02.301 in a complex with these Guanali binding

NOTE Confidence: 0.85330483

00:38:02.301 --> 00:38:05.120 proteins which you know need this GTP.

NOTE Confidence: 0.85330483

00:38:05.120 --> 00:38:07.388 So we think that there's a whole

NOTE Confidence: 0.85330483

00:38:07.388 --> 00:38:09.587 nother pathway or metabolism that

NOTE Confidence: 0.85330483

00:38:09.587 --> 00:38:12.122 pulls the substrate away from

NOTE Confidence: 0.85330483

00:38:12.122 --> 00:38:15.231 maintaining high levels of cyclic GMP

NOTE Confidence: 0.85330483

00:38:15.231 --> 00:38:17.721 and you can essentially accelerate

NOTE Confidence: 0.85330483

00:38:17.721 --> 00:38:20.719 that and we'll get back to that,

NOTE Confidence: 0.85330483

00:38:20.720 --> 00:38:23.960 oops, going too fast if we

NOTE Confidence: 0.85330483

00:38:23.960 --> 00:38:24.840 inhibit phosphodiesterases.

NOTE Confidence: 0.85330483

00:38:24.840 --> 00:38:28.320 So you can imagine if we block

NOTE Confidence: 0.85330483

00:38:28.320 --> 00:38:29.838 phosphodiesterases here,

NOTE Confidence: 0.85330483

00:38:29.840 --> 00:38:31.748 this is going to build up and you can

NOTE Confidence: 0.85330483

00:38:31.748 --> 00:38:33.480 trigger the cells to undergo apoptosis.

NOTE Confidence: 0.85330483

00:38:33.480 --> 00:38:35.088 So that's kind of the hypothesis

NOTE Confidence: 0.85330483

00:38:35.088 --> 00:38:36.959 that I want to keep in mind.

NOTE Confidence: 0.85330483

00:38:36.960 --> 00:38:37.288 OK,

NOTE Confidence: 0.85330483

00:38:37.288 --> 00:38:38.600 so let's move on.

NOTE Confidence: 0.85330483

00:38:38.600 --> 00:38:40.966 We've moved to the next era where

NOTE Confidence: 0.85330483

00:38:40.966 --> 00:38:43.639 we're now using single cell sequencing.

NOTE Confidence: 0.85330483

00:38:43.640 --> 00:38:48.040 And I want to point out again that we're

NOTE Confidence: 0.85330483

00:38:48.040 --> 00:38:51.384 reinforcing what we initially observed

NOTE Confidence: 0.85330483

00:38:51.384 --> 00:38:54.120 and I just want you to this is published,

NOTE Confidence: 0.85330483

00:38:54.120 --> 00:38:57.348 but you can see here in our

NOTE Confidence: 0.85330483

00:38:57.348 --> 00:39:00.396 go enrichment for this is the,

NOTE Confidence: 0.85330483

00:39:00.400 --> 00:39:02.080 you know spring plot that won't

NOTE Confidence: 0.85330483

00:39:02.080 --> 00:39:03.720 bore you with all of that,

NOTE Confidence: 0.85330483

00:39:03.720 --> 00:39:06.520 but you'll notice that the go enrichment,

NOTE Confidence: 0.85330483

00:39:06.520 --> 00:39:07.608 Gtpas activity,

NOTE Confidence: 0.85330483

00:39:07.608 --> 00:39:08.696 GTP binding.

NOTE Confidence: 0.85330483

00:39:08.696 --> 00:39:13.918 So again a lot of the genes even in the

NOTE Confidence: 0.85330483

00:39:13.920 --> 00:39:15.972 doing the single cell sequencing seem

NOTE Confidence: 0.85330483

00:39:15.972 --> 00:39:20.120 to take us to these Gtpas types of proteins.

NOTE Confidence: 0.85330483

00:39:20.120 --> 00:39:23.330 I want to highlight though this

NOTE Confidence: 0.85330483

00:39:23.330 --> 00:39:25.088 region here which kind of didn't

NOTE Confidence: 0.85330483

00:39:25.088 --> 00:39:26.559 blow up quite as big as it should.

NOTE Confidence: 0.85330483

00:39:26.560 --> 00:39:30.208 But what we were kind of surprised about

NOTE Confidence: 0.85330483

00:39:30.208 --> 00:39:34.512 is that there's really three groups,

NOTE Confidence: 0.85330483

00:39:34.512 --> 00:39:36.032 low, medium,

NOTE Confidence: 0.85330483

00:39:36.032 --> 00:39:36.704 medium,

NOTE Confidence: 0.85330483

00:39:36.704 --> 00:39:39.824 high and high expressors of Schlafen.

NOTE Confidence: 0.85330483

00:39:39.824 --> 00:39:42.032 And this is what we're finding

NOTE Confidence: 0.85330483

00:39:42.032 --> 00:39:44.774 many times as you start to get into

NOTE Confidence: 0.85330483

00:39:44.774 --> 00:39:46.394 single cell sequencing is that

NOTE Confidence: 0.85330483

00:39:46.394 --> 00:39:48.712 many of these cells exist in sort

NOTE Confidence: 0.85330483

00:39:48.712 --> 00:39:51.240 of different activation states.

NOTE Confidence: 0.85330483

00:39:51.240 --> 00:39:53.970 I we haven't quite gotten to

NOTE Confidence: 0.85330483

00:39:53.970 --> 00:39:55.145 the pseudo trajectory.

NOTE Confidence: 0.85330483

00:39:55.145 --> 00:39:57.000 Somebody's working on that 'cause you need,

NOTE Confidence: 0.85330483

00:39:57.000 --> 00:39:59.000 you need a different program.

NOTE Confidence: 0.85330483

00:39:59.000 --> 00:40:01.208 But what you can kind of see is

NOTE Confidence: 0.85330483

00:40:01.208 --> 00:40:04.000 that the Low Expressors Group 3,

NOTE Confidence: 0.85330483

00:40:04.000 --> 00:40:08.364 which is this blue, actually it has

NOTE Confidence: 0.85330483

00:40:08.364 --> 00:40:11.685 more of the neutrophil genotype,

NOTE Confidence: 0.85330483

00:40:11.685 --> 00:40:15.013 so that would be I guess no.

NOTE Confidence: 0.85330483

00:40:15.013 --> 00:40:17.078 Anyway, I won't point it.

NOTE Confidence: 0.85330483

00:40:17.080 --> 00:40:19.360 I guess this group here.

NOTE Confidence: 0.85330483

00:40:19.360 --> 00:40:23.920 And whereas the higher expressing ones,

NOTE Confidence: 0.85330483

00:40:23.920 --> 00:40:28.918 there's one group number two that

NOTE Confidence: 0.85330483

00:40:28.920 --> 00:40:32.000 tends to be and so that's this

NOTE Confidence: 0.85330483

00:40:32.000 --> 00:40:34.556 cluster here higher in nitric oxide

NOTE Confidence: 0.85330483

00:40:34.556 --> 00:40:37.070 2 which is actually a different

NOTE Confidence: 0.85330483

00:40:37.155 --> 00:40:39.720 group than that express arginate.

NOTE Confidence: 0.85330483

00:40:39.720 --> 00:40:42.120 So this is just the mouse.

NOTE Confidence: 0.85330483

00:40:42.120 --> 00:40:46.600 So even that mouse cluster that we are,

NOTE Confidence: 0.85330483

00:40:46.600 --> 00:40:49.000 we're already thinking that we're

NOTE Confidence: 0.85330483

00:40:49.000 --> 00:40:51.230 polarizing and becoming myeloid

NOTE Confidence: 0.85330483

00:40:51.230 --> 00:40:53.594 derived suppressor cells from

NOTE Confidence: 0.85330483

00:40:53.594 --> 00:40:55.958 a granulocyte or neutrophil.

NOTE Confidence: 0.931444244761905

00:40:55.960 --> 00:40:59.332 They actually have different sort of

NOTE Confidence: 0.931444244761905

00:40:59.332 --> 00:41:02.116 activation states or different gene

NOTE Confidence: 0.931444244761905

00:41:02.116 --> 00:41:04.828 clusters that you can now identify

NOTE Confidence: 0.931444244761905

00:41:04.828 --> 00:41:07.520 by single cell sequencing. OK.

NOTE Confidence: 0.931444244761905

00:41:07.520 --> 00:41:10.080 So I've given you a lot of information.

NOTE Confidence: 0.931444244761905

00:41:10.080 --> 00:41:13.596 So essentially from the mouse model,

NOTE Confidence: 0.931444244761905

00:41:13.600 --> 00:41:16.240 what we're saying is that,

NOTE Confidence: 0.931444244761905

00:41:16.240 --> 00:41:17.950 and I didn't really give you

NOTE Confidence: 0.931444244761905

00:41:17.950 --> 00:41:20.199 the sort of how this all begins,

NOTE Confidence: 0.931444244761905

00:41:20.200 --> 00:41:22.368 but essentially when Helicobacter

NOTE Confidence: 0.931444244761905

00:41:22.368 --> 00:41:24.990 infects the stomach, it can,

NOTE Confidence: 0.931444244761905

00:41:24.990 --> 00:41:27.465 the dying parietal cells or

NOTE Confidence: 0.931444244761905

00:41:27.465 --> 00:41:29.506 intraparietal cells actually can

NOTE Confidence: 0.931444244761905

00:41:29.506 --> 00:41:32.356 release Sonic Hedgehog into the plasma.

NOTE Confidence: 0.931444244761905

00:41:32.360 --> 00:41:34.712 So some of the papers that I didn't

NOTE Confidence: 0.931444244761905

00:41:34.712 --> 00:41:37.025 talk about in detail actually you can

NOTE Confidence: 0.931444244761905

00:41:37.025 --> 00:41:39.315 pick up Sonic Hedgehog in the plasma

NOTE Confidence: 0.931444244761905

00:41:39.315 --> 00:41:41.830 of the mice within two or three days

NOTE Confidence: 0.931444244761905

00:41:41.830 --> 00:41:44.120 these cells track to the stomach.

NOTE Confidence: 0.931444244761905

00:41:44.120 --> 00:41:46.352 But the first two months or so of

NOTE Confidence: 0.931444244761905

00:41:46.352 --> 00:41:48.276 the infection it's we're still in

NOTE Confidence: 0.931444244761905

00:41:48.276 --> 00:41:50.232 more of the pro inflammatory stage.

NOTE Confidence: 0.931444244761905

00:41:50.240 --> 00:41:52.652 It's not till about when we did a formal

NOTE Confidence: 0.931444244761905

00:41:52.652 --> 00:41:54.716 time course about five and a half,

NOTE Confidence: 0.931444244761905

00:41:54.720 --> 00:41:56.695 six months of a Helicobacter

NOTE Confidence: 0.931444244761905

00:41:56.695 --> 00:41:57.880 infection in mice.

NOTE Confidence: 0.931444244761905

00:41:57.880 --> 00:42:01.396 Do you actually see these cells

NOTE Confidence: 0.931444244761905

00:42:01.396 --> 00:42:03.688 actually generate enough interferon

NOTE Confidence: 0.931444244761905

00:42:03.688 --> 00:42:05.800 alpha in the tissue?

NOTE Confidence: 0.931444244761905

00:42:05.800 --> 00:42:06.980 That and I'm the reason

NOTE Confidence: 0.931444244761905

00:42:06.980 --> 00:42:08.160 why I'm crossing that out,

NOTE Confidence: 0.931444244761905

00:42:08.160 --> 00:42:11.220 is that we actually infuse interferon

NOTE Confidence: 0.931444244761905

00:42:11.220 --> 00:42:14.395 antibody in our 2022 paper to show

NOTE Confidence: 0.931444244761905

00:42:14.395 --> 00:42:17.151 that we could actually block the

NOTE Confidence: 0.931444244761905

00:42:17.151 --> 00:42:20.199 polarization of the Schloffen for MDS,

NOTE Confidence: 0.931444244761905

00:42:20.200 --> 00:42:23.400 CS and we did not get the spim.

NOTE Confidence: 0.931444244761905

00:42:23.400 --> 00:42:25.200 Is the the term metaplasia that

NOTE Confidence: 0.931444244761905

00:42:25.200 --> 00:42:26.679 we use for the mice,

NOTE Confidence: 0.931444244761905

00:42:26.680 --> 00:42:28.964 it stands for spasmolytic

NOTE Confidence: 0.931444244761905

00:42:28.964 --> 00:42:30.677 polypeptide expressing metaplasia,

NOTE Confidence: 0.931444244761905

00:42:30.680 --> 00:42:32.498 but we just call it SPM because in the

NOTE Confidence: 0.931444244761905

00:42:32.498 --> 00:42:34.637 mice you actually don't see the goblet cells.

NOTE Confidence: 0.931444244761905

00:42:34.640 --> 00:42:37.104 So they had to come up with

NOTE Confidence: 0.931444244761905

00:42:37.104 --> 00:42:38.840 another way to market.

NOTE Confidence: 0.931444244761905

00:42:38.840 --> 00:42:41.892 And so again what we're proposing is

NOTE Confidence: 0.931444244761905

00:42:41.892 --> 00:42:44.660 that if we block the phosphodiesterases

NOTE Confidence: 0.931444244761905

00:42:44.660 --> 00:42:47.810 and maybe these along with the GTP

NOTE Confidence: 0.931444244761905

00:42:47.810 --> 00:42:50.516 Azes that we can do the same thing.

NOTE Confidence: 0.931444244761905

00:42:50.520 --> 00:42:54.240 So what I've shown you is more in vitro data,

NOTE Confidence: 0.931444244761905

00:42:54.240 --> 00:42:56.184 but now I'm going to show you what

NOTE Confidence: 0.931444244761905

00:42:56.184 --> 00:42:59.120 it looks like with the knockout.

NOTE Confidence: 0.931444244761905

00:42:59.120 --> 00:43:03.344 So as I mentioned this is a normal

NOTE Confidence: 0.931444244761905

00:43:03.344 --> 00:43:06.103 mouse and like I said we can goose

NOTE Confidence: 0.931444244761905

00:43:06.103 --> 00:43:09.586 up the the whole signal and and get

NOTE Confidence: 0.931444244761905

00:43:09.586 --> 00:43:12.456 the metaplastic change faster if we

NOTE Confidence: 0.931444244761905

00:43:12.456 --> 00:43:14.716 over express with Sonic Hedgehog.

NOTE Confidence: 0.931444244761905

00:43:14.720 --> 00:43:17.345 So the green staining you saw before

NOTE Confidence: 0.931444244761905

00:43:17.345 --> 00:43:19.839 is the metaplastic change in the mice.

NOTE Confidence: 0.931444244761905

00:43:19.840 --> 00:43:24.480 And when we do the conditional deletion

NOTE Confidence: 0.931444244761905

00:43:24.480 --> 00:43:27.077 and we're deleting it using Glee one,

NOTE Confidence: 0.931444244761905

00:43:27.080 --> 00:43:28.223 Cree ERT two.

NOTE Confidence: 0.931444244761905

00:43:28.223 --> 00:43:30.890 So we're deleting it in that those

NOTE Confidence: 0.931444244761905

00:43:30.979 --> 00:43:33.829 myeloid cells that we originally

NOTE Confidence: 0.931444244761905

00:43:33.829 --> 00:43:35.588 identified the Schlafen cells in.

NOTE Confidence: 0.931444244761905

00:43:35.588 --> 00:43:38.561 And you can see that you start to read

NOTE Confidence: 0.931444244761905

00:43:38.561 --> 00:43:40.799 the normal architecture of the stomach.

NOTE Confidence: 0.931444244761905

00:43:40.800 --> 00:43:43.480 The parietal cells are shown here in white,

NOTE Confidence: 0.931444244761905

00:43:43.480 --> 00:43:46.360 are starting to come back.

NOTE Confidence: 0.931444244761905

00:43:46.360 --> 00:43:47.998 What about Sildenafil?

NOTE Confidence: 0.931444244761905

00:43:47.998 --> 00:43:49.636 Didn't take much.

NOTE Confidence: 0.931444244761905

00:43:49.640 --> 00:43:52.760 We did two injections of sildenafil,

NOTE Confidence: 0.931444244761905

00:43:52.760 --> 00:43:53.460 same thing.

NOTE Confidence: 0.931444244761905

00:43:53.460 --> 00:43:56.306 And here I'm showing you an H&E where

NOTE Confidence: 0.931444244761905

00:43:56.306 --> 00:43:58.917 you can really see the parietal cells,

NOTE Confidence: 0.931444244761905

00:43:58.920 --> 00:44:01.080 which I'm I'm used to looking at it.

NOTE Confidence: 0.931444244761905

00:44:01.080 --> 00:44:03.896 But these big pink cells are

NOTE Confidence: 0.931444244761905

00:44:03.896 --> 00:44:05.144 your parietal cells,

NOTE Confidence: 0.931444244761905

00:44:05.144 --> 00:44:07.640 starting to return in the presence

NOTE Confidence: 0.931444244761905

00:44:07.715 --> 00:44:10.253 of just after two injections of

NOTE Confidence: 0.931444244761905

00:44:10.253 --> 00:44:12.428 sildenafil and very recently within

NOTE Confidence: 0.931444244761905

00:44:12.428 --> 00:44:15.050 the last couple of months going

NOTE Confidence: 0.931444244761905

00:44:15.133 --> 00:44:17.737 back to our aisle 1 overexpressing

NOTE Confidence: 0.931444244761905

00:44:17.737 --> 00:44:19.039 mice with those

NOTE Confidence: 0.8161020075

00:44:19.040 --> 00:44:20.240 big ugly tumors.

NOTE Confidence: 0.8161020075

00:44:20.240 --> 00:44:23.400 So here you can see in this low power view.

NOTE Confidence: 0.8161020075

00:44:23.400 --> 00:44:26.277 Here is the villi of the intestine.

NOTE Confidence: 0.8161020075

00:44:26.280 --> 00:44:28.260 Here is the pyloris,

NOTE Confidence: 0.8161020075

00:44:28.260 --> 00:44:31.734 the junction between the stomach or the

NOTE Confidence: 0.8161020075

00:44:31.734 --> 00:44:35.220 antrum and the in the small intestine.

NOTE Confidence: 0.8161020075

00:44:35.220 --> 00:44:36.560 These are Bruner's glands.

NOTE Confidence: 0.8161020075

00:44:36.560 --> 00:44:39.000 Here the tumors develop and

NOTE Confidence: 0.8161020075

00:44:39.000 --> 00:44:41.976 we're able to accelerate it if

NOTE Confidence: 0.8161020075

00:44:41.976 --> 00:44:44.640 you give it the MNU nitrosamine.

NOTE Confidence: 0.8161020075

00:44:44.640 --> 00:44:47.160 So instead of 40% of the mice alone,

NOTE Confidence: 0.8161020075

00:44:47.160 --> 00:44:50.560 we get about 60% of the mice we'll

NOTE Confidence: 0.8161020075

00:44:50.560 --> 00:44:53.560 develop these ugly dysplastic tumors.

NOTE Confidence: 0.8161020075

00:44:53.560 --> 00:44:55.295 But two injections of SILDENAFIL

NOTE Confidence: 0.8161020075

00:44:55.295 --> 00:44:57.840 were able to melt those tumors down.

NOTE Confidence: 0.8161020075

00:44:57.840 --> 00:44:58.560 And

NOTE Confidence: 0.96508010875

00:45:00.960 --> 00:45:02.440 the reason why I put this in here,

NOTE Confidence: 0.96508010875

00:45:02.440 --> 00:45:05.158 this is again kind of hot off the presses.

NOTE Confidence: 0.96508010875

00:45:05.160 --> 00:45:07.028 I want to come back to, OK,

NOTE Confidence: 0.96508010875

00:45:07.028 --> 00:45:09.434 I told you that I mean Schlafen

NOTE Confidence: 0.96508010875

00:45:09.434 --> 00:45:12.758 is AER protein, well guess what,

NOTE Confidence: 0.96508010875

00:45:12.760 --> 00:45:15.040 it's an RNA binding protein.

NOTE Confidence: 0.96508010875

00:45:15.040 --> 00:45:20.136 And so we actually have recently done a

NOTE Confidence: 0.96508010875

00:45:20.136 --> 00:45:23.272 pull down again with the Schlafen antibody.

NOTE Confidence: 0.96508010875

00:45:23.280 --> 00:45:27.445 These are transfer RNAs and what's very

NOTE Confidence: 0.96508010875

00:45:27.445 --> 00:45:30.638 interesting is that it actually binds to

NOTE Confidence: 0.96508010875

00:45:30.638 --> 00:45:33.880 very specifically in an inducible manner,

NOTE Confidence: 0.96508010875

00:45:33.880 --> 00:45:37.678 glycine and tyrosine specific transfer RNAs.

NOTE Confidence: 0.96508010875

00:45:37.680 --> 00:45:39.440 I don't have time to get into it right now,

NOTE Confidence: 0.96508010875

00:45:39.440 --> 00:45:41.160 but we can come back to it at the end.

NOTE Confidence: 0.96508010875

00:45:41.160 --> 00:45:43.923 But I just wanted to start to close the

NOTE Confidence: 0.96508010875

00:45:43.923 --> 00:45:46.354 loop of this is very interesting protein

NOTE Confidence: 0.96508010875

00:45:46.354 --> 00:45:49.399 and why is it so important and why an

NOTE Confidence: 0.96508010875

00:45:49.400 --> 00:45:51.680 ERRNA binding protein is involved.

NOTE Confidence: 0.96508010875

00:45:51.680 --> 00:45:54.837 OK. I'm going to because of time,

NOTE Confidence: 0.96508010875

00:45:54.840 --> 00:45:57.072 I'm going to come back to this diagram

NOTE Confidence: 0.96508010875

00:45:57.072 --> 00:45:59.279 which I know is pretty complicated

NOTE Confidence: 0.96508010875

00:45:59.280 --> 00:46:01.121 because I wanted to show you our

NOTE Confidence: 0.96508010875

00:46:01.121 --> 00:46:02.280 phase two clinical trial.

NOTE Confidence: 0.96508010875

00:46:02.280 --> 00:46:07.168 So this is a collaboration with primarily a a

NOTE Confidence: 0.96508010875

00:46:07.168 --> 00:46:10.932 really talented junior faculty in oncology,

NOTE Confidence: 0.96508010875

00:46:10.932 --> 00:46:11.998 Junaid Arshad,

NOTE Confidence: 0.96508010875

00:46:12.000 --> 00:46:17.232 Rosten Schroff is our Chief of he Monk and

NOTE Confidence: 0.96508010875

00:46:17.232 --> 00:46:22.408 Aaron Scott are the trio of GI oncologists.

NOTE Confidence: 0.96508010875

00:46:22.408 --> 00:46:26.600 And so when I presented this to them,

NOTE Confidence: 0.96508010875

00:46:26.600 --> 00:46:27.884 they Janae suggested,

NOTE Confidence: 0.96508010875

00:46:27.884 --> 00:46:30.880 well you know why not just try,

NOTE Confidence: 0.96508010875

00:46:30.880 --> 00:46:32.140 let's try and see if we

NOTE Confidence: 0.96508010875

00:46:32.140 --> 00:46:33.799 can set up a window trial.

NOTE Confidence: 0.96508010875

00:46:33.800 --> 00:46:36.135 And so essentially I didn't

NOTE Confidence: 0.96508010875

00:46:36.135 --> 00:46:38.920 know what a window trial was,

NOTE Confidence: 0.96508010875

00:46:38.920 --> 00:46:40.945 but he said you know what we can do

NOTE Confidence: 0.96508010875

00:46:40.945 --> 00:46:42.675 because most of these patients are going

NOTE Confidence: 0.96508010875

00:46:42.675 --> 00:46:45.008 to have to go to receive standard of care,

NOTE Confidence: 0.96508010875

00:46:45.008 --> 00:46:47.440 flot therapy and then go for a gastrectomy

NOTE Confidence: 0.96508010875

00:46:47.440 --> 00:46:49.680 if we if there's stage one to three.

NOTE Confidence: 0.96508010875

00:46:49.680 --> 00:46:50.835 So we're only dealing with

NOTE Confidence: 0.96508010875

00:46:50.835 --> 00:46:51.759 stage one to three,

NOTE Confidence: 0.96508010875

00:46:51.760 --> 00:46:58.106 well 1B to to three and so these

NOTE Confidence: 0.96508010875

00:46:58.106 --> 00:47:01.436 are the window trial objectives.

NOTE Confidence: 0.96508010875

00:47:01.440 --> 00:47:03.170 So the primary objective and

NOTE Confidence: 0.96508010875

00:47:03.170 --> 00:47:04.554 I didn't realize this,

NOTE Confidence: 0.96508010875

00:47:04.560 --> 00:47:06.786 we can't just give patients to

NOTE Confidence: 0.96508010875

00:47:06.786 --> 00:47:09.070 Dalafail even though it the safety

NOTE Confidence: 0.96508010875

00:47:09.070 --> 00:47:11.236 profile we know is pretty good.

NOTE Confidence: 0.96508010875

00:47:11.240 --> 00:47:13.193 I'm not supposed to I guess because of CME,

NOTE Confidence: 0.96508010875

00:47:13.200 --> 00:47:14.520 I'm not supposed to say the trade name.

NOTE Confidence: 0.96508010875

00:47:14.520 --> 00:47:15.628 But anyway,

NOTE Confidence: 0.96508010875

00:47:15.628 --> 00:47:18.952 so they're just focused on this

NOTE Confidence: 0.96508010875

00:47:18.952 --> 00:47:22.691 feasibility and safety and but the

NOTE Confidence: 0.96508010875

00:47:22.691 --> 00:47:25.319 secondary objectives shown here,

NOTE Confidence: 0.96508010875

00:47:25.320 --> 00:47:26.008 you know,

NOTE Confidence: 0.96508010875

00:47:26.008 --> 00:47:28.072 to to see whether there's some

NOTE Confidence: 0.96508010875

00:47:28.072 --> 00:47:28.760 pathologic response.

NOTE Confidence: 0.96508010875

00:47:28.760 --> 00:47:31.592 But my interest in what I'll show you

NOTE Confidence: 0.96508010875

00:47:31.592 --> 00:47:34.040 because the study is still ongoing,

NOTE Confidence: 0.96508010875

00:47:34.040 --> 00:47:36.357 I'll just show you that of what

NOTE Confidence: 0.96508010875

00:47:36.357 --> 00:47:38.832 we're looking at in terms of does

NOTE Confidence: 0.96508010875

00:47:38.832 --> 00:47:40.944 tadalafil in a patient with actual

NOTE Confidence: 0.96508010875

00:47:41.015 --> 00:47:43.408 gastric cancer do anything, right.

NOTE Confidence: 0.96508010875

00:47:43.408 --> 00:47:47.104 So remember we've got to follow 12

NOTE Confidence: 0.96508010875

00:47:47.104 --> 00:47:50.840 L these are the exclusion criteria,

NOTE Confidence: 0.96508010875

00:47:50.840 --> 00:47:54.040 study feasibility.

NOTE Confidence: 0.96508010875

00:47:54.040 --> 00:47:56.800 So we've been going for about a year.

NOTE Confidence: 0.96508010875

00:47:56.800 --> 00:47:58.480 We've got six patients enrolled,

NOTE Confidence: 0.96508010875

00:47:58.480 --> 00:48:00.436 2 patients have finished the study.

NOTE Confidence: 0.96508010875

00:48:00.440 --> 00:48:02.720 But what I want to show,

NOTE Confidence: 0.96508010875

00:48:02.720 --> 00:48:05.195 so we're our goal is to enroll 10 patients.

NOTE Confidence: 0.90682155

00:48:07.240 --> 00:48:09.536 When I moved to Arizona,

NOTE Confidence: 0.90682155

00:48:09.536 --> 00:48:13.280 I set up a repository for our endoscopy lab.

NOTE Confidence: 0.90682155

00:48:13.280 --> 00:48:16.898 So I or one of the other endoscopists will

NOTE Confidence: 0.90682155

00:48:16.898 --> 00:48:20.084 do a if if the patient is not referred

NOTE Confidence: 0.90682155

00:48:20.084 --> 00:48:22.855 in at their not referring him from the

NOTE Confidence: 0.90682155

00:48:22.855 --> 00:48:24.853 outside that becomes a problem because

NOTE Confidence: 0.90682155

00:48:24.853 --> 00:48:27.125 we actually want to try to do single

NOTE Confidence: 0.90682155

00:48:27.125 --> 00:48:29.675 cell sequencing at each of these intervals.

NOTE Confidence: 0.90682155

00:48:29.680 --> 00:48:30.886 So that really means that we

NOTE Confidence: 0.90682155

00:48:30.886 --> 00:48:32.440 have to do the endoscopy here.

NOTE Confidence: 0.90682155

00:48:32.440 --> 00:48:34.600 So just with the biopsies,

NOTE Confidence: 0.90682155

00:48:34.600 --> 00:48:36.625 jumbo biopsies we can do

NOTE Confidence: 0.90682155

00:48:36.625 --> 00:48:37.840 single cell sequencing.

NOTE Confidence: 0.90682155

00:48:37.840 --> 00:48:39.712 And I just wanted to show you that

NOTE Confidence: 0.90682155

00:48:39.712 --> 00:48:41.639 even in a gastric cancer patient,

NOTE Confidence: 0.90682155

00:48:41.640 --> 00:48:45.033 we can stain for Schlaf and 12 L So

NOTE Confidence: 0.90682155

00:48:45.033 --> 00:48:48.305 it's there in the immune cells in

NOTE Confidence: 0.90682155

00:48:48.305 --> 00:48:51.548 the lamina propria of these tumors.

NOTE Confidence: 0.90682155

00:48:51.548 --> 00:48:55.760 So I'll just show you a little bit of,

NOTE Confidence: 0.90682155

00:48:55.760 --> 00:48:59.952 let's see and I'm sorry it ends up

NOTE Confidence: 0.90682155

00:48:59.952 --> 00:49:02.044 going counterclockwise because of the

NOTE Confidence: 0.90682155

00:49:02.044 --> 00:49:04.480 way the data gets uploaded into the

NOTE Confidence: 0.90682155

00:49:04.558 --> 00:49:07.000 cloud for the 10X genomic analysis.

NOTE Confidence: 0.90682155

00:49:07.000 --> 00:49:10.600 So what we are able to do because

NOTE Confidence: 0.90682155

00:49:10.600 --> 00:49:14.480 obviously we run into problems with we're

NOTE Confidence: 0.90682155

00:49:14.480 --> 00:49:18.408 able to capture the 2nd interval endoscopy,

NOTE Confidence: 0.90682155

00:49:18.408 --> 00:49:19.392 so this one,

NOTE Confidence: 0.90682155

00:49:19.392 --> 00:49:22.518 but if the patient comes in from the outside,

NOTE Confidence: 0.90682155

00:49:22.520 --> 00:49:24.920 we basically do single cell sequencing.

NOTE Confidence: 0.90682155

00:49:24.920 --> 00:49:28.231 We have plenty of normal referrals to

NOTE Confidence: 0.90682155

00:49:28.231 --> 00:49:30.839 endoscopy that there's nothing there.

NOTE Confidence: 0.90682155

00:49:30.840 --> 00:49:34.017 They don't have gastritis and so we can do

NOTE Confidence: 0.90682155

00:49:34.017 --> 00:49:37.119 single cell sequencing on on those patients.

NOTE Confidence: 0.90682155

00:49:37.120 --> 00:49:41.290 So what I have circled here is the

NOTE Confidence: 0.90682155

00:49:41.290 --> 00:49:45.040 Myeloid cluster in a normal patient,

NOTE Confidence: 0.90682155

00:49:45.040 --> 00:49:47.144 one of my patients that I had referred

NOTE Confidence: 0.90682155

00:49:47.144 --> 00:49:49.905 for endos because I knew that I was

NOTE Confidence: 0.90682155

00:49:49.905 --> 00:49:51.353 having trouble eradicating Helicobacter.

NOTE Confidence: 0.90682155

00:49:51.360 --> 00:49:54.680 So they had Helicobacter gastritis

NOTE Confidence: 0.90682155

00:49:54.680 --> 00:49:56.584 and here intestinal metaplasia.

NOTE Confidence: 0.90682155

00:49:56.584 --> 00:50:00.031 And then this was one of the

NOTE Confidence: 0.90682155

00:50:00.031 --> 00:50:02.536 patients that the first patient

NOTE Confidence: 0.90682155

00:50:02.536 --> 00:50:05.288 that was enrolled in the study.

NOTE Confidence: 0.90682155

00:50:05.288 --> 00:50:08.796 And so they actually have a lot more

NOTE Confidence: 0.90682155

00:50:08.796 --> 00:50:12.275 of these Schlafen 12 L positive cells,

NOTE Confidence: 0.90682155

00:50:12.280 --> 00:50:18.906 which if you look at the just that gene,

NOTE Confidence: 0.90682155

00:50:18.906 --> 00:50:22.155 you can see here that this is

NOTE Confidence: 0.90682155

00:50:22.155 --> 00:50:23.680 where the myeloid cells are.

NOTE Confidence: 0.90682155

00:50:23.680 --> 00:50:26.280 But look at the normal

NOTE Confidence: 0.90682155

00:50:26.280 --> 00:50:27.624 gastritis intestinal atoplasia,

NOTE Confidence: 0.90682155

00:50:27.624 --> 00:50:30.312 I'm sort of going in order.

NOTE Confidence: 0.90682155

00:50:30.320 --> 00:50:33.748 Sorry, I didn't give you the preya paradigm,

NOTE Confidence: 0.90682155

00:50:33.748 --> 00:50:37.864 but Schlafen 12 L doesn't come on

NOTE Confidence: 0.90682155

00:50:37.864 --> 00:50:40.360 until you very strong, strongly,

NOTE Confidence: 0.90682155

00:50:40.360 --> 00:50:43.960 maybe a little bit in the metaplastic stage,

NOTE Confidence: 0.90682155

00:50:43.960 --> 00:50:46.840 but until these patients are actually,

NOTE Confidence: 0.90682155

00:50:46.840 --> 00:50:49.870 you actually have gastric cancer

NOTE Confidence: 0.90682155

00:50:49.870 --> 00:50:51.580 now you're gonna say, well,

NOTE Confidence: 0.90682155

00:50:51.580 --> 00:50:52.955 what are these other cells?

NOTE Confidence: 0.90682155

00:50:52.960 --> 00:50:54.043 They're T cells.

NOTE Confidence: 0.90682155

00:50:54.043 --> 00:50:57.044 So this was the big surprise as we

NOTE Confidence: 0.90682155

00:50:57.044 --> 00:50:59.432 move and not surprisingly when you

NOTE Confidence: 0.90682155

00:50:59.432 --> 00:51:03.560 move from mouse models to people,

NOTE Confidence: 0.90682155

00:51:03.560 --> 00:51:07.000 you know, sometimes all bets are off.

NOTE Confidence: 0.90682155

00:51:07.000 --> 00:51:10.717 So we now also have to understand

NOTE Confidence: 0.90682155

00:51:10.720 --> 00:51:13.779 what's going on in these T cells

NOTE Confidence: 0.90682155

00:51:13.779 --> 00:51:16.281 because you can see again Schlafen

NOTE Confidence: 0.90682155

00:51:16.281 --> 00:51:18.810 12 LS picked up in the T cells and

NOTE Confidence: 0.90682155

00:51:18.882 --> 00:51:21.238 gastritis and intestinal metaplasia.

NOTE Confidence: 0.90682155

00:51:21.240 --> 00:51:23.560 Now I think I have one slide here.

NOTE Confidence: 0.90682155

00:51:23.560 --> 00:51:25.200 It turns out that

NOTE Confidence: 0.9529675

00:51:27.400 --> 00:51:30.600 in the actual cancer,

NOTE Confidence: 0.9529675

00:51:30.600 --> 00:51:32.938 the T cells that are most prominent

NOTE Confidence: 0.9529675

00:51:32.938 --> 00:51:35.349 that you don't see in the other

NOTE Confidence: 0.9529675

00:51:35.349 --> 00:51:37.353 groups are the exhausted T cells.

NOTE Confidence: 0.9529675

00:51:37.360 --> 00:51:40.555 So that's going to be a whole other project

NOTE Confidence: 0.9529675

00:51:40.555 --> 00:51:43.584 to understand what is this molecule

NOTE Confidence: 0.9529675

00:51:43.584 --> 00:51:48.960 doing in terms of the metabolism of T cells.

NOTE Confidence: 0.9529675

00:51:48.960 --> 00:51:50.517 So we have our work cut out for us.

NOTE Confidence: 0.9529675

00:51:50.520 --> 00:51:54.400 I finally wanted to show you what happens

NOTE Confidence: 0.9529675

00:51:54.400 --> 00:51:58.920 with Tadalafil and so here's a cancer,

NOTE Confidence: 0.9529675

00:51:58.920 --> 00:52:01.179 so this was one of the patients where we

NOTE Confidence: 0.9529675

00:52:01.179 --> 00:52:03.000 the first, this was our first patient.

NOTE Confidence: 0.9529675

00:52:03.000 --> 00:52:04.400 So we didn't have this was they

NOTE Confidence: 0.9529675

00:52:04.400 --> 00:52:05.760 were referred in from the outside.

NOTE Confidence: 0.9529675

00:52:05.760 --> 00:52:11.120 So we only had slides and so this

NOTE Confidence: 0.9529675

00:52:11.120 --> 00:52:13.850 is sustaining for CD11B myeloid

NOTE Confidence: 0.9529675

00:52:13.850 --> 00:52:17.680 marker and our Schlofen 12 L Co

NOTE Confidence: 0.9529675

00:52:17.680 --> 00:52:19.600 localized here in the merge view,

NOTE Confidence: 0.9529675

00:52:19.600 --> 00:52:22.560 but here the high-powered view in the cancer,

NOTE Confidence: 0.9529675

00:52:22.560 --> 00:52:24.960 but with with Cialis, oh sorry,

NOTE Confidence: 0.9529675

00:52:24.960 --> 00:52:31.120 Tadalafil that we are eliminating

NOTE Confidence: 0.9529675

00:52:31.120 --> 00:52:34.640 the these Schlafen positive MDSCS.

NOTE Confidence: 0.825844932

00:52:37.440 --> 00:52:43.424 OK. So the take away there seems to be

NOTE Confidence: 0.825844932

00:52:43.424 --> 00:52:46.304 overlap between the pathways regulating

NOTE Confidence: 0.825844932

00:52:46.304 --> 00:52:50.000 Schlafen 4 and we also believe 12 L and

NOTE Confidence: 0.825844932

00:52:50.000 --> 00:52:53.040 cyclic GMP dependent phosphodiesterases

NOTE Confidence: 0.825844932

00:52:53.040 --> 00:52:55.400 and these inhibitors allow cyclic

NOTE Confidence: 0.825844932

00:52:55.400 --> 00:52:58.220 GMP to accumulate and induce MDSE

NOTE Confidence: 0.825844932

00:52:58.220 --> 00:53:00.520 apoptosis and that's the mechanism.

NOTE Confidence: 0.825844932

00:53:00.520 --> 00:53:02.592 Their elimination we think is we can

NOTE Confidence: 0.825844932

00:53:02.592 --> 00:53:04.878 at least see it in our mouse model.

NOTE Confidence: 0.825844932

00:53:04.880 --> 00:53:07.617 The big question will be as we

NOTE Confidence: 0.825844932

00:53:07.617 --> 00:53:10.677 expand this trial and get past the

NOTE Confidence: 0.825844932

00:53:10.677 --> 00:53:12.922 safety stage that this potentially

NOTE Confidence: 0.825844932

00:53:12.922 --> 00:53:15.424 may be a neoadjuvant for gastric.

NOTE Confidence: 0.825844932

00:53:15.424 --> 00:53:18.080 But again these cells are in a lot

NOTE Confidence: 0.825844932

00:53:18.157 --> 00:53:20.757 of cancers and we need to you know

NOTE Confidence: 0.825844932

00:53:20.757 --> 00:53:23.039 think about it in several cancers.

NOTE Confidence: 0.825844932

00:53:23.040 --> 00:53:25.973 So that I just want to certainly

NOTE Confidence: 0.825844932

00:53:25.973 --> 00:53:28.117 acknowledge linding who moved with

NOTE Confidence: 0.825844932

00:53:28.117 --> 00:53:30.541 me from Michigan and has really

NOTE Confidence: 0.825844932

00:53:30.541 --> 00:53:32.999 carried out all of these studies.

NOTE Confidence: 0.825844932

00:53:33.000 --> 00:53:36.515 Acknowledge again our HE monk GI

NOTE Confidence: 0.825844932

00:53:36.515 --> 00:53:39.290 group division and our targets

NOTE Confidence: 0.825844932

00:53:39.290 --> 00:53:43.683 by a repository and to thank the

NOTE Confidence: 0.825844932

00:53:43.683 --> 00:53:46.435 patients for their participation.

NOTE Confidence: 0.825844932

00:53:46.440 --> 00:53:47.106 Thank you.

NOTE Confidence: 0.825844932

00:53:47.106 --> 00:53:48.438 I'll take any questions

NOTE Confidence: 0.633809843333333

00:53:52.920 --> 00:53:55.132 and I should, yes,

NOTE Confidence: 0.633809843333333

00:53:55.132 --> 00:53:57.035 I don't know you can.

NOTE Confidence: 0.633809843333333

00:53:57.035 --> 00:53:58.360 There's also two questions online.

NOTE Confidence: 0.633809843333333

00:53:58.360 --> 00:53:58.840 So thank you for

NOTE Confidence: 0.59843657

00:54:04.240 --> 00:54:06.640 this education. But my question is the

NOTE Confidence: 0.59843657

00:54:06.640 --> 00:54:10.720 degree of expression in the myeloid cells.

NOTE Confidence: 0.9386269

00:54:10.720 --> 00:54:12.940 Is it something innate or is

NOTE Confidence: 0.9386269

00:54:12.940 --> 00:54:14.600 it acquired? Do we know? Is

NOTE Confidence: 0.909235881428571

00:54:14.600 --> 00:54:16.724 it like, is it something that's

NOTE Confidence: 0.909235881428571

00:54:16.724 --> 00:54:18.440 hereditary tendency to have higher

NOTE Confidence: 0.9116056725

00:54:18.440 --> 00:54:19.960 expression in certain individuals

NOTE Confidence: 0.5869538825

00:54:19.960 --> 00:54:20.960 and lower in others

NOTE Confidence: 0.19609609

00:54:23.360 --> 00:54:23.520 maybe

NOTE Confidence: 0.36984032

00:54:25.720 --> 00:54:25.800 are

NOTE Confidence: 0.805796806666667

00:54:28.080 --> 00:54:30.960 people. So your question is whether

NOTE Confidence: 0.805796806666667

00:54:30.960 --> 00:54:32.690 people are predisposed because

NOTE Confidence: 0.805796806666667

00:54:32.690 --> 00:54:35.160 they have snips or mutations.

NOTE Confidence: 0.805796806666667

00:54:35.160 --> 00:54:36.399 I'm just saying is it does it

NOTE Confidence: 0.805796806666667

00:54:36.399 --> 00:54:37.720 take like a two hit phenomena

NOTE Confidence: 0.832497478

00:54:37.720 --> 00:54:39.808 where you have H pylori infection

NOTE Confidence: 0.832497478

00:54:39.808 --> 00:54:42.080 but there is innate over expression

NOTE Confidence: 0.832497478

00:54:42.080 --> 00:54:44.042 of certain of these proteins and

NOTE Confidence: 0.832497478

00:54:44.042 --> 00:54:46.200 then that's when cancer happens? And

NOTE Confidence: 0.913102905

00:54:46.200 --> 00:54:47.436 I also had a second question.

NOTE Confidence: 0.913102905

00:54:47.440 --> 00:54:48.560 Do you think that some of the same

NOTE Confidence: 0.827958842857143

00:54:48.560 --> 00:54:50.395 pathways are involved in other

NOTE Confidence: 0.827958842857143

00:54:50.395 --> 00:54:52.230 types of gastric cancer like

NOTE Confidence: 0.827958842857143

00:54:52.300 --> 00:54:53.920 smoking related or others.

NOTE Confidence: 0.918313658333333

00:54:54.480 --> 00:54:58.560 So this pathway I think and

NOTE Confidence: 0.918514968

00:55:00.640 --> 00:55:04.840 is similar. I shouldn't because of

NOTE Confidence: 0.918514968

00:55:04.840 --> 00:55:08.052 the type 1 interferon regulation,

NOTE Confidence: 0.918514968

00:55:08.052 --> 00:55:10.112 is it similar to like

NOTE Confidence: 0.918514968

00:55:10.112 --> 00:55:12.520 the Sting C gas pathway?

NOTE Confidence: 0.918514968

00:55:12.520 --> 00:55:14.782 I haven't looked to see where

NOTE Confidence: 0.918514968

00:55:14.782 --> 00:55:17.200 the parallel and the overlap is,

NOTE Confidence: 0.918514968

00:55:17.200 --> 00:55:22.877 but I would emphasize that you know DAMPS,

NOTE Confidence: 0.918514968

00:55:22.880 --> 00:55:25.988 but probably even Pamps certainly can

NOTE Confidence: 0.918514968

00:55:25.988 --> 00:55:28.560 activate these plasma cytodendritic cells.

NOTE Confidence: 0.918514968

00:55:28.560 --> 00:55:30.560 The reason why I I like focusing on

NOTE Confidence: 0.918514968

00:55:30.560 --> 00:55:32.262 the Schlafen is because we're able to

NOTE Confidence: 0.918514968

00:55:32.262 --> 00:55:34.560 take it all the way down to the promoter.

NOTE Confidence: 0.918514968

00:55:34.560 --> 00:55:37.488 We know why that promoter and

NOTE Confidence: 0.918514968

00:55:37.488 --> 00:55:39.440 those cells get marked.

NOTE Confidence: 0.918514968

00:55:39.440 --> 00:55:43.160 So it suggests that you really

NOTE Confidence: 0.918514968

00:55:43.160 --> 00:55:46.091 need a very strong induction

NOTE Confidence: 0.918514968

00:55:46.091 --> 00:55:48.797 of Type 1 interferons or maybe

NOTE Confidence: 0.918514968

00:55:48.797 --> 00:55:51.040 there's mutations in those Irfs,

NOTE Confidence: 0.918514968

00:55:51.040 --> 00:55:52.150 etcetera constitutive.

NOTE Confidence: 0.918514968

00:55:52.150 --> 00:55:55.930 I mean it gets pretty complicated where

NOTE Confidence: 0.918514968

00:55:55.930 --> 00:55:59.080 whether people may be predisposed or not,

NOTE Confidence: 0.918514968

00:55:59.080 --> 00:56:03.695 we are some of the endpoints that

NOTE Confidence: 0.918514968

00:56:03.695 --> 00:56:07.158 we're looking at it are so TLR 9

NOTE Confidence: 0.918514968

00:56:07.158 --> 00:56:09.412 mainly because there is already

NOTE Confidence: 0.918514968

00:56:09.412 --> 00:56:11.348 information actually related to

NOTE Confidence: 0.918514968

00:56:11.348 --> 00:56:13.735 gastric cancer and Helicobacter that

NOTE Confidence: 0.918514968

00:56:13.735 --> 00:56:16.724 patients that have mutations in TLR 9

NOTE Confidence: 0.918514968

00:56:16.724 --> 00:56:19.609 May have a more aggressive response

NOTE Confidence: 0.918514968

00:56:19.609 --> 00:56:21.994 to an infection with Helicobacter.

NOTE Confidence: 0.918514968

00:56:22.000 --> 00:56:25.400 So that's we're starting with more upstream.

NOTE Confidence: 0.786846705

00:56:27.640 --> 00:56:29.380 Yes, thank you. That was a

NOTE Confidence: 0.786846705

00:56:29.380 --> 00:56:31.920 great talk. So Tadalphil is,

NOTE Confidence: 0.93450597

00:56:32.720 --> 00:56:34.220 you know, prescribed for

NOTE Confidence: 0.93450597

00:56:34.220 --> 00:56:35.720 other things as well.

NOTE Confidence: 0.93450597

00:56:35.720 --> 00:56:36.920 Do you, have you considered

NOTE Confidence: 0.93450597

00:56:36.920 --> 00:56:38.184 doing like a retrospective

NOTE Confidence: 0.93450597

00:56:38.184 --> 00:56:40.080 study and looking at you know,

NOTE Confidence: 0.93450597

00:56:40.080 --> 00:56:42.360 maybe stomach cancer versus people

NOTE Confidence: 0.93450597

00:56:42.360 --> 00:56:44.640 who've been prescribed to Dalafil,

NOTE Confidence: 0.85302366375

00:56:46.040 --> 00:56:47.900 a retrospective study? Yeah.

NOTE Confidence: 0.85302366375

00:56:47.900 --> 00:56:51.440 So in other words, it's in wide use.

NOTE Confidence: 0.865781166666667

00:56:53.800 --> 00:56:55.655 The problem is and I think we're

NOTE Confidence: 0.865781166666667

00:56:55.655 --> 00:56:58.165 going to need AI to do these kinds of

NOTE Confidence: 0.865781166666667

00:56:58.165 --> 00:57:00.055 things because it's it's really being

NOTE Confidence: 0.865781166666667

00:57:00.055 --> 00:57:02.680 someone has to mine the clinical data.

NOTE Confidence: 0.865781166666667

00:57:02.680 --> 00:57:04.145 I'd have to see whether

NOTE Confidence: 0.865781166666667

00:57:04.145 --> 00:57:05.317 it's already out there.

NOTE Confidence: 0.865781166666667

00:57:05.320 --> 00:57:08.386 Most likely it's not for gastric

NOTE Confidence: 0.865781166666667

00:57:08.386 --> 00:57:12.071 cancer maybe for one of the bigger

NOTE Confidence: 0.865781166666667

00:57:12.071 --> 00:57:15.155 cancers like lung or colon cancer.

NOTE Confidence: 0.865781166666667

00:57:15.160 --> 00:57:17.224 But I still think it's going to take

NOTE Confidence: 0.865781166666667

00:57:17.224 --> 00:57:19.375 some energy to pull it out of the

NOTE Confidence: 0.865781166666667

00:57:19.375 --> 00:57:21.080 clinical records and really analyze it.

NOTE Confidence: 0.865781166666667

00:57:21.080 --> 00:57:23.684 I really offhand I haven't seen any

NOTE Confidence: 0.865781166666667

00:57:23.684 --> 00:57:26.000 papers really looking at that but

NOTE Confidence: 0.865781166666667

00:57:26.000 --> 00:57:27.880 it's that's an excellent question.

NOTE Confidence: 0.865781166666667

00:57:27.880 --> 00:57:32.360 Thank you, Clara. Hello.

NOTE Confidence: 0.865781166666667

00:57:32.360 --> 00:57:33.040 2 questions.

NOTE Confidence: 0.886043567142857

00:57:33.040 --> 00:57:36.197 One, back to the inflammatory cytokine role.

NOTE Confidence: 0.886043567142857

00:57:36.200 --> 00:57:38.620 And you showed that overexpressing

NOTE Confidence: 0.886043567142857

00:57:38.620 --> 00:57:40.556 is sufficient to contribute.

NOTE Confidence: 0.886043567142857

00:57:40.560 --> 00:57:42.415 But if you sort of throw in

NOTE Confidence: 0.886043567142857

00:57:42.415 --> 00:57:44.290 inhibitors or utilize cell specific

NOTE Confidence: 0.886043567142857

00:57:44.290 --> 00:57:46.600 deletion of Aisle 1 beta TNF,

NOTE Confidence: 0.886043567142857

00:57:46.600 --> 00:57:48.679 you had a range of different cytokines.

NOTE Confidence: 0.886043567142857

00:57:48.680 --> 00:57:51.394 What's the effect of deletion in

NOTE Confidence: 0.886043567142857

00:57:51.394 --> 00:57:53.038 your model on the end outcome?

NOTE Confidence: 0.886043567142857

00:57:53.040 --> 00:57:57.080 So deletion of like PNF or we we haven't,

NOTE Confidence: 0.807212166

00:57:57.760 --> 00:57:58.960 yeah, we haven't gone there.

NOTE Confidence: 0.807212166

00:57:58.960 --> 00:58:00.920 You can imagine how many mice my

NOTE Confidence: 0.807212166

00:58:00.920 --> 00:58:04.384 my mouse bill is out of control and

NOTE Confidence: 0.807212166

00:58:04.384 --> 00:58:06.600 I just it's reading all of those

NOTE Confidence: 0.807212166

00:58:06.600 --> 00:58:08.240 yeah mice onto those backgrounds

NOTE Confidence: 0.807212166

00:58:08.240 --> 00:58:10.800 which I I haven't that's why we did

NOTE Confidence: 0.807212166

00:58:10.800 --> 00:58:12.800 the antibodies a little cheaper.

NOTE Confidence: 0.807212166

00:58:12.800 --> 00:58:14.478 And then I guess the second question

NOTE Confidence: 0.880993492727273

00:58:14.880 --> 00:58:16.714 is a little bit related to the

NOTE Confidence: 0.880993492727273

00:58:16.714 --> 00:58:18.120 spectrum of Schlafen expression.

NOTE Confidence: 0.880993492727273

00:58:18.120 --> 00:58:19.793 If I know you mentioned in the

NOTE Confidence: 0.880993492727273

00:58:19.793 --> 00:58:21.080 mouse model that you can't,

NOTE Confidence: 0.880993492727273

00:58:21.080 --> 00:58:23.840 you don't see progression to the to cancer,

NOTE Confidence: 0.880993492727273

00:58:23.840 --> 00:58:25.408 it's more than metaplasia.

NOTE Confidence: 0.880993492727273

00:58:25.408 --> 00:58:28.872 But in human if you try and sort

NOTE Confidence: 0.880993492727273

00:58:28.872 --> 00:58:32.832 of consider the transition between

NOTE Confidence: 0.880993492727273

00:58:32.832 --> 00:58:36.000 metaplasia to gastric cancer.

NOTE Confidence: 0.880993492727273

00:58:36.000 --> 00:58:36.800 Well, I guess the first,

NOTE Confidence: 0.880993492727273

00:58:36.800 --> 00:58:39.136 can you speak to some of the things

NOTE Confidence: 0.880993492727273

00:58:39.136 --> 00:58:42.488 that you think are contributing to that

NOTE Confidence: 0.880993492727273

00:58:42.488 --> 00:58:45.302 enabling that transition into the in

NOTE Confidence: 0.880993492727273

00:58:45.302 --> 00:58:48.005 the 1 to 3% that sort of overlap with

NOTE Confidence: 0.880993492727273

00:58:48.005 --> 00:58:50.160 some of the pathways you've highlighted.

NOTE Confidence: 0.880993492727273

00:58:50.160 --> 00:58:50.700 In other words,

NOTE Confidence: 0.880993492727273

00:58:50.700 --> 00:58:52.395 you got the 10% that have metaplasia and

NOTE Confidence: 0.880993492727273

00:58:52.395 --> 00:58:54.832 then one to 3% actual gastric cancer,

NOTE Confidence: 0.880993492727273

00:58:54.832 --> 00:58:55.336 right.

NOTE Confidence: 0.880993492727273

00:58:55.336 --> 00:58:58.087 And and so in I guess in your

NOTE Confidence: 0.880993492727273

00:58:58.087 --> 00:58:59.955 studies that you're doing where

NOTE Confidence: 0.880993492727273

00:58:59.955 --> 00:59:02.316 you're looking at are you able

NOTE Confidence: 0.880993492727273

00:59:02.316 --> 00:59:04.548 to look at spectrum of Schlafen

NOTE Confidence: 0.880993492727273

00:59:04.548 --> 00:59:06.088 expression in that subset that

NOTE Confidence: 0.880993492727273

00:59:06.088 --> 00:59:07.840 goes on to gastric cancer relative

NOTE Confidence: 0.880993492727273

00:59:07.895 --> 00:59:09.677 to those that stay in metaplasia.

NOTE Confidence: 0.824670795238095

00:59:10.840 --> 00:59:13.264 OK. So I'm I'm trying to so have

NOTE Confidence: 0.824670795238095

00:59:13.264 --> 00:59:15.470 we looked at so you're taking

NOTE Confidence: 0.824670795238095

00:59:15.470 --> 00:59:17.762 gastric cancer or you mean taking

NOTE Confidence: 0.824670795238095

00:59:17.839 --> 00:59:21.040 metaplasia patients with metaplasia, I

NOTE Confidence: 0.868682635

00:59:21.080 --> 00:59:23.132 mean in the pathway are you and and it

NOTE Confidence: 0.868682635

00:59:23.132 --> 00:59:25.088 can be Schlafen and can be you know

NOTE Confidence: 0.868682635

00:59:25.088 --> 00:59:26.999 for the full for the full pathway.

NOTE Confidence: 0.868682635

00:59:27.000 --> 00:59:29.275 In general are you able to see

NOTE Confidence: 0.868682635

00:59:29.275 --> 00:59:31.598 that those that progress to cancer

NOTE Confidence: 0.868682635

00:59:31.600 --> 00:59:34.629 are fit on the higher end of of

NOTE Confidence: 0.868682635

00:59:34.629 --> 00:59:36.461 sort of or on the altered end of

NOTE Confidence: 0.868682635

00:59:36.461 --> 00:59:37.902 expression of the pathway relative

NOTE Confidence: 0.868682635

00:59:37.902 --> 00:59:39.636 to those that remain in metaplasia

NOTE Confidence: 0.524150561666667

00:59:41.440 --> 00:59:44.956 altered of I'm so I'm sorry

NOTE Confidence: 0.524150561666667

00:59:44.960 --> 00:59:46.640 of your can you segregate

NOTE Confidence: 0.789262433076923

00:59:46.800 --> 00:59:48.789 like in in in any number of thing can

NOTE Confidence: 0.789262433076923

00:59:48.789 --> 00:59:52.186 you segregate the high versus low in the

NOTE Confidence: 0.789262433076923

00:59:52.186 --> 00:59:54.377 shop and pathway for those that progress

NOTE Confidence: 0.789262433076923

00:59:54.377 --> 00:59:57.920 versus that remain in metaplasia Oh

NOTE Confidence: 0.813621394

00:59:57.920 --> 01:00:01.296 so but in people or or in the in

NOTE Confidence: 0.813621394

01:00:01.296 --> 01:00:03.000 people in other words we have

NOTE Confidence: 0.753566116666667

01:00:03.120 --> 01:00:05.118 from bulk RNA or from other

NOTE Confidence: 0.753566116666667

01:00:05.120 --> 01:00:07.096 types of data sets that may

NOTE Confidence: 0.753566116666667

01:00:07.096 --> 01:00:08.440 have been done in the stomach.

NOTE Confidence: 0.8566534925

01:00:09.520 --> 01:00:11.960 You know it just really hasn't been done.

NOTE Confidence: 0.8566534925

01:00:11.960 --> 01:00:16.979 We haven't really segregated the subtypes of

NOTE Confidence: 0.8566534925

01:00:16.979 --> 01:00:21.840 Schlafen 12 L cells in the patients at all.

NOTE Confidence: 0.8566534925

01:00:21.840 --> 01:00:25.412 I I mean it it's we're just a lot of

NOTE Confidence: 0.8566534925

01:00:25.412 --> 01:00:28.500 it is just numbers and we're just happy

NOTE Confidence: 0.8566534925

01:00:28.592 --> 01:00:31.328 to be able to to well you know with

NOTE Confidence: 0.8566534925

01:00:31.328 --> 01:00:33.353 the repository the logistics is not

NOTE Confidence: 0.8566534925

01:00:33.353 --> 01:00:36.127 as tricky because I have to have our

NOTE Confidence: 0.8566534925

01:00:36.127 --> 01:00:38.710 inpatient teams let us know there's a

NOTE Confidence: 0.8566534925

01:00:38.710 --> 01:00:41.012 patient in house patient has to agree

NOTE Confidence: 0.8566534925

01:00:41.012 --> 01:00:43.335 many times they don't come or they

NOTE Confidence: 0.8566534925

01:00:43.335 --> 01:00:45.267 come and they we've already gotten

NOTE Confidence: 0.8566534925

01:00:45.267 --> 01:00:47.428 the biopsies and our hospital will

NOTE Confidence: 0.8566534925

01:00:47.428 --> 01:00:49.730 not release that the even the tissue.

NOTE Confidence: 0.8566534925

01:00:49.730 --> 01:00:52.313 So we have a lot of just sort of

NOTE Confidence: 0.8566534925

01:00:52.313 --> 01:00:54.600 logistical issues but I'll keep that in

NOTE Confidence: 0.8566534925

01:00:54.600 --> 01:00:57.717 mind as we or I can send you the data.

NOTE Confidence: 0.8566534925

01:00:57.720 --> 01:00:59.640 Yeah, the data sets out

NOTE Confidence: 0.842874333

01:00:59.640 --> 01:01:01.020 there from the stomach and

NOTE Confidence: 0.842874333

01:01:01.020 --> 01:01:02.400 then look at high versus,

NOTE Confidence: 0.842874333

01:01:02.400 --> 01:01:04.560 you know the high versus lower

NOTE Confidence: 0.842874333

01:01:04.560 --> 01:01:05.598 expressors. Yeah, ends of the

NOTE Confidence: 0.56026433125

01:01:07.840 --> 01:01:09.950 I, I, I mean I I will look, I haven't,

NOTE Confidence: 0.56026433125

01:01:09.950 --> 01:01:11.240 I just haven't come across it,

NOTE Confidence: 0.56026433125

01:01:11.240 --> 01:01:13.000 but it's a good question.

NOTE Confidence: 0.56026433125

01:01:13.000 --> 01:01:13.918 You've stumped me.

NOTE Confidence: 0.936968044

01:01:16.320 --> 01:01:17.120 I may have missed this,

NOTE Confidence: 0.936968044

01:01:17.120 --> 01:01:19.472 but is persistent hedgehog sibling in

NOTE Confidence: 0.936968044

01:01:19.472 --> 01:01:22.240 the MDSC cells required to maintain

NOTE Confidence: 0.936968044

01:01:22.240 --> 01:01:24.123 the dysplastic tumors and if so is

NOTE Confidence: 0.936968044

01:01:24.123 --> 01:01:26.478 there a role for smoothened inhibitors?

NOTE Confidence: 0.936968044

01:01:26.480 --> 01:01:31.262 Oh that Doctor Kaplan had

NOTE Confidence: 0.936968044

01:01:31.262 --> 01:01:32.838 raised that issue yesterday.

NOTE Confidence: 0.936968044

01:01:32.840 --> 01:01:36.840 We could think about Vesmotogib to

NOTE Confidence: 0.936968044

01:01:36.840 --> 01:01:40.990 revisit that I it's a good question and

NOTE Confidence: 0.936968044

01:01:40.990 --> 01:01:44.356 I I mean I would try it out in our mouse

NOTE Confidence: 0.936968044

01:01:44.356 --> 01:01:46.719 models probably first I I do know that.

NOTE Confidence: 0.936968044

01:01:46.720 --> 01:01:49.114 So if you use a a Glee one null,

NOTE Confidence: 0.936968044

01:01:49.120 --> 01:01:53.220 we we didn't, we haven't used any

NOTE Confidence: 0.936968044

01:01:53.220 --> 01:01:55.396 hedgehog inhibitors but basically you

NOTE Confidence: 0.936968044

01:01:55.396 --> 01:01:58.114 as I showed you with the in vitro data,

NOTE Confidence: 0.936968044

01:01:58.120 --> 01:01:59.176 you need hedgehog,

NOTE Confidence: 0.936968044

01:01:59.176 --> 01:02:00.936 some kind of hedgehog signalling

NOTE Confidence: 0.936968044

01:02:00.936 --> 01:02:02.877 for that promoter to come on.

NOTE Confidence: 0.936968044

01:02:02.880 --> 01:02:05.505 The assumption is that the

NOTE Confidence: 0.936968044

01:02:05.505 --> 01:02:07.370 cells aren't or polarizing,

NOTE Confidence: 0.936968044

01:02:07.370 --> 01:02:09.395 but we haven't gone back

NOTE Confidence: 0.936968044

01:02:09.395 --> 01:02:11.040 to really explore that.

NOTE Confidence: 0.3446184875

01:02:14.080 --> 01:02:16.880 Oh, they were listening.

NOTE Confidence: 0.3446184875

01:02:16.880 --> 01:02:17.996 Oh, OK. I thought there was,

NOTE Confidence: 0.3446184875

01:02:18.000 --> 01:02:19.596 there was two things on the line,

NOTE Confidence: 0.3446184875

01:02:19.600 --> 01:02:21.718 but it was just the CME.

NOTE Confidence: 0.3446184875

01:02:21.720 --> 01:02:25.000 OK, no questions. All right.