

WEBVTT

NOTE duration:"00:54:26"

NOTE recognizability:0.859

NOTE language:en-us

NOTE Confidence: 0.90888099

00:00:04.850 --> 00:00:08.714 So today I'm delighted to introduce Dr.

NOTE Confidence: 0.90888099

00:00:08.720 --> 00:00:11.575 Bluma Lesch as our pathology

NOTE Confidence: 0.90888099

00:00:11.575 --> 00:00:13.288 grand rounds speaker.

NOTE Confidence: 0.90888099

00:00:13.290 --> 00:00:15.446 Many of you may know Doctor Lash

NOTE Confidence: 0.90888099

00:00:15.446 --> 00:00:17.340 is an assistant professor here

NOTE Confidence: 0.90888099

00:00:17.340 --> 00:00:19.140 in the genetics department,

NOTE Confidence: 0.90888099

00:00:19.140 --> 00:00:23.076 but what you may not know is that LUMO is

NOTE Confidence: 0.90888099

00:00:23.076 --> 00:00:26.364 actually a graduate of Yale University.

NOTE Confidence: 0.90888099

00:00:26.370 --> 00:00:30.350 Before she went on to the MD PhD

NOTE Confidence: 0.90888099

00:00:30.350 --> 00:00:32.550 program at the Tri Institutional

NOTE Confidence: 0.90888099

00:00:32.550 --> 00:00:35.330 Program at Weill Cornell.

NOTE Confidence: 0.90888099

00:00:35.330 --> 00:00:36.720 Rockefeller MSKCC,

NOTE Confidence: 0.90888099

00:00:36.720 --> 00:00:39.317 which did her pH D with Cori

NOTE Confidence: 0.90888099

00:00:39.317 --> 00:00:42.658 Bargmann and then she went on to do
NOTE Confidence: 0.90888099

00:00:42.658 --> 00:00:44.798 postdoc at the Whitehead Institute.
NOTE Confidence: 0.90888099

00:00:44.800 --> 00:00:46.725 With David Page and Richard
NOTE Confidence: 0.90888099

00:00:46.725 --> 00:00:48.265 Young as Co advisors.
NOTE Confidence: 0.920912913333333

00:00:50.380 --> 00:00:53.122 Her research focuses on the mechanisms
NOTE Confidence: 0.920912913333333

00:00:53.122 --> 00:00:54.885 of transcriptional regulation in
NOTE Confidence: 0.920912913333333

00:00:54.885 --> 00:00:57.195 the context of both development and
NOTE Confidence: 0.920912913333333

00:00:57.195 --> 00:00:59.764 evolution and in the short time since
NOTE Confidence: 0.920912913333333

00:00:59.764 --> 00:01:02.200 she started her lab here in 2017.
NOTE Confidence: 0.920912913333333

00:01:02.200 --> 00:01:04.320 She's actually been awarded the
NOTE Confidence: 0.920912913333333

00:01:04.320 --> 00:01:06.016 prestigious steel Cyril Scholar
NOTE Confidence: 0.920912913333333

00:01:06.016 --> 00:01:08.948 Award and and just received the Pew
NOTE Confidence: 0.920912913333333

00:01:08.948 --> 00:01:12.350 Biomedical Scholar Award in 2021.
NOTE Confidence: 0.920912913333333

00:01:12.350 --> 00:01:14.910 And so, without further ado,
NOTE Confidence: 0.920912913333333

00:01:14.910 --> 00:01:17.172 I'd like to introduce Dr Lash
NOTE Confidence: 0.920912913333333

00:01:17.172 --> 00:01:18.680 and her grand rounds.

NOTE Confidence: 0.920912913333333

00:01:18.680 --> 00:01:21.900 Talk will be an intergenerational,

NOTE Confidence: 0.920912913333333

00:01:21.900 --> 00:01:25.530 epigenetic, epigenetic inheritance of cancer.

NOTE Confidence: 0.909786081

00:01:33.100 --> 00:01:34.725 Alright, thank you, let me

NOTE Confidence: 0.909786081

00:01:34.725 --> 00:01:36.350 just share my screen here.

NOTE Confidence: 0.7797568175

00:02:06.310 --> 00:02:10.600 Can everyone see that? Yes, OK,

NOTE Confidence: 0.7797568175

00:02:10.600 --> 00:02:12.840 so thanks to the lobby for inviting me.

NOTE Confidence: 0.7797568175

00:02:12.840 --> 00:02:14.709 I'm I'm really excited to tell you

NOTE Confidence: 0.7797568175

00:02:14.709 --> 00:02:16.440 about what we're working on and

NOTE Confidence: 0.7797568175

00:02:16.440 --> 00:02:18.186 also looking forward to helping me,

NOTE Confidence: 0.7797568175

00:02:18.190 --> 00:02:19.783 hopefully making some

NOTE Confidence: 0.7797568175

00:02:19.783 --> 00:02:21.907 connections in your department.

NOTE Confidence: 0.7797568175

00:02:21.910 --> 00:02:23.998 So I'm going to talk about

NOTE Confidence: 0.7797568175

00:02:23.998 --> 00:02:24.694 Internet intergenerational

NOTE Confidence: 0.7797568175

00:02:24.694 --> 00:02:25.899 epigenetic inheritance of cancer,

NOTE Confidence: 0.7797568175

00:02:25.900 --> 00:02:28.918 which is a fairly dense topic

NOTE Confidence: 0.7797568175

00:02:28.920 --> 00:02:32.156 and I want to start out actually
NOTE Confidence: 0.7797568175

00:02:32.156 --> 00:02:35.186 with a fairly simple video.
NOTE Confidence: 0.7797568175

00:02:35.190 --> 00:02:36.784 This is a video of, UM,
NOTE Confidence: 0.7797568175

00:02:36.784 --> 00:02:39.388 the first cell division and an
NOTE Confidence: 0.7797568175

00:02:39.388 --> 00:02:42.518 embryo single cell zygote with two.
NOTE Confidence: 0.7797568175

00:02:42.518 --> 00:02:46.040 The two pronuclei coming together to
NOTE Confidence: 0.7797568175

00:02:46.040 --> 00:02:48.840 meet and undergo the first cell division
NOTE Confidence: 0.7797568175

00:02:48.840 --> 00:02:51.147 and generate the two cell embryo,
NOTE Confidence: 0.7797568175

00:02:51.150 --> 00:02:53.328 and I'm showing this video both
NOTE Confidence: 0.7797568175

00:02:53.328 --> 00:02:55.170 because it's just really cool.
NOTE Confidence: 0.7797568175

00:02:55.170 --> 00:02:57.249 This is one of the most amazing
NOTE Confidence: 0.7797568175

00:02:57.249 --> 00:02:59.233 points in the life cycle and
NOTE Confidence: 0.7797568175

00:02:59.233 --> 00:03:00.928 I really like watching it,
NOTE Confidence: 0.7797568175

00:03:00.930 --> 00:03:04.098 but also because I want to make a point.
NOTE Confidence: 0.7797568175

00:03:04.100 --> 00:03:06.494 In this video that that sort of sets up
NOTE Confidence: 0.7797568175

00:03:06.494 --> 00:03:08.876 the problem that we're interested in.

NOTE Confidence: 0.7797568175

00:03:08.880 --> 00:03:11.064 And the point is so here you

NOTE Confidence: 0.7797568175

00:03:11.064 --> 00:03:13.179 can see the two pronuclei.

NOTE Confidence: 0.7797568175

00:03:13.180 --> 00:03:15.156 Hopefully you can see that one of them

NOTE Confidence: 0.7797568175

00:03:15.156 --> 00:03:17.217 is much brighter than the other one.

NOTE Confidence: 0.7797568175

00:03:17.220 --> 00:03:20.094 The brighter one is the paternal

NOTE Confidence: 0.7797568175

00:03:20.094 --> 00:03:22.580 pronucleus coming from the sperm,

NOTE Confidence: 0.7797568175

00:03:22.580 --> 00:03:26.676 and the reason it's brighter is because it's

NOTE Confidence: 0.7797568175

00:03:26.676 --> 00:03:30.640 loaded up with histones tagged with GFP,

NOTE Confidence: 0.7797568175

00:03:30.640 --> 00:03:32.470 and this GFP tagged histone

NOTE Confidence: 0.7797568175

00:03:32.470 --> 00:03:34.300 was coming from the oocyte.

NOTE Confidence: 0.7797568175

00:03:34.300 --> 00:03:36.309 The fact that this nucleus this nucleus

NOTE Confidence: 0.7797568175

00:03:36.309 --> 00:03:39.005 is so much brighter means that all of its.

NOTE Confidence: 0.7797568175

00:03:39.010 --> 00:03:39.836 The stones,

NOTE Confidence: 0.7797568175

00:03:39.836 --> 00:03:42.314 all of it's upper genetic protein

NOTE Confidence: 0.7797568175

00:03:42.314 --> 00:03:45.227 information has been removed and completely

NOTE Confidence: 0.7797568175

00:03:45.227 --> 00:03:47.747 replaced with oocyte provided histones.

NOTE Confidence: 0.7797568175

00:03:47.750 --> 00:03:49.370 So this is a you know,

NOTE Confidence: 0.7797568175

00:03:49.370 --> 00:03:51.465 kind of the common conventional

NOTE Confidence: 0.7797568175

00:03:51.465 --> 00:03:54.010 wisdom in the field that come,

NOTE Confidence: 0.7797568175

00:03:54.010 --> 00:03:56.265 that all epigenetic information coming

NOTE Confidence: 0.7797568175

00:03:56.265 --> 00:03:59.174 from sperm at least is completely

NOTE Confidence: 0.7797568175

00:03:59.174 --> 00:04:02.069 replaced at fertilization and reset.

NOTE Confidence: 0.7797568175

00:04:02.070 --> 00:04:03.432 And and so.

NOTE Confidence: 0.7797568175

00:04:03.432 --> 00:04:05.248 With that in mind.

NOTE Confidence: 0.896484545925926

00:04:08.420 --> 00:04:10.708 This is a question one of the questions

NOTE Confidence: 0.896484545925926

00:04:10.708 --> 00:04:12.781 that my lab is especially interested

NOTE Confidence: 0.896484545925926

00:04:12.781 --> 00:04:15.358 in two life experiences of the parents

NOTE Confidence: 0.896484545925926

00:04:15.358 --> 00:04:17.500 affect the health of the progeny,

NOTE Confidence: 0.896484545925926

00:04:17.500 --> 00:04:20.524 and one would think since life experience

NOTE Confidence: 0.896484545925926

00:04:20.524 --> 00:04:23.779 tends to be encoded in epigenetics,

NOTE Confidence: 0.896484545925926

00:04:23.780 --> 00:04:26.276 but the fact that all of this epigenetic

NOTE Confidence: 0.896484545925926
00:04:26.276 --> 00:04:28.262 information is reset at fertilization would
NOTE Confidence: 0.896484545925926
00:04:28.262 --> 00:04:31.119 mean that the answer to this question is no.
NOTE Confidence: 0.896484545925926
00:04:31.120 --> 00:04:33.550 But what I'm going to try and get across in
NOTE Confidence: 0.896484545925926
00:04:33.612 --> 00:04:36.159 this talk is that the answer is actually yes,
NOTE Confidence: 0.896484545925926
00:04:36.160 --> 00:04:37.714 and we're going to try and
NOTE Confidence: 0.896484545925926
00:04:37.714 --> 00:04:39.030 uncover what some of the.
NOTE Confidence: 0.896484545925926
00:04:39.030 --> 00:04:41.400 Mechanisms for that might be.
NOTE Confidence: 0.896484545925926
00:04:41.400 --> 00:04:43.745 And we can break down this question
NOTE Confidence: 0.896484545925926
00:04:43.745 --> 00:04:46.130 into two more specific questions.
NOTE Confidence: 0.896484545925926
00:04:46.130 --> 00:04:48.990 One is gene regulatory information
NOTE Confidence: 0.896484545925926
00:04:48.990 --> 00:04:51.439 inherited across generations. So is this.
NOTE Confidence: 0.896484545925926
00:04:51.439 --> 00:04:52.654 This is a molecular question.
NOTE Confidence: 0.896484545925926
00:04:52.660 --> 00:04:55.456 What's happening at the biochemical level?
NOTE Confidence: 0.896484545925926
00:04:55.460 --> 00:04:56.870 And then the second question is,
NOTE Confidence: 0.896484545925926
00:04:56.870 --> 00:04:59.278 is this inherited regulatory
NOTE Confidence: 0.896484545925926

00:04:59.278 --> 00:05:01.084 information biologically meaningful?
NOTE Confidence: 0.896484545925926

00:05:01.090 --> 00:05:02.023 In other words,
NOTE Confidence: 0.896484545925926

00:05:02.023 --> 00:05:03.578 does it actually affect phenotype
NOTE Confidence: 0.896484545925926

00:05:03.578 --> 00:05:05.509 or is it just a biochemical
NOTE Confidence: 0.896484545925926

00:05:05.509 --> 00:05:07.375 signature that we can follow with
NOTE Confidence: 0.896484545925926

00:05:07.439 --> 00:05:09.307 our various molecular techniques?
NOTE Confidence: 0.896484545925926

00:05:09.310 --> 00:05:11.370 Uhm?
NOTE Confidence: 0.896484545925926

00:05:11.370 --> 00:05:14.226 Before I get too deeply into the problem,
NOTE Confidence: 0.896484545925926

00:05:14.230 --> 00:05:16.295 I'm going to give you a quick
NOTE Confidence: 0.896484545925926

00:05:16.295 --> 00:05:17.180 introduction to epigenetics.
NOTE Confidence: 0.896484545925926

00:05:17.180 --> 00:05:19.336 This is probably review for most people,
NOTE Confidence: 0.896484545925926

00:05:19.340 --> 00:05:20.908 but I just want to make sure
NOTE Confidence: 0.896484545925926

00:05:20.908 --> 00:05:22.656 everybody is on the same page and
NOTE Confidence: 0.896484545925926

00:05:22.656 --> 00:05:25.148 what I'm showing here is a consensus
NOTE Confidence: 0.896484545925926

00:05:25.148 --> 00:05:26.578 definition for what epigenetics
NOTE Confidence: 0.896484545925926

00:05:26.578 --> 00:05:29.170 is that came out of a cold Spring

NOTE Confidence: 0.896484545925926

00:05:29.236 --> 00:05:31.438 Harbor meeting about 10 years ago,

NOTE Confidence: 0.896484545925926

00:05:31.440 --> 00:05:34.439 and it has four key components stably

NOTE Confidence: 0.896484545925926

00:05:34.439 --> 00:05:36.155 heritable phenotype resulting from

NOTE Confidence: 0.896484545925926

00:05:36.155 --> 00:05:38.300 changes in a chromosome without

NOTE Confidence: 0.896484545925926

00:05:38.359 --> 00:05:40.239 alterations in the DNA sequence,

NOTE Confidence: 0.896484545925926

00:05:40.240 --> 00:05:41.430 and I want to make the point.

NOTE Confidence: 0.896484545925926

00:05:41.430 --> 00:05:43.694 That come off when we talk about epigenetics.

NOTE Confidence: 0.896484545925926

00:05:43.700 --> 00:05:45.877 We're talking about the second half of

NOTE Confidence: 0.896484545925926

00:05:45.877 --> 00:05:47.585 this sentence changes their chromosome

NOTE Confidence: 0.896484545925926

00:05:47.585 --> 00:05:49.727 without alterations in a DNA sequence,

NOTE Confidence: 0.896484545925926

00:05:49.730 --> 00:05:52.250 and those are the things shown here

NOTE Confidence: 0.896484545925926

00:05:52.250 --> 00:05:55.337 that are generally considered to be the

NOTE Confidence: 0.896484545925926

00:05:55.337 --> 00:05:57.550 carriers of opportunistic information.

NOTE Confidence: 0.896484545925926

00:05:57.550 --> 00:05:59.070 Covalent modifications to DNA,

NOTE Confidence: 0.896484545925926

00:05:59.070 --> 00:06:02.240 mostly in the form of DNA methylation,

NOTE Confidence: 0.896484545925926

00:06:02.240 --> 00:06:04.628 positioning of nucleosomes
NOTE Confidence: 0.896484545925926

00:06:04.628 --> 00:06:07.016 along the chromosome.
NOTE Confidence: 0.896484545925926

00:06:07.020 --> 00:06:08.996 Covalent modifications to histones,
NOTE Confidence: 0.896484545925926

00:06:08.996 --> 00:06:11.466 which can affect positioning along
NOTE Confidence: 0.896484545925926

00:06:11.466 --> 00:06:13.670 the chromosome transcription factor
NOTE Confidence: 0.896484545925926

00:06:13.670 --> 00:06:16.405 binding and large scale structural
NOTE Confidence: 0.896484545925926

00:06:16.405 --> 00:06:18.639 arrangements of the chromosomes.
NOTE Confidence: 0.896484545925926

00:06:18.640 --> 00:06:20.313 These are the kinds of things that
NOTE Confidence: 0.896484545925926

00:06:20.313 --> 00:06:22.393 you see a lot of data on that we
NOTE Confidence: 0.896484545925926

00:06:22.393 --> 00:06:24.248 tend to study and pay attention to,
NOTE Confidence: 0.896484545925926

00:06:24.250 --> 00:06:26.509 but I want to point out that a key
NOTE Confidence: 0.896484545925926

00:06:26.509 --> 00:06:28.691 aspect of this definition is that
NOTE Confidence: 0.896484545925926

00:06:28.691 --> 00:06:31.824 this effects phenotype and but it's
NOTE Confidence: 0.896484545925926

00:06:31.824 --> 00:06:34.616 heritable so so I and I want to make
NOTE Confidence: 0.896484545925926

00:06:34.616 --> 00:06:36.230 sure that that we're addressing.
NOTE Confidence: 0.896484545925926

00:06:36.230 --> 00:06:38.840 So those questions during this talk.

NOTE Confidence: 0.836415338461539

00:06:41.500 --> 00:06:45.276 My love is especially interested in in one

NOTE Confidence: 0.836415338461539

00:06:45.276 --> 00:06:48.188 particular aspect of epidemic information,

NOTE Confidence: 0.836415338461539

00:06:48.190 --> 00:06:50.686 we tend to focus on this level of

NOTE Confidence: 0.836415338461539

00:06:50.686 --> 00:06:52.340 organization at the nucleosome.

NOTE Confidence: 0.836415338461539

00:06:52.340 --> 00:06:55.095 The nucleosome is the basic

NOTE Confidence: 0.836415338461539

00:06:55.095 --> 00:06:57.299 structural unit of chromatin,

NOTE Confidence: 0.836415338461539

00:06:57.300 --> 00:06:59.980 and it's composed of an

NOTE Confidence: 0.836415338461539

00:06:59.980 --> 00:07:02.660 octamer of eight of eight,

NOTE Confidence: 0.836415338461539

00:07:02.660 --> 00:07:05.996 histone 8 histone proteins,

NOTE Confidence: 0.836415338461539

00:07:05.996 --> 00:07:08.498 so two tetramers.

NOTE Confidence: 0.836415338461539

00:07:08.500 --> 00:07:11.752 And 147 base pairs of DNA

NOTE Confidence: 0.836415338461539

00:07:11.752 --> 00:07:13.690 wrapped around its optimer.

NOTE Confidence: 0.79615179875

00:07:16.360 --> 00:07:18.370 Each of these histones has a

NOTE Confidence: 0.79615179875

00:07:18.370 --> 00:07:20.076 globular domain that makes up

NOTE Confidence: 0.79615179875

00:07:20.076 --> 00:07:21.596 the core of the nucleosome,

NOTE Confidence: 0.79615179875

00:07:21.600 --> 00:07:23.784 but importantly also has an end
NOTE Confidence: 0.79615179875

00:07:23.784 --> 00:07:25.560 terminal tail that sticks out,
NOTE Confidence: 0.79615179875

00:07:25.560 --> 00:07:29.344 and it's this floppy tail that gets modified.
NOTE Confidence: 0.79615179875

00:07:29.350 --> 00:07:31.268 I'm currently and so we tend to.
NOTE Confidence: 0.79615179875

00:07:31.270 --> 00:07:33.055 This is the structure we tend to
NOTE Confidence: 0.79615179875

00:07:33.055 --> 00:07:34.631 portray this as a cartoon like
NOTE Confidence: 0.79615179875

00:07:34.631 --> 00:07:36.381 this and this is what you'll see
NOTE Confidence: 0.79615179875

00:07:36.438 --> 00:07:38.088 throughout the rest of the top,
NOTE Confidence: 0.79615179875

00:07:38.090 --> 00:07:40.730 but at the biochemical level,
NOTE Confidence: 0.79615179875

00:07:40.730 --> 00:07:42.774 covalent modifications to these
NOTE Confidence: 0.79615179875

00:07:42.774 --> 00:07:45.329 histone tails can affect the
NOTE Confidence: 0.79615179875

00:07:45.329 --> 00:07:47.439 stability of this nucleosome and
NOTE Confidence: 0.79615179875

00:07:47.439 --> 00:07:50.255 in turn effects the extent of gene
NOTE Confidence: 0.79615179875

00:07:50.255 --> 00:07:52.565 regulation of a particular locus.
NOTE Confidence: 0.79615179875

00:07:52.570 --> 00:07:56.924 Uhm? So when we talk about resetting
NOTE Confidence: 0.79615179875

00:07:56.924 --> 00:07:58.790 of epigenetic information,

NOTE Confidence: 0.79615179875
00:07:58.790 --> 00:08:00.006 there are,
NOTE Confidence: 0.79615179875
00:08:00.006 --> 00:08:03.654 and we're focusing on on his
NOTE Confidence: 0.79615179875
00:08:03.654 --> 00:08:04.870 own modifications.
NOTE Confidence: 0.79615179875
00:08:04.870 --> 00:08:06.970 There are actually two aspects of this.
NOTE Confidence: 0.79615179875
00:08:06.970 --> 00:08:09.250 There's one that I showed already
NOTE Confidence: 0.79615179875
00:08:09.250 --> 00:08:11.458 in the in the in the early embryo
NOTE Confidence: 0.79615179875
00:08:11.458 --> 00:08:14.087 where his zones are kicked out of the
NOTE Confidence: 0.79615179875
00:08:14.087 --> 00:08:16.283 eternal nucleus and some extent reset
NOTE Confidence: 0.79615179875
00:08:16.283 --> 00:08:18.647 in the maternal practically as well.
NOTE Confidence: 0.79615179875
00:08:18.650 --> 00:08:20.810 And there's also a resetting
NOTE Confidence: 0.79615179875
00:08:20.810 --> 00:08:22.970 that happens in sperm before
NOTE Confidence: 0.79615179875
00:08:23.053 --> 00:08:25.328 you even get to fertilization.
NOTE Confidence: 0.79615179875
00:08:25.330 --> 00:08:26.870 So sperm actually removed
NOTE Confidence: 0.79615179875
00:08:26.870 --> 00:08:28.410 most of their histones.
NOTE Confidence: 0.79615179875
00:08:28.410 --> 00:08:30.360 Most of their nucleosomes as they
NOTE Confidence: 0.79615179875

00:08:30.360 --> 00:08:32.103 mature and replaced them with
NOTE Confidence: 0.79615179875

00:08:32.103 --> 00:08:34.008 another protein and their packaging
NOTE Confidence: 0.79615179875

00:08:34.008 --> 00:08:35.532 protein called crudo means,
NOTE Confidence: 0.79615179875

00:08:35.540 --> 00:08:37.958 and that's so that they can
NOTE Confidence: 0.79615179875

00:08:37.958 --> 00:08:39.781 compact their their their genome.
NOTE Confidence: 0.79615179875

00:08:39.781 --> 00:08:40.118 Very,
NOTE Confidence: 0.79615179875

00:08:40.118 --> 00:08:42.900 very small and fitted into a sperm head.
NOTE Confidence: 0.79615179875

00:08:42.900 --> 00:08:45.132 As we've all seen.
NOTE Confidence: 0.79615179875

00:08:45.132 --> 00:08:46.248 And so.
NOTE Confidence: 0.79615179875

00:08:46.250 --> 00:08:47.725 There's a loss of epigenetic
NOTE Confidence: 0.79615179875

00:08:47.725 --> 00:08:48.905 information at this stage,
NOTE Confidence: 0.79615179875

00:08:48.910 --> 00:08:51.112 and there's a loss of epigenetic
NOTE Confidence: 0.79615179875

00:08:51.112 --> 00:08:52.580 information at this stage.
NOTE Confidence: 0.79615179875

00:08:52.580 --> 00:08:53.404 But importantly,
NOTE Confidence: 0.79615179875

00:08:53.404 --> 00:08:55.876 there is a little bit of
NOTE Confidence: 0.79615179875

00:08:55.876 --> 00:08:58.312 retention of histones in this

NOTE Confidence: 0.79615179875

00:08:58.312 --> 00:09:00.156 during this protamine transition,

NOTE Confidence: 0.79615179875

00:09:00.160 --> 00:09:02.362 and we're actually not sure the

NOTE Confidence: 0.79615179875

00:09:02.362 --> 00:09:04.399 extent to which those retained

NOTE Confidence: 0.79615179875

00:09:04.399 --> 00:09:06.379 histones actually passed through

NOTE Confidence: 0.79615179875

00:09:06.379 --> 00:09:08.898 into the into the early embryo.

NOTE Confidence: 0.940186819411765

00:09:11.610 --> 00:09:15.012 So in complete counterpoint to the extent

NOTE Confidence: 0.940186819411765

00:09:15.012 --> 00:09:18.316 of epigenetic resetting that happens at

NOTE Confidence: 0.940186819411765

00:09:18.316 --> 00:09:20.668 fertilization and before fertilization,

NOTE Confidence: 0.940186819411765

00:09:20.670 --> 00:09:23.624 there's quite a lot of evidence indicating

NOTE Confidence: 0.940186819411765

00:09:23.624 --> 00:09:27.302 that phenotype can be affected by paternal

NOTE Confidence: 0.940186819411765

00:09:27.302 --> 00:09:30.510 experience or by parental experience.

NOTE Confidence: 0.940186819411765

00:09:30.510 --> 00:09:32.175 And what I'm showing here

NOTE Confidence: 0.940186819411765

00:09:32.175 --> 00:09:33.507 are two classic examples.

NOTE Confidence: 0.940186819411765

00:09:33.510 --> 00:09:36.780 These are phenotypes that are actually

NOTE Confidence: 0.940186819411765

00:09:36.780 --> 00:09:39.910 conveyed generally by DNA methylation.

NOTE Confidence: 0.940186819411765

00:09:39.910 --> 00:09:42.451 But these are papers that that in
NOTE Confidence: 0.940186819411765

00:09:42.451 --> 00:09:44.708 some ways kicked off this field.
NOTE Confidence: 0.940186819411765

00:09:44.710 --> 00:09:47.758 This is a locus called agouti viable yellow
NOTE Confidence: 0.940186819411765

00:09:47.758 --> 00:09:51.265 which is an allele of the agouti gene that
NOTE Confidence: 0.940186819411765

00:09:51.265 --> 00:09:53.878 affects coat color among other things.
NOTE Confidence: 0.940186819411765

00:09:53.880 --> 00:09:56.472 And these mice are all genetically
NOTE Confidence: 0.940186819411765

00:09:56.472 --> 00:09:58.662 identical but carry different levels
NOTE Confidence: 0.940186819411765

00:09:58.662 --> 00:10:00.972 of DNA methylation at this locus
NOTE Confidence: 0.940186819411765

00:10:00.972 --> 00:10:03.349 which affects the extent to which
NOTE Confidence: 0.940186819411765

00:10:03.349 --> 00:10:05.647 they they express or don't express.
NOTE Confidence: 0.940186819411765

00:10:05.650 --> 00:10:08.920 This brown agouti coat color.
NOTE Confidence: 0.940186819411765

00:10:08.920 --> 00:10:12.756 And it turns out that the maternal
NOTE Confidence: 0.940186819411765

00:10:12.760 --> 00:10:15.714 epigenetic state can affect the chances of
NOTE Confidence: 0.940186819411765

00:10:15.714 --> 00:10:18.215 the offspring having the same epigenetic
NOTE Confidence: 0.940186819411765

00:10:18.215 --> 00:10:20.931 state and having a similar code color.
NOTE Confidence: 0.940186819411765

00:10:20.940 --> 00:10:21.634 These again,

NOTE Confidence: 0.940186819411765
00:10:21.634 --> 00:10:24.063 this has nothing to do with being
NOTE Confidence: 0.940186819411765
00:10:24.063 --> 00:10:25.827 encoded in the genome itself.
NOTE Confidence: 0.940186819411765
00:10:25.830 --> 00:10:28.054 So this is a maternal effect just to
NOTE Confidence: 0.940186819411765
00:10:28.054 --> 00:10:30.600 show you that it's not only maternal is.
NOTE Confidence: 0.940186819411765
00:10:30.600 --> 00:10:32.712 Similar effects can be seen and
NOTE Confidence: 0.940186819411765
00:10:32.712 --> 00:10:34.120 another locust called Accent,
NOTE Confidence: 0.940186819411765
00:10:34.120 --> 00:10:36.465 and this causes a kick tail and
NOTE Confidence: 0.940186819411765
00:10:36.465 --> 00:10:38.209 can be transmitted either from
NOTE Confidence: 0.940186819411765
00:10:38.209 --> 00:10:40.219 a father or from the mother.
NOTE Confidence: 0.940186819411765
00:10:40.220 --> 00:10:40.750 Uhm?
NOTE Confidence: 0.842131356153846
00:10:43.210 --> 00:10:45.148 A whole pile of other studies
NOTE Confidence: 0.842131356153846
00:10:45.148 --> 00:10:47.450 has looked at this kind of thing,
NOTE Confidence: 0.842131356153846
00:10:47.450 --> 00:10:49.676 not just in terms of morphology
NOTE Confidence: 0.842131356153846
00:10:49.676 --> 00:10:52.218 and coat color, but in terms of
NOTE Confidence: 0.842131356153846
00:10:52.218 --> 00:10:54.003 things like metabolism and behavior.
NOTE Confidence: 0.842131356153846

00:10:54.010 --> 00:10:56.250 So I'm showing here a couple of the
NOTE Confidence: 0.842131356153846

00:10:56.250 --> 00:10:58.276 most common types of phenotypes that
NOTE Confidence: 0.842131356153846

00:10:58.276 --> 00:11:00.382 have been studied in this context.
NOTE Confidence: 0.842131356153846

00:11:00.390 --> 00:11:02.170 A fairly well established
NOTE Confidence: 0.842131356153846

00:11:02.170 --> 00:11:03.950 one is paternal diet,
NOTE Confidence: 0.842131356153846

00:11:03.950 --> 00:11:07.873 so a high fat diet in the father can
NOTE Confidence: 0.842131356153846

00:11:07.873 --> 00:11:10.351 result in altered insulin response and
NOTE Confidence: 0.842131356153846

00:11:10.351 --> 00:11:12.490 altered glucose processing and offspring.
NOTE Confidence: 0.842131356153846

00:11:12.490 --> 00:11:15.802 This is an example from a paper in 2015.
NOTE Confidence: 0.842131356153846

00:11:15.810 --> 00:11:18.057 Uhm, a number of papers have looked
NOTE Confidence: 0.842131356153846

00:11:18.057 --> 00:11:19.928 at drug exposures in the father,
NOTE Confidence: 0.842131356153846

00:11:19.930 --> 00:11:23.374 so here's an example where a father
NOTE Confidence: 0.842131356153846

00:11:23.374 --> 00:11:26.188 exposed to nicotine has offspring that
NOTE Confidence: 0.842131356153846

00:11:26.188 --> 00:11:28.864 actually are better at processing nicotine.
NOTE Confidence: 0.842131356153846

00:11:28.870 --> 00:11:30.890 So this is actually survival.
NOTE Confidence: 0.842131356153846

00:11:30.890 --> 00:11:34.236 Or if you give them toxic doses.

NOTE Confidence: 0.842131356153846

00:11:34.240 --> 00:11:36.550 The offspring of exposed fathers are

NOTE Confidence: 0.842131356153846

00:11:36.550 --> 00:11:39.015 better able to process those doses

NOTE Confidence: 0.842131356153846

00:11:39.015 --> 00:11:41.160 and survive compared to offspring.

NOTE Confidence: 0.842131356153846

00:11:41.160 --> 00:11:42.588 If not you fathers.

NOTE Confidence: 0.842131356153846

00:11:42.588 --> 00:11:44.730 It also affects some sort of

NOTE Confidence: 0.842131356153846

00:11:44.806 --> 00:11:48.092 addictive behaviors and and and

NOTE Confidence: 0.842131356153846

00:11:48.092 --> 00:11:51.440 responses to to drugs at that level.

NOTE Confidence: 0.842131356153846

00:11:51.440 --> 00:11:52.770 And then finally there are a number

NOTE Confidence: 0.842131356153846

00:11:52.770 --> 00:11:54.317 of ways you can stress out a mouse.

NOTE Confidence: 0.842131356153846

00:11:54.320 --> 00:11:56.865 Essentially they all result in

NOTE Confidence: 0.842131356153846

00:11:56.865 --> 00:11:59.410 increased cortisol levels and offspring

NOTE Confidence: 0.842131356153846

00:11:59.486 --> 00:12:02.042 of stressed out fathers tend to

NOTE Confidence: 0.842131356153846

00:12:02.042 --> 00:12:04.247 have altered responses to stress.

NOTE Confidence: 0.842131356153846

00:12:04.250 --> 00:12:04.901 Specifically,

NOTE Confidence: 0.842131356153846

00:12:04.901 --> 00:12:09.458 a lower a smaller increase in cortisone

NOTE Confidence: 0.842131356153846

00:12:09.460 --> 00:12:12.043 following a stressful event and in some
NOTE Confidence: 0.842131356153846

00:12:12.043 --> 00:12:15.037 cases they have behavioral changes as well.
NOTE Confidence: 0.842131356153846

00:12:15.040 --> 00:12:16.750 So this is all in rodents.
NOTE Confidence: 0.842131356153846

00:12:16.750 --> 00:12:18.545 This has been looked at
NOTE Confidence: 0.842131356153846

00:12:18.545 --> 00:12:20.340 to some extent in humans,
NOTE Confidence: 0.842131356153846

00:12:20.340 --> 00:12:23.105 although obviously it's harder to do these
NOTE Confidence: 0.842131356153846

00:12:23.105 --> 00:12:25.488 kinds of experiments in human subjects.
NOTE Confidence: 0.842131356153846

00:12:25.490 --> 00:12:28.340 The best examples are in.
NOTE Confidence: 0.842131356153846

00:12:28.340 --> 00:12:31.316 One example is in a cohort from Sweden
NOTE Confidence: 0.842131356153846

00:12:31.316 --> 00:12:34.008 from the 19th century where they
NOTE Confidence: 0.842131356153846

00:12:34.008 --> 00:12:36.810 had very careful records of harvest
NOTE Confidence: 0.842131356153846

00:12:36.810 --> 00:12:40.990 yields and health outcomes overtime,
NOTE Confidence: 0.842131356153846

00:12:40.990 --> 00:12:43.798 and in that study their studies from the
NOTE Confidence: 0.842131356153846

00:12:43.798 --> 00:12:46.459 early 2000s they were able to show that.
NOTE Confidence: 0.842131356153846

00:12:46.460 --> 00:12:50.528 Good nutrition in the paternal grandfather
NOTE Confidence: 0.842131356153846

00:12:50.528 --> 00:12:53.240 resulted in increased cardiovascular

NOTE Confidence: 0.842131356153846

00:12:53.332 --> 00:12:56.547 events and diabetes in grandchildren.

NOTE Confidence: 0.842131356153846

00:12:56.550 --> 00:12:59.558 This is a follow-up study that was done

NOTE Confidence: 0.842131356153846

00:12:59.558 --> 00:13:02.271 more recently in a cohort of of almost

NOTE Confidence: 0.842131356153846

00:13:02.271 --> 00:13:04.350 30,000 people over three generations,

NOTE Confidence: 0.842131356153846

00:13:04.350 --> 00:13:05.670 also in Sweden,

NOTE Confidence: 0.842131356153846

00:13:05.670 --> 00:13:08.582 and here they actually see an effect on

NOTE Confidence: 0.842131356153846

00:13:08.582 --> 00:13:11.470 cancer so well nourished grandfathers,

NOTE Confidence: 0.842131356153846

00:13:11.470 --> 00:13:13.798 well nourished paternal grandfathers

NOTE Confidence: 0.842131356153846

00:13:13.798 --> 00:13:18.105 have a a correlation with a significantly

NOTE Confidence: 0.842131356153846

00:13:18.105 --> 00:13:22.395 increase rate of cancer in grandchildren.

NOTE Confidence: 0.842131356153846

00:13:22.400 --> 00:13:23.810 Uhm?

NOTE Confidence: 0.842131356153846

00:13:23.810 --> 00:13:25.220 So.

NOTE Confidence: 0.842131356153846

00:13:25.220 --> 00:13:27.621 The answer to this question do life

NOTE Confidence: 0.842131356153846

00:13:27.621 --> 00:13:29.333 experiences of parents affect the

NOTE Confidence: 0.842131356153846

00:13:29.333 --> 00:13:31.496 health of progeny appears to be yes,

NOTE Confidence: 0.842131356153846

00:13:31.500 --> 00:13:32.068 but.
NOTE Confidence: 0.842131356153846

00:13:32.068 --> 00:13:35.476 The molecular mechanism by which these
NOTE Confidence: 0.842131356153846

00:13:35.476 --> 00:13:37.913 these experiences are transmitted
NOTE Confidence: 0.842131356153846

00:13:37.913 --> 00:13:41.735 remains a pretty significant black box,
NOTE Confidence: 0.842131356153846

00:13:41.740 --> 00:13:43.844 and so we're trying to get at these
NOTE Confidence: 0.842131356153846

00:13:43.844 --> 00:13:45.661 questions of what information is
NOTE Confidence: 0.842131356153846

00:13:45.661 --> 00:13:47.716 transmitted and whether it's meaningful,
NOTE Confidence: 0.842131356153846

00:13:47.720 --> 00:13:49.652 and we've decided to do this
NOTE Confidence: 0.842131356153846

00:13:49.652 --> 00:13:50.940 by simplifying the system.
NOTE Confidence: 0.842131356153846

00:13:50.940 --> 00:13:53.873 So rather than expose then making an
NOTE Confidence: 0.842131356153846

00:13:53.873 --> 00:13:55.529 environmental exposure change like
NOTE Confidence: 0.842131356153846

00:13:55.529 --> 00:13:57.509 diet or stress or drug treatments
NOTE Confidence: 0.842131356153846

00:13:57.509 --> 00:13:59.484 were going to make a genetic
NOTE Confidence: 0.842131356153846

00:13:59.484 --> 00:14:01.619 change where we have a little bit
NOTE Confidence: 0.842131356153846

00:14:01.620 --> 00:14:03.678 more control over the effects of.
NOTE Confidence: 0.842131356153846

00:14:03.680 --> 00:14:06.954 Add change on epigenetic state and

NOTE Confidence: 0.842131356153846
00:14:06.954 --> 00:14:09.438 then evaluate what those effects are
NOTE Confidence: 0.842131356153846
00:14:09.438 --> 00:14:12.388 in offspring and try and connect that
NOTE Confidence: 0.842131356153846
00:14:12.388 --> 00:14:14.830 molecular chain at each point along
NOTE Confidence: 0.935687288636364
00:14:14.908 --> 00:14:17.530 the way. So here is our strategy.
NOTE Confidence: 0.935687288636364
00:14:17.530 --> 00:14:19.480 Make the make a genetic change.
NOTE Confidence: 0.935687288636364
00:14:19.480 --> 00:14:22.531 In my father we examine the sperm and we
NOTE Confidence: 0.935687288636364
00:14:22.531 --> 00:14:25.160 examine the offspring within this firm.
NOTE Confidence: 0.935687288636364
00:14:25.160 --> 00:14:27.740 There are three main modalities of
NOTE Confidence: 0.935687288636364
00:14:27.740 --> 00:14:30.298 epigenetic information that will look at.
NOTE Confidence: 0.935687288636364
00:14:30.300 --> 00:14:31.170 One is small.
NOTE Confidence: 0.935687288636364
00:14:31.170 --> 00:14:33.525 RNA is so actually this is something that
NOTE Confidence: 0.935687288636364
00:14:33.525 --> 00:14:35.874 we in my lab had paid less attention to.
NOTE Confidence: 0.935687288636364
00:14:35.880 --> 00:14:36.755 Although there are plenty of
NOTE Confidence: 0.935687288636364
00:14:36.755 --> 00:14:37.630 other people in the field,
NOTE Confidence: 0.935687288636364
00:14:37.630 --> 00:14:40.450 but I've looked at from DNA metalation
NOTE Confidence: 0.935687288636364

00:14:40.450 --> 00:14:43.810 so it could be like modifications to
NOTE Confidence: 0.935687288636364

00:14:43.810 --> 00:14:47.492 the DNA and histone modifications. Uhm?
NOTE Confidence: 0.935687288636364

00:14:47.492 --> 00:14:50.444 Our general strategy is very simple,
NOTE Confidence: 0.935687288636364

00:14:50.450 --> 00:14:52.662 so we're taking advantage of the fact
NOTE Confidence: 0.935687288636364

00:14:52.662 --> 00:14:54.928 that males have only One X chromosome
NOTE Confidence: 0.935687288636364

00:14:54.930 --> 00:14:58.008 and that the X chromosome encodes
NOTE Confidence: 0.935687288636364

00:14:58.008 --> 00:15:01.150 a variety of epigenetic regulators.
NOTE Confidence: 0.935687288636364

00:15:01.150 --> 00:15:03.154 So if we delete and epigenetic
NOTE Confidence: 0.935687288636364

00:15:03.154 --> 00:15:05.990 regulator on the X chromosome in a male,
NOTE Confidence: 0.935687288636364

00:15:05.990 --> 00:15:08.828 we make a complete knockout and we
NOTE Confidence: 0.935687288636364

00:15:08.828 --> 00:15:11.042 knock that we crossed that mail
NOTE Confidence: 0.935687288636364

00:15:11.042 --> 00:15:14.270 to a genetically wildtype female.
NOTE Confidence: 0.935687288636364

00:15:14.270 --> 00:15:16.382 If you remember your Punnett squares
NOTE Confidence: 0.935687288636364

00:15:16.382 --> 00:15:18.406 from high school biology, all male.
NOTE Confidence: 0.935687288636364

00:15:18.406 --> 00:15:20.562 Offspring of that cross are going to
NOTE Confidence: 0.935687288636364

00:15:20.562 --> 00:15:22.853 get a normal X chromosome from their

NOTE Confidence: 0.935687288636364
00:15:22.853 --> 00:15:24.963 mother and a normal Y chromosome
NOTE Confidence: 0.935687288636364
00:15:24.963 --> 00:15:26.109 from their father.
NOTE Confidence: 0.935687288636364
00:15:26.110 --> 00:15:28.378 Even though the father was a
NOTE Confidence: 0.935687288636364
00:15:28.378 --> 00:15:30.380 complete knockout for this scene.
NOTE Confidence: 0.935687288636364
00:15:30.380 --> 00:15:32.462 Which means we can evaluate the
NOTE Confidence: 0.935687288636364
00:15:32.462 --> 00:15:34.876 phenotype of these F1 males and if
NOTE Confidence: 0.935687288636364
00:15:34.876 --> 00:15:37.116 we see a phenotype that implies that
NOTE Confidence: 0.935687288636364
00:15:37.191 --> 00:15:39.543 it's a result of epigenetic changes
NOTE Confidence: 0.935687288636364
00:15:39.543 --> 00:15:41.854 in the paternal germline rather than
NOTE Confidence: 0.935687288636364
00:15:41.854 --> 00:15:43.689 genetic changes that are inherited.
NOTE Confidence: 0.795618613
00:15:46.600 --> 00:15:47.912 As a genetic target,
NOTE Confidence: 0.795618613
00:15:47.912 --> 00:15:49.880 we picked the gene called JTX.
NOTE Confidence: 0.795618613
00:15:49.880 --> 00:15:51.620 It's also called KDM 6A,
NOTE Confidence: 0.795618613
00:15:51.620 --> 00:15:54.788 and you may see that name pop up later
NOTE Confidence: 0.795618613
00:15:54.788 --> 00:15:57.580 on in the slides and we picked this
NOTE Confidence: 0.795618613

00:15:57.580 --> 00:15:59.440 gene first because it's X linked,
NOTE Confidence: 0.795618613

00:15:59.440 --> 00:16:01.798 so it meets our first criterion.
NOTE Confidence: 0.795618613

00:16:01.800 --> 00:16:04.260 It's also a well established
NOTE Confidence: 0.795618613

00:16:04.260 --> 00:16:05.244 chromatin regulator,
NOTE Confidence: 0.795618613

00:16:05.250 --> 00:16:08.010 and we know a specific enzymatic
NOTE Confidence: 0.795618613

00:16:08.010 --> 00:16:10.509 activity that this gene has it.
NOTE Confidence: 0.795618613

00:16:10.510 --> 00:16:12.382 See methylates metalation
NOTE Confidence: 0.795618613

00:16:12.382 --> 00:16:16.126 at Lysine 27 of histone H3.
NOTE Confidence: 0.795618613

00:16:16.130 --> 00:16:18.489 This is a well studied histone modification
NOTE Confidence: 0.795618613

00:16:18.489 --> 00:16:21.509 and a well established enzymatic activity.
NOTE Confidence: 0.795618613

00:16:21.510 --> 00:16:22.647 For this protein.
NOTE Confidence: 0.795618613

00:16:22.647 --> 00:16:25.951 We also know that it has non non
NOTE Confidence: 0.795618613

00:16:25.951 --> 00:16:28.756 enzymatic effects on chromatin so
NOTE Confidence: 0.795618613

00:16:28.756 --> 00:16:31.540 it regulates enhancer assembly by
NOTE Confidence: 0.795618613

00:16:31.540 --> 00:16:33.810 by interacting with a complex.
NOTE Confidence: 0.795618613

00:16:33.810 --> 00:16:36.250 That place is a different

NOTE Confidence: 0.795618613

00:16:36.250 --> 00:16:37.226 chromatin modification.

NOTE Confidence: 0.795618613

00:16:37.230 --> 00:16:39.430 These are both relatively well

NOTE Confidence: 0.795618613

00:16:39.430 --> 00:16:41.630 defined functions for this protein

NOTE Confidence: 0.795618613

00:16:41.701 --> 00:16:43.829 and gives us some hope of being

NOTE Confidence: 0.795618613

00:16:43.829 --> 00:16:46.239 able to trace this molecular chain.

NOTE Confidence: 0.795618613

00:16:46.240 --> 00:16:49.630 From sperm to the next generation.

NOTE Confidence: 0.795618613

00:16:49.630 --> 00:16:51.850 We also know that UTX is

NOTE Confidence: 0.795618613

00:16:51.850 --> 00:16:52.590 biologically significant.

NOTE Confidence: 0.795618613

00:16:52.590 --> 00:16:54.374 It's a developmental regulator.

NOTE Confidence: 0.795618613

00:16:54.374 --> 00:16:56.604 It's been implicated in cardiac

NOTE Confidence: 0.795618613

00:16:56.604 --> 00:16:58.762 development and in about police this and

NOTE Confidence: 0.795618613

00:16:58.762 --> 00:17:01.049 we know that it's a tumor suppressor,

NOTE Confidence: 0.795618613

00:17:01.050 --> 00:17:02.730 which I'll come back through

NOTE Confidence: 0.795618613

00:17:02.730 --> 00:17:04.592 a little bit later. Uhm?

NOTE Confidence: 0.795618613

00:17:04.592 --> 00:17:08.688 So, uhm, here's how we set this up.

NOTE Confidence: 0.795618613

00:17:08.690 --> 00:17:10.874 For those of you who are interested
NOTE Confidence: 0.795618613

00:17:10.874 --> 00:17:11.810 in the details,
NOTE Confidence: 0.795618613

00:17:11.810 --> 00:17:13.970 we set this up as a conditional knockout.
NOTE Confidence: 0.795618613

00:17:13.970 --> 00:17:16.742 So the TX is deleted only in the germline,
NOTE Confidence: 0.795618613

00:17:16.750 --> 00:17:19.318 not in the somatic tissue of the parents,
NOTE Confidence: 0.795618613

00:17:19.320 --> 00:17:21.635 which reduces the possibility of
NOTE Confidence: 0.795618613

00:17:21.635 --> 00:17:23.950 having secondary or indirect effects.
NOTE Confidence: 0.795618613

00:17:23.950 --> 00:17:26.960 And we're using a creed that that is
NOTE Confidence: 0.795618613

00:17:26.960 --> 00:17:29.865 basically complete to the excision by birth,
NOTE Confidence: 0.795618613

00:17:29.870 --> 00:17:33.664 so U TX is lost throughout surmounted
NOTE Confidence: 0.795618613

00:17:33.664 --> 00:17:35.230 Genesis from starting from.
NOTE Confidence: 0.795618613

00:17:35.230 --> 00:17:38.130 Very early in the lifetime of the animal.
NOTE Confidence: 0.795618613

00:17:38.130 --> 00:17:39.780 Uhm?
NOTE Confidence: 0.795618613

00:17:39.780 --> 00:17:42.860 We can confirm that this knockout it's
NOTE Confidence: 0.795618613

00:17:42.860 --> 00:17:45.267 complete using Western blot for UT X.
NOTE Confidence: 0.795618613

00:17:45.270 --> 00:17:47.403 There's a tiny bit of a residual band here,

NOTE Confidence: 0.795618613

00:17:47.410 --> 00:17:48.754 and that's because this is done

NOTE Confidence: 0.795618613

00:17:48.754 --> 00:17:49.426 on whole testis,

NOTE Confidence: 0.795618613

00:17:49.430 --> 00:17:52.246 which has some somatic tissue which

NOTE Confidence: 0.795618613

00:17:52.246 --> 00:17:55.390 therefore still expresses UTX.

NOTE Confidence: 0.795618613

00:17:55.390 --> 00:17:58.046 Uh, the first thing to note is that,

NOTE Confidence: 0.795618613

00:17:58.050 --> 00:17:58.614 UM,

NOTE Confidence: 0.795618613

00:17:58.614 --> 00:18:01.434 that blossom PTX has essentially

NOTE Confidence: 0.795618613

00:18:01.434 --> 00:18:03.690 no effect on fertility,

NOTE Confidence: 0.795618613

00:18:03.690 --> 00:18:06.586 so I'm showing here a cross section of

NOTE Confidence: 0.795618613

00:18:06.586 --> 00:18:08.698 the seminiferous tubule in a control,

NOTE Confidence: 0.795618613

00:18:08.700 --> 00:18:11.610 and the UTX conditional knockout,

NOTE Confidence: 0.795618613

00:18:11.610 --> 00:18:14.233 which will be shown as Cao and

NOTE Confidence: 0.795618613

00:18:14.233 --> 00:18:17.148 the tubules are pretty identical.

NOTE Confidence: 0.795618613

00:18:17.150 --> 00:18:19.100 They contain all the different

NOTE Confidence: 0.795618613

00:18:19.100 --> 00:18:21.812 fault mental cell types in this

NOTE Confidence: 0.795618613

00:18:21.812 --> 00:18:23.867 developing seminiferous epithelium.
NOTE Confidence: 0.795618613

00:18:23.870 --> 00:18:26.208 Sperm look normal and the numbers of
NOTE Confidence: 0.795618613

00:18:26.208 --> 00:18:28.518 sperm are about the same and these
NOTE Confidence: 0.795618613

00:18:28.518 --> 00:18:31.209 minds can produce pops at the same levels.
NOTE Confidence: 0.795618613

00:18:31.210 --> 00:18:32.194 So this is.
NOTE Confidence: 0.795618613

00:18:32.194 --> 00:18:34.871 This is whatever we see is not due
NOTE Confidence: 0.795618613

00:18:34.871 --> 00:18:37.344 to some sort of secondary effect
NOTE Confidence: 0.795618613

00:18:37.344 --> 00:18:40.554 of just screwing up fertility.
NOTE Confidence: 0.795618613

00:18:40.560 --> 00:18:40.882 Uhm,
NOTE Confidence: 0.795618613

00:18:40.882 --> 00:18:43.136 so then we start to look at
NOTE Confidence: 0.795618613

00:18:43.136 --> 00:18:45.195 offspring and the first thing that
NOTE Confidence: 0.795618613

00:18:45.195 --> 00:18:47.346 we noticed was that offspring of
NOTE Confidence: 0.795618613

00:18:47.346 --> 00:18:49.440 these mice have a reduced lifespan.
NOTE Confidence: 0.795618613

00:18:49.440 --> 00:18:51.498 They still live a good long time,
NOTE Confidence: 0.795618613

00:18:51.500 --> 00:18:53.732 so they make it out to about a year.
NOTE Confidence: 0.795618613

00:18:53.740 --> 00:18:55.728 But then they start dying and then

NOTE Confidence: 0.795618613

00:18:55.728 --> 00:18:57.423 another cohort of them lives a

NOTE Confidence: 0.795618613

00:18:57.423 --> 00:18:58.995 little bit longer and then dies

NOTE Confidence: 0.795618613

00:18:58.995 --> 00:19:00.784 out in about a year and a half.

NOTE Confidence: 0.795618613

00:19:00.790 --> 00:19:03.210 Uhm? And we did this.

NOTE Confidence: 0.795618613

00:19:03.210 --> 00:19:05.202 Our initial cohort was in a

NOTE Confidence: 0.795618613

00:19:05.202 --> 00:19:06.198 mixed genetic background.

NOTE Confidence: 0.874118577777778

00:19:06.200 --> 00:19:09.350 Just to you know, make sure this was real.

NOTE Confidence: 0.874118577777778

00:19:09.350 --> 00:19:11.730 We also did this in an inbred

NOTE Confidence: 0.874118577777778

00:19:11.730 --> 00:19:14.249 background and can confirm same effect.

NOTE Confidence: 0.874118577777778

00:19:14.250 --> 00:19:16.819 Incidentally, and sort of fascinating to me.

NOTE Confidence: 0.874118577777778

00:19:16.820 --> 00:19:18.764 The shape of the curve is actually the same,

NOTE Confidence: 0.874118577777778

00:19:18.770 --> 00:19:21.767 so there's a drop off around the year and

NOTE Confidence: 0.874118577777778

00:19:21.767 --> 00:19:24.414 another set of deaths a little bit later.

NOTE Confidence: 0.874118577777778

00:19:24.420 --> 00:19:26.244 And then of course, what we want to

NOTE Confidence: 0.874118577777778

00:19:26.244 --> 00:19:28.206 do is look into what's going on.

NOTE Confidence: 0.874118577777778

00:19:28.210 --> 00:19:29.386 What's causing these deaths,
NOTE Confidence: 0.874118577777778

00:19:29.386 --> 00:19:31.468 and to do that we took each
NOTE Confidence: 0.874118577777778

00:19:31.468 --> 00:19:33.246 mouse that died as they died and
NOTE Confidence: 0.874118577777778

00:19:33.246 --> 00:19:34.970 did it complete necropsies,
NOTE Confidence: 0.874118577777778

00:19:34.970 --> 00:19:39.638 sampling each of about 12 tissues.
NOTE Confidence: 0.874118577777778

00:19:39.640 --> 00:19:41.476 And I'll tell you right away,
NOTE Confidence: 0.874118577777778

00:19:41.480 --> 00:19:43.358 we actually have no idea what's
NOTE Confidence: 0.874118577777778

00:19:43.358 --> 00:19:45.250 causing this first set of deaths.
NOTE Confidence: 0.874118577777778

00:19:45.250 --> 00:19:48.458 These mice drop dead overnight and
NOTE Confidence: 0.874118577777778

00:19:48.458 --> 00:19:51.668 don't appear to have any histologic
NOTE Confidence: 0.874118577777778

00:19:51.668 --> 00:19:54.740 differences relative to controls.
NOTE Confidence: 0.874118577777778

00:19:54.740 --> 00:19:56.840 But in the second set of dots,
NOTE Confidence: 0.874118577777778

00:19:56.840 --> 00:19:58.376 we found something interesting,
NOTE Confidence: 0.874118577777778

00:19:58.376 --> 00:20:01.128 so this is just raw data showing
NOTE Confidence: 0.874118577777778

00:20:01.128 --> 00:20:02.259 counts by age,
NOTE Confidence: 0.874118577777778

00:20:02.260 --> 00:20:04.020 and obviously the controls guide

NOTE Confidence: 0.874118577777778
00:20:04.020 --> 00:20:06.274 to the controls also have various
NOTE Confidence: 0.874118577777778
00:20:06.274 --> 00:20:08.770 issues because they're just old mice.
NOTE Confidence: 0.874118577777778
00:20:08.770 --> 00:20:10.033 But most strikingly,
NOTE Confidence: 0.874118577777778
00:20:10.033 --> 00:20:12.980 and there was a substantial increase in
NOTE Confidence: 0.874118577777778
00:20:13.053 --> 00:20:15.805 the number of tumors we found in offspring
NOTE Confidence: 0.874118577777778
00:20:15.805 --> 00:20:18.739 of JTX knockouts compared to controls.
NOTE Confidence: 0.874118577777778
00:20:18.740 --> 00:20:20.380 And this is tumors found
NOTE Confidence: 0.874118577777778
00:20:20.380 --> 00:20:21.364 across multiple tissues.
NOTE Confidence: 0.874118577777778
00:20:21.370 --> 00:20:23.890 The most common that we saw in
NOTE Confidence: 0.874118577777778
00:20:23.890 --> 00:20:25.192 histiocytic sarcoma, and then,
NOTE Confidence: 0.874118577777778
00:20:25.192 --> 00:20:26.647 which is common in mice.
NOTE Confidence: 0.874118577777778
00:20:26.650 --> 00:20:29.850 But we saw many more in EU TX
NOTE Confidence: 0.874118577777778
00:20:29.850 --> 00:20:31.490 offspring compared to controls.
NOTE Confidence: 0.874118577777778
00:20:31.490 --> 00:20:33.524 And then the next most common
NOTE Confidence: 0.874118577777778
00:20:33.524 --> 00:20:35.250 are cellular carcinoma and lung.
NOTE Confidence: 0.874118577777778

00:20:35.250 --> 00:20:36.045 Various lung tumors,
NOTE Confidence: 0.874118577777778

00:20:36.045 --> 00:20:37.900 which I will also come back to
NOTE Confidence: 0.874118577777778

00:20:37.956 --> 00:20:38.836 a bit at the end.
NOTE Confidence: 0.33267832

00:20:41.290 --> 00:20:44.185 Uhm? So that was very interesting
NOTE Confidence: 0.33267832

00:20:44.185 --> 00:20:46.019 and we also wanted to know what
NOTE Confidence: 0.33267832

00:20:46.019 --> 00:20:47.375 happens across multiple generations.
NOTE Confidence: 0.33267832

00:20:47.380 --> 00:20:49.720 So we did this follow-up experiments
NOTE Confidence: 0.33267832

00:20:49.720 --> 00:20:51.790 where I'm not showing details here,
NOTE Confidence: 0.33267832

00:20:51.790 --> 00:20:54.769 but basically we set it up so that we
NOTE Confidence: 0.33267832

00:20:54.769 --> 00:20:57.835 could look at F2 mice that were the
NOTE Confidence: 0.33267832

00:20:57.835 --> 00:20:59.950 product of two successive generations
NOTE Confidence: 0.33267832

00:21:00.025 --> 00:21:02.244 of loss of BTX in the germline.
NOTE Confidence: 0.33267832

00:21:02.250 --> 00:21:03.414 So in other words,
NOTE Confidence: 0.33267832

00:21:03.414 --> 00:21:05.689 the germ cells never have a chance
NOTE Confidence: 0.33267832

00:21:05.689 --> 00:21:08.009 to reset their epigenetic information
NOTE Confidence: 0.33267832

00:21:08.010 --> 00:21:10.345 because you taxes is continually

NOTE Confidence: 0.33267832

00:21:10.345 --> 00:21:12.680 lost across these two generations.

NOTE Confidence: 0.858737492857143

00:21:16.170 --> 00:21:18.249 When we look at these F2 mice,

NOTE Confidence: 0.858737492857143

00:21:18.250 --> 00:21:22.016 we see a similar reduction in lifespan.

NOTE Confidence: 0.858737492857143

00:21:22.020 --> 00:21:24.636 Uhm, and and the similar sort

NOTE Confidence: 0.858737492857143

00:21:24.636 --> 00:21:27.360 of shape overall of the curve.

NOTE Confidence: 0.858737492857143

00:21:27.360 --> 00:21:30.520 Although this first drop off is his absence.

NOTE Confidence: 0.858737492857143

00:21:30.520 --> 00:21:33.120 Interesting like.

NOTE Confidence: 0.858737492857143

00:21:33.120 --> 00:21:35.160 And again we saw a significant

NOTE Confidence: 0.858737492857143

00:21:35.160 --> 00:21:37.262 increase in the in the numbers

NOTE Confidence: 0.858737492857143

00:21:37.262 --> 00:21:39.586 of tumors that came up in mice.

NOTE Confidence: 0.858737492857143

00:21:39.590 --> 00:21:40.596 And interestingly,

NOTE Confidence: 0.858737492857143

00:21:40.596 --> 00:21:44.620 although the overall tumor rate was about the

NOTE Confidence: 0.858737492857143

00:21:44.701 --> 00:21:48.157 same between in the F1 and F2 mouse cohorts,

NOTE Confidence: 0.858737492857143

00:21:48.160 --> 00:21:51.028 there was a a noticeable difference

NOTE Confidence: 0.858737492857143

00:21:51.028 --> 00:21:54.009 in the severity of the tumors.

NOTE Confidence: 0.858737492857143

00:21:54.010 --> 00:21:56.178 So we see a lot more aggressive tumors
NOTE Confidence: 0.858737492857143

00:21:56.178 --> 00:21:58.945 and F and F2 minutes compared to F1 mice.
NOTE Confidence: 0.858737492857143

00:21:58.950 --> 00:22:00.670 They tend to be in the same tissue.
NOTE Confidence: 0.858737492857143

00:22:00.670 --> 00:22:03.830 They look a lot worse, and relatedly,
NOTE Confidence: 0.858737492857143

00:22:03.830 --> 00:22:07.850 each individual mouse has more tumors.
NOTE Confidence: 0.858737492857143

00:22:07.850 --> 00:22:09.620 And, and here we're counting
NOTE Confidence: 0.858737492857143

00:22:09.620 --> 00:22:10.328 independent tumors,
NOTE Confidence: 0.858737492857143

00:22:10.330 --> 00:22:11.850 either within the same teacher
NOTE Confidence: 0.858737492857143

00:22:11.850 --> 00:22:13.066 or in multiple tissues.
NOTE Confidence: 0.858737492857143

00:22:13.070 --> 00:22:15.698 It was not uncommon to see mice with with.
NOTE Confidence: 0.810070235

00:22:17.890 --> 00:22:19.690 323 independent tumors and
NOTE Confidence: 0.810070235

00:22:19.690 --> 00:22:21.490 occasionally four or five.
NOTE Confidence: 0.810070235

00:22:21.490 --> 00:22:23.326 And so something is.
NOTE Confidence: 0.810070235

00:22:23.326 --> 00:22:25.162 This implies that something
NOTE Confidence: 0.810070235

00:22:25.162 --> 00:22:26.706 is accumulating epigenetically
NOTE Confidence: 0.810070235

00:22:26.706 --> 00:22:28.890 across generations in the

NOTE Confidence: 0.810070235
00:22:28.890 --> 00:22:31.074 absence of this chromatin
NOTE Confidence: 0.810070235
00:22:31.074 --> 00:22:33.199 regulator in the male germline.
NOTE Confidence: 0.85750261125
00:22:36.110 --> 00:22:38.326 Uhm, so here. So we have a phenotype.
NOTE Confidence: 0.85750261125
00:22:38.330 --> 00:22:40.256 So this now we're at the level of the
NOTE Confidence: 0.85750261125
00:22:40.256 --> 00:22:41.998 studies that I showed at the beginning.
NOTE Confidence: 0.85750261125
00:22:42.000 --> 00:22:44.772 We see a phenomenon of a change in in
NOTE Confidence: 0.85750261125
00:22:44.772 --> 00:22:47.307 phenotype in the offspring of males that
NOTE Confidence: 0.85750261125
00:22:47.307 --> 00:22:49.670 have undergone a certain perturbation,
NOTE Confidence: 0.85750261125
00:22:49.670 --> 00:22:51.506 and we can conclude that perturbing
NOTE Confidence: 0.85750261125
00:22:51.506 --> 00:22:53.718 epigenetic state in the male germ cells
NOTE Confidence: 0.85750261125
00:22:53.718 --> 00:22:55.584 reduces lifespan and increases tumor rate
NOTE Confidence: 0.85750261125
00:22:55.584 --> 00:22:57.769 in the genetically wildtype offspring.
NOTE Confidence: 0.85750261125
00:22:57.770 --> 00:22:59.121 And now we want to go back
NOTE Confidence: 0.85750261125
00:22:59.121 --> 00:23:00.120 to the original purpose,
NOTE Confidence: 0.85750261125
00:23:00.120 --> 00:23:01.875 which is to understand what
NOTE Confidence: 0.85750261125

00:23:01.875 --> 00:23:02.928 genetic regulatory improvement
NOTE Confidence: 0.85750261125

00:23:02.928 --> 00:23:04.870 with gene regulatory information.
NOTE Confidence: 0.85750261125

00:23:04.870 --> 00:23:06.410 In other words, what epigenetic.
NOTE Confidence: 0.85750261125

00:23:06.410 --> 00:23:10.498 Information is actually inherited.
NOTE Confidence: 0.85750261125

00:23:10.500 --> 00:23:12.924 Uhm, and I'll just remind you that we
NOTE Confidence: 0.85750261125

00:23:12.924 --> 00:23:15.338 know that UT X is a tumor suppressor,
NOTE Confidence: 0.85750261125

00:23:15.340 --> 00:23:17.764 so when UTX is actually lost
NOTE Confidence: 0.85750261125

00:23:17.764 --> 00:23:19.380 in the tissue itself,
NOTE Confidence: 0.85750261125

00:23:19.380 --> 00:23:22.405 it promotes tumor formation and
NOTE Confidence: 0.85750261125

00:23:22.405 --> 00:23:24.825 variety of different tumors.
NOTE Confidence: 0.85750261125

00:23:24.830 --> 00:23:26.456 And just in case you're wondering
NOTE Confidence: 0.85750261125

00:23:26.456 --> 00:23:28.149 how much people care about this,
NOTE Confidence: 0.85750261125

00:23:28.150 --> 00:23:30.075 this is a paper that came out
NOTE Confidence: 0.85750261125

00:23:30.075 --> 00:23:32.109 in nature a month or two ago,
NOTE Confidence: 0.85750261125

00:23:32.110 --> 00:23:36.282 again showing that UT X axis tumor
NOTE Confidence: 0.85750261125

00:23:36.282 --> 00:23:38.720 suppressor and attributing this

NOTE Confidence: 0.85750261125

00:23:38.720 --> 00:23:41.990 to formation of a phase separated.

NOTE Confidence: 0.85750261125

00:23:41.990 --> 00:23:43.646 Regions in the nucleus,

NOTE Confidence: 0.85750261125

00:23:43.646 --> 00:23:45.716 based on an intrinsically disordered

NOTE Confidence: 0.85750261125

00:23:45.716 --> 00:23:48.180 domain at the center of the TX protein.

NOTE Confidence: 0.9080008675

00:23:52.030 --> 00:23:54.333 Alright, so now we wanna know what

NOTE Confidence: 0.9080008675

00:23:54.333 --> 00:23:55.723 gene regulatory information is

NOTE Confidence: 0.9080008675

00:23:55.723 --> 00:23:57.448 inherited from the knockout fathers.

NOTE Confidence: 0.9080008675

00:23:57.450 --> 00:23:59.592 And can we link this to what's

NOTE Confidence: 0.9080008675

00:23:59.592 --> 00:24:01.349 known about JTX molecular function

NOTE Confidence: 0.9080008675

00:24:01.349 --> 00:24:03.647 as a as a tumor suppressor?

NOTE Confidence: 0.9080008675

00:24:03.650 --> 00:24:06.234 To do that, we're going to look again,

NOTE Confidence: 0.9080008675

00:24:06.240 --> 00:24:09.610 not so much at noncoding RNA's, but at.

NOTE Confidence: 0.9080008675

00:24:09.610 --> 00:24:12.690 DNA methylations and histone modifications.

NOTE Confidence: 0.9080008675

00:24:12.690 --> 00:24:15.186 And we started out by by thinking about

NOTE Confidence: 0.9080008675

00:24:15.186 --> 00:24:17.050 histone modifications because as I mentioned,

NOTE Confidence: 0.9080008675

00:24:17.050 --> 00:24:20.648 we know that UTX has enzymatic activity

NOTE Confidence: 0.9080008675

00:24:20.648 --> 00:24:24.208 as a demethylase of this modification.

NOTE Confidence: 0.9080008675

00:24:24.210 --> 00:24:26.720 H3K27 travel.

NOTE Confidence: 0.9080008675

00:24:26.720 --> 00:24:28.688 So the first thing we did was look

NOTE Confidence: 0.9080008675

00:24:28.688 --> 00:24:30.768 at this modification and we performed

NOTE Confidence: 0.9080008675

00:24:30.768 --> 00:24:33.054 the chip seek experiments in sperm.

NOTE Confidence: 0.9080008675

00:24:33.060 --> 00:24:35.727 And now we expect that use because

NOTE Confidence: 0.9080008675

00:24:35.727 --> 00:24:38.179 you TX is a demethylase.

NOTE Confidence: 0.9080008675

00:24:38.180 --> 00:24:40.904 It removes this modification when we

NOTE Confidence: 0.9080008675

00:24:40.904 --> 00:24:44.237 delete JTX we should see an increase in

NOTE Confidence: 0.9080008675

00:24:44.240 --> 00:24:47.216 K27 trimethyl signal and that is in fact

NOTE Confidence: 0.9080008675

00:24:47.216 --> 00:24:50.755 what we see across two replicates in sperm.

NOTE Confidence: 0.9080008675

00:24:50.760 --> 00:24:53.480 A moderate increase globally

NOTE Confidence: 0.9080008675

00:24:53.480 --> 00:24:56.530 in K27 Trimethylation.

NOTE Confidence: 0.9080008675

00:24:56.530 --> 00:24:57.446 So we thought create.

NOTE Confidence: 0.9080008675

00:24:57.446 --> 00:24:58.820 This is exactly what we predict.

NOTE Confidence: 0.9080008675

00:24:58.820 --> 00:25:01.277 Now we all have all we have to do

NOTE Confidence: 0.9080008675

00:25:01.277 --> 00:25:04.130 is figure out exactly what genes are

NOTE Confidence: 0.9080008675

00:25:04.130 --> 00:25:07.062 most affected by this change in K27

NOTE Confidence: 0.9080008675

00:25:07.062 --> 00:25:10.074 TRIMETHYLATION and we'll have our answer.

NOTE Confidence: 0.9080008675

00:25:10.080 --> 00:25:11.868 So we started looking at individual

NOTE Confidence: 0.9080008675

00:25:11.868 --> 00:25:13.928 genes and it turned out as usually

NOTE Confidence: 0.9080008675

00:25:13.928 --> 00:25:15.825 happens that the story was a little

NOTE Confidence: 0.9080008675

00:25:15.879 --> 00:25:17.829 bit more complicated than I thought.

NOTE Confidence: 0.9080008675

00:25:17.830 --> 00:25:20.720 So here is an example of our chip seek data.

NOTE Confidence: 0.9080008675

00:25:20.720 --> 00:25:22.856 This is shown as signal tracks

NOTE Confidence: 0.9080008675

00:25:22.856 --> 00:25:25.323 on the genome browser and so here

NOTE Confidence: 0.9080008675

00:25:25.323 --> 00:25:26.948 gene models at the bottom.

NOTE Confidence: 0.9080008675

00:25:26.950 --> 00:25:29.894 And if you look at the gene promoters

NOTE Confidence: 0.9080008675

00:25:29.894 --> 00:25:33.062 and Gray is controlled data and in in

NOTE Confidence: 0.9080008675

00:25:33.062 --> 00:25:36.230 oranges data from EU T X knockout sperm.

NOTE Confidence: 0.9080008675

00:25:36.230 --> 00:25:38.246 And you look at the promoter regions.
NOTE Confidence: 0.9080008675

00:25:38.250 --> 00:25:40.978 You actually see a drop in signal in
NOTE Confidence: 0.9080008675

00:25:40.978 --> 00:25:43.398 the knockout relative to the control.
NOTE Confidence: 0.9080008675

00:25:43.400 --> 00:25:45.416 So this is the opposite direction
NOTE Confidence: 0.9080008675

00:25:45.416 --> 00:25:47.460 of what we had expected.
NOTE Confidence: 0.9080008675

00:25:47.460 --> 00:25:48.692 And it turns out,
NOTE Confidence: 0.9080008675

00:25:48.692 --> 00:25:51.080 if we look across the entire genome.
NOTE Confidence: 0.9080008675

00:25:51.080 --> 00:25:53.579 What's happening is that in the knockout,
NOTE Confidence: 0.9080008675

00:25:53.580 --> 00:25:56.100 the signal is dropping right at the
NOTE Confidence: 0.9080008675

00:25:56.100 --> 00:25:58.019 promoter with where normally the
NOTE Confidence: 0.9080008675

00:25:58.019 --> 00:26:00.335 signal is highest and it's increasing
NOTE Confidence: 0.9080008675

00:26:00.335 --> 00:26:02.420 in these intergenic regions,
NOTE Confidence: 0.9080008675

00:26:02.420 --> 00:26:04.656 so it's essentially redistributing
NOTE Confidence: 0.9080008675

00:26:04.656 --> 00:26:08.010 across the genome and flattening out.
NOTE Confidence: 0.9080008675

00:26:08.010 --> 00:26:10.640 We could interpret that as
NOTE Confidence: 0.9080008675

00:26:10.640 --> 00:26:12.744 randomization or overall remodeling,

NOTE Confidence: 0.9080008675

00:26:12.750 --> 00:26:15.486 but the punchline for us was that this

NOTE Confidence: 0.9080008675

00:26:15.486 --> 00:26:17.681 doesn't actually allow us to identify

NOTE Confidence: 0.9080008675

00:26:17.681 --> 00:26:19.746 specific genes that are being MIS

NOTE Confidence: 0.9080008675

00:26:19.746 --> 00:26:21.750 regulated and contributing to the phenotype.

NOTE Confidence: 0.9080008675

00:26:21.750 --> 00:26:23.521 It just tells us that something is

NOTE Confidence: 0.9080008675

00:26:23.521 --> 00:26:25.539 wrong with K27 trimethylation sperm.

NOTE Confidence: 0.9080008675

00:26:25.539 --> 00:26:29.060 So we decided to take an alternate

NOTE Confidence: 0.9080008675

00:26:29.145 --> 00:26:33.488 tack and we know that.

NOTE Confidence: 0.9080008675

00:26:33.490 --> 00:26:37.912 That K 27 Trimethylation is is

NOTE Confidence: 0.9080008675

00:26:37.912 --> 00:26:40.860 antagonistic with DNA methylation.

NOTE Confidence: 0.9080008675

00:26:40.860 --> 00:26:41.132 Uhm,

NOTE Confidence: 0.9080008675

00:26:41.132 --> 00:26:42.764 so this is they actually have

NOTE Confidence: 0.9080008675

00:26:42.764 --> 00:26:44.360 a very complex relationship,

NOTE Confidence: 0.9080008675

00:26:44.360 --> 00:26:46.957 but in general we see that this

NOTE Confidence: 0.9080008675

00:26:46.957 --> 00:26:49.262 modification and DNA match DNA

NOTE Confidence: 0.9080008675

00:26:49.262 --> 00:26:51.498 metalation are anticorrelated genome.
NOTE Confidence: 0.9080008675

00:26:51.500 --> 00:26:53.684 So we decided to look at what
NOTE Confidence: 0.9080008675

00:26:53.684 --> 00:26:56.656 happens to DNA methylation in the
NOTE Confidence: 0.9080008675

00:26:56.656 --> 00:26:59.596 sperm of these knockout mice.
NOTE Confidence: 0.9080008675

00:26:59.600 --> 00:27:01.000 When we did that,
NOTE Confidence: 0.9080008675

00:27:01.000 --> 00:27:03.660 we found actually a very striking effect.
NOTE Confidence: 0.9080008675

00:27:03.660 --> 00:27:06.210 So it's only a relatively small
NOTE Confidence: 0.9080008675

00:27:06.210 --> 00:27:08.544 subset of regions that exhibit
NOTE Confidence: 0.9080008675

00:27:08.544 --> 00:27:10.748 changes in DNA methylation.
NOTE Confidence: 0.9080008675

00:27:10.750 --> 00:27:12.528 If you look globally across the genome,
NOTE Confidence: 0.9080008675

00:27:12.530 --> 00:27:14.590 there's no global change,
NOTE Confidence: 0.9080008675

00:27:14.590 --> 00:27:17.680 but among these regions that exhibit
NOTE Confidence: 0.8537157972727

00:27:17.765 --> 00:27:20.425 changes. The vast majority of them
NOTE Confidence: 0.8537157972727

00:27:20.425 --> 00:27:22.420 have increases in DNA metalation,
NOTE Confidence: 0.8537157972727

00:27:22.420 --> 00:27:24.190 so there's some bias or it's
NOTE Confidence: 0.8537157972727

00:27:24.190 --> 00:27:25.370 game of DNA methylation.

NOTE Confidence: 0.853715797272727

00:27:25.370 --> 00:27:28.646 In the context of this disruption is

NOTE Confidence: 0.853715797272727

00:27:28.646 --> 00:27:32.390 overall disruption in K27 TRIMETHYLATION.

NOTE Confidence: 0.853715797272727

00:27:32.390 --> 00:27:35.114 Uhm? Interestingly, if we then look

NOTE Confidence: 0.853715797272727

00:27:35.114 --> 00:27:38.150 in somatic tissue of the offspring,

NOTE Confidence: 0.853715797272727

00:27:38.150 --> 00:27:40.460 we see the same effect.

NOTE Confidence: 0.853715797272727

00:27:40.460 --> 00:27:42.998 So again, there's an overall game

NOTE Confidence: 0.853715797272727

00:27:42.998 --> 00:27:45.872 at DNA metalation at a subset of

NOTE Confidence: 0.853715797272727

00:27:45.872 --> 00:27:48.448 LOCI and a clear bias towards gain,

NOTE Confidence: 0.853715797272727

00:27:48.450 --> 00:27:51.843 as opposed to lots of DNA metalation in this.

NOTE Confidence: 0.853715797272727

00:27:51.850 --> 00:27:56.170 In this case, bone marrow of the offspring.

NOTE Confidence: 0.853715797272727

00:27:56.170 --> 00:27:58.753 Alright, so now the question in your

NOTE Confidence: 0.853715797272727

00:27:58.753 --> 00:28:01.725 mind should be how many of these sites

NOTE Confidence: 0.853715797272727

00:28:01.725 --> 00:28:04.330 that game DNA metalation in offspring

NOTE Confidence: 0.853715797272727

00:28:04.330 --> 00:28:06.280 were also gaining DNA methylation

NOTE Confidence: 0.853715797272727

00:28:06.280 --> 00:28:08.970 in the sperm of the knockout.

NOTE Confidence: 0.853715797272727

00:28:08.970 --> 00:28:12.522 And the answer is that not all of them,
NOTE Confidence: 0.853715797272727

00:28:12.522 --> 00:28:14.866 but many of them are are hypermethylated
NOTE Confidence: 0.853715797272727

00:28:14.866 --> 00:28:17.806 in both the sperm and the bone
NOTE Confidence: 0.853715797272727

00:28:17.806 --> 00:28:19.480 marrow of offspring,
NOTE Confidence: 0.853715797272727

00:28:19.480 --> 00:28:22.012 which implies that this DNA metalation
NOTE Confidence: 0.853715797272727

00:28:22.012 --> 00:28:24.212 change may be persisting across
NOTE Confidence: 0.853715797272727

00:28:24.212 --> 00:28:26.422 generations and helping to alter
NOTE Confidence: 0.853715797272727

00:28:26.422 --> 00:28:28.730 gene expression in somatic tissue.
NOTE Confidence: 0.853715797272727

00:28:28.730 --> 00:28:32.258 This turns out to be about 200 low side.
NOTE Confidence: 0.853715797272727

00:28:32.260 --> 00:28:34.480 Uhm?
NOTE Confidence: 0.853715797272727

00:28:34.480 --> 00:28:37.360 And we can convince is an example of just
NOTE Confidence: 0.853715797272727

00:28:37.360 --> 00:28:39.768 showing the signal at one particular look.
NOTE Confidence: 0.853715797272727

00:28:39.768 --> 00:28:40.794 It's almost two,
NOTE Confidence: 0.853715797272727

00:28:40.800 --> 00:28:43.222 and then we can actually validate it
NOTE Confidence: 0.853715797272727

00:28:43.222 --> 00:28:48.038 using a different assay at the same locus.
NOTE Confidence: 0.853715797272727

00:28:48.040 --> 00:28:48.363 Uhm,

NOTE Confidence: 0.853715797272727

00:28:48.363 --> 00:28:49.978 so now we wanna know.

NOTE Confidence: 0.853715797272727

00:28:49.980 --> 00:28:52.948 OK this seems like a a important set

NOTE Confidence: 0.853715797272727

00:28:52.948 --> 00:28:55.668 of targets that may be contributing

NOTE Confidence: 0.853715797272727

00:28:55.668 --> 00:28:57.090 to our phenotype.

NOTE Confidence: 0.853715797272727

00:28:57.090 --> 00:28:58.920 We wanna know what's special

NOTE Confidence: 0.853715797272727

00:28:58.920 --> 00:29:01.420 about this set of 200 regions.

NOTE Confidence: 0.853715797272727

00:29:01.420 --> 00:29:02.939 Turns out there's not really much bias

NOTE Confidence: 0.853715797272727

00:29:02.939 --> 00:29:04.898 in terms of where they are in the genome.

NOTE Confidence: 0.853715797272727

00:29:04.900 --> 00:29:06.184 There's a bit of a cluster

NOTE Confidence: 0.853715797272727

00:29:06.184 --> 00:29:07.040 here on chromosome 5,

NOTE Confidence: 0.853715797272727

00:29:07.040 --> 00:29:08.872 but generally they're scattered

NOTE Confidence: 0.853715797272727

00:29:08.872 --> 00:29:10.246 across the genome,

NOTE Confidence: 0.853715797272727

00:29:10.250 --> 00:29:11.858 and I'll summarize a whole bunch

NOTE Confidence: 0.853715797272727

00:29:11.858 --> 00:29:13.562 of analysis by telling you that

NOTE Confidence: 0.853715797272727

00:29:13.562 --> 00:29:14.438 they're not enriched.

NOTE Confidence: 0.853715797272727

00:29:14.440 --> 00:29:15.204 It repeats,
NOTE Confidence: 0.853715797272727

00:29:15.204 --> 00:29:17.496 they're not enrich step imprinted regions.
NOTE Confidence: 0.853715797272727

00:29:17.500 --> 00:29:19.104 They're not particularly enriched
NOTE Confidence: 0.853715797272727

00:29:19.104 --> 00:29:19.906 near promoters.
NOTE Confidence: 0.853715797272727

00:29:19.910 --> 00:29:21.775 With jeans and they're not
NOTE Confidence: 0.853715797272727

00:29:21.775 --> 00:29:23.267 enriched at CPG islands,
NOTE Confidence: 0.853715797272727

00:29:23.270 --> 00:29:26.502 which is another dumb class that we might
NOTE Confidence: 0.853715797272727

00:29:26.502 --> 00:29:29.859 expect to see biases and DNA methylation.
NOTE Confidence: 0.853715797272727

00:29:29.860 --> 00:29:32.030 Uhm?
NOTE Confidence: 0.853715797272727

00:29:32.030 --> 00:29:35.198 What they are enriched for is
NOTE Confidence: 0.853715797272727

00:29:35.198 --> 00:29:37.310 changes in K27 Trimethylation,
NOTE Confidence: 0.853715797272727

00:29:37.310 --> 00:29:39.935 which is where we started.
NOTE Confidence: 0.853715797272727

00:29:39.940 --> 00:29:42.474 So the regions that have the biggest
NOTE Confidence: 0.853715797272727

00:29:42.474 --> 00:29:45.345 perturbation in K27 tend to also have
NOTE Confidence: 0.853715797272727

00:29:45.345 --> 00:29:48.680 the greatest gains in DNA methylation,
NOTE Confidence: 0.853715797272727

00:29:48.680 --> 00:29:52.296 so there may be a functional link there.

NOTE Confidence: 0.853715797272727

00:29:52.300 --> 00:29:55.246 They're also enriched and enhancer regions,

NOTE Confidence: 0.853715797272727

00:29:55.250 --> 00:29:57.714 and this is marked by a different

NOTE Confidence: 0.853715797272727

00:29:57.714 --> 00:29:58.770 histone modification that's

NOTE Confidence: 0.853715797272727

00:29:58.837 --> 00:30:00.917 generally associated with enhancers.

NOTE Confidence: 0.853715797272727

00:30:00.920 --> 00:30:03.755 We see that these persistence

NOTE Confidence: 0.853715797272727

00:30:03.755 --> 00:30:06.590 hypermethylated regions tend to occur

NOTE Confidence: 0.853715797272727

00:30:06.678 --> 00:30:09.978 in regions that have enhancer activity.

NOTE Confidence: 0.853715797272727

00:30:09.980 --> 00:30:11.552 And that was nice,

NOTE Confidence: 0.853715797272727

00:30:11.552 --> 00:30:13.124 because 'cause enhancers we

NOTE Confidence: 0.853715797272727

00:30:13.124 --> 00:30:15.060 can potentially linked to genes

NOTE Confidence: 0.853715797272727

00:30:15.060 --> 00:30:16.508 and linked to functions.

NOTE Confidence: 0.853715797272727

00:30:16.510 --> 00:30:19.240 So we did that using an established

NOTE Confidence: 0.853715797272727

00:30:19.240 --> 00:30:21.921 software for making those kinds of

NOTE Confidence: 0.853715797272727

00:30:21.921 --> 00:30:24.052 associations and what I'm showing

NOTE Confidence: 0.853715797272727

00:30:24.052 --> 00:30:27.670 here is actually all of the enriched

NOTE Confidence: 0.853715797272727

00:30:27.670 --> 00:30:30.760 phenotypes associated with with the
NOTE Confidence: 0.853715797272727

00:30:30.760 --> 00:30:34.160 the persistent hypermethylated region.
NOTE Confidence: 0.853715797272727

00:30:34.160 --> 00:30:35.290 So there's a clear link.
NOTE Confidence: 0.853715797272727

00:30:35.290 --> 00:30:38.032 There's a clear functional link here
NOTE Confidence: 0.853715797272727

00:30:38.032 --> 00:30:41.062 to tumorigenesis as sort of evidence.
NOTE Confidence: 0.853715797272727

00:30:41.062 --> 00:30:44.380 By past phenotypes that have been
NOTE Confidence: 0.853715797272727

00:30:44.380 --> 00:30:46.940 associated with these enhancer regions.
NOTE Confidence: 0.928311184615385

00:30:48.970 --> 00:30:51.026 To get a little bit more at how
NOTE Confidence: 0.928311184615385

00:30:51.026 --> 00:30:52.960 this might actually be occurring,
NOTE Confidence: 0.928311184615385

00:30:52.960 --> 00:30:55.600 we took a closer look at the sequences
NOTE Confidence: 0.928311184615385

00:30:55.600 --> 00:30:57.633 associated with these 200 or the
NOTE Confidence: 0.928311184615385

00:30:57.633 --> 00:30:59.263 sequences of these 200 regions,
NOTE Confidence: 0.928311184615385

00:30:59.270 --> 00:31:01.598 and we looked for enriched motifs
NOTE Confidence: 0.928311184615385

00:31:01.598 --> 00:31:04.925 and we were able to find 3 enriched
NOTE Confidence: 0.928311184615385

00:31:04.925 --> 00:31:07.040 DNA motifs in these sequences.
NOTE Confidence: 0.928311184615385

00:31:07.040 --> 00:31:09.368 All of which contain CPG sites,

NOTE Confidence: 0.928311184615385

00:31:09.370 --> 00:31:11.362 so these are the sites that

NOTE Confidence: 0.928311184615385

00:31:11.362 --> 00:31:12.358 game DNA metalation,

NOTE Confidence: 0.928311184615385

00:31:12.360 --> 00:31:14.736 so these are probably where the

NOTE Confidence: 0.928311184615385

00:31:14.736 --> 00:31:16.800 DNA replication is seeking place.

NOTE Confidence: 0.928311184615385

00:31:16.800 --> 00:31:17.708 And interestingly,

NOTE Confidence: 0.928311184615385

00:31:17.708 --> 00:31:20.432 two of these three have been

NOTE Confidence: 0.928311184615385

00:31:20.432 --> 00:31:23.295 tested to see if the presence or

NOTE Confidence: 0.928311184615385

00:31:23.295 --> 00:31:25.620 absence of DNA methylation effects

NOTE Confidence: 0.928311184615385

00:31:25.620 --> 00:31:28.389 binding of a transcription factor.

NOTE Confidence: 0.928311184615385

00:31:28.390 --> 00:31:30.718 So this is a site that is usually

NOTE Confidence: 0.928311184615385

00:31:30.718 --> 00:31:32.174 bound by transcription factor

NOTE Confidence: 0.928311184615385

00:31:32.174 --> 00:31:34.988 called elk one in the presence of

NOTE Confidence: 0.928311184615385

00:31:34.988 --> 00:31:37.468 DNA methylation elk when binding.

NOTE Confidence: 0.928311184615385

00:31:37.470 --> 00:31:39.045 Is significantly inhibited

NOTE Confidence: 0.928311184615385

00:31:39.045 --> 00:31:41.145 and same thing here.

NOTE Confidence: 0.928311184615385

00:31:41.150 --> 00:31:43.638 This is normally bound by GPA and the
NOTE Confidence: 0.928311184615385

00:31:43.638 --> 00:31:46.201 presence of DNA metalation there's a
NOTE Confidence: 0.928311184615385

00:31:46.201 --> 00:31:48.073 significant inhibition of binding,
NOTE Confidence: 0.928311184615385

00:31:48.080 --> 00:31:50.810 which implies that these regions
NOTE Confidence: 0.928311184615385

00:31:50.810 --> 00:31:54.150 that gained DNA metalation and sperm.
NOTE Confidence: 0.928311184615385

00:31:54.150 --> 00:31:56.475 And then retain that DNA
NOTE Confidence: 0.928311184615385

00:31:56.475 --> 00:31:57.870 metalation in offspring.
NOTE Confidence: 0.928311184615385

00:31:57.870 --> 00:32:00.460 There may be an effect on transcription
NOTE Confidence: 0.928311184615385

00:32:00.460 --> 00:32:02.694 factor activity and G and downstream
NOTE Confidence: 0.928311184615385

00:32:02.694 --> 00:32:04.800 gene expression that may in turn
NOTE Confidence: 0.928311184615385

00:32:04.800 --> 00:32:06.951 affect the phenotype and maybe
NOTE Confidence: 0.928311184615385

00:32:06.951 --> 00:32:08.679 tumorigenesis in those tissues.
NOTE Confidence: 0.928311184615385

00:32:08.680 --> 00:32:09.008 Interestingly,
NOTE Confidence: 0.928311184615385

00:32:09.008 --> 00:32:10.976 at around the same time that
NOTE Confidence: 0.928311184615385

00:32:10.976 --> 00:32:12.679 that we did this study,
NOTE Confidence: 0.928311184615385

00:32:12.680 --> 00:32:14.577 another paper came out looking at you.

NOTE Confidence: 0.928311184615385

00:32:14.580 --> 00:32:17.526 T X function in magnetic tissue.

NOTE Confidence: 0.928311184615385

00:32:17.530 --> 00:32:19.876 And and they found almost exactly

NOTE Confidence: 0.928311184615385

00:32:19.876 --> 00:32:22.513 the same enriched set of motifs among

NOTE Confidence: 0.928311184615385

00:32:22.513 --> 00:32:24.851 a set of genes where they found

NOTE Confidence: 0.928311184615385

00:32:24.924 --> 00:32:27.458 when they knockout EX they see a

NOTE Confidence: 0.928311184615385

00:32:27.458 --> 00:32:29.488 miss regulation of gene expression

NOTE Confidence: 0.928311184615385

00:32:29.488 --> 00:32:32.771 and they see they see that UTX

NOTE Confidence: 0.928311184615385

00:32:32.771 --> 00:32:35.857 binds directly to these promoters.

NOTE Confidence: 0.928311184615385

00:32:35.860 --> 00:32:38.316 So here you see out for a while

NOTE Confidence: 0.928311184615385

00:32:38.316 --> 00:32:41.086 and GPA coming right out of this

NOTE Confidence: 0.928311184615385

00:32:41.086 --> 00:32:42.328 analysis as well.

NOTE Confidence: 0.928311184615385

00:32:42.330 --> 00:32:45.126 So this implies that UTX may

NOTE Confidence: 0.928311184615385

00:32:45.126 --> 00:32:47.490 actually directly bind these sites

NOTE Confidence: 0.928311184615385

00:32:47.490 --> 00:32:50.300 in developing sperm altered DNA

NOTE Confidence: 0.928311184615385

00:32:50.300 --> 00:32:53.430 methylation at those sites, the DNA.

NOTE Confidence: 0.928311184615385

00:32:53.430 --> 00:32:56.070 The DNA methylation is retained in
NOTE Confidence: 0.928311184615385

00:32:56.070 --> 00:32:58.608 matter poetic tissue of offspring.
NOTE Confidence: 0.928311184615385

00:32:58.610 --> 00:33:01.110 And effects from binding and
NOTE Confidence: 0.928311184615385

00:33:01.110 --> 00:33:03.610 downstream expression based on these.
NOTE Confidence: 0.928311184615385

00:33:03.610 --> 00:33:05.640 These classes of transcription factors.
NOTE Confidence: 0.803412997272727

00:33:07.820 --> 00:33:10.190 One example of this effect
NOTE Confidence: 0.803412997272727

00:33:10.190 --> 00:33:13.180 is that the rank 2 gene,
NOTE Confidence: 0.803412997272727

00:33:13.180 --> 00:33:15.448 so this is one of the hypermethylated
NOTE Confidence: 0.803412997272727

00:33:15.448 --> 00:33:17.650 DMR is that we identify it within
NOTE Confidence: 0.803412997272727

00:33:17.650 --> 00:33:19.814 that DMR we see an elk one
NOTE Confidence: 0.803412997272727

00:33:19.814 --> 00:33:21.600 binding site within that elk.
NOTE Confidence: 0.803412997272727

00:33:21.600 --> 00:33:24.499 When binding site is a CPG site and
NOTE Confidence: 0.803412997272727

00:33:24.499 --> 00:33:27.705 that site has more population in
NOTE Confidence: 0.803412997272727

00:33:27.705 --> 00:33:31.288 knockout sperm compared to controls and
NOTE Confidence: 0.803412997272727

00:33:31.288 --> 00:33:34.768 more methylation in healthy bone marrow.
NOTE Confidence: 0.803412997272727

00:33:34.770 --> 00:33:37.055 And knockout an offspring of

NOTE Confidence: 0.803412997272727

00:33:37.055 --> 00:33:38.883 knockouts compared to controls.

NOTE Confidence: 0.803412997272727

00:33:38.890 --> 00:33:40.689 Since is any absence of any disease,

NOTE Confidence: 0.803412997272727

00:33:40.690 --> 00:33:43.070 phenotype, and implies that they

NOTE Confidence: 0.803412997272727

00:33:43.070 --> 00:33:46.114 made that this may predispose these

NOTE Confidence: 0.803412997272727

00:33:46.114 --> 00:33:48.450 healthy offspring to generating.

NOTE Confidence: 0.803412997272727

00:33:48.450 --> 00:33:50.934 Blood tumors this is a analysis

NOTE Confidence: 0.803412997272727

00:33:50.934 --> 00:33:53.310 of of ranks to target.

NOTE Confidence: 0.803412997272727

00:33:53.310 --> 00:33:55.740 Genes are now looking downstream in

NOTE Confidence: 0.803412997272727

00:33:55.740 --> 00:33:58.949 the in the gene regulatory network.

NOTE Confidence: 0.803412997272727

00:33:58.950 --> 00:34:02.038 This set of genes sort of as significantly

NOTE Confidence: 0.803412997272727

00:34:02.038 --> 00:34:03.732 perturbed and gene expression

NOTE Confidence: 0.803412997272727

00:34:03.732 --> 00:34:06.270 space in the presence of disease.

NOTE Confidence: 0.803412997272727

00:34:06.270 --> 00:34:08.148 But even before we see disease,

NOTE Confidence: 0.803412997272727

00:34:08.150 --> 00:34:10.424 there's a shift in the expression

NOTE Confidence: 0.803412997272727

00:34:10.424 --> 00:34:12.369 of these downstream genes towards

NOTE Confidence: 0.803412997272727

00:34:12.369 --> 00:34:14.189 a more disease like state,
NOTE Confidence: 0.803412997272727

00:34:14.190 --> 00:34:17.208 again implying that may be predisposed
NOTE Confidence: 0.803412997272727

00:34:17.208 --> 00:34:20.152 by these epigenetic changes induced by
NOTE Confidence: 0.803412997272727

00:34:20.152 --> 00:34:23.120 by UTX last in the previous generation.
NOTE Confidence: 0.8230942415

00:34:28.200 --> 00:34:30.965 Alright, so from that we can conclude
NOTE Confidence: 0.8230942415

00:34:30.965 --> 00:34:34.703 that the sperm of beauty X knockout males
NOTE Confidence: 0.8230942415

00:34:34.703 --> 00:34:37.173 carries changes in histone methylation
NOTE Confidence: 0.8230942415

00:34:37.180 --> 00:34:39.900 K27 trimethylation and DNA methylation,
NOTE Confidence: 0.8230942415

00:34:39.900 --> 00:34:43.050 some of which persists offspring.
NOTE Confidence: 0.8230942415

00:34:43.050 --> 00:34:45.598 And it leaves open two questions that
NOTE Confidence: 0.8230942415

00:34:45.598 --> 00:34:48.699 we're sort of in the process of pursuing.
NOTE Confidence: 0.8230942415

00:34:48.700 --> 00:34:50.482 One is, how are these changes
NOTE Confidence: 0.8230942415

00:34:50.482 --> 00:34:52.230 established in the developing germ line?
NOTE Confidence: 0.8230942415

00:34:52.230 --> 00:34:53.987 So we we what we've added so
NOTE Confidence: 0.8230942415

00:34:53.987 --> 00:34:55.160 far is mature sperm.
NOTE Confidence: 0.8230942415

00:34:55.160 --> 00:34:57.266 But we know that UTX is lost at the

NOTE Confidence: 0.8230942415

00:34:57.266 --> 00:34:58.857 beginning of spring out of Genesis.

NOTE Confidence: 0.8230942415

00:34:58.860 --> 00:35:01.086 So what are those initial changes

NOTE Confidence: 0.8230942415

00:35:01.086 --> 00:35:02.199 in epigenetic state?

NOTE Confidence: 0.8230942415

00:35:02.200 --> 00:35:04.408 That's set up views?

NOTE Confidence: 0.8230942415

00:35:04.408 --> 00:35:06.064 DNA methylation differences

NOTE Confidence: 0.8230942415

00:35:06.064 --> 00:35:08.510 that appear to persist?

NOTE Confidence: 0.8230942415

00:35:08.510 --> 00:35:11.022 A second question is how are they maintained

NOTE Confidence: 0.8230942415

00:35:11.022 --> 00:35:12.848 in developing tissues of offspring?

NOTE Confidence: 0.8230942415

00:35:12.850 --> 00:35:15.928 So again we have a time point of sperm.

NOTE Confidence: 0.8230942415

00:35:15.930 --> 00:35:17.436 And then we have a time

NOTE Confidence: 0.8230942415

00:35:17.436 --> 00:35:18.440 point of adult offspring.

NOTE Confidence: 0.8230942415

00:35:18.440 --> 00:35:20.240 Actually pretty old adult offspring

NOTE Confidence: 0.8230942415

00:35:20.240 --> 00:35:22.490 that are starting to develop tumors.

NOTE Confidence: 0.8230942415

00:35:22.490 --> 00:35:25.106 What happens during all the time in between?

NOTE Confidence: 0.8230942415

00:35:25.110 --> 00:35:28.225 How do we maintain these epigenetic marks?

NOTE Confidence: 0.8230942415

00:35:28.230 --> 00:35:32.316 Even in the context of of rapid changes in
NOTE Confidence: 0.8230942415

00:35:32.316 --> 00:35:34.969 developmental gene expression and so on?
NOTE Confidence: 0.8230942415

00:35:34.970 --> 00:35:35.742 And finally,
NOTE Confidence: 0.8230942415

00:35:35.742 --> 00:35:37.672 how do they actually predispose
NOTE Confidence: 0.8230942415

00:35:37.672 --> 00:35:38.444 to tumorigenesis?
NOTE Confidence: 0.8230942415

00:35:38.450 --> 00:35:41.124 I showed you one example in the
NOTE Confidence: 0.8230942415

00:35:41.124 --> 00:35:44.070 in the alteration of ETS binding
NOTE Confidence: 0.8230942415

00:35:44.070 --> 00:35:45.786 transcription factor binding,
NOTE Confidence: 0.8230942415

00:35:45.790 --> 00:35:48.618 but we'd like to identify sort of
NOTE Confidence: 0.8230942415

00:35:48.618 --> 00:35:51.204 some more global rules about how
NOTE Confidence: 0.8230942415

00:35:51.204 --> 00:35:53.790 this effect may be taking place.
NOTE Confidence: 0.8230942415

00:35:53.790 --> 00:35:55.534 So what I'm going to show you is
NOTE Confidence: 0.8230942415

00:35:55.534 --> 00:35:57.218 just a little bit of preliminary data
NOTE Confidence: 0.8230942415

00:35:57.218 --> 00:35:59.009 to try and address these questions.
NOTE Confidence: 0.8230942415

00:35:59.010 --> 00:36:01.866 These are things that were very much in
NOTE Confidence: 0.8230942415

00:36:01.866 --> 00:36:04.756 the process of trying to understand still.

NOTE Confidence: 0.8230942415

00:36:04.760 --> 00:36:07.440 So First off we looked at where you

NOTE Confidence: 0.8230942415

00:36:07.440 --> 00:36:10.422 at when you text is expressed during

NOTE Confidence: 0.8230942415

00:36:10.422 --> 00:36:12.796 strategy MC developments and what I'm

NOTE Confidence: 0.8230942415

00:36:12.796 --> 00:36:15.190 showing here is single cell RNA seek

NOTE Confidence: 0.8230942415

00:36:15.263 --> 00:36:19.260 data that's been put onto a pseudo time axis.

NOTE Confidence: 0.8230942415

00:36:19.260 --> 00:36:21.555 So these different colors are

NOTE Confidence: 0.8230942415

00:36:21.555 --> 00:36:23.391 progressive stages of schematic

NOTE Confidence: 0.8230942415

00:36:23.391 --> 00:36:25.183 demik development starting here

NOTE Confidence: 0.8230942415

00:36:25.183 --> 00:36:27.697 in red or starting over here,

NOTE Confidence: 0.8230942415

00:36:27.700 --> 00:36:30.295 and the sporadic janitors progressing

NOTE Confidence: 0.8230942415

00:36:30.295 --> 00:36:32.371 through meiosis and through

NOTE Confidence: 0.8230942415

00:36:32.371 --> 00:36:34.617 the final stages of sperm.

NOTE Confidence: 0.8230942415

00:36:34.620 --> 00:36:36.530 Developments and intimate tours firm.

NOTE Confidence: 0.882411649230769

00:36:38.960 --> 00:36:41.109 DMC1 is a marker for a specific

NOTE Confidence: 0.882411649230769

00:36:41.109 --> 00:36:43.258 cell type and a specific stage.

NOTE Confidence: 0.882411649230769

00:36:43.260 --> 00:36:45.696 This is the very beginning of the
NOTE Confidence: 0.882411649230769

00:36:45.696 --> 00:36:47.626 entry into meiosis when chromosomes
NOTE Confidence: 0.882411649230769

00:36:47.626 --> 00:36:49.841 are actually inducing double strand
NOTE Confidence: 0.882411649230769

00:36:49.841 --> 00:36:52.100 breaks and starting recombination.
NOTE Confidence: 0.882411649230769

00:36:52.100 --> 00:36:53.840 So this is a critical time
NOTE Confidence: 0.882411649230769

00:36:53.840 --> 00:36:54.710 during spermatic Genesis,
NOTE Confidence: 0.882411649230769

00:36:54.710 --> 00:36:57.214 and it has to be very highly regulated,
NOTE Confidence: 0.882411649230769

00:36:57.220 --> 00:36:59.680 and you can see that U TX is most strongly
NOTE Confidence: 0.882411649230769

00:36:59.746 --> 00:37:01.918 expressed right exactly at this time.
NOTE Confidence: 0.882411649230769

00:37:01.920 --> 00:37:04.136 So it's a very specific time in Toronto,
NOTE Confidence: 0.882411649230769

00:37:04.140 --> 00:37:06.072 Genesis, and implies that it may
NOTE Confidence: 0.882411649230769

00:37:06.072 --> 00:37:08.180 have for very specific developments.
NOTE Confidence: 0.882411649230769

00:37:08.180 --> 00:37:09.704 Functions, and there's also
NOTE Confidence: 0.882411649230769

00:37:09.704 --> 00:37:11.228 a bit of expression,
NOTE Confidence: 0.882411649230769

00:37:11.230 --> 00:37:13.558 and the earlier strategem excels and
NOTE Confidence: 0.882411649230769

00:37:13.558 --> 00:37:16.538 a little bit in the somatic cells.

NOTE Confidence: 0.882411649230769

00:37:16.540 --> 00:37:18.290 And we can confirm this.

NOTE Confidence: 0.882411649230769

00:37:18.290 --> 00:37:22.010 Uhm, this is using single molecule RNA fish,

NOTE Confidence: 0.882411649230769

00:37:22.010 --> 00:37:26.114 so each of the green points here is a

NOTE Confidence: 0.882411649230769

00:37:26.114 --> 00:37:29.997 single molecule of RNA ATX RNA in blue.

NOTE Confidence: 0.882411649230769

00:37:30.000 --> 00:37:32.562 Is DAPI showing the chromatin and

NOTE Confidence: 0.882411649230769

00:37:32.562 --> 00:37:35.964 you can see that there's JTX RNA

NOTE Confidence: 0.882411649230769

00:37:35.964 --> 00:37:38.174 molecules in these cells that are at

NOTE Confidence: 0.882411649230769

00:37:38.174 --> 00:37:40.690 the edge of the seminiferous tubule.

NOTE Confidence: 0.882411649230769

00:37:40.690 --> 00:37:42.916 These are the progenitor and early meiotic

NOTE Confidence: 0.882411649230769

00:37:42.916 --> 00:37:46.702 cells that I referred to just a minute ago.

NOTE Confidence: 0.882411649230769

00:37:46.702 --> 00:37:48.464 And but expression persists

NOTE Confidence: 0.882411649230769

00:37:48.464 --> 00:37:50.546 actually a little bit into later

NOTE Confidence: 0.882411649230769

00:37:50.546 --> 00:37:52.109 stages from out of Genesis,

NOTE Confidence: 0.882411649230769

00:37:52.110 --> 00:37:54.475 but is definitely highest in

NOTE Confidence: 0.882411649230769

00:37:54.475 --> 00:37:56.367 these early progenitor cells,

NOTE Confidence: 0.882411649230769

00:37:56.370 --> 00:37:57.695 confirming what we saw from
NOTE Confidence: 0.882411649230769

00:37:57.695 --> 00:37:59.020 the single cell RNA seed.
NOTE Confidence: 0.8645121415

00:38:01.440 --> 00:38:04.272 In addition, I told you at the very
NOTE Confidence: 0.8645121415

00:38:04.272 --> 00:38:08.007 beginning of this talk that some lots of VTX
NOTE Confidence: 0.8645121415

00:38:08.007 --> 00:38:10.164 doesn't affect fertility, which is true.
NOTE Confidence: 0.8645121415

00:38:10.164 --> 00:38:11.654 These mice are completely fertile.
NOTE Confidence: 0.8645121415

00:38:11.660 --> 00:38:13.640 There's no change in sperm count,
NOTE Confidence: 0.8645121415

00:38:13.640 --> 00:38:15.456 but we do see a little bit of
NOTE Confidence: 0.8645121415

00:38:15.456 --> 00:38:17.080 an effect on spermatogenesis.
NOTE Confidence: 0.8645121415

00:38:17.080 --> 00:38:19.870 This is an extremely mild change,
NOTE Confidence: 0.8645121415

00:38:19.870 --> 00:38:22.522 but we see a statistically significant
NOTE Confidence: 0.8645121415

00:38:22.522 --> 00:38:25.599 increase in the number of spermatogonia,
NOTE Confidence: 0.8645121415

00:38:25.600 --> 00:38:29.050 so these early stragetic genitor cells.
NOTE Confidence: 0.8645121415

00:38:29.050 --> 00:38:30.898 As I said, either by market,
NOTE Confidence: 0.8645121415

00:38:30.900 --> 00:38:33.522 by this solid four marker or
NOTE Confidence: 0.8645121415

00:38:33.522 --> 00:38:37.930 by sort of counting by Ajani.

NOTE Confidence: 0.8645121415

00:38:37.930 --> 00:38:40.950 And that implies that although

NOTE Confidence: 0.8645121415

00:38:40.950 --> 00:38:42.626 nothing is affecting fertility,

NOTE Confidence: 0.8645121415

00:38:42.626 --> 00:38:45.140 something is off in these cells.

NOTE Confidence: 0.8645121415

00:38:45.140 --> 00:38:47.975 Something has been changed in the gene

NOTE Confidence: 0.8645121415

00:38:47.975 --> 00:38:50.150 regulatory network that's causing them

NOTE Confidence: 0.8645121415

00:38:50.150 --> 00:38:52.370 to not progress completely smoothly,

NOTE Confidence: 0.8645121415

00:38:52.370 --> 00:38:54.880 so through their normal development.

NOTE Confidence: 0.8714695225

00:38:57.150 --> 00:39:02.254 And we also looked at gene expression in in

NOTE Confidence: 0.8714695225

00:39:02.254 --> 00:39:05.222 testis and whole testis and consistent with

NOTE Confidence: 0.8714695225

00:39:05.222 --> 00:39:08.682 the fact that we see very that we see very

NOTE Confidence: 0.8714695225

00:39:08.682 --> 00:39:11.270 little change in phenotype in the knockout.

NOTE Confidence: 0.8714695225

00:39:11.270 --> 00:39:14.132 And in the fact that you TX is expressed

NOTE Confidence: 0.8714695225

00:39:14.132 --> 00:39:16.786 only in a very small subset of cells,

NOTE Confidence: 0.8714695225

00:39:16.790 --> 00:39:18.158 we don't see massive changes at

NOTE Confidence: 0.8714695225

00:39:18.158 --> 00:39:19.640 the level of the whole test.

NOTE Confidence: 0.8714695225

00:39:19.640 --> 00:39:21.390 So that's what we expect.
NOTE Confidence: 0.8714695225

00:39:21.390 --> 00:39:23.574 But we do see a couple of interesting
NOTE Confidence: 0.8714695225

00:39:23.574 --> 00:39:25.887 changes, and one of them is KLF 10.
NOTE Confidence: 0.8714695225

00:39:25.890 --> 00:39:28.284 So Cliften is a transcription factor
NOTE Confidence: 0.8714695225

00:39:28.284 --> 00:39:31.550 that's known to be a direct targeted VTX,
NOTE Confidence: 0.8714695225

00:39:31.550 --> 00:39:36.030 significantly downregulated in JTX knockouts,
NOTE Confidence: 0.8714695225

00:39:36.030 --> 00:39:37.774 and we know that it acts in a
NOTE Confidence: 0.8714695225

00:39:37.774 --> 00:39:39.530 variety of developmental contexts,
NOTE Confidence: 0.8714695225

00:39:39.530 --> 00:39:41.890 often along with TGF beta.
NOTE Confidence: 0.8714695225

00:39:41.890 --> 00:39:44.557 And so this is a good candidate for, UM.
NOTE Confidence: 0.8714695225

00:39:44.557 --> 00:39:48.106 For it, sort of for understanding how
NOTE Confidence: 0.8714695225

00:39:48.106 --> 00:39:50.508 transcriptional networks may be perturbed,
NOTE Confidence: 0.8714695225

00:39:50.510 --> 00:39:52.322 starting from the very beginning of
NOTE Confidence: 0.8714695225

00:39:52.322 --> 00:39:54.667 loss of BTX turns for how to Genesis,
NOTE Confidence: 0.8714695225

00:39:54.670 --> 00:39:56.358 and we're actually waiting
NOTE Confidence: 0.8714695225

00:39:56.358 --> 00:39:58.046 for single cell RNA.

NOTE Confidence: 0.8714695225

00:39:58.050 --> 00:39:59.900 Seek data to come back.

NOTE Confidence: 0.8714695225

00:39:59.900 --> 00:40:02.612 That will hopefully allow us to look at

NOTE Confidence: 0.8714695225

00:40:02.612 --> 00:40:04.450 gene expression changes specifically in

NOTE Confidence: 0.8714695225

00:40:04.450 --> 00:40:07.310 the subset of cells that do express JTX,

NOTE Confidence: 0.8714695225

00:40:07.310 --> 00:40:08.782 which hopefully will be.

NOTE Confidence: 0.8714695225

00:40:08.782 --> 00:40:10.622 A little bit more expensive.

NOTE Confidence: 0.893852786206897

00:40:12.820 --> 00:40:14.168 And then finally, uhm,

NOTE Confidence: 0.893852786206897

00:40:14.168 --> 00:40:17.867 I getting into sort of to the other end of

NOTE Confidence: 0.893852786206897

00:40:17.867 --> 00:40:20.267 the spectrum trying to understand what's

NOTE Confidence: 0.893852786206897

00:40:20.346 --> 00:40:23.116 actually happening in these offspring

NOTE Confidence: 0.893852786206897

00:40:23.116 --> 00:40:25.332 tissues to promote tumorigenesis.

NOTE Confidence: 0.893852786206897

00:40:25.340 --> 00:40:26.804 We've actually shifted our

NOTE Confidence: 0.893852786206897

00:40:26.804 --> 00:40:27.536 attention recently.

NOTE Confidence: 0.893852786206897

00:40:27.540 --> 00:40:30.500 We have been focusing on Magic Poesis based

NOTE Confidence: 0.893852786206897

00:40:30.500 --> 00:40:33.538 on the histiocytic sarcoma phenotype,

NOTE Confidence: 0.893852786206897

00:40:33.540 --> 00:40:34.860 but have started focusing
NOTE Confidence: 0.893852786206897

00:40:34.860 --> 00:40:36.840 a little bit more on lung.
NOTE Confidence: 0.893852786206897

00:40:36.840 --> 00:40:38.352 And there are a couple of reasons for that.
NOTE Confidence: 0.893852786206897

00:40:38.360 --> 00:40:40.872 One is that slang is a little bit
NOTE Confidence: 0.893852786206897

00:40:40.872 --> 00:40:43.398 easier to collect than bone marrow,
NOTE Confidence: 0.893852786206897

00:40:43.400 --> 00:40:46.564 but also that we saw this really
NOTE Confidence: 0.893852786206897

00:40:46.564 --> 00:40:49.553 interesting effect in the F1 and F2's,
NOTE Confidence: 0.893852786206897

00:40:49.553 --> 00:40:51.518 which is just actually there
NOTE Confidence: 0.893852786206897

00:40:51.518 --> 00:40:53.400 are two parts of it.
NOTE Confidence: 0.893852786206897

00:40:53.400 --> 00:40:55.539 One is that.
NOTE Confidence: 0.893852786206897

00:40:55.540 --> 00:40:58.060 Long is the only tumor that we never
NOTE Confidence: 0.893852786206897

00:40:58.060 --> 00:40:59.800 saw spontaneously occur in controls,
NOTE Confidence: 0.893852786206897

00:40:59.800 --> 00:41:01.830 and we see it only in the
NOTE Confidence: 0.893852786206897

00:41:01.830 --> 00:41:03.470 offspring of JTX knockouts,
NOTE Confidence: 0.893852786206897

00:41:03.470 --> 00:41:05.906 so it seems to be fairly specific.
NOTE Confidence: 0.893852786206897

00:41:05.910 --> 00:41:07.779 And two is that it has this.

NOTE Confidence: 0.893852786206897
00:41:07.780 --> 00:41:08.920 It had a very strong,
NOTE Confidence: 0.893852786206897
00:41:08.920 --> 00:41:11.180 effective anticipation where the
NOTE Confidence: 0.893852786206897
00:41:11.180 --> 00:41:14.038 tumors in the F2's were significantly
NOTE Confidence: 0.893852786206897
00:41:14.038 --> 00:41:16.952 worse than the tumors in the F1F ones
NOTE Confidence: 0.893852786206897
00:41:16.952 --> 00:41:19.024 tended to be small self contained data
NOTE Confidence: 0.893852786206897
00:41:19.024 --> 00:41:21.104 nomas and the F2 is often they would
NOTE Confidence: 0.893852786206897
00:41:21.104 --> 00:41:23.020 take over the entire chest cavity.
NOTE Confidence: 0.893852786206897
00:41:23.020 --> 00:41:25.498 So it seems like there's something
NOTE Confidence: 0.893852786206897
00:41:25.498 --> 00:41:27.505 especially sensitive in the in
NOTE Confidence: 0.893852786206897
00:41:27.505 --> 00:41:29.507 the lung that may be picking up
NOTE Confidence: 0.893852786206897
00:41:29.507 --> 00:41:32.146 on these changes that do not get
NOTE Confidence: 0.893852786206897
00:41:32.146 --> 00:41:34.141 reset from generation to generation.
NOTE Confidence: 0.893852786206897
00:41:34.150 --> 00:41:35.702 In keeping with that,
NOTE Confidence: 0.893852786206897
00:41:35.702 --> 00:41:38.855 we see a substantial set of genes that
NOTE Confidence: 0.893852786206897
00:41:38.855 --> 00:41:42.310 are miss regulated in both F1 and F2 long.
NOTE Confidence: 0.893852786206897

00:41:42.310 --> 00:41:45.340 So this is these are completely
NOTE Confidence: 0.893852786206897

00:41:45.340 --> 00:41:47.360 genetically wildtype mice and
NOTE Confidence: 0.893852786206897

00:41:47.450 --> 00:41:50.598 completely histologically normal lung,
NOTE Confidence: 0.893852786206897

00:41:50.600 --> 00:41:52.630 so this is pre any disease and
NOTE Confidence: 0.893852786206897

00:41:52.630 --> 00:41:54.731 yet they share about 200 genes
NOTE Confidence: 0.893852786206897

00:41:54.731 --> 00:41:56.666 that are commonly MIS regulated,
NOTE Confidence: 0.893852786206897

00:41:56.670 --> 00:41:58.716 implying that there's some sort of
NOTE Confidence: 0.893852786206897

00:41:58.716 --> 00:42:00.629 common process that's going on there,
NOTE Confidence: 0.893852786206897

00:42:00.630 --> 00:42:03.241 and these genes are enriched for a
NOTE Confidence: 0.893852786206897

00:42:03.241 --> 00:42:05.100 variety of biological processes.
NOTE Confidence: 0.893852786206897

00:42:05.100 --> 00:42:07.300 And just as an example,
NOTE Confidence: 0.893852786206897

00:42:07.300 --> 00:42:09.500 the most enriched processes relate
NOTE Confidence: 0.893852786206897

00:42:09.500 --> 00:42:12.420 to protein targeting to the membrane,
NOTE Confidence: 0.893852786206897

00:42:12.420 --> 00:42:15.178 and these are some of the genes
NOTE Confidence: 0.893852786206897

00:42:15.180 --> 00:42:16.860 included in that category.
NOTE Confidence: 0.893852786206897

00:42:16.860 --> 00:42:19.444 And I'm showing this where each

NOTE Confidence: 0.893852786206897

00:42:19.444 --> 00:42:21.704 column is an individual mouse.

NOTE Confidence: 0.893852786206897

00:42:21.710 --> 00:42:24.350 To emphasize that these effects are

NOTE Confidence: 0.893852786206897

00:42:24.350 --> 00:42:26.110 very consistent from individual

NOTE Confidence: 0.893852786206897

00:42:26.180 --> 00:42:27.100 to individual.

NOTE Confidence: 0.893852786206897

00:42:27.100 --> 00:42:27.511 Again,

NOTE Confidence: 0.893852786206897

00:42:27.511 --> 00:42:29.566 despite the fact that they're

NOTE Confidence: 0.893852786206897

00:42:29.566 --> 00:42:31.617 genetically identical and there is

NOTE Confidence: 0.893852786206897

00:42:31.617 --> 00:42:33.687 no apparent disease in these tissues.

NOTE Confidence: 0.970967156666667

00:42:35.990 --> 00:42:39.289 And finally, in trying to understand again

NOTE Confidence: 0.970967156666667

00:42:39.289 --> 00:42:42.321 what the links are between these sets of

NOTE Confidence: 0.970967156666667

00:42:42.321 --> 00:42:45.308 miss regulated genes and tumorigenesis,

NOTE Confidence: 0.970967156666667

00:42:45.310 --> 00:42:48.254 we've also noticed that the sets of genes

NOTE Confidence: 0.970967156666667

00:42:48.254 --> 00:42:51.382 that are commonly miss regulated in F1 and

NOTE Confidence: 0.970967156666667

00:42:51.382 --> 00:42:57.160 F2 lungs are enriched for being Mick targets.

NOTE Confidence: 0.970967156666667

00:42:57.160 --> 00:43:00.360 To make, of course is a is a.

NOTE Confidence: 0.970967156666667

00:43:00.360 --> 00:43:01.998 Extremely common oncogene,
NOTE Confidence: 0.970967156666667

00:43:01.998 --> 00:43:05.274 and it's been implicated previously in
NOTE Confidence: 0.970967156666667

00:43:05.274 --> 00:43:07.979 regulating a brass dependent lung cancer,
NOTE Confidence: 0.970967156666667

00:43:07.980 --> 00:43:11.804 so this may be sort of an interesting
NOTE Confidence: 0.970967156666667

00:43:11.810 --> 00:43:13.442 connection to what's actually
NOTE Confidence: 0.970967156666667

00:43:13.442 --> 00:43:15.482 happening to initiate these tumors.
NOTE Confidence: 0.970967156666667

00:43:15.490 --> 00:43:19.676 To predispose these lung tissues to tumors.
NOTE Confidence: 0.970967156666667

00:43:19.680 --> 00:43:22.998 Uh. So so in conclusion,
NOTE Confidence: 0.970967156666667

00:43:22.998 --> 00:43:25.233 basically we've found that perturbing
NOTE Confidence: 0.970967156666667

00:43:25.233 --> 00:43:27.659 epigenetic state in male germ cells
NOTE Confidence: 0.970967156666667

00:43:27.659 --> 00:43:29.569 reduces the lifespan and increases
NOTE Confidence: 0.970967156666667

00:43:29.640 --> 00:43:31.908 tumor rate and wild type offspring,
NOTE Confidence: 0.970967156666667

00:43:31.910 --> 00:43:34.220 and that's perma VTX knockout.
NOTE Confidence: 0.970967156666667

00:43:34.220 --> 00:43:37.260 Males carries changes in histone
NOTE Confidence: 0.970967156666667

00:43:37.260 --> 00:43:38.836 modification K27 TRIMETHYLATION,
NOTE Confidence: 0.970967156666667

00:43:38.836 --> 00:43:40.768 and in DNA METALATION,

NOTE Confidence: 0.970967156666667

00:43:40.770 --> 00:43:43.125 and some of those changes

NOTE Confidence: 0.970967156666667

00:43:43.125 --> 00:43:44.538 persist into offspring.

NOTE Confidence: 0.970967156666667

00:43:44.540 --> 00:43:45.329 And to me,

NOTE Confidence: 0.970967156666667

00:43:45.329 --> 00:43:47.170 this implies that a common set of

NOTE Confidence: 0.970967156666667

00:43:47.237 --> 00:43:49.332 regulatory networks may be sensitive

NOTE Confidence: 0.970967156666667

00:43:49.332 --> 00:43:51.427 to epigenetic perturbation in the

NOTE Confidence: 0.970967156666667

00:43:51.492 --> 00:43:53.288 germline and in tumorigenesis.

NOTE Confidence: 0.970967156666667

00:43:53.290 --> 00:43:56.888 In other words, there are some jeans,

NOTE Confidence: 0.970967156666667

00:43:56.890 --> 00:43:58.154 some promoters,

NOTE Confidence: 0.970967156666667

00:43:58.154 --> 00:44:01.314 some regulatory regions that are

NOTE Confidence: 0.970967156666667

00:44:01.314 --> 00:44:04.506 especially sensitive to any kind of

NOTE Confidence: 0.970967156666667

00:44:04.506 --> 00:44:07.530 epigenetic change be at loss of BTX

NOTE Confidence: 0.970967156666667

00:44:07.626 --> 00:44:10.570 or potentially an environmental.

NOTE Confidence: 0.970967156666667

00:44:10.570 --> 00:44:14.560 Influence or or toxin and that.

NOTE Confidence: 0.970967156666667

00:44:14.560 --> 00:44:18.118 The germ line is particularly prone

NOTE Confidence: 0.970967156666667

00:44:18.118 --> 00:44:21.370 to misregulation of those regions,
NOTE Confidence: 0.970967156666667

00:44:21.370 --> 00:44:26.160 and those regions are especially.
NOTE Confidence: 0.970967156666667

00:44:26.160 --> 00:44:29.334 Have an especially strong tendency to
NOTE Confidence: 0.970967156666667

00:44:29.334 --> 00:44:32.510 contribute to initiation of pyrogenesis,
NOTE Confidence: 0.970967156666667

00:44:32.510 --> 00:44:34.934 so there's a correlation that may
NOTE Confidence: 0.970967156666667

00:44:34.934 --> 00:44:37.400 actually be causation across generations,
NOTE Confidence: 0.970967156666667

00:44:37.400 --> 00:44:39.392 but at least is an interesting
NOTE Confidence: 0.970967156666667

00:44:39.392 --> 00:44:41.340 set of networks to explore.
NOTE Confidence: 0.970967156666667

00:44:41.340 --> 00:44:42.308 And finally,
NOTE Confidence: 0.970967156666667

00:44:42.308 --> 00:44:45.696 this sort of fascinating idea that although
NOTE Confidence: 0.970967156666667

00:44:45.696 --> 00:44:48.929 you TX is not required for fertility,
NOTE Confidence: 0.970967156666667

00:44:48.930 --> 00:44:49.408 it may.
NOTE Confidence: 0.970967156666667

00:44:49.408 --> 00:44:51.320 It may have a role in the germline,
NOTE Confidence: 0.970967156666667

00:44:51.320 --> 00:44:53.820 and tuning heritable epigenetic information.
NOTE Confidence: 0.970967156666667

00:44:53.820 --> 00:44:55.120 So in other words,
NOTE Confidence: 0.970967156666667

00:44:55.120 --> 00:44:57.070 the Organism has an interest in

NOTE Confidence: 0.970967156666667
00:44:57.144 --> 00:44:59.392 controlling what epigenetic information
NOTE Confidence: 0.970967156666667
00:44:59.392 --> 00:45:01.640 is passed across generations,
NOTE Confidence: 0.970967156666667
00:45:01.640 --> 00:45:04.720 and that U TX may be one of the tools
NOTE Confidence: 0.970967156666667
00:45:04.810 --> 00:45:08.226 that it uses to control that information.
NOTE Confidence: 0.970967156666667
00:45:08.230 --> 00:45:10.990 So finally I just want to acknowledge a
NOTE Confidence: 0.970967156666667
00:45:10.990 --> 00:45:14.350 bunch of people who have contributed to this,
NOTE Confidence: 0.970967156666667
00:45:14.350 --> 00:45:14.695 uhm,
NOTE Confidence: 0.970967156666667
00:45:14.695 --> 00:45:17.455 Ben Walters is a postdoc who's done most
NOTE Confidence: 0.970967156666667
00:45:17.455 --> 00:45:20.385 of the work on this project in my lab,
NOTE Confidence: 0.970967156666667
00:45:20.390 --> 00:45:22.645 Shannon created the fertilization video
NOTE Confidence: 0.970967156666667
00:45:22.645 --> 00:45:26.009 that I showed and Allison is underground.
NOTE Confidence: 0.970967156666667
00:45:26.010 --> 00:45:28.314 He's been helping Ben out how Ming
NOTE Confidence: 0.970967156666667
00:45:28.314 --> 00:45:30.277 is a student who has done some
NOTE Confidence: 0.970967156666667
00:45:30.277 --> 00:45:31.879 really cool work on this project
NOTE Confidence: 0.970967156666667
00:45:31.879 --> 00:45:33.648 that I actually did not show here,
NOTE Confidence: 0.970967156666667

00:45:33.650 --> 00:45:35.514 and I want to make sure to acknowledge
NOTE Confidence: 0.970967156666667

00:45:35.514 --> 00:45:37.397 this is a project that I initiated.
NOTE Confidence: 0.970967156666667

00:45:37.400 --> 00:45:40.384 As a postdoc at Whitehead and David Page,
NOTE Confidence: 0.970967156666667

00:45:40.390 --> 00:45:41.256 my mentor,
NOTE Confidence: 0.970967156666667

00:45:41.256 --> 00:45:43.421 there was extremely generous and
NOTE Confidence: 0.970967156666667

00:45:43.421 --> 00:45:46.621 letting me start this very risky and
NOTE Confidence: 0.970967156666667

00:45:46.621 --> 00:45:48.896 very expensive project without much
NOTE Confidence: 0.970967156666667

00:45:48.896 --> 00:45:51.668 promise of of where it was going to go,
NOTE Confidence: 0.970967156666667

00:45:51.670 --> 00:45:54.580 and likewise hope funds for Cancer
NOTE Confidence: 0.970967156666667

00:45:54.580 --> 00:45:56.520 Research initially funded it.
NOTE Confidence: 0.970967156666667

00:45:56.520 --> 00:46:00.420 Similarly had a very risky stage.
NOTE Confidence: 0.970967156666667

00:46:00.420 --> 00:46:02.796 Rod Brunson is a veterinary Paul
NOTE Confidence: 0.970967156666667

00:46:02.796 --> 00:46:05.733 tough Ologist who did the the looked
NOTE Confidence: 0.970967156666667

00:46:05.733 --> 00:46:07.858 at actually every single necropsy
NOTE Confidence: 0.970967156666667

00:46:07.858 --> 00:46:10.888 slide for this project she's on and
NOTE Confidence: 0.970967156666667

00:46:10.888 --> 00:46:12.918 Ben are hematologists who helped

NOTE Confidence: 0.970967156666667
00:46:12.918 --> 00:46:14.700 with that phenotyping.
NOTE Confidence: 0.970967156666667
00:46:14.700 --> 00:46:16.825 Elizabeth Morgan as apologists at
NOTE Confidence: 0.970967156666667
00:46:16.825 --> 00:46:18.950 Brigham Hill helps validate some
NOTE Confidence: 0.762290705384615
00:46:19.018 --> 00:46:21.845 of our results and grant gave us the
NOTE Confidence: 0.762290705384615
00:46:21.845 --> 00:46:24.736 TX mice and Tyler provided advice for
NOTE Confidence: 0.762290705384615
00:46:24.736 --> 00:46:27.610 the project and thank you again for
NOTE Confidence: 0.762290705384615
00:46:27.610 --> 00:46:29.600 the invitation and for listening.
NOTE Confidence: 0.762290705384615
00:46:29.600 --> 00:46:31.490 And I'm looking forward to.
NOTE Confidence: 0.762290705384615
00:46:31.490 --> 00:46:32.678 Answering any questions.
NOTE Confidence: 0.873334588
00:46:37.280 --> 00:46:38.840 Thank you so much Bluma.
NOTE Confidence: 0.873334588
00:46:38.840 --> 00:46:41.605 Uhm that was it was really fantastic.
NOTE Confidence: 0.873334588
00:46:41.610 --> 00:46:45.213 I think a lot of us think about changes
NOTE Confidence: 0.873334588
00:46:45.213 --> 00:46:48.314 to methylation marks a lot in in
NOTE Confidence: 0.873334588
00:46:48.314 --> 00:46:51.028 terms of you know, different tumors,
NOTE Confidence: 0.873334588
00:46:51.028 --> 00:46:55.380 but we don't really get to think a lot about.
NOTE Confidence: 0.873334588

00:46:55.380 --> 00:46:57.070 The mechanisms underlying what sort
NOTE Confidence: 0.873334588

00:46:57.070 --> 00:46:59.259 of what those changes are sort of.
NOTE Confidence: 0.873334588

00:46:59.260 --> 00:47:00.842 What is the origin of those changes
NOTE Confidence: 0.873334588

00:47:00.842 --> 00:47:02.995 and and and sort of all the different
NOTE Confidence: 0.873334588

00:47:02.995 --> 00:47:04.415 contexts that you mentioned here,
NOTE Confidence: 0.873334588

00:47:04.420 --> 00:47:05.740 and the germ line.
NOTE Confidence: 0.873334588

00:47:05.740 --> 00:47:07.574 So thank you so much.
NOTE Confidence: 0.873334588

00:47:07.574 --> 00:47:10.608 There are actually a couple of questions
NOTE Confidence: 0.873334588

00:47:10.608 --> 00:47:13.252 already, so doctor Sklar asked.
NOTE Confidence: 0.873334588

00:47:13.252 --> 00:47:15.692 Where the tumor types heritable
NOTE Confidence: 0.873334588

00:47:15.692 --> 00:47:18.307 between the F1 and F2 generations.
NOTE Confidence: 0.850852887777778

00:47:20.670 --> 00:47:22.950 Uhm, meaning oh, so if you have a
NOTE Confidence: 0.850852887777778

00:47:22.950 --> 00:47:25.441 specific if you have an F1 with a
NOTE Confidence: 0.850852887777778

00:47:25.441 --> 00:47:27.062 particular tumor, do the offspring
NOTE Confidence: 0.850852887777778

00:47:27.062 --> 00:47:29.700 of that F1 get the same tumor so?
NOTE Confidence: 0.812778536

00:47:32.020 --> 00:47:33.060 Uh, yeah, I think that.

NOTE Confidence: 0.812778536

00:47:33.060 --> 00:47:34.530 I think that's the question.

NOTE Confidence: 0.907904933043478

00:47:34.700 --> 00:47:37.080 OK yeah, that's a great question and

NOTE Confidence: 0.907904933043478

00:47:37.080 --> 00:47:40.178 one that we do not have data to answer

NOTE Confidence: 0.907904933043478

00:47:40.178 --> 00:47:43.008 because the we never actually bred those.

NOTE Confidence: 0.907904933043478

00:47:43.010 --> 00:47:45.187 Come the F1 that we phenotypes we

NOTE Confidence: 0.907904933043478

00:47:45.187 --> 00:47:47.459 never bread and F ones that we bred.

NOTE Confidence: 0.907904933043478

00:47:47.460 --> 00:47:49.511 We never phenotype so we were never

NOTE Confidence: 0.907904933043478

00:47:49.511 --> 00:47:51.550 able to make that specific connection

NOTE Confidence: 0.907904933043478

00:47:51.550 --> 00:47:53.746 from the F1 to F2 generation.

NOTE Confidence: 0.907904933043478

00:47:53.750 --> 00:47:56.240 It's only at the population level but yeah,

NOTE Confidence: 0.907904933043478

00:47:56.240 --> 00:47:57.220 that's a great question.

NOTE Confidence: 0.844743998

00:47:59.030 --> 00:48:02.458 OK and then come from Katie

NOTE Confidence: 0.844743998

00:48:02.458 --> 00:48:04.398 Politi bloomer really nice talk.

NOTE Confidence: 0.844743998

00:48:04.400 --> 00:48:06.984 Have you looked at the lung tumors to

NOTE Confidence: 0.844743998

00:48:06.984 --> 00:48:09.406 see whether they have K Ras mutations?

NOTE Confidence: 0.844743998

00:48:09.410 --> 00:48:10.995 Mice can develop them spontaneously
NOTE Confidence: 0.844743998

00:48:10.995 --> 00:48:12.580 and as you mentioned K.
NOTE Confidence: 0.844743998

00:48:12.580 --> 00:48:14.380 Ruskin cooperate with MIC.
NOTE Confidence: 0.799510418

00:48:14.960 --> 00:48:18.059 Yeah also a great question. We have not.
NOTE Confidence: 0.799510418

00:48:18.059 --> 00:48:20.414 We haven't looked at any genetics
NOTE Confidence: 0.799510418

00:48:20.414 --> 00:48:23.770 yet in these mice so we haven't
NOTE Confidence: 0.799510418

00:48:23.770 --> 00:48:26.150 looked to see what kind of underlying
NOTE Confidence: 0.799510418

00:48:26.217 --> 00:48:28.547 spontaneous mutations there may be.
NOTE Confidence: 0.799510418

00:48:28.550 --> 00:48:31.091 We're in the process of setting up
NOTE Confidence: 0.799510418

00:48:31.091 --> 00:48:33.907 to try and do some XM sequencing
NOTE Confidence: 0.799510418

00:48:33.907 --> 00:48:36.373 from the slides that we have.
NOTE Confidence: 0.799510418

00:48:36.380 --> 00:48:38.246 It's sort of variable in quality,
NOTE Confidence: 0.799510418

00:48:38.250 --> 00:48:40.378 but but we definitely want to look
NOTE Confidence: 0.799510418

00:48:40.378 --> 00:48:41.280 at that, yeah?
NOTE Confidence: 0.889154753846154

00:48:43.780 --> 00:48:47.748 OK, and then there's also a question in
NOTE Confidence: 0.889154753846154

00:48:47.748 --> 00:48:51.952 the Q&A box from Chen and many of these

NOTE Confidence: 0.889154753846154
00:48:51.952 --> 00:48:56.109 top dogs in F1 and F2 lunks are RP.
NOTE Confidence: 0.889154753846154
00:48:56.109 --> 00:48:59.252 LRPS jeans. Do you see any changes
NOTE Confidence: 0.889154753846154
00:48:59.252 --> 00:49:02.109 of translation translational changes?
NOTE Confidence: 0.920915255
00:49:03.170 --> 00:49:04.400 We have not looked at it.
NOTE Confidence: 0.920915255
00:49:04.400 --> 00:49:06.068 Yeah, we we definitely want to,
NOTE Confidence: 0.920915255
00:49:06.070 --> 00:49:07.764 but we haven't collected that data yet.
NOTE Confidence: 0.920915255
00:49:07.770 --> 00:49:09.420 This is all pretty new.
NOTE Confidence: 0.920915255
00:49:09.420 --> 00:49:10.880 All that like data, yeah?
NOTE Confidence: 0.920723748
00:49:11.850 --> 00:49:13.974 OK, so there's lots of there's
NOTE Confidence: 0.920723748
00:49:13.974 --> 00:49:16.050 a lot of interest, so Krishna,
NOTE Confidence: 0.920723748
00:49:16.050 --> 00:49:18.030 who's one of our residents asked,
NOTE Confidence: 0.920723748
00:49:18.030 --> 00:49:20.485 does such findings have potential
NOTE Confidence: 0.920723748
00:49:20.485 --> 00:49:22.449 impact on epigenetic paternal
NOTE Confidence: 0.920723748
00:49:22.449 --> 00:49:24.619 screening and or genetic counseling
NOTE Confidence: 0.920723748
00:49:24.619 --> 00:49:26.634 in couples planning to conceive
NOTE Confidence: 0.920723748

00:49:26.634 --> 00:49:29.058 or with male infertility issues?
NOTE Confidence: 0.677390901666667

00:49:29.970 --> 00:49:33.558 Uhm, that's a great question I.
NOTE Confidence: 0.677390901666667

00:49:33.560 --> 00:49:34.752 So yes and no.
NOTE Confidence: 0.677390901666667

00:49:34.752 --> 00:49:37.008 I think on a practical level it
NOTE Confidence: 0.677390901666667

00:49:37.008 --> 00:49:39.773 would be very difficult to do any
NOTE Confidence: 0.677390901666667

00:49:39.773 --> 00:49:41.610 epigenetic screening at this point.
NOTE Confidence: 0.677390901666667

00:49:41.610 --> 00:49:43.969 I think it that's some future goal
NOTE Confidence: 0.677390901666667

00:49:43.969 --> 00:49:46.887 might be to identify a set in humans,
NOTE Confidence: 0.677390901666667

00:49:46.890 --> 00:49:49.375 a set of sort of high risk
NOTE Confidence: 0.677390901666667

00:49:49.375 --> 00:49:51.583 epigenetic loci that we could do
NOTE Confidence: 0.677390901666667

00:49:51.583 --> 00:49:54.068 some sort of array on or something.
NOTE Confidence: 0.677390901666667

00:49:54.070 --> 00:49:55.987 And then we could look at things like that.
NOTE Confidence: 0.677390901666667

00:49:55.990 --> 00:49:58.060 Or right now we just don't have any idea
NOTE Confidence: 0.677390901666667

00:49:58.060 --> 00:50:00.120 we can't like whole genome sequence,
NOTE Confidence: 0.677390901666667

00:50:00.120 --> 00:50:02.322 every infertile couple or whole genome
NOTE Confidence: 0.677390901666667

00:50:02.322 --> 00:50:03.790 bisulfite sequence every infertile.

NOTE Confidence: 0.677390901666667
00:50:03.790 --> 00:50:04.686 Couple uhm.
NOTE Confidence: 0.677390901666667
00:50:04.686 --> 00:50:07.374 But I actually think like looking
NOTE Confidence: 0.677390901666667
00:50:07.374 --> 00:50:10.043 for germline mutations of epigenetic
NOTE Confidence: 0.677390901666667
00:50:10.043 --> 00:50:12.863 regulators is a potentially really
NOTE Confidence: 0.677390901666667
00:50:12.863 --> 00:50:15.615 fruitful thing that people don't do
NOTE Confidence: 0.677390901666667
00:50:15.615 --> 00:50:18.000 right now because I think what one
NOTE Confidence: 0.677390901666667
00:50:18.000 --> 00:50:20.539 thing that our study has shown is that
NOTE Confidence: 0.677390901666667
00:50:20.540 --> 00:50:23.804 increase rates of mutation of these
NOTE Confidence: 0.677390901666667
00:50:23.804 --> 00:50:26.625 regulators can affect phenotype even if
NOTE Confidence: 0.677390901666667
00:50:26.625 --> 00:50:29.820 the mutation itself is not inherited.
NOTE Confidence: 0.677390901666667
00:50:29.820 --> 00:50:30.956 So in other words,
NOTE Confidence: 0.677390901666667
00:50:30.956 --> 00:50:31.808 if there are,
NOTE Confidence: 0.677390901666667
00:50:31.810 --> 00:50:34.127 if you're if the father is producing
NOTE Confidence: 0.677390901666667
00:50:34.127 --> 00:50:36.189 sperm that carry these mutations.
NOTE Confidence: 0.677390901666667
00:50:36.190 --> 00:50:38.150 Even if the sperm that creates the
NOTE Confidence: 0.677390901666667

00:50:38.150 --> 00:50:39.709 embryo doesn't carry the mutation,
NOTE Confidence: 0.677390901666667

00:50:39.710 --> 00:50:41.942 it may actually be relevant information
NOTE Confidence: 0.677390901666667

00:50:41.942 --> 00:50:44.258 for understanding the health of the embryo.
NOTE Confidence: 0.677390901666667

00:50:44.260 --> 00:50:45.580 So and that's something that we
NOTE Confidence: 0.677390901666667

00:50:45.580 --> 00:50:47.345 may be might be able to do at
NOTE Confidence: 0.677390901666667

00:50:47.345 --> 00:50:48.385 kind of a screening level.
NOTE Confidence: 0.793740314

00:50:50.690 --> 00:50:54.346 And finally, Doctor Prasad asked, can these
NOTE Confidence: 0.793740314

00:50:54.346 --> 00:50:56.736 heritable epigenetic changes be reverted?
NOTE Confidence: 0.80029936

00:50:57.880 --> 00:51:01.036 Uhm? So far, no, at least
NOTE Confidence: 0.80029936

00:51:01.036 --> 00:51:03.140 not a controllable way.
NOTE Confidence: 0.846175212222222

00:51:05.830 --> 00:51:08.974 They are in a very exploratory
NOTE Confidence: 0.846175212222222

00:51:08.974 --> 00:51:10.546 set of experiments.
NOTE Confidence: 0.846175212222222

00:51:10.550 --> 00:51:13.814 It would be cool to try using sort
NOTE Confidence: 0.846175212222222

00:51:13.814 --> 00:51:15.424 of epigenetic drugs and seeing
NOTE Confidence: 0.846175212222222

00:51:15.424 --> 00:51:17.349 what that would affect that has,
NOTE Confidence: 0.846175212222222

00:51:17.350 --> 00:51:20.326 although that's obviously not locus specific,

NOTE Confidence: 0.846175212222222

00:51:20.330 --> 00:51:22.738 so that may have a lot of secondary

NOTE Confidence: 0.846175212222222

00:51:22.738 --> 00:51:24.659 changes that we're not expecting.

NOTE Confidence: 0.846175212222222

00:51:24.660 --> 00:51:26.472 My lab has thought about using

NOTE Confidence: 0.846175212222222

00:51:26.472 --> 00:51:27.988 CRISPR type approaches to do

NOTE Confidence: 0.846175212222222

00:51:27.988 --> 00:51:29.470 this in a locus specific way,

NOTE Confidence: 0.846175212222222

00:51:29.470 --> 00:51:32.098 but that's obviously not.

NOTE Confidence: 0.846175212222222

00:51:32.100 --> 00:51:34.680 Sort of applicable then it

NOTE Confidence: 0.846175212222222

00:51:34.680 --> 00:51:36.228 potentially clinically applicable

NOTE Confidence: 0.846175212222222

00:51:36.230 --> 00:51:39.190 and is a experimentally challenging,

NOTE Confidence: 0.846175212222222

00:51:39.190 --> 00:51:42.106 so I haven't managed to actually do it yet,

NOTE Confidence: 0.846175212222222

00:51:42.110 --> 00:51:43.944 so that's a great question as well.

NOTE Confidence: 0.846175212222222

00:51:43.950 --> 00:51:45.147 We don't yet know the answer to

NOTE Confidence: 0.701810683333333

00:51:46.320 --> 00:51:48.550 bloom. I thought I really enjoyed your

NOTE Confidence: 0.701810683333333

00:51:48.550 --> 00:51:51.764 talk and I thought it's fascinating that

NOTE Confidence: 0.701810683333333

00:51:51.764 --> 00:51:56.121 you have mice with with different code

NOTE Confidence: 0.701810683333333

00:51:56.121 --> 00:51:59.748 colors and that was epic genetically
NOTE Confidence: 0.9095217533333333

00:52:00.540 --> 00:52:05.040 determined. And and which brings me to.
NOTE Confidence: 0.9095217533333333

00:52:05.040 --> 00:52:07.420 Is that possible that the skin color in
NOTE Confidence: 0.9095217533333333

00:52:07.420 --> 00:52:10.976 humans is also epigenetically determined?
NOTE Confidence: 0.9095217533333333

00:52:10.976 --> 00:52:14.055 Because clearly there is a correlation to
NOTE Confidence: 0.9095217533333333

00:52:14.055 --> 00:52:17.105 environment and sun exposure and different
NOTE Confidence: 0.9095217533333333

00:52:17.105 --> 00:52:22.160 regions in the world and the skin color.
NOTE Confidence: 0.9095217533333333

00:52:22.160 --> 00:52:25.639 Yeah yeah. So. So on one level.
NOTE Confidence: 0.9095217533333333

00:52:25.640 --> 00:52:27.304 Certainly there's an epigenetic
NOTE Confidence: 0.9095217533333333

00:52:27.304 --> 00:52:28.968 component because it's responsive,
NOTE Confidence: 0.9095217533333333

00:52:28.970 --> 00:52:31.268 as you said, responsive to environment.
NOTE Confidence: 0.9095217533333333

00:52:31.270 --> 00:52:34.380 So if you if you spend a lot of time
NOTE Confidence: 0.9095217533333333

00:52:34.474 --> 00:52:37.080 in the sun then generally your skin
NOTE Confidence: 0.9095217533333333

00:52:37.080 --> 00:52:39.255 gets darker and that's epigenetic.
NOTE Confidence: 0.9095217533333333

00:52:39.260 --> 00:52:40.856 It's there's there's.
NOTE Confidence: 0.9095217533333333

00:52:40.856 --> 00:52:44.048 It's not necessarily gene regulatory based,

NOTE Confidence: 0.9095217533333333
00:52:44.050 --> 00:52:46.240 but then the second question might
NOTE Confidence: 0.9095217533333333
00:52:46.240 --> 00:52:48.519 be to wet expenses that heritable
NOTE Confidence: 0.9095217533333333
00:52:48.519 --> 00:52:50.389 and that we don't know.
NOTE Confidence: 0.9095217533333333
00:52:50.390 --> 00:52:52.217 I think in the in the case of mice.
NOTE Confidence: 0.9095217533333333
00:52:52.220 --> 00:52:54.434 We had a specific locus that
NOTE Confidence: 0.9095217533333333
00:52:54.434 --> 00:52:56.674 we knew is responsible for, UM,
NOTE Confidence: 0.9095217533333333
00:52:56.674 --> 00:52:59.432 for coat color and and and then
NOTE Confidence: 0.9095217533333333
00:52:59.432 --> 00:53:01.850 a specific regulatory change.
NOTE Confidence: 0.9095217533333333
00:53:01.850 --> 00:53:02.726 In that case,
NOTE Confidence: 0.9095217533333333
00:53:02.726 --> 00:53:04.770 there was a transposon that was inserted
NOTE Confidence: 0.9095217533333333
00:53:04.828 --> 00:53:06.871 in the locus so we could try or the
NOTE Confidence: 0.9095217533333333
00:53:06.871 --> 00:53:08.776 people who did the study could track,
NOTE Confidence: 0.9095217533333333
00:53:08.780 --> 00:53:10.556 you know, the extent to which
NOTE Confidence: 0.9095217533333333
00:53:10.556 --> 00:53:11.740 that transposon was methylated.
NOTE Confidence: 0.9095217533333333
00:53:11.740 --> 00:53:12.163 Basically,
NOTE Confidence: 0.9095217533333333

00:53:12.163 --> 00:53:15.547 in humans I don't know if we know
NOTE Confidence: 0.9095217533333333

00:53:15.547 --> 00:53:18.496 of alleles that could do that.
NOTE Confidence: 0.9095217533333333

00:53:18.500 --> 00:53:20.930 Sort of an analogous situation
NOTE Confidence: 0.9095217533333333

00:53:20.930 --> 00:53:22.366 so we don't have.
NOTE Confidence: 0.9095217533333333

00:53:22.366 --> 00:53:24.161 Any specific data sort of
NOTE Confidence: 0.9095217533333333

00:53:24.161 --> 00:53:25.969 demonstrating that it could be true,
NOTE Confidence: 0.9095217533333333

00:53:25.970 --> 00:53:27.340 although we don't have anything
NOTE Confidence: 0.9095217533333333

00:53:27.340 --> 00:53:29.350 showing that it can't be true either.
NOTE Confidence: 0.43887408

00:53:36.240 --> 00:53:38.728 K I think I don't
NOTE Confidence: 0.945543644

00:53:38.740 --> 00:53:41.124 have any other questions.
NOTE Confidence: 0.945543644

00:53:41.124 --> 00:53:43.680 I'd really just like to thank you again.
NOTE Confidence: 0.945543644

00:53:43.680 --> 00:53:47.280 Bluma, it's really fantastic talk and
NOTE Confidence: 0.945543644

00:53:47.280 --> 00:53:51.930 I just like look forward to you know,
NOTE Confidence: 0.945543644

00:53:51.930 --> 00:53:54.852 helping you connect with anyone in our
NOTE Confidence: 0.945543644

00:53:54.852 --> 00:53:58.790 department and it'll be really great too.
NOTE Confidence: 0.945543644

00:53:58.790 --> 00:54:00.870 You know work work together

NOTE Confidence: 0.945543644

00:54:00.870 --> 00:54:02.534 in in whatever capacity?

NOTE Confidence: 0.75465924

00:54:03.740 --> 00:54:04.950 Yeah, no thank you again,

NOTE Confidence: 0.75465924

00:54:04.950 --> 00:54:06.819 it was great to to be here.

NOTE Confidence: 0.775924158571429

00:54:09.210 --> 00:54:13.354 Hey, uhm. I guess we can't come.

NOTE Confidence: 0.8176172

00:54:15.450 --> 00:54:17.330 Uh, I guess that that's sort of

NOTE Confidence: 0.8176172

00:54:17.330 --> 00:54:20.186 it so we can come log off there.

NOTE Confidence: 0.8176172

00:54:20.190 --> 00:54:22.206 I've there aren't any other questions.

NOTE Confidence: 0.8176172

00:54:22.210 --> 00:54:23.833 Thank you again.

NOTE Confidence: 0.8176172

00:54:23.833 --> 00:54:25.997 Thanks everyone for attending.