WEBVTT

- NOTE duration:"00:54:26"
- NOTE recognizability:0.859
- NOTE language:en-us
- NOTE Confidence: 0.90888099
- $00:00:04.850 \rightarrow 00:00:08.714$ So today I'm delighted to introduce Dr.
- NOTE Confidence: 0.90888099
- $00{:}00{:}08.720 \dashrightarrow 00{:}00{:}11.575$ Bluma Lesch as our pathology
- NOTE Confidence: 0.90888099
- 00:00:11.575 --> 00:00:13.288 grand rounds speaker.
- NOTE Confidence: 0.90888099
- $00{:}00{:}13.290 \dashrightarrow 00{:}00{:}15.446$ Many of you may know Doctor Lash
- NOTE Confidence: 0.90888099
- $00:00:15.446 \longrightarrow 00:00:17.340$ is an assistant professor here
- NOTE Confidence: 0.90888099
- $00{:}00{:}17{.}340 \dashrightarrow 00{:}00{:}19{.}140$ 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
- $00{:}00{:}26.370 \dashrightarrow 00{:}00{:}30.350$ Before she went on to the MD PhD
- NOTE Confidence: 0.90888099
- $00{:}00{:}30{.}350 \dashrightarrow 00{:}00{:}32{.}550$ program at the Tri Institutional
- NOTE Confidence: 0.90888099
- $00{:}00{:}32.550 \dashrightarrow 00{:}00{:}35.330$ Program at Weill Cornell.
- NOTE Confidence: 0.90888099
- $00:00:35.330 \longrightarrow 00:00:36.720$ Rockefeller MSKCC,
- NOTE Confidence: 0.90888099
- $00{:}00{:}36.720 \dashrightarrow 00{:}00{:}39.317$ which did her pH D with Cori
- NOTE Confidence: 0.90888099

 $00:00:39.317 \longrightarrow 00:00:42.658$ Bargmann and then she went on to do

NOTE Confidence: 0.90888099

 $00:00:42.658 \rightarrow 00:00:44.798$ 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

 $00{:}00{:}50{.}380 \dashrightarrow 00{:}00{:}53{.}122$ Her research focuses on the mechanisms

NOTE Confidence: 0.920912913333333

 $00{:}00{:}53.122 \dashrightarrow 00{:}00{:}54.885$ of transcriptional regulation in

NOTE Confidence: 0.920912913333333

 $00{:}00{:}54.885 \dashrightarrow 00{:}00{:}57.195$ the context of both development and

NOTE Confidence: 0.920912913333333

 $00:00:57.195 \rightarrow 00:00:59.764$ evolution and in the short time since

NOTE Confidence: 0.920912913333333

 $00:00:59.764 \longrightarrow 00:01:02.200$ she started her lab here in 2017.

NOTE Confidence: 0.920912913333333

 $00:01:02.200 \longrightarrow 00:01:04.320$ 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

 $00:01:06.016 \rightarrow 00:01:08.948$ 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

 $00:01:12.350 \longrightarrow 00:01:14.910$ 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

 $00:01:17.172 \longrightarrow 00:01:18.680$ 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
- $00:01:34.725 \longrightarrow 00:01:36.350$ 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
- $00:02:10.600 \dashrightarrow 00:02:12.840$ so thanks to the lobby for inviting me.
- NOTE Confidence: 0.7797568175
- $00:02:12.840 \dashrightarrow 00:02:14.709$ I'm I'm really excited to tell you
- NOTE Confidence: 0.7797568175
- $00:02:14.709 \longrightarrow 00:02:16.440$ 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
- $00{:}02{:}19.783 \dashrightarrow 00{:}02{:}21.907$ connections in your department.
- NOTE Confidence: 0.7797568175
- $00{:}02{:}21{.}910 \dashrightarrow 00{:}02{:}23{.}998$ So I'm going to talk about
- NOTE Confidence: 0.7797568175
- $00{:}02{:}23.998 \dashrightarrow 00{:}02{:}24.694$ Internet intergenerational
- NOTE Confidence: 0.7797568175
- 00:02:24.694 --> 00:02:25.899 epigenetic inheritance of cancer,
- NOTE Confidence: 0.7797568175
- $00:02:25.900 \longrightarrow 00:02:28.918$ 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

 $00{:}02{:}32{.}156 \dashrightarrow 00{:}02{:}35{.}186$ 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

 $00:02:36.784 \longrightarrow 00:02:39.388$ the first cell division and an

NOTE Confidence: 0.7797568175

 $00:02:39.388 \longrightarrow 00:02:42.518$ 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

NOTE confidence. 0.1151506115

 $00{:}02{:}46{.}040 \dashrightarrow 00{:}02{:}48{.}840$ 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

 $00{:}02{:}51{.}150 \dashrightarrow 00{:}02{:}53{.}328$ and I'm showing this video both

NOTE Confidence: 0.7797568175

 $00:02:53.328 \rightarrow 00:02:55.170$ because it's just really cool.

NOTE Confidence: 0.7797568175

 $00{:}02{:}55{.}170 \dashrightarrow 00{:}02{:}57{.}249$ This is one of the most a mazing

NOTE Confidence: 0.7797568175

 $00:02:57.249 \longrightarrow 00:02:59.233$ 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

 $00:03:00.930 \longrightarrow 00:03:04.098$ but also because I want to make a point.

NOTE Confidence: 0.7797568175

 $00:03:04.100 \longrightarrow 00:03:06.494$ In this video that that sort of sets up

NOTE Confidence: 0.7797568175

 $00:03:06.494 \rightarrow 00:03:08.876$ the problem that we're interested in.

- NOTE Confidence: 0.7797568175
- $00:03:08.880 \longrightarrow 00:03:11.064$ And the point is so here you

 $00:03:11.064 \rightarrow 00:03:13.179$ can see the two pronuclei.

NOTE Confidence: 0.7797568175

 $00:03:13.180 \rightarrow 00:03:15.156$ Hopefully you can see that one of them

NOTE Confidence: 0.7797568175

 $00:03:15.156 \rightarrow 00:03:17.217$ is much brighter than the other one.

NOTE Confidence: 0.7797568175

 $00:03:17.220 \dashrightarrow 00:03:20.094$ The brighter one is the paternal

NOTE Confidence: 0.7797568175

 $00:03:20.094 \dashrightarrow 00:03:22.580$ pronucleus coming from the sperm,

NOTE Confidence: 0.7797568175

 $00:03:22.580 \rightarrow 00:03:26.676$ and the reason it's brighter is because it's

NOTE Confidence: 0.7797568175

 $00:03:26.676 \rightarrow 00:03:30.640$ loaded up with histories tagged with GFP,

NOTE Confidence: 0.7797568175

 $00:03:30.640 \dashrightarrow 00:03:32.470$ and this GFP tagged histone

NOTE Confidence: 0.7797568175

 $00:03:32.470 \longrightarrow 00:03:34.300$ was coming from the oocyte.

NOTE Confidence: 0.7797568175

 $00:03:34.300 \longrightarrow 00:03:36.309$ The fact that this nucleus this nucleus

NOTE Confidence: 0.7797568175

 $00{:}03{:}36{.}309 \dashrightarrow 00{:}03{:}39{.}005$ 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

 $00:03:42.314 \rightarrow 00:03:45.227$ information has been removed and completely

 $00:03:45.227 \rightarrow 00:03:47.747$ replaced with oocyte provided histones.

NOTE Confidence: 0.7797568175

 $00{:}03{:}47.750 \dashrightarrow 00{:}03{:}49.370$ So this is a you know,

NOTE Confidence: 0.7797568175

 $00{:}03{:}49{.}370 \dashrightarrow 00{:}03{:}51{.}465$ 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

 $00:03:54.010 \rightarrow 00:03:56.265$ that all epigenetic information coming

NOTE Confidence: 0.7797568175

 $00:03:56.265 \rightarrow 00:03:59.174$ from sperm at least is completely

NOTE Confidence: 0.7797568175

 $00:03:59.174 \rightarrow 00:04:02.069$ replaced at fertilization and reset.

NOTE Confidence: 0.7797568175

 $00:04:02.070 \longrightarrow 00:04:03.432$ And and so.

NOTE Confidence: 0.7797568175

 $00:04:03.432 \longrightarrow 00:04:05.248$ With that in mind.

NOTE Confidence: 0.896484545925926

 $00:04:08.420 \longrightarrow 00:04:10.708$ This is a question one of the questions

NOTE Confidence: 0.896484545925926

 $00{:}04{:}10.708 \dashrightarrow 00{:}04{:}12.781$ that my lab is especially interested

NOTE Confidence: 0.896484545925926

 $00:04:12.781 \longrightarrow 00:04:15.358$ in two life experiences of the parents

NOTE Confidence: 0.896484545925926

 $00:04:15.358 \rightarrow 00:04:17.500$ affect the health of the progeny,

NOTE Confidence: 0.896484545925926

 $00{:}04{:}17{.}500 \dashrightarrow 00{:}04{:}20{.}524$ and one would think since life experience

NOTE Confidence: 0.896484545925926

 $00:04:20.524 \rightarrow 00:04:23.779$ tends to be encoded in epigenetics,

NOTE Confidence: 0.896484545925926

 $00:04:23.780 \longrightarrow 00:04:26.276$ but the fact that all of this epigenetic

- NOTE Confidence: 0.896484545925926
- $00{:}04{:}26.276 \dashrightarrow 00{:}04{:}28.262$ information is reset at fertilization would
- NOTE Confidence: 0.896484545925926
- $00:04:28.262 \longrightarrow 00:04:31.119$ mean that the answer to this question is no.
- NOTE Confidence: 0.896484545925926
- $00{:}04{:}31{.}120 \dashrightarrow 00{:}04{:}33{.}550$ But what I'm going to try and get across in
- NOTE Confidence: 0.896484545925926
- $00:04:33.612 \rightarrow 00:04:36.159$ this talk is that the answer is actually yes,
- NOTE Confidence: 0.896484545925926
- $00:04:36.160 \longrightarrow 00:04:37.714$ and we're going to try and
- NOTE Confidence: 0.896484545925926
- $00:04:37.714 \longrightarrow 00:04:39.030$ uncover what some of the.
- NOTE Confidence: 0.896484545925926
- $00:04:39.030 \longrightarrow 00:04:41.400$ Mechanisms for that might be.
- NOTE Confidence: 0.896484545925926
- $00{:}04{:}41{.}400 \dashrightarrow 00{:}04{:}43{.}745$ And we can break down this question
- NOTE Confidence: 0.896484545925926
- $00:04:43.745 \rightarrow 00:04:46.130$ 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
- $00:04:48.990 \longrightarrow 00:04:51.439$ inherited across generations. So is this.
- NOTE Confidence: 0.896484545925926
- $00{:}04{:}51{.}439 \dashrightarrow 00{:}04{:}52{.}654$ This is a molecular question.
- NOTE Confidence: 0.896484545925926
- $00:04:52.660 \rightarrow 00:04:55.456$ What's happening at the biochemical level?
- NOTE Confidence: 0.896484545925926
- $00:04:55.460 \rightarrow 00:04:56.870$ And then the second question is,
- NOTE Confidence: 0.896484545925926
- $00:04:56.870 \longrightarrow 00:04:59.278$ is this inherited regulatory
- NOTE Confidence: 0.896484545925926

 $00:04:59.278 \rightarrow 00:05:01.084$ information biologically meaningful?

NOTE Confidence: 0.896484545925926

 $00{:}05{:}01.090 \dashrightarrow 00{:}05{:}02.023$ In other words,

NOTE Confidence: 0.896484545925926

 $00:05:02.023 \rightarrow 00:05:03.578$ does it actually affect phenotype

NOTE Confidence: 0.896484545925926

 $00:05:03.578 \rightarrow 00:05:05.509$ or is it just a biochemical

NOTE Confidence: 0.896484545925926

 $00{:}05{:}05{.}509 \dashrightarrow 00{:}05{:}07{.}375$ signature that we can follow with

NOTE Confidence: 0.896484545925926

 $00:05:07.439 \rightarrow 00:05:09.307$ our various molecular techniques?

NOTE Confidence: 0.896484545925926

00:05:09.310 --> 00:05:11.370 Uhm?

NOTE Confidence: 0.896484545925926

 $00:05:11.370 \longrightarrow 00:05:14.226$ 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

 $00:05:16.295 \rightarrow 00:05:17.180$ introduction to epigenetics.

NOTE Confidence: 0.896484545925926

 $00:05:17.180 \rightarrow 00:05:19.336$ This is probably review for most people,

NOTE Confidence: 0.896484545925926

 $00:05:19.340 \longrightarrow 00:05:20.908$ but I just want to make sure

NOTE Confidence: 0.896484545925926

 $00:05:20.908 \rightarrow 00:05:22.656$ everybody is on the same page and

NOTE Confidence: 0.896484545925926

 $00:05:22.656 \rightarrow 00:05:25.148$ what I'm showing here is a consensus

NOTE Confidence: 0.896484545925926

 $00:05:25.148 \rightarrow 00:05:26.578$ definition for what epigenetics

NOTE Confidence: 0.896484545925926

 $00:05:26.578 \rightarrow 00:05:29.170$ 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
- $00:05:31.440 \longrightarrow 00:05:34.439$ and it has four key components stably
- NOTE Confidence: 0.896484545925926
- $00:05:34.439 \rightarrow 00:05:36.155$ heritable phenotype resulting from
- NOTE Confidence: 0.896484545925926
- $00{:}05{:}36{.}155 \dashrightarrow 00{:}05{:}38{.}300$ changes in a chromosome without
- NOTE Confidence: 0.896484545925926
- $00:05:38.359 \dashrightarrow 00:05:40.239$ alterations in the DNA sequence,
- NOTE Confidence: 0.896484545925926
- $00{:}05{:}40{.}240 \dashrightarrow 00{:}05{:}41{.}430$ and I want to make the point.
- NOTE Confidence: 0.896484545925926
- $00:05:41.430 \rightarrow 00:05:43.694$ That come off when we talk about epigenetics.
- NOTE Confidence: 0.896484545925926
- $00:05:43.700 \longrightarrow 00:05:45.877$ We're talking about the second half of
- NOTE Confidence: 0.896484545925926
- $00{:}05{:}45{.}877 \dashrightarrow 00{:}05{:}47{.}585$ this sentence changes their chromosome
- NOTE Confidence: 0.896484545925926
- $00:05:47.585 \rightarrow 00:05:49.727$ without alterations in a DNA sequence,
- NOTE Confidence: 0.896484545925926
- $00:05:49.730 \longrightarrow 00:05:52.250$ and those are the things shown here
- NOTE Confidence: 0.896484545925926
- $00{:}05{:}52{.}250 \dashrightarrow 00{:}05{:}55{.}337$ that are generally considered to be the
- NOTE Confidence: 0.896484545925926
- $00{:}05{:}55{.}337 \dashrightarrow 00{:}05{:}57{.}550$ carriers of opportunistic information.
- NOTE Confidence: 0.896484545925926
- $00{:}05{:}57{.}550 \dashrightarrow 00{:}05{:}59{.}070$ Covalent modifications to DNA,
- NOTE Confidence: 0.896484545925926
- $00:05:59.070 \rightarrow 00:06:02.240$ 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

 $00{:}06{:}04.628 \dashrightarrow 00{:}06{:}07.016$ along the chromosome.

NOTE Confidence: 0.896484545925926

 $00:06:07.020 \rightarrow 00:06:08.996$ Covalent modifications to histones,

NOTE Confidence: 0.896484545925926

 $00:06:08.996 \rightarrow 00:06:11.466$ 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

 $00{:}06{:}13.670 \dashrightarrow 00{:}06{:}16.405$ binding and large scale structural

NOTE Confidence: 0.896484545925926

 $00{:}06{:}16{.}405 \dashrightarrow 00{:}06{:}18{.}639$ arrangements of the chromosomes.

NOTE Confidence: 0.896484545925926

 $00:06:18.640 \longrightarrow 00:06:20.313$ These are the kinds of things that

NOTE Confidence: 0.896484545925926

 $00{:}06{:}20{.}313 \dashrightarrow 00{:}06{:}22{.}393$ you see a lot of data on that we

NOTE Confidence: 0.896484545925926

 $00{:}06{:}22.393 \dashrightarrow 00{:}06{:}24.248$ tend to study and pay attention to,

NOTE Confidence: 0.896484545925926

 $00:06:24.250 \longrightarrow 00:06:26.509$ but I want to point out that a key

NOTE Confidence: 0.896484545925926

 $00:06:26.509 \longrightarrow 00:06:28.691$ aspect of this definition is that

NOTE Confidence: 0.896484545925926

 $00:06:28.691 \rightarrow 00:06:31.824$ this effects phenotype and but it's

NOTE Confidence: 0.896484545925926

 $00{:}06{:}31{.}824 \dashrightarrow 00{:}06{:}34{.}616$ heritable so so I and I want to make

NOTE Confidence: 0.896484545925926

 $00:06:34.616 \dashrightarrow 00:06:36.230$ sure that that we're addressing.

NOTE Confidence: 0.896484545925926

 $00:06:36.230 \rightarrow 00:06:38.840$ So those questions during this talk.

- NOTE Confidence: 0.836415338461539
- $00:06:41.500 \rightarrow 00:06:45.276$ 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
- $00:06:48.190 \longrightarrow 00:06:50.686$ we tend to focus on this level of
- NOTE Confidence: 0.836415338461539
- $00:06:50.686 \rightarrow 00:06:52.340$ organization at the nucleosome.
- NOTE Confidence: 0.836415338461539
- $00:06:52.340 \longrightarrow 00:06:55.095$ 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
- $00:06:57.300 \longrightarrow 00:06:59.980$ and it's composed of an
- NOTE Confidence: 0.836415338461539
- $00:06:59.980 \longrightarrow 00:07:02.660$ 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
- $00:07:05.996 \longrightarrow 00:07:08.498$ 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
- $00:07:11.752 \longrightarrow 00:07:13.690$ wrapped around its optimer.
- NOTE Confidence: 0.79615179875
- $00:07:16.360 \longrightarrow 00:07:18.370$ Each of these histores has a
- NOTE Confidence: 0.79615179875
- $00{:}07{:}18.370 \dashrightarrow 00{:}07{:}20.076$ globular domain that makes up
- NOTE Confidence: 0.79615179875
- $00:07:20.076 \longrightarrow 00:07:21.596$ the core of the nucleosome,
- NOTE Confidence: 0.79615179875

 $00:07:21.600 \longrightarrow 00:07:23.784$ but importantly also has an end

NOTE Confidence: 0.79615179875

 $00{:}07{:}23.784 \dashrightarrow 00{:}07{:}25.560$ terminal tail that sticks out,

NOTE Confidence: 0.79615179875

 $00:07:25.560 \rightarrow 00:07:29.344$ and it's this floppy tail that gets modified.

NOTE Confidence: 0.79615179875

 $00:07:29.350 \longrightarrow 00:07:31.268$ I'm currently and so we tend to.

NOTE Confidence: 0.79615179875

 $00{:}07{:}31.270 \dashrightarrow 00{:}07{:}33.055$ 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

 $00:07:34.631 \longrightarrow 00:07:36.381$ this and this is what you'll see

NOTE Confidence: 0.79615179875

 $00:07:36.438 \rightarrow 00:07:38.088$ throughout the rest of the top,

NOTE Confidence: 0.79615179875

 $00:07:38.090 \longrightarrow 00:07:40.730$ but at the biochemical level,

NOTE Confidence: 0.79615179875

 $00{:}07{:}40.730 \dashrightarrow 00{:}07{:}42.774$ 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

 $00{:}07{:}45{.}329 \dashrightarrow 00{:}07{:}47{.}439$ stability of this nucleosome and

NOTE Confidence: 0.79615179875

 $00{:}07{:}47.439 \dashrightarrow 00{:}07{:}50.255$ in turn effects the extent of gene

NOTE Confidence: 0.79615179875

 $00{:}07{:}50.255 \dashrightarrow 00{:}07{:}52.565$ regulation of a particular locus.

NOTE Confidence: 0.79615179875

 $00:07:52.570 \dashrightarrow 00:07:56.924$ Uhm? So when we talk about resetting

NOTE Confidence: 0.79615179875

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

 $00:07:58.790 \longrightarrow 00:08:00.006$ there are,

NOTE Confidence: 0.79615179875

 $00{:}08{:}00{.}006 \dashrightarrow 00{:}08{:}03{.}654$ and we're focusing on on his

NOTE Confidence: 0.79615179875

 $00:08:03.654 \longrightarrow 00:08:04.870$ own modifications.

NOTE Confidence: 0.79615179875

 $00:08:04.870 \rightarrow 00:08:06.970$ There are actually two aspects of this.

NOTE Confidence: 0.79615179875

 $00{:}08{:}06{.}970 \dashrightarrow 00{:}08{:}09{.}250$ There's one that I showed already

NOTE Confidence: 0.79615179875

 $00:08:09.250 \longrightarrow 00:08:11.458$ in the in the in the early embryo

NOTE Confidence: 0.79615179875

 $00{:}08{:}11.458 \dashrightarrow 00{:}08{:}14.087$ where his zones are kicked out of the

NOTE Confidence: 0.79615179875

 $00{:}08{:}14.087 \dashrightarrow 00{:}08{:}16.283$ eternal nucleus and some extent reset

NOTE Confidence: 0.79615179875

 $00{:}08{:}16.283 \dashrightarrow 00{:}08{:}18.647$ in the maternal practically as well.

NOTE Confidence: 0.79615179875

 $00:08:18.650 \longrightarrow 00:08:20.810$ And there's also a resetting

NOTE Confidence: 0.79615179875

 $00:08:20.810 \longrightarrow 00:08:22.970$ that happens in sperm before

NOTE Confidence: 0.79615179875

 $00{:}08{:}23.053 \dashrightarrow 00{:}08{:}25.328$ you even get to fertilization.

NOTE Confidence: 0.79615179875

 $00:08:25.330 \longrightarrow 00:08:26.870$ So sperm actually removed

NOTE Confidence: 0.79615179875

 $00{:}08{:}26.870 \dashrightarrow 00{:}08{:}28.410$ most of their histones.

NOTE Confidence: 0.79615179875

 $00{:}08{:}28{.}410 \dashrightarrow 00{:}08{:}30{.}360$ Most of their nucleosomes as they

 $00:08:30.360 \longrightarrow 00:08:32.103$ mature and replaced them with

NOTE Confidence: 0.79615179875

 $00:08:32.103 \rightarrow 00:08:34.008$ 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

 $00:08:35.540 \longrightarrow 00:08:37.958$ and that's so that they can

NOTE Confidence: 0.79615179875

 $00{:}08{:}37{.}958 \dashrightarrow 00{:}08{:}39{.}781$ 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

 $00:08:42.900 \longrightarrow 00:08:45.132$ As we've all seen.

NOTE Confidence: 0.79615179875

 $00{:}08{:}45{.}132 \dashrightarrow 00{:}08{:}46{.}248$ And so.

NOTE Confidence: 0.79615179875

 $00:08:46.250 \longrightarrow 00:08:47.725$ There's a loss of epigenetic

NOTE Confidence: 0.79615179875

 $00:08:47.725 \longrightarrow 00:08:48.905$ information at this stage,

NOTE Confidence: 0.79615179875

 $00{:}08{:}48{.}910 \dashrightarrow 00{:}08{:}51{.}112$ and there's a loss of epigenetic

NOTE Confidence: 0.79615179875

 $00{:}08{:}51{.}112 \dashrightarrow 00{:}08{:}52{.}580$ information at this stage.

NOTE Confidence: 0.79615179875

 $00:08:52.580 \longrightarrow 00:08:53.404$ But importantly,

NOTE Confidence: 0.79615179875

 $00{:}08{:}53{.}404 \dashrightarrow 00{:}08{:}55{.}876$ there is a little bit of

NOTE Confidence: 0.79615179875

 $00:08:55.876 \longrightarrow 00:08:58.312$ retention of histories in this

 $00:08:58.312 \rightarrow 00:09:00.156$ during this protamine transition,

NOTE Confidence: 0.79615179875

 $00:09:00.160 \longrightarrow 00:09:02.362$ and we're actually not sure the

NOTE Confidence: 0.79615179875

 $00:09:02.362 \longrightarrow 00:09:04.399$ extent to which those retained

NOTE Confidence: 0.79615179875

 $00:09:04.399 \rightarrow 00:09:06.379$ histones actually passed through

NOTE Confidence: 0.79615179875

 $00:09:06.379 \rightarrow 00:09:08.898$ into the into the early embryo.

NOTE Confidence: 0.940186819411765

 $00{:}09{:}11.610 \dashrightarrow 00{:}09{:}15.012$ So in complete counterpoint to the extent

NOTE Confidence: 0.940186819411765

 $00:09:15.012 \longrightarrow 00:09:18.316$ 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

 $00:09:23.624 \rightarrow 00:09:27.302$ that phenotype can be affected by paternal

NOTE Confidence: 0.940186819411765

 $00:09:27.302 \rightarrow 00:09:30.510$ experience or by parental experience.

NOTE Confidence: 0.940186819411765

 $00:09:30.510 \longrightarrow 00:09:32.175$ And what I'm showing here

NOTE Confidence: 0.940186819411765

 $00{:}09{:}32.175 \dashrightarrow 00{:}09{:}33.507$ are two classic examples.

NOTE Confidence: 0.940186819411765

 $00{:}09{:}33.510 \dashrightarrow 00{:}09{:}36.780$ These are phenotypes that are actually

NOTE Confidence: 0.940186819411765

 $00:09:36.780 \dashrightarrow 00:09:39.910$ conveyed generally by DNA methylation.

 $00:09:39.910 \longrightarrow 00:09:42.451$ 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 agout
i viable yellow

NOTE Confidence: 0.940186819411765

 $00:09:47.758 \dashrightarrow 00:09:51.265$ which is an allele of the agouti gene that

NOTE Confidence: 0.940186819411765

 $00:09:51.265 \dashrightarrow 00:09:53.878$ affects coat color among other things.

NOTE Confidence: 0.940186819411765

 $00:09:53.880 \rightarrow 00:09:56.472$ And these mice are all genetically

NOTE Confidence: 0.940186819411765

 $00:09:56.472 \rightarrow 00:09:58.662$ identical but carry different levels

NOTE Confidence: 0.940186819411765

 $00:09:58.662 \rightarrow 00:10:00.972$ of DNA methylation at this locus

NOTE Confidence: 0.940186819411765

 $00{:}10{:}00{.}972 \dashrightarrow 00{:}10{:}03{.}349$ which affects the extent to which

NOTE Confidence: 0.940186819411765

 $00:10:03.349 \rightarrow 00:10:05.647$ they they express or don't express.

NOTE Confidence: 0.940186819411765

 $00:10:05.650 \longrightarrow 00:10:08.920$ This brown agouti coat color.

NOTE Confidence: 0.940186819411765

 $00{:}10{:}08{.}920 \dashrightarrow 00{:}10{:}12{.}756$ And it turns out that the maternal

NOTE Confidence: 0.940186819411765

 $00{:}10{:}12{.}760 \dashrightarrow 00{:}10{:}15{.}714$ epigenetic state can affect the chances of

NOTE Confidence: 0.940186819411765

 $00:10:15.714 \rightarrow 00:10:18.215$ the offspring having the same epigenetic

NOTE Confidence: 0.940186819411765

 $00{:}10{:}18{.}215 \dashrightarrow 00{:}10{:}20{.}931$ state and having a similar code color.

NOTE Confidence: 0.940186819411765

 $00:10:20.940 \longrightarrow 00:10:21.634$ These again,

 $00:10:21.634 \rightarrow 00:10:24.063$ this has nothing to do with being

NOTE Confidence: 0.940186819411765

 $00:10:24.063 \rightarrow 00:10:25.827$ encoded in the genome itself.

NOTE Confidence: 0.940186819411765

 $00:10:25.830 \longrightarrow 00:10:28.054$ So this is a maternal effect just to

NOTE Confidence: 0.940186819411765

 $00:10:28.054 \rightarrow 00:10:30.600$ show you that it's not only maternal is.

NOTE Confidence: 0.940186819411765

 $00{:}10{:}30{.}600 \dashrightarrow 00{:}10{:}32{.}712$ Similar effects can be seen and

NOTE Confidence: 0.940186819411765

 $00:10:32.712 \longrightarrow 00:10:34.120$ another locust called Accent,

NOTE Confidence: 0.940186819411765

 $00{:}10{:}34{.}120 \dashrightarrow 00{:}10{:}36{.}465$ and this causes a kick tail and

NOTE Confidence: 0.940186819411765

 $00{:}10{:}36.465 \dashrightarrow 00{:}10{:}38.209$ can be transmitted either from

NOTE Confidence: 0.940186819411765

 $00:10:38.209 \longrightarrow 00:10:40.219$ a father or from the mother.

NOTE Confidence: 0.940186819411765

00:10:40.220 --> 00:10:40.750 Uhm?

NOTE Confidence: 0.842131356153846

 $00:10:43.210 \longrightarrow 00:10:45.148$ A whole pile of other studies

NOTE Confidence: 0.842131356153846

 $00:10:45.148 \rightarrow 00:10:47.450$ has looked at this kind of thing,

NOTE Confidence: 0.842131356153846

 $00:10:47.450 \longrightarrow 00:10:49.676$ not just in terms of morphology

NOTE Confidence: 0.842131356153846

 $00{:}10{:}49.676 \dashrightarrow 00{:}10{:}52.218$ and coat color, but in terms of

NOTE Confidence: 0.842131356153846

 $00{:}10{:}52{.}218$ --> $00{:}10{:}54{.}003$ things like metabolism and behavior.

 $00:10:54.010 \rightarrow 00:10:56.250$ So I'm showing here a couple of the

NOTE Confidence: 0.842131356153846

 $00:10:56.250 \rightarrow 00:10:58.276$ most common types of phenotypes that

NOTE Confidence: 0.842131356153846

 $00{:}10{:}58.276 \dashrightarrow 00{:}11{:}00.382$ 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

 $00:11:02.170 \longrightarrow 00:11:03.950$ one is paternal diet,

NOTE Confidence: 0.842131356153846

 $00{:}11{:}03{.}950 \dashrightarrow 00{:}11{:}07{.}873$ so a high fat diet in the father can

NOTE Confidence: 0.842131356153846

 $00:11:07.873 \longrightarrow 00:11:10.351$ 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

 $00:11:12.490 \rightarrow 00:11:15.802$ This is an example from a paper in 2015.

NOTE Confidence: 0.842131356153846

 $00{:}11{:}15{.}810 \dashrightarrow 00{:}11{:}18{.}057$ 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

 $00{:}11{:}19{.}930 \dashrightarrow 00{:}11{:}23{.}374$ so here's an example where a father

NOTE Confidence: 0.842131356153846

 $00{:}11{:}23.374 \dashrightarrow 00{:}11{:}26.188$ exposed to nicotine has offspring that

NOTE Confidence: 0.842131356153846

 $00{:}11{:}26.188 \dashrightarrow 00{:}11{:}28.864$ actually are better at processing nicotine.

NOTE Confidence: 0.842131356153846

 $00:11:28.870 \rightarrow 00:11:30.890$ So this is actually survival.

NOTE Confidence: 0.842131356153846

 $00:11:30.890 \rightarrow 00:11:34.236$ Or if you give them toxic doses.

 $00:11:34.240 \rightarrow 00:11:36.550$ The offspring of exposed fathers are

NOTE Confidence: 0.842131356153846

 $00{:}11{:}36{.}550 \dashrightarrow 00{:}11{:}39{.}015$ better able to process those doses

NOTE Confidence: 0.842131356153846

 $00:11:39.015 \rightarrow 00:11:41.160$ and survive compared to offspring.

NOTE Confidence: 0.842131356153846

 $00{:}11{:}41{.}160 \dashrightarrow 00{:}11{:}42{.}588$ 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

 $00{:}11{:}44.806 \dashrightarrow 00{:}11{:}48.092$ addictive behaviors and and and

NOTE Confidence: 0.842131356153846

 $00:11:48.092 \rightarrow 00:11:51.440$ responses to to drugs at that level.

NOTE Confidence: 0.842131356153846

 $00:11:51.440 \rightarrow 00:11:52.770$ And then finally there are a number

NOTE Confidence: 0.842131356153846

 $00{:}11{:}52.770 \dashrightarrow 00{:}11{:}54.317$ of ways you can stress out a mouse.

NOTE Confidence: 0.842131356153846

 $00:11:54.320 \longrightarrow 00:11:56.865$ 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

 $00{:}11{:}59{.}486 \dashrightarrow 00{:}12{:}02{.}042$ of stressed out fathers tend to

NOTE Confidence: 0.842131356153846

 $00{:}12{:}02{.}042 \dashrightarrow 00{:}12{:}04{.}247$ have altered responses to stress.

NOTE Confidence: 0.842131356153846

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

NOTE Confidence: 0.842131356153846

 $00{:}12{:}04{.}901 \dashrightarrow 00{:}12{:}09{.}458$ a lower a smaller increase in cortisone

 $00:12:09.460 \longrightarrow 00:12:12.043$ following a stressful event and in some

NOTE Confidence: 0.842131356153846

 $00:12:12.043 \rightarrow 00:12:15.037$ cases they have behavioral changes as well.

NOTE Confidence: 0.842131356153846

 $00:12:15.040 \longrightarrow 00:12:16.750$ So this is all in rodents.

NOTE Confidence: 0.842131356153846

 $00{:}12{:}16.750 \dashrightarrow 00{:}12{:}18.545$ This has been looked at

NOTE Confidence: 0.842131356153846

 $00:12:18.545 \longrightarrow 00:12:20.340$ to some extent in humans,

NOTE Confidence: 0.842131356153846

 $00{:}12{:}20{.}340 \dashrightarrow 00{:}12{:}23{.}105$ although obviously it's harder to do these

NOTE Confidence: 0.842131356153846

 $00:12:23.105 \rightarrow 00:12:25.488$ kinds of experiments in human subjects.

NOTE Confidence: 0.842131356153846

 $00:12:25.490 \longrightarrow 00:12:28.340$ The best examples are in.

NOTE Confidence: 0.842131356153846

 $00{:}12{:}28{.}340 \dashrightarrow 00{:}12{:}31{.}316$ One example is in a cohort from Sweden

NOTE Confidence: 0.842131356153846

 $00:12:31.316 \rightarrow 00:12:34.008$ from the 19th century where they

NOTE Confidence: 0.842131356153846

 $00:12:34.008 \longrightarrow 00:12:36.810$ had very careful records of harvest

NOTE Confidence: 0.842131356153846

 $00:12:36.810 \longrightarrow 00:12:40.990$ yields and health outcomes overtime,

NOTE Confidence: 0.842131356153846

 $00{:}12{:}40{.}990 \dashrightarrow 00{:}12{:}43{.}798$ and in that study their studies from the

NOTE Confidence: 0.842131356153846

 $00:12:43.798 \longrightarrow 00:12:46.459$ early 2000s they were able to show that.

NOTE Confidence: 0.842131356153846

 $00:12:46.460 \rightarrow 00:12:50.528$ Good nutrition in the paternal granfather

NOTE Confidence: 0.842131356153846

 $00{:}12{:}50{.}528$ --> $00{:}12{:}53{.}240$ resulted in increased cardiovascular

 $00:12:53.332 \rightarrow 00:12:56.547$ events and diabetes in grandchildren.

NOTE Confidence: 0.842131356153846

 $00{:}12{:}56{.}550 \dashrightarrow 00{:}12{:}59{.}558$ This is a follow-up study that was done

NOTE Confidence: 0.842131356153846

 $00{:}12{:}59{.}558 \dashrightarrow 00{:}13{:}02{.}271$ more recently in a cohort of almost

NOTE Confidence: 0.842131356153846

 $00:13:02.271 \rightarrow 00:13:04.350 \ 30,000$ people over three generations,

NOTE Confidence: 0.842131356153846

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

NOTE Confidence: 0.842131356153846

 $00{:}13{:}05.670 \dashrightarrow 00{:}13{:}08.582$ and here they actually see an effect on

NOTE Confidence: 0.842131356153846

 $00:13:08.582 \rightarrow 00:13:11.470$ 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

 $00:13:13.798 \rightarrow 00:13:18.105$ have 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

 $00{:}13{:}23.810 \dashrightarrow 00{:}13{:}25.220$ So.

NOTE Confidence: 0.842131356153846

 $00{:}13{:}25{.}220 \dashrightarrow 00{:}13{:}27{.}621$ 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

 $00{:}13{:}29{.}333 \dashrightarrow 00{:}13{:}31{.}496$ health of progeny appears to be yes,

 $00:13:31.500 \longrightarrow 00:13:32.068$ but.

NOTE Confidence: 0.842131356153846

 $00:13:32.068 \rightarrow 00:13:35.476$ The molecular mechanism by which these

NOTE Confidence: 0.842131356153846

 $00:13:35.476 \rightarrow 00:13:37.913$ these experiences are transmitted

NOTE Confidence: 0.842131356153846

 $00:13:37.913 \rightarrow 00:13:41.735$ remains a pretty significant black box,

NOTE Confidence: 0.842131356153846

 $00:13:41.740 \longrightarrow 00:13:43.844$ and so we're trying to get at these

NOTE Confidence: 0.842131356153846

 $00{:}13{:}43{.}844 \dashrightarrow 00{:}13{:}45{.}661$ questions of what information is

NOTE Confidence: 0.842131356153846

 $00:13:45.661 \rightarrow 00:13:47.716$ transmitted and whether it's meaningful,

NOTE Confidence: 0.842131356153846

 $00{:}13{:}47.720 \dashrightarrow 00{:}13{:}49.652$ and we've decided to do this

NOTE Confidence: 0.842131356153846

 $00:13:49.652 \longrightarrow 00:13:50.940$ by simplifying the system.

NOTE Confidence: 0.842131356153846

 $00{:}13{:}50{.}940 \dashrightarrow 00{:}13{:}53{.}873$ So rather than expose then making an

NOTE Confidence: 0.842131356153846

 $00{:}13{:}53.873 \dashrightarrow 00{:}13{:}55.529$ environmental exposure change like

NOTE Confidence: 0.842131356153846

 $00{:}13{:}55{.}529 \dashrightarrow 00{:}13{:}57{.}509$ 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

 $00:13:59.484 \longrightarrow 00:14:01.619$ change where we have a little bit

NOTE Confidence: 0.842131356153846

 $00{:}14{:}01.620 \dashrightarrow 00{:}14{:}03.678$ 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
- $00{:}14{:}06{.}954 \dashrightarrow 00{:}14{:}09{.}438$ then evaluate what those effects are
- NOTE Confidence: 0.842131356153846
- $00:14:09.438 \longrightarrow 00:14:12.388$ 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
- $00:14:14.908 \rightarrow 00:14:17.530$ the way. So here is our strategy.
- NOTE Confidence: 0.935687288636364
- $00:14:17.530 \rightarrow 00:14:19.480$ Make the make a genetic change.
- NOTE Confidence: 0.935687288636364
- $00{:}14{:}19{.}480 \dashrightarrow 00{:}14{:}22{.}531$ In my father we examine the sperm and we
- NOTE Confidence: 0.935687288636364
- $00:14:22.531 \rightarrow 00:14:25.160$ examine the offspring within this firm.
- NOTE Confidence: 0.935687288636364
- $00{:}14{:}25{.}160 \dashrightarrow 00{:}14{:}27{.}740$ There are three main modalities of
- NOTE Confidence: 0.935687288636364
- $00{:}14{:}27.740 \dashrightarrow 00{:}14{:}30.298$ epigenetic information that will look at.
- NOTE Confidence: 0.935687288636364
- $00:14:30.300 \longrightarrow 00:14:31.170$ One is small.
- NOTE Confidence: 0.935687288636364
- $00:14:31.170 \longrightarrow 00:14:33.525$ RNA is so actually this is something that
- NOTE Confidence: 0.935687288636364
- $00{:}14{:}33{.}525 \dashrightarrow 00{:}14{:}35{.}874$ we in my lab had paid less attention to.
- NOTE Confidence: 0.935687288636364
- $00:14:35.880 \longrightarrow 00:14:36.755$ Although there are plenty of
- NOTE Confidence: 0.935687288636364
- $00{:}14{:}36.755 \dashrightarrow 00{:}14{:}37.630$ other people in the field,
- NOTE Confidence: 0.935687288636364
- $00{:}14{:}37.630 \dashrightarrow 00{:}14{:}40.450$ but I've looked at from DNA metalation
- NOTE Confidence: 0.935687288636364

 $00{:}14{:}40{.}450 \dashrightarrow 00{:}14{:}43{.}810$ so it could be like modifications to

NOTE Confidence: 0.935687288636364

 $00{:}14{:}43{.}810 \dashrightarrow 00{:}14{:}47{.}492$ 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

 $00:14:50.450 \rightarrow 00:14:52.662$ so we're taking advantage of the fact

NOTE Confidence: 0.935687288636364

 $00{:}14{:}52.662 \dashrightarrow 00{:}14{:}54.928$ that males have only One X chromosome

NOTE Confidence: 0.935687288636364

 $00{:}14{:}54{.}930 \dashrightarrow 00{:}14{:}58{.}008$ and that the X chromosome encodes

NOTE Confidence: 0.935687288636364

 $00:14:58.008 \rightarrow 00:15:01.150$ a variety of epigenetic regulators.

NOTE Confidence: 0.935687288636364

 $00:15:01.150 \longrightarrow 00:15:03.154$ So if we delete and epigenetic

NOTE Confidence: 0.935687288636364

 $00{:}15{:}03{.}154 \dashrightarrow 00{:}15{:}05{.}990$ regulator on the X chromosome in a male,

NOTE Confidence: 0.935687288636364

 $00{:}15{:}05{.}990 \dashrightarrow 00{:}15{:}08{.}828$ we make a complete knock out and we

NOTE Confidence: 0.935687288636364

 $00{:}15{:}08.828 \dashrightarrow 00{:}15{:}11.042$ knock that we crossed that mail

NOTE Confidence: 0.935687288636364

 $00:15:11.042 \rightarrow 00:15:14.270$ to a genetically wildtype female.

NOTE Confidence: 0.935687288636364

 $00{:}15{:}14.270 \dashrightarrow 00{:}15{:}16.382$ 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

 $00{:}15{:}18{.}406 \dashrightarrow 00{:}15{:}20{.}562$ Offspring of that cross are going to

NOTE Confidence: 0.935687288636364

 $00{:}15{:}20.562 \dashrightarrow 00{:}15{:}22.853$ get a normal X chromosome from their

- NOTE Confidence: 0.935687288636364
- $00{:}15{:}22.853 \dashrightarrow 00{:}15{:}24.963$ mother and a normal Y chromosome
- NOTE Confidence: 0.935687288636364
- $00{:}15{:}24{.}963 \dashrightarrow 00{:}15{:}26{.}109$ from their father.
- NOTE Confidence: 0.935687288636364
- $00:15:26.110 \longrightarrow 00:15:28.378$ Even though the father was a
- NOTE Confidence: 0.935687288636364
- $00:15:28.378 \rightarrow 00:15:30.380$ complete knockout for this scene.
- NOTE Confidence: 0.935687288636364
- $00{:}15{:}30{.}380 \dashrightarrow 00{:}15{:}32{.}462$ Which means we can evaluate the
- NOTE Confidence: 0.935687288636364
- $00{:}15{:}32{.}462 \dashrightarrow 00{:}15{:}34{.}876$ phenotype of these F1 males and if
- NOTE Confidence: 0.935687288636364
- $00:15:34.876 \rightarrow 00:15:37.116$ we see a phenotype that implies that
- NOTE Confidence: 0.935687288636364
- $00:15:37.191 \rightarrow 00:15:39.543$ it's a result of epigenetic changes
- NOTE Confidence: 0.935687288636364
- $00{:}15{:}39{.}543 \dashrightarrow 00{:}15{:}41{.}854$ in the paternal germline rather than
- NOTE Confidence: 0.935687288636364
- $00:15:41.854 \rightarrow 00:15:43.689$ genetic changes that are inherited.
- NOTE Confidence: 0.795618613
- $00:15:46.600 \rightarrow 00:15:47.912$ As a genetic target,
- NOTE Confidence: 0.795618613
- $00:15:47.912 \rightarrow 00:15:49.880$ 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
- $00{:}15{:}51{.}620 \dashrightarrow 00{:}15{:}54{.}788$ and you may see that name pop up later
- NOTE Confidence: 0.795618613
- $00{:}15{:}54.788 \dashrightarrow 00{:}15{:}57.580$ 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

 $00{:}15{:}59{.}440 \dashrightarrow 00{:}16{:}01{.}798$ so it meets our first criterion.

NOTE Confidence: 0.795618613

 $00{:}16{:}01.800 \dashrightarrow 00{:}16{:}04.260$ It's also a well established

NOTE Confidence: 0.795618613

 $00:16:04.260 \rightarrow 00:16:05.244$ chromatin regulator,

NOTE Confidence: 0.795618613

 $00{:}16{:}05{.}250 \dashrightarrow 00{:}16{:}08{.}010$ and we know a specific enzymatic

NOTE Confidence: 0.795618613

 $00:16:08.010 \longrightarrow 00:16:10.509$ activity that this gene has it.

NOTE Confidence: 0.795618613

 $00:16:10.510 \longrightarrow 00:16:12.382$ See methylates metalation

NOTE Confidence: 0.795618613

 $00:16:12.382 \longrightarrow 00:16:16.126$ at Lysine 27 of histone H3.

NOTE Confidence: 0.795618613

 $00{:}16{:}16{.}130 \dashrightarrow 00{:}16{:}18{.}489$ This is a well studied histone modification

NOTE Confidence: 0.795618613

 $00:16:18.489 \rightarrow 00:16:21.509$ and a well established enzymatic activity.

NOTE Confidence: 0.795618613

 $00:16:21.510 \longrightarrow 00:16:22.647$ For this protein.

NOTE Confidence: 0.795618613

 $00{:}16{:}22.647 \dashrightarrow 00{:}16{:}25.951$ We also know that it has non non

NOTE Confidence: 0.795618613

 $00:16:25.951 \rightarrow 00:16:28.756$ enzymatic effects on chromatin so

NOTE Confidence: 0.795618613

 $00{:}16{:}28.756 \dashrightarrow 00{:}16{:}31.540$ it regulates enhancer assembly by

NOTE Confidence: 0.795618613

 $00:16:31.540 \dashrightarrow 00:16:33.810$ by interacting with a complex.

NOTE Confidence: 0.795618613

 $00:16:33.810 \longrightarrow 00:16:36.250$ That place is a different

- NOTE Confidence: 0.795618613
- $00:16:36.250 \longrightarrow 00:16:37.226$ chromatin modification.
- NOTE Confidence: 0.795618613
- $00:16:37.230 \longrightarrow 00:16:39.430$ These are both relatively well
- NOTE Confidence: 0.795618613
- $00:16:39.430 \longrightarrow 00:16:41.630$ defined functions for this protein
- NOTE Confidence: 0.795618613
- $00:16:41.701 \longrightarrow 00:16:43.829$ and gives us some hope of being
- NOTE Confidence: 0.795618613
- $00{:}16{:}43.829 \dashrightarrow 00{:}16{:}46.239$ able to trace this molecular chain.
- NOTE Confidence: 0.795618613
- $00{:}16{:}46.240 \dashrightarrow 00{:}16{:}49.630$ From sperm to the next generation.
- NOTE Confidence: 0.795618613
- $00:16:49.630 \longrightarrow 00:16:51.850$ We also know that UTX is
- NOTE Confidence: 0.795618613
- $00:16:51.850 \longrightarrow 00:16:52.590$ biologically significant.
- NOTE Confidence: 0.795618613
- $00{:}16{:}52{.}590 \dashrightarrow 00{:}16{:}54{.}374$ It's a developmental regulator.
- NOTE Confidence: 0.795618613
- $00{:}16{:}54{.}374 \dashrightarrow 00{:}16{:}56{.}604$ It's been implicated in cardiac
- NOTE Confidence: 0.795618613
- $00{:}16{:}56{.}604 \dashrightarrow 00{:}16{:}58{.}762$ development and in about police this and
- NOTE Confidence: 0.795618613
- $00{:}16{:}58.762 \dashrightarrow 00{:}17{:}01.049$ we know that it's a tumor suppressor,
- NOTE Confidence: 0.795618613
- $00{:}17{:}01.050 \dashrightarrow 00{:}17{:}02.730$ 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
- $00{:}17{:}04.592 \dashrightarrow 00{:}17{:}08.688$ So, uhm, here's how we set this up.
- NOTE Confidence: 0.795618613

 $00{:}17{:}08.690 \dashrightarrow 00{:}17{:}10.874$ For those of you who are interested

NOTE Confidence: 0.795618613

 $00{:}17{:}10.874 \dashrightarrow 00{:}17{:}11.810$ in the details,

NOTE Confidence: 0.795618613

 $00{:}17{:}11.810 \dashrightarrow 00{:}17{:}13.970$ we set this up as a conditional knock out.

NOTE Confidence: 0.795618613

 $00:17:13.970 \rightarrow 00:17:16.742$ So the TX is deleted only in the germline,

NOTE Confidence: 0.795618613

 $00{:}17{:}16.750 \dashrightarrow 00{:}17{:}19.318$ not in the somatic tissue of the parents,

NOTE Confidence: 0.795618613

 $00{:}17{:}19{.}320 \dashrightarrow 00{:}17{:}21{.}635$ which reduces the possibility of

NOTE Confidence: 0.795618613

 $00:17:21.635 \rightarrow 00:17:23.950$ having secondary or indirect effects.

NOTE Confidence: 0.795618613

 $00{:}17{:}23.950 \dashrightarrow 00{:}17{:}26.960$ And we're using a creed that that is

NOTE Confidence: 0.795618613

 $00{:}17{:}26.960 \dashrightarrow 00{:}17{:}29.865$ basically complete to the excision by birth,

NOTE Confidence: 0.795618613

 $00{:}17{:}29.870 \dashrightarrow 00{:}17{:}33.664$ so U TX is lost throughout surmounted

NOTE Confidence: 0.795618613

 $00:17:33.664 \rightarrow 00:17:35.230$ Genesis from starting from.

NOTE Confidence: 0.795618613

 $00:17:35.230 \rightarrow 00:17:38.130$ Very early in the lifetime of the animal.

NOTE Confidence: 0.795618613

 $00:17:38.130 \longrightarrow 00:17:39.780$ Uhm?

NOTE Confidence: 0.795618613

 $00{:}17{:}39{.}780 \dashrightarrow 00{:}17{:}42{.}860$ We can confirm that this knock out it's

NOTE Confidence: 0.795618613

 $00:17:42.860 \dashrightarrow 00:17:45.267$ complete using Western blot for UT X.

NOTE Confidence: 0.795618613

 $00:17:45.270 \rightarrow 00:17:47.403$ There's a tiny bit of a residual band here,

- NOTE Confidence: 0.795618613
- $00:17:47.410 \longrightarrow 00:17:48.754$ and that's because this is done
- NOTE Confidence: 0.795618613
- $00:17:48.754 \longrightarrow 00:17:49.426$ on whole testis,
- NOTE Confidence: 0.795618613
- $00:17:49.430 \longrightarrow 00:17:52.246$ which has some somatic tissue which
- NOTE Confidence: 0.795618613
- $00:17:52.246 \longrightarrow 00:17:55.390$ therefore still expresses UTX.
- NOTE Confidence: 0.795618613
- $00:17:55.390 \rightarrow 00:17:58.046$ 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
- $00:17:58.614 \rightarrow 00:18:01.434$ 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
- $00:18:06.586 \rightarrow 00:18:08.698$ 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
- $00{:}18{:}11{.}610 \dashrightarrow 00{:}18{:}14{.}233$ which will be shown as Cao and
- NOTE Confidence: 0.795618613
- $00:18:14.233 \rightarrow 00:18:17.148$ the tubules are pretty identical.
- NOTE Confidence: 0.795618613
- $00{:}18{:}17{.}150 \dashrightarrow 00{:}18{:}19{.}100$ They contain all the different
- NOTE Confidence: 0.795618613
- $00:18:19.100 \longrightarrow 00:18:21.812$ fault mental cell types in this
- NOTE Confidence: 0.795618613

 $00:18:21.812 \rightarrow 00:18:23.867$ developing seminiferous epithelium.

NOTE Confidence: 0.795618613

 $00{:}18{:}23.870 \dashrightarrow 00{:}18{:}26.208$ Sperm look normal and the numbers of

NOTE Confidence: 0.795618613

 $00{:}18{:}26.208 \dashrightarrow 00{:}18{:}28.518$ sperm are about the same and these

NOTE Confidence: 0.795618613

 $00:18:28.518 \rightarrow 00:18:31.209$ minds can produce pops at the same levels.

NOTE Confidence: 0.795618613

 $00:18:31.210 \longrightarrow 00:18:32.194$ So this is.

NOTE Confidence: 0.795618613

 $00{:}18{:}32{.}194 \dashrightarrow 00{:}18{:}34{.}871$ This is whatever we see is not due

NOTE Confidence: 0.795618613

 $00:18:34.871 \rightarrow 00:18:37.344$ 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

 $00{:}18{:}40.882 \dashrightarrow 00{:}18{:}43.136$ so then we start to look at

NOTE Confidence: 0.795618613

 $00{:}18{:}43.136 \dashrightarrow 00{:}18{:}45.195$ offspring and the first thing that

NOTE Confidence: 0.795618613

 $00{:}18{:}45{.}195 \dashrightarrow 00{:}18{:}47{.}346$ we noticed was that offspring of

NOTE Confidence: 0.795618613

 $00{:}18{:}47{.}346 \dashrightarrow 00{:}18{:}49{.}440$ 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

 $00:18:51.500 \longrightarrow 00:18:53.732$ so they make it out to about a year.

NOTE Confidence: 0.795618613

 $00:18:53.740 \rightarrow 00:18:55.728$ But then they start dying and then

 $00:18:55.728 \longrightarrow 00:18:57.423$ another cohort of them lives a

NOTE Confidence: 0.795618613

 $00:18:57.423 \longrightarrow 00:18:58.995$ little bit longer and then dies

NOTE Confidence: 0.795618613

 $00{:}18{:}58{.}995 \dashrightarrow 00{:}19{:}00{.}784$ out in about a year and a half.

NOTE Confidence: 0.795618613

 $00:19:00.790 \longrightarrow 00:19:03.210$ 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: 0.87411857777778

 $00:19:09.350 \longrightarrow 00:19:11.730$ We also did this in an inbred

NOTE Confidence: 0.874118577777778

 $00{:}19{:}11.730 \dashrightarrow 00{:}19{:}14.249$ 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

 $00:19:16.820 \rightarrow 00:19:18.764$ The shape of the curve is actually the same,

NOTE Confidence: 0.87411857777778

 $00{:}19{:}18{.}770 \dashrightarrow 00{:}19{:}21{.}767$ so there's a drop off around the year and

NOTE Confidence: 0.87411857777778

 $00{:}19{:}21.767 \dashrightarrow 00{:}19{:}24.414$ another set of deaths a little bit later.

NOTE Confidence: 0.874118577777778

 $00{:}19{:}24{.}420 \dashrightarrow 00{:}19{:}26{.}244$ And then of course, what we want to

NOTE Confidence: 0.874118577777778

 $00{:}19{:}26{.}244 \dashrightarrow 00{:}19{:}28{.}206$ do is look into what's going on.

 $00:19:28.210 \rightarrow 00:19:29.386$ What's causing these deaths,

NOTE Confidence: 0.874118577777778

 $00:19:29.386 \longrightarrow 00:19:31.468$ and to do that we took each

NOTE Confidence: 0.874118577777778

 $00:19:31.468 \rightarrow 00:19:33.246$ 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

 $00{:}19{:}34{.}970 \dashrightarrow 00{:}19{:}39{.}638$ sampling each of about 12 tissues.

NOTE Confidence: 0.87411857777778

 $00{:}19{:}39{.}640 \dashrightarrow 00{:}19{:}41{.}476$ And I'll tell you right away,

NOTE Confidence: 0.874118577777778

 $00:19:41.480 \longrightarrow 00:19:43.358$ we actually have no idea what's

NOTE Confidence: 0.87411857777778

 $00:19:43.358 \longrightarrow 00:19:45.250$ causing this first set of deaths.

NOTE Confidence: 0.87411857777778

 $00{:}19{:}45{.}250 \dashrightarrow 00{:}19{:}48{.}458$ These mice drop dead overnight and

NOTE Confidence: 0.874118577777778

 $00:19:48.458 \rightarrow 00:19:51.668$ don't appear to have any histologic

NOTE Confidence: 0.874118577777778

 $00{:}19{:}51.668 \dashrightarrow 00{:}19{:}54.740$ differences relative to controls.

NOTE Confidence: 0.874118577777778

 $00:19:54.740 \longrightarrow 00:19:56.840$ But in the second set of dots,

NOTE Confidence: 0.874118577777778

 $00:19:56.840 \rightarrow 00:19:58.376$ we found something interesting,

NOTE Confidence: 0.87411857777778

 $00:19:58.376 \rightarrow 00:20:01.128$ so this is just raw data showing

NOTE Confidence: 0.874118577777778

 $00:20:01.128 \longrightarrow 00:20:02.259$ counts by age,

NOTE Confidence: 0.87411857777778

 $00:20:02.260 \longrightarrow 00:20:04.020$ and obviously the controls guide

 $00{:}20{:}04.020 \dashrightarrow 00{:}20{:}06.274$ to the controls also have various

NOTE Confidence: 0.87411857777778

 $00:20:06.274 \rightarrow 00:20:08.770$ issues because they're just old mice.

NOTE Confidence: 0.87411857777778

00:20:08.770 --> 00:20:10.033 But most strikingly,

NOTE Confidence: 0.874118577777778

 $00{:}20{:}10.033 \dashrightarrow 00{:}20{:}12.980$ and there was a substantial increase in

NOTE Confidence: 0.874118577777778

 $00:20:13.053 \rightarrow 00:20:15.805$ the number of tumors we found in offspring

NOTE Confidence: 0.87411857777778

00:20:15.805 --> 00:20:18.739 of JTX knockouts compared to controls.

NOTE Confidence: 0.874118577777778

 $00:20:18.740 \longrightarrow 00:20:20.380$ And this is tumors found

NOTE Confidence: 0.87411857777778

 $00:20:20.380 \longrightarrow 00:20:21.364$ across multiple tissues.

NOTE Confidence: 0.87411857777778

 $00:20:21.370 \longrightarrow 00:20:23.890$ The most common that we saw in

NOTE Confidence: 0.874118577777778

 $00:20:23.890 \rightarrow 00:20:25.192$ histiocytic sarcoma, and then,

NOTE Confidence: 0.874118577777778

 $00:20:25.192 \longrightarrow 00:20:26.647$ which is common in mice.

NOTE Confidence: 0.87411857777778

00:20:26.650 --> 00:20:29.850 But we saw many more in EU TX

NOTE Confidence: 0.87411857777778

 $00{:}20{:}29{.}850 \dashrightarrow 00{:}20{:}31{.}490$ offspring compared to controls.

NOTE Confidence: 0.87411857777778

 $00{:}20{:}31{.}490 \dashrightarrow 00{:}20{:}33{.}524$ And then the next most common

NOTE Confidence: 0.874118577777778

 $00{:}20{:}33{.}524$ --> $00{:}20{:}35{.}250$ are cellular carcinoma and lung.

00:20:35.250 --> 00:20:36.045 Various lung tumors,

NOTE Confidence: 0.87411857777778

 $00{:}20{:}36{.}045 \dashrightarrow 00{:}20{:}37{.}900$ which I will also come back to

NOTE Confidence: 0.87411857777778

 $00{:}20{:}37{.}956 \dashrightarrow 00{:}20{:}38{.}836$ a bit at the end.

NOTE Confidence: 0.33267832

 $00:20:41.290 \longrightarrow 00:20:44.185$ Uhm? So that was very interesting

NOTE Confidence: 0.33267832

 $00{:}20{:}44.185 \dashrightarrow 00{:}20{:}46.019$ 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

 $00{:}20{:}47{.}380 \dashrightarrow 00{:}20{:}49{.}720$ 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

 $00:20:51.790 \rightarrow 00:20:54.769$ but basically we set it up so that we NOTE Confidence: 0.33267832

 $00{:}20{:}54.769 \dashrightarrow 00{:}20{:}57.835$ could look at F2 mice that were the NOTE Confidence: 0.33267832

 $00{:}20{:}57.835 \dashrightarrow 00{:}20{:}59.950$ product of two successive generations NOTE Confidence: 0.33267832

 $00:21:00.025 \rightarrow 00:21:02.244$ of loss of BTX in the germline.

NOTE Confidence: 0.33267832

 $00:21:02.250 \longrightarrow 00:21:03.414$ So in other words,

NOTE Confidence: 0.33267832

 $00:21:03.414 \rightarrow 00:21:05.689$ the germ cells never have a chance

NOTE Confidence: 0.33267832

 $00{:}21{:}05{.}689 \dashrightarrow 00{:}21{:}08{.}009$ to reset their epigenetic information

NOTE Confidence: 0.33267832

 $00:21:08.010 \rightarrow 00:21:10.345$ because you taxes is continually

- NOTE Confidence: 0.33267832
- $00:21:10.345 \rightarrow 00:21:12.680$ lost across these two generations.
- NOTE Confidence: 0.858737492857143
- $00:21:16.170 \longrightarrow 00:21:18.249$ When we look at these F2 mice,
- NOTE Confidence: 0.858737492857143
- $00:21:18.250 \longrightarrow 00:21:22.016$ we see a similar reduction in lifespan.
- NOTE Confidence: 0.858737492857143
- $00:21:22.020 \longrightarrow 00:21:24.636$ Uhm, and the similar sort
- NOTE Confidence: 0.858737492857143
- $00{:}21{:}24.636 \dashrightarrow 00{:}21{:}27.360$ of shape overall of the curve.
- NOTE Confidence: 0.858737492857143
- $00:21:27.360 \rightarrow 00:21:30.520$ 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
- $00{:}21{:}33{.}120 \dashrightarrow 00{:}21{:}35{.}160$ And again we saw a significant
- NOTE Confidence: 0.858737492857143
- $00:21:35.160 \longrightarrow 00:21:37.262$ increase in the in the numbers
- NOTE Confidence: 0.858737492857143
- $00:21:37.262 \longrightarrow 00:21:39.586$ 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
- $00:21:40.596 \rightarrow 00:21:44.620$ although the overall tumor rate was about the
- NOTE Confidence: 0.858737492857143
- $00:21:44.701 \rightarrow 00:21:48.157$ 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
- $00:21:51.028 \longrightarrow 00:21:54.009$ in the severity of the tumors.
- NOTE Confidence: 0.858737492857143

 $00:21:54.010 \rightarrow 00:21:56.178$ So we see a lot more aggressive tumors

NOTE Confidence: 0.858737492857143

 $00{:}21{:}56{.}178 \dashrightarrow 00{:}21{:}58{.}945$ and F and F2 minutes compared to F1 mice.

NOTE Confidence: 0.858737492857143

 $00{:}21{:}58{.}950 \dashrightarrow 00{:}22{:}00{.}670$ 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

 $00{:}22{:}03.830 \dashrightarrow 00{:}22{:}07.850$ each individual mouse has more tumors.

NOTE Confidence: 0.858737492857143

 $00:22:07.850 \longrightarrow 00:22:09.620$ And, and here we're counting

NOTE Confidence: 0.858737492857143

00:22:09.620 --> 00:22:10.328 independent tumors,

NOTE Confidence: 0.858737492857143

 $00{:}22{:}10{.}330 \dashrightarrow 00{:}22{:}11{.}850$ either within the same teacher

NOTE Confidence: 0.858737492857143

 $00{:}22{:}11.850 \dashrightarrow 00{:}22{:}13.066$ or in multiple tissues.

NOTE Confidence: 0.858737492857143

 $00{:}22{:}13.070 \dashrightarrow 00{:}22{:}15.698$ It was not uncommon to see mice with with.

NOTE Confidence: 0.810070235

 $00:22:17.890 \longrightarrow 00:22:19.690$ 323 independent tumors and

NOTE Confidence: 0.810070235

 $00:22:19.690 \longrightarrow 00:22:21.490$ occasionally four or five.

NOTE Confidence: 0.810070235

 $00:22:21.490 \longrightarrow 00:22:23.326$ And so something is.

NOTE Confidence: 0.810070235

 $00:22:23.326 \longrightarrow 00:22:25.162$ This implies that something

NOTE Confidence: 0.810070235

 $00:22:25.162 \rightarrow 00:22:26.706$ is accumulating epigenetically

NOTE Confidence: 0.810070235

 $00:22:26.706 \longrightarrow 00:22:28.890$ across generations in the
$00:22:28.890 \longrightarrow 00:22:31.074$ absence of this chromatin

NOTE Confidence: 0.810070235

 $00{:}22{:}31.074 \dashrightarrow 00{:}22{:}33.199$ 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

 $00:22:38.330 \longrightarrow 00:22:40.256$ 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

 $00:22:42.000 \rightarrow 00:22:44.772$ We see a phenomenon of a change in in

NOTE Confidence: 0.85750261125

 $00{:}22{:}44{.}772 \dashrightarrow 00{:}22{:}47{.}307$ phenotype in the offspring of males that

NOTE Confidence: 0.85750261125

 $00:22:47.307 \rightarrow 00:22:49.670$ have undergone a certain perturbation,

NOTE Confidence: 0.85750261125

 $00{:}22{:}49.670 \dashrightarrow 00{:}22{:}51.506$ and we can conclude that perturbing

NOTE Confidence: 0.85750261125

 $00:22:51.506 \rightarrow 00:22:53.718$ epigenetic state in the male germ cells

NOTE Confidence: 0.85750261125

 $00{:}22{:}53.718 \dashrightarrow 00{:}22{:}55.584$ reduces lifespan and increases tumor rate

NOTE Confidence: 0.85750261125

 $00{:}22{:}55{.}584 \dashrightarrow 00{:}22{:}57{.}769$ in the genetically wild type offspring.

NOTE Confidence: 0.85750261125

 $00{:}22{:}57{.}770 \dashrightarrow 00{:}22{:}59{.}121$ And now we want to go back

NOTE Confidence: 0.85750261125

 $00{:}22{:}59{.}121 \dashrightarrow 00{:}23{:}00{.}120$ to the original purpose,

NOTE Confidence: 0.85750261125

 $00{:}23{:}00{.}120 \dashrightarrow 00{:}23{:}01{.}875$ which is to understand what

 $00:23:01.875 \rightarrow 00:23:02.928$ genetic regulatory improvement

NOTE Confidence: 0.85750261125

 $00{:}23{:}02{.}928 \dashrightarrow 00{:}23{:}04{.}870$ 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

 $00:23:06.410 \rightarrow 00:23:10.498$ Information is actually inherited.

NOTE Confidence: 0.85750261125

 $00{:}23{:}10.500 \dashrightarrow 00{:}23{:}12.924$ Uhm, and I'll just remind you that we

NOTE Confidence: 0.85750261125

 $00{:}23{:}12{.}924 \dashrightarrow 00{:}23{:}15{.}338$ know that UT X is a tumor suppressor,

NOTE Confidence: 0.85750261125

 $00:23:15.340 \longrightarrow 00:23:17.764$ so when UTX is actually lost

NOTE Confidence: 0.85750261125

 $00:23:17.764 \longrightarrow 00:23:19.380$ in the tissue itself,

NOTE Confidence: 0.85750261125

 $00:23:19.380 \longrightarrow 00:23:22.405$ it promotes tumor formation and

NOTE Confidence: 0.85750261125

 $00:23:22.405 \rightarrow 00:23:24.825$ 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

 $00:23:26.456 \rightarrow 00:23:28.149$ how much people care about this,

NOTE Confidence: 0.85750261125

 $00:23:28.150 \longrightarrow 00:23:30.075$ 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

 $00{:}23{:}32{.}110 \dashrightarrow 00{:}23{:}36{.}282$ again showing that UT X axis tumor

NOTE Confidence: 0.85750261125

 $00:23:36.282 \rightarrow 00:23:38.720$ suppressor and attributing this

- NOTE Confidence: 0.85750261125
- $00:23:38.720 \rightarrow 00:23:41.990$ to formation of a phase separated.
- NOTE Confidence: 0.85750261125
- $00:23:41.990 \longrightarrow 00:23:43.646$ Regions in the nucleus,
- NOTE Confidence: 0.85750261125
- $00:23:43.646 \rightarrow 00:23:45.716$ based on an intrinsically disordered
- NOTE Confidence: 0.85750261125
- $00:23:45.716 \longrightarrow 00:23:48.180$ 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
- $00:23:54.333 \rightarrow 00:23:55.723$ gene regulatory information is
- NOTE Confidence: 0.9080008675
- $00:23:55.723 \rightarrow 00:23:57.448$ inherited from the knockout fathers.
- NOTE Confidence: 0.9080008675
- $00{:}23{:}57{.}450 \dashrightarrow 00{:}23{:}59{.}592$ 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
- $00:24:01.349 \longrightarrow 00:24:03.647$ as a sa a tumor suppressor?
- NOTE Confidence: 0.9080008675
- $00:24:03.650 \rightarrow 00:24:06.234$ To do that, we're going to look again,
- NOTE Confidence: 0.9080008675
- $00{:}24{:}06{.}240 \dashrightarrow 00{:}24{:}09{.}610$ not so much at noncoding RNA's, but at.
- NOTE Confidence: 0.9080008675
- $00:24:09.610 \rightarrow 00:24:12.690$ DNA methylations and histone modifications.
- NOTE Confidence: 0.9080008675
- $00{:}24{:}12.690 \dashrightarrow 00{:}24{:}15.186$ 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

 $00:24:17.050 \rightarrow 00:24:20.648$ we know that UTX has enzymatic activity

NOTE Confidence: 0.9080008675

 $00{:}24{:}20.648 \dashrightarrow 00{:}24{:}24.208$ as a demethylase of this modification.

NOTE Confidence: 0.9080008675

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

NOTE Confidence: 0.9080008675

 $00:24:26.720 \longrightarrow 00:24:28.688$ So the first thing we did was look

NOTE Confidence: 0.9080008675

 $00{:}24{:}28.688 \dashrightarrow 00{:}24{:}30.768$ at this modification and we performed

NOTE Confidence: 0.9080008675

 $00{:}24{:}30.768 \dashrightarrow 00{:}24{:}33.054$ the chip seek experiments in sperm.

NOTE Confidence: 0.9080008675

 $00{:}24{:}33.060 \dashrightarrow 00{:}24{:}35.727$ And now we expect that use because

NOTE Confidence: 0.9080008675

 $00:24:35.727 \longrightarrow 00:24:38.179$ you TX is a demethylase.

NOTE Confidence: 0.9080008675

 $00{:}24{:}38.180 \dashrightarrow 00{:}24{:}40.904$ 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

 $00{:}24{:}44{.}240 \dashrightarrow 00{:}24{:}47{.}216$ K27 trimethyl signal and that is in fact

NOTE Confidence: 0.9080008675

 $00:24:47.216 \rightarrow 00:24:50.755$ 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

 $00{:}24{:}53{.}480 \dashrightarrow 00{:}24{:}56{.}530$ in K27 Trimethylation.

NOTE Confidence: 0.9080008675

 $00{:}24{:}56{.}530 \dashrightarrow 00{:}24{:}57{.}446$ So we thought create.

NOTE Confidence: 0.9080008675

 $00:24:57.446 \longrightarrow 00:24:58.820$ This is exactly what we predict.

- NOTE Confidence: 0.9080008675
- $00:24:58.820 \longrightarrow 00:25:01.277$ 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
- $00:25:04.130 \longrightarrow 00:25:07.062 \text{ most affected by this change in K27}$
- NOTE Confidence: 0.9080008675
- 00:25:07.062 --> 00:25:10.074 TRIMETHYLATION and we'll have our answer.
- NOTE Confidence: 0.9080008675
- $00{:}25{:}10.080 \dashrightarrow 00{:}25{:}11.868$ So we started looking at individual
- NOTE Confidence: 0.9080008675
- $00{:}25{:}11.868 \dashrightarrow 00{:}25{:}13.928$ genes and it turned out as usually
- NOTE Confidence: 0.9080008675
- $00:25:13.928 \rightarrow 00:25:15.825$ happens that the story was a little
- NOTE Confidence: 0.9080008675
- $00:25:15.879 \rightarrow 00:25:17.829$ bit more complicated than I thought.
- NOTE Confidence: 0.9080008675
- $00{:}25{:}17.830 \dashrightarrow 00{:}25{:}20.720$ So here is an example of our chip seek data.
- NOTE Confidence: 0.9080008675
- $00:25:20.720 \longrightarrow 00:25:22.856$ This is shown as signal tracks
- NOTE Confidence: 0.9080008675
- $00:25:22.856 \rightarrow 00:25:25.323$ on the genome browser and so here
- NOTE Confidence: 0.9080008675
- $00{:}25{:}25{.}323 \dashrightarrow 00{:}25{:}26{.}948$ gene models at the bottom.
- NOTE Confidence: 0.9080008675
- $00:25:26.950 \rightarrow 00:25:29.894$ And if you look at the gene promoters
- NOTE Confidence: 0.9080008675
- $00{:}25{:}29{.}894 \dashrightarrow 00{:}25{:}33{.}062$ and Gray is controlled data and in in
- NOTE Confidence: 0.9080008675
- $00:25:33.062 \rightarrow 00:25:36.230$ oranges data from EU T X knockout sperm.
- NOTE Confidence: 0.9080008675

 $00:25:36.230 \rightarrow 00:25:38.246$ And you look at the promoter regions.

NOTE Confidence: 0.9080008675

 $00{:}25{:}38{.}250 \dashrightarrow 00{:}25{:}40{.}978$ You actually see a drop in signal in

NOTE Confidence: 0.9080008675

 $00{:}25{:}40{.}978 \dashrightarrow 00{:}25{:}43{.}398$ the knockout relative to the control.

NOTE Confidence: 0.9080008675

 $00:25:43.400 \longrightarrow 00:25:45.416$ So this is the opposite direction

NOTE Confidence: 0.9080008675

 $00{:}25{:}45{.}416 \dashrightarrow 00{:}25{:}47{.}460$ of what we had expected.

NOTE Confidence: 0.9080008675

 $00:25:47.460 \longrightarrow 00:25:48.692$ And it turns out,

NOTE Confidence: 0.9080008675

 $00:25:48.692 \rightarrow 00:25:51.080$ if we look across the entire genome.

NOTE Confidence: 0.9080008675

 $00:25:51.080 \rightarrow 00:25:53.579$ What's happening is that in the knockout,

NOTE Confidence: 0.9080008675

 $00{:}25{:}53.580 \dashrightarrow 00{:}25{:}56.100$ the signal is dropping right at the

NOTE Confidence: 0.9080008675

 $00{:}25{:}56{.}100 \dashrightarrow 00{:}25{:}58{.}019$ promoter with where normally the

NOTE Confidence: 0.9080008675

 $00{:}25{:}58.019 \dashrightarrow 00{:}26{:}00{.}335$ 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

 $00:26:02.420 \rightarrow 00:26:04.656$ so it's essentially redistributing

NOTE Confidence: 0.9080008675

 $00:26:04.656 \rightarrow 00:26:08.010$ across the genome and flattening out.

NOTE Confidence: 0.9080008675

 $00{:}26{:}08.010 \dashrightarrow 00{:}26{:}10.640$ We could interpret that as

NOTE Confidence: 0.9080008675

 $00:26:10.640 \rightarrow 00:26:12.744$ randomization or overall remodeling,

- NOTE Confidence: 0.9080008675
- $00{:}26{:}12.750 \dashrightarrow 00{:}26{:}15.486$ 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
- $00:26:17.681 \rightarrow 00:26:19.746$ specific genes that are being MIS
- NOTE Confidence: 0.9080008675
- $00:26:19.746 \rightarrow 00:26:21.750$ regulated and contributing to the phenotype.
- NOTE Confidence: 0.9080008675
- $00{:}26{:}21.750 \dashrightarrow 00{:}26{:}23.521$ It just tells us that something is
- NOTE Confidence: 0.9080008675
- $00{:}26{:}23.521 \dashrightarrow 00{:}26{:}25.539$ wrong with K27 trimethylation sperm.
- NOTE Confidence: 0.9080008675
- $00{:}26{:}25{.}539 \dashrightarrow 00{:}26{:}29{.}060$ So we decided to take an alternate
- NOTE Confidence: 0.9080008675
- $00{:}26{:}29{.}145 \dashrightarrow 00{:}26{:}33{.}488$ tack and we know that.
- NOTE Confidence: 0.9080008675
- $00:26:33.490 \longrightarrow 00:26:37.912$ That K 27 Trimethylation is is
- NOTE Confidence: 0.9080008675
- $00:26:37.912 \longrightarrow 00:26:40.860$ antagonistic with DNA methylation.
- NOTE Confidence: 0.9080008675
- 00:26:40.860 --> 00:26:41.132 Uhm,
- NOTE Confidence: 0.9080008675
- $00:26:41.132 \longrightarrow 00:26:42.764$ 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
- $00:26:44.360 \longrightarrow 00:26:46.957$ but in general we see that this
- NOTE Confidence: 0.9080008675
- $00{:}26{:}46{.}957 \dashrightarrow 00{:}26{:}49{.}262$ modification and DNA match DNA
- NOTE Confidence: 0.9080008675

 $00:26:49.262 \rightarrow 00:26:51.498$ metalation are anticorrelated genome.

NOTE Confidence: 0.9080008675

 $00:26:51.500 \longrightarrow 00:26:53.684$ So we decided to look at what

NOTE Confidence: 0.9080008675

 $00{:}26{:}53.684 \dashrightarrow 00{:}26{:}56.656$ happens to DNA methylation in the

NOTE Confidence: 0.9080008675

 $00:26:56.656 \rightarrow 00:26:59.596$ sperm of these knockout mice.

NOTE Confidence: 0.9080008675

 $00:26:59.600 \longrightarrow 00:27:01.000$ When we did that,

NOTE Confidence: 0.9080008675

 $00:27:01.000 \rightarrow 00:27:03.660$ 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

 $00:27:06.210 \longrightarrow 00:27:08.544$ subset of regions that exhibit

NOTE Confidence: 0.9080008675

 $00{:}27{:}08{.}544 \dashrightarrow 00{:}27{:}10{.}748$ changes in DNA methylation.

NOTE Confidence: 0.9080008675

 $00:27:10.750 \longrightarrow 00:27:12.528$ If you look globally across the genome,

NOTE Confidence: 0.9080008675

 $00:27:12.530 \longrightarrow 00:27:14.590$ there's no global change,

NOTE Confidence: 0.9080008675

 $00{:}27{:}14.590 \dashrightarrow 00{:}27{:}17.680$ but among these regions that exhibit

NOTE Confidence: 0.853715797272727

 $00{:}27{:}17.765 \dashrightarrow 00{:}27{:}20.425$ changes. The vast majority of them

NOTE Confidence: 0.853715797272727

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

NOTE Confidence: 0.853715797272727

 $00{:}27{:}22.420 \dashrightarrow 00{:}27{:}24.190$ so there's some bias or it's

NOTE Confidence: 0.853715797272727

 $00:27:24.190 \longrightarrow 00:27:25.370$ game of DNA methylation.

- NOTE Confidence: 0.853715797272727
- $00{:}27{:}25{.}370 \dashrightarrow 00{:}27{:}28{.}646$ 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
- $00:27:35.114 \rightarrow 00:27:38.150$ in somatic tissue of the offspring,
- NOTE Confidence: 0.853715797272727
- $00{:}27{:}38{.}150 \dashrightarrow 00{:}27{:}40{.}460$ we see the same effect.
- NOTE Confidence: 0.853715797272727
- $00{:}27{:}40.460 \dashrightarrow 00{:}27{:}42.998$ So again, there's an overall game
- NOTE Confidence: 0.853715797272727
- $00{:}27{:}42.998 \dashrightarrow 00{:}27{:}45.872$ 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
- $00:27:48.450 \longrightarrow 00:27:51.843$ as opposed to lots of DNA metalation in this.
- NOTE Confidence: 0.853715797272727
- $00:27:51.850 \rightarrow 00:27:56.170$ 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
- $00{:}28{:}01{.}725 \dashrightarrow 00{:}28{:}04{.}330$ that game DNA metalation in offspring
- NOTE Confidence: 0.853715797272727
- $00{:}28{:}04{.}330 \dashrightarrow 00{:}28{:}06{.}280$ were also gaining DNA methylation
- NOTE Confidence: 0.853715797272727
- $00:28:06.280 \longrightarrow 00:28:08.970$ 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

 $00{:}28{:}12{.}522 \dashrightarrow 00{:}28{:}14{.}866$ but many of them are are hypermethylated

NOTE Confidence: 0.853715797272727

 $00:28:14.866 \longrightarrow 00:28:17.806$ 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

 $00{:}28{:}19{.}480 \dashrightarrow 00{:}28{:}22{.}012$ 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

 $00:28:24.212 \rightarrow 00:28:26.422$ generations and helping to alter

NOTE Confidence: 0.853715797272727

 $00:28:26.422 \rightarrow 00:28:28.730$ gene expression in somatic tissue.

NOTE Confidence: 0.853715797272727

 $00{:}28{:}28{.}730 \dashrightarrow 00{:}28{:}32{.}258$ This turns out to be about 200 low side.

NOTE Confidence: 0.853715797272727

 $00:28:32.260 \rightarrow 00:28:34.480$ Uhm?

NOTE Confidence: 0.853715797272727

 $00{:}28{:}34{.}480 \dashrightarrow 00{:}28{:}37{.}360$ And we can convince is an example of just

NOTE Confidence: 0.853715797272727

 $00{:}28{:}37{.}360 \dashrightarrow 00{:}28{:}39{.}768$ 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

 $00:28:40.800 \longrightarrow 00:28:43.222$ and then we can actually validate it

NOTE Confidence: 0.853715797272727

 $00{:}28{:}43{.}222 \dashrightarrow 00{:}28{:}48{.}038$ using a different assay at the same locus.

NOTE Confidence: 0.853715797272727

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

 $00:28:48.363 \longrightarrow 00:28:49.978$ so now we wanna know.

NOTE Confidence: 0.853715797272727

 $00{:}28{:}49{.}980 \dashrightarrow 00{:}28{:}52{.}948$ OK this seems like a a important set

NOTE Confidence: 0.853715797272727

 $00:28:52.948 \rightarrow 00:28:55.668$ 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

 $00{:}28{:}57{.}090 \dashrightarrow 00{:}28{:}58{.}920$ We wanna know what's special

NOTE Confidence: 0.853715797272727

 $00:28:58.920 \longrightarrow 00:29:01.420$ about this set of 200 regions.

NOTE Confidence: 0.853715797272727

 $00:29:01.420 \longrightarrow 00:29:02.939$ Turns out there's not really much bias

NOTE Confidence: 0.853715797272727

 $00:29:02.939 \rightarrow 00:29:04.898$ in terms of where they are in the genome.

NOTE Confidence: 0.853715797272727

 $00{:}29{:}04{.}900 \dashrightarrow 00{:}29{:}06{.}184$ There's a bit of a cluster

NOTE Confidence: 0.853715797272727

 $00:29:06.184 \longrightarrow 00:29:07.040$ 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

 $00{:}29{:}08.872 \dashrightarrow 00{:}29{:}10.246$ across the genome,

NOTE Confidence: 0.853715797272727

 $00{:}29{:}10{.}250 \dashrightarrow 00{:}29{:}11{.}858$ 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

 $00{:}29{:}13.562 \dashrightarrow 00{:}29{:}14.438$ they're not enriched.

- $00:29:14.440 \longrightarrow 00:29:15.204$ 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
- $00:29:19.104 \rightarrow 00:29:19.906$ near promoters.
- NOTE Confidence: 0.853715797272727
- $00{:}29{:}19{.}910 \dashrightarrow 00{:}29{:}21{.}775$ With jeans and they're not
- NOTE Confidence: 0.853715797272727
- $00{:}29{:}21.775 \dashrightarrow 00{:}29{:}23.267$ enriched at CPG islands,
- NOTE Confidence: 0.853715797272727
- $00{:}29{:}23{.}270 \dashrightarrow 00{:}29{:}26{.}502$ which is another dumb class that we might
- NOTE Confidence: 0.853715797272727
- $00{:}29{:}26.502 \dashrightarrow 00{:}29{:}29.859$ expect to see biases and DNA methylation.
- NOTE Confidence: 0.853715797272727
- 00:29:29.860 --> 00:29:32.030 Uhm?
- NOTE Confidence: 0.853715797272727
- $00:29:32.030 \longrightarrow 00:29:35.198$ 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
- $00:29:37.310 \longrightarrow 00:29:39.935$ which is where we started.
- NOTE Confidence: 0.853715797272727
- $00{:}29{:}39{.}940 \dashrightarrow 00{:}29{:}42{.}474$ So the regions that have the biggest
- NOTE Confidence: 0.853715797272727
- $00:29:42.474 \longrightarrow 00:29:45.345$ perturbation in K27 tend to also have
- NOTE Confidence: 0.853715797272727
- $00:29:45.345 \rightarrow 00:29:48.680$ the greatest gains in DNA methylation,
- NOTE Confidence: 0.853715797272727
- $00:29:48.680 \rightarrow 00:29:52.296$ so there may be a functional link there.

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

NOTE Confidence: 0.853715797272727

 $00{:}29{:}55{.}250 \dashrightarrow 00{:}29{:}57{.}714$ and this is marked by a different

NOTE Confidence: 0.853715797272727

 $00:29:57.714 \longrightarrow 00:29:58.770$ histone modification that's

NOTE Confidence: 0.853715797272727

 $00:29:58.837 \rightarrow 00:30:00.917$ generally associated with enhancers.

NOTE Confidence: 0.853715797272727

 $00{:}30{:}00{.}920 \dashrightarrow 00{:}30{:}03{.}755$ We see that these persistence

NOTE Confidence: 0.853715797272727

 $00{:}30{:}03{.}755 \dashrightarrow 00{:}30{:}06{.}590$ hypermethylated regions tend to occur

NOTE Confidence: 0.853715797272727

 $00:30:06.678 \rightarrow 00:30:09.978$ in regions that have enhancer activity.

NOTE Confidence: 0.853715797272727

 $00:30:09.980 \longrightarrow 00:30:11.552$ And that was nice,

NOTE Confidence: 0.853715797272727

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

NOTE Confidence: 0.853715797272727

 $00:30:13.124 \rightarrow 00:30:15.060$ can potentially linked to genes

NOTE Confidence: 0.853715797272727

 $00:30:15.060 \longrightarrow 00:30:16.508$ and linked to functions.

NOTE Confidence: 0.853715797272727

 $00{:}30{:}16{.}510 \dashrightarrow 00{:}30{:}19{.}240$ 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

 $00{:}30{:}24.052 \dashrightarrow 00{:}30{:}27.670$ here is actually all of the enriched

 $00:30:27.670 \rightarrow 00:30:30.760$ phenotypes associated with with the

NOTE Confidence: 0.853715797272727

 $00:30:30.760 \longrightarrow 00:30:34.160$ the persistent hypermethylated region.

NOTE Confidence: 0.853715797272727

 $00{:}30{:}34{.}160 \dashrightarrow 00{:}30{:}35{.}290$ So there's a clear link.

NOTE Confidence: 0.853715797272727

 $00{:}30{:}35{.}290 \dashrightarrow 00{:}30{:}38{.}032$ There's a clear functional link here

NOTE Confidence: 0.853715797272727

 $00:30:38.032 \longrightarrow 00:30:41.062$ to tumorigenesis as sort of evidence.

NOTE Confidence: 0.853715797272727

 $00{:}30{:}41.062 \dashrightarrow 00{:}30{:}44.380$ By past phenotypes that have been

NOTE Confidence: 0.853715797272727

 $00:30:44.380 \longrightarrow 00:30:46.940$ associated with these enhancer regions.

NOTE Confidence: 0.928311184615385

 $00:30:48.970 \longrightarrow 00:30:51.026$ To get a little bit more at how

NOTE Confidence: 0.928311184615385

 $00:30:51.026 \rightarrow 00:30:52.960$ this might actually be occurring,

NOTE Confidence: 0.928311184615385

 $00{:}30{:}52{.}960 \dashrightarrow 00{:}30{:}55{.}600$ we took a closer look at the sequences

NOTE Confidence: 0.928311184615385

 $00{:}30{:}55{.}600 \dashrightarrow 00{:}30{:}57{.}633$ associated with these 200 or the

NOTE Confidence: 0.928311184615385

 $00:30:57.633 \rightarrow 00:30:59.263$ sequences of these 200 regions,

NOTE Confidence: 0.928311184615385

 $00{:}30{:}59{.}270 \dashrightarrow 00{:}31{:}01{.}598$ and we looked for enriched motifs

NOTE Confidence: 0.928311184615385

 $00:31:01.598 \dashrightarrow 00:31:04.925$ and we were able to find 3 enriched

NOTE Confidence: 0.928311184615385

 $00:31:04.925 \dashrightarrow 00:31:07.040$ 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
- $00:31:09.370 \longrightarrow 00:31:11.362$ 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
- $00:31:12.360 \longrightarrow 00:31:14.736$ 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
- $00{:}31{:}16.800 \dashrightarrow 00{:}31{:}17.708$ And interestingly,
- NOTE Confidence: 0.928311184615385
- 00:31:17.708 --> 00:31:20.432 two of these three have been
- NOTE Confidence: 0.928311184615385
- $00{:}31{:}20{.}432 \dashrightarrow 00{:}31{:}23{.}295$ tested to see if the presence or
- NOTE Confidence: 0.928311184615385
- $00:31:23.295 \rightarrow 00:31:25.620$ absence of DNA methylation effects
- NOTE Confidence: 0.928311184615385
- $00{:}31{:}25.620 \dashrightarrow 00{:}31{:}28.389$ binding of a transcription factor.
- NOTE Confidence: 0.928311184615385
- $00:31:28.390 \longrightarrow 00:31:30.718$ 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
- $00:31:32.174 \longrightarrow 00:31:34.988$ called elk one in the presence of
- NOTE Confidence: 0.928311184615385
- $00:31:34.988 \dashrightarrow 00:31:37.468$ DNA methylation elk when binding.
- NOTE Confidence: 0.928311184615385
- $00:31:37.470 \longrightarrow 00:31:39.045$ Is significantly inhibited
- NOTE Confidence: 0.928311184615385
- $00:31:39.045 \rightarrow 00:31:41.145$ and same thing here.
- NOTE Confidence: 0.928311184615385

 $00:31:41.150 \rightarrow 00:31:43.638$ This is normally bound by GPA and the

NOTE Confidence: 0.928311184615385

 $00{:}31{:}43.638 \dashrightarrow 00{:}31{:}46.201$ 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

 $00:31:48.080 \rightarrow 00:31:50.810$ 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

 $00{:}31{:}54{.}150 \dashrightarrow 00{:}31{:}56{.}475$ And then retain that DNA

NOTE Confidence: 0.928311184615385

 $00:31:56.475 \longrightarrow 00:31:57.870$ metalation in offspring.

NOTE Confidence: 0.928311184615385

 $00:31:57.870 \longrightarrow 00:32:00.460$ There may be an effect on transcription

NOTE Confidence: 0.928311184615385

 $00{:}32{:}00{.}460 \dashrightarrow 00{:}32{:}02{.}694$ factor activity and G and downstream

NOTE Confidence: 0.928311184615385

 $00:32:02.694 \rightarrow 00:32:04.800$ gene expression that may in turn

NOTE Confidence: 0.928311184615385

 $00{:}32{:}04{.}800 \dashrightarrow 00{:}32{:}06{.}951$ affect the phenotype and may be

NOTE Confidence: 0.928311184615385

 $00:32:06.951 \dashrightarrow 00:32:08.679$ tumorigenesis in those tissues.

NOTE Confidence: 0.928311184615385

 $00:32:08.680 \dashrightarrow 00:32:09.008$ Interestingly,

NOTE Confidence: 0.928311184615385

 $00{:}32{:}09{.}008 \dashrightarrow 00{:}32{:}10{.}976$ at around the same time that

NOTE Confidence: 0.928311184615385

 $00:32:10.976 \longrightarrow 00:32:12.679$ that we did this study,

NOTE Confidence: 0.928311184615385

 $00:32:12.680 \rightarrow 00:32:14.577$ another paper came out looking at you.

 $00:32:14.580 \dashrightarrow 00:32:17.526$ T X function in magnetic tissue.

NOTE Confidence: 0.928311184615385

 $00:32:17.530 \longrightarrow 00:32:19.876$ And and they found almost exactly

NOTE Confidence: 0.928311184615385

 $00:32:19.876 \longrightarrow 00:32:22.513$ the same enriched set of motifs among

NOTE Confidence: 0.928311184615385

 $00:32:22.513 \longrightarrow 00:32:24.851$ a set of genes where they found

NOTE Confidence: 0.928311184615385

 $00{:}32{:}24{.}924 \dashrightarrow 00{:}32{:}27{.}458$ when they knock out EX they see a

NOTE Confidence: 0.928311184615385

 $00:32:27.458 \rightarrow 00:32:29.488$ miss regulation of gene expression

NOTE Confidence: 0.928311184615385

 $00:32:29.488 \rightarrow 00:32:32.771$ and they see that UTX

NOTE Confidence: 0.928311184615385

 $00:32:32.771 \rightarrow 00:32:35.857$ binds directly to these promoters.

NOTE Confidence: 0.928311184615385

 $00:32:35.860 \longrightarrow 00:32:38.316$ So here you see out for a while

NOTE Confidence: 0.928311184615385

 $00:32:38.316 \dashrightarrow 00:32:41.086$ and GPA coming right out of this

NOTE Confidence: 0.928311184615385

 $00:32:41.086 \longrightarrow 00:32:42.328$ analysis as well.

NOTE Confidence: 0.928311184615385

 $00:32:42.330 \longrightarrow 00:32:45.126$ So this implies that UTX may

NOTE Confidence: 0.928311184615385

 $00:32:45.126 \longrightarrow 00:32:47.490$ actually directly bind these sites

NOTE Confidence: 0.928311184615385

 $00{:}32{:}47{.}490 \dashrightarrow 00{:}32{:}50{.}300$ in developing sperm altered DNA

NOTE Confidence: 0.928311184615385

 $00:32:50.300 \dashrightarrow 00:32:53.430$ methylation at those sites, the DNA.

 $00:32:53.430 \longrightarrow 00:32:56.070$ The DNA metalation is retained in

NOTE Confidence: 0.928311184615385

 $00{:}32{:}56{.}070 \dashrightarrow 00{:}32{:}58{.}608$ matter poetic tissue of offspring.

NOTE Confidence: 0.928311184615385

 $00{:}32{:}58{.}610 \dashrightarrow 00{:}33{:}01{.}110$ And effects from binding and

NOTE Confidence: 0.928311184615385

 $00:33:01.110 \longrightarrow 00:33:03.610$ downstream expression based on these.

NOTE Confidence: 0.928311184615385

 $00:33:03.610 \dashrightarrow 00:33:05.640$ 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

 $00:33:10.190 \longrightarrow 00:33:13.180$ is that the ranks 2 gene,

NOTE Confidence: 0.803412997272727

 $00:33:13.180 \longrightarrow 00:33:15.448$ so this is one of the hypermethylated

NOTE Confidence: 0.803412997272727

 $00{:}33{:}15.448 \dashrightarrow 00{:}33{:}17.650$ DMR is that we identify it within

NOTE Confidence: 0.803412997272727

 $00{:}33{:}17.650 \dashrightarrow 00{:}33{:}19.814$ that DMR we see an elk one

NOTE Confidence: 0.803412997272727

 $00:33:19.814 \longrightarrow 00:33:21.600$ binding site within that elk.

NOTE Confidence: 0.803412997272727

 $00:33:21.600 \dashrightarrow 00:33:24.499$ When binding site is a CPG site and

NOTE Confidence: 0.803412997272727

 $00:33:24.499 \longrightarrow 00:33:27.705$ that site has more population in

NOTE Confidence: 0.803412997272727

 $00{:}33{:}27.705 \dashrightarrow 00{:}33{:}31.288$ knockout sperm compared to controls and

NOTE Confidence: 0.803412997272727

 $00:33:31.288 \rightarrow 00:33:34.768$ more methylation in healthy bone marrow.

NOTE Confidence: 0.803412997272727

 $00:33:34.770 \longrightarrow 00:33:37.055$ And knockout an offspring of

- NOTE Confidence: 0.803412997272727
- $00{:}33{:}37.055 \dashrightarrow 00{:}33{:}38.883$ knockouts compared to controls.

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

 $00:33:43.070 \rightarrow 00:33:46.114$ 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

 $00{:}33{:}48{.}450 \dashrightarrow 00{:}33{:}50{.}934$ Blood tumors this is a analysis

NOTE Confidence: 0.803412997272727

 $00:33:50.934 \longrightarrow 00:33:53.310$ of of ranks to target.

NOTE Confidence: 0.803412997272727

 $00:33:53.310 \longrightarrow 00:33:55.740$ Genes are now looking downstream in

NOTE Confidence: 0.803412997272727

 $00{:}33{:}55{.}740 \dashrightarrow 00{:}33{:}58{.}949$ the in the gene regulatory network.

NOTE Confidence: 0.803412997272727

 $00:33:58.950 \rightarrow 00:34:02.038$ This set of genes sort of as significantly

NOTE Confidence: 0.803412997272727

 $00:34:02.038 \rightarrow 00:34:03.732$ perturbed and gene expression

NOTE Confidence: 0.803412997272727

 $00:34:03.732 \longrightarrow 00:34:06.270$ space in the presence of disease.

NOTE Confidence: 0.803412997272727

 $00:34:06.270 \longrightarrow 00:34:08.148$ But even before we see disease,

NOTE Confidence: 0.803412997272727

 $00{:}34{:}08{.}150 \dashrightarrow 00{:}34{:}10{.}424$ there's a shift in the expression

NOTE Confidence: 0.803412997272727

 $00{:}34{:}10{.}424 \dashrightarrow 00{:}34{:}12{.}369$ of these downstream genes towards

 $00:34:12.369 \longrightarrow 00:34:14.189$ a more disease like state,

NOTE Confidence: 0.803412997272727

 $00:34:14.190 \rightarrow 00:34:17.208$ again implying that may be predisposed

NOTE Confidence: 0.803412997272727

 $00{:}34{:}17{.}208 \dashrightarrow 00{:}34{:}20{.}152$ by these epigenetic changes induced by

NOTE Confidence: 0.803412997272727

 $00:34:20.152 \dashrightarrow 00:34:23.120$ by UTX last in the previous generation.

NOTE Confidence: 0.8230942415

 $00:34:28.200 \dashrightarrow 00:34:30.965$ 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

 $00:34:34.703 \longrightarrow 00:34:37.173$ 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

 $00:34:39.900 \dashrightarrow 00:34:43.050$ some of which persists offspring.

NOTE Confidence: 0.8230942415

 $00{:}34{:}43.050 \dashrightarrow 00{:}34{:}45.598$ And it leaves open two questions that

NOTE Confidence: 0.8230942415

 $00{:}34{:}45{.}598 \dashrightarrow 00{:}34{:}48{.}699$ 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

 $00:34:50.482 \rightarrow 00:34:52.230$ established in the developing germ line?

NOTE Confidence: 0.8230942415

 $00:34:52.230 \longrightarrow 00:34:53.987$ 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

 $00{:}34{:}55{.}160 \dashrightarrow 00{:}34{:}57{.}266$ 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
- $00{:}34{:}58{.}860 \dashrightarrow 00{:}35{:}01{.}086$ 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
- $00:35:02.200 \longrightarrow 00:35:04.408$ That's set up views?
- NOTE Confidence: 0.8230942415
- 00:35:04.408 --> 00:35:06.064 DNA methylation differences
- NOTE Confidence: 0.8230942415
- $00:35:06.064 \rightarrow 00:35:08.510$ that appear to persist?
- NOTE Confidence: 0.8230942415
- $00:35:08.510 \rightarrow 00:35:11.022$ A second question is how are they maintained
- NOTE Confidence: 0.8230942415
- $00:35:11.022 \rightarrow 00:35:12.848$ in developing tissues of offspring?
- NOTE Confidence: 0.8230942415
- $00{:}35{:}12.850 \dashrightarrow 00{:}35{:}15.928$ So again we have a time point of sperm.
- NOTE Confidence: 0.8230942415
- $00{:}35{:}15{.}930 \dashrightarrow 00{:}35{:}17{.}436$ 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
- $00{:}35{:}18{.}440 \dashrightarrow 00{:}35{:}20{.}240$ Actually pretty old a dult offspring
- NOTE Confidence: 0.8230942415
- $00:35:20.240 \rightarrow 00:35:22.490$ that are starting to develop tumors.
- NOTE Confidence: 0.8230942415
- $00:35:22.490 \rightarrow 00:35:25.106$ What happens during all the time in between?
- NOTE Confidence: 0.8230942415
- $00:35:25.110 \rightarrow 00:35:28.225$ How do we maintain these epigenetic marks?
- NOTE Confidence: 0.8230942415

 $00:35:28.230 \longrightarrow 00:35:32.316$ Even in the context of of rapid changes in

NOTE Confidence: 0.8230942415

 $00:35:32.316 \longrightarrow 00:35:34.969$ developmental gene expression and so on?

NOTE Confidence: 0.8230942415

00:35:34.970 --> 00:35:35.742 And finally,

NOTE Confidence: 0.8230942415

 $00:35:35.742 \rightarrow 00:35:37.672$ how do they actually predispose

NOTE Confidence: 0.8230942415

 $00:35:37.672 \longrightarrow 00:35:38.444$ to tumorigenesis?

NOTE Confidence: 0.8230942415

 $00{:}35{:}38{.}450 \dashrightarrow 00{:}35{:}41{.}124$ I showed you one example in the

NOTE Confidence: 0.8230942415

 $00{:}35{:}41{.}124 \dashrightarrow 00{:}35{:}44{.}070$ 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

 $00{:}35{:}45{.}790 \dashrightarrow 00{:}35{:}48{.}618$ but we'd like to identify sort of

NOTE Confidence: 0.8230942415

 $00{:}35{:}48.618 \dashrightarrow 00{:}35{:}51.204$ some more global rules about how

NOTE Confidence: 0.8230942415

 $00:35:51.204 \dashrightarrow 00:35:53.790$ this effect may be taking place.

NOTE Confidence: 0.8230942415

 $00:35:53.790 \rightarrow 00:35:55.534$ So what I'm going to show you is

NOTE Confidence: 0.8230942415

 $00{:}35{:}55{.}534 \dashrightarrow 00{:}35{:}57{.}218$ 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

 $00{:}35{:}59{.}010 \dashrightarrow 00{:}36{:}01.866$ These are things that were very much in

NOTE Confidence: 0.8230942415

 $00:36:01.866 \rightarrow 00:36:04.756$ the process of trying to understand still.

 $00:36:04.760 \dashrightarrow 00:36:07.440$ So First off we looked at where you

NOTE Confidence: 0.8230942415

 $00:36:07.440 \longrightarrow 00:36:10.422$ at when you text is expressed during

NOTE Confidence: 0.8230942415

 $00{:}36{:}10.422 \dashrightarrow 00{:}36{:}12.796$ strategy MC developments and what I'm

NOTE Confidence: 0.8230942415

 $00:36:12.796 \rightarrow 00:36:15.190$ showing here is single cell RNA seek

NOTE Confidence: 0.8230942415

 $00:36:15.263 \rightarrow 00:36:19.260$ data that's been put onto a pseudo time axis.

NOTE Confidence: 0.8230942415

 $00:36:19.260 \longrightarrow 00:36:21.555$ So these different colors are

NOTE Confidence: 0.8230942415

 $00:36:21.555 \rightarrow 00:36:23.391$ progressive stages of schematic

NOTE Confidence: 0.8230942415

 $00:36:23.391 \rightarrow 00:36:25.183$ demik development starting here

NOTE Confidence: 0.8230942415

 $00:36:25.183 \longrightarrow 00:36:27.697$ in red or starting over here,

NOTE Confidence: 0.8230942415

 $00:36:27.700 \rightarrow 00:36:30.295$ and the sporadic janitors progressing

NOTE Confidence: 0.8230942415

 $00:36:30.295 \longrightarrow 00:36:32.371$ through meiosis and through

NOTE Confidence: 0.8230942415

 $00{:}36{:}32{.}371 \dashrightarrow 00{:}36{:}34{.}617$ the final stages of sperm.

NOTE Confidence: 0.8230942415

 $00{:}36{:}34{.}620 \dashrightarrow 00{:}36{:}36{.}530$ Developments and intimate tours firm.

NOTE Confidence: 0.882411649230769

 $00{:}36{:}38{.}960 \dashrightarrow 00{:}36{:}41{.}109$ DMC1 is a marker for a specific

NOTE Confidence: 0.882411649230769

 $00{:}36{:}41.109 \dashrightarrow 00{:}36{:}43.258$ cell type and a specific stage.

00:36:43.260 - > 00:36:45.696 This is the very beginning of the

NOTE Confidence: 0.882411649230769

 $00{:}36{:}45.696 \dashrightarrow 00{:}36{:}47.626$ entry into meiosis when chromosomes

NOTE Confidence: 0.882411649230769

 $00:36:47.626 \rightarrow 00:36:49.841$ are actually inducing double strand

NOTE Confidence: 0.882411649230769

 $00:36:49.841 \rightarrow 00:36:52.100$ breaks and starting recombination.

NOTE Confidence: 0.882411649230769

 $00:36:52.100 \longrightarrow 00:36:53.840$ 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

 $00:36:54.710 \longrightarrow 00:36:57.214$ and it has to be very highly regulated,

NOTE Confidence: 0.882411649230769

 $00:36:57.220 \rightarrow 00:36:59.680$ and you can see that U TX is most strongly

NOTE Confidence: 0.882411649230769

 $00:36:59.746 \longrightarrow 00:37:01.918$ 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

 $00{:}37{:}04{.}140 \dashrightarrow 00{:}37{:}06{.}072$ Genesis, and implies that it may

NOTE Confidence: 0.882411649230769

 $00:37:06.072 \dashrightarrow 00:37:08.180$ have for very specific developments.

NOTE Confidence: 0.882411649230769

 $00:37:08.180 \longrightarrow 00:37:09.704$ Functions, and there's also

NOTE Confidence: 0.882411649230769

 $00:37:09.704 \longrightarrow 00:37:11.228$ a bit of expression,

NOTE Confidence: 0.882411649230769

 $00{:}37{:}11{.}230 \dashrightarrow 00{:}37{:}13{.}558$ and the earlier strategem excels and

NOTE Confidence: 0.882411649230769

 $00:37:13.558 \rightarrow 00:37:16.538$ a little bit in the somatic cells.

- NOTE Confidence: 0.882411649230769
- $00:37:16.540 \longrightarrow 00:37:18.290$ And we can confirm this.
- NOTE Confidence: 0.882411649230769
- $00{:}37{:}18.290 \dashrightarrow 00{:}37{:}22.010$ Uhm, this is using single molecule RNA fish,
- NOTE Confidence: 0.882411649230769
- $00:37:22.010 \rightarrow 00:37:26.114$ so each of the green points here is a
- NOTE Confidence: 0.882411649230769
- $00:37:26.114 \rightarrow 00:37:29.997$ single molecule of RNA ATX RNA in blue.
- NOTE Confidence: 0.882411649230769
- $00{:}37{:}30.000 \dashrightarrow 00{:}37{:}32.562$ Is DAPI showing the chromatin and
- NOTE Confidence: 0.882411649230769
- $00{:}37{:}32.562 \dashrightarrow 00{:}37{:}35.964$ you can see that there's JTX RNA
- NOTE Confidence: 0.882411649230769
- $00{:}37{:}35{.}964 \dashrightarrow 00{:}37{:}38{.}174$ molecules in these cells that are at
- NOTE Confidence: 0.882411649230769
- $00:37:38.174 \dashrightarrow 00:37:40.690$ the edge of the seminiferous tubule.
- NOTE Confidence: 0.882411649230769
- $00{:}37{:}40.690 \dashrightarrow 00{:}37{:}42.916$ These are the progenitor and early meiotic
- NOTE Confidence: 0.882411649230769
- $00:37:42.916 \longrightarrow 00:37:46.702$ 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
- $00:37:48.464 \longrightarrow 00:37:50.546$ actually a little bit into later
- NOTE Confidence: 0.882411649230769
- $00:37:50.546 \longrightarrow 00:37:52.109$ stages from out of Genesis,
- NOTE Confidence: 0.882411649230769
- $00{:}37{:}52{.}110 \dashrightarrow 00{:}37{:}54{.}475$ but is definitely highest in
- NOTE Confidence: 0.882411649230769
- $00:37:54.475 \longrightarrow 00:37:56.367$ these early progenitor cells,
- NOTE Confidence: 0.882411649230769

 $00:37:56.370 \longrightarrow 00:37:57.695$ confirming what we saw from

NOTE Confidence: 0.882411649230769

 $00{:}37{:}57{.}695 \dashrightarrow 00{:}37{:}59{.}020$ the single cell RNA seed.

NOTE Confidence: 0.8645121415

 $00:38:01.440 \longrightarrow 00:38:04.272$ In addition, I told you at the very

NOTE Confidence: 0.8645121415

 $00:38:04.272 \rightarrow 00:38:08.007$ beginning of this talk that some lots of VTX

NOTE Confidence: 0.8645121415

 $00:38:08.007 \rightarrow 00:38:10.164$ doesn't affect fertility, which is true.

NOTE Confidence: 0.8645121415

 $00:38:10.164 \dashrightarrow 00:38:11.654$ 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

 $00:38:13.640 \longrightarrow 00:38:15.456$ 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

 $00{:}38{:}19{.}870 \dashrightarrow 00{:}38{:}22{.}522$ but we see a statistically significant

NOTE Confidence: 0.8645121415

 $00{:}38{:}22.522 \dashrightarrow 00{:}38{:}25.599$ increase in the number of spermatogonia,

NOTE Confidence: 0.8645121415

 $00:38:25.600 \rightarrow 00:38:29.050$ 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

 $00{:}38{:}30{.}900 \dashrightarrow 00{:}38{:}33{.}522$ by this solid four marker or

NOTE Confidence: 0.8645121415

 $00:38:33.522 \rightarrow 00:38:37.930$ by sort of counting by Ajani.

 $00:38:37.930 \longrightarrow 00:38:40.950$ And that implies that although

NOTE Confidence: 0.8645121415

 $00:38:40.950 \longrightarrow 00:38:42.626$ nothing is affecting fertility,

NOTE Confidence: 0.8645121415

 $00:38:42.626 \rightarrow 00:38:45.140$ something is off in these cells.

NOTE Confidence: 0.8645121415

 $00:38:45.140 \rightarrow 00:38:47.975$ Something has been changed in the gene

NOTE Confidence: 0.8645121415

 $00:38:47.975 \rightarrow 00:38:50.150$ regulatory network that's causing them

NOTE Confidence: 0.8645121415

 $00:38:50.150 \rightarrow 00:38:52.370$ to not progress completely smoothly,

NOTE Confidence: 0.8645121415

 $00:38:52.370 \rightarrow 00:38:54.880$ so through their normal development.

NOTE Confidence: 0.8714695225

 $00{:}38{:}57{.}150 \dashrightarrow 00{:}39{:}02{.}254$ And we also looked at gene expression in in

NOTE Confidence: 0.8714695225

 $00{:}39{:}02{.}254$ --> $00{:}39{:}05{.}222$ test is and whole test is and consistent with NOTE Confidence: 0.8714695225

 $00:39:05.222 \dashrightarrow 00:39:08.682$ the fact that we see very that we see very

NOTE Confidence: 0.8714695225

 $00:39:08.682 \dashrightarrow 00:39:11.270$ little change in phenotype in the knockout.

NOTE Confidence: 0.8714695225

 $00:39{:}11.270 \dashrightarrow 00{:}39{:}14.132$ And in the fact that you TX is expressed

NOTE Confidence: 0.8714695225

 $00{:}39{:}14.132 \dashrightarrow 00{:}39{:}16.786$ only in a very small subset of cells,

NOTE Confidence: 0.8714695225

 $00{:}39{:}16.790 \dashrightarrow 00{:}39{:}18.158$ we don't see massive changes at

NOTE Confidence: 0.8714695225

 $00:39:18.158 \longrightarrow 00:39:19.640$ the level of the whole test.

 $00:39:19.640 \longrightarrow 00:39:21.390$ So that's what we expect.

NOTE Confidence: 0.8714695225

 $00:39:21.390 \longrightarrow 00:39:23.574$ But we do see a couple of interesting

NOTE Confidence: 0.8714695225

 $00:39:23.574 \rightarrow 00:39:25.887$ changes, and one of them is KLF 10.

NOTE Confidence: 0.8714695225

 $00{:}39{:}25{.}890 \dashrightarrow 00{:}39{:}28{.}284$ 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

 $00{:}39{:}36{.}030 \dashrightarrow 00{:}39{:}37{.}774$ and we know that it acts in a

NOTE Confidence: 0.8714695225

 $00:39:37.774 \rightarrow 00:39:39.530$ variety of developmental contacts,

NOTE Confidence: 0.8714695225

 $00{:}39{:}39{.}530 \dashrightarrow 00{:}39{:}41{.}890$ often along with TGF beta.

NOTE Confidence: 0.8714695225

 $00{:}39{:}41.890 \dashrightarrow 00{:}39{:}44.557$ And so this is a good candidate for, UM.

NOTE Confidence: 0.8714695225

 $00{:}39{:}44.557 \dashrightarrow 00{:}39{:}48.106$ 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

 $00:39:50.510 \rightarrow 00:39:52.322$ 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

 $00:39:54.670 \rightarrow 00:39:56.358$ and we're actually waiting

NOTE Confidence: 0.8714695225

 $00:39:56.358 \rightarrow 00:39:58.046$ for single cell RNA.

- NOTE Confidence: 0.8714695225
- $00{:}39{:}58.050 \dashrightarrow 00{:}39{:}59.900$ Seek data to come back.
- NOTE Confidence: 0.8714695225
- $00:39:59.900 \dashrightarrow 00:40:02.612$ That will hopefully allow us to look at
- NOTE Confidence: 0.8714695225
- $00:40:02.612 \rightarrow 00:40:04.450$ gene expression changes specifically in
- NOTE Confidence: 0.8714695225
- $00:40:04.450 \rightarrow 00:40:07.310$ the subset of cells that do express JTX,
- NOTE Confidence: 0.8714695225
- $00:40:07.310 \longrightarrow 00:40:08.782$ which hopefully will be.
- NOTE Confidence: 0.8714695225
- $00{:}40{:}08.782 \dashrightarrow 00{:}40{:}10.622$ 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
- $00{:}40{:}14.168 \dashrightarrow 00{:}40{:}17.867$ I getting into sort of to the other end of
- NOTE Confidence: 0.893852786206897
- $00{:}40{:}17.867 \dashrightarrow 00{:}40{:}20.267$ 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
- $00:40:23.116 \rightarrow 00:40:25.332$ tissues to promote tumorigenesis.
- NOTE Confidence: 0.893852786206897
- $00:40:25.340 \longrightarrow 00:40:26.804$ We've actually shifted our
- NOTE Confidence: 0.893852786206897
- $00:40:26.804 \longrightarrow 00:40:27.536$ attention recently.
- NOTE Confidence: 0.893852786206897
- $00{:}40{:}27{.}540 \dashrightarrow 00{:}40{:}30{.}500$ We have been focusing on Magic Poesis based
- NOTE Confidence: 0.893852786206897
- $00{:}40{:}30{.}500 \dashrightarrow 00{:}40{:}33{.}538$ on the histiocytic sarcoma phenotype,
- NOTE Confidence: 0.893852786206897

 $00:40:33.540 \longrightarrow 00:40:34.860$ but have started focusing

NOTE Confidence: 0.893852786206897

 $00{:}40{:}34.860 \dashrightarrow 00{:}40{:}36.840$ a little bit more on lung.

NOTE Confidence: 0.893852786206897

 $00:40:36.840 \rightarrow 00:40:38.352$ And there are a couple of reasons for that.

NOTE Confidence: 0.893852786206897

 $00:40:38.360 \longrightarrow 00:40:40.872$ One is that slang is a little bit

NOTE Confidence: 0.893852786206897

 $00:40:40.872 \longrightarrow 00:40:43.398$ easier to collect than bone marrow,

NOTE Confidence: 0.893852786206897

 $00:40:43.400 \longrightarrow 00:40:46.564$ but also that we saw this really

NOTE Confidence: 0.893852786206897

 $00:40:46.564 \rightarrow 00:40:49.553$ interesting effect in the F1 and F2's,

NOTE Confidence: 0.893852786206897

 $00:40:49.553 \rightarrow 00:40:51.518$ which is just actually there

NOTE Confidence: 0.893852786206897

 $00:40:51.518 \longrightarrow 00:40:53.400$ are two parts of it.

NOTE Confidence: 0.893852786206897

 $00:40:53.400 \longrightarrow 00:40:55.539$ One is that.

NOTE Confidence: 0.893852786206897

 $00:40:55.540 \rightarrow 00:40:58.060$ Long is the only tumor that we never

NOTE Confidence: 0.893852786206897

 $00:40:58.060 \rightarrow 00:40:59.800$ saw spontaneously occur in controls,

NOTE Confidence: 0.893852786206897

 $00:40:59.800 \longrightarrow 00:41:01.830$ 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

 $00:41:03.470 \longrightarrow 00:41:05.906$ so it seems to be fairly specific.

NOTE Confidence: 0.893852786206897

 $00:41:05.910 \longrightarrow 00:41:07.779$ 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
- $00{:}41{:}08{.}920 \dashrightarrow 00{:}41{:}11{.}180$ effective anticipation where the
- NOTE Confidence: 0.893852786206897
- $00:41:11.180 \rightarrow 00:41:14.038$ tumors in the F2's were significantly
- NOTE Confidence: 0.893852786206897
- $00{:}41{:}14.038 \dashrightarrow 00{:}41{:}16.952$ worse than the tumors in the F1F ones
- NOTE Confidence: 0.893852786206897
- $00:41:16.952 \dashrightarrow 00:41:19.024$ tended to be small self contained data
- NOTE Confidence: 0.893852786206897
- 00:41:19.024 --> 00:41:21.104 no
mas and the F2 is often they would
- NOTE Confidence: 0.893852786206897
- $00:41:21.104 \rightarrow 00:41:23.020$ take over the entire chest cavity.
- NOTE Confidence: 0.893852786206897
- $00:41:23.020 \rightarrow 00:41:25.498$ So it seems like there's something
- NOTE Confidence: 0.893852786206897
- $00{:}41{:}25{.}498 \dashrightarrow 00{:}41{:}27{.}505$ especially sensitive in the in
- NOTE Confidence: 0.893852786206897
- $00:41:27.505 \longrightarrow 00:41:29.507$ the lung that may be picking up
- NOTE Confidence: 0.893852786206897
- $00:41:29.507 \longrightarrow 00:41:32.146$ on these changes that do not get
- NOTE Confidence: 0.893852786206897
- $00{:}41{:}32.146 \dashrightarrow 00{:}41{:}34.141$ 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
- $00{:}41{:}35{.}702 \dashrightarrow 00{:}41{:}38{.}855$ we see a substantial set of genes that
- NOTE Confidence: 0.893852786206897
- $00:41:38.855 \rightarrow 00:41:42.310$ are miss regulated in both F1 and F2 long.
- NOTE Confidence: 0.893852786206897

 $00:41:42.310 \longrightarrow 00:41:45.340$ 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

 $00:41:47.450 \rightarrow 00:41:50.598$ completely histologically normal lung,

NOTE Confidence: 0.893852786206897

 $00:41:50.600 \rightarrow 00:41:52.630$ so this is pre any disease and

NOTE Confidence: 0.893852786206897

 $00:41:52.630 \longrightarrow 00:41:54.731$ yet they share about 200 genes

NOTE Confidence: 0.893852786206897

 $00:41:54.731 \rightarrow 00:41:56.666$ that are commonly MIS regulated,

NOTE Confidence: 0.893852786206897

 $00:41:56.670 \rightarrow 00:41:58.716$ implying that there's some sort of

NOTE Confidence: 0.893852786206897

 $00:41:58.716 \rightarrow 00:42:00.629$ common process that's going on there,

NOTE Confidence: 0.893852786206897

 $00{:}42{:}00{.}630 \dashrightarrow 00{:}42{:}03{.}241$ and these genes are enriched for a

NOTE Confidence: 0.893852786206897

 $00:42:03.241 \rightarrow 00:42:05.100$ 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

 $00:42:07.300 \longrightarrow 00:42:09.500$ the most enriched processes relate

NOTE Confidence: 0.893852786206897

 $00:42:09.500 \rightarrow 00:42:12.420$ to protein targeting to the membrane,

NOTE Confidence: 0.893852786206897

 $00{:}42{:}12{.}420 \dashrightarrow 00{:}42{:}15{.}178$ and these are some of the genes

NOTE Confidence: 0.893852786206897

 $00:42:15.180 \longrightarrow 00:42:16.860$ included in that category.

NOTE Confidence: 0.893852786206897

 $00:42:16.860 \longrightarrow 00:42:19.444$ 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
- $00:42:21.710 \longrightarrow 00:42:24.350$ To emphasize that these effects are
- NOTE Confidence: 0.893852786206897
- $00:42:24.350 \rightarrow 00:42:26.110$ very consistent from individual
- NOTE Confidence: 0.893852786206897
- $00{:}42{:}26.180 \dashrightarrow 00{:}42{:}27.100$ to individual.
- NOTE Confidence: 0.893852786206897
- 00:42:27.100 --> 00:42:27.511 Again,
- NOTE Confidence: 0.893852786206897
- $00:42:27.511 \longrightarrow 00:42:29.566$ despite the fact that they're
- NOTE Confidence: 0.893852786206897
- $00:42:29.566 \rightarrow 00:42:31.617$ genetically identical and there is
- NOTE Confidence: 0.893852786206897
- $00:42:31.617 \rightarrow 00:42:33.687$ no apparent disease in these tissues.
- NOTE Confidence: 0.9709671566666667
- $00{:}42{:}35{.}990 \dashrightarrow 00{:}42{:}39{.}289$ And finally, in trying to understand again
- NOTE Confidence: 0.9709671566666667
- $00:42:39.289 \longrightarrow 00:42:42.321$ what the links are between these sets of
- NOTE Confidence: 0.9709671566666667
- $00{:}42{:}42{.}321 \dashrightarrow 00{:}42{:}45{.}308$ miss regulated genes and tumorigenesis,
- NOTE Confidence: 0.9709671566666667
- $00{:}42{:}45{.}310 \dashrightarrow 00{:}42{:}48{.}254$ we've also noticed that the sets of genes
- NOTE Confidence: 0.9709671566666667
- $00{:}42{:}48{.}254 \dashrightarrow 00{:}42{:}51{.}382$ that are commonly miss regulated in F1 and
- NOTE Confidence: 0.9709671566666667
- $00{:}42{:}51{.}382 \dashrightarrow 00{:}42{:}57{.}160$ F2 lungs are enriched for being Mick targets.
- NOTE Confidence: 0.9709671566666667
- $00:42:57.160 \longrightarrow 00:43:00.360$ To make, of course is a is a.
- NOTE Confidence: 0.9709671566666667

00:43:00.360 --> 00:43:01.998 Extremely common oncogene,

NOTE Confidence: 0.9709671566666667

 $00:43:01.998 \rightarrow 00:43:05.274$ and it's been implicated previously in

NOTE Confidence: 0.9709671566666667

 $00:43:05.274 \rightarrow 00:43:07.979$ regulating abrass dependent lung cancer,

NOTE Confidence: 0.9709671566666667

 $00:43:07.980 \rightarrow 00:43:11.804$ so this may be sort of an interesting

NOTE Confidence: 0.9709671566666667

 $00:43:11.810 \longrightarrow 00:43:13.442$ connection to what's actually

NOTE Confidence: 0.9709671566666667

 $00:43:13.442 \rightarrow 00:43:15.482$ happening to initiate these tumors.

NOTE Confidence: 0.9709671566666667

 $00:43:15.490 \rightarrow 00:43:19.676$ To predispose these lung tissues to tumors.

NOTE Confidence: 0.9709671566666667

00:43:19.680 --> 00:43:22.998 Uh. So so in conclusion,

NOTE Confidence: 0.9709671566666667

 $00:43:22.998 \rightarrow 00:43:25.233$ basically we've found that perturbing

NOTE Confidence: 0.9709671566666667

 $00:43:25.233 \rightarrow 00:43:27.659$ epigenetic state in male germ cells

NOTE Confidence: 0.9709671566666667

 $00{:}43{:}27.659 \dashrightarrow 00{:}43{:}29.569$ reduces the lifespan and increases

NOTE Confidence: 0.9709671566666667

00:43:29.640 --> 00:43:31.908 tumor rate and wild type offspring,

NOTE Confidence: 0.9709671566666667

 $00:43:31.910 \longrightarrow 00:43:34.220$ and that's perma VTX knockout.

NOTE Confidence: 0.9709671566666667

 $00{:}43{:}34{.}220 \dashrightarrow 00{:}43{:}37{.}260$ Males carries changes in histone

NOTE Confidence: 0.9709671566666667

00:43:37.260 --> 00:43:38.836 modification K27 TRIMETHYLATION,

NOTE Confidence: 0.9709671566666667

00:43:38.836 --> 00:43:40.768 and in DNA METALATION,

- NOTE Confidence: 0.9709671566666667
- $00:43:40.770 \longrightarrow 00:43:43.125$ and some of those changes
- NOTE Confidence: 0.9709671566666667
- 00:43:43.125 00:43:44.538 persist into offspring.
- NOTE Confidence: 0.9709671566666667
- $00{:}43{:}44{.}540 \dashrightarrow 00{:}43{:}45{.}329$ And to me,
- NOTE Confidence: 0.9709671566666667
- $00{:}43{:}45{.}329 \dashrightarrow 00{:}43{:}47{.}170$ this implies that a common set of
- NOTE Confidence: 0.9709671566666667
- $00:43:47.237 \rightarrow 00:43:49.332$ regulatory networks may be sensitive
- NOTE Confidence: 0.9709671566666667
- $00:43:49.332 \longrightarrow 00:43:51.427$ to epigenetic perturbation in the
- NOTE Confidence: 0.9709671566666667
- $00:43:51.492 \rightarrow 00:43:53.288$ germline and in tumorigenesis.
- NOTE Confidence: 0.9709671566666667
- $00:43:53.290 \rightarrow 00:43:56.888$ In other words, there are some jeans,
- NOTE Confidence: 0.9709671566666667
- $00:43:56.890 \rightarrow 00:43:58.154$ some promoters,
- NOTE Confidence: 0.9709671566666667
- $00:43:58.154 \rightarrow 00:44:01.314$ some regulatory regions that are
- NOTE Confidence: 0.9709671566666667
- $00:44:01.314 \rightarrow 00:44:04.506$ especially sensitive to any kind of
- NOTE Confidence: 0.9709671566666667
- $00{:}44{:}04{.}506 \dashrightarrow 00{:}44{:}07{.}530$ epigenetic change be at loss of BTX
- NOTE Confidence: 0.9709671566666667
- $00:44:07.626 \rightarrow 00:44:10.570$ or potentially an environmental.
- NOTE Confidence: 0.9709671566666667
- $00{:}44{:}10.570 \dashrightarrow 00{:}44{:}14.560$ Influence or or toxin and that.
- NOTE Confidence: 0.9709671566666667
- $00{:}44{:}14{.}560 \dashrightarrow 00{:}44{:}18{.}118$ The germ line is particularly prone
- NOTE Confidence: 0.9709671566666667

 $00:44:18.118 \rightarrow 00:44:21.370$ to misregulation of those regions,

NOTE Confidence: 0.9709671566666667

 $00:44:21.370 \rightarrow 00:44:26.160$ and those regions are especially.

NOTE Confidence: 0.9709671566666667

 $00:44:26.160 \rightarrow 00:44:29.334$ Have an especially strong tendency to

NOTE Confidence: 0.9709671566666667

 $00:44:29.334 \rightarrow 00:44:32.510$ contribute to initiation of pyrogenesis,

NOTE Confidence: 0.9709671566666667

 $00:44:32.510 \longrightarrow 00:44:34.934$ so there's a correlation that may

NOTE Confidence: 0.9709671566666667

 $00:44:34.934 \rightarrow 00:44:37.400$ actually be causation across generations,

NOTE Confidence: 0.9709671566666667

 $00:44:37.400 \longrightarrow 00:44:39.392$ but at least is an interesting

NOTE Confidence: 0.9709671566666667

 $00:44:39.392 \rightarrow 00:44:41.340$ set of networks to explore.

NOTE Confidence: 0.9709671566666667

00:44:41.340 --> 00:44:42.308 And finally,

NOTE Confidence: 0.9709671566666667

 $00:44:42.308 \rightarrow 00:44:45.696$ this sort of fascinating idea that although

NOTE Confidence: 0.9709671566666667

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: 0.9709671566666667

00:44:49.408 - 00:44:51.320 It may have a role in the germline,

NOTE Confidence: 0.9709671566666667

 $00{:}44{:}51{.}320 \dashrightarrow 00{:}44{:}53{.}820$ and tuning heritable epigenetic information.

NOTE Confidence: 0.9709671566666667

 $00:44:53.820 \longrightarrow 00:44:55.120$ So in other words,

NOTE Confidence: 0.9709671566666667

 $00:44:55.120 \longrightarrow 00:44:57.070$ the Organism has an interest in
NOTE Confidence: 0.9709671566666667

 $00:44:57.144 \rightarrow 00:44:59.392$ controlling what epigenetic information

NOTE Confidence: 0.9709671566666667

 $00:44:59.392 \rightarrow 00:45:01.640$ is passed across generations,

NOTE Confidence: 0.9709671566666667

 $00:45:01.640 \longrightarrow 00:45:04.720$ and that U TX may be one of the tools

NOTE Confidence: 0.9709671566666667

 $00:45:04.810 \longrightarrow 00:45:08.226$ that it uses to control that information.

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}08{.}230 \dashrightarrow 00{:}45{:}10{.}990$ So finally I just want to acknowledge a

NOTE Confidence: 0.9709671566666667

 $00:45:10.990 \rightarrow 00:45:14.350$ bunch of people who have contributed to this,

NOTE Confidence: 0.9709671566666667

 $00:45:14.350 \longrightarrow 00:45:14.695$ uhm,

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}14.695 \dashrightarrow 00{:}45{:}17.455$ Ben Walters is a postdoc who's done most

NOTE Confidence: 0.9709671566666667

 $00:45:17.455 \longrightarrow 00:45:20.385$ of the work on this project in my lab,

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}20{.}390 \dashrightarrow 00{:}45{:}22{.}645$ Shannon created the fertilization video

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}22.645 \dashrightarrow 00{:}45{:}26.009$ that I showed and Allison is underground.

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}26.010 \dashrightarrow 00{:}45{:}28.314$ He's been helping Ben out how Ming

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}28{.}314 \dashrightarrow 00{:}45{:}30{.}277$ is a student who has done some

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}30{.}277 \dashrightarrow 00{:}45{:}31{.}879$ really cool work on this project

NOTE Confidence: 0.9709671566666667

 $00:45:31.879 \longrightarrow 00:45:33.648$ that I actually did not show here,

NOTE Confidence: 0.9709671566666667

 $00:45:33.650 \rightarrow 00:45:35.514$ and I want to make sure to acknowledge

NOTE Confidence: 0.9709671566666667

 $00:45:35.514 \longrightarrow 00:45:37.397$ this is a project that I initiated.

NOTE Confidence: 0.9709671566666667

00:45:37.400 --> 00:45:40.384 As a postdoc at Whitehead and David Page,

NOTE Confidence: 0.9709671566666667

 $00:45:40.390 \longrightarrow 00:45:41.256$ my mentor,

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}41{.}256 \dashrightarrow 00{:}45{:}43{.}421$ there was extremely generous and

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}43{.}421 \dashrightarrow 00{:}45{:}46{.}621$ letting me start this very risky and

NOTE Confidence: 0.9709671566666667

 $00:45:46.621 \rightarrow 00:45:48.896$ very expensive project without much

NOTE Confidence: 0.9709671566666667

 $00:45:48.896 \rightarrow 00:45:51.668$ promise of of where it was going to go,

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}51{.}670 \dashrightarrow 00{:}45{:}54{.}580$ and likewise hope funds for Cancer

NOTE Confidence: 0.9709671566666667

 $00:45:54.580 \longrightarrow 00:45:56.520$ Research initially funded it.

NOTE Confidence: 0.9709671566666667

 $00{:}45{:}56{.}520 \dashrightarrow 00{:}46{:}00{.}420$ Similarly had a very risky stage.

NOTE Confidence: 0.9709671566666667

00:46:00.420 --> 00:46:02.796 Rod Brunson is a veterinary Paul

NOTE Confidence: 0.9709671566666667

00:46:02.796 --> 00:46:05.733 tough Ologist who did the the looked

NOTE Confidence: 0.9709671566666667

 $00:46:05.733 \rightarrow 00:46:07.858$ at actually every single necropsy

NOTE Confidence: 0.9709671566666667

 $00:46:07.858 \longrightarrow 00:46:10.888$ slide for this project she's on and

NOTE Confidence: 0.9709671566666667

 $00{:}46{:}10.888 \dashrightarrow 00{:}46{:}12.918$ Ben are hematologists who helped

- NOTE Confidence: 0.9709671566666667
- $00:46:12.918 \longrightarrow 00:46:14.700$ with that phenotyping.
- NOTE Confidence: 0.9709671566666667
- $00{:}46{:}14.700 \dashrightarrow 00{:}46{:}16.825$ Elizabeth Morgan as apologists at
- NOTE Confidence: 0.9709671566666667
- 00:46:16.825 --> 00:46:18.950 Brigham Hill helps validate some
- NOTE Confidence: 0.762290705384615
- $00{:}46{:}19.018 \dashrightarrow 00{:}46{:}21.845$ 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
- $00{:}46{:}24.736 \dashrightarrow 00{:}46{:}27.610$ 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
- $00:46:31.490 \longrightarrow 00:46:32.678$ Answering any questions.
- NOTE Confidence: 0.873334588
- 00:46:37.280 --> 00:46:38.840 Thank you so much Bluma.
- NOTE Confidence: 0.873334588
- $00:46:38.840 \longrightarrow 00:46:41.605$ Uhm that was it was really fantastic.
- NOTE Confidence: 0.873334588
- $00{:}46{:}41.610 \dashrightarrow 00{:}46{:}45.213$ I think a lot of us think about changes
- NOTE Confidence: 0.873334588
- $00:46:45.213 \longrightarrow 00:46:48.314$ 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
- $00:46:51.028 \rightarrow 00:46:55.380$ but we don't really get to think a lot about.
- NOTE Confidence: 0.873334588

 $00:46:55.380 \longrightarrow 00:46:57.070$ The mechanisms underlying what sort

NOTE Confidence: 0.873334588

 $00{:}46{:}57.070 \dashrightarrow 00{:}46{:}59.259$ of what those changes are sort of.

NOTE Confidence: 0.873334588

 $00{:}46{:}59{.}260 \dashrightarrow 00{:}47{:}00{.}842$ What is the origin of those changes

NOTE Confidence: 0.873334588

 $00{:}47{:}00{.}842 \dashrightarrow 00{:}47{:}02{.}995$ and and sort of all the different

NOTE Confidence: 0.873334588

 $00:47:02.995 \longrightarrow 00:47:04.415$ contexts that you mentioned here,

NOTE Confidence: 0.873334588

 $00{:}47{:}04{.}420 \dashrightarrow 00{:}47{:}05{.}740$ and the germ line.

NOTE Confidence: 0.873334588

 $00{:}47{:}05{.}740 \dashrightarrow 00{:}47{:}07{.}574$ So thank you so much.

NOTE Confidence: 0.873334588

 $00:47:07.574 \rightarrow 00:47:10.608$ There are actually a couple of questions

NOTE Confidence: 0.873334588

 $00{:}47{:}10.608 \dashrightarrow 00{:}47{:}13.252$ already, so doctor Sklar asked.

NOTE Confidence: 0.873334588

 $00{:}47{:}13.252 \dashrightarrow 00{:}47{:}15.692$ Where the tumor types heritable

NOTE Confidence: 0.873334588

 $00{:}47{:}15.692 \dashrightarrow 00{:}47{:}18.307$ between the F1 and F2 generations.

NOTE Confidence: 0.850852887777778

 $00:47:20.670 \longrightarrow 00:47:22.950$ Uhm, meaning oh, so if you have a

NOTE Confidence: 0.850852887777778

 $00{:}47{:}22.950 \dashrightarrow 00{:}47{:}25.441$ specific if you have an F1 with a

NOTE Confidence: 0.850852887777778

 $00{:}47{:}25{.}441 \dashrightarrow 00{:}47{:}27{.}062$ particular tumor, do the offspring

NOTE Confidence: 0.850852887777778

 $00:47:27.062 \rightarrow 00:47:29.700$ of that F1 get the same tumor so?

NOTE Confidence: 0.812778536

 $00:47:32.020 \longrightarrow 00:47:33.060$ Uh, yeah, I think that.

NOTE Confidence: 0.812778536

 $00{:}47{:}33.060 \dashrightarrow 00{:}47{:}34.530$ I think that's the question.

NOTE Confidence: 0.907904933043478

 $00{:}47{:}34.700 \dashrightarrow 00{:}47{:}37.080$ OK yeah, that's a great question and

NOTE Confidence: 0.907904933043478

 $00{:}47{:}37{.}080 \dashrightarrow 00{:}47{:}40{.}178$ one that we do not have data to answer

NOTE Confidence: 0.907904933043478

 $00:47:40.178 \rightarrow 00:47:43.008$ because the we never actually bred those.

NOTE Confidence: 0.907904933043478

 $00{:}47{:}43.010 \dashrightarrow 00{:}47{:}45.187$ Come the F1 that we phenotypes we

NOTE Confidence: 0.907904933043478

 $00{:}47{:}45{.}187 \dashrightarrow 00{:}47{:}47{.}459$ 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

 $00{:}47{:}49{.}511 \dashrightarrow 00{:}47{:}51{.}550$ able to make that specific connection

NOTE Confidence: 0.907904933043478

 $00:47:51.550 \longrightarrow 00:47:53.746$ from the F1 to F2 generation.

NOTE Confidence: 0.907904933043478

 $00{:}47{:}53.750 \dashrightarrow 00{:}47{:}56.240$ It's only at the population level but yeah,

NOTE Confidence: 0.907904933043478

 $00{:}47{:}56{.}240 \dashrightarrow 00{:}47{:}57{.}220$ that's a great question.

NOTE Confidence: 0.844743998

 $00{:}47{:}59{.}030 \dashrightarrow 00{:}48{:}02{.}458$ OK and then come from Katie

NOTE Confidence: 0.844743998

 $00{:}48{:}02{.}458 \dashrightarrow 00{:}48{:}04{.}398$ Politi bloomer really nice talk.

NOTE Confidence: 0.844743998

 $00{:}48{:}04{.}400 \dashrightarrow 00{:}48{:}06{.}984$ Have you looked at the lung tumors to

NOTE Confidence: 0.844743998

 $00:48:06.984 \rightarrow 00:48:09.406$ see whether they have K Ras mutations?

NOTE Confidence: 0.844743998

 $00:48:09.410 \longrightarrow 00:48:10.995$ Mice can develop them spontaneously

NOTE Confidence: 0.844743998

 $00:48:10.995 \longrightarrow 00:48:12.580$ and as you mentioned K.

NOTE Confidence: 0.844743998

 $00:48:12.580 \longrightarrow 00:48:14.380$ Ruskin cooperate with MIC.

NOTE Confidence: 0.799510418

 $00:48:14.960 \longrightarrow 00:48:18.059$ Yeah also a great question. We have not.

NOTE Confidence: 0.799510418

 $00:48:18.059 \longrightarrow 00:48:20.414$ We haven't looked at any genetics

NOTE Confidence: 0.799510418

 $00:48:20.414 \longrightarrow 00:48:23.770$ yet in these mice so we haven't

NOTE Confidence: 0.799510418

 $00:48:23.770 \longrightarrow 00:48:26.150$ looked to see what kind of underlying

NOTE Confidence: 0.799510418

 $00:48:26.217 \rightarrow 00:48:28.547$ 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

 $00{:}48{:}31{.}091 \dashrightarrow 00{:}48{:}33{.}907$ to try and do some XM sequencing

NOTE Confidence: 0.799510418

 $00:48:33.907 \longrightarrow 00:48:36.373$ 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

 $00:48:38.250 \longrightarrow 00:48:40.378$ but but we definitely want to look

NOTE Confidence: 0.799510418

 $00:48:40.378 \longrightarrow 00:48:41.280$ at that, yeah?

NOTE Confidence: 0.889154753846154

 $00{:}48{:}43.780 \dashrightarrow 00{:}48{:}47.748$ OK, and then there's also a question in

NOTE Confidence: 0.889154753846154

 $00{:}48{:}47{.}748 \dashrightarrow 00{:}48{:}51{.}952$ the Q&A box from Chen and many of these

- NOTE Confidence: 0.889154753846154
- $00:48:51.952 \longrightarrow 00:48:56.109$ top dogs in F1 and F2 lungs 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
- $00:48:59.252 \rightarrow 00:49:02.109$ of translation translational changes?
- NOTE Confidence: 0.920915255
- $00:49:03.170 \longrightarrow 00:49:04.400$ 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
- $00{:}49{:}06{.}070 \dashrightarrow 00{:}49{:}07{.}764$ but we haven't collected that data yet.
- NOTE Confidence: 0.920915255
- $00:49:07.770 \longrightarrow 00:49:09.420$ This is all pretty new.
- NOTE Confidence: 0.920915255
- $00:49:09.420 \longrightarrow 00:49:10.880$ 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
- $00:49:18.030 \rightarrow 00:49:20.485$ 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
- $00{:}49{:}22{.}449 \dashrightarrow 00{:}49{:}24{.}619$ screening and or genetic counseling
- NOTE Confidence: 0.920723748
- $00:49:24.619 \rightarrow 00:49:26.634$ in couples planning to conceive
- NOTE Confidence: 0.920723748

 $00:49:26.634 \rightarrow 00:49:29.058$ or with male infertility issues?

NOTE Confidence: 0.6773909016666667

 $00{:}49{:}29{.}970 \dashrightarrow 00{:}49{:}33{.}558$ Uhm, that's a great question I.

NOTE Confidence: 0.677390901666667

 $00:49:33.560 \longrightarrow 00:49:34.752$ So yes and no.

NOTE Confidence: 0.6773909016666667

 $00:49:34.752 \longrightarrow 00:49:37.008$ I think on a practical level it

NOTE Confidence: 0.6773909016666667

00:49:37.008 -> 00:49:39.773 would be very difficult to do any

NOTE Confidence: 0.677390901666667

 $00:49:39.773 \rightarrow 00:49:41.610$ epigenetic screening at this point.

NOTE Confidence: 0.6773909016666667

 $00{:}49{:}41.610 \dashrightarrow 00{:}49{:}43.969$ I think it that's some future goal

NOTE Confidence: 0.6773909016666667

 $00:49:43.969 \rightarrow 00:49:46.887$ might be to identify a set in humans,

NOTE Confidence: 0.6773909016666667

 $00{:}49{:}46{.}890 \dashrightarrow 00{:}49{:}49{.}375$ a set of sort of high risk

NOTE Confidence: 0.6773909016666667

 $00:49:49.375 \longrightarrow 00:49:51.583$ epigenetic loci that we could do

NOTE Confidence: 0.6773909016666667

 $00{:}49{:}51{.}583 \dashrightarrow 00{:}49{:}54.068$ some sort of array on or something.

NOTE Confidence: 0.6773909016666667

 $00{:}49{:}54{.}070 \dashrightarrow 00{:}49{:}55{.}987$ And then we could look at things like that.

NOTE Confidence: 0.6773909016666667

00:49:55.990 --> 00:49:58.060 Or right now we just don't have any idea

NOTE Confidence: 0.6773909016666667

 $00:49:58.060 \rightarrow 00:50:00.120$ we can't like whole genome sequence,

NOTE Confidence: 0.6773909016666667

 $00:50:00.120 \rightarrow 00:50:02.322$ every infertile couple or whole genome

NOTE Confidence: 0.6773909016666667

 $00:50:02.322 \rightarrow 00:50:03.790$ bisulfite sequence every infertile.

- NOTE Confidence: 0.6773909016666667
- 00:50:03.790 --> 00:50:04.686 Couple uhm.
- NOTE Confidence: 0.6773909016666667
- 00:50:04.686 --> 00:50:07.374 But I actually think like looking
- NOTE Confidence: 0.6773909016666667
- $00:50:07.374 \rightarrow 00:50:10.043$ for germline mutations of epigenetic
- NOTE Confidence: 0.6773909016666667
- $00:50:10.043 \rightarrow 00:50:12.863$ regulators is a potentially really
- NOTE Confidence: 0.6773909016666667
- $00{:}50{:}12.863 \dashrightarrow 00{:}50{:}15.615$ fruitful thing that people don't do
- NOTE Confidence: 0.6773909016666667
- $00{:}50{:}15.615 \dashrightarrow 00{:}50{:}18.000$ right now because I think what one
- NOTE Confidence: 0.6773909016666667
- $00:50:18.000 \rightarrow 00:50:20.539$ thing that our study has shown is that
- NOTE Confidence: 0.677390901666667
- $00{:}50{:}20{.}540 \dashrightarrow 00{:}50{:}23{.}804$ increase rates of mutation of these
- NOTE Confidence: 0.6773909016666667
- $00{:}50{:}23.804 \dashrightarrow 00{:}50{:}26.625$ regulators can affect phenotype even if
- NOTE Confidence: 0.677390901666667
- $00:50:26.625 \rightarrow 00:50:29.820$ the mutation itself is not inherited.
- NOTE Confidence: 0.6773909016666667
- $00:50:29.820 \longrightarrow 00:50:30.956$ So in other words,
- NOTE Confidence: 0.6773909016666667
- $00{:}50{:}30{.}956 \dashrightarrow 00{:}50{:}31{.}808$ if there are,
- NOTE Confidence: 0.6773909016666667
- $00:50:31.810 \longrightarrow 00:50:34.127$ if you're if the father is producing
- NOTE Confidence: 0.6773909016666667
- $00{:}50{:}34{.}127 \dashrightarrow 00{:}50{:}36{.}189$ sperm that carry these mutations.
- NOTE Confidence: 0.6773909016666667
- $00{:}50{:}36{.}190 \dashrightarrow 00{:}50{:}38{.}150$ Even if the sperm that creates the
- NOTE Confidence: 0.6773909016666667

00:50:38.150 --> 00:50:39.709 embryo doesn't carry the mutation,

NOTE Confidence: 0.6773909016666667

 $00:50:39.710 \longrightarrow 00:50:41.942$ it may actually be relevant information

NOTE Confidence: 0.677390901666667

 $00:50:41.942 \longrightarrow 00:50:44.258$ for understanding the health of the embryo.

NOTE Confidence: 0.6773909016666667

 $00:50:44.260 \longrightarrow 00:50:45.580$ So and that's something that we

NOTE Confidence: 0.6773909016666667

 $00:50:45.580 \longrightarrow 00:50:47.345$ may be might be able to do at

NOTE Confidence: 0.6773909016666667

 $00{:}50{:}47{.}345 \dashrightarrow 00{:}50{:}48{.}385$ kind of a screening level.

NOTE Confidence: 0.793740314

 $00:50:50.690 \rightarrow 00:50:54.346$ And finally, Doctor Prasad asked, can these

NOTE Confidence: 0.793740314

 $00:50:54.346 \rightarrow 00:50:56.736$ 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

 $00:51:01.036 \rightarrow 00:51:03.140$ 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

 $00:51:08.974 \longrightarrow 00:51:10.546$ 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

 $00:51:13.814 \rightarrow 00:51:15.424$ of epigenetic drugs and seeing

NOTE Confidence: 0.846175212222222

 $00:51:15.424 \rightarrow 00:51:17.349$ what that would affect that has,

NOTE Confidence: 0.846175212222222

 $00:51:17.350 \rightarrow 00:51:20.326$ although that's obviously not locus specific,

- NOTE Confidence: 0.846175212222222
- $00:51:20.330 \rightarrow 00:51:22.738$ so that may have a lot of secondary
- NOTE Confidence: 0.846175212222222
- $00{:}51{:}22.738 \dashrightarrow 00{:}51{:}24.659$ changes that we're not expecting.
- NOTE Confidence: 0.846175212222222
- $00:51:24.660 \rightarrow 00:51:26.472$ My lab has thought about using
- NOTE Confidence: 0.846175212222222
- $00{:}51{:}26{.}472 \dashrightarrow 00{:}51{:}27{.}988$ CRISPR type approaches to do
- NOTE Confidence: 0.846175212222222
- $00:51:27.988 \longrightarrow 00:51:29.470$ this in a locus specific way,
- NOTE Confidence: 0.846175212222222
- $00:51:29.470 \longrightarrow 00:51:32.098$ but that's obviously not.
- NOTE Confidence: 0.846175212222222
- $00:51:32.100 \longrightarrow 00:51:34.680$ Sort of applicable then it
- NOTE Confidence: 0.846175212222222
- 00:51:34.680 --> 00:51:36.228 potentially clinically applicable
- NOTE Confidence: 0.846175212222222
- $00:51:36.230 \rightarrow 00:51:39.190$ 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
- $00:51:42.110 \longrightarrow 00:51:43.944$ so that's a great question as well.
- NOTE Confidence: 0.846175212222222
- $00{:}51{:}43{.}950 \dashrightarrow 00{:}51{:}45{.}147$ 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
- $00{:}51{:}48{.}550 \dashrightarrow 00{:}51{:}51{.}764$ talk and I thought it's fascinating that
- NOTE Confidence: 0.701810683333333
- $00{:}51{:}51{.}764 \dashrightarrow 00{:}51{:}56{.}121$ you have mice with with different code
- NOTE Confidence: 0.701810683333333

 $00:51:56.121 \rightarrow 00:51:59.748$ colors and that was epic genetically

NOTE Confidence: 0.909521753333333

 $00:52:00.540 \rightarrow 00:52:05.040$ determined. And and which brings me to.

NOTE Confidence: 0.909521753333333

 $00:52:05.040 \longrightarrow 00:52:07.420$ Is that possible that the skin color in

NOTE Confidence: 0.909521753333333

 $00:52:07.420 \rightarrow 00:52:10.976$ humans is also epigenetically determined?

NOTE Confidence: 0.909521753333333

 $00{:}52{:}10.976 \dashrightarrow 00{:}52{:}14.055$ Because clearly there is a correlation to

NOTE Confidence: 0.909521753333333

 $00{:}52{:}14.055 \dashrightarrow 00{:}52{:}17.105$ environment and sun exposure and different NOTE Confidence: 0.909521753333333

 $00:52:17.105 \longrightarrow 00:52:22.160$ regions in the world and the skin color.

NOTE Confidence: 0.909521753333333

00:52:22.160 --> 00:52:25.639 Yeah yeah. So. So on one level.

NOTE Confidence: 0.909521753333333

 $00:52:25.640 \rightarrow 00:52:27.304$ Certainly there's an epigenetic

NOTE Confidence: 0.909521753333333

 $00:52:27.304 \rightarrow 00:52:28.968$ component because it's responsive,

NOTE Confidence: 0.909521753333333

 $00:52:28.970 \dashrightarrow 00:52:31.268$ as you said, responsive to environment.

NOTE Confidence: 0.909521753333333

 $00:52:31.270 \longrightarrow 00:52:34.380$ So if you if you spend a lot of time

NOTE Confidence: 0.909521753333333

 $00:52:34.474 \rightarrow 00:52:37.080$ in the sun then generally your skin

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 $00:52:37.080 \rightarrow 00:52:39.255$ gets darker and that's epigenetic.

NOTE Confidence: 0.909521753333333

 $00:52:39.260 \longrightarrow 00:52:40.856$ It's there's there's.

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 $00:52:40.856 \rightarrow 00:52:44.048$ It's not necessarily gene regulatory based,

- NOTE Confidence: 0.909521753333333
- $00:52:44.050 \rightarrow 00:52:46.240$ but then the second question might
- NOTE Confidence: 0.909521753333333
- $00:52:46.240 \longrightarrow 00:52:48.519$ be to wet expenses that heritable
- NOTE Confidence: 0.909521753333333
- $00{:}52{:}48{.}519 \dashrightarrow 00{:}52{:}50{.}389$ and that we don't know.
- NOTE Confidence: 0.909521753333333
- $00:52:50.390 \longrightarrow 00:52:52.217$ I think in the in the case of mice.
- NOTE Confidence: 0.909521753333333
- $00:52:52.220 \longrightarrow 00:52:54.434$ We had a specific locus that
- NOTE Confidence: 0.909521753333333
- $00:52:54.434 \longrightarrow 00:52:56.674$ we knew is responsible for, UM,
- NOTE Confidence: 0.909521753333333
- $00:52:56.674 \rightarrow 00:52:59.432$ for coat color and and then
- NOTE Confidence: 0.909521753333333
- 00:52:59.432 --> 00:53:01.850 a specific regulatory change.
- NOTE Confidence: 0.909521753333333
- $00:53:01.850 \longrightarrow 00:53:02.726$ In that case,
- NOTE Confidence: 0.909521753333333
- $00:53:02.726 \longrightarrow 00:53:04.770$ there was a transposon that was inserted
- NOTE Confidence: 0.909521753333333
- $00:53:04.828 \longrightarrow 00:53:06.871$ in the locus so we could try or the
- NOTE Confidence: 0.909521753333333
- 00:53:06.871 00:53:08.776 people who did the study could track,
- NOTE Confidence: 0.909521753333333
- $00:53:08.780 \longrightarrow 00:53:10.556$ you know, the extent to which
- NOTE Confidence: 0.909521753333333
- $00{:}53{:}10{.}556 \dashrightarrow 00{:}53{:}11{.}740$ that transposon was methylated.
- NOTE Confidence: 0.909521753333333
- $00:53:11.740 \longrightarrow 00:53:12.163$ Basically,
- NOTE Confidence: 0.909521753333333

 $00{:}53{:}12.163 \dashrightarrow 00{:}53{:}15.547$ in humans I don't know if we know

NOTE Confidence: 0.909521753333333

 $00:53:15.547 \longrightarrow 00:53:18.496$ of alleles that could do that.

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00:53:18.500 --> 00:53:20.930 Sort of an analogous situation

NOTE Confidence: 0.909521753333333

 $00:53:20.930 \longrightarrow 00:53:22.366$ so we don't have.

NOTE Confidence: 0.909521753333333

00:53:22.366 --> 00:53:24.161 Any specific data sort of

NOTE Confidence: 0.909521753333333

 $00:53:24.161 \rightarrow 00:53:25.969$ demonstrating that it could be true,

NOTE Confidence: 0.909521753333333

 $00:53:25.970 \rightarrow 00:53:27.340$ although we don't have anything

NOTE Confidence: 0.909521753333333

 $00:53:27.340 \rightarrow 00:53:29.350$ 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

 $00:53:38.740 \longrightarrow 00:53:41.124$ have any other questions.

NOTE Confidence: 0.945543644

 $00{:}53{:}41{.}124 \dashrightarrow 00{:}53{:}43{.}680$ 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

 $00{:}53{:}51{.}930 \dashrightarrow 00{:}53{:}54{.}852$ helping you connect with anyone in our

NOTE Confidence: 0.945543644

 $00{:}53{:}54{.}852 \dashrightarrow 00{:}53{:}58{.}790$ 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
- $00:54:00.870 \longrightarrow 00:54:02.534$ in in whatever capacity?

NOTE Confidence: 0.75465924

 $00:54:03.740 \longrightarrow 00:54:04.950$ Yeah, no thank you again,

NOTE Confidence: 0.75465924

 $00:54:04.950 \longrightarrow 00:54:06.819$ it was great to to be here.

NOTE Confidence: 0.775924158571429

 $00{:}54{:}09{.}210 \dashrightarrow 00{:}54{:}13{.}354$ Hey, uhm. I guess we can't come.

NOTE Confidence: 0.8176172

 $00:54:15.450 \longrightarrow 00:54:17.330$ Uh, I guess that that's sort of

NOTE Confidence: 0.8176172

 $00{:}54{:}17{.}330 \dashrightarrow 00{:}54{:}20{.}186$ it so we can come log off there.

NOTE Confidence: 0.8176172

 $00:54:20.190 \longrightarrow 00:54:22.206$ 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.