WEBVTT

NOTE duration:"00:48:35.8080000"

NOTE language:en-us

NOTE Confidence: 0.818772971630096

00:00:00.000 --> 00:00:02.116 Alright everyone, good afternoon,

NOTE Confidence: 0.818772971630096

 $00:00:02.116 \rightarrow 00:00:05.769$  let's go ahead and get started so

NOTE Confidence: 0.818772971630096

 $00:00:05.769 \longrightarrow 00:00:08.513$  everyone can get on with their day.

NOTE Confidence: 0.818772971630096

 $00{:}00{:}08{.}520 \dashrightarrow 00{:}00{:}11{.}224$  It is our great pleasure today to welcome

NOTE Confidence: 0.818772971630096

 $00{:}00{:}11.224 \dashrightarrow 00{:}00{:}13.845$  Doctor Jian Xu as our distinguished speaker

NOTE Confidence: 0.818772971630096

 $00:00:13.845 \rightarrow 00:00:16.291$  of Hematology for that Yale Cooperative

NOTE Confidence: 0.818772971630096

00:00:16.291 --> 00:00:18.786 Center of Excellence in Hematology.

NOTE Confidence: 0.818772971630096

 $00:00:18.790 \longrightarrow 00:00:21.065$  We are in enjoyed very glad to

NOTE Confidence: 0.818772971630096

00:00:21.065 --> 00:00:23.831 welcome him not just on behalf of

NOTE Confidence: 0.818772971630096

 $00{:}00{:}23.831 \dashrightarrow 00{:}00{:}25.981$  the Yellow Cooperative Center of

NOTE Confidence: 0.818772971630096

00:00:25.981 --> 00:00:27.479 Excellence of Hematology,

NOTE Confidence: 0.818772971630096

 $00{:}00{:}27.480 \dashrightarrow 00{:}00{:}30.504$  but also for all of the Centers of excellence

NOTE Confidence: 0.818772971630096

 $00:00:30.504 \rightarrow 00:00:33.436$  in hematology across the United States.

NOTE Confidence: 0.818772971630096

 $00:00:33.440 \longrightarrow 00:00:35.825$  As you can see, the title of his talk

- NOTE Confidence: 0.818772971630096
- $00:00:35.825 \rightarrow 00:00:38.554$  is decoding the noncoding genome in
- NOTE Confidence: 0.818772971630096
- $00:00:38.554 \rightarrow 00:00:40.470$  blood development and disorders.
- NOTE Confidence: 0.818772971630096
- $00:00:40.470 \longrightarrow 00:00:42.320$  He was trained at UCLA.
- NOTE Confidence: 0.818772971630096
- 00:00:42.320 --> 00:00:44.910 He did a postdoc at Boston Children's,
- NOTE Confidence: 0.818772971630096
- $00:00:44.910 \longrightarrow 00:00:46.760$  and he's now an associate
- NOTE Confidence: 0.818772971630096
- 00:00:46.760 --> 00:00:48.610 professor at you T Southwestern.
- NOTE Confidence: 0.818772971630096
- $00{:}00{:}48.610 \dashrightarrow 00{:}00{:}50.420$  His lab studies the molecular
- NOTE Confidence: 0.818772971630096
- 00:00:50.420 -> 00:00:51.868 mechanisms that regulate gene
- NOTE Confidence: 0.818772971630096
- $00{:}00{:}51.868 \dashrightarrow 00{:}00{:}53.788$  expression and hematopoies is and cancer,
- NOTE Confidence: 0.818772971630096
- $00:00:53.790 \longrightarrow 00:00:54.900$  especially transcriptional enhancers
- NOTE Confidence: 0.818772971630096
- $00:00:54.900 \rightarrow 00:00:56.380$  and epigenetic regulatory regions.
- NOTE Confidence: 0.818772971630096
- $00{:}00{:}56.380 \dashrightarrow 00{:}00{:}59.710$  So we're just very excited to have him work.
- NOTE Confidence: 0.818772971630096
- 00:00:59.710 --> 00:01:01.222 We're grateful he's allowed
- NOTE Confidence: 0.818772971630096
- $00{:}01{:}01{.}222 \dashrightarrow 00{:}01{:}03{.}490$  us to record his talk today.
- NOTE Confidence: 0.818772971630096
- $00:01:03.490 \longrightarrow 00:01:05.310$  I'm at the end of his talk.
- NOTE Confidence: 0.818772971630096

 $00:01:05.310 \rightarrow 00:01:07.130$  We ask that if you have questions,

NOTE Confidence: 0.818772971630096

 $00:01:07.130 \longrightarrow 00:01:08.636$  you put your questions in the

NOTE Confidence: 0.818772971630096

00:01:08.636 --> 00:01:09.990 Q&A or in the chat.

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00:01:09.990 --> 00:01:12.070 I think I will have difficulty unmuting you,

NOTE Confidence: 0.818772971630096

 $00{:}01{:}12.070 \dashrightarrow 00{:}01{:}14.110$  so if you type your question I will

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 $00{:}01{:}14.110 \dashrightarrow 00{:}01{:}16.227$  read it and then he can answer it.

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 $00:01:16.230 \longrightarrow 00:01:16.852$  So again,

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 $00{:}01{:}16.852 \dashrightarrow 00{:}01{:}19.340$  thank you so much and we were quite

NOTE Confidence: 0.818772971630096

00:01:19.414 --> 00:01:21.489 excited about your talk today.

NOTE Confidence: 0.818772971630096

 $00{:}01{:}21{.}490 \dashrightarrow 00{:}01{:}24{.}542$  Thank you so much Jeannie for that

NOTE Confidence: 0.818772971630096

 $00{:}01{:}24.542 \dashrightarrow 00{:}01{:}26.920$  really nice introduction and I want

NOTE Confidence: 0.818772971630096

00:01:26.920 --> 00:01:29.244 to sort of start up before sinking

NOTE Confidence: 0.818772971630096

00:01:29.324 $\operatorname{-->}$ 00:01:31.892 Pat Gallagher Anadan across for the

NOTE Confidence: 0.818772971630096

 $00{:}01{:}31{.}892 \dashrightarrow 00{:}01{:}34{.}867$  opportunity and a kind invitation to a

NOTE Confidence: 0.818772971630096

 $00{:}01{:}34.867 \dashrightarrow 00{:}01{:}36.543$  virtually visitor cooperative center

NOTE Confidence: 0.818772971630096

 $00:01:36.543 \rightarrow 00:01:39.270$  of excellence of hematology at year and,

 $00{:}01{:}39{.}270 \dashrightarrow 00{:}01{:}41{.}930$  and I'm excited to share some more

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 $00{:}01{:}41{.}930 \dashrightarrow 00{:}01{:}44{.}544$  recent work related to the study of

NOTE Confidence: 0.818772971630096

 $00:01:44.544 \dashrightarrow 00:01:46.650$  noncoding genome in the context of

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 $00:01:46.728 \rightarrow 00:01:48.980$  blood development and disorders.

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00:01:48.980 --> 00:01:52.956 So just a brief introduction of my lab,

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 $00{:}01{:}52{.}960 \dashrightarrow 00{:}01{:}55{.}654$  so we started the mechanism that

NOTE Confidence: 0.818772971630096

 $00:01:55.654 \rightarrow 00:01:57.450$  regulate gene expression during

NOTE Confidence: 0.818772971630096

 $00:01:57.524 \rightarrow 00:01:59.420$  blood cell differentiation,

NOTE Confidence: 0.818772971630096

 $00{:}01{:}59{.}420 \dashrightarrow 00{:}02{:}02{.}836$  and how deregulation these process on the

NOTE Confidence: 0.818772971630096

00:02:02.836 --> 00:02:05.880 lines of development of blood disorders,

NOTE Confidence: 0.818772971630096

 $00:02:05.880 \longrightarrow 00:02:08.729$  and more specifically we aim to understand

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 $00{:}02{:}08.729 \dashrightarrow 00{:}02{:}12.368$  how we need specific transcription factors.

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 $00{:}02{:}12.370 \dashrightarrow 00{:}02{:}14.474$  Epigenetic regulators cooperate with

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 $00{:}02{:}14.474 \dashrightarrow 00{:}02{:}16.578$  environmental signals to control

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 $00:02:16.578 \longrightarrow 00:02:19.345$  cell identity by acting on a set

 $00:02:19.345 \rightarrow 00:02:20.990$  of non coding regulatory elements

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 $00{:}02{:}21.063 \dashrightarrow 00{:}02{:}23.219$  such as transcriptional enhancers,

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 $00:02:23.220 \longrightarrow 00:02:26.424$  which can be the central focus

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 $00:02:26.424 \rightarrow 00:02:28.560$  of my talk today.

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 $00{:}02{:}28.560 \dashrightarrow 00{:}02{:}32.240$  So as we all know that a noncoding

NOTE Confidence: 0.818772971630096

 $00:02:32.240 \longrightarrow 00:02:35.232$  genome occupies nearly 99% of the

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 $00:02:35.232 \rightarrow 00:02:37.862$  human genomics space and consistent

NOTE Confidence: 0.818772971630096

 $00:02:37.862 \rightarrow 00:02:40.288$  various regulatory elements as well

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 $00{:}02{:}40.288 \dashrightarrow 00{:}02{:}42.598$  as many of the pulley characters.

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 $00:02:42.600 \rightarrow 00:02:45.876$  Repetitive element an other genomic DNA is,

NOTE Confidence: 0.818772971630096

 $00:02:45.880 \longrightarrow 00:02:47.464$  on the other hand,

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 $00{:}02{:}47.464 \dashrightarrow 00{:}02{:}49.840$  from genetic studies we know vast

NOTE Confidence: 0.818772971630096

 $00:02:49.920 \dashrightarrow 00:02:52.355$  majority of disease associated genetic

NOTE Confidence: 0.818772971630096

00:02:52.355 --> 00:02:56.170 variants are located in a noncoding genome,

NOTE Confidence: 0.818772971630096

 $00:02:56.170 \rightarrow 00:02:58.570$  but identify the causal mechanism.

NOTE Confidence: 0.818772971630096

 $00:02:58.570 \longrightarrow 00:03:00.382$  Has remained a significant

- NOTE Confidence: 0.818772971630096
- $00:03:00.382 \longrightarrow 00:03:02.194$  challenge for the field.
- NOTE Confidence: 0.818772971630096
- 00:03:02.200 --> 00:03:03.048 An an.
- NOTE Confidence: 0.818772971630096
- 00:03:03.048 --> 00:03:06.016 In select cases we know our careful
- NOTE Confidence: 0.818772971630096
- $00:03:06.016 \rightarrow 00:03:08.351$  dissection of the underlying pathways
- NOTE Confidence: 0.818772971630096
- $00:03:08.351 \longrightarrow 00:03:12.158$  can often lead to new insights in Human
- NOTE Confidence: 0.818772971630096
- $00{:}03{:}12.158 \dashrightarrow 00{:}03{:}14.618$  Genetics and an even the rapeutics,
- NOTE Confidence: 0.818772971630096
- $00:03:14.620 \longrightarrow 00:03:15.742$  for example,
- NOTE Confidence: 0.818772971630096
- $00:03:15.742 \longrightarrow 00:03:17.986$  by associating common genetic
- NOTE Confidence: 0.818772971630096
- $00{:}03{:}17.986 \dashrightarrow 00{:}03{:}20.230$  variations with certain block
- NOTE Confidence: 0.818772971630096
- $00:03:20.312 \longrightarrow 00:03:23.308$  trades such as feeding him a globin
- NOTE Confidence: 0.818772971630096
- $00:03:23.308 \rightarrow 00:03:25.800$  expression levels a gene called BCL
- NOTE Confidence: 0.818772971630096
- $00{:}03{:}25{.}800 \dashrightarrow 00{:}03{:}28{.}418$ 11 A was identified more than 10
- NOTE Confidence: 0.749307191371918
- 00:03:28.420 --> 00:03:31.172 years ago. OK, I did as opposed to
- NOTE Confidence: 0.749307191371918
- $00{:}03{:}31{.}172 \dashrightarrow 00{:}03{:}34{.}052$  Federal in Boston Children's with walking
- NOTE Confidence: 0.749307191371918
- $00:03:34.052 \rightarrow 00:03:37.220$  and together with Vijay Sankar Anadem.
- NOTE Confidence: 0.749307191371918

 $00:03:37.220 \rightarrow 00:03:40.136$  Bawa have shown that this genetic

NOTE Confidence: 0.749307191371918

 $00{:}03{:}40{.}136 \dashrightarrow 00{:}03{:}42{.}574$  variants that were identified forms

NOTE Confidence: 0.749307191371918

 $00{:}03{:}42{.}574 \dashrightarrow 00{:}03{:}45{.}486$  you are status actually do not affect

NOTE Confidence: 0.749307191371918

 $00:03:45.486 \rightarrow 00:03:48.097$  the coding sequences of BCL 11 A.

NOTE Confidence: 0.749307191371918

 $00{:}03{:}48{.}100 \dashrightarrow 00{:}03{:}50{.}656$  But instead that a tissue specific

NOTE Confidence: 0.749307191371918

 $00:03:50.656 \rightarrow 00:03:52.880$  enhancer for this transcription factor,

NOTE Confidence: 0.749307191371918

 $00:03:52.880 \rightarrow 00:03:55.055$  so normally as nicely illustrated

NOTE Confidence: 0.749307191371918

00:03:55.055 --> 00:03:57.230 by Los Harrison Global Bill,

NOTE Confidence: 0.749307191371918

 $00{:}03{:}57{.}230 \dashrightarrow 00{:}03{:}59{.}870$  that PC anime is activated in.

NOTE Confidence: 0.749307191371918

 $00:03:59.870 \dashrightarrow 00:04:01.334$  Definitive hematopoietic cells

NOTE Confidence: 0.749307191371918

 $00{:}04{:}01{.}334 \dashrightarrow 00{:}04{:}02{.}798$  by this tissue,

NOTE Confidence: 0.749307191371918

 $00:04:02.800 \longrightarrow 00:04:05.575$  especially enhancer to request fitting

NOTE Confidence: 0.749307191371918

 $00:04:05.575 \rightarrow 00:04:08.350$  hemoglobin expression and impatient when

NOTE Confidence: 0.749307191371918

 $00:04:08.420 \dashrightarrow 00:04:11.087$  the adult beta globin gene is mutated,

NOTE Confidence: 0.749307191371918

 $00:04:11.090 \rightarrow 00:04:15.482$  such as in the context of sickle cell anemia,

NOTE Confidence: 0.749307191371918

 $00:04:15.490 \longrightarrow 00:04:17.930$  and this is permissive for

- NOTE Confidence: 0.749307191371918
- $00:04:17.930 \longrightarrow 00:04:20.370$  developping as sickle cell disease.
- NOTE Confidence: 0.749307191371918
- 00:04:20.370 --> 00:04:22.730 The GEOHASH variant basically
- NOTE Confidence: 0.749307191371918
- $00{:}04{:}22.730 \dashrightarrow 00{:}04{:}25.090$  functions to attenuate enhance
- NOTE Confidence: 0.749307191371918
- $00:04:25.090 \rightarrow 00:04:27.687$  activity leads to less of a PCR.
- NOTE Confidence: 0.749307191371918
- $00:04:27.690 \longrightarrow 00:04:30.155$  My expression an and reactivation
- NOTE Confidence: 0.749307191371918
- 00:04:30.155 --> 00:04:31.634 of feeling hemoglobin.
- NOTE Confidence: 0.749307191371918
- 00:04:31.640 --> 00:04:33.155 Question 2A milli.
- NOTE Confidence: 0.749307191371918
- 00:04:33.155 --> 00:04:34.670 Ameliorated disease symptoms.
- NOTE Confidence: 0.749307191371918
- $00:04:34.670 \rightarrow 00:04:38.205$  So this is how the genetics works,
- NOTE Confidence: 0.749307191371918
- $00:04:38.210 \longrightarrow 00:04:41.006$  but this fine is not only
- NOTE Confidence: 0.749307191371918
- $00:04:41.006 \rightarrow 00:04:42.870$  established the underlying genetic
- NOTE Confidence: 0.749307191371918
- $00{:}04{:}42{.}949 \dashrightarrow 00{:}04{:}45{.}277$  basis of hemoglobin switching,
- NOTE Confidence: 0.749307191371918
- $00:04:45.280 \longrightarrow 00:04:48.154$  but also raise the possibility that
- NOTE Confidence: 0.749307191371918
- 00:04:48.154 --> 00:04:50.830 teach you specific enhancer elements.
- NOTE Confidence: 0.749307191371918
- $00:04:50.830 \longrightarrow 00:04:52.762$  Maybe potential the rapeutic targets
- NOTE Confidence: 0.749307191371918

 $00:04:52.762 \longrightarrow 00:04:55.660$  and this idea actually has led

NOTE Confidence: 0.749307191371918

 $00:04:55.734 \rightarrow 00:04:58.848$  to an ongoing clinical trials by

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00:04:58.848 --> 00:05:00.924 Christmas Therapeutics in partnership.

NOTE Confidence: 0.749307191371918

 $00{:}05{:}00{.}930 \dashrightarrow 00{:}05{:}01{.}922$  Vertex Pharmaceuticals.

NOTE Confidence: 0.749307191371918

00:05:01.922 --> 00:05:05.394 To target PCR 11 Enhancer in sickle

NOTE Confidence: 0.749307191371918

 $00{:}05{:}05{.}394 \dashrightarrow 00{:}05{:}07{.}986$  cell disease and beta thal assemia

NOTE Confidence: 0.749307191371918

00:05:07.986 --> 00:05:11.010 patients using CAS 9 genome editing.

NOTE Confidence: 0.749307191371918

00:05:11.010 -> 00:05:13.716 So when you walk since first

NOTE Confidence: 0.749307191371918

 $00:05:13.716 \longrightarrow 00:05:15.520$  to mobilize our city.

NOTE Confidence: 0.749307191371918

 $00{:}05{:}15{.}520 \dashrightarrow 00{:}05{:}17{.}668$  Sorry for positive hematopoietic

NOTE Confidence: 0.749307191371918

 $00{:}05{:}17.668 \dashrightarrow 00{:}05{:}20.353$  stem progenitor cells from affecting

NOTE Confidence: 0.749307191371918

 $00{:}05{:}20.353 \dashrightarrow 00{:}05{:}22.735$  individuals and transducer cells with

NOTE Confidence: 0.749307191371918

 $00{:}05{:}22.735 \dashrightarrow 00{:}05{:}24.511$  rubber nuclear proteins containing

NOTE Confidence: 0.749307191371918

 $00{:}05{:}24.511 \dashrightarrow 00{:}05{:}27.259$  cost 9 and a single godani that

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00:05:27.259 --> 00:05:29.049 target the PCL away enhancer,

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 $00{:}05{:}29.050 \dashrightarrow 00{:}05{:}31.305$  which leads to disruption of

 $00:05:31.305 \longrightarrow 00:05:32.658$  the enhancer function,

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 $00:05:32.660 \longrightarrow 00:05:34.910$  and then these edited cells.

NOTE Confidence: 0.749307191371918

 $00{:}05{:}34{.}910 \dashrightarrow 00{:}05{:}38{.}630$  We are well reinfused back to the same

NOTE Confidence: 0.749307191371918

 $00:05:38.630 \rightarrow 00:05:42.550$  patient and observe for disease phenotypes.

NOTE Confidence: 0.749307191371918

 $00{:}05{:}42.550 \dashrightarrow 00{:}05{:}43.914$  As you may know,

NOTE Confidence: 0.749307191371918

 $00{:}05{:}43{.}914 \dashrightarrow 00{:}05{:}46{.}935$  the result of the first 2 patient one

NOTE Confidence: 0.749307191371918

00:05:46.935 --> 00:05:50.503 sickle cell patient in one Peter Self well,

NOTE Confidence: 0.749307191371918

 $00:05:50.510 \longrightarrow 00:05:52.946$  recently reported in a paper at

NOTE Confidence: 0.749307191371918

 $00{:}05{:}52{.}946 \dashrightarrow 00{:}05{:}54{.}570$  publishing Union General Medicine

NOTE Confidence: 0.749307191371918

 $00:05:54.641 \rightarrow 00:05:56.927$  with more cases recently reported in

NOTE Confidence: 0.749307191371918

 $00{:}05{:}56{.}927 \dashrightarrow 00{:}05{:}58{.}912$  the Ash American Society Hematology

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 $00:05:58.912 \rightarrow 00:06:01.649$  Annual Meeting just a couple weeks ago.

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 $00{:}06{:}01{.}650 \dashrightarrow 00{:}06{:}04{.}604$  So as one example showing here that

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 $00{:}06{:}04{.}604 \dashrightarrow 00{:}06{:}07{.}981$  here's the result for the first bit of

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 $00:06:07.981 \dashrightarrow 00:06:10.810$  cell patients that are treated by CAS 9,

00:06:10.810 --> 00:06:13.798 editing of the PCL 11 Enhancer.

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00:06:13.800 --> 00:06:17.552 As you can see on the left graph

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 $00:06:17.552 \rightarrow 00:06:20.549$  before infusion of the edited cells,

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 $00:06:20.550 \rightarrow 00:06:23.178$  the patient had a hemoglobin level

NOTE Confidence: 0.749307191371918

 $00{:}06{:}23.178 \dashrightarrow 00{:}06{:}26.516$  of nine .0 gram per deciliter with

NOTE Confidence: 0.749307191371918

00:06:26.516 --> 00:06:30.009 feeding him global level only .3 grams NOTE Confidence: 0.749307191371918

 $00{:}06{:}30{.}102 \dashrightarrow 00{:}06{:}33{.}532$  per deciliter but just a couple months

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 $00:06:33.532 \longrightarrow 00:06:36.468$  after infusion of the edited cells,

NOTE Confidence: 0.749307191371918

 $00{:}06{:}36{.}468 \dashrightarrow 00{:}06{:}38{.}412$  the feeling hemoglobin level

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 $00{:}06{:}38{.}412 \dashrightarrow 00{:}06{:}41{.}366$  increased to 6.5 gram per deciliter

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 $00{:}06{:}41{.}366 \dashrightarrow 00{:}06{:}44{.}192$  an letter 1113.1 gram per deciliter.

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 $00{:}06{:}44.200 \dashrightarrow 00{:}06{:}46.915$  With total hemoglobin increased to

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 $00:06:46.915 \rightarrow 00:06:50.526$  14.1 and this is accompanied by nearly

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 $00{:}06{:}50{.}526 \dashrightarrow 00{:}06{:}53{.}978$  100% F cells or these feeding him

NOTE Confidence: 0.749307191371918

 $00:06:53.978 \longrightarrow 00:06:57.355$  globin positive cells and up to 18

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 $00:06:57.355 \rightarrow 00:07:00.253$  months of follow up so this patient

 $00:07:00.354 \rightarrow 00:07:03.370$  is clinically cured technically,

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 $00:07:03.370 \longrightarrow 00:07:05.795$  therefore this proof of principle

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 $00:07:05.795 \dashrightarrow 00:07:08.859$  studies are very encouraging not only

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 $00:07:08.859 \rightarrow 00:07:11.654$  to show that the rapeutic targeting

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 $00{:}07{:}11.654 \dashrightarrow 00{:}07{:}14.260$  disease associated enhancer elements can.

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 $00{:}07{:}14.260 \dashrightarrow 00{:}07{:}17.424$  Likely provide a cure for the most

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 $00:07:17.424 \rightarrow 00:07:20.113$  common monogenic disease that was first

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 $00:07:20.113 \rightarrow 00:07:22.615$  described more than a century ago,

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 $00:07:22.620 \longrightarrow 00:07:25.014$  but also open up new ideas

NOTE Confidence: 0.749307191371918

 $00:07:25.014 \rightarrow 00:07:26.610$  and opportunities for people

NOTE Confidence: 0.855561494827271

 $00:07:26.684 \rightarrow 00:07:29.660$  to understand biology and more important,

NOTE Confidence: 0.855561494827271

 $00{:}07{:}29.660 \dashrightarrow 00{:}07{:}32.740$  it develop approaches to target this disease.

NOTE Confidence: 0.855561494827271

00:07:32.740 --> 00:07:36.460 Associated noncoding regulatory elements.

NOTE Confidence: 0.855561494827271

 $00{:}07{:}36{.}460 \dashrightarrow 00{:}07{:}39{.}270$  So. First question we ask when

NOTE Confidence: 0.855561494827271

 $00{:}07{:}39{.}270$  -->  $00{:}07{:}42{.}524$  when I started my lap at you T

 $00:07:42.524 \rightarrow 00:07:44.679$  Southwestern is what are enhancers?

NOTE Confidence: 0.855561494827271

 $00:07:44.680 \rightarrow 00:07:46.710$  How enhancer was initially discovered?

NOTE Confidence: 0.855561494827271

00:07:46.710 --> 00:07:48.326 So Enhancer was first

NOTE Confidence: 0.855561494827271

 $00:07:48.326 \rightarrow 00:07:50.346$  discovered nearly 40 years ago,

NOTE Confidence: 0.855561494827271

 $00:07:50.350 \longrightarrow 00:07:53.995$  an actually from a viral genome as a shot.

NOTE Confidence: 0.855561494827271

 $00{:}07{:}54.000 \dashrightarrow 00{:}07{:}56.380$  Deer sequences in the SV 40 Gino

NOTE Confidence: 0.855561494827271

 $00{:}07{:}56.380 \dashrightarrow 00{:}07{:}58.557$  that can enhance the expression of

NOTE Confidence: 0.855561494827271

 $00{:}07{:}58.557 \dashrightarrow 00{:}08{:}01.084$  a rabbit bitter globin gene in the

NOTE Confidence: 0.855561494827271

 $00:08:01.156 \longrightarrow 00:08:03.310$  orientation independent manner.

NOTE Confidence: 0.855561494827271

 $00{:}08{:}03{.}310 \dashrightarrow 00{:}08{:}04{.}822$  In a transient transfection

NOTE Confidence: 0.855561494827271

 $00{:}08{:}04{.}822 \dashrightarrow 00{:}08{:}07{.}090$  as says soon after the 1st century

NOTE Confidence: 0.855561494827271

 $00:08:07.160 \longrightarrow 00:08:08.648$  enhancer was discovered.

NOTE Confidence: 0.855561494827271

 $00:08:08.650 \dashrightarrow 00:08:11.548$  From the mouth immuno globin gene.

NOTE Confidence: 0.855561494827271

 $00{:}08{:}11.550 \dashrightarrow 00{:}08{:}14.714$  In a tissue specific manner so therefore

NOTE Confidence: 0.855561494827271

 $00:08:14.714 \rightarrow 00:08:18.301$  even from the very early days enhancer

NOTE Confidence: 0.855561494827271

 $00:08:18.301 \longrightarrow 00:08:21.517$  at defined as SESAC ingenious sequences

 $00{:}08{:}21.601 \dashrightarrow 00{:}08{:}25.145$  that function at often at a distance to

NOTE Confidence: 0.855561494827271

 $00:08:25.145 \longrightarrow 00:08:27.696$  activate gene transcription in orientation

NOTE Confidence: 0.855561494827271

 $00:08:27.696 \rightarrow 00:08:30.456$  independent and tissue specific manner.

NOTE Confidence: 0.855561494827271

 $00:08:30.460 \longrightarrow 00:08:32.788$  As such, it has been very

NOTE Confidence: 0.855561494827271

 $00:08:32.788 \dashrightarrow 00:08:34.340$  difficult to studying answers,

NOTE Confidence: 0.855561494827271

 $00:08:34.340 \longrightarrow 00:08:36.668$  and an still remains very tickled.

NOTE Confidence: 0.855561494827271

00:08:36.670 --> 00:08:38.222 To identify enhancer target

NOTE Confidence: 0.855561494827271

 $00:08:38.222 \rightarrow 00:08:40.550$  genes and their in vivo function,

NOTE Confidence: 0.855561494827271

 $00:08:40.550 \longrightarrow 00:08:43.005$  largely due to the lack

NOTE Confidence: 0.855561494827271

00:08:43.005 - 00:08:44.478 of experimental tools.

NOTE Confidence: 0.855561494827271

 $00{:}08{:}44{.}480 \dashrightarrow 00{:}08{:}46{.}690$  So therefore there are several

NOTE Confidence: 0.855561494827271

 $00:08:46.690 \rightarrow 00:08:48.458$  important questions enhancer biology

NOTE Confidence: 0.855561494827271

 $00{:}08{:}48{.}458 \dashrightarrow 00{:}08{:}50{.}688$  that remain to be addressed Anan.

NOTE Confidence: 0.855561494827271

 $00{:}08{:}50.690 \dashrightarrow 00{:}08{:}53.480$  This is some of the questions that we are

NOTE Confidence: 0.855561494827271

 $00{:}08{:}53{.}480 \dashrightarrow 00{:}08{:}56{.}488$  very particularly interesting excited about,

 $00{:}08{:}56{.}490 \dashrightarrow 00{:}08{:}59{.}378$  and I would like to share some recent

NOTE Confidence: 0.855561494827271

 $00{:}08{:}59{.}378 \dashrightarrow 00{:}09{:}02{.}671$  work that we have done trying to address

NOTE Confidence: 0.855561494827271

 $00:09:02.671 \longrightarrow 00:09:05.180$  some of these important questions.

NOTE Confidence: 0.855561494827271

 $00:09:05.180 \rightarrow 00:09:07.616$  He has a biology and particularly

NOTE Confidence: 0.855561494827271

 $00:09:07.616 \rightarrow 00:09:10.150$  how to identify enhances and housing,

NOTE Confidence: 0.855561494827271

 $00{:}09{:}10.150 \dashrightarrow 00{:}09{:}12.550$  has a regular their target gene

NOTE Confidence: 0.855561494827271

 $00:09:12.550 \rightarrow 00:09:15.589$  expression and how it has it themselves.

NOTE Confidence: 0.855561494827271

00:09:15.590 --> 00:09:17.096 Regulated and finally,

NOTE Confidence: 0.855561494827271

 $00{:}09{:}17.096 \dashrightarrow 00{:}09{:}20.108$  how do he has alterations contribute

NOTE Confidence: 0.855561494827271

 $00:09:20.108 \longrightarrow 00:09:21.430$  to diseases,

NOTE Confidence: 0.855561494827271

 $00:09:21.430 \longrightarrow 00:09:24.650$  typically in the context of

NOTE Confidence: 0.855561494827271

00:09:24.650 --> 00:09:25.938 hematopoietic malignancy?

NOTE Confidence: 0.855561494827271

 $00:09:25.940 \longrightarrow 00:09:28.484$  So the first question is how

NOTE Confidence: 0.855561494827271

 $00:09:28.484 \longrightarrow 00:09:29.756$  to identify Hazard.

NOTE Confidence: 0.855561494827271

 $00:09:29.760 \rightarrow 00:09:31.220$  This has been challenging,

NOTE Confidence: 0.855561494827271

 $00{:}09{:}31{.}220 \dashrightarrow 00{:}09{:}33{.}905$  but with the advances in next Gen

- NOTE Confidence: 0.855561494827271
- $00:09:33.905 \rightarrow 00:09:36.055$  sequencing technologies coupled with an
- NOTE Confidence: 0.855561494827271
- $00{:}09{:}36.055 \dashrightarrow 00{:}09{:}39.080$  analysis of variety of chromatin features,
- NOTE Confidence: 0.855561494827271
- $00:09:39.080 \dashrightarrow 00:09:41.666$  we can now easily annotate these
- NOTE Confidence: 0.855561494827271
- $00:09:41.666 \rightarrow 00:09:44.695$  noncoding genome using a number of methods
- NOTE Confidence: 0.855561494827271
- $00{:}09{:}44.695 \dashrightarrow 00{:}09{:}47.551$  such as chip sequencing as you know,
- NOTE Confidence: 0.855561494827271
- $00:09:47.560 \longrightarrow 00:09:48.832$  to examine protein,
- NOTE Confidence: 0.855561494827271
- $00:09:48.832 \longrightarrow 00:09:49.680$  DNA interactions,
- NOTE Confidence: 0.855561494827271
- $00:09:49.680 \longrightarrow 00:09:52.284$  air taxi or dinner sequencing to
- NOTE Confidence: 0.855561494827271
- $00{:}09{:}52.284 \dashrightarrow 00{:}09{:}54.020$  examine chromatin Accessibility as
- NOTE Confidence: 0.855561494827271
- $00:09:54.093 \rightarrow 00:09:56.584$  a surrogate for open property, or.
- NOTE Confidence: 0.855561494827271
- 00:09:56.584 --> 00:09:59.304 Active transcription and more recently
- NOTE Confidence: 0.855561494827271
- 00:09:59.304 --> 00:10:00.936 chromatin confirmation capture
- NOTE Confidence: 0.855561494827271
- $00:10:00.936 \rightarrow 00:10:04.061$  or three CBEST methods to examine
- NOTE Confidence: 0.855561494827271
- $00{:}10{:}04.061 \dashrightarrow 00{:}10{:}06.065$  high order chromatin structures.
- NOTE Confidence: 0.855561494827271
- $00:10:06.070 \longrightarrow 00:10:07.814$  So now we can.
- NOTE Confidence: 0.855561494827271

00:10:07.814 --> 00:10:09.994 Fairly easily to identify putative

NOTE Confidence: 0.855561494827271

 $00:10:09.994 \rightarrow 00:10:12.430$  enhances other regulatory elements in

NOTE Confidence: 0.855561494827271

 $00:10:12.430 \longrightarrow 00:10:15.316$  a systematic manner and using these

NOTE Confidence: 0.855561494827271

 $00:10:15.392 \rightarrow 00:10:18.544$  tools are we can use a simple combination.

NOTE Confidence: 0.855561494827271

 $00{:}10{:}18.550 \dashrightarrow 00{:}10{:}20.735$  We enhance associated histone Marks

NOTE Confidence: 0.855561494827271

 $00{:}10{:}20.735 \dashrightarrow 00{:}10{:}22.920$  and chromatin Accessibility to identify

NOTE Confidence: 0.855561494827271

 $00{:}10{:}22.986 \dashrightarrow 00{:}10{:}25.056$  putative active enhancers or other

NOTE Confidence: 0.855561494827271

 $00{:}10{:}25.056 \dashrightarrow 00{:}10{:}27.126$  regulatory elements across the Gina.

NOTE Confidence: 0.855561494827271

 $00{:}10{:}27.130 \dashrightarrow 00{:}10{:}29.986$  So using our favorite local that human

NOTE Confidence: 0.855561494827271

 $00:10:29.986 \dashrightarrow 00:10:32.699$  beta globin gene cluster as example.

NOTE Confidence: 0.855561494827271

 $00{:}10{:}32.700 \dashrightarrow 00{:}10{:}36.140$  As you can see from this genome browser,

NOTE Confidence: 0.855561494827271

 $00:10:36.140 \longrightarrow 00:10:38.732$  tracks that we can easily identify

NOTE Confidence: 0.855561494827271

 $00:10:38.732 \longrightarrow 00:10:40.028$  the upstream enhancer.

NOTE Confidence: 0.855561494827271

 $00{:}10{:}40{.}030 \dashrightarrow 00{:}10{:}42{.}298$  Pass this on Locus control region

NOTE Confidence: 0.855561494827271

 $00:10:42.298 \longrightarrow 00:10:45.447$  or else are by the presence of

NOTE Confidence: 0.855561494827271

 $00{:}10{:}45{.}447 \dashrightarrow 00{:}10{:}47{.}519$  dinners will have sensitivity.

- NOTE Confidence: 0.855561494827271
- $00{:}10{:}47{.}520 \dashrightarrow 00{:}10{:}49{.}645$  He can 27 simulation and
- NOTE Confidence: 0.855561494827271
- $00{:}10{:}49.645 \dashrightarrow 00{:}10{:}51.345$  HCC for modern isolation.
- NOTE Confidence: 0.855561494827271
- $00:10:51.350 \longrightarrow 00:10:54.192$  On the other side you can also
- NOTE Confidence: 0.855561494827271
- $00:10:54.192 \longrightarrow 00:10:55.939$  identify active promoters by
- NOTE Confidence: 0.855561494827271
- $00:10:55.939 \longrightarrow 00:10:57.739$  the presence of translation.
- NOTE Confidence: 0.855561494827271
- $00{:}10{:}57{.}740 \dashrightarrow 00{:}11{:}01{.}116$  At 3K four there's all done in primary
- NOTE Confidence: 0.855561494827271
- $00:11:01.116 \rightarrow 00:11:03.988$  humour as well progenitor cells.
- NOTE Confidence: 0.855561494827271
- $00:11:03.990 \longrightarrow 00:11:05.738$  So using this approach,
- NOTE Confidence: 0.855561494827271
- $00:11:05.738 \rightarrow 00:11:08.360$  we and others have previously compared
- NOTE Confidence: 0.855561494827271
- 00:11:08.430 --> 00:11:11.390 enhancer landscapes between human primary,
- NOTE Confidence: 0.798697412014008
- 00:11:11.390 --> 00:11:13.358 hematopoietic stem progenitor cells
- NOTE Confidence: 0.798697412014008
- $00{:}11{:}13.358 \dashrightarrow 00{:}11{:}15.326$  and differentiated industry sales,
- NOTE Confidence: 0.798697412014008
- $00{:}11{:}15{.}330 \dashrightarrow 00{:}11{:}17{.}718$  and we notice that initially that
- NOTE Confidence: 0.798697412014008
- $00{:}11{:}17{.}718 \dashrightarrow 00{:}11{:}20{.}052$  enhances undergoes a pretty progressive
- NOTE Confidence: 0.798697412014008
- $00{:}11{:}20.052 \dashrightarrow 00{:}11{:}22.720$  turnover during limits differentiation,
- NOTE Confidence: 0.798697412014008

 $00:11:22.720 \rightarrow 00:11:25.744$  such that about 2/3 of the enhancer

NOTE Confidence: 0.798697412014008

 $00{:}11{:}25{.}744 \dashrightarrow 00{:}11{:}28{.}124$  that were found in undifferentiated

NOTE Confidence: 0.798697412014008

00:11:28.124 --> 00:11:31.118 City City for positive cell or

NOTE Confidence: 0.798697412014008

 $00:11:31.118 \longrightarrow 00:11:34.354$  loss and replaced by a similar

NOTE Confidence: 0.798697412014008

00:11:34.354 --> 00:11:37.034 number of Linux specific enhancers.

NOTE Confidence: 0.798697412014008

00:11:37.040 --> 00:11:39.638 In just a few cell divisions,

NOTE Confidence: 0.798697412014008

 $00{:}11{:}39{.}640 \dashrightarrow 00{:}11{:}41{.}508$  we then identified transcription

NOTE Confidence: 0.798697412014008

 $00:11:41.508 \rightarrow 00:11:43.843$  factors and their combinations that

NOTE Confidence: 0.798697412014008

 $00{:}11{:}43.843 \dashrightarrow 00{:}11{:}46.949$  are required for this image and a

NOTE Confidence: 0.798697412014008

 $00:11:46.949 \longrightarrow 00:11:48.661$  developmental stage specific enhance

NOTE Confidence: 0.798697412014008

 $00{:}11{:}48.733 \dashrightarrow 00{:}11{:}51.456$  activities and I should say that similar

NOTE Confidence: 0.798697412014008

 $00:11:51.456 \rightarrow 00:11:53.466$  results obtained by elegant studies

NOTE Confidence: 0.798697412014008

 $00:11:53.466 \rightarrow 00:11:56.810$  for pack animals group here at the Yell

NOTE Confidence: 0.798697412014008

 $00{:}11{:}56{.}891 \dashrightarrow 00{:}11{:}59{.}556$  and Ross Hardison, and many others,

NOTE Confidence: 0.798697412014008

00:11:59.556 --> 00:12:01.284 in different model systems.

NOTE Confidence: 0.798697412014008

 $00{:}12{:}01{.}290 \dashrightarrow 00{:}12{:}03{.}546$  And this really has provided a

- NOTE Confidence: 0.798697412014008
- $00:12:03.546 \rightarrow 00:12:05.672$  useful resource for the community
- NOTE Confidence: 0.798697412014008
- $00:12:05.672 \rightarrow 00:12:07.848$  to understand the regulatory.
- NOTE Confidence: 0.798697412014008
- $00:12:07.850 \longrightarrow 00:12:08.952$  Basketball hematopoietic
- NOTE Confidence: 0.798697412014008
- $00:12:08.952 \longrightarrow 00:12:10.054$  cell differentiation.
- NOTE Confidence: 0.798697412014008
- $00:12:10.054 \rightarrow 00:12:12.809$  So with this increasing availability
- NOTE Confidence: 0.798697412014008
- $00:12:12.809 \longrightarrow 00:12:15.228$  of this large genomic data set,
- NOTE Confidence: 0.798697412014008
- $00{:}12{:}15{.}230 \dashrightarrow 00{:}12{:}17{.}848$  so we wonder whether we could use
- NOTE Confidence: 0.798697412014008
- $00{:}12{:}17.848 \dashrightarrow 00{:}12{:}19.425$  this information to understand
- NOTE Confidence: 0.798697412014008
- $00:12:19.425 \longrightarrow 00:12:21.310$  how it has a regular,
- NOTE Confidence: 0.798697412014008
- $00:12:21.310 \longrightarrow 00:12:23.326$  their target genes blushing.
- NOTE Confidence: 0.798697412014008
- 00:12:23.326 --> 00:12:23.830 Anne,
- NOTE Confidence: 0.798697412014008
- $00{:}12{:}23.830 \dashrightarrow 00{:}12{:}26.710$  this let us to focus a set of these
- NOTE Confidence: 0.798697412014008
- $00:12:26.710 \longrightarrow 00:12:29.089$  linear specific enhancer clusters or
- NOTE Confidence: 0.798697412014008
- $00{:}12{:}29.089 \dashrightarrow 00{:}12{:}32.370$  super enhancers as some people call it,
- NOTE Confidence: 0.798697412014008
- $00{:}12{:}32{.}370 \dashrightarrow 00{:}12{:}35{.}208$  including one showing here that's located
- NOTE Confidence: 0.798697412014008

00:12:35.208 --> 00:12:38.477 upstream of the gene call SLC 25 S 37,

NOTE Confidence: 0.798697412014008

 $00{:}12{:}38{.}480 \dashrightarrow 00{:}12{:}40{.}922$  which is a includes iron transporter

NOTE Confidence: 0.798697412014008

 $00:12:40.922 \rightarrow 00:12:42.550$  critical for hematopoietic cells.

NOTE Confidence: 0.798697412014008

 $00:12:42.550 \longrightarrow 00:12:44.580$  So as you can see,

NOTE Confidence: 0.798697412014008

 $00{:}12{:}44.580 \dashrightarrow 00{:}12{:}46.500$  these tissue specific enhancer that

NOTE Confidence: 0.798697412014008

 $00{:}12{:}46{.}500 \dashrightarrow 00{:}12{:}48{.}925$  are conserved between mouse and human

NOTE Confidence: 0.798697412014008

 $00{:}12{:}48{.}925 \dashrightarrow 00{:}12{:}51{.}160$  are contains 3 individual enhancers

NOTE Confidence: 0.798697412014008

 $00:12:51.160 \rightarrow 00:12:52.948$  that are virtually indistinguishable

NOTE Confidence: 0.798697412014008

 $00{:}12{:}53.008 \dashrightarrow 00{:}12{:}55.258$  in terms of histone Marks and

NOTE Confidence: 0.798697412014008

 $00:12:55.258 \rightarrow 00:12:56.383$  transcription factor binding.

NOTE Confidence: 0.798697412014008

 $00:12:56.390 \rightarrow 00:12:58.430$  In this case got one.

NOTE Confidence: 0.798697412014008

 $00:12:58.430 \longrightarrow 00:13:01.064$  Inhuman amounts are extra cells so

NOTE Confidence: 0.798697412014008

 $00:13:01.064 \rightarrow 00:13:02.820$  therefore the critical question

NOTE Confidence: 0.798697412014008

 $00:13:02.893 \rightarrow 00:13:05.875$  we had initially was how do these

NOTE Confidence: 0.798697412014008

 $00{:}13{:}05{.}875 \dashrightarrow 00{:}13{:}07{.}153$  individual constitute enhances

NOTE Confidence: 0.798697412014008

 $00:13:07.223 \longrightarrow 00:13:09.018$  contribute to the function of

 $00:13:09.018 \rightarrow 00:13:11.169$  this super enhancer as a whole.

NOTE Confidence: 0.798697412014008

 $00:13:11.169 \longrightarrow 00:13:13.263$  So we decided to use CRISPR

NOTE Confidence: 0.798697412014008

00:13:13.263 --> 00:13:15.395 knockout to knockout each individual

NOTE Confidence: 0.798697412014008

 $00:13:15.395 \rightarrow 00:13:17.427$  enhances and their combinations.

NOTE Confidence: 0.798697412014008

 $00:13:17.430 \rightarrow 00:13:20.046$  We found that quite surprisingly that

NOTE Confidence: 0.798697412014008

 $00{:}13{:}20.046 \dashrightarrow 00{:}13{:}23.711$  this thing has a seems to be organized

NOTE Confidence: 0.798697412014008

 $00:13:23.711 \longrightarrow 00:13:26.471$  as a functional hierarchy such that

NOTE Confidence: 0.798697412014008

 $00{:}13{:}26.553 \dashrightarrow 00{:}13{:}29.460$  not card enhances 3 E 3 or the most.

NOTE Confidence: 0.798697412014008

 $00:13:29.460 \longrightarrow 00:13:31.350$  This thing has us completely

NOTE Confidence: 0.798697412014008

 $00:13:31.350 \longrightarrow 00:13:32.862$  abolished in has activity,

NOTE Confidence: 0.798697412014008

 $00{:}13{:}32{.}870 \dashrightarrow 00{:}13{:}34{.}765$  whereas knock out the other two

NOTE Confidence: 0.798697412014008

 $00:13:34.765 \longrightarrow 00:13:36.660$  neighboring hazards had little effect.

NOTE Confidence: 0.798697412014008

 $00{:}13{:}36.660 \dashrightarrow 00{:}13{:}39.524$  And this was also seen by others in

NOTE Confidence: 0.798697412014008

 $00{:}13{:}39{.}524 \dashrightarrow 00{:}13{:}41{.}967$  different hazard clusters and cell types.

NOTE Confidence: 0.798697412014008

 $00{:}13{:}41{.}970 \dashrightarrow 00{:}13{:}44{.}539$  So therefore the key question is what

 $00:13:44.539 \rightarrow 00:13:46.888$  is unique about this enhanced E3?

NOTE Confidence: 0.798697412014008

 $00{:}13{:}46.890 \dashrightarrow 00{:}13{:}49.228$  In fact they are hard to distinguish

NOTE Confidence: 0.798697412014008

 $00{:}13{:}49{.}228 \dashrightarrow 00{:}13{:}51{.}186$  based on the chromatin features

NOTE Confidence: 0.798697412014008

 $00:13:51.186 \longrightarrow 00:13:52.958$  and how to identify.

NOTE Confidence: 0.798697412014008

 $00:13:52.960 \longrightarrow 00:13:55.066$  This seems to be functionally more

NOTE Confidence: 0.798697412014008

 $00{:}13{:}55{.}066 \dashrightarrow 00{:}13{:}57{.}347$  important or or predominant enhancers in

NOTE Confidence: 0.798697412014008

00:13:57.347 --> 00:13:59.807 super enhancer function and more importantly.

NOTE Confidence: 0.798697412014008

 $00:13:59.810 \rightarrow 00:14:01.765$  This list another important question

NOTE Confidence: 0.798697412014008

 $00:14:01.765 \longrightarrow 00:14:04.210$  that we've been studying is how

NOTE Confidence: 0.798697412014008

 $00:14:04.210 \rightarrow 00:14:05.898$  enhancer themselves are regulated

NOTE Confidence: 0.798697412014008

00:14:05.898 --> 00:14:08.008 or organized in native quality.

NOTE Confidence: 0.798697412014008

 $00:14:08.010 \longrightarrow 00:14:11.196$  In, in, in, in prime itself.

NOTE Confidence: 0.798697412014008

 $00{:}14{:}11{.}200 \dashrightarrow 00{:}14{:}14{.}469$  So you attempt to address this question.

NOTE Confidence: 0.798697412014008

 $00:14:14.470 \longrightarrow 00:14:17.646$  We thought that we will ideally be able

NOTE Confidence: 0.798697412014008

 $00{:}14{:}17.646 \dashrightarrow 00{:}14{:}20.698$  to isolating hazard from this native

NOTE Confidence: 0.798697412014008

 $00:14:20.698 \rightarrow 00:14:22.874$  quality environment and bisector.

- NOTE Confidence: 0.798697412014008
- $00:14:22.880 \rightarrow 00:14:24.335$  Regularly composed compositions.
- NOTE Confidence: 0.798697412014008
- $00:14:24.335 \longrightarrow 00:14:27.245$  So we ended up engineering are
- NOTE Confidence: 0.798697412014008
- $00:14:27.245 \longrightarrow 00:14:29.552$  inside your capture as say by
- NOTE Confidence: 0.798697412014008
- $00{:}14{:}29{.}552 \dashrightarrow 00{:}14{:}31{.}742$  leveraging CRISPR CAS 9 technology.
- NOTE Confidence: 0.798697412014008
- $00{:}14{:}31.750 \dashrightarrow 00{:}14{:}35.638$  So briefly many of new by combining a
- NOTE Confidence: 0.798697412014008
- $00{:}14{:}35{.}638 \dashrightarrow 00{:}14{:}38{.}695$  gene specific garden sequence with a
- NOTE Confidence: 0.798697412014008
- 00:14:38.695 --> 00:14:42.529 nucleus in activity cost 9 or D CAS 9.
- NOTE Confidence: 0.798697412014008
- $00:14:42.530 \longrightarrow 00:14:45.370$  The crisper cast 9 Rd CAS 9 can
- NOTE Confidence: 0.798697412014008
- $00:14:45.370 \longrightarrow 00:14:46.080$  be targeted
- NOTE Confidence: 0.77639240026474
- $00:14:46.163 \longrightarrow 00:14:48.935$  to the proximity of any answer
- NOTE Confidence: 0.77639240026474
- 00:14:48.935 --> 00:14:51.391 that you might be interested
- NOTE Confidence: 0.77639240026474
- $00:14:51.391 \longrightarrow 00:14:53.755$  or other regulatory elements.
- NOTE Confidence: 0.77639240026474
- $00:14:53.760 \longrightarrow 00:14:55.488$  We then met further
- NOTE Confidence: 0.77639240026474
- $00{:}14{:}55{.}488 \dashrightarrow 00{:}14{:}57{.}216$  modifications of the system,
- NOTE Confidence: 0.77639240026474
- $00{:}14{:}57{.}220 \dashrightarrow 00{:}14{:}59{.}160$  including adding an epitope tag
- NOTE Confidence: 0.77639240026474

 $00:14:59.160 \longrightarrow 00:15:01.970$  that can be enabled by terminated,

NOTE Confidence: 0.77639240026474

00:15:01.970 --> 00:15:04.130 then using high affinity stood

NOTE Confidence: 0.77639240026474

 $00{:}15{:}04{.}130 \dashrightarrow 00{:}15{:}05{.}858$  averaging biotin based application.

NOTE Confidence: 0.77639240026474

 $00{:}15{:}05{.}860 \dashrightarrow 00{:}15{:}08{.}541$  We can isolate the enhancer complex and

NOTE Confidence: 0.77639240026474

00:15:08.541 --> 00:15:10.263 all associated molecular interactions

NOTE Confidence: 0.77639240026474

 $00{:}15{:}10.263 \dashrightarrow 00{:}15{:}12.808$  and determine has associated proteins.

NOTE Confidence: 0.77639240026474

 $00:15:12.810 \rightarrow 00:15:16.872$  Amaze and DNA complexes by proteomics

NOTE Confidence: 0.77639240026474

 $00:15:16.872 \rightarrow 00:15:19.580$  and next generation sequences.

NOTE Confidence: 0.77639240026474

 $00{:}15{:}19{.}580 \dashrightarrow 00{:}15{:}22{.}684$  So as a proof of principle this approach

NOTE Confidence: 0.77639240026474

 $00:15:22.684 \rightarrow 00:15:25.140$  we started with human telomeres,

NOTE Confidence: 0.77639240026474

 $00:15:25.140 \rightarrow 00:15:28.542$  which contains many copies of repetitive's

NOTE Confidence: 0.77639240026474

 $00:15:28.542 \rightarrow 00:15:31.230$  at telemetric repeat sequence that

NOTE Confidence: 0.77639240026474

 $00{:}15{:}31{.}230 \dashrightarrow 00{:}15{:}34{.}272$  can be targeted by a single God on it.

NOTE Confidence: 0.77639240026474

00:15:34.280 --> 00:15:35.944 Upon inside your capture,

NOTE Confidence: 0.77639240026474

 $00:15:35.944 \longrightarrow 00:15:38.871$  we found out that email can be

NOTE Confidence: 0.77639240026474

00:15:38.871 -> 00:15:41.279 labeled by image Ng if you fuse,

- NOTE Confidence: 0.77639240026474
- $00:15:41.280 \rightarrow 00:15:43.752$  because now with the GOP molecule
- NOTE Confidence: 0.77639240026474
- $00:15:43.752 \longrightarrow 00:15:45.949$  for example also by Q PCR,
- NOTE Confidence: 0.77639240026474
- $00:15:45.950 \longrightarrow 00:15:47.502$  we identified chilling your
- NOTE Confidence: 0.77639240026474
- 00:15:47.502 --> 00:15:49.054 DNA are highly enriched,
- NOTE Confidence: 0.77639240026474
- $00:15:49.060 \rightarrow 00:15:51.825$  ANAN more important by Western blot and
- NOTE Confidence: 0.77639240026474
- $00{:}15{:}51.825 \dashrightarrow 00{:}15{:}54.507$  subsequent in mass spec based pre omics.
- NOTE Confidence: 0.77639240026474
- $00:15:54.510 \rightarrow 00:15:57.226$  We can identify many of the noise,
- NOTE Confidence: 0.77639240026474
- 00:15:57.230 --> 00:15:57.634 artillery,
- NOTE Confidence: 0.77639240026474
- $00:15:57.634 \rightarrow 00:16:00.058$  associated proteins and many of the
- NOTE Confidence: 0.77639240026474
- $00:16:00.058 \rightarrow 00:16:02.071$  unknown factors that she annualizing
- NOTE Confidence: 0.77639240026474
- $00:16:02.071 \rightarrow 00:16:04.285$  to how telomere may be regulated.
- NOTE Confidence: 0.77639240026474
- $00:16:04.290 \rightarrow 00:16:06.690$  This is a highly repetitive sequences.
- NOTE Confidence: 0.77639240026474
- $00:16:06.690 \rightarrow 00:16:08.690$  What about a single copy?
- NOTE Confidence: 0.77639240026474
- $00{:}16{:}08.690 \dashrightarrow 00{:}16{:}10.690$  Locals in the human genome?
- NOTE Confidence: 0.77639240026474
- $00{:}16{:}10.690 \dashrightarrow 00{:}16{:}13.890$  So we choose to focus on our favorite.
- NOTE Confidence: 0.77639240026474

00:16:13.890 --> 00:16:15.984 Locals are human beta globin gene

NOTE Confidence: 0.77639240026474

 $00:16:15.984 \longrightarrow 00:16:18.121$  cluster as you know that these

NOTE Confidence: 0.77639240026474

 $00{:}16{:}18{.}121 \dashrightarrow 00{:}16{:}20{.}473$  cluster contains a set of five beta

NOTE Confidence: 0.77639240026474

 $00:16:20.473 \rightarrow 00:16:23.061$  like globin genes that undergoes

NOTE Confidence: 0.77639240026474

 $00{:}16{:}23.061 \dashrightarrow 00{:}16{:}24.699$  developmental switching doing.

NOTE Confidence: 0.77639240026474

 $00{:}16{:}24.700 \dashrightarrow 00{:}16{:}26.665$  Insurance cell differentiation and all

NOTE Confidence: 0.77639240026474

 $00:16:26.665 \rightarrow 00:16:29.210$  these things are controlled by a shield.

NOTE Confidence: 0.77639240026474

00:16:29.210 --> 00:16:31.300 Locals control raging or super

NOTE Confidence: 0.77639240026474

 $00{:}16{:}31{.}300 \dashrightarrow 00{:}16{:}34{.}271$  enhancer if you wish and look at

NOTE Confidence: 0.77639240026474

00:16:34.271 -> 00:16:36.665 it upstream of this gene clusters.

NOTE Confidence: 0.77639240026474

 $00{:}16{:}36{.}670 \dashrightarrow 00{:}16{:}39{.}040$  So using a single godani that

NOTE Confidence: 0.77639240026474

 $00{:}16{:}39{.}040 \dashrightarrow 00{:}16{:}41{.}583$  are designed to be specific for

NOTE Confidence: 0.77639240026474

 $00:16:41.583 \rightarrow 00:16:43.339$  the three Prime HS,

NOTE Confidence: 0.77639240026474

 $00:16:43.340 \longrightarrow 00:16:45.914$  one insulator element we found by

NOTE Confidence: 0.77639240026474

 $00{:}16{:}45{.}914 \dashrightarrow 00{:}16{:}48{.}900$  chip sequencing of the DCAS 9 capture

NOTE Confidence: 0.77639240026474

 $00:16:48.900 \rightarrow 00:16:51.686$  DNA that only three primary chest one

 $00:16:51.766 \rightarrow 00:16:54.594$  and no other regions and across loci,

NOTE Confidence: 0.77639240026474

 $00:16:54.600 \rightarrow 00:16:55.872$  is highly enriched.

NOTE Confidence: 0.77639240026474

00:16:55.872 --> 00:16:56.296 Similarly,

NOTE Confidence: 0.77639240026474

00:16:56.296 --> 00:16:59.190 if you use a gardener targeting HPV,

NOTE Confidence: 0.77639240026474

 $00{:}16{:}59{.}190 \dashrightarrow 00{:}17{:}02{.}368$  you will see a single peak antagony

NOTE Confidence: 0.77639240026474

 $00{:}17{:}02.368 \dashrightarrow 00{:}17{:}04.935$  HPP promoter regions we know in

NOTE Confidence: 0.77639240026474

 $00:17:04.935 \longrightarrow 00:17:07.546$  the human genome the gamma gene is.

NOTE Confidence: 0.77639240026474

00:17:07.550 --> 00:17:09.896 Duplicate it at pgy and beaches.

NOTE Confidence: 0.77639240026474

 $00{:}17{:}09{.}900 \dashrightarrow 00{:}17{:}12.644$  SVG two, so therefore a single God,

NOTE Confidence: 0.77639240026474

00:17:12.650 --> 00:17:14.218 an actual capture both,

NOTE Confidence: 0.77639240026474

 $00:17:14.218 \rightarrow 00:17:16.570$  and that's exactly what we're seeing,

NOTE Confidence: 0.77639240026474

 $00{:}17{:}16.570 \dashrightarrow 00{:}17{:}19.307$  and then we can simply by design

NOTE Confidence: 0.77639240026474

 $00{:}17{:}19{.}307 \dashrightarrow 00{:}17{:}20{.}089$  different God.

NOTE Confidence: 0.77639240026474

00:17:20.090 --> 00:17:22.050 Honest, having different regulatory elements,

NOTE Confidence: 0.77639240026474

 $00:17:22.050 \longrightarrow 00:17:23.229$  enhancers for example,

 $00:17:23.229 \rightarrow 00:17:25.980$  and we can capture each individual enhances.

NOTE Confidence: 0.77639240026474

 $00{:}17{:}25{.}980 \dashrightarrow 00{:}17{:}27{.}680$  Using this card on is,

NOTE Confidence: 0.77639240026474

00:17:27.680 --> 00:17:28.637 and more importantly,

NOTE Confidence: 0.77639240026474

 $00:17:28.637 \longrightarrow 00:17:30.870$  if we pull all these God honors

NOTE Confidence: 0.77639240026474

 $00{:}17{:}30{.}939 \dashrightarrow 00{:}17{:}32{.}853$  together an echo expressing the same

NOTE Confidence: 0.77639240026474

 $00{:}17{:}32.853 \dashrightarrow 00{:}17{:}35.302$  cell that we can capture all five

NOTE Confidence: 0.77639240026474

 $00:17:35.302 \rightarrow 00:17:37.142$  enhancers suggestion that this system

NOTE Confidence: 0.77639240026474

 $00:17:37.142 \rightarrow 00:17:39.684$  can be multiplexed to capture many

NOTE Confidence: 0.77639240026474

 $00{:}17{:}39{.}684 \dashrightarrow 00{:}17{:}43{.}600$  enhances at the same time in the same cell.

NOTE Confidence: 0.77639240026474

 $00:17:43.600 \rightarrow 00:17:45.540$  So based on these findings,

NOTE Confidence: 0.77639240026474

 $00:17:45.540 \longrightarrow 00:17:46.964$  but we went ahead,

NOTE Confidence: 0.77639240026474

 $00{:}17{:}46{.}964 \dashrightarrow 00{:}17{:}48{.}388$  developed a capture proteomics

NOTE Confidence: 0.77639240026474

 $00{:}17{:}48.388 \dashrightarrow 00{:}17{:}50.200$  to determine decathlon capture,

NOTE Confidence: 0.77639240026474

 $00:17:50.200 \rightarrow 00:17:52.378$  look locals are specific podium and

NOTE Confidence: 0.77639240026474

 $00{:}17{:}52{.}378 \dashrightarrow 00{:}17{:}54{.}600$  identify in this case again using

NOTE Confidence: 0.77639240026474

 $00:17:54.600 \rightarrow 00:17:56.700$  beta globin gene cluster as example

- NOTE Confidence: 0.77639240026474
- 00:17:56.700 00:17:58.407 that we identify manufacturers
- NOTE Confidence: 0.77639240026474
- $00:17:58.407 \longrightarrow 00:18:00.275$  that are social with,
- NOTE Confidence: 0.77639240026474
- $00{:}18{:}00{.}280 \dashrightarrow 00{:}18{:}02{.}536$  for example HS2 enhance at the
- NOTE Confidence: 0.77639240026474
- $00{:}18{:}02{.}536 \dashrightarrow 00{:}18{:}04{.}511$  LCR region including some familiar
- NOTE Confidence: 0.77639240026474
- 00:18:04.511 --> 00:18:05.720 faces like God.
- NOTE Confidence: 0.77639240026474
- $00:18:05.720 \longrightarrow 00:18:08.121$  I want a long beyond the four
- NOTE Confidence: 0.77639240026474
- $00{:}18{:}08{.}121 \dashrightarrow 00{:}18{:}11{.}017$  etc and but also some other new
- NOTE Confidence: 0.77639240026474
- $00{:}18{:}11.017 \dashrightarrow 00{:}18{:}13.681$  factors that we decided to follow
- NOTE Confidence: 0.778671443462372
- 00:18:13.767 --> 00:18:16.352 up on. Such as a nuclear pore proteins
- NOTE Confidence: 0.778671443462372
- $00:18:16.352 \rightarrow 00:18:19.417$  and you can see some of these factors
- NOTE Confidence: 0.778671443462372
- $00:18:19.417 \rightarrow 00:18:22.332$  also present at the gamma globin gene
- NOTE Confidence: 0.778671443462372
- $00:18:22.332 \rightarrow 00:18:25.433$  promoters and other factors are present in.
- NOTE Confidence: 0.778671443462372
- $00{:}18{:}25{.}440 \dashrightarrow 00{:}18{:}27{.}556$  Beta globin gene clusters.
- NOTE Confidence: 0.778671443462372
- $00{:}18{:}27{.}556$  -->  $00{:}18{:}30{.}730$  So this analysis provides the initial
- NOTE Confidence: 0.778671443462372
- $00{:}18{:}30{.}814 \dashrightarrow 00{:}18{:}33{.}539$  evidence for the composition based
- NOTE Confidence: 0.778671443462372

 $00:18:33.539 \longrightarrow 00:18:36.264$  organization of the beta globin

NOTE Confidence: 0.778671443462372

00:18:36.353 - > 00:18:38.749 gene enhancers and promoters.

NOTE Confidence: 0.778671443462372

 $00{:}18{:}38{.}750 \dashrightarrow 00{:}18{:}41{.}614$  We all know that the human genome is

NOTE Confidence: 0.778671443462372

 $00:18:41.614 \rightarrow 00:18:44.018$  organized into a multilayer structure.

NOTE Confidence: 0.778671443462372

 $00:18:44.020 \longrightarrow 00:18:46.045$  Units are organized by Long

NOTE Confidence: 0.778671443462372

 $00:18:46.045 \longrightarrow 00:18:47.260$  range dinner interactions,

NOTE Confidence: 0.778671443462372

00:18:47.260 --> 00:18:48.475 or chromatin looping,

NOTE Confidence: 0.778671443462372

 $00{:}18{:}48{.}475 \dashrightarrow 00{:}18{:}50{.}500$  so we never saw that.

NOTE Confidence: 0.778671443462372

 $00{:}18{:}50{.}500 \dashrightarrow 00{:}18{:}52{.}719$  Can we combine this DCAS 9 capture

NOTE Confidence: 0.778671443462372

 $00{:}18{:}52{.}719 \dashrightarrow 00{:}18{:}55{.}714$  with three C analysis to identify local

NOTE Confidence: 0.778671443462372

 $00{:}18{:}55{.}714$  -->  $00{:}18{:}58{.}184$  specific long range thing interactions?

NOTE Confidence: 0.778671443462372

 $00{:}18{:}58{.}190 \dashrightarrow 00{:}19{:}00{.}953$  So the way it works is we first using

NOTE Confidence: 0.778671443462372

 $00:19:00.953 \longrightarrow 00:19:03.833$  in vivo bite Internet DCAS 9 to

NOTE Confidence: 0.778671443462372

 $00{:}19{:}03.833 \dashrightarrow 00{:}19{:}06.648$  isolate enhances that you might be

NOTE Confidence: 0.778671443462372

 $00{:}19{:}06{.}648 \dashrightarrow 00{:}19{:}09{.}338$  interested and Cromartie is crosslinked.

NOTE Confidence: 0.778671443462372

 $00:19:09.340 \longrightarrow 00:19:11.488$  Followed by enzyme digestion.

- NOTE Confidence: 0.778671443462372
- 00:19:11.488 --> 00:19:14.173 Usually we use frequent Cadillac
- NOTE Confidence: 0.778671443462372
- $00{:}19{:}14.173 \dashrightarrow 00{:}19{:}16.868$  DPM two and this is followed
- NOTE Confidence: 0.778671443462372
- $00:19:16.868 \rightarrow 00:19:19.350$  by a proximity ligation of the.
- NOTE Confidence: 0.778671443462372
- 00:19:19.350 --> 00:19:21.550 Adjusted genomic DNA Anan followed
- NOTE Confidence: 0.778671443462372
- $00:19:21.550 \longrightarrow 00:19:23.750$  by fragmentation and then the
- NOTE Confidence: 0.778671443462372
- $00:19:23.824 \rightarrow 00:19:26.264$  enhancer can be directly isolated
- NOTE Confidence: 0.778671443462372
- 00:19:26.264 --> 00:19:28.704 using strip having best purification,
- NOTE Confidence: 0.778671443462372
- $00{:}19{:}28{.}710 \dashrightarrow 00{:}19{:}31{.}650$  ANAN together with all the DF
- NOTE Confidence: 0.778671443462372
- $00:19:31.650 \rightarrow 00:19:34.330$  fragment that will really get it,
- NOTE Confidence: 0.778671443462372
- $00:19:34.330 \rightarrow 00:19:36.808$  and using pale and sequencing we
- NOTE Confidence: 0.778671443462372
- $00:19:36.808 \rightarrow 00:19:39.556$  can identify all the long range
- NOTE Confidence: 0.778671443462372
- $00{:}19{:}39{.}556 \dashrightarrow 00{:}19{:}42{.}091$  interactions that are social with
- NOTE Confidence: 0.778671443462372
- $00:19:42.091 \longrightarrow 00:19:44.626$  this target enhances and more
- NOTE Confidence: 0.778671443462372
- $00{:}19{:}44.626 \dashrightarrow 00{:}19{:}46.498$  importantly by combining capture
- NOTE Confidence: 0.778671443462372
- $00{:}19{:}46{.}498 \dashrightarrow 00{:}19{:}49{.}048$  as we see analysis with capture.
- NOTE Confidence: 0.778671443462372

 $00:19:49.048 \longrightarrow 00:19:51.421$  Baryonyx we hope to be able to

NOTE Confidence: 0.778671443462372

00:19:51.421 --> 00:19:52.470 identify causality.

NOTE Confidence: 0.778671443462372

 $00:19:52.470 \longrightarrow 00:19:54.528$  What are the factors that might

NOTE Confidence: 0.778671443462372

 $00:19:54.528 \longrightarrow 00:19:56.553$  be responsible for this Sweetie

NOTE Confidence: 0.778671443462372

 $00:19:56.553 \longrightarrow 00:19:57.719$  Genome organization?

NOTE Confidence: 0.778671443462372

 $00:19:57.720 \longrightarrow 00:20:00.205$  This is just showing one of the

NOTE Confidence: 0.778671443462372

 $00:20:00.205 \rightarrow 00:20:02.887$  example of the data how this works,

NOTE Confidence: 0.778671443462372

 $00:20:02.890 \rightarrow 00:20:05.170$  so here we're showing capture 3C

NOTE Confidence: 0.778671443462372

 $00{:}20{:}05{.}170 \dashrightarrow 00{:}20{:}07{.}310$  analysis for the active HP Gigi.

NOTE Confidence: 0.778671443462372

 $00:20:07.310 \longrightarrow 00:20:09.900$  This was done in Cape RC2 sales.

NOTE Confidence: 0.778671443462372

 $00:20:09.900 \longrightarrow 00:20:12.154$  Now you will see that is active

NOTE Confidence: 0.778671443462372

00:20:12.154 --> 00:20:14.411 Edge BGM contains many long range

NOTE Confidence: 0.778671443462372

 $00{:}20{:}14.411 \dashrightarrow 00{:}20{:}16.446$  interactions with other six element

NOTE Confidence: 0.778671443462372

 $00{:}20{:}16.446 \dashrightarrow 00{:}20{:}19.140$  across the low side but not the

NOTE Confidence: 0.778671443462372

 $00:20:19.140 \longrightarrow 00:20:20.223$  nearby repressed genes.

NOTE Confidence: 0.778671443462372

 $00:20:20.230 \longrightarrow 00:20:22.323$  But first I if you capture the

 $00:20:22.323 \rightarrow 00:20:24.426$  repressions HPB you will see the

NOTE Confidence: 0.778671443462372

 $00{:}20{:}24{.}426 \dashrightarrow 00{:}20{:}26{.}336$  HPV forms of predominant shorter

NOTE Confidence: 0.778671443462372

 $00{:}20{:}26{.}336 \dashrightarrow 00{:}20{:}28{.}064$  range interactions and downstream

NOTE Confidence: 0.778671443462372

 $00:20:28.064 \rightarrow 00:20:29.856$  sweeper matches one insulator.

NOTE Confidence: 0.778671443462372

 $00{:}20{:}29{.}860 \dashrightarrow 00{:}20{:}31{.}995$  There's no interaction between active

NOTE Confidence: 0.778671443462372

 $00{:}20{:}31{.}995 \dashrightarrow 00{:}20{:}35{.}248$  and repressed genes on when we capture this.

NOTE Confidence: 0.778671443462372

 $00{:}20{:}35{.}250 \dashrightarrow 00{:}20{:}37{.}285$  We next capture each individual

NOTE Confidence: 0.778671443462372

 $00:20:37.285 \longrightarrow 00:20:38.506$  in hazard within,

NOTE Confidence: 0.778671443462372

 $00{:}20{:}38{.}510 \dashrightarrow 00{:}20{:}40{.}520$  else are an interesting and we

NOTE Confidence: 0.778671443462372

 $00{:}20{:}40{.}520 \dashrightarrow 00{:}20{:}43{.}210$  found that H S3 has a contains

NOTE Confidence: 0.778671443462372

00:20:43.210 --> 00:20:45.325 many more long range interaction

NOTE Confidence: 0.778671443462372

 $00:20:45.325 \longrightarrow 00:20:47.489$  then other nearby enhancers,

NOTE Confidence: 0.778671443462372

 $00{:}20{:}47.490 \dashrightarrow 00{:}20{:}49.250$  including access to and.

NOTE Confidence: 0.778671443462372

 $00{:}20{:}49{.}250 \dashrightarrow 00{:}20{:}51{.}450$  We further validated this using

NOTE Confidence: 0.778671443462372

 $00{:}20{:}51{.}450 \dashrightarrow 00{:}20{:}53{.}279$  independent God honest and we

 $00:20:53.279 \rightarrow 00:20:55.259$  notice that H3 has a consistently

NOTE Confidence: 0.778671443462372

 $00:20:55.326 \longrightarrow 00:20:57.086$  contained many more interactions

NOTE Confidence: 0.778671443462372

 $00:20:57.086 \rightarrow 00:20:59.726$  than the nearby actions to enhance,

NOTE Confidence: 0.778671443462372

 $00:20:59.730 \longrightarrow 00:21:02.467$  and this was interesting to us because

NOTE Confidence: 0.778671443462372

 $00:21:02.467 \longrightarrow 00:21:05.827$  it's just too has been sought to be

NOTE Confidence: 0.778671443462372

 $00{:}21{:}05{.}827 \dashrightarrow 00{:}21{:}07{.}932$  the strongest enhancer within LCR.

NOTE Confidence: 0.778671443462372

00:21:07.940 --> 00:21:09.544 By transgenic enhancer Reporter,

NOTE Confidence: 0.778671443462372

00:21:09.544 --> 00:21:11.950 access YH Three was also shown

NOTE Confidence: 0.778671443462372

 $00:21:12.020 \longrightarrow 00:21:13.040$  to be important,

NOTE Confidence: 0.778671443462372

 $00:21:13.040 \rightarrow 00:21:16.168$  but only in the context of native quality.

NOTE Confidence: 0.778671443462372

 $00{:}21{:}16.170 \dashrightarrow 00{:}21{:}18.642$  So therefore our findings may help

NOTE Confidence: 0.778671443462372

 $00{:}21{:}18.642 \dashrightarrow 00{:}21{:}20.763$  to explain these findings and

NOTE Confidence: 0.778671443462372

 $00{:}21{:}20.763 \dashrightarrow 00{:}21{:}23.151$  support a model that the hierarchy

NOTE Confidence: 0.778671443462372

 $00:21:23.151 \longrightarrow 00:21:25.473$  organization with a beta globin LCR

NOTE Confidence: 0.778671443462372

 $00:21:25.473 \rightarrow 00:21:27.923$  in which that itches to my function

NOTE Confidence: 0.778671443462372

 $00:21:27.930 \rightarrow 00:21:30.394$  to recruit a trans acting factors and

- NOTE Confidence: 0.778671443462372
- 00:21:30.394 --> 00:21:33.028 function more like a conventional enhancer,
- NOTE Confidence: 0.778671443462372
- $00{:}21{:}33.030 \dashrightarrow 00{:}21{:}35.767$  yhs 3 might might be more important,
- NOTE Confidence: 0.778671443462372
- $00:21:35.770 \longrightarrow 00:21:38.584$  immediate and long ranged in actions of.
- NOTE Confidence: 0.778671443462372
- $00:21:38.590 \longrightarrow 00:21:39.006$  Formative,
- NOTE Confidence: 0.778671443462372
- 00:21:39.006 --> 00:21:39.422 loopy,
- NOTE Confidence: 0.778671443462372
- $00:21:39.422 \longrightarrow 00:21:40.254$  and really,
- NOTE Confidence: 0.778671443462372
- 00:21:40.254 --> 00:21:42.334 it's a combination posing hazard.
- NOTE Confidence: 0.716553509235382
- $00:21:42.340 \longrightarrow 00:21:45.259$  Am I dictating what the locals control?
- NOTE Confidence: 0.716553509235382
- 00:21:45.260 --> 00:21:47.276 Regional Super Enhancer will
- NOTE Confidence: 0.716553509235382
- 00:21:47.276 --> 00:21:49.796 function in its native quality.
- NOTE Confidence: 0.716553509235382
- 00:21:49.800 --> 00:21:52.010 So as a brief summary,
- NOTE Confidence: 0.716553509235382
- $00{:}21{:}52.010 \dashrightarrow 00{:}21{:}54.308$  so we think that this decath lon
- NOTE Confidence: 0.716553509235382
- 00:21:54.308 --> 00:21:56.361 capture my provider are useful
- NOTE Confidence: 0.716553509235382
- 00:21:56.361 --> 00:21:58.621 tool for multi omic dissection
- NOTE Confidence: 0.716553509235382
- $00:21:58.621 \rightarrow 00:22:00.978$  of this regulatory elements from
- NOTE Confidence: 0.716553509235382
$00:22:00.978 \longrightarrow 00:22:03.343$  their endogenous loci and this

NOTE Confidence: 0.716553509235382

00:22:03.343 --> 00:22:05.235 biotin scribbling based affinity

NOTE Confidence: 0.716553509235382

 $00:22:05.240 \rightarrow 00:22:07.092$  capture provides high specificity

NOTE Confidence: 0.716553509235382

 $00:22:07.092 \rightarrow 00:22:09.870$  and sensitivity and this SGI based

NOTE Confidence: 0.716553509235382

 $00{:}22{:}09{.}946 \dashrightarrow 00{:}22{:}11.662$  targeting allows for Multiplex

NOTE Confidence: 0.716553509235382

00:22:11.662 --> 00:22:14.236 analysis which are going to show

NOTE Confidence: 0.716553509235382

 $00:22:14.310 \rightarrow 00:22:16.806$  in a minute and more importantly

NOTE Confidence: 0.716553509235382

 $00:22:16.806 \rightarrow 00:22:18.965$  the simultaneous analysis of local

NOTE Confidence: 0.716553509235382

 $00:22:18.965 \rightarrow 00:22:21.440$  specific proteome and 3D interactions.

NOTE Confidence: 0.716553509235382

 $00:22:21.440 \longrightarrow 00:22:23.650$  Help to establish causality and

NOTE Confidence: 0.716553509235382

 $00:22:23.650 \longrightarrow 00:22:26.387$  the system should be brought it

NOTE Confidence: 0.716553509235382

 $00:22:26.387 \rightarrow 00:22:28.632$  up application applicable to other

NOTE Confidence: 0.716553509235382

00:22:28.632 --> 00:22:31.100 genomic locals or model systems.

NOTE Confidence: 0.716553509235382

00:22:31.100 --> 00:22:31.523 However,

NOTE Confidence: 0.716553509235382

 $00:22:31.523 \longrightarrow 00:22:34.061$  one of the major limitation of

NOTE Confidence: 0.716553509235382

 $00:22:34.061 \rightarrow 00:22:36.489$  the original capture Mesa was that

- NOTE Confidence: 0.716553509235382
- 00:22:36.489 --> 00:22:38.649 it requires large number of cells
- NOTE Confidence: 0.716553509235382
- $00:22:38.649 \longrightarrow 00:22:40.746$  and typically 10s of sometime
- NOTE Confidence: 0.716553509235382
- $00:22:40.746 \longrightarrow 00:22:43.242$  hundreds of millions of sales for
- NOTE Confidence: 0.716553509235382
- 00:22:43.250 --> 00:22:44.866 local specific proteomic studies,
- NOTE Confidence: 0.716553509235382
- $00:22:44.866 \rightarrow 00:22:47.756$  and thus was not applicable to primary
- NOTE Confidence: 0.716553509235382
- $00{:}22{:}47.756 \dashrightarrow 00{:}22{:}50.138$  cell types or male cell populations.
- NOTE Confidence: 0.716553509235382
- $00{:}22{:}50{.}140 \dashrightarrow 00{:}22{:}52{.}548$  So we wonder whether we could improve
- NOTE Confidence: 0.716553509235382
- $00:22:52.548 \rightarrow 00:22:54.594$  the design to increase capture
- NOTE Confidence: 0.716553509235382
- $00{:}22{:}54{.}594 \dashrightarrow 00{:}22{:}57{.}426$  efficiency so you know original design.
- NOTE Confidence: 0.716553509235382
- $00:22:57.430 \longrightarrow 00:23:00.041$  We fuse the biotin tag to the
- NOTE Confidence: 0.716553509235382
- 00:23:00.041 --> 00:23:02.289 N terminus of the kastein.
- NOTE Confidence: 0.716553509235382
- $00:23:02.290 \longrightarrow 00:23:04.714$  We just close to the nucleotide
- NOTE Confidence: 0.716553509235382
- $00:23:04.714 \longrightarrow 00:23:06.330$  protein interacting pocket that
- NOTE Confidence: 0.716553509235382
- 00:23:06.400 --> 00:23:08.068 might cause are pa tomaski,
- NOTE Confidence: 0.716553509235382
- $00{:}23{:}08.070 \dashrightarrow 00{:}23{:}10.730$  whereas the C terminus of CAS 9
- NOTE Confidence: 0.716553509235382

 $00:23:10.730 \longrightarrow 00:23:13.029$  proteins largely exposed an unstructured.

NOTE Confidence: 0.716553509235382

 $00:23:13.030 \rightarrow 00:23:15.718$  So we have tried tagging the seat

NOTE Confidence: 0.716553509235382

 $00:23:15.718 \longrightarrow 00:23:17.980$  owners instead for by connection.

NOTE Confidence: 0.716553509235382

00:23:17.980 --> 00:23:20.050 Moreover, in our original design,

NOTE Confidence: 0.716553509235382

 $00{:}23{:}20.050 \dashrightarrow 00{:}23{:}22.618$  we use the conventional every tag

NOTE Confidence: 0.716553509235382

 $00:23:22.618 \rightarrow 00:23:25.176$  together with the bacteria puje biotin

NOTE Confidence: 0.716553509235382

 $00:23:25.176 \longrightarrow 00:23:27.480$  ligase for in vivo bike nation.

NOTE Confidence: 0.716553509235382

 $00:23:27.480 \rightarrow 00:23:30.784$  So this will make a three vector system.

NOTE Confidence: 0.716553509235382

 $00:23:30.790 \longrightarrow 00:23:32.478$  However there are other.

NOTE Confidence: 0.716553509235382

 $00:23:32.478 \rightarrow 00:23:35.010$  Peptide sequence that can be bought

NOTE Confidence: 0.716553509235382

00:23:35.090 --> 00:23:37.538 in an area using endogenous biting

NOTE Confidence: 0.716553509235382

 $00:23:37.538 \rightarrow 00:23:40.179$  like is that expressing my man in

NOTE Confidence: 0.716553509235382

 $00{:}23{:}40{.}179 \dashrightarrow 00{:}23{:}42{.}349$  sales so we have been testing some

NOTE Confidence: 0.716553509235382

 $00:23:42.350 \rightarrow 00:23:44.768$  of those sequences and more recently

NOTE Confidence: 0.716553509235382

 $00:23:44.768 \rightarrow 00:23:46.899$  approximately biting ligands such as APEX.

NOTE Confidence: 0.716553509235382

00:23:46.900 --> 00:23:49.388 Two was shown to be able to buy

00:23:49.388 --> 00:23:51.192 terminate nearby proteins on comity

NOTE Confidence: 0.716553509235382

 $00{:}23{:}51{.}192 \dashrightarrow 00{:}23{:}53{.}782$  which may increase the signal to noise

NOTE Confidence: 0.716553509235382

 $00:23:53.848 \rightarrow 00:23:56.378$  ratio for identification by proteomics.

NOTE Confidence: 0.716553509235382

 $00:23:56.380 \longrightarrow 00:23:58.906$  So we have been trying and

NOTE Confidence: 0.716553509235382

 $00:23:58.906 \rightarrow 00:24:01.310$  adapting those systems for capture.

NOTE Confidence: 0.716553509235382

 $00{:}24{:}01{.}310 \dashrightarrow 00{:}24{:}03{.}638$  So with this improved capture system

NOTE Confidence: 0.716553509235382

 $00:24:03.638 \rightarrow 00:24:05.720$  with first attempted Multiplex capture,

NOTE Confidence: 0.716553509235382

 $00:24:05.720 \rightarrow 00:24:08.126$  many answers in a single experiment,

NOTE Confidence: 0.716553509235382

 $00{:}24{:}08{.}130 \dashrightarrow 00{:}24{:}10.713$  so we started with the LCI enhancer

NOTE Confidence: 0.716553509235382

 $00:24:10.713 \longrightarrow 00:24:12.749$  with 10 individual gardeners to

NOTE Confidence: 0.716553509235382

 $00{:}24{:}12.749 \dashrightarrow 00{:}24{:}15.759$  capture all 5H S enhances and observe

NOTE Confidence: 0.716553509235382

 $00{:}24{:}15.759 \dashrightarrow 00{:}24{:}17.820$  interactions social with all enhancers

NOTE Confidence: 0.716553509235382

 $00{:}24{:}17.820 \dashrightarrow 00{:}24{:}20.154$  in a single experiment and more

NOTE Confidence: 0.716553509235382

 $00:24:20.160 \longrightarrow 00:24:21.940$  importantly you actually can resolve

NOTE Confidence: 0.716553509235382

 $00{:}24{:}21{.}940 \dashrightarrow 00{:}24{:}24{.}970$  this data into a single enhancer resolution.

 $00:24:24.970 \longrightarrow 00:24:27.376$  Look at what other enhancer mediated

NOTE Confidence: 0.716553509235382

 $00{:}24{:}27{.}376 \dashrightarrow 00{:}24{:}28{.}980$  by each individual enhances,

NOTE Confidence: 0.716553509235382

 $00:24:28.980 \longrightarrow 00:24:30.588$  as you may recall,

NOTE Confidence: 0.716553509235382

 $00:24:30.588 \rightarrow 00:24:33.000$  the pattern looks almost the same.

NOTE Confidence: 0.716553509235382

 $00:24:33.000 \longrightarrow 00:24:35.556$  As we did previously for the

NOTE Confidence: 0.716553509235382

00:24:35.556 --> 00:24:36.408 individual capture,

NOTE Confidence: 0.716553509235382

 $00:24:36.410 \rightarrow 00:24:38.110$  you negating that multiplicative

NOTE Confidence: 0.716553509235382

00:24:38.110 --> 00:24:38.960 multipliers capture.

NOTE Confidence: 0.716553509235382

 $00{:}24{:}38{.}960 \dashrightarrow 00{:}24{:}42{.}266$  We tend the native permitting architecture.

NOTE Confidence: 0.716553509235382

 $00{:}24{:}42{.}270 \dashrightarrow 00{:}24{:}43{.}978$  So based on this,

NOTE Confidence: 0.716553509235382

 $00{:}24{:}43{.}978 \dashrightarrow 00{:}24{:}46{.}540$  we next performed much less capture

NOTE Confidence: 0.716553509235382

 $00:24:46.623 \longrightarrow 00:24:48.879$  of actually super enhancers.

NOTE Confidence: 0.716553509235382

00:24:48.880 --> 00:24:51.706 Using this super enhancer calling algorithm,

NOTE Confidence: 0.716553509235382

 $00{:}24{:}51{.}710 \dashrightarrow 00{:}24{:}54{.}370$  and in this experiment we use nearly

NOTE Confidence: 0.716553509235382

 $00:24:54.370 \longrightarrow 00:24:57.091$  2000 God on his targeting more

NOTE Confidence: 0.716553509235382

00:24:57.091 -> 00:24:59.586 than 150 super enhances containing

 $00:24:59.586 \longrightarrow 00:25:02.570$  more than 800 individual enhances.

NOTE Confidence: 0.716553509235382

 $00{:}25{:}02{.}570 \dashrightarrow 00{:}25{:}04{.}274$  A very large panel.

NOTE Confidence: 0.716553509235382

 $00{:}25{:}04{.}274 \dashrightarrow 00{:}25{:}07{.}385$  And that data shows that we can

NOTE Confidence: 0.716553509235382

00:25:07.385 - > 00:25:10.157 capture the vast majority of that

NOTE Confidence: 0.716553509235382

 $00{:}25{:}10{.}157 \dashrightarrow 00{:}25{:}13{.}270$  enhances in a single experiment.

NOTE Confidence: 0.716553509235382

 $00{:}25{:}13{.}270 \dashrightarrow 00{:}25{:}15{.}545$  So with these high resolution

NOTE Confidence: 0.716553509235382

 $00:25:15.545 \rightarrow 00:25:16.455$  multiplus capture,

NOTE Confidence: 0.823797523975372

 $00:25:16.460 \longrightarrow 00:25:19.280$  we notice that some interesting features

NOTE Confidence: 0.823797523975372

 $00{:}25{:}19{.}280 \dashrightarrow 00{:}25{:}21{.}631$  about this special configuration of

NOTE Confidence: 0.823797523975372

 $00:25:21.631 \rightarrow 00:25:23.281$  these super enhancers, specifically,

NOTE Confidence: 0.823797523975372

 $00:25:23.281 \longrightarrow 00:25:26.368$  we can often identify one or few

NOTE Confidence: 0.823797523975372

 $00{:}25{:}26{.}368 \dashrightarrow 00{:}25{:}28{.}796$  enhances within a super enhancer

NOTE Confidence: 0.823797523975372

 $00:25:28.796 \longrightarrow 00:25:31.251$  that have unusually higher frequency

NOTE Confidence: 0.823797523975372

00:25:31.251 --> 00:25:33.559 of interactions compared to other

NOTE Confidence: 0.823797523975372

00:25:33.559 --> 00:25:35.649 nearby enhances we call this.

00:25:35.650 - 00:25:38.320 He has a happy hanses.

NOTE Confidence: 0.823797523975372

 $00{:}25{:}38{.}320 \dashrightarrow 00{:}25{:}40{.}145$  We further developed a computational

NOTE Confidence: 0.823797523975372

 $00{:}25{:}40.145 \dashrightarrow 00{:}25{:}42.352$  workflow and a fund at about

NOTE Confidence: 0.823797523975372

 $00:25:42.352 \rightarrow 00:25:44.242 1/4$  of the Super enhancers are

NOTE Confidence: 0.823797523975372

 $00{:}25{:}44{.}242 \dashrightarrow 00{:}25{:}46{.}422$  organized as a hierarchy structure

NOTE Confidence: 0.823797523975372

 $00:25:46.422 \rightarrow 00:25:48.168$  containing hopping answers,

NOTE Confidence: 0.823797523975372

 $00{:}25{:}48.170 \dashrightarrow 00{:}25{:}50.543$  and here just showing a snapshot of

NOTE Confidence: 0.823797523975372

 $00:25:50.543 \rightarrow 00:25:53.334$  1 example of a hierarchy of super

NOTE Confidence: 0.823797523975372

 $00{:}25{:}53{.}334 \dashrightarrow 00{:}25{:}55{.}454$  enhancer that contains a hopping

NOTE Confidence: 0.823797523975372

 $00{:}25{:}55{.}454 \dashrightarrow 00{:}25{:}58{.}374$  answer that you can see that has

NOTE Confidence: 0.823797523975372

 $00{:}25{:}58{.}374 \dashrightarrow 00{:}25{:}59{.}986$  more frequent interactions with

NOTE Confidence: 0.823797523975372

 $00{:}25{:}59{.}990 \dashrightarrow 00{:}26{:}01{.}566$  other enhancers and promoters

NOTE Confidence: 0.823797523975372

00:26:01.566 - 00:26:03.536 within the same genomic region,

NOTE Confidence: 0.823797523975372

 $00{:}26{:}03{.}540 \dashrightarrow 00{:}26{:}06{.}053$  and what I won't show you the

NOTE Confidence: 0.823797523975372

 $00:26:06.053 \rightarrow 00:26:08.499$  data we actually went ahead using

NOTE Confidence: 0.823797523975372

 $00:26:08.499 \rightarrow 00:26:10.644$  crisper cast 9 to knockout.

 $00:26:10.650 \longrightarrow 00:26:12.546$  These hopping hazard.

NOTE Confidence: 0.823797523975372

 $00{:}26{:}12.546 \dashrightarrow 00{:}26{:}16.970$  Versus the nearby non hop enhances and

NOTE Confidence: 0.823797523975372

 $00{:}26{:}17.083 \dashrightarrow 00{:}26{:}20.875$  almost all the time that we can see,

NOTE Confidence: 0.823797523975372

 $00:26:20.880 \longrightarrow 00:26:23.848$  knockout hopping has at least a more

NOTE Confidence: 0.823797523975372

 $00{:}26{:}23.848 \dashrightarrow 00{:}26{:}26.324$  profound effect and target gene

NOTE Confidence: 0.823797523975372

 $00{:}26{:}26{.}324 \dashrightarrow 00{:}26{:}28{.}568$  expression comparing to knock out

NOTE Confidence: 0.823797523975372

 $00{:}26{:}28{.}568 \dashrightarrow 00{:}26{:}31{.}397$  an unhappy hazards suggestion that

NOTE Confidence: 0.823797523975372

 $00:26:31.397 \rightarrow 00:26:33.937$  this enhancer might be functionally

NOTE Confidence: 0.823797523975372

 $00:26:33.937 \longrightarrow 00:26:35.969$  more potent enhances that.

NOTE Confidence: 0.823797523975372

 $00{:}26{:}35{.}970 \dashrightarrow 00{:}26{:}38{.}742$  Functioning within a super has a

NOTE Confidence: 0.823797523975372

00:26:38.742 --> 00:26:41.760 gene cluster. So as a brief summary.

NOTE Confidence: 0.823797523975372

 $00{:}26{:}41.760 \dashrightarrow 00{:}26{:}44.070$  So here we showcase our several

NOTE Confidence: 0.823797523975372

 $00{:}26{:}44.070 \dashrightarrow 00{:}26{:}46.077$  potential implications for the D

NOTE Confidence: 0.823797523975372

00:26:46.077 -> 00:26:48.465 cast net capture system for high

NOTE Confidence: 0.823797523975372

00:26:48.465 --> 00:26:50.219 resolution Multiplex analysis and

 $00:26:50.219 \rightarrow 00:26:52.207$  local specific quality interactions.

NOTE Confidence: 0.823797523975372

 $00{:}26{:}52{.}210 \dashrightarrow 00{:}26{:}54{.}527$  We hope that the capture system can

NOTE Confidence: 0.823797523975372

 $00{:}26{:}54{.}527 \dashrightarrow 00{:}26{:}57{.}111$  enable us to determine a special

NOTE Confidence: 0.823797523975372

 $00:26:57.111 \longrightarrow 00:26:59.135$  configuration enhances and their

NOTE Confidence: 0.823797523975372

 $00{:}26{:}59{.}135 \dashrightarrow 00{:}27{:}00{.}147$  target genes,

NOTE Confidence: 0.823797523975372

 $00{:}27{:}00{.}150 \dashrightarrow 00{:}27{:}02{.}658$  as well as a temporal regulation

NOTE Confidence: 0.823797523975372

 $00:27:02.658 \longrightarrow 00:27:03.494$  during development.

NOTE Confidence: 0.823797523975372

 $00:27:03.500 \longrightarrow 00:27:04.541$  So with this,

NOTE Confidence: 0.823797523975372

 $00{:}27{:}04{.}541 \dashrightarrow 00{:}27{:}07{.}544$  we started to one of the next important

NOTE Confidence: 0.823797523975372

 $00:27:07.544 \rightarrow 00:27:11.488$  question that that would be interested in is.

NOTE Confidence: 0.823797523975372

 $00{:}27{:}11{.}490 \dashrightarrow 00{:}27{:}15{.}210$  How do we have to actually control tagger?

NOTE Confidence: 0.823797523975372

00:27:15.210 --> 00:27:15.610 Jinx,

NOTE Confidence: 0.823797523975372

 $00:27:15.610 \rightarrow 00:27:16.010$  brushing?

NOTE Confidence: 0.823797523975372

 $00{:}27{:}16.010 \dashrightarrow 00{:}27{:}17.210$  Inside to it,

NOTE Confidence: 0.823797523975372

 $00:27:17.210 \longrightarrow 00:27:19.660$  particularly doing in people development.

NOTE Confidence: 0.823797523975372

 $00:27:19.660 \longrightarrow 00:27:22.006$  And this has not been trivial.

- NOTE Confidence: 0.823797523975372
- 00:27:22.010 --> 00:27:23.960 Trivial as you can imagine,
- NOTE Confidence: 0.823797523975372
- $00{:}27{:}23.960 \dashrightarrow 00{:}27{:}26.306$  you can knock out this individual enhancers,
- NOTE Confidence: 0.823797523975372
- $00:27:26.310 \longrightarrow 00:27:28.650$  but offering you're not getting answer.
- NOTE Confidence: 0.823797523975372
- 00:27:28.650 --> 00:27:31.778 Look at in a cell grows best answer,
- NOTE Confidence: 0.823797523975372
- 00:27:31.780 --> 00:27:33.826 you don't really see a difference
- NOTE Confidence: 0.823797523975372
- $00:27:33.826 \longrightarrow 00:27:36.176$  is so we thought that to address
- NOTE Confidence: 0.823797523975372
- $00:27:36.176 \longrightarrow 00:27:38.318$  this we will need a tool that
- NOTE Confidence: 0.823797523975372
- $00:27:38.395 \rightarrow 00:27:40.950$  allow us to systematically bisector
- NOTE Confidence: 0.823797523975372
- $00{:}27{:}40{.}950 \dashrightarrow 00{:}27{:}42{.}994$  functional requirement of this
- NOTE Confidence: 0.823797523975372
- $00:27:42.994 \rightarrow 00:27:45.098$  enhances in their native comity.
- NOTE Confidence: 0.823797523975372
- 00:27:45.098 --> 00:27:47.083 Ideally doing in people development
- NOTE Confidence: 0.823797523975372
- $00{:}27{:}47.083 \dashrightarrow 00{:}27{:}49.380$  and such as human quality limits,
- NOTE Confidence: 0.823797523975372
- $00{:}27{:}49{.}380 \dashrightarrow 00{:}27{:}50{.}264$  differentiation so.
- NOTE Confidence: 0.823797523975372
- $00{:}27{:}50{.}264 \dashrightarrow 00{:}27{:}52{.}916$  We recently redesigned the Cast 9
- NOTE Confidence: 0.823797523975372
- $00{:}27{:}52{.}916 \dashrightarrow 00{:}27{:}55{.}639$  best so called epigenetic editing
- NOTE Confidence: 0.823797523975372

 $00:27:55.639 \rightarrow 00:27:58.574$  system that can efficiently perturb

NOTE Confidence: 0.823797523975372

 $00:27:58.574 \rightarrow 00:28:01.083$  enhancer activities by modulating

NOTE Confidence: 0.823797523975372

 $00{:}28{:}01{.}083 \dashrightarrow 00{:}28{:}03{.}595$  enhance associated chromatin features.

NOTE Confidence: 0.823797523975372

 $00:28:03.600 \rightarrow 00:28:06.942$  Particularly careful and K 27 simulation

NOTE Confidence: 0.823797523975372

 $00:28:06.942 \rightarrow 00:28:09.170$  specifically for enhanced activation,

NOTE Confidence: 0.823797523975372

 $00:28:09.170 \longrightarrow 00:28:11.398$  refused ecaster with P300,

NOTE Confidence: 0.823797523975372

00:28:11.398 --> 00:28:13.069 which catalyze H3K27

NOTE Confidence: 0.823797523975372

 $00:28:13.069 \rightarrow 00:28:14.740$  assimilation within adapted,

NOTE Confidence: 0.823797523975372

 $00{:}28{:}14.740 \dashrightarrow 00{:}28{:}17.818$  helping actimel Ms 2 on the

NOTE Confidence: 0.823797523975372

 $00:28:17.818 \rightarrow 00:28:20.880$  SG and sequence to recruit.

NOTE Confidence: 0.823797523975372

 $00{:}28{:}20{.}880 \dashrightarrow 00{:}28{:}23{.}604$  Another activated VP 64 similarly for

NOTE Confidence: 0.823797523975372

 $00:28:23.604 \rightarrow 00:28:26.119$  the repression that refused the cast.

NOTE Confidence: 0.823797523975372

 $00{:}28{:}26{.}120 \dashrightarrow 00{:}28{:}28{.}305$  Now with LC-1 which catalyze

NOTE Confidence: 0.823797523975372

00:28:28.305 - 00:28:30.053 the removal of H3K,

NOTE Confidence: 0.823797523975372

 $00{:}28{:}30.060 \dashrightarrow 00{:}28{:}31.804$  four born monogamous flashing

NOTE Confidence: 0.823797523975372

 $00:28:31.804 \rightarrow 00:28:33.548$  and then as geometry,

- NOTE Confidence: 0.823797523975372
- 00:28:33.550 --> 00:28:35.566 could another repressor correct,
- NOTE Confidence: 0.823797523975372
- 00:28:35.566 --> 00:28:38.590 so therefore the main advantage of
- NOTE Confidence: 0.823797523975372
- $00:28:38.673 \rightarrow 00:28:41.109$  this system which we call increased
- NOTE Confidence: 0.823797523975372
- $00:28:41.109 \longrightarrow 00:28:43.969$  by or increase for a or enhancer
- NOTE Confidence: 0.823797523975372
- $00{:}28{:}43.969 \dashrightarrow 00{:}28{:}46.657$  targeting increased bio quiz for a is
- NOTE Confidence: 0.823797523975372
- $00:28:46.660 \rightarrow 00:28:48.865$  that this system combines effectors
- NOTE Confidence: 0.823797523975372
- $00:28:48.865 \rightarrow 00:28:51.070$  with distinct mechanism for modulating.
- NOTE Confidence: 0.823797523975372
- $00{:}28{:}51{.}070 \dashrightarrow 00{:}28{:}52{.}998$  Enhancer associated genetic marks.
- NOTE Confidence: 0.823797523975372
- $00:28:52.998 \longrightarrow 00:28:56.350$  So we have used this system in
- NOTE Confidence: 0.823797523975372
- $00:28:56.350 \longrightarrow 00:28:58.588$  a variety of cell models and
- NOTE Confidence: 0.823797523975372
- $00:28:58.588 \rightarrow 00:28:59.707$  showing that the
- NOTE Confidence: 0.78987539211909
- 00:28:59.793 --> 00:29:02.499 new system is superior than the
- NOTE Confidence: 0.78987539211909
- 00:29:02.499 --> 00:29:04.700 original crisper I whisper in
- NOTE Confidence: 0.78987539211909
- $00{:}29{:}04.700 \dashrightarrow 00{:}29{:}06.260$  system for enhancing perturbations.
- NOTE Confidence: 0.78987539211909
- $00{:}29{:}06{.}260 \dashrightarrow 00{:}29{:}08{.}432$  However, the main challenges analysis of
- NOTE Confidence: 0.78987539211909

00:29:08.432 --> 00:29:10.540 enhancer function doing illegal development.

NOTE Confidence: 0.78987539211909

00:29:10.540 --> 00:29:13.200 To address this, we are when I

NOTE Confidence: 0.78987539211909

00:29:13.200 --> 00:29:15.638 generate a knock in mouse model.

NOTE Confidence: 0.78987539211909

00:29:15.640 --> 00:29:18.335 10 D CAS. Nine care app converging

NOTE Confidence: 0.78987539211909

 $00{:}29{:}18.335 \dashrightarrow 00{:}29{:}20.404$  under the docs inducible promoter

NOTE Confidence: 0.78987539211909

 $00:29:20.404 \rightarrow 00:29:23.732$  in College in one in one low side.

NOTE Confidence: 0.78987539211909

 $00:29:23.740 \rightarrow 00:29:26.948$  So we then developed by in Vivo Enhancer

NOTE Confidence: 0.78987539211909

 $00{:}29{:}26{.}948 \dashrightarrow 00{:}29{:}29{.}428$  perturbation asset you then there's no

NOTE Confidence: 0.78987539211909

 $00{:}29{:}29{.}428 \dashrightarrow 00{:}29{:}31{.}834$  key mouse to determine hazard function.

NOTE Confidence: 0.78987539211909

 $00:29:31.840 \rightarrow 00:29:34.129$  Doing him at opposes so briefly the

NOTE Confidence: 0.78987539211909

 $00{:}29{:}34{.}129 \dashrightarrow 00{:}29{:}36{.}659$  way it works is that we reasoned

NOTE Confidence: 0.78987539211909

 $00:29:36.659 \rightarrow 00:29:38.499$  that by ABBA genetic modulation

NOTE Confidence: 0.78987539211909

00:29:38.499 --> 00:29:41.525 of Venus physic enhancers in HCS

NOTE Confidence: 0.78987539211909

 $00{:}29{:}41.525 \dashrightarrow 00{:}29{:}43.589$  followed by pulmonary transplantation.

NOTE Confidence: 0.78987539211909

 $00{:}29{:}43.590 \dashrightarrow 00{:}29{:}46.092$  We could access the HSE deriving

NOTE Confidence: 0.78987539211909

 $00:29:46.092 \rightarrow 00:29:47.343$  mature cell images.

 $00{:}29{:}47.350 \dashrightarrow 00{:}29{:}49.492$  As a read out for the functional

NOTE Confidence: 0.78987539211909

 $00:29:49.492 \longrightarrow 00:29:51.934$  impact of he has a population

NOTE Confidence: 0.78987539211909

 $00{:}29{:}51{.}934 \dashrightarrow 00{:}29{:}53{.}874$  doing HSC Danish differentiation.

NOTE Confidence: 0.78987539211909

 $00:29:53.880 \longrightarrow 00:29:56.568$  So that way you would do it.

NOTE Confidence: 0.78987539211909

 $00{:}29{:}56{.}570 \dashrightarrow 00{:}29{:}59{.}244$  You will isolate him out of politics.

NOTE Confidence: 0.78987539211909

 $00{:}29{:}59{.}250 \dashrightarrow 00{:}30{:}01{.}180$  Tampa general sales from this

NOTE Confidence: 0.78987539211909

 $00{:}30{:}01{.}180 \dashrightarrow 00{:}30{:}03{.}110$  knocking Mouse and then transduced

NOTE Confidence: 0.78987539211909

 $00:30:03.170 \longrightarrow 00:30:05.486$  with God only library with Garnet

NOTE Confidence: 0.78987539211909

 $00{:}30{:}05{.}486 \dashrightarrow 00{:}30{:}07{.}030$  design against each individual

NOTE Confidence: 0.78987539211909

 $00{:}30{:}07{.}091 \dashrightarrow 00{:}30{:}09{.}293$  enhancer that you might be interested

NOTE Confidence: 0.78987539211909

 $00:30:09.293 \longrightarrow 00:30:11.161$  followed by bone marrow transplant.

NOTE Confidence: 0.78987539211909

00:30:11.161 $\operatorname{-->}$ 00:30:13.898 Then D<br/> Kastner Kara will be induced

NOTE Confidence: 0.78987539211909

 $00{:}30{:}13.898 \dashrightarrow 00{:}30{:}15.880$  by docs admin administration in

NOTE Confidence: 0.78987539211909

 $00{:}30{:}15{.}880 \dashrightarrow 00{:}30{:}18{.}512$  the period of 12 to 16 weeks.

NOTE Confidence: 0.78987539211909

00:30:18.520 --> 00:30:21.736 Then you want to isolate a

 $00:30:21.736 \longrightarrow 00:30:24.896$  mature cells cells and perform

NOTE Confidence: 0.78987539211909

 $00{:}30{:}24.896 \dashrightarrow 00{:}30{:}28.488$  amplicon sequencing to determine.

NOTE Confidence: 0.78987539211909

 $00{:}30{:}28{.}490 \dashrightarrow 00{:}30{:}31{.}568$  The abundance of SG and a in a starting

NOTE Confidence: 0.78987539211909

 $00:30:31.568 \rightarrow 00:30:34.303$  population before transplant an the

NOTE Confidence: 0.78987539211909

 $00:30:34.303 \rightarrow 00:30:36.627$  resulting population after transplantation.

NOTE Confidence: 0.78987539211909

 $00:30:36.630 \longrightarrow 00:30:38.742$  So as a proof of principle this we

NOTE Confidence: 0.78987539211909

 $00:30:38.742 \rightarrow 00:30:40.804$  focus on several key hematopoietic

NOTE Confidence: 0.78987539211909

 $00:30:40.804 \rightarrow 00:30:42.768$  transcription factors and their

NOTE Confidence: 0.78987539211909

 $00:30:42.768 \longrightarrow 00:30:44.550$  annotating enhances an and.

NOTE Confidence: 0.78987539211909

 $00{:}30{:}44{.}550 \dashrightarrow 00{:}30{:}46{.}832$  Design multiplies got an A plus for

NOTE Confidence: 0.78987539211909

 $00{:}30{:}46.832 \dashrightarrow 00{:}30{:}49.069$  in vivo enhancer population squeeze,

NOTE Confidence: 0.78987539211909

00:30:49.070 --> 00:30:51.644 so I would like to show you the CBF

NOTE Confidence: 0.78987539211909

 $00:30:51.644 \dashrightarrow 00:30:54.595$  and locals as a first example which

NOTE Confidence: 0.78987539211909

 $00:30:54.595 \rightarrow 00:30:56.990$  contains out for annotating hazards,

NOTE Confidence: 0.78987539211909

 $00{:}30{:}56{.}990 \dashrightarrow 00{:}30{:}59{.}524$  look at it in a different upstream

NOTE Confidence: 0.78987539211909

 $00:30:59.524 \longrightarrow 00:31:01.420$  or downstream regions to the

- NOTE Confidence: 0.78987539211909
- $00:31:01.420 \rightarrow 00:31:03.265$  transcription start site by enhance
- NOTE Confidence: 0.78987539211909
- $00:31:03.265 \longrightarrow 00:31:05.280$  in billing has a population.
- NOTE Confidence: 0.78987539211909
- $00{:}31{:}05{.}280 \dashrightarrow 00{:}31{:}08{.}376$  We found that SGML for CDL 4 plus.
- NOTE Confidence: 0.78987539211909
- $00{:}31{:}08{.}380 \dashrightarrow 00{:}31{:}10{.}196$  So disable.
- NOTE Confidence: 0.78987539211909
- $00:31:10.196 \rightarrow 00:31:16.552$  Enhancer all year for Enhancer in this.
- NOTE Confidence: 0.78987539211909
- $00{:}31{:}16.560 \dashrightarrow 00{:}31{:}18.685$  A significantly depleted in mylow
- NOTE Confidence: 0.78987539211909
- $00:31:18.685 \rightarrow 00:31:21.370$  cells but not in B&T cells.
- NOTE Confidence: 0.78987539211909
- $00:31:21.370 \longrightarrow 00:31:22.726$  This is interesting,
- NOTE Confidence: 0.78987539211909
- $00:31:22.726 \dashrightarrow 00:31:25.438$  as previously has been shown that
- NOTE Confidence: 0.78987539211909
- $00{:}31{:}25{.}438 \dashrightarrow 00{:}31{:}28{.}760$  CBF on gene knock out or the plus 37
- NOTE Confidence: 0.78987539211909
- 00:31:28.760 --> 00:31:31.364 Hanson AKA annoying to be required
- NOTE Confidence: 0.78987539211909
- $00{:}31{:}31{.}364 \dashrightarrow 00{:}31{:}33{.}584$  by more minor cell differentiation
- NOTE Confidence: 0.78987539211909
- 00:31:33.584 --> 00:31:35.354 but not for lymphopoiesis,
- NOTE Confidence: 0.78987539211909
- $00{:}31{:}35{.}354 \dashrightarrow 00{:}31{:}37{.}976$  so our result not only validate
- NOTE Confidence: 0.78987539211909
- $00:31:37.976 \longrightarrow 00:31:38.850$  these findings,
- NOTE Confidence: 0.78987539211909

 $00:31:38.850 \longrightarrow 00:31:41.531$  but also show that the plus a

NOTE Confidence: 0.78987539211909

00:31:41.531 --> 00:31:43.769 keeping hazard is E2 enhancer

NOTE Confidence: 0.78987539211909

 $00:31:43.769 \rightarrow 00:31:46.769$  showing over here are also important.

NOTE Confidence: 0.78987539211909

 $00:31:46.770 \rightarrow 00:31:47.802$  For modeling differentiation,

NOTE Confidence: 0.78987539211909

 $00{:}31{:}47.802 \dashrightarrow 00{:}31{:}49.866$  but the other two enhancer seems

NOTE Confidence: 0.78987539211909

 $00:31:49.866 \rightarrow 00:31:51.169$  to be indispensable,

NOTE Confidence: 0.78987539211909

 $00{:}31{:}51{.}170 \dashrightarrow 00{:}31{:}54{.}682$  and none of these enhancer seems to be

NOTE Confidence: 0.78987539211909

 $00{:}31{:}54.682 \dashrightarrow 00{:}31{:}57.419$  important for B&T cell development.

NOTE Confidence: 0.78987539211909

 $00{:}31{:}57{.}420 \dashrightarrow 00{:}32{:}00{.}192$  The second example is a SPI one

NOTE Confidence: 0.78987539211909

00:32:00.192 --> 00:32:01.939 locus or PU .1 G,

NOTE Confidence: 0.78987539211909

 $00{:}32{:}01{.}940 \dashrightarrow 00{:}32{:}05{.}164$  and we observed this gene has a single

NOTE Confidence: 0.78987539211909

 $00:32:05.164 \rightarrow 00:32:07.219$  enhancer located at 14 KP option.

NOTE Confidence: 0.78987539211909

 $00:32:07.220 \longrightarrow 00:32:09.782$  With this gene we notice that the

NOTE Confidence: 0.78987539211909

 $00{:}32{:}09{.}782 \dashrightarrow 00{:}32{:}11{.}767$  three independent guard on it

NOTE Confidence: 0.78987539211909

 $00{:}32{:}11.767 \dashrightarrow 00{:}32{:}13.411$  against its enhancer significantly

NOTE Confidence: 0.78987539211909

 $00:32:13.411 \rightarrow 00:32:15.890$  depleted in my loiselle and B cells,

 $00:32:15.890 \rightarrow 00:32:18.917$  but not in T cells, and this result,

NOTE Confidence: 0.78987539211909

 $00:32:18.917 \rightarrow 00:32:21.930$  again are consistent with the role of SPI.

NOTE Confidence: 0.78987539211909

 $00{:}32{:}21{.}930 \dashrightarrow 00{:}32{:}24{.}562$  One Pu .1 for normal Milo and

NOTE Confidence: 0.78987539211909

 $00:32:24.562 \rightarrow 00:32:25.314$  busier development,

NOTE Confidence: 0.78987539211909

 $00:32:25.320 \dashrightarrow 00:32:28.254$  but not for teacher development, so again.

NOTE Confidence: 0.78987539211909

 $00{:}32{:}28{.}254 \dashrightarrow 00{:}32{:}31{.}943$  I did that this initial genetic studies.

NOTE Confidence: 0.830534815788269

 $00:32:31.950 \longrightarrow 00:32:34.470$  Using mouse models.

NOTE Confidence: 0.830534815788269

 $00{:}32{:}34{.}470 \dashrightarrow 00{:}32{:}37{.}152$  And next time I want to show is that

NOTE Confidence: 0.830534815788269

 $00{:}32{:}37{.}152 \dashrightarrow 00{:}32{:}39{.}850$  the wrong Swan Locust so runs well?

NOTE Confidence: 0.830534815788269

00:32:39.850 --> 00:32:41.182 Actually have two annotated

NOTE Confidence: 0.830534815788269

 $00{:}32{:}41{.}182 \dashrightarrow 00{:}32{:}42{.}847$  transcription start site with three

NOTE Confidence: 0.830534815788269

 $00{:}32{:}42.847 \dashrightarrow 00{:}32{:}44.547$  enhancers at different genomic regions.

NOTE Confidence: 0.830534815788269

 $00:32:44.550 \rightarrow 00:32:46.762$  Again using this perturbation we find that

NOTE Confidence: 0.830534815788269

 $00:32:46.762 \rightarrow 00:32:49.588$  none of the enhancer seems to be important.

NOTE Confidence: 0.830534815788269

00:32:49.590 --> 00:32:51.270 Actually, in myeloid B&T cells,

 $00:32:51.270 \longrightarrow 00:32:52.950$  but the promoter garden is

NOTE Confidence: 0.830534815788269

 $00{:}32{:}52{.}950 \dashrightarrow 00{:}32{:}55{.}022$  somewhat you reached in my low

NOTE Confidence: 0.830534815788269

 $00:32:55.022 \rightarrow 00:32:56.978$  self but depleted and B&T cells,

NOTE Confidence: 0.830534815788269

 $00:32:56.980 \longrightarrow 00:32:59.668$  so this is one of the first example.

NOTE Confidence: 0.830534815788269

 $00{:}32{:}59{.}670 \dashrightarrow 00{:}33{:}01{.}415$  We actually see the opposite

NOTE Confidence: 0.830534815788269

00:33:01.415 --> 00:33:03.160 phenotype in different cell images NOTE Confidence: 0.830534815788269

 $00:33:03.215 \dashrightarrow 00:33:04.790$  and this is interesting because

NOTE Confidence: 0.830534815788269

00:33:04.790 --> 00:33:06.760 ranks will knock out your mouth.

NOTE Confidence: 0.830534815788269

 $00:33:06.760 \longrightarrow 00:33:10.210$  Has shown to to develop Mylar

NOTE Confidence: 0.830534815788269

 $00:33:10.210 \rightarrow 00:33:11.935$  preffective phenotype characterized

NOTE Confidence: 0.830534815788269

00:33:11.935 --> 00:33:14.880 by myeloid enhanced my lawyer.

NOTE Confidence: 0.830534815788269

00:33:14.880 --> 00:33:17.885 Refreshing but defective B&T cell

NOTE Confidence: 0.830534815788269

 $00{:}33{:}17.885 \dashrightarrow 00{:}33{:}20.890$  maturation so therefore our results

NOTE Confidence: 0.830534815788269

 $00{:}33{:}20.985 \dashrightarrow 00{:}33{:}23.730$  also consistent with this and

NOTE Confidence: 0.830534815788269

 $00:33:23.730 \rightarrow 00:33:26.475$  recapture the phenotype of ranks.

NOTE Confidence: 0.830534815788269

 $00:33:26.480 \rightarrow 00:33:29.360$  One deficiency showcasing that this

- NOTE Confidence: 0.830534815788269
- $00:33:29.360 \longrightarrow 00:33:32.910$  crisp Ohio increased by best epigenetic
- NOTE Confidence: 0.830534815788269
- $00{:}33{:}32{.}910 \dashrightarrow 00{:}33{:}36{.}928$  editing and can be convenient as say too.
- NOTE Confidence: 0.830534815788269
- $00:33:36.930 \longrightarrow 00:33:38.782$  Isaca regulatory elements that
- NOTE Confidence: 0.830534815788269
- $00:33:38.782 \longrightarrow 00:33:41.097$  are required for this linear
- NOTE Confidence: 0.830534815788269
- $00{:}33{:}41.097 \dashrightarrow 00{:}33{:}43.129$  specific transcription factors.
- NOTE Confidence: 0.830534815788269
- 00:33:43.130 --> 00:33:44.046 And finally,
- NOTE Confidence: 0.830534815788269
- $00:33:44.046 \longrightarrow 00:33:46.336$  we perform a Multiplex perturbation
- NOTE Confidence: 0.830534815788269
- $00:33:46.336 \longrightarrow 00:33:48.871$  by pulling all the God are
- NOTE Confidence: 0.830534815788269
- $00{:}33{:}48.871 \dashrightarrow 00{:}33{:}50.686$  made in a single experiment.
- NOTE Confidence: 0.830534815788269
- $00:33:50.690 \rightarrow 00:33:52.018$  Anan by this analysis.
- NOTE Confidence: 0.830534815788269
- 00:33:52.018 --> 00:33:55.079 Now you can have a ranking order of
- NOTE Confidence: 0.830534815788269
- $00{:}33{:}55{.}079 \dashrightarrow 00{:}33{:}57{.}559$  different enhancers and promoters that
- NOTE Confidence: 0.830534815788269
- $00:33:57.559 \dashrightarrow 00:33:59.929$  are specifically enriched or depleted.
- NOTE Confidence: 0.830534815788269
- 00:33:59.930 --> 00:34:02.030 In my lawyer B&T cells,
- NOTE Confidence: 0.830534815788269
- $00{:}34{:}02{.}030 \dashrightarrow 00{:}34{:}04{.}172$  for example with Dan I fied that
- NOTE Confidence: 0.830534815788269

00:34:04.172 --> 00:34:07.212 CB back on cartoon has a required

NOTE Confidence: 0.830534815788269

00:34:07.212 --> 00:34:08.748 for myeloid differentiation,

NOTE Confidence: 0.830534815788269

 $00:34:08.750 \rightarrow 00:34:10.850$  while ranks one enhancer promoters

NOTE Confidence: 0.830534815788269

 $00:34:10.850 \longrightarrow 00:34:12.950$  are required for PMT sales.

NOTE Confidence: 0.830534815788269

 $00{:}34{:}12.950 \dashrightarrow 00{:}34{:}15.130$  Therefore, this enhanced CRISPR editing.

NOTE Confidence: 0.830534815788269

 $00{:}34{:}15{.}130 \dashrightarrow 00{:}34{:}18{.}021$  I could provide a useful tool for

NOTE Confidence: 0.830534815788269

 $00:34:18.021 \rightarrow 00:34:19.817$  functional interrogation of SIS

NOTE Confidence: 0.830534815788269

 $00:34:19.817 \rightarrow 00:34:21.741$  element doing illegal development

NOTE Confidence: 0.830534815788269

 $00:34:21.741 \longrightarrow 00:34:24.146$  and more importantly by combining

NOTE Confidence: 0.830534815788269

 $00{:}34{:}24{.}221 \dashrightarrow 00{:}34{:}26{.}286$  these knocking mouse model with

NOTE Confidence: 0.830534815788269

 $00:34:26.286 \dashrightarrow 00:34:28.825$  other disease models we might be

NOTE Confidence: 0.830534815788269

 $00{:}34{:}28.825 \dashrightarrow 00{:}34{:}31.150$  able to study enhancer function

NOTE Confidence: 0.830534815788269

 $00:34:31.150 \rightarrow 00:34:33.010$  doing different biological process

NOTE Confidence: 0.830534815788269

 $00:34:33.084 \rightarrow 00:34:35.550$  of pathological process and this is

NOTE Confidence: 0.830534815788269

 $00:34:35.550 \rightarrow 00:34:38.128$  something that we're very excited about

NOTE Confidence: 0.830534815788269

 $00:34:38.128 \rightarrow 00:34:40.708$  and certainly looking forward to any.

- NOTE Confidence: 0.830534815788269
- 00:34:40.710 --> 00:34:42.550 Collaborations whom I simply
- NOTE Confidence: 0.830534815788269
- $00:34:42.550 \longrightarrow 00:34:45.310$  store might be useful for their
- NOTE Confidence: 0.830534815788269
- $00:34:45.394 \longrightarrow 00:34:47.389$  respective disease models.
- NOTE Confidence: 0.830534815788269
- $00{:}34{:}47{.}390 \dashrightarrow 00{:}34{:}51{.}458$  So as a brief summary for for this part,
- NOTE Confidence: 0.830534815788269
- $00:34:51.460 \longrightarrow 00:34:54.166$  so we've shown that enhance the
- NOTE Confidence: 0.830534815788269
- 00:34:54.166 --> 00:34:55.522 control limits, differentiation,
- NOTE Confidence: 0.830534815788269
- $00{:}34{:}55{.}522 \dashrightarrow 00{:}34{:}55{.}974$  disease,
- NOTE Confidence: 0.830534815788269
- $00:34:55.974 \rightarrow 00:34:57.782$  phenotype and undergoes profound
- NOTE Confidence: 0.830534815788269
- $00{:}34{:}57{.}782 \dashrightarrow 00{:}34{:}59{.}138$  turnover during development.
- NOTE Confidence: 0.830534815788269
- $00:34:59.140 \longrightarrow 00:35:01.996$  We've developed the Constine best capture
- NOTE Confidence: 0.830534815788269
- $00:35:01.996 \rightarrow 00:35:04.569$  tools for multimeric analysis of local,
- NOTE Confidence: 0.830534815788269
- $00{:}35{:}04{.}570 \dashrightarrow 00{:}35{:}05{.}923$  specific quality interactions.
- NOTE Confidence: 0.830534815788269
- $00{:}35{:}05{.}923 \dashrightarrow 00{:}35{:}08{.}178$  We also redesign enhancing target,
- NOTE Confidence: 0.830534815788269
- $00{:}35{:}08{.}180 \dashrightarrow 00{:}35{:}10{.}255$  increase pain response system that
- NOTE Confidence: 0.830534815788269
- $00{:}35{:}10.255 \dashrightarrow 00{:}35{:}12.330$  will enable in vivo functional
- NOTE Confidence: 0.830534815788269

 $00:35:12.398 \longrightarrow 00:35:14.060$  interrogation of enhancer.

NOTE Confidence: 0.830534815788269

 $00{:}35{:}14.060 \dashrightarrow 00{:}35{:}17.708$  As we have other success element doing in.

NOTE Confidence: 0.830534815788269

 $00:35:17.710 \dashrightarrow 00:35:19.265$  We want development and we're

NOTE Confidence: 0.830534815788269

 $00:35:19.265 \longrightarrow 00:35:21.595$  happy to share the tools or the

NOTE Confidence: 0.830534815788269

 $00:35:21.595 \dashrightarrow 00:35:23.365$  construct has been deposited action.

NOTE Confidence: 0.830534815788269

 $00:35:23.370 \longrightarrow 00:35:25.701$  And if you are any of your

NOTE Confidence: 0.830534815788269

00:35:25.701 --> 00:35:26.700 colleagues are interested,

NOTE Confidence: 0.830534815788269

 $00:35:26.700 \longrightarrow 00:35:29.530$  feel free to reach out.

NOTE Confidence: 0.830534815788269

 $00{:}35{:}29{.}530 \dashrightarrow 00{:}35{:}32{.}314$  So in the last few minutes I want

NOTE Confidence: 0.830534815788269

 $00:35:32.314 \dashrightarrow 00:35:35.278$  to switch gears a little bit and I

NOTE Confidence: 0.830534815788269

 $00{:}35{:}35{.}278 \dashrightarrow 00{:}35{:}38{.}035$  want to discuss some of the recent

NOTE Confidence: 0.830534815788269

 $00{:}35{:}38.035 \dashrightarrow 00{:}35{:}40.870$  effort we trying to address the last

NOTE Confidence: 0.830534815788269

 $00:35:40.870 \dashrightarrow 00:35:43.054$  question that is how to pathological

NOTE Confidence: 0.830534815788269

 $00:35:43.054 \rightarrow 00:35:45.030$  enhance alterations contribute to diseases,

NOTE Confidence: 0.830534815788269

 $00:35:45.030 \rightarrow 00:35:47.500$  particularly the development block answers.

NOTE Confidence: 0.830534815788269

 $00:35:47.500 \longrightarrow 00:35:48.712$  As we know,

- NOTE Confidence: 0.830534815788269
- $00:35:48.712 \rightarrow 00:35:51.540$  much of our knowledge on cancer driver
- NOTE Confidence: 0.830534815788269
- $00{:}35{:}51{.}629 \dashrightarrow 00{:}35{:}54{.}259$  mutations is based on alterations
- NOTE Confidence: 0.830534815788269
- $00:35:54.259 \rightarrow 00:35:56.889$  of protein coding sequences and
- NOTE Confidence: 0.830534815788269
- 00:35:56.971 -> 00:35:59.396 little is knowing whether man,
- NOTE Confidence: 0.830534815788269
- $00:35:59.400 \rightarrow 00:36:01.780$  how noncoding alterations may contribute
- NOTE Confidence: 0.830534815788269
- 00:36:01.780 --> 00:36:04.160 to disease on passive biology,
- NOTE Confidence: 0.830534815788269
- $00:36:04.160 \longrightarrow 00:36:06.064$  especially in the developer
- NOTE Confidence: 0.830534815788269
- 00:36:06.064 --> 00:36:07.016 hematopoietic malignancies.
- NOTE Confidence: 0.830534815788269
- $00{:}36{:}07{.}020 \dashrightarrow 00{:}36{:}09{.}410$  So we started this rather
- NOTE Confidence: 0.830534815788269
- $00:36:09.410 \longrightarrow 00:36:11.800$  ambitious project several years ago
- NOTE Confidence: 0.803040623664856
- $00:36:11.884 \rightarrow 00:36:14.626$  with the goal to identify leukemia,
- NOTE Confidence: 0.803040623664856
- $00{:}36{:}14.630 \dashrightarrow 00{:}36{:}16.139$  associating handsome mutations
- NOTE Confidence: 0.803040623664856
- $00:36:16.139 \rightarrow 00:36:17.648$  by targeted sequencing.
- NOTE Confidence: 0.803040623664856
- $00{:}36{:}17.650 \dashrightarrow 00{:}36{:}21.097$  So the way it works is that we first
- NOTE Confidence: 0.803040623664856
- $00{:}36{:}21.097 \dashrightarrow 00{:}36{:}23.572$  annotated plot Vinny specific enhancers
- NOTE Confidence: 0.803040623664856

00:36:23.572 - > 00:36:27.080 based on chip sequencing and a taxi,

NOTE Confidence: 0.803040623664856

 $00{:}36{:}27.080 \dashrightarrow 00{:}36{:}30.216$  just like every body else is doing that,

NOTE Confidence: 0.803040623664856

 $00:36:30.220 \dashrightarrow 00:36:33.820$  I introduced earlier and then we can gather.

NOTE Confidence: 0.803040623664856

 $00:36:33.820 \rightarrow 00:36:36.472$  This game is almost twenty 2000s

NOTE Confidence: 0.803040623664856

 $00{:}36{:}36{.}472 \dashrightarrow 00{:}36{:}38{.}857$  of enhancers that are present

NOTE Confidence: 0.803040623664856

 $00{:}36{:}38{.}857 \dashrightarrow 00{:}36{:}41{.}517$  in variety of different normal.

NOTE Confidence: 0.803040623664856

 $00{:}36{:}41.520 \dashrightarrow 00{:}36{:}44.292$  Gmail cell lines that we have gathered

NOTE Confidence: 0.803040623664856

 $00:36:44.292 \rightarrow 00:36:47.908$  and then we can design target sequencing

NOTE Confidence: 0.803040623664856

 $00{:}36{:}47{.}908 \dashrightarrow 00{:}36{:}50{.}252$  panel to specifically resequence

NOTE Confidence: 0.803040623664856

 $00{:}36{:}50{.}252 \dashrightarrow 00{:}36{:}53{.}379$  the enhancer sequences in a panel

NOTE Confidence: 0.803040623664856

 $00:36:53.379 \rightarrow 00:36:55.247$  of human hematopoietic malignancy

NOTE Confidence: 0.803040623664856

 $00:36:55.247 \longrightarrow 00:36:58.142$  is a particularly in an email.

NOTE Confidence: 0.803040623664856

 $00{:}36{:}58{.}142 \dashrightarrow 00{:}36{:}59{.}606$  An NDS conditions.

NOTE Confidence: 0.803040623664856

 $00{:}36{:}59{.}610 \dashrightarrow 00{:}37{:}02{.}622$  We also included some informal samples

NOTE Confidence: 0.803040623664856

 $00:37:02.622 \dashrightarrow 00:37:04.990$  an acute lymphoblastic leukemia and,

NOTE Confidence: 0.803040623664856

 $00:37:04.990 \rightarrow 00:37:07.930$  importantly, thirty. One of these samples.

 $00:37:07.930 \longrightarrow 00:37:10.370$  We actually have tumor normal

NOTE Confidence: 0.803040623664856

 $00:37:10.370 \longrightarrow 00:37:12.322$  pairs that we can.

NOTE Confidence: 0.803040623664856

 $00:37:12.330 \longrightarrow 00:37:14.082$  Identify somatic mutations in

NOTE Confidence: 0.803040623664856

 $00:37:14.082 \rightarrow 00:37:16.710$  the in the non coding Gina.

NOTE Confidence: 0.803040623664856

 $00:37:16.710 \longrightarrow 00:37:19.851$  Pen and if you do this and like other

NOTE Confidence: 0.803040623664856

 $00{:}37{:}19.851 \dashrightarrow 00{:}37{:}22.309$  people doing a protein coding sequence

NOTE Confidence: 0.803040623664856

 $00:37:22.309 \rightarrow 00:37:25.752$  as well you you can easily identify

NOTE Confidence: 0.803040623664856

 $00:37:25.752 \rightarrow 00:37:29.097$  thousands of recurrently mutated mutations.

NOTE Confidence: 0.803040623664856

 $00{:}37{:}29{.}100 \dashrightarrow 00{:}37{:}31{.}302$  In this case we identify almost

NOTE Confidence: 0.803040623664856

 $00:37:31.302 \rightarrow 00:37:33.516$  slightly over a 4000 frequently

NOTE Confidence: 0.803040623664856

 $00:37:33.516 \rightarrow 00:37:35.529$  mutated noncoding elements.

NOTE Confidence: 0.803040623664856

 $00{:}37{:}35{.}530 \dashrightarrow 00{:}37{:}38{.}687$  We call them mutational Hotspot Ann and

NOTE Confidence: 0.803040623664856

 $00{:}37{:}38.687 \dashrightarrow 00{:}37{:}41.497$  these overlays about 1800 enhances that

NOTE Confidence: 0.803040623664856

 $00{:}37{:}41.497 \dashrightarrow 00{:}37{:}44.710$  we have identified from the initial steps.

NOTE Confidence: 0.803040623664856

 $00{:}37{:}44.710 \dashrightarrow 00{:}37{:}47.015$  So these are the enhancement

00:37:47.015 --> 00:37:48.398 carries somatic mutations.

NOTE Confidence: 0.803040623664856

00:37:48.400 - 00:37:50.435 That are frequently mutated in

NOTE Confidence: 0.803040623664856

 $00:37:50.435 \rightarrow 00:37:51.656$  human hematopoietic malignancy.

NOTE Confidence: 0.803040623664856

 $00:37:51.660 \rightarrow 00:37:54.924$  The key question is and the key challenges.

NOTE Confidence: 0.803040623664856

 $00:37:54.930 \longrightarrow 00:37:57.457$  How do you know whether they are

NOTE Confidence: 0.803040623664856

 $00{:}37{:}57{.}457 \dashrightarrow 00{:}38{:}00{.}855$  functional an what is how to access their NOTE Confidence: 0.803040623664856

 $00:38:00.855 \rightarrow 00:38:03.090$  functional roles in cancer pathogenesis?

NOTE Confidence: 0.803040623664856

 $00:38:03.090 \rightarrow 00:38:05.428$  So Fortunately with the crisper a quiz

NOTE Confidence: 0.803040623664856

 $00{:}38{:}05{.}428 \dashrightarrow 00{:}38{:}07{.}985$  by system that we have engineered that

NOTE Confidence: 0.803040623664856

 $00:38:07.985 \rightarrow 00:38:10.217$  especially for enhances so we could

NOTE Confidence: 0.803040623664856

 $00{:}38{:}10.283 \dashrightarrow 00{:}38{:}12.803$  perform a functional interrogation of

NOTE Confidence: 0.803040623664856

 $00:38:12.803 \rightarrow 00:38:15.323$  functional perturbation screens using God.

NOTE Confidence: 0.803040623664856

 $00{:}38{:}15{.}330 \dashrightarrow 00{:}38{:}17{.}380$  RNAs that are designed to

NOTE Confidence: 0.803040623664856

 $00:38:17.380 \longrightarrow 00:38:18.610$  target this enhances.

NOTE Confidence: 0.803040623664856

 $00:38:18.610 \rightarrow 00:38:21.106$  Then we perform the screening and

NOTE Confidence: 0.803040623664856

00:38:21.106 --> 00:38:22.770 multiple leukemia cell lines.

 $00:38:22.770 \longrightarrow 00:38:26.170$  And by this we can identify hundreds of

NOTE Confidence: 0.803040623664856

 $00{:}38{:}26.170 \dashrightarrow 00{:}38{:}29.425$  enhances that seems to be a putative tumor.

NOTE Confidence: 0.803040623664856

 $00:38:29.430 \longrightarrow 00:38:31.090$  Suppressive or uncle genic.

NOTE Confidence: 0.803040623664856

 $00:38:31.090 \rightarrow 00:38:32.335$  In other ways,

NOTE Confidence: 0.803040623664856

 $00:38:32.340 \longrightarrow 00:38:35.211$  we use cell growth as a reader so that

NOTE Confidence: 0.803040623664856

 $00{:}38{:}35{.}211 \dashrightarrow 00{:}38{:}37{.}799$  that perturbation of this enhances often

NOTE Confidence: 0.803040623664856

 $00{:}38{:}37{.}799 \dashrightarrow 00{:}38{:}41{.}016$  can lead to an enhanced or inhibited

NOTE Confidence: 0.803040623664856

 $00:38:41.016 \rightarrow 00:38:43.866$  cell growth phenotype and this really

NOTE Confidence: 0.803040623664856

 $00{:}38{:}43.866 \dashrightarrow 00{:}38{:}46.508$  have provided a number of candidate

NOTE Confidence: 0.803040623664856

 $00:38:46.508 \rightarrow 00:38:48.618$  enhances an associated genetic loci.

NOTE Confidence: 0.803040623664856

 $00:38:48.620 \longrightarrow 00:38:49.430$  Subsequence studies.

NOTE Confidence: 0.803040623664856

00:38:49.430 --> 00:38:52.670 So I would like to focus on one

NOTE Confidence: 0.803040623664856

 $00{:}38{:}52{.}748 \dashrightarrow 00{:}38{:}55{.}576$  of the enhancer that we follow up

NOTE Confidence: 0.803040623664856

 $00{:}38{:}55{.}576 \dashrightarrow 00{:}38{:}57{.}793$  with more detailed analysis and

NOTE Confidence: 0.803040623664856

 $00{:}38{:}57{.}793 \dashrightarrow 00{:}39{:}00{.}088$  this enhances located about 150

00:39:00.088 --> 00:39:02.664 KB upstream of the gene called

NOTE Confidence: 0.803040623664856

 $00{:}39{:}02.664 \dashrightarrow 00{:}39{:}04.654$  carrots that contains several non

NOTE Confidence: 0.803040623664856

00:39:04.654 --> 00:39:06.429 coding variants in AML samples,

NOTE Confidence: 0.803040623664856

 $00:39:06.430 \rightarrow 00:39:08.722$  and by chromatin profiling and 3D

NOTE Confidence: 0.803040623664856

 $00:39:08.722 \rightarrow 00:39:09.868$  chromatin confirmation capture.

NOTE Confidence: 0.803040623664856

 $00{:}39{:}09{.}870 \dashrightarrow 00{:}39{:}12{.}622$  We found this thing has it seems to

NOTE Confidence: 0.803040623664856

 $00:39:12.622 \rightarrow 00:39:14.752$  be physically interact with Akira's

NOTE Confidence: 0.803040623664856

 $00:39:14.752 \rightarrow 00:39:17.488$  promoter regions which is located about

NOTE Confidence: 0.803040623664856

 $00{:}39{:}17.488 \dashrightarrow 00{:}39{:}20.197$  150 KB downstream of this enhancer.

NOTE Confidence: 0.803040623664856

 $00:39:20.200 \longrightarrow 00:39:21.277$  And more importantly,

NOTE Confidence: 0.803040623664856

 $00{:}39{:}21{.}277 \dashrightarrow 00{:}39{:}24{.}890$  when we use CRISPR CAS 9 to knock out this,

NOTE Confidence: 0.803040623664856

 $00:39:24.890 \longrightarrow 00:39:27.042$  he has a in a leukemia cell line

NOTE Confidence: 0.803040623664856

 $00{:}39{:}27.042 \dashrightarrow 00{:}39{:}29.787$  and we found that Carros expression

NOTE Confidence: 0.803040623664856

 $00:39:29.787 \rightarrow 00:39:31.923$  was significantly down regulated.

NOTE Confidence: 0.803040623664856

 $00:39:31.930 \rightarrow 00:39:34.478$  But none of these other genes within

NOTE Confidence: 0.803040623664856

 $00:39:34.478 \longrightarrow 00:39:36.080$  the same neighborhood affected

- NOTE Confidence: 0.803040623664856
- $00:39:36.080 \longrightarrow 00:39:37.400$  suggestion at this.
- NOTE Confidence: 0.803040623664856
- $00:39:37.400 \rightarrow 00:39:39.612$  Enhancer is selectively required
- NOTE Confidence: 0.803040623664856
- $00{:}39{:}39{.}612 \dashrightarrow 00{:}39{:}42{.}377$  for the expression of casting.
- NOTE Confidence: 0.803040623664856
- $00{:}39{:}42{.}380 \dashrightarrow 00{:}39{:}45{.}344$  So is this was interesting because
- NOTE Confidence: 0.803040623664856
- $00:39:45.344 \rightarrow 00:39:47.680$  unlike any grass care US,
- NOTE Confidence: 0.803040623664856
- $00:39:47.680 \rightarrow 00:39:50.090$  protein coding mutations are rarely
- NOTE Confidence: 0.803040623664856
- $00:39:50.090 \dashrightarrow 00:39:52.500$  found in human animal patients.
- NOTE Confidence: 0.757966220378876
- 00:39:52.500 --> 00:39:53.898 However, high care,
- NOTE Confidence: 0.757966220378876
- $00{:}39{:}53{.}898 \dashrightarrow 00{:}39{:}57{.}160$  high level of care as expression in
- NOTE Confidence: 0.757966220378876
- $00{:}39{:}57{.}253 \dashrightarrow 00{:}40{:}00{.}103$  AML is associated with poor survival
- NOTE Confidence: 0.757966220378876
- $00:40:00.103 \rightarrow 00:40:03.109$  using data from the TCG cohorts.
- NOTE Confidence: 0.757966220378876
- 00:40:03.110 --> 00:40:06.995 So we thought that Miss May identify
- NOTE Confidence: 0.757966220378876
- $00{:}40{:}06{.}995 \dashrightarrow 00{:}40{:}09{.}128$  potential functional enhancer that
- NOTE Confidence: 0.757966220378876
- $00{:}40{:}09{.}128 \dashrightarrow 00{:}40{:}12.724$  plays a role in a male biology. So too.
- NOTE Confidence: 0.757966220378876
- $00{:}40{:}12.724 \dashrightarrow 00{:}40{:}15.084$  Establish the functionality of whether
- NOTE Confidence: 0.757966220378876

 $00:40:15.084 \rightarrow 00:40:18.477$  not is kerosene has is important for AML.

NOTE Confidence: 0.757966220378876

00:40:18.480 --> 00:40:20.244 We generate Caroline Hanson

NOTE Confidence: 0.757966220378876

00:40:20.244 --> 00:40:22.008 AKA AML cell line.

NOTE Confidence: 0.757966220378876

 $00:40:22.010 \rightarrow 00:40:24.936$  This is Daniels is selling called Mkpo

NOTE Confidence: 0.757966220378876

 $00{:}40{:}24{.}936 \dashrightarrow 00{:}40{:}27{.}619$  one and observe the significant less

NOTE Confidence: 0.757966220378876

 $00{:}40{:}27.619$  -->  $00{:}40{:}30.762$  tumor burden in bone marrow cells and

NOTE Confidence: 0.757966220378876

 $00:40:30.845 \dashrightarrow 00:40:33.479$  blood of the Xeno graft recipient.

NOTE Confidence: 0.757966220378876

 $00:40:33.480 \rightarrow 00:40:35.372$  Using two independent enhancer

NOTE Confidence: 0.757966220378876

00:40:35.372 --> 00:40:37.737 single Cell developed in Hazen

NOTE Confidence: 0.757966220378876

 $00{:}40{:}37{.}737 \dashrightarrow 00{:}40{:}39{.}647$  Okok looms as a control,

NOTE Confidence: 0.757966220378876

 $00{:}40{:}39.650 \dashrightarrow 00{:}40{:}41.910$  we also knock out the carrots

NOTE Confidence: 0.757966220378876

 $00:40:41.910 \longrightarrow 00:40:43.266$  protein coding gene.

NOTE Confidence: 0.757966220378876

 $00{:}40{:}43.270 \dashrightarrow 00{:}40{:}46.822$  And we see that he has a knock out

NOTE Confidence: 0.757966220378876

 $00{:}40{:}46.822 \dashrightarrow 00{:}40{:}49.376$  almost recalculate the care as GM

NOTE Confidence: 0.757966220378876

 $00:40:49.376 \longrightarrow 00:40:51.734$  lockout in this access and just

NOTE Confidence: 0.757966220378876

 $00:40:51.825 \rightarrow 00:40:54.645$  showing more data showing that this

 $00:40:54.645 \rightarrow 00:40:57.422$  is reflected by Les Plus constant

NOTE Confidence: 0.757966220378876

 $00:40:57.422 \longrightarrow 00:41:00.098$  prefer block as well as less.

NOTE Confidence: 0.757966220378876

 $00:41:00.100 \longrightarrow 00:41:02.764$  And number of frequency of the

NOTE Confidence: 0.757966220378876

 $00:41:02.764 \rightarrow 00:41:05.036$  Premier sales in xenograft animals

NOTE Confidence: 0.757966220378876

 $00:41:05.036 \longrightarrow 00:41:07.508$  in the bone marrow and blood.

NOTE Confidence: 0.757966220378876

 $00{:}41{:}07{.}510 \dashrightarrow 00{:}41{:}10{.}006$  So this result demonstrator care us

NOTE Confidence: 0.757966220378876

 $00{:}41{:}10.006 \dashrightarrow 00{:}41{:}12.162$  and this semantic enhance associated

NOTE Confidence: 0.757966220378876

00:41:12.162 --> 00:41:14.700 enhancer are required for AML cell

NOTE Confidence: 0.757966220378876

 $00:41:14.700 \longrightarrow 00:41:17.060$  grows in virtual and an illegal.

NOTE Confidence: 0.757966220378876

 $00:41:17.060 \longrightarrow 00:41:19.130$  So then we went ahead.

NOTE Confidence: 0.757966220378876

 $00{:}41{:}19{.}130 \dashrightarrow 00{:}41{:}21{.}578$  Get the motif analysis and found

NOTE Confidence: 0.757966220378876

00:41:21.578 --> 00:41:23.675 this recurrent carers enhancer that

NOTE Confidence: 0.757966220378876

 $00:41:23.675 \rightarrow 00:41:26.045$  we found the AML patient highly

NOTE Confidence: 0.757966220378876

 $00{:}41{:}26.045 \dashrightarrow 00{:}41{:}27.728$  colocalized with binding site

NOTE Confidence: 0.757966220378876

 $00{:}41{:}27.728 \dashrightarrow 00{:}41{:}29.868$  of interest in nuclear hormone

00:41:29.868 --> 00:41:31.580 receptors in particularly par,

NOTE Confidence: 0.757966220378876

 $00{:}41{:}31{.}580 \dashrightarrow 00{:}41{:}34{.}996$  gamma and ice are showing over here.

NOTE Confidence: 0.757966220378876

 $00{:}41{:}35{.}000 \dashrightarrow 00{:}41{:}37{.}322$  I'm so interested in the cameras

NOTE Confidence: 0.757966220378876

 $00:41:37.322 \longrightarrow 00:41:40.241$  in has are also found in has

NOTE Confidence: 0.757966220378876

 $00{:}41{:}40{.}241 \dashrightarrow 00{:}41{:}42{.}809$  mutations are also found in other

NOTE Confidence: 0.757966220378876

 $00:41:42.809 \dashrightarrow 00:41:45.575$  cancer types based on TCG and pain.

NOTE Confidence: 0.757966220378876

 $00{:}41{:}45{.}580 \dashrightarrow 00{:}41{:}48{.}072$  Cancer pan cancer data set here showing

NOTE Confidence: 0.757966220378876

 $00:41:48.072 \rightarrow 00:41:51.687$  this is a leukemia reputation that we found,

NOTE Confidence: 0.757966220378876

00:41:51.690 --> 00:41:54.126 but hole in has actually carries

NOTE Confidence: 0.757966220378876

 $00:41:54.126 \rightarrow 00:41:55.344$  many recovery mutations.

NOTE Confidence: 0.757966220378876

 $00{:}41{:}55{.}350 \dashrightarrow 00{:}41{:}57{.}672$  Many of these mutations are also

NOTE Confidence: 0.757966220378876

 $00:41:57.672 \longrightarrow 00:41:59.220$  overlap with predicted nuclear

NOTE Confidence: 0.757966220378876

00:41:59.287 --> 00:42:00.640 hormone binding sites,

NOTE Confidence: 0.757966220378876

 $00{:}42{:}00{.}640 \dashrightarrow 00{:}42{:}02{.}686$  and this was interesting as nuclear

NOTE Confidence: 0.757966220378876

 $00:42:02.686 \longrightarrow 00:42:04.722$  hormones are family of lichen

NOTE Confidence: 0.757966220378876

 $00:42:04.722 \longrightarrow 00:42:05.938$  regulated transcription.

- NOTE Confidence: 0.757966220378876
- $00:42:05.940 \rightarrow 00:42:09.108$  Factors that are activated by hormones,
- NOTE Confidence: 0.757966220378876
- $00{:}42{:}09{.}110 \dashrightarrow 00{:}42{:}11.605$  ligands or growth factors and
- NOTE Confidence: 0.757966220378876
- 00:42:11.605 00:42:14.920 usually in the absence of ligands,
- NOTE Confidence: 0.757966220378876
- $00{:}42{:}14.920 \dashrightarrow 00{:}42{:}17.782$  PPL comma AXA dimer will recruit
- NOTE Confidence: 0.757966220378876
- 00:42:17.782 --> 00:42:19.690 Corey Presser complex immediate
- NOTE Confidence: 0.757966220378876
- $00{:}42{:}19.772 \dashrightarrow 00{:}42{:}22.308$  derepression appan liggen binding.
- NOTE Confidence: 0.757966220378876
- $00:42:22.310 \longrightarrow 00:42:25.340$  This time are actually cutco
- NOTE Confidence: 0.757966220378876
- $00{:}42{:}25{.}340 \dashrightarrow 00{:}42{:}27{.}158$  activist coactivators through
- NOTE Confidence: 0.757966220378876
- $00:42:27.158 \longrightarrow 00:42:28.370$  activating transcription.
- NOTE Confidence: 0.757966220378876
- $00{:}42{:}28.370 \dashrightarrow 00{:}42{:}30.830$  So we wonder whether cameras enhance
- NOTE Confidence: 0.757966220378876
- $00:42:30.830 \longrightarrow 00:42:33.112$  it might actually be regulated
- NOTE Confidence: 0.757966220378876
- $00{:}42{:}33{.}112 \dashrightarrow 00{:}42{:}35{.}360$  by nuclear hormone signaling,
- NOTE Confidence: 0.757966220378876
- $00{:}42{:}35{.}360 \dashrightarrow 00{:}42{:}38{.}874$  so to validate days we perform chip
- NOTE Confidence: 0.757966220378876
- $00{:}42{:}38.874 \dashrightarrow 00{:}42{:}41.321$  sequencing analysis in multiple AML
- NOTE Confidence: 0.757966220378876
- $00:42:41.321 \longrightarrow 00:42:44.282$  cell line as well as non email.
- NOTE Confidence: 0.757966220378876

 $00:42:44.290 \longrightarrow 00:42:45.496$  Tumor cell lines.

NOTE Confidence: 0.757966220378876

 $00{:}42{:}45{.}496$  -->  $00{:}42{:}48{.}868$  We found a strong PPR gamma and I

NOTE Confidence: 0.757966220378876

 $00:42:48.868 \rightarrow 00:42:51.676$  saw binding at the very associated

NOTE Confidence: 0.757966220378876

 $00:42:51.676 \rightarrow 00:42:54.415$  enhancer element and if you zoom in

NOTE Confidence: 0.757966220378876

 $00:42:54.415 \rightarrow 00:42:57.412$  you can see some of the speaker really.

NOTE Confidence: 0.757966220378876

 $00{:}42{:}57{.}412 \dashrightarrow 00{:}43{:}00{.}217$  Directly overlapping the variant that NOTE Confidence: 0.757966220378876

 $00:43:00.217 \rightarrow 00:43:03.558$  that was found in the AML samples.

NOTE Confidence: 0.757966220378876

 $00:43:03.560 \longrightarrow 00:43:06.146$  To directly test whether this email

NOTE Confidence: 0.757966220378876

 $00{:}43{:}06.146 \dashrightarrow 00{:}43{:}07.870$  associated non coding variants

NOTE Confidence: 0.757966220378876

 $00{:}43{:}07{.}944 \dashrightarrow 00{:}43{:}09{.}972$  indeed modulate nuclear hormone

NOTE Confidence: 0.757966220378876

 $00:43:09.972 \longrightarrow 00:43:12.000$  binding and enhancer function,

NOTE Confidence: 0.757966220378876

 $00:43:12.000 \longrightarrow 00:43:13.410$  we went ahead,

NOTE Confidence: 0.757966220378876

 $00{:}43{:}13{.}410 \dashrightarrow 00{:}43{:}16{.}230$  generate a knocking audio and this

NOTE Confidence: 0.757966220378876

 $00:43:16.230 \longrightarrow 00:43:17.859$  was not trivial.

NOTE Confidence: 0.757966220378876

 $00:43:17.860 \rightarrow 00:43:20.926$  That efficiency is still not very high,

NOTE Confidence: 0.757966220378876

00:43:20.930 --> 00:43:23.708 but anyway we achieved by knocking

 $00:43:23.708 \longrightarrow 00:43:26.377$  by Christmas targeting of the either

NOTE Confidence: 0.757966220378876

 $00:43:26.377 \rightarrow 00:43:29.337$  the white type or the mutant value in

NOTE Confidence: 0.757966220378876

 $00{:}43{:}29{.}418 \dashrightarrow 00{:}43{:}32{.}346$  two K562 leukemia cells within screen.

NOTE Confidence: 0.757966220378876

00:43:32.350 --> 00:43:34.314 Single cell derived knocking

NOTE Confidence: 0.757966220378876

 $00{:}43{:}34{.}314 \dashrightarrow 00{:}43{:}36{.}769$  clones and measure nuclear Homer

NOTE Confidence: 0.757966220378876

 $00:43:36.769 \longrightarrow 00:43:39.190$  by name by chip experiment.

NOTE Confidence: 0.745472967624664

 $00{:}43{:}39{.}190 \dashrightarrow 00{:}43{:}42{.}022$  So the data showing on the top right

NOTE Confidence: 0.745472967624664

 $00:43:42.022 \longrightarrow 00:43:44.883$  corner so you will see in the input

NOTE Confidence: 0.745472967624664

 $00{:}43{:}44{.}883 \dashrightarrow 00{:}43{:}47{.}148$  dinner you will see this expecting

NOTE Confidence: 0.745472967624664

 $00:43:47.148 \longrightarrow 00:43:49.948$  one to one ratio of the whiter

NOTE Confidence: 0.745472967624664

 $00{:}43{:}49{.}948 \dashrightarrow 00{:}43{:}52{.}030$  versus knocking earlier because we

NOTE Confidence: 0.745472967624664

 $00{:}43{:}52.030 \dashrightarrow 00{:}43{:}54.130$  generate the heroes actors knocking

NOTE Confidence: 0.745472967624664

 $00{:}43{:}54{.}130 \dashrightarrow 00{:}43{:}55{.}930$  values in in this cell lines.

NOTE Confidence: 0.745472967624664

00:43:55.930 --> 00:43:57.844 However, if you look at abundance

NOTE Confidence: 0.745472967624664

 $00{:}43{:}57{.}844 \dashrightarrow 00{:}44{:}00{.}501$  of this of the ratio of the
00:44:00.501 --> 00:44:02.249 knocking mutually versus Vytorin,

NOTE Confidence: 0.745472967624664

 $00:44:02.250 \rightarrow 00:44:04.762$  the chipped in and you see the knocking

NOTE Confidence: 0.745472967624664

 $00:44:04.762 \rightarrow 00:44:07.089$  mutant value are significantly enriched,

NOTE Confidence: 0.745472967624664

 $00:44:07.090 \rightarrow 00:44:09.736$  and this suggests that the mutant value.

NOTE Confidence: 0.745472967624664

 $00:44:09.740 \longrightarrow 00:44:11.560$  Actually have stronger Association

NOTE Confidence: 0.745472967624664

 $00{:}44{:}11.560 \dashrightarrow 00{:}44{:}13.835$  with the nuclear hormone receptors

NOTE Confidence: 0.745472967624664

 $00:44:13.835 \rightarrow 00:44:16.066$  by chip experiment and consistent

NOTE Confidence: 0.745472967624664

 $00:44:16.066 \rightarrow 00:44:18.206$  with this and nuclear agonist,

NOTE Confidence: 0.745472967624664

 $00{:}44{:}18{.}210 \dashrightarrow 00{:}44{:}20{.}919$  I can list more enhanced CARROS expression

NOTE Confidence: 0.745472967624664

 $00:44:20.919 \longrightarrow 00:44:24.313$  in a knock in sales compared to the

NOTE Confidence: 0.745472967624664

 $00:44:24.313 \rightarrow 00:44:27.049$  wild type cells against suggestion that

NOTE Confidence: 0.745472967624664

 $00{:}44{:}27.049 \dashrightarrow 00{:}44{:}29.569$  these mutant assume associated cameras

NOTE Confidence: 0.745472967624664

 $00:44:29.569 \rightarrow 00:44:32.005$  enhancer are regulated by nuclear

NOTE Confidence: 0.745472967624664

 $00:44:32.005 \rightarrow 00:44:34.080$  hormone receptors and this recurrent

NOTE Confidence: 0.745472967624664

 $00:44:34.080 \rightarrow 00:44:36.303$  mutations my function to enhance

NOTE Confidence: 0.745472967624664

 $00:44:36.303 \rightarrow 00:44:38.279$  nuclear hormone receptor binding.

- NOTE Confidence: 0.745472967624664
- $00:44:38.280 \longrightarrow 00:44:40.570$  To trans activate Cara sticks.
- NOTE Confidence: 0.745472967624664
- 00:44:40.570 -> 00:44:43.230 Watching you email sales.
- NOTE Confidence: 0.745472967624664
- $00:44:43.230 \longrightarrow 00:44:46.014$  So we also valid that is finding other
- NOTE Confidence: 0.745472967624664
- $00{:}44{:}46.014 \dashrightarrow 00{:}44{:}48.869$  enhances that I won't have time to show
- NOTE Confidence: 0.745472967624664
- $00{:}44{:}48.869 \dashrightarrow 00{:}44{:}51.510$  an including a interesting Lee has a
- NOTE Confidence: 0.745472967624664
- $00:44:51.510 \rightarrow 00:44:53.475$  controlling our security engine code,
- NOTE Confidence: 0.745472967624664
- $00:44:53.480 \longrightarrow 00:44:55.310$  PO2 this is all publisher
- NOTE Confidence: 0.745472967624664
- $00:44:55.310 \longrightarrow 00:44:56.408$  if you're interested.
- NOTE Confidence: 0.745472967624664
- $00{:}44{:}56{.}410 \dashrightarrow 00{:}44{:}58{.}245$  You're more than happy to
- NOTE Confidence: 0.745472967624664
- $00{:}44{:}58{.}245 \dashrightarrow 00{:}45{:}00{.}080$  read about the details so.
- NOTE Confidence: 0.745472967624664
- $00:45:00.080 \longrightarrow 00:45:03.006$  Moreover, we are in a global analysis.
- NOTE Confidence: 0.745472967624664
- 00:45:03.010 --> 00:45:05.100 We found his nuclear hormone,
- NOTE Confidence: 0.745472967624664
- $00{:}45{:}05{.}100 \dashrightarrow 00{:}45{:}07{.}802$  our finest artist seems to be frequent
- NOTE Confidence: 0.745472967624664
- $00{:}45{:}07.802 \dashrightarrow 00{:}45{:}09.690$  targets of noncoding mutations,
- NOTE Confidence: 0.745472967624664
- $00:45:09.690 \rightarrow 00:45:10.944$  in particular email,
- NOTE Confidence: 0.745472967624664

 $00:45:10.944 \rightarrow 00:45:13.034$  but also other hematological malignancy,

NOTE Confidence: 0.745472967624664

00:45:13.040 --> 00:45:13.458 suggestion,

NOTE Confidence: 0.745472967624664

 $00{:}45{:}13{.}458$  -->  $00{:}45{:}15{.}548$  perhaps a more generalizable mechanisms.

NOTE Confidence: 0.745472967624664

 $00:45:15.550 \rightarrow 00:45:17.704$  So therefore we seek our findings

NOTE Confidence: 0.745472967624664

 $00{:}45{:}17.704 \dashrightarrow 00{:}45{:}20.658$  support model that is pathogenic and non

NOTE Confidence: 0.745472967624664

 $00:45:20.658 \rightarrow 00:45:23.068$  coding variants are noncoding mutations,

NOTE Confidence: 0.745472967624664

 $00:45:23.070 \rightarrow 00:45:24.742$  might cooperate with signal

NOTE Confidence: 0.745472967624664

00:45:24.742 --> 00:45:25.996 independent transcriptional machinery.

NOTE Confidence: 0.745472967624664

00:45:26.000 --> 00:45:27.970 In this particular case nuclear

NOTE Confidence: 0.745472967624664

 $00:45:27.970 \rightarrow 00:45:29.940$  receptors to rewire signal dependent

NOTE Confidence: 0.745472967624664

00:45:30.001 -> 00:45:31.450 gene expression programs.

NOTE Confidence: 0.745472967624664

 $00{:}45{:}31{.}450 \dashrightarrow 00{:}45{:}34{.}105$  Then my potentially promote are

NOTE Confidence: 0.745472967624664

 $00{:}45{:}34.105 \dashrightarrow 00{:}45{:}36.760$  functionally that contribute to the

NOTE Confidence: 0.745472967624664

 $00:45:36.840 \longrightarrow 00:45:40.088$  development of hematopoetic malignancies.

NOTE Confidence: 0.745472967624664

 $00:45:40.090 \longrightarrow 00:45:43.300$  So as a final summary.

NOTE Confidence: 0.745472967624664

 $00:45:43.300 \longrightarrow 00:45:46.150$  Is that an explosion of genomic

- NOTE Confidence: 0.745472967624664
- $00:45:46.150 \longrightarrow 00:45:47.575$  and epigenomic information?
- NOTE Confidence: 0.745472967624664
- $00{:}45{:}47{.}580 \dashrightarrow 00{:}45{:}50{.}079$  In recent years we have learned a
- NOTE Confidence: 0.745472967624664
- $00{:}45{:}50.079 \dashrightarrow 00{:}45{:}52.864$  great deal of how gene regulation
- NOTE Confidence: 0.745472967624664
- $00{:}45{:}52{.}864 \dashrightarrow 00{:}45{:}55{.}048$  controls normal development and
- NOTE Confidence: 0.745472967624664
- $00{:}45{:}55{.}048 \dashrightarrow 00{:}45{:}57{.}832$  how dys regulation of this process
- NOTE Confidence: 0.745472967624664
- $00{:}45{:}57.832 \dashrightarrow 00{:}45{:}59.956$  contribute to human diseases.
- NOTE Confidence: 0.745472967624664
- $00:45:59.960 \longrightarrow 00:46:00.828$  How what.
- NOTE Confidence: 0.745472967624664
- $00:46:00.828 \longrightarrow 00:46:02.998$  We currently know only represents
- NOTE Confidence: 0.745472967624664
- $00:46:02.998 \longrightarrow 00:46:06.013$  a very small portion of the
- NOTE Confidence: 0.745472967624664
- $00:46:06.013 \rightarrow 00:46:07.099$  complicated complex.
- NOTE Confidence: 0.745472967624664
- 00:46:07.100 --> 00:46:08.573 The human genome,
- NOTE Confidence: 0.745472967624664
- $00:46:08.573 \longrightarrow 00:46:11.028$  and in retrospect and maybe
- NOTE Confidence: 0.745472967624664
- $00{:}46{:}11.028 \dashrightarrow 00{:}46{:}13.348$  more relevant to our studies.
- NOTE Confidence: 0.745472967624664
- $00{:}46{:}13.350 \dashrightarrow 00{:}46{:}14.679$  As we know,
- NOTE Confidence: 0.745472967624664
- $00{:}46{:}14.679 \dashrightarrow 00{:}46{:}16.894$  the first documented cases of
- NOTE Confidence: 0.745472967624664

00:46:16.894 --> 00:46:19.166 sickle cell disease was described

NOTE Confidence: 0.745472967624664

 $00{:}46{:}19{.}166 \dashrightarrow 00{:}46{:}22{.}204$  by an James Herrick and in 90.

NOTE Confidence: 0.745472967624664

00:46:22.210 --> 00:46:24.184 Early 90 app.

NOTE Confidence: 0.745472967624664

00:46:24.184 --> 00:46:26.816 Centuries and 9010 specifically,

NOTE Confidence: 0.745472967624664

 $00{:}46{:}26{.}820 \dashrightarrow 00{:}46{:}29{.}900$  which was later dropped as a first

NOTE Confidence: 0.745472967624664

 $00:46:29.900 \rightarrow 00:46:32.578$  molecular disease by a Linus Pauling.

NOTE Confidence: 0.745472967624664

00:46:32.580 --> 00:46:35.118 In 1947 an enhancer was not

NOTE Confidence: 0.745472967624664

 $00:46:35.118 \longrightarrow 00:46:36.810$  discovered until early 1980s

NOTE Confidence: 0.745472967624664

 $00{:}46{:}36{.}887 \dashrightarrow 00{:}46{:}39{.}227$  and followed by the completion.

NOTE Confidence: 0.745472967624664

00:46:39.230 --> 00:46:41.440 The first draft of human

NOTE Confidence: 0.745472967624664

 $00:46:41.440 \longrightarrow 00:46:43.208$  genome in early 2000s.

NOTE Confidence: 0.745472967624664

 $00{:}46{:}43.210 \dashrightarrow 00{:}46{:}45.964$  Now more than a century after

NOTE Confidence: 0.745472967624664

 $00{:}46{:}45{.}964 \dashrightarrow 00{:}46{:}48{.}287$  discovering sickle cell disease and

NOTE Confidence: 0.745472967624664

00:46:48.287 --> 00:46:50.735 40 years of discovery of enhances,

NOTE Confidence: 0.745472967624664

 $00:46:50.740 \rightarrow 00:46:53.561$  we might have a first enhancer targeting

NOTE Confidence: 0.745472967624664

 $00:46:53.561 \rightarrow 00:46:56.080$  therapist for this molecular disease.

- NOTE Confidence: 0.745472967624664
- $00:46:56.080 \rightarrow 00:46:56.900$  Very soon,
- NOTE Confidence: 0.745472967624664
- $00:46:56.900 \longrightarrow 00:46:59.360$  and we certainly hope that by
- NOTE Confidence: 0.745472967624664
- $00:46:59.360 \longrightarrow 00:47:02.251$  focusing on your hands as another
- NOTE Confidence: 0.745472967624664
- 00:47:02.251 --> 00:47:04.736 non coding regulatory at genomic
- NOTE Confidence: 0.745472967624664
- $00{:}47{:}04.736 \dashrightarrow 00{:}47{:}07.727$  elements that we might be able to
- NOTE Confidence: 0.745472967624664
- $00:47:07.727 \rightarrow 00:47:09.797$  identify new mechanism and genetic
- NOTE Confidence: 0.745472967624664
- $00:47:09.797 \longrightarrow 00:47:12.539$  pathways that contribute to a normal
- NOTE Confidence: 0.745472967624664
- $00:47:12.539 \rightarrow 00:47:14.669$  blood cell development an animal.
- NOTE Confidence: 0.745472967624664
- $00{:}47{:}14.670 \dashrightarrow 00{:}47{:}16.680$  Long term that we might be
- NOTE Confidence: 0.745472967624664
- $00:47:16.680 \longrightarrow 00:47:18.020$  able to develop our
- NOTE Confidence: 0.830641567707062
- $00:47:18.098 \rightarrow 00:47:19.994$  enhanced targeting therapeutics
- NOTE Confidence: 0.830641567707062
- $00:47:19.994 \longrightarrow 00:47:21.890$  for blood disorders.
- NOTE Confidence: 0.830641567707062
- $00{:}47{:}21.890 \dashrightarrow 00{:}47{:}23.930$  So with that most important,
- NOTE Confidence: 0.830641567707062
- 00:47:23.930 --> 00:47:25.915 I want to acknowledge all
- NOTE Confidence: 0.830641567707062
- $00:47:25.915 \longrightarrow 00:47:28.400$  the people who met his work,
- NOTE Confidence: 0.830641567707062

 $00:47:28.400 \longrightarrow 00:47:30.205$  possible the initial study PCL

NOTE Confidence: 0.830641567707062

00:47:30.205 --> 00:47:32.522 PCL Evan Hansen was done in

NOTE Confidence: 0.830641567707062

 $00{:}47{:}32{.}522 \dashrightarrow 00{:}47{:}34{.}306$  Stockings Lab in collaboration

NOTE Confidence: 0.830641567707062

00:47:34.306 --> 00:47:36.536 with Stambaugh and Vicious Ankara,

NOTE Confidence: 0.830641567707062

 $00{:}47{:}36{.}540 \dashrightarrow 00{:}47{:}39{.}030$  and profiling work done in primary

NOTE Confidence: 0.830641567707062

 $00{:}47{:}39{.}030 \dashrightarrow 00{:}47{:}41{.}141$  hematopoietic cells was done in

NOTE Confidence: 0.830641567707062

 $00{:}47{:}41{.}141 \dashrightarrow 00{:}47{:}43{.}433$  collaboration with the formal post or

NOTE Confidence: 0.830641567707062

00:47:43.433 --> 00:47:45.899 fellow John Huang from Stalking Slab.

NOTE Confidence: 0.830641567707062

 $00{:}47{:}45{.}900 \dashrightarrow 00{:}47{:}50{.}094$  Now he has his own lab in Sherman University.

NOTE Confidence: 0.830641567707062

 $00{:}47{:}50{.}100 \dashrightarrow 00{:}47{:}53{.}180$  The development of the cast net capture

NOTE Confidence: 0.830641567707062

 $00{:}47{:}53.180 \dashrightarrow 00{:}47{:}55.829$  was spearheaded by a former poster in

NOTE Confidence: 0.830641567707062

 $00{:}47{:}55{.}829 \dashrightarrow 00{:}47{:}59{.}094$  my lap as she knew now has his own

NOTE Confidence: 0.830641567707062

 $00:47:59.094 \rightarrow 00:48:01.728$  app together with another poster fellow.

NOTE Confidence: 0.830641567707062

 $00:48:01.730 \longrightarrow 00:48:03.735$  Again using the developer of

NOTE Confidence: 0.830641567707062

00:48:03.735 --> 00:48:04.938 Enhancer targeting CRISPR,

NOTE Confidence: 0.830641567707062

 $00{:}48{:}04{.}940 \dashrightarrow 00{:}48{:}07{.}185$  Aquifer was spearheaded by another

NOTE Confidence: 0.830641567707062

00:48:07.185 --> 00:48:09.824 poster fellow Kyle only think is

NOTE Confidence: 0.830641567707062

 $00:48:09.824 \longrightarrow 00:48:11.750$  one of the fellows over here.

NOTE Confidence: 0.830641567707062

00:48:11.750 --> 00:48:14.312 If I can move my brows anyway

NOTE Confidence: 0.830641567707062

 $00:48:14.312 \rightarrow 00:48:16.569$  together with another Postal federal,

NOTE Confidence: 0.830641567707062

 $00{:}48{:}16.570 \dashrightarrow 00{:}48{:}18.600$  most of them are transitioned

NOTE Confidence: 0.830641567707062

 $00{:}48{:}18.600 \dashrightarrow 00{:}48{:}20.224$  to their independent positions.

NOTE Confidence: 0.830641567707062

 $00{:}48{:}20{.}230 \dashrightarrow 00{:}48{:}21{.}386$  Together with other collaborators

NOTE Confidence: 0.830641567707062

 $00{:}48{:}21{.}386 \dashrightarrow 00{:}48{:}23{.}525$  and we couldn't do this with a

NOTE Confidence: 0.830641567707062

 $00{:}48{:}23.525 \dashrightarrow 00{:}48{:}24.941$  wonderful collaboration from Boston

NOTE Confidence: 0.830641567707062

 $00{:}48{:}24{.}941 \dashrightarrow 00{:}48{:}26{.}711$  Children's and our local collaborators

NOTE Confidence: 0.830641567707062

 $00{:}48{:}26.766 \dashrightarrow 00{:}48{:}28.260$  at you T Southwestern UT Dallas.

NOTE Confidence: 0.830641567707062

00:48:28.260 --> 00:48:29.472 I will stop here.

NOTE Confidence: 0.830641567707062

 $00:48:29.472 \longrightarrow 00:48:31.290$  I'm happy to take any questions

NOTE Confidence: 0.830641567707062

 $00{:}48{:}31{.}353 \dashrightarrow 00{:}48{:}32{.}589$  that you might have.

NOTE Confidence: 0.830641567707062

 $00{:}48{:}32{.}590 \dashrightarrow 00{:}48{:}35{.}803$  Thank you very much for your time.