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 --> 00:00:05.769 let's go ahead and get started so

NOTE Confidence: 0.818772971630096

00:00:05.769 --> 00:00:08.513 everyone can get on with their day.

NOTE Confidence: 0.818772971630096

00:00:08.520 --> 00:00:11.224 It is our great pleasure today to welcome

NOTE Confidence: 0.818772971630096

00:00:11.224 --> 00:00:13.845 Doctor Jian Xu as our distinguished speaker

NOTE Confidence: 0.818772971630096

00:00:13.845 --> 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 --> 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 --> 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 --> 00:00:30.504 but also for all of the Centers of excellence

NOTE Confidence: 0.818772971630096

00:00:30.504 --> 00:00:33.436 in hematology across the United States.

NOTE Confidence: 0.818772971630096

00:00:33.440 --> 00:00:35.825 As you can see, the title of his talk

NOTE Confidence: 0.818772971630096

00:00:35.825 --> 00:00:38.554 is decoding the noncoding genome in

NOTE Confidence: 0.818772971630096

00:00:38.554 --> 00:00:40.470 blood development and disorders.

NOTE Confidence: 0.818772971630096

00:00:40.470 --> 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 --> 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 --> 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 --> 00:00:53.788 expression and hematopoiesis and cancer,

NOTE Confidence: 0.818772971630096

00:00:53.790 --> 00:00:54.900 especially transcriptional enhancers

NOTE Confidence: 0.818772971630096

00:00:54.900 --> 00:00:56.380 and epigenetic regulatory regions.

NOTE Confidence: 0.818772971630096

00:00:56.380 --> 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 --> 00:01:03.490 us to record his talk today.

NOTE Confidence: 0.818772971630096

00:01:03.490 --> 00:01:05.310 I'm at the end of his talk.

NOTE Confidence: 0.818772971630096

00:01:05.310 --> 00:01:07.130 We ask that if you have questions,

NOTE Confidence: 0.818772971630096

00:01:07.130 --> 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.

NOTE Confidence: 0.818772971630096

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

NOTE Confidence: 0.818772971630096

00:01:12.070 --> 00:01:14.110 so if you type your question I will

NOTE Confidence: 0.818772971630096

00:01:14.110 --> 00:01:16.227 read it and then he can answer it.

NOTE Confidence: 0.818772971630096

00:01:16.230 --> 00:01:16.852 So again,

NOTE Confidence: 0.818772971630096

00:01:16.852 --> 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 --> 00:01:24.542 Thank you so much Jeannie for that

NOTE Confidence: 0.818772971630096

00:01:24.542 --> 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 --> 00:01:31.892 Pat Gallagher Anadan across for the

NOTE Confidence: 0.818772971630096

00:01:31.892 --> 00:01:34.867 opportunity and a kind invitation to a

NOTE Confidence: 0.818772971630096

00:01:34.867 --> 00:01:36.543 virtually visitor cooperative center

NOTE Confidence: 0.818772971630096

00:01:36.543 --> 00:01:39.270 of excellence of hematology at year and,

NOTE Confidence: 0.818772971630096

00:01:39.270 --> 00:01:41.930 and I'm excited to share some more

NOTE Confidence: 0.818772971630096

00:01:41.930 --> 00:01:44.544 recent work related to the study of

NOTE Confidence: 0.818772971630096

00:01:44.544 --> 00:01:46.650 noncoding genome in the context of

NOTE Confidence: 0.818772971630096

00:01:46.728 --> 00:01:48.980 blood development and disorders.

NOTE Confidence: 0.818772971630096

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

NOTE Confidence: 0.818772971630096

00:01:52.960 --> 00:01:55.654 so we started the mechanism that

NOTE Confidence: 0.818772971630096

00:01:55.654 --> 00:01:57.450 regulate gene expression during

NOTE Confidence: 0.818772971630096

00:01:57.524 --> 00:01:59.420 blood cell differentiation,

NOTE Confidence: 0.818772971630096

00:01:59.420 --> 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 --> 00:02:08.729 and more specifically we aim to understand

NOTE Confidence: 0.818772971630096

00:02:08.729 --> 00:02:12.368 how we need specific transcription factors.

NOTE Confidence: 0.818772971630096

00:02:12.370 --> 00:02:14.474 Epigenetic regulators cooperate with

NOTE Confidence: 0.818772971630096

00:02:14.474 --> 00:02:16.578 environmental signals to control

NOTE Confidence: 0.818772971630096

00:02:16.578 --> 00:02:19.345 cell identity by acting on a set

NOTE Confidence: 0.818772971630096

00:02:19.345 --> 00:02:20.990 of non coding regulatory elements

NOTE Confidence: 0.818772971630096

00:02:21.063 --> 00:02:23.219 such as transcriptional enhancers,

NOTE Confidence: 0.818772971630096

00:02:23.220 --> 00:02:26.424 which can be the central focus

NOTE Confidence: 0.818772971630096

00:02:26.424 --> 00:02:28.560 of my talk today.

NOTE Confidence: 0.818772971630096

00:02:28.560 --> 00:02:32.240 So as we all know that a noncoding

NOTE Confidence: 0.818772971630096

00:02:32.240 --> 00:02:35.232 genome occupies nearly 99% of the

NOTE Confidence: 0.818772971630096

00:02:35.232 --> 00:02:37.862 human genomics space and consistent

NOTE Confidence: 0.818772971630096

00:02:37.862 --> 00:02:40.288 various regulatory elements as well

NOTE Confidence: 0.818772971630096

00:02:40.288 --> 00:02:42.598 as many of the pulley characters.

NOTE Confidence: 0.818772971630096

00:02:42.600 --> 00:02:45.876 Repetitive element an other genomic DNA is,

NOTE Confidence: 0.818772971630096

00:02:45.880 --> 00:02:47.464 on the other hand,

NOTE Confidence: 0.818772971630096

00:02:47.464 --> 00:02:49.840 from genetic studies we know vast

NOTE Confidence: 0.818772971630096

00:02:49.920 --> 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 --> 00:02:58.570 but identify the causal mechanism.

NOTE Confidence: 0.818772971630096

00:02:58.570 --> 00:03:00.382 Has remained a significant

NOTE Confidence: 0.818772971630096

00:03:00.382 --> 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 --> 00:03:08.351 dissection of the underlying pathways

NOTE Confidence: 0.818772971630096

00:03:08.351 --> 00:03:12.158 can often lead to new insights in Human

NOTE Confidence: 0.818772971630096

00:03:12.158 --> 00:03:14.618 Genetics and an even therapeutics,

NOTE Confidence: 0.818772971630096

00:03:14.620 --> 00:03:15.742 for example,

NOTE Confidence: 0.818772971630096

00:03:15.742 --> 00:03:17.986 by associating common genetic

NOTE Confidence: 0.818772971630096

00:03:17.986 --> 00:03:20.230 variations with certain block

NOTE Confidence: 0.818772971630096

00:03:20.312 --> 00:03:23.308 trades such as feeding him a globin

NOTE Confidence: 0.818772971630096

00:03:23.308 --> 00:03:25.800 expression levels a gene called BCL

NOTE Confidence: 0.818772971630096

00:03:25.800 --> 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 --> 00:03:34.052 Federal in Boston Children's with walking

NOTE Confidence: 0.749307191371918

00:03:34.052 --> 00:03:37.220 and together with Vijay Sankar Anadem.

NOTE Confidence: 0.749307191371918

00:03:37.220 --> 00:03:40.136 Bawa have shown that this genetic

NOTE Confidence: 0.749307191371918

00:03:40.136 --> 00:03:42.574 variants that were identified forms

NOTE Confidence: 0.749307191371918

00:03:42.574 --> 00:03:45.486 you are status actually do not affect

NOTE Confidence: 0.749307191371918

00:03:45.486 --> 00:03:48.097 the coding sequences of BCL 11 A.

NOTE Confidence: 0.749307191371918

00:03:48.100 --> 00:03:50.656 But instead that a tissue specific

NOTE Confidence: 0.749307191371918

00:03:50.656 --> 00:03:52.880 enhancer for this transcription factor,

NOTE Confidence: 0.749307191371918

00:03:52.880 --> 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 --> 00:03:59.870 that PC anime is activated in.

NOTE Confidence: 0.749307191371918

00:03:59.870 --> 00:04:01.334 Definitive hematopoietic cells

NOTE Confidence: 0.749307191371918

00:04:01.334 --> 00:04:02.798 by this tissue,

NOTE Confidence: 0.749307191371918

00:04:02.800 --> 00:04:05.575 especially enhancer to request fitting

NOTE Confidence: 0.749307191371918

00:04:05.575 --> 00:04:08.350 hemoglobin expression and impatient when

NOTE Confidence: 0.749307191371918

00:04:08.420 --> 00:04:11.087 the adult beta globin gene is mutated,

NOTE Confidence: 0.749307191371918

00:04:11.090 --> 00:04:15.482 such as in the context of sickle cell anemia,

NOTE Confidence: 0.749307191371918

00:04:15.490 --> 00:04:17.930 and this is permissive for

NOTE Confidence: 0.749307191371918

00:04:17.930 --> 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 --> 00:04:25.090 functions to attenuate enhance

NOTE Confidence: 0.749307191371918

00:04:25.090 --> 00:04:27.687 activity leads to less of a PCR.

NOTE Confidence: 0.749307191371918

00:04:27.690 --> 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 --> 00:04:38.205 So this is how the genetics works,

NOTE Confidence: 0.749307191371918

00:04:38.210 --> 00:04:41.006 but this fine is not only

NOTE Confidence: 0.749307191371918

00:04:41.006 --> 00:04:42.870 established the underlying genetic

NOTE Confidence: 0.749307191371918

00:04:42.949 --> 00:04:45.277 basis of hemoglobin switching,

NOTE Confidence: 0.749307191371918

00:04:45.280 --> 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 --> 00:04:52.762 Maybe potential therapeutic targets

NOTE Confidence: 0.749307191371918

00:04:52.762 --> 00:04:55.660 and this idea actually has led

NOTE Confidence: 0.749307191371918

00:04:55.734 --> 00:04:58.848 to an ongoing clinical trials by

NOTE Confidence: 0.749307191371918

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

NOTE Confidence: 0.749307191371918

00:05:00.930 --> 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 --> 00:05:07.986 cell disease and beta thalassemia

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 --> 00:05:15.520 to mobilize our city.

NOTE Confidence: 0.749307191371918

00:05:15.520 --> 00:05:17.668 Sorry for positive hematopoietic

NOTE Confidence: 0.749307191371918

00:05:17.668 --> 00:05:20.353 stem progenitor cells from affecting

NOTE Confidence: 0.749307191371918

00:05:20.353 --> 00:05:22.735 individuals and transducer cells with

NOTE Confidence: 0.749307191371918

00:05:22.735 --> 00:05:24.511 rubber nuclear proteins containing

NOTE Confidence: 0.749307191371918

00:05:24.511 --> 00:05:27.259 cost 9 and a single godani that

NOTE Confidence: 0.749307191371918

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

NOTE Confidence: 0.749307191371918

00:05:29.050 --> 00:05:31.305 which leads to disruption of

NOTE Confidence: 0.749307191371918

00:05:31.305 --> 00:05:32.658 the enhancer function,

NOTE Confidence: 0.749307191371918

00:05:32.660 --> 00:05:34.910 and then these edited cells.

NOTE Confidence: 0.749307191371918

00:05:34.910 --> 00:05:38.630 We are well reinfused back to the same

NOTE Confidence: 0.749307191371918

00:05:38.630 --> 00:05:42.550 patient and observe for disease phenotypes.

NOTE Confidence: 0.749307191371918

00:05:42.550 --> 00:05:43.914 As you may know,

NOTE Confidence: 0.749307191371918

00:05:43.914 --> 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 --> 00:05:52.946 recently reported in a paper at

NOTE Confidence: 0.749307191371918

00:05:52.946 --> 00:05:54.570 publishing Union General Medicine

NOTE Confidence: 0.749307191371918

00:05:54.641 --> 00:05:56.927 with more cases recently reported in

NOTE Confidence: 0.749307191371918

00:05:56.927 --> 00:05:58.912 the Ash American Society Hematology

NOTE Confidence: 0.749307191371918

00:05:58.912 --> 00:06:01.649 Annual Meeting just a couple weeks ago.

NOTE Confidence: 0.749307191371918

00:06:01.650 --> 00:06:04.604 So as one example showing here that

NOTE Confidence: 0.749307191371918

00:06:04.604 --> 00:06:07.981 here's the result for the first bit of

NOTE Confidence: 0.749307191371918

00:06:07.981 --> 00:06:10.810 cell patients that are treated by CAS 9,

NOTE Confidence: 0.749307191371918

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

NOTE Confidence: 0.749307191371918

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

NOTE Confidence: 0.749307191371918

00:06:17.552 --> 00:06:20.549 before infusion of the edited cells,

NOTE Confidence: 0.749307191371918

00:06:20.550 --> 00:06:23.178 the patient had a hemoglobin level

NOTE Confidence: 0.749307191371918

00:06:23.178 --> 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 --> 00:06:33.532 per deciliter but just a couple months

NOTE Confidence: 0.749307191371918

00:06:33.532 --> 00:06:36.468 after infusion of the edited cells,

NOTE Confidence: 0.749307191371918

00:06:36.468 --> 00:06:38.412 the feeling hemoglobin level

NOTE Confidence: 0.749307191371918

00:06:38.412 --> 00:06:41.366 increased to 6.5 gram per deciliter

NOTE Confidence: 0.749307191371918

00:06:41.366 --> 00:06:44.192 an letter 1113.1 gram per deciliter.

NOTE Confidence: 0.749307191371918

00:06:44.200 --> 00:06:46.915 With total hemoglobin increased to

NOTE Confidence: 0.749307191371918

00:06:46.915 --> 00:06:50.526 14.1 and this is accompanied by nearly

NOTE Confidence: 0.749307191371918

00:06:50.526 --> 00:06:53.978 100% F cells or these feeding him

NOTE Confidence: 0.749307191371918

00:06:53.978 --> 00:06:57.355 globin positive cells and up to 18

NOTE Confidence: 0.749307191371918

00:06:57.355 --> 00:07:00.253 months of follow up so this patient

NOTE Confidence: 0.749307191371918

00:07:00.354 --> 00:07:03.370 is clinically cured technically,

NOTE Confidence: 0.749307191371918

00:07:03.370 --> 00:07:05.795 therefore this proof of principle

NOTE Confidence: 0.749307191371918

00:07:05.795 --> 00:07:08.859 studies are very encouraging not only

NOTE Confidence: 0.749307191371918

00:07:08.859 --> 00:07:11.654 to show that therapeutic targeting

NOTE Confidence: 0.749307191371918

00:07:11.654 --> 00:07:14.260 disease associated enhancer elements can.

NOTE Confidence: 0.749307191371918

00:07:14.260 --> 00:07:17.424 Likely provide a cure for the most

NOTE Confidence: 0.749307191371918

00:07:17.424 --> 00:07:20.113 common monogenic disease that was first

NOTE Confidence: 0.749307191371918

00:07:20.113 --> 00:07:22.615 described more than a century ago,

NOTE Confidence: 0.749307191371918

00:07:22.620 --> 00:07:25.014 but also open up new ideas

NOTE Confidence: 0.749307191371918

00:07:25.014 --> 00:07:26.610 and opportunities for people

NOTE Confidence: 0.855561494827271

00:07:26.684 --> 00:07:29.660 to understand biology and more important,

NOTE Confidence: 0.855561494827271

00:07:29.660 --> 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 --> 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

NOTE Confidence: 0.855561494827271

00:07:42.524 --> 00:07:44.679 Southwestern is what are enhancers?

NOTE Confidence: 0.855561494827271

00:07:44.680 --> 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 --> 00:07:50.346 discovered nearly 40 years ago,

NOTE Confidence: 0.855561494827271

00:07:50.350 --> 00:07:53.995 an actually from a viral genome as a shot.

NOTE Confidence: 0.855561494827271

00:07:54.000 --> 00:07:56.380 Deer sequences in the SV 40 Gino

NOTE Confidence: 0.855561494827271

00:07:56.380 --> 00:07:58.557 that can enhance the expression of

NOTE Confidence: 0.855561494827271

00:07:58.557 --> 00:08:01.084 a rabbit bitter globin gene in the

NOTE Confidence: 0.855561494827271

00:08:01.156 --> 00:08:03.310 orientation independent manner.

NOTE Confidence: 0.855561494827271

00:08:03.310 --> 00:08:04.822 In a transient transfection

NOTE Confidence: 0.855561494827271

00:08:04.822 --> 00:08:07.090 assays soon after the 1st century

NOTE Confidence: 0.855561494827271

00:08:07.160 --> 00:08:08.648 enhancer was discovered.

NOTE Confidence: 0.855561494827271

00:08:08.650 --> 00:08:11.548 From the mouth immuno globin gene.

NOTE Confidence: 0.855561494827271

00:08:11.550 --> 00:08:14.714 In a tissue specific manner so therefore

NOTE Confidence: 0.855561494827271

00:08:14.714 --> 00:08:18.301 even from the very early days enhancer

NOTE Confidence: 0.855561494827271

00:08:18.301 --> 00:08:21.517 at defined as SESAC ingenious sequences

NOTE Confidence: 0.855561494827271

00:08:21.601 --> 00:08:25.145 that function at often at a distance to

NOTE Confidence: 0.855561494827271

00:08:25.145 --> 00:08:27.696 activate gene transcription in orientation

NOTE Confidence: 0.855561494827271

00:08:27.696 --> 00:08:30.456 independent and tissue specific manner.

NOTE Confidence: 0.855561494827271

00:08:30.460 --> 00:08:32.788 As such, it has been very

NOTE Confidence: 0.855561494827271

00:08:32.788 --> 00:08:34.340 difficult to studying answers,

NOTE Confidence: 0.855561494827271

00:08:34.340 --> 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 --> 00:08:40.550 genes and their in vivo function,

NOTE Confidence: 0.855561494827271

00:08:40.550 --> 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 --> 00:08:46.690 So therefore there are several

NOTE Confidence: 0.855561494827271

00:08:46.690 --> 00:08:48.458 important questions enhancer biology

NOTE Confidence: 0.855561494827271

00:08:48.458 --> 00:08:50.688 that remain to be addressed Anan.

NOTE Confidence: 0.855561494827271

00:08:50.690 --> 00:08:53.480 This is some of the questions that we are

NOTE Confidence: 0.855561494827271

00:08:53.480 --> 00:08:56.488 very particularly interesting excited about,

NOTE Confidence: 0.855561494827271

00:08:56.490 --> 00:08:59.378 and I would like to share some recent

NOTE Confidence: 0.855561494827271

00:08:59.378 --> 00:09:02.671 work that we have done trying to address

NOTE Confidence: 0.855561494827271

00:09:02.671 --> 00:09:05.180 some of these important questions.

NOTE Confidence: 0.855561494827271

00:09:05.180 --> 00:09:07.616 He has a biology and particularly

NOTE Confidence: 0.855561494827271

00:09:07.616 --> 00:09:10.150 how to identify enhances and housing,

NOTE Confidence: 0.855561494827271

00:09:10.150 --> 00:09:12.550 has a regular their target gene

NOTE Confidence: 0.855561494827271

00:09:12.550 --> 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 --> 00:09:20.108 how do he has alterations contribute

NOTE Confidence: 0.855561494827271

00:09:20.108 --> 00:09:21.430 to diseases,

NOTE Confidence: 0.855561494827271

00:09:21.430 --> 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 --> 00:09:28.484 So the first question is how

NOTE Confidence: 0.855561494827271

00:09:28.484 --> 00:09:29.756 to identify Hazard.

NOTE Confidence: 0.855561494827271

00:09:29.760 --> 00:09:31.220 This has been challenging,

NOTE Confidence: 0.855561494827271

00:09:31.220 --> 00:09:33.905 but with the advances in next Gen

NOTE Confidence: 0.855561494827271

00:09:33.905 --> 00:09:36.055 sequencing technologies coupled with an

NOTE Confidence: 0.855561494827271

00:09:36.055 --> 00:09:39.080 analysis of variety of chromatin features,

NOTE Confidence: 0.855561494827271

00:09:39.080 --> 00:09:41.666 we can now easily annotate these

NOTE Confidence: 0.855561494827271

00:09:41.666 --> 00:09:44.695 noncoding genome using a number of methods

NOTE Confidence: 0.855561494827271

00:09:44.695 --> 00:09:47.551 such as chip sequencing as you know,

NOTE Confidence: 0.855561494827271

00:09:47.560 --> 00:09:48.832 to examine protein,

NOTE Confidence: 0.855561494827271

00:09:48.832 --> 00:09:49.680 DNA interactions,

NOTE Confidence: 0.855561494827271

00:09:49.680 --> 00:09:52.284 air taxi or dinner sequencing to

NOTE Confidence: 0.855561494827271

00:09:52.284 --> 00:09:54.020 examine chromatin Accessibility as

NOTE Confidence: 0.855561494827271

00:09:54.093 --> 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 --> 00:10:04.061 or three CBEST methods to examine

NOTE Confidence: 0.855561494827271

00:10:04.061 --> 00:10:06.065 high order chromatin structures.

NOTE Confidence: 0.855561494827271

00:10:06.070 --> 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 --> 00:10:12.430 enhances other regulatory elements in

NOTE Confidence: 0.855561494827271

00:10:12.430 --> 00:10:15.316 a systematic manner and using these

NOTE Confidence: 0.855561494827271

00:10:15.392 --> 00:10:18.544 tools are we can use a simple combination.

NOTE Confidence: 0.855561494827271

00:10:18.550 --> 00:10:20.735 We enhance associated histone Marks

NOTE Confidence: 0.855561494827271

00:10:20.735 --> 00:10:22.920 and chromatin Accessibility to identify

NOTE Confidence: 0.855561494827271

00:10:22.986 --> 00:10:25.056 putative active enhancers or other

NOTE Confidence: 0.855561494827271

00:10:25.056 --> 00:10:27.126 regulatory elements across the Gina.

NOTE Confidence: 0.855561494827271

00:10:27.130 --> 00:10:29.986 So using our favorite local that human

NOTE Confidence: 0.855561494827271

00:10:29.986 --> 00:10:32.699 beta globin gene cluster as example.

NOTE Confidence: 0.855561494827271

00:10:32.700 --> 00:10:36.140 As you can see from this genome browser,

NOTE Confidence: 0.855561494827271

00:10:36.140 --> 00:10:38.732 tracks that we can easily identify

NOTE Confidence: 0.855561494827271

00:10:38.732 --> 00:10:40.028 the upstream enhancer.

NOTE Confidence: 0.855561494827271

00:10:40.030 --> 00:10:42.298 Pass this on Locus control region

NOTE Confidence: 0.855561494827271

00:10:42.298 --> 00:10:45.447 or else are by the presence of

NOTE Confidence: 0.855561494827271

00:10:45.447 --> 00:10:47.519 dinners will have sensitivity.

NOTE Confidence: 0.855561494827271

00:10:47.520 --> 00:10:49.645 He can 27 simulation and

NOTE Confidence: 0.855561494827271

00:10:49.645 --> 00:10:51.345 HCC for modern isolation.

NOTE Confidence: 0.855561494827271

00:10:51.350 --> 00:10:54.192 On the other side you can also

NOTE Confidence: 0.855561494827271

00:10:54.192 --> 00:10:55.939 identify active promoters by

NOTE Confidence: 0.855561494827271

00:10:55.939 --> 00:10:57.739 the presence of translation.

NOTE Confidence: 0.855561494827271

00:10:57.740 --> 00:11:01.116 At 3K four there's all done in primary

NOTE Confidence: 0.855561494827271

00:11:01.116 --> 00:11:03.988 humour as well progenitor cells.

NOTE Confidence: 0.855561494827271

00:11:03.990 --> 00:11:05.738 So using this approach,

NOTE Confidence: 0.855561494827271

00:11:05.738 --> 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 --> 00:11:15.326 and differentiated industry sales,

NOTE Confidence: 0.798697412014008

00:11:15.330 --> 00:11:17.718 and we notice that initially that

NOTE Confidence: 0.798697412014008

00:11:17.718 --> 00:11:20.052 enhances undergoes a pretty progressive

NOTE Confidence: 0.798697412014008

00:11:20.052 --> 00:11:22.720 turnover during limits differentiation,

NOTE Confidence: 0.798697412014008

00:11:22.720 --> 00:11:25.744 such that about 2/3 of the enhancer

NOTE Confidence: 0.798697412014008

00:11:25.744 --> 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 --> 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 --> 00:11:41.508 we then identified transcription

NOTE Confidence: 0.798697412014008

00:11:41.508 --> 00:11:43.843 factors and their combinations that

NOTE Confidence: 0.798697412014008

00:11:43.843 --> 00:11:46.949 are required for this image and a

NOTE Confidence: 0.798697412014008

00:11:46.949 --> 00:11:48.661 developmental stage specific enhance

NOTE Confidence: 0.798697412014008

00:11:48.733 --> 00:11:51.456 activities and I should say that similar

NOTE Confidence: 0.798697412014008

00:11:51.456 --> 00:11:53.466 results obtained by elegant studies

NOTE Confidence: 0.798697412014008

00:11:53.466 --> 00:11:56.810 for pack animals group here at the Yell

NOTE Confidence: 0.798697412014008

00:11:56.891 --> 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 --> 00:12:03.546 And this really has provided a

NOTE Confidence: 0.798697412014008

00:12:03.546 --> 00:12:05.672 useful resource for the community

NOTE Confidence: 0.798697412014008

00:12:05.672 --> 00:12:07.848 to understand the regulatory.

NOTE Confidence: 0.798697412014008

00:12:07.850 --> 00:12:08.952 Basketball hematopoietic

NOTE Confidence: 0.798697412014008

00:12:08.952 --> 00:12:10.054 cell differentiation.

NOTE Confidence: 0.798697412014008

00:12:10.054 --> 00:12:12.809 So with this increasing availability

NOTE Confidence: 0.798697412014008

00:12:12.809 --> 00:12:15.228 of this large genomic data set,

NOTE Confidence: 0.798697412014008

00:12:15.230 --> 00:12:17.848 so we wonder whether we could use

NOTE Confidence: 0.798697412014008

00:12:17.848 --> 00:12:19.425 this information to understand

NOTE Confidence: 0.798697412014008

00:12:19.425 --> 00:12:21.310 how it has a regular,

NOTE Confidence: 0.798697412014008

00:12:21.310 --> 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 --> 00:12:26.710 this let us to focus a set of these

NOTE Confidence: 0.798697412014008

00:12:26.710 --> 00:12:29.089 linear specific enhancer clusters or

NOTE Confidence: 0.798697412014008

00:12:29.089 --> 00:12:32.370 super enhancers as some people call it,

NOTE Confidence: 0.798697412014008

00:12:32.370 --> 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 --> 00:12:40.922 which is a includes iron transporter

NOTE Confidence: 0.798697412014008

00:12:40.922 --> 00:12:42.550 critical for hematopoietic cells.

NOTE Confidence: 0.798697412014008

00:12:42.550 --> 00:12:44.580 So as you can see,

NOTE Confidence: 0.798697412014008

00:12:44.580 --> 00:12:46.500 these tissue specific enhancer that

NOTE Confidence: 0.798697412014008

00:12:46.500 --> 00:12:48.925 are conserved between mouse and human

NOTE Confidence: 0.798697412014008

00:12:48.925 --> 00:12:51.160 are contains 3 individual enhancers

NOTE Confidence: 0.798697412014008

00:12:51.160 --> 00:12:52.948 that are virtually indistinguishable

NOTE Confidence: 0.798697412014008

00:12:53.008 --> 00:12:55.258 in terms of histone Marks and

NOTE Confidence: 0.798697412014008

00:12:55.258 --> 00:12:56.383 transcription factor binding.

NOTE Confidence: 0.798697412014008

00:12:56.390 --> 00:12:58.430 In this case got one.

NOTE Confidence: 0.798697412014008

00:12:58.430 --> 00:13:01.064 Inhuman amounts are extra cells so

NOTE Confidence: 0.798697412014008

00:13:01.064 --> 00:13:02.820 therefore the critical question

NOTE Confidence: 0.798697412014008

00:13:02.893 --> 00:13:05.875 we had initially was how do these

NOTE Confidence: 0.798697412014008

00:13:05.875 --> 00:13:07.153 individual constitute enhances

NOTE Confidence: 0.798697412014008

00:13:07.223 --> 00:13:09.018 contribute to the function of

NOTE Confidence: 0.798697412014008

00:13:09.018 --> 00:13:11.169 this super enhancer as a whole.

NOTE Confidence: 0.798697412014008

00:13:11.169 --> 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 --> 00:13:17.427 enhances and their combinations.

NOTE Confidence: 0.798697412014008

00:13:17.430 --> 00:13:20.046 We found that quite surprisingly that

NOTE Confidence: 0.798697412014008

00:13:20.046 --> 00:13:23.711 this thing has a seems to be organized

NOTE Confidence: 0.798697412014008

00:13:23.711 --> 00:13:26.471 as a functional hierarchy such that

NOTE Confidence: 0.798697412014008

00:13:26.553 --> 00:13:29.460 not card enhances 3 E 3 or the most.

NOTE Confidence: 0.798697412014008

00:13:29.460 --> 00:13:31.350 This thing has us completely

NOTE Confidence: 0.798697412014008

00:13:31.350 --> 00:13:32.862 abolished in has activity,

NOTE Confidence: 0.798697412014008

00:13:32.870 --> 00:13:34.765 whereas knockout the other two

NOTE Confidence: 0.798697412014008

00:13:34.765 --> 00:13:36.660 neighboring hazards had little effect.

NOTE Confidence: 0.798697412014008

00:13:36.660 --> 00:13:39.524 And this was also seen by others in

NOTE Confidence: 0.798697412014008

00:13:39.524 --> 00:13:41.967 different hazard clusters and cell types.

NOTE Confidence: 0.798697412014008

00:13:41.970 --> 00:13:44.539 So therefore the key question is what

NOTE Confidence: 0.798697412014008

00:13:44.539 --> 00:13:46.888 is unique about this enhanced E3?

NOTE Confidence: 0.798697412014008

00:13:46.890 --> 00:13:49.228 In fact they are hard to distinguish

NOTE Confidence: 0.798697412014008

00:13:49.228 --> 00:13:51.186 based on the chromatin features

NOTE Confidence: 0.798697412014008

00:13:51.186 --> 00:13:52.958 and how to identify.

NOTE Confidence: 0.798697412014008

00:13:52.960 --> 00:13:55.066 This seems to be functionally more

NOTE Confidence: 0.798697412014008

00:13:55.066 --> 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 --> 00:14:01.765 This list another important question

NOTE Confidence: 0.798697412014008

00:14:01.765 --> 00:14:04.210 that we've been studying is how

NOTE Confidence: 0.798697412014008

00:14:04.210 --> 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 --> 00:14:11.196 In, in, in, in prime itself.

NOTE Confidence: 0.798697412014008

00:14:11.200 --> 00:14:14.469 So you attempt to address this question.

NOTE Confidence: 0.798697412014008

00:14:14.470 --> 00:14:17.646 We thought that we will ideally be able

NOTE Confidence: 0.798697412014008

00:14:17.646 --> 00:14:20.698 to isolating hazard from this native

NOTE Confidence: 0.798697412014008

00:14:20.698 --> 00:14:22.874 quality environment and bisector.

NOTE Confidence: 0.798697412014008

00:14:22.880 --> 00:14:24.335 Regularly composed compositions.

NOTE Confidence: 0.798697412014008

00:14:24.335 --> 00:14:27.245 So we ended up engineering are

NOTE Confidence: 0.798697412014008

00:14:27.245 --> 00:14:29.552 inside your capture assay by

NOTE Confidence: 0.798697412014008

00:14:29.552 --> 00:14:31.742 leveraging CRISPR CAS 9 technology.

NOTE Confidence: 0.798697412014008

00:14:31.750 --> 00:14:35.638 So briefly many of new by combining a

NOTE Confidence: 0.798697412014008

00:14:35.638 --> 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 --> 00:14:45.370 The crisper cast 9 Rd CAS 9 can

NOTE Confidence: 0.798697412014008

00:14:45.370 --> 00:14:46.080 be targeted

NOTE Confidence: 0.77639240026474

00:14:46.163 --> 00:14:48.935 to the proximity of 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 --> 00:14:53.755 or other regulatory elements.

NOTE Confidence: 0.77639240026474

00:14:53.760 --> 00:14:55.488 We then met further

NOTE Confidence: 0.77639240026474

00:14:55.488 --> 00:14:57.216 modifications of the system,

NOTE Confidence: 0.77639240026474

00:14:57.220 --> 00:14:59.160 including adding an epitope tag

NOTE Confidence: 0.77639240026474

00:14:59.160 --> 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 --> 00:15:05.858 averaging biotin based application.

NOTE Confidence: 0.77639240026474

00:15:05.860 --> 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 --> 00:15:12.808 and determine has associated proteins.

NOTE Confidence: 0.77639240026474

00:15:12.810 --> 00:15:16.872 Amaze and DNA complexes by proteomics

NOTE Confidence: 0.77639240026474

00:15:16.872 --> 00:15:19.580 and next generation sequences.

NOTE Confidence: 0.77639240026474

00:15:19.580 --> 00:15:22.684 So as a proof of principle this approach

NOTE Confidence: 0.77639240026474

00:15:22.684 --> 00:15:25.140 we started with human telomeres,

NOTE Confidence: 0.77639240026474

00:15:25.140 --> 00:15:28.542 which contains many copies of repetitive's

NOTE Confidence: 0.77639240026474

00:15:28.542 --> 00:15:31.230 at telemetric repeat sequence that

NOTE Confidence: 0.77639240026474

00:15:31.230 --> 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 --> 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 --> 00:15:43.752 because now with the GOP molecule

NOTE Confidence: 0.77639240026474

00:15:43.752 --> 00:15:45.949 for example also by Q PCR,

NOTE Confidence: 0.77639240026474

00:15:45.950 --> 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 --> 00:15:51.825 ANAN more important by Western blot and

NOTE Confidence: 0.77639240026474

00:15:51.825 --> 00:15:54.507 subsequent in mass spec based pre omics.

NOTE Confidence: 0.77639240026474

00:15:54.510 --> 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 --> 00:16:00.058 associated proteins and many of the

NOTE Confidence: 0.77639240026474

00:16:00.058 --> 00:16:02.071 unknown factors that she annualizing

NOTE Confidence: 0.77639240026474

00:16:02.071 --> 00:16:04.285 to how telomere may be regulated.

NOTE Confidence: 0.77639240026474

00:16:04.290 --> 00:16:06.690 This is a highly repetitive sequences.

NOTE Confidence: 0.77639240026474

00:16:06.690 --> 00:16:08.690 What about a single copy?

NOTE Confidence: 0.77639240026474

00:16:08.690 --> 00:16:10.690 Locals in the human genome?

NOTE Confidence: 0.77639240026474

00:16:10.690 --> 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 --> 00:16:18.121 cluster as you know that these

NOTE Confidence: 0.77639240026474

00:16:18.121 --> 00:16:20.473 cluster contains a set of five beta

NOTE Confidence: 0.77639240026474

00:16:20.473 --> 00:16:23.061 like globin genes that undergoes

NOTE Confidence: 0.77639240026474

00:16:23.061 --> 00:16:24.699 developmental switching doing.

NOTE Confidence: 0.77639240026474

00:16:24.700 --> 00:16:26.665 Insurance cell differentiation and all

NOTE Confidence: 0.77639240026474

00:16:26.665 --> 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 --> 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 --> 00:16:39.040 So using a single godani that

NOTE Confidence: 0.77639240026474

00:16:39.040 --> 00:16:41.583 are designed to be specific for

NOTE Confidence: 0.77639240026474

00:16:41.583 --> 00:16:43.339 the three Prime HS,

NOTE Confidence: 0.77639240026474

00:16:43.340 --> 00:16:45.914 one insulator element we found by

NOTE Confidence: 0.77639240026474

00:16:45.914 --> 00:16:48.900 chip sequencing of the DCAS 9 capture

NOTE Confidence: 0.77639240026474

00:16:48.900 --> 00:16:51.686 DNA that only three primary chest one

NOTE Confidence: 0.77639240026474

00:16:51.766 --> 00:16:54.594 and no other regions and across loci,

NOTE Confidence: 0.77639240026474

00:16:54.600 --> 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 --> 00:17:02.368 you will see a single peak antagony

NOTE Confidence: 0.77639240026474

00:17:02.368 --> 00:17:04.935 HPP promoter regions we know in

NOTE Confidence: 0.77639240026474

00:17:04.935 --> 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 --> 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 --> 00:17:16.570 and that's exactly what we're seeing,

NOTE Confidence: 0.77639240026474

00:17:16.570 --> 00:17:19.307 and then we can simply by design

NOTE Confidence: 0.77639240026474

00:17:19.307 --> 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 --> 00:17:23.229 enhancers for example,

NOTE Confidence: 0.77639240026474

00:17:23.229 --> 00:17:25.980 and we can capture each individual enhances.

NOTE Confidence: 0.77639240026474

00:17:25.980 --> 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 --> 00:17:30.870 if we pull all these God honors

NOTE Confidence: 0.77639240026474

00:17:30.939 --> 00:17:32.853 together an echo expressing the same

NOTE Confidence: 0.77639240026474

00:17:32.853 --> 00:17:35.302 cell that we can capture all five

NOTE Confidence: 0.77639240026474

00:17:35.302 --> 00:17:37.142 enhancers suggestion that this system

NOTE Confidence: 0.77639240026474

00:17:37.142 --> 00:17:39.684 can be multiplexed to capture many

NOTE Confidence: 0.77639240026474

00:17:39.684 --> 00:17:43.600 enhances at the same time in the same cell.

NOTE Confidence: 0.77639240026474

00:17:43.600 --> 00:17:45.540 So based on these findings,

NOTE Confidence: 0.77639240026474

00:17:45.540 --> 00:17:46.964 but we went ahead,

NOTE Confidence: 0.77639240026474

00:17:46.964 --> 00:17:48.388 developed a capture proteomics

NOTE Confidence: 0.77639240026474

00:17:48.388 --> 00:17:50.200 to determine decathlon capture,

NOTE Confidence: 0.77639240026474

00:17:50.200 --> 00:17:52.378 look locals are specific podium and

NOTE Confidence: 0.77639240026474

00:17:52.378 --> 00:17:54.600 identify in this case again using

NOTE Confidence: 0.77639240026474

00:17:54.600 --> 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 --> 00:18:00.275 that are social with,

NOTE Confidence: 0.77639240026474

00:18:00.280 --> 00:18:02.536 for example HS2 enhance at the

NOTE Confidence: 0.77639240026474

00:18:02.536 --> 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 --> 00:18:08.121 I want a long beyond the four

NOTE Confidence: 0.77639240026474

00:18:08.121 --> 00:18:11.017 etc and but also some other new

NOTE Confidence: 0.77639240026474

00:18:11.017 --> 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 --> 00:18:19.417 and you can see some of these factors

NOTE Confidence: 0.778671443462372

00:18:19.417 --> 00:18:22.332 also present at the gamma globin gene

NOTE Confidence: 0.778671443462372

00:18:22.332 --> 00:18:25.433 promoters and other factors are present in.

NOTE Confidence: 0.778671443462372

00:18:25.440 --> 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 --> 00:18:33.539 evidence for the composition based

NOTE Confidence: 0.778671443462372

00:18:33.539 --> 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 --> 00:18:41.614 We all know that the human genome is

NOTE Confidence: 0.778671443462372

00:18:41.614 --> 00:18:44.018 organized into a multilayer structure.

NOTE Confidence: 0.778671443462372

00:18:44.020 --> 00:18:46.045 Units are organized by Long

NOTE Confidence: 0.778671443462372

00:18:46.045 --> 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 --> 00:18:50.500 so we never saw that.

NOTE Confidence: 0.778671443462372

00:18:50.500 --> 00:18:52.719 Can we combine this DCAS 9 capture

NOTE Confidence: 0.778671443462372

00:18:52.719 --> 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 --> 00:19:00.953 So the way it works is we first using

NOTE Confidence: 0.778671443462372

00:19:00.953 --> 00:19:03.833 in vivo bite Internet DCAS 9 to

NOTE Confidence: 0.778671443462372

00:19:03.833 --> 00:19:06.648 isolate enhances that you might be

NOTE Confidence: 0.778671443462372

00:19:06.648 --> 00:19:09.338 interested and Cromartie is crosslinked.

NOTE Confidence: 0.778671443462372

00:19:09.340 --> 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 --> 00:19:16.868 DPM two and this is followed

NOTE Confidence: 0.778671443462372

00:19:16.868 --> 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 --> 00:19:23.750 by fragmentation and then the

NOTE Confidence: 0.778671443462372

00:19:23.824 --> 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 --> 00:19:31.650 ANAN together with all the DF

NOTE Confidence: 0.778671443462372

00:19:31.650 --> 00:19:34.330 fragment that will really get it,

NOTE Confidence: 0.778671443462372

00:19:34.330 --> 00:19:36.808 and using pale and sequencing we

NOTE Confidence: 0.778671443462372

00:19:36.808 --> 00:19:39.556 can identify all the long range

NOTE Confidence: 0.778671443462372

00:19:39.556 --> 00:19:42.091 interactions that are social with

NOTE Confidence: 0.778671443462372

00:19:42.091 --> 00:19:44.626 this target enhances and more

NOTE Confidence: 0.778671443462372

00:19:44.626 --> 00:19:46.498 importantly by combining capture

NOTE Confidence: 0.778671443462372

00:19:46.498 --> 00:19:49.048 as we see analysis with capture.

NOTE Confidence: 0.778671443462372

00:19:49.048 --> 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 --> 00:19:54.528 What are the factors that might

NOTE Confidence: 0.778671443462372

00:19:54.528 --> 00:19:56.553 be responsible for this Sweetie

NOTE Confidence: 0.778671443462372

00:19:56.553 --> 00:19:57.719 Genome organization?

NOTE Confidence: 0.778671443462372

00:19:57.720 --> 00:20:00.205 This is just showing one of the

NOTE Confidence: 0.778671443462372

00:20:00.205 --> 00:20:02.887 example of the data how this works,

NOTE Confidence: 0.778671443462372

00:20:02.890 --> 00:20:05.170 so here we're showing capture 3C

NOTE Confidence: 0.778671443462372

00:20:05.170 --> 00:20:07.310 analysis for the active HP Gigi.

NOTE Confidence: 0.778671443462372

00:20:07.310 --> 00:20:09.900 This was done in Cape RC2 sales.

NOTE Confidence: 0.778671443462372

00:20:09.900 --> 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 --> 00:20:16.446 interactions with other six element

NOTE Confidence: 0.778671443462372

00:20:16.446 --> 00:20:19.140 across the low side but not the

NOTE Confidence: 0.778671443462372

00:20:19.140 --> 00:20:20.223 nearby repressed genes.

NOTE Confidence: 0.778671443462372

00:20:20.230 --> 00:20:22.323 But first I if you capture the

NOTE Confidence: 0.778671443462372

00:20:22.323 --> 00:20:24.426 repressions HPB you will see the

NOTE Confidence: 0.778671443462372

00:20:24.426 --> 00:20:26.336 HPV forms of predominant shorter

NOTE Confidence: 0.778671443462372

00:20:26.336 --> 00:20:28.064 range interactions and downstream

NOTE Confidence: 0.778671443462372

00:20:28.064 --> 00:20:29.856 sweeper matches one insulator.

NOTE Confidence: 0.778671443462372

00:20:29.860 --> 00:20:31.995 There's no interaction between active

NOTE Confidence: 0.778671443462372

00:20:31.995 --> 00:20:35.248 and repressed genes on when we capture this.

NOTE Confidence: 0.778671443462372

00:20:35.250 --> 00:20:37.285 We next capture each individual

NOTE Confidence: 0.778671443462372

00:20:37.285 --> 00:20:38.506 in hazard within,

NOTE Confidence: 0.778671443462372

00:20:38.510 --> 00:20:40.520 else are an interesting and we

NOTE Confidence: 0.778671443462372

00:20:40.520 --> 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 --> 00:20:47.489 then other nearby enhancers,

NOTE Confidence: 0.778671443462372

00:20:47.490 --> 00:20:49.250 including access to and.

NOTE Confidence: 0.778671443462372

00:20:49.250 --> 00:20:51.450 We further validated this using

NOTE Confidence: 0.778671443462372

00:20:51.450 --> 00:20:53.279 independent God honest and we

NOTE Confidence: 0.778671443462372

00:20:53.279 --> 00:20:55.259 notice that H3 has a consistently

NOTE Confidence: 0.778671443462372

00:20:55.326 --> 00:20:57.086 contained many more interactions

NOTE Confidence: 0.778671443462372

00:20:57.086 --> 00:20:59.726 than the nearby actions to enhance,

NOTE Confidence: 0.778671443462372

00:20:59.730 --> 00:21:02.467 and this was interesting to us because

NOTE Confidence: 0.778671443462372

00:21:02.467 --> 00:21:05.827 it's just too has been sought to be

NOTE Confidence: 0.778671443462372

00:21:05.827 --> 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 --> 00:21:13.040 to be important,

NOTE Confidence: 0.778671443462372

00:21:13.040 --> 00:21:16.168 but only in the context of native quality.

NOTE Confidence: 0.778671443462372

00:21:16.170 --> 00:21:18.642 So therefore our findings may help

NOTE Confidence: 0.778671443462372

00:21:18.642 --> 00:21:20.763 to explain these findings and

NOTE Confidence: 0.778671443462372

00:21:20.763 --> 00:21:23.151 support a model that the hierarchy

NOTE Confidence: 0.778671443462372

00:21:23.151 --> 00:21:25.473 organization with a beta globin LCR

NOTE Confidence: 0.778671443462372

00:21:25.473 --> 00:21:27.923 in which that itches to my function

NOTE Confidence: 0.778671443462372

00:21:27.930 --> 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 --> 00:21:35.767 yhs 3 might might be more important,

NOTE Confidence: 0.778671443462372

00:21:35.770 --> 00:21:38.584 immediate and long ranged in actions of.

NOTE Confidence: 0.778671443462372

00:21:38.590 --> 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 --> 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 --> 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 --> 00:21:54.308 so we think that this decathlon

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 --> 00:22:00.978 of this regulatory elements from

NOTE Confidence: 0.716553509235382

00:22:00.978 --> 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 --> 00:22:07.092 capture provides high specificity

NOTE Confidence: 0.716553509235382

00:22:07.092 --> 00:22:09.870 and sensitivity and this SGI based

NOTE Confidence: 0.716553509235382

00:22:09.946 --> 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 --> 00:22:16.806 in a minute and more importantly

NOTE Confidence: 0.716553509235382

00:22:16.806 --> 00:22:18.965 the simultaneous analysis of local

NOTE Confidence: 0.716553509235382

00:22:18.965 --> 00:22:21.440 specific proteome and 3D interactions.

NOTE Confidence: 0.716553509235382

00:22:21.440 --> 00:22:23.650 Help to establish causality and

NOTE Confidence: 0.716553509235382

00:22:23.650 --> 00:22:26.387 the system should be brought it

NOTE Confidence: 0.716553509235382

00:22:26.387 --> 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 --> 00:22:34.061 one of the major limitation of

NOTE Confidence: 0.716553509235382

00:22:34.061 --> 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 --> 00:22:40.746 and typically 10s of sometime

NOTE Confidence: 0.716553509235382

00:22:40.746 --> 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 --> 00:22:47.756 and thus was not applicable to primary

NOTE Confidence: 0.716553509235382

00:22:47.756 --> 00:22:50.138 cell types or male cell populations.

NOTE Confidence: 0.716553509235382

00:22:50.140 --> 00:22:52.548 So we wonder whether we could improve

NOTE Confidence: 0.716553509235382

00:22:52.548 --> 00:22:54.594 the design to increase capture

NOTE Confidence: 0.716553509235382

00:22:54.594 --> 00:22:57.426 efficiency so you know original design.

NOTE Confidence: 0.716553509235382

00:22:57.430 --> 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 --> 00:23:04.714 We just close to the nucleotide

NOTE Confidence: 0.716553509235382

00:23:04.714 --> 00:23:06.330 protein interacting pocket that

NOTE Confidence: 0.716553509235382

00:23:06.400 --> 00:23:08.068 might cause arepa tomaski,

NOTE Confidence: 0.716553509235382

00:23:08.070 --> 00:23:10.730 whereas the C terminus of CAS 9

NOTE Confidence: 0.716553509235382

00:23:10.730 --> 00:23:13.029 proteins largely exposed an unstructured.

NOTE Confidence: 0.716553509235382

00:23:13.030 --> 00:23:15.718 So we have tried tagging the seat

NOTE Confidence: 0.716553509235382

00:23:15.718 --> 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 --> 00:23:22.618 we use the conventional every tag

NOTE Confidence: 0.716553509235382

00:23:22.618 --> 00:23:25.176 together with the bacteria puje biotin

NOTE Confidence: 0.716553509235382

00:23:25.176 --> 00:23:27.480 ligase for in vivo bike nation.

NOTE Confidence: 0.716553509235382

00:23:27.480 --> 00:23:30.784 So this will make a three vector system.

NOTE Confidence: 0.716553509235382

00:23:30.790 --> 00:23:32.478 However there are other.

NOTE Confidence: 0.716553509235382

00:23:32.478 --> 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 --> 00:23:40.179 like is that expressing my man in

NOTE Confidence: 0.716553509235382

00:23:40.179 --> 00:23:42.349 sales so we have been testing some

NOTE Confidence: 0.716553509235382

00:23:42.350 --> 00:23:44.768 of those sequences and more recently

NOTE Confidence: 0.716553509235382

00:23:44.768 --> 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

NOTE Confidence: 0.716553509235382

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

NOTE Confidence: 0.716553509235382

00:23:51.192 --> 00:23:53.782 which may increase the signal to noise

NOTE Confidence: 0.716553509235382

00:23:53.848 --> 00:23:56.378 ratio for identification by proteomics.

NOTE Confidence: 0.716553509235382

00:23:56.380 --> 00:23:58.906 So we have been trying and

NOTE Confidence: 0.716553509235382

00:23:58.906 --> 00:24:01.310 adapting those systems for capture.

NOTE Confidence: 0.716553509235382

00:24:01.310 --> 00:24:03.638 So with this improved capture system

NOTE Confidence: 0.716553509235382

00:24:03.638 --> 00:24:05.720 with first attempted Multiplex capture,

NOTE Confidence: 0.716553509235382

00:24:05.720 --> 00:24:08.126 many answers in a single experiment,

NOTE Confidence: 0.716553509235382

00:24:08.130 --> 00:24:10.713 so we started with the LCI enhancer

NOTE Confidence: 0.716553509235382

00:24:10.713 --> 00:24:12.749 with 10 individual gardeners to

NOTE Confidence: 0.716553509235382

00:24:12.749 --> 00:24:15.759 capture all 5H S enhances and observe

NOTE Confidence: 0.716553509235382

00:24:15.759 --> 00:24:17.820 interactions social with all enhancers

NOTE Confidence: 0.716553509235382

00:24:17.820 --> 00:24:20.154 in a single experiment and more

NOTE Confidence: 0.716553509235382

00:24:20.160 --> 00:24:21.940 importantly you actually can resolve

NOTE Confidence: 0.716553509235382

00:24:21.940 --> 00:24:24.970 this data into a single enhancer resolution.

NOTE Confidence: 0.716553509235382

00:24:24.970 --> 00:24:27.376 Look at what other enhancer mediated

NOTE Confidence: 0.716553509235382

00:24:27.376 --> 00:24:28.980 by each individual enhances,

NOTE Confidence: 0.716553509235382

00:24:28.980 --> 00:24:30.588 as you may recall,

NOTE Confidence: 0.716553509235382

00:24:30.588 --> 00:24:33.000 the pattern looks almost the same.

NOTE Confidence: 0.716553509235382

00:24:33.000 --> 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 --> 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 --> 00:24:42.266 We tend the native permitting architecture.

NOTE Confidence: 0.716553509235382

00:24:42.270 --> 00:24:43.978 So based on this,

NOTE Confidence: 0.716553509235382

00:24:43.978 --> 00:24:46.540 we next performed much less capture

NOTE Confidence: 0.716553509235382

00:24:46.623 --> 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 --> 00:24:54.370 and in this experiment we use nearly

NOTE Confidence: 0.716553509235382

00:24:54.370 --> 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

NOTE Confidence: 0.716553509235382

00:24:59.586 --> 00:25:02.570 more than 800 individual enhances.

NOTE Confidence: 0.716553509235382

00:25:02.570 --> 00:25:04.274 A very large panel.

NOTE Confidence: 0.716553509235382

00:25:04.274 --> 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 --> 00:25:13.270 enhances in a single experiment.

NOTE Confidence: 0.716553509235382

00:25:13.270 --> 00:25:15.545 So with these high resolution

NOTE Confidence: 0.716553509235382

00:25:15.545 --> 00:25:16.455 multiplus capture,

NOTE Confidence: 0.823797523975372

00:25:16.460 --> 00:25:19.280 we notice that some interesting features

NOTE Confidence: 0.823797523975372

00:25:19.280 --> 00:25:21.631 about this special configuration of

NOTE Confidence: 0.823797523975372

00:25:21.631 --> 00:25:23.281 these super enhancers, specifically,

NOTE Confidence: 0.823797523975372

00:25:23.281 --> 00:25:26.368 we can often identify one or few

NOTE Confidence: 0.823797523975372

00:25:26.368 --> 00:25:28.796 enhances within a super enhancer

NOTE Confidence: 0.823797523975372

00:25:28.796 --> 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.

NOTE Confidence: 0.823797523975372

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

NOTE Confidence: 0.823797523975372

00:25:38.320 --> 00:25:40.145 We further developed a computational

NOTE Confidence: 0.823797523975372

00:25:40.145 --> 00:25:42.352 workflow and a fund at about

NOTE Confidence: 0.823797523975372

00:25:42.352 --> 00:25:44.242 1/4 of the Super enhancers are

NOTE Confidence: 0.823797523975372

00:25:44.242 --> 00:25:46.422 organized as a hierarchy structure

NOTE Confidence: 0.823797523975372

00:25:46.422 --> 00:25:48.168 containing hopping answers,

NOTE Confidence: 0.823797523975372

00:25:48.170 --> 00:25:50.543 and here just showing a snapshot of

NOTE Confidence: 0.823797523975372

00:25:50.543 --> 00:25:53.334 1 example of a hierarchy of super

NOTE Confidence: 0.823797523975372

00:25:53.334 --> 00:25:55.454 enhancer that contains a hopping

NOTE Confidence: 0.823797523975372

00:25:55.454 --> 00:25:58.374 answer that you can see that has

NOTE Confidence: 0.823797523975372

00:25:58.374 --> 00:25:59.986 more frequent interactions with

NOTE Confidence: 0.823797523975372

00:25:59.990 --> 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 --> 00:26:06.053 and what I won't show you the

NOTE Confidence: 0.823797523975372

00:26:06.053 --> 00:26:08.499 data we actually went ahead using

NOTE Confidence: 0.823797523975372

00:26:08.499 --> 00:26:10.644 crisper cast 9 to knockout.

NOTE Confidence: 0.823797523975372

00:26:10.650 --> 00:26:12.546 These hopping hazard.

NOTE Confidence: 0.823797523975372

00:26:12.546 --> 00:26:16.970 Versus the nearby non hop enhances and

NOTE Confidence: 0.823797523975372

00:26:17.083 --> 00:26:20.875 almost all the time that we can see,

NOTE Confidence: 0.823797523975372

00:26:20.880 --> 00:26:23.848 knockout hopping has at least a more

NOTE Confidence: 0.823797523975372

00:26:23.848 --> 00:26:26.324 profound effect and target gene

NOTE Confidence: 0.823797523975372

00:26:26.324 --> 00:26:28.568 expression comparing to knockout

NOTE Confidence: 0.823797523975372

00:26:28.568 --> 00:26:31.397 an unhappy hazards suggestion that

NOTE Confidence: 0.823797523975372

00:26:31.397 --> 00:26:33.937 this enhancer might be functionally

NOTE Confidence: 0.823797523975372

00:26:33.937 --> 00:26:35.969 more potent enhances that.

NOTE Confidence: 0.823797523975372

00:26:35.970 --> 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 --> 00:26:44.070 So here we showcase our several

NOTE Confidence: 0.823797523975372

00:26:44.070 --> 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

NOTE Confidence: 0.823797523975372

00:26:50.219 --> 00:26:52.207 local specific quality interactions.

NOTE Confidence: 0.823797523975372

00:26:52.210 --> 00:26:54.527 We hope that the capture system can

NOTE Confidence: 0.823797523975372

00:26:54.527 --> 00:26:57.111 enable us to determine a special

NOTE Confidence: 0.823797523975372

00:26:57.111 --> 00:26:59.135 configuration enhances and their

NOTE Confidence: 0.823797523975372

00:26:59.135 --> 00:27:00.147 target genes,

NOTE Confidence: 0.823797523975372

00:27:00.150 --> 00:27:02.658 as well as a temporal regulation

NOTE Confidence: 0.823797523975372

00:27:02.658 --> 00:27:03.494 during development.

NOTE Confidence: 0.823797523975372

00:27:03.500 --> 00:27:04.541 So with this,

NOTE Confidence: 0.823797523975372

00:27:04.541 --> 00:27:07.544 we started to one of the next important

NOTE Confidence: 0.823797523975372

00:27:07.544 --> 00:27:11.488 question that that would be interested in is.

NOTE Confidence: 0.823797523975372

00:27:11.490 --> 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 --> 00:27:16.010 brushing?

NOTE Confidence: 0.823797523975372

00:27:16.010 --> 00:27:17.210 Inside to it,

NOTE Confidence: 0.823797523975372

00:27:17.210 --> 00:27:19.660 particularly doing in people development.

NOTE Confidence: 0.823797523975372

00:27:19.660 --> 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 --> 00:27:26.306 you can knockout this individual enhancers,

NOTE Confidence: 0.823797523975372

00:27:26.310 --> 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 --> 00:27:36.176 is so we thought that to address

NOTE Confidence: 0.823797523975372

00:27:36.176 --> 00:27:38.318 this we will need a tool that

NOTE Confidence: 0.823797523975372

00:27:38.395 --> 00:27:40.950 allow us to systematically bisector

NOTE Confidence: 0.823797523975372

00:27:40.950 --> 00:27:42.994 functional requirement of this

NOTE Confidence: 0.823797523975372

00:27:42.994 --> 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 --> 00:27:49.380 and such as human quality limits,

NOTE Confidence: 0.823797523975372

00:27:49.380 --> 00:27:50.264 differentiation so.

NOTE Confidence: 0.823797523975372

00:27:50.264 --> 00:27:52.916 We recently redesigned the Cast 9

NOTE Confidence: 0.823797523975372

00:27:52.916 --> 00:27:55.639 best so called epigenetic editing

NOTE Confidence: 0.823797523975372

00:27:55.639 --> 00:27:58.574 system that can efficiently perturb

NOTE Confidence: 0.823797523975372

00:27:58.574 --> 00:28:01.083 enhancer activities by modulating

NOTE Confidence: 0.823797523975372

00:28:01.083 --> 00:28:03.595 enhance associated chromatin features.

NOTE Confidence: 0.823797523975372

00:28:03.600 --> 00:28:06.942 Particularly careful and K 27 simulation

NOTE Confidence: 0.823797523975372

00:28:06.942 --> 00:28:09.170 specifically for enhanced activation,

NOTE Confidence: 0.823797523975372

00:28:09.170 --> 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 --> 00:28:14.740 assimilation within adapted,

NOTE Confidence: 0.823797523975372

00:28:14.740 --> 00:28:17.818 helping actimel Ms 2 on the

NOTE Confidence: 0.823797523975372

00:28:17.818 --> 00:28:20.880 SG and sequence to recruit.

NOTE Confidence: 0.823797523975372

00:28:20.880 --> 00:28:23.604 Another activated VP 64 similarly for

NOTE Confidence: 0.823797523975372

00:28:23.604 --> 00:28:26.119 the repression that refused the cast.

NOTE Confidence: 0.823797523975372

00:28:26.120 --> 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 --> 00:28:31.804 four born monogamous flashing

NOTE Confidence: 0.823797523975372

00:28:31.804 --> 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 --> 00:28:41.109 this system which we call increased

NOTE Confidence: 0.823797523975372

00:28:41.109 --> 00:28:43.969 by or increase for a or enhancer

NOTE Confidence: 0.823797523975372

00:28:43.969 --> 00:28:46.657 targeting increased bio quiz for a is

NOTE Confidence: 0.823797523975372

00:28:46.660 --> 00:28:48.865 that this system combines effectors

NOTE Confidence: 0.823797523975372

00:28:48.865 --> 00:28:51.070 with distinct mechanism for modulating.

NOTE Confidence: 0.823797523975372

00:28:51.070 --> 00:28:52.998 Enhancer associated genetic marks.

NOTE Confidence: 0.823797523975372

00:28:52.998 --> 00:28:56.350 So we have used this system in

NOTE Confidence: 0.823797523975372

00:28:56.350 --> 00:28:58.588 a variety of cell models and

NOTE Confidence: 0.823797523975372

00:28:58.588 --> 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 --> 00:29:06.260 system for enhancing perturbations.

NOTE Confidence: 0.78987539211909

00:29:06.260 --> 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 --> 00:29:20.404 under the docs inducible promoter

NOTE Confidence: 0.78987539211909

00:29:20.404 --> 00:29:23.732 in College in one in one low side.

NOTE Confidence: 0.78987539211909

00:29:23.740 --> 00:29:26.948 So we then developed by in Vivo Enhancer

NOTE Confidence: 0.78987539211909

00:29:26.948 --> 00:29:29.428 perturbation asset you then there's no

NOTE Confidence: 0.78987539211909

00:29:29.428 --> 00:29:31.834 key mouse to determine hazard function.

NOTE Confidence: 0.78987539211909

00:29:31.840 --> 00:29:34.129 Doing him at opposes so briefly the

NOTE Confidence: 0.78987539211909

00:29:34.129 --> 00:29:36.659 way it works is that we reasoned

NOTE Confidence: 0.78987539211909

00:29:36.659 --> 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 --> 00:29:43.589 followed by pulmonary transplantation.

NOTE Confidence: 0.78987539211909

00:29:43.590 --> 00:29:46.092 We could access the HSE deriving

NOTE Confidence: 0.78987539211909

00:29:46.092 --> 00:29:47.343 mature cell images.

NOTE Confidence: 0.78987539211909

00:29:47.350 --> 00:29:49.492 As a read out for the functional

NOTE Confidence: 0.78987539211909

00:29:49.492 --> 00:29:51.934 impact of he has a population

NOTE Confidence: 0.78987539211909

00:29:51.934 --> 00:29:53.874 doing HSC Danish differentiation.

NOTE Confidence: 0.78987539211909

00:29:53.880 --> 00:29:56.568 So that way you would do it.

NOTE Confidence: 0.78987539211909

00:29:56.570 --> 00:29:59.244 You will isolate him out of politics.

NOTE Confidence: 0.78987539211909

00:29:59.250 --> 00:30:01.180 Tampa general sales from this

NOTE Confidence: 0.78987539211909

00:30:01.180 --> 00:30:03.110 knocking Mouse and then transduced

NOTE Confidence: 0.78987539211909

00:30:03.170 --> 00:30:05.486 with God only library with Garnet

NOTE Confidence: 0.78987539211909

00:30:05.486 --> 00:30:07.030 design against each individual

NOTE Confidence: 0.78987539211909

00:30:07.091 --> 00:30:09.293 enhancer that you might be interested

NOTE Confidence: 0.78987539211909

00:30:09.293 --> 00:30:11.161 followed by bone marrow transplant.

NOTE Confidence: 0.78987539211909

00:30:11.161 --> 00:30:13.898 Then D Kastner Kara will be induced

NOTE Confidence: 0.78987539211909

00:30:13.898 --> 00:30:15.880 by docs admin administration in

NOTE Confidence: 0.78987539211909

00:30:15.880 --> 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

NOTE Confidence: 0.78987539211909

00:30:21.736 --> 00:30:24.896 mature cells cells and perform

NOTE Confidence: 0.78987539211909

00:30:24.896 --> 00:30:28.488 amplicon sequencing to determine.

NOTE Confidence: 0.78987539211909

00:30:28.490 --> 00:30:31.568 The abundance of SG and a in a starting

NOTE Confidence: 0.78987539211909

00:30:31.568 --> 00:30:34.303 population before transplant an the

NOTE Confidence: 0.78987539211909

00:30:34.303 --> 00:30:36.627 resulting population after transplantation.

NOTE Confidence: 0.78987539211909

00:30:36.630 --> 00:30:38.742 So as a proof of principle this we

NOTE Confidence: 0.78987539211909

00:30:38.742 --> 00:30:40.804 focus on several key hematopoietic

NOTE Confidence: 0.78987539211909

00:30:40.804 --> 00:30:42.768 transcription factors and their

NOTE Confidence: 0.78987539211909

00:30:42.768 --> 00:30:44.550 annotating enhances an and.

NOTE Confidence: 0.78987539211909

00:30:44.550 --> 00:30:46.832 Design multiplies got an A plus for

NOTE Confidence: 0.78987539211909

00:30:46.832 --> 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 --> 00:30:54.595 and locals as a first example which

NOTE Confidence: 0.78987539211909

00:30:54.595 --> 00:30:56.990 contains out for annotating hazards,

NOTE Confidence: 0.78987539211909

00:30:56.990 --> 00:30:59.524 look at it in a different upstream

NOTE Confidence: 0.78987539211909

00:30:59.524 --> 00:31:01.420 or downstream regions to the

NOTE Confidence: 0.78987539211909

00:31:01.420 --> 00:31:03.265 transcription start site by enhance

NOTE Confidence: 0.78987539211909

00:31:03.265 --> 00:31:05.280 in billing has a population.

NOTE Confidence: 0.78987539211909

00:31:05.280 --> 00:31:08.376 We found that SGML for CDL 4 plus.

NOTE Confidence: 0.78987539211909

00:31:08.380 --> 00:31:10.196 So disable.

NOTE Confidence: 0.78987539211909

00:31:10.196 --> 00:31:16.552 Enhancer all year for Enhancer in this.

NOTE Confidence: 0.78987539211909

00:31:16.560 --> 00:31:18.685 A significantly depleted in mylow

NOTE Confidence: 0.78987539211909

00:31:18.685 --> 00:31:21.370 cells but not in B&T cells.

NOTE Confidence: 0.78987539211909

00:31:21.370 --> 00:31:22.726 This is interesting,

NOTE Confidence: 0.78987539211909

00:31:22.726 --> 00:31:25.438 as previously has been shown that

NOTE Confidence: 0.78987539211909

00:31:25.438 --> 00:31:28.760 CBF on gene knockout 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 --> 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 --> 00:31:37.976 so our result not only validate

NOTE Confidence: 0.78987539211909

00:31:37.976 --> 00:31:38.850 these findings,

NOTE Confidence: 0.78987539211909

00:31:38.850 --> 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 --> 00:31:46.769 showing over here are also important.

NOTE Confidence: 0.78987539211909

00:31:46.770 --> 00:31:47.802 For modeling differentiation,

NOTE Confidence: 0.78987539211909

00:31:47.802 --> 00:31:49.866 but the other two enhancer seems

NOTE Confidence: 0.78987539211909

00:31:49.866 --> 00:31:51.169 to be indispensable,

NOTE Confidence: 0.78987539211909

00:31:51.170 --> 00:31:54.682 and none of these enhancer seems to be

NOTE Confidence: 0.78987539211909

00:31:54.682 --> 00:31:57.419 important for B&T cell development.

NOTE Confidence: 0.78987539211909

00:31:57.420 --> 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 --> 00:32:05.164 and we observed this gene has a single

NOTE Confidence: 0.78987539211909

00:32:05.164 --> 00:32:07.219 enhancer located at 14 KP option.

NOTE Confidence: 0.78987539211909

00:32:07.220 --> 00:32:09.782 With this gene we notice that the

NOTE Confidence: 0.78987539211909

00:32:09.782 --> 00:32:11.767 three independent guard on it

NOTE Confidence: 0.78987539211909

00:32:11.767 --> 00:32:13.411 against its enhancer significantly

NOTE Confidence: 0.78987539211909

00:32:13.411 --> 00:32:15.890 depleted in my loiselle and B cells,

NOTE Confidence: 0.78987539211909

00:32:15.890 --> 00:32:18.917 but not in T cells, and this result,

NOTE Confidence: 0.78987539211909

00:32:18.917 --> 00:32:21.930 again are consistent with the role of SPI.

NOTE Confidence: 0.78987539211909

00:32:21.930 --> 00:32:24.562 One Pu .1 for normal Milo and

NOTE Confidence: 0.78987539211909

00:32:24.562 --> 00:32:25.314 busier development,

NOTE Confidence: 0.78987539211909

00:32:25.320 --> 00:32:28.254 but not for teacher development, so again.

NOTE Confidence: 0.78987539211909

00:32:28.254 --> 00:32:31.943 I did that this initial genetic studies.

NOTE Confidence: 0.830534815788269

00:32:31.950 --> 00:32:34.470 Using mouse models.

NOTE Confidence: 0.830534815788269

00:32:34.470 --> 00:32:37.152 And next time I want to show is that

NOTE Confidence: 0.830534815788269

00:32:37.152 --> 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 --> 00:32:42.847 transcription start site with three

NOTE Confidence: 0.830534815788269

00:32:42.847 --> 00:32:44.547 enhancers at different genomic regions.

NOTE Confidence: 0.830534815788269

00:32:44.550 --> 00:32:46.762 Again using this perturbation we find that

NOTE Confidence: 0.830534815788269

00:32:46.762 --> 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,

NOTE Confidence: 0.830534815788269

00:32:51.270 --> 00:32:52.950 but the promoter garden is

NOTE Confidence: 0.830534815788269

00:32:52.950 --> 00:32:55.022 somewhat you reached in my low

NOTE Confidence: 0.830534815788269

00:32:55.022 --> 00:32:56.978 self but depleted and B&T cells,

NOTE Confidence: 0.830534815788269

00:32:56.980 --> 00:32:59.668 so this is one of the first example.

NOTE Confidence: 0.830534815788269

00:32:59.670 --> 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 --> 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 --> 00:33:10.210 Has shown to to develop Mylar

NOTE Confidence: 0.830534815788269

00:33:10.210 --> 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 --> 00:33:20.890 maturation so therefore our results

NOTE Confidence: 0.830534815788269

00:33:20.985 --> 00:33:23.730 also consistent with this and

NOTE Confidence: 0.830534815788269

00:33:23.730 --> 00:33:26.475 recapture the phenotype of ranks.

NOTE Confidence: 0.830534815788269

00:33:26.480 --> 00:33:29.360 One deficiency showcasing that this

NOTE Confidence: 0.830534815788269

00:33:29.360 --> 00:33:32.910 crisp Ohio increased by best epigenetic

NOTE Confidence: 0.830534815788269

00:33:32.910 --> 00:33:36.928 editing and can be convenient assay too.

NOTE Confidence: 0.830534815788269

00:33:36.930 --> 00:33:38.782 Isaca regulatory elements that

NOTE Confidence: 0.830534815788269

00:33:38.782 --> 00:33:41.097 are required for this linear

NOTE Confidence: 0.830534815788269

00:33:41.097 --> 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 --> 00:33:46.336 we perform a Multiplex perturbation

NOTE Confidence: 0.830534815788269

00:33:46.336 --> 00:33:48.871 by pulling all the God are

NOTE Confidence: 0.830534815788269

00:33:48.871 --> 00:33:50.686 made in a single experiment.

NOTE Confidence: 0.830534815788269

00:33:50.690 --> 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 --> 00:33:57.559 different enhancers and promoters that

NOTE Confidence: 0.830534815788269

00:33:57.559 --> 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 --> 00:34:04.172 for example with Dan Ified 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 --> 00:34:10.850 while ranks one enhancer promoters

NOTE Confidence: 0.830534815788269

00:34:10.850 --> 00:34:12.950 are required for PMT sales.

NOTE Confidence: 0.830534815788269

00:34:12.950 --> 00:34:15.130 Therefore, this enhanced CRISPR editing.

NOTE Confidence: 0.830534815788269

00:34:15.130 --> 00:34:18.021 I could provide a useful tool for

NOTE Confidence: 0.830534815788269

00:34:18.021 --> 00:34:19.817 functional interrogation of SIS

NOTE Confidence: 0.830534815788269

00:34:19.817 --> 00:34:21.741 element doing illegal development

NOTE Confidence: 0.830534815788269

00:34:21.741 --> 00:34:24.146 and more importantly by combining

NOTE Confidence: 0.830534815788269

00:34:24.221 --> 00:34:26.286 these knocking mouse model with

NOTE Confidence: 0.830534815788269

00:34:26.286 --> 00:34:28.825 other disease models we might be

NOTE Confidence: 0.830534815788269

00:34:28.825 --> 00:34:31.150 able to study enhancer function

NOTE Confidence: 0.830534815788269

00:34:31.150 --> 00:34:33.010 doing different biological process

NOTE Confidence: 0.830534815788269

00:34:33.084 --> 00:34:35.550 of pathological process and this is

NOTE Confidence: 0.830534815788269

00:34:35.550 --> 00:34:38.128 something that we're very excited about

NOTE Confidence: 0.830534815788269

00:34:38.128 --> 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 --> 00:34:45.310 store might be useful for their

NOTE Confidence: 0.830534815788269

00:34:45.394 --> 00:34:47.389 respective disease models.

NOTE Confidence: 0.830534815788269

00:34:47.390 --> 00:34:51.458 So as a brief summary for for this part,

NOTE Confidence: 0.830534815788269

00:34:51.460 --> 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 --> 00:34:55.974 disease,

NOTE Confidence: 0.830534815788269

00:34:55.974 --> 00:34:57.782 phenotype and undergoes profound

NOTE Confidence: 0.830534815788269

00:34:57.782 --> 00:34:59.138 turnover during development.

NOTE Confidence: 0.830534815788269

00:34:59.140 --> 00:35:01.996 We've developed the Constine best capture

NOTE Confidence: 0.830534815788269

00:35:01.996 --> 00:35:04.569 tools for multimeric analysis of local,

NOTE Confidence: 0.830534815788269

00:35:04.570 --> 00:35:05.923 specific quality interactions.

NOTE Confidence: 0.830534815788269

00:35:05.923 --> 00:35:08.178 We also redesign enhancing target,

NOTE Confidence: 0.830534815788269

00:35:08.180 --> 00:35:10.255 increase pain response system that

NOTE Confidence: 0.830534815788269

00:35:10.255 --> 00:35:12.330 will enable in vivo functional

NOTE Confidence: 0.830534815788269

00:35:12.398 --> 00:35:14.060 interrogation of enhancer.

NOTE Confidence: 0.830534815788269

00:35:14.060 --> 00:35:17.708 As we have other success element doing in.

NOTE Confidence: 0.830534815788269

00:35:17.710 --> 00:35:19.265 We want development and we're

NOTE Confidence: 0.830534815788269

00:35:19.265 --> 00:35:21.595 happy to share the tools or the

NOTE Confidence: 0.830534815788269

00:35:21.595 --> 00:35:23.365 construct has been deposited action.

NOTE Confidence: 0.830534815788269

00:35:23.370 --> 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 --> 00:35:29.530 feel free to reach out.

NOTE Confidence: 0.830534815788269

00:35:29.530 --> 00:35:32.314 So in the last few minutes I want

NOTE Confidence: 0.830534815788269

00:35:32.314 --> 00:35:35.278 to switch gears a little bit and I

NOTE Confidence: 0.830534815788269

00:35:35.278 --> 00:35:38.035 want to discuss some of the recent

NOTE Confidence: 0.830534815788269

00:35:38.035 --> 00:35:40.870 effort we trying to address the last

NOTE Confidence: 0.830534815788269

00:35:40.870 --> 00:35:43.054 question that is how to pathological

NOTE Confidence: 0.830534815788269

00:35:43.054 --> 00:35:45.030 enhance alterations contribute to diseases,

NOTE Confidence: 0.830534815788269

00:35:45.030 --> 00:35:47.500 particularly the development block answers.

NOTE Confidence: 0.830534815788269

00:35:47.500 --> 00:35:48.712 As we know,

NOTE Confidence: 0.830534815788269

00:35:48.712 --> 00:35:51.540 much of our knowledge on cancer driver

NOTE Confidence: 0.830534815788269

00:35:51.629 --> 00:35:54.259 mutations is based on alterations

NOTE Confidence: 0.830534815788269

00:35:54.259 --> 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 --> 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 --> 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 --> 00:36:09.410 So we started this rather

NOTE Confidence: 0.830534815788269

00:36:09.410 --> 00:36:11.800 ambitious project several years ago

NOTE Confidence: 0.803040623664856

00:36:11.884 --> 00:36:14.626 with the goal to identify leukemia,

NOTE Confidence: 0.803040623664856

00:36:14.630 --> 00:36:16.139 associating handsome mutations

NOTE Confidence: 0.803040623664856

00:36:16.139 --> 00:36:17.648 by targeted sequencing.

NOTE Confidence: 0.803040623664856

00:36:17.650 --> 00:36:21.097 So the way it works is that we first

NOTE Confidence: 0.803040623664856

00:36:21.097 --> 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 --> 00:36:30.216 just like everybody else is doing that,

NOTE Confidence: 0.803040623664856

00:36:30.220 --> 00:36:33.820 I introduced earlier and then we can gather.

NOTE Confidence: 0.803040623664856

00:36:33.820 --> 00:36:36.472 This game is almost twenty 2000s

NOTE Confidence: 0.803040623664856

00:36:36.472 --> 00:36:38.857 of enhancers that are present

NOTE Confidence: 0.803040623664856

00:36:38.857 --> 00:36:41.517 in variety of different normal.

NOTE Confidence: 0.803040623664856

00:36:41.520 --> 00:36:44.292 Gmail cell lines that we have gathered

NOTE Confidence: 0.803040623664856

00:36:44.292 --> 00:36:47.908 and then we can design target sequencing

NOTE Confidence: 0.803040623664856

00:36:47.908 --> 00:36:50.252 panel to specifically resequence

NOTE Confidence: 0.803040623664856

00:36:50.252 --> 00:36:53.379 the enhancer sequences in a panel

NOTE Confidence: 0.803040623664856

00:36:53.379 --> 00:36:55.247 of human hematopoietic malignancy

NOTE Confidence: 0.803040623664856

00:36:55.247 --> 00:36:58.142 is a particularly in an email.

NOTE Confidence: 0.803040623664856

00:36:58.142 --> 00:36:59.606 An NDS conditions.

NOTE Confidence: 0.803040623664856

00:36:59.610 --> 00:37:02.622 We also included some informal samples

NOTE Confidence: 0.803040623664856

00:37:02.622 --> 00:37:04.990 an acute lymphoblastic leukemia and,

NOTE Confidence: 0.803040623664856

00:37:04.990 --> 00:37:07.930 importantly, thirty. One of these samples.

NOTE Confidence: 0.803040623664856

00:37:07.930 --> 00:37:10.370 We actually have tumor normal

NOTE Confidence: 0.803040623664856

00:37:10.370 --> 00:37:12.322 pairs that we can.

NOTE Confidence: 0.803040623664856

00:37:12.330 --> 00:37:14.082 Identify somatic mutations in

NOTE Confidence: 0.803040623664856

00:37:14.082 --> 00:37:16.710 the in the non coding Gina.

NOTE Confidence: 0.803040623664856

00:37:16.710 --> 00:37:19.851 Pen and if you do this and like other

NOTE Confidence: 0.803040623664856

00:37:19.851 --> 00:37:22.309 people doing a protein coding sequence

NOTE Confidence: 0.803040623664856

00:37:22.309 --> 00:37:25.752 as well you you can easily identify

NOTE Confidence: 0.803040623664856

00:37:25.752 --> 00:37:29.097 thousands of recurrently mutated mutations.

NOTE Confidence: 0.803040623664856

00:37:29.100 --> 00:37:31.302 In this case we identify almost

NOTE Confidence: 0.803040623664856

00:37:31.302 --> 00:37:33.516 slightly over a 4000 frequently

NOTE Confidence: 0.803040623664856

00:37:33.516 --> 00:37:35.529 mutated noncoding elements.

NOTE Confidence: 0.803040623664856

00:37:35.530 --> 00:37:38.687 We call them mutational Hotspot Ann and

NOTE Confidence: 0.803040623664856

00:37:38.687 --> 00:37:41.497 these overlays about 1800 enhances that

NOTE Confidence: 0.803040623664856

00:37:41.497 --> 00:37:44.710 we have identified from the initial steps.

NOTE Confidence: 0.803040623664856

00:37:44.710 --> 00:37:47.015 So these are the enhancement

NOTE Confidence: 0.803040623664856

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 --> 00:37:51.656 human hematopoietic malignancy.

NOTE Confidence: 0.803040623664856

00:37:51.660 --> 00:37:54.924 The key question is and the key challenges.

NOTE Confidence: 0.803040623664856

00:37:54.930 --> 00:37:57.457 How do you know whether they are

NOTE Confidence: 0.803040623664856

00:37:57.457 --> 00:38:00.855 functional an what is how to access their

NOTE Confidence: 0.803040623664856

00:38:00.855 --> 00:38:03.090 functional roles in cancer pathogenesis?

NOTE Confidence: 0.803040623664856

00:38:03.090 --> 00:38:05.428 So Fortunately with the crisper a quiz

NOTE Confidence: 0.803040623664856

00:38:05.428 --> 00:38:07.985 by system that we have engineered that

NOTE Confidence: 0.803040623664856

00:38:07.985 --> 00:38:10.217 especially for enhances so we could

NOTE Confidence: 0.803040623664856

00:38:10.283 --> 00:38:12.803 perform a functional interrogation of

NOTE Confidence: 0.803040623664856

00:38:12.803 --> 00:38:15.323 functional perturbation screens using God.

NOTE Confidence: 0.803040623664856

00:38:15.330 --> 00:38:17.380 RNAs that are designed to

NOTE Confidence: 0.803040623664856

00:38:17.380 --> 00:38:18.610 target this enhances.

NOTE Confidence: 0.803040623664856

00:38:18.610 --> 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.

NOTE Confidence: 0.803040623664856

00:38:22.770 --> 00:38:26.170 And by this we can identify hundreds of

NOTE Confidence: 0.803040623664856

00:38:26.170 --> 00:38:29.425 enhances that seems to be a putative tumor.

NOTE Confidence: 0.803040623664856

00:38:29.430 --> 00:38:31.090 Suppressive or uncle genic.

NOTE Confidence: 0.803040623664856

00:38:31.090 --> 00:38:32.335 In other ways,

NOTE Confidence: 0.803040623664856

00:38:32.340 --> 00:38:35.211 we use cell growth as a reader so that

NOTE Confidence: 0.803040623664856

00:38:35.211 --> 00:38:37.799 that perturbation of this enhances often

NOTE Confidence: 0.803040623664856

00:38:37.799 --> 00:38:41.016 can lead to an enhanced or inhibited

NOTE Confidence: 0.803040623664856

00:38:41.016 --> 00:38:43.866 cell growth phenotype and this really

NOTE Confidence: 0.803040623664856

00:38:43.866 --> 00:38:46.508 have provided a number of candidate

NOTE Confidence: 0.803040623664856

00:38:46.508 --> 00:38:48.618 enhances an associated genetic loci.

NOTE Confidence: 0.803040623664856

00:38:48.620 --> 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 --> 00:38:55.576 of the enhancer that we follow up

NOTE Confidence: 0.803040623664856

00:38:55.576 --> 00:38:57.793 with more detailed analysis and

NOTE Confidence: 0.803040623664856

00:38:57.793 --> 00:39:00.088 this enhances located about 150

NOTE Confidence: 0.803040623664856

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

NOTE Confidence: 0.803040623664856

00:39:02.664 --> 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 --> 00:39:08.722 and by chromatin profiling and 3D

NOTE Confidence: 0.803040623664856

00:39:08.722 --> 00:39:09.868 chromatin confirmation capture.

NOTE Confidence: 0.803040623664856

00:39:09.870 --> 00:39:12.622 We found this thing has it seems to

NOTE Confidence: 0.803040623664856

00:39:12.622 --> 00:39:14.752 be physically interact with Akira's

NOTE Confidence: 0.803040623664856

00:39:14.752 --> 00:39:17.488 promoter regions which is located about

NOTE Confidence: 0.803040623664856

00:39:17.488 --> 00:39:20.197 150 KB downstream of this enhancer.

NOTE Confidence: 0.803040623664856

00:39:20.200 --> 00:39:21.277 And more importantly,

NOTE Confidence: 0.803040623664856

00:39:21.277 --> 00:39:24.890 when we use CRISPR CAS 9 to knockout this,

NOTE Confidence: 0.803040623664856

00:39:24.890 --> 00:39:27.042 he has a in a leukemia cell line

NOTE Confidence: 0.803040623664856

00:39:27.042 --> 00:39:29.787 and we found that Carros expression

NOTE Confidence: 0.803040623664856

00:39:29.787 --> 00:39:31.923 was significantly down regulated.

NOTE Confidence: 0.803040623664856

00:39:31.930 --> 00:39:34.478 But none of these other genes within

NOTE Confidence: 0.803040623664856

00:39:34.478 --> 00:39:36.080 the same neighborhood affected

NOTE Confidence: 0.803040623664856

00:39:36.080 --> 00:39:37.400 suggestion at this.

NOTE Confidence: 0.803040623664856

00:39:37.400 --> 00:39:39.612 Enhancer is selectively required

NOTE Confidence: 0.803040623664856

00:39:39.612 --> 00:39:42.377 for the expression of casting.

NOTE Confidence: 0.803040623664856

00:39:42.380 --> 00:39:45.344 So is this was interesting because

NOTE Confidence: 0.803040623664856

00:39:45.344 --> 00:39:47.680 unlike any grass care US,

NOTE Confidence: 0.803040623664856

00:39:47.680 --> 00:39:50.090 protein coding mutations are rarely

NOTE Confidence: 0.803040623664856

00:39:50.090 --> 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 --> 00:39:57.160 high level of care as expression in

NOTE Confidence: 0.757966220378876

00:39:57.253 --> 00:40:00.103 AML is associated with poor survival

NOTE Confidence: 0.757966220378876

00:40:00.103 --> 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 --> 00:40:09.128 potential functional enhancer that

NOTE Confidence: 0.757966220378876

00:40:09.128 --> 00:40:12.724 plays a role in a male biology. So too.

NOTE Confidence: 0.757966220378876

00:40:12.724 --> 00:40:15.084 Establish the functionality of whether

NOTE Confidence: 0.757966220378876

00:40:15.084 --> 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 --> 00:40:24.936 This is Daniels is selling called Mkpo

NOTE Confidence: 0.757966220378876

00:40:24.936 --> 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 --> 00:40:33.479 blood of the Xeno graft recipient.

NOTE Confidence: 0.757966220378876

00:40:33.480 --> 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 --> 00:40:39.647 Okok looms as a control,

NOTE Confidence: 0.757966220378876

00:40:39.650 --> 00:40:41.910 we also knockout the carrots

NOTE Confidence: 0.757966220378876

00:40:41.910 --> 00:40:43.266 protein coding gene.

NOTE Confidence: 0.757966220378876

00:40:43.270 --> 00:40:46.822 And we see that he has a knockout

NOTE Confidence: 0.757966220378876

00:40:46.822 --> 00:40:49.376 almost recalculate the care as GM

NOTE Confidence: 0.757966220378876

00:40:49.376 --> 00:40:51.734 lockout in this access and just

NOTE Confidence: 0.757966220378876

00:40:51.825 --> 00:40:54.645 showing more data showing that this

NOTE Confidence: 0.757966220378876

00:40:54.645 --> 00:40:57.422 is reflected by Les Plus constant

NOTE Confidence: 0.757966220378876

00:40:57.422 --> 00:41:00.098 prefer block as well as less.

NOTE Confidence: 0.757966220378876

00:41:00.100 --> 00:41:02.764 And number of frequency of the

NOTE Confidence: 0.757966220378876

00:41:02.764 --> 00:41:05.036 Premier sales in xenograft animals

NOTE Confidence: 0.757966220378876

00:41:05.036 --> 00:41:07.508 in the bone marrow and blood.

NOTE Confidence: 0.757966220378876

00:41:07.510 --> 00:41:10.006 So this result demonstrator care us

NOTE Confidence: 0.757966220378876

00:41:10.006 --> 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 --> 00:41:17.060 grows in virtual and an illegal.

NOTE Confidence: 0.757966220378876

00:41:17.060 --> 00:41:19.130 So then we went ahead.

NOTE Confidence: 0.757966220378876

00:41:19.130 --> 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 --> 00:41:26.045 we found the AML patient highly

NOTE Confidence: 0.757966220378876

00:41:26.045 --> 00:41:27.728 colocalized with binding site

NOTE Confidence: 0.757966220378876

00:41:27.728 --> 00:41:29.868 of interest in nuclear hormone

NOTE Confidence: 0.757966220378876

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

NOTE Confidence: 0.757966220378876

00:41:31.580 --> 00:41:34.996 gamma and ice are showing over here.

NOTE Confidence: 0.757966220378876

00:41:35.000 --> 00:41:37.322 I'm so interested in the cameras

NOTE Confidence: 0.757966220378876

00:41:37.322 --> 00:41:40.241 in has are also found in has

NOTE Confidence: 0.757966220378876

00:41:40.241 --> 00:41:42.809 mutations are also found in other

NOTE Confidence: 0.757966220378876

00:41:42.809 --> 00:41:45.575 cancer types based on TCG and pain.

NOTE Confidence: 0.757966220378876

00:41:45.580 --> 00:41:48.072 Cancer pan cancer data set here showing

NOTE Confidence: 0.757966220378876

00:41:48.072 --> 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 --> 00:41:55.344 many recovery mutations.

NOTE Confidence: 0.757966220378876

00:41:55.350 --> 00:41:57.672 Many of these mutations are also

NOTE Confidence: 0.757966220378876

00:41:57.672 --> 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 --> 00:42:02.686 and this was interesting as nuclear

NOTE Confidence: 0.757966220378876

00:42:02.686 --> 00:42:04.722 hormones are family of lichen

NOTE Confidence: 0.757966220378876

00:42:04.722 --> 00:42:05.938 regulated transcription.

NOTE Confidence: 0.757966220378876

00:42:05.940 --> 00:42:09.108 Factors that are activated by hormones,

NOTE Confidence: 0.757966220378876

00:42:09.110 --> 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 --> 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 --> 00:42:22.308 derepression appan liggen binding.

NOTE Confidence: 0.757966220378876

00:42:22.310 --> 00:42:25.340 This time are actually cutco

NOTE Confidence: 0.757966220378876

00:42:25.340 --> 00:42:27.158 activist coactivators through

NOTE Confidence: 0.757966220378876

00:42:27.158 --> 00:42:28.370 activating transcription.

NOTE Confidence: 0.757966220378876

00:42:28.370 --> 00:42:30.830 So we wonder whether cameras enhance

NOTE Confidence: 0.757966220378876

00:42:30.830 --> 00:42:33.112 it might actually be regulated

NOTE Confidence: 0.757966220378876

00:42:33.112 --> 00:42:35.360 by nuclear hormone signaling,

NOTE Confidence: 0.757966220378876

00:42:35.360 --> 00:42:38.874 so to validate days we perform chip

NOTE Confidence: 0.757966220378876

00:42:38.874 --> 00:42:41.321 sequencing analysis in multiple AML

NOTE Confidence: 0.757966220378876

00:42:41.321 --> 00:42:44.282 cell line as well as non email.

NOTE Confidence: 0.757966220378876

00:42:44.290 --> 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 --> 00:42:51.676 saw binding at the very associated

NOTE Confidence: 0.757966220378876

00:42:51.676 --> 00:42:54.415 enhancer element and if you zoom in

NOTE Confidence: 0.757966220378876

00:42:54.415 --> 00:42:57.412 you can see some of the speaker really.

NOTE Confidence: 0.757966220378876

00:42:57.412 --> 00:43:00.217 Directly overlapping the variant that

NOTE Confidence: 0.757966220378876

00:43:00.217 --> 00:43:03.558 that was found in the AML samples.

NOTE Confidence: 0.757966220378876

00:43:03.560 --> 00:43:06.146 To directly test whether this email

NOTE Confidence: 0.757966220378876

00:43:06.146 --> 00:43:07.870 associated non coding variants

NOTE Confidence: 0.757966220378876

00:43:07.944 --> 00:43:09.972 indeed modulate nuclear hormone

NOTE Confidence: 0.757966220378876

00:43:09.972 --> 00:43:12.000 binding and enhancer function,

NOTE Confidence: 0.757966220378876

00:43:12.000 --> 00:43:13.410 we went ahead,

NOTE Confidence: 0.757966220378876

00:43:13.410 --> 00:43:16.230 generate a knocking audio and this

NOTE Confidence: 0.757966220378876

00:43:16.230 --> 00:43:17.859 was not trivial.

NOTE Confidence: 0.757966220378876

00:43:17.860 --> 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

NOTE Confidence: 0.757966220378876

00:43:23.708 --> 00:43:26.377 by Christmas targeting of the either

NOTE Confidence: 0.757966220378876

00:43:26.377 --> 00:43:29.337 the white type or the mutant value in

NOTE Confidence: 0.757966220378876

00:43:29.418 --> 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 --> 00:43:36.769 clones and measure nuclear Homer

NOTE Confidence: 0.757966220378876

00:43:36.769 --> 00:43:39.190 by name by chip experiment.

NOTE Confidence: 0.745472967624664

00:43:39.190 --> 00:43:42.022 So the data showing on the top right

NOTE Confidence: 0.745472967624664

00:43:42.022 --> 00:43:44.883 corner so you will see in the input

NOTE Confidence: 0.745472967624664

00:43:44.883 --> 00:43:47.148 dinner you will see this expecting

NOTE Confidence: 0.745472967624664

00:43:47.148 --> 00:43:49.948 one to one ratio of the whiter

NOTE Confidence: 0.745472967624664

00:43:49.948 --> 00:43:52.030 versus knocking earlier because we

NOTE Confidence: 0.745472967624664

00:43:52.030 --> 00:43:54.130 generate the heroes actors knocking

NOTE Confidence: 0.745472967624664

00:43:54.130 --> 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 --> 00:44:00.501 of this of the ratio of the

NOTE Confidence: 0.745472967624664

00:44:00.501 --> 00:44:02.249 knocking mutually versus Vytorin,

NOTE Confidence: 0.745472967624664

00:44:02.250 --> 00:44:04.762 the chipped in and you see the knocking

NOTE Confidence: 0.745472967624664

00:44:04.762 --> 00:44:07.089 mutant value are significantly enriched,

NOTE Confidence: 0.745472967624664

00:44:07.090 --> 00:44:09.736 and this suggests that the mutant value.

NOTE Confidence: 0.745472967624664

00:44:09.740 --> 00:44:11.560 Actually have stronger Association

NOTE Confidence: 0.745472967624664

00:44:11.560 --> 00:44:13.835 with the nuclear hormone receptors

NOTE Confidence: 0.745472967624664

00:44:13.835 --> 00:44:16.066 by chip experiment and consistent

NOTE Confidence: 0.745472967624664

00:44:16.066 --> 00:44:18.206 with this and nuclear agonist,

NOTE Confidence: 0.745472967624664

00:44:18.210 --> 00:44:20.919 I can list more enhanced CARROS expression

NOTE Confidence: 0.745472967624664

00:44:20.919 --> 00:44:24.313 in a knock in sales compared to the

NOTE Confidence: 0.745472967624664

00:44:24.313 --> 00:44:27.049 wild type cells against suggestion that

NOTE Confidence: 0.745472967624664

00:44:27.049 --> 00:44:29.569 these mutant assume associated cameras

NOTE Confidence: 0.745472967624664

00:44:29.569 --> 00:44:32.005 enhancer are regulated by nuclear

NOTE Confidence: 0.745472967624664

00:44:32.005 --> 00:44:34.080 hormone receptors and this recurrent

NOTE Confidence: 0.745472967624664

00:44:34.080 --> 00:44:36.303 mutations my function to enhance

NOTE Confidence: 0.745472967624664

00:44:36.303 --> 00:44:38.279 nuclear hormone receptor binding.

NOTE Confidence: 0.745472967624664

00:44:38.280 --> 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 --> 00:44:46.014 So we also valid that is finding other

NOTE Confidence: 0.745472967624664

00:44:46.014 --> 00:44:48.869 enhances that I won't have time to show

NOTE Confidence: 0.745472967624664

00:44:48.869 --> 00:44:51.510 an including a interesting Lee has a

NOTE Confidence: 0.745472967624664

00:44:51.510 --> 00:44:53.475 controlling our security engine code,

NOTE Confidence: 0.745472967624664

00:44:53.480 --> 00:44:55.310 PO2 this is all publisher

NOTE Confidence: 0.745472967624664

00:44:55.310 --> 00:44:56.408 if you're interested.

NOTE Confidence: 0.745472967624664

00:44:56.410 --> 00:44:58.245 You're more than happy to

NOTE Confidence: 0.745472967624664

00:44:58.245 --> 00:45:00.080 read about the details so.

NOTE Confidence: 0.745472967624664

00:45:00.080 --> 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 --> 00:45:07.802 our finest artist seems to be frequent

NOTE Confidence: 0.745472967624664

00:45:07.802 --> 00:45:09.690 targets of noncoding mutations,

NOTE Confidence: 0.745472967624664

00:45:09.690 --> 00:45:10.944 in particular email,

NOTE Confidence: 0.745472967624664

00:45:10.944 --> 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 --> 00:45:17.704 So therefore we seek our findings

NOTE Confidence: 0.745472967624664

00:45:17.704 --> 00:45:20.658 support model that is pathogenic and non

NOTE Confidence: 0.745472967624664

00:45:20.658 --> 00:45:23.068 coding variants are noncoding mutations,

NOTE Confidence: 0.745472967624664

00:45:23.070 --> 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 --> 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 --> 00:45:34.105 Then my potentially promote are

NOTE Confidence: 0.745472967624664

00:45:34.105 --> 00:45:36.760 functionally that contribute to the

NOTE Confidence: 0.745472967624664

00:45:36.840 --> 00:45:40.088 development of hematopoetic malignancies.

NOTE Confidence: 0.745472967624664

00:45:40.090 --> 00:45:43.300 So as a final summary.

NOTE Confidence: 0.745472967624664

00:45:43.300 --> 00:45:46.150 Is that an explosion of genomic

NOTE Confidence: 0.745472967624664

00:45:46.150 --> 00:45:47.575 and epigenomic information?

NOTE Confidence: 0.745472967624664

00:45:47.580 --> 00:45:50.079 In recent years we have learned a

NOTE Confidence: 0.745472967624664

00:45:50.079 --> 00:45:52.864 great deal of how gene regulation

NOTE Confidence: 0.745472967624664

00:45:52.864 --> 00:45:55.048 controls normal development and

NOTE Confidence: 0.745472967624664

00:45:55.048 --> 00:45:57.832 how dysregulation of this process

NOTE Confidence: 0.745472967624664

00:45:57.832 --> 00:45:59.956 contribute to human diseases.

NOTE Confidence: 0.745472967624664

00:45:59.960 --> 00:46:00.828 How what.

NOTE Confidence: 0.745472967624664

00:46:00.828 --> 00:46:02.998 We currently know only represents

NOTE Confidence: 0.745472967624664

00:46:02.998 --> 00:46:06.013 a very small portion of the

NOTE Confidence: 0.745472967624664

00:46:06.013 --> 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 --> 00:46:11.028 and in retrospect and maybe

NOTE Confidence: 0.745472967624664

00:46:11.028 --> 00:46:13.348 more relevant to our studies.

NOTE Confidence: 0.745472967624664

00:46:13.350 --> 00:46:14.679 As we know,

NOTE Confidence: 0.745472967624664

00:46:14.679 --> 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 --> 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 --> 00:46:29.900 which was later dropped as a first

NOTE Confidence: 0.745472967624664

00:46:29.900 --> 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 --> 00:46:36.810 discovered until early 1980s

NOTE Confidence: 0.745472967624664

00:46:36.887 --> 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 --> 00:46:43.208 genome in early 2000s.

NOTE Confidence: 0.745472967624664

00:46:43.210 --> 00:46:45.964 Now more than a century after

NOTE Confidence: 0.745472967624664

00:46:45.964 --> 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 --> 00:46:53.561 we might have a first enhancer targeting

NOTE Confidence: 0.745472967624664

00:46:53.561 --> 00:46:56.080 therapist for this molecular disease.

NOTE Confidence: 0.745472967624664

00:46:56.080 --> 00:46:56.900 Very soon,

NOTE Confidence: 0.745472967624664

00:46:56.900 --> 00:46:59.360 and we certainly hope that by

NOTE Confidence: 0.745472967624664

00:46:59.360 --> 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 --> 00:47:07.727 elements that we might be able to

NOTE Confidence: 0.745472967624664

00:47:07.727 --> 00:47:09.797 identify new mechanism and genetic

NOTE Confidence: 0.745472967624664

00:47:09.797 --> 00:47:12.539 pathways that contribute to a normal

NOTE Confidence: 0.745472967624664

00:47:12.539 --> 00:47:14.669 blood cell development an animal.

NOTE Confidence: 0.745472967624664

00:47:14.670 --> 00:47:16.680 Long term that we might be

NOTE Confidence: 0.745472967624664

00:47:16.680 --> 00:47:18.020 able to develop our

NOTE Confidence: 0.830641567707062

00:47:18.098 --> 00:47:19.994 enhanced targeting therapeutics

NOTE Confidence: 0.830641567707062

00:47:19.994 --> 00:47:21.890 for blood disorders.

NOTE Confidence: 0.830641567707062

00:47:21.890 --> 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 --> 00:47:28.400 the people who met his work,

NOTE Confidence: 0.830641567707062

00:47:28.400 --> 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 --> 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 --> 00:47:39.030 and profiling work done in primary

NOTE Confidence: 0.830641567707062

00:47:39.030 --> 00:47:41.141 hematopoietic cells was done in

NOTE Confidence: 0.830641567707062

00:47:41.141 --> 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 --> 00:47:50.094 Now he has his own lab in Sherman University.

NOTE Confidence: 0.830641567707062

00:47:50.100 --> 00:47:53.180 The development of the cast net capture

NOTE Confidence: 0.830641567707062

00:47:53.180 --> 00:47:55.829 was spearheaded by a former poster in

NOTE Confidence: 0.830641567707062

00:47:55.829 --> 00:47:59.094 my lap as she knew now has his own

NOTE Confidence: 0.830641567707062

00:47:59.094 --> 00:48:01.728 app together with another poster fellow.

NOTE Confidence: 0.830641567707062

00:48:01.730 --> 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 --> 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 --> 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 --> 00:48:16.569 together with another Postal federal,

NOTE Confidence: 0.830641567707062

00:48:16.570 --> 00:48:18.600 most of them are transitioned

NOTE Confidence: 0.830641567707062

00:48:18.600 --> 00:48:20.224 to their independent positions.

NOTE Confidence: 0.830641567707062

00:48:20.230 --> 00:48:21.386 Together with other collaborators

NOTE Confidence: 0.830641567707062

00:48:21.386 --> 00:48:23.525 and we couldn't do this with a

NOTE Confidence: 0.830641567707062

00:48:23.525 --> 00:48:24.941 wonderful collaboration from Boston

NOTE Confidence: 0.830641567707062

00:48:24.941 --> 00:48:26.711 Children's and our local collaborators

NOTE Confidence: 0.830641567707062

00:48:26.766 --> 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 --> 00:48:31.290 I'm happy to take any questions

NOTE Confidence: 0.830641567707062

00:48:31.353 --> 00:48:32.589 that you might have.

NOTE Confidence: 0.830641567707062

00:48:32.590 --> 00:48:35.803 Thank you very much for your time.