WEBVTT

NOTE duration:”00:33:50.2490000”

NOTE language:en-us

NOTE Confidence: 0.8749004

00:00:00.000 --> 00:00:02.808 Why don't we go ahead and get started?

NOTE Confidence: 0.8749004

00:00:02.810 --> 00:00:04.286 So I'm Jeannie Hendrickson.

NOTE Confidence: 0.8749004

00:00:04.286 --> 00:00:05.762 I'm representing the enrichment

NOTE Confidence: 0.8749004

00:00:05.762 --> 00:00:07.663 program of the Yale Cooperative

NOTE Confidence: 0.8749004

00:00:07.663 --> 00:00:09.508 Center of Excellence in Hematology,

NOTE Confidence: 0.8749004

00:00:09.510 --> 00:00:11.862 or super excited on this Snowy Friday

NOTE Confidence: 0.8749004

00:00:11.862 --> 00:00:13.627 afternoon to have Marjorie Brands

NOTE Confidence: 0.8749004

00:00:13.627 --> 00:00:16.063 visiting us for a talk that's called

NOTE Confidence: 0.8749004

00:00:16.063 --> 00:00:18.427 cell fate decisions in hematopoiesis.

NOTE Confidence: 0.8749004

00:00:18.430 --> 00:00:19.408 She's visiting us,

NOTE Confidence: 0.8749004

00:00:19.408 --> 00:00:21.690 and virtually she's a professor in the

NOTE Confidence: 0.8749004

00:00:21.752 --> 00:00:23.697 Department of Cellular and Molecular

NOTE Confidence: 0.8749004

00:00:23.697 --> 00:00:26.506 Medicine and a senior scientist at the

NOTE Confidence: 0.8749004

00:00:26.506 --> 00:00:28.110 Ottawa Hospital Research Institute,

NOTE Confidence: 0.8749004

00:00:28.110 --> 00:00:31.449 and really enjoy the picture of her lab here.

NOTE Confidence: 0.8749004

00:00:31.450 --> 00:00:32.668 So we're thrilled.

NOTE Confidence: 0.8749004

00:00:32.668 --> 00:00:34.698 She's with us this afternoon.

NOTE Confidence: 0.8749004

00:00:34.700 --> 00:00:37.308 And at the end of her talk we

NOTE Confidence: 0.8749004

00:00:37.308 --> 00:00:39.834 should be able to have some

NOTE Confidence: 0.8749004

00:00:39.834 --> 00:00:42.064 questions and answers as well.

NOTE Confidence: 0.8749004

00:00:42.070 --> 00:00:44.398 So thanks again Marjorie for visiting.

NOTE Confidence: 0.8749004

00:00:44.400 --> 00:00:45.948 We really appreciate it.

NOTE Confidence: 0.8749004

00:00:45.948 --> 00:00:47.496 Thank you very much.

NOTE Confidence: 0.8749004

00:00:47.500 --> 00:00:50.216 It's a great pleasure to be here.

NOTE Confidence: 0.8749004

00:00:50.220 --> 00:00:53.188 Thanks Pat for the invitation and I really

NOTE Confidence: 0.8749004

00:00:53.188 --> 00:00:56.037 enjoyed my discussions that I had today,

NOTE Confidence: 0.8749004

00:00:56.040 --> 00:00:58.756 so I'm going to start by 10.

NOTE Confidence: 0.8749004

00:00:58.760 --> 00:01:01.076 So the as we all know,

NOTE Confidence: 0.8749004

00:01:01.080 --> 00:01:03.810 hematopoiesis is a multi step process

NOTE Confidence: 0.8749004

00:01:03.810 --> 00:01:06.360 through which the hematopoietic stem cell.

NOTE Confidence: 0.8749004

00:01:06.360 --> 00:01:09.336 Shades to give rise to all the cells

NOTE Confidence: 0.8749004

00:01:09.336 --> 00:01:11.900 that are present in the blood,

NOTE Confidence: 0.8749004

00:01:11.900 --> 00:01:13.826 and this process is highly regulated

NOTE Confidence: 0.8749004

00:01:13.826 --> 00:01:15.747 by a number of transcription

NOTE Confidence: 0.8749004

00:01:15.747 --> 00:01:17.448 factors and cofactors,

NOTE Confidence: 0.8749004

00:01:17.450 --> 00:01:20.030 and these factors work together as

NOTE Confidence: 0.8749004

00:01:20.030 --> 00:01:22.159 networks to promote differentiation to

NOTE Confidence: 0.8749004

00:01:22.159 --> 00:01:24.574 our specific lineages such As for example,

NOTE Confidence: 0.8749004

00:01:24.580 --> 00:01:27.555 the average ridlen age that I'm going

NOTE Confidence: 0.8749004

00:01:27.555 --> 00:01:31.573 to focus on today and at the same

NOTE Confidence: 0.8749004

00:01:31.573 --> 00:01:33.693 time these transcription factors.

NOTE Confidence: 0.8749004

00:01:33.700 --> 00:01:35.500 Inhibiting the other alternate

NOTE Confidence: 0.8749004

00:01:35.500 --> 00:01:36.400 hematopoietic lineages.

NOTE Confidence: 0.8749004

00:01:36.400 --> 00:01:38.962 Now what's interesting is that the

NOTE Confidence: 0.8749004

00:01:38.962 --> 00:01:40.670 transcription factors that drive

NOTE Confidence: 0.8749004

00:01:40.735 --> 00:01:43.100 every trade or other lineages

NOTE Confidence: 0.8749004

00:01:43.100 --> 00:01:44.046 drive differentiation.

NOTE Confidence: 0.8749004

00:01:44.050 --> 00:01:46.857 There are expressed at very high levels

NOTE Confidence: 0.8749004

00:01:46.857 --> 00:01:50.140 at the specific stage when they are

NOTE Confidence: 0.8749004

00:01:50.140 --> 00:01:52.144 important to drive differentiation,

NOTE Confidence: 0.8749004

00:01:52.150 --> 00:01:54.400 usually towards the later stages.

NOTE Confidence: 0.8749004

00:01:54.400 --> 00:01:57.016 But most of these factors are

NOTE Confidence: 0.8749004

00:01:57.016 --> 00:01:58.760 also expressed in hematopoietic

NOTE Confidence: 0.8749004

00:01:58.839 --> 00:02:00.699 stem and progenitor cells,

NOTE Confidence: 0.8749004

00:02:00.700 --> 00:02:03.330 although at very low levels.

NOTE Confidence: 0.8749004

00:02:03.330 --> 00:02:06.558 Which suggests that the amount also

NOTE Confidence: 0.8749004

00:02:06.558 --> 00:02:09.333 dosage of transcription factors play

NOTE Confidence: 0.8749004

00:02:09.333 --> 00:02:12.567 critical role for cell fate determination.

NOTE Confidence: 0.8749004

00:02:12.570 --> 00:02:15.012 Now the importance of the dosage

NOTE Confidence: 0.8749004

00:02:15.012 --> 00:02:17.112 of transcription factors for the

NOTE Confidence: 0.8749004

00:02:17.112 --> 00:02:19.112 process of cell fate decision

NOTE Confidence: 0.8749004

00:02:19.112 --> 00:02:21.665 has been established early on by

NOTE Confidence: 0.8749004

00:02:21.665 --> 00:02:23.860 reprogramming experiments in cell lines.

NOTE Confidence: 0.8749004

00:02:23.860 --> 00:02:24.952 So, for example,

NOTE Confidence: 0.8749004

00:02:24.952 --> 00:02:27.500 the lab of tumors graph in 1995

NOTE Confidence: 0.8749004

00:02:27.583 --> 00:02:29.973 was able to reprogram myeloblastic

NOTE Confidence: 0.8749004

00:02:29.973 --> 00:02:32.834 cell lines 2 hours different fate

NOTE Confidence: 0.8749004

00:02:32.834 --> 00:02:35.557 depending on the amount of the data.

NOTE Confidence: 0.8749004

00:02:35.560 --> 00:02:37.645 One footings that was Ectopically

NOTE Confidence: 0.8749004

00:02:37.645 --> 00:02:38.896 expressed so specifically,

NOTE Confidence: 0.8749004

00:02:38.900 --> 00:02:42.008 the lab showed that if that high

NOTE Confidence: 0.8749004

00:02:42.008 --> 00:02:44.020 levels of get a one.

NOTE Confidence: 0.8749004

00:02:44.020 --> 00:02:46.444 We drive differentiation to us every

NOTE Confidence: 0.8749004

00:02:46.444 --> 00:02:48.060 trade lineages or megakaryocytes,

NOTE Confidence: 0.8749004

00:02:48.060 --> 00:02:50.270 while intermediate levels of get

NOTE Confidence: 0.8749004

00:02:50.270 --> 00:02:52.480 a one will drive differentiation

NOTE Confidence: 0.8749004

00:02:52.554 --> 00:02:54.119 too as the elzina fear.

NOTE Confidence: 0.8749004

00:02:54.120 --> 00:02:56.650 Now these early experiment really

NOTE Confidence: 0.8749004

00:02:56.650 --> 00:02:58.168 demonstrated that different

NOTE Confidence: 0.8749004

00:02:58.168 --> 00:03:01.078 amounts of the data one put in

NOTE Confidence: 0.8749004

00:03:01.078 --> 00:03:02.903 can promote alternate cell fate.

NOTE Confidence: 0.8749004

00:03:02.910 --> 00:03:04.356 Now, more recently,

NOTE Confidence: 0.8749004

00:03:04.356 --> 00:03:06.284 linear programming experiment in

NOTE Confidence: 0.8749004

00:03:06.284 --> 00:03:09.084 in primary cells have also shown

NOTE Confidence: 0.8749004

00:03:09.084 --> 00:03:11.640 the importance of the dosage of

NOTE Confidence: 0.8749004

00:03:11.640 --> 00:03:13.373 transcription factors for the

NOTE Confidence: 0.8749004

00:03:13.373 --> 00:03:15.423 process of cell fate decisions.

NOTE Confidence: 0.8749004

00:03:15.430 --> 00:03:18.559 So for example, in this publication here,

NOTE Confidence: 0.8749004

00:03:18.560 --> 00:03:20.728 the authors have reprogrammed

NOTE Confidence: 0.8749004

00:03:20.728 --> 00:03:23.438 human fibroblasts into every trade

NOTE Confidence: 0.8749004

00:03:23.438 --> 00:03:25.795 progenitors by using this cocktail

NOTE Confidence: 0.8749004

00:03:25.795 --> 00:03:27.970 of four transcription factors get

NOTE Confidence: 0.8749004

00:03:27.970 --> 00:03:30.614 away until one element 2 and C myc,

NOTE Confidence: 0.8040973

00:03:30.620 --> 00:03:33.040 which they called the GTLM.

NOTE Confidence: 0.8040973

00:03:33.040 --> 00:03:34.855 Cocktail, and for these reprogramming

NOTE Confidence: 0.8040973

00:03:34.855 --> 00:03:37.450 experiments they have used a retroviruses,

NOTE Confidence: 0.8040973

00:03:37.450 --> 00:03:39.455 and each retrovirus expresses one

NOTE Confidence: 0.8040973

00:03:39.455 --> 00:03:41.059 of these transcription factors.

NOTE Confidence: 0.8040973

00:03:41.060 --> 00:03:43.256 And what's very interesting is they

NOTE Confidence: 0.8040973

00:03:43.256 --> 00:03:45.569 found that depending on the relative

NOTE Confidence: 0.8040973

00:03:45.569 --> 00:03:47.133 levels between their retroviruses

NOTE Confidence: 0.8040973

00:03:47.133 --> 00:03:49.880 that they use in their experiments,

NOTE Confidence: 0.8040973

00:03:49.880 --> 00:03:52.286 they can obtain completely different results.

NOTE Confidence: 0.8040973

00:03:52.290 --> 00:03:53.472 So for example,

NOTE Confidence: 0.8040973

00:03:53.472 --> 00:03:57.100 if they use a GT LM ratio of 2111,

NOTE Confidence: 0.8040973

00:03:57.100 --> 00:03:59.458 then these these reprogram cells will

NOTE Confidence: 0.8040973

00:03:59.458 --> 00:04:01.510 produce exclusively red cell colony,

NOTE Confidence: 0.8040973

00:04:01.510 --> 00:04:03.760 which suggests that those are

NOTE Confidence: 0.8040973

00:04:03.760 --> 00:04:05.560 functionally which would progenitors.

NOTE Confidence: 0.8040973

00:04:05.560 --> 00:04:07.485 However, if they use a

NOTE Confidence: 0.8040973

00:04:07.485 --> 00:04:09.410 slightly different GT LM ratio,

NOTE Confidence: 0.8040973

00:04:09.410 --> 00:04:10.532 for example 1112,

NOTE Confidence: 0.8040973

00:04:10.532 --> 00:04:12.402 then the reprogram cells will

NOTE Confidence: 0.8040973

00:04:12.402 --> 00:04:14.418 not produce red cells colonies,

NOTE Confidence: 0.8040973

00:04:14.420 --> 00:04:16.730 suggesting that these are not functional.

NOTE Confidence: 0.8040973

00:04:16.730 --> 00:04:18.465 So these these experiments have

NOTE Confidence: 0.8040973

00:04:18.465 --> 00:04:21.102 shown that it's not only the dosage

NOTE Confidence: 0.8040973

00:04:21.102 --> 00:04:23.182 of the amount of transcription

NOTE Confidence: 0.8040973

00:04:23.182 --> 00:04:24.430 factors that's important,

NOTE Confidence: 0.8040973

00:04:24.430 --> 00:04:26.740 but really the whole ative levels,

NOTE Confidence: 0.8040973

00:04:26.740 --> 00:04:29.050 or just to comma tree of

NOTE Confidence: 0.8040973

00:04:29.050 --> 00:04:29.820 transcription factors.

NOTE Confidence: 0.8040973

00:04:29.820 --> 00:04:32.130 That is key for reprogramming efficiency,

NOTE Confidence: 0.8040973

00:04:32.130 --> 00:04:35.586 and it is the same for native hematopoiesis.

NOTE Confidence: 0.8040973

00:04:35.590 --> 00:04:38.481 Where it has been proposed that the

NOTE Confidence: 0.8040973

00:04:38.481 --> 00:04:40.462 transcription factors that drive

NOTE Confidence: 0.8040973

00:04:40.462 --> 00:04:42.463 differentiation towards alternate

NOTE Confidence: 0.8040973

00:04:42.463 --> 00:04:45.131 hematopoietic lineages Co expressing

NOTE Confidence: 0.8040973

00:04:45.131 --> 00:04:47.436 bipotential progenitors and that those

NOTE Confidence: 0.8040973

00:04:47.436 --> 00:04:50.095 changes in us to comma tree is what

NOTE Confidence: 0.8040973

00:04:50.095 --> 00:04:52.870 is important to drive differentiation

NOTE Confidence: 0.8040973

00:04:52.870 --> 00:04:56.559 to US1 fate or another phase.

NOTE Confidence: 0.8040973

00:04:56.560 --> 00:04:58.948 Now a number of gene regulatory

NOTE Confidence: 0.8040973

00:04:58.948 --> 00:05:00.912 networks have been established in

NOTE Confidence: 0.8040973

00:05:00.912 --> 00:05:02.730 an attempt to model this self,

NOTE Confidence: 0.8040973

00:05:02.730 --> 00:05:04.908 a choice that occur in this

NOTE Confidence: 0.8040973

00:05:04.908 --> 00:05:05.634 bipotential progenitors,

NOTE Confidence: 0.8040973

00:05:05.640 --> 00:05:06.663 and for example,

NOTE Confidence: 0.8040973

00:05:06.663 --> 00:05:09.050 here is a network model of the

NOTE Confidence: 0.8040973

00:05:09.124 --> 00:05:11.805 selfish choice that occur in the MVP,

NOTE Confidence: 0.8040973

00:05:11.810 --> 00:05:13.510 just the megakaryocytes every

NOTE Confidence: 0.8040973

00:05:13.510 --> 00:05:15.635 trade progenitors and those cells

NOTE Confidence: 0.8040973

00:05:15.635 --> 00:05:17.759 must choose between an arbitrate

NOTE Confidence: 0.8040973

00:05:17.759 --> 00:05:19.804 fate or a megakaryocytic faith.

NOTE Confidence: 0.8040973

00:05:19.810 --> 00:05:20.235 Now,

NOTE Confidence: 0.8040973

00:05:20.235 --> 00:05:21.935 this hematopoietic tree of

NOTE Confidence: 0.8040973

00:05:21.935 --> 00:05:24.060 differentiation that I have shown

NOTE Confidence: 0.8040973

00:05:24.127 --> 00:05:26.780 you so far was a commonly accepted

NOTE Confidence: 0.8040973

00:05:26.780 --> 00:05:28.321 model for hematopoiesis until

NOTE Confidence: 0.8040973

00:05:28.321 --> 00:05:30.337 about 6:00 or seven years ago,

NOTE Confidence: 0.8040973

00:05:30.340 --> 00:05:32.881 when the use of single cell RNA

NOTE Confidence: 0.8040973

00:05:32.881 --> 00:05:34.881 seek transformed it into something

NOTE Confidence: 0.8040973

00:05:34.881 --> 00:05:36.966 that looks more like this.

NOTE Confidence: 0.8040973

00:05:36.970 --> 00:05:37.360 Now,

NOTE Confidence: 0.8040973

00:05:37.360 --> 00:05:39.310 in this knew continuous model

NOTE Confidence: 0.8040973

00:05:39.310 --> 00:05:40.090 of hematopoiesis,

NOTE Confidence: 0.8040973

00:05:40.090 --> 00:05:42.430 there are no differentiation steps process,

NOTE Confidence: 0.8040973

00:05:42.430 --> 00:05:44.770 but instead the cells are gradually

NOTE Confidence: 0.8040973

00:05:44.770 --> 00:05:46.330 transitioning along hematopoietic lineages.

NOTE Confidence: 0.8040973

00:05:46.330 --> 00:05:49.060 And really in these types of models,

NOTE Confidence: 0.8040973

00:05:49.060 --> 00:05:49.431 the.

NOTE Confidence: 0.8040973

00:05:49.431 --> 00:05:51.657 Hematopoiesis is actually based on a

NOTE Confidence: 0.8040973

00:05:51.657 --> 00:05:53.960 continuum of changing failed probability.

NOTE Confidence: 0.8040973

00:05:53.960 --> 00:05:56.642 So in in that type of model they are

NOTE Confidence: 0.8040973

00:05:56.642 --> 00:05:58.930 known by potential opportunities,

NOTE Confidence: 0.8040973

00:05:58.930 --> 00:06:00.514 but they're only hematopoietic.

NOTE Confidence: 0.8040973

00:06:00.514 --> 00:06:02.098 For generators with sulfate

NOTE Confidence: 0.8040973

00:06:02.098 --> 00:06:03.551 probabilities that are becoming

NOTE Confidence: 0.8040973

00:06:03.551 --> 00:06:05.375 more and more restricted as the

NOTE Confidence: 0.8040973

00:06:05.375 --> 00:06:07.016 cells gradually transition along

NOTE Confidence: 0.8040973

00:06:07.016 --> 00:06:08.477 the hematopoietic trajectories.

NOTE Confidence: 0.8040973

00:06:08.480 --> 00:06:11.056 Now in his new types of models

NOTE Confidence: 0.8040973

00:06:11.056 --> 00:06:13.060 for him at a crisis,

NOTE Confidence: 0.8040973

00:06:13.060 --> 00:06:15.238 and the exact exact role of

NOTE Confidence: 0.8040973

00:06:15.238 --> 00:06:16.690 transcription factors and the

NOTE Confidence: 0.8040973

00:06:16.762 --> 00:06:18.418 importance of their quantitative

NOTE Confidence: 0.8040973

00:06:18.418 --> 00:06:20.902 changes for the process of self.

NOTE Confidence: 0.8040973

00:06:20.910 --> 00:06:22.182 Decision remains unclear,

NOTE Confidence: 0.8040973

00:06:22.182 --> 00:06:25.826 so our goal is to establish a dynamic

NOTE Confidence: 0.8040973

00:06:25.826 --> 00:06:28.796 model of erythropoiesis that can

NOTE Confidence: 0.8040973

00:06:28.796 --> 00:06:31.770 integrate those quantitative changes in

NOTE Confidence: 0.8040973

00:06:31.770 --> 00:06:34.878 the level of transcription factors overtime.

NOTE Confidence: 0.8040973

00:06:34.880 --> 00:06:35.927 Now I will.

NOTE Confidence: 0.8040973

00:06:35.927 --> 00:06:38.370 I will model system to study human.

NOTE Confidence: 0.8040973

00:06:38.370 --> 00:06:40.799 Every troop Oasis is an ex vivo

NOTE Confidence: 0.8040973

00:06:40.799 --> 00:06:42.277 differentiation protocol where we

NOTE Confidence: 0.8040973

00:06:42.277 --> 00:06:44.177 isolate the city certified positive

NOTE Confidence: 0.8040973

00:06:44.177 --> 00:06:46.068 stomach progenitor cells from cord

NOTE Confidence: 0.8040973

00:06:46.068 --> 00:06:47.910 blood or peripheral blood or bone

NOTE Confidence: 0.8040973

00:06:47.910 --> 00:06:50.085 marrow and those cells are then

NOTE Confidence: 0.8040973

00:06:50.085 --> 00:06:51.745 differentiated to observe Richard

NOTE Confidence: 0.8040973

00:06:51.745 --> 00:06:54.213 lineages by using a cocktail of

NOTE Confidence: 0.8040973

00:06:54.213 --> 00:06:55.757 growth factors and cytokines.

NOTE Confidence: 0.8208043

00:06:55.760 --> 00:06:57.678 Now here are the sum of the

NOTE Confidence: 0.8208043

00:06:57.678 --> 00:06:58.910 morphological changes that occur

NOTE Confidence: 0.8208043

00:06:58.910 --> 00:07:00.685 during this ex vivo electrophoresis.

NOTE Confidence: 0.8208043

00:07:00.690 --> 00:07:02.886 You can see at the at the beginning at

NOTE Confidence: 0.8208043

00:07:02.886 --> 00:07:05.241 Day zero we can see the hematopoietic

NOTE Confidence: 0.8208043

00:07:05.241 --> 00:07:07.651 stem and progenitor cells and then there

NOTE Confidence: 0.8208043

00:07:07.651 --> 00:07:09.601 are dramatic changes in morphology and

NOTE Confidence: 0.8208043

00:07:09.601 --> 00:07:12.372 at the end of differentiation we obtain

NOTE Confidence: 0.8208043

00:07:12.372 --> 00:07:14.440 complete indication on those cells.

NOTE Confidence: 0.8208043

00:07:14.440 --> 00:07:16.673 That we wanted to further study every

NOTE Confidence: 0.8208043

00:07:16.673 --> 00:07:18.997 true policies at the single cell level.

NOTE Confidence: 0.8208043

00:07:19.000 --> 00:07:21.254 And for this we decided to use

NOTE Confidence: 0.8208043

00:07:21.254 --> 00:07:22.920 my cytometry or site off,

NOTE Confidence: 0.8208043

00:07:22.920 --> 00:07:24.935 which allows one to measure

NOTE Confidence: 0.8208043

00:07:24.935 --> 00:07:26.547 putains in single cell.

NOTE Confidence: 0.8208043

00:07:26.550 --> 00:07:29.010 So for the site of experiment,

NOTE Confidence: 0.8208043

00:07:29.010 --> 00:07:31.060 we harvested cells at regular

NOTE Confidence: 0.8208043

00:07:31.060 --> 00:07:32.700 intervals during the crossover.

NOTE Confidence: 0.8208043

00:07:32.700 --> 00:07:34.320 Every trait differentiation and

NOTE Confidence: 0.8208043

00:07:34.320 --> 00:07:36.750 then we barcoded those cells are

NOTE Confidence: 0.8208043

00:07:36.821 --> 00:07:38.976 separately at different time points

NOTE Confidence: 0.8208043

00:07:38.976 --> 00:07:41.131 with Palladium isotopes prior to

NOTE Confidence: 0.8208043

00:07:41.196 --> 00:07:43.096 combining them and standing them

NOTE Confidence: 0.8208043

00:07:43.096 --> 00:07:45.504 together with a cocktail of antibodies

NOTE Confidence: 0.8208043

00:07:45.504 --> 00:07:48.024 contain including cell surface markers

NOTE Confidence: 0.8208043

00:07:48.024 --> 00:07:50.660 as well as transcription factors.

NOTE Confidence: 0.8208043

00:07:50.660 --> 00:07:52.865 And then we did a clustering analysis

NOTE Confidence: 0.8208043

00:07:52.865 --> 00:07:55.701 on the 27 markers at a different time

NOTE Confidence: 0.8208043

00:07:55.701 --> 00:07:58.427 points and this allowed us to identify

NOTE Confidence: 0.8208043

00:07:58.427 --> 00:08:00.537 18 clusters or cell populations.

NOTE Confidence: 0.8208043

00:08:00.540 --> 00:08:02.496 And because we did a temporal

NOTE Confidence: 0.8208043

00:08:02.496 --> 00:08:05.091 because we did re bar coded the

NOTE Confidence: 0.8208043

00:08:05.091 --> 00:08:07.126 samples at different time points,

NOTE Confidence: 0.8208043

00:08:07.130 --> 00:08:09.510 we could do a temporal analysis of

NOTE Confidence: 0.8208043

00:08:09.510 --> 00:08:11.719 those cell populations which allowed us

NOTE Confidence: 0.8208043

00:08:11.719 --> 00:08:13.599 to reconstruct the dynamic trajectory

NOTE Confidence: 0.8208043

00:08:13.599 --> 00:08:16.260 from the early March put on progenitor

NOTE Confidence: 0.8208043

00:08:16.260 --> 00:08:18.490 cells to the differentiated auto chromatic,

NOTE Confidence: 0.8208043

00:08:18.490 --> 00:08:19.250 which replies.

NOTE Confidence: 0.8208043

00:08:19.250 --> 00:08:21.150 And then we looked at.

NOTE Confidence: 0.8208043

00:08:21.150 --> 00:08:22.974 The transcription factors expression

NOTE Confidence: 0.8208043

00:08:22.974 --> 00:08:25.710 in single cells within these different

NOTE Confidence: 0.8208043

00:08:25.775 --> 00:08:28.270 populations along the retreat trajectory.

NOTE Confidence: 0.8208043

00:08:28.270 --> 00:08:30.226 And our first question was whether

NOTE Confidence: 0.8208043

00:08:30.226 --> 00:08:32.519 there is Co expression of antagonist

NOTE Confidence: 0.8208043

00:08:32.519 --> 00:08:34.844 transcription factors in early progenitors.

NOTE Confidence: 0.8208043

00:08:34.850 --> 00:08:37.384 So we looked at fly one which

NOTE Confidence: 0.8208043

00:08:37.384 --> 00:08:38.470 promotes differentiation towards

NOTE Confidence: 0.8208043

00:08:38.535 --> 00:08:39.879 megakaryocytes and PLF,

NOTE Confidence: 0.8208043

00:08:39.880 --> 00:08:41.428 one which promotes differentiation

NOTE Confidence: 0.8208043

00:08:41.428 --> 00:08:42.589 to repair itself,

NOTE Confidence: 0.8208043

00:08:42.590 --> 00:08:45.486 and we looked at them in the MVP

NOTE Confidence: 0.8208043

00:08:45.486 --> 00:08:48.059 populations that we gated with this

NOTE Confidence: 0.8208043

00:08:48.059 --> 00:08:50.274 combination of seven cell surface

NOTE Confidence: 0.8208043

00:08:50.274 --> 00:08:53.178 markers and what we found is that the

NOTE Confidence: 0.8208043

00:08:53.178 --> 00:08:55.748 vast majority of the MVP Dooku Express

NOTE Confidence: 0.8208043

00:08:55.748 --> 00:08:57.296 is antagonist transcription factors,

NOTE Confidence: 0.8208043

00:08:57.300 --> 00:08:59.520 KLF one and fly one.

NOTE Confidence: 0.8208043

00:08:59.520 --> 00:09:00.519 In single serve.

NOTE Confidence: 0.8208043

00:09:00.519 --> 00:09:02.850 So next we wanted to follow the

NOTE Confidence: 0.8208043

00:09:02.929 --> 00:09:05.321 changes in put in levels of KLF one

NOTE Confidence: 0.8208043

00:09:05.321 --> 00:09:08.319 and fly one as the sales proceeds

NOTE Confidence: 0.8208043

00:09:08.319 --> 00:09:09.717 towards irritated differentiation

NOTE Confidence: 0.8208043

00:09:09.717 --> 00:09:12.405 and you can see these results at

NOTE Confidence: 0.8208043

00:09:12.405 --> 00:09:14.965 the single cell level here and when

NOTE Confidence: 0.8208043

00:09:14.965 --> 00:09:17.155 we aggregate the results we found

NOTE Confidence: 0.8208043

00:09:17.155 --> 00:09:19.198 that there is a gradual increase

NOTE Confidence: 0.8208043

00:09:19.198 --> 00:09:21.776 in put in levels of KLF one and

NOTE Confidence: 0.8208043

00:09:21.776 --> 00:09:23.924 at the same time gradual decrease

NOTE Confidence: 0.8208043

00:09:23.924 --> 00:09:26.257 in foot in levels of fly one.

NOTE Confidence: 0.8208043

00:09:26.260 --> 00:09:28.342 But there is no abrupt switch

NOTE Confidence: 0.8208043

00:09:28.342 --> 00:09:29.730 after a specific population.

NOTE Confidence: 0.8208043

00:09:29.730 --> 00:09:31.680 What happens is that those

NOTE Confidence: 0.8208043

00:09:31.680 --> 00:09:32.850 gradual changes actually.

NOTE Confidence: 0.8208043

00:09:32.850 --> 00:09:36.240 Taking several populations to occur

NOTE Confidence: 0.8208043

00:09:36.240 --> 00:09:39.630 belongs in between the trajectory.

NOTE Confidence: 0.8208043

00:09:39.630 --> 00:09:42.920 And then we we decided to Ectopically

NOTE Confidence: 0.8208043

00:09:42.920 --> 00:09:46.149 Express a flag tag version of fly,

NOTE Confidence: 0.8208043

00:09:46.150 --> 00:09:48.166 one in early progenitors.

NOTE Confidence: 0.8208043

00:09:48.166 --> 00:09:49.678 And then again,

NOTE Confidence: 0.8208043

00:09:49.680 --> 00:09:51.176 we followed differentiation by

NOTE Confidence: 0.8208043

00:09:51.176 --> 00:09:53.838 site of analysis and this time we

NOTE Confidence: 0.8208043

00:09:53.838 --> 00:09:55.938 identified not one but two trajectories

NOTE Confidence: 0.8208043

00:09:55.938 --> 00:09:58.072 in addition to the average rate

NOTE Confidence: 0.8208043

00:09:58.072 --> 00:10:00.118 trajectory that you can see here.

NOTE Confidence: 0.8208043

00:10:00.120 --> 00:10:02.318 By high level of expression of the

NOTE Confidence: 0.8208043

00:10:02.318 --> 00:10:04.812 Alpha globin we also found a second

NOTE Confidence: 0.8208043

00:10:04.812 --> 00:10:06.667 trajectory here which correspond to

NOTE Confidence: 0.8208043

00:10:06.667 --> 00:10:08.326 the megakaryocytic trajectory as

NOTE Confidence: 0.8208043

00:10:08.326 --> 00:10:11.182 shown by high level of expression of

NOTE Confidence: 0.821070433333334

00:10:11.190 --> 00:10:12.738 the city 41 marker.

NOTE Confidence: 0.821070433333334

00:10:12.738 --> 00:10:15.550 And then when we followed the cells

NOTE Confidence: 0.821070433333334

00:10:15.550 --> 00:10:18.371 that express flag fly one by including

NOTE Confidence: 0.821070433333334

00:10:18.371 --> 00:10:21.238 a flag antibody in our cocktail,

NOTE Confidence: 0.821070433333334

00:10:21.240 --> 00:10:23.280 we could determine that only the

NOTE Confidence: 0.821070433333334

00:10:23.280 --> 00:10:25.938 cells that express flag fly one shown

NOTE Confidence: 0.821070433333334

00:10:25.938 --> 00:10:27.998 in blue are differentiating towards

NOTE Confidence: 0.821070433333334

00:10:27.998 --> 00:10:29.560 the megakaryocytic trajectory,

NOTE Confidence: 0.821070433333334

00:10:29.560 --> 00:10:31.744 while the cells that do not

NOTE Confidence: 0.821070433333334

00:10:31.744 --> 00:10:34.247 express factor one shown here in

NOTE Confidence: 0.821070433333334

00:10:34.247 --> 00:10:36.183 green continue to differentiate

NOTE Confidence: 0.821070433333334

00:10:36.183 --> 00:10:38.119 along the imagery trajectory.

NOTE Confidence: 0.821070433333334

00:10:38.120 --> 00:10:40.598 So this experiment showed that the

NOTE Confidence: 0.821070433333334

00:10:40.598 --> 00:10:42.988 ectopic expression of Flight 1 is

NOTE Confidence: 0.821070433333334

00:10:42.988 --> 00:10:45.326 able to deviate the cells from their

NOTE Confidence: 0.821070433333334

00:10:45.326 --> 00:10:47.253 preferred every trade tragic tree

NOTE Confidence: 0.821070433333334

00:10:47.253 --> 00:10:49.533 to take on a megakaryocytic faith.

NOTE Confidence: 0.821070433333334

00:10:49.540 --> 00:10:50.398 So overall,

NOTE Confidence: 0.821070433333334

00:10:50.398 --> 00:10:52.543 these results are supports the

NOTE Confidence: 0.821070433333334

00:10:52.543 --> 00:10:54.352 concepts that quantitative changes

NOTE Confidence: 0.821070433333334

00:10:54.352 --> 00:10:56.622 in transcription factor put in

NOTE Confidence: 0.821070433333334

00:10:56.622 --> 00:10:58.438 levels in individual hematopoietic

NOTE Confidence: 0.821070433333334

00:10:58.505 --> 00:11:00.165 progenitors are key determinants

NOTE Confidence: 0.821070433333334

00:11:00.165 --> 00:11:02.240 of the cell fate decisions.

NOTE Confidence: 0.821070433333334

00:11:02.240 --> 00:11:04.697 Now in our site of experiment we

NOTE Confidence: 0.821070433333334

00:11:04.697 --> 00:11:07.231 could account for all older cell

NOTE Confidence: 0.821070433333334

00:11:07.231 --> 00:11:09.111 populations that were present

NOTE Confidence: 0.821070433333334

00:11:09.111 --> 00:11:11.671 in our differentiation media and

NOTE Confidence: 0.821070433333334

00:11:11.671 --> 00:11:13.823 that includes the hematopoetic

NOTE Confidence: 0.821070433333334

00:11:13.823 --> 00:11:15.437 progenitors erythroid cells.

NOTE Confidence: 0.821070433333334

00:11:15.440 --> 00:11:18.170 Also some megakaryocytes and Milo itself.

NOTE Confidence: 0.821070433333334

00:11:18.170 --> 00:11:18.674 However,

NOTE Confidence: 0.821070433333334

00:11:18.674 --> 00:11:22.202 there was one major cell population here

NOTE Confidence: 0.821070433333334

00:11:22.202 --> 00:11:25.687 for which the identity was less clear.

NOTE Confidence: 0.821070433333334

00:11:25.690 --> 00:11:27.680 And as you can see,

NOTE Confidence: 0.821070433333334

00:11:27.680 --> 00:11:29.804 the cell population starts to accumulate

NOTE Confidence: 0.821070433333334

00:11:29.804 --> 00:11:32.045 from day four of differentiation and

NOTE Confidence: 0.821070433333334

00:11:32.045 --> 00:11:34.319 then it increases until the 11th

NOTE Confidence: 0.821070433333334

00:11:34.319 --> 00:11:36.484 and then starts to progressively

NOTE Confidence: 0.821070433333334

00:11:36.484 --> 00:11:38.272 decrease and then completely

NOTE Confidence: 0.821070433333334

00:11:38.272 --> 00:11:41.560 disappears from our differentiation.

NOTE Confidence: 0.821070433333334

00:11:41.560 --> 00:11:43.240 Such a medium.

NOTE Confidence: 0.821070433333334

00:11:43.240 --> 00:11:45.292 Now looking at the cell surface

NOTE Confidence: 0.821070433333334

00:11:45.292 --> 00:11:46.660 markers for this population,

NOTE Confidence: 0.821070433333334

00:11:46.660 --> 00:11:48.400 we notice that it expresses

NOTE Confidence: 0.821070433333334

00:11:48.400 --> 00:11:50.420 very high levels of CD 44,

NOTE Confidence: 0.821070433333334

00:11:50.420 --> 00:11:53.498 which you can see here on the heat map,

NOTE Confidence: 0.821070433333334

00:11:53.500 --> 00:11:55.546 but also on this Disney plot.

NOTE Confidence: 0.821070433333334

00:11:55.550 --> 00:11:57.692 And we also notice that this

NOTE Confidence: 0.821070433333334

00:11:57.692 --> 00:11:58.763 sector population expresses

NOTE Confidence: 0.821070433333334

00:11:58.763 --> 00:12:00.000 intermediate levels of CD123.

NOTE Confidence: 0.821070433333334

00:12:00.000 --> 00:12:03.078 But when we look closer on a Disney product,

NOTE Confidence: 0.821070433333334

00:12:03.080 --> 00:12:04.785 you can see the expression

NOTE Confidence: 0.821070433333334

00:12:04.785 --> 00:12:06.149 of CD123 is heterogeneous,

NOTE Confidence: 0.821070433333334

00:12:06.150 --> 00:12:07.746 with some cells expressing

NOTE Confidence: 0.821070433333334

00:12:07.746 --> 00:12:09.741 extremely high levels an other

NOTE Confidence: 0.821070433333334

00:12:09.741 --> 00:12:12.038 cells are moderate levels of CD123.

NOTE Confidence: 0.821070433333334

00:12:12.040 --> 00:12:14.074 We also notice that these cells

NOTE Confidence: 0.821070433333334

00:12:14.074 --> 00:12:15.979 express very high levels of data.

NOTE Confidence: 0.821070433333334

00:12:15.980 --> 00:12:16.407 Two,

NOTE Confidence: 0.821070433333334

00:12:16.407 --> 00:12:18.969 it's actually the cell population that

NOTE Confidence: 0.821070433333334

00:12:18.969 --> 00:12:21.767 expresses the highest level of of getting 2.

NOTE Confidence: 0.821070433333334

00:12:21.770 --> 00:12:23.938 In in our experiment,

NOTE Confidence: 0.821070433333334

00:12:23.938 --> 00:12:27.190 and it does express graded levels

NOTE Confidence: 0.821070433333334

00:12:27.297 --> 00:12:30.307 of the transferring receptor CD

NOTE Confidence: 0.821070433333334

00:12:30.307 --> 00:12:33.317 71 but is completely negative

NOTE Confidence: 0.821070433333334

00:12:33.415 --> 00:12:36.079 for the early marker CD 34.

NOTE Confidence: 0.821070433333334

00:12:36.080 --> 00:12:38.055 So based on these combination

NOTE Confidence: 0.821070433333334

00:12:38.055 --> 00:12:39.635 of cell surface markers,

NOTE Confidence: 0.821070433333334

00:12:39.640 --> 00:12:41.810 it suggested that these populations

NOTE Confidence: 0.821070433333334

00:12:41.810 --> 00:12:43.546 could represent battlefields which

NOTE Confidence: 0.821070433333334

00:12:43.546 --> 00:12:45.790 at first we found a surprising

NOTE Confidence: 0.821070433333334

00:12:45.790 --> 00:12:47.540 because basil fees are supposed

NOTE Confidence: 0.821070433333334

00:12:47.607 --> 00:12:49.507 to emerge from the granulocytic.

NOTE Confidence: 0.821070433333334

00:12:49.510 --> 00:12:52.275 So the model with branch of differentiation,

NOTE Confidence: 0.821070433333334

00:12:52.280 --> 00:12:54.250 not the average rate branch.

NOTE Confidence: 0.821070433333334

00:12:54.250 --> 00:12:54.678 However,

NOTE Confidence: 0.821070433333334

00:12:54.678 --> 00:12:56.818 these results are consistent with

NOTE Confidence: 0.821070433333334

00:12:56.818 --> 00:12:59.319 a single scientific data that have

NOTE Confidence: 0.821070433333334

00:12:59.319 --> 00:13:01.467 been published both from mouse bone

NOTE Confidence: 0.821070433333334

00:13:01.467 --> 00:13:03.835 marrow and from human bone marrow

NOTE Confidence: 0.821070433333334

00:13:03.835 --> 00:13:06.211 that have identified a cell population.

NOTE Confidence: 0.821070433333334

00:13:06.220 --> 00:13:08.705 In close proximity to the error rate,

NOTE Confidence: 0.821070433333334

00:13:08.710 --> 00:13:10.402 cells that with the gene expression

NOTE Confidence: 0.821070433333334

00:13:10.402 --> 00:13:12.943 profile that that is consistent with the

NOTE Confidence: 0.821070433333334

00:13:12.943 --> 00:13:14.755 battlefield identity transcription factors.

NOTE Confidence: 0.821070433333334

00:13:14.760 --> 00:13:16.896 Now why do we want to

NOTE Confidence: 0.821070433333334

00:13:16.896 --> 00:13:17.964 know Putin's documetary?

NOTE Confidence: 0.821070433333334

00:13:17.970 --> 00:13:19.017 First of all,

NOTE Confidence: 0.821070433333334

00:13:19.017 --> 00:13:21.111 because we want to better understand

NOTE Confidence: 0.821070433333334

00:13:21.111 --> 00:13:22.947 how this changes in stock.

NOTE Confidence: 0.821070433333334

00:13:22.950 --> 00:13:24.018 Yama tree, Dr,

NOTE Confidence: 0.821070433333334

00:13:24.018 --> 00:13:25.086 Cell fate decisions.

NOTE Confidence: 0.821070433333334

00:13:25.090 --> 00:13:26.815 But also because despite everything

NOTE Confidence: 0.821070433333334

00:13:26.815 --> 00:13:28.973 that we have learned from genomic

NOTE Confidence: 0.821070433333334

00:13:28.973 --> 00:13:30.813 studies and cheap seek about

NOTE Confidence: 0.821070433333334

00:13:30.813 --> 00:13:32.285 the binding of transcription

NOTE Confidence: 0.821070433333334

00:13:32.346 --> 00:13:33.986 factors to their target side,

NOTE Confidence: 0.7989812

00:13:33.990 --> 00:13:35.845 we still don't know how

NOTE Confidence: 0.7989812

00:13:35.845 --> 00:13:36.958 many transcription factors.

NOTE Confidence: 0.7989812

00:13:36.960 --> 00:13:39.382 Are there compared to the number of

NOTE Confidence: 0.7989812

00:13:39.382 --> 00:13:41.606 binding sites and we still don't

NOTE Confidence: 0.7989812

00:13:41.606 --> 00:13:43.466 know if cofactors are limiting

NOTE Confidence: 0.7989812

00:13:43.466 --> 00:13:45.720 compared to transcription factors,

NOTE Confidence: 0.7989812

00:13:45.720 --> 00:13:47.715 in which case the transcription

NOTE Confidence: 0.7989812

00:13:47.715 --> 00:13:50.090 factors must compete to recruit them,

NOTE Confidence: 0.7989812

00:13:50.090 --> 00:13:51.682 or whether cofactors are

NOTE Confidence: 0.7989812

00:13:51.682 --> 00:13:53.274 present in large excess,

NOTE Confidence: 0.7989812

00:13:53.280 --> 00:13:56.328 in which case there equipment would

NOTE Confidence: 0.7989812

00:13:56.328 --> 00:13:57.852 be highly facilitated.

NOTE Confidence: 0.7989812

00:13:57.860 --> 00:14:00.350 Now, if one wants to measure

NOTE Confidence: 0.7989812

00:14:00.350 --> 00:14:01.595 documetary between Putin's,

NOTE Confidence: 0.7989812

00:14:01.600 --> 00:14:03.802 it is necessary to use approaches

NOTE Confidence: 0.7989812

00:14:03.802 --> 00:14:05.270 that provide an absolute

NOTE Confidence: 0.7989812

00:14:05.339 --> 00:14:07.427 quantification of these proteins.

NOTE Confidence: 0.7989812

00:14:07.430 --> 00:14:10.342 So we decided to use a targeted

NOTE Confidence: 0.7989812

00:14:10.342 --> 00:14:11.590 mass spectrometry approach,

NOTE Confidence: 0.7989812

00:14:11.590 --> 00:14:13.670 which is called selected reaction

NOTE Confidence: 0.7989812

00:14:13.670 --> 00:14:15.267 monitoring our SRM, which,

NOTE Confidence: 0.7989812

00:14:15.267 --> 00:14:17.696 when coupled with the spiking of known

NOTE Confidence: 0.7989812

00:14:17.696 --> 00:14:20.318 amounts of isotopically labeled peptides,

NOTE Confidence: 0.7989812

00:14:20.320 --> 00:14:21.988 can provide an absolute

NOTE Confidence: 0.7989812

00:14:21.988 --> 00:14:23.239 quantification of footings.

NOTE Confidence: 0.7989812

00:14:23.240 --> 00:14:24.036 Now recently,

NOTE Confidence: 0.7989812

00:14:24.036 --> 00:14:26.026 a number of publications came

NOTE Confidence: 0.7989812

00:14:26.026 --> 00:14:27.872 out using quantitative mass

NOTE Confidence: 0.7989812

00:14:27.872 --> 00:14:29.040 spectrometry approaches.

NOTE Confidence: 0.7989812

00:14:29.040 --> 00:14:31.010 Which we are not SRM,

NOTE Confidence: 0.7989812

00:14:31.010 --> 00:14:33.914 so I just wanted to take a few

NOTE Confidence: 0.7989812

00:14:33.914 --> 00:14:36.569 minutes to explain why we have

NOTE Confidence: 0.7989812

00:14:36.569 --> 00:14:39.329 decided to use this SRM approach

NOTE Confidence: 0.7989812

00:14:39.422 --> 00:14:41.990 for our for our own purposes.

NOTE Confidence: 0.7989812

00:14:41.990 --> 00:14:44.182 So first of all I will start by

NOTE Confidence: 0.7989812

00:14:44.182 --> 00:14:46.411 saying that my spectrometry is not

NOTE Confidence: 0.7989812

00:14:46.411 --> 00:14:48.421 inherently quantitative an what it

NOTE Confidence: 0.7989812

00:14:48.421 --> 00:14:50.887 means is that the intensity of the

NOTE Confidence: 0.7989812

00:14:50.887 --> 00:14:53.174 signal that is measured by the mass

NOTE Confidence: 0.7989812

00:14:53.174 --> 00:14:54.764 spectrometer does not only depend

NOTE Confidence: 0.7989812

00:14:54.764 --> 00:14:56.989 on the abundance of the peptide,

NOTE Confidence: 0.7989812

00:14:56.990 --> 00:14:59.718 but also on a number of other criteria,

NOTE Confidence: 0.7989812

00:14:59.720 --> 00:15:01.766 such as the amino acid composition

NOTE Confidence: 0.7989812

00:15:01.766 --> 00:15:03.130 or the ionization efficiency,

NOTE Confidence: 0.7989812

00:15:03.130 --> 00:15:05.170 or other parameters that are

NOTE Confidence: 0.7989812

00:15:05.170 --> 00:15:07.578 not fully understood and what it

NOTE Confidence: 0.7989812

00:15:07.578 --> 00:15:09.643 means is that it's not unusual to

NOTE Confidence: 0.7989812

00:15:09.643 --> 00:15:11.998 be in situation like this one.

NOTE Confidence: 0.7989812

00:15:12.000 --> 00:15:14.380 When you have a very high abundant

NOTE Confidence: 0.7989812

00:15:14.380 --> 00:15:16.349 peptide like the blue peptide

NOTE Confidence: 0.7989812

00:15:16.349 --> 00:15:18.989 producing a low intensity signal by

NOTE Confidence: 0.7989812

00:15:18.989 --> 00:15:21.138 mass spectrometry or lower opponents

NOTE Confidence: 0.7989812

00:15:21.138 --> 00:15:23.138 peptide like the red peptide,

NOTE Confidence: 0.7989812

00:15:23.140 --> 00:15:26.500 producing a very high intensity signal.

NOTE Confidence: 0.7989812

00:15:26.500 --> 00:15:28.510 Now to overcome this limitation and

NOTE Confidence: 0.7989812

00:15:28.510 --> 00:15:30.806 still being able to extract quantitative

NOTE Confidence: 0.7989812

00:15:30.806 --> 00:15:33.026 information from my spec data,

NOTE Confidence: 0.7989812

00:15:33.030 --> 00:15:35.718 a number of strategies have been proposed.

NOTE Confidence: 0.7989812

00:15:35.720 --> 00:15:37.640 Anna very popular strategy is

NOTE Confidence: 0.7989812

00:15:37.640 --> 00:15:39.560 called the Proteomic Ruler Method,

NOTE Confidence: 0.7989812

00:15:39.560 --> 00:15:41.672 which has been established by the

NOTE Confidence: 0.7989812

00:15:41.672 --> 00:15:43.984 lab of Matthias Mann to estimate

NOTE Confidence: 0.7989812

00:15:43.984 --> 00:15:46.079 copy number of proteins preserve,

NOTE Confidence: 0.7989812

00:15:46.080 --> 00:15:48.656 so this method is using the mass

NOTE Confidence: 0.7989812

00:15:48.656 --> 00:15:50.197 spectrometry signals from histones

NOTE Confidence: 0.7989812

00:15:50.197 --> 00:15:52.405 as an internal standard to quantify

NOTE Confidence: 0.7989812

00:15:52.405 --> 00:15:54.150 all the other footings,

NOTE Confidence: 0.7989812

00:15:54.150 --> 00:15:56.710 and this is this is a very effective

NOTE Confidence: 0.7989812

00:15:56.710 --> 00:15:59.520 method to estimate putting copy numbers.

NOTE Confidence: 0.7989812

00:15:59.520 --> 00:16:01.236 It's also high throughput.

NOTE Confidence: 0.7989812

00:16:01.236 --> 00:16:03.381 You can measure thousands of

NOTE Confidence: 0.7989812

00:16:03.381 --> 00:16:05.418 proteins in a single experiment,

NOTE Confidence: 0.7989812

00:16:05.420 --> 00:16:07.877 and it is quite easy to do and it

NOTE Confidence: 0.7989812

00:16:07.877 --> 00:16:11.247 has been used in and in a lot of

NOTE Confidence: 0.7989812

00:16:11.247 --> 00:16:13.366 different publications and I have

NOTE Confidence: 0.7989812

00:16:13.366 --> 00:16:15.511 highlighted some of these publications

NOTE Confidence: 0.7989812

00:16:15.511 --> 00:16:18.020 here for high throughput studies.

NOTE Confidence: 0.7989812

00:16:18.020 --> 00:16:18.570 So,

NOTE Confidence: 0.7989812

00:16:18.570 --> 00:16:19.120 however,

NOTE Confidence: 0.7989812

00:16:19.120 --> 00:16:21.160 in our case we want it to be

NOTE Confidence: 0.7989812

00:16:21.160 --> 00:16:23.555 able to distinguish even subtle

NOTE Confidence: 0.7989812

00:16:23.555 --> 00:16:25.967 differences in the circulatory

NOTE Confidence: 0.7989812

00:16:25.967 --> 00:16:27.776 between transcription factors.

NOTE Confidence: 0.7989812

00:16:27.780 --> 00:16:30.378 So so instead we decided to

NOTE Confidence: 0.7989812

00:16:30.378 --> 00:16:32.110 use a different approach,

NOTE Confidence: 0.7989812

00:16:32.110 --> 00:16:34.532 which is based on the spiking of

NOTE Confidence: 0.7989812

00:16:34.532 --> 00:16:36.683 known amount of isotopically labeled

NOTE Confidence: 0.7989812

00:16:36.683 --> 00:16:40.323 peptides that are used as internal controls.

NOTE Confidence: 0.7989812

00:16:40.330 --> 00:16:41.986 So in this approach,

NOTE Confidence: 0.7989812

00:16:41.986 --> 00:16:43.642 each individual peptide is

NOTE Confidence: 0.7989812

00:16:43.642 --> 00:16:45.446 quantified using an isotopically

NOTE Confidence: 0.7989812

00:16:45.446 --> 00:16:47.258 labeled version of itself,

NOTE Confidence: 0.7989812

00:16:47.260 --> 00:16:48.502 as illustrated here.

NOTE Confidence: 0.7989812

00:16:48.502 --> 00:16:50.986 Which we called the the silk

NOTE Confidence: 0.7989812

00:16:50.986 --> 00:16:53.581 peptide and this approach has been

NOTE Confidence: 0.7989812

00:16:53.581 --> 00:16:55.686 shown to be extremely sensitive

NOTE Confidence: 0.843861926086957

00:16:55.764 --> 00:16:57.000 to dynamic range,

NOTE Confidence: 0.843861926086957

00:16:57.000 --> 00:16:59.316 is very large and it's currently

NOTE Confidence: 0.843861926086957

00:16:59.316 --> 00:17:02.715 considered as a gold standard for putting

NOTE Confidence: 0.843861926086957

00:17:02.715 --> 00:17:05.087 quantification by mass spectrometry.

NOTE Confidence: 0.843861926086957

00:17:05.090 --> 00:17:08.079 So to use to establish SRM assay

NOTE Confidence: 0.843861926086957

00:17:08.079 --> 00:17:09.360 for putting quantification,

NOTE Confidence: 0.843861926086957

00:17:09.360 --> 00:17:11.718 we collaborated with Jeff and Ishan

NOTE Confidence: 0.843861926086957

00:17:11.718 --> 00:17:13.832 Margulis pee from the Institute

NOTE Confidence: 0.843861926086957

00:17:13.832 --> 00:17:16.187 for Systems Biology in Seattle,

NOTE Confidence: 0.843861926086957

00:17:16.190 --> 00:17:18.800 and we developed SRM assay and

NOTE Confidence: 0.843861926086957

00:17:18.800 --> 00:17:21.410 optimize Sri massive over 100 Putin's

NOTE Confidence: 0.843861926086957

00:17:21.410 --> 00:17:24.182 and we decided to use a different

NOTE Confidence: 0.843861926086957

00:17:24.182 --> 00:17:26.144 types of proteins, including.

NOTE Confidence: 0.843861926086957

00:17:26.144 --> 00:17:28.360 DNA binding transcription factors,

NOTE Confidence: 0.843861926086957

00:17:28.360 --> 00:17:30.064 but also compressors, coactivators,

NOTE Confidence: 0.843861926086957

00:17:30.064 --> 00:17:31.768 some chromatin remodeling enzyme,

NOTE Confidence: 0.843861926086957

00:17:31.770 --> 00:17:34.752 as well as some subunits of the

NOTE Confidence: 0.843861926086957

00:17:34.752 --> 00:17:36.030 general transcription machinery.

NOTE Confidence: 0.843861926086957

00:17:36.030 --> 00:17:37.865 And overall we quantified 103

NOTE Confidence: 0.843861926086957

00:17:37.865 --> 00:17:40.794 proteins at 13 time points during the

NOTE Confidence: 0.843861926086957

00:17:40.794 --> 00:17:42.846 course of erythroid differentiation.

NOTE Confidence: 0.843861926086957

00:17:42.850 --> 00:17:45.734 Now I should mention that even though

NOTE Confidence: 0.843861926086957

00:17:45.734 --> 00:17:48.347 these SRM assay are quite expensive

NOTE Confidence: 0.843861926086957

00:17:48.347 --> 00:17:50.939 to develop and they take time,

NOTE Confidence: 0.843861926086957

00:17:50.940 --> 00:17:54.540 but once they have been developed

NOTE Confidence: 0.843861926086957

00:17:54.540 --> 00:17:56.940 they can be reused.

NOTE Confidence: 0.843861926086957

00:17:56.940 --> 00:17:59.924 Much cheaper way and fast way to be

NOTE Confidence: 0.843861926086957

00:17:59.924 --> 00:18:03.583 able to quantify the same protein in

NOTE Confidence: 0.843861926086957

00:18:03.583 --> 00:18:06.403 in a different cellular environment.

NOTE Confidence: 0.843861926086957

00:18:06.410 --> 00:18:08.630 So because we wanted to build

NOTE Confidence: 0.843861926086957

00:18:08.630 --> 00:18:09.740 gene regulatory network,

NOTE Confidence: 0.843861926086957

00:18:09.740 --> 00:18:11.960 we also had to measure changes

NOTE Confidence: 0.843861926086957

00:18:11.960 --> 00:18:13.440 in our near levels.

NOTE Confidence: 0.843861926086957

00:18:13.440 --> 00:18:14.172 So again,

NOTE Confidence: 0.843861926086957

00:18:14.172 --> 00:18:16.734 we have just excels at regular intervals

NOTE Confidence: 0.843861926086957

00:18:16.734 --> 00:18:19.356 during the course of their true policies,

NOTE Confidence: 0.843861926086957

00:18:19.360 --> 00:18:23.545 and we measured our in a level by RNA

NOTE Confidence: 0.843861926086957

00:18:23.545 --> 00:18:26.630 sequencing and put in levels by SRAM.

NOTE Confidence: 0.843861926086957

00:18:26.630 --> 00:18:27.394 And first,

NOTE Confidence: 0.843861926086957

00:18:27.394 --> 00:18:29.304 focusing on the RNA data.

NOTE Confidence: 0.843861926086957

00:18:29.310 --> 00:18:31.524 Here I'm showing this irony Sickbay

NOTE Confidence: 0.843861926086957

00:18:31.524 --> 00:18:33.000 Suretrade trajectory overtime along

NOTE Confidence: 0.843861926086957

00:18:33.057 --> 00:18:34.669 these two principal components,

NOTE Confidence: 0.843861926086957

00:18:34.670 --> 00:18:36.590 and as you can see,

NOTE Confidence: 0.843861926086957

00:18:36.590 --> 00:18:39.481 there is a nice purple nice progression

NOTE Confidence: 0.843861926086957

00:18:39.481 --> 00:18:41.576 from the hematopoietic stem and

NOTE Confidence: 0.843861926086957

00:18:41.576 --> 00:18:44.327 progenitor cells at day zero to the

NOTE Confidence: 0.843861926086957

00:18:44.327 --> 00:18:46.590 differentiated erythroid cells shown here.

NOTE Confidence: 0.843861926086957

00:18:46.590 --> 00:18:48.942 Now looking at the proteins that we

NOTE Confidence: 0.843861926086957

00:18:48.942 --> 00:18:51.309 have measured by hospital clustering,

NOTE Confidence: 0.843861926086957

00:18:51.310 --> 00:18:54.397 you can see that there are different

NOTE Confidence: 0.843861926086957

00:18:54.397 --> 00:18:56.743 clusters and these clusters appear

NOTE Confidence: 0.843861926086957

00:18:56.743 --> 00:18:59.569 to be a temporary Co regulated.

NOTE Confidence: 0.843861926086957

00:18:59.570 --> 00:19:01.682 Now the first question we wanted

NOTE Confidence: 0.843861926086957

00:19:01.682 --> 00:19:04.604 to ask was whether there is a good

NOTE Confidence: 0.843861926086957

00:19:04.604 --> 00:19:06.399 correlation between putting an M

NOTE Confidence: 0.843861926086957

00:19:06.399 --> 00:19:08.910 RNA during erythropoiesis and 1st.

NOTE Confidence: 0.843861926086957

00:19:08.910 --> 00:19:10.850 We looked at global correlation

NOTE Confidence: 0.843861926086957

00:19:10.850 --> 00:19:12.014 as illustrated here.

NOTE Confidence: 0.843861926086957

00:19:12.020 --> 00:19:14.180 Looking at M RNA level versus

NOTE Confidence: 0.843861926086957

00:19:14.180 --> 00:19:16.616 protein levels and what we found is

NOTE Confidence: 0.843861926086957

00:19:16.616 --> 00:19:18.758 that there is really quite a good

NOTE Confidence: 0.843861926086957

00:19:18.830 --> 00:19:21.350 correlation in differentiating cells.

NOTE Confidence: 0.843861926086957

00:19:21.350 --> 00:19:21.718 However,

NOTE Confidence: 0.843861926086957

00:19:21.718 --> 00:19:23.926 the correlation is extremely low in

NOTE Confidence: 0.843861926086957

00:19:23.926 --> 00:19:26.020 hematopoietic stem and progenitor cells,

NOTE Confidence: 0.843861926086957

00:19:26.020 --> 00:19:27.940 which is consistent with published

NOTE Confidence: 0.843861926086957

00:19:27.940 --> 00:19:30.395 data that have shown that the

NOTE Confidence: 0.843861926086957

00:19:30.395 --> 00:19:31.787 protein translation rate.

NOTE Confidence: 0.843861926086957

00:19:31.790 --> 00:19:34.460 Is extremely low in the hematopoietic

NOTE Confidence: 0.843861926086957

00:19:34.460 --> 00:19:36.240 stem and progenitor cells.

NOTE Confidence: 0.843861926086957

00:19:36.240 --> 00:19:38.976 So next we wanted to look at the

NOTE Confidence: 0.843861926086957

00:19:38.976 --> 00:19:41.156 correlation between our input in

NOTE Confidence: 0.843861926086957

00:19:41.156 --> 00:19:43.052 changes overtime during differentiation

NOTE Confidence: 0.843861926086957

00:19:43.052 --> 00:19:45.456 as illustrated here and what we

NOTE Confidence: 0.843861926086957

00:19:45.456 --> 00:19:47.577 found is that for most genes there

NOTE Confidence: 0.843861926086957

00:19:47.580 --> 00:19:49.092 is a positive correlation.

NOTE Confidence: 0.843861926086957

00:19:49.092 --> 00:19:49.470 However,

NOTE Confidence: 0.843861926086957

00:19:49.470 --> 00:19:51.899 for some genes there is low correlation

NOTE Confidence: 0.843861926086957

00:19:51.899 --> 00:19:54.380 and even sometimes a negative correlation.

NOTE Confidence: 0.843861926086957

00:19:54.380 --> 00:19:57.117 So for example here if we look

NOTE Confidence: 0.843861926086957

00:19:57.117 --> 00:20:00.197 at the fly one or get the two.

NOTE Confidence: 0.843861926086957

00:20:00.200 --> 00:20:02.424 She and you can see that there is

NOTE Confidence: 0.843861926086957

00:20:02.424 --> 00:20:04.301 a very good correlation between

NOTE Confidence: 0.843861926086957

00:20:04.301 --> 00:20:07.220 changes in putting an M RNA levels.

NOTE Confidence: 0.843861926086957

00:20:07.220 --> 00:20:07.571 However,

NOTE Confidence: 0.843861926086957

00:20:07.571 --> 00:20:10.730 for other genes such as get our Nortel one,

NOTE Confidence: 0.843861926086957

00:20:10.730 --> 00:20:13.257 you can see the Putin level is

NOTE Confidence: 0.843861926086957

00:20:13.257 --> 00:20:15.637 increasing much faster than the our name,

NOTE Confidence: 0.843861926086957

00:20:15.640 --> 00:20:17.456 suggesting an important contribution

NOTE Confidence: 0.843861926086957

00:20:17.456 --> 00:20:19.272 of the post transcriptional

NOTE Confidence: 0.843861926086957

00:20:19.272 --> 00:20:20.180 regulatory mechanisms.

NOTE Confidence: 0.843861926086957

00:20:20.180 --> 00:20:21.950 So if you are interested

NOTE Confidence: 0.843861926086957

00:20:21.950 --> 00:20:23.720 in looking at other genes

NOTE Confidence: 0.87455606

00:20:23.792 --> 00:20:25.348 that we have measured,

NOTE Confidence: 0.87455606

00:20:25.350 --> 00:20:28.318 we have we have done a website here

NOTE Confidence: 0.87455606

00:20:28.318 --> 00:20:31.404 which I'm going to try to access and I

NOTE Confidence: 0.87455606

00:20:31.404 --> 00:20:34.831 hope it is going to work so I'm just

NOTE Confidence: 0.87455606

00:20:34.831 --> 00:20:37.833 gonna stop sharing for a few seconds.

NOTE Confidence: 0.87455606

00:20:37.833 --> 00:20:39.717 And try to share.

NOTE Confidence: 0.856727264285714

00:20:45.730 --> 00:20:47.362 My other sites. OK,

NOTE Confidence: 0.856727264285714

00:20:47.362 --> 00:20:51.608 so I hope you can see it so so perfect.

NOTE Confidence: 0.856727264285714

00:20:51.610 --> 00:20:53.787 Thank you so on these websites we

NOTE Confidence: 0.856727264285714

00:20:53.787 --> 00:20:56.690 have to drop down menu here with the

NOTE Confidence: 0.856727264285714

00:20:56.690 --> 00:20:58.585 proteins that you have measured.

NOTE Confidence: 0.856727264285714

00:20:58.590 --> 00:21:00.782 So I just wanted to show you an

NOTE Confidence: 0.856727264285714

00:21:00.782 --> 00:21:03.236 example of proteins that going up

NOTE Confidence: 0.856727264285714

00:21:03.236 --> 00:21:05.068 during differentiation where there

NOTE Confidence: 0.856727264285714

00:21:05.068 --> 00:21:06.953 is extremely good correlation so

NOTE Confidence: 0.856727264285714

00:21:06.953 --> 00:21:09.418 you can see so on the left side.

NOTE Confidence: 0.856727264285714

00:21:09.418 --> 00:21:12.282 Here we have put in copy number per

NOTE Confidence: 0.856727264285714

00:21:12.282 --> 00:21:14.825 cell and the blue graph correspond to

NOTE Confidence: 0.856727264285714

00:21:14.825 --> 00:21:18.340 put in an on the right we have the RNA.

NOTE Confidence: 0.856727264285714

00:21:18.340 --> 00:21:20.566 And from left to right we have

NOTE Confidence: 0.856727264285714

00:21:20.566 --> 00:21:22.300 a differentiation from MPP to

NOTE Confidence: 0.856727264285714

00:21:22.300 --> 00:21:23.380 Basel figurative glass,

NOTE Confidence: 0.856727264285714

00:21:23.380 --> 00:21:25.918 so you can see this two hour and then

NOTE Confidence: 0.856727264285714

00:21:25.918 --> 00:21:28.755 put in correlate extremely well for six,

NOTE Confidence: 0.856727264285714

00:21:28.760 --> 00:21:31.208 6, but actually for for a lot of

NOTE Confidence: 0.856727264285714

00:21:31.208 --> 00:21:33.423 proteins there is a very low correlation

NOTE Confidence: 0.856727264285714

00:21:33.423 --> 00:21:35.810 or or even a negative correlation.

NOTE Confidence: 0.856727264285714

00:21:35.810 --> 00:21:38.834 I just want to show you one more one.

NOTE Confidence: 0.856727264285714

00:21:38.840 --> 00:21:41.020 Another example kept away which

NOTE Confidence: 0.856727264285714

00:21:41.020 --> 00:21:43.891 is a histo nasty transfer is also

NOTE Confidence: 0.856727264285714

00:21:43.891 --> 00:21:46.339 called GCN 5 and you can see for

NOTE Confidence: 0.856727264285714

00:21:46.417 --> 00:21:48.785 this put in the RNA and put in.

NOTE Confidence: 0.856727264285714

00:21:48.790 --> 00:21:50.834 Growth curves have almost

NOTE Confidence: 0.856727264285714

00:21:50.834 --> 00:21:53.900 nothing to do with each other,

NOTE Confidence: 0.856727264285714

00:21:53.900 --> 00:21:56.880 suggesting a highly complex

NOTE Confidence: 0.856727264285714

00:21:56.880 --> 00:21:59.115 posttranscriptional regulation mechanism.

NOTE Confidence: 0.856727264285714

00:21:59.120 --> 00:22:00.780 So.

NOTE Confidence: 0.856727264285714

00:22:00.780 --> 00:22:05.613 I will just go back to my presentation now.

NOTE Confidence: 0.856727264285714

00:22:05.620 --> 00:22:06.416 OK, perfect,

NOTE Confidence: 0.856727264285714

00:22:06.416 --> 00:22:08.406 so as you could see,

NOTE Confidence: 0.856727264285714

00:22:08.410 --> 00:22:11.200 we found that there are really

NOTE Confidence: 0.856727264285714

00:22:11.200 --> 00:22:12.595 major discrepancies between

NOTE Confidence: 0.856727264285714

00:22:12.595 --> 00:22:14.769 mRNA and put in and put in.

NOTE Confidence: 0.856727264285714

00:22:14.770 --> 00:22:15.964 Abundance is an.

NOTE Confidence: 0.856727264285714

00:22:15.964 --> 00:22:17.954 This is for master regulators

NOTE Confidence: 0.856727264285714

00:22:17.954 --> 00:22:18.750 of erythropoiesis,

NOTE Confidence: 0.856727264285714

00:22:18.750 --> 00:22:21.080 suggesting that gene regulatory networks

NOTE Confidence: 0.856727264285714

00:22:21.080 --> 00:22:24.640 should not be limited to M RNA but

NOTE Confidence: 0.856727264285714

00:22:24.640 --> 00:22:26.565 should also integrate put things.

NOTE Confidence: 0.856727264285714

00:22:26.570 --> 00:22:28.747 And this is what we tried to

NOTE Confidence: 0.856727264285714

00:22:28.747 --> 00:22:30.678 do in collaboration with the

NOTE Confidence: 0.856727264285714

00:22:30.678 --> 00:22:32.076 computational biology step.

NOTE Confidence: 0.856727264285714

00:22:32.080 --> 00:22:33.810 Perkins and Daniel Sanchez start

NOTE Confidence: 0.856727264285714

00:22:33.810 --> 00:22:35.540 level from our Institute and

NOTE Confidence: 0.856727264285714

00:22:35.599 --> 00:22:37.603 basically they they wanted to build

NOTE Confidence: 0.856727264285714

00:22:37.603 --> 00:22:39.820 a dynamic network model of every

NOTE Confidence: 0.856727264285714

00:22:39.820 --> 00:22:41.452 trade commitments that incorporates

NOTE Confidence: 0.856727264285714

00:22:41.452 --> 00:22:43.084 the quantitative changes in

NOTE Confidence: 0.856727264285714

00:22:43.090 --> 00:22:44.554 transcription factor protein levels.

NOTE Confidence: 0.856727264285714

00:22:44.554 --> 00:22:46.018 So in the model,

NOTE Confidence: 0.856727264285714

00:22:46.020 --> 00:22:48.604 M RNA are considered as the targets and

NOTE Confidence: 0.856727264285714

00:22:48.604 --> 00:22:51.160 Putin's are considered as the regulators.

NOTE Confidence: 0.856727264285714

00:22:51.160 --> 00:22:53.435 Putins can be activated so

NOTE Confidence: 0.856727264285714

00:22:53.435 --> 00:22:55.255 they can be repressors.

NOTE Confidence: 0.856727264285714

00:22:55.260 --> 00:22:58.711 And basically what they did is to

NOTE Confidence: 0.856727264285714

00:22:58.711 --> 00:23:00.719 use ordinary differential equations

NOTE Confidence: 0.856727264285714

00:23:00.719 --> 00:23:03.377 to try to predict the kinetic

NOTE Confidence: 0.856727264285714

00:23:03.377 --> 00:23:06.880 of the change in M RNA levels by

NOTE Confidence: 0.856727264285714

00:23:06.880 --> 00:23:08.970 the changes in the quantitative

NOTE Confidence: 0.856727264285714

00:23:08.970 --> 00:23:10.450 changes in protein levels.

NOTE Confidence: 0.856727264285714

00:23:10.450 --> 00:23:13.242 And here is the the models that

NOTE Confidence: 0.856727264285714

00:23:13.242 --> 00:23:15.722 they they established around 14

NOTE Confidence: 0.856727264285714

00:23:15.722 --> 00:23:17.706 transcription factors at different

NOTE Confidence: 0.856727264285714

00:23:17.782 --> 00:23:19.738 days during differentiation.

NOTE Confidence: 0.856727264285714

00:23:19.740 --> 00:23:21.985 Now what distinguishes this model

NOTE Confidence: 0.856727264285714

00:23:21.985 --> 00:23:24.230 from previously published model is

NOTE Confidence: 0.856727264285714

00:23:24.302 --> 00:23:27.236 that in quantifies the strength of

NOTE Confidence: 0.856727264285714

00:23:27.236 --> 00:23:29.192 the identified regulatory relationships

NOTE Confidence: 0.856727264285714

00:23:29.262 --> 00:23:31.663 as a measure of the contribution of

NOTE Confidence: 0.856727264285714

00:23:31.663 --> 00:23:34.728 all proteins and this is shown by

NOTE Confidence: 0.856727264285714

00:23:34.728 --> 00:23:36.756 different levels of transparency.

NOTE Confidence: 0.856727264285714

00:23:36.760 --> 00:23:38.032 So for example here,

NOTE Confidence: 0.856727264285714

00:23:38.032 --> 00:23:41.029 if we look at ranks one and get it to,

NOTE Confidence: 0.856727264285714

00:23:41.030 --> 00:23:42.680 you can see that the activation

NOTE Confidence: 0.856727264285714

00:23:42.680 --> 00:23:45.157 of getting 2 by ranks one is much

NOTE Confidence: 0.856727264285714

00:23:45.157 --> 00:23:47.125 stronger than the activation of ranks.

NOTE Confidence: 0.856727264285714

00:23:47.130 --> 00:23:49.398 One by getting 2.

NOTE Confidence: 0.856727264285714

00:23:49.400 --> 00:23:51.326 The model is also dynamic in

NOTE Confidence: 0.856727264285714

00:23:51.326 --> 00:23:53.736 that it reveals changes in these

NOTE Confidence: 0.856727264285714

00:23:53.736 --> 00:23:55.329 regulatory relationships overtime,

NOTE Confidence: 0.856727264285714

00:23:55.330 --> 00:23:57.700 so you can see, for example,

NOTE Confidence: 0.856727264285714

00:23:57.700 --> 00:23:59.116 at day zero,

NOTE Confidence: 0.856727264285714

00:23:59.116 --> 00:24:01.004 the strongest regulatory relationships.

NOTE Confidence: 0.856727264285714

00:24:01.010 --> 00:24:03.135 Involve proteins that are important

NOTE Confidence: 0.856727264285714

00:24:03.135 --> 00:24:04.410 in progenitor cells,

NOTE Confidence: 0.856727264285714

00:24:04.410 --> 00:24:06.710 but those links are progressively

NOTE Confidence: 0.856727264285714

00:24:06.710 --> 00:24:09.010 decreasing in strength and they

NOTE Confidence: 0.812685

00:24:09.085 --> 00:24:10.995 are fading away and that

NOTE Confidence: 0.812685

00:24:10.995 --> 00:24:12.905 they tend in committed cells.

NOTE Confidence: 0.812685

00:24:12.910 --> 00:24:16.725 They have been replaced by other links.

NOTE Confidence: 0.812685

00:24:16.730 --> 00:24:19.425 That that binds proteins that are known

NOTE Confidence: 0.812685

00:24:19.425 --> 00:24:22.340 to be important in differentiated cells.

NOTE Confidence: 0.812685

00:24:22.340 --> 00:24:24.923 We also notice that our model is able to

NOTE Confidence: 0.812685

00:24:24.923 --> 00:24:27.448 correctly recapitulates the timing of the

NOTE Confidence: 0.812685

00:24:27.448 --> 00:24:29.192 transcription factor across antagonisms

NOTE Confidence: 0.812685

00:24:29.192 --> 00:24:31.638 that underlies the cell fate decisions.

NOTE Confidence: 0.812685

00:24:31.640 --> 00:24:34.616 So here you can see at day zero,

NOTE Confidence: 0.812685

00:24:34.620 --> 00:24:37.588 the model was able to capture the P1,

NOTE Confidence: 0.812685

00:24:37.590 --> 00:24:39.450 get a one across antagonism,

NOTE Confidence: 0.812685

00:24:39.450 --> 00:24:41.676 which regulates a very early self,

NOTE Confidence: 0.812685

00:24:41.680 --> 00:24:43.564 a choice between my

NOTE Confidence: 0.812685

00:24:43.564 --> 00:24:44.977 Louisiana Richard lineage.

NOTE Confidence: 0.812685

00:24:44.980 --> 00:24:47.660 And that they too were able to capture

NOTE Confidence: 0.812685

00:24:47.660 --> 00:24:50.410 a second subsequent cross antagonism,

NOTE Confidence: 0.812685

00:24:50.410 --> 00:24:51.508 the KLF one,

NOTE Confidence: 0.812685

00:24:51.508 --> 00:24:53.704 Fly 1 cross antagonism that regulates

NOTE Confidence: 0.812685

00:24:53.704 --> 00:24:56.545 cell fate decision that took on later

NOTE Confidence: 0.812685

00:24:56.545 --> 00:24:58.687 between the erythroid cells Anna

NOTE Confidence: 0.812685

00:24:58.687 --> 00:25:01.052 megakaryocytes and both of these

NOTE Confidence: 0.812685

00:25:01.052 --> 00:25:02.944 cross antagonisms have completely

NOTE Confidence: 0.812685

00:25:02.950 --> 00:25:07.297 disappeared at day 10 in committed cells.

NOTE Confidence: 0.812685

00:25:07.300 --> 00:25:08.810 Now I will another interesting

NOTE Confidence: 0.812685

00:25:08.810 --> 00:25:11.205 aspect of the model is that it allows

NOTE Confidence: 0.812685

00:25:11.205 --> 00:25:13.123 us to compare the strength of the

NOTE Confidence: 0.812685

00:25:13.180 --> 00:25:14.824 different transcription factors to

NOTE Confidence: 0.812685

00:25:14.824 --> 00:25:17.290 the regulation of their target genes.

NOTE Confidence: 0.812685

00:25:17.290 --> 00:25:18.244 So for example,

NOTE Confidence: 0.812685

00:25:18.244 --> 00:25:20.950 if we look at the data 1 gene,

NOTE Confidence: 0.812685

00:25:20.950 --> 00:25:23.274 you can see that the contribution of

NOTE Confidence: 0.812685

00:25:23.274 --> 00:25:25.587 tell one to the activation of get

NOTE Confidence: 0.812685

00:25:25.587 --> 00:25:27.951 a one is about twice as important

NOTE Confidence: 0.812685

00:25:27.951 --> 00:25:30.919 compared to the contribution of GATA 2.

NOTE Confidence: 0.812685

00:25:30.920 --> 00:25:31.512 And surprisingly,

NOTE Confidence: 0.812685

00:25:31.512 --> 00:25:33.880 this is not because tell one is a

NOTE Confidence: 0.812685

00:25:33.947 --> 00:25:35.807 stronger activator of this gene,

NOTE Confidence: 0.812685

00:25:35.810 --> 00:25:38.458 because when we look.

NOTE Confidence: 0.812685

00:25:38.460 --> 00:25:39.906 Get the activation strength and one

NOTE Confidence: 0.812685

00:25:39.906 --> 00:25:42.087 is in fact a weaker activator of the

NOTE Confidence: 0.812685

00:25:42.087 --> 00:25:44.090 ghetto engine compared to get that too.

NOTE Confidence: 0.812685

00:25:44.090 --> 00:25:46.482 But what happens is that 10 one is

NOTE Confidence: 0.812685

00:25:46.482 --> 00:25:49.075 3 times more abundant than get a 2.

NOTE Confidence: 0.812685

00:25:49.080 --> 00:25:51.192 So basically what this shows is

NOTE Confidence: 0.812685

00:25:51.192 --> 00:25:53.040 that Taiwan is a week,

NOTE Confidence: 0.812685

00:25:53.040 --> 00:25:55.218 but opponents of activators of the

NOTE Confidence: 0.812685

00:25:55.218 --> 00:25:58.486 data 1 gene and get a 2 even though

NOTE Confidence: 0.812685

00:25:58.486 --> 00:26:00.960 it's a stronger activator of the gene.

NOTE Confidence: 0.812685

00:26:00.960 --> 00:26:03.024 Overall it contributes less to its

NOTE Confidence: 0.812685

00:26:03.024 --> 00:26:05.279 activation because it is less abundant.

NOTE Confidence: 0.812685

00:26:05.280 --> 00:26:07.037 So with this type of models we

NOTE Confidence: 0.812685

00:26:07.037 --> 00:26:09.274 are really able to dissect the

NOTE Confidence: 0.812685

00:26:09.274 --> 00:26:10.696 quantitative relationships between

NOTE Confidence: 0.812685

00:26:10.696 --> 00:26:12.118 these transcription factors.

NOTE Confidence: 0.812685

00:26:12.120 --> 00:26:14.526 And that's very important if we

NOTE Confidence: 0.812685

00:26:14.526 --> 00:26:17.573 want to be able to control every

NOTE Confidence: 0.812685

00:26:17.573 --> 00:26:20.737 trapezes either in vitro or in vivo.

NOTE Confidence: 0.812685

00:26:20.740 --> 00:26:23.638 So because they built different gene

NOTE Confidence: 0.812685

00:26:23.638 --> 00:26:26.489 regulatory networks at different time points,

NOTE Confidence: 0.812685

00:26:26.490 --> 00:26:28.938 we pieced them all together and

NOTE Confidence: 0.812685

00:26:28.938 --> 00:26:32.150 made little movies where you can see

NOTE Confidence: 0.812685

00:26:32.150 --> 00:26:34.660 the quantitative changes in this

NOTE Confidence: 0.812685

00:26:34.660 --> 00:26:37.303 regulatory relationships as the cells

NOTE Confidence: 0.812685

00:26:37.303 --> 00:26:39.898 proceed towards every trait differentiation.

NOTE Confidence: 0.812685

00:26:39.900 --> 00:26:42.896 So you can see that this early

NOTE Confidence: 0.812685

00:26:42.896 --> 00:26:44.180 regulatory here relationships

NOTE Confidence: 0.812685

00:26:44.257 --> 00:26:47.257 decreases with time and are replaced

NOTE Confidence: 0.812685

00:26:47.257 --> 00:26:49.257 by other regulatory relationships

NOTE Confidence: 0.812685

00:26:49.329 --> 00:26:51.397 in more differentiated cells.

NOTE Confidence: 0.83764976

00:26:54.030 --> 00:26:56.030 OK, So what about cofactors?

NOTE Confidence: 0.83764976

00:26:56.030 --> 00:26:58.901 So everything I showed you so far was about

NOTE Confidence: 0.83764976

00:26:58.901 --> 00:27:01.608 the DNA binding transcription factors,

NOTE Confidence: 0.83764976

00:27:01.610 --> 00:27:04.305 but we know that these proteins works

NOTE Confidence: 0.83764976

00:27:04.305 --> 00:27:06.399 with the recruitment of cofactors,

NOTE Confidence: 0.83764976

00:27:06.400 --> 00:27:10.810 so we also wanted to measure cofactors by SM.

NOTE Confidence: 0.83764976

00:27:10.810 --> 00:27:13.295 And we started with the

NOTE Confidence: 0.83764976

00:27:13.295 --> 00:27:15.283 histone acety transfers P300.

NOTE Confidence: 0.83764976

00:27:15.290 --> 00:27:17.486 Now, according to the current literature,

NOTE Confidence: 0.83764976

00:27:17.490 --> 00:27:19.947 P300 has been shown to interact with

NOTE Confidence: 0.83764976

00:27:19.947 --> 00:27:21.530 dozens of transcription factors,

NOTE Confidence: 0.83764976

00:27:21.530 --> 00:27:24.226 so we expected it to be highly abundant

NOTE Confidence: 0.83764976

00:27:24.226 --> 00:27:26.668 in the nucleus, but much more,

NOTE Confidence: 0.83764976

00:27:26.668 --> 00:27:27.400 well, surprise.

NOTE Confidence: 0.83764976

00:27:27.400 --> 00:27:30.190 We found that not only P 300 is not in

NOTE Confidence: 0.83764976

00:27:30.265 --> 00:27:32.910 excess of the transcription factors,

NOTE Confidence: 0.83764976

00:27:32.910 --> 00:27:35.454 it is in fact present at a lower

NOTE Confidence: 0.83764976

00:27:35.454 --> 00:27:37.899 opponents than almost every single

NOTE Confidence: 0.83764976

00:27:37.899 --> 00:27:40.219 transcription factor taken individually.

NOTE Confidence: 0.83764976

00:27:40.220 --> 00:27:44.332 So then we looked at the other histone

NOTE Confidence: 0.83764976

00:27:44.332 --> 00:27:46.493 acetyltransferase is CBP and catuara

NOTE Confidence: 0.83764976

00:27:46.493 --> 00:27:49.821 GCN 5 and as you can see those are

NOTE Confidence: 0.83764976

00:27:49.821 --> 00:27:53.021 just as well in the nucleus as P300.

NOTE Confidence: 0.83764976

00:27:53.030 --> 00:27:54.860 So the next logical thing was

NOTE Confidence: 0.83764976

00:27:54.860 --> 00:27:56.920 to look at the antagonist,

NOTE Confidence: 0.83764976

00:27:56.920 --> 00:27:57.985 enzymes, histone deacetylase,

NOTE Confidence: 0.83764976

00:27:57.985 --> 00:27:59.760 and as you can see,

NOTE Confidence: 0.83764976

00:27:59.760 --> 00:28:01.884 those are much more abundant than

NOTE Confidence: 0.83764976

00:28:01.884 --> 00:28:03.300 the histo nasty transparency.

NOTE Confidence: 0.83764976

00:28:03.300 --> 00:28:05.115 So there is a quantitative

NOTE Confidence: 0.83764976

00:28:05.115 --> 00:28:06.930 imbalance between the edge ducks

NOTE Confidence: 0.83764976

00:28:06.991 --> 00:28:08.959 and their hearts in the nucleus.

NOTE Confidence: 0.83764976

00:28:08.960 --> 00:28:11.907 And then we looked at a broader

NOTE Confidence: 0.83764976

00:28:11.907 --> 00:28:13.170 range of cofactors.

NOTE Confidence: 0.83764976

00:28:13.170 --> 00:28:15.200 And what we found is all the

NOTE Confidence: 0.83764976

00:28:15.200 --> 00:28:16.876 coactivators that we have measured

NOTE Confidence: 0.83764976

00:28:16.876 --> 00:28:18.741 are actually really low abundance

NOTE Confidence: 0.83764976

00:28:18.741 --> 00:28:20.630 compared to the compressors.

NOTE Confidence: 0.83764976

00:28:20.630 --> 00:28:21.695 So for example,

NOTE Confidence: 0.83764976

00:28:21.695 --> 00:28:24.180 if we focus on CHD for sociology,

NOTE Confidence: 0.83764976

00:28:24.180 --> 00:28:26.329 far is one of the enzymatic subunits

NOTE Confidence: 0.83764976

00:28:26.329 --> 00:28:28.790 of the Nerd core oppressor complex.

NOTE Confidence: 0.83764976

00:28:28.790 --> 00:28:30.570 And as you can see,

NOTE Confidence: 0.83764976

00:28:30.570 --> 00:28:32.747 there is an almost 50 fold excess

NOTE Confidence: 0.83764976

00:28:32.747 --> 00:28:35.335 of CHD 4 compared to the to

NOTE Confidence: 0.83764976

00:28:35.335 --> 00:28:37.310 the Co activators in nucleus,

NOTE Confidence: 0.83764976

00:28:37.310 --> 00:28:39.344 and these results likely explain the

NOTE Confidence: 0.83764976

00:28:39.344 --> 00:28:41.900 fact that they're not complex has been

NOTE Confidence: 0.83764976

00:28:41.900 --> 00:28:43.800 identified as an interacting Putin.

NOTE Confidence: 0.83764976

00:28:43.800 --> 00:28:46.520 In almost every single put on the screen,

NOTE Confidence: 0.83764976

00:28:46.520 --> 00:28:49.509 now that have been published so far.

NOTE Confidence: 0.83764976

00:28:49.510 --> 00:28:51.868 So we found that the compressors

NOTE Confidence: 0.83764976

00:28:51.868 --> 00:28:53.047 are highly opponent.

NOTE Confidence: 0.83764976

00:28:53.050 --> 00:28:55.054 The coactivators are rare,

NOTE Confidence: 0.83764976

00:28:55.054 --> 00:28:57.559 so where do the transcription

NOTE Confidence: 0.83764976

00:28:57.559 --> 00:28:59.810 factor of fit on that scale?

NOTE Confidence: 0.83764976

00:28:59.810 --> 00:29:01.802 And the answer is that they

NOTE Confidence: 0.83764976

00:29:01.802 --> 00:29:03.690 fit somewhere in the middle.

NOTE Confidence: 0.83764976

00:29:03.690 --> 00:29:06.410 So here on this graph we have the

NOTE Confidence: 0.83764976

00:29:06.410 --> 00:29:08.988 copy number of Putin's in log scale,

NOTE Confidence: 0.83764976

00:29:08.990 --> 00:29:10.750 and as you can see,

NOTE Confidence: 0.83764976

00:29:10.750 --> 00:29:12.808 there is about an order of magnitude

NOTE Confidence: 0.83764976

00:29:12.808 --> 00:29:15.034 difference in your balance between Co

NOTE Confidence: 0.83764976

00:29:15.034 --> 00:29:16.746 activators and transcription factors.

NOTE Confidence: 0.83764976

00:29:16.750 --> 00:29:18.970 And then another order of magnitude

NOTE Confidence: 0.83764976

00:29:18.970 --> 00:29:20.450 difference between the transcription

NOTE Confidence: 0.83764976

00:29:20.506 --> 00:29:22.046 factors and the Co oppressors.

NOTE Confidence: 0.83764976

00:29:22.050 --> 00:29:22.938 And Interestingly,

NOTE Confidence: 0.83764976

00:29:22.938 --> 00:29:25.158 we could detect these differences

NOTE Confidence: 0.83764976

00:29:25.158 --> 00:29:27.201 in abundance only because we

NOTE Confidence: 0.83764976

00:29:27.201 --> 00:29:29.139 looked at Putin's because when we

NOTE Confidence: 0.83764976

00:29:29.139 --> 00:29:31.439 do the same analysis with M RNA.

NOTE Confidence: 0.83764976

00:29:31.440 --> 00:29:33.052 As you can see,

NOTE Confidence: 0.83764976

00:29:33.052 --> 00:29:35.067 there is no statistically significant

NOTE Confidence: 0.83764976

00:29:35.067 --> 00:29:36.904 differences in the abundance of

NOTE Confidence: 0.83764976

00:29:36.904 --> 00:29:38.609 the transcripts that code for

NOTE Confidence: 0.83764976

00:29:38.609 --> 00:29:40.819 these different classes of factors,

NOTE Confidence: 0.83764976

00:29:40.820 --> 00:29:42.725 which suggests that these very

NOTE Confidence: 0.83764976

00:29:42.725 --> 00:29:44.630 large differences in abundance are

NOTE Confidence: 0.83764976

00:29:44.693 --> 00:29:46.628 regulated post transcriptionally.

NOTE Confidence: 0.83764976

00:29:46.630 --> 00:29:48.620 And indeed, consistent with that,

NOTE Confidence: 0.83764976

00:29:48.620 --> 00:29:50.852 we found that when we inhibits

NOTE Confidence: 0.83764976

00:29:50.852 --> 00:29:52.835 protein translation by using by

NOTE Confidence: 0.83764976

00:29:52.835 --> 00:29:54.990 treating the cells with cycloheximide,

NOTE Confidence: 0.83764976

00:29:54.990 --> 00:29:57.240 you can see that the coactivators

NOTE Confidence: 0.83764976

00:29:57.240 --> 00:30:00.288 appear to be much less stable compare.

NOTE Confidence: 0.83764976

00:30:00.290 --> 00:30:01.676 This occurred pressers.

NOTE Confidence: 0.83764976

00:30:01.676 --> 00:30:05.406 So at least one of the reason why

NOTE Confidence: 0.83764976

00:30:05.406 --> 00:30:07.812 the coactivators are so where in

NOTE Confidence: 0.83764976

00:30:07.812 --> 00:30:09.015 a cell is

NOTE Confidence: 0.814414732142857

00:30:09.108 --> 00:30:12.108 because those appears to be

NOTE Confidence: 0.814414732142857

00:30:12.108 --> 00:30:13.908 extremely unstable footing.

NOTE Confidence: 0.814414732142857

00:30:13.910 --> 00:30:17.254 And this is true throughout every trip Oasis.

NOTE Confidence: 0.814414732142857

00:30:17.260 --> 00:30:19.840 Here I have plotted the Putin

NOTE Confidence: 0.814414732142857

00:30:19.840 --> 00:30:22.983 transcript average and as you can see

NOTE Confidence: 0.814414732142857

00:30:22.983 --> 00:30:25.213 the coactivators here are present

NOTE Confidence: 0.814414732142857

00:30:25.213 --> 00:30:28.415 between 100 and 1000 copies per

NOTE Confidence: 0.814414732142857

00:30:28.415 --> 00:30:30.643 Nicholas there transcription factors.

NOTE Confidence: 0.814414732142857

00:30:30.650 --> 00:30:34.913 On average, between 1000 and 10,000 and

NOTE Confidence: 0.814414732142857

00:30:34.913 --> 00:30:38.708 the oppressors between 10,000 and 100,000.

NOTE Confidence: 0.814414732142857

00:30:38.710 --> 00:30:40.756 So overall, these results suggest that

NOTE Confidence: 0.814414732142857

00:30:40.756 --> 00:30:43.289 the nucleus is a highly repressive

NOTE Confidence: 0.814414732142857

00:30:43.289 --> 00:30:46.039 environment where coactivators are limiting,

NOTE Confidence: 0.814414732142857

00:30:46.040 --> 00:30:48.692 which implies that the DNA bound

NOTE Confidence: 0.814414732142857

00:30:48.692 --> 00:30:50.916 transcription factors must compete with

NOTE Confidence: 0.814414732142857

00:30:50.916 --> 00:30:53.214 each other to mediate the recruitment

NOTE Confidence: 0.814414732142857

00:30:53.214 --> 00:30:55.948 of this limited number of coactivators.

NOTE Confidence: 0.814414732142857

00:30:55.950 --> 00:30:58.626 Now, one way through which the

NOTE Confidence: 0.814414732142857

00:30:58.626 --> 00:31:00.885 transcription factors can increase their

NOTE Confidence: 0.814414732142857

00:31:00.885 --> 00:31:03.706 likelihood of being able to recruit them,

NOTE Confidence: 0.814414732142857

00:31:03.710 --> 00:31:06.300 the limiting coactivators is through

NOTE Confidence: 0.814414732142857

00:31:06.300 --> 00:31:08.372 assembling themselves onto enhancers.

NOTE Confidence: 0.814414732142857

00:31:08.380 --> 00:31:10.956 So we wanted to ask the question,

NOTE Confidence: 0.814414732142857

00:31:10.960 --> 00:31:13.445 how do the number of active enhancers

NOTE Confidence: 0.814414732142857

00:31:13.445 --> 00:31:15.020 and coactivator molecules compare?

NOTE Confidence: 0.814414732142857

00:31:15.020 --> 00:31:17.508 So we looked at Co activators that are

NOTE Confidence: 0.814414732142857

00:31:17.508 --> 00:31:20.190 known to associate to active enhancers,

NOTE Confidence: 0.814414732142857

00:31:20.190 --> 00:31:22.398 which are the histone acetyl transferases,

NOTE Confidence: 0.814414732142857

00:31:22.400 --> 00:31:25.718 CPP 300 and the HTK for monometer

NOTE Confidence: 0.814414732142857

00:31:25.718 --> 00:31:29.016 transfer is is a mileage 3 MLN 4?

NOTE Confidence: 0.814414732142857

00:31:29.020 --> 00:31:31.673 And we have estimated the number of

NOTE Confidence: 0.814414732142857

00:31:31.673 --> 00:31:34.045 active enhancers by doing a taxic

NOTE Confidence: 0.814414732142857

00:31:34.045 --> 00:31:36.361 experiments which we have analyzed by

NOTE Confidence: 0.814414732142857

00:31:36.361 --> 00:31:38.918 hint Attack to identify transcription

NOTE Confidence: 0.814414732142857

00:31:38.918 --> 00:31:41.538 factor footprint and then intersected

NOTE Confidence: 0.814414732142857

00:31:41.538 --> 00:31:44.250 these with predicted enhancers from database.

NOTE Confidence: 0.814414732142857

00:31:44.250 --> 00:31:47.582 And this is the number of estimated

NOTE Confidence: 0.814414732142857

00:31:47.582 --> 00:31:50.329 active enhancers that we have obtained

NOTE Confidence: 0.814414732142857

00:31:50.329 --> 00:31:53.686 and as you can see these numbers are

NOTE Confidence: 0.814414732142857

00:31:53.686 --> 00:31:56.894 in the same order of magnitude as the

NOTE Confidence: 0.814414732142857

00:31:56.894 --> 00:31:59.176 number of molecules of coactivators.

NOTE Confidence: 0.814414732142857

00:31:59.176 --> 00:32:01.990 Suggesting that maybe the formation of

NOTE Confidence: 0.814414732142857

00:32:02.059 --> 00:32:04.761 these active in home sales depend on

NOTE Confidence: 0.814414732142857

00:32:04.761 --> 00:32:07.300 the availability of these coactivators.

NOTE Confidence: 0.814414732142857

00:32:07.300 --> 00:32:10.300 So this is of all our model where we have

NOTE Confidence: 0.814414732142857

00:32:10.375 --> 00:32:12.395 the transcription factors recruiting

NOTE Confidence: 0.814414732142857

00:32:12.395 --> 00:32:16.086 the RECO activators and the rest of

NOTE Confidence: 0.814414732142857

00:32:16.086 --> 00:32:18.426 the nucleus containing corepressor's.

NOTE Confidence: 0.814414732142857

00:32:18.430 --> 00:32:20.650 And we think that this.

NOTE Confidence: 0.7799415

00:32:23.000 --> 00:32:25.835 Hello hello hi how are you doing?

NOTE Confidence: 0.75336707

00:32:28.140 --> 00:32:30.090 Well, not there are you in

NOTE Confidence: 0.75336707

00:32:30.090 --> 00:32:32.090 the wilderness or in the camp.

NOTE Confidence: 0.75336707

00:32:32.090 --> 00:32:33.730 Sorry, my treat doctor Wiseman.

NOTE Confidence: 0.75336707

00:32:33.730 --> 00:32:36.810 Can you hear me OK?

NOTE Confidence: 0.75336707

00:32:36.810 --> 00:32:39.150 Actually going out on Sunday.

NOTE Confidence: 0.75336707

00:32:39.150 --> 00:32:42.230 So OK, so you missed some buddies

NOTE Confidence: 0.75336707

00:32:42.230 --> 00:32:44.280 working before Doctor Wiseman.

NOTE Confidence: 0.75336707

00:32:44.280 --> 00:32:46.338 Please mute yourself.

NOTE Confidence: 0.75336707

00:32:46.338 --> 00:32:49.414 I muted him. Thank you.

NOTE Confidence: 0.75336707

00:32:49.414 --> 00:32:51.949 I I'm almost done anyway.

NOTE Confidence: 0.75336707

00:32:51.950 --> 00:32:54.785 Thank you so so we think basically

NOTE Confidence: 0.75336707

00:32:54.785 --> 00:32:57.006 that this restriction of abundance

NOTE Confidence: 0.75336707

00:32:57.006 --> 00:32:59.321 of coactivators could be an

NOTE Confidence: 0.75336707

00:32:59.321 --> 00:33:01.232 important mechanism for concerted

NOTE Confidence: 0.75336707

00:33:01.232 --> 00:33:03.884 gene regulation and we think it

NOTE Confidence: 0.75336707

00:33:03.884 --> 00:33:06.044 may be particularly important in

NOTE Confidence: 0.75336707

00:33:06.044 --> 00:33:07.712 multipotent progenitors to prevent

NOTE Confidence: 0.75336707

00:33:07.712 --> 00:33:10.394 high levels of Co expression of

NOTE Confidence: 0.75336707

00:33:10.394 --> 00:33:12.278 genes from different lineages.

NOTE Confidence: 0.75336707

00:33:12.280 --> 00:33:14.048 So basically decreasing the

NOTE Confidence: 0.75336707

00:33:14.048 --> 00:33:15.816 transcriptional noise as well.

NOTE Confidence: 0.79514533

00:33:18.340 --> 00:33:20.330 And I will stop here.

NOTE Confidence: 0.79514533

00:33:20.330 --> 00:33:23.506 And I've knowledge people who did the work,

NOTE Confidence: 0.79514533

00:33:23.510 --> 00:33:25.525 so I already acknowledged all

NOTE Confidence: 0.79514533

00:33:25.525 --> 00:33:27.890 our collaborators an from my lab.

NOTE Confidence: 0.79514533

00:33:27.890 --> 00:33:30.599 This project was done mainly by two

NOTE Confidence: 0.79514533

00:33:30.599 --> 00:33:32.270 very talented postdoctoral fellow,

NOTE Confidence: 0.79514533

00:33:32.270 --> 00:33:36.250 common Poly who did most of the wet lab work.

NOTE Confidence: 0.79514533

00:33:36.250 --> 00:33:39.280 Xena Motory, who did the informatic.

NOTE Confidence: 0.79514533

00:33:39.280 --> 00:33:40.692 Analysis, With some help

NOTE Confidence: 0.79514533

00:33:40.692 --> 00:33:42.104 from a Kathy Silverman,

NOTE Confidence: 0.79514533

00:33:42.110 --> 00:33:44.240 who also did the informatic analysis,

NOTE Confidence: 0.79514533

00:33:44.240 --> 00:33:47.200 and I thank you all for listening and

NOTE Confidence: 0.79514533

00:33:47.200 --> 00:33:50.246 I'll be happy to take any question.