WEBVTT

NOTE duration:"00:23:44.5970000"

NOTE language:en-us

NOTE Confidence: 0.81004965

00:00:00.000 --> 00:00:02.121 Thanks, Diane, I'm so sorry that I

NOTE Confidence: 0.81004965

00:00:02.121 --> 00:00:04.459 don't get to meet you in person's,

NOTE Confidence: 0.81004965

00:00:04.460 --> 00:00:06.788 of course, but it's always fun to to

NOTE Confidence: 0.81004965

00:00:06.788 --> 00:00:09.170 see you and talk science with you.

NOTE Confidence: 0.81004965

00:00:09.170 --> 00:00:10.934 So yeah, today I'm going to

NOTE Confidence: 0.81004965

00:00:10.934 --> 00:00:12.837 talk about 2 two main aspects

NOTE Confidence: 0.81004965

00:00:12.837 --> 00:00:15.126 of what we studying in the lab.

NOTE Confidence: 0.81004965

00:00:15.130 --> 00:00:17.111 The first one is really going to

NOTE Confidence: 0.81004965

00:00:17.111 --> 00:00:19.701 be from my first love and what I've

NOTE Confidence: 0.81004965

00:00:19.701 --> 00:00:22.040 been studying for the past 12 years,

NOTE Confidence: 0.81004965

00:00:22.040 --> 00:00:23.610 which is a ritual poiesis.

NOTE Confidence: 0.81004965

00:00:23.610 --> 00:00:26.032 And in the second part we're going

NOTE Confidence: 0.81004965

00:00:26.032 --> 00:00:28.056 to move towards something that I

NOTE Confidence: 0.81004965

00:00:28.056 --> 00:00:30.540 I was totally a Neo fit for the.

1

00:00:30.540 --> 00:00:33.676 And I would say, five years ago,

00:00:33.680 --> 00:00:35.210 four years ago,

00:00:35.210 --> 00:00:37.760 which is really looking into

00:00:37.760 --> 00:00:40.292 skeletal defects in this disease

00:00:40.292 --> 00:00:43.136 called Diamond Black fan anemia so.

00:00:43.140 --> 00:00:45.198 Here is my computer of course.

00:00:45.200 --> 00:00:47.174 OK, here is an overview of the

00:00:47.174 --> 00:00:49.544 talk in the first spot I'm going

00:00:49.544 --> 00:00:51.722 to give a general introduction on

00:00:51.791 --> 00:00:53.636 Diamond Black fan anemia because

00:00:53.636 --> 00:00:55.832 I'm not sure about the audience,

00:00:55.832 --> 00:00:57.884 but everyone knows about the disease.

00:00:57.890 --> 00:01:00.074 Then I'm going to get right into

00:01:00.074 --> 00:01:02.409 the subject and talk to you about

00:01:02.409 --> 00:01:04.401 this study that we published last

00:01:04.468 --> 00:01:06.694 year on the mechanism of action

NOTE Confidence: 0.81004965

00:01:06.694 --> 00:01:08.524 of steroids during normal and

NOTE Confidence: 0.81004965

00:01:08.524 --> 00:01:10.244 disordered humanary choices with a

NOTE Confidence: 0.81004965

00:01:10.244 --> 00:01:12.299 focus on Diamond black fan anemia,

NOTE Confidence: 0.81004965

00:01:12.300 --> 00:01:13.904 and I'll try to.

NOTE Confidence: 0.81004965

00:01:13.904 --> 00:01:15.909 To insist on understanding the

NOTE Confidence: 0.81004965

00:01:15.909 --> 00:01:17.048 developmental differences and

NOTE Confidence: 0.81004965

00:01:17.048 --> 00:01:19.400 the role of this protein P 57.

NOTE Confidence: 0.81004965

00:01:19.400 --> 00:01:21.950 Keep two in the mechanism of

NOTE Confidence: 0.81004965

00:01:21.950 --> 00:01:24.150 action of steroids and then.

NOTE Confidence: 0.81004965

00:01:24.150 --> 00:01:27.078 I will go to modeling the skeletal defects,

NOTE Confidence: 0.81004965

00:01:27.080 --> 00:01:29.312 observing DBA and I'll get back

NOTE Confidence: 0.81004965

00:01:29.312 --> 00:01:31.469 to Erato places at the end.

NOTE Confidence: 0.81004965

00:01:31.470 --> 00:01:33.270 But really the main take home

NOTE Confidence: 0.81004965

00:01:33.270 --> 00:01:34.933 message here is to understand

NOTE Confidence: 0.81004965

00:01:34.933 --> 00:01:36.933 that skeletal defects in Diamond

NOTE Confidence: 0.81004965

00:01:36.933 --> 00:01:39.160 Black fan anemia are mediated.

NOTE Confidence: 0.81004965

00:01:39.160 --> 00:01:42.445 In part, I would say by failure of Leo.

NOTE Confidence: 0.81004965

00:01:42.450 --> 00:01:42.926 Yeah,

NOTE Confidence: 0.81004965

00:01:42.926 --> 00:01:47.210 have you moved past the first slide or no?

NOTE Confidence: 0.81004965

00:01:47.210 --> 00:01:50.318 Yeah, it's not advancing on the screen.

NOTE Confidence: 0.81004965

00:01:50.320 --> 00:01:54.904 I don't know why I think we should.

NOTE Confidence: 0.81004965

00:01:54.910 --> 00:01:57.964 I shouldn't be the cohost Genie

NOTE Confidence: 0.81004965

00:01:57.964 --> 00:02:00.370 because it keeps popping in.

NOTE Confidence: 0.81004965

00:02:00.370 --> 00:02:02.446 You want to be the host?

NOTE Confidence: 0.81004965

00:02:02.450 --> 00:02:02.764 No,

NOTE Confidence: 0.81004965

00:02:02.764 --> 00:02:05.590 I don't want to be the host because I

NOTE Confidence: 0.81004965

00:02:05.668 --> 00:02:08.349 see all the people popping in here.

NOTE Confidence: 0.81004965

00:02:08.350 --> 00:02:10.090 So let me do something.

NOTE Confidence: 0.81004965

00:02:10.090 --> 00:02:12.211 What I was saying is really the

NOTE Confidence: 0.81004965

00:02:12.211 --> 00:02:14.009 take home that the skeletal

NOTE Confidence: 0.81004965

00:02:14.009 --> 00:02:15.637 defects in IVR mediated,

NOTE Confidence: 0.81004965

00:02:15.640 --> 00:02:18.090 in part by the failure of the

NOTE Confidence: 0.81004965

00:02:18.090 --> 00:02:20.316 mesenchymal lineages and how DBA can

NOTE Confidence: 0.81004965

00:02:20.316 --> 00:02:22.161 be a cancer predisposition syndrome

NOTE Confidence: 0.81004965

00:02:22.161 --> 00:02:24.659 and touch a little bit on that idea.

NOTE Confidence: 0.842228368

00:02:27.040 --> 00:02:29.941 Other side moving now. Yes, perfect.

NOTE Confidence: 0.842228368

00:02:29.941 --> 00:02:32.589 So as I mentioned just a little bit

NOTE Confidence: 0.842228368

00:02:32.589 --> 00:02:34.855 of introduction on the clinical

NOTE Confidence: 0.842228368

00:02:34.855 --> 00:02:37.645 features of Diamond Black fan anemia,

NOTE Confidence: 0.842228368

00:02:37.650 --> 00:02:39.924 it Sahara trade hyperplasia an you

NOTE Confidence: 0.842228368

00:02:39.924 --> 00:02:42.878 can see on this bone marrow smear.

NOTE Confidence: 0.842228368

00:02:42.880 --> 00:02:45.764 Although in the US physician don't do

NOTE Confidence: 0.842228368

00:02:45.764 --> 00:02:48.762 a smear anymore on this patients that

NOTE Confidence: 0.842228368

00:02:48.762 --> 00:02:51.718 the bone marrow is pretty normal except

NOTE Confidence: 0.842228368

00:02:51.718 --> 00:02:54.931 for a Pau city of era trade pictures is

NOTE Confidence: 0.842228368

00:02:54.940 --> 00:02:56.950 the patients have congenital anomalies.

00:02:56.950 --> 00:02:59.100 They have skeletal and growth

00:02:59.100 --> 00:03:00.820 defects which will be.

00:03:00.820 --> 00:03:03.925 Focus of the talk today in the second part.

00:03:03.930 --> 00:03:06.006 Here you can observe, for example,

00:03:06.010 --> 00:03:08.086 try financial firm in this patient.

00:03:08.090 --> 00:03:10.322 This was documented by Adriana Blouse

00:03:10.322 --> 00:03:12.498 and Jeff Lipton several times in

00:03:12.498 --> 00:03:14.364 the literature and they also have

00:03:14.364 --> 00:03:16.415 a cancer predisposition and I will

00:03:16.415 --> 00:03:18.821 insist on that because I think that's

00:03:18.821 --> 00:03:20.927 one of the most fascinating questions

00:03:20.927 --> 00:03:22.620 that remained in the field.

00:03:25.420 --> 00:03:28.660 So just a little bit of history here.

00:03:28.660 --> 00:03:30.690 The Diamond Black fan anemia,

00:03:30.690 --> 00:03:32.890 the classic diagnostic criteria was

00:03:32.890 --> 00:03:35.878 described by Joseph in 1936 and then

NOTE Confidence: 0.8252814

00:03:35.878 --> 00:03:38.377 rebuilt by Diamond Black Fan in 1938.

NOTE Confidence: 0.8252814

00:03:38.380 --> 00:03:40.810 First as pure red cell aplasia.

NOTE Confidence: 0.8252814

00:03:40.810 --> 00:03:43.602 That led to the classic definition of a

NOTE Confidence: 0.8252814

00:03:43.602 --> 00:03:46.079 moderate to severe microcytic anemia.

NOTE Confidence: 0.8252814

00:03:46.080 --> 00:03:49.590 And I'll get back to that at the end

NOTE Confidence: 0.8252814

00:03:49.590 --> 00:03:52.631 because that's what I've been a big

NOTE Confidence: 0.8252814

00:03:52.631 --> 00:03:55.490 problem in the field is to model.

NOTE Confidence: 0.8252814

00:03:55.490 --> 00:03:58.731 Diamond Black fan anemia in the classic

NOTE Confidence: 0.8252814

00:03:58.731 --> 00:04:01.399 mouse model systems that we have

NOTE Confidence: 0.8252814

00:04:01.399 --> 00:04:04.199 because it's very difficult to model A

NOTE Confidence: 0.8252814

00:04:04.279 --> 00:04:07.339 macrocytic anemia with an increase MCV.

NOTE Confidence: 0.8252814

00:04:07.340 --> 00:04:08.236 That is.

NOTE Confidence: 0.8252814

00:04:08.236 --> 00:04:10.476 I complained by reticular cytopenia,

NOTE Confidence: 0.8252814

00:04:10.480 --> 00:04:13.280 a decrease in reticular site due to

NOTE Confidence: 0.8252814

00:04:13.280 --> 00:04:15.382 stress erythropoiesis that happens in the

NOTE Confidence: 0.8252814

00:04:15.382 --> 00:04:18.040 spring in the mouse and as I mentioned,

NOTE Confidence: 0.8252814

00:04:18.040 --> 00:04:19.990 bone marrow is normal cylinder with

NOTE Confidence: 0.8252814

00:04:19.990 --> 00:04:22.000 opacity of red cell precursors.

NOTE Confidence: 0.8252814

00:04:22.000 --> 00:04:26.608 It's diagnosed at an age less than a year.

NOTE Confidence: 0.8252814

00:04:26.610 --> 00:04:29.004 But now we have expanded the definition

NOTE Confidence: 0.8252814

00:04:29.004 --> 00:04:31.662 of DBA with criteria that come with

NOTE Confidence: 0.8252814

00:04:31.662 --> 00:04:34.569 from a more robust Epidemiology as a

NOTE Confidence: 0.8252814

00:04:34.569 --> 00:04:36.557 result of international registries,

NOTE Confidence: 0.8252814

00:04:36.560 --> 00:04:39.360 and I will point out the importance

NOTE Confidence: 0.8252814

00:04:39.360 --> 00:04:41.789 of this clinical registries such as

NOTE Confidence: 0.8252814

00:04:41.789 --> 00:04:44.521 the one we have, a defined Steam,

NOTE Confidence: 0.8252814

00:04:44.521 --> 00:04:46.506 the diamond black fan anemia,

NOTE Confidence: 0.8252814

00:04:46.510 --> 00:04:48.238 registry of North America,

NOTE Confidence: 0.8252814

00:04:48.238 --> 00:04:51.679 but also the ones from Europe in the UK,

NOTE Confidence: 0.8252814

00:04:51.680 --> 00:04:52.874 Germany, Italy, Sweden.

NOTE Confidence: 0.8252814

00:04:52.874 --> 00:04:55.262 Of course France and many others.

NOTE Confidence: 0.8252814

00:04:55.270 --> 00:04:58.126 Gene discovery was very important in helping.

NOTE Confidence: 0.8252814

00:04:58.130 --> 00:05:00.260 Redefined the disease diamond black

NOTE Confidence: 0.8252814

00:05:00.260 --> 00:05:03.388 fan and 23 genes now like categorized

NOTE Confidence: 0.8252814

00:05:03.388 --> 00:05:04.759 as DBA jeans,

NOTE Confidence: 0.8252814

00:05:04.760 --> 00:05:07.382 11 of them discovered through the

NOTE Confidence: 0.8252814

00:05:07.382 --> 00:05:09.664 Diamond Black fan anemia registry

NOTE Confidence: 0.8252814

00:05:09.664 --> 00:05:12.877 and this led to a modern diagnostic

NOTE Confidence: 0.8252814

00:05:12.877 --> 00:05:15.118 criteria because at first Diamond

NOTE Confidence: 0.8252814

00:05:15.118 --> 00:05:18.016 Black fan was discovered as a mutation

NOTE Confidence: 0.8252814

00:05:18.020 --> 00:05:20.666 in a gene encoding ribosomal protein.

NOTE Confidence: 0.8252814

00:05:20.670 --> 00:05:23.322 Whether in the small subunit or

NOTE Confidence: 0.8252814

00:05:23.322 --> 00:05:25.090 in the large subunit.

NOTE Confidence: 0.8252814

00:05:25.090 --> 00:05:27.736 But now we've studies from Vigesaa,

NOTE Confidence: 0.8252814

00:05:27.740 --> 00:05:28.961 Karen and Overs.

NOTE Confidence: 0.8252814

00:05:28.961 --> 00:05:31.403 Getting one mutations and over new

NOTE Confidence: 0.8252814

00:05:31.403 --> 00:05:33.712 mutations found and we're rather call

NOTE Confidence: 0.8252814

00:05:33.712 --> 00:05:36.062 it Diamond black fan anemia syndromes

NOTE Confidence: 0.8252814

00:05:36.062 --> 00:05:38.750 rather than Diamond black fan anemia.

NOTE Confidence: 0.88067997

00:05:40.870 --> 00:05:45.014 OK, so from there where are we going?

NOTE Confidence: 0.88067997

00:05:45.020 --> 00:05:47.780 The damn little bit of wording of the

NOTE Confidence: 0.88067997

00:05:47.780 --> 00:05:49.900 Diamond Black fan anemia registry.

NOTE Confidence: 0.88067997

00:05:49.900 --> 00:05:53.266 As I told you DBA is a rare disease.

NOTE Confidence: 0.88067997

00:05:53.270 --> 00:05:56.098 It's about the incidence is about 7

NOTE Confidence: 0.88067997

00:05:56.098 --> 00:05:58.402 chameleon birth and that computes to

NOTE Confidence: 0.88067997

00:05:58.402 --> 00:06:01.578 about 25 to 30 new patients a year in

NOTE Confidence: 0.88067997

00:06:01.578 --> 00:06:03.780 the United States here at Feinstein

NOTE Confidence: 0.88067997

00:06:03.780 --> 00:06:06.420 in the registry we have about 800

NOTE Confidence: 0.88067997

00:06:06.420 --> 00:06:08.650 patients that are enrolled from Dad.

NOTE Confidence: 0.88067997

00:06:08.650 --> 00:06:11.947 About 788 are coming from North America

NOTE Confidence: 0.88067997

00:06:11.947 --> 00:06:16.000 and the male to female ratio is 1 to one.

NOTE Confidence: 0.88067997

00:06:16.000 --> 00:06:19.276 In the demographics we have 670 patients

NOTE Confidence: 0.88067997

00:06:19.276 --> 00:06:22.130 that are alive which allows us.

NOTE Confidence: 0.88067997

00:06:22.130 --> 00:06:24.706 Kind of a decent access to samples,

NOTE Confidence: 0.88067997

00:06:24.710 --> 00:06:26.558 and that's that's pretty good when

NOTE Confidence: 0.88067997

00:06:26.558 --> 00:06:28.776 you want to do translational research

NOTE Confidence: 0.88067997

00:06:28.776 --> 00:06:31.700 element back to that, 118 are dead.

NOTE Confidence: 0.88067997

00:06:31.700 --> 00:06:32.060 Unfortunately,

NOTE Confidence: 0.88067997

00:06:32.060 --> 00:06:34.680 the median age is 20 three years,

NOTE Confidence: 0.88067997

00:06:34.680 --> 00:06:36.888 So what did they die from?

NOTE Confidence: 0.88067997

00:06:36.890 --> 00:06:39.008 They died from stem cell transplant

NOTE Confidence: 0.88067997

00:06:39.008 --> 00:06:40.950 related complications from iron overload,

NOTE Confidence: 0.88067997

00:06:40.950 --> 00:06:43.366 which is a big issue and I'll get

NOTE Confidence: 0.88067997

00:06:43.366 --> 00:06:45.750 to that because these patients,

NOTE Confidence: 0.88067997

00:06:45.750 --> 00:06:47.958 when they are not steroid responsive,

NOTE Confidence: 0.88067997

00:06:47.960 --> 00:06:49.815 OK they are transfusion dependent

NOTE Confidence: 0.88067997

00:06:49.815 --> 00:06:52.020 and when they get transfusions over,

NOTE Confidence: 0.88067997

00:06:52.020 --> 00:06:53.181 transfusions over transfusions.

NOTE Confidence: 0.88067997

00:06:53.181 --> 00:06:54.729 Of course they accumulate.

NOTE Confidence: 0.88067997

00:06:54.730 --> 00:06:57.754 Iran and Iran is a big issue.

NOTE Confidence: 0.88067997

00:06:57.760 --> 00:06:59.930 They also die from infection,

NOTE Confidence: 0.88067997

00:06:59.930 --> 00:07:01.614 sepsis, often colon cancer,

NOTE Confidence: 0.88067997

00:07:01.614 --> 00:07:04.690 and obviously tumors or from other cancer.

NOTE Confidence: 0.837899

00:07:07.870 --> 00:07:10.582 OK, the current therapies I touched on the

NOTE Confidence: 0.837899

00:07:10.582 --> 00:07:12.820 peripheral red blood cells transfusions,

NOTE Confidence: 0.837899

00:07:12.820 --> 00:07:15.316 but the mainstay of the treatment when a

NOTE Confidence: 0.837899

00:07:15.316 --> 00:07:17.807 patient is diagnosed with diamond black

NOTE Confidence: 0.837899

00:07:17.807 --> 00:07:20.052 fan anemia is really corticosteroids.

NOTE Confidence: 0.837899

00:07:20.060 --> 00:07:22.349 OK, the only cure for the patient

NOTE Confidence: 0.837899

00:07:22.349 --> 00:07:24.629 is a stem cell transplant.

NOTE Confidence: 0.837899

00:07:24.630 --> 00:07:26.780 However Anile insist on that

NOTE Confidence: 0.837899

00:07:26.780 --> 00:07:28.930 the stem cell transplant doesn't

NOTE Confidence: 0.837899

00:07:29.003 --> 00:07:31.328 protect them from getting cancer.

NOTE Confidence: 0.837899

00:07:31.330 --> 00:07:34.912 So this is a family that agreed of course

NOTE Confidence: 0.837899

00:07:34.912 --> 00:07:38.385 to provide this picture and the dad.

NOTE Confidence: 0.837899

00:07:38.390 --> 00:07:41.060 Is actually.

NOTE Confidence: 0.837899

00:07:41.060 --> 00:07:43.934 Responsive to steroids and the two

NOTE Confidence: 0.837899

00:07:43.934 --> 00:07:46.390 daughters have a different phenotype

NOTE Confidence: 0.837899

00:07:46.390 --> 00:07:49.150 and so that the first daughter.

NOTE Confidence: 0.837899

00:07:49.150 --> 00:07:52.146 OK here is also having anemia that

NOTE Confidence: 0.837899

00:07:52.146 --> 00:07:54.526 is responsive to steroid while

NOTE Confidence: 0.837899

00:07:54.526 --> 00:07:57.046 the second one is transfusion

NOTE Confidence: 0.837899

00:07:57.046 --> 00:08:00.076 dependent and we really don't know

NOTE Confidence: 0.837899

00:08:00.076 --> 00:08:02.944 why steroids within the same family

NOTE Confidence: 0.837899

00:08:02.944 --> 00:08:07.216 can for example lead to a response.

NOTE Confidence: 0.837899

00:08:07.220 --> 00:08:08.495 Or a resistance,

NOTE Confidence: 0.837899

00:08:08.495 --> 00:08:12.339 and so that's a problem that one of my MD,

NOTE Confidence: 0.837899

00:08:12.340 --> 00:08:13.808 PhD student, Ryan Ashley,

NOTE Confidence: 0.837899

00:08:13.808 --> 00:08:16.516 decided to back off for his PhD

NOTE Confidence: 0.837899

00:08:16.516 --> 00:08:19.132 is to understand the mechanism of

NOTE Confidence: 0.837899

00:08:19.132 --> 00:08:21.204 action of glucocorticoids to increase

NOTE Confidence: 0.837899

00:08:21.204 --> 00:08:22.588 the red cell mass.

NOTE Confidence: 0.837899

00:08:22.590 --> 00:08:24.162 Because, as I mentioned,

NOTE Confidence: 0.837899

00:08:24.162 --> 00:08:25.734 it was really unknown.

NOTE Confidence: 0.837899

00:08:25.740 --> 00:08:27.076 It was really unclear.

NOTE Confidence: 0.837899

00:08:27.076 --> 00:08:30.072 I should say not unknown but unclear at

NOTE Confidence: 0.837899

00:08:30.072 --> 00:08:32.826 which stage during era trade differentiation,

NOTE Confidence: 0.837899

00:08:32.830 --> 00:08:33.724 the glucocorticoids.

NOTE Confidence: 0.837899

00:08:33.724 --> 00:08:36.853 And here I'm going to just mention

NOTE Confidence: 0.837899

00:08:36.853 --> 00:08:38.789 dexamethasone in culture was acting.

NOTE Confidence: 0.837899

00:08:38.790 --> 00:08:40.815 There was some studies that

NOTE Confidence: 0.837899

00:08:40.815 --> 00:08:42.435 were saying that yeah,

NOTE Confidence: 0.837899

00:08:42.440 --> 00:08:43.655 glucocorticoid acts early

NOTE Confidence: 0.837899

14

00:08:43.655 --> 00:08:45.680 at the BFUE stage OK,

NOTE Confidence: 0.837899

00:08:45.680 --> 00:08:47.336 especially in the mouse.

NOTE Confidence: 0.837899

00:08:47.336 --> 00:08:50.268 While over more recent studies by mayor

NOTE Confidence: 0.837899

00:08:50.268 --> 00:08:52.865 of Sokolowski had shown it was acting

NOTE Confidence: 0.837899

00:08:52.865 --> 00:08:55.397 later on on the later progenitor,

NOTE Confidence: 0.837899

00:08:55.400 --> 00:08:56.238 the CFV,

NOTE Confidence: 0.837899

00:08:56.238 --> 00:08:59.171 while in the human aritro places early

NOTE Confidence: 0.837899

00:08:59.171 --> 00:09:01.313 studies had showed demonstrated that

NOTE Confidence: 0.837899

00:09:01.313 --> 00:09:04.700 it was acting on the late progenitor.

NOTE Confidence: 0.837899

00:09:04.700 --> 00:09:05.181 Indeed,

NOTE Confidence: 0.837899

00:09:05.181 --> 00:09:08.067 we're not reinventing the wheel right?

NOTE Confidence: 0.837899

00:09:08.070 --> 00:09:10.198 In 1976 already studies.

NOTE Confidence: 0.837899

00:09:10.198 --> 00:09:13.390 Beautiful studies had been done showing

NOTE Confidence: 0.837899

00:09:13.479 --> 00:09:16.371 that demonstrating that the CFU in

NOTE Confidence: 0.837899

00:09:16.371 --> 00:09:19.853 number was increased as we increase

NOTE Confidence: 0.837899

00:09:19.853 --> 00:09:22.049 the dexamethasone concentration.

NOTE Confidence: 0.837899

00:09:22.050 --> 00:09:24.890 So if we go into human arixtra places

NOTE Confidence: 0.837899

00:09:24.890 --> 00:09:27.685 now everything is happening in the bone

NOTE Confidence: 0.837899

00:09:27.685 --> 00:09:30.110 marrow from the hematopoietic stem cell,

NOTE Confidence: 0.837899

00:09:30.110 --> 00:09:32.030 hematopoietic stem and progenitor cell,

NOTE Confidence: 0.837899

00:09:32.030 --> 00:09:35.110 and here Diane will have to excuse me.

NOTE Confidence: 0.837899

00:09:35.110 --> 00:09:38.006 But I'm going to bypass all the stages

NOTE Confidence: 0.837899

00:09:38.006 --> 00:09:41.246 and not argue about which one is which.

NOTE Confidence: 0.837899

00:09:41.250 --> 00:09:43.254 I'm just going to go directly

NOTE Confidence: 0.837899

00:09:43.254 --> 00:09:45.975 to the BFG and to the BFUECFUE

NOTE Confidence: 0.837899

00:09:45.975 --> 00:09:48.155 to the area trade progenitors,

NOTE Confidence: 0.837899

00:09:48.160 --> 00:09:50.152 which is what is really of

NOTE Confidence: 0.837899

00:09:50.152 --> 00:09:52.094 our interest today because the

NOTE Confidence: 0.837899

00:09:52.094 --> 00:09:53.738 terminal differentiation wants.

NOTE Confidence: 0.837899

00:09:53.740 --> 00:09:56.260 And progenitor is entering the terminal.

NOTE Confidence: 0.837899

00:09:56.260 --> 00:09:57.940 Differentiation there is not

NOTE Confidence: 0.837899

00:09:57.940 --> 00:10:00.068 so much that happens, it's.

NOTE Confidence: 0.837899

00:10:00.068 --> 00:10:00.516 Committed,

NOTE Confidence: 0.837899

00:10:00.516 --> 00:10:03.204 it's differentiated and you just have

NOTE Confidence: 0.837899

00:10:03.204 --> 00:10:06.486 four to five cell divisions over 5 days.

NOTE Confidence: 0.837899

00:10:06.490 --> 00:10:08.762 That leads to the

NOTE Confidence: 0.837899

00:10:08.762 --> 00:10:09.898 orthochromatic erythrocytes.

NOTE Confidence: 0.837899

00:10:09.900 --> 00:10:12.378 And the processes of a new creation

NOTE Confidence: 0.837899

00:10:12.378 --> 00:10:15.178 that we still don't fully understand.

NOTE Confidence: 0.837899

00:10:15.180 --> 00:10:17.616 Leading to the reticular site that

NOTE Confidence: 0.837899

00:10:17.616 --> 00:10:19.240 remodels its plasma membrane,

NOTE Confidence: 0.837899

00:10:19.240 --> 00:10:21.256 degrades all the internal

NOTE Confidence: 0.837899

00:10:21.256 --> 00:10:23.776 compartments and become the red

NOTE Confidence: 0.837899

00:10:23.776 --> 00:10:26.760 blood cell that leaves for 120 days.

NOTE Confidence: 0.837899

00:10:26.760 --> 00:10:28.910 OK.

NOTE Confidence: 0.837899

00:10:28.910 --> 00:10:32.501 So we started this study by an

NOTE Confidence: 0.837899

00:10:32.501 --> 00:10:35.310 observation very crude observation.

NOTE Confidence: 0.837899

00:10:35.310 --> 00:10:37.830 We took CD 34 positive cells the

NOTE Confidence: 0.837899

00:10:37.830 --> 00:10:39.839 so called hematopoietic stem and

NOTE Confidence: 0.837899

00:10:39.839 --> 00:10:41.994 progenitor cells that were derived

NOTE Confidence: 0.837899

00:10:41.994 --> 00:10:43.878 weather from peripheral blood PB

NOTE Confidence: 0.837899

00:10:43.878 --> 00:10:45.982 for the rest of the talk or from

NOTE Confidence: 0.837423

00:10:45.990 --> 00:10:48.188 cold blood CB and what we observe

NOTE Confidence: 0.837423

00:10:48.188 --> 00:10:50.476 this that when we treated these

NOTE Confidence: 0.837423

00:10:50.476 --> 00:10:52.601 cells with dexamethasone we observed

NOTE Confidence: 0.837423

00:10:52.601 --> 00:10:54.781 an increase in the cell expansion

NOTE Confidence: 0.837423

00:10:54.781 --> 00:10:57.054 for the cells that will be derived,

NOTE Confidence: 0.837423

00:10:57.054 --> 00:10:59.358 derived from an adult source compared

NOTE Confidence: 0.837423

00:10:59.358 --> 00:11:01.988 to the ones that were derived from

NOTE Confidence: 0.837423

00:11:01.988 --> 00:11:04.094 the cold blood and actually we

NOTE Confidence: 0.837423

00:11:04.167 --> 00:11:06.285 saw a decrease in the expansion.

NOTE Confidence: 0.837423

00:11:06.290 --> 00:11:08.747 And this to us was really intriguing.

NOTE Confidence: 0.837423

00:11:08.750 --> 00:11:10.118 What was happening here?

NOTE Confidence: 0.837423

00:11:10.118 --> 00:11:12.610 This was going against not the dogma,

NOTE Confidence: 0.837423

00:11:12.610 --> 00:11:15.088 but against all the protocols that had

NOTE Confidence: 0.837423

00:11:15.088 --> 00:11:17.170 been using dexamethasone in their culture.

NOTE Confidence: 0.837423

00:11:17.170 --> 00:11:20.082 Here we were using a culture systems that

NOTE Confidence: 0.837423

00:11:20.082 --> 00:11:23.197 was not using any steroids at baseline.

NOTE Confidence: 0.837423

00:11:23.200 --> 00:11:26.329 So we decided to go deeper into

NOTE Confidence: 0.837423

00:11:26.329 --> 00:11:27.223 the mechanism.

NOTE Confidence: 0.837423

00:11:27.230 --> 00:11:29.966 And what we found thanks to the method

NOTE Confidence: 0.837423

00:11:29.966 --> 00:11:32.477 and that Manada had developed to

NOTE Confidence: 0.837423

00:11:32.477 --> 00:11:35.099 study the surface markers for Louise

NOTE Confidence: 0.837423

00:11:35.175 --> 00:11:37.580 and then we validated everything.

NOTE Confidence: 0.837423

00:11:37.580 --> 00:11:40.058 Of course, with colony forming assays,

NOTE Confidence: 0.837423

00:11:40.060 --> 00:11:42.279 we observed that it's actually the CFU

NOTE Confidence: 0.837423

00:11:42.279 --> 00:11:44.884 E from the peripheral blood treated

NOTE Confidence: 0.837423

00:11:44.884 --> 00:11:47.519 with dexamethasone that we're expanding.

19

NOTE Confidence: 0.837423

00:11:47.520 --> 00:11:49.872 You can observe here that none

NOTE Confidence: 0.837423

00:11:49.872 --> 00:11:52.070 of the BFU is order.

NOTE Confidence: 0.837423

00:11:52.070 --> 00:11:54.140 CFU is affected except for

NOTE Confidence: 0.837423

00:11:54.140 --> 00:11:55.796 the peripheral blood treated.

NOTE Confidence: 0.7586687

00:12:00.090 --> 00:12:02.142 When we when we then sorted

NOTE Confidence: 0.7586687

00:12:02.142 --> 00:12:05.026 to cells OK on based on this

NOTE Confidence: 0.7586687

00:12:05.026 --> 00:12:07.416 surface marker expression by fax.

NOTE Confidence: 0.7586687

00:12:07.420 --> 00:12:10.269 By flow cytometry we started the cells.

NOTE Confidence: 0.7586687

00:12:10.270 --> 00:12:13.105 We observed that again it was DCF,

NOTE Confidence: 0.7586687

00:12:13.110 --> 00:12:14.518 UE so-called CFU Ian.

NOTE Confidence: 0.7586687

00:12:14.518 --> 00:12:17.477 Here on code on code because they were

NOTE Confidence: 0.7586687

00:12:17.477 --> 00:12:19.799 not derived from colony forming assays

NOTE Confidence: 0.7586687

00:12:19.799 --> 00:12:22.478 but by surface marker expression.

NOTE Confidence: 0.7586687

00:12:22.480 --> 00:12:24.880 We observed that these were the

NOTE Confidence: 0.7586687

00:12:24.880 --> 00:12:26.950 ones derived from peripheral blood.

NOTE Confidence: 0.7586687

00:12:26.950 --> 00:12:29.080 When we then validated the

00:12:29.080 --> 00:12:30.358 findings by Colony.

00:12:30.360 --> 00:12:31.198 Coming essays,

00:12:31.198 --> 00:12:33.712 we observed that indeed the surface

00:12:33.712 --> 00:12:36.514 area the colony area for the CFO

00:12:36.514 --> 00:12:38.898 is formed by peripheral blood were

00:12:38.898 --> 00:12:41.454 indeed the ones that were responding,

00:12:41.460 --> 00:12:44.393 and I would not hear that very

00:12:44.393 --> 00:12:46.514 puzzling and interesting here was

00:12:46.514 --> 00:12:48.860 that the cold blood at baseline,

00:12:48.860 --> 00:12:49.646 without dexamethasone,

00:12:49.646 --> 00:12:52.397 we're having kind of the same size

00:12:52.397 --> 00:12:54.554 surface area as the peripheral

00:12:54.554 --> 00:12:56.250 blood treated with dexamethasone,

00:12:56.250 --> 00:12:58.305 meaning that maybe and here

00:12:58.305 --> 00:12:59.538 is just speculation,

NOTE Confidence: 0.7586687

00:12:59.540 --> 00:13:03.083 because I have no proof of that, but.

NOTE Confidence: 0.7586687

00:13:03.083 --> 00:13:06.398 Maybe this cells were already.

NOTE Confidence: 0.7586687

00:13:06.400 --> 00:13:08.168 Maximum in their response.

NOTE Confidence: 0.8278979

00:13:11.040 --> 00:13:13.816 The best proof to us would be to

NOTE Confidence: 0.8278979

00:13:13.816 --> 00:13:16.239 go back to the patient, right?

NOTE Confidence: 0.8278979

00:13:16.239 --> 00:13:18.951 Because if we are writing what we are

NOTE Confidence: 0.8278979

00:13:18.951 --> 00:13:21.386 asserting that it's a late progenitor

NOTE Confidence: 0.8278979

00:13:21.386 --> 00:13:23.006 that respond to dexamethasone,

NOTE Confidence: 0.8278979

00:13:23.010 --> 00:13:26.750 we have to prove that in a patient with DB.

NOTE Confidence: 0.8278979

00:13:26.750 --> 00:13:28.620 So we took three patients.

NOTE Confidence: 0.8278979

00:13:28.620 --> 00:13:31.460 OK, that are known to respond to steroids

NOTE Confidence: 0.8278979

00:13:31.460 --> 00:13:34.671 and what we did is that we measure the

NOTE Confidence: 0.8278979

00:13:34.671 --> 00:13:37.004 response to steroid by measuring simply

NOTE Confidence: 0.8278979

00:13:37.004 --> 00:13:39.832 the reticle sight count in the blood.

NOTE Confidence: 0.8278979

00:13:39.840 --> 00:13:41.472 OK, in this patients.

NOTE Confidence: 0.8278979

00:13:41.472 --> 00:13:43.512 After treatment with steroids and

NOTE Confidence: 0.8278979

00:13:43.512 --> 00:13:46.465 so my good friend I knew Nola in her

NOTE Confidence: 0.8278979

00:13:46.465 --> 00:13:48.652 clinic had three patients that she

NOTE Confidence: 0.8278979

00:13:48.652 --> 00:13:51.634 was following and what we did is that

NOTE Confidence: 0.8278979

00:13:51.634 --> 00:13:53.866 she treated them with Prednisone in

NOTE Confidence: 0.8278979

00:13:53.866 --> 00:13:56.730 that case because it was in the clinic,

NOTE Confidence: 0.8278979

00:13:56.730 --> 00:14:00.015 not in vitro and then measure the blood cast.

NOTE Confidence: 0.8278979

00:14:00.020 --> 00:14:01.745 What she observed is that

NOTE Confidence: 0.8278979

00:14:01.745 --> 00:14:04.399 within 7 to 10 days a response.

NOTE Confidence: 0.8278979

00:14:04.400 --> 00:14:06.220 Heretical site response was observed.

NOTE Confidence: 0.8278979

00:14:06.220 --> 00:14:09.226 This if we go back to the basics of

NOTE Confidence: 0.8278979

00:14:09.226 --> 00:14:11.904 very true Poesis tells us that it

NOTE Confidence: 0.8278979

00:14:11.904 --> 00:14:14.998 has to come from a late progenitor.

NOTE Confidence: 0.8278979

00:14:15.000 --> 00:14:17.401 It cannot come for a very early

NOTE Confidence: 0.8278979

00:14:17.401 --> 00:14:18.820 progenitor very early BFUE,

NOTE Confidence: 0.8278979

00:14:18.820 --> 00:14:20.518 because as I showed you before

NOTE Confidence: 0.8278979

00:14:20.518 --> 00:14:22.637 in the diagram in the schematics

NOTE Confidence: 0.8278979

00:14:22.637 --> 00:14:24.020 of human erythropoiesis,

NOTE Confidence: 0.8278979

00:14:24.020 --> 00:14:26.701 it will take way much longer to

NOTE Confidence: 0.8278979

00:14:26.701 --> 00:14:29.419 come from an early progenitor.

NOTE Confidence: 0.8278979

00:14:29.420 --> 00:14:31.620 So having said that,

NOTE Confidence: 0.8278979

00:14:31.620 --> 00:14:34.370 having showed that probably it's.

NOTE Confidence: 0.8278979

00:14:34.370 --> 00:14:36.470 Kind of late for genital that

NOTE Confidence: 0.8278979

00:14:36.470 --> 00:14:37.520 respond to steroids.

NOTE Confidence: 0.8278979

00:14:37.520 --> 00:14:39.270 We decided to go further

NOTE Confidence: 0.8278979

00:14:39.270 --> 00:14:40.670 down into the mechanism,

NOTE Confidence: 0.8278979

00:14:40.670 --> 00:14:42.740 but before going further down

NOTE Confidence: 0.8278979

00:14:42.740 --> 00:14:45.110 into the mechanism we need it.

NOTE Confidence: 0.8278979

00:14:45.110 --> 00:14:47.270 To figure out this,

NOTE Confidence: 0.8278979

00:14:47.270 --> 00:14:49.970 heterogeneity of human error trade

NOTE Confidence: 0.8278979

00:14:49.970 --> 00:14:52.685 progenitors to really try to understand

NOTE Confidence: 0.8278979

00:14:52.685 --> 00:14:55.270 better what is going on here,

NOTE Confidence: 0.8278979

00:14:55.270 --> 00:14:56.348 because this.

NOTE Confidence: 0.8278979

00:14:56.348 --> 00:14:59.043 Hierarchy here, and you're not

NOTE Confidence: 0.8278979

00:14:59.043 --> 00:15:01.679 going to contradict me on that.

NOTE Confidence: 0.8278979

00:15:01.680 --> 00:15:02.532 Is that?

NOTE Confidence: 0.8278979

00:15:02.532 --> 00:15:03.810 Yeah, it's nice,

NOTE Confidence: 0.8278979

00:15:03.810 --> 00:15:06.360 but really it's BFU E2 CFUE,

NOTE Confidence: 0.8278979

00:15:06.360 --> 00:15:08.490 but what else in between?

NOTE Confidence: 0.8278979

00:15:08.490 --> 00:15:11.898 When you look at them under the microscope,

NOTE Confidence: 0.8278979

00:15:11.900 --> 00:15:14.462 the colony forming assays and here

NOTE Confidence: 0.8278979

00:15:14.462 --> 00:15:17.010 provided by young Cheyenne Mohans lab?

NOTE Confidence: 0.8278979

00:15:17.010 --> 00:15:19.140 This is the same plate.

NOTE Confidence: 0.8278979

00:15:19.140 --> 00:15:19.547 Well,

NOTE Confidence: 0.8278979

00:15:19.547 --> 00:15:21.582 it's kind of subjective because

NOTE Confidence: 0.8278979

00:15:21.582 --> 00:15:23.785 all these colonies have different

NOTE Confidence: 0.8278979

00:15:23.785 --> 00:15:25.813 sizes showing probably heterogeneity

NOTE Confidence: 0.8278979

00:15:25.813 --> 00:15:28.348 of the era trade progenitors.

NOTE Confidence: 0.8278979

00:15:28.350 --> 00:15:31.521 An indeed in a previous study we

NOTE Confidence: 0.8278979

00:15:31.521 --> 00:15:34.330 published in 2018 based on these

NOTE Confidence: 0.8278979

00:15:34.330 --> 00:15:37.048 two surface markers CD34 CD 36

NOTE Confidence: 0.8278979

00:15:37.048 --> 00:15:39.717 that would define the BF you

NOTE Confidence: 0.8278979

00:15:39.717 --> 00:15:42.300 here in the lower right quadrant,

NOTE Confidence: 0.8278979

00:15:42.300 --> 00:15:46.350 or the CFU is in the upper left quadrant.

NOTE Confidence: 0.8278979

00:15:46.350 --> 00:15:48.870 We observed again a difference

NOTE Confidence: 0.8278979

00:15:48.870 --> 00:15:50.886 between cornbread and peripheral

NOTE Confidence: 0.8278979

00:15:50.886 --> 00:15:53.844 blood because we observed a double

NOTE Confidence: 0.8278979

00:15:53.844 --> 00:15:55.744 positive population that was

NOTE Confidence: 0.8278979

00:15:55.744 --> 00:15:58.270 present for a long time in culture.

NOTE Confidence: 0.8278979

00:15:58.270 --> 00:16:01.030 In cells derived from peripheral blood,

NOTE Confidence: 0.8278979

00:16:01.030 --> 00:16:04.970 but not much more transient, incorporated.

NOTE Confidence: 0.8278979

00:16:04.970 --> 00:16:07.310 And so we took the bed.

NOTE Confidence: 0.8278979

00:16:07.310 --> 00:16:10.226 Kind of crazy bet that maybe.

NOTE Confidence: 0.8278979

00:16:10.230 --> 00:16:12.695 This double positive population was

NOTE Confidence: 0.8278979

00:16:12.695 --> 00:16:16.179 the one that was responding to steroids.

NOTE Confidence: 0.8278979

00:16:16.180 --> 00:16:16.711 So.

NOTE Confidence: 0.8278979

00:16:16.711 --> 00:16:19.897 We went further and decided to

NOTE Confidence: 0.8278979

00:16:19.897 --> 00:16:21.490 characterize this population.

NOTE Confidence: 0.8278979

00:16:21.490 --> 00:16:23.630 We added surface markers OK,

NOTE Confidence: 0.8278979

00:16:23.630 --> 00:16:25.334 we tested on SA,

NOTE Confidence: 0.8278979

00:16:25.334 --> 00:16:27.464 tested 10s of surface markers.

NOTE Confidence: 0.8278979

00:16:27.470 --> 00:16:30.368 I think an she observed that city

NOTE Confidence: 0.8278979

00:16:30.368 --> 00:16:34.621 105 and CD 71 was giving the best

NOTE Confidence: 0.8278979

00:16:34.621 --> 00:16:36.953 resolution to discriminate between

NOTE Confidence: 0.8278979

00:16:36.953 --> 00:16:39.831 what we call now the immature

NOTE Confidence: 0.8278979

00:16:39.831 --> 00:16:41.587 and mature CFU E.

NOTE Confidence: 0.8278979

00:16:41.590 --> 00:16:45.622 And indeed, when we put them plated them in.

NOTE Confidence: 0.79175115

00:16:45.630 --> 00:16:48.700 People only that give rise to see a few E.

NOTE Confidence: 0.79175115

00:16:48.700 --> 00:16:50.849 This is the definition of a CFU.

NOTE Confidence: 0.79175115

00:16:50.850 --> 00:16:53.050 It responds to Ipoh only.

NOTE Confidence: 0.79175115

00:16:53.050 --> 00:16:55.878 Or incomplete media to generate the beer,

NOTE Confidence: 0.79175115

00:16:55.880 --> 00:16:57.676 and so we there.

NOTE Confidence: 0.79175115

00:16:57.676 --> 00:17:00.370 It's indeed consistent with what she

NOTE Confidence: 0.79175115

00:17:00.457 --> 00:17:03.661 says is that it's it is this image you

NOTE Confidence: 0.79175115

00:17:03.661 --> 00:17:06.824 see FUE that has the potential that I

NOTE Confidence: 0.79175115

00:17:06.824 --> 00:17:10.780 didn't get a chance to answer yet as

NOTE Confidence: 0.79175115

00:17:10.780 --> 00:17:14.190 the potential forming both of them.

NOTE Confidence: 0.79175115

00:17:14.190 --> 00:17:17.010 The BSU and the CFU.

NOTE Confidence: 0.79175115

00:17:17.010 --> 00:17:21.896 OK, when it's placed under any media.

NOTE Confidence: 0.79175115

00:17:21.900 --> 00:17:24.508 So it's not yet a fully committed CFU,

NOTE Confidence: 0.79175115

00:17:24.510 --> 00:17:28.082 E, but it's not a BF UA also, of course.

NOTE Confidence: 0.79175115

00:17:28.082 --> 00:17:31.449 We need single sarony seek for that.

NOTE Confidence: 0.79175115

00:17:31.450 --> 00:17:33.490 To really look at them deeply

NOTE Confidence: 0.79175115

00:17:33.490 --> 00:17:34.510 and characterize them,

NOTE Confidence: 0.79175115

00:17:34.510 --> 00:17:36.890 but it's consistent with what Miraf said,

NOTE Confidence: 0.79175115

00:17:36.890 --> 00:17:40.090 and I'm going to go further down with

NOTE Confidence: 0.79175115

00:17:40.090 --> 00:17:43.130 that because of the mechanism of action.

NOTE Confidence: 0.79175115

00:17:43.130 --> 00:17:45.405 So I'm I'm not going to spend

NOTE Confidence: 0.79175115

00:17:45.405 --> 00:17:47.329 a lot of time here.

NOTE Confidence: 0.79175115

00:17:47.330 --> 00:17:50.130 It's basically this image you see a few.

NOTE Confidence: 0.79175115

00:17:50.130 --> 00:17:52.460 We did respond, but importantly.

NOTE Confidence: 0.79175115

00:17:52.460 --> 00:17:54.050 When we treat.

NOTE Confidence: 0.79175115

00:17:54.050 --> 00:17:55.110 With dexamethasone,

NOTE Confidence: 0.79175115

00:17:55.110 --> 00:17:57.483 we see a reduction of the S

NOTE Confidence: 0.79175115

00:17:57.483 --> 00:17:59.180 phase as may arrive.

NOTE Confidence: 0.79175115

00:17:59.180 --> 00:18:02.960 Did in the mature CFD population.

NOTE Confidence: 0.79175115

00:18:02.960 --> 00:18:05.584 And how is that working so we get

NOTE Confidence: 0.79175115

00:18:05.584 --> 00:18:08.474 into the cell cycle and into the

NOTE Confidence: 0.79175115

00:18:08.474 --> 00:18:11.114 mechanism of Regulation an yeah may

NOTE Confidence: 0.79175115

00:18:11.114 --> 00:18:13.984 have had done everything in the mouse,

NOTE Confidence: 0.79175115

00:18:13.990 --> 00:18:16.662 so that was pretty easy, quote, unquote.

NOTE Confidence: 0.79175115

00:18:16.662 --> 00:18:17.364 To answer,

NOTE Confidence: 0.79175115

00:18:17.364 --> 00:18:20.851 we had P 57 keep to that she had

NOTE Confidence: 0.79175115

00:18:20.851 --> 00:18:23.449 published in cell in Science Advances.

NOTE Confidence: 0.79175115

00:18:23.450 --> 00:18:26.690 OK, that was involved in the

NOTE Confidence: 0.79175115

00:18:26.690 --> 00:18:28.310 regulation of steroids.

NOTE Confidence: 0.79175115

00:18:28.310 --> 00:18:28.686 Indeed,

NOTE Confidence: 0.79175115

00:18:28.686 --> 00:18:31.694 what we observed is that in peripheral blood.

NOTE Confidence: 0.79175115

00:18:31.700 --> 00:18:34.444 OK, there was a downregulation of P57 very

NOTE Confidence: 0.79175115

00:18:34.444 --> 00:18:37.359 early on by the seven of differentiation.

NOTE Confidence: 0.79175115

00:18:37.360 --> 00:18:39.240 Here, we observed that P.

NOTE Confidence: 0.79175115

00:18:39.240 --> 00:18:40.972 57 was totally down,

NOTE Confidence: 0.79175115

00:18:40.972 --> 00:18:43.570 while in the cold blood it

NOTE Confidence: 0.79175115

00:18:43.666 --> 00:18:45.508 was still remaining.

NOTE Confidence: 0.79175115

00:18:45.510 --> 00:18:47.037 P 27 however,

NOTE Confidence: 0.79175115

00:18:47.037 --> 00:18:49.073 was gradually increasing over

NOTE Confidence: 0.79175115

00:18:49.073 --> 00:18:51.710 the 14 days of culture,

NOTE Confidence: 0.79175115

00:18:51.710 --> 00:18:54.818 and here is Alpha Globin's control.

NOTE Confidence: 0.90529215

00:18:56.980 --> 00:18:57.700 Then

NOTE Confidence: 0.8127419

00:18:59.990 --> 00:19:02.478 we looked at the purified CFU E and

NOTE Confidence: 0.8127419

00:19:02.478 --> 00:19:04.635 here really not looking at image

NOTE Confidence: 0.8127419

00:19:04.635 --> 00:19:06.825 services mature because we did not

NOTE Confidence: 0.8127419

00:19:06.891 --> 00:19:09.278 have enough cells to do the Western.

NOTE Confidence: 0.8127419

00:19:09.280 --> 00:19:12.926 So when I say see if you hear is the mix

NOTE Confidence: 0.8127419

00:19:12.926 --> 00:19:16.409 of the two and we observe an increase in

NOTE Confidence: 0.8127419

00:19:16.503 --> 00:19:19.847 the expression levels OK of P57 Kip 2.

NOTE Confidence: 0.8127419

00:19:19.850 --> 00:19:22.060 Under CFIA, derived from peripheral

NOTE Confidence: 0.8127419

00:19:22.060 --> 00:19:24.270 blood but not cold blood.

NOTE Confidence: 0.8127419

00:19:24.270 --> 00:19:26.086 P. 27 wasn't changed.

NOTE Confidence: 0.8127419

00:19:26.086 --> 00:19:29.999 So how do we relate that to DBA now?

NOTE Confidence: 0.8546087

00:19:33.260 --> 00:19:35.479 Well, we went back to our patients

NOTE Confidence: 0.8546087

00:19:35.479 --> 00:19:38.200 with DBA and as I told you the benefit

NOTE Confidence: 0.8546087

00:19:38.200 --> 00:19:40.541 of being part of the Diamond Black

NOTE Confidence: 0.8546087

00:19:40.541 --> 00:19:42.809 fan registries that you have access

NOTE Confidence: 0.8546087

00:19:42.809 --> 00:19:44.845 to samples and patients are really

NOTE Confidence: 0.8546087

00:19:44.845 --> 00:19:46.500 eager to contribute to studies.

NOTE Confidence: 0.8546087

00:19:46.500 --> 00:19:48.484 As I'm sure you know and so we

NOTE Confidence: 0.8546087

00:19:48.484 --> 00:19:50.711 had a transfusion dependent or

NOTE Confidence: 0.8546087

00:19:50.711 --> 00:19:52.367 the steroid responsive.

NOTE Confidence: 0.8546087

00:19:52.370 --> 00:19:54.426 Just a note, it's much easier to get

NOTE Confidence: 0.8546087

00:19:54.426 --> 00:19:56.312 blood from transfusion dependent than

NOTE Confidence: 0.8546087

00:19:56.312 --> 00:19:58.502 the steroid responsive because the

NOTE Confidence: 0.8546087

00:19:58.502 --> 00:20:00.198 steroid responsive don't come to.

NOTE Confidence: 0.8546087

00:20:00.200 --> 00:20:02.237 Clinic they just called to get a

NOTE Confidence: 0.8546087

00:20:02.237 --> 00:20:03.884 refill on their steroids because

NOTE Confidence: 0.8546087

00:20:03.884 --> 00:20:05.996 the treatment works so they don't

00:20:05.996 --> 00:20:07.680 need to come to clinic.

00:20:07.680 --> 00:20:09.200 However, the transfusion dependent

00:20:09.200 --> 00:20:11.940 come over and So what we observe

00:20:11.940 --> 00:20:13.488 is that the expansion.

00:20:13.490 --> 00:20:15.325 Was indeed very effective in

00:20:15.325 --> 00:20:16.426 the series responsive,

00:20:16.430 --> 00:20:19.496 but not in the transfusion dependent.

00:20:19.500 --> 00:20:22.139 And here I have to give credit

00:20:22.139 --> 00:20:25.443 to Ryan because he did a lot of

00:20:25.443 --> 00:20:27.115 experiments working on about

00:20:27.115 --> 00:20:29.826 20,000 cells to get Western blots.

00:20:29.830 --> 00:20:33.134 Because you have a pool city of very

00:20:33.134 --> 00:20:35.190 trade progenitors as I mentioned.

00:20:35.190 --> 00:20:37.668 But what we observed is exactly

00:20:37.668 --> 00:20:39.320 what Diane was asking.

00:20:39.320 --> 00:20:43.450 OK, and what we what we published is that P.

00:20:43.450 --> 00:20:47.158 57 OK is actually up regulated.

00:20:47.160 --> 00:20:49.965 Industry responsive and not into

00:20:49.965 --> 00:20:51.648 transfusion dependent patients.

00:20:53.770 --> 00:20:55.406 And so we leave.

00:20:55.406 --> 00:20:58.580 We left it here on that paper,

00:20:58.580 --> 00:21:00.970 although we undertook some proteomics

00:21:00.970 --> 00:21:04.586 and the data are available and in the

00:21:04.586 --> 00:21:06.878 paper that was published last year,

00:21:06.880 --> 00:21:10.222 if I can change the slide

00:21:10.222 --> 00:21:13.780 in JCI and there are over.

00:21:13.780 --> 00:21:16.306 The targets, notably one that I'm

00:21:16.306 --> 00:21:19.419 sure is of interest of several people

00:21:19.419 --> 00:21:22.190 in the audience, such as NL 41,

00:21:22.190 --> 00:21:23.965 another cell cycle regulator that

34

00:21:23.965 --> 00:21:26.517 has been involved in proliferation

NOTE Confidence: 0.8211199

00:21:26.517 --> 00:21:28.637 and differentiation and cancer,

NOTE Confidence: 0.8211199

00:21:28.640 --> 00:21:32.784 and we are actively following up on that.

NOTE Confidence: 0.8211199

00:21:32.790 --> 00:21:37.170 With Pat and Lori Steiner so.

NOTE Confidence: 0.8211199

00:21:37.170 --> 00:21:38.740 In conclusion, for this spot,

NOTE Confidence: 0.8211199

00:21:38.740 --> 00:21:42.560 what I can tell you now is that we start.

NOTE Confidence: 0.8211199

00:21:42.560 --> 00:21:43.913 Understanding not completely,

NOTE Confidence: 0.8211199

00:21:43.913 --> 00:21:46.619 we don't have a complete picture,

NOTE Confidence: 0.8211199

00:21:46.620 --> 00:21:48.875 but still with starting making

NOTE Confidence: 0.8211199

00:21:48.875 --> 00:21:51.130 progress in response to steroid,

NOTE Confidence: 0.8211199

00:21:51.130 --> 00:21:54.490 we think that we can draw a comparison

NOTE Confidence: 0.8211199

00:21:54.490 --> 00:21:57.439 between healthy control patients with TBI,

NOTE Confidence: 0.8211199

00:21:57.440 --> 00:21:59.652 an adult versus neonet.

NOTE Confidence: 0.8211199

00:21:59.652 --> 00:22:01.864 Hematopoietic stem and progenitor

NOTE Confidence: 0.8211199

00:22:01.864 --> 00:22:04.934 cells and probably P 57 Kip, too,

NOTE Confidence: 0.8211199

00:22:04.934 --> 00:22:07.238 is central to the response to

NOTE Confidence: 0.8211199

00:22:07.238 --> 00:22:09.900 steroids on this imagery population.

NOTE Confidence: 0.8211199

00:22:09.900 --> 00:22:12.777 The image you see FUE population that

NOTE Confidence: 0.8211199

00:22:12.777 --> 00:22:15.525 we still have to further characterize

NOTE Confidence: 0.8211199

00:22:15.525 --> 00:22:18.375 an we actively doing that an.

NOTE Confidence: 0.8265596

00:22:20.760 --> 00:22:23.616 Leading to self renewal of this population

NOTE Confidence: 0.8265596

00:22:23.616 --> 00:22:25.859 an increasing the red cell mass.

NOTE Confidence: 0.8265596

00:22:25.860 --> 00:22:27.820 Thinking a lot of people.

NOTE Confidence: 0.8265596

00:22:27.820 --> 00:22:30.557 Of course, the members of the lab.

NOTE Confidence: 0.8265596

00:22:30.560 --> 00:22:32.954 Julian, who's been my partner in

NOTE Confidence: 0.8265596

00:22:32.954 --> 00:22:35.760 crime for the past 10 years with

NOTE Confidence: 0.8265596

00:22:35.760 --> 00:22:38.004 who I probably would be lost.

NOTE Confidence: 0.8265596

00:22:38.010 --> 00:22:40.938 The people in the lab who do an

NOTE Confidence: 0.8265596

00:22:40.938 --> 00:22:43.497 amazing work and the past members.

NOTE Confidence: 0.8265596

00:22:43.500 --> 00:22:45.426 My MD, PhD students that all

NOTE Confidence: 0.8265596

00:22:45.426 --> 00:22:47.326 graduated now and I'll collaborators

NOTE Confidence: 0.8265596

00:22:47.326 --> 00:22:51.590 within the Feinstein, Jeff and and.

NOTE Confidence: 0.8265596

00:22:51.590 --> 00:22:52.964 And of course,

NOTE Confidence: 0.8265596

00:22:52.964 --> 00:22:55.254 our outside collaborators my as

NOTE Confidence: 0.8265596

00:22:55.254 --> 00:22:58.419 I call him my my scientific dad,

NOTE Confidence: 0.8265596

00:22:58.420 --> 00:23:03.508 more Han Bat, who has been following me.

NOTE Confidence: 0.8265596

00:23:03.510 --> 00:23:05.778 I would say listening to me and

NOTE Confidence: 0.8265596

00:23:05.778 --> 00:23:08.734 for the past 10 years also or 12

NOTE Confidence: 0.8265596

00:23:08.734 --> 00:23:10.644 years listening to my complaints

NOTE Confidence: 0.8265596

00:23:10.727 --> 00:23:12.200 and everything very,

NOTE Confidence: 0.8265596

00:23:12.200 --> 00:23:14.468 very patient with me and then

NOTE Confidence: 0.8265596

00:23:14.468 --> 00:23:15.980 this will help us.

NOTE Confidence: 0.8265596

00:23:15.980 --> 00:23:18.152 We've all done older single serving

NOTE Confidence: 0.8265596

00:23:18.152 --> 00:23:21.099 is sick that I didn't have time to

NOTE Confidence: 0.8265596

00:23:21.099 --> 00:23:23.714 present today and you and all our

NOTE Confidence: 0.8265596

00:23:23.714 --> 00:23:26.570 collaborators from the USA and in France.

NOTE Confidence: 0.8265596

00:23:26.570 --> 00:23:28.838 And of course our funding source

NOTE Confidence: 0.8265596

00:23:28.838 --> 00:23:30.350 from NIH hanovers foundations.

NOTE Confidence: 0.8265596

00:23:30.350 --> 00:23:32.630 If you have any questions feel

NOTE Confidence: 0.8265596

00:23:32.630 --> 00:23:34.980 free to send me an email.

NOTE Confidence: 0.8265596

00:23:34.980 --> 00:23:36.080 Thanks for your attention,

NOTE Confidence: 0.8265596

00:23:36.080 --> 00:23:38.320 will be happy to take any questions.

NOTE Confidence: 0.79174405

00:23:42.210 --> 00:23:44.597 Thank you, Leo, for truly excellent talk.