

WEBVTT

NOTE duration:"00:54:03"

NOTE recognizability:0.771

NOTE language:en-us

NOTE Confidence: 0.764020417

00:00:00.000 --> 00:00:03.485 Today's speaker is Karen Feinberg.

NOTE Confidence: 0.764020417

00:00:03.485 --> 00:00:06.273 Doctor Feinberg needs no

NOTE Confidence: 0.764020417

00:00:06.273 --> 00:00:08.060 introduction introduction.

NOTE Confidence: 0.764020417

00:00:08.060 --> 00:00:10.470 However, we have several new

NOTE Confidence: 0.764020417

00:00:10.470 --> 00:00:12.398 members in the department,

NOTE Confidence: 0.764020417

00:00:12.400 --> 00:00:15.412 so for their sake I will

NOTE Confidence: 0.764020417

00:00:15.412 --> 00:00:16.918 introduce Doctor Feinberg.

NOTE Confidence: 0.764020417

00:00:16.920 --> 00:00:21.272 She's been at Yale for a long, long time.

NOTE Confidence: 0.764020417

00:00:21.272 --> 00:00:25.619 She came to Yale to do her

NOTE Confidence: 0.764020417

00:00:25.619 --> 00:00:28.558 undergraduate education and she

NOTE Confidence: 0.764020417

00:00:28.558 --> 00:00:32.138 graduated BS Magna \*\*\* laude.

NOTE Confidence: 0.764020417

00:00:32.140 --> 00:00:36.070 And then Doctor Feinberg stayed on to

NOTE Confidence: 0.764020417

00:00:36.070 --> 00:00:41.700 do an MPhil, followed by an MD PhD.

NOTE Confidence: 0.764020417

00:00:41.700 --> 00:00:46.447 She went on to Mass General Hospital to  
NOTE Confidence: 0.764020417

00:00:46.447 --> 00:00:49.789 do a residency in clinical pathology,  
NOTE Confidence: 0.764020417

00:00:49.790 --> 00:00:52.600 followed by a fellowship in  
NOTE Confidence: 0.764020417

00:00:52.600 --> 00:00:55.126 molecular genetic pathology at  
NOTE Confidence: 0.764020417

00:00:55.126 --> 00:00:57.430 Brigham and Women's Hospital.  
NOTE Confidence: 0.764020417

00:00:57.430 --> 00:00:58.902 So after that, however,  
NOTE Confidence: 0.764020417

00:00:58.902 --> 00:01:02.108 it looks like Doctor Feinberg's interest's  
NOTE Confidence: 0.764020417

00:01:02.108 --> 00:01:05.882 basic interest was in iron metabolism  
NOTE Confidence: 0.764020417

00:01:05.882 --> 00:01:09.081 and she did a research fellowship  
NOTE Confidence: 0.764020417

00:01:09.081 --> 00:01:12.880 at BWH and then she was recruited.  
NOTE Confidence: 0.764020417

00:01:12.880 --> 00:01:14.674 At Duke University,  
NOTE Confidence: 0.764020417

00:01:14.674 --> 00:01:18.860 where she spent another four years building  
NOTE Confidence: 0.764020417

00:01:18.957 --> 00:01:23.038 her research until thanks to Doctor Morrow,  
NOTE Confidence: 0.764020417

00:01:23.040 --> 00:01:28.374 Karen was recruited here at Yale in  
NOTE Confidence: 0.764020417

00:01:28.380 --> 00:01:33.450 2013 to continue her research work.  
NOTE Confidence: 0.764020417

00:01:33.450 --> 00:01:36.394 Doctor Feinberg's track record

NOTE Confidence: 0.764020417

00:01:36.394 --> 00:01:40.074 track record of Excellence was

NOTE Confidence: 0.764020417

00:01:40.074 --> 00:01:43.464 established early on during her

NOTE Confidence: 0.764020417

00:01:43.464 --> 00:01:46.654 undergraduate education when she was.

NOTE Confidence: 0.764020417

00:01:46.660 --> 00:01:51.748 Became member of the Phi Beta Kappa Society

NOTE Confidence: 0.764020417

00:01:51.748 --> 00:01:55.979 for Excellence in Humanities and in Arts.

NOTE Confidence: 0.764020417

00:01:55.980 --> 00:01:58.584 But at Yale College,

NOTE Confidence: 0.764020417

00:01:58.584 --> 00:02:01.899 she also became a member of

NOTE Confidence: 0.764020417

00:02:01.900 --> 00:02:04.080 prestigious Honor Society,

NOTE Confidence: 0.764020417

00:02:04.080 --> 00:02:06.820 Alpha Omega Alpha Society

NOTE Confidence: 0.764020417

00:02:06.820 --> 00:02:08.875 for medical students.

NOTE Confidence: 0.764020417

00:02:08.880 --> 00:02:13.029 She received a Yale MD PhD Alumni Award and

NOTE Confidence: 0.764020417

00:02:13.029 --> 00:02:17.417 she received two Young Investigator Awards,

NOTE Confidence: 0.764020417

00:02:17.420 --> 00:02:21.446 one in 2006 from the Association

NOTE Confidence: 0.764020417

00:02:21.446 --> 00:02:23.459 of Molecular Pathology.

NOTE Confidence: 0.764020417

00:02:23.460 --> 00:02:25.987 While she was still a fellow and.

NOTE Confidence: 0.764020417

00:02:25.990 --> 00:02:30.470 Another in 2013 from International  
NOTE Confidence: 0.764020417

00:02:30.470 --> 00:02:33.158 BioWare and Society.  
NOTE Confidence: 0.764020417

00:02:33.160 --> 00:02:36.562 Doctor Finberg has been a Co  
NOTE Confidence: 0.764020417

00:02:36.562 --> 00:02:39.680 investigator on several grounds at Yale,  
NOTE Confidence: 0.764020417

00:02:39.680 --> 00:02:42.656 and I will not enumerate them.  
NOTE Confidence: 0.764020417

00:02:42.660 --> 00:02:44.804 She's currently associate director  
NOTE Confidence: 0.764020417

00:02:44.804 --> 00:02:48.020 of tumor Profiling Lab and she  
NOTE Confidence: 0.764020417

00:02:48.111 --> 00:02:50.900 plays a seminar where she played  
NOTE Confidence: 0.764020417

00:02:50.900 --> 00:02:54.900 a Seminole role in implementing  
NOTE Confidence: 0.764020417

00:02:54.900 --> 00:02:58.100 clinical next generation sequencing.  
NOTE Confidence: 0.764020417

00:02:58.100 --> 00:03:00.320 She is associate director  
NOTE Confidence: 0.764020417

00:03:00.320 --> 00:03:02.540 of Yale Molecular Genetic.  
NOTE Confidence: 0.764020417

00:03:02.540 --> 00:03:04.848 Pathology fellowship and assistant  
NOTE Confidence: 0.764020417

00:03:04.848 --> 00:03:08.310 Director of Education for the Yale,  
NOTE Confidence: 0.764020417

00:03:08.310 --> 00:03:10.095 MD, PhD program.  
NOTE Confidence: 0.764020417

00:03:10.095 --> 00:03:14.260 Her research focus is primarily primarily on

NOTE Confidence: 0.764020417

00:03:14.358 --> 00:03:18.648 molecular basis of inherited iron disorders.

NOTE Confidence: 0.764020417

00:03:18.650 --> 00:03:22.470 Mechanisms of systemic iron regulation,

NOTE Confidence: 0.764020417

00:03:22.470 --> 00:03:24.936 and physiological consequences

NOTE Confidence: 0.764020417

00:03:24.936 --> 00:03:28.224 of iron deficiency anemia.

NOTE Confidence: 0.764020417

00:03:28.230 --> 00:03:30.612 So, with that I'll let Doctor

NOTE Confidence: 0.764020417

00:03:30.612 --> 00:03:32.789 Feinberg start for those of you.

NOTE Confidence: 0.764020417

00:03:32.790 --> 00:03:34.760 Who would have questions at

NOTE Confidence: 0.764020417

00:03:34.760 --> 00:03:36.730 the end of the talk?

NOTE Confidence: 0.764020417

00:03:36.730 --> 00:03:39.605 Feel free to unmute yourself

NOTE Confidence: 0.764020417

00:03:39.605 --> 00:03:41.330 and ask questions.

NOTE Confidence: 0.764020417

00:03:41.330 --> 00:03:43.030 Those who are on zoom.

NOTE Confidence: 0.764020417

00:03:43.030 --> 00:03:43.900 Thank you.

NOTE Confidence: 0.775845432111111

00:03:44.890 --> 00:03:47.186 So thank you Doctor Prasad and I wanted

NOTE Confidence: 0.775845432111111

00:03:47.186 --> 00:03:49.706 to say that it's a particular honor

NOTE Confidence: 0.775845432111111

00:03:49.706 --> 00:03:52.004 to follow Doctor Keshishian who spoke

NOTE Confidence: 0.775845432111111

00:03:52.004 --> 00:03:54.146 in ground grand Grounds last week.  
NOTE Confidence: 0.775845432111111  
00:03:54.150 --> 00:03:55.662 So Doctor Cashiering was one of  
NOTE Confidence: 0.775845432111111  
00:03:55.662 --> 00:03:57.288 my mentors when I was an MDP.  
NOTE Confidence: 0.775845432111111  
00:03:57.290 --> 00:03:59.089 She sitting here and he's actually the  
NOTE Confidence: 0.775845432111111  
00:03:59.089 --> 00:04:01.085 first person that really told me to think  
NOTE Confidence: 0.775845432111111  
00:04:01.085 --> 00:04:02.770 seriously about a career in pathology,  
NOTE Confidence: 0.775845432111111  
00:04:02.770 --> 00:04:04.170 so perhaps he's listening today.  
NOTE Confidence: 0.775845432111111  
00:04:04.170 --> 00:04:08.170 I hope so. I have nothing to disclose.  
NOTE Confidence: 0.775845432111111  
00:04:08.170 --> 00:04:10.739 So today we have a diverse audience  
NOTE Confidence: 0.775845432111111  
00:04:10.739 --> 00:04:12.712 and our department, so I'm going to  
NOTE Confidence: 0.775845432111111  
00:04:12.712 --> 00:04:16.260 try and cover a lot of ground. My talk.  
NOTE Confidence: 0.775845432111111  
00:04:16.260 --> 00:04:18.366 I'll start with an introduction to  
NOTE Confidence: 0.775845432111111  
00:04:18.366 --> 00:04:20.340 the iron regulatory hormone hepcidin,  
NOTE Confidence: 0.775845432111111  
00:04:20.340 --> 00:04:22.548 and talk about its dysregulation and  
NOTE Confidence: 0.775845432111111  
00:04:22.548 --> 00:04:24.859 human genetic disorder of iron loading.  
NOTE Confidence: 0.775845432111111  
00:04:24.860 --> 00:04:27.660 But I'll move on to the condition iron

NOTE Confidence: 0.775845432111111

00:04:27.660 --> 00:04:30.320 refractory iron deficiency anemia, or Rita,

NOTE Confidence: 0.775845432111111

00:04:30.320 --> 00:04:33.890 a genetic disorder of hepcidin, excess.

NOTE Confidence: 0.775845432111111

00:04:33.890 --> 00:04:36.305 Then we'll move to new insights into

NOTE Confidence: 0.775845432111111

00:04:36.305 --> 00:04:37.842 mechanisms of iron mobilization

NOTE Confidence: 0.775845432111111

00:04:37.842 --> 00:04:39.159 from the liver.

NOTE Confidence: 0.775845432111111

00:04:39.160 --> 00:04:41.460 From my laboratory work here and

NOTE Confidence: 0.775845432111111

00:04:41.460 --> 00:04:43.092 finally some collaborative studies.

NOTE Confidence: 0.775845432111111

00:04:43.100 --> 00:04:44.471 I've done it.

NOTE Confidence: 0.775845432111111

00:04:44.471 --> 00:04:44.928 Yeah,

NOTE Confidence: 0.775845432111111

00:04:44.928 --> 00:04:47.213 looking at the physiological consequences

NOTE Confidence: 0.775845432111111

00:04:47.213 --> 00:04:49.890 of iron deficiency beyond anemia.

NOTE Confidence: 0.775845432111111

00:04:49.890 --> 00:04:53.256 So let's start with iron regulation.

NOTE Confidence: 0.775845432111111

00:04:53.260 --> 00:04:55.870 As this audience is well aware,

NOTE Confidence: 0.775845432111111

00:04:55.870 --> 00:04:57.570 the maintenance of systemic iron

NOTE Confidence: 0.775845432111111

00:04:57.570 --> 00:04:59.710 balance is really critical for health.

NOTE Confidence: 0.775845432111111

00:04:59.710 --> 00:05:02.014 2 little iron impairs of production  
NOTE Confidence: 0.775845432111111

00:05:02.014 --> 00:05:03.550 of many essential proteins,  
NOTE Confidence: 0.775845432111111

00:05:03.550 --> 00:05:05.218 most notable of course.  
NOTE Confidence: 0.775845432111111

00:05:05.218 --> 00:05:06.886 Hemoglobin leading to anemia,  
NOTE Confidence: 0.775845432111111

00:05:06.890 --> 00:05:09.104 and I'll remind you that iron  
NOTE Confidence: 0.775845432111111

00:05:09.104 --> 00:05:11.932 deficiency anemia is the most common  
NOTE Confidence: 0.775845432111111

00:05:11.932 --> 00:05:13.858 micronutrient deficiency worldwide.  
NOTE Confidence: 0.775845432111111

00:05:13.860 --> 00:05:16.200 About 80% of the global  
NOTE Confidence: 0.775845432111111

00:05:16.200 --> 00:05:18.540 population has low iron stores,  
NOTE Confidence: 0.775845432111111

00:05:18.540 --> 00:05:20.540 as estimated by The Who,  
NOTE Confidence: 0.775845432111111

00:05:20.540 --> 00:05:23.473 and about 30% of the global population  
NOTE Confidence: 0.775845432111111

00:05:23.473 --> 00:05:26.570 has overt anemia due to iron deficiency.  
NOTE Confidence: 0.775845432111111

00:05:26.570 --> 00:05:26.894 Conversely,  
NOTE Confidence: 0.775845432111111

00:05:26.894 --> 00:05:29.486 too much higher the problem for the body,  
NOTE Confidence: 0.775845432111111

00:05:29.490 --> 00:05:31.975 because iron causes oxidative damage  
NOTE Confidence: 0.775845432111111

00:05:31.975 --> 00:05:34.218 to tissues and this iron overload



NOTE Confidence: 0.775845432111111

00:05:34.218 --> 00:05:35.778 can be acquired through chronic

NOTE Confidence: 0.775845432111111

00:05:35.778 --> 00:05:37.446 blood transfusions and also in

NOTE Confidence: 0.775845432111111

00:05:37.446 --> 00:05:39.066 a variety of genetic disorders,

NOTE Confidence: 0.775845432111111

00:05:39.070 --> 00:05:41.410 including for example HFE

NOTE Confidence: 0.775845432111111

00:05:41.410 --> 00:05:43.165 hereditary can chromatolysis,

NOTE Confidence: 0.775845432111111

00:05:43.170 --> 00:05:45.480 as well as several iron loading remias.

NOTE Confidence: 0.834830914444444

00:05:47.770 --> 00:05:50.380 Iron Physiology involves a complex

NOTE Confidence: 0.834830914444444

00:05:50.380 --> 00:05:52.468 interplay between multiple organs.

NOTE Confidence: 0.834830914444444

00:05:52.470 --> 00:05:54.717 Iron is absorbed in the duodenum and

NOTE Confidence: 0.834830914444444

00:05:54.717 --> 00:05:57.166 it's transported into the Plasma, where it

NOTE Confidence: 0.834830914444444

00:05:57.166 --> 00:05:59.356 finds the carrier protein transparent.

NOTE Confidence: 0.834830914444444

00:05:59.360 --> 00:06:01.022 Iron Dentist delivered to the bone

NOTE Confidence: 0.834830914444444

00:06:01.022 --> 00:06:02.940 marrow for red blood cell synthesis.

NOTE Confidence: 0.834830914444444

00:06:02.940 --> 00:06:05.108 These red cells circulate and when they age,

NOTE Confidence: 0.834830914444444

00:06:05.110 --> 00:06:06.364 they're phagocytosis by

NOTE Confidence: 0.834830914444444

00:06:06.364 --> 00:06:08.036 macrophages in the spleen.  
NOTE Confidence: 0.834830914444444

00:06:08.040 --> 00:06:10.819 This allows the iron to be reclaimed  
NOTE Confidence: 0.834830914444444

00:06:10.820 --> 00:06:12.648 from hemoglobin and exported  
NOTE Confidence: 0.834830914444444

00:06:12.648 --> 00:06:14.933 back into circulation to support  
NOTE Confidence: 0.834830914444444

00:06:14.933 --> 00:06:17.248 further rounds of auricular crisis.  
NOTE Confidence: 0.834830914444444

00:06:17.250 --> 00:06:17.970 Iron, of course,  
NOTE Confidence: 0.834830914444444

00:06:17.970 --> 00:06:19.650 can also be used by other organs,  
NOTE Confidence: 0.834830914444444

00:06:19.650 --> 00:06:20.850 such as the heart, muscle,  
NOTE Confidence: 0.834830914444444

00:06:20.850 --> 00:06:23.307 pancreas and of course iron is needed  
NOTE Confidence: 0.834830914444444

00:06:23.307 --> 00:06:25.609 for the fetus during pregnancy.  
NOTE Confidence: 0.834830914444444

00:06:25.610 --> 00:06:28.538 The liver is the body's main iron Depot,  
NOTE Confidence: 0.834830914444444

00:06:28.540 --> 00:06:32.810 the main site of iron storage.  
NOTE Confidence: 0.834830914444444

00:06:32.810 --> 00:06:34.796 And daily we actually lose very  
NOTE Confidence: 0.834830914444444

00:06:34.796 --> 00:06:36.510 little iron from the body.  
NOTE Confidence: 0.834830914444444

00:06:36.510 --> 00:06:38.456 We have small losses from shedding of  
NOTE Confidence: 0.834830914444444

00:06:38.456 --> 00:06:40.438 the lining of the of the GI tract.

NOTE Confidence: 0.834830914444444

00:06:40.440 --> 00:06:42.010 The Gu tracks the skin.

NOTE Confidence: 0.834830914444444

00:06:42.010 --> 00:06:44.110 And of course menstruation and women.

NOTE Confidence: 0.834830914444444

00:06:44.110 --> 00:06:46.846 But there's no known regulated mechanism

NOTE Confidence: 0.834830914444444

00:06:46.846 --> 00:06:49.390 for iron excretion from the body.

NOTE Confidence: 0.834830914444444

00:06:49.390 --> 00:06:50.620 As a result,

NOTE Confidence: 0.834830914444444

00:06:50.620 --> 00:06:52.670 it's become clear that systemic

NOTE Confidence: 0.834830914444444

00:06:52.670 --> 00:06:55.394 iron balance is regulated at the

NOTE Confidence: 0.834830914444444

00:06:55.394 --> 00:06:57.226 level of intestinal absorption.

NOTE Confidence: 0.834830914444444

00:06:57.230 --> 00:06:58.298 And so I thought,

NOTE Confidence: 0.834830914444444

00:06:58.298 --> 00:06:59.366 inspired by Doctor Kashgari

NOTE Confidence: 0.834830914444444

00:06:59.366 --> 00:07:01.108 and I show a little history.

NOTE Confidence: 0.834830914444444

00:07:01.110 --> 00:07:02.490 So this is George H.

NOTE Confidence: 0.834830914444444

00:07:02.490 --> 00:07:02.746 Whipple,

NOTE Confidence: 0.834830914444444

00:07:02.746 --> 00:07:03.770 who was a pathologist,

NOTE Confidence: 0.834830914444444

00:07:03.770 --> 00:07:06.608 actually a Yale undergraduate as well.

NOTE Confidence: 0.834830914444444

00:07:06.610 --> 00:07:08.326 He's the whipple of Whipple's disease,  
NOTE Confidence: 0.834830914444444

00:07:08.330 --> 00:07:09.412 not procedure,  
NOTE Confidence: 0.834830914444444

00:07:09.412 --> 00:07:12.804 and he shared the 1934 Nobel Prize  
NOTE Confidence: 0.834830914444444

00:07:12.804 --> 00:07:14.436 for discovering it's concerning  
NOTE Confidence: 0.834830914444444

00:07:14.436 --> 00:07:16.730 liver therapy in cases of anemia.  
NOTE Confidence: 0.834830914444444

00:07:16.730 --> 00:07:18.662 This is a publication from his  
NOTE Confidence: 0.834830914444444

00:07:18.662 --> 00:07:20.510 group from 1943 in the Journal  
NOTE Confidence: 0.834830914444444

00:07:20.510 --> 00:07:21.410 of Experimental Medicine,  
NOTE Confidence: 0.834830914444444

00:07:21.410 --> 00:07:24.464 where they looked at radioactive iron  
NOTE Confidence: 0.834830914444444

00:07:24.464 --> 00:07:26.500 absorption by the gastrointestinal  
NOTE Confidence: 0.834830914444444

00:07:26.570 --> 00:07:27.560 tract of dogs.  
NOTE Confidence: 0.834830914444444

00:07:27.560 --> 00:07:31.165 And he made some summer lovations that  
NOTE Confidence: 0.834830914444444

00:07:31.165 --> 00:07:33.318 the gastrointestinal mucosa accepts  
NOTE Confidence: 0.834830914444444

00:07:33.318 --> 00:07:35.880 iron readily when the Iron Reserve  
NOTE Confidence: 0.834830914444444

00:07:35.880 --> 00:07:38.160 stores are depleted by chronic anemia,  
NOTE Confidence: 0.834830914444444

00:07:38.160 --> 00:07:39.920 but in a plethoric state when there is,

NOTE Confidence: 0.834830914444444

00:07:39.920 --> 00:07:41.620 there is very little absorption

NOTE Confidence: 0.834830914444444

00:07:41.620 --> 00:07:44.508 of iron and the body has no ready

NOTE Confidence: 0.834830914444444

00:07:44.508 --> 00:07:47.079 means of disposing of surplus iron.

NOTE Confidence: 0.834830914444444

00:07:47.080 --> 00:07:50.615 The body can protect itself against a

NOTE Confidence: 0.834830914444444

00:07:50.615 --> 00:07:53.337 large accumulation of iron with the body,

NOTE Confidence: 0.834830914444444

00:07:53.337 --> 00:07:55.150 which can cause damage to important organs,

NOTE Confidence: 0.834830914444444

00:07:55.150 --> 00:07:56.702 as in hemochromatosis and

NOTE Confidence: 0.834830914444444

00:07:56.702 --> 00:07:57.478 Mediterranean anemia.

NOTE Confidence: 0.834830914444444

00:07:57.480 --> 00:07:59.958 The traditional name for a historical

NOTE Confidence: 0.834830914444444

00:07:59.958 --> 00:08:01.610 name for beta thalassemia.

NOTE Confidence: 0.834830914444444

00:08:01.610 --> 00:08:03.674 And the mechanism of this acceptance

NOTE Confidence: 0.834830914444444

00:08:03.674 --> 00:08:06.770 or refusal of iron is of great interest

NOTE Confidence: 0.834830914444444

00:08:06.770 --> 00:08:08.426 to physiologists and physicians.

NOTE Confidence: 0.834830914444444

00:08:08.430 --> 00:08:11.198 So it took a long time for that

NOTE Confidence: 0.834830914444444

00:08:11.198 --> 00:08:13.069 mechanism to be discovered,

NOTE Confidence: 0.834830914444444

00:08:13.070 --> 00:08:15.037 but in the early 2000s it became  
NOTE Confidence: 0.834830914444444

00:08:15.037 --> 00:08:16.718 clear that the hormone called  
NOTE Confidence: 0.834830914444444

00:08:16.718 --> 00:08:18.658 hepcidin is the central regulator  
NOTE Confidence: 0.834830914444444

00:08:18.658 --> 00:08:20.370 of systemic iron balance.  
NOTE Confidence: 0.834830914444444

00:08:20.370 --> 00:08:21.681 So upside Nessa,  
NOTE Confidence: 0.834830914444444

00:08:21.681 --> 00:08:23.429 small peptide hormone produced  
NOTE Confidence: 0.834830914444444

00:08:23.429 --> 00:08:25.605 by hepatocytes you can detect it  
NOTE Confidence: 0.834830914444444

00:08:25.605 --> 00:08:27.674 in both blood and urine,  
NOTE Confidence: 0.834830914444444

00:08:27.674 --> 00:08:29.929 and hepcidin regulates iron balance  
NOTE Confidence: 0.834830914444444

00:08:29.929 --> 00:08:31.936 primarily by acting it to sites.  
NOTE Confidence: 0.834830914444444

00:08:31.940 --> 00:08:34.614 So upside and acts on enterocytes to  
NOTE Confidence: 0.834830914444444

00:08:34.614 --> 00:08:36.899 limit the absorption of dietary iron.  
NOTE Confidence: 0.834830914444444

00:08:36.900 --> 00:08:38.994 And hepcidin also acts on macrophages  
NOTE Confidence: 0.834830914444444

00:08:38.994 --> 00:08:41.479 to limit iron export from these cells.  
NOTE Confidence: 0.834830914444444

00:08:41.480 --> 00:08:44.182 This is the iron that has been  
NOTE Confidence: 0.834830914444444

00:08:44.182 --> 00:08:46.538 reclaimed from senescent red blood cells.

NOTE Confidence: 0.834830914444444

00:08:46.540 --> 00:08:48.856 To have side and limits the

NOTE Confidence: 0.834830914444444

00:08:48.856 --> 00:08:50.400 recycling of iron stores.

NOTE Confidence: 0.834830914444444

00:08:50.400 --> 00:08:52.638 And molecular level have sided mediate

NOTE Confidence: 0.834830914444444

00:08:52.638 --> 00:08:55.140 these effects by binding to fair portion,

NOTE Confidence: 0.834830914444444

00:08:55.140 --> 00:08:57.384 which is a cellular iron exporter

NOTE Confidence: 0.834830914444444

00:08:57.384 --> 00:08:58.880 present on the basolateral

NOTE Confidence: 0.844623677142857

00:08:58.949 --> 00:09:01.079 surface of enterocytes and also on

NOTE Confidence: 0.844623677142857

00:09:01.079 --> 00:09:03.320 the plasma membrane of macrophages.

NOTE Confidence: 0.844623677142857

00:09:03.320 --> 00:09:05.450 Have side in binding to Fairport

NOTE Confidence: 0.844623677142857

00:09:05.450 --> 00:09:06.515 and causes ferroportin,

NOTE Confidence: 0.844623677142857

00:09:06.520 --> 00:09:10.460 endocytosis and degradation in lysosomes.

NOTE Confidence: 0.844623677142857

00:09:10.460 --> 00:09:11.985 Additionally more recent work on

NOTE Confidence: 0.844623677142857

00:09:11.985 --> 00:09:13.885 from the Group of elements has

NOTE Confidence: 0.844623677142857

00:09:13.885 --> 00:09:15.465 shown that upside and actually

NOTE Confidence: 0.844623677142857

00:09:15.465 --> 00:09:17.171 also includes the Fairport and

NOTE Confidence: 0.844623677142857

00:09:17.171 --> 00:09:18.940 transporter blocking iron transport.  
NOTE Confidence: 0.706172645

00:09:21.130 --> 00:09:22.798 Have side an expression is modulated  
NOTE Confidence: 0.706172645

00:09:22.798 --> 00:09:24.550 in response to liver iron stores.  
NOTE Confidence: 0.706172645

00:09:24.550 --> 00:09:27.054 This is the basic regulation in the normal  
NOTE Confidence: 0.706172645

00:09:27.054 --> 00:09:29.949 state so that when body iron stores decrease,  
NOTE Confidence: 0.706172645

00:09:29.950 --> 00:09:32.442 have side and production is reduced and  
NOTE Confidence: 0.706172645

00:09:32.442 --> 00:09:34.952 this allows iron and iron absorption from  
NOTE Confidence: 0.706172645

00:09:34.952 --> 00:09:38.234 the intestine promoted as well as the iron  
NOTE Confidence: 0.706172645

00:09:38.234 --> 00:09:40.970 release from macrophage stores to proceed.  
NOTE Confidence: 0.706172645

00:09:40.970 --> 00:09:43.382 The net result here of course is to maintain  
NOTE Confidence: 0.706172645

00:09:43.382 --> 00:09:45.857 the level of iron in the circulation to  
NOTE Confidence: 0.706172645

00:09:45.857 --> 00:09:48.009 maintain the supply of iron for replaces,  
NOTE Confidence: 0.706172645

00:09:48.010 --> 00:09:50.398 the net effect being the prevention  
NOTE Confidence: 0.706172645

00:09:50.398 --> 00:09:51.990 of systemic iron deficiency.  
NOTE Confidence: 0.706172645

00:09:51.990 --> 00:09:52.826 And conversely,  
NOTE Confidence: 0.706172645

00:09:52.826 --> 00:09:55.334 when body iron stores increase liver



NOTE Confidence: 0.706172645

00:09:55.334 --> 00:09:57.269 increases hepcidin production inhibiting

NOTE Confidence: 0.706172645

00:09:57.269 --> 00:09:59.791 further dietary iron absorption and

NOTE Confidence: 0.706172645

00:09:59.791 --> 00:10:01.996 inhibiting iron released from macrophages.

NOTE Confidence: 0.76499848

00:10:05.820 --> 00:10:08.502 So genetic defects impacting the website

NOTE Confidence: 0.76499848

00:10:08.502 --> 00:10:11.984 in Fairport and access underlie the major

NOTE Confidence: 0.76499848

00:10:11.984 --> 00:10:14.689 inherited primary iron overload disorders.

NOTE Confidence: 0.76499848

00:10:14.690 --> 00:10:18.288 There are five major disorders shown here.

NOTE Confidence: 0.76499848

00:10:18.290 --> 00:10:20.124 I'm going to focus first on these.

NOTE Confidence: 0.76499848

00:10:20.130 --> 00:10:22.566 These first three categories, SHFE related,

NOTE Confidence: 0.76499848

00:10:22.570 --> 00:10:24.946 hemochromatosis juvenile hemochromatosis,

NOTE Confidence: 0.76499848

00:10:24.946 --> 00:10:28.906 and TFR 2 related hemochromatosis.

NOTE Confidence: 0.76499848

00:10:28.910 --> 00:10:31.320 So all of these disorders

NOTE Confidence: 0.76499848

00:10:31.320 --> 00:10:32.766 are recessive disorders.

NOTE Confidence: 0.76499848

00:10:32.770 --> 00:10:34.190 And characterized by similar patterns

NOTE Confidence: 0.76499848

00:10:34.190 --> 00:10:35.950 of iron loading in the liver,

NOTE Confidence: 0.76499848

00:10:35.950 --> 00:10:38.294 heart, and endocrine glands.

NOTE Confidence: 0.76499848

00:10:38.294 --> 00:10:41.224 And the stilar iron accumulation

NOTE Confidence: 0.76499848

00:10:41.224 --> 00:10:42.920 pattern is prankowl.

NOTE Confidence: 0.76499848

00:10:42.920 --> 00:10:44.576 The gene products that are mutated

NOTE Confidence: 0.76499848

00:10:44.576 --> 00:10:46.700 in these forms of hemochromatosis H,

NOTE Confidence: 0.76499848

00:10:46.700 --> 00:10:49.468 Fe HJV or Hematoxylin.

NOTE Confidence: 0.76499848

00:10:49.468 --> 00:10:52.545 HAMP, which is the hepcidin gene

NOTE Confidence: 0.76499848

00:10:52.545 --> 00:10:54.453 itself or transparent receptor

NOTE Confidence: 0.76499848

00:10:54.460 --> 00:10:56.325 2A homologue of the transferrin

NOTE Confidence: 0.76499848

00:10:56.325 --> 00:10:57.817 receptor on erythroid cells.

NOTE Confidence: 0.76499848

00:10:57.820 --> 00:11:01.106 All of these gene products are are

NOTE Confidence: 0.76499848

00:11:01.106 --> 00:11:03.344 acts in in parasites to promote

NOTE Confidence: 0.76499848

00:11:03.344 --> 00:11:05.210 upside and transcription,

NOTE Confidence: 0.76499848

00:11:05.210 --> 00:11:07.328 and I'll show you in a second the

NOTE Confidence: 0.76499848

00:11:07.328 --> 00:11:10.016 other class of iron overload disorder

NOTE Confidence: 0.76499848

00:11:10.016 --> 00:11:12.668 in this table are you Lisa disorders?

NOTE Confidence: 0.76499848

00:11:12.668 --> 00:11:14.630 Between mutations in Fairport and itself

NOTE Confidence: 0.76499848

00:11:14.689 --> 00:11:16.429 and there are two different forms.

NOTE Confidence: 0.76499848

00:11:16.430 --> 00:11:17.826 They show autosomal dominant

NOTE Confidence: 0.76499848

00:11:17.826 --> 00:11:19.571 inheritance and the features differ

NOTE Confidence: 0.76499848

00:11:19.571 --> 00:11:21.249 depending upon the mutations or gain.

NOTE Confidence: 0.76499848

00:11:21.250 --> 00:11:23.987 A function or loss of function mutations.

NOTE Confidence: 0.76499848

00:11:23.990 --> 00:11:27.716 But I want to mostly focus on these non

NOTE Confidence: 0.76499848

00:11:27.716 --> 00:11:30.556 Fairport and types of iron overload.

NOTE Confidence: 0.76499848

00:11:30.560 --> 00:11:33.000 Because they all seem to converge on a

NOTE Confidence: 0.76499848

00:11:33.000 --> 00:11:34.837 common signaling pathway in the liver,

NOTE Confidence: 0.76499848

00:11:34.840 --> 00:11:35.476 so bone,

NOTE Confidence: 0.76499848

00:11:35.476 --> 00:11:37.066 repressed protein or BMP SMAD

NOTE Confidence: 0.76499848

00:11:37.066 --> 00:11:39.466 signaling is the major signaling pathway

NOTE Confidence: 0.76499848

00:11:39.466 --> 00:11:41.314 promoting upside and transcription.

NOTE Confidence: 0.76499848

00:11:41.320 --> 00:11:43.960 Perhaps sites in this pathway.

NOTE Confidence: 0.76499848

00:11:43.960 --> 00:11:47.120 The BMP 6 ligand binds to receptor complex.

NOTE Confidence: 0.76499848

00:11:47.120 --> 00:11:48.916 Promote the phosphorylation of

NOTE Confidence: 0.76499848

00:11:48.916 --> 00:11:50.712 intracellular SMAD proteins which

NOTE Confidence: 0.76499848

00:11:50.712 --> 00:11:52.340 translocates to the nucleus,

NOTE Confidence: 0.76499848

00:11:52.340 --> 00:11:54.116 promoting the transcription of

NOTE Confidence: 0.76499848

00:11:54.116 --> 00:11:56.780 upside and other BMP target genes.

NOTE Confidence: 0.76499848

00:11:56.780 --> 00:11:58.904 The light interior BMP 6 interestingly

NOTE Confidence: 0.76499848

00:11:58.904 --> 00:12:01.137 appears to be produced by liver

NOTE Confidence: 0.76499848

00:12:01.137 --> 00:12:02.268 sinusoidal endothelial cells

NOTE Confidence: 0.76499848

00:12:02.268 --> 00:12:04.153 in response to iron levels.

NOTE Confidence: 0.76499848

00:12:04.160 --> 00:12:06.355 Although the mechanism by which

NOTE Confidence: 0.76499848

00:12:06.355 --> 00:12:08.111 liver sinusoidal endothelial cells

NOTE Confidence: 0.76499848

00:12:08.111 --> 00:12:10.016 sense iron to express the MP,

NOTE Confidence: 0.76499848

00:12:10.020 --> 00:12:13.250 six is still under investigation.

NOTE Confidence: 0.76499848

00:12:13.250 --> 00:12:15.602 Hema Jubelin but one of the gene

NOTE Confidence: 0.76499848

00:12:15.602 --> 00:12:17.133 products mutated in juvenile

NOTE Confidence: 0.76499848

00:12:17.133 --> 00:12:19.398 hemochromatosis is the GPI anchored

NOTE Confidence: 0.76499848

00:12:19.398 --> 00:12:21.865 protein is the coreceptor for BMP's

NOTE Confidence: 0.76499848

00:12:21.865 --> 00:12:23.445 and hepatocytes and hemoglobin

NOTE Confidence: 0.76499848

00:12:23.445 --> 00:12:25.970 augment signaling to the BMP pathway.

NOTE Confidence: 0.615097638

00:12:28.330 --> 00:12:31.168 HFE, the well known hereditary can

NOTE Confidence: 0.615097638

00:12:31.168 --> 00:12:33.464 comatose this protein and transparent

NOTE Confidence: 0.615097638

00:12:33.464 --> 00:12:35.649 receptor 2 are transmembrane proteins

NOTE Confidence: 0.615097638

00:12:35.649 --> 00:12:37.694 that interact with the classic

NOTE Confidence: 0.615097638

00:12:37.694 --> 00:12:39.698 transferrin receptor TNFR 1 to form

NOTE Confidence: 0.615097638

00:12:39.698 --> 00:12:42.432 what is believed to be an iron sensing

NOTE Confidence: 0.615097638

00:12:42.432 --> 00:12:44.700 complex that responds to levels of

NOTE Confidence: 0.615097638

00:12:44.700 --> 00:12:47.025 transparent bound iron and circulation

NOTE Confidence: 0.615097638

00:12:47.030 --> 00:12:48.710 and through and through the sensing,

NOTE Confidence: 0.615097638

00:12:48.710 --> 00:12:51.550 modulate herbicide and transcription.

NOTE Confidence: 0.615097638

00:12:51.550 --> 00:12:53.495 It's thought that perhaps these

NOTE Confidence: 0.615097638

00:12:53.495 --> 00:12:55.440 proteins all participate in a  
NOTE Confidence: 0.615097638

00:12:55.513 --> 00:12:57.429 giant so-called super complex,  
NOTE Confidence: 0.615097638

00:12:57.430 --> 00:12:59.180 that that still remains to  
NOTE Confidence: 0.615097638

00:12:59.180 --> 00:13:00.230 be fully demonstrated,  
NOTE Confidence: 0.615097638

00:13:00.230 --> 00:13:03.137 but it seems likely that HFB and TFR 2  
NOTE Confidence: 0.615097638

00:13:03.137 --> 00:13:05.689 signaling also impact on the in peace man,  
NOTE Confidence: 0.615097638

00:13:05.690 --> 00:13:08.960 the B and PEACEMAN pathway.  
NOTE Confidence: 0.615097638

00:13:08.960 --> 00:13:11.670 So I'd like to move on now to from a  
NOTE Confidence: 0.615097638

00:13:11.751 --> 00:13:14.916 disorder disorders of hepcidin deficiency.  
NOTE Confidence: 0.615097638

00:13:14.920 --> 00:13:17.524 In the previous slide to disorders  
NOTE Confidence: 0.615097638

00:13:17.524 --> 00:13:19.260 of upside in excess.  
NOTE Confidence: 0.615097638

00:13:19.260 --> 00:13:21.900 So when I started my postdoc  
NOTE Confidence: 0.615097638

00:13:21.900 --> 00:13:23.220 with Nancy Andrews,  
NOTE Confidence: 0.615097638

00:13:23.220 --> 00:13:25.460 she marked Fleming and Matt  
NOTE Confidence: 0.615097638

00:13:25.460 --> 00:13:27.252 Henry at Children's Hospital.  
NOTE Confidence: 0.615097638

00:13:27.260 --> 00:13:30.164 Boston had collected DNA from a

NOTE Confidence: 0.615097638

00:13:30.164 --> 00:13:32.859 number of children and never kindreds,

NOTE Confidence: 0.615097638

00:13:32.859 --> 00:13:35.337 in which the children had iron

NOTE Confidence: 0.615097638

00:13:35.337 --> 00:13:37.043 deficiency anemia that was

NOTE Confidence: 0.615097638

00:13:37.043 --> 00:13:39.073 refractory to oral iron therapy.

NOTE Confidence: 0.615097638

00:13:39.080 --> 00:13:40.544 And they called this condition a

NOTE Confidence: 0.615097638

00:13:40.544 --> 00:13:42.744 red for this. For this phenotype.

NOTE Confidence: 0.615097638

00:13:42.744 --> 00:13:45.672 The key clinical features were congenital,

NOTE Confidence: 0.615097638

00:13:45.680 --> 00:13:46.350 hypochromic,

NOTE Confidence: 0.615097638

00:13:46.350 --> 00:13:49.700 microcytic anemia and extremely low.

NOTE Confidence: 0.615097638

00:13:49.700 --> 00:13:51.212 Erythrocyte mean corpuscular volume,

NOTE Confidence: 0.615097638

00:13:51.212 --> 00:13:53.102 sometimes down into the 40s.

NOTE Confidence: 0.615097638

00:13:53.110 --> 00:13:54.226 So extremely low.

NOTE Confidence: 0.615097638

00:13:54.226 --> 00:13:56.092 Very low, transparent saturation.

NOTE Confidence: 0.615097638

00:13:56.092 --> 00:14:00.019 A failure to respond to oral iron.

NOTE Confidence: 0.615097638

00:14:00.020 --> 00:14:01.310 And a sluggish,

NOTE Confidence: 0.615097638

00:14:01.310 --> 00:14:03.030 incomplete response to intravenous  
NOTE Confidence: 0.615097638

00:14:03.030 --> 00:14:04.840 or intramuscular iron and looking  
NOTE Confidence: 0.615097638

00:14:04.840 --> 00:14:05.620 at the pedigrees,  
NOTE Confidence: 0.615097638

00:14:05.620 --> 00:14:07.900 particularly this first pedigree from Turkey.  
NOTE Confidence: 0.615097638

00:14:07.900 --> 00:14:08.832 With consanguinity,  
NOTE Confidence: 0.615097638

00:14:08.832 --> 00:14:11.628 you can appreciate that transmission was  
NOTE Confidence: 0.615097638

00:14:11.628 --> 00:14:13.969 compatible with recessive inheritance.  
NOTE Confidence: 0.615097638

00:14:13.970 --> 00:14:15.854 Here's the typical blood smear from  
NOTE Confidence: 0.615097638

00:14:15.854 --> 00:14:17.860 one of the affected individuals,  
NOTE Confidence: 0.615097638

00:14:17.860 --> 00:14:20.850 showing classic signs of asphere  
NOTE Confidence: 0.615097638

00:14:20.850 --> 00:14:22.644 iron deficiency anemia.  
NOTE Confidence: 0.615097638

00:14:22.650 --> 00:14:25.980 So when I came to Nancy's lab and Eliza  
NOTE Confidence: 0.615097638

00:14:25.980 --> 00:14:29.648 assay to measure hepcidin levels in patients,  
NOTE Confidence: 0.615097638

00:14:29.650 --> 00:14:32.884 blood and urine had just become available  
NOTE Confidence: 0.615097638

00:14:32.890 --> 00:14:34.738 and looking at the phenotype individuals,  
NOTE Confidence: 0.615097638

00:14:34.740 --> 00:14:35.556 we were suspicious.



NOTE Confidence: 0.615097638

00:14:35.556 --> 00:14:36.916 The phenotype of these individuals

NOTE Confidence: 0.615097638

00:14:36.916 --> 00:14:38.598 and we were suspicious that they

NOTE Confidence: 0.615097638

00:14:38.598 --> 00:14:40.230 had a defect in hepcidin regulation

NOTE Confidence: 0.615097638

00:14:40.281 --> 00:14:41.807 and sure enough we found that have

NOTE Confidence: 0.615097638

00:14:41.807 --> 00:14:43.714 side levels in these individuals

NOTE Confidence: 0.615097638

00:14:43.714 --> 00:14:45.580 were inappropriately elevated.

NOTE Confidence: 0.615097638

00:14:45.580 --> 00:14:48.004 So this of course explains the

NOTE Confidence: 0.615097638

00:14:48.004 --> 00:14:49.620 pathophysiology of this disorder.

NOTE Confidence: 0.615097638

00:14:49.620 --> 00:14:51.005 Normally an iron deficiency have

NOTE Confidence: 0.615097638

00:14:51.005 --> 00:14:52.640 side and level should be low,

NOTE Confidence: 0.615097638

00:14:52.640 --> 00:14:54.212 but in these in these individuals

NOTE Confidence: 0.615097638

00:14:54.212 --> 00:14:55.640 who had decreased iron stores,

NOTE Confidence: 0.615097638

00:14:55.640 --> 00:14:57.120 there have a side,

NOTE Confidence: 0.615097638

00:14:57.120 --> 00:14:58.600 and it's paradoxically increased.

NOTE Confidence: 0.615097638

00:14:58.600 --> 00:15:00.658 So it's explains both their failure to

NOTE Confidence: 0.615097638

00:15:00.658 --> 00:15:03.093 respond to oral iron as well as their  
NOTE Confidence: 0.615097638

00:15:03.093 --> 00:15:04.588 failure to respond to intravenous  
NOTE Confidence: 0.615097638

00:15:04.650 --> 00:15:06.340 or intramuscular forms of iron.  
NOTE Confidence: 0.615097638

00:15:06.340 --> 00:15:08.602 Because these forms of iron require  
NOTE Confidence: 0.615097638

00:15:08.602 --> 00:15:10.110 processing by macrophages before  
NOTE Confidence: 0.615097638

00:15:10.169 --> 00:15:12.262 this iron can be exported into the  
NOTE Confidence: 0.615097638

00:15:12.262 --> 00:15:14.219 circulation for use in erythropoiesis.  
NOTE Confidence: 0.903718927142857

00:15:16.440 --> 00:15:20.855 So this is this was back in 2007  
NOTE Confidence: 0.903718927142857

00:15:20.855 --> 00:15:23.630 and before exome sequencing was,  
NOTE Confidence: 0.903718927142857

00:15:23.630 --> 00:15:26.772 it's cheap as it is today, and so I did.  
NOTE Confidence: 0.903718927142857

00:15:26.772 --> 00:15:28.056 Traditional linkage analysis,  
NOTE Confidence: 0.903718927142857

00:15:28.060 --> 00:15:29.815 mapping to map the phenotype  
NOTE Confidence: 0.903718927142857

00:15:29.815 --> 00:15:31.594 to region of chromosome 22.  
NOTE Confidence: 0.903718927142857

00:15:31.594 --> 00:15:34.212 This was a region of about 100  
NOTE Confidence: 0.903718927142857

00:15:34.212 --> 00:15:36.719 megabases many genes to sift through.  
NOTE Confidence: 0.903718927142857

00:15:36.720 --> 00:15:38.880 And as I was sifting through a particular

NOTE Confidence: 0.903718927142857

00:15:38.880 --> 00:15:40.639 gene that came to our attention,

NOTE Confidence: 0.903718927142857

00:15:40.640 --> 00:15:42.194 which is a gene called tempra 6,

NOTE Confidence: 0.903718927142857

00:15:42.200 --> 00:15:44.640 also known as matriptase 2.

NOTE Confidence: 0.903718927142857

00:15:44.640 --> 00:15:47.784 So this encodes a type 2

NOTE Confidence: 0.903718927142857

00:15:47.784 --> 00:15:49.356 transmembrane serine protease.

NOTE Confidence: 0.903718927142857

00:15:49.360 --> 00:15:50.722 Transmembrane serine protease

NOTE Confidence: 0.903718927142857

00:15:50.722 --> 00:15:53.446 6 is now it's official name.

NOTE Confidence: 0.903718927142857

00:15:53.450 --> 00:15:55.762 That was known at that time to be

NOTE Confidence: 0.903718927142857

00:15:55.762 --> 00:15:57.108 primarily expressed in the liver,

NOTE Confidence: 0.903718927142857

00:15:57.110 --> 00:15:58.860 and had been found to be localized

NOTE Confidence: 0.903718927142857

00:15:58.860 --> 00:16:00.441 to the plasma membrane when

NOTE Confidence: 0.903718927142857

00:16:00.441 --> 00:16:02.376 overexpressed themselves at that time,

NOTE Confidence: 0.903718927142857

00:16:02.380 --> 00:16:04.355 there were only two publications

NOTE Confidence: 0.903718927142857

00:16:04.355 --> 00:16:05.540 on this protein.

NOTE Confidence: 0.860873481111111

00:16:07.590 --> 00:16:09.282 Structurally, this protein consists

NOTE Confidence: 0.860873481111111

00:16:09.282 --> 00:16:11.397 of a short intracellular region,  
NOTE Confidence: 0.8608734811111111

00:16:11.400 --> 00:16:12.537 a transmembrane domain,  
NOTE Confidence: 0.8608734811111111

00:16:12.537 --> 00:16:14.053 and a large extracellular  
NOTE Confidence: 0.8608734811111111

00:16:14.053 --> 00:16:15.640 domain with several motifs,  
NOTE Confidence: 0.8608734811111111

00:16:15.640 --> 00:16:17.432 including most notably AC,  
NOTE Confidence: 0.8608734811111111

00:16:17.432 --> 00:16:20.658 terminal, serial, protease, domain.  
NOTE Confidence: 0.8608734811111111

00:16:20.660 --> 00:16:23.980 What caught my eye was in the abstract  
NOTE Confidence: 0.8608734811111111

00:16:23.980 --> 00:16:26.282 book for the 2007 ASH Annual meeting,  
NOTE Confidence: 0.8608734811111111

00:16:26.282 --> 00:16:27.950 where the group of Ernie and  
NOTE Confidence: 0.8608734811111111

00:16:28.003 --> 00:16:29.419 Bruce Boiler reported this.  
NOTE Confidence: 0.8608734811111111

00:16:29.420 --> 00:16:32.420 Mouse munit temper 60 and new new mutant,  
NOTE Confidence: 0.8608734811111111

00:16:32.420 --> 00:16:34.598 which is a mouse that you can see from  
NOTE Confidence: 0.8608734811111111

00:16:34.598 --> 00:16:36.350 this picture, has hair on its head,  
NOTE Confidence: 0.8608734811111111

00:16:36.350 --> 00:16:38.774 but it's all for the rest of his  
NOTE Confidence: 0.8608734811111111

00:16:38.774 --> 00:16:40.560 body called the Mask Mutant.  
NOTE Confidence: 0.8608734811111111

00:16:40.560 --> 00:16:42.936 The baldness relates to iron deficiency.

NOTE Confidence: 0.8608734811111111

00:16:42.940 --> 00:16:45.583 It's cured by feeding iron and they show

NOTE Confidence: 0.8608734811111111

00:16:45.583 --> 00:16:47.060 that these mice of course they they.

NOTE Confidence: 0.8608734811111111

00:16:47.060 --> 00:16:49.238 They map the temper 16 and the strain and

NOTE Confidence: 0.8608734811111111

00:16:49.238 --> 00:16:51.279 they showed that this was a recessive.

NOTE Confidence: 0.8608734811111111

00:16:51.280 --> 00:16:53.068 The phenotype where the mice had

NOTE Confidence: 0.8608734811111111

00:16:53.068 --> 00:16:54.589 iron deficiency anemia due to

NOTE Confidence: 0.8608734811111111

00:16:54.589 --> 00:16:55.954 impaired and absorption and looking

NOTE Confidence: 0.8608734811111111

00:16:55.954 --> 00:16:58.290 at the liver of these mice they had

NOTE Confidence: 0.8608734811111111

00:16:58.290 --> 00:16:59.780 elevated have side messenger RNA,

NOTE Confidence: 0.8608734811111111

00:16:59.780 --> 00:17:01.856 so obviously this was an excellent

NOTE Confidence: 0.8608734811111111

00:17:01.856 --> 00:17:03.922 candidate for the erythema type and I

NOTE Confidence: 0.8608734811111111

00:17:03.922 --> 00:17:06.040 went on to look at 10% as a candidate

NOTE Confidence: 0.8608734811111111

00:17:06.040 --> 00:17:08.933 in kinders with a Rita and we found a

NOTE Confidence: 0.8608734811111111

00:17:08.933 --> 00:17:11.309 number of mutations across the molecule,

NOTE Confidence: 0.8608734811111111

00:17:11.310 --> 00:17:11.725 classic,

NOTE Confidence: 0.8608734811111111

00:17:11.725 --> 00:17:12.555 frameshift mutations,  
NOTE Confidence: 0.8608734811111111

00:17:12.555 --> 00:17:14.215 nonsense mutations and a  
NOTE Confidence: 0.8608734811111111

00:17:14.215 --> 00:17:16.558 variety of missense mutations at  
NOTE Confidence: 0.8608734811111111

00:17:16.558 --> 00:17:18.118 evolutionarily conserved residues.  
NOTE Confidence: 0.83107

00:17:20.170 --> 00:17:24.296 So. Distinguishing Arita from other  
NOTE Confidence: 0.83107

00:17:24.296 --> 00:17:27.350 required forms of iron deficiency anemia  
NOTE Confidence: 0.83107

00:17:27.430 --> 00:17:29.980 cannot always be so straightforward.  
NOTE Confidence: 0.83107

00:17:29.980 --> 00:17:31.936 I worked with Matt Heaney at  
NOTE Confidence: 0.83107

00:17:31.936 --> 00:17:32.914 Children's Hospital Boston,  
NOTE Confidence: 0.83107

00:17:32.920 --> 00:17:34.084 develop some diagnostic  
NOTE Confidence: 0.83107

00:17:34.084 --> 00:17:35.636 algorithms for the disorder,  
NOTE Confidence: 0.83107

00:17:35.640 --> 00:17:37.251 and I want to point out one of the  
NOTE Confidence: 0.83107

00:17:37.251 --> 00:17:38.672 key aspects of these algorithms  
NOTE Confidence: 0.83107

00:17:38.672 --> 00:17:40.157 is to consider how patients  
NOTE Confidence: 0.83107

00:17:40.157 --> 00:17:41.736 respond to an oral iron challenge.  
NOTE Confidence: 0.83107

00:17:41.740 --> 00:17:43.780 So you really want to look at how

NOTE Confidence: 0.83107

00:17:43.780 --> 00:17:45.491 their serum iron levels change after

NOTE Confidence: 0.83107

00:17:45.491 --> 00:17:47.879 you give them iron in the short term.

NOTE Confidence: 0.83107

00:17:47.880 --> 00:17:48.576 Short term,

NOTE Confidence: 0.83107

00:17:48.576 --> 00:17:49.968 after a fire administration

NOTE Confidence: 0.83107

00:17:49.968 --> 00:17:51.012 to help differentiate.

NOTE Confidence: 0.83107

00:17:51.020 --> 00:17:52.280 This is truly an absorptive.

NOTE Confidence: 0.83107

00:17:52.280 --> 00:17:54.132 Effect before proceeding.

NOTE Confidence: 0.83107

00:17:54.132 --> 00:17:57.504 Then at that time you know when genetic

NOTE Confidence: 0.83107

00:17:57.504 --> 00:18:00.366 testing was a little more expensive.

NOTE Confidence: 0.83107

00:18:00.370 --> 00:18:02.377 You know we we weren't going to think about

NOTE Confidence: 0.83107

00:18:02.377 --> 00:18:03.957 testing temper 6 immediately up front.

NOTE Confidence: 0.83107

00:18:03.960 --> 00:18:04.980 I think now with Exos,

NOTE Confidence: 0.83107

00:18:04.980 --> 00:18:05.260 a little

NOTE Confidence: 0.940471478

00:18:05.270 --> 00:18:06.350 bit of a different story.

NOTE Confidence: 0.850175888366667

00:18:07.890 --> 00:18:10.872 I also collaborated with Matt and Mark

NOTE Confidence: 0.850175888366667

00:18:10.872 --> 00:18:13.512 Fleming to look at hepcidin levels  
NOTE Confidence: 0.850175888366667

00:18:13.512 --> 00:18:16.494 in patients with Arita and how they  
NOTE Confidence: 0.850175888366667

00:18:16.578 --> 00:18:19.704 compared to other patients with iron  
NOTE Confidence: 0.850175888366667

00:18:19.704 --> 00:18:22.127 refractory anemia that wasn't couldn't  
NOTE Confidence: 0.850175888366667

00:18:22.127 --> 00:18:24.486 be attributed to 10 per six mutation.  
NOTE Confidence: 0.850175888366667

00:18:24.490 --> 00:18:25.906 And indeed you know, as expected,  
NOTE Confidence: 0.850175888366667

00:18:25.910 --> 00:18:27.830 the hepcidin levels in patients with  
NOTE Confidence: 0.850175888366667

00:18:27.830 --> 00:18:30.065 temper 6 mutation based on our original  
NOTE Confidence: 0.850175888366667

00:18:30.065 --> 00:18:32.158 court where again seemed to be increased  
NOTE Confidence: 0.850175888366667

00:18:32.213 --> 00:18:34.152 but there was some overlap with patients  
NOTE Confidence: 0.850175888366667

00:18:34.152 --> 00:18:37.980 who did not have a temper 6 mutation.  
NOTE Confidence: 0.850175888366667

00:18:37.980 --> 00:18:39.882 And so we looked more closely  
NOTE Confidence: 0.850175888366667

00:18:39.882 --> 00:18:41.150 at various laboratory indices,  
NOTE Confidence: 0.850175888366667

00:18:41.150 --> 00:18:42.734 and you can see with these  
NOTE Confidence: 0.850175888366667

00:18:42.734 --> 00:18:44.037 receiver operating curves the red  
NOTE Confidence: 0.850175888366667

00:18:44.037 --> 00:18:45.437 curve here is to have side in.



NOTE Confidence: 0.850175888366667

00:18:45.440 --> 00:18:47.920 This is a fairly good job of predicting

NOTE Confidence: 0.850175888366667

00:18:47.920 --> 00:18:50.441 temper 6 mutation status in patients

NOTE Confidence: 0.850175888366667

00:18:50.441 --> 00:18:52.736 with chronic iron refractory anemia,

NOTE Confidence: 0.850175888366667

00:18:52.740 --> 00:18:54.910 but better indices turn out to be

NOTE Confidence: 0.850175888366667

00:18:54.910 --> 00:18:56.582 indices where you normalize the

NOTE Confidence: 0.850175888366667

00:18:56.582 --> 00:18:58.622 helpside into either the serum iron

NOTE Confidence: 0.850175888366667

00:18:58.622 --> 00:19:01.009 or the the transparent saturation.

NOTE Confidence: 0.798722157611111

00:19:03.420 --> 00:19:05.268 So of course I wanted to actually

NOTE Confidence: 0.798722157611111

00:19:05.268 --> 00:19:07.215 figure out how society was working

NOTE Confidence: 0.798722157611111

00:19:07.215 --> 00:19:09.040 to regulate upside in production.

NOTE Confidence: 0.798722157611111

00:19:09.040 --> 00:19:11.896 The Group of Cleric and Michaela did

NOTE Confidence: 0.798722157611111

00:19:11.896 --> 00:19:13.970 some beautiful invitro work showing

NOTE Confidence: 0.798722157611111

00:19:13.970 --> 00:19:16.266 the temper 6 cleaves Hema, Julian,

NOTE Confidence: 0.798722157611111

00:19:16.266 --> 00:19:18.828 the BMP coreceptor from the plasma membrane.

NOTE Confidence: 0.798722157611111

00:19:18.830 --> 00:19:20.405 This is the gene product I showed

NOTE Confidence: 0.798722157611111

00:19:20.405 --> 00:19:22.475 you a few minutes ago with one of  
NOTE Confidence: 0.798722157611111

00:19:22.475 --> 00:19:24.500 the genes that's mutated in juvenile  
NOTE Confidence: 0.798722157611111

00:19:24.500 --> 00:19:26.300 hemochromatosis and I went on and  
NOTE Confidence: 0.798722157611111

00:19:26.300 --> 00:19:28.186 now smodels to show that mice lacking  
NOTE Confidence: 0.798722157611111

00:19:28.186 --> 00:19:30.160 temper 6 show excess signaling through  
NOTE Confidence: 0.798722157611111

00:19:30.160 --> 00:19:32.311 the BMP pathway that is dependent  
NOTE Confidence: 0.798722157611111

00:19:32.311 --> 00:19:34.106 upon the presence of hemoglobin.  
NOTE Confidence: 0.791357212333333

00:19:38.930 --> 00:19:41.144 And then wait additional studies looking  
NOTE Confidence: 0.791357212333333

00:19:41.144 --> 00:19:43.865 at genetic loss of temper sticks and  
NOTE Confidence: 0.791357212333333

00:19:43.865 --> 00:19:46.229 other mouse models of clinical iron  
NOTE Confidence: 0.791357212333333

00:19:46.229 --> 00:19:48.787 overloads where iron overload is due to  
NOTE Confidence: 0.791357212333333

00:19:48.787 --> 00:19:50.578 have side insufficiency in particular,  
NOTE Confidence: 0.791357212333333

00:19:50.578 --> 00:19:53.682 predatory tosis due to HF mutation and also  
NOTE Confidence: 0.791357212333333

00:19:53.682 --> 00:19:56.710 non transfusion dependent beta thalassemia.  
NOTE Confidence: 0.791357212333333

00:19:56.710 --> 00:19:58.740 I won't get into the mechanism there  
NOTE Confidence: 0.791357212333333

00:19:58.740 --> 00:20:01.083 but let's just say briefly that inherent

NOTE Confidence: 0.791357212333333  
00:20:01.083 --> 00:20:03.201 in a congenital iron loading anemias  
NOTE Confidence: 0.791357212333333  
00:20:03.259 --> 00:20:05.377 have signed news also low promoted  
NOTE Confidence: 0.791357212333333  
00:20:05.377 --> 00:20:07.202 which promotes iron loading and our  
NOTE Confidence: 0.791357212333333  
00:20:07.202 --> 00:20:08.644 group as well as the canvas shell.  
NOTE Confidence: 0.791357212333333  
00:20:08.650 --> 00:20:10.414 Group demonstrated that indeed,  
NOTE Confidence: 0.791357212333333  
00:20:10.414 --> 00:20:13.926 temper six loss is a way to raise  
NOTE Confidence: 0.791357212333333  
00:20:13.926 --> 00:20:16.284 upside and limit iron loading in  
NOTE Confidence: 0.791357212333333  
00:20:16.284 --> 00:20:18.970 in these iron loading disorders.  
NOTE Confidence: 0.791357212333333  
00:20:18.970 --> 00:20:21.320 So approaches to modulate temperance  
NOTE Confidence: 0.791357212333333  
00:20:21.320 --> 00:20:23.200 expression or under investigation.  
NOTE Confidence: 0.791357212333333  
00:20:23.200 --> 00:20:25.174 So in addition to just doing the  
NOTE Confidence: 0.791357212333333  
00:20:25.174 --> 00:20:26.020 classic knockout experiments,  
NOTE Confidence: 0.791357212333333  
00:20:26.020 --> 00:20:28.568 groups have looked at small interfering RNA  
NOTE Confidence: 0.791357212333333  
00:20:28.568 --> 00:20:31.119 S RNA formulated in lipid nanoparticles,  
NOTE Confidence: 0.791357212333333  
00:20:31.120 --> 00:20:33.370 as well as antisense oligonucleotides.  
NOTE Confidence: 0.791357212333333

00:20:33.370 --> 00:20:36.418 The target temper 6 M RNA.  
NOTE Confidence: 0.791357212333333

00:20:36.420 --> 00:20:38.424 Here's here's a diagram showing the  
NOTE Confidence: 0.791357212333333

00:20:38.424 --> 00:20:40.113 antisense approach and the commentary  
NOTE Confidence: 0.791357212333333

00:20:40.113 --> 00:20:42.592 Rd on that paper and the idea here  
NOTE Confidence: 0.791357212333333

00:20:42.592 --> 00:20:44.908 of course is to cause degradation of  
NOTE Confidence: 0.791357212333333

00:20:44.908 --> 00:20:47.899 the temper 6 M RNA with these oligos.  
NOTE Confidence: 0.791357212333333

00:20:47.900 --> 00:20:49.909 Lose temper 6 from the plasma membrane  
NOTE Confidence: 0.791357212333333

00:20:49.909 --> 00:20:52.210 of these cells and now promote signaling  
NOTE Confidence: 0.791357212333333

00:20:52.210 --> 00:20:54.620 through these pathways to elevate have side.  
NOTE Confidence: 0.791357212333333

00:20:54.620 --> 00:20:57.236 Now I'll point out that currently  
NOTE Confidence: 0.791357212333333

00:20:57.236 --> 00:20:59.860 temper 6 antisense oligos,  
NOTE Confidence: 0.791357212333333

00:20:59.860 --> 00:21:01.715 specifically those that have been  
NOTE Confidence: 0.791357212333333

00:21:01.715 --> 00:21:03.970 caught conjugated to a liver specific  
NOTE Confidence: 0.791357212333333

00:21:03.970 --> 00:21:06.480 ligand and a settled Galactus demeanor.  
NOTE Confidence: 0.791357212333333

00:21:06.480 --> 00:21:09.448 Galac are in phase two clinical trials  
NOTE Confidence: 0.791357212333333

00:21:09.448 --> 00:21:12.290 for humans with pathological media.

NOTE Confidence: 0.791357212333333  
00:21:12.290 --> 00:21:13.793 I also want to point out that you know,  
NOTE Confidence: 0.791357212333333  
00:21:13.800 --> 00:21:16.640 I showed you the complex CMP pathway earlier,  
NOTE Confidence: 0.791357212333333  
00:21:16.640 --> 00:21:19.088 and while multiple proteins in that  
NOTE Confidence: 0.791357212333333  
00:21:19.088 --> 00:21:21.040 pathways might be considered path  
NOTE Confidence: 0.791357212333333  
00:21:21.040 --> 00:21:22.872 possibilities to modulate upside  
NOTE Confidence: 0.791357212333333  
00:21:22.872 --> 00:21:23.788 and expression,  
NOTE Confidence: 0.791357212333333  
00:21:23.790 --> 00:21:25.600 I want to point out that temper 6 is is  
NOTE Confidence: 0.791357212333333  
00:21:25.653 --> 00:21:27.411 a particularly attractive target in my  
NOTE Confidence: 0.791357212333333  
00:21:27.411 --> 00:21:29.261 mind because unlike many of the other  
NOTE Confidence: 0.791357212333333  
00:21:29.261 --> 00:21:31.218 proteins I showed you in the BMP pathway,  
NOTE Confidence: 0.791357212333333  
00:21:31.218 --> 00:21:34.146 this is a liver specific gene.  
NOTE Confidence: 0.791357212333333  
00:21:34.150 --> 00:21:35.345 So hopefully you could reduce  
NOTE Confidence: 0.791357212333333  
00:21:35.345 --> 00:21:36.980 a lot of off target effects.  
NOTE Confidence: 0.876092818636364  
00:21:39.370 --> 00:21:41.410 So I'd like to move on now and  
NOTE Confidence: 0.876092818636364  
00:21:41.410 --> 00:21:43.176 talk about new insights we've  
NOTE Confidence: 0.876092818636364

00:21:43.176 --> 00:21:45.166 made into the mechanisms of  
NOTE Confidence: 0.876092818636364

00:21:45.166 --> 00:21:46.770 iron mobilization and deliver.  
NOTE Confidence: 0.91608775

00:21:49.830 --> 00:21:51.446 So from what I've told you so far,  
NOTE Confidence: 0.91608775

00:21:51.450 --> 00:21:55.218 have sided therapies would seem like.  
NOTE Confidence: 0.91608775

00:21:55.220 --> 00:21:57.680 Reasonable approach to limit iron loading,  
NOTE Confidence: 0.91608775

00:21:57.680 --> 00:21:59.795 but one of the problems I see with those  
NOTE Confidence: 0.91608775

00:21:59.795 --> 00:22:01.798 types of therapies is they don't really  
NOTE Confidence: 0.91608775

00:22:01.798 --> 00:22:03.660 address the problem of iron loading.  
NOTE Confidence: 0.91608775

00:22:03.660 --> 00:22:04.752 It's already present once,  
NOTE Confidence: 0.91608775

00:22:04.752 --> 00:22:06.820 once in a dual mileage is loaded,  
NOTE Confidence: 0.91608775

00:22:06.820 --> 00:22:08.724 lowering raising their upside level is not  
NOTE Confidence: 0.91608775

00:22:08.724 --> 00:22:10.950 going to help eliminate the iron the iron.  
NOTE Confidence: 0.91608775

00:22:10.950 --> 00:22:12.534 This morning the body,  
NOTE Confidence: 0.91608775

00:22:12.534 --> 00:22:14.514 you know hereditary hemochromatosis sewers  
NOTE Confidence: 0.91608775

00:22:14.514 --> 00:22:16.920 are classically treated by phlebotomy.  
NOTE Confidence: 0.91608775

00:22:16.920 --> 00:22:18.820 Most patients can tolerate slotomania,

NOTE Confidence: 0.91608775

00:22:18.820 --> 00:22:20.536 although it's definitely inconvenient

NOTE Confidence: 0.91608775

00:22:20.536 --> 00:22:24.053 to have to be closed on a regular

NOTE Confidence: 0.91608775

00:22:24.053 --> 00:22:25.789 basis throughout your life.

NOTE Confidence: 0.91608775

00:22:25.790 --> 00:22:27.505 And although this is the classic therapy,

NOTE Confidence: 0.91608775

00:22:27.510 --> 00:22:29.142 the mechanisms that promote

NOTE Confidence: 0.91608775

00:22:29.142 --> 00:22:30.774 our immobilization are really

NOTE Confidence: 0.91608775

00:22:30.774 --> 00:22:32.769 not well understood at all.

NOTE Confidence: 0.91608775

00:22:32.770 --> 00:22:35.024 So this was an area I was

NOTE Confidence: 0.91608775

00:22:35.024 --> 00:22:35.990 interested in exploring.

NOTE Confidence: 0.91608775

00:22:35.990 --> 00:22:37.484 What are the mechanisms that regulate

NOTE Confidence: 0.91608775

00:22:37.484 --> 00:22:39.179 the release of iron from the liver?

NOTE Confidence: 0.8129131075

00:22:41.280 --> 00:22:45.640 And I became more intrigued by this area.

NOTE Confidence: 0.8129131075

00:22:45.640 --> 00:22:49.408 When? With these this work from the

NOTE Confidence: 0.8129131075

00:22:49.408 --> 00:22:52.667 Group of Joe Mancius at Harvard and also

NOTE Confidence: 0.8129131075

00:22:52.667 --> 00:22:54.852 group from Novartis characterizing a

NOTE Confidence: 0.8129131075

00:22:54.852 --> 00:22:57.773 role of protein nuclear color receptor  
NOTE Confidence: 0.8129131075

00:22:57.773 --> 00:22:59.482 coactivator 4 previously thought  
NOTE Confidence: 0.8129131075

00:22:59.482 --> 00:23:01.337 to be a transcriptional regulator,  
NOTE Confidence: 0.8129131075

00:23:01.340 --> 00:23:04.068 a new role in the regulation of ferritin,  
NOTE Confidence: 0.8129131075

00:23:04.070 --> 00:23:06.478 trafficking within cells and  
NOTE Confidence: 0.8129131075

00:23:06.478 --> 00:23:08.220 specifically in cancer cells.  
NOTE Confidence: 0.8129131075

00:23:08.220 --> 00:23:11.901 These groups showed that NC A4 is a cargo  
NOTE Confidence: 0.8129131075

00:23:11.901 --> 00:23:14.727 receptor that that shuttles the iron  
NOTE Confidence: 0.8129131075

00:23:14.727 --> 00:23:17.275 transport complex ferritin to the lysosome.  
NOTE Confidence: 0.8129131075

00:23:17.275 --> 00:23:19.358 We're fair to him, can be degraded,  
NOTE Confidence: 0.8129131075

00:23:19.358 --> 00:23:21.074 and the iron can be released  
NOTE Confidence: 0.8129131075

00:23:21.074 --> 00:23:22.219 into the cytoplasm,  
NOTE Confidence: 0.8129131075

00:23:22.220 --> 00:23:23.900 potentially made available for  
NOTE Confidence: 0.8129131075

00:23:23.900 --> 00:23:25.580 export cancel as well.  
NOTE Confidence: 0.8129131075

00:23:25.580 --> 00:23:27.068 We were interested in this gene  
NOTE Confidence: 0.8129131075

00:23:27.068 --> 00:23:28.342 actually was interested in gene



NOTE Confidence: 0.8129131075

00:23:28.342 --> 00:23:29.517 before these papers came up,

NOTE Confidence: 0.8129131075

00:23:29.520 --> 00:23:32.000 because I found it in some micro experiments.

NOTE Confidence: 0.8129131075

00:23:32.000 --> 00:23:33.352 Looking at, you know,

NOTE Confidence: 0.8129131075

00:23:33.352 --> 00:23:36.469 M RNA from livers of mice when iron

NOTE Confidence: 0.8129131075

00:23:36.469 --> 00:23:38.485 overload versus iron deficiency.

NOTE Confidence: 0.8129131075

00:23:38.490 --> 00:23:39.573 So Jay Lee,

NOTE Confidence: 0.8129131075

00:23:39.573 --> 00:23:41.378 who was a phenomenal Xpath

NOTE Confidence: 0.8129131075

00:23:41.378 --> 00:23:42.829 graduate student in my lab.

NOTE Confidence: 0.8129131075

00:23:42.830 --> 00:23:45.166 He graduated last year as well as Larissa.

NOTE Confidence: 0.8129131075

00:23:45.170 --> 00:23:47.020 Loads of Oscar Research Assistant

NOTE Confidence: 0.8129131075

00:23:47.020 --> 00:23:49.228 lab decided to really try and

NOTE Confidence: 0.8129131075

00:23:49.228 --> 00:23:51.286 define if insula forward had a role

NOTE Confidence: 0.8129131075

00:23:51.286 --> 00:23:52.760 in iron mobilization,

NOTE Confidence: 0.8129131075

00:23:52.760 --> 00:23:55.370 the mobilization of iron from ferritin

NOTE Confidence: 0.8129131075

00:23:55.370 --> 00:23:57.580 stores specifically in the liver.

NOTE Confidence: 0.8129131075

00:23:57.580 --> 00:23:59.440 So to do this,  
NOTE Confidence: 0.8129131075

00:23:59.440 --> 00:24:01.770 we utilize chemically modified srna.  
NOTE Confidence: 0.8129131075

00:24:01.770 --> 00:24:04.120 Since the galnet conjugated srna,  
NOTE Confidence: 0.8129131075

00:24:04.120 --> 00:24:07.072 the targets have had ascites to lower NC  
NOTE Confidence: 0.8129131075

00:24:07.072 --> 00:24:09.558 4 expression to participates in vivo,  
NOTE Confidence: 0.8129131075

00:24:09.560 --> 00:24:10.362 and this,  
NOTE Confidence: 0.8129131075

00:24:10.362 --> 00:24:11.164 of course,  
NOTE Confidence: 0.8129131075

00:24:11.164 --> 00:24:12.768 was after thoroughly validating  
NOTE Confidence: 0.8129131075

00:24:12.768 --> 00:24:14.380 these sarnas and invitro.  
NOTE Confidence: 0.8129131075

00:24:14.380 --> 00:24:17.638 Before we started the annual work.  
NOTE Confidence: 0.8129131075

00:24:17.640 --> 00:24:20.139 So we looked at the responses of  
NOTE Confidence: 0.8129131075

00:24:20.139 --> 00:24:22.116 animals that were treated with  
NOTE Confidence: 0.8129131075

00:24:22.116 --> 00:24:23.772 either vehicle luciferase control  
NOTE Confidence: 0.8129131075

00:24:23.772 --> 00:24:26.281 or end to a forward targeting  
NOTE Confidence: 0.8129131075

00:24:26.281 --> 00:24:28.875 Sir and A and then subjected to a  
NOTE Confidence: 0.8129131075

00:24:28.875 --> 00:24:30.675 large volume for botany and then

NOTE Confidence: 0.8129131075

00:24:30.675 --> 00:24:32.838 looking a week later to to see

NOTE Confidence: 0.8129131075

00:24:32.838 --> 00:24:34.080 their physiological responses.

NOTE Confidence: 0.8129131075

00:24:34.080 --> 00:24:37.104 So would the srna we see we

NOTE Confidence: 0.8129131075

00:24:37.104 --> 00:24:38.822 obtained excellent knocked out

NOTE Confidence: 0.8129131075

00:24:38.822 --> 00:24:40.874 of entry for in the liver.

NOTE Confidence: 0.8129131075

00:24:40.880 --> 00:24:43.664 And you can see that one week after

NOTE Confidence: 0.8129131075

00:24:43.664 --> 00:24:46.712 spodni mice treated with vehicle

NOTE Confidence: 0.8129131075

00:24:46.712 --> 00:24:49.404 control or luciferase control.

NOTE Confidence: 0.8129131075

00:24:49.410 --> 00:24:51.468 So to mark reduction hepatic Iron store,

NOTE Confidence: 0.8129131075

00:24:51.470 --> 00:24:52.578 the iron was exciting,

NOTE Confidence: 0.8129131075

00:24:52.578 --> 00:24:54.850 but in mice with Intuit for knockdown,

NOTE Confidence: 0.8129131075

00:24:54.850 --> 00:24:57.202 we didn't see that massive reduction

NOTE Confidence: 0.8129131075

00:24:57.202 --> 00:24:59.132 librarian stores and similarly

NOTE Confidence: 0.8129131075

00:24:59.132 --> 00:25:01.987 looking at ferritin protein levels,

NOTE Confidence: 0.8129131075

00:25:01.990 --> 00:25:04.097 we see that compared to the baseline

NOTE Confidence: 0.8129131075

00:25:04.097 --> 00:25:05.897 state mice treated with vehicle  
NOTE Confidence: 0.8129131075

00:25:05.897 --> 00:25:07.581 luciferase controls showed marked  
NOTE Confidence: 0.8129131075

00:25:07.581 --> 00:25:09.265 reduction to ferritin protein,  
NOTE Confidence: 0.8129131075

00:25:09.270 --> 00:25:11.391 which is not seen in mice with  
NOTE Confidence: 0.8129131075

00:25:11.391 --> 00:25:12.690 ensued 4 knocked down.  
NOTE Confidence: 0.8129131075

00:25:12.690 --> 00:25:14.030 And we did further characterization  
NOTE Confidence: 0.8129131075

00:25:14.030 --> 00:25:15.740 to just make sure that ensued.  
NOTE Confidence: 0.8129131075

00:25:15.740 --> 00:25:17.590 Mice within two four knockdown  
NOTE Confidence: 0.8129131075

00:25:17.590 --> 00:25:19.440 showed similar degrees of anemia,  
NOTE Confidence: 0.8129131075

00:25:19.440 --> 00:25:19.822 transferrin,  
NOTE Confidence: 0.8129131075

00:25:19.822 --> 00:25:20.204 saturation,  
NOTE Confidence: 0.8129131075

00:25:20.204 --> 00:25:21.732 and have silence suppression  
NOTE Confidence: 0.8129131075

00:25:21.732 --> 00:25:22.878 after full bodies.  
NOTE Confidence: 0.8129131075

00:25:22.880 --> 00:25:24.782 So these other factors we couldn't  
NOTE Confidence: 0.8129131075

00:25:24.782 --> 00:25:26.773 explain the difference in the liver  
NOTE Confidence: 0.8129131075

00:25:26.773 --> 00:25:28.759 iron loading phenotype that we observed.

NOTE Confidence: 0.8129131075

00:25:28.760 --> 00:25:31.632 So and so if we're appears to be

NOTE Confidence: 0.8129131075

00:25:31.632 --> 00:25:33.530 limiting hepatic remobilization.

NOTE Confidence: 0.8129131075

00:25:33.530 --> 00:25:34.916 And this led us to question,

NOTE Confidence: 0.8129131075

00:25:34.920 --> 00:25:37.314 you know how is endogenous and two

NOTE Confidence: 0.8129131075

00:25:37.314 --> 00:25:39.188 for activity regulated and what's

NOTE Confidence: 0.8129131075

00:25:39.188 --> 00:25:41.158 the stimulus for iron mobilization?

NOTE Confidence: 0.645353680315789

00:25:43.170 --> 00:25:45.095 So we then we just shifted to

NOTE Confidence: 0.645353680315789

00:25:45.095 --> 00:25:46.978 work and hepatoma cells have the

NOTE Confidence: 0.645353680315789

00:25:46.978 --> 00:25:48.638 cities are have three hepatoma

NOTE Confidence: 0.645353680315789

00:25:48.638 --> 00:25:51.245 cells and we treated them first

NOTE Confidence: 0.645353680315789

00:25:51.245 --> 00:25:53.930 with a chelator just proximity DFO.

NOTE Confidence: 0.645353680315789

00:25:53.930 --> 00:25:57.339 And we found that this caused an

NOTE Confidence: 0.645353680315789

00:25:57.339 --> 00:26:00.288 upregulation inside for a messenger RNA.

NOTE Confidence: 0.645353680315789

00:26:00.290 --> 00:26:01.950 We realized in these experiments,

NOTE Confidence: 0.645353680315789

00:26:01.950 --> 00:26:03.930 not only is DFO keliher,

NOTE Confidence: 0.645353680315789

00:26:03.930 --> 00:26:06.678 but it's also a stabilizer of  
NOTE Confidence: 0.645353680315789

00:26:06.678 --> 00:26:08.510 hip hypoxia inducible factor.  
NOTE Confidence: 0.645353680315789

00:26:08.510 --> 00:26:10.922 And we treated hepatoma cells with  
NOTE Confidence: 0.645353680315789

00:26:10.922 --> 00:26:13.100 other chemicals known to stabilize  
NOTE Confidence: 0.645353680315789

00:26:13.100 --> 00:26:15.585 hip calcium chloride and demog  
NOTE Confidence: 0.645353680315789

00:26:15.585 --> 00:26:17.573 and observe similar upregulation  
NOTE Confidence: 0.645353680315789

00:26:17.573 --> 00:26:19.558 in institute for expression.  
NOTE Confidence: 0.645353680315789

00:26:19.558 --> 00:26:21.560 So you remember that the  
NOTE Confidence: 0.645353680315789

00:26:21.560 --> 00:26:22.760 poor little hydroxylases,  
NOTE Confidence: 0.645353680315789

00:26:22.760 --> 00:26:25.728 the HIF prolyl hydroxylases?  
NOTE Confidence: 0.645353680315789

00:26:25.728 --> 00:26:28.688 Or oxygen and iron dependent enzymes  
NOTE Confidence: 0.645353680315789

00:26:28.688 --> 00:26:30.660 that promote the degradation  
NOTE Confidence: 0.645353680315789

00:26:30.660 --> 00:26:32.939 of health HIF alpha subunits.  
NOTE Confidence: 0.645353680315789

00:26:32.939 --> 00:26:37.524 So in the normoxic and iron sufficient state.  
NOTE Confidence: 0.645353680315789

00:26:37.524 --> 00:26:40.150 HIF alpha subunits undergo post  
NOTE Confidence: 0.645353680315789

00:26:40.150 --> 00:26:42.246 translational modification and targeting

NOTE Confidence: 0.645353680315789  
00:26:42.246 --> 00:26:44.178 to the proteasome for degradation.  
NOTE Confidence: 0.645353680315789  
00:26:44.178 --> 00:26:46.810 But, in the hypoxic or the iron,  
NOTE Confidence: 0.645353680315789  
00:26:46.810 --> 00:26:48.628 sufficient insufficient state.  
NOTE Confidence: 0.645353680315789  
00:26:48.628 --> 00:26:52.230 For example, in the setting of chelation.  
NOTE Confidence: 0.645353680315789  
00:26:52.230 --> 00:26:54.095 Hips subunits alpha subunits are  
NOTE Confidence: 0.645353680315789  
00:26:54.095 --> 00:26:55.960 available to translocate to the  
NOTE Confidence: 0.645353680315789  
00:26:56.022 --> 00:26:58.094 nucleus where they can heterodyne  
NOTE Confidence: 0.645353680315789  
00:26:58.094 --> 00:27:00.174 rise with the constitutive beta  
NOTE Confidence: 0.645353680315789  
00:27:00.174 --> 00:27:02.449 subunit to criminal gene expression.  
NOTE Confidence: 0.645353680315789  
00:27:02.450 --> 00:27:03.656 I'll remind you that they're both.  
NOTE Confidence: 0.645353680315789  
00:27:03.660 --> 00:27:07.100 They're both the hip 1A and a hip 2A subunit.  
NOTE Confidence: 0.645353680315789  
00:27:07.100 --> 00:27:08.978 So we wanted to investigate if  
NOTE Confidence: 0.645353680315789  
00:27:08.978 --> 00:27:10.800 the answer for induction wouldn't,  
NOTE Confidence: 0.645353680315789  
00:27:10.800 --> 00:27:12.980 if one HIF dependent process.  
NOTE Confidence: 0.645353680315789  
00:27:12.980 --> 00:27:14.860 So using end to if we're knocked down.  
NOTE Confidence: 0.645353680315789

00:27:14.860 --> 00:27:18.580 Sorry using hip knockdown experiments  
NOTE Confidence: 0.645353680315789

00:27:18.580 --> 00:27:21.325 we were able to show first that in the  
NOTE Confidence: 0.645353680315789

00:27:21.325 --> 00:27:24.211 absence of knockdown we see a marked  
NOTE Confidence: 0.645353680315789

00:27:24.211 --> 00:27:25.883 induction of interferon chelation.  
NOTE Confidence: 0.645353680315789

00:27:25.890 --> 00:27:28.326 The treatment with the FL chelator  
NOTE Confidence: 0.645353680315789

00:27:28.330 --> 00:27:30.855 and this induction is abrogated  
NOTE Confidence: 0.645353680315789

00:27:30.855 --> 00:27:33.770 by knockdown of 51 or 52,  
NOTE Confidence: 0.645353680315789

00:27:33.770 --> 00:27:37.290 particularly the double combination together.  
NOTE Confidence: 0.645353680315789

00:27:37.290 --> 00:27:39.066 Jade went on to do some data mining.  
NOTE Confidence: 0.645353680315789

00:27:39.070 --> 00:27:42.283 We found a data set from the lava Peter  
NOTE Confidence: 0.645353680315789

00:27:42.283 --> 00:27:45.014 Ratcliffe in the UK who had done a  
NOTE Confidence: 0.645353680315789

00:27:45.014 --> 00:27:48.050 GMY chip seek experiment in hepatoma cells.  
NOTE Confidence: 0.645353680315789

00:27:48.050 --> 00:27:50.036 These are hep 3G hepatoma cells  
NOTE Confidence: 0.645353680315789

00:27:50.036 --> 00:27:50.698 under conditions.  
NOTE Confidence: 0.645353680315789

00:27:50.700 --> 00:27:53.964 Hypoxia and Jade was able to  
NOTE Confidence: 0.645353680315789

00:27:53.964 --> 00:27:56.140 identify in their data.



NOTE Confidence: 0.645353680315789

00:27:56.140 --> 00:27:58.345 It hits one binding site actually hit

NOTE Confidence: 0.645353680315789

00:27:58.345 --> 00:28:01.158 one hit two and HIF 1 beta binding site,

NOTE Confidence: 0.645353680315789

00:28:01.160 --> 00:28:03.524 about 1.5 KB upstream of the

NOTE Confidence: 0.645353680315789

00:28:03.524 --> 00:28:05.440 first exon and two A4.

NOTE Confidence: 0.645353680315789

00:28:05.440 --> 00:28:07.618 So this LED us to a model in which

NOTE Confidence: 0.645353680315789

00:28:07.618 --> 00:28:09.945 the hip one transcription factors

NOTE Confidence: 0.645353680315789

00:28:09.945 --> 00:28:11.957 under HIP stabilizing conditions.

NOTE Confidence: 0.645353680315789

00:28:11.960 --> 00:28:14.718 So either iron deficiency or hypoxia promote,

NOTE Confidence: 0.645353680315789

00:28:14.720 --> 00:28:17.080 and so if we're transcription

NOTE Confidence: 0.645353680315789

00:28:17.080 --> 00:28:19.204 increasing the supply of this protein

NOTE Confidence: 0.645353680315789

00:28:19.204 --> 00:28:21.220 to participate in the ferritin,

NOTE Confidence: 0.645353680315789

00:28:21.220 --> 00:28:23.330 not for the process described

NOTE Confidence: 0.645353680315789

00:28:23.330 --> 00:28:25.018 by the Mancias group,

NOTE Confidence: 0.645353680315789

00:28:25.020 --> 00:28:27.130 allowing ferret to be degraded.

NOTE Confidence: 0.645353680315789

00:28:27.130 --> 00:28:29.474 An iron to be made available for use

NOTE Confidence: 0.645353680315789

00:28:29.474 --> 00:28:31.588 and perhaps exported from the South.  
NOTE Confidence: 0.645353680315789

00:28:31.590 --> 00:28:33.466 So I think this has been relieved,  
NOTE Confidence: 0.645353680315789

00:28:33.470 --> 00:28:35.510 revealed a pathway with some  
NOTE Confidence: 0.645353680315789

00:28:35.510 --> 00:28:37.142 potential for our immobilization.  
NOTE Confidence: 0.645353680315789

00:28:37.150 --> 00:28:39.033 I think whether this could be capitalized  
NOTE Confidence: 0.645353680315789

00:28:39.033 --> 00:28:40.760 in iron disorders remains to be seen,  
NOTE Confidence: 0.645353680315789

00:28:40.760 --> 00:28:42.430 but could be very interesting  
NOTE Confidence: 0.645353680315789

00:28:42.430 --> 00:28:43.590 to investigate further.  
NOTE Confidence: 0.863935014285714

00:28:46.390 --> 00:28:49.801 So finally I'd like to move on to some  
NOTE Confidence: 0.863935014285714

00:28:49.801 --> 00:28:51.708 collaborative work I've done here,  
NOTE Confidence: 0.863935014285714

00:28:51.710 --> 00:28:53.635 switching now to thinking about  
NOTE Confidence: 0.863935014285714

00:28:53.635 --> 00:28:54.790 the physiological consequences,  
NOTE Confidence: 0.863935014285714

00:28:54.790 --> 00:28:56.618 iron deficiency beyond anemia,  
NOTE Confidence: 0.863935014285714

00:28:56.618 --> 00:28:59.360 and I'll talk about two collaborations.  
NOTE Confidence: 0.863935014285714

00:28:59.360 --> 00:29:01.222 One is looking at the relationship of  
NOTE Confidence: 0.863935014285714

00:29:01.222 --> 00:29:02.829 iron deficiency to platelet counts,

NOTE Confidence: 0.863935014285714

00:29:02.830 --> 00:29:05.478 and the 2nd is the relationship of iron

NOTE Confidence: 0.863935014285714

00:29:05.478 --> 00:29:07.712 deficiency to production of the hormone

NOTE Confidence: 0.863935014285714

00:29:07.712 --> 00:29:10.310 fibroblast growth factor 23 or FGF 23.

NOTE Confidence: 0.774963462

00:29:14.400 --> 00:29:16.488 So as as many in the

NOTE Confidence: 0.774963462

00:29:16.488 --> 00:29:17.880 audience are probably aware,

NOTE Confidence: 0.774963462

00:29:17.880 --> 00:29:20.334 iron deficiency media is often associated

NOTE Confidence: 0.774963462

00:29:20.334 --> 00:29:21.970 with elevated platelet counts.

NOTE Confidence: 0.774963462

00:29:21.970 --> 00:29:26.639 In humans. This is a age1 observation.

NOTE Confidence: 0.774963462

00:29:26.640 --> 00:29:28.117 I went back and looked at the

NOTE Confidence: 0.774963462

00:29:28.117 --> 00:29:29.460 platelet counts and the patients with

NOTE Confidence: 0.774963462

00:29:29.460 --> 00:29:31.000 a ride up and we've been focusing

NOTE Confidence: 0.774963462

00:29:31.047 --> 00:29:32.297 on their red cell phenotypes.

NOTE Confidence: 0.774963462

00:29:32.300 --> 00:29:33.875 Not thinking so much about their playlists,

NOTE Confidence: 0.774963462

00:29:33.880 --> 00:29:35.945 but indeed if you look graph their

NOTE Confidence: 0.774963462

00:29:35.945 --> 00:29:37.680 hemoglobin levels versus their platelets,

NOTE Confidence: 0.774963462

00:29:37.680 --> 00:29:40.968 you see a really nice inverse  
NOTE Confidence: 0.774963462

00:29:40.968 --> 00:29:44.559 correlation between these parameters.  
NOTE Confidence: 0.774963462

00:29:44.560 --> 00:29:46.737 And so we wondered if we could  
NOTE Confidence: 0.774963462

00:29:46.737 --> 00:29:48.857 capitalize on the temper 6 knockout  
NOTE Confidence: 0.774963462

00:29:48.857 --> 00:29:50.988 model a mouse model of chronic iron  
NOTE Confidence: 0.774963462

00:29:50.988 --> 00:29:52.626 deficiency anemia to gain insight  
NOTE Confidence: 0.774963462

00:29:52.626 --> 00:29:54.246 into the underlying mechanism.  
NOTE Confidence: 0.774963462

00:29:54.250 --> 00:29:55.210 So you might just ask,  
NOTE Confidence: 0.774963462

00:29:55.210 --> 00:29:57.127 but why not just feed mice and you know  
NOTE Confidence: 0.774963462

00:29:57.127 --> 00:29:58.819 regular mice and iron deficient diet  
NOTE Confidence: 0.774963462

00:29:58.819 --> 00:30:00.249 and induce iron deficiency anemia.  
NOTE Confidence: 0.774963462

00:30:00.250 --> 00:30:01.638 It's actually quite technically  
NOTE Confidence: 0.774963462

00:30:01.638 --> 00:30:03.026 challenging to do that.  
NOTE Confidence: 0.774963462

00:30:03.030 --> 00:30:05.798 Mice have much such small daily iron needs,  
NOTE Confidence: 0.774963462

00:30:05.800 --> 00:30:07.288 and there's so much iron available  
NOTE Confidence: 0.774963462

00:30:07.288 --> 00:30:08.989 in their caging in their bedding.

NOTE Confidence: 0.774963462

00:30:08.990 --> 00:30:12.630 It's very hard to conduct studies of

NOTE Confidence: 0.774963462

00:30:12.630 --> 00:30:14.610 in which iron deficiency anemia is.

NOTE Confidence: 0.774963462

00:30:14.610 --> 00:30:16.233 Consistently induced through

NOTE Confidence: 0.774963462

00:30:16.233 --> 00:30:17.856 dietary means alone.

NOTE Confidence: 0.774963462

00:30:17.860 --> 00:30:19.848 So This is why we're interested in

NOTE Confidence: 0.774963462

00:30:19.848 --> 00:30:22.234 using the mouse model where we had a

NOTE Confidence: 0.774963462

00:30:22.234 --> 00:30:24.170 genetic form of iron deficiency anemia.

NOTE Confidence: 0.774963462

00:30:24.170 --> 00:30:26.706 We confirmed that the temper 6 knockout mice.

NOTE Confidence: 0.774963462

00:30:26.710 --> 00:30:27.612 Of course,

NOTE Confidence: 0.774963462

00:30:27.612 --> 00:30:30.769 as we move previously had low hemoglobin,

NOTE Confidence: 0.774963462

00:30:30.770 --> 00:30:32.858 low MCV but also elevated platelets

NOTE Confidence: 0.774963462

00:30:32.858 --> 00:30:34.703 and we also confirmed their

NOTE Confidence: 0.774963462

00:30:34.703 --> 00:30:36.638 public plate elevation by facts.

NOTE Confidence: 0.774963462

00:30:36.640 --> 00:30:38.410 This was actually quite important.

NOTE Confidence: 0.774963462

00:30:38.410 --> 00:30:40.818 Those of you who remember your lab

NOTE Confidence: 0.774963462

00:30:40.818 --> 00:30:43.203 medicine know that microsites so small  
NOTE Confidence: 0.774963462

00:30:43.203 --> 00:30:45.007 erythrocytes can easily miscounted  
NOTE Confidence: 0.774963462

00:30:45.007 --> 00:30:47.250 for platelets by cell counter.  
NOTE Confidence: 0.774963462

00:30:47.250 --> 00:30:48.972 This is a particular issue for  
NOTE Confidence: 0.774963462

00:30:48.972 --> 00:30:51.084 mice where the red cell MCV is  
NOTE Confidence: 0.774963462

00:30:51.084 --> 00:30:52.584 much smaller than the humans.  
NOTE Confidence: 0.774963462

00:30:52.590 --> 00:30:54.546 So we confirmed the plate elevation.  
NOTE Confidence: 0.774963462

00:30:54.550 --> 00:30:55.642 And here you can see the  
NOTE Confidence: 0.774963462

00:30:55.642 --> 00:30:56.188 peripheral blood smears,  
NOTE Confidence: 0.774963462

00:30:56.190 --> 00:30:57.982 and I think you can appreciate even  
NOTE Confidence: 0.774963462

00:30:57.982 --> 00:30:59.803 on the temper 6 knockouts where  
NOTE Confidence: 0.774963462

00:30:59.803 --> 00:31:01.468 it increased number of platelets.  
NOTE Confidence: 0.898929906666667

00:31:03.890 --> 00:31:07.530 So to make sure we could observe plate  
NOTE Confidence: 0.898929906666667

00:31:07.530 --> 00:31:09.510 elevation in mice with normal hepcidin  
NOTE Confidence: 0.898929906666667

00:31:09.510 --> 00:31:11.277 regulation we collaborated with Mark  
NOTE Confidence: 0.898929906666667

00:31:11.277 --> 00:31:13.027 Flemmings Group at Children's Hospital

NOTE Confidence: 0.898929906666667  
00:31:13.027 --> 00:31:15.334 boss and they were doing some studies  
NOTE Confidence: 0.898929906666667  
00:31:15.334 --> 00:31:16.884 of iron deficiency and pregnancy.  
NOTE Confidence: 0.898929906666667  
00:31:16.890 --> 00:31:18.745 So in pregnant mice that an iron  
NOTE Confidence: 0.898929906666667  
00:31:18.745 --> 00:31:20.238 deficient diet they were able  
NOTE Confidence: 0.898929906666667  
00:31:20.238 --> 00:31:21.530 to induce consistent anemia.  
NOTE Confidence: 0.898929906666667  
00:31:21.530 --> 00:31:23.070 But of course that's a very difficult  
NOTE Confidence: 0.898929906666667  
00:31:23.070 --> 00:31:24.571 experience for a long term experiment  
NOTE Confidence: 0.898929906666667  
00:31:24.571 --> 00:31:26.426 because the mice will eventually give birth,  
NOTE Confidence: 0.898929906666667  
00:31:26.430 --> 00:31:27.774 so it's it's not a practical  
NOTE Confidence: 0.898929906666667  
00:31:27.774 --> 00:31:29.110 way to study this problem,  
NOTE Confidence: 0.898929906666667  
00:31:29.110 --> 00:31:30.670 but it confirmed that this is  
NOTE Confidence: 0.898929906666667  
00:31:30.670 --> 00:31:32.330 a not this played elevation.  
NOTE Confidence: 0.898929906666667  
00:31:32.330 --> 00:31:34.247 We seen the temper 6 knockout might it's not.  
NOTE Confidence: 0.898929906666667  
00:31:34.250 --> 00:31:35.558 It's not something specifically  
NOTE Confidence: 0.898929906666667  
00:31:35.558 --> 00:31:37.520 related to their website and defect.  
NOTE Confidence: 0.898929906666667

00:31:37.520 --> 00:31:39.560 It's more general phenomena related in  
NOTE Confidence: 0.898929906666667

00:31:39.560 --> 00:31:42.388 some way to their iron deficiency anemia.  
NOTE Confidence: 0.898929906666667

00:31:42.390 --> 00:31:44.170 And oh, I wanted to point out, of course,  
NOTE Confidence: 0.898929906666667

00:31:44.170 --> 00:31:45.885 this is the collaboration with a group  
NOTE Confidence: 0.898929906666667

00:31:45.885 --> 00:31:48.165 of Diane Kraus 2 proposed excellent postdocs,  
NOTE Confidence: 0.898929906666667

00:31:48.170 --> 00:31:49.673 a former postdocs,  
NOTE Confidence: 0.898929906666667

00:31:49.673 --> 00:31:51.677 now Julianna Shaviv Trucchio  
NOTE Confidence: 0.898929906666667

00:31:51.677 --> 00:31:53.180 and Vanessa Scanlon.  
NOTE Confidence: 0.898929906666667

00:31:53.180 --> 00:31:54.460 Jade in my lab,  
NOTE Confidence: 0.898929906666667

00:31:54.460 --> 00:31:56.870 and Larissa in my lab as well.  
NOTE Confidence: 0.898929906666667

00:31:56.870 --> 00:31:59.108 So as many of you know,  
NOTE Confidence: 0.898929906666667

00:31:59.110 --> 00:32:01.930 Diane is very interested in hematopoiesis.  
NOTE Confidence: 0.898929906666667

00:32:01.930 --> 00:32:04.768 This is the classic hematopoiesis tree.  
NOTE Confidence: 0.898929906666667

00:32:04.770 --> 00:32:07.008 And here we have the megakaryocyte  
NOTE Confidence: 0.898929906666667

00:32:07.008 --> 00:32:08.127 erythroid progenitor cell.  
NOTE Confidence: 0.898929906666667

00:32:08.130 --> 00:32:10.490 So this is a cell that can decorate



NOTE Confidence: 0.898929906666667  
00:32:10.490 --> 00:32:13.001 down the megakaryocyte for the erythroid  
NOTE Confidence: 0.898929906666667  
00:32:13.001 --> 00:32:15.779 lineage and Diane is very interesting  
NOTE Confidence: 0.898929906666667  
00:32:15.846 --> 00:32:18.528 factors that control this fake decision.  
NOTE Confidence: 0.898929906666667  
00:32:18.530 --> 00:32:21.278 So we hypothesized that the megakaryocyte  
NOTE Confidence: 0.898929906666667  
00:32:21.278 --> 00:32:23.520 erythroid progenitor cell from iron  
NOTE Confidence: 0.898929906666667  
00:32:23.520 --> 00:32:25.542 deficient mice would show a bias  
NOTE Confidence: 0.898929906666667  
00:32:25.542 --> 00:32:28.088 towards the mid career site MK lineage.  
NOTE Confidence: 0.898929906666667  
00:32:28.090 --> 00:32:29.510 Diane's lab has an excellent  
NOTE Confidence: 0.898929906666667  
00:32:29.510 --> 00:32:30.646 assay to assess this,  
NOTE Confidence: 0.898929906666667  
00:32:30.650 --> 00:32:32.930 so this is a colony forming assay to  
NOTE Confidence: 0.898929906666667  
00:32:32.930 --> 00:32:35.455 assess the MK erythroid lineage potential  
NOTE Confidence: 0.898929906666667  
00:32:35.455 --> 00:32:37.815 where the megakaryocyte erythroid peak,  
NOTE Confidence: 0.898929906666667  
00:32:37.820 --> 00:32:40.214 which your cells or MP's or  
NOTE Confidence: 0.898929906666667  
00:32:40.214 --> 00:32:42.362 isolated from mouse bone marrow  
NOTE Confidence: 0.898929906666667  
00:32:42.362 --> 00:32:44.727 by facts grown with cytokines.  
NOTE Confidence: 0.898929906666667

00:32:44.730 --> 00:32:46.865 To promote the growth of  
NOTE Confidence: 0.898929906666667

00:32:46.865 --> 00:32:48.573 MK and erythroid progeny.  
NOTE Confidence: 0.898929906666667

00:32:48.580 --> 00:32:49.780 And after several days,  
NOTE Confidence: 0.898929906666667

00:32:49.780 --> 00:32:51.580 the colonies are fixed and stained  
NOTE Confidence: 0.898929906666667

00:32:51.637 --> 00:32:53.347 specifically for me to carry site  
NOTE Confidence: 0.898929906666667

00:32:53.347 --> 00:32:55.115 markers shown here in Green CD  
NOTE Confidence: 0.898929906666667

00:32:55.115 --> 00:32:56.555 41 and northward markers here.  
NOTE Confidence: 0.898929906666667

00:32:56.560 --> 00:32:58.425 City 71 the transferring receptor  
NOTE Confidence: 0.898929906666667

00:32:58.425 --> 00:33:01.153 shown in red so you can get  
NOTE Confidence: 0.898929906666667

00:33:01.153 --> 00:33:03.517 develop colonies that are MK only  
NOTE Confidence: 0.898929906666667

00:33:03.517 --> 00:33:05.785 erythroid only or a mix of the two.  
NOTE Confidence: 0.898929906666667

00:33:05.790 --> 00:33:08.870 And we found that compared to wild  
NOTE Confidence: 0.898929906666667

00:33:08.870 --> 00:33:11.294 type animals MEP's from temper 6  
NOTE Confidence: 0.898929906666667

00:33:11.294 --> 00:33:13.801 knockout mice showed an increased  
NOTE Confidence: 0.898929906666667

00:33:13.801 --> 00:33:16.109 percentage of colonies that  
NOTE Confidence: 0.898929906666667

00:33:16.109 --> 00:33:18.470 were only forming MK progeny.

NOTE Confidence: 0.898929906666667

00:33:18.470 --> 00:33:21.350 So the MEP's from 10 per six knockout

NOTE Confidence: 0.898929906666667

00:33:21.350 --> 00:33:23.943 mice were MK biased and in similar

NOTE Confidence: 0.898929906666667

00:33:23.943 --> 00:33:26.558 studies we found that there was also

NOTE Confidence: 0.898929906666667

00:33:26.558 --> 00:33:29.127 bias in mice would be dietary induced

NOTE Confidence: 0.898929906666667

00:33:29.130 --> 00:33:33.580 our inefficiency anemia during pregnancy.

NOTE Confidence: 0.898929906666667

00:33:33.580 --> 00:33:35.280 So the next question became,

NOTE Confidence: 0.898929906666667

00:33:35.280 --> 00:33:38.076 does the low iron environment itself

NOTE Confidence: 0.898929906666667

00:33:38.076 --> 00:33:41.237 promote the mercury site bias of the MEP?

NOTE Confidence: 0.898929906666667

00:33:41.240 --> 00:33:43.445 So to address this we moved on to some

NOTE Confidence: 0.898929906666667

00:33:43.445 --> 00:33:45.750 bone marrow transplantation experiments.

NOTE Confidence: 0.898929906666667

00:33:45.750 --> 00:33:47.162 So in this experiment.

NOTE Confidence: 0.898929906666667

00:33:47.162 --> 00:33:50.118 We took temper 6 wild type mice and

NOTE Confidence: 0.898929906666667

00:33:50.118 --> 00:33:52.792 iron balance hosts or temper 6 knockout

NOTE Confidence: 0.898929906666667

00:33:52.792 --> 00:33:55.838 mice and iron deficient host and they

NOTE Confidence: 0.898929906666667

00:33:55.838 --> 00:33:58.058 were transplanted each with wild type.

NOTE Confidence: 0.898929906666667

00:33:58.058 --> 00:33:59.766 Were not that bone marrow and I  
NOTE Confidence: 0.898929906666667

00:33:59.766 --> 00:34:01.663 want to remind you 10 per six is  
NOTE Confidence: 0.898929906666667

00:34:01.663 --> 00:34:03.239 not expressed in the bone marrow.  
NOTE Confidence: 0.898929906666667

00:34:03.240 --> 00:34:04.392 So, 12 weeks later,  
NOTE Confidence: 0.898929906666667

00:34:04.392 --> 00:34:06.120 we looked at the blood parameters  
NOTE Confidence: 0.7975412164

00:34:06.177 --> 00:34:08.353 these animals and you can see that whenever  
NOTE Confidence: 0.7975412164

00:34:08.353 --> 00:34:10.416 the we had a well typed recipient,  
NOTE Confidence: 0.7975412164

00:34:10.420 --> 00:34:12.310 serum iron, blood, hemoglobin and plate  
NOTE Confidence: 0.7975412164

00:34:12.310 --> 00:34:14.550 levels were all in the normal range.  
NOTE Confidence: 0.7975412164

00:34:14.550 --> 00:34:16.580 The donor genotype for the  
NOTE Confidence: 0.7975412164

00:34:16.580 --> 00:34:17.798 marriage didn't matter.  
NOTE Confidence: 0.7975412164

00:34:17.800 --> 00:34:20.691 When we put knockout or wall table  
NOTE Confidence: 0.7975412164

00:34:20.691 --> 00:34:22.760 mirror into knockout recipient.  
NOTE Confidence: 0.7975412164

00:34:22.760 --> 00:34:24.835 They showed the animals showed  
NOTE Confidence: 0.7975412164

00:34:24.835 --> 00:34:26.495 cerebral blood parameters consistent  
NOTE Confidence: 0.7975412164

00:34:26.495 --> 00:34:28.299 with iron deficiency anemia,

NOTE Confidence: 0.7975412164  
00:34:28.300 --> 00:34:31.396 and they showed elevation of platelets.  
NOTE Confidence: 0.7975412164  
00:34:31.400 --> 00:34:34.067 So we then used the Colony formation  
NOTE Confidence: 0.7975412164  
00:34:34.067 --> 00:34:36.580 assay to assess the MK erythroid  
NOTE Confidence: 0.7975412164  
00:34:36.580 --> 00:34:38.866 lineage potential of the MEP's and  
NOTE Confidence: 0.7975412164  
00:34:38.866 --> 00:34:40.564 you can see that when wildtype  
NOTE Confidence: 0.7975412164  
00:34:40.564 --> 00:34:42.375 mice were transplanted with wild  
NOTE Confidence: 0.7975412164  
00:34:42.375 --> 00:34:43.959 type were knockout marrow,  
NOTE Confidence: 0.7975412164  
00:34:43.960 --> 00:34:45.390 there was no significant difference.  
NOTE Confidence: 0.7975412164  
00:34:45.390 --> 00:34:47.722 The number of megakaryocyte  
NOTE Confidence: 0.7975412164  
00:34:47.722 --> 00:34:48.888 colonies produced.  
NOTE Confidence: 0.7975412164  
00:34:48.890 --> 00:34:49.372 However,  
NOTE Confidence: 0.7975412164  
00:34:49.372 --> 00:34:52.746 when the recipient was a knockout mouse,  
NOTE Confidence: 0.7975412164  
00:34:52.750 --> 00:34:56.334 we saw an increase in MK number of  
NOTE Confidence: 0.7975412164  
00:34:56.334 --> 00:34:59.346 the number of colonies that were  
NOTE Confidence: 0.7975412164  
00:34:59.350 --> 00:35:00.886 MP's that needed that yielded MK.  
NOTE Confidence: 0.7975412164

00:35:00.890 --> 00:35:03.550 Only colonies to say that.  
NOTE Confidence: 0.7975412164

00:35:03.550 --> 00:35:06.189 And a similar increase when wild type  
NOTE Confidence: 0.7975412164

00:35:06.189 --> 00:35:09.128 mice was put into the knockout host.  
NOTE Confidence: 0.7975412164

00:35:09.130 --> 00:35:10.778 So it was really the iron status of  
NOTE Confidence: 0.7975412164

00:35:10.778 --> 00:35:12.357 the host was that was determined.  
NOTE Confidence: 0.7975412164

00:35:12.360 --> 00:35:14.670 This commitment to the MK lineage  
NOTE Confidence: 0.7975412164

00:35:14.670 --> 00:35:16.308 and in a number of further studies  
NOTE Confidence: 0.7975412164

00:35:16.308 --> 00:35:18.230 that I'm not going to get into detail  
NOTE Confidence: 0.7975412164

00:35:18.230 --> 00:35:19.987 here today we tried to get some  
NOTE Confidence: 0.7975412164

00:35:19.987 --> 00:35:21.595 insight into the mechanism by which  
NOTE Confidence: 0.7975412164

00:35:21.595 --> 00:35:23.763 this fake decision was occurring.  
NOTE Confidence: 0.7975412164

00:35:23.763 --> 00:35:24.304 First,  
NOTE Confidence: 0.7975412164

00:35:24.304 --> 00:35:26.842 we tried knocking down expression  
NOTE Confidence: 0.7975412164

00:35:26.842 --> 00:35:28.330 of the transfer receptor,  
NOTE Confidence: 0.7975412164

00:35:28.330 --> 00:35:29.810 one which mediates iron uptake,  
NOTE Confidence: 0.7975412164

00:35:29.810 --> 00:35:32.962 but unfortunately that was that you know,

NOTE Confidence: 0.7975412164

00:35:32.962 --> 00:35:34.226 toxic to the cells,

NOTE Confidence: 0.7975412164

00:35:34.230 --> 00:35:35.460 so that that wasn't a viable.

NOTE Confidence: 0.7975412164

00:35:35.460 --> 00:35:38.470 Approach but in Human MP's we were

NOTE Confidence: 0.7975412164

00:35:38.470 --> 00:35:41.682 able to recapitulate this MK bias by

NOTE Confidence: 0.7975412164

00:35:41.682 --> 00:35:43.982 knocking down transparent receptor 2.

NOTE Confidence: 0.7975412164

00:35:43.990 --> 00:35:45.586 So this is the transformer receptor 2.

NOTE Confidence: 0.7975412164

00:35:45.590 --> 00:35:47.726 I just showed you that in the table

NOTE Confidence: 0.7975412164

00:35:47.726 --> 00:35:49.041 of hemochromatosis genes and it's

NOTE Confidence: 0.7975412164

00:35:49.041 --> 00:35:50.493 not only expressed in liver but

NOTE Confidence: 0.7975412164

00:35:50.493 --> 00:35:52.522 it also seems to play a role in

NOTE Confidence: 0.7975412164

00:35:52.522 --> 00:35:54.136 erythroid cells where it modulates

NOTE Confidence: 0.7975412164

00:35:54.136 --> 00:35:55.868 signaling through equation receptor.

NOTE Confidence: 0.7975412164

00:35:55.870 --> 00:35:58.096 So reducing expression of TFR 2

NOTE Confidence: 0.7975412164

00:35:58.096 --> 00:36:01.375 which is thought to be more of an

NOTE Confidence: 0.7975412164

00:36:01.375 --> 00:36:03.520 iron sensor rather than immediately

NOTE Confidence: 0.7975412164

00:36:03.520 --> 00:36:05.779 requiring uptake seem to modulate.  
NOTE Confidence: 0.7975412164

00:36:05.780 --> 00:36:06.968 This MK bias.  
NOTE Confidence: 0.760224992

00:36:10.300 --> 00:36:11.440 For the last few minutes,  
NOTE Confidence: 0.760224992

00:36:11.440 --> 00:36:13.736 I want to talk about a collaboration we've  
NOTE Confidence: 0.760224992

00:36:13.736 --> 00:36:15.876 had with Jackie Fretz and Orthopedics  
NOTE Confidence: 0.760224992

00:36:15.876 --> 00:36:17.761 looking at emerging links between  
NOTE Confidence: 0.760224992

00:36:17.761 --> 00:36:20.196 iron deficiency and the hormone FGF.  
NOTE Confidence: 0.760224992

00:36:20.196 --> 00:36:24.000 23 fibroblast growth factor 23 so.  
NOTE Confidence: 0.760224992

00:36:24.000 --> 00:36:27.812 FGF 23. Is a hormone produced,  
NOTE Confidence: 0.760224992

00:36:27.812 --> 00:36:29.384 thought to produce classically  
NOTE Confidence: 0.760224992

00:36:29.384 --> 00:36:30.760 by osteocytes and bone,  
NOTE Confidence: 0.760224992

00:36:30.760 --> 00:36:32.755 and it plays a critical role in  
NOTE Confidence: 0.760224992

00:36:32.755 --> 00:36:34.055 skeletal health by regulating  
NOTE Confidence: 0.760224992

00:36:34.055 --> 00:36:35.960 the phosphate vitamin D axis,  
NOTE Confidence: 0.760224992

00:36:35.960 --> 00:36:37.520 circulating levels of FGF,  
NOTE Confidence: 0.760224992

00:36:37.520 --> 00:36:39.860 23 rise in patients with chronic



NOTE Confidence: 0.760224992

00:36:39.928 --> 00:36:42.261 kidney disease, and this FGF.

NOTE Confidence: 0.760224992

00:36:42.261 --> 00:36:44.943 23 elevation is associated with adverse

NOTE Confidence: 0.760224992

00:36:44.943 --> 00:36:46.988 cardiovascular outcomes and all cause

NOTE Confidence: 0.760224992

00:36:46.988 --> 00:36:48.893 mortality in patients both with

NOTE Confidence: 0.760224992

00:36:48.893 --> 00:36:51.389 and without chronic kidney disease.

NOTE Confidence: 0.760224992

00:36:51.390 --> 00:36:54.216 Whether or not FGF 23 is a direct mediator.

NOTE Confidence: 0.760224992

00:36:54.220 --> 00:36:56.668 A biomarker I think is still under debate,

NOTE Confidence: 0.760224992

00:36:56.670 --> 00:36:58.482 but what was interesting to us

NOTE Confidence: 0.760224992

00:36:58.482 --> 00:37:00.390 and why others had approached me

NOTE Confidence: 0.760224992

00:37:00.390 --> 00:37:02.595 about our model is the fact that

NOTE Confidence: 0.760224992

00:37:02.595 --> 00:37:04.868 iron deficiency had been found to

NOTE Confidence: 0.760224992

00:37:04.868 --> 00:37:06.959 correlate with FGF 23 elevation

NOTE Confidence: 0.760224992

00:37:06.959 --> 00:37:09.617 in the circulation of both humans,

NOTE Confidence: 0.760224992

00:37:09.620 --> 00:37:12.940 healthy humans and mouse models.

NOTE Confidence: 0.760224992

00:37:12.940 --> 00:37:14.588 And so of course we wanted to turn

NOTE Confidence: 0.760224992

00:37:14.588 --> 00:37:16.311 to the temperance model again to see  
NOTE Confidence: 0.760224992

00:37:16.311 --> 00:37:18.380 if we could use that as a tool here,  
NOTE Confidence: 0.760224992

00:37:18.380 --> 00:37:20.508 and we found that temper 6 knockout  
NOTE Confidence: 0.760224992

00:37:20.508 --> 00:37:22.847 mice compared to wild type where  
NOTE Confidence: 0.760224992

00:37:22.847 --> 00:37:24.987 heterozygous controlled so it increased  
NOTE Confidence: 0.760224992

00:37:24.987 --> 00:37:27.441 urine phosphate to creatinine ratios as  
NOTE Confidence: 0.760224992

00:37:27.441 --> 00:37:29.546 expected based on the known function  
NOTE Confidence: 0.760224992

00:37:29.546 --> 00:37:32.519 of FGF 23 and increased phosphate excretion.  
NOTE Confidence: 0.760224992

00:37:32.520 --> 00:37:33.500 And looking in their blood,  
NOTE Confidence: 0.760224992

00:37:33.500 --> 00:37:35.100 we saw level increased levels  
NOTE Confidence: 0.760224992

00:37:35.100 --> 00:37:37.280 of the active FGF 23 hormone,  
NOTE Confidence: 0.760224992

00:37:37.280 --> 00:37:39.890 as well as total FGF 23,  
NOTE Confidence: 0.760224992

00:37:39.890 --> 00:37:40.970 probably because it's a different.  
NOTE Confidence: 0.760224992

00:37:40.970 --> 00:37:42.937 A lot of apps say that analyzes.  
NOTE Confidence: 0.760224992

00:37:42.940 --> 00:37:45.310 Both inactive and active forms,  
NOTE Confidence: 0.760224992

00:37:45.310 --> 00:37:48.880 the hormone which undergoes cleavage.

NOTE Confidence: 0.760224992  
00:37:48.880 --> 00:37:49.230 So.  
NOTE Confidence: 0.760224992  
00:37:49.230 --> 00:37:51.680 We thought we would be looking at  
NOTE Confidence: 0.760224992  
00:37:51.680 --> 00:37:54.299 FGF 20 regulation of the bone.  
NOTE Confidence: 0.760224992  
00:37:54.300 --> 00:37:57.486 But when we isolated bone mRNA  
NOTE Confidence: 0.760224992  
00:37:57.486 --> 00:37:59.079 from bone cortex,  
NOTE Confidence: 0.760224992  
00:37:59.080 --> 00:38:01.372 we actually found that FGF 23  
NOTE Confidence: 0.760224992  
00:38:01.372 --> 00:38:03.284 elevation was not increased in  
NOTE Confidence: 0.760224992  
00:38:03.284 --> 00:38:05.180 the temper of 6 knockout mice.  
NOTE Confidence: 0.760224992  
00:38:05.180 --> 00:38:06.656 And we discovered 2 the better.  
NOTE Confidence: 0.760224992  
00:38:06.660 --> 00:38:07.588 We clean the bone,  
NOTE Confidence: 0.760224992  
00:38:07.588 --> 00:38:08.980 the clearer this cleaner that she  
NOTE Confidence: 0.760224992  
00:38:09.033 --> 00:38:10.599 was all came showing no difference.  
NOTE Confidence: 0.760224992  
00:38:10.600 --> 00:38:12.052 So it became very suspicious of  
NOTE Confidence: 0.760224992  
00:38:12.052 --> 00:38:13.020 the Bone Arrow itself.  
NOTE Confidence: 0.760224992  
00:38:13.020 --> 00:38:13.960 May be the source def.  
NOTE Confidence: 0.760224992

00:38:13.960 --> 00:38:14.902 Chapter 23.  
NOTE Confidence: 0.760224992

00:38:14.902 --> 00:38:16.786 Elevation iron deficiency anemia.  
NOTE Confidence: 0.760224992

00:38:16.790 --> 00:38:18.632 And indeed that's what we saw  
NOTE Confidence: 0.760224992

00:38:18.632 --> 00:38:20.574 when we looked at expression by  
NOTE Confidence: 0.760224992

00:38:20.574 --> 00:38:22.359 qPCR on the bone marrow.  
NOTE Confidence: 0.771646292222222

00:38:24.700 --> 00:38:28.017 So to get for more of a grip on what the cell  
NOTE Confidence: 0.771646292222222

00:38:28.017 --> 00:38:30.816 type was that produced was producing FGF,  
NOTE Confidence: 0.771646292222222

00:38:30.816 --> 00:38:33.896 23 we introduced an FGF 23 EGF reporter,  
NOTE Confidence: 0.771646292222222

00:38:33.896 --> 00:38:36.420 or little into the upper 6 mouse line,  
NOTE Confidence: 0.771646292222222

00:38:36.420 --> 00:38:38.184 so this is a well characterized  
NOTE Confidence: 0.771646292222222

00:38:38.184 --> 00:38:40.343 allele in which the the enhanced  
NOTE Confidence: 0.771646292222222

00:38:40.343 --> 00:38:42.624 green fluorescence protein, or egfp,  
NOTE Confidence: 0.771646292222222

00:38:42.624 --> 00:38:45.664 is knocked into the endogenous FGF 23  
NOTE Confidence: 0.771646292222222

00:38:45.664 --> 00:38:48.076 locus immediately after the start codon.  
NOTE Confidence: 0.771646292222222

00:38:48.080 --> 00:38:52.147 So this is a reporter allele that  
NOTE Confidence: 0.771646292222222

00:38:52.147 --> 00:38:55.195 also knocks out FGF 23 transcription

NOTE Confidence: 0.771646292222222

00:38:55.195 --> 00:38:56.935 from the same allele.

NOTE Confidence: 0.771646292222222

00:38:56.940 --> 00:38:59.256 And mice heterozygous for the supporter,

NOTE Confidence: 0.771646292222222

00:38:59.260 --> 00:39:01.356 so the mice that have one functional FGF,

NOTE Confidence: 0.771646292222222

00:39:01.360 --> 00:39:03.635 23 little only are known to maintain

NOTE Confidence: 0.771646292222222

00:39:03.635 --> 00:39:05.130 normal hot phosphate balance.

NOTE Confidence: 0.771646292222222

00:39:05.130 --> 00:39:06.467 So we bred the soul into the

NOTE Confidence: 0.771646292222222

00:39:06.467 --> 00:39:07.876 temporal six months line and I won't

NOTE Confidence: 0.771646292222222

00:39:07.876 --> 00:39:09.070 show you all the supporting data,

NOTE Confidence: 0.771646292222222

00:39:09.070 --> 00:39:11.002 but basically wanted to prove that

NOTE Confidence: 0.771646292222222

00:39:11.002 --> 00:39:13.195 temper 6 knockout mice carrying reporter

NOTE Confidence: 0.771646292222222

00:39:13.195 --> 00:39:15.295 were still equally iron deficient.

NOTE Confidence: 0.771646292222222

00:39:15.300 --> 00:39:17.197 Had equal degrees of anemia and retained

NOTE Confidence: 0.771646292222222

00:39:17.197 --> 00:39:19.396 after you have 23 elevation in the plasma,

NOTE Confidence: 0.771646292222222

00:39:19.400 --> 00:39:21.338 which they did.

NOTE Confidence: 0.771646292222222

00:39:21.340 --> 00:39:23.356 One little a piece of data I'll show

NOTE Confidence: 0.771646292222222

00:39:23.356 --> 00:39:25.624 you is inside is temper 6 knockout  
NOTE Confidence: 0.771646292222222

00:39:25.624 --> 00:39:27.713 mice also have elevated levels of  
NOTE Confidence: 0.771646292222222

00:39:27.713 --> 00:39:29.974 risk reports and we looked at various  
NOTE Confidence: 0.771646292222222

00:39:29.974 --> 00:39:31.980 lab parameters trying to see if we  
NOTE Confidence: 0.771646292222222

00:39:31.980 --> 00:39:33.340 found certain parameters that seemed  
NOTE Confidence: 0.771646292222222

00:39:33.396 --> 00:39:35.100 to correlate with FGF 23 elevation,  
NOTE Confidence: 0.771646292222222

00:39:35.100 --> 00:39:37.180 and in fact it was the erythropoietin level.  
NOTE Confidence: 0.771646292222222

00:39:37.180 --> 00:39:39.956 If we look across mice at different genotypes  
NOTE Confidence: 0.771646292222222

00:39:39.956 --> 00:39:42.360 that seemed to correlate best with FGF,  
NOTE Confidence: 0.771646292222222

00:39:42.360 --> 00:39:45.000 23 three levels in circulation,  
NOTE Confidence: 0.771646292222222

00:39:45.000 --> 00:39:48.234 and just hold that thought for now.  
NOTE Confidence: 0.771646292222222

00:39:48.240 --> 00:39:50.417 So we had a GFP reporter mouse.  
NOTE Confidence: 0.771646292222222

00:39:50.420 --> 00:39:51.624 We did flow cytometry.  
NOTE Confidence: 0.771646292222222

00:39:51.624 --> 00:39:53.800 The total bone marrow to try and  
NOTE Confidence: 0.771646292222222

00:39:53.800 --> 00:39:55.850 see if population and you can see  
NOTE Confidence: 0.771646292222222

00:39:55.850 --> 00:39:57.530 that in mice carrying the portfolio

NOTE Confidence: 0.771646292222222

00:39:57.592 --> 00:39:59.783 both temper 6 knockout and temper 6

NOTE Confidence: 0.771646292222222

00:39:59.783 --> 00:40:01.610 heterozygous with the reporter allele

NOTE Confidence: 0.771646292222222

00:40:01.610 --> 00:40:03.370 heterozygous for the reporter level.

NOTE Confidence: 0.771646292222222

00:40:03.370 --> 00:40:05.458 Just a very small fraction of

NOTE Confidence: 0.771646292222222

00:40:05.458 --> 00:40:07.310 the population with GFP right?

NOTE Confidence: 0.771646292222222

00:40:07.310 --> 00:40:09.235 But we did not see these small

NOTE Confidence: 0.771646292222222

00:40:09.235 --> 00:40:09.785 fractions right.

NOTE Confidence: 0.771646292222222

00:40:09.790 --> 00:40:11.990 Cells in my selected reporter.

NOTE Confidence: 0.771646292222222

00:40:11.990 --> 00:40:14.550 This turned out to be less than .02% of

NOTE Confidence: 0.771646292222222

00:40:14.550 --> 00:40:17.350 power cells and so Jade was very frustrated.

NOTE Confidence: 0.771646292222222

00:40:17.350 --> 00:40:18.259 A bit heartbroken.

NOTE Confidence: 0.771646292222222

00:40:18.259 --> 00:40:20.380 She thought these were going to be

NOTE Confidence: 0.771646292222222

00:40:20.444 --> 00:40:22.850 incredibly difficult animals to work with.

NOTE Confidence: 0.771646292222222

00:40:22.850 --> 00:40:25.972 So we we then took a look at the bone

NOTE Confidence: 0.771646292222222

00:40:25.972 --> 00:40:28.624 marrow biopsies in these mice with

NOTE Confidence: 0.771646292222222

00:40:28.624 --> 00:40:31.538 Jackie frats and here's confocal of.  
NOTE Confidence: 0.7716462922222222

00:40:31.540 --> 00:40:33.787 Core biopsies after this very brief fixation,  
NOTE Confidence: 0.7716462922222222

00:40:33.790 --> 00:40:35.260 you can see green fluorescent  
NOTE Confidence: 0.7716462922222222

00:40:35.260 --> 00:40:36.436 throughout the Marina patterns,  
NOTE Confidence: 0.7716462922222222

00:40:36.440 --> 00:40:39.820 suggesting localization to the vasculature.  
NOTE Confidence: 0.7716462922222222

00:40:39.820 --> 00:40:42.430 So this led us to think more about our  
NOTE Confidence: 0.7716462922222222

00:40:42.430 --> 00:40:44.918 flow cytometry and using a protocol  
NOTE Confidence: 0.7716462922222222

00:40:44.918 --> 00:40:47.043 to enrich for endothelial cells.  
NOTE Confidence: 0.7716462922222222

00:40:47.050 --> 00:40:49.384 We look specifically at GFP expression  
NOTE Confidence: 0.7716462922222222

00:40:49.384 --> 00:40:52.488 within cells in the endothelial cell gate.  
NOTE Confidence: 0.7716462922222222

00:40:52.490 --> 00:40:53.418 In mice,  
NOTE Confidence: 0.7716462922222222

00:40:53.418 --> 00:40:56.666 the various temper 6 FGF 23 genotypes,  
NOTE Confidence: 0.7716462922222222

00:40:56.670 --> 00:40:59.071 and we found that looking within the  
NOTE Confidence: 0.7716462922222222

00:40:59.071 --> 00:41:01.119 endothelial cell gate mice that carry  
NOTE Confidence: 0.7716462922222222

00:41:01.119 --> 00:41:03.033 the reporter allele showed a subset  
NOTE Confidence: 0.7716462922222222

00:41:03.033 --> 00:41:05.308 of salt with breaking fluorescence,



NOTE Confidence: 0.771646292222222

00:41:05.310 --> 00:41:07.928 which was not seen in my slacking

NOTE Confidence: 0.771646292222222

00:41:07.928 --> 00:41:08.676 airport earlier.

NOTE Confidence: 0.771646292222222

00:41:08.680 --> 00:41:11.102 And the percentage of cells in the

NOTE Confidence: 0.771646292222222

00:41:11.102 --> 00:41:13.281 endothelial gate that were GFP bright

NOTE Confidence: 0.771646292222222

00:41:13.281 --> 00:41:15.423 was higher in temperate 6 knockouts.

NOTE Confidence: 0.771646292222222

00:41:15.430 --> 00:41:17.458 The iron deficiency type compared to

NOTE Confidence: 0.771646292222222

00:41:17.458 --> 00:41:19.357 the non iron deficient heterozygous

NOTE Confidence: 0.771646292222222

00:41:19.357 --> 00:41:20.818 controlled unit type.

NOTE Confidence: 0.824266841666667

00:41:24.690 --> 00:41:27.960 So to gain further expression for

NOTE Confidence: 0.824266841666667

00:41:27.960 --> 00:41:29.775 FGF 2323 elevation in expression

NOTE Confidence: 0.824266841666667

00:41:29.775 --> 00:41:32.030 in bone marrow and Ophelia cells,

NOTE Confidence: 0.824266841666667

00:41:32.030 --> 00:41:34.046 we mind a published data set from the lab.

NOTE Confidence: 0.824266841666667

00:41:34.050 --> 00:41:36.726 David David Scadden in the study,

NOTE Confidence: 0.824266841666667

00:41:36.730 --> 00:41:39.466 the author use single cell RNA seek of bone

NOTE Confidence: 0.824266841666667

00:41:39.466 --> 00:41:42.027 marrow stromal cells from blastic mite sex,

NOTE Confidence: 0.824266841666667

00:41:42.030 --> 00:41:44.090 6 mice at steady state.  
NOTE Confidence: 0.824266841666667

00:41:44.090 --> 00:41:45.510 So these are normal mice.  
NOTE Confidence: 0.824266841666667

00:41:45.510 --> 00:41:46.608 Normal iron balance,  
NOTE Confidence: 0.824266841666667

00:41:46.608 --> 00:41:47.706 normal phosphate balance,  
NOTE Confidence: 0.824266841666667

00:41:47.710 --> 00:41:49.354 and in their study they were  
NOTE Confidence: 0.824266841666667

00:41:49.354 --> 00:41:51.231 able to identify 17 stromal cell  
NOTE Confidence: 0.824266841666667

00:41:51.231 --> 00:41:53.026 clusters and mining their data.  
NOTE Confidence: 0.824266841666667

00:41:53.030 --> 00:41:55.186 We found FGF 23.  
NOTE Confidence: 0.824266841666667

00:41:55.186 --> 00:41:57.881 Expression in the population they  
NOTE Confidence: 0.824266841666667

00:41:57.881 --> 00:42:01.487 defined as sinusoidal endothelial cells.  
NOTE Confidence: 0.824266841666667

00:42:01.490 --> 00:42:03.490 Looking more at the individual  
NOTE Confidence: 0.824266841666667

00:42:03.490 --> 00:42:04.690 single cell data,  
NOTE Confidence: 0.824266841666667

00:42:04.690 --> 00:42:06.839 you can see that the cells that  
NOTE Confidence: 0.824266841666667

00:42:06.839 --> 00:42:08.998 express FGF 23 also express,  
NOTE Confidence: 0.824266841666667

00:42:08.998 --> 00:42:10.846 and Ophelia cell markers,  
NOTE Confidence: 0.824266841666667

00:42:10.850 --> 00:42:12.886 Pecan 1 and amusin.

NOTE Confidence: 0.824266841666667

00:42:12.886 --> 00:42:17.340 And they do not express classic bone markers.

NOTE Confidence: 0.824266841666667

00:42:17.340 --> 00:42:19.215 These blue populations of the

NOTE Confidence: 0.824266841666667

00:42:19.215 --> 00:42:20.340 osteon lineage populations,

NOTE Confidence: 0.824266841666667

00:42:20.340 --> 00:42:21.980 which traditionally are thought to

NOTE Confidence: 0.824266841666667

00:42:21.980 --> 00:42:23.620 be the populations producing FGF.

NOTE Confidence: 0.824266841666667

00:42:23.620 --> 00:42:23.996 23,

NOTE Confidence: 0.824266841666667

00:42:23.996 --> 00:42:26.252 And I'll point out one interesting

NOTE Confidence: 0.824266841666667

00:42:26.252 --> 00:42:27.760 observation you found here,

NOTE Confidence: 0.824266841666667

00:42:27.760 --> 00:42:29.932 is that erythropoietin express

NOTE Confidence: 0.824266841666667

00:42:29.932 --> 00:42:32.055 receptor expression is also detected

NOTE Confidence: 0.824266841666667

00:42:32.055 --> 00:42:33.780 in these sinusoidal endothelial cells,

NOTE Confidence: 0.824266841666667

00:42:33.780 --> 00:42:35.621 which is why I mentioned the hypo

NOTE Confidence: 0.824266841666667

00:42:35.621 --> 00:42:37.720 levels earlier in the correlation with FGF.

NOTE Confidence: 0.824266841666667

00:42:37.720 --> 00:42:38.730 23 upregulation.

NOTE Confidence: 0.723181633333333

00:42:42.180 --> 00:42:44.958 So to assess expression of the

NOTE Confidence: 0.723181633333333

00:42:44.960 --> 00:42:46.898 FGF 23 reporter allele in the  
NOTE Confidence: 0.7231816333333333

00:42:46.898 --> 00:42:48.190 context of tissue architecture  
NOTE Confidence: 0.7231816333333333

00:42:48.244 --> 00:42:50.020 we employed immunohistochemistry,  
NOTE Confidence: 0.7231816333333333

00:42:50.020 --> 00:42:52.372 good old immunohistochemistry with anti GFP  
NOTE Confidence: 0.7231816333333333

00:42:52.372 --> 00:42:54.939 antibody and fixed bone marrow sections.  
NOTE Confidence: 0.7231816333333333

00:42:54.940 --> 00:42:57.236 And you can see that mice carrying  
NOTE Confidence: 0.7231816333333333

00:42:57.236 --> 00:42:59.304 the reporter allele showed staining  
NOTE Confidence: 0.7231816333333333

00:42:59.304 --> 00:43:02.014 sign your little initial cells.  
NOTE Confidence: 0.7231816333333333

00:43:02.020 --> 00:43:03.988 And the staining was not observed in mice  
NOTE Confidence: 0.7231816333333333

00:43:03.988 --> 00:43:06.037 that do not carry the reporter allele.  
NOTE Confidence: 0.7231816333333333

00:43:06.040 --> 00:43:08.539 The staining is more intense and the  
NOTE Confidence: 0.7231816333333333

00:43:08.539 --> 00:43:10.853 iron deficient temporal 6 knockout mice  
NOTE Confidence: 0.7231816333333333

00:43:10.853 --> 00:43:12.813 than the heterozygous control mice.  
NOTE Confidence: 0.7231816333333333

00:43:12.820 --> 00:43:15.439 And looking at lower power in one of the  
NOTE Confidence: 0.7231816333333333

00:43:15.439 --> 00:43:17.580 temporal 6 knockouts with the reporter,  
NOTE Confidence: 0.7231816333333333

00:43:17.580 --> 00:43:19.404 you can appreciate that this and

NOTE Confidence: 0.7231816333333333  
00:43:19.404 --> 00:43:21.103 it still still staining  
NOTE Confidence: 0.7231816333333333  
00:43:21.103 --> 00:43:23.208 extends throughout the bone marrow.  
NOTE Confidence: 0.802502598421053  
00:43:25.320 --> 00:43:27.406 We also looked at other organs from  
NOTE Confidence: 0.802502598421053  
00:43:27.406 --> 00:43:29.336 these animals and we detected GFP  
NOTE Confidence: 0.802502598421053  
00:43:29.336 --> 00:43:31.286 expression rare cells of the thymus,  
NOTE Confidence: 0.802502598421053  
00:43:31.290 --> 00:43:33.585 but not in in a variety of other organs,  
NOTE Confidence: 0.802502598421053  
00:43:33.590 --> 00:43:34.535 including liver, spleen,  
NOTE Confidence: 0.802502598421053  
00:43:34.535 --> 00:43:35.795 heart, muscle or kidney.  
NOTE Confidence: 0.802502598421053  
00:43:35.800 --> 00:43:37.688 And I again want to give a special  
NOTE Confidence: 0.802502598421053  
00:43:37.688 --> 00:43:39.556 shout out to Amos Brooks from  
NOTE Confidence: 0.802502598421053  
00:43:39.556 --> 00:43:40.896 Yale Tissue pathology service,  
NOTE Confidence: 0.802502598421053  
00:43:40.900 --> 00:43:42.965 who optimizes IHC staining which  
NOTE Confidence: 0.802502598421053  
00:43:42.965 --> 00:43:45.640 which turned out to be really,  
NOTE Confidence: 0.802502598421053  
00:43:45.640 --> 00:43:48.624 really beautiful. So.  
NOTE Confidence: 0.802502598421053  
00:43:48.624 --> 00:43:53.106 We had shown temper 6 mice expressing  
NOTE Confidence: 0.802502598421053

00:43:53.106 --> 00:43:55.886 shave evidence of expressing FGF.  
NOTE Confidence: 0.802502598421053

00:43:55.890 --> 00:43:57.146 23 instinctual endothelial cells.  
NOTE Confidence: 0.802502598421053

00:43:57.146 --> 00:43:59.030 The catch here is that these  
NOTE Confidence: 0.802502598421053

00:43:59.080 --> 00:44:00.650 mice have upside and elevation,  
NOTE Confidence: 0.802502598421053

00:44:00.650 --> 00:44:03.650 so the question is now.  
NOTE Confidence: 0.802502598421053

00:44:03.650 --> 00:44:04.574 Our bone marrow,  
NOTE Confidence: 0.802502598421053

00:44:04.574 --> 00:44:07.418 signal hill and ethyl cells is cited FGF 23,  
NOTE Confidence: 0.802502598421053

00:44:07.418 --> 00:44:09.138 elevation in anemic might have  
NOTE Confidence: 0.802502598421053

00:44:09.138 --> 00:44:10.890 attacked outside of regulation.  
NOTE Confidence: 0.802502598421053

00:44:10.890 --> 00:44:12.906 So to test this we use the  
NOTE Confidence: 0.802502598421053

00:44:12.910 --> 00:44:15.240 FGF 23 Egfp reporter mice,  
NOTE Confidence: 0.802502598421053

00:44:15.240 --> 00:44:16.962 and this case these mice carried  
NOTE Confidence: 0.802502598421053

00:44:16.962 --> 00:44:18.570 2 well tempered 6 wheels,  
NOTE Confidence: 0.802502598421053

00:44:18.570 --> 00:44:19.866 so they're not anemic.  
NOTE Confidence: 0.802502598421053

00:44:19.866 --> 00:44:22.352 They have normal iron status and we  
NOTE Confidence: 0.802502598421053

00:44:22.352 --> 00:44:24.938 subjected them to large volume colotomy

NOTE Confidence: 0.802502598421053

00:44:24.938 --> 00:44:26.774 with intraperitoneal saline volume

NOTE Confidence: 0.802502598421053

00:44:26.774 --> 00:44:29.029 replacement to induce acute anemia,

NOTE Confidence: 0.802502598421053

00:44:29.030 --> 00:44:31.766 and you can see that 18 hours after flatter

NOTE Confidence: 0.802502598421053

00:44:31.766 --> 00:44:34.220 you were successful inducing anemia.

NOTE Confidence: 0.802502598421053

00:44:34.220 --> 00:44:36.405 People elevation and elevation of

NOTE Confidence: 0.802502598421053

00:44:36.405 --> 00:44:39.718 plasma after you have 23 in the plasma.

NOTE Confidence: 0.802502598421053

00:44:39.720 --> 00:44:40.956 And looking at their bone marrow

NOTE Confidence: 0.802502598421053

00:44:40.956 --> 00:44:42.060 section at this time point,

NOTE Confidence: 0.802502598421053

00:44:42.060 --> 00:44:44.263 you can see upregulation of FGF

NOTE Confidence: 0.802502598421053

00:44:44.263 --> 00:44:46.384 23 and sinusoidal of the sorry of

NOTE Confidence: 0.802502598421053

00:44:46.384 --> 00:44:48.287 the reporter allele in sinusoidal

NOTE Confidence: 0.802502598421053

00:44:48.287 --> 00:44:50.347 endothelial cells of the phlebotomist

NOTE Confidence: 0.802502598421053

00:44:50.347 --> 00:44:53.100 mice with the reporter compared to non

NOTE Confidence: 0.802502598421053

00:44:53.100 --> 00:44:56.440 phlebotomist mice carrying reporter allele.

NOTE Confidence: 0.802502598421053

00:44:56.440 --> 00:44:58.380 So this raises some questions.

NOTE Confidence: 0.802502598421053

00:44:58.380 --> 00:45:00.473 Does does FGF 23 have a local  
NOTE Confidence: 0.802502598421053

00:45:00.473 --> 00:45:02.320 role in the bone marrow?  
NOTE Confidence: 0.802502598421053

00:45:02.320 --> 00:45:04.805 Is this a protective or  
NOTE Confidence: 0.802502598421053

00:45:04.805 --> 00:45:06.296 a pathological response?  
NOTE Confidence: 0.802502598421053

00:45:06.300 --> 00:45:08.612 There is a paper that came out in  
NOTE Confidence: 0.802502598421053

00:45:08.612 --> 00:45:10.765 blood from a Japanese group last  
NOTE Confidence: 0.802502598421053

00:45:10.765 --> 00:45:12.926 year that suggested that FGF 23  
NOTE Confidence: 0.802502598421053

00:45:12.926 --> 00:45:14.864 from a rifter blast is involved  
NOTE Confidence: 0.802502598421053

00:45:14.864 --> 00:45:16.400 in hematopoietic progenitor cell  
NOTE Confidence: 0.802502598421053

00:45:16.400 --> 00:45:18.460 mobilization for the bone marrow,  
NOTE Confidence: 0.802502598421053

00:45:18.460 --> 00:45:18.768 particularly,  
NOTE Confidence: 0.802502598421053

00:45:18.768 --> 00:45:21.540 this is in the context of induction of G.  
NOTE Confidence: 0.802502598421053

00:45:21.540 --> 00:45:23.710 CSF.  
NOTE Confidence: 0.802502598421053

00:45:23.710 --> 00:45:26.125 So exactly how their data fit together  
NOTE Confidence: 0.802502598421053

00:45:26.125 --> 00:45:27.900 with ours remains to be seen.  
NOTE Confidence: 0.802502598421053

00:45:27.900 --> 00:45:30.004 I I will say that in in their



NOTE Confidence: 0.802502598421053

00:45:30.004 --> 00:45:31.977 paper they do also have expression

NOTE Confidence: 0.802502598421053

00:45:31.977 --> 00:45:34.696 of FGF 23 detected in in flow,

NOTE Confidence: 0.802502598421053

00:45:34.700 --> 00:45:35.930 sort of populations.

NOTE Confidence: 0.802502598421053

00:45:35.930 --> 00:45:37.570 That would include the

NOTE Confidence: 0.802502598421053

00:45:37.570 --> 00:45:38.800 sinusoidal endothelial cells,

NOTE Confidence: 0.802502598421053

00:45:38.800 --> 00:45:40.924 although they don't specifically

NOTE Confidence: 0.802502598421053

00:45:40.924 --> 00:45:43.048 look at that population.

NOTE Confidence: 0.802502598421053

00:45:43.050 --> 00:45:45.402 So with that I just wanted to

NOTE Confidence: 0.802502598421053

00:45:45.402 --> 00:45:47.694 acknowledge a huge number of people

NOTE Confidence: 0.802502598421053

00:45:47.694 --> 00:45:49.709 that made this work possible.

NOTE Confidence: 0.802502598421053

00:45:49.710 --> 00:45:51.330 It always takes the village

NOTE Confidence: 0.802502598421053

00:45:51.330 --> 00:45:52.950 to do to do research,

NOTE Confidence: 0.802502598421053

00:45:52.950 --> 00:45:54.670 starting with the original patients,

NOTE Confidence: 0.802502598421053

00:45:54.670 --> 00:45:56.299 their family members,

NOTE Confidence: 0.802502598421053

00:45:56.299 --> 00:45:58.394 and referring physicians at Yale.

NOTE Confidence: 0.802502598421053

00:45:58.394 --> 00:46:00.018 I've mentioned Jade in my lab who  
NOTE Confidence: 0.802502598421053

00:46:00.018 --> 00:46:01.570 was a phenomenal PhD student,  
NOTE Confidence: 0.802502598421053

00:46:01.570 --> 00:46:05.490 Larissa and Outstanding Research assistant.  
NOTE Confidence: 0.802502598421053

00:46:05.490 --> 00:46:07.032 My mentor at Nancy who got  
NOTE Confidence: 0.802502598421053

00:46:07.032 --> 00:46:08.470 me started in the field.  
NOTE Confidence: 0.802502598421053

00:46:08.470 --> 00:46:10.090 I've mentioned collaborations with Mark,  
NOTE Confidence: 0.802502598421053

00:46:10.090 --> 00:46:12.340 Plumbing Group and Matheny at  
NOTE Confidence: 0.802502598421053

00:46:12.340 --> 00:46:13.690 Children's Hospital Boston.  
NOTE Confidence: 0.802502598421053

00:46:13.690 --> 00:46:15.805 Stefano Rebello was instrumental in  
NOTE Confidence: 0.802502598421053

00:46:15.805 --> 00:46:18.720 providing me with the Palace comic mice.  
NOTE Confidence: 0.802502598421053

00:46:18.720 --> 00:46:19.374 At Yale,  
NOTE Confidence: 0.802502598421053

00:46:19.374 --> 00:46:21.336 Jackie's been an excellent collaborator here,  
NOTE Confidence: 0.802502598421053

00:46:21.340 --> 00:46:22.560 as well as common Bergson,  
NOTE Confidence: 0.802502598421053

00:46:22.560 --> 00:46:24.140 endocrinology and then my main  
NOTE Confidence: 0.802502598421053

00:46:24.140 --> 00:46:25.720 collaborators have been the Yale  
NOTE Confidence: 0.802502598421053

00:46:25.780 --> 00:46:27.440 Cooperative Center of Excellence.

NOTE Confidence: 0.802502598421053  
00:46:27.440 --> 00:46:27.788 Hematology,  
NOTE Confidence: 0.802502598421053  
00:46:27.788 --> 00:46:29.876 where I've been serving on the  
NOTE Confidence: 0.802502598421053  
00:46:29.876 --> 00:46:30.920 steering committee Dianne,  
NOTE Confidence: 0.802502598421053  
00:46:30.920 --> 00:46:32.033 Vanessa and Juliana,  
NOTE Confidence: 0.802502598421053  
00:46:32.033 --> 00:46:34.630 and her in Diane's lab were absolutely  
NOTE Confidence: 0.778610553571429  
00:46:34.699 --> 00:46:36.399 incredible for our studies.  
NOTE Confidence: 0.778610553571429  
00:46:36.400 --> 00:46:38.520 Steffie Helenus Group has contributed.  
NOTE Confidence: 0.778610553571429  
00:46:38.520 --> 00:46:40.240 Gene Hendrickson's group Pat Gallagher  
NOTE Confidence: 0.778610553571429  
00:46:40.240 --> 00:46:42.451 and also some of the clinical  
NOTE Confidence: 0.778610553571429  
00:46:42.451 --> 00:46:45.037 hematologists who referred me some very  
NOTE Confidence: 0.778610553571429  
00:46:45.037 --> 00:46:46.977 interesting studies where I've been  
NOTE Confidence: 0.778610553571429  
00:46:46.977 --> 00:46:49.014 looking at some exome data on some.  
NOTE Confidence: 0.778610553571429  
00:46:49.020 --> 00:46:51.370 Never look phenotypes as well.  
NOTE Confidence: 0.778610553571429  
00:46:51.370 --> 00:46:54.493 So with that I will stop and take questions.  
NOTE Confidence: 0.78017205  
00:47:03.180 --> 00:47:07.110 Very nice. I have several  
NOTE Confidence: 0.78017205

00:47:07.110 --> 00:47:08.820 questions actually first.  
NOTE Confidence: 0.484349052

00:47:11.160 --> 00:47:13.456 So many different families here  
NOTE Confidence: 0.484349052

00:47:13.456 --> 00:47:16.421 in your planning and reaction  
NOTE Confidence: 0.484349052

00:47:16.421 --> 00:47:18.200 relationship with erythrocytes.  
NOTE Confidence: 0.484349052

00:47:18.200 --> 00:47:22.068 Tempress backup cameras 6.  
NOTE Confidence: 0.484349052

00:47:22.070 --> 00:47:25.010 That's also it appears the delivery  
NOTE Confidence: 0.484349052

00:47:25.010 --> 00:47:27.570 of Iron Company backer pitch.  
NOTE Confidence: 0.484349052

00:47:27.570 --> 00:47:29.058 So the Brotherhood islands  
NOTE Confidence: 0.484349052

00:47:29.058 --> 00:47:30.546 in the bone marrow.  
NOTE Confidence: 0.484349052

00:47:30.550 --> 00:47:33.052 Of course he contact with therapist  
NOTE Confidence: 0.484349052

00:47:33.052 --> 00:47:35.469 and order to survive and grow,  
NOTE Confidence: 0.484349052

00:47:35.470 --> 00:47:37.745 so could some of this effect and  
NOTE Confidence: 0.484349052

00:47:37.745 --> 00:47:39.770 ship complete the differentiation  
NOTE Confidence: 0.484349052

00:47:39.770 --> 00:47:41.950 via failure of the Riverside  
NOTE Confidence: 0.484349052

00:47:41.950 --> 00:47:43.694 support by the macrophage.  
NOTE Confidence: 0.484349052

00:47:43.700 --> 00:47:44.108 The other?

NOTE Confidence: 0.484349052  
00:47:44.108 --> 00:47:45.128 Maybe they need to sense  
NOTE Confidence: 0.484349052  
00:47:45.128 --> 00:47:46.180 the iron in the back.  
NOTE Confidence: 0.96249638  
00:47:50.090 --> 00:47:53.697 I think it's possible, but well,  
NOTE Confidence: 0.96249638  
00:47:53.697 --> 00:47:55.405 you're thinking about specifically  
NOTE Confidence: 0.96249638  
00:47:55.405 --> 00:47:57.540 upside and effect or just  
NOTE Confidence: 0.96249638  
00:47:57.613 --> 00:47:59.130 a low iron effect. I think  
NOTE Confidence: 0.611700668  
00:47:59.140 --> 00:48:01.530 you know about your knockout.  
NOTE Confidence: 0.771885047142857  
00:48:03.450 --> 00:48:04.717 They would have trap. They would have.  
NOTE Confidence: 0.771885047142857  
00:48:04.720 --> 00:48:06.490 They should have some relative.  
NOTE Confidence: 0.771885047142857  
00:48:06.490 --> 00:48:08.709 They they may have some relative Miron  
NOTE Confidence: 0.771885047142857  
00:48:08.709 --> 00:48:11.248 trapping in those in bone marrow macrophages,  
NOTE Confidence: 0.6541913087  
00:48:11.260 --> 00:48:14.850 yeah, but if there is we could that be a.  
NOTE Confidence: 0.6541913087  
00:48:14.850 --> 00:48:18.690 I remember in style selection.  
NOTE Confidence: 0.6541913087  
00:48:18.690 --> 00:48:21.216 The grip right precursor is not  
NOTE Confidence: 0.6541913087  
00:48:21.216 --> 00:48:23.880 in contact with that macro page.  
NOTE Confidence: 0.657250543333333

00:48:27.120 --> 00:48:30.312 You predicted it would shift it to  
NOTE Confidence: 0.657250543333333

00:48:30.312 --> 00:48:33.540 a plant. Spontaneous. By default.  
NOTE Confidence: 0.437752976666667

00:48:36.160 --> 00:48:37.318 Violence and everything.  
NOTE Confidence: 0.702928065103448

00:48:38.200 --> 00:48:40.594 No, I I will say that the effect of  
NOTE Confidence: 0.702928065103448

00:48:40.594 --> 00:48:42.649 hepcidin on bone marrow macrophages is  
NOTE Confidence: 0.702928065103448

00:48:42.649 --> 00:48:45.092 much less well studied than the effect  
NOTE Confidence: 0.702928065103448

00:48:45.092 --> 00:48:47.395 of macrophages in the spleen or liver.  
NOTE Confidence: 0.702928065103448

00:48:47.400 --> 00:48:48.385 You know, just people who  
NOTE Confidence: 0.702928065103448

00:48:48.385 --> 00:48:49.173 were studying mouse models.  
NOTE Confidence: 0.702928065103448

00:48:49.180 --> 00:48:50.776 It's somewhat easier to to be looking  
NOTE Confidence: 0.702928065103448

00:48:50.776 --> 00:48:52.060 at these assessments in the screen,  
NOTE Confidence: 0.702928065103448

00:48:52.060 --> 00:48:54.062 so I don't think it's been quite  
NOTE Confidence: 0.702928065103448

00:48:54.062 --> 00:48:55.616 as well characterized in mouse  
NOTE Confidence: 0.702928065103448

00:48:55.616 --> 00:48:57.206 models and have sided regulation.  
NOTE Confidence: 0.247896505

00:48:58.290 --> 00:49:00.870 Just regulation.  
NOTE Confidence: 0.247896505

00:49:00.870 --> 00:49:05.220 And then. Clearly the.

NOTE Confidence: 0.247896505

00:49:05.220 --> 00:49:07.052 Most of these models show the

NOTE Confidence: 0.247896505

00:49:07.052 --> 00:49:08.808 iron passing through the cell.

NOTE Confidence: 0.247896505

00:49:08.810 --> 00:49:12.186 Either it's faster, it's it's

NOTE Confidence: 0.247896505

00:49:12.186 --> 00:49:16.010 liberated in the auto light lights.

NOTE Confidence: 0.247896505

00:49:16.010 --> 00:49:17.430 And then it is airborne

NOTE Confidence: 0.247896505

00:49:17.430 --> 00:49:19.354 and puts it out right?

NOTE Confidence: 0.247896505

00:49:19.354 --> 00:49:22.318 So we're talking about circulating iron.

NOTE Confidence: 0.247896505

00:49:22.320 --> 00:49:25.320 To this cell is every cell have breakfast

NOTE Confidence: 0.247896505

00:49:25.320 --> 00:49:27.398 control its internal iron levels,

NOTE Confidence: 0.247896505

00:49:27.398 --> 00:49:29.484 and that must be a big important

NOTE Confidence: 0.247896505

00:49:29.484 --> 00:49:31.400 thing in parasitosis control.

NOTE Confidence: 0.247896505

00:49:31.400 --> 00:49:32.770 And now it's a bit

NOTE Confidence: 0.663194246153846

00:49:32.780 --> 00:49:36.434 right. So so this is this is

NOTE Confidence: 0.663194246153846

00:49:36.434 --> 00:49:39.899 another whole side of iron biology.

NOTE Confidence: 0.663194246153846

00:49:39.900 --> 00:49:41.996 There's a great review called 2 to Tango,

NOTE Confidence: 0.663194246153846

00:49:42.000 --> 00:49:43.184 written by Martina Buffet,  
NOTE Confidence: 0.663194246153846

00:49:43.184 --> 00:49:44.960 Baller and and several other leaders  
NOTE Confidence: 0.663194246153846

00:49:44.960 --> 00:49:47.064 in the field where you know upside and  
NOTE Confidence: 0.663194246153846

00:49:47.064 --> 00:49:48.369 regulations systemic are in regulation  
NOTE Confidence: 0.663194246153846

00:49:48.369 --> 00:49:49.858 but upside and acts on Fairport.  
NOTE Confidence: 0.663194246153846

00:49:49.860 --> 00:49:51.106 And of course which is expressed not  
NOTE Confidence: 0.663194246153846

00:49:51.106 --> 00:49:52.569 only in the cell types I showed you.  
NOTE Confidence: 0.663194246153846

00:49:52.570 --> 00:49:54.682 In fact, probably on most if  
NOTE Confidence: 0.663194246153846

00:49:54.682 --> 00:49:57.070 not all cell types in the body.  
NOTE Confidence: 0.663194246153846

00:49:57.070 --> 00:49:59.668 Cells also regulate iron status through  
NOTE Confidence: 0.663194246153846

00:49:59.668 --> 00:50:01.920 the iron regulatory protein system,  
NOTE Confidence: 0.663194246153846

00:50:01.920 --> 00:50:03.328 which stabilizes the messenger  
NOTE Confidence: 0.663194246153846

00:50:03.328 --> 00:50:05.088 RNA proteins that are involved  
NOTE Confidence: 0.663194246153846

00:50:05.088 --> 00:50:07.148 in iron transport into the cells.  
NOTE Confidence: 0.663194246153846

00:50:07.150 --> 00:50:09.150 The transferrin receptors normally  
NOTE Confidence: 0.663194246153846

00:50:09.150 --> 00:50:11.150 stabilized during iron deficiency



NOTE Confidence: 0.663194246153846

00:50:11.150 --> 00:50:13.229 and during iron deficiency.

NOTE Confidence: 0.663194246153846

00:50:13.230 --> 00:50:15.965 The translation of proteins involved

NOTE Confidence: 0.663194246153846

00:50:15.965 --> 00:50:18.654 in iron exports, such as fair cordon,

NOTE Confidence: 0.663194246153846

00:50:18.654 --> 00:50:20.723 is reduced so the cell have means

NOTE Confidence: 0.663194246153846

00:50:20.723 --> 00:50:22.067 of compensating throughout.

NOTE Confidence: 0.663194246153846

00:50:22.070 --> 00:50:23.696 Tosis is very interesting because the

NOTE Confidence: 0.663194246153846

00:50:23.696 --> 00:50:25.308 transfer receptor is not behaving the

NOTE Confidence: 0.663194246153846

00:50:25.308 --> 00:50:27.002 way you predict based on that system.

NOTE Confidence: 0.663194246153846

00:50:27.010 --> 00:50:28.658 That's something actually asked

NOTE Confidence: 0.663194246153846

00:50:28.658 --> 00:50:31.130 during his work talk last week,

NOTE Confidence: 0.663194246153846

00:50:31.130 --> 00:50:32.240 I think, yeah.

NOTE Confidence: 0.53470733175

00:50:33.630 --> 00:50:37.086 That that's the big thing now

NOTE Confidence: 0.53470733175

00:50:37.086 --> 00:50:39.308 turn immunity. To regulate that.

NOTE Confidence: 0.35102296

00:50:42.980 --> 00:50:45.230 Absolutely. Right?

NOTE Confidence: 0.40567447425

00:50:49.560 --> 00:50:53.280 Check chat, there's only one request that

NOTE Confidence: 0.66330616

00:50:53.490 --> 00:50:55.200 people can hear questions.  
NOTE Confidence: 0.59701

00:50:57.640 --> 00:51:03.460 Otherwise the ohh OK. The problem.  
NOTE Confidence: 0.33173567

00:51:09.160 --> 00:51:13.690 Yeah. Stick around.  
NOTE Confidence: 0.33173567

00:51:13.690 --> 00:51:15.922 There's a respect box here in  
NOTE Confidence: 0.33173567

00:51:15.922 --> 00:51:18.290 the body that are regulated.  
NOTE Confidence: 0.33173567

00:51:18.290 --> 00:51:20.570 This is level sheets, traumatic.  
NOTE Confidence: 0.33173567

00:51:20.570 --> 00:51:23.310 It's. My death was gross.  
NOTE Confidence: 0.77323309375

00:51:25.910 --> 00:51:30.730 So, so I think this area has been explored.  
NOTE Confidence: 0.77323309375

00:51:30.730 --> 00:51:33.842 Oh, sorry, so the question is how that  
NOTE Confidence: 0.77323309375

00:51:33.842 --> 00:51:36.210 there are areas in the body where his  
NOTE Confidence: 0.77323309375

00:51:36.278 --> 00:51:38.938 levels can change dramatically and our iron  
NOTE Confidence: 0.77323309375

00:51:38.938 --> 00:51:41.688 levels in those areas regulated as well.  
NOTE Confidence: 0.77323309375

00:51:41.690 --> 00:51:43.714 So the individual I know who's probably done  
NOTE Confidence: 0.77323309375

00:51:43.714 --> 00:51:45.847 the most work in this area is Yatrik Shah,  
NOTE Confidence: 0.77323309375

00:51:45.850 --> 00:51:47.290 Michigan, who's particularly focused  
NOTE Confidence: 0.77323309375

00:51:47.290 --> 00:51:50.410 on the role of HIF one and hip two

NOTE Confidence: 0.77323309375

00:51:50.410 --> 00:51:52.551 in the intestinal cells where they

NOTE Confidence: 0.77323309375

00:51:52.551 --> 00:51:54.849 also appear to be modulating iron.

NOTE Confidence: 0.77323309375

00:51:54.850 --> 00:51:56.859 Of taking the cells in addition to

NOTE Confidence: 0.77323309375

00:51:56.859 --> 00:51:59.101 Fairport and so there is a more complex

NOTE Confidence: 0.77323309375

00:51:59.101 --> 00:52:01.293 story than what I told you today but,

NOTE Confidence: 0.77323309375

00:52:01.293 --> 00:52:03.051 but that's definitely an area under

NOTE Confidence: 0.77323309375

00:52:03.051 --> 00:52:04.210 active investigation as well.

NOTE Confidence: 0.793803008

00:52:07.170 --> 00:52:09.380 I was thinking more like you.

NOTE Confidence: 0.27733737

00:52:12.180 --> 00:52:13.010 Took my soul.

NOTE Confidence: 0.758194675

00:52:16.460 --> 00:52:16.870 Of course.

NOTE Confidence: 0.55843451

00:52:20.560 --> 00:52:21.400 Just in those.

NOTE Confidence: 0.131269635

00:52:23.860 --> 00:52:24.710 Higher results.

NOTE Confidence: 0.85485744

00:52:26.960 --> 00:52:27.170 Right?

NOTE Confidence: 0.885264783333333

00:52:29.650 --> 00:52:31.138 I think it's it's certainly possible.

NOTE Confidence: 0.885264783333333

00:52:31.140 --> 00:52:33.660 I'm not sure if anyone he's really looking.

NOTE Confidence: 0.7280365075

00:52:36.390 --> 00:52:39.547 So you know, truthfully we use an  
NOTE Confidence: 0.7280365075

00:52:39.547 --> 00:52:41.779 old-fashioned Perls Prussian blue stain.  
NOTE Confidence: 0.7280365075

00:52:41.780 --> 00:52:44.174 There certainly dies that people will  
NOTE Confidence: 0.7280365075

00:52:44.174 --> 00:52:47.330 use for for self culture experiments.  
NOTE Confidence: 0.7280365075

00:52:47.330 --> 00:52:48.638 Often we use expression  
NOTE Confidence: 0.7280365075

00:52:48.638 --> 00:52:49.946 of the transfer receptor.  
NOTE Confidence: 0.7280365075

00:52:49.950 --> 00:52:52.140 Messenger RNA is a simple  
NOTE Confidence: 0.7280365075

00:52:52.140 --> 00:52:53.892 surrogate because that's so  
NOTE Confidence: 0.7280365075

00:52:53.892 --> 00:52:56.532 responsive to the intracellular ion  
NOTE Confidence: 0.7280365075

00:52:56.532 --> 00:52:58.656 concentrations of iron concentration.  
NOTE Confidence: 0.7280365075

00:52:58.660 --> 00:53:00.914 But I you know that work may  
NOTE Confidence: 0.7280365075

00:53:00.914 --> 00:53:03.098 be going on in in this field.  
NOTE Confidence: 0.7280365075

00:53:03.100 --> 00:53:04.906 I think I tend to gravitate  
NOTE Confidence: 0.7280365075

00:53:04.906 --> 00:53:06.572 towards meetings where the focus  
NOTE Confidence: 0.7280365075

00:53:06.572 --> 00:53:08.180 is on hematological disorders.  
NOTE Confidence: 0.7280365075

00:53:08.180 --> 00:53:09.620 So so that I'm just probably

NOTE Confidence: 0.7280365075

00:53:09.620 --> 00:53:11.820 less familiar with that area now.

NOTE Confidence: 0.414910599

00:53:15.890 --> 00:53:18.090 Affairs versus fairy these families.

NOTE Confidence: 0.817501398571428

00:53:20.000 --> 00:53:22.996 So there are oxidases and reductases around.

NOTE Confidence: 0.817501398571428

00:53:23.000 --> 00:53:24.412 Many of these transmembrane.

NOTE Confidence: 0.817501398571428

00:53:24.412 --> 00:53:26.177 Passage steps that are also

NOTE Confidence: 0.817501398571428

00:53:26.177 --> 00:53:27.600 part of the story. There.

NOTE Confidence: 0.817501398571428

00:53:27.600 --> 00:53:28.850 There are many additional players.

NOTE Confidence: 0.817501398571428

00:53:28.850 --> 00:53:31.088 These cartoons you know for iron

NOTE Confidence: 0.817501398571428

00:53:31.088 --> 00:53:33.021 uptake that I've shipped friend

NOTE Confidence: 0.817501398571428

00:53:33.021 --> 00:53:34.978 showed you yeah. I mean no.

NOTE Confidence: 0.89717738

00:53:45.260 --> 00:53:46.634 OK, thank you so much for

NOTE Confidence: 0.89717738

00:53:46.634 --> 00:53:47.550 the opportunity to present.

NOTE Confidence: 0.577667

00:53:51.570 --> 00:53:51.860 So.

NOTE Confidence: 0.15366933

00:53:58.540 --> 00:53:59.160 Discovered.