WEBVTT

NOTE duration: ”00:59:11.378”

NOTE Confidence: 0.9051418

00:00:00.719 --> 00:00:02.159 It's my great honor to

NOTE Confidence: 0.9051418

00:00:02.159 --> 00:00:04.240 introduce Doctor. Peng Jie as

NOTE Confidence: 0.9051418

00:00:04.240 --> 00:00:05.779 our Grand Rounds speaker today.

NOTE Confidence: 0.97184014

00:00:06.559 --> 00:00:07.919 Doctor. Jie is a physician

NOTE Confidence: 0.97184014

00:00:07.919 --> 00:00:08.420 scientist,

NOTE Confidence: 0.97160554

00:00:09.039 --> 00:00:10.639 and tenured professor of pathology

NOTE Confidence: 0.97160554

00:00:10.639 --> 00:00:11.860 at Northwestern University,

NOTE Confidence: 0.95496416

00:00:12.320 --> 00:00:13.725 where he serves as vice

NOTE Confidence: 0.95496416

00:00:13.725 --> 00:00:15.245 chair for research and holds

NOTE Confidence: 0.95496416

00:00:15.245 --> 00:00:16.545 the Marie a Fleming

NOTE Confidence: 0.9541774

00:00:16.925 --> 00:00:17.425 professorship.

NOTE Confidence: 0.9817021

00:00:18.605 --> 00:00:20.385 His work is advancing experimental

NOTE Confidence: 0.9817021

00:00:20.525 --> 00:00:22.545 hematology as well as clinical

NOTE Confidence: 0.9817021

00:00:22.605 --> 00:00:23.105 hematopathology.

NOTE Confidence: 0.9839093

00:00:24.285 --> 00:00:25.885 After earning an MD from

NOTE Confidence: 0.9839093

00:00:25.885 --> 00:00:26.785 Peking University,

NOTE Confidence: 0.94923615

00:00:27.400 --> 00:00:29.080 PhD from Albert Einstein, and

NOTE Confidence: 0.94923615

00:00:29.080 --> 00:00:31.100 completing a postdoc at MIT,

NOTE Confidence: 0.94923615

00:00:31.400 --> 00:00:33.720 he joined Northwestern's pathology physician

NOTE Confidence: 0.94923615

00:00:33.720 --> 00:00:35.320 scientist training program in twenty

NOTE Confidence: 0.94923615

00:00:35.320 --> 00:00:37.739 eleven, later gaining board certification

NOTE Confidence: 0.94923615

00:00:37.960 --> 00:00:40.040 in clinical hematop clinical pathology

NOTE Confidence: 0.94923615

00:00:40.040 --> 00:00:40.780 and hematopathology.

NOTE Confidence: 0.9793668

00:00:41.885 --> 00:00:43.325 He has received many awards

NOTE Confidence: 0.9793668

00:00:43.325 --> 00:00:45.345 and recognitions, including being inducted

NOTE Confidence: 0.9793668

00:00:45.405 --> 00:00:47.085 into the American Society for

NOTE Confidence: 0.9793668

00:00:47.085 --> 00:00:48.065 Clinical Investigation.

NOTE Confidence: 0.94215304

00:00:49.405 --> 00:00:50.845 He also received the Pamela

NOTE Confidence: 0.94215304

00:00:50.845 --> 00:00:53.085 Catton Memorial Leukemia Research Award

NOTE Confidence: 0.94215304

00:00:53.085 --> 00:00:54.580 in twenty nineteen and the

NOTE Confidence: 0.94215304

00:00:54.580 --> 00:00:56.500 Ramsey Cotran Award from USCAP

NOTE Confidence: 0.94215304

00:00:56.500 --> 00:00:57.940 in twenty twenty two. He

NOTE Confidence: 0.94215304

00:00:57.940 --> 00:00:59.640 is currently an associate editor,

NOTE Confidence: 0.94167507

00:01:00.580 --> 00:01:01.320 of JCI,

NOTE Confidence: 0.9972392

00:01:01.860 --> 00:01:03.540 and he was recently appointed

NOTE Confidence: 0.9972392

00:01:03.540 --> 00:01:04.440 to the NIDDK

NOTE Confidence: 0.75322783

00:01:04.980 --> 00:01:06.040 Advisory Council.

NOTE Confidence: 0.94986403

00:01:06.515 --> 00:01:08.034 Since starting his independent lab

NOTE Confidence: 0.94986403

00:01:08.034 --> 00:01:09.635 in twenty eleven, doctor Gee

NOTE Confidence: 0.94986403

00:01:09.635 --> 00:01:11.895 has maintained continuous extramural support,

NOTE Confidence: 0.94986403

00:01:12.115 --> 00:01:13.875 securing twelve NIH grants. He

NOTE Confidence: 0.94986403

00:01:13.875 --> 00:01:15.155 is currently PI on three

NOTE Confidence: 0.94986403

00:01:15.155 --> 00:01:16.694 r o ones, an NSF

NOTE Confidence: 0.94986403

00:01:16.755 --> 00:01:18.515 award, two DOD grants, and

NOTE Confidence: 0.94986403

00:01:18.515 --> 00:01:19.895 fourteen foundation awards.

NOTE Confidence: 0.9932639

00:01:20.490 --> 00:01:21.550 A committed mentor,

NOTE Confidence: 0.9847038

00:01:22.090 --> 00:01:23.069 he directs Northwestern's

NOTE Confidence: 0.9219584

00:01:23.370 --> 00:01:25.610 pathology physician scientist training program

NOTE Confidence: 0.9219584

00:01:25.610 --> 00:01:27.550 and cofounded the Starzl Academy,

NOTE Confidence: 0.9219584

00:01:27.850 --> 00:01:29.130 guiding the next generation of

NOTE Confidence: 0.9219584

00:01:29.130 --> 00:01:30.190 clinician scientists.

NOTE Confidence: 0.9944274

00:01:30.569 --> 00:01:31.610 Today, we are honored to

NOTE Confidence: 0.9944274

00:01:31.610 --> 00:01:32.490 have him speak to us

NOTE Confidence: 0.9944274

00:01:32.490 --> 00:01:34.110 directly on this exciting story

NOTE Confidence: 0.9944274

00:01:34.345 --> 00:01:35.704 about the role of inflammation

NOTE Confidence: 0.9944274

00:01:35.704 --> 00:01:37.145 in the evolution from clonal

NOTE Confidence: 0.9944274

00:01:37.145 --> 00:01:37.645 hematopoiesis.

NOTE Confidence: 0.9983419

00:01:38.024 --> 00:01:38.845 Thank you.

NOTE Confidence: 0.7748345

00:01:45.225 --> 00:01:47.110 Thank you, Amina and Huapin

NOTE Confidence: 0.7748345

00:01:47.110 --> 00:01:48.330 and whole department,

NOTE Confidence: 0.7485759

00:01:48.790 --> 00:01:49.530 year pathology,

NOTE Confidence: 0.9038263

00:01:49.990 --> 00:01:51.590 for inviting me. It's really

NOTE Confidence: 0.9038263

00:01:51.590 --> 00:01:52.790 great great honor to be

NOTE Confidence: 0.9038263

00:01:52.790 --> 00:01:53.290 here.

NOTE Confidence: 0.9867228

00:01:53.909 --> 00:01:54.310 So,

NOTE Confidence: 0.94062996

00:01:54.710 --> 00:01:55.990 so today I'm just going

NOTE Confidence: 0.94062996

00:01:55.990 --> 00:01:57.110 to talk to you about

NOTE Confidence: 0.94062996

00:01:57.110 --> 00:01:58.550 the role of information in

NOTE Confidence: 0.94062996

00:01:58.550 --> 00:01:59.690 evolution from

NOTE Confidence: 0.9613294

00:02:00.005 --> 00:02:02.265 clonal hematopoiesis to MDS and

NOTE Confidence: 0.9613294

00:02:02.405 --> 00:02:02.905 AML.

NOTE Confidence: 0.9228226

00:02:04.005 --> 00:02:05.365 Before I start, I just

NOTE Confidence: 0.9228226

00:02:05.365 --> 00:02:06.725 have a quick disclosure. I'm

NOTE Confidence: 0.9228226

00:02:06.725 --> 00:02:07.845 a founder and co board

NOTE Confidence: 0.9228226

00:02:07.845 --> 00:02:09.365 members of two companies that

NOTE Confidence: 0.9228226

00:02:09.365 --> 00:02:10.825 I, co established.

NOTE Confidence: 0.9917038

00:02:11.605 --> 00:02:13.044 But today today's talk has

NOTE Confidence: 0.9917038

00:02:13.044 --> 00:02:14.345 nothing to do with that.

NOTE Confidence: 0.96921945

00:02:15.680 --> 00:02:17.519 Before I talk, really go

NOTE Confidence: 0.96921945

00:02:17.519 --> 00:02:19.060 into details about inflammation

NOTE Confidence: 0.87324697

00:02:19.360 --> 00:02:20.900 and myeloid disease,

NOTE Confidence: 0.97947645

00:02:21.200 --> 00:02:22.739 I just want to cover

NOTE Confidence: 0.97947645

00:02:22.799 --> 00:02:23.919 a little bit about what

NOTE Confidence: 0.97947645

00:02:23.919 --> 00:02:25.760 the major research is ongoing

NOTE Confidence: 0.97947645

00:02:25.760 --> 00:02:27.379 in my lab. So,

NOTE Confidence: 0.9498105

00:02:28.724 --> 00:02:29.764 ever since I started my

NOTE Confidence: 0.9498105

00:02:29.764 --> 00:02:31.125 own lab, back in two

NOTE Confidence: 0.9498105

00:02:31.125 --> 00:02:32.105 thousand twelve,

NOTE Confidence: 0.8784591

00:02:32.805 --> 00:02:35.364 I continue my postdoctoral work

NOTE Confidence: 0.8784591

00:02:35.364 --> 00:02:37.044 on universal poiseis. I was

NOTE Confidence: 0.8784591

00:02:37.044 --> 00:02:38.185 with Harvey Lodish,

NOTE Confidence: 0.9508877

00:02:38.885 --> 00:02:40.424 working on chromatin condensation

NOTE Confidence: 0.97150123

00:02:40.724 --> 00:02:41.544 and enucleation

NOTE Confidence: 0.6988436

00:02:41.845 --> 00:02:43.065 in rest cell development.

NOTE Confidence: 0.90988535

00:02:43.580 --> 00:02:44.780 So we have still our

NOTE Confidence: 0.90988535

00:02:44.780 --> 00:02:46.540 effort on doing in doing

NOTE Confidence: 0.90988535

00:02:46.540 --> 00:02:48.560 mechanistic studies in metapoisis

NOTE Confidence: 0.89313483

00:02:48.860 --> 00:02:50.299 as well as terminal erosive

NOTE Confidence: 0.89313483

00:02:50.299 --> 00:02:50.799 poiesis.

NOTE Confidence: 0.995491

00:02:51.340 --> 00:02:52.459 Much of the effort on

NOTE Confidence: 0.995491

00:02:52.459 --> 00:02:54.379 that part is, working on

NOTE Confidence: 0.995491

00:02:54.379 --> 00:02:54.879 how

NOTE Confidence: 0.8681585

00:02:55.340 --> 00:02:57.819 using novel technologies including spatial

NOTE Confidence: 0.8681585

00:02:57.819 --> 00:02:59.084 omics studies to see

NOTE Confidence: 0.9903462

00:02:59.805 --> 00:03:01.105 to to tell the differences

NOTE Confidence: 0.9903462

00:03:01.165 --> 00:03:02.385 between mouse and human

NOTE Confidence: 0.96744835

00:03:02.845 --> 00:03:03.424 in hematopoiesis

NOTE Confidence: 0.9228729

00:03:03.724 --> 00:03:04.864 as well as urosopoiesis.

NOTE Confidence: 0.94938034

00:03:06.125 --> 00:03:07.805 The second major part is

NOTE Confidence: 0.94938034

00:03:07.805 --> 00:03:08.465 on myeloprolifera

NOTE Confidence: 0.8881964

00:03:08.845 --> 00:03:10.685 neoplasm. We focus on this

NOTE Confidence: 0.8881964

00:03:10.685 --> 00:03:12.544 protein called PLAGSTRING two,

NOTE Confidence: 0.9657104

00:03:13.020 --> 00:03:14.300 which is really a downstream

NOTE Confidence: 0.9657104

00:03:14.300 --> 00:03:15.600 target of JAK STAT5.

NOTE Confidence: 0.87749255

00:03:16.220 --> 00:03:17.980 And this protein is highly

NOTE Confidence: 0.87749255

00:03:17.980 --> 00:03:20.080 upregulated in patient with myeloproliferative

NOTE Confidence: 0.87749255

00:03:20.300 --> 00:03:21.740 neoplasm as well as in

NOTE Confidence: 0.87749255

00:03:21.740 --> 00:03:22.480 most models,

NOTE Confidence: 0.985455

00:03:23.180 --> 00:03:24.480 with JAK2 mutation.

NOTE Confidence: 0.9490664

00:03:25.455 --> 00:03:26.355 So we are,

NOTE Confidence: 0.838316

00:03:26.735 --> 00:03:28.415 we figure out how it

NOTE Confidence: 0.838316

00:03:28.415 --> 00:03:29.775 works as a com o

NOTE Confidence: 0.838316

00:03:29.775 --> 00:03:31.315 con, sacralin complex,

NOTE Confidence: 0.9450425

00:03:32.334 --> 00:03:34.655 activate AKT pathway, and we

NOTE Confidence: 0.9450425

00:03:34.655 --> 00:03:35.855 develop a small molecule,

NOTE Confidence: 0.7718928

00:03:36.175 --> 00:03:37.715 inhibitor of plaque two,

NOTE Confidence: 0.85770845

00:03:38.190 --> 00:03:39.629 to treat, hopefully to treat

NOTE Confidence: 0.85770845

00:03:39.629 --> 00:03:40.129 myelodysplast

NOTE Confidence: 0.8926299

00:03:40.430 --> 00:03:40.930 syndromes,

NOTE Confidence: 0.90082914

00:03:41.390 --> 00:03:41.890 myeloproliferative

NOTE Confidence: 0.9954338

00:03:42.190 --> 00:03:42.690 neoplasms.

NOTE Confidence: 0.9501773

00:03:44.030 --> 00:03:45.470 The third major part of

NOTE Confidence: 0.9501773

00:03:45.470 --> 00:03:46.989 my research lab, which is

NOTE Confidence: 0.9501773

00:03:46.989 --> 00:03:48.030 I'm going to talk about

NOTE Confidence: 0.9501773

00:03:48.030 --> 00:03:49.650 in detail today, is inflammation

NOTE Confidence: 0.72198564

00:03:50.030 --> 00:03:51.310 in innate immune signaling in

NOTE Confidence: 0.72198564

00:03:51.310 --> 00:03:51.810 myeloneoplasms.

NOTE Confidence: 0.88930404

00:03:53.665 --> 00:03:54.545 Major model, we use,

NOTE Confidence: 0.91943336

00:03:55.985 --> 00:03:56.805 mouse models,

NOTE Confidence: 0.9635751

00:03:57.105 --> 00:03:59.425 to mimic MDS as well

NOTE Confidence: 0.9635751

00:03:59.425 --> 00:03:59.925 as,

NOTE Confidence: 0.9267263

00:04:00.705 --> 00:04:02.165 bone marrow organoid models,

NOTE Confidence: 0.89786834

00:04:02.785 --> 00:04:05.125 and also human human's data,

NOTE Confidence: 0.999683

00:04:05.665 --> 00:04:06.405 as well.

NOTE Confidence: 0.98298514

00:04:08.280 --> 00:04:08.780 So,

NOTE Confidence: 0.957232

00:04:10.040 --> 00:04:12.219 so talking about myeloid diseases

NOTE Confidence: 0.957232

00:04:12.439 --> 00:04:14.040 as well as inflammation, so

NOTE Confidence: 0.957232

00:04:14.040 --> 00:04:15.420 we're really talking about,

NOTE Confidence: 0.8548673

00:04:16.039 --> 00:04:17.479 some of the disease or

NOTE Confidence: 0.8548673

00:04:17.479 --> 00:04:17.979 entities,

NOTE Confidence: 0.9496521

00:04:18.600 --> 00:04:20.895 that, listed here. So we're,

NOTE Confidence: 0.94590396

00:04:21.455 --> 00:04:23.395 so starting from non clonal

NOTE Confidence: 0.94590396

00:04:23.455 --> 00:04:23.955 idiopathic

NOTE Confidence: 0.91903335

00:04:24.335 --> 00:04:26.355 cytopenia of unknown significance,

NOTE Confidence: 0.8938133

00:04:27.455 --> 00:04:28.175 these kind of,

NOTE Confidence: 0.91076076

00:04:28.895 --> 00:04:30.015 we we don't call it

NOTE Confidence: 0.91076076

00:04:30.015 --> 00:04:31.455 disease, but this kind of,

NOTE Confidence: 0.9253056

00:04:32.335 --> 00:04:32.835 situation,

NOTE Confidence: 0.96333927

00:04:33.615 --> 00:04:35.450 where we cannot call them

NOTE Confidence: 0.96333927

00:04:35.450 --> 00:04:37.550 patients, but individuals will have

NOTE Confidence: 0.96333927

00:04:37.610 --> 00:04:38.110 unknown,

NOTE Confidence: 0.90256655

00:04:38.890 --> 00:04:39.390 cytopenias,

NOTE Confidence: 0.9909453

00:04:39.850 --> 00:04:41.070 and they don't have any

NOTE Confidence: 0.9909453

00:04:41.210 --> 00:04:42.270 detectable mutations.

NOTE Confidence: 0.85648006

00:04:43.690 --> 00:04:45.290 And these patients oftentimes, they

NOTE Confidence: 0.85648006

00:04:45.290 --> 00:04:45.690 can,

NOTE Confidence: 0.9760225

00:04:46.570 --> 00:04:47.890 they they can also have

NOTE Confidence: 0.9760225

00:04:48.090 --> 00:04:49.950 can further develop into

NOTE Confidence: 0.88995993

00:04:51.585 --> 00:04:51.904 chronic,

NOTE Confidence: 0.79333466

00:04:52.464 --> 00:04:54.384 so called clonal hematopoiesis of

NOTE Confidence: 0.79333466

00:04:54.384 --> 00:04:56.164 different inter determined potential.

NOTE Confidence: 0.9518281

00:04:56.625 --> 00:04:57.745 And in this patient, you

NOTE Confidence: 0.9518281

00:04:57.745 --> 00:04:58.944 can also you can you

NOTE Confidence: 0.9518281

00:04:58.944 --> 00:04:59.925 can also have,

NOTE Confidence: 0.8269972

00:05:01.025 --> 00:05:02.324 with or without cytopenia,

NOTE Confidence: 0.92337644

00:05:02.625 --> 00:05:02.944 but,

NOTE Confidence: 0.83698756

00:05:03.450 --> 00:05:05.710 oftentimes these patient, these individuals

NOTE Confidence: 0.83698756

00:05:05.850 --> 00:05:06.170 have,

NOTE Confidence: 0.96771485

00:05:06.890 --> 00:05:07.950 mutations detectable

NOTE Confidence: 0.9703718

00:05:08.330 --> 00:05:09.610 that I'm gonna talk about

NOTE Confidence: 0.9703718

00:05:09.610 --> 00:05:10.910 in detail later on.

NOTE Confidence: 0.9131904

00:05:11.290 --> 00:05:12.890 And then we have, entities

NOTE Confidence: 0.9131904

00:05:12.890 --> 00:05:14.650 called the clonal cytopenia on

NOTE Confidence: 0.9131904

00:05:14.650 --> 00:05:16.430 determined potential significance.

NOTE Confidence: 0.8800609

00:05:17.050 --> 00:05:18.430 And in these individuals,

NOTE Confidence: 0.8706161

00:05:19.025 --> 00:05:20.305 we not only have set

NOTE Confidence: 0.8706161

00:05:20.305 --> 00:05:21.925 opinions as well as have,

NOTE Confidence: 0.94216114

00:05:22.705 --> 00:05:23.205 mutations

NOTE Confidence: 0.9495004

00:05:24.064 --> 00:05:25.425 in many genes that I'm

NOTE Confidence: 0.9495004

00:05:25.425 --> 00:05:27.044 gonna talk about later on.

NOTE Confidence: 0.9837246

00:05:27.425 --> 00:05:29.344 So these patients all can,

NOTE Confidence: 0.9301954

00:05:30.064 --> 00:05:31.525 many of them can further

NOTE Confidence: 0.9301954

00:05:31.824 --> 00:05:33.525 progress to MDS,

NOTE Confidence: 0.8242002

00:05:34.410 --> 00:05:35.950 that's myelodysplastic syndrome.

NOTE Confidence: 0.92851686

00:05:36.490 --> 00:05:37.950 And we have low blast

NOTE Confidence: 0.92851686

00:05:38.250 --> 00:05:40.029 MDS and high blast MDS,

NOTE Confidence: 0.92851686

00:05:40.090 --> 00:05:41.370 and that's still based on

NOTE Confidence: 0.92851686

00:05:41.370 --> 00:05:42.510 previous WSL,

NOTE Confidence: 0.9980809

00:05:43.450 --> 00:05:43.950 classifications.

NOTE Confidence: 0.9246989

00:05:44.810 --> 00:05:45.950 And in these patients,

NOTE Confidence: 0.95406

00:05:46.745 --> 00:05:47.785 most of them will have

NOTE Confidence: 0.95406

00:05:47.785 --> 00:05:49.725 mutations or chromosome abnormalities.

NOTE Confidence: 0.95159584

00:05:50.585 --> 00:05:51.865 And, of course, they have

NOTE Confidence: 0.95159584

00:05:51.865 --> 00:05:54.125 bone marrow abnormalities with dysplasia

NOTE Confidence: 0.95159584

00:05:54.185 --> 00:05:56.125 in different kinds of lineages,

NOTE Confidence: 0.8772174

00:05:57.065 --> 00:05:59.225 as well as different percentage

NOTE Confidence: 0.8772174

00:05:59.225 --> 00:06:00.285 of, blasts

NOTE Confidence: 0.9632759

00:06:01.099 --> 00:06:02.800 that gives them different entities.

NOTE Confidence: 0.9346819

00:06:03.660 --> 00:06:05.039 And then, eventually,

NOTE Confidence: 0.99817383

00:06:06.139 --> 00:06:07.819 many of those patients can

NOTE Confidence: 0.99817383

00:06:07.819 --> 00:06:09.759 progress to acute myeloid leukemia

NOTE Confidence: 0.8997165

00:06:10.220 --> 00:06:11.339 where they have more than

NOTE Confidence: 0.8997165

00:06:11.339 --> 00:06:12.940 twenty percent of blasts either

NOTE Confidence: 0.8997165

00:06:12.940 --> 00:06:13.979 in the profile blood or

NOTE Confidence: 0.8997165

00:06:13.979 --> 00:06:14.960 in bone marrow.

NOTE Confidence: 0.95366955

00:06:15.425 --> 00:06:16.245 And they oftentimes,

NOTE Confidence: 0.961637

00:06:16.785 --> 00:06:18.885 share similar mutations or chromosome

NOTE Confidence: 0.961637

00:06:18.945 --> 00:06:19.445 abnormalities,

NOTE Confidence: 0.91373384

00:06:20.065 --> 00:06:21.845 as those patient with MDS.

NOTE Confidence: 0.98113203

00:06:23.745 --> 00:06:24.145 So,

NOTE Confidence: 0.9670082

00:06:24.705 --> 00:06:27.045 across all these, different entities,

NOTE Confidence: 0.9670082

00:06:27.265 --> 00:06:28.705 inflammation really play a big

NOTE Confidence: 0.9670082

00:06:28.705 --> 00:06:29.985 role, and there are a

NOTE Confidence: 0.9670082

00:06:29.985 --> 00:06:30.885 lot of studies,

NOTE Confidence: 0.8616988

00:06:32.700 --> 00:06:33.600 has been reported,

NOTE Confidence: 0.97076386

00:06:33.980 --> 00:06:35.760 in different aspects of inflammation,

NOTE Confidence: 0.84646285

00:06:37.180 --> 00:06:38.460 that seem, you know, that

NOTE Confidence: 0.84646285

00:06:38.460 --> 00:06:39.820 plays a role in different

NOTE Confidence: 0.84646285

00:06:39.820 --> 00:06:40.320 entities.

NOTE Confidence: 0.9227539

00:06:41.339 --> 00:06:41.820 But,

NOTE Confidence: 0.95967704

00:06:42.300 --> 00:06:43.120 as I mentioned,

NOTE Confidence: 0.83372074

00:06:43.580 --> 00:06:45.660 these entities have a lot

NOTE Confidence: 0.83372074

00:06:45.660 --> 00:06:46.160 of

NOTE Confidence: 0.9267127

00:06:46.985 --> 00:06:48.824 commonly shared in between these,

NOTE Confidence: 0.9267127

00:06:49.145 --> 00:06:50.664 entities as well as acute

NOTE Confidence: 0.9267127

00:06:50.664 --> 00:06:51.645 myeloid leukemia.

NOTE Confidence: 0.9973488

00:06:52.185 --> 00:06:53.805 The most common ones are,

NOTE Confidence: 0.97243243

00:06:54.425 --> 00:06:55.865 these are all called clonal

NOTE Confidence: 0.97243243

00:06:55.865 --> 00:06:56.365 hematopoietic

NOTE Confidence: 0.9870166

00:06:56.745 --> 00:06:58.365 clonal hematopoiesis mutations.

NOTE Confidence: 0.94518846

00:06:59.370 --> 00:07:00.490 The most common ones are

NOTE Confidence: 0.94518846

00:07:00.490 --> 00:07:02.089 DMT three a and tattoo

NOTE Confidence: 0.94518846

00:07:02.089 --> 00:07:02.589 mutations,

NOTE Confidence: 0.99193317

00:07:03.370 --> 00:07:04.330 as you can see from

NOTE Confidence: 0.99193317

00:07:04.330 --> 00:07:04.830 this,

NOTE Confidence: 0.8728032

00:07:05.850 --> 00:07:07.790 review paper we recently published.

NOTE Confidence: 0.93409383

00:07:09.920 --> 00:07:10.170 And,

NOTE Confidence: 0.92499983

00:07:10.810 --> 00:07:11.310 these

NOTE Confidence: 0.95551515

00:07:11.995 --> 00:07:12.815 common mutations,

NOTE Confidence: 0.8880536

00:07:13.435 --> 00:07:14.955 for example, DMT three a

NOTE Confidence: 0.8880536

00:07:14.955 --> 00:07:15.615 and tattoo,

NOTE Confidence: 0.9835375

00:07:16.074 --> 00:07:18.014 are commonly related to epigenetic

NOTE Confidence: 0.9835375

00:07:18.235 --> 00:07:19.595 modification, but they are also

NOTE Confidence: 0.9835375

00:07:19.595 --> 00:07:21.914 closely related to inflammation and

NOTE Confidence: 0.9835375

00:07:21.914 --> 00:07:23.435 inflammatory changes in the bone

NOTE Confidence: 0.9835375

00:07:23.435 --> 00:07:24.655 marrow overall environment.

NOTE Confidence: 0.9378322

00:07:26.315 --> 00:07:26.815 So,

NOTE Confidence: 0.88303524

00:07:28.850 --> 00:07:29.330 and and,

NOTE Confidence: 0.8908841

00:07:30.290 --> 00:07:31.490 and we are talking also

NOTE Confidence: 0.8908841

00:07:31.490 --> 00:07:33.470 about MDS when these,

NOTE Confidence: 0.8618805

00:07:34.130 --> 00:07:36.450 clonal hematopoietic mutation, patient with

NOTE Confidence: 0.8618805

00:07:36.450 --> 00:07:38.389 these mutations for the develop.

NOTE Confidence: 0.9944562

00:07:38.770 --> 00:07:40.870 And this MDS is really

NOTE Confidence: 0.74021274

00:07:41.330 --> 00:07:42.070 a a clonal,

NOTE Confidence: 0.95305854

00:07:43.485 --> 00:07:45.165 disorder that arrived from the

NOTE Confidence: 0.95305854

00:07:45.165 --> 00:07:45.905 bone marrow.

NOTE Confidence: 0.9886994

00:07:46.285 --> 00:07:47.165 And you have,

NOTE Confidence: 0.8690926

00:07:48.365 --> 00:07:50.705 a group of symptoms including

NOTE Confidence: 0.8690926

00:07:50.765 --> 00:07:53.645 cytopenia, dysplasia, and major and

NOTE Confidence: 0.8690926

00:07:53.645 --> 00:07:55.345 these can all cause to

NOTE Confidence: 0.8690926

00:07:55.485 --> 00:07:56.705 infective hematopoiesis

NOTE Confidence: 0.8754086

00:07:57.730 --> 00:07:59.650 and increase development to, acute

NOTE Confidence: 0.8754086

00:07:59.650 --> 00:08:01.650 myeloid leukemia. So mainly we

NOTE Confidence: 0.8754086

00:08:01.650 --> 00:08:03.090 have three lineages as you

NOTE Confidence: 0.8754086

00:08:03.090 --> 00:08:04.290 may you you know that

NOTE Confidence: 0.8754086

00:08:04.290 --> 00:08:04.870 in in

NOTE Confidence: 0.92950785

00:08:05.330 --> 00:08:06.710 the bone marrow environment.

NOTE Confidence: 0.9504749

00:08:07.250 --> 00:08:08.130 We have a red cell

NOTE Confidence: 0.9504749

00:08:08.130 --> 00:08:09.990 lineage. If you have dysplasia

NOTE Confidence: 0.9504749

00:08:10.050 --> 00:08:11.170 in the red cell lineage,

NOTE Confidence: 0.9504749

00:08:11.170 --> 00:08:12.230 you will have anemia.

NOTE Confidence: 0.94900215

00:08:13.534 --> 00:08:14.655 And we also have,

NOTE Confidence: 0.85671604

00:08:15.534 --> 00:08:16.034 myelolinage,

NOTE Confidence: 0.9359822

00:08:16.735 --> 00:08:18.014 that give rise to white

NOTE Confidence: 0.9359822

00:08:18.014 --> 00:08:19.935 blood cells. So dysplasia in

NOTE Confidence: 0.9359822

00:08:19.935 --> 00:08:20.914 white, myelolinage

NOTE Confidence: 0.9356977

00:08:21.215 --> 00:08:21.955 will cause,

NOTE Confidence: 0.9196343

00:08:22.735 --> 00:08:24.094 reduction in the red in

NOTE Confidence: 0.9196343

00:08:24.094 --> 00:08:25.134 the white blood cell count,

NOTE Confidence: 0.9196343

00:08:25.134 --> 00:08:26.014 and then it can lead

NOTE Confidence: 0.9196343

00:08:26.014 --> 00:08:27.235 to frequent infection,

NOTE Confidence: 0.90999335

00:08:28.080 --> 00:08:29.280 as well as weaken the

NOTE Confidence: 0.90999335

00:08:29.280 --> 00:08:29.780 immunity.

NOTE Confidence: 0.9619854

00:08:30.320 --> 00:08:31.780 And reduction in the megakaryocytic

NOTE Confidence: 0.98628443

00:08:32.320 --> 00:08:33.860 lineage that can cause,

NOTE Confidence: 0.9420444

00:08:34.640 --> 00:08:36.640 the reduction in in in

NOTE Confidence: 0.9420444

00:08:36.640 --> 00:08:38.240 platelets count, and that can

NOTE Confidence: 0.9420444

00:08:38.240 --> 00:08:39.679 lead to easy bleeding and,

NOTE Confidence: 0.9420444

00:08:39.920 --> 00:08:40.420 bruising.

NOTE Confidence: 0.97118

00:08:40.960 --> 00:08:42.339 So these are all important

NOTE Confidence: 0.97118

00:08:42.400 --> 00:08:43.925 symptoms that we, should keep

NOTE Confidence: 0.97118

00:08:43.925 --> 00:08:44.565 in mind,

NOTE Confidence: 0.94268775

00:08:44.885 --> 00:08:46.404 and when we try to

NOTE Confidence: 0.94268775

00:08:46.404 --> 00:08:48.084 model these diseases in using

NOTE Confidence: 0.94268775

00:08:48.084 --> 00:08:48.584 animal

NOTE Confidence: 0.94630814

00:08:48.964 --> 00:08:50.105 models or other,

NOTE Confidence: 0.94066495

00:08:50.644 --> 00:08:51.785 nonhuman models.

NOTE Confidence: 0.9611935

00:08:53.764 --> 00:08:55.285 So we got interested in

NOTE Confidence: 0.9611935

00:08:55.285 --> 00:08:56.024 this field,

NOTE Confidence: 0.6958355

00:08:58.245 --> 00:08:58.745 especially,

NOTE Confidence: 0.78826547

00:08:59.980 --> 00:09:01.900 this specific entity called a

NOTE Confidence: 0.78826547

00:09:01.900 --> 00:09:03.100 delta five q m d

NOTE Confidence: 0.78826547

00:09:03.100 --> 00:09:03.920 s where

NOTE Confidence: 0.97143096

00:09:04.380 --> 00:09:05.020 the long,

NOTE Confidence: 0.98530984

00:09:05.580 --> 00:09:07.260 long arm of chromosome five

NOTE Confidence: 0.98530984

00:09:07.260 --> 00:09:08.480 is commonly deleted.

NOTE Confidence: 0.9978671

00:09:08.940 --> 00:09:09.820 And there are a lot

NOTE Confidence: 0.9978671

00:09:09.820 --> 00:09:10.320 of

NOTE Confidence: 0.6313819

00:09:11.340 --> 00:09:11.840 genes

NOTE Confidence: 0.9511673

00:09:12.220 --> 00:09:13.580 on chromosome five, as you

NOTE Confidence: 0.9511673

00:09:13.580 --> 00:09:14.320 can imagine.

NOTE Confidence: 0.94819385

00:09:14.675 --> 00:09:15.814 And one of the gene,

NOTE Confidence: 0.91788596

00:09:17.074 --> 00:09:18.834 is called, so one of

NOTE Confidence: 0.91788596

00:09:18.834 --> 00:09:20.754 the gene is, microRNA that

NOTE Confidence: 0.91788596

00:09:20.754 --> 00:09:22.115 has been shown before to

NOTE Confidence: 0.91788596

00:09:22.115 --> 00:09:22.855 be involved

NOTE Confidence: 0.98497325

00:09:23.795 --> 00:09:24.375 in thrombocytosis

NOTE Confidence: 0.7631676

00:09:24.915 --> 00:09:25.235 and,

NOTE Confidence: 0.8505366

00:09:26.035 --> 00:09:26.535 hypo,

NOTE Confidence: 0.74528176

00:09:27.154 --> 00:09:29.394 lobulated omega kerasocytes in in

NOTE Confidence: 0.74528176

00:09:29.394 --> 00:09:29.894 MDS.

NOTE Confidence: 0.8885205

00:09:31.459 --> 00:09:33.380 We are also interest interested

NOTE Confidence: 0.8885205

00:09:33.380 --> 00:09:34.579 in a gene called d

NOTE Confidence: 0.8885205

00:09:34.579 --> 00:09:36.019 I p h one, which

NOTE Confidence: 0.8885205

00:09:36.019 --> 00:09:37.459 encode protein called m dye

NOTE Confidence: 0.8885205

00:09:37.459 --> 00:09:38.579 one. So the the reason

NOTE Confidence: 0.8885205

00:09:38.579 --> 00:09:39.079 I'm

NOTE Confidence: 0.89317924

00:09:39.459 --> 00:09:40.980 getting to the MDS field

NOTE Confidence: 0.89317924

00:09:40.980 --> 00:09:41.720 is because,

NOTE Confidence: 0.8228061

00:09:43.355 --> 00:09:45.115 EIPH one, which encode m

NOTE Confidence: 0.8228061

00:09:45.115 --> 00:09:46.955 dye one, is actually involving

NOTE Confidence: 0.8228061

00:09:46.955 --> 00:09:47.934 acting cytoskeleton,

NOTE Confidence: 0.91814446

00:09:49.355 --> 00:09:50.575 modification. So

NOTE Confidence: 0.89217037

00:09:51.195 --> 00:09:52.795 we have discovered previously in

NOTE Confidence: 0.89217037

00:09:52.795 --> 00:09:53.835 our rest of your field

NOTE Confidence: 0.89217037

00:09:53.835 --> 00:09:55.115 that m dye one is

NOTE Confidence: 0.89217037

00:09:55.115 --> 00:09:57.370 important for rest of rest

NOTE Confidence: 0.89217037

00:09:57.370 --> 00:09:57.949 cell nucleation

NOTE Confidence: 0.8710589

00:09:58.329 --> 00:09:59.309 as well as,

NOTE Confidence: 0.7955045

00:10:00.170 --> 00:10:01.850 later stage of terminal universal

NOTE Confidence: 0.7955045

00:10:01.850 --> 00:10:02.350 poiseis.

NOTE Confidence: 0.93215925

00:10:02.730 --> 00:10:03.850 But it turns out that

NOTE Confidence: 0.93215925

00:10:03.850 --> 00:10:05.610 this gene is located on

NOTE Confidence: 0.93215925

00:10:05.610 --> 00:10:06.970 chromosome five q. So I

NOTE Confidence: 0.93215925

00:10:06.970 --> 00:10:08.730 am I've become very interested

NOTE Confidence: 0.93215925

00:10:08.730 --> 00:10:10.350 in chromosome five q division

NOTE Confidence: 0.9962287

00:10:10.809 --> 00:10:11.550 in MDS.

NOTE Confidence: 0.94779706

00:10:12.455 --> 00:10:13.895 So what we actually find

NOTE Confidence: 0.94779706

00:10:13.895 --> 00:10:15.575 out, that was back in

NOTE Confidence: 0.94779706

00:10:15.575 --> 00:10:16.875 more than ten years ago,

NOTE Confidence: 0.8194663

00:10:17.815 --> 00:10:19.815 using MDI one or dmp

NOTE Confidence: 0.8194663

00:10:19.975 --> 00:10:21.015 d I d I a

NOTE Confidence: 0.8194663

00:10:21.015 --> 00:10:22.955 ph one knockout mouse model,

NOTE Confidence: 0.8194663

00:10:23.255 --> 00:10:24.955 we found that these mice

NOTE Confidence: 0.8194663

00:10:25.175 --> 00:10:26.295 with when they are eight

NOTE Confidence: 0.8194663

00:10:26.535 --> 00:10:28.020 when they are about one

NOTE Confidence: 0.8194663

00:10:28.020 --> 00:10:28.760 year for

NOTE Confidence: 0.92179227

00:10:29.060 --> 00:10:31.300 old, they develop MDS like

NOTE Confidence: 0.92179227

00:10:31.300 --> 00:10:31.800 symptoms,

NOTE Confidence: 0.97896177

00:10:32.820 --> 00:10:34.440 where we found that actually

NOTE Confidence: 0.97896177

00:10:34.500 --> 00:10:35.000 CD14

NOTE Confidence: 0.92750263

00:10:35.460 --> 00:10:36.200 is overexpressed

NOTE Confidence: 0.87331015

00:10:36.660 --> 00:10:39.560 in apparently overexpressed on granular

NOTE Confidence: 0.87331015

00:10:39.620 --> 00:10:39.915 sites.

NOTE Confidence: 0.84949744

00:10:40.475 --> 00:10:41.755 Usually, a CD fourteen is

NOTE Confidence: 0.84949744

00:10:41.755 --> 00:10:44.014 over, overexpressed in monocytes.

NOTE Confidence: 0.8984469

00:10:44.875 --> 00:10:46.394 But in this, in this

NOTE Confidence: 0.8984469

00:10:46.394 --> 00:10:48.074 MOS model, CD fourteen is

NOTE Confidence: 0.8984469

00:10:48.074 --> 00:10:49.454 upregulated in granulocytes,

NOTE Confidence: 0.9565773

00:10:49.915 --> 00:10:51.195 and CD fourteen is a

NOTE Confidence: 0.9565773

00:10:51.195 --> 00:10:53.454 coreceptor with Tollac receptor four.

NOTE Confidence: 0.9742643

00:10:53.755 --> 00:10:54.495 And as

NOTE Confidence: 0.8983953

00:10:54.929 --> 00:10:56.610 TR four is commonly involved

NOTE Confidence: 0.8983953

00:10:56.610 --> 00:10:57.570 in the immune,

NOTE Confidence: 0.7006678

00:10:58.290 --> 00:10:59.970 abnormally in the immune signaling

NOTE Confidence: 0.7006678

00:10:59.970 --> 00:11:00.470 pathway,

NOTE Confidence: 0.9935473

00:11:00.929 --> 00:11:01.830 this activation

NOTE Confidence: 0.9386298

00:11:02.210 --> 00:11:04.050 or overexpression of CD fourteen

NOTE Confidence: 0.9386298

00:11:04.050 --> 00:11:04.790 leads to,

NOTE Confidence: 0.8993265

00:11:05.410 --> 00:11:07.570 inflammatory changes in this mouse

NOTE Confidence: 0.8993265

00:11:07.570 --> 00:11:09.350 model in their bone marrow,

NOTE Confidence: 0.8993265

00:11:09.375 --> 00:11:10.835 and that can lead to,

NOTE Confidence: 0.91820216

00:11:11.775 --> 00:11:12.275 granulocytopenia

NOTE Confidence: 0.97208625

00:11:12.975 --> 00:11:14.115 as well as dysplasia

NOTE Confidence: 0.8877377

00:11:14.735 --> 00:11:15.695 in in a variety of

NOTE Confidence: 0.8877377

00:11:15.695 --> 00:11:18.175 different lineages. And this, study

NOTE Confidence: 0.8877377

00:11:18.175 --> 00:11:20.575 was, led by, Ganesha Keith

NOTE Confidence: 0.8877377

00:11:20.575 --> 00:11:22.830 Forsen. He's currently has his

NOTE Confidence: 0.8877377

00:11:22.830 --> 00:11:24.429 own actually, he's in the

NOTE Confidence: 0.8877377

00:11:24.429 --> 00:11:26.270 business field, and actually he's

NOTE Confidence: 0.8877377

00:11:26.270 --> 00:11:27.490 running his own company.

NOTE Confidence: 0.98792404

00:11:29.550 --> 00:11:30.450 So with that,

NOTE Confidence: 0.92169124

00:11:31.150 --> 00:11:32.510 Yang Mei took over the

NOTE Confidence: 0.92169124

00:11:32.510 --> 00:11:33.010 project,

NOTE Confidence: 0.9907147

00:11:33.470 --> 00:11:35.505 after Ganesha left the lab.

NOTE Confidence: 0.9288251

00:11:36.065 --> 00:11:37.745 What Yang did is that,

NOTE Confidence: 0.9288251

00:11:37.745 --> 00:11:39.205 as I mentioned to you,

NOTE Confidence: 0.8096396

00:11:40.545 --> 00:11:42.945 m MDI1 is involved in

NOTE Confidence: 0.8096396

00:11:42.945 --> 00:11:44.325 the upper regulation of CD14,

NOTE Confidence: 0.60247743

00:11:44.785 --> 00:11:45.605 that corecept

NOTE Confidence: 0.8388999

00:11:45.985 --> 00:11:46.485 coreceptor

NOTE Confidence: 0.8219026

00:11:47.265 --> 00:11:49.445 with, colac receptor four pathway.

NOTE Confidence: 0.9162065

00:11:49.950 --> 00:11:50.990 And it has been shown

NOTE Confidence: 0.9162065

00:11:50.990 --> 00:11:52.510 that miR-one forty six,

NOTE Confidence: 0.91642433

00:11:52.910 --> 00:11:54.590 forty six a that I

NOTE Confidence: 0.91642433

00:11:54.590 --> 00:11:55.710 showed you before in the

NOTE Confidence: 0.91642433

00:11:55.710 --> 00:11:56.210 cartoon,

NOTE Confidence: 0.96317047

00:11:57.150 --> 00:11:58.910 is also involved in the

NOTE Confidence: 0.96317047

00:11:58.910 --> 00:11:59.410 upregulation

NOTE Confidence: 0.97374284

00:11:59.790 --> 00:12:01.950 or overactivation of Tollac receptor

NOTE Confidence: 0.97374284

00:12:01.950 --> 00:12:02.690 four pathway.

NOTE Confidence: 0.9965836

00:12:04.415 --> 00:12:04.815 So,

NOTE Confidence: 0.90720505

00:12:05.535 --> 00:12:07.934 Yang actually decided to cross

NOTE Confidence: 0.90720505

00:12:07.934 --> 00:12:09.615 these two knockout mice and

NOTE Confidence: 0.90720505

00:12:09.615 --> 00:12:11.315 make double knockout mice

NOTE Confidence: 0.8732627

00:12:11.695 --> 00:12:13.774 to more closely mimic patients

NOTE Confidence: 0.8732627

00:12:13.774 --> 00:12:15.695 with MDS, five weeks five

NOTE Confidence: 0.8732627

00:12:15.695 --> 00:12:16.355 q deletion.

NOTE Confidence: 0.9105113

00:12:17.210 --> 00:12:18.110 So this is,

NOTE Confidence: 0.8833299

00:12:19.050 --> 00:12:19.550 the

NOTE Confidence: 0.70602417

00:12:19.929 --> 00:12:21.309 ResCell count hemoglobin

NOTE Confidence: 0.6970798

00:12:21.929 --> 00:12:22.750 and metacritic

NOTE Confidence: 0.8697758

00:12:23.130 --> 00:12:23.370 count,

NOTE Confidence: 0.8515078

00:12:25.770 --> 00:12:26.270 entities,

NOTE Confidence: 0.70909065

00:12:26.730 --> 00:12:27.870 in this individually

NOTE Confidence: 0.97269505

00:12:28.250 --> 00:12:29.610 knockout mice. As you can

NOTE Confidence: 0.97269505

00:12:29.610 --> 00:12:30.809 see, compared to the to

NOTE Confidence: 0.97269505

00:12:30.809 --> 00:12:32.030 the wild type mice,

NOTE Confidence: 0.64246005

00:12:32.714 --> 00:12:33.934 the neuromphoresisait

NOTE Confidence: 0.8949063

00:12:34.714 --> 00:12:36.554 knockout mice as well as

NOTE Confidence: 0.8949063

00:12:36.554 --> 00:12:37.915 m by one knockout mice,

NOTE Confidence: 0.8949063

00:12:37.915 --> 00:12:39.675 they they show some phenotype

NOTE Confidence: 0.8949063

00:12:39.675 --> 00:12:40.815 but not as severe,

NOTE Confidence: 0.9991782

00:12:41.434 --> 00:12:42.554 compared to the wild type

NOTE Confidence: 0.9991782

00:12:42.554 --> 00:12:43.054 mice.

NOTE Confidence: 0.9905171

00:12:44.650 --> 00:12:45.450 And when he,

NOTE Confidence: 0.9319391

00:12:46.410 --> 00:12:48.429 checked the double knockout mice,

NOTE Confidence: 0.97044957

00:12:48.890 --> 00:12:50.010 you you can see really

NOTE Confidence: 0.97044957

00:12:50.010 --> 00:12:52.410 severe, significant difference compared to

NOTE Confidence: 0.97044957

00:12:52.410 --> 00:12:53.390 the single knockout.

NOTE Confidence: 0.9255031

00:12:53.929 --> 00:12:55.790 These mice with aging develop

NOTE Confidence: 0.9255031

00:12:55.850 --> 00:12:56.330 severe,

NOTE Confidence: 0.99985874

00:12:56.730 --> 00:12:57.230 anemia

NOTE Confidence: 0.94309336

00:12:57.575 --> 00:12:59.175 with reduction in RBC count

NOTE Confidence: 0.94309336

00:12:59.175 --> 00:13:01.175 and hemoglobin count as well

NOTE Confidence: 0.94309336

00:13:01.175 --> 00:13:01.995 as HCT.

NOTE Confidence: 0.9978544

00:13:02.855 --> 00:13:03.654 And if you look at

NOTE Confidence: 0.9978544

00:13:03.654 --> 00:13:05.595 their survival, these mice really,

NOTE Confidence: 0.9489027

00:13:06.615 --> 00:13:07.995 really die of the disease,

NOTE Confidence: 0.78672713

00:13:10.740 --> 00:13:12.660 at around one one around

NOTE Confidence: 0.78672713

00:13:12.660 --> 00:13:13.639 one year old

NOTE Confidence: 0.88334113

00:13:14.339 --> 00:13:15.860 compared to the single knockout

NOTE Confidence: 0.88334113

00:13:15.860 --> 00:13:16.360 mice.

NOTE Confidence: 0.9890393

00:13:18.019 --> 00:13:19.959 And, he also checked

NOTE Confidence: 0.95566744

00:13:20.339 --> 00:13:21.959 the different cytokine expression,

NOTE Confidence: 0.52459335

00:13:22.500 --> 00:13:23.000 inflammation

NOTE Confidence: 0.90754557

00:13:23.459 --> 00:13:24.855 in the bone marrow, And

NOTE Confidence: 0.90754557

00:13:24.855 --> 00:13:26.135 he found out that r

NOTE Confidence: 0.90754557

00:13:26.135 --> 00:13:27.355 six specifically,

NOTE Confidence: 0.7309792

00:13:29.095 --> 00:13:30.214 r six as well as

NOTE Confidence: 0.7309792

00:13:30.214 --> 00:13:32.615 TFR four are specifically highly

NOTE Confidence: 0.7309792

00:13:32.615 --> 00:13:33.115 operated

NOTE Confidence: 0.79457533

00:13:33.815 --> 00:13:35.334 in patient in mice with

NOTE Confidence: 0.79457533

00:13:35.334 --> 00:13:37.110 double knockout versus two genes.

NOTE Confidence: 0.9953735

00:13:38.230 --> 00:13:39.610 And he also checked

NOTE Confidence: 0.8767958

00:13:39.990 --> 00:13:41.589 the r six level in,

NOTE Confidence: 0.8767958

00:13:41.829 --> 00:13:43.029 g g one g r

NOTE Confidence: 0.8767958

00:13:43.029 --> 00:13:44.390 one positive mac one positive

NOTE Confidence: 0.8767958

00:13:44.390 --> 00:13:44.890 granulocytes.

NOTE Confidence: 0.89221036

00:13:45.990 --> 00:13:47.670 He found that, in both

NOTE Confidence: 0.89221036

00:13:47.670 --> 00:13:48.630 the bone marrow and the

NOTE Confidence: 0.89221036

00:13:48.630 --> 00:13:49.130 spleen,

NOTE Confidence: 0.9668895

00:13:49.475 --> 00:13:50.755 the double knockout mice have

NOTE Confidence: 0.9668895

00:13:50.755 --> 00:13:52.775 finally expressed our six levels,

NOTE Confidence: 0.9796303

00:13:53.395 --> 00:13:54.775 compared to the single knockout.

NOTE Confidence: 0.91054124

00:13:55.715 --> 00:13:56.995 This is also true for

NOTE Confidence: 0.91054124

00:13:56.995 --> 00:13:58.215 TNFr file expression.

NOTE Confidence: 0.93976265

00:13:58.835 --> 00:13:59.955 So this is a really,

NOTE Confidence: 0.93976265

00:14:00.195 --> 00:14:01.475 you know, it makes sense

NOTE Confidence: 0.93976265

00:14:01.475 --> 00:14:03.415 that double knockout mice, because

NOTE Confidence: 0.93976265

00:14:03.715 --> 00:14:04.375 they cotarget

NOTE Confidence: 0.89426845

00:14:06.819 --> 00:14:08.100 the TNF- Tollak receptor four

NOTE Confidence: 0.89426845

00:14:08.100 --> 00:14:09.779 pathway, they have this high

NOTE Confidence: 0.89426845

00:14:09.779 --> 00:14:10.279 upregulation,

NOTE Confidence: 0.96728796

00:14:10.740 --> 00:14:12.579 highly inflammatory changes in their

NOTE Confidence: 0.96728796

00:14:12.579 --> 00:14:14.019 bone marrow that lead to

NOTE Confidence: 0.96728796

00:14:14.019 --> 00:14:15.000 the eventual

NOTE Confidence: 0.91605186

00:14:15.459 --> 00:14:16.519 MDS development.

NOTE Confidence: 0.96025395

00:14:18.554 --> 00:14:18.995 So,

NOTE Confidence: 0.9400951

00:14:19.435 --> 00:14:20.634 here's the model that we,

NOTE Confidence: 0.9400951

00:14:20.875 --> 00:14:22.235 this paper was published in

NOTE Confidence: 0.9400951

00:14:22.235 --> 00:14:23.295 twenty eighteen

NOTE Confidence: 0.85367936

00:14:23.675 --> 00:14:24.334 in leukemia.

NOTE Confidence: 0.8846079

00:14:24.875 --> 00:14:27.435 So with the, we propose

NOTE Confidence: 0.8846079

00:14:27.435 --> 00:14:28.495 that with aging,

NOTE Confidence: 0.98419905

00:14:29.035 --> 00:14:31.115 and aging will lead to

NOTE Confidence: 0.98419905

00:14:31.115 --> 00:14:31.615 more

NOTE Confidence: 0.94702286

00:14:32.680 --> 00:14:34.280 damaged social molecular patterns and

NOTE Confidence: 0.94702286

00:14:34.280 --> 00:14:35.980 passage of social molecular pattern

NOTE Confidence: 0.94702286

00:14:36.280 --> 00:14:36.780 accumulation

NOTE Confidence: 0.83300686

00:14:37.560 --> 00:14:39.100 in individuals or particularly

NOTE Confidence: 0.94640326

00:14:39.880 --> 00:14:41.400 in this mouse model. And

NOTE Confidence: 0.94640326

00:14:41.400 --> 00:14:42.680 if you have both of

NOTE Confidence: 0.94640326

00:14:42.680 --> 00:14:44.760 these genes knocked out, you

NOTE Confidence: 0.94640326

00:14:44.760 --> 00:14:45.420 will have,

NOTE Confidence: 0.8572252

00:14:46.745 --> 00:14:47.865 especially you have a,

NOTE Confidence: 0.9219449

00:14:48.904 --> 00:14:51.065 myeloid derived suppressor cells. They

NOTE Confidence: 0.9219449

00:14:51.065 --> 00:14:52.345 are very sensitive to this

NOTE Confidence: 0.9219449

00:14:52.345 --> 00:14:53.545 environment, to the loss of

NOTE Confidence: 0.9219449

00:14:53.545 --> 00:14:54.745 these two genes, and they

NOTE Confidence: 0.9219449

00:14:54.745 --> 00:14:55.885 will over secrete

NOTE Confidence: 0.87538534

00:14:57.065 --> 00:14:58.840 TFR file as well as

NOTE Confidence: 0.87538534

00:14:58.840 --> 00:15:00.280 as r six. And these

NOTE Confidence: 0.87538534

00:15:00.280 --> 00:15:02.120 two cytokines actually have different

NOTE Confidence: 0.87538534

00:15:02.120 --> 00:15:02.620 mechanisms

NOTE Confidence: 0.96533704

00:15:03.400 --> 00:15:04.700 in, in,

NOTE Confidence: 0.9947541

00:15:05.320 --> 00:15:05.820 blocking

NOTE Confidence: 0.8565246

00:15:06.200 --> 00:15:07.880 common or universal voices for

NOTE Confidence: 0.8565246

00:15:08.280 --> 00:15:10.360 so for r six, they

NOTE Confidence: 0.8565246

00:15:10.360 --> 00:15:11.420 will lead to upregulation

NOTE Confidence: 0.64890957

00:15:11.720 --> 00:15:12.300 of ROS,

NOTE Confidence: 0.9380153

00:15:12.600 --> 00:15:13.825 that lead to upregulation

NOTE Confidence: 0.9497351

00:15:14.285 --> 00:15:15.885 activation of caspase three and

NOTE Confidence: 0.9497351

00:15:15.885 --> 00:15:17.325 seven. So that leads to

NOTE Confidence: 0.9497351

00:15:17.325 --> 00:15:18.464 the, apoptosis

NOTE Confidence: 0.80150706

00:15:18.765 --> 00:15:20.464 cell test. But for tnFR

NOTE Confidence: 0.80150706

00:15:20.525 --> 00:15:21.245 alpha that,

NOTE Confidence: 0.9680542

00:15:21.645 --> 00:15:22.385 they target,

NOTE Confidence: 0.95003766

00:15:23.325 --> 00:15:25.325 the GATA one. And GATA

NOTE Confidence: 0.95003766

00:15:25.325 --> 00:15:26.685 one is, as you know,

NOTE Confidence: 0.95003766

00:15:26.685 --> 00:15:27.425 is critical

NOTE Confidence: 0.7958951

00:15:27.899 --> 00:15:29.600 transferring factor for erosapoisis,

NOTE Confidence: 0.8327205

00:15:30.060 --> 00:15:31.040 and that leads

NOTE Confidence: 0.8853238

00:15:31.420 --> 00:15:32.720 to ineffective erosapoisis,

NOTE Confidence: 0.96223575

00:15:33.500 --> 00:15:35.040 and that leads to defective,

NOTE Confidence: 0.6877091

00:15:35.579 --> 00:15:36.560 rest cell production.

NOTE Confidence: 0.88776726

00:15:37.100 --> 00:15:39.180 So overall, this, this,

NOTE Confidence: 0.95876294

00:15:39.660 --> 00:15:41.040 these two kind of cytokines

NOTE Confidence: 0.9143193

00:15:41.495 --> 00:15:43.654 lead to ineffective rosuquoiesis and

NOTE Confidence: 0.9143193

00:15:43.654 --> 00:15:44.375 lead to a lot of

NOTE Confidence: 0.9143193

00:15:44.375 --> 00:15:46.134 cell death, and that can

NOTE Confidence: 0.9143193

00:15:46.134 --> 00:15:46.634 refuse,

NOTE Confidence: 0.91010016

00:15:48.214 --> 00:15:49.435 damage to sort of molecular

NOTE Confidence: 0.91010016

00:15:49.495 --> 00:15:50.615 patterns. And this is kind

NOTE Confidence: 0.91010016

00:15:50.615 --> 00:15:52.375 of like a positive feedback

NOTE Confidence: 0.91010016

00:15:52.375 --> 00:15:54.954 loop that promote the progression

NOTE Confidence: 0.91010016

00:15:55.014 --> 00:15:56.154 of this disease.

NOTE Confidence: 0.9779042

00:15:59.860 --> 00:16:00.360 So,

NOTE Confidence: 0.6987661

00:16:01.300 --> 00:16:01.800 Yang,

NOTE Confidence: 0.8968844

00:16:02.180 --> 00:16:03.460 kind of continue with this

NOTE Confidence: 0.8968844

00:16:03.460 --> 00:16:03.960 project.

NOTE Confidence: 0.9413945

00:16:04.660 --> 00:16:05.720 What he actually,

NOTE Confidence: 0.9560696

00:16:07.220 --> 00:16:09.380 did that we actually missed,

NOTE Confidence: 0.9560696

00:16:09.700 --> 00:16:11.220 in the previous publication in

NOTE Confidence: 0.9560696

00:16:11.220 --> 00:16:11.720 leukemia,

NOTE Confidence: 0.98385257

00:16:12.904 --> 00:16:14.105 because these mice,

NOTE Confidence: 0.9857481

00:16:14.824 --> 00:16:15.865 when they are one year

NOTE Confidence: 0.9857481

00:16:15.865 --> 00:16:17.884 old, they kind

NOTE Confidence: 0.9765118

00:16:18.264 --> 00:16:19.464 of die very quickly of

NOTE Confidence: 0.9765118

00:16:19.464 --> 00:16:20.204 the disease.

NOTE Confidence: 0.86899984

00:16:20.824 --> 00:16:22.845 But, in the follow-up study,

NOTE Confidence: 0.86899984

00:16:22.904 --> 00:16:24.985 he, Young really carefully looked

NOTE Confidence: 0.86899984

00:16:24.985 --> 00:16:27.029 at those moribund mice. And

NOTE Confidence: 0.86899984

00:16:27.029 --> 00:16:28.390 he found that there's a

NOTE Confidence: 0.86899984

00:16:28.390 --> 00:16:28.790 lot of,

NOTE Confidence: 0.9296738

00:16:29.830 --> 00:16:31.750 fibrotic changes in these mice

NOTE Confidence: 0.9296738

00:16:31.750 --> 00:16:33.110 in the bone marrow, as

NOTE Confidence: 0.9296738

00:16:33.110 --> 00:16:33.610 well

NOTE Confidence: 0.8366604

00:16:34.390 --> 00:16:35.829 as, a really accumulation of

NOTE Confidence: 0.8366604

00:16:35.829 --> 00:16:37.370 the, blast looking,

NOTE Confidence: 0.91744983

00:16:38.070 --> 00:16:38.570 cells,

NOTE Confidence: 0.9405178

00:16:39.404 --> 00:16:41.105 in their bone marrow, environment.

NOTE Confidence: 0.93378377

00:16:41.485 --> 00:16:43.324 And these, blast looking cells

NOTE Confidence: 0.93378377

00:16:43.324 --> 00:16:44.764 can also be found in

NOTE Confidence: 0.93378377

00:16:44.764 --> 00:16:45.904 the peripheral blood.

NOTE Confidence: 0.9866681

00:16:48.125 --> 00:16:49.404 So, we just,

NOTE Confidence: 0.81226593

00:16:49.884 --> 00:16:51.805 wonder whether because IL six

NOTE Confidence: 0.81226593

00:16:51.805 --> 00:16:53.665 and TRF are highly upregulated

NOTE Confidence: 0.81226593

00:16:53.884 --> 00:16:54.860 in the in this patient

NOTE Confidence: 0.81226593

00:16:55.019 --> 00:16:55.500 in this,

NOTE Confidence: 0.9419807

00:16:56.060 --> 00:16:57.579 in this MOS model, we

NOTE Confidence: 0.9419807

00:16:57.579 --> 00:16:59.500 just wonder whether r six

NOTE Confidence: 0.9419807

00:16:59.500 --> 00:17:00.000 particularly

NOTE Confidence: 0.9976426

00:17:00.620 --> 00:17:01.360 is critical

NOTE Confidence: 0.9962081

00:17:01.899 --> 00:17:03.279 to mediate this process.

NOTE Confidence: 0.9001833

00:17:03.820 --> 00:17:04.559 So, again,

NOTE Confidence: 0.87032366

00:17:05.340 --> 00:17:05.820 this is,

NOTE Confidence: 0.76621795

00:17:06.619 --> 00:17:07.119 the,

NOTE Confidence: 0.880352

00:17:08.705 --> 00:17:10.545 all type comparison to double

NOTE Confidence: 0.880352

00:17:10.545 --> 00:17:11.045 knockout

NOTE Confidence: 0.8167772

00:17:11.505 --> 00:17:12.244 of MDI1

NOTE Confidence: 0.7526119

00:17:12.705 --> 00:17:13.445 and miR46a.

NOTE Confidence: 0.86149913

00:17:14.705 --> 00:17:16.244 Again you can see dramatic,

NOTE Confidence: 0.9995628

00:17:16.865 --> 00:17:17.365 reduction

NOTE Confidence: 0.81364125

00:17:17.665 --> 00:17:18.885 in RBC, hemoglobin,

NOTE Confidence: 0.814436

00:17:20.109 --> 00:17:21.409 as well as significant,

NOTE Confidence: 0.9979159

00:17:21.869 --> 00:17:22.369 thrombocytopenia

NOTE Confidence: 0.94924545

00:17:22.909 --> 00:17:23.950 in these mice when they

NOTE Confidence: 0.94924545

00:17:23.950 --> 00:17:24.690 are moribund.

NOTE Confidence: 0.9815881

00:17:26.429 --> 00:17:27.169 And then

NOTE Confidence: 0.99152476

00:17:27.470 --> 00:17:28.770 what he did is,

NOTE Confidence: 0.84835196

00:17:29.149 --> 00:17:30.750 on top of that, he

NOTE Confidence: 0.84835196

00:17:30.750 --> 00:17:32.270 additionally knocked out the r

NOTE Confidence: 0.84835196

00:17:32.270 --> 00:17:33.549 six. So he made triple

NOTE Confidence: 0.84835196

00:17:33.549 --> 00:17:34.450 knockout mice.

NOTE Confidence: 0.8523119

00:17:36.494 --> 00:17:38.015 So we thought at originally

NOTE Confidence: 0.8523119

00:17:38.015 --> 00:17:39.315 when we designed this experiment,

NOTE Confidence: 0.7758928

00:17:39.695 --> 00:17:41.135 because our supposed r six

NOTE Confidence: 0.7758928

00:17:41.135 --> 00:17:42.175 and t r four are

NOTE Confidence: 0.7758928

00:17:42.175 --> 00:17:42.675 regulated,

NOTE Confidence: 0.95114285

00:17:43.535 --> 00:17:45.695 probably r six knockout by

NOTE Confidence: 0.95114285

00:17:45.695 --> 00:17:46.975 itself may not be able

NOTE Confidence: 0.95114285

00:17:46.975 --> 00:17:48.655 to completely rescue the disease

NOTE Confidence: 0.95114285

00:17:48.655 --> 00:17:50.399 phenotype. But to our big

NOTE Confidence: 0.95114285

00:17:50.399 --> 00:17:52.179 surprise, this really dramatically

NOTE Confidence: 0.8585335

00:17:52.720 --> 00:17:54.639 the knockout of, R6 really

NOTE Confidence: 0.8585335

00:17:54.639 --> 00:17:56.820 dramatically rescued the disease phenotype.

NOTE Confidence: 0.9761155

00:17:57.440 --> 00:17:58.639 As you can see that,

NOTE Confidence: 0.8771993

00:18:00.000 --> 00:18:00.500 RBC

NOTE Confidence: 0.9569115

00:18:00.880 --> 00:18:02.320 goes back to almost like

NOTE Confidence: 0.9569115

00:18:02.320 --> 00:18:02.820 normal.

NOTE Confidence: 0.728283

00:18:03.945 --> 00:18:04.445 Hemoglobin

NOTE Confidence: 0.9292921

00:18:04.744 --> 00:18:05.565 is normalized.

NOTE Confidence: 0.955542

00:18:06.025 --> 00:18:07.465 Platelets is still a little

NOTE Confidence: 0.955542

00:18:07.465 --> 00:18:09.304 bit low, but, it's really

NOTE Confidence: 0.955542

00:18:09.304 --> 00:18:10.525 dramatically improved.

NOTE Confidence: 0.933121

00:18:10.905 --> 00:18:11.945 Monocyte, which is,

NOTE Confidence: 0.82809275

00:18:12.585 --> 00:18:15.225 also highly upregulated in these

NOTE Confidence: 0.82809275

00:18:15.225 --> 00:18:17.470 double knockout mice, are also,

NOTE Confidence: 0.84207404

00:18:17.770 --> 00:18:19.450 their level also dropped down

NOTE Confidence: 0.84207404

00:18:19.450 --> 00:18:21.230 with, knockout to r six.

NOTE Confidence: 0.9727952

00:18:22.570 --> 00:18:24.090 And looking at their spleen,

NOTE Confidence: 0.9727952

00:18:24.410 --> 00:18:25.290 you can see that there

NOTE Confidence: 0.9727952

00:18:25.290 --> 00:18:26.170 is a this is a

NOTE Confidence: 0.9727952

00:18:26.170 --> 00:18:27.369 huge spleen in the double

NOTE Confidence: 0.9727952

00:18:27.369 --> 00:18:29.325 knockout mice. This is probably

NOTE Confidence: 0.9727952

00:18:29.625 --> 00:18:31.145 the the the biggest spleen

NOTE Confidence: 0.9727952

00:18:31.145 --> 00:18:32.105 I have ever seen in

NOTE Confidence: 0.9727952

00:18:32.105 --> 00:18:33.645 my in my research career.

NOTE Confidence: 0.9956905

00:18:34.905 --> 00:18:35.405 But

NOTE Confidence: 0.8803117

00:18:35.705 --> 00:18:37.244 knock out of our six

NOTE Confidence: 0.8803117

00:18:37.385 --> 00:18:37.885 completely

NOTE Confidence: 0.9160438

00:18:38.185 --> 00:18:39.885 normalized the spleen size,

NOTE Confidence: 0.98971087

00:18:40.425 --> 00:18:42.365 and their survival is also

NOTE Confidence: 0.98971087

00:18:42.585 --> 00:18:43.085 dramatically,

NOTE Confidence: 0.99965155

00:18:43.785 --> 00:18:44.285 improved.

NOTE Confidence: 0.9837699

00:18:46.560 --> 00:18:48.000 So, you know, I'm a

NOTE Confidence: 0.9837699

00:18:48.000 --> 00:18:48.500 hematopathologist,

NOTE Confidence: 0.9758203

00:18:48.960 --> 00:18:49.760 so I like to look

NOTE Confidence: 0.9758203

00:18:49.760 --> 00:18:50.580 at the morphology.

NOTE Confidence: 0.9424706

00:18:51.119 --> 00:18:52.560 So again, when we look

NOTE Confidence: 0.9424706

00:18:52.560 --> 00:18:54.080 at the double knockout mice,

NOTE Confidence: 0.9424706

00:18:54.080 --> 00:18:55.220 you can see that,

NOTE Confidence: 0.9789577

00:18:55.760 --> 00:18:57.619 again, these are moribond mice

NOTE Confidence: 0.9789577

00:18:57.680 --> 00:18:58.660 about to die.

NOTE Confidence: 0.8262682

00:18:59.015 --> 00:19:00.135 They are bone marrow is

NOTE Confidence: 0.8262682

00:19:00.135 --> 00:19:00.635 completely

NOTE Confidence: 0.7418824

00:19:01.015 --> 00:19:01.335 if,

NOTE Confidence: 0.95728886

00:19:01.895 --> 00:19:03.415 kind of infiltrated with these

NOTE Confidence: 0.95728886

00:19:03.415 --> 00:19:05.175 blast looking cells, including, you

NOTE Confidence: 0.95728886

00:19:05.175 --> 00:19:07.255 know, apoptotic bodies as well

NOTE Confidence: 0.95728886

00:19:07.255 --> 00:19:08.395 as mitotic bodies.

NOTE Confidence: 0.8797524

00:19:09.015 --> 00:19:09.515 There's

NOTE Confidence: 0.8433399

00:19:09.815 --> 00:19:10.555 no basic,

NOTE Confidence: 0.91420585

00:19:11.015 --> 00:19:11.515 differentiated,

NOTE Confidence: 0.8941661

00:19:12.350 --> 00:19:13.250 normal differentiated,

NOTE Confidence: 0.8488744

00:19:14.190 --> 00:19:15.869 cell types. For example, what

NOTE Confidence: 0.8488744

00:19:15.869 --> 00:19:17.230 you can see in the

NOTE Confidence: 0.8488744

00:19:17.230 --> 00:19:18.590 bowel type mice as well

NOTE Confidence: 0.8488744

00:19:18.590 --> 00:19:19.790 as our six knockout mice.

NOTE Confidence: 0.8488744

00:19:19.790 --> 00:19:20.770 It's nice megakaryocytes

NOTE Confidence: 0.90046215

00:19:21.150 --> 00:19:22.350 as, as well as these,

NOTE Confidence: 0.88512117

00:19:23.230 --> 00:19:23.730 granulocytes

NOTE Confidence: 0.8313761

00:19:24.030 --> 00:19:25.550 and the universal cells. They

NOTE Confidence: 0.8313761

00:19:25.550 --> 00:19:26.210 are completely,

NOTE Confidence: 0.93522483

00:19:27.175 --> 00:19:28.475 occupied by blasts.

NOTE Confidence: 0.9096297

00:19:29.175 --> 00:19:30.375 And if you have r

NOTE Confidence: 0.9096297

00:19:30.375 --> 00:19:31.115 six knockout,

NOTE Confidence: 0.7652695

00:19:32.135 --> 00:19:32.875 they are

NOTE Confidence: 0.94632924

00:19:33.175 --> 00:19:34.775 the the this phenotype is

NOTE Confidence: 0.94632924

00:19:34.775 --> 00:19:35.915 completely reworked.

NOTE Confidence: 0.9256399

00:19:36.615 --> 00:19:37.734 You can you you have

NOTE Confidence: 0.9256399

00:19:37.734 --> 00:19:38.234 megakaryocyte

NOTE Confidence: 0.8639487

00:19:38.615 --> 00:19:40.055 back into the shape. You

NOTE Confidence: 0.8639487

00:19:40.055 --> 00:19:42.075 have all these, segmented neutrophils.

NOTE Confidence: 0.9204088

00:19:42.559 --> 00:19:44.080 Actually, in neutrophils in mice

NOTE Confidence: 0.9204088

00:19:44.080 --> 00:19:45.600 are different from human. They're

NOTE Confidence: 0.9204088

00:19:45.600 --> 00:19:46.980 kind of like donut shaped.

NOTE Confidence: 0.97929394

00:19:49.040 --> 00:19:50.400 So you have you have

NOTE Confidence: 0.97929394

00:19:50.400 --> 00:19:52.500 full differentiation of different lineages.

NOTE Confidence: 0.8834962

00:19:53.280 --> 00:19:54.320 And the my and the

NOTE Confidence: 0.8834962

00:19:54.320 --> 00:19:56.320 fibrosis is also, back to

NOTE Confidence: 0.8834962

00:19:56.320 --> 00:19:56.820 the,

NOTE Confidence: 0.86522627

00:19:57.685 --> 00:19:59.185 is also significantly reduced.

NOTE Confidence: 0.89356256

00:19:59.725 --> 00:20:01.405 Also, spleen size, as shown,

NOTE Confidence: 0.89356256

00:20:01.565 --> 00:20:03.244 they are significantly reduced, and

NOTE Confidence: 0.89356256

00:20:03.244 --> 00:20:05.325 their, normal morphology where you

NOTE Confidence: 0.89356256

00:20:05.325 --> 00:20:06.925 can see both the red

NOTE Confidence: 0.89356256

00:20:06.925 --> 00:20:08.705 pulp and white pulp

NOTE Confidence: 0.88409793

00:20:09.085 --> 00:20:11.005 are also normalized with the

NOTE Confidence: 0.88409793

00:20:11.005 --> 00:20:12.465 knockout of r six.

NOTE Confidence: 0.9089651

00:20:15.080 --> 00:20:16.279 So all these are all

NOTE Confidence: 0.9089651

00:20:16.279 --> 00:20:16.760 happen,

NOTE Confidence: 0.9650859

00:20:17.080 --> 00:20:18.359 in most models. So what

NOTE Confidence: 0.9650859

00:20:18.359 --> 00:20:19.179 about human?

NOTE Confidence: 0.97645265

00:20:19.720 --> 00:20:21.019 So we actually,

NOTE Confidence: 0.73508143

00:20:21.960 --> 00:20:22.760 check the,

NOTE Confidence: 0.87015736

00:20:23.080 --> 00:20:24.279 published I think this is

NOTE Confidence: 0.87015736

00:20:24.279 --> 00:20:25.159 a form of one of

NOTE Confidence: 0.87015736

00:20:25.159 --> 00:20:26.760 the published dataset where we

NOTE Confidence: 0.87015736

00:20:26.760 --> 00:20:27.980 look at r six

NOTE Confidence: 0.97524476

00:20:28.575 --> 00:20:29.075 expression

NOTE Confidence: 0.96204346

00:20:29.615 --> 00:20:31.635 in different subtypes of MDS,

NOTE Confidence: 0.96204346

00:20:31.855 --> 00:20:32.355 including,

NOTE Confidence: 0.9535882

00:20:33.695 --> 00:20:35.075 again again, these are still

NOTE Confidence: 0.9535882

00:20:35.215 --> 00:20:35.695 previous,

NOTE Confidence: 0.8957709

00:20:36.174 --> 00:20:38.414 entities that from the previous

NOTE Confidence: 0.8957709

00:20:38.414 --> 00:20:40.115 WHO and, classification.

NOTE Confidence: 0.9977082

00:20:40.734 --> 00:20:41.789 So when you look at,

NOTE Confidence: 0.8982984

00:20:42.590 --> 00:20:43.730 compared to the control,

NOTE Confidence: 0.8928462

00:20:44.190 --> 00:20:45.010 healthy individuals,

NOTE Confidence: 0.86090946

00:20:45.789 --> 00:20:47.950 MDS with brain cellophiles have,

NOTE Confidence: 0.87218374

00:20:48.350 --> 00:20:50.109 not much upregulation of IL

NOTE Confidence: 0.87218374

00:20:50.109 --> 00:20:50.850 six receptor.

NOTE Confidence: 0.95494235

00:20:51.950 --> 00:20:53.809 MDS with single lineage dysplasia,

NOTE Confidence: 0.95494235

00:20:53.869 --> 00:20:55.549 not much, but MDS with

NOTE Confidence: 0.95494235

00:20:55.549 --> 00:20:56.775 those high risk MDS.

NOTE Confidence: 0.87362957

00:20:57.335 --> 00:20:59.015 MDS with excess plus one

NOTE Confidence: 0.87362957

00:20:59.015 --> 00:21:00.315 as well as plus two,

NOTE Confidence: 0.87362957

00:21:00.615 --> 00:21:02.795 have dramatically statistically significant

NOTE Confidence: 0.8413561

00:21:03.494 --> 00:21:05.275 upregulation of r six receptor.

NOTE Confidence: 0.85562307

00:21:05.655 --> 00:21:06.935 And this is, this is

NOTE Confidence: 0.85562307

00:21:06.935 --> 00:21:08.615 the correlate with their worst,

NOTE Confidence: 0.89271986

00:21:09.095 --> 00:21:09.595 survival,

NOTE Confidence: 0.8151937

00:21:10.740 --> 00:21:12.680 with increased r six receptor

NOTE Confidence: 0.8151937

00:21:12.820 --> 00:21:13.320 expression.

NOTE Confidence: 0.98557997

00:21:14.340 --> 00:21:15.460 So we we can also

NOTE Confidence: 0.98557997

00:21:15.460 --> 00:21:15.780 do,

NOTE Confidence: 0.97478455

00:21:16.980 --> 00:21:17.480 immunohistochemical

NOTE Confidence: 0.83684254

00:21:18.100 --> 00:21:18.580 stain,

NOTE Confidence: 0.91788894

00:21:18.900 --> 00:21:19.880 in these patients.

NOTE Confidence: 0.9568267

00:21:20.340 --> 00:21:20.840 So,

NOTE Confidence: 0.98247457

00:21:21.460 --> 00:21:22.820 with r six receptor, you

NOTE Confidence: 0.98247457

00:21:22.820 --> 00:21:24.500 can see that, for in

NOTE Confidence: 0.98247457

00:21:24.500 --> 00:21:25.000 both

NOTE Confidence: 0.957536

00:21:25.575 --> 00:21:26.475 MDS with

NOTE Confidence: 0.95896435

00:21:27.494 --> 00:21:29.654 multilinear dysplasia, those are also

NOTE Confidence: 0.95896435

00:21:29.654 --> 00:21:30.635 high risk MDS

NOTE Confidence: 0.89364946

00:21:31.095 --> 00:21:32.615 as well as, MDS with

NOTE Confidence: 0.89364946

00:21:32.615 --> 00:21:33.595 excess plus.

NOTE Confidence: 0.8301616

00:21:33.895 --> 00:21:35.734 There are six receptor level

NOTE Confidence: 0.8301616

00:21:35.734 --> 00:21:36.715 are highly upregulated

NOTE Confidence: 0.9402316

00:21:37.335 --> 00:21:38.909 compared to the control ones,

NOTE Confidence: 0.9402316

00:21:38.909 --> 00:21:39.409 and

NOTE Confidence: 0.87308985

00:21:39.710 --> 00:21:41.169 and and there's a mildly

NOTE Confidence: 0.87308985

00:21:41.389 --> 00:21:42.429 upregulated out,

NOTE Confidence: 0.9570357

00:21:42.830 --> 00:21:44.429 r six receptor in MDS

NOTE Confidence: 0.9570357

00:21:44.429 --> 00:21:45.090 with rinsuloplasts.

NOTE Confidence: 0.87503237

00:21:46.830 --> 00:21:48.289 There's also a particular,

NOTE Confidence: 0.95837444

00:21:48.909 --> 00:21:50.750 subtype of r six receptor

NOTE Confidence: 0.95837444

00:21:50.750 --> 00:21:51.570 that's soluble.

NOTE Confidence: 0.9847651

00:21:52.335 --> 00:21:54.335 And we wonder whether this

NOTE Confidence: 0.9847651

00:21:54.335 --> 00:21:54.835 soluble,

NOTE Confidence: 0.9331854

00:21:56.255 --> 00:21:58.015 isoform of IR six is

NOTE Confidence: 0.9331854

00:21:58.015 --> 00:22:00.494 particularly upregulated in those MDS

NOTE Confidence: 0.9331854

00:22:00.494 --> 00:22:00.994 patients.

NOTE Confidence: 0.9436198

00:22:01.455 --> 00:22:02.815 And that's indeed the case,

NOTE Confidence: 0.9436198

00:22:02.815 --> 00:22:04.655 but, the upregulation of IR

NOTE Confidence: 0.9436198

00:22:04.655 --> 00:22:06.355 six, soluble IR six receptor

NOTE Confidence: 0.9634504

00:22:06.740 --> 00:22:07.940 is not something that you

NOTE Confidence: 0.9634504

00:22:07.940 --> 00:22:08.980 can see in the peripheral

NOTE Confidence: 0.9634504

00:22:08.980 --> 00:22:10.820 blood. But only if you,

NOTE Confidence: 0.9662616

00:22:11.380 --> 00:22:13.000 harvest the bone marrow solution,

NOTE Confidence: 0.9662616

00:22:13.220 --> 00:22:14.600 you can see the significant

NOTE Confidence: 0.9662616

00:22:14.740 --> 00:22:15.240 upregulation

NOTE Confidence: 0.9220772

00:22:15.540 --> 00:22:17.960 R6 receptor. And this also

NOTE Confidence: 0.9220772

00:22:18.020 --> 00:22:19.960 closely correlate with their disease,

NOTE Confidence: 0.75289845

00:22:20.500 --> 00:22:21.000 stage.

NOTE Confidence: 0.99627197

00:22:21.525 --> 00:22:23.465 Again, high risk MDS have

NOTE Confidence: 0.98014927

00:22:23.845 --> 00:22:24.665 much higher,

NOTE Confidence: 0.75677776

00:22:25.205 --> 00:22:27.465 or statistically significant upper regulation,

NOTE Confidence: 0.8363398

00:22:28.005 --> 00:22:29.385 soluble R6 receptor.

NOTE Confidence: 0.94941133

00:22:31.605 --> 00:22:33.285 So with that, we wonder

NOTE Confidence: 0.94941133

00:22:33.285 --> 00:22:33.785 whether,

NOTE Confidence: 0.90865135

00:22:34.565 --> 00:22:36.725 you target R6 receptor or

NOTE Confidence: 0.90865135

00:22:36.725 --> 00:22:38.630 R6 pathway can really,

NOTE Confidence: 0.9571414

00:22:40.130 --> 00:22:41.270 provide some therapeutic,

NOTE Confidence: 0.98370254

00:22:41.890 --> 00:22:42.390 effect

NOTE Confidence: 0.97938025

00:22:42.690 --> 00:22:43.990 in patient with MDS.

NOTE Confidence: 0.9805031

00:22:44.770 --> 00:22:46.690 So we actually took the,

NOTE Confidence: 0.58555275

00:22:47.970 --> 00:22:49.270 four patient samples,

NOTE Confidence: 0.9499386

00:22:49.970 --> 00:22:51.350 and this is a colony

NOTE Confidence: 0.9499386

00:22:51.410 --> 00:22:53.484 assay. And we treat the,

NOTE Confidence: 0.7339907

00:22:53.885 --> 00:22:54.045 these,

NOTE Confidence: 0.89306504

00:22:55.325 --> 00:22:56.705 CD thirty four derived,

NOTE Confidence: 0.75343966

00:22:57.244 --> 00:22:58.545 bone marrow colonies,

NOTE Confidence: 0.9996412

00:22:59.244 --> 00:22:59.744 using

NOTE Confidence: 0.75633353

00:23:00.045 --> 00:23:00.545 tocilizumab,

NOTE Confidence: 0.9278514

00:23:01.645 --> 00:23:03.185 which is our six receptor

NOTE Confidence: 0.9278514

00:23:03.325 --> 00:23:03.825 antibody.

NOTE Confidence: 0.89749014

00:23:04.859 --> 00:23:06.400 I think our six antibody,

NOTE Confidence: 0.9799364

00:23:06.780 --> 00:23:08.400 and that that can significantly,

NOTE Confidence: 0.83441895

00:23:09.260 --> 00:23:11.119 lead to the reduction specifically

NOTE Confidence: 0.9078661

00:23:11.420 --> 00:23:13.020 in MDS patient samples, but

NOTE Confidence: 0.9078661

00:23:13.020 --> 00:23:14.400 not in the normal CD34

NOTE Confidence: 0.9078661

00:23:14.619 --> 00:23:15.119 positive

NOTE Confidence: 0.9936011

00:23:15.500 --> 00:23:16.000 colonies.

NOTE Confidence: 0.92147404

00:23:16.635 --> 00:23:18.315 So this again demonstrate that,

NOTE Confidence: 0.92147404

00:23:18.635 --> 00:23:19.994 this, is I think these

NOTE Confidence: 0.92147404

00:23:19.994 --> 00:23:21.115 are all from high risk

NOTE Confidence: 0.92147404

00:23:21.115 --> 00:23:22.795 MDS patients. So these high

NOTE Confidence: 0.92147404

00:23:22.795 --> 00:23:23.615 risk MDS

NOTE Confidence: 0.917842

00:23:24.315 --> 00:23:25.835 samples are very sensitive to

NOTE Confidence: 0.917842

00:23:25.835 --> 00:23:26.815 our six receptor

NOTE Confidence: 0.99786323

00:23:27.355 --> 00:23:27.855 pathways.

NOTE Confidence: 0.98164314

00:23:30.340 --> 00:23:31.460 So with that, I just

NOTE Confidence: 0.98164314

00:23:31.460 --> 00:23:31.859 want to,

NOTE Confidence: 0.86873615

00:23:33.700 --> 00:23:34.980 summarize this part of my

NOTE Confidence: 0.86873615

00:23:34.980 --> 00:23:36.820 talk. So I think I

NOTE Confidence: 0.86873615

00:23:36.820 --> 00:23:38.020 I showed you that, double

NOTE Confidence: 0.86873615

00:23:38.020 --> 00:23:40.020 knockout mDY one as well

NOTE Confidence: 0.86873615

00:23:40.020 --> 00:23:41.460 as miRIF forty six a,

NOTE Confidence: 0.86873615

00:23:41.925 --> 00:23:43.865 causes age related to anemia

NOTE Confidence: 0.86873615

00:23:43.925 --> 00:23:45.305 and ineffective rosuploidosis

NOTE Confidence: 0.9168987

00:23:46.325 --> 00:23:48.805 and, damage associated molecular patterns

NOTE Confidence: 0.9168987

00:23:48.805 --> 00:23:49.705 that are increased

NOTE Confidence: 0.61513066

00:23:50.085 --> 00:23:51.305 in overaging.

NOTE Confidence: 0.9802637

00:23:51.605 --> 00:23:52.965 That that actually happens to

NOTE Confidence: 0.9802637

00:23:52.965 --> 00:23:54.905 everybody, not just MDS patients.

NOTE Confidence: 0.9141677

00:23:55.800 --> 00:23:56.540 That can trigger,

NOTE Confidence: 0.9123438

00:23:57.480 --> 00:23:58.920 the overproduction of r six

NOTE Confidence: 0.9123438

00:23:58.920 --> 00:23:59.900 and t alpha

NOTE Confidence: 0.88000065

00:24:00.280 --> 00:24:01.400 in in in these MOS

NOTE Confidence: 0.88000065

00:24:01.400 --> 00:24:01.900 models.

NOTE Confidence: 0.93560725

00:24:03.080 --> 00:24:04.700 And we show that pathological

NOTE Confidence: 0.93560725

00:24:04.920 --> 00:24:06.300 levels of these, proinflammatory

NOTE Confidence: 0.908291

00:24:06.840 --> 00:24:09.100 cytokines can induce ineffective erosuppoiesis.

NOTE Confidence: 0.92933804

00:24:09.915 --> 00:24:10.955 And r six play a

NOTE Confidence: 0.92933804

00:24:10.955 --> 00:24:12.895 pivotal role in MDS progression

NOTE Confidence: 0.92933804

00:24:12.955 --> 00:24:14.575 to acute myeloid leukemia.

NOTE Confidence: 0.90445524

00:24:15.035 --> 00:24:15.994 And I would think that

NOTE Confidence: 0.90445524

00:24:15.994 --> 00:24:17.675 targeting r six pathway could

NOTE Confidence: 0.90445524

00:24:17.675 --> 00:24:18.415 be a therapeutic

NOTE Confidence: 0.82083595

00:24:18.875 --> 00:24:19.375 effective,

NOTE Confidence: 0.9955239

00:24:19.675 --> 00:24:21.295 in treating high risk MDS

NOTE Confidence: 0.97319037

00:24:21.980 --> 00:24:23.500 when they progress to acute

NOTE Confidence: 0.97319037

00:24:23.500 --> 00:24:24.560 myeloid leukemia.

NOTE Confidence: 0.9946833

00:24:26.220 --> 00:24:26.540 So,

NOTE Confidence: 0.9516207

00:24:27.100 --> 00:24:28.700 so with that, we kind

NOTE Confidence: 0.9516207

00:24:28.700 --> 00:24:29.520 of more,

NOTE Confidence: 0.9849131

00:24:29.980 --> 00:24:32.160 looking at inflammation overall,

NOTE Confidence: 0.88198566

00:24:32.619 --> 00:24:34.240 in in myeloid diseases,

NOTE Confidence: 0.8855961

00:24:34.934 --> 00:24:36.615 And this is a really

NOTE Confidence: 0.8855961

00:24:36.615 --> 00:24:39.195 simplified cartoon showing the basic

NOTE Confidence: 0.8855961

00:24:39.255 --> 00:24:39.755 inflammatory

NOTE Confidence: 0.99729586

00:24:40.135 --> 00:24:40.635 pathways.

NOTE Confidence: 0.89307886

00:24:41.015 --> 00:24:42.054 So once you have the

NOTE Confidence: 0.89307886

00:24:42.054 --> 00:24:43.575 damage associated molecular pattern or

NOTE Confidence: 0.89307886

00:24:43.575 --> 00:24:45.414 passage associated molecular patterns, that

NOTE Confidence: 0.89307886

00:24:45.414 --> 00:24:47.174 can trigger the activation of

NOTE Confidence: 0.89307886

00:24:47.174 --> 00:24:47.835 the inflammasomes,

NOTE Confidence: 0.87378603

00:24:48.980 --> 00:24:50.660 both from an RRP3 or

NOTE Confidence: 0.87378603

00:24:50.660 --> 00:24:51.880 as well as ASC.

NOTE Confidence: 0.93036747

00:24:52.260 --> 00:24:54.020 And this, together with the

NOTE Confidence: 0.93036747

00:24:54.020 --> 00:24:55.540 procaspace one, this can lead

NOTE Confidence: 0.93036747

00:24:55.540 --> 00:24:57.300 to the activation of caspace

NOTE Confidence: 0.93036747

00:24:57.300 --> 00:24:59.300 one, procaspace one to caspace

NOTE Confidence: 0.93036747

00:24:59.300 --> 00:25:01.400 one. And the activated caspace

NOTE Confidence: 0.93036747

00:25:01.460 --> 00:25:02.980 one can cleave pro IL

NOTE Confidence: 0.93036747

00:25:02.980 --> 00:25:03.720 one beta

NOTE Confidence: 0.84206927

00:25:04.365 --> 00:25:05.325 as as well as a

NOTE Confidence: 0.84206927

00:25:05.325 --> 00:25:06.465 pro r eighteen

NOTE Confidence: 0.91531956

00:25:06.925 --> 00:25:08.365 and lead to the, the

NOTE Confidence: 0.91531956

00:25:08.365 --> 00:25:09.645 the mature r one beta

NOTE Confidence: 0.91531956

00:25:09.645 --> 00:25:11.244 and r eighteen. And these,

NOTE Confidence: 0.91531956

00:25:11.484 --> 00:25:11.984 proinflammatory

NOTE Confidence: 0.9962937

00:25:12.365 --> 00:25:12.865 cytokines

NOTE Confidence: 0.91464365

00:25:13.645 --> 00:25:15.005 can secret out of this,

NOTE Confidence: 0.91464365

00:25:15.244 --> 00:25:17.085 this inflammatory cell into the,

NOTE Confidence: 0.9826189

00:25:17.890 --> 00:25:19.410 into the environment through this,

NOTE Confidence: 0.8060029

00:25:21.570 --> 00:25:23.330 this gas seventy immediately pore

NOTE Confidence: 0.8060029

00:25:23.330 --> 00:25:25.410 formation. So this actually was

NOTE Confidence: 0.8060029

00:25:25.410 --> 00:25:26.790 a really exciting discovery,

NOTE Confidence: 0.9758927

00:25:27.970 --> 00:25:29.429 I think, around

NOTE Confidence: 0.9804379

00:25:29.885 --> 00:25:31.245 a decade or so ago,

NOTE Confidence: 0.83223003

00:25:31.725 --> 00:25:33.885 mainly driven by, Feng Shao's

NOTE Confidence: 0.83223003

00:25:33.885 --> 00:25:35.105 group in China.

NOTE Confidence: 0.8839651

00:25:35.565 --> 00:25:37.405 And, so what happens is

NOTE Confidence: 0.8839651

00:25:37.405 --> 00:25:39.085 that activated the caspase one

NOTE Confidence: 0.8839651

00:25:39.085 --> 00:25:40.285 can also cleave the full

NOTE Confidence: 0.8839651

00:25:40.285 --> 00:25:41.485 length gas from a d

NOTE Confidence: 0.8839651

00:25:41.485 --> 00:25:42.845 and that d should so

NOTE Confidence: 0.8839651

00:25:42.845 --> 00:25:43.805 once you have the n

NOTE Confidence: 0.8839651

00:25:43.805 --> 00:25:44.305 terminal

NOTE Confidence: 0.9818515

00:25:44.820 --> 00:25:47.299 cleaved gastrimin d by caspase

NOTE Confidence: 0.9818515

00:25:47.299 --> 00:25:47.799 one,

NOTE Confidence: 0.99137247

00:25:48.179 --> 00:25:49.880 they can form a really

NOTE Confidence: 0.99137247

00:25:50.019 --> 00:25:51.059 beautiful pore,

NOTE Confidence: 0.9543123

00:25:51.380 --> 00:25:52.119 on the,

NOTE Confidence: 0.96809405

00:25:52.580 --> 00:25:54.580 cytoplasm membrane, and that leads

NOTE Confidence: 0.96809405

00:25:54.580 --> 00:25:55.779 to the release of these,

NOTE Confidence: 0.8217905

00:25:56.580 --> 00:25:57.080 proinflammatory

NOTE Confidence: 0.9954524

00:25:57.460 --> 00:25:57.960 cytokines.

NOTE Confidence: 0.9481723

00:25:59.515 --> 00:26:01.355 And here is, another cartoon

NOTE Confidence: 0.9481723

00:26:01.355 --> 00:26:03.135 that really shows vividly

NOTE Confidence: 0.9458643

00:26:03.755 --> 00:26:05.535 how this pore was formed.

NOTE Confidence: 0.9395371

00:26:05.915 --> 00:26:08.075 And actually, the crystal structure

NOTE Confidence: 0.9395371

00:26:08.075 --> 00:26:09.915 of, this n terminal domain

NOTE Confidence: 0.9395371

00:26:09.915 --> 00:26:10.155 of,

NOTE Confidence: 0.87638617

00:26:10.955 --> 00:26:12.975 gastrinomy d has been resolved

NOTE Confidence: 0.947279

00:26:13.519 --> 00:26:14.639 And they form once you

NOTE Confidence: 0.947279

00:26:14.639 --> 00:26:16.480 have this, n terminal domain

NOTE Confidence: 0.947279

00:26:16.480 --> 00:26:18.000 cleave, they kind of form,

NOTE Confidence: 0.920897

00:26:19.679 --> 00:26:21.220 kind of line up closely,

NOTE Confidence: 0.9623578

00:26:22.000 --> 00:26:22.799 and form this,

NOTE Confidence: 0.89551705

00:26:23.519 --> 00:26:25.039 palm like structure. And they

NOTE Confidence: 0.89551705

00:26:25.039 --> 00:26:26.419 they insert the,

NOTE Confidence: 0.9454582

00:26:27.475 --> 00:26:28.375 plasma membrane,

NOTE Confidence: 0.98886

00:26:28.835 --> 00:26:30.135 with all these fingers

NOTE Confidence: 0.91427773

00:26:30.515 --> 00:26:32.515 into the and definitely form

NOTE Confidence: 0.91427773

00:26:32.515 --> 00:26:33.794 a kind of a really

NOTE Confidence: 0.91427773

00:26:33.794 --> 00:26:35.695 a beautiful circle and a

NOTE Confidence: 0.91427773

00:26:35.715 --> 00:26:36.914 big hole on the plasma

NOTE Confidence: 0.91427773

00:26:36.914 --> 00:26:38.515 membrane so that all those

NOTE Confidence: 0.91427773

00:26:38.515 --> 00:26:40.195 cytokines can be released from

NOTE Confidence: 0.91427773

00:26:40.195 --> 00:26:41.335 the, cytoplasm.

NOTE Confidence: 0.84669346

00:26:43.840 --> 00:26:45.840 So, we are interested in

NOTE Confidence: 0.84669346

00:26:45.840 --> 00:26:47.220 whether gas SMG

NOTE Confidence: 0.93703026

00:26:47.600 --> 00:26:49.359 is involved in the whole

NOTE Confidence: 0.93703026

00:26:49.359 --> 00:26:50.580 MDS inflammation,

NOTE Confidence: 0.9900931

00:26:51.760 --> 00:26:52.260 situation.

NOTE Confidence: 0.9797802

00:26:52.799 --> 00:26:54.400 So what we actually this

NOTE Confidence: 0.9797802

00:26:54.400 --> 00:26:54.900 is

NOTE Confidence: 0.8850402

00:26:55.280 --> 00:26:56.880 a data we this has

NOTE Confidence: 0.8850402

00:26:56.880 --> 00:26:58.320 not been published, but, they

NOTE Confidence: 0.8850402

00:26:58.320 --> 00:27:00.135 said the data we accumulated,

NOTE Confidence: 0.8850402

00:27:00.534 --> 00:27:01.514 many years ago.

NOTE Confidence: 0.9951375

00:27:01.975 --> 00:27:02.715 And we,

NOTE Confidence: 0.8346248

00:27:03.335 --> 00:27:04.615 again, we look at the

NOTE Confidence: 0.8346248

00:27:04.615 --> 00:27:06.134 control patient as well as

NOTE Confidence: 0.8346248

00:27:06.134 --> 00:27:07.434 delta five q MDS,

NOTE Confidence: 0.8651304

00:27:08.054 --> 00:27:09.195 MDS with reinstereoblast,

NOTE Confidence: 0.88427013

00:27:09.654 --> 00:27:11.654 MDS with high risk, excess

NOTE Confidence: 0.88427013

00:27:11.654 --> 00:27:13.119 of last one. You can

NOTE Confidence: 0.88427013

00:27:13.119 --> 00:27:15.299 see that, gastrin d expression

NOTE Confidence: 0.88427013

00:27:15.520 --> 00:27:16.900 is also highly

NOTE Confidence: 0.7537746

00:27:17.760 --> 00:27:18.260 increased,

NOTE Confidence: 0.99474555

00:27:19.200 --> 00:27:20.559 compared to the control patient

NOTE Confidence: 0.99474555

00:27:20.559 --> 00:27:22.100 in different MDS patients.

NOTE Confidence: 0.7740658

00:27:22.880 --> 00:27:24.720 Seems like MDS, derrick five

NOTE Confidence: 0.7740658

00:27:24.720 --> 00:27:25.760 q, we also is a

NOTE Confidence: 0.7740658

00:27:25.760 --> 00:27:27.280 low risk MDS. It the

NOTE Confidence: 0.7740658

00:27:27.280 --> 00:27:29.674 level of, carcinoid are also

NOTE Confidence: 0.9905594

00:27:30.215 --> 00:27:31.595 high, compared to

NOTE Confidence: 0.71053696

00:27:31.895 --> 00:27:33.895 the patient with, MDS ring

NOTE Confidence: 0.71053696

00:27:33.895 --> 00:27:34.395 cellophilus.

NOTE Confidence: 0.89016664

00:27:36.455 --> 00:27:38.075 So here's a quantification.

NOTE Confidence: 0.9763346

00:27:38.375 --> 00:27:39.655 Again, these are from the

NOTE Confidence: 0.9763346

00:27:39.895 --> 00:27:40.955 one of the database

NOTE Confidence: 0.85193527

00:27:42.480 --> 00:27:44.480 shared by, Amit Verma from

NOTE Confidence: 0.85193527

00:27:44.480 --> 00:27:46.180 Albert Einstein College of Medicine,

NOTE Confidence: 0.8484303

00:27:46.560 --> 00:27:47.760 and we can see that,

NOTE Confidence: 0.8484303

00:27:48.160 --> 00:27:50.240 EV patient with EMDS EV

NOTE Confidence: 0.8484303

00:27:50.240 --> 00:27:51.300 one, EV two,

NOTE Confidence: 0.9868782

00:27:51.760 --> 00:27:52.320 as well as,

NOTE Confidence: 0.8485409

00:27:52.880 --> 00:27:54.020 not much on retinoblast,

NOTE Confidence: 0.85977936

00:27:54.480 --> 00:27:55.440 but so they have a

NOTE Confidence: 0.85977936

00:27:55.440 --> 00:27:56.720 really high expression of a

NOTE Confidence: 0.85977936

00:27:56.720 --> 00:27:57.220 CasaMed.

NOTE Confidence: 0.9927578

00:27:58.135 --> 00:27:59.674 And looking back to our,

NOTE Confidence: 0.8972398

00:28:00.294 --> 00:28:01.734 double knockout mouse model that

NOTE Confidence: 0.8972398

00:28:01.734 --> 00:28:02.715 I just described,

NOTE Confidence: 0.9057445

00:28:03.255 --> 00:28:04.775 their level of and they

NOTE Confidence: 0.9057445

00:28:04.775 --> 00:28:06.315 can you can see clearly

NOTE Confidence: 0.9057445

00:28:06.375 --> 00:28:08.615 cleaved and terminal Casa MD

NOTE Confidence: 0.9057445

00:28:08.615 --> 00:28:09.115 here,

NOTE Confidence: 0.9434463

00:28:09.494 --> 00:28:10.609 compared to the wild type

NOTE Confidence: 0.9434463

00:28:10.609 --> 00:28:12.550 mice. So that indicate that

NOTE Confidence: 0.9434463

00:28:12.609 --> 00:28:14.869 these really double knockout mice,

NOTE Confidence: 0.910552

00:28:15.250 --> 00:28:17.010 and this is specifically from

NOTE Confidence: 0.910552

00:28:17.010 --> 00:28:19.090 the disease model because it

NOTE Confidence: 0.910552

00:28:19.090 --> 00:28:20.369 takes time for these mice

NOTE Confidence: 0.910552

00:28:20.369 --> 00:28:21.430 to develop MDS.

NOTE Confidence: 0.97777367

00:28:21.810 --> 00:28:23.325 It takes about eight months.

NOTE Confidence: 0.97777367

00:28:23.404 --> 00:28:25.024 So these are really samples

NOTE Confidence: 0.97777367

00:28:25.164 --> 00:28:26.284 from eight months to one

NOTE Confidence: 0.97777367

00:28:26.284 --> 00:28:27.264 year old mice.

NOTE Confidence: 0.8502184

00:28:27.565 --> 00:28:29.325 They are they they are

NOTE Confidence: 0.8502184

00:28:29.325 --> 00:28:31.565 really inflammatory being indicated by

NOTE Confidence: 0.8502184

00:28:31.565 --> 00:28:33.904 this cleaved and terminal guesstimate

NOTE Confidence: 0.96186125

00:28:34.205 --> 00:28:34.705 expression.

NOTE Confidence: 0.8455858

00:28:37.419 --> 00:28:39.899 So, this project was taken

NOTE Confidence: 0.8455858

00:28:39.899 --> 00:28:41.679 by Doctor Kehaan Ren.

NOTE Confidence: 0.9529747

00:28:42.779 --> 00:28:43.600 He's actually,

NOTE Confidence: 0.9376628

00:28:44.620 --> 00:28:45.500 he is going to,

NOTE Confidence: 0.9899008

00:28:46.380 --> 00:28:48.220 establish his own research lab

NOTE Confidence: 0.9899008

00:28:48.220 --> 00:28:50.059 at SUNY Stony Brook early

NOTE Confidence: 0.9899008

00:28:50.059 --> 00:28:50.880 next year.

NOTE Confidence: 0.872482

00:28:52.065 --> 00:28:53.505 What he is trying to

NOTE Confidence: 0.872482

00:28:53.505 --> 00:28:55.424 figure out is how weather

NOTE Confidence: 0.872482

00:28:55.424 --> 00:28:56.405 gas m d,

NOTE Confidence: 0.9758181

00:28:56.945 --> 00:28:58.325 is really involving

NOTE Confidence: 0.9289884

00:28:58.945 --> 00:29:00.625 MDS as I mentioned, but

NOTE Confidence: 0.9289884

00:29:00.625 --> 00:29:02.465 particularly using the MOS model

NOTE Confidence: 0.9289884

00:29:02.465 --> 00:29:03.664 I just described to you,

NOTE Confidence: 0.9289884

00:29:03.664 --> 00:29:05.265 the double knockout of MDI

NOTE Confidence: 0.9289884

00:29:05.265 --> 00:29:07.130 one and neuron forty six

NOTE Confidence: 0.9289884

00:29:07.130 --> 00:29:07.630 a.

NOTE Confidence: 0.99333894

00:29:08.890 --> 00:29:09.049 So,

NOTE Confidence: 0.77292573

00:29:09.850 --> 00:29:11.210 he started with a single

NOTE Confidence: 0.77292573

00:29:11.210 --> 00:29:12.330 cell or R and C,

NOTE Confidence: 0.96457833

00:29:13.130 --> 00:29:14.809 experiment. And you can see

NOTE Confidence: 0.96457833

00:29:14.809 --> 00:29:16.330 here that compared to the

NOTE Confidence: 0.96457833

00:29:16.330 --> 00:29:17.049 wild type,

NOTE Confidence: 0.887473

00:29:17.610 --> 00:29:18.110 mice,

NOTE Confidence: 0.9648075

00:29:18.784 --> 00:29:20.144 bone marrow cells from the

NOTE Confidence: 0.9648075

00:29:20.144 --> 00:29:22.225 double knockout mice have really

NOTE Confidence: 0.9648075

00:29:22.225 --> 00:29:23.524 increased, expression,

NOTE Confidence: 0.96385044

00:29:24.465 --> 00:29:26.304 in this particular population, which

NOTE Confidence: 0.96385044

00:29:26.304 --> 00:29:27.044 is the,

NOTE Confidence: 0.84494257

00:29:27.745 --> 00:29:29.664 the green is, monocyte and

NOTE Confidence: 0.84494257

00:29:29.664 --> 00:29:30.725 macrophage population.

NOTE Confidence: 0.76901156

00:29:31.669 --> 00:29:32.169 Is

NOTE Confidence: 0.86474454

00:29:33.110 --> 00:29:34.630 is, first of all, the

NOTE Confidence: 0.86474454

00:29:34.630 --> 00:29:36.410 the expression level of SMD

NOTE Confidence: 0.86474454

00:29:36.470 --> 00:29:38.250 is increased. And second,

NOTE Confidence: 0.94271904

00:29:38.950 --> 00:29:40.390 the double knockout mice, they

NOTE Confidence: 0.94271904

00:29:40.390 --> 00:29:41.289 have expanded

NOTE Confidence: 0.81755656

00:29:41.669 --> 00:29:43.049 monocytic and megakarousid

NOTE Confidence: 0.94159675

00:29:43.669 --> 00:29:44.809 macrophage population.

NOTE Confidence: 0.949377

00:29:46.115 --> 00:29:47.875 So that's very interesting because

NOTE Confidence: 0.949377

00:29:47.875 --> 00:29:50.035 monocyte is, is commonly known

NOTE Confidence: 0.949377

00:29:50.035 --> 00:29:50.535 as,

NOTE Confidence: 0.9661944

00:29:50.915 --> 00:29:52.035 as as a cell type

NOTE Confidence: 0.9661944

00:29:52.035 --> 00:29:53.235 that secrete a lot of

NOTE Confidence: 0.9661944

00:29:53.235 --> 00:29:54.295 inflammatory cytokines.

NOTE Confidence: 0.9992723

00:29:56.115 --> 00:29:56.615 So

NOTE Confidence: 0.999616

00:29:57.075 --> 00:29:58.695 he took the same approach

NOTE Confidence: 0.9591072

00:29:59.100 --> 00:30:00.860 as we did before, with

NOTE Confidence: 0.9591072

00:30:00.860 --> 00:30:01.920 our six knockout.

NOTE Confidence: 0.9877383

00:30:02.460 --> 00:30:03.580 And what he did here

NOTE Confidence: 0.9877383

00:30:03.580 --> 00:30:04.080 is,

NOTE Confidence: 0.993891

00:30:04.460 --> 00:30:04.960 again,

NOTE Confidence: 0.89988583

00:30:05.660 --> 00:30:07.840 crossing double knockout mouse mouse

NOTE Confidence: 0.89988583

00:30:07.900 --> 00:30:08.380 with,

NOTE Confidence: 0.92462873

00:30:09.020 --> 00:30:10.620 Gethsemane d knockout. So he

NOTE Confidence: 0.92462873

00:30:10.620 --> 00:30:12.160 made Gethsemane d

NOTE Confidence: 0.81929886

00:30:13.075 --> 00:30:13.735 and GSMD

NOTE Confidence: 0.861433

00:30:14.355 --> 00:30:15.715 neuron forty six a and

NOTE Confidence: 0.861433

00:30:15.715 --> 00:30:17.635 DHP one MDI one triple

NOTE Confidence: 0.861433

00:30:17.635 --> 00:30:18.455 knockout mice.

NOTE Confidence: 0.96924573

00:30:20.115 --> 00:30:21.955 And he used a different

NOTE Confidence: 0.96924573

00:30:21.955 --> 00:30:22.455 approach,

NOTE Confidence: 0.8692814

00:30:23.315 --> 00:30:24.135 than before,

NOTE Confidence: 0.83768445

00:30:24.435 --> 00:30:26.135 our six model, where he

NOTE Confidence: 0.7818312

00:30:26.510 --> 00:30:28.110 got these mouse models and

NOTE Confidence: 0.7818312

00:30:28.110 --> 00:30:29.010 he transplant

NOTE Confidence: 0.82728463

00:30:29.630 --> 00:30:30.670 the either wild type of

NOTE Confidence: 0.82728463

00:30:30.670 --> 00:30:32.190 double knockout or triple knockout

NOTE Confidence: 0.82728463

00:30:32.190 --> 00:30:32.690 might,

NOTE Confidence: 0.9030256

00:30:33.230 --> 00:30:35.070 bone marrow cells into the

NOTE Confidence: 0.9030256

00:30:35.070 --> 00:30:37.170 lethally irradiated recipient mice.

NOTE Confidence: 0.9570861

00:30:37.550 --> 00:30:38.350 So you can have a

NOTE Confidence: 0.9570861

00:30:38.350 --> 00:30:39.790 lot of mice, at the

NOTE Confidence: 0.9570861

00:30:39.790 --> 00:30:41.294 same time. And he looked

NOTE Confidence: 0.9570861

00:30:41.294 --> 00:30:42.414 at the survival of these

NOTE Confidence: 0.9570861

00:30:42.414 --> 00:30:42.914 mice,

NOTE Confidence: 0.98767245

00:30:43.375 --> 00:30:44.575 and you can see that,

NOTE Confidence: 0.8111568

00:30:45.455 --> 00:30:47.135 with double double knockout really

NOTE Confidence: 0.8111568

00:30:47.135 --> 00:30:48.815 die quickly as we've shown

NOTE Confidence: 0.8111568

00:30:48.815 --> 00:30:49.695 before. And,

NOTE Confidence: 0.97536165

00:30:51.054 --> 00:30:52.515 sort of as we expected,

NOTE Confidence: 0.4037303

00:30:52.975 --> 00:30:54.195 guess SMAD knockout,

NOTE Confidence: 0.91823334

00:30:54.500 --> 00:30:55.700 just as our six knock

NOTE Confidence: 0.91823334

00:30:55.700 --> 00:30:57.620 out, really significantly rescued their

NOTE Confidence: 0.91823334

00:30:57.620 --> 00:30:58.120 lethality.

NOTE Confidence: 0.9534817

00:30:58.660 --> 00:31:00.100 And there is also significant

NOTE Confidence: 0.9534817

00:31:00.100 --> 00:31:01.380 rescue of red blood cell

NOTE Confidence: 0.9534817

00:31:01.380 --> 00:31:01.880 count.

NOTE Confidence: 0.92362005

00:31:02.660 --> 00:31:04.500 Platelet count not much, but

NOTE Confidence: 0.92362005

00:31:04.500 --> 00:31:06.500 also a significant rescue of

NOTE Confidence: 0.92362005

00:31:06.500 --> 00:31:08.680 the increased monocyte count.

NOTE Confidence: 0.76628774

00:31:11.365 --> 00:31:13.205 This this, study also,

NOTE Confidence: 0.8797974

00:31:13.525 --> 00:31:15.525 demonstrate that, this disease is

NOTE Confidence: 0.8797974

00:31:15.525 --> 00:31:16.105 a hematopoietic

NOTE Confidence: 0.9388825

00:31:16.405 --> 00:31:18.985 intrinsic because it's trans transferable

NOTE Confidence: 0.9267394

00:31:19.365 --> 00:31:20.325 to, you know, to the

NOTE Confidence: 0.9267394

00:31:20.405 --> 00:31:21.465 to different mouse.

NOTE Confidence: 0.8358124

00:31:24.890 --> 00:31:26.170 So we show that there's

NOTE Confidence: 0.8358124

00:31:26.170 --> 00:31:27.870 an expansion of this

NOTE Confidence: 0.87045515

00:31:28.250 --> 00:31:28.750 monocytic,

NOTE Confidence: 0.7055199

00:31:29.290 --> 00:31:29.790 microphage,

NOTE Confidence: 0.8879881

00:31:30.410 --> 00:31:30.910 population.

NOTE Confidence: 0.9317161

00:31:31.690 --> 00:31:33.710 So we look, more closely,

NOTE Confidence: 0.91758347

00:31:34.410 --> 00:31:36.350 using this flow cytometry assay.

NOTE Confidence: 0.9285604

00:31:36.890 --> 00:31:37.905 As you can see that

NOTE Confidence: 0.9285604

00:31:37.905 --> 00:31:39.365 in the double knockout mice

NOTE Confidence: 0.9285604

00:31:39.585 --> 00:31:40.945 in the bone marrow, you

NOTE Confidence: 0.9285604

00:31:40.945 --> 00:31:42.325 have, not only,

NOTE Confidence: 0.83288676

00:31:42.945 --> 00:31:44.945 a growth overall overall growth

NOTE Confidence: 0.83288676

00:31:45.025 --> 00:31:47.285 overall expansion of monocyte macrophage

NOTE Confidence: 0.83288676

00:31:47.345 --> 00:31:47.845 population.

NOTE Confidence: 0.9982202

00:31:48.225 --> 00:31:49.265 You can also see the

NOTE Confidence: 0.9982202

00:31:49.265 --> 00:31:50.725 accumulation of this immature

NOTE Confidence: 0.92434883

00:31:51.425 --> 00:31:52.245 where you have

NOTE Confidence: 0.7188769

00:31:53.510 --> 00:31:55.610 RY six g negative negativity

NOTE Confidence: 0.9407223

00:31:56.149 --> 00:31:57.669 and low expression of r

NOTE Confidence: 0.9407223

00:31:58.230 --> 00:31:59.590 RY six c, which is

NOTE Confidence: 0.9407223

00:31:59.590 --> 00:32:00.950 a monocyte marker. So this

NOTE Confidence: 0.9407223

00:32:00.950 --> 00:32:02.250 is a kind of immature

NOTE Confidence: 0.9407223

00:32:02.309 --> 00:32:03.289 monocyte population.

NOTE Confidence: 0.98749673

00:32:03.669 --> 00:32:04.409 It's particularly

NOTE Confidence: 0.97029096

00:32:04.710 --> 00:32:05.990 increased in in the in

NOTE Confidence: 0.97029096

00:32:05.990 --> 00:32:07.485 the double knockout mouse model.

NOTE Confidence: 0.9735672

00:32:07.965 --> 00:32:10.465 And this, phenotype is reverted

NOTE Confidence: 0.91235274

00:32:11.005 --> 00:32:12.545 with a knockout of gastronomy

NOTE Confidence: 0.91235274

00:32:12.684 --> 00:32:13.184 d.

NOTE Confidence: 0.7921516

00:32:13.565 --> 00:32:13.965 So,

NOTE Confidence: 0.9060271

00:32:14.365 --> 00:32:15.424 this is a quantified,

NOTE Confidence: 0.91559744

00:32:16.765 --> 00:32:18.304 of the flow flow data.

NOTE Confidence: 0.9325676

00:32:21.070 --> 00:32:22.429 So this is again the,

NOTE Confidence: 0.8768218

00:32:23.309 --> 00:32:25.230 single cell, RNA seq data

NOTE Confidence: 0.8768218

00:32:25.230 --> 00:32:26.509 so you can, you know,

NOTE Confidence: 0.8768218

00:32:26.509 --> 00:32:27.789 as you can as you

NOTE Confidence: 0.8768218

00:32:27.789 --> 00:32:29.230 can imagine, you can characterize

NOTE Confidence: 0.8768218

00:32:29.230 --> 00:32:30.429 a lot of different cell

NOTE Confidence: 0.8768218

00:32:30.429 --> 00:32:30.929 populations,

NOTE Confidence: 0.9784543

00:32:31.230 --> 00:32:32.450 not only hematopoietic,

NOTE Confidence: 0.9467894

00:32:33.184 --> 00:32:34.865 but also stromal cells as

NOTE Confidence: 0.9467894

00:32:34.865 --> 00:32:35.924 well as mesenchymal

NOTE Confidence: 0.83041304

00:32:37.825 --> 00:32:38.885 stem cell populations.

NOTE Confidence: 0.96112823

00:32:40.865 --> 00:32:41.345 So,

NOTE Confidence: 0.9836871

00:32:42.465 --> 00:32:43.684 so but interestingly,

NOTE Confidence: 0.7734354

00:32:44.145 --> 00:32:46.225 if you transplant this double

NOTE Confidence: 0.7734354

00:32:46.225 --> 00:32:47.525 knockout mouse model,

NOTE Confidence: 0.98338324

00:32:48.059 --> 00:32:49.259 bone marrow cells into the

NOTE Confidence: 0.98338324

00:32:49.259 --> 00:32:50.159 recipient mice,

NOTE Confidence: 0.99148995

00:32:51.259 --> 00:32:53.019 the changes are not just

NOTE Confidence: 0.99148995

00:32:53.019 --> 00:32:54.539 happening in the double knockout

NOTE Confidence: 0.99148995

00:32:54.539 --> 00:32:56.539 donor cells. These donor cells

NOTE Confidence: 0.99148995

00:32:56.539 --> 00:32:57.279 can also,

NOTE Confidence: 0.7964858

00:32:58.139 --> 00:33:00.639 remodel the recipients non hematopoietic

NOTE Confidence: 0.6756582

00:33:01.179 --> 00:33:02.159 bone marrow environment,

NOTE Confidence: 0.96261513

00:33:02.460 --> 00:33:03.795 where you can see that,

NOTE Confidence: 0.8812522

00:33:04.355 --> 00:33:06.915 as as expected, neutrophils from

NOTE Confidence: 0.8812522

00:33:06.915 --> 00:33:08.515 the donor double knockout mouse

NOTE Confidence: 0.8812522

00:33:08.515 --> 00:33:10.275 model, they have once you

NOTE Confidence: 0.8812522

00:33:10.275 --> 00:33:12.035 have knockout of SNMD, they

NOTE Confidence: 0.8812522

00:33:12.035 --> 00:33:13.895 have reduction of these inflammatory

NOTE Confidence: 0.8812522

00:33:14.115 --> 00:33:14.615 markers,

NOTE Confidence: 0.87323827

00:33:15.075 --> 00:33:16.355 for example, s s one

NOTE Confidence: 0.87323827

00:33:16.355 --> 00:33:17.495 hundred and eighty nine,

NOTE Confidence: 0.8720727

00:33:18.210 --> 00:33:19.410 as well as the urethral

NOTE Confidence: 0.8720727

00:33:19.410 --> 00:33:19.910 population.

NOTE Confidence: 0.9221585

00:33:20.290 --> 00:33:21.510 But the in the fibroblast

NOTE Confidence: 0.9221585

00:33:21.730 --> 00:33:22.690 population as well as the

NOTE Confidence: 0.9221585

00:33:22.690 --> 00:33:24.530 mesenchymal stromal cells where they

NOTE Confidence: 0.9221585

00:33:24.530 --> 00:33:25.809 do not have these kind

NOTE Confidence: 0.9221585

00:33:25.809 --> 00:33:26.470 of genetic

NOTE Confidence: 0.80477095

00:33:27.730 --> 00:33:28.230 manipulations,

NOTE Confidence: 0.9972237

00:33:29.010 --> 00:33:30.210 their levels are also

NOTE Confidence: 0.9382009

00:33:31.654 --> 00:33:33.014 their level s one hundred

NOTE Confidence: 0.9382009

00:33:33.014 --> 00:33:33.894 and eighty nine levels are

NOTE Confidence: 0.9382009

00:33:33.894 --> 00:33:34.715 also decreased.

NOTE Confidence: 0.92625654

00:33:35.335 --> 00:33:36.794 So that's that's an interesting,

NOTE Confidence: 0.9995886

00:33:37.095 --> 00:33:38.475 finding from this model.

NOTE Confidence: 0.96543276

00:33:41.735 --> 00:33:42.235 So,

NOTE Confidence: 0.99349254

00:33:43.014 --> 00:33:44.455 so that also leads us

NOTE Confidence: 0.99349254

00:33:44.455 --> 00:33:45.514 to wonder whether

NOTE Confidence: 0.7783818

00:33:46.070 --> 00:33:47.190 what if you knock out

NOTE Confidence: 0.7783818

00:33:47.190 --> 00:33:48.710 the guesstimate in the bone

NOTE Confidence: 0.7783818

00:33:48.710 --> 00:33:49.450 marrow microenvironment?

NOTE Confidence: 0.9893142

00:33:49.910 --> 00:33:51.210 Would that also can,

NOTE Confidence: 0.9324009

00:33:51.590 --> 00:33:53.190 you know, revert the disease

NOTE Confidence: 0.9324009

00:33:53.190 --> 00:33:53.690 phenotype?

NOTE Confidence: 0.9984247

00:33:53.990 --> 00:33:55.370 So that's what he did.

NOTE Confidence: 0.95945466

00:33:55.990 --> 00:33:57.350 So he, again, he took

NOTE Confidence: 0.95945466

00:33:57.350 --> 00:33:58.570 the wild type mice,

NOTE Confidence: 0.94946206

00:33:59.585 --> 00:34:00.705 wild type donor cells,

NOTE Confidence: 0.9123184

00:34:02.065 --> 00:34:03.285 this oh, sorry.

NOTE Confidence: 0.8756158

00:34:03.665 --> 00:34:04.705 He he he took the

NOTE Confidence: 0.8756158

00:34:04.705 --> 00:34:06.805 top knockout mice and transplant

NOTE Confidence: 0.8756158

00:34:06.865 --> 00:34:08.225 them into wild type, either

NOTE Confidence: 0.8756158

00:34:08.225 --> 00:34:10.405 wild type or guesstimating knockout

NOTE Confidence: 0.8756158

00:34:10.625 --> 00:34:12.705 recipient mice. So in this,

NOTE Confidence: 0.8756158

00:34:13.025 --> 00:34:13.925 in these mice,

NOTE Confidence: 0.934273

00:34:14.450 --> 00:34:16.130 SMD are completely knocked out

NOTE Confidence: 0.934273

00:34:16.130 --> 00:34:17.890 in in every tissue type

NOTE Confidence: 0.934273

00:34:17.890 --> 00:34:18.390 type,

NOTE Confidence: 0.9138238

00:34:18.930 --> 00:34:20.050 in in this in this

NOTE Confidence: 0.9138238

00:34:20.050 --> 00:34:20.550 mice.

NOTE Confidence: 0.9038083

00:34:21.170 --> 00:34:22.770 And then, actually, he, kind

NOTE Confidence: 0.9038083

00:34:22.770 --> 00:34:23.830 of, disappointed,

NOTE Confidence: 0.946697

00:34:24.210 --> 00:34:25.810 that he didn't find any

NOTE Confidence: 0.946697

00:34:25.810 --> 00:34:27.430 rescue of the of,

NOTE Confidence: 0.99784267

00:34:28.175 --> 00:34:28.755 the phenotypes

NOTE Confidence: 0.982563

00:34:29.455 --> 00:34:30.815 as what we have shown

NOTE Confidence: 0.982563

00:34:30.815 --> 00:34:31.315 before,

NOTE Confidence: 0.86767805

00:34:32.255 --> 00:34:34.094 using whole body guesstimate did

NOTE Confidence: 0.86767805

00:34:34.094 --> 00:34:35.775 not count. So that indicate

NOTE Confidence: 0.86767805

00:34:35.775 --> 00:34:36.175 that,

NOTE Confidence: 0.99901366

00:34:36.575 --> 00:34:37.075 probably

NOTE Confidence: 0.81534165

00:34:37.375 --> 00:34:38.735 not caught of GastroMD in

NOTE Confidence: 0.81534165

00:34:38.735 --> 00:34:39.875 the bone marrow microenvironment

NOTE Confidence: 0.9859491

00:34:40.415 --> 00:34:40.915 only

NOTE Confidence: 0.9994893

00:34:41.270 --> 00:34:42.630 may not be sufficient to

NOTE Confidence: 0.9994893

00:34:42.630 --> 00:34:43.130 rescue

NOTE Confidence: 0.8872598

00:34:43.510 --> 00:34:45.270 this disease phenotype because we

NOTE Confidence: 0.8872598

00:34:45.270 --> 00:34:46.010 thought that

NOTE Confidence: 0.9012819

00:34:46.310 --> 00:34:48.069 this, disease is quite strong

NOTE Confidence: 0.9012819

00:34:48.069 --> 00:34:49.270 because they can change from

NOTE Confidence: 0.9012819

00:34:49.270 --> 00:34:51.290 MDS to acute myeloid leukemia.

NOTE Confidence: 0.9012819

00:34:51.589 --> 00:34:53.190 And the inflammation is pretty

NOTE Confidence: 0.9012819

00:34:53.190 --> 00:34:55.109 pretty strong, so knockout of,

NOTE Confidence: 0.9012819

00:34:55.589 --> 00:34:56.089 or

NOTE Confidence: 0.9026681

00:34:56.805 --> 00:34:58.085 reduction in the inflammation in

NOTE Confidence: 0.9026681

00:34:58.085 --> 00:34:59.065 the bone marrow microenvironment

NOTE Confidence: 0.9926846

00:34:59.364 --> 00:35:00.505 may not be sufficient

NOTE Confidence: 0.9833128

00:35:00.885 --> 00:35:02.505 to revert this disease phenotype.

NOTE Confidence: 0.8612154

00:35:04.005 --> 00:35:05.685 So, so we then turn

NOTE Confidence: 0.8612154

00:35:05.685 --> 00:35:07.385 to a more milder,

NOTE Confidence: 0.95555747

00:35:08.325 --> 00:35:08.580 model

NOTE Confidence: 0.8261632

00:35:13.060 --> 00:35:13.800 MOS model.

NOTE Confidence: 0.9571108

00:35:14.180 --> 00:35:15.219 And tattoo, I mentioned a

NOTE Confidence: 0.9571108

00:35:15.219 --> 00:35:16.340 little bit in the beginning,

NOTE Confidence: 0.9571108

00:35:16.340 --> 00:35:18.100 but we know that tattoo

NOTE Confidence: 0.9571108

00:35:18.100 --> 00:35:19.480 is, is evolving

NOTE Confidence: 0.80097884

00:35:19.780 --> 00:35:20.760 in in the

NOTE Confidence: 0.8655287

00:35:21.665 --> 00:35:22.165 demystylation

NOTE Confidence: 0.94021535

00:35:22.705 --> 00:35:23.025 of,

NOTE Confidence: 0.8626444

00:35:23.825 --> 00:35:25.585 of chromatin and where they

NOTE Confidence: 0.8626444

00:35:25.585 --> 00:35:26.405 change from,

NOTE Confidence: 0.8135426

00:35:27.025 --> 00:35:27.844 five mysocerosine

NOTE Confidence: 0.9149888

00:35:28.305 --> 00:35:29.285 to five hydroxyamysocerosine

NOTE Confidence: 0.8037017

00:35:30.385 --> 00:35:31.665 and that lead to eventual

NOTE Confidence: 0.8037017

00:35:31.665 --> 00:35:32.165 demystylation.

NOTE Confidence: 0.98468035

00:35:33.025 --> 00:35:34.484 And they are also involved,

NOTE Confidence: 0.9593629

00:35:35.239 --> 00:35:37.020 in showing multiple publications

NOTE Confidence: 0.99104583

00:35:37.719 --> 00:35:38.380 that can,

NOTE Confidence: 0.93247026

00:35:38.760 --> 00:35:40.359 you know, tattoo is can

NOTE Confidence: 0.93247026

00:35:40.359 --> 00:35:42.359 repress the secretion of different

NOTE Confidence: 0.93247026

00:35:42.359 --> 00:35:44.119 cytokines including r one beta

NOTE Confidence: 0.93247026

00:35:44.119 --> 00:35:45.880 and r six in different

NOTE Confidence: 0.93247026

00:35:45.880 --> 00:35:46.780 tissue types.

NOTE Confidence: 0.9971308

00:35:47.655 --> 00:35:48.795 So we just wonder

NOTE Confidence: 0.983002

00:35:49.175 --> 00:35:50.695 if we do the same

NOTE Confidence: 0.983002

00:35:50.695 --> 00:35:51.195 experiment

NOTE Confidence: 0.8732384

00:35:51.575 --> 00:35:53.915 and transplant tattoo knockout mice

NOTE Confidence: 0.8732384

00:35:54.135 --> 00:35:55.575 where people have shown well

NOTE Confidence: 0.8732384

00:35:55.575 --> 00:35:57.355 established that they develop,

NOTE Confidence: 0.7084762

00:35:59.015 --> 00:35:59.515 inflammatory,

NOTE Confidence: 0.94964814

00:36:01.119 --> 00:36:02.260 myeloid disorders

NOTE Confidence: 0.90259904

00:36:02.800 --> 00:36:03.700 in these mice.

NOTE Confidence: 0.87939996

00:36:04.160 --> 00:36:05.760 Whether we transplant these knock

NOTE Confidence: 0.87939996

00:36:05.760 --> 00:36:06.080 on,

NOTE Confidence: 0.77017003

00:36:06.560 --> 00:36:08.320 bone marrow cells into the

NOTE Confidence: 0.77017003

00:36:08.320 --> 00:36:09.680 water into water type or

NOTE Confidence: 0.77017003

00:36:09.680 --> 00:36:10.560 a gas and the knock

NOTE Confidence: 0.77017003

00:36:10.560 --> 00:36:11.520 on it to see if

NOTE Confidence: 0.77017003

00:36:11.520 --> 00:36:12.580 there's any differences.

NOTE Confidence: 0.99925345

00:36:14.005 --> 00:36:15.125 So that's what we did.

NOTE Confidence: 0.9178498

00:36:16.005 --> 00:36:16.965 We can see that you

NOTE Confidence: 0.9178498

00:36:16.965 --> 00:36:18.645 can see that, once you

NOTE Confidence: 0.9178498

00:36:18.645 --> 00:36:20.565 have tattoo transplanting to wild

NOTE Confidence: 0.9178498

00:36:20.565 --> 00:36:21.285 type, there's a

NOTE Confidence: 0.9176033

00:36:21.844 --> 00:36:22.905 as we expected,

NOTE Confidence: 0.97022724

00:36:23.364 --> 00:36:25.285 the spleen is huge because

NOTE Confidence: 0.97022724

00:36:25.285 --> 00:36:26.425 they have this inflammation,

NOTE Confidence: 0.8595371

00:36:28.080 --> 00:36:29.580 and the extra medullary erossoposis,

NOTE Confidence: 0.8595371

00:36:29.719 --> 00:36:31.080 that's how they lead that

NOTE Confidence: 0.8595371

00:36:31.080 --> 00:36:32.840 lead to the enlargement of

NOTE Confidence: 0.8595371

00:36:32.840 --> 00:36:33.340 spleen.

NOTE Confidence: 0.9563259

00:36:33.800 --> 00:36:35.180 So if you knock out

NOTE Confidence: 0.73508483

00:36:35.560 --> 00:36:37.400 guess if you transplant tattoo

NOTE Confidence: 0.73508483

00:36:37.400 --> 00:36:38.920 into Casem D, knock out

NOTE Confidence: 0.73508483

00:36:38.920 --> 00:36:39.900 bone marrow microenvironment,

NOTE Confidence: 0.9727311

00:36:41.325 --> 00:36:42.785 This isn't the the

NOTE Confidence: 0.9209186

00:36:43.165 --> 00:36:44.145 the splenomegaly

NOTE Confidence: 0.9888413

00:36:44.445 --> 00:36:45.505 is not there anymore.

NOTE Confidence: 0.9723044

00:36:46.445 --> 00:36:47.964 And looking at the bone

NOTE Confidence: 0.9723044

00:36:47.964 --> 00:36:48.464 marrow,

NOTE Confidence: 0.96162415

00:36:49.005 --> 00:36:50.045 you can see that if

NOTE Confidence: 0.96162415

00:36:50.045 --> 00:36:52.205 you transplant knockout tattoo knockout

NOTE Confidence: 0.96162415

00:36:52.205 --> 00:36:53.165 into the wild type bone

NOTE Confidence: 0.96162415

00:36:53.165 --> 00:36:53.665 marrow,

NOTE Confidence: 0.9885426

00:36:54.125 --> 00:36:55.105 wild type recipient,

NOTE Confidence: 0.9478539

00:36:55.500 --> 00:36:57.040 You can see this inflammatory

NOTE Confidence: 0.9478539

00:36:57.180 --> 00:36:58.880 changes as well as dysplasia

NOTE Confidence: 0.68649554

00:36:59.500 --> 00:37:00.800 kind of infiltration

NOTE Confidence: 0.9692579

00:37:01.100 --> 00:37:03.260 of, immature appearance cells. It's

NOTE Confidence: 0.9692579

00:37:03.260 --> 00:37:04.400 not the full blown,

NOTE Confidence: 0.8227782

00:37:05.020 --> 00:37:05.520 leukemia,

NOTE Confidence: 0.94559693

00:37:06.300 --> 00:37:07.600 but they have some dysplastic

NOTE Confidence: 0.94559693

00:37:07.660 --> 00:37:08.160 changes.

NOTE Confidence: 0.9208729

00:37:08.700 --> 00:37:09.520 You know, most

NOTE Confidence: 0.9796298

00:37:10.215 --> 00:37:11.175 morphology is a little bit

NOTE Confidence: 0.9796298

00:37:11.175 --> 00:37:12.535 difficult compared to a human

NOTE Confidence: 0.9796298

00:37:12.535 --> 00:37:13.895 morphology, but I can see

NOTE Confidence: 0.9796298

00:37:13.975 --> 00:37:14.695 all I can see is

NOTE Confidence: 0.9796298

00:37:14.695 --> 00:37:15.195 there's

NOTE Confidence: 0.8346975

00:37:15.575 --> 00:37:17.275 a there's a, ineffective

NOTE Confidence: 0.95028067

00:37:17.575 --> 00:37:18.075 hematopoiesis

NOTE Confidence: 0.9900255

00:37:18.455 --> 00:37:19.755 in this in this model.

NOTE Confidence: 0.96846247

00:37:20.135 --> 00:37:21.435 And you can see splenomegaly

NOTE Confidence: 0.8999088

00:37:21.735 --> 00:37:23.335 as well as disruption of

NOTE Confidence: 0.8999088

00:37:23.335 --> 00:37:23.835 normal

NOTE Confidence: 0.9875319

00:37:24.295 --> 00:37:25.114 spleen architecture

NOTE Confidence: 0.9812169

00:37:25.950 --> 00:37:26.770 when you have

NOTE Confidence: 0.86754876

00:37:27.150 --> 00:37:29.230 tattoo knockout transplant into wild

NOTE Confidence: 0.86754876

00:37:29.230 --> 00:37:29.969 type recipient.

NOTE Confidence: 0.95661765

00:37:30.510 --> 00:37:31.250 This is,

NOTE Confidence: 0.9908099

00:37:32.430 --> 00:37:33.230 I would say,

NOTE Confidence: 0.9679539

00:37:33.630 --> 00:37:34.130 predominantly

NOTE Confidence: 0.997806

00:37:34.589 --> 00:37:35.089 reverted

NOTE Confidence: 0.9256969

00:37:35.469 --> 00:37:36.910 when the tattoo knockout mice,

NOTE Confidence: 0.9256969

00:37:37.150 --> 00:37:38.670 bone marrow cells are transplanted

NOTE Confidence: 0.9256969

00:37:38.670 --> 00:37:40.750 into gastronomy d knockout bone

NOTE Confidence: 0.9256969

00:37:40.750 --> 00:37:41.475 marrow recipient,

NOTE Confidence: 0.99736613

00:37:42.435 --> 00:37:43.495 recipient mice.

NOTE Confidence: 0.8969404

00:37:46.835 --> 00:37:47.235 So,

NOTE Confidence: 0.981261

00:37:47.875 --> 00:37:48.995 and when we look at

NOTE Confidence: 0.981261

00:37:48.995 --> 00:37:49.975 the flow cytometry,

NOTE Confidence: 0.9811637

00:37:50.755 --> 00:37:52.195 you can see, as we

NOTE Confidence: 0.9811637

00:37:52.195 --> 00:37:52.695 expected,

NOTE Confidence: 0.944884

00:37:53.155 --> 00:37:54.295 our six g,

NOTE Confidence: 0.8602416

00:37:54.995 --> 00:37:56.820 negative and our c our

NOTE Confidence: 0.8602416

00:37:56.820 --> 00:37:58.040 y six c molecule

NOTE Confidence: 0.9333238

00:37:58.500 --> 00:37:59.720 monocytic population

NOTE Confidence: 0.85703313

00:38:00.180 --> 00:38:01.960 that are increased with tattoo

NOTE Confidence: 0.85703313

00:38:02.020 --> 00:38:03.640 transplantation to water recipient

NOTE Confidence: 0.9746393

00:38:04.260 --> 00:38:05.000 are reduced,

NOTE Confidence: 0.94003105

00:38:05.300 --> 00:38:06.920 when they transplant into guesstimating

NOTE Confidence: 0.94003105

00:38:06.980 --> 00:38:07.880 knockout mice,

NOTE Confidence: 0.93380785

00:38:09.455 --> 00:38:10.495 both in the bone marrow,

NOTE Confidence: 0.93380785

00:38:10.735 --> 00:38:11.855 in the peripheral blood as

NOTE Confidence: 0.93380785

00:38:11.855 --> 00:38:12.575 well as in the bone

NOTE Confidence: 0.93380785

00:38:12.575 --> 00:38:13.075 marrow.

NOTE Confidence: 0.7827212

00:38:13.455 --> 00:38:14.515 CD eleven b,

NOTE Confidence: 0.94761926

00:38:14.975 --> 00:38:15.475 granulocytic,

NOTE Confidence: 0.9830464

00:38:16.175 --> 00:38:16.675 cells,

NOTE Confidence: 0.92207825

00:38:17.295 --> 00:38:19.055 myeloid cells as well are

NOTE Confidence: 0.92207825

00:38:19.055 --> 00:38:19.875 also reduced,

NOTE Confidence: 0.982135

00:38:20.415 --> 00:38:22.114 when you transplant into guesstimating

NOTE Confidence: 0.982135

00:38:22.255 --> 00:38:22.755 knockout.

NOTE Confidence: 0.8455639

00:38:23.989 --> 00:38:25.349 B cells that are re

NOTE Confidence: 0.8455639

00:38:25.510 --> 00:38:27.829 repressed when tattoo are transplanted

NOTE Confidence: 0.8455639

00:38:27.829 --> 00:38:28.569 into WALTAP

NOTE Confidence: 0.9662536

00:38:29.030 --> 00:38:30.790 are, are recovered when they

NOTE Confidence: 0.9662536

00:38:30.790 --> 00:38:32.569 transplant into GSMD knockout.

NOTE Confidence: 0.89594364

00:38:33.030 --> 00:38:34.969 And the c especially, significantly,

NOTE Confidence: 0.8094886

00:38:35.270 --> 00:38:37.210 CD seventy one that represent

NOTE Confidence: 0.6667893

00:38:38.614 --> 00:38:39.994 extra medullary erossopoises,

NOTE Confidence: 0.9169561

00:38:40.775 --> 00:38:42.075 the expansion of erossoprogenerate

NOTE Confidence: 0.9973527

00:38:42.535 --> 00:38:43.035 populations

NOTE Confidence: 0.9251258

00:38:43.414 --> 00:38:44.315 in the spleen,

NOTE Confidence: 0.6192625

00:38:44.934 --> 00:38:45.434 remarkably

NOTE Confidence: 0.75973135

00:38:45.974 --> 00:38:47.734 reverted when they transplanted into

NOTE Confidence: 0.75973135

00:38:47.734 --> 00:38:49.035 Casimod knock out.

NOTE Confidence: 0.89161015

00:38:50.934 --> 00:38:53.239 So this this data demonstrate

NOTE Confidence: 0.89161015

00:38:53.300 --> 00:38:54.040 that SMD,

NOTE Confidence: 0.8885684

00:38:54.420 --> 00:38:55.860 knock out of SMD in

NOTE Confidence: 0.8885684

00:38:55.860 --> 00:38:57.160 the bone marrow microenvironment

NOTE Confidence: 0.9304108

00:38:58.500 --> 00:38:59.320 can significantly

NOTE Confidence: 0.92060417

00:38:59.700 --> 00:39:02.200 revert the inflammatory changes or

NOTE Confidence: 0.92060417

00:39:02.260 --> 00:39:04.040 tetra mediated myeloid diseases,

NOTE Confidence: 0.9306909

00:39:05.344 --> 00:39:05.844 when,

NOTE Confidence: 0.9025353

00:39:07.344 --> 00:39:09.025 in this particular mouse model.

NOTE Confidence: 0.9025353

00:39:09.025 --> 00:39:10.385 So we also see that,

NOTE Confidence: 0.9025353

00:39:10.704 --> 00:39:12.085 the different cytokines,

NOTE Confidence: 0.88689214

00:39:12.785 --> 00:39:13.505 different side,

NOTE Confidence: 0.99568224

00:39:13.905 --> 00:39:14.964 inflammatory pathways

NOTE Confidence: 0.91786194

00:39:15.344 --> 00:39:16.724 are also upregulated.

NOTE Confidence: 0.90462536

00:39:17.480 --> 00:39:19.160 One tattoo are transplanted into

NOTE Confidence: 0.90462536

00:39:19.160 --> 00:39:20.140 wild type group,

NOTE Confidence: 0.8844145

00:39:20.520 --> 00:39:21.799 but, I don't see have

NOTE Confidence: 0.8844145

00:39:21.799 --> 00:39:23.319 data here, but I these

NOTE Confidence: 0.8844145

00:39:23.319 --> 00:39:25.020 changes are kind of reverted

NOTE Confidence: 0.8844145

00:39:25.160 --> 00:39:26.440 when they are transplanted into

NOTE Confidence: 0.8844145

00:39:26.440 --> 00:39:28.299 calcium D knockout group.

NOTE Confidence: 0.96741945

00:39:31.035 --> 00:39:32.094 So we can also,

NOTE Confidence: 0.92667556

00:39:32.714 --> 00:39:33.214 really,

NOTE Confidence: 0.9718593

00:39:34.075 --> 00:39:34.974 look at this,

NOTE Confidence: 0.8910327

00:39:35.594 --> 00:39:36.734 through a microscope,

NOTE Confidence: 0.99019146

00:39:37.755 --> 00:39:38.895 by doing immunofluorescence.

NOTE Confidence: 0.8549563

00:39:40.234 --> 00:39:41.454 And this is a

NOTE Confidence: 0.98395574

00:39:43.530 --> 00:39:44.670 confocal immunofluorescence

NOTE Confidence: 0.86966014

00:39:45.210 --> 00:39:45.710 study,

NOTE Confidence: 0.8577429

00:39:46.969 --> 00:39:48.250 and where you can see

NOTE Confidence: 0.8577429

00:39:48.250 --> 00:39:49.290 what we we stained the

NOTE Confidence: 0.8577429

00:39:49.290 --> 00:39:50.650 gas MND in N terminal

NOTE Confidence: 0.8577429

00:39:50.650 --> 00:39:52.010 domain. This is a specific

NOTE Confidence: 0.8577429

00:39:52.010 --> 00:39:53.370 for N terminal domain that

NOTE Confidence: 0.8577429

00:39:53.370 --> 00:39:54.969 indicate the inflammation in the

NOTE Confidence: 0.8577429

00:39:54.969 --> 00:39:56.855 bone marrow. We also stained

NOTE Confidence: 0.8577429

00:39:56.855 --> 00:39:58.135 CD two seventy one's,

NOTE Confidence: 0.85313004

00:39:58.775 --> 00:40:00.315 mesenchymal stromal marker,

NOTE Confidence: 0.88902783

00:40:00.614 --> 00:40:01.974 as well as UEA one

NOTE Confidence: 0.88902783

00:40:01.974 --> 00:40:03.815 that's also a, I think

NOTE Confidence: 0.88902783

00:40:03.815 --> 00:40:04.474 the it's,

NOTE Confidence: 0.9373211

00:40:05.415 --> 00:40:07.035 also a stromal cell marker.

NOTE Confidence: 0.9373211

00:40:07.175 --> 00:40:08.315 You can see that,

NOTE Confidence: 0.89248943

00:40:10.270 --> 00:40:11.550 water to water type, there's

NOTE Confidence: 0.89248943

00:40:11.550 --> 00:40:13.330 not much upregulation of guesstimating

NOTE Confidence: 0.7804637

00:40:13.790 --> 00:40:14.370 n terminals.

NOTE Confidence: 0.9080404

00:40:14.750 --> 00:40:16.110 But tattooed to water type,

NOTE Confidence: 0.9080404

00:40:16.110 --> 00:40:16.990 you can see a whole

NOTE Confidence: 0.9080404

00:40:16.990 --> 00:40:18.590 bone marrow is inflamed. It's

NOTE Confidence: 0.9080404

00:40:18.590 --> 00:40:20.430 kind of everywhere is has

NOTE Confidence: 0.9080404

00:40:20.430 --> 00:40:22.910 this red guesstimating n terminal

NOTE Confidence: 0.9080404

00:40:22.910 --> 00:40:23.410 deletion,

NOTE Confidence: 0.97954625

00:40:23.870 --> 00:40:25.010 deleted mutant,

NOTE Confidence: 0.8388026

00:40:25.825 --> 00:40:26.405 not mutant,

NOTE Confidence: 0.973521

00:40:26.945 --> 00:40:28.085 isoform expression.

NOTE Confidence: 0.9941114

00:40:28.705 --> 00:40:29.844 But if you transplant

NOTE Confidence: 0.8344456

00:40:30.145 --> 00:40:32.565 tattoo knockout to GSMD knockout,

NOTE Confidence: 0.90307266

00:40:32.945 --> 00:40:34.405 model, recipient model,

NOTE Confidence: 0.9910148

00:40:35.025 --> 00:40:36.965 this inflammation is significantly

NOTE Confidence: 0.9973147

00:40:37.265 --> 00:40:37.765 reduced.

NOTE Confidence: 0.9548037

00:40:39.290 --> 00:40:40.730 Specifically, you can see the

NOTE Confidence: 0.9548037

00:40:40.730 --> 00:40:43.130 co, localization of the stromal

NOTE Confidence: 0.9548037

00:40:43.130 --> 00:40:43.630 markers

NOTE Confidence: 0.7905007

00:40:44.170 --> 00:40:45.770 with GSM d. So that

NOTE Confidence: 0.7905007

00:40:45.770 --> 00:40:46.750 indicate that

NOTE Confidence: 0.8715318

00:40:47.130 --> 00:40:48.810 it's not just the donor

NOTE Confidence: 0.8715318

00:40:48.810 --> 00:40:50.430 cells that with TAT2 mutation

NOTE Confidence: 0.9780485

00:40:50.810 --> 00:40:51.710 that are inflammatory.

NOTE Confidence: 0.97802037

00:40:52.525 --> 00:40:53.645 The bone marrow whole bone

NOTE Confidence: 0.97802037

00:40:53.645 --> 00:40:55.185 marrow environment is inflammatory.

NOTE Confidence: 0.82767725

00:40:55.805 --> 00:40:57.585 But with GASMAD knockout,

NOTE Confidence: 0.96634716

00:40:58.605 --> 00:40:59.725 you don't you don't have

NOTE Confidence: 0.96634716

00:41:00.045 --> 00:41:01.165 of course, you don't have

NOTE Confidence: 0.96634716

00:41:01.165 --> 00:41:02.364 GASMAD in the bone marrow

NOTE Confidence: 0.96634716

00:41:02.364 --> 00:41:04.364 microenvironment, but the the the

NOTE Confidence: 0.96634716

00:41:04.364 --> 00:41:06.445 the donor hematopoietic cells, their

NOTE Confidence: 0.96634716

00:41:06.445 --> 00:41:07.620 inflammation is also

NOTE Confidence: 0.98964065

00:41:10.180 --> 00:41:11.080 reduced. So,

NOTE Confidence: 0.9180067

00:41:11.780 --> 00:41:13.240 back to the single cell

NOTE Confidence: 0.9180067

00:41:13.380 --> 00:41:13.880 experiment,

NOTE Confidence: 0.9905112

00:41:14.820 --> 00:41:16.440 when we took the,

NOTE Confidence: 0.9630094

00:41:16.980 --> 00:41:18.340 bone marrow cells from these

NOTE Confidence: 0.9630094

00:41:18.340 --> 00:41:20.260 mice, from these transplanted mice,

NOTE Confidence: 0.9630094

00:41:20.260 --> 00:41:22.040 you can see that, as

NOTE Confidence: 0.7081975

00:41:22.434 --> 00:41:24.275 as expected, there's a outbreak

NOTE Confidence: 0.7081975

00:41:24.434 --> 00:41:26.934 significant outbreak of this inflammatory

NOTE Confidence: 0.85007864

00:41:27.555 --> 00:41:29.094 macrophages or monocytes

NOTE Confidence: 0.927675

00:41:29.714 --> 00:41:31.555 when you transplant tattoo knockout

NOTE Confidence: 0.927675

00:41:31.555 --> 00:41:33.015 to wild type, mice.

NOTE Confidence: 0.81274873

00:41:34.035 --> 00:41:35.395 But you can also see

NOTE Confidence: 0.81274873

00:41:35.395 --> 00:41:37.154 a significant outbreak ratio of

NOTE Confidence: 0.81274873

00:41:37.154 --> 00:41:39.080 CD four poly T cells,

NOTE Confidence: 0.81274873

00:41:39.080 --> 00:41:40.140 which is a reverted

NOTE Confidence: 0.68403023

00:41:40.520 --> 00:41:41.340 when tattoo

NOTE Confidence: 0.7723836

00:41:41.640 --> 00:41:43.080 knock out or transplanted to

NOTE Confidence: 0.7723836

00:41:43.080 --> 00:41:44.620 get SMD knock out mice.

NOTE Confidence: 0.98137033

00:41:45.080 --> 00:41:46.860 So this is interesting because,

NOTE Confidence: 0.9255846

00:41:49.080 --> 00:41:49.960 so I can I can

NOTE Confidence: 0.9255846

00:41:49.960 --> 00:41:51.180 go back to this slide,

NOTE Confidence: 0.9360916

00:41:52.015 --> 00:41:53.455 because you can you can

NOTE Confidence: 0.9360916

00:41:53.455 --> 00:41:54.895 see that, if we once

NOTE Confidence: 0.9360916

00:41:54.895 --> 00:41:55.395 we,

NOTE Confidence: 0.9289819

00:41:57.295 --> 00:41:58.575 took once we took this

NOTE Confidence: 0.9289819

00:41:58.575 --> 00:41:59.715 CD four polypropagation

NOTE Confidence: 0.9374855

00:42:00.255 --> 00:42:01.475 and further,

NOTE Confidence: 0.92068875

00:42:02.494 --> 00:42:04.094 some you know, subdivide them

NOTE Confidence: 0.92068875

00:42:04.094 --> 00:42:05.670 into different groups of CD

NOTE Confidence: 0.92068875

00:42:05.670 --> 00:42:07.190 four poly cells? You can

NOTE Confidence: 0.92068875

00:42:07.190 --> 00:42:08.150 see that compared to the

NOTE Confidence: 0.92068875

00:42:08.150 --> 00:42:09.190 wild type as well as

NOTE Confidence: 0.92068875

00:42:09.190 --> 00:42:10.890 get tattooed to guesstimate knockout,

NOTE Confidence: 0.99927586

00:42:11.349 --> 00:42:12.730 this particular population

NOTE Confidence: 0.97501594

00:42:13.270 --> 00:42:14.809 is is strongly upregulated.

NOTE Confidence: 0.91296744

00:42:15.430 --> 00:42:17.349 And this population expressed, of

NOTE Confidence: 0.91296744

00:42:17.349 --> 00:42:19.175 course, CD four, but also

NOTE Confidence: 0.91296744

00:42:19.175 --> 00:42:21.015 CD forty ligand and c,

NOTE Confidence: 0.91296744

00:42:21.335 --> 00:42:23.255 IL twenty one. So to

NOTE Confidence: 0.91296744

00:42:23.255 --> 00:42:24.635 us, this population,

NOTE Confidence: 0.8682564

00:42:24.935 --> 00:42:26.135 this CD four T cell

NOTE Confidence: 0.8682564

00:42:26.135 --> 00:42:26.635 population,

NOTE Confidence: 0.69583845

00:42:27.094 --> 00:42:27.594 express,

NOTE Confidence: 0.92534035

00:42:27.895 --> 00:42:29.915 t follicular helper cell like

NOTE Confidence: 0.92534035

00:42:30.135 --> 00:42:30.635 phenotype.

NOTE Confidence: 0.9911702

00:42:30.935 --> 00:42:32.455 So we are really thinking

NOTE Confidence: 0.9911702

00:42:32.455 --> 00:42:32.955 that,

NOTE Confidence: 0.9995012

00:42:33.950 --> 00:42:35.329 this could play a role

NOTE Confidence: 0.81559294

00:42:35.630 --> 00:42:37.730 in in kind of, communication

NOTE Confidence: 0.97949266

00:42:38.190 --> 00:42:38.589 between the,

NOTE Confidence: 0.8895942

00:42:40.109 --> 00:42:41.869 the CD4 poly T cells

NOTE Confidence: 0.8895942

00:42:41.869 --> 00:42:42.849 as well as

NOTE Confidence: 0.7536713

00:42:43.390 --> 00:42:45.410 the inflammatory macrophage and monocytes

NOTE Confidence: 0.9580874

00:42:45.950 --> 00:42:47.390 to to promote this co

NOTE Confidence: 0.9580874

00:42:47.390 --> 00:42:47.890 inflammatory

NOTE Confidence: 0.97850186

00:42:48.684 --> 00:42:49.505 bone marrow microenvironment.

NOTE Confidence: 0.9657322

00:42:51.325 --> 00:42:53.244 Back to this, data. So

NOTE Confidence: 0.9657322

00:42:53.244 --> 00:42:54.125 we also did,

NOTE Confidence: 0.7294182

00:42:55.404 --> 00:42:57.724 spatial transportomic studies. Here we

NOTE Confidence: 0.7294182

00:42:57.724 --> 00:43:00.145 use the 10x Visium platform,

NOTE Confidence: 0.95870477

00:43:00.684 --> 00:43:01.885 and you can see that,

NOTE Confidence: 0.9103992

00:43:02.780 --> 00:43:04.619 here is, so we spoke

NOTE Confidence: 0.9103992

00:43:04.619 --> 00:43:06.940 specifically looking at macrophages as

NOTE Confidence: 0.9103992

00:43:06.940 --> 00:43:08.859 well as, stromal cells. You

NOTE Confidence: 0.9103992

00:43:08.859 --> 00:43:10.140 can see that when you

NOTE Confidence: 0.9103992

00:43:10.140 --> 00:43:12.140 transplant tattoo knockout into wild

NOTE Confidence: 0.9103992

00:43:12.140 --> 00:43:12.960 type mice,

NOTE Confidence: 0.86888474

00:43:13.500 --> 00:43:14.560 there's a closer,

NOTE Confidence: 0.8984369

00:43:15.114 --> 00:43:16.735 not only there's a upregulation

NOTE Confidence: 0.9690017

00:43:17.114 --> 00:43:18.094 of, both,

NOTE Confidence: 0.9209865

00:43:18.955 --> 00:43:19.455 macrophages,

NOTE Confidence: 0.977133

00:43:19.835 --> 00:43:20.815 of these macrophages,

NOTE Confidence: 0.89254665

00:43:21.675 --> 00:43:23.855 but these macrophages tend to,

NOTE Confidence: 0.9022487

00:43:25.275 --> 00:43:25.775 spatially,

NOTE Confidence: 0.8554997

00:43:27.000 --> 00:43:28.360 get closer or there is

NOTE Confidence: 0.8554997

00:43:28.360 --> 00:43:29.320 a space there is a

NOTE Confidence: 0.8554997

00:43:29.320 --> 00:43:30.219 spatial proximity

NOTE Confidence: 0.84160924

00:43:30.920 --> 00:43:33.020 of this inflammatory macrophages

NOTE Confidence: 0.93172854

00:43:33.320 --> 00:43:35.000 with the stromal cells. But

NOTE Confidence: 0.93172854

00:43:35.000 --> 00:43:37.260 if you use tattoo knockout,

NOTE Confidence: 0.8589993

00:43:37.719 --> 00:43:39.580 transplant into Casamine knockout,

NOTE Confidence: 0.8867189

00:43:41.295 --> 00:43:42.655 Of course, the microphage is

NOTE Confidence: 0.8867189

00:43:42.655 --> 00:43:43.155 reduced,

NOTE Confidence: 0.85399395

00:43:43.694 --> 00:43:44.734 and there's this,

NOTE Confidence: 0.645214

00:43:45.454 --> 00:43:45.954 spatial

NOTE Confidence: 0.899749

00:43:46.415 --> 00:43:48.194 proximity is not there anymore.

NOTE Confidence: 0.92320037

00:43:50.175 --> 00:43:50.994 So overall,

NOTE Confidence: 0.8795958

00:43:51.454 --> 00:43:52.415 we think this,

NOTE Confidence: 0.98247993

00:43:52.815 --> 00:43:54.114 this model like this.

NOTE Confidence: 0.87032825

00:43:55.200 --> 00:43:57.160 So we have operators in

NOTE Confidence: 0.87032825

00:43:57.319 --> 00:43:57.819 this,

NOTE Confidence: 0.61494815

00:43:58.640 --> 00:43:59.859 tattoo transplantation

NOTE Confidence: 0.87680894

00:44:00.239 --> 00:44:01.520 to to the wall to

NOTE Confidence: 0.87680894

00:44:01.520 --> 00:44:02.820 the not wall type recipient.

NOTE Confidence: 0.7852551

00:44:03.280 --> 00:44:04.880 You have, upper regulation of

NOTE Confidence: 0.7852551

00:44:04.880 --> 00:44:06.260 this inflammatory microphages

NOTE Confidence: 0.8233782

00:44:06.800 --> 00:44:08.080 and upper region for CD

NOTE Confidence: 0.8233782

00:44:08.080 --> 00:44:09.645 four poly T cells, where

NOTE Confidence: 0.8233782

00:44:09.805 --> 00:44:11.005 these CD four poly T

NOTE Confidence: 0.8233782

00:44:11.005 --> 00:44:11.505 cells,

NOTE Confidence: 0.91135347

00:44:12.125 --> 00:44:13.325 have CD,

NOTE Confidence: 0.9545342

00:44:13.645 --> 00:44:15.165 have high expression of CD

NOTE Confidence: 0.9545342

00:44:15.165 --> 00:44:16.545 forty ligand signaling,

NOTE Confidence: 0.92811865

00:44:17.085 --> 00:44:18.765 IR twenty one, which has

NOTE Confidence: 0.92811865

00:44:18.765 --> 00:44:20.285 been shown before that can

NOTE Confidence: 0.92811865

00:44:20.285 --> 00:44:21.985 induce macrophage proliferation.

NOTE Confidence: 0.87305146

00:44:22.610 --> 00:44:24.870 And macrophage these inflammatory macrophages,

NOTE Confidence: 0.90522665

00:44:25.730 --> 00:44:26.930 we we also have data

NOTE Confidence: 0.90522665

00:44:26.930 --> 00:44:28.530 showing that they also secret

NOTE Confidence: 0.90522665

00:44:28.530 --> 00:44:29.570 a lot of r one

NOTE Confidence: 0.90522665

00:44:29.730 --> 00:44:30.390 r twelve

NOTE Confidence: 0.9278022

00:44:30.770 --> 00:44:32.450 that can further enhance the

NOTE Confidence: 0.9278022

00:44:32.450 --> 00:44:33.890 expression or activation of the

NOTE Confidence: 0.9278022

00:44:33.890 --> 00:44:35.410 CD four positive T cells.

NOTE Confidence: 0.9278022

00:44:35.410 --> 00:44:36.770 So this kind of positive

NOTE Confidence: 0.9278022

00:44:36.770 --> 00:44:37.270 feedback

NOTE Confidence: 0.96646184

00:44:37.755 --> 00:44:39.035 really promoted the,

NOTE Confidence: 0.9069034

00:44:39.515 --> 00:44:41.454 the inflammation and disease progression

NOTE Confidence: 0.97496396

00:44:41.994 --> 00:44:43.375 of this particular model.

NOTE Confidence: 0.9324824

00:44:45.194 --> 00:44:46.255 And and overall,

NOTE Confidence: 0.94682217

00:44:47.114 --> 00:44:48.974 this, this is our overall,

NOTE Confidence: 0.94682217

00:44:49.194 --> 00:44:49.694 hypothesis.

NOTE Confidence: 0.83953834

00:44:50.395 --> 00:44:51.330 This This has not been

NOTE Confidence: 0.83953834

00:44:51.330 --> 00:44:52.850 published. We're still working,

NOTE Confidence: 0.8485729

00:44:53.890 --> 00:44:55.330 on really fine tune the

NOTE Confidence: 0.8485729

00:44:55.330 --> 00:44:56.850 different CD four part,

NOTE Confidence: 0.87484837

00:44:57.489 --> 00:44:59.410 cell populations and really try

NOTE Confidence: 0.87484837

00:44:59.410 --> 00:45:01.170 to figure out whether this,

NOTE Confidence: 0.6766748

00:45:01.730 --> 00:45:03.330 t follicular like helper cell

NOTE Confidence: 0.6766748

00:45:03.330 --> 00:45:03.830 population

NOTE Confidence: 0.9671329

00:45:04.290 --> 00:45:04.950 is truly

NOTE Confidence: 0.9130173

00:45:05.415 --> 00:45:06.635 really promote the,

NOTE Confidence: 0.8546346

00:45:07.094 --> 00:45:08.635 expansion of these, macrophages.

NOTE Confidence: 0.94350827

00:45:09.975 --> 00:45:11.255 And we can use some,

NOTE Confidence: 0.94350827

00:45:11.255 --> 00:45:12.395 you know, antibodies

NOTE Confidence: 0.9981206

00:45:12.935 --> 00:45:13.435 targeting

NOTE Confidence: 0.9082271

00:45:13.815 --> 00:45:15.495 CD forty ligand or r

NOTE Confidence: 0.9082271

00:45:15.495 --> 00:45:17.550 twenty one to demonstrate this

NOTE Confidence: 0.9082271

00:45:17.550 --> 00:45:18.930 pathway. So that's something,

NOTE Confidence: 0.9397089

00:45:19.550 --> 00:45:20.450 work in progress.

NOTE Confidence: 0.9469877

00:45:20.750 --> 00:45:21.489 But overall,

NOTE Confidence: 0.826677

00:45:22.750 --> 00:45:24.030 so you you have this

NOTE Confidence: 0.826677

00:45:24.030 --> 00:45:25.570 with with a tattoo mutation,

NOTE Confidence: 0.97809345

00:45:25.870 --> 00:45:27.489 you have this clonal hematopoietic

NOTE Confidence: 0.9595833

00:45:27.790 --> 00:45:28.290 population,

NOTE Confidence: 0.9746602

00:45:29.390 --> 00:45:30.850 that can, really

NOTE Confidence: 0.9897926

00:45:31.535 --> 00:45:32.195 have closer,

NOTE Confidence: 0.9302643

00:45:33.695 --> 00:45:35.455 spatial proximity to the wild

NOTE Confidence: 0.9302643

00:45:35.455 --> 00:45:36.594 type stromal cells

NOTE Confidence: 0.90608764

00:45:37.215 --> 00:45:39.055 and, whole and this whole

NOTE Confidence: 0.90608764

00:45:39.055 --> 00:45:41.075 bone marrow inflammatory environment,

NOTE Confidence: 0.89124155

00:45:41.775 --> 00:45:43.075 with the type two mutated

NOTE Confidence: 0.89124155

00:45:43.295 --> 00:45:45.295 microphases can really provide kind

NOTE Confidence: 0.89124155

00:45:45.295 --> 00:45:47.079 of positive feedback loop to

NOTE Confidence: 0.89124155

00:45:47.079 --> 00:45:48.680 promote the disease. But if

NOTE Confidence: 0.89124155

00:45:48.680 --> 00:45:50.540 you knock out guesstimate d,

NOTE Confidence: 0.99876016

00:45:50.920 --> 00:45:51.819 in this background,

NOTE Confidence: 0.9203964

00:45:52.440 --> 00:45:53.160 you kind of,

NOTE Confidence: 0.97653556

00:45:53.800 --> 00:45:54.700 disrupt this,

NOTE Confidence: 0.93783426

00:45:55.239 --> 00:45:57.160 positive feedback loop, and that

NOTE Confidence: 0.93783426

00:45:57.160 --> 00:45:58.520 leads to the reduction in

NOTE Confidence: 0.93783426

00:45:58.520 --> 00:45:59.260 the inflammatory,

NOTE Confidence: 0.90349895

00:46:00.385 --> 00:46:02.625 monocyte or macrophage population, and

NOTE Confidence: 0.90349895

00:46:02.625 --> 00:46:03.745 that leads to the also

NOTE Confidence: 0.90349895

00:46:03.745 --> 00:46:05.445 reduction in the CD4 populate

NOTE Confidence: 0.90349895

00:46:05.665 --> 00:46:06.565 positive population.

NOTE Confidence: 0.8984685

00:46:08.705 --> 00:46:09.205 So,

NOTE Confidence: 0.9605435

00:46:09.585 --> 00:46:10.085 again,

NOTE Confidence: 0.90588284

00:46:10.625 --> 00:46:12.245 this is still a working,

NOTE Confidence: 0.90559894

00:46:13.105 --> 00:46:14.485 work in progress model.

NOTE Confidence: 0.9319262

00:46:14.829 --> 00:46:17.069 So hopefully, we can once

NOTE Confidence: 0.9319262

00:46:17.069 --> 00:46:18.750 we get this antibody treatment

NOTE Confidence: 0.9319262

00:46:18.750 --> 00:46:20.430 experiment, we will be able

NOTE Confidence: 0.9319262

00:46:20.430 --> 00:46:22.030 to submit this manuscript by

NOTE Confidence: 0.9319262

00:46:22.030 --> 00:46:22.750 the end of this or

NOTE Confidence: 0.9319262

00:46:22.750 --> 00:46:23.809 early next year.

NOTE Confidence: 0.9536006

00:46:24.910 --> 00:46:25.869 So with that, I would

NOTE Confidence: 0.9536006

00:46:25.869 --> 00:46:27.150 like to thank people in

NOTE Confidence: 0.9536006

00:46:27.150 --> 00:46:28.049 my lab specifically,

NOTE Confidence: 0.71763873

00:46:28.795 --> 00:46:29.835 and as I mentioned, Yang

NOTE Confidence: 0.71763873

00:46:29.835 --> 00:46:31.375 Mei and Ke Han Ren

NOTE Confidence: 0.71763873

00:46:31.515 --> 00:46:32.015 really

NOTE Confidence: 0.84875727

00:46:32.395 --> 00:46:33.755 is the driving force of

NOTE Confidence: 0.84875727

00:46:33.755 --> 00:46:34.895 these these projects.

NOTE Confidence: 0.97986907

00:46:35.755 --> 00:46:37.275 And, other members of my

NOTE Confidence: 0.97986907

00:46:37.275 --> 00:46:38.635 lab, many of them are

NOTE Confidence: 0.97986907

00:46:38.635 --> 00:46:39.435 involved in,

NOTE Confidence: 0.84338033

00:46:39.995 --> 00:46:43.295 different projects including MDS, MTN,

NOTE Confidence: 0.88020724

00:46:43.940 --> 00:46:45.320 and spatialomic studies.

NOTE Confidence: 0.9968767

00:46:45.620 --> 00:46:46.420 And we also have a

NOTE Confidence: 0.9968767

00:46:46.420 --> 00:46:46.739 lot of,

NOTE Confidence: 0.69172597

00:46:47.540 --> 00:46:48.920 great colleagues in Northwestern,

NOTE Confidence: 0.9851498

00:46:49.540 --> 00:46:50.680 many people working

NOTE Confidence: 0.8699866

00:46:52.500 --> 00:46:53.960 on, different aspects of,

NOTE Confidence: 0.81324065

00:46:54.900 --> 00:46:57.320 myeloid diseases including Lucy Gottlieb,

NOTE Confidence: 0.7065991

00:46:58.100 --> 00:46:58.760 a collaboration

NOTE Confidence: 0.9363326

00:46:59.220 --> 00:47:00.494 on the germline mutated,

NOTE Confidence: 0.95488614

00:47:00.815 --> 00:47:01.315 MDS,

NOTE Confidence: 0.8657615

00:47:01.694 --> 00:47:02.194 models,

NOTE Confidence: 0.67017543

00:47:02.494 --> 00:47:04.035 Ian Liu, Liz Eklund.

NOTE Confidence: 0.85687065

00:47:04.575 --> 00:47:05.535 And we also have a

NOTE Confidence: 0.85687065

00:47:05.535 --> 00:47:08.015 a fantastic immunology group so

NOTE Confidence: 0.85687065

00:47:08.015 --> 00:47:09.474 where I can learn immunology

NOTE Confidence: 0.85687065

00:47:09.614 --> 00:47:11.555 from and inflammation from them,

NOTE Confidence: 0.85687065

00:47:11.775 --> 00:47:14.674 including Roman Ronan, Sumajin, Douyifang.

NOTE Confidence: 0.92680836

00:47:15.440 --> 00:47:16.640 And we also have a

NOTE Confidence: 0.92680836

00:47:16.640 --> 00:47:17.140 beautiful

NOTE Confidence: 0.8872063

00:47:18.400 --> 00:47:18.900 hematology,

NOTE Confidence: 0.8059689

00:47:19.280 --> 00:47:19.780 hematoposology

NOTE Confidence: 0.8203432

00:47:20.160 --> 00:47:22.100 group. Yihua Cheng is our

NOTE Confidence: 0.822596

00:47:23.520 --> 00:47:25.780 program director, and Madina Suguna

NOTE Confidence: 0.822596

00:47:25.840 --> 00:47:28.320 Hona is also collaborating on

NOTE Confidence: 0.822596

00:47:28.320 --> 00:47:29.300 many of the

NOTE Confidence: 0.8564806

00:47:29.600 --> 00:47:30.820 projects I mentioned.

NOTE Confidence: 0.95964885

00:47:31.545 --> 00:47:32.444 And this is,

NOTE Confidence: 0.9309177

00:47:34.905 --> 00:47:36.825 so we also collaborated with,

NOTE Confidence: 0.9309177

00:47:37.065 --> 00:47:38.825 the drug discovery group at

NOTE Confidence: 0.9309177

00:47:38.825 --> 00:47:39.325 Northwestern.

NOTE Confidence: 0.8900918

00:47:40.265 --> 00:47:41.464 Many of them are involved

NOTE Confidence: 0.8900918

00:47:41.464 --> 00:47:42.925 in, you know, drug testing,

NOTE Confidence: 0.8900918

00:47:42.984 --> 00:47:44.344 as I mentioned, our six

NOTE Confidence: 0.8900918

00:47:44.344 --> 00:47:44.844 inhibit

NOTE Confidence: 0.68309736

00:47:45.305 --> 00:47:46.525 antibody testing

NOTE Confidence: 0.95722723

00:47:46.950 --> 00:47:48.410 as well as small molecule

NOTE Confidence: 0.95722723

00:47:48.469 --> 00:47:50.710 inhibitor development for the lab

NOTE Confidence: 0.95722723

00:47:50.710 --> 00:47:51.849 two study in MPN,

NOTE Confidence: 0.9684253

00:47:52.310 --> 00:47:53.430 and these are my funding

NOTE Confidence: 0.9684253

00:47:53.430 --> 00:47:53.930 resources.

NOTE Confidence: 0.9556453

00:47:54.550 --> 00:47:56.070 So I'll be happy to

NOTE Confidence: 0.9556453

00:47:56.070 --> 00:47:57.190 take any question you may

NOTE Confidence: 0.9556453

00:47:57.190 --> 00:47:57.690 have.

NOTE Confidence: 0.6812239

00:48:24.469 --> 00:48:25.623 So you're asking about r

NOTE Confidence: 0.6812239

00:48:25.623 --> 00:48:25.709 one signaling in your house

NOTE Confidence: 0.6812239

00:48:25.709 --> 00:48:25.810 slot. Can you put your

NOTE Confidence: 0.6812239

00:48:25.810 --> 00:48:25.895 way off? It's at work

NOTE Confidence: 0.6812239

00:48:25.895 --> 00:48:25.980 stands and aim here on

NOTE Confidence: 0.6812239

00:48:25.980 --> 00:48:26.065 our wall and stuff like

NOTE Confidence: 0.6812239

00:48:26.065 --> 00:48:26.150 that. So you're asking about

NOTE Confidence: 0.6812239

00:48:26.150 --> 00:48:26.890 r one

NOTE Confidence: 0.8468647

00:48:27.190 --> 00:48:29.130 signaling in this mouse model.

NOTE Confidence: 0.9537792

00:48:30.915 --> 00:48:32.675 So we, this model actually

NOTE Confidence: 0.9537792

00:48:32.835 --> 00:48:34.135 so based on our cytokine

NOTE Confidence: 0.9537792

00:48:34.275 --> 00:48:35.555 array data, r one is

NOTE Confidence: 0.9537792

00:48:35.555 --> 00:48:36.375 not particularly

NOTE Confidence: 0.9158212

00:48:36.675 --> 00:48:38.595 upregulated compared to you know,

NOTE Confidence: 0.9158212

00:48:38.595 --> 00:48:40.695 it's upregulated. It's the pan

NOTE Confidence: 0.9158212

00:48:40.915 --> 00:48:42.855 inflammatory cytokines are all upregulated.

NOTE Confidence: 0.857208

00:48:43.200 --> 00:48:44.560 But compared to r six

NOTE Confidence: 0.857208

00:48:44.560 --> 00:48:45.700 and t r alpha,

NOTE Confidence: 0.9619362

00:48:46.000 --> 00:48:47.540 r one is not dramatically

NOTE Confidence: 0.9619362

00:48:47.760 --> 00:48:49.200 high. So that's why we

NOTE Confidence: 0.9619362

00:48:49.200 --> 00:48:50.400 focused on r six and

NOTE Confidence: 0.9619362

00:48:50.400 --> 00:48:51.680 t r alpha instead of,

NOTE Confidence: 0.9619362

00:48:51.839 --> 00:48:53.119 r one beta. But r

NOTE Confidence: 0.9619362

00:48:53.119 --> 00:48:54.560 one has been studied in

NOTE Confidence: 0.9619362

00:48:54.560 --> 00:48:55.780 many other models

NOTE Confidence: 0.98567736

00:48:56.160 --> 00:48:57.440 in MDS as well as

NOTE Confidence: 0.98567736

00:48:57.440 --> 00:48:58.560 acute myeloid leukemia.

NOTE Confidence: 0.96959484

00:48:59.415 --> 00:49:01.015 It definitely play a big

NOTE Confidence: 0.96959484

00:49:01.015 --> 00:49:02.795 role in in this, pathogenesis

NOTE Confidence: 0.9217944

00:49:03.335 --> 00:49:04.475 myeloid diseases.

NOTE Confidence: 0.5300984

00:49:12.670 --> 00:49:13.870 Sorry. Okay? Do you know

NOTE Confidence: 0.5300984

00:49:13.870 --> 00:49:15.330 for the adaptive immune

NOTE Confidence: 0.63486373

00:49:15.710 --> 00:49:16.210 system?

NOTE Confidence: 0.97431767

00:49:18.030 --> 00:49:19.710 So far, that's where we

NOTE Confidence: 0.97431767

00:49:19.710 --> 00:49:21.810 are looking at. So we

NOTE Confidence: 0.97431767

00:49:21.870 --> 00:49:24.290 haven't really touched the adaptive

NOTE Confidence: 0.97431767

00:49:24.350 --> 00:49:25.570 immune system yet,

NOTE Confidence: 0.9900077

00:49:26.165 --> 00:49:27.224 but that's a good question.

NOTE Confidence: 0.96984786

00:49:28.724 --> 00:49:29.224 Whether

NOTE Confidence: 0.95788753

00:49:29.525 --> 00:49:30.885 b cell any types of

NOTE Confidence: 0.95788753

00:49:30.885 --> 00:49:31.864 b cells are involved,

NOTE Confidence: 0.91839474

00:49:32.244 --> 00:49:33.065 I don't know.

NOTE Confidence: 0.7532629

00:49:33.525 --> 00:49:34.025 Probably,

NOTE Confidence: 0.9723471

00:49:35.364 --> 00:49:37.285 but yeah. But I'm very

NOTE Confidence: 0.9723471

00:49:37.285 --> 00:49:39.285 interested in looking at the

NOTE Confidence: 0.9723471

00:49:39.285 --> 00:49:39.785 spatial

NOTE Confidence: 0.83836746

00:49:40.484 --> 00:49:41.385 omics studies

NOTE Confidence: 0.8891404

00:49:41.925 --> 00:49:43.040 in in these mouse models

NOTE Confidence: 0.8891404

00:49:43.100 --> 00:49:44.300 as well as patients to

NOTE Confidence: 0.8891404

00:49:44.300 --> 00:49:44.960 see their

NOTE Confidence: 0.93770766

00:49:45.500 --> 00:49:47.420 different adaptive immune system. In

NOTE Confidence: 0.93770766

00:49:47.420 --> 00:49:48.480 the immune system,

NOTE Confidence: 0.9594167

00:49:49.580 --> 00:49:50.860 there are any changes in

NOTE Confidence: 0.9594167

00:49:50.860 --> 00:49:52.000 the myeloid diseases,

NOTE Confidence: 0.8718432

00:49:52.780 --> 00:49:54.219 but not particularly in this

NOTE Confidence: 0.8718432

00:49:54.219 --> 00:49:55.980 model yet. And and they

NOTE Confidence: 0.8718432

00:49:55.980 --> 00:49:57.100 have already come in. I

NOTE Confidence: 0.8718432

00:49:57.100 --> 00:49:57.600 apologize.

NOTE Confidence: 0.97755456

00:49:58.224 --> 00:49:58.805 Is there

NOTE Confidence: 0.7020393

00:49:59.105 --> 00:50:00.404 a role

NOTE Confidence: 0.92205215

00:50:00.704 --> 00:50:01.204 for,

NOTE Confidence: 0.28952616

00:50:02.065 --> 00:50:02.565 program

NOTE Confidence: 0.7201546

00:50:03.905 --> 00:50:05.585 so that we basically wanna

NOTE Confidence: 0.7201546

00:50:05.984 --> 00:50:07.344 because everything here was, like,

NOTE Confidence: 0.7201546

00:50:07.344 --> 00:50:08.945 this this this is their

NOTE Confidence: 0.7201546

00:50:08.945 --> 00:50:10.805 update from a membrane.

NOTE Confidence: 0.102462

00:50:12.590 --> 00:50:13.090 They

NOTE Confidence: 0.21717437

00:50:13.390 --> 00:50:14.210 assisted learning?

NOTE Confidence: 0.9892191

00:50:14.910 --> 00:50:16.670 Yes. Again, we haven't touched

NOTE Confidence: 0.9892191

00:50:16.670 --> 00:50:17.410 that yet,

NOTE Confidence: 0.8539731

00:50:17.790 --> 00:50:19.310 but it's possible. I mean,

NOTE Confidence: 0.8539731

00:50:19.310 --> 00:50:20.430 type two is, you know,

NOTE Confidence: 0.8539731

00:50:20.430 --> 00:50:23.010 commonly involving epigenetic and modifications,

NOTE Confidence: 0.95601624

00:50:23.925 --> 00:50:25.285 But that's, I think that's

NOTE Confidence: 0.95601624

00:50:25.285 --> 00:50:26.565 well known. So we we

NOTE Confidence: 0.95601624

00:50:26.565 --> 00:50:28.745 really didn't really touch specifically

NOTE Confidence: 0.95601624

00:50:28.805 --> 00:50:30.645 on epigenetic changes in this

NOTE Confidence: 0.95601624

00:50:30.645 --> 00:50:31.145 in

NOTE Confidence: 0.73838913

00:50:31.844 --> 00:50:32.425 this particular

NOTE Confidence: 0.7887194

00:50:32.965 --> 00:50:33.785 model system.

NOTE Confidence: 0.9456413

00:50:35.045 --> 00:50:35.545 Yeah.

NOTE Confidence: 0.71187204

00:50:45.350 --> 00:50:46.470 You see the effect in

NOTE Confidence: 0.71187204

00:50:46.470 --> 00:50:47.850 the tattoo not passed

NOTE Confidence: 0.73150414

00:50:48.470 --> 00:50:50.070 by limiting gas turbine in

NOTE Confidence: 0.73150414

00:50:50.070 --> 00:50:51.610 the host. Yeah. Right?

NOTE Confidence: 0.84234816

00:50:53.714 --> 00:50:55.954 Is as you expand those

NOTE Confidence: 0.84234816

00:50:55.954 --> 00:50:57.395 cells you put in, they're

NOTE Confidence: 0.84234816

00:50:57.395 --> 00:50:58.755 bringing with the wild type

NOTE Confidence: 0.84234816

00:50:58.755 --> 00:51:00.375 gas turbine into that environment,

NOTE Confidence: 0.84234816

00:51:00.594 --> 00:51:02.135 the transplanted cells.

NOTE Confidence: 0.8646812

00:51:02.835 --> 00:51:04.035 Do that does that play

NOTE Confidence: 0.8646812

00:51:04.035 --> 00:51:05.734 a role or link disease

NOTE Confidence: 0.8646812

00:51:05.954 --> 00:51:06.515 that become

NOTE Confidence: 0.66600245

00:51:07.850 --> 00:51:09.930 But the transplanted factor in

NOTE Confidence: 0.66600245

00:51:09.930 --> 00:51:10.930 and of itself. But the

NOTE Confidence: 0.66600245

00:51:11.050 --> 00:51:12.330 the diversity, what happens if

NOTE Confidence: 0.66600245

00:51:12.330 --> 00:51:13.530 you cannot help that strand

NOTE Confidence: 0.66600245

00:51:13.530 --> 00:51:15.310 and walk with that two

NOTE Confidence: 0.66600245

00:51:15.450 --> 00:51:16.570 and put into a wild

NOTE Confidence: 0.66600245

00:51:16.570 --> 00:51:18.090 type of person. That's that's

NOTE Confidence: 0.66600245

00:51:18.090 --> 00:51:18.989 the big thing.

NOTE Confidence: 0.9977749

00:51:19.450 --> 00:51:19.950 So

NOTE Confidence: 0.82681286

00:51:20.484 --> 00:51:22.244 the the transplanted cells are

NOTE Confidence: 0.82681286

00:51:22.244 --> 00:51:23.945 all tied to knockout. Right?

NOTE Confidence: 0.82681286

00:51:24.085 --> 00:51:25.165 Right. But they're gas terminus

NOTE Confidence: 0.82681286

00:51:25.165 --> 00:51:26.325 in wild. Yeah. Of course,

NOTE Confidence: 0.82681286

00:51:26.325 --> 00:51:27.445 they mean wild type. So

NOTE Confidence: 0.82681286

00:51:27.445 --> 00:51:28.484 that we have the data

NOTE Confidence: 0.82681286

00:51:28.484 --> 00:51:29.785 in, you know, this immunohoressence.

NOTE Confidence: 0.91409314

00:51:30.405 --> 00:51:30.905 They,

NOTE Confidence: 0.8806036

00:51:32.165 --> 00:51:33.204 with the knockout of the

NOTE Confidence: 0.8806036

00:51:33.204 --> 00:51:35.045 gastrin d, they suppress the

NOTE Confidence: 0.8806036

00:51:35.045 --> 00:51:37.000 expression of n terminal gasramin

NOTE Confidence: 0.8806036

00:51:37.060 --> 00:51:38.119 d in the transplanted

NOTE Confidence: 0.9564334

00:51:38.980 --> 00:51:39.480 mice,

NOTE Confidence: 0.97523606

00:51:40.099 --> 00:51:41.000 donor cells.

NOTE Confidence: 0.908421

00:51:41.700 --> 00:51:43.640 Yes. Right. Right. But

NOTE Confidence: 0.6907186

00:51:44.020 --> 00:51:45.219 is to turn the experiment

NOTE Confidence: 0.6907186

00:51:45.219 --> 00:51:46.819 around, not have not just

NOTE Confidence: 0.6907186

00:51:46.819 --> 00:51:48.020 that tube, but also the

NOTE Confidence: 0.6907186

00:51:48.020 --> 00:51:49.640 gastric d in the

NOTE Confidence: 0.7966851

00:51:50.375 --> 00:51:52.954 transplant cells Yeah. Does that

NOTE Confidence: 0.93687254

00:51:54.295 --> 00:51:55.575 they are better when put

NOTE Confidence: 0.93687254

00:51:55.575 --> 00:51:56.935 into a wild type mice.

NOTE Confidence: 0.93687254

00:51:56.935 --> 00:51:58.295 So that won't that won't

NOTE Confidence: 0.93687254

00:51:58.295 --> 00:51:59.655 have disease, I I would

NOTE Confidence: 0.93687254

00:51:59.655 --> 00:52:01.175 say, because we we already

NOTE Confidence: 0.93687254

00:52:01.175 --> 00:52:02.214 did that with whole bone

NOTE Confidence: 0.93687254

00:52:02.375 --> 00:52:04.474 whole whole knockout mice. Right?

NOTE Confidence: 0.9811609

00:52:05.230 --> 00:52:06.590 So we we so that's

NOTE Confidence: 0.9811609

00:52:06.590 --> 00:52:07.730 that's what we showed.

NOTE Confidence: 0.97910994

00:52:08.910 --> 00:52:10.190 Yeah. So that's what we

NOTE Confidence: 0.97910994

00:52:10.190 --> 00:52:11.330 showed here.

NOTE Confidence: 0.9825759

00:52:13.630 --> 00:52:14.130 Here.

NOTE Confidence: 0.92371184

00:52:14.430 --> 00:52:15.790 So we did a triple

NOTE Confidence: 0.92371184

00:52:15.790 --> 00:52:16.290 knockout.

NOTE Confidence: 0.91699505

00:52:18.075 --> 00:52:19.675 Oh, sorry. You're talking about

NOTE Confidence: 0.91699505

00:52:19.675 --> 00:52:21.594 tattoo. Yeah. I would say

NOTE Confidence: 0.91699505

00:52:21.594 --> 00:52:22.795 it's will be similar to

NOTE Confidence: 0.91699505

00:52:22.795 --> 00:52:24.255 this. Similar to that? Yeah.

NOTE Confidence: 0.7854149

00:52:24.875 --> 00:52:26.795 So that's so even knocking

NOTE Confidence: 0.7854149

00:52:26.795 --> 00:52:28.235 out gas theremin in the

NOTE Confidence: 0.7854149

00:52:28.235 --> 00:52:28.735 cells,

NOTE Confidence: 0.7540043

00:52:30.750 --> 00:52:31.950 you don't need gas thermometer

NOTE Confidence: 0.7540043

00:52:31.950 --> 00:52:33.489 back out in the post.

NOTE Confidence: 0.7540043

00:52:33.630 --> 00:52:34.130 Right.

NOTE Confidence: 0.8829454

00:52:35.070 --> 00:52:37.650 Because that suppressed the intrinsic

NOTE Confidence: 0.8829454

00:52:37.870 --> 00:52:39.090 inflammatory changes.

NOTE Confidence: 0.8630234

00:52:39.390 --> 00:52:41.070 So they wouldn't induce the

NOTE Confidence: 0.9209987

00:52:42.885 --> 00:52:44.165 that's what I that's side

NOTE Confidence: 0.9209987

00:52:44.165 --> 00:52:46.105 of the equation works. Yeah.

NOTE Confidence: 0.8774126

00:52:46.565 --> 00:52:47.925 I think so. I think

NOTE Confidence: 0.8774126

00:52:47.925 --> 00:52:49.525 so. Yeah. So it play

NOTE Confidence: 0.8774126

00:52:49.685 --> 00:52:51.205 I think SMD play both

NOTE Confidence: 0.8774126

00:52:51.205 --> 00:52:53.625 intrinsic and extrinsic way role.

NOTE Confidence: 0.94850934

00:52:55.619 --> 00:52:56.819 That's what I'm like, we

NOTE Confidence: 0.94850934

00:52:56.819 --> 00:52:58.599 haven't done that experiment, but

NOTE Confidence: 0.96383095

00:52:59.219 --> 00:53:00.119 I think that's

NOTE Confidence: 0.9355219

00:53:00.500 --> 00:53:01.700 with this with this model,

NOTE Confidence: 0.9355219

00:53:01.700 --> 00:53:02.739 I think that's because this

NOTE Confidence: 0.9355219

00:53:02.739 --> 00:53:04.039 is a more stronger model.

NOTE Confidence: 0.94886696

00:53:04.739 --> 00:53:05.940 So I would I would

NOTE Confidence: 0.94886696

00:53:05.940 --> 00:53:08.119 imagine that tattoo knockout would

NOTE Confidence: 0.94886696

00:53:08.180 --> 00:53:09.160 be the same.

NOTE Confidence: 0.84674716

00:53:11.795 --> 00:53:12.295 Okay.

NOTE Confidence: 0.8043896

00:53:29.410 --> 00:53:30.630 Knockout? Oh. In that triple

NOTE Confidence: 0.9422601

00:53:30.930 --> 00:53:32.230 knockout? That's a good question.

NOTE Confidence: 0.9836018

00:53:33.090 --> 00:53:34.210 We haven't looked at that

NOTE Confidence: 0.9836018

00:53:34.210 --> 00:53:34.710 yet,

NOTE Confidence: 0.9575982

00:53:36.369 --> 00:53:37.989 but I would imagine because

NOTE Confidence: 0.91003585

00:53:39.734 --> 00:53:41.015 r six should still be

NOTE Confidence: 0.91003585

00:53:41.015 --> 00:53:41.515 upregulated,

NOTE Confidence: 0.99329585

00:53:43.255 --> 00:53:43.755 because

NOTE Confidence: 0.73842746

00:53:44.135 --> 00:53:45.594 not called r six.

NOTE Confidence: 0.6888736

00:53:46.214 --> 00:53:47.015 I don't know. It's not

NOTE Confidence: 0.6888736

00:53:47.094 --> 00:53:48.375 What happens to get? Yeah.

NOTE Confidence: 0.6888736

00:53:48.375 --> 00:53:49.815 Sturm is still upregulated. I

NOTE Confidence: 0.6888736

00:53:49.815 --> 00:53:51.515 mean, Destiny is still upregulated.

NOTE Confidence: 0.70253503

00:53:52.440 --> 00:53:53.000 It's not called the six.

NOTE Confidence: 0.70253503

00:53:53.400 --> 00:53:55.079 It's upregulated in all the

NOTE Confidence: 0.70253503

00:53:55.079 --> 00:53:55.579 activity

NOTE Confidence: 0.82490504

00:53:56.040 --> 00:53:57.480 that Gascam is doing is

NOTE Confidence: 0.82490504

00:53:57.480 --> 00:53:58.920 through y l six. I

NOTE Confidence: 0.82490504

00:53:58.920 --> 00:54:00.359 would imagine, but I I

NOTE Confidence: 0.82490504

00:54:00.359 --> 00:54:01.260 don't know yet,

NOTE Confidence: 0.9771225

00:54:02.040 --> 00:54:03.319 because we don't have that

NOTE Confidence: 0.9771225

00:54:03.319 --> 00:54:03.819 model.

NOTE Confidence: 0.9428894

00:54:04.599 --> 00:54:05.800 But that's a good question.

NOTE Confidence: 0.9428894

00:54:05.800 --> 00:54:06.300 Yeah.

NOTE Confidence: 0.8105321

00:54:08.535 --> 00:54:09.035 Mitra?

NOTE Confidence: 0.31466705

00:54:13.295 --> 00:54:13.795 I

NOTE Confidence: 0.95382845

00:54:18.055 --> 00:54:19.175 would think so. I would

NOTE Confidence: 0.95382845

00:54:19.175 --> 00:54:20.614 think so. There are there

NOTE Confidence: 0.95382845

00:54:20.694 --> 00:54:21.734 so we we also I

NOTE Confidence: 0.95382845

00:54:21.734 --> 00:54:22.860 didn't have data because we're

NOTE Confidence: 0.95382845

00:54:22.860 --> 00:54:24.140 still working on that. We

NOTE Confidence: 0.95382845

00:54:24.140 --> 00:54:26.400 use SMD inhibitors. There are

NOTE Confidence: 0.95382845

00:54:26.460 --> 00:54:28.480 different kinds of SMD inhibitors

NOTE Confidence: 0.81573725

00:54:29.180 --> 00:54:30.700 that can that has shown

NOTE Confidence: 0.81573725

00:54:30.700 --> 00:54:31.740 some effect in our most

NOTE Confidence: 0.81573725

00:54:31.740 --> 00:54:33.580 model, but we still find

NOTE Confidence: 0.81573725

00:54:33.580 --> 00:54:34.880 true that the datasets.

NOTE Confidence: 0.8689884

00:54:37.425 --> 00:54:39.045 Yeah. It's really great stuff.

NOTE Confidence: 0.8689884

00:54:39.105 --> 00:54:40.245 Thank you. My

NOTE Confidence: 0.85253423

00:54:40.625 --> 00:54:42.245 I really like this observation

NOTE Confidence: 0.85253423

00:54:42.385 --> 00:54:42.885 that

NOTE Confidence: 0.93064135

00:54:43.265 --> 00:54:45.125 the t follicular helper cells,

NOTE Confidence: 0.7180581

00:54:45.905 --> 00:54:47.285 the CD four t follicular

NOTE Confidence: 0.7180581

00:54:47.344 --> 00:54:48.645 helper software upregulated.

NOTE Confidence: 0.8499102

00:54:50.469 --> 00:54:51.670 That's how it comes. Right?

NOTE Confidence: 0.8499102

00:54:51.670 --> 00:54:52.790 And so those are gonna

NOTE Confidence: 0.8499102

00:54:52.790 --> 00:54:53.530 be active,

NOTE Confidence: 0.8562644

00:54:54.150 --> 00:54:55.610 you know, managing precipitation

NOTE Confidence: 0.91394466

00:54:56.390 --> 00:54:57.430 in the really in the

NOTE Confidence: 0.91394466

00:54:57.430 --> 00:54:58.570 dendritic cells

NOTE Confidence: 0.79801285

00:54:59.030 --> 00:54:59.530 primarily.

NOTE Confidence: 0.997255

00:55:00.230 --> 00:55:00.730 So

NOTE Confidence: 0.88284653

00:55:01.030 --> 00:55:02.310 then that gets into this

NOTE Confidence: 0.88284653

00:55:02.310 --> 00:55:02.810 question.

NOTE Confidence: 0.7338666

00:55:05.895 --> 00:55:07.255 Can you, let's say, knock

NOTE Confidence: 0.7338666

00:55:07.255 --> 00:55:08.935 out sting just in the

NOTE Confidence: 0.7338666

00:55:08.935 --> 00:55:10.075 dead zone and

NOTE Confidence: 0.9766468

00:55:11.415 --> 00:55:11.915 modulate

NOTE Confidence: 0.6331817

00:55:12.855 --> 00:55:14.395 the ten to knock out?

NOTE Confidence: 0.78923655

00:55:14.855 --> 00:55:17.355 That's that's my question. Yeah.

NOTE Confidence: 0.78923655

00:55:17.415 --> 00:55:18.383 And I know that if

NOTE Confidence: 0.78923655

00:55:18.383 --> 00:55:18.431 I have made that maybe

NOTE Confidence: 0.78923655

00:55:18.431 --> 00:55:19.205 you don't wanna No.

NOTE Confidence: 0.9391513

00:55:21.550 --> 00:55:22.670 No. We we haven't done

NOTE Confidence: 0.9391513

00:55:22.670 --> 00:55:24.109 that yet. I think that

NOTE Confidence: 0.9391513

00:55:24.109 --> 00:55:25.230 would be something to think

NOTE Confidence: 0.9391513

00:55:25.230 --> 00:55:25.730 about.

NOTE Confidence: 0.96921104

00:55:26.109 --> 00:55:27.390 And the other question I

NOTE Confidence: 0.96921104

00:55:27.390 --> 00:55:28.670 I have related to that

NOTE Confidence: 0.96921104

00:55:28.670 --> 00:55:28.750 is,

NOTE Confidence: 0.98396325

00:55:30.190 --> 00:55:30.589 the,

NOTE Confidence: 0.8346222

00:55:31.630 --> 00:55:33.730 the gas and the phenotype,

NOTE Confidence: 0.8346222

00:55:33.869 --> 00:55:34.530 you know,

NOTE Confidence: 0.8590932

00:55:35.325 --> 00:55:36.525 it forms a four, I

NOTE Confidence: 0.8590932

00:55:36.525 --> 00:55:37.805 guess, in the cells. Right?

NOTE Confidence: 0.8590932

00:55:37.805 --> 00:55:39.165 Mhmm. And is that need

NOTE Confidence: 0.8590932

00:55:39.165 --> 00:55:40.605 to have a product cell

NOTE Confidence: 0.8590932

00:55:40.605 --> 00:55:41.645 debris? Is it does it

NOTE Confidence: 0.8590932

00:55:41.645 --> 00:55:42.625 kill the cells?

NOTE Confidence: 0.912438

00:55:43.405 --> 00:55:44.925 Not really. It doesn't really

NOTE Confidence: 0.912438

00:55:45.165 --> 00:55:46.625 so it depends on how

NOTE Confidence: 0.912438

00:55:46.765 --> 00:55:48.285 how strongly gas in the

NOTE Confidence: 0.912438

00:55:48.285 --> 00:55:50.559 internal domain is expressed, is

NOTE Confidence: 0.912438

00:55:50.559 --> 00:55:52.160 cleaved. Right? So if you

NOTE Confidence: 0.912438

00:55:52.160 --> 00:55:53.280 don't have enough gas in

NOTE Confidence: 0.912438

00:55:53.280 --> 00:55:54.319 the that has been shown.

NOTE Confidence: 0.912438

00:55:54.319 --> 00:55:55.920 That's not my major focus,

NOTE Confidence: 0.912438

00:55:55.920 --> 00:55:57.119 but that has been shown

NOTE Confidence: 0.912438

00:55:57.119 --> 00:55:58.180 by many publications.

NOTE Confidence: 0.9281122

00:55:58.559 --> 00:55:59.760 You have don't have enough

NOTE Confidence: 0.9281122

00:55:59.760 --> 00:56:00.800 gas in the n terminal

NOTE Confidence: 0.9281122

00:56:00.800 --> 00:56:01.300 domain.

NOTE Confidence: 0.82004637

00:56:01.680 --> 00:56:04.400 That cell inflammatory cells is

NOTE Confidence: 0.82004637

00:56:04.400 --> 00:56:05.984 not is is dying, but

NOTE Confidence: 0.82004637

00:56:05.984 --> 00:56:07.765 not truly die dead yet.

NOTE Confidence: 0.82004637

00:56:07.984 --> 00:56:09.204 Kind of like a zombie

NOTE Confidence: 0.82004637

00:56:09.344 --> 00:56:10.625 kind of stage. Is it

NOTE Confidence: 0.82004637

00:56:10.625 --> 00:56:12.645 release chromatin and nucleic acid?

NOTE Confidence: 0.915623

00:56:14.785 --> 00:56:15.905 Could be. There is there

NOTE Confidence: 0.915623

00:56:16.065 --> 00:56:17.125 I mean, if it does,

NOTE Confidence: 0.915623

00:56:17.344 --> 00:56:18.565 right, that would suggest

NOTE Confidence: 0.77103424

00:56:19.680 --> 00:56:21.120 that a might be activated

NOTE Confidence: 0.77103424

00:56:21.120 --> 00:56:22.560 with the dead brain cells.

NOTE Confidence: 0.77103424

00:56:22.560 --> 00:56:23.859 I'm just trying to establish

NOTE Confidence: 0.77103424

00:56:24.000 --> 00:56:24.500 why

NOTE Confidence: 0.7299894

00:56:25.200 --> 00:56:26.320 Right. People living in their

NOTE Confidence: 0.7299894

00:56:26.320 --> 00:56:28.339 apple cells are increased. Yeah.

NOTE Confidence: 0.9166398

00:56:29.119 --> 00:56:30.719 It's so bay so what

NOTE Confidence: 0.9166398

00:56:30.719 --> 00:56:31.619 we hypothesize

NOTE Confidence: 0.9762848

00:56:31.935 --> 00:56:33.635 is that, the inflammatory

NOTE Confidence: 0.72485036

00:56:34.094 --> 00:56:34.594 monocytosis,

NOTE Confidence: 0.638003

00:56:35.135 --> 00:56:35.635 microphages,

NOTE Confidence: 0.9098992

00:56:38.734 --> 00:56:39.635 provide this,

NOTE Confidence: 0.9785569

00:56:41.215 --> 00:56:41.955 kind of

NOTE Confidence: 0.86001694

00:56:42.335 --> 00:56:44.335 this has the highest r

NOTE Confidence: 0.86001694

00:56:44.335 --> 00:56:46.175 o twelve secondretion that has

NOTE Confidence: 0.86001694

00:56:46.175 --> 00:56:47.295 been shown to promote this

NOTE Confidence: 0.86001694

00:56:47.295 --> 00:56:49.510 t follicular help cell expansion.

NOTE Confidence: 0.9957942

00:56:50.050 --> 00:56:51.510 So that's our hypothesis,

NOTE Confidence: 0.994228

00:56:51.810 --> 00:56:53.410 but we need to really

NOTE Confidence: 0.994228

00:56:53.410 --> 00:56:54.950 show that experimentally.

NOTE Confidence: 0.9217238

00:57:11.525 --> 00:57:13.445 That yeah. That that could,

NOTE Confidence: 0.9217238

00:57:13.445 --> 00:57:14.950 yeah, that could also be

NOTE Confidence: 0.9217238

00:57:14.950 --> 00:57:16.250 the case. Yeah.

NOTE Confidence: 0.7067696

00:57:17.750 --> 00:57:18.950 Yeah. But that move back

NOTE Confidence: 0.7067696

00:57:18.950 --> 00:57:19.530 to the.

NOTE Confidence: 0.7317486

00:57:20.390 --> 00:57:21.450 We That's that's

NOTE Confidence: 0.9115319

00:57:21.750 --> 00:57:23.190 an interesting question. So we

NOTE Confidence: 0.9115319

00:57:23.190 --> 00:57:25.210 probably can make some generative

NOTE Confidence: 0.9115319

00:57:25.350 --> 00:57:26.090 cell specific,

NOTE Confidence: 0.8042411

00:57:27.110 --> 00:57:27.610 knockout

NOTE Confidence: 0.8696914

00:57:28.345 --> 00:57:29.785 model. In in these mouse

NOTE Confidence: 0.8696914

00:57:29.785 --> 00:57:31.545 models, have have you challenged

NOTE Confidence: 0.8696914

00:57:31.545 --> 00:57:33.545 them with an inflammatory signals

NOTE Confidence: 0.8696914

00:57:33.545 --> 00:57:35.225 like LPS or sepsis, like,

NOTE Confidence: 0.8696914

00:57:35.225 --> 00:57:35.725 conditionally?

NOTE Confidence: 0.80672264

00:57:36.585 --> 00:57:36.905 Right.

NOTE Confidence: 0.8710619

00:57:37.385 --> 00:57:38.825 Good question. But you don't

NOTE Confidence: 0.8710619

00:57:38.825 --> 00:57:40.105 need to. Yeah. I don't

NOTE Confidence: 0.8710619

00:57:40.105 --> 00:57:41.305 need to. So that that

NOTE Confidence: 0.8710619

00:57:41.305 --> 00:57:42.745 double knockout mouse model is

NOTE Confidence: 0.8710619

00:57:42.745 --> 00:57:44.025 very severe. I noticed the

NOTE Confidence: 0.8710619

00:57:44.025 --> 00:57:45.280 time time scale was months.

NOTE Confidence: 0.8710619

00:57:45.280 --> 00:57:46.559 And Yeah. But if you

NOTE Confidence: 0.8710619

00:57:46.559 --> 00:57:48.000 if you stimulate the LPS,

NOTE Confidence: 0.8710619

00:57:48.000 --> 00:57:49.039 do they just go down

NOTE Confidence: 0.8710619

00:57:49.039 --> 00:57:50.240 the next We we act

NOTE Confidence: 0.8710619

00:57:50.319 --> 00:57:51.920 we actually challenged the m

NOTE Confidence: 0.8710619

00:57:51.920 --> 00:57:53.539 by one single knockout

NOTE Confidence: 0.99295723

00:57:53.839 --> 00:57:55.380 in our original publication

NOTE Confidence: 0.8628856

00:57:55.680 --> 00:57:57.520 use using our PS. That

NOTE Confidence: 0.8628856

00:57:57.520 --> 00:57:58.980 can promote their disease.

NOTE Confidence: 0.92291987

00:57:59.625 --> 00:58:01.085 Because they may go down

NOTE Confidence: 0.92291987

00:58:01.305 --> 00:58:03.065 very fast because they're all

NOTE Confidence: 0.92291987

00:58:03.065 --> 00:58:04.765 primed for either metosis

NOTE Confidence: 0.6303278

00:58:05.145 --> 00:58:05.645 or

NOTE Confidence: 0.8174432

00:58:06.265 --> 00:58:06.765 metosis,

NOTE Confidence: 0.9648935

00:58:07.145 --> 00:58:08.505 which is you're having a

NOTE Confidence: 0.9648935

00:58:08.505 --> 00:58:09.005 macrophage

NOTE Confidence: 0.86811715

00:58:09.545 --> 00:58:11.465 enhancement in your and those

NOTE Confidence: 0.86811715

00:58:11.465 --> 00:58:12.585 are all prime all these

NOTE Confidence: 0.86811715

00:58:12.585 --> 00:58:13.680 signals are all the same.

NOTE Confidence: 0.86811715

00:58:13.760 --> 00:58:15.040 The IL one b Yeah.

NOTE Confidence: 0.86811715

00:58:15.119 --> 00:58:16.500 Gas derm and d for,

NOTE Confidence: 0.9722103

00:58:17.280 --> 00:58:18.420 macrophage extracellular

NOTE Confidence: 0.91984

00:58:18.800 --> 00:58:20.720 traps too. And those they

NOTE Confidence: 0.91984

00:58:20.720 --> 00:58:22.240 don't really kill the mouse.

NOTE Confidence: 0.91984

00:58:22.240 --> 00:58:23.599 What happens is there's an

NOTE Confidence: 0.91984

00:58:23.599 --> 00:58:25.200 occlusion somewhere else in a

NOTE Confidence: 0.91984

00:58:25.200 --> 00:58:26.880 vital organ that causes organ

NOTE Confidence: 0.91984

00:58:26.880 --> 00:58:28.355 failure. Nice die. Right. I

NOTE Confidence: 0.91984

00:58:28.355 --> 00:58:29.395 wonder if you've been looking

NOTE Confidence: 0.91984

00:58:29.395 --> 00:58:30.295 both of those,

NOTE Confidence: 0.8137751

00:58:30.674 --> 00:58:32.135 nettosis and metosis,

NOTE Confidence: 0.61682326

00:58:32.914 --> 00:58:34.055 or by citrullinated,

NOTE Confidence: 0.9830993

00:58:35.155 --> 00:58:36.434 of the histone Yeah. And

NOTE Confidence: 0.9830993

00:58:36.434 --> 00:58:38.115 if you did any work

NOTE Confidence: 0.9830993

00:58:38.115 --> 00:58:39.015 with a citrullinated

NOTE Confidence: 0.9991731

00:58:39.315 --> 00:58:39.815 antibody

NOTE Confidence: 0.94341797

00:58:40.434 --> 00:58:42.660 in your analysis. Yeah. Yeah.

NOTE Confidence: 0.94341797

00:58:42.819 --> 00:58:43.859 Yeah. That's work to be

NOTE Confidence: 0.94341797

00:58:43.859 --> 00:58:44.980 done. We haven't done that,

NOTE Confidence: 0.94341797

00:58:44.980 --> 00:58:45.480 unfortunately.

NOTE Confidence: 0.9448206

00:58:46.500 --> 00:58:47.940 Yeah. But that's, yeah. You

NOTE Confidence: 0.9448206

00:58:47.940 --> 00:58:48.579 can definitely

NOTE Confidence: 0.96543896

00:58:49.299 --> 00:58:50.660 I I don't remember if

NOTE Confidence: 0.96543896

00:58:50.660 --> 00:58:51.960 people have challenged

NOTE Confidence: 0.8113511

00:58:52.260 --> 00:58:53.940 the tattoo knock on. Must

NOTE Confidence: 0.8113511

00:58:53.940 --> 00:58:55.380 be, but that's a widely

NOTE Confidence: 0.8113511

00:58:55.380 --> 00:58:56.359 available model.

NOTE Confidence: 0.81344265

00:58:57.115 --> 00:58:58.635 I bet everything is primed

NOTE Confidence: 0.81344265

00:58:58.635 --> 00:58:59.135 for

NOTE Confidence: 0.75218356

00:58:59.435 --> 00:59:00.015 a catastrophic

NOTE Confidence: 0.80615216

00:59:00.955 --> 00:59:03.375 and vascular occlusions Right. From

NOTE Confidence: 0.88580126

00:59:04.235 --> 00:59:05.615 these extracellular Yeah.

NOTE Confidence: 0.95622563

00:59:07.755 --> 00:59:08.255 Yeah.

NOTE Confidence: 0.99251527

00:59:08.635 --> 00:59:09.915 Thank you so much. Thank

NOTE Confidence: 0.99251527

00:59:09.915 --> 00:59:10.415 you.