WEBVTT

00:00:00.000 --> 00:00:02.640 So next, it's my pleasure to

00:00:02.640 --> 00:00:04.400 introduce Doctor Deep Dixit,

00:00:04.400 --> 00:00:05.588 who studied veterinary medicine

00:00:05.588 --> 00:00:07.760 in India and did his PhD research

00:00:07.760 --> 00:00:09.440 at the University of Hanover,

00:00:09.440 --> 00:00:10.948 Germany, and postdoctoral research

00:00:10.948 --> 00:00:12.833 at Morehouse School of Medicine,

00:00:12.840 --> 00:00:15.440 Atlanta and the National Institutes

00:00:15.440 --> 00:00:18.040 of On Aging in Baltimore.

00:00:18.040 --> 00:00:20.518 He currently holds the Valdemar von

00:00:20.518 --> 00:00:23.490 Zewitz Endowed Chair and is the professor

00:00:23.490 --> 00:00:25.560 in the Department of Pathology,

00:00:25.560 --> 00:00:27.306 Comparative Medicine and

00:00:27.306 --> 00:00:29.634 Immunobiology at Yale University.

NOTE Confidence: 0.875200872

00:00:29.640 --> 00:00:32.125 Doctor Dixit is also the director of

NOTE Confidence: 0.875200872

00:00:32.125 --> 00:00:34.758 the Yale Center for Research on Aging,

NOTE Confidence: 0.875200872

00:00:34.760 --> 00:00:40.758 or Y age, at Yale School of Medicine.

NOTE Confidence: 0.875200872

00:00:40.760 --> 00:00:41.560 Doctor Dixit,

NOTE Confidence: 0.863808744

00:00:46.360 --> 00:00:47.920 thank you. Thank you, Anya.

NOTE Confidence: 0.863808744

00:00:47.920 --> 00:00:49.396 You know, it's always the hardest

NOTE Confidence: 0.863808744

00:00:49.396 --> 00:00:51.199 thing to do is to give a talk,

NOTE Confidence: 0.863808744

00:00:51.200 --> 00:00:53.798 intramural talk, in a Yale symposium

NOTE Confidence: 0.863808744

00:00:53.800 --> 00:00:55.480 among the audience from Yale.

NOTE Confidence: 0.863808744

00:00:55.480 --> 00:00:57.300 Because it's the hardest

NOTE Confidence: 0.863808744

00:00:57.300 --> 00:00:59.120 because everybody's so great.

NOTE Confidence: 0.863808744

00:00:59.120 --> 00:01:02.040 So let me see if I can do justice to it.

NOTE Confidence: 0.863808744

00:01:02.040 --> 00:01:03.615 Now I think we've heard about obesity

NOTE Confidence: 0.863808744

00:01:03.615 --> 00:01:05.159 and we'll talk more about obesity.

NOTE Confidence: 0.863808744

00:01:05.160 --> 00:01:08.160 But I just want to remind those of you who

NOTE Confidence: 0.863808744

00:01:08.160 --> 00:01:11.436 don't think about this as much as we do,

NOTE Confidence: 0.863808744

00:01:11.440 --> 00:01:14.464 which is that if you compare the

NOTE Confidence: 0.863808744

00:01:14.464 --> 00:01:16.586 risk factors of various situations

NOTE Confidence: 0.863808744

00:01:16.586 --> 00:01:19.477 that we are dealing with in life,

NOTE Confidence: 0.863808744

00:01:19.480 --> 00:01:22.080 actually aging, just getting old,

NOTE Confidence: 0.863808744

00:01:22.080 --> 00:01:24.342 the process of getting old is

NOTE Confidence: 0.863808744

00:01:24.342 --> 00:01:26.317 the single biggest risk factor

NOTE Confidence: 0.863808744

00:01:26.317 --> 00:01:28.639 for each one of these diseases,

NOTE Confidence: 0.863808744

00:01:28.640 --> 00:01:30.278 including heart disease,

NOTE Confidence: 0.863808744

00:01:30.278 --> 00:01:31.916 Alzheimer's and cancers.

NOTE Confidence: 0.863808744

00:01:31.920 --> 00:01:33.850 And this is something that

NOTE Confidence: 0.863808744

00:01:33.850 --> 00:01:35.394 we're extremely interested in.

NOTE Confidence: 0.863808744

00:01:35.400 --> 00:01:37.668 And what we are also extremely

NOTE Confidence: 0.863808744

00:01:37.668 --> 00:01:40.080 interested in is the interaction

NOTE Confidence: 0.863808744

00:01:40.080 --> 00:01:43.935 that occurs between development of

NOTE Confidence: 0.863808744

00:01:43.935 --> 00:01:47.790 obesity and chronic obesity that

NOTE Confidence: 0.863808744

00:01:47.912 --> 00:01:51.016 spills into age as we get older.

NOTE Confidence: 0.863808744

00:01:51.016 --> 00:01:53.480 So these are data from CDC and

NOTE Confidence: 0.863808744

00:01:53.480 --> 00:01:56.946 you can see that individuals that

NOTE Confidence: 0.863808744

00:01:56.946 --> 00:01:59.660 are older adults that are between

NOTE Confidence: 0.863808744

00:01:59.660 --> 00:02:01.560 the ages of 65 and 74,

NOTE Confidence: 0.863808744

00:02:01.560 --> 00:02:03.726 in this case the the incidence

NOTE Confidence: 0.863808744

00:02:03.726 --> 00:02:05.600 of obesity is fairly high,

NOTE Confidence: 0.863808744

00:02:05.600 --> 00:02:09.674 almost 40% of older adults have obesity.

NOTE Confidence: 0.863808744

00:02:09.680 --> 00:02:12.116 And what in terms of mechanisms,

NOTE Confidence: 0.863808744

00:02:12.120 --> 00:02:15.216 we know very little about how

NOTE Confidence: 0.863808744

00:02:15.216 --> 00:02:18.623 the basic biology of aging and

NOTE Confidence: 0.863808744

00:02:18.623 --> 00:02:21.718 the aging processes are impacted

NOTE Confidence: 0.863808744

00:02:21.720 --> 00:02:24.084 when we have this chronic obesity

NOTE Confidence: 0.863808744

00:02:24.084 --> 00:02:26.200 that is present in aging.

NOTE Confidence: 0.863808744

00:02:26.200 --> 00:02:28.140 There are some studies,

NOTE Confidence: 0.863808744

00:02:28.140 --> 00:02:30.080 including some from Yale.

NOTE Confidence: 0.863808744

00:02:30.080 --> 00:02:34.280 But what's very intriguing is this

NOTE Confidence: 0.863808744

00:02:34.280 --> 00:02:37.080 response that you see in all 'cause

NOTE Confidence: 0.863808744

00:02:37.080 --> 00:02:40.424 mortality and the BMI with age, right.

NOTE Confidence: 0.863808744

00:02:40.424 --> 00:02:41.960 So it's a paradox.

NOTE Confidence: 0.863808744

00:02:41.960 --> 00:02:45.268 So you will notice that on the Y axis,

NOTE Confidence: 0.863808744

00:02:45.268 --> 00:02:46.903 this is the mortality hazard

NOTE Confidence: 0.863808744

00:02:46.903 --> 00:02:48.837 ratio and the BMI listed here

NOTE Confidence: 0.863808744

00:02:48.840 --> 00:02:51.312 that if as we get older and the

NOTE Confidence: 0.863808744

00:02:51.312 --> 00:02:53.479 chances of mortality increases.

NOTE Confidence: 0.863808744

00:02:53.480 --> 00:02:55.360 If the BMI is high,

NOTE Confidence: 0.863808744

00:02:55.360 --> 00:02:57.240 obviously that is expected.

NOTE Confidence: 0.863808744

00:02:57.240 --> 00:03:00.060 But also the chances of mortality

NOTE Confidence: 0.863808744

00:03:00.141 --> 00:03:02.725 are much higher if the BMI is on

NOTE Confidence: 0.863808744

00:03:02.725 --> 00:03:04.998 the lower end of the spectrum.

NOTE Confidence: 0.863808744

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00:03:05.000 --> 00:03:08.150 How these things are actually mechanistically

NOTE Confidence: 0.863808744

00:03:08.150 --> 00:03:10.720 related are not very well known.

NOTE Confidence: 0.863808744

00:03:10.720 --> 00:03:12.640 It's also not known whether you know the

NOTE Confidence: 0.699415944545455

00:03:16.680 --> 00:03:19.557 point of time. But it's also well

NOTE Confidence: 0.699415944545455

00:03:19.557 --> 00:03:22.180 not known whether if one carries on

NOTE Confidence: 0.699415944545455

00:03:22.180 --> 00:03:24.840 obesity and aging risk all this way,

NOTE Confidence: 0.699415944545455

00:03:24.840 --> 00:03:27.199 whether this is already a fait accompli,

NOTE Confidence: 0.699415944545455

00:03:27.200 --> 00:03:29.752 Is there anything we can do to this

NOTE Confidence: 0.699415944545455

00:03:29.752 --> 00:03:32.118 process that would enhance our health?

NOTE Confidence: 0.699415944545455

00:03:32.120 --> 00:03:34.256 So we have been interested in

NOTE Confidence: 0.699415944545455

00:03:34.256 --> 00:03:36.091 negative energy balance and how

NOTE Confidence: 0.699415944545455

00:03:36.091 --> 00:03:37.836 to induce negative energy balance

NOTE Confidence: 0.699415944545455

00:03:37.836 --> 00:03:40.200 and what that does to Physiology.

NOTE Confidence: 0.699415944545455

00:03:40.200 --> 00:03:42.600 And as Tomas had mentioned,

NOTE Confidence: 0.699415944545455

00:03:42.600 --> 00:03:45.258 one of the key interventions that

NOTE Confidence: 0.699415944545455

00:03:45.258 --> 00:03:47.542 was discovered almost 100 years

NOTE Confidence: 0.699415944545455

00:03:47.542 --> 00:03:49.717 ago that extends lifespan and

NOTE Confidence: 0.699415944545455

00:03:49.717 --> 00:03:52.440 health span is caloric restriction.

NOTE Confidence: 0.699415944545455

00:03:52.440 --> 00:03:56.691 And so as you know obesity is a

NOTE Confidence: 0.699415944545455

00:03:56.691 --> 00:03:58.999 fundamental disorder of thermodynamics.

NOTE Confidence: 0.699415944545455

00:03:59.000 --> 00:04:01.163 So you have energy intake and you

NOTE Confidence: 0.699415944545455

00:04:01.163 --> 00:04:03.359 have energy out energy expenditure.

NOTE Confidence: 0.699415944545455

00:04:03.360 --> 00:04:05.202 We heard a lot about everything

NOTE Confidence: 0.699415944545455

00:04:05.202 --> 00:04:06.760 that's currently is known about

NOTE Confidence: 0.699415944545455

00:04:06.760 --> 00:04:07.694 obesity interventions,

NOTE Confidence: 0.699415944545455

00:04:07.694 --> 00:04:09.095 pharmacologic interventions are

NOTE Confidence: 0.699415944545455

00:04:09.095 --> 00:04:11.848 all on energy intake which is

NOTE Confidence: 0.699415944545455

00:04:11.848 --> 00:04:13.276 inhibiting your food intake.

NOTE Confidence: 0.699415944545455

00:04:13.280 --> 00:04:15.360 And we are very much interested to see

NOTE Confidence: 0.699415944545455

00:04:15.360 --> 00:04:17.158 what's the other side of the axis,

NOTE Confidence: 0.699415944545455

00:04:17.160 --> 00:04:19.638 Is there a way to expend energy?

NOTE Confidence: 0.699415944545455

00:04:19.640 --> 00:04:19.884 Anyway,

NOTE Confidence: 0.699415944545455

00:04:19.884 --> 00:04:22.400 I'm not going to go into the details of this,

NOTE Confidence: 0.699415944545455

00:04:22.400 --> 00:04:24.031 but we know that when the host

NOTE Confidence: 0.699415944545455

00:04:24.031 --> 00:04:25.559 is in negative energy balance,

NOTE Confidence: 0.699415944545455

00:04:25.560 --> 00:04:27.000 you get lifespan extension.

NOTE Confidence: 0.699415944545455

00:04:27.000 --> 00:04:28.800 Actually you have less diseases,

NOTE Confidence: 0.699415944545455

00:04:28.800 --> 00:04:31.558 except there's a dirty little secret here,

NOTE Confidence: 0.699415944545455

00:04:31.560 --> 00:04:34.794 which is as we get this longevity,

NOTE Confidence: 0.699415944545455

00:04:34.800 --> 00:04:38.960 this longevity dividend comes at

NOTE Confidence: 0.699415944545455

00:04:38.960 --> 00:04:41.040 with the risks of these trade-offs.

NOTE Confidence: 0.955366636666667

00:04:43.760 --> 00:04:47.099 So animal models that live long,

NOTE Confidence: 0.955366636666667

00:04:47.099 --> 00:04:48.266 all of them, they live,

NOTE Confidence: 0.955366636666667

00:04:48.266 --> 00:04:50.319 they do live long, but they have,

NOTE Confidence: 0.955366636666667

00:04:50.319 --> 00:04:52.648 they're growth ******** they do not breed.

NOTE Confidence: 0.955366636666667

00:04:52.648 --> 00:04:54.914 If you take them out from a specific

NOTE Confidence: 0.955366636666667

00:04:54.914 --> 00:04:58.278 pathogen free facility, they fall dead.

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NOTE Confidence: 0.955366636666667

00:04:58.280 --> 00:04:59.044 And we've been studying

NOTE Confidence: 0.955366636666667

00:04:59.044 --> 00:04:59.999 this for almost 100 years.

NOTE Confidence: 0.955366636666667

00:05:00.000 --> 00:05:02.338 And the question has been if this

NOTE Confidence: 0.955366636666667

00:05:02.338 --> 00:05:03.808 intervention that extends lifespan

NOTE Confidence: 0.955366636666667

00:05:03.808 --> 00:05:05.838 has this multiple health benefits.

NOTE Confidence: 0.955366636666667

00:05:05.840 --> 00:05:08.054 If are we going to ever harness any of

NOTE Confidence: 0.955366636666667

00:05:08.054 --> 00:05:09.752 the so-called Pella restriction mimetics?

NOTE Confidence: 0.955366636666667

00:05:09.752 --> 00:05:12.560 Is it actually relevant to human Physiology?

NOTE Confidence: 0.955366636666667

00:05:12.560 --> 00:05:14.536 And this is what we have been trying

NOTE Confidence: 0.955366636666667

00:05:14.536 --> 00:05:16.800 to do over the past 15 years or so.

NOTE Confidence: 0.955366636666667

00:05:16.800 --> 00:05:18.375 I'm not going to go into the

NOTE Confidence: 0.955366636666667

00:05:18.375 --> 00:05:19.600 details of model organisms.

NOTE Confidence: 0.955366636666667

00:05:19.600 --> 00:05:21.399 Both Tomas and I are failed veterinarians.

NOTE Confidence: 0.955366636666667

00:05:21.400 --> 00:05:23.392 It's very nice to give a

NOTE Confidence: 0.955366636666667

00:05:23.392 --> 00:05:25.700 talk right after him. So.

NOTE Confidence: 0.955366636666667

00:05:25.700 --> 00:05:29.735 But the idea here is that the

NOTE Confidence: 0.955366636666667

00:05:29.735 --> 00:05:30.645 dietary interventions,

NOTE Confidence: 0.955366636666667

00:05:30.645 --> 00:05:32.920 especially things like caloric restriction,

NOTE Confidence: 0.955366636666667

00:05:32.920 --> 00:05:35.520 if you do in animals, you know,

NOTE Confidence: 0.955366636666667

00:05:35.520 --> 00:05:39.360 animal in a cage does not sign consent forms.

NOTE Confidence: 0.955366636666667

00:05:39.360 --> 00:05:40.956 It doesn't know if you're going to,

NOTE Confidence: 0.955366636666667

00:05:40.960 --> 00:05:42.598 you know, give 40% less calories.

NOTE Confidence: 0.955366636666667

00:05:42.600 --> 00:05:44.595 Animal doesn't know what's going to happen.

NOTE Confidence: 0.955366636666667

00:05:44.600 --> 00:05:46.872 So the idea is to actually do a

NOTE Confidence: 0.955366636666667

00:05:46.872 --> 00:05:48.359 randomized controlled study in people,

NOTE Confidence: 0.955366636666667

00:05:48.360 --> 00:05:50.403 see if it is relevant to human Physiology in

NOTE Confidence: 0.955366636666667

00:05:50.403 --> 00:05:52.719 in terms of inducing negative energy balance,

NOTE Confidence: 0.955366636666667

00:05:52.720 --> 00:05:54.400 most importantly without

NOTE Confidence: 0.955366636666667

00:05:54.400 --> 00:05:56.080 inducing these trade-offs.

NOTE Confidence: 0.955366636666667

00:05:56.080 --> 00:05:57.420 And many of these trade-offs

NOTE Confidence: 0.955366636666667

00:05:57.420 --> 00:05:58.760 actually come from stress signaling.

NOTE Confidence: 0.955366636666667

00:05:58.760 --> 00:05:59.292 All right.

NOTE Confidence: 0.955366636666667

00:05:59.292 --> 00:06:01.154 And see if that is actually relevant.

NOTE Confidence: 0.955366636666667

00:06:01.160 --> 00:06:03.848 Can we harness those endogenous factors

NOTE Confidence: 0.955366636666667

00:06:03.848 --> 00:06:05.995 assigned causality using the animal models?

NOTE Confidence: 0.955366636666667

00:06:05.995 --> 00:06:08.246 And this was a trial that was funded

NOTE Confidence: 0.955366636666667

00:06:08.246 --> 00:06:10.238 by the National Institute on Aging.

NOTE Confidence: 0.955366636666667

00:06:10.240 --> 00:06:11.488 It's now complete.

NOTE Confidence: 0.955366636666667

00:06:11.488 --> 00:06:13.984 This trial was initiated while I

NOTE Confidence: 0.955366636666667

00:06:13.984 --> 00:06:15.740 was starting my faculty position

NOTE Confidence: 0.955366636666667

00:06:15.740 --> 00:06:17.080 in Pennington in Louisiana.

NOTE Confidence: 0.955366636666667

00:06:17.080 --> 00:06:19.355 And the idea that NIH wanted was

NOTE Confidence: 0.955366636666667

00:06:19.360 --> 00:06:21.450 that we take healthy people, OK?

NOTE Confidence: 0.955366636666667

00:06:21.450 --> 00:06:21.820 See,

NOTE Confidence: 0.955366636666667

00:06:21.820 --> 00:06:23.670 if we restrict the calories

NOTE Confidence: 0.955366636666667

00:06:23.670 --> 00:06:26.216 by 25% for two years,

NOTE Confidence: 0.955366636666667

00:06:26.216 --> 00:06:28.936 would that delay the trajectory

NOTE Confidence: 0.955366636666667

00:06:28.936 --> 00:06:31.480 of reducing the risk of disease

NOTE Confidence: 0.955366636666667

00:06:31.480 --> 00:06:34.800 and slowing the process of aging?

NOTE Confidence: 0.955366636666667

00:06:34.800 --> 00:06:36.732 It was a really an ambitious goal

NOTE Confidence: 0.955366636666667

00:06:36.732 --> 00:06:38.657 because there is no way to know after

NOTE Confidence: 0.955366636666667

00:06:38.657 --> 00:06:40.456 two years how you have actually traject

NOTE Confidence: 0.955366636666667

00:06:40.456 --> 00:06:41.920 changed the trajectory of aging.

NOTE Confidence: 0.955366636666667

00:06:41.920 --> 00:06:43.078 You know there are no markers,

NOTE Confidence: 0.955366636666667

00:06:43.080 --> 00:06:44.480 there are no biomarkers or

NOTE Confidence: 0.955366636666667

00:06:44.480 --> 00:06:45.880 or any of those things.

NOTE Confidence: 0.955366636666667

00:06:45.880 --> 00:06:47.760 Anyway,

NOTE Confidence: 0.955366636666667

00:06:47.760 --> 00:06:50.200 what we have been interested in is to see if

NOTE Confidence: 0.955366636666667

00:06:50.263 --> 00:06:52.594 it is indeed relevant to human Physiology.

NOTE Confidence: 0.955366636666667

00:06:52.600 --> 00:06:54.625 Can we harness some of

NOTE Confidence: 0.955366636666667

00:06:54.625 --> 00:06:55.840 those endogenous factors?

NOTE Confidence: 0.955366636666667

00:06:55.840 --> 00:06:58.444 So this is what happens when people

NOTE Confidence: 0.955366636666667

00:06:58.444 --> 00:06:59.560 undergo caloric restriction.

NOTE Confidence: 0.955366636666667

00:06:59.560 --> 00:07:01.738 So actually humans in free living

NOTE Confidence: 0.955366636666667

00:07:01.738 --> 00:07:03.527 condition can only undergo about

NOTE Confidence: 0.955366636666667

00:07:03.527 --> 00:07:05.008 14% or 15% caloric restriction.

NOTE Confidence: 0.955366636666667

00:07:05.008 --> 00:07:06.820 The reason why we have obesity

NOTE Confidence: 0.955366636666667

00:07:06.872 --> 00:07:08.612 epidemic is because exercise and

NOTE Confidence: 0.955366636666667

00:07:08.612 --> 00:07:10.352 reducing food intake doesn't work.

NOTE Confidence: 0.955366636666667

00:07:10.360 --> 00:07:12.160 That's why we have pharmacology.

NOTE Confidence: 0.955366636666667

00:07:12.160 --> 00:07:13.438 The key point here is that,

NOTE Confidence: 0.955366636666667

00:07:13.440 --> 00:07:15.490 so this is transcriptional data

NOTE Confidence: 0.955366636666667

00:07:15.490 --> 00:07:16.720 from adipose transcriptome,

NOTE Confidence: 0.955366636666667

00:07:16.720 --> 00:07:18.000 data from adipose tissue.

NOTE Confidence: 0.955366636666667

00:07:18.000 --> 00:07:20.048 These are individuals at the baseline.

NOTE Confidence: 0.955366636666667

00:07:20.048 --> 00:07:21.104 These are individuals

NOTE Confidence: 0.955366636666667

00:07:21.104 --> 00:07:22.160 after caloric restriction.

NOTE Confidence: 0.955366636666667

00:07:22.160 --> 00:07:24.496 And you can see the remarkable change in

00:07:24.496 --> 00:07:26.240 the transcriptome of the adipose tissue.

00:07:26.240 --> 00:07:27.840 And I recall that when we were doing

00:07:27.840 --> 00:07:28.852 this analysis, my collaborator,

00:07:28.852 --> 00:07:30.076 Washu Mike Sardomoff says,

00:07:30.080 --> 00:07:31.142 oh, you know,

00:07:31.142 --> 00:07:32.558 your mice look amazing.

00:07:32.560 --> 00:07:34.600 These are not inbred 99.9%

00:07:34.600 --> 00:07:35.545 genetically identical animals.

00:07:35.545 --> 00:07:37.120 As far as I know.

00:07:37.120 --> 00:07:38.848 They're all human beings.

00:07:38.848 --> 00:07:40.430 Yeah. So I'm not going to

00:07:40.430 --> 00:07:41.920 go into the detail of that,

00:07:41.920 --> 00:07:44.860 but share some really new data

00:07:44.860 --> 00:07:48.385 in next 5 minutes or so that is I

00:07:48.385 --> 00:07:49.960 think is quite serendipitous in,

NOTE Confidence: 0.896328714

00:07:49.960 --> 00:07:51.955 in many ways that we have found

NOTE Confidence: 0.896328714

00:07:51.960 --> 00:07:53.330 suggesting that there are several

NOTE Confidence: 0.896328714

00:07:53.330 --> 00:07:55.060 other pathways that could be really

NOTE Confidence: 0.896328714

00:07:55.060 --> 00:07:56.920 interesting and important for weight loss.

NOTE Confidence: 0.896328714

00:07:56.920 --> 00:07:58.512 So one of the things that we have

NOTE Confidence: 0.896328714

00:07:58.512 --> 00:07:59.994 been very interested to see is

NOTE Confidence: 0.896328714

00:07:59.994 --> 00:08:01.289 also the changes in metabolism

NOTE Confidence: 0.896328714

00:08:01.289 --> 00:08:03.107 that that occurs when individuals

NOTE Confidence: 0.896328714

00:08:03.107 --> 00:08:04.238 undergo caloric restriction.

NOTE Confidence: 0.896328714

00:08:04.240 --> 00:08:05.476 So when we did the metabolomics,

NOTE Confidence: 0.896328714

00:08:05.480 --> 00:08:08.000 the the pathway that really lit up

NOTE Confidence: 0.896328714

00:08:08.000 --> 00:08:10.675 was the pathway that is associated

NOTE Confidence: 0.896328714

00:08:10.675 --> 00:08:13.200 with taurine and cysteine metabolism,

NOTE Confidence: 0.896328714

00:08:13.200 --> 00:08:15.444 which led me into this area that

NOTE Confidence: 0.896328714

00:08:15.444 --> 00:08:17.154 we had never thought about,

NOTE Confidence: 0.896328714

00:08:17.160 --> 00:08:19.200 which is the transalphuration path.

NOTE Confidence: 0.896328714

00:08:19.200 --> 00:08:20.060 Please don't hate me.

NOTE Confidence: 0.896328714

00:08:20.060 --> 00:08:21.912 This is not meant for you to kind of

NOTE Confidence: 0.896328714

00:08:21.912 --> 00:08:23.520 really look into it in any details.

NOTE Confidence: 0.896328714

00:08:23.520 --> 00:08:25.480 We've we've all suffered through TCA cycle.

NOTE Confidence: 0.896328714

00:08:25.480 --> 00:08:25.749 OK.

NOTE Confidence: 0.896328714

00:08:25.749 --> 00:08:27.632 The key point here is I want

NOTE Confidence: 0.896328714

00:08:27.632 --> 00:08:29.880 you to focus on cysteine, OK.

NOTE Confidence: 0.896328714

00:08:29.880 --> 00:08:33.080 This is a fundamental pathway that is really,

NOTE Confidence: 0.896328714

00:08:33.080 --> 00:08:35.299 really critical for us in terms of

NOTE Confidence: 0.896328714

00:08:35.299 --> 00:08:37.560 maintenance of sulfur amino acid metabolism.

NOTE Confidence: 0.896328714

00:08:37.560 --> 00:08:37.873 OK.

NOTE Confidence: 0.896328714

00:08:37.873 --> 00:08:39.751 Why is this metabolism showing up

NOTE Confidence: 0.896328714

00:08:39.751 --> 00:08:41.878 in this calorie restriction we had?

NOTE Confidence: 0.896328714

00:08:41.880 --> 00:08:43.623 This is not what we predicted and

NOTE Confidence: 0.896328714

00:08:43.623 --> 00:08:45.600 that's the beauty of science in many ways.

NOTE Confidence: 0.896328714

00:08:45.600 --> 00:08:49.132 So this is the enzyme just quickly.

NOTE Confidence: 0.896328714

00:08:49.132 --> 00:08:52.210 So cysteine is made from this

NOTE Confidence: 0.896328714

00:08:52.210 --> 00:08:54.435 enzyme here cystathione gamma lyase.

NOTE Confidence: 0.896328714

00:08:54.440 --> 00:08:56.155 And when we checked our transcriptional data,

NOTE Confidence: 0.896328714

00:08:56.160 --> 00:08:57.830 indeed this enzyme is very

NOTE Confidence: 0.896328714

00:08:57.830 --> 00:09:00.162 critical and it gets up regulated

NOTE Confidence: 0.896328714

00:09:00.162 --> 00:09:01.920 upon caloric restriction.

NOTE Confidence: 0.896328714

00:09:01.920 --> 00:09:03.805 So prediction would be that

NOTE Confidence: 0.896328714

00:09:03.805 --> 00:09:05.313 you have more cysteine,

NOTE Confidence: 0.896328714

00:09:05.320 --> 00:09:08.280 well actually just before that

NOTE Confidence: 0.896328714

00:09:08.280 --> 00:09:09.546 and this increase of this enzyme

NOTE Confidence: 0.896328714

00:09:09.546 --> 00:09:11.000 while we were doing these studies,

NOTE Confidence: 0.896328714

00:09:11.000 --> 00:09:13.166 this paper came out from vitamin

NOTE Confidence: 0.896328714

00:09:13.166 --> 00:09:15.394 Gladyshave's lab that this enzyme is

NOTE Confidence: 0.896328714

00:09:15.394 --> 00:09:17.199 also increase in multiple intervention

NOTE Confidence: 0.896328714

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00:09:17.199 --> 00:09:20.120 that in in in mice that extend lifespan.

NOTE Confidence: 0.896328714

00:09:20.120 --> 00:09:20.800 So we thought that OK,

NOTE Confidence: 0.896328714

00:09:20.800 --> 00:09:22.676 we are probably on the right trajectory,

NOTE Confidence: 0.896328714

00:09:22.680 --> 00:09:22.998 right.

NOTE Confidence: 0.896328714

00:09:22.998 --> 00:09:25.542 And and this is the kind of a

NOTE Confidence: 0.896328714

00:09:25.542 --> 00:09:28.027 snapshot of how cysteine metabolism

NOTE Confidence: 0.896328714

00:09:28.027 --> 00:09:30.115 and transulphuration looks like.

NOTE Confidence: 0.896328714

00:09:30.120 --> 00:09:32.280 So this is the methionine cycle.

NOTE Confidence: 0.896328714

00:09:32.280 --> 00:09:34.226 All of you know that cysteine is

NOTE Confidence: 0.896328714

00:09:34.226 --> 00:09:36.171 dietary non essential and I'm going to

NOTE Confidence: 0.896328714

00:09:36.171 --> 00:09:38.320 show you that it's actually really essential.

NOTE Confidence: 0.896328714

00:09:38.320 --> 00:09:39.839 It may be dietary is not essential,

NOTE Confidence: 0.896328714

00:09:39.840 --> 00:09:41.560 it's really essential for Physiology.

NOTE Confidence: 0.896328714

00:09:41.560 --> 00:09:44.266 So this enzyme increases by caloric

NOTE Confidence: 0.896328714

00:09:44.266 --> 00:09:46.592 restriction and what it does is it

NOTE Confidence: 0.896328714

00:09:46.592 --> 00:09:47.840 converts histathionine into cysteine.

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NOTE Confidence: 0.896328714

00:09:47.840 --> 00:09:50.080 And as you know cysteine is a very

NOTE Confidence: 0.896328714

00:09:50.080 --> 00:09:51.648 important substrate for multiple

NOTE Confidence: 0.896328714

00:09:51.648 --> 00:09:53.160 things including glutathione.

NOTE Confidence: 0.896328714

00:09:53.160 --> 00:09:55.477 And the key part of cysteine is,

NOTE Confidence: 0.896328714

00:09:55.480 --> 00:09:58.605 is this very critical modification

NOTE Confidence: 0.896328714

00:09:58.605 --> 00:10:00.480 here thiol group.

NOTE Confidence: 0.896328714

00:10:00.480 --> 00:10:02.771 It's the only amino acid that

NOTE Confidence: 0.896328714

00:10:02.771 --> 00:10:04.404 has a thiol group in it, OK.

NOTE Confidence: 0.896328714

00:10:04.404 --> 00:10:06.224 And that is absolutely essential

NOTE Confidence: 0.896328714

00:10:06.224 --> 00:10:07.316 for its function.

NOTE Confidence: 0.896328714

00:10:07.320 --> 00:10:08.259 But you know,

NOTE Confidence: 0.896328714

00:10:08.259 --> 00:10:10.137 prediction would be that if the

NOTE Confidence: 0.896328714

00:10:10.137 --> 00:10:11.910 cysteine levels are high, oh, sorry,

NOTE Confidence: 0.896328714

00:10:11.910 --> 00:10:13.555 the if the Cth levels are high,

NOTE Confidence: 0.896328714

00:10:13.560 --> 00:10:15.102 then the cysteine levels are going

NOTE Confidence: 0.896328714

00:10:15.102 --> 00:10:16.930 to be higher in calorie restriction,

NOTE Confidence: 0.896328714

00:10:16.930 --> 00:10:18.680 but it's actually the opposite.

NOTE Confidence: 0.896328714

00:10:18.680 --> 00:10:20.960 So what happens is in individuals

NOTE Confidence: 0.896328714

00:10:20.960 --> 00:10:22.480 that undergo calorie restriction,

NOTE Confidence: 0.817405406666667

00:10:22.480 --> 00:10:24.216 if you measure cysteine levels in the

NOTE Confidence: 0.817405406666667

00:10:24.216 --> 00:10:25.728 adipose tissue, it's actually lower.

NOTE Confidence: 0.817405406666667

00:10:25.728 --> 00:10:28.902 So Cth is in terms of going up to

NOTE Confidence: 0.817405406666667

00:10:28.902 --> 00:10:31.158 kind of maintain the cysteine levels.

NOTE Confidence: 0.817405406666667

00:10:31.160 --> 00:10:33.650 So what we decided to do was to see if

NOTE Confidence: 0.817405406666667

00:10:33.719 --> 00:10:36.551 we can target CDH and create a artificial

NOTE Confidence: 0.817405406666667

00:10:36.551 --> 00:10:38.640 condition of regulating cysteine.

NOTE Confidence: 0.817405406666667

00:10:38.640 --> 00:10:39.858 And the way you do that because

NOTE Confidence: 0.817405406666667

00:10:39.858 --> 00:10:41.160 if you just restrict cysteine,

NOTE Confidence: 0.817405406666667

00:10:41.160 --> 00:10:43.168 it's not going to make any difference because

NOTE Confidence: 0.817405406666667

00:10:43.168 --> 00:10:45.240 body is going to make cysteine from CDH.

NOTE Confidence: 0.817405406666667

00:10:45.240 --> 00:10:46.880 So what we did was create this mouse.

00:10:46.880 --> 00:10:49.124 This work was done by my

00:10:49.124 --> 00:10:51.000 former PhD student Eileen Lee.

00:10:51.000 --> 00:10:52.914 So she created these animals that

00:10:52.914 --> 00:10:54.994 lack Cth enzyme and then restricted

00:10:54.994 --> 00:10:56.478 cysteine in the diet.

00:10:56.480 --> 00:10:58.432 And what it does is that in this

00:10:58.432 --> 00:11:00.200 case there is no cysteine being

00:11:00.200 --> 00:11:02.036 made or is either being consumed.

00:11:02.040 --> 00:11:03.620 The mice are normal.

00:11:03.620 --> 00:11:06.382 Most of these mice in in when

00:11:06.382 --> 00:11:07.958 they're in the cysteine.

00:11:07.960 --> 00:11:09.115 When you give cysteine in the diet,

00:11:09.120 --> 00:11:10.347 they're totally fine.

00:11:10.347 --> 00:11:13.210 But notice what happens to the knockouts

00:11:13.278 --> 00:11:15.714 when you remove cysteine in the diet,

00:11:15.720 --> 00:11:17.238 they undergo massive,

NOTE Confidence: 0.817405406666667

00:11:17.238 --> 00:11:18.756 massive weight loss.

NOTE Confidence: 0.817405406666667

00:11:18.760 --> 00:11:20.084 And this weight loss,

NOTE Confidence: 0.817405406666667

00:11:20.084 --> 00:11:22.680 weight loss is really specific to cysteine.

NOTE Confidence: 0.817405406666667

00:11:22.680 --> 00:11:24.912 So if we so this is the weight loss

NOTE Confidence: 0.817405406666667

00:11:24.912 --> 00:11:26.840 here with restricting cysteine.

NOTE Confidence: 0.817405406666667

00:11:26.840 --> 00:11:29.080 If you put cysteine back in the diet

NOTE Confidence: 0.817405406666667

00:11:29.080 --> 00:11:31.872 they gain weight back up and you know

NOTE Confidence: 0.817405406666667

00:11:31.872 --> 00:11:35.437 we did this for three cycles just for fun.

NOTE Confidence: 0.817405406666667

00:11:35.440 --> 00:11:37.200 These animals don't have disease,

NOTE Confidence: 0.817405406666667

00:11:37.200 --> 00:11:37.688 OK,

NOTE Confidence: 0.817405406666667

00:11:37.688 --> 00:11:39.640 they don't have malaise.

NOTE Confidence: 0.817405406666667

00:11:39.640 --> 00:11:41.182 So these are the knockouts on

NOTE Confidence: 0.817405406666667

00:11:41.182 --> 00:11:41.953 cysteine free diet.

NOTE Confidence: 0.817405406666667

00:11:41.960 --> 00:11:44.277 They are pretty they are pretty healthy.

NOTE Confidence: 0.817405406666667

00:11:44.280 --> 00:11:46.268 So the question is what are these

NOTE Confidence: 0.817405406666667

00:11:46.268 --> 00:11:48.116 mice dying of or what is actually

NOTE Confidence: 0.817405406666667

00:11:48.116 --> 00:11:49.610 happening in terms of weight loss

NOTE Confidence: 0.817405406666667

00:11:49.661 --> 00:11:51.101 because we know that weight loss

NOTE Confidence: 0.817405406666667

00:11:51.101 --> 00:11:52.720 can be healthy and UN unhealthy.

NOTE Confidence: 0.817405406666667

00:11:52.720 --> 00:11:55.445 What was really striking in

NOTE Confidence: 0.817405406666667

00:11:55.445 --> 00:11:58.115 these animals was that when we

NOTE Confidence: 0.817405406666667

00:11:58.115 --> 00:11:59.840 depleted cysteine from the system,

NOTE Confidence: 0.817405406666667

00:11:59.840 --> 00:12:02.420 what it did was it completely

NOTE Confidence: 0.817405406666667

00:12:02.420 --> 00:12:04.718 changed the white adipose tissue

NOTE Confidence: 0.817405406666667

00:12:04.718 --> 00:12:07.110 into brown adipose tissue and it

NOTE Confidence: 0.817405406666667

00:12:07.110 --> 00:12:08.280 was not like a minor response,

NOTE Confidence: 0.817405406666667

00:12:08.280 --> 00:12:09.980 it was total conversion of

NOTE Confidence: 0.817405406666667

00:12:09.980 --> 00:12:11.000 the adipose tissue,

NOTE Confidence: 0.817405406666667

00:12:11.000 --> 00:12:13.520 both subcutaneous as well as visceral.

NOTE Confidence: 0.817405406666667

00:12:13.520 --> 00:12:14.880 All right.

NOTE Confidence: 0.817405406666667

00:12:14.880 --> 00:12:17.000 And this is just the marker UCP one,

00:12:17.000 --> 00:12:19.000 which is critical for uncoupling.

00:12:19.000 --> 00:12:20.200 We all know that mice,

00:12:20.200 --> 00:12:21.760 you know they show this response

00:12:21.760 --> 00:12:23.526 typically if they're in sub thermal

00:12:23.526 --> 00:12:25.206 neutral temperature because our animal

00:12:25.206 --> 00:12:27.480 facilities are 22°C whereas you and I,

00:12:27.480 --> 00:12:29.436 we all live in thermal neutrality.

00:12:29.440 --> 00:12:31.344 So what Eileen did was did the

00:12:31.344 --> 00:12:32.758 same experiment in animals that

00:12:32.758 --> 00:12:34.840 are kept at 30°C which is thermal

00:12:34.840 --> 00:12:37.096 neutral zone and it is independent

00:12:37.096 --> 00:12:39.116 of thermal neutrality or cold.

00:12:39.120 --> 00:12:41.040 So these animals still lose weight,

00:12:41.040 --> 00:12:42.066 dramatic weight loss.

00:12:42.066 --> 00:12:44.460 And this weight loss in animals is

NOTE Confidence: 0.817405406666667

00:12:44.527 --> 00:12:46.873 considered lethal because they have to

NOTE Confidence: 0.817405406666667

00:12:46.873 --> 00:12:49.359 euthanize animals at this point of time.

NOTE Confidence: 0.817405406666667

00:12:49.360 --> 00:12:52.636 So idea is what is actually happening.

NOTE Confidence: 0.817405406666667

00:12:52.640 --> 00:12:54.760 There is increased energy expenditure

NOTE Confidence: 0.817405406666667

00:12:54.760 --> 00:12:56.880 in these in these animals.

NOTE Confidence: 0.817405406666667

00:12:56.880 --> 00:12:59.320 So they're expending more energy.

NOTE Confidence: 0.817405406666667

00:12:59.320 --> 00:13:01.154 They're eating the same amount of food,

NOTE Confidence: 0.817405406666667

00:13:01.160 --> 00:13:03.440 but they're expending more energy.

NOTE Confidence: 0.817405406666667

00:13:03.440 --> 00:13:05.200 So we collaborated with Famid

NOTE Confidence: 0.817405406666667

00:13:05.200 --> 00:13:06.946 Heider and Daniel Komen here and

NOTE Confidence: 0.817405406666667

00:13:06.946 --> 00:13:08.958 and Famid's lab has this fantastic

NOTE Confidence: 0.817405406666667

00:13:08.958 --> 00:13:10.526 technique to actually measure

NOTE Confidence: 0.817405406666667

00:13:10.526 --> 00:13:12.094 actual temperature in the

NOTE Confidence: 0.85218012173913

00:13:12.158 --> 00:13:14.608 brown adipose tissue using a probe which

NOTE Confidence: 0.85218012173913

00:13:14.608 --> 00:13:17.059 with with which you can actually measure

NOTE Confidence: 0.85218012173913

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00:13:17.059 --> 00:13:19.405 the proton relaxation and the proton

NOTE Confidence: 0.85218012173913

00:13:19.405 --> 00:13:21.462 leak and and you can actually measure

NOTE Confidence: 0.85218012173913

00:13:21.462 --> 00:13:23.560 temperature that way in a very precise way.

NOTE Confidence: 0.85218012173913

00:13:23.560 --> 00:13:25.756 And you can see that the there's the brown

NOTE Confidence: 0.85218012173913

00:13:25.756 --> 00:13:27.715 adipose tissue in this case is indeed hot.

NOTE Confidence: 0.85218012173913

00:13:27.720 --> 00:13:29.763 So I will summarize what we have which is

NOTE Confidence: 0.85218012173913

00:13:29.763 --> 00:13:31.957 so this is the transalphuration pathway,

NOTE Confidence: 0.85218012173913

00:13:31.960 --> 00:13:33.200 this is what is happening.

NOTE Confidence: 0.85218012173913

00:13:33.200 --> 00:13:34.635 So when we get rid of cysteine,

NOTE Confidence: 0.85218012173913

00:13:34.640 --> 00:13:36.540 when you deplete cysteine,

NOTE Confidence: 0.85218012173913

00:13:36.540 --> 00:13:40.400 what you do is you always have this case,

NOTE Confidence: 0.85218012173913

00:13:40.400 --> 00:13:42.476 this loss of cysteine which is

NOTE Confidence: 0.85218012173913

00:13:42.476 --> 00:13:44.342 associated with loss of glutathione

NOTE Confidence: 0.85218012173913

00:13:44.342 --> 00:13:47.254 and then cysteine and also go into

NOTE Confidence: 0.85218012173913

00:13:47.254 --> 00:13:49.438 different pathways that are noted here.

NOTE Confidence: 0.85218012173913

00:13:49.440 --> 00:13:51.372 But what happens when you completely

NOTE Confidence: 0.85218012173913

00:13:51.372 --> 00:13:54.069 get rid of cysteine in this in in the

NOTE Confidence: 0.85218012173913

00:13:54.069 --> 00:13:56.135 animals is activation of this arm which

NOTE Confidence: 0.85218012173913

00:13:56.135 --> 00:13:58.097 had previously not been studied in

NOTE Confidence: 0.85218012173913

00:13:58.097 --> 00:13:59.932 great detail which leads to formation

NOTE Confidence: 0.85218012173913

00:13:59.932 --> 00:14:01.397 of this gamma glutamil peptides.

NOTE Confidence: 0.85218012173913

00:14:01.400 --> 00:14:02.920 I don't have time to go into that.

NOTE Confidence: 0.85218012173913

00:14:02.920 --> 00:14:03.880 The question you would ask is,

NOTE Confidence: 0.85218012173913

00:14:03.880 --> 00:14:05.320 is this dependent on UCP one?

NOTE Confidence: 0.85218012173913

00:14:05.320 --> 00:14:07.168 Because UCP one has been thought

NOTE Confidence: 0.85218012173913

00:14:07.168 --> 00:14:09.538 to be the Holy Grail of energy

NOTE Confidence: 0.85218012173913

00:14:09.538 --> 00:14:11.680 expenditure and the answer is no.

NOTE Confidence: 0.85218012173913

00:14:11.680 --> 00:14:14.928 OK, so so we created animals that

NOTE Confidence: 0.85218012173913

00:14:14.928 --> 00:14:18.080 lack Cth as well as UCP one,

NOTE Confidence: 0.85218012173913

00:14:18.080 --> 00:14:19.285 There's really no response if

NOTE Confidence: 0.85218012173913

00:14:19.285 --> 00:14:20.919 you if you don't have UCP one,

NOTE Confidence: 0.85218012173913

00:14:20.920 --> 00:14:22.396 the animals brown, they lose weight,

NOTE Confidence: 0.85218012173913

00:14:22.400 --> 00:14:24.760 they die.

NOTE Confidence: 0.85218012173913

00:14:24.760 --> 00:14:26.716 So how does it actually work?

NOTE Confidence: 0.85218012173913

00:14:26.720 --> 00:14:28.561 What happens is that when you deplete

NOTE Confidence: 0.85218012173913

00:14:28.561 --> 00:14:30.136 cysteine you get the activation

NOTE Confidence: 0.85218012173913

00:14:30.136 --> 00:14:31.600 of sympathetic nervous system,

NOTE Confidence: 0.85218012173913

00:14:31.600 --> 00:14:33.360 you get increase in norepinephrine

NOTE Confidence: 0.85218012173913

00:14:33.360 --> 00:14:35.936 shown here in the red bar and if

NOTE Confidence: 0.85218012173913

00:14:35.936 --> 00:14:37.470 you block norepinephrine receptors

NOTE Confidence: 0.85218012173913

00:14:37.470 --> 00:14:40.560 beta 3 adenergic receptor by this

NOTE Confidence: 0.85218012173913

00:14:40.560 --> 00:14:42.890 compound L70 four in the blue,

NOTE Confidence: 0.85218012173913

00:14:42.890 --> 00:14:44.440 you can protect the animal's

NOTE Confidence: 0.85218012173913

00:14:44.440 --> 00:14:46.079 death from the weight loss.

NOTE Confidence: 0.85218012173913

00:14:46.080 --> 00:14:47.838 I'll end by just showing you

NOTE Confidence: 0.85218012173913

00:14:47.840 --> 00:14:49.856 last pieces of data which is pre

NOTE Confidence: 0.85218012173913

00:14:49.856 --> 00:14:51.432 clinical data in animal models

NOTE Confidence: 0.85218012173913

00:14:51.432 --> 00:14:53.920 which is fine we're killing animals,

NOTE Confidence: 0.85218012173913

00:14:53.920 --> 00:14:56.226 normal animals with by disrupting

NOTE Confidence: 0.85218012173913

00:14:56.226 --> 00:14:58.074 this key pathway which.

NOTE Confidence: 0.85218012173913

00:14:58.080 --> 00:14:59.802 But the question really is whether

NOTE Confidence: 0.85218012173913

00:14:59.802 --> 00:15:01.276 this can be potentially be

NOTE Confidence: 0.85218012173913

00:15:01.276 --> 00:15:02.636 harnessed in terms of therapy.

NOTE Confidence: 0.85218012173913

00:15:02.640 --> 00:15:04.840 And here are animals that

NOTE Confidence: 0.85218012173913

00:15:04.840 --> 00:15:07.040 were fed high fat diet.

NOTE Confidence: 0.85218012173913

00:15:07.040 --> 00:15:08.140 These animals are fed high

NOTE Confidence: 0.85218012173913

00:15:08.140 --> 00:15:09.240 fat diet for eight weeks.

NOTE Confidence: 0.85218012173913

00:15:09.240 --> 00:15:11.920 Then we switched the high fat diet into

NOTE Confidence: 0.85218012173913

00:15:11.920 --> 00:15:14.759 high fat diet that only lacks cysteine,

NOTE Confidence: 0.85218012173913

00:15:14.760 --> 00:15:15.080 OK.

NOTE Confidence: 0.85218012173913

00:15:15.080 --> 00:15:17.320 And they consume same amount of calories.

NOTE Confidence: 0.85218012173913

00:15:17.320 --> 00:15:19.759 And what you get is again a dramatic 30%

NOTE Confidence: 0.85218012173913

00:15:19.760 --> 00:15:22.556 weight loss within seven days actually.

NOTE Confidence: 0.85218012173913

00:15:22.560 --> 00:15:23.490 All right.

NOTE Confidence: 0.85218012173913

00:15:23.490 --> 00:15:25.815 And this is associated again

NOTE Confidence: 0.85218012173913

00:15:25.815 --> 00:15:27.703 with this massive Browning

NOTE Confidence: 0.85218012173913

00:15:27.703 --> 00:15:30.920 of the of the adipose tissue.

NOTE Confidence: 0.85218012173913

00:15:30.920 --> 00:15:34.316 So what we ended up discovering in

NOTE Confidence: 0.85218012173913

00:15:34.316 --> 00:15:36.430 a way serendipitously through this

NOTE Confidence: 0.85218012173913

00:15:36.430 --> 00:15:38.560 study that was initiated in humans

NOTE Confidence: 0.85218012173913

00:15:38.560 --> 00:15:42.106 is that the cysteine is actually

NOTE Confidence: 0.85218012173913

00:15:42.106 --> 00:15:43.879 critical thermogenic checkpoint.

NOTE Confidence: 0.85218012173913

00:15:43.880 --> 00:15:45.280 And if you get rid of cysteine,

NOTE Confidence: 0.85218012173913

00:15:45.280 --> 00:15:46.852 the body tries to keep cysteine

NOTE Confidence: 0.85218012173913

00:15:46.852 --> 00:15:48.480 because if you get rid of it,

NOTE Confidence: 0.85218012173913

00:15:48.480 --> 00:15:51.318 you get this uncontrolled energy expenditure.

NOTE Confidence: 0.85218012173913

00:15:51.320 --> 00:15:52.520 So in a normal situation,

NOTE Confidence: 0.85218012173913

00:15:52.520 --> 00:15:54.720 you're consuming a cysteine in

NOTE Confidence: 0.85218012173913

00:15:54.720 --> 00:15:56.576 your diet and this is required

NOTE Confidence: 0.85218012173913

00:15:56.576 --> 00:15:57.796 for your normal energy storage.

NOTE Confidence: 0.85218012173913

00:15:57.800 --> 00:15:59.930 You don't really get engagement

NOTE Confidence: 0.85218012173913

00:15:59.930 --> 00:16:01.634 of trans sulfuration pathway.

NOTE Confidence: 0.85218012173913

00:16:01.640 --> 00:16:03.040 OK, because you're consuming cysteine,

NOTE Confidence: 0.820726718333333

00:16:03.040 --> 00:16:05.080 you don't need to make cysteine.

NOTE Confidence: 0.820726718333333

00:16:05.080 --> 00:16:08.368 However, if you create an artificial

NOTE Confidence: 0.820726718333333

00:16:08.368 --> 00:16:11.600 situation where trans alteration is required,

NOTE Confidence: 0.820726718333333

00:16:11.600 --> 00:16:13.616 what you get in this case is this is

NOTE Confidence: 0.820726718333333

00:16:13.616 --> 00:16:15.576 the methionine cycle and when the

NOTE Confidence: 0.820726718333333

00:16:15.576 --> 00:16:17.696 cysteine levels go down, it triggers.

NOTE Confidence: 0.820726718333333

00:16:17.696 --> 00:16:19.248 We don't actually know

NOTE Confidence: 0.820726718333333

00:16:19.248 --> 00:16:21.200 exactly how it triggers this.

NOTE Confidence: 0.820726718333333

00:16:21.200 --> 00:16:22.950 This loss of cysteine is sensed by

NOTE Confidence: 0.820726718333333

00:16:22.950 --> 00:16:24.955 the nervous system in a way that

NOTE Confidence: 0.820726718333333

00:16:24.955 --> 00:16:26.159 basically increases sympathetic tone,

NOTE Confidence: 0.820726718333333

00:16:26.160 --> 00:16:27.336 it increases Browning,

NOTE Confidence: 0.820726718333333

00:16:27.336 --> 00:16:29.688 there is increased proton leak and

NOTE Confidence: 0.820726718333333

00:16:29.688 --> 00:16:31.920 heat production in these animals.

NOTE Confidence: 0.820726718333333

00:16:31.920 --> 00:16:33.700 It's UCP one independent.

NOTE Confidence: 0.820726718333333

00:16:33.700 --> 00:16:35.480 And this is basically,

NOTE Confidence: 0.820726718333333

00:16:35.480 --> 00:16:38.600 you know, how it works. So.

NOTE Confidence: 0.820726718333333

00:16:38.600 --> 00:16:40.608 So what I've told you is that the

NOTE Confidence: 0.820726718333333

00:16:40.608 --> 00:16:42.146 defense of cysteine actually is

NOTE Confidence: 0.820726718333333

00:16:42.146 --> 00:16:43.771 absolutely critical and I think

NOTE Confidence: 0.820726718333333

00:16:43.771 --> 00:16:45.800 is a thermogenic checkpoint.

NOTE Confidence: 0.820726718333333

00:16:45.800 --> 00:16:46.652 And this is the,

NOTE Confidence: 0.820726718333333

00:16:46.652 --> 00:16:47.717 as far as I know,

NOTE Confidence: 0.820726718333333

00:16:47.720 --> 00:16:49.440 the only study that I know in the

NOTE Confidence: 0.820726718333333

00:16:49.440 --> 00:16:50.689 literature where you can actually

NOTE Confidence: 0.820726718333333

00:16:50.689 --> 00:16:52.237 kill a mouse by lethal thermogenesis.

00:16:52.240 --> 00:16:55.488 OK, so I've shown you that cysteine

00:16:55.488 --> 00:16:56.720 starvation causes uncontrolled Browning.

00:16:56.720 --> 00:16:57.716 If you get rid of cysteine,

00:16:57.720 --> 00:16:59.468 it causes uncontrolled Browning

00:16:59.468 --> 00:17:01.653 and the trans alphuration pathway

00:17:01.653 --> 00:17:03.539 which is activated in color

00:17:03.539 --> 00:17:05.609 illustration is actually a way for

00:17:05.674 --> 00:17:07.399 the body to conserve energy.

00:17:07.400 --> 00:17:09.731 So obviously the future this is just

00:17:09.731 --> 00:17:11.772 you know really emerging work which

00:17:11.772 --> 00:17:14.000 we are very interested and excited by

00:17:14.000 --> 00:17:16.208 and will time will tell how far this

00:17:16.208 --> 00:17:18.720 goes in terms of clinical translation.

00:17:18.720 --> 00:17:20.440 All this work was done by Eileen Lee,

00:17:20.440 --> 00:17:21.916 a graduate student in the lab.

00:17:21.920 --> 00:17:23.648 This project is now being LED

NOTE Confidence: 0.820726718333333

00:17:23.648 --> 00:17:25.400 very ably by Lucy Urliegue and

NOTE Confidence: 0.820726718333333

00:17:25.400 --> 00:17:27.552 and Abby Lee in the lab and and

NOTE Confidence: 0.820726718333333

00:17:27.620 --> 00:17:29.520 of course all my collaborators.

NOTE Confidence: 0.820726718333333

00:17:29.520 --> 00:17:32.520 I'm not as organized as Tomas to finish

NOTE Confidence: 0.958623666666667

00:17:32.520 --> 00:17:33.639 on time. Sorry.

NOTE Confidence: 0.821519966

00:17:41.670 --> 00:17:44.270 Thank you. Wonderful questions. Please.

NOTE Confidence: 0.87201145

00:17:49.700 --> 00:17:52.682 No, it does not affect energy

NOTE Confidence: 0.87201145

00:17:52.682 --> 00:17:53.780 intake. Yeah. Marcelo,

NOTE Confidence: 0.6110673

00:17:57.740 --> 00:18:01.375 hello. My question is more general and it's

NOTE Confidence: 0.856527193

00:18:01.380 --> 00:18:04.228 I was wondering if in the in the

NOTE Confidence: 0.856527193

00:18:04.228 --> 00:18:07.131 trials with these drugs in general if

NOTE Confidence: 0.856527193

00:18:07.131 --> 00:18:10.632 there is any evidence that so we know

NOTE Confidence: 0.856527193

00:18:10.632 --> 00:18:13.416 from that there's more brown adipose

NOTE Confidence: 0.856527193

00:18:13.416 --> 00:18:16.420 tissue in humans presumably in the

NOTE Confidence: 0.856527193

00:18:16.420 --> 00:18:19.740 winter here or in cold climates versus

NOTE Confidence: 0.856527193

00:18:19.740 --> 00:18:22.880 people that live in tropical climates.

NOTE Confidence: 0.856527193

00:18:22.880 --> 00:18:26.079 So in terms of this thermogenic checkpoint,

NOTE Confidence: 0.856527193

00:18:26.080 --> 00:18:29.072 if there is any evidence that these drugs

NOTE Confidence: 0.856527193

00:18:29.072 --> 00:18:32.112 and to visit the drugs work more or

NOTE Confidence: 0.856527193

00:18:32.112 --> 00:18:35.370 less in the winter versus the summer in

NOTE Confidence: 0.856527193

00:18:35.370 --> 00:18:38.600 the tropics versus in the cold climate,

NOTE Confidence: 0.856527193

00:18:38.600 --> 00:18:42.168 if there is any, There's so many people.

NOTE Confidence: 0.856527193

00:18:42.168 --> 00:18:43.920 So if there's any evidence there,

NOTE Confidence: 0.856527193

00:18:43.920 --> 00:18:45.520 there's some interaction with

NOTE Confidence: 0.856527193

00:18:45.520 --> 00:18:46.720 the thermogenic checkpoint.

NOTE Confidence: 0.890015322

00:18:47.720 --> 00:18:49.160 Yeah, I don't know, Marcelo.

NOTE Confidence: 0.890015322

00:18:49.160 --> 00:18:50.536 I mean this is a question that you

NOTE Confidence: 0.890015322

00:18:50.536 --> 00:18:51.727 know folks that study thermogenesis

NOTE Confidence: 0.890015322

00:18:51.727 --> 00:18:52.799 have been asked several,

NOTE Confidence: 0.890015322

00:18:52.800 --> 00:18:54.366 several times that you know there

NOTE Confidence: 0.890015322

00:18:54.366 --> 00:18:55.710 are people living in Scandinavia

NOTE Confidence: 0.890015322

00:18:55.710 --> 00:18:57.404 in an Arctic and are there is

NOTE Confidence: 0.890015322

00:18:57.404 --> 00:18:58.958 the less incidence of obesity,

NOTE Confidence: 0.890015322

00:18:58.960 --> 00:19:00.808 there is some association but association

NOTE Confidence: 0.890015322

00:19:00.808 --> 00:19:02.850 is not causalities but and most of

NOTE Confidence: 0.890015322

00:19:02.850 --> 00:19:04.356 those times people are still majority

NOTE Confidence: 0.890015322

00:19:04.356 --> 00:19:06.200 of the times in thermal neutrality.

NOTE Confidence: 0.890015322

00:19:06.200 --> 00:19:07.742 You know we still are in

NOTE Confidence: 0.890015322

00:19:07.742 --> 00:19:08.513 thermal neutral condition.

NOTE Confidence: 0.890015322

00:19:08.520 --> 00:19:10.440 So they're never though these pathways

NOTE Confidence: 0.890015322

00:19:10.440 --> 00:19:13.145 are never you know kind of activated.

NOTE Confidence: 0.890015322

00:19:13.145 --> 00:19:16.639 So it's not really clear hopefully in time,

NOTE Confidence: 0.6933973

00:19:19.680 --> 00:19:19.960 right

NOTE Confidence: 0.350200956666667

00:19:22.120 --> 00:19:24.480 expands quite substantially in the

NOTE Confidence: 0.697018664166667

00:19:26.520 --> 00:19:28.725 winter. It tells us that even though

NOTE Confidence: 0.697018664166667

00:19:28.725 --> 00:19:30.440 we are regulating our climate,

NOTE Confidence: 0.697018664166667

00:19:30.440 --> 00:19:32.800 we are not absolutely determinate

NOTE Confidence: 0.697018664166667

00:19:32.800 --> 00:19:34.918 otherwise, you know, yeah,

NOTE Confidence: 0.697018664166667

00:19:34.920 --> 00:19:36.580 counter regulation for increasing.

NOTE Confidence: 0.697018664166667

00:19:36.580 --> 00:19:38.240 So my point is

NOTE Confidence: 0.715704338

00:19:38.560 --> 00:19:40.646 to see if the cysteine pathway

NOTE Confidence: 0.715704338

00:19:40.646 --> 00:19:42.476 is potentially affected in there

NOTE Confidence: 0.502148814444444

00:19:44.160 --> 00:19:46.026 in the winter. They are taking

NOTE Confidence: 0.502148814444444

00:19:46.026 --> 00:19:48.160 some appetite and all the, yeah

NOTE Confidence: 0.45717192

00:19:51.960 --> 00:19:53.595 are more effective like the

NOTE Confidence: 0.45717192

00:19:53.595 --> 00:19:55.720 individual that you were studying.

NOTE Confidence: 0.45717192

00:19:55.720 --> 00:19:58.800 Yeah, gender question. Yeah, potentially.

NOTE Confidence: 0.938694187142857

00:20:00.080 --> 00:20:02.194 Yeah, clinically we haven't seen that yet,

NOTE Confidence: 0.938694187142857

00:20:02.200 --> 00:20:04.400 but it's something to consider.

NOTE Confidence: 0.938694187142857

00:20:04.400 --> 00:20:05.600 One more quick question shot.

NOTE Confidence: 0.436012798

00:20:09.800 --> 00:20:10.640 Yeah, the bill will work.

NOTE Confidence: 0.436012798

00:20:10.640 --> 00:20:15.230 The what is what do you think primary

NOTE Confidence: 0.436012798

00:20:15.230 --> 00:20:17.840 side of action of positive restriction,

NOTE Confidence: 0.436012798

00:20:17.840 --> 00:20:20.080 whether when wrong type self or

NOTE Confidence: 0.436012798

00:20:20.080 --> 00:20:22.240 what type self or the mother? Yeah.

NOTE Confidence: 0.69485578

00:20:22.520 --> 00:20:24.704 So, so Shawn Yang is asking

NOTE Confidence: 0.69485578

00:20:24.704 --> 00:20:26.160 how does cysteine work?

NOTE Confidence: 0.69485578

00:20:26.160 --> 00:20:27.944 Where is it acting?

NOTE Confidence: 0.69485578

00:20:27.944 --> 00:20:29.785 And the answer is complex.

NOTE Confidence: 0.69485578

00:20:29.785 --> 00:20:33.408 So we have knocked it out in multiple places,

NOTE Confidence: 0.69485578

00:20:33.408 --> 00:20:35.108 including liver, adipose tissue.

NOTE Confidence: 0.69485578

00:20:35.108 --> 00:20:37.680 And if you knock it out in specific cells,

NOTE Confidence: 0.69485578

00:20:37.680 --> 00:20:40.410 there is no effect because cysteine

NOTE Confidence: 0.69485578

00:20:40.410 --> 00:20:43.710 is so important for the host that

NOTE Confidence: 0.69485578

00:20:43.710 --> 00:20:46.035 other organs compensate for it.

NOTE Confidence: 0.69485578

00:20:46.040 --> 00:20:47.438 As far as brain is concerned,

NOTE Confidence: 0.69485578

00:20:47.440 --> 00:20:49.316 this is a really a great question.

NOTE Confidence: 0.69485578

00:20:49.320 --> 00:20:50.804 We don't really know.

NOTE Confidence: 0.69485578

00:20:50.804 --> 00:20:52.659 We only have preliminary evidence

NOTE Confidence: 0.69485578

00:20:52.659 --> 00:20:54.920 as at this point of time and I

NOTE Confidence: 0.69485578

00:20:54.920 --> 00:20:56.360 think we are working with Tomasha's

NOTE Confidence: 0.69485578

00:20:56.360 --> 00:20:57.997 lab to see and Bernardo here,

NOTE Confidence: 0.69485578

00:20:58.000 --> 00:21:00.310 who's in I guess in the audience

NOTE Confidence: 0.69485578

00:21:00.310 --> 00:21:01.536 somewhere to see if cysteine

NOTE Confidence: 0.69485578

00:21:01.536 --> 00:21:02.880 is being sensed in the brain.

NOTE Confidence: 0.69485578

00:21:02.880 --> 00:21:04.158 If you get rid of cysteine in the brain,

NOTE Confidence: 0.69485578

00:21:04.160 --> 00:21:06.477 is that the one that is triggering

NOTE Confidence: 0.69485578

00:21:06.477 --> 00:21:07.880 the sympathetic nervous system

NOTE Confidence: 0.69485578

00:21:07.880 --> 00:21:09.200 outflow into the adipose tissue?

NOTE Confidence: 0.69485578

00:21:09.200 --> 00:21:10.020 But yes,

NOTE Confidence: 0.69485578

00:21:10.020 --> 00:21:12.976 one thing is very clear that that

NOTE Confidence: 0.69485578

00:21:12.976 --> 00:21:15.439 the lack of cysteine triggers

NOTE Confidence: 0.69485578

00:21:15.439 --> 00:21:17.355 the upstream sympathetic activity

NOTE Confidence: 0.69485578

00:21:17.355 --> 00:21:20.333 that basically then leads to the

NOTE Confidence: 0.69485578

00:21:20.333 --> 00:21:22.085 thermogenic major thermogenic response.

NOTE Confidence: 0.69485578

00:21:22.085 --> 00:21:24.160 And most of the thermogenic

NOTE Confidence: 0.69485578

00:21:24.160 --> 00:21:26.265 response is independent of all

NOTE Confidence: 0.69485578

00:21:26.265 --> 00:21:28.280 the known current currently known

NOTE Confidence: 0.69485578

00:21:28.280 --> 00:21:29.990 pathways that people have been

NOTE Confidence: 0.69485578

00:21:29.990 --> 00:21:31.893 publishing in terms of uncoupling.

NOTE Confidence: 0.69485578

00:21:31.893 --> 00:21:34.558 None of those are involved.

NOTE Confidence: 0.69485578

00:21:34.560 --> 00:21:34.920 Great.

NOTE Confidence: 0.940140543076923

00:21:34.920 --> 00:21:37.026 OK, With that we're going to go ahead and

NOTE Confidence: 0.940140543076923

00:21:37.026 --> 00:21:39.080 move into our break. Thank you so much.