WEBVTT

NOTE duration:”00:59:29”

NOTE recognizability:0.757

NOTE language:en-us

NOTE Confidence: 0.914125553636364

00:00:00.000 --> 00:00:04.272 OK. Good afternoon and welcome to

NOTE Confidence: 0.914125553636364

00:00:04.272 --> 00:00:08.500 today's grand rounds in pathology.

NOTE Confidence: 0.914125553636364

00:00:08.500 --> 00:00:12.595 I would like to introduce today's speaker,

NOTE Confidence: 0.914125553636364

00:00:12.600 --> 00:00:14.538 doctor Patricia Dossantos.

NOTE Confidence: 0.914125553636364

00:00:14.538 --> 00:00:18.372 A professor and associate chair of

NOTE Confidence: 0.914125553636364

00:00:18.372 --> 00:00:21.878 chemistry from Wake Forest University.

NOTE Confidence: 0.914125553636364

00:00:21.880 --> 00:00:24.196 Patricia received her bachelor's

NOTE Confidence: 0.914125553636364

00:00:24.196 --> 00:00:27.670 at the Federal University of Rio

NOTE Confidence: 0.914125553636364

00:00:27.767 --> 00:00:30.418 Grande in Porto Alegre, Brazil.

NOTE Confidence: 0.914125553636364

00:00:30.418 --> 00:00:35.940 And then came to the United States to do

NOTE Confidence: 0.914125553636364

00:00:35.940 --> 00:00:39.790 a PhD in biochemistry at Virginia Tech.

NOTE Confidence: 0.914125553636364

00:00:39.790 --> 00:00:41.906 After completing her PhD,

NOTE Confidence: 0.914125553636364

00:00:41.906 --> 00:00:44.618 she stayed at Virginia Tech for

NOTE Confidence: 0.914125553636364

00:00:44.618 --> 00:00:47.457 three years as a postdoc associate.

NOTE Confidence: 0.914125553636364

00:00:47.460 --> 00:00:49.560 And was then recruited to the

NOTE Confidence: 0.914125553636364

00:00:49.560 --> 00:00:51.982 Department of Chemistry at Wake Forest

NOTE Confidence: 0.914125553636364

00:00:51.982 --> 00:00:53.898 University as assistant professor,

NOTE Confidence: 0.914125553636364

00:00:53.900 --> 00:00:56.570 where she very quickly wrote through

NOTE Confidence: 0.914125553636364

00:00:56.570 --> 00:00:59.387 rose through the ranks to full

NOTE Confidence: 0.914125553636364

00:00:59.387 --> 00:01:01.299 professor and associate chair.

NOTE Confidence: 0.914125553636364

00:01:01.300 --> 00:01:03.920 Throughout her academic development,

NOTE Confidence: 0.914125553636364

00:01:03.920 --> 00:01:07.195 Patricia has always been outstanding.

NOTE Confidence: 0.914125553636364

00:01:07.200 --> 00:01:11.117 In the year she graduated with her doctorate,

NOTE Confidence: 0.914125553636364

00:01:11.117 --> 00:01:13.212 she received the Outstanding Graduate

NOTE Confidence: 0.914125553636364

00:01:13.212 --> 00:01:15.120 Student Award at Virginia Tech,

NOTE Confidence: 0.914125553636364

00:01:15.120 --> 00:01:18.858 and she was also the commencement speaker

NOTE Confidence: 0.914125553636364

00:01:18.858 --> 00:01:22.907 at the graduation ceremony at Virginia Tech.

NOTE Confidence: 0.914125553636364

00:01:22.910 --> 00:01:26.123 She further received at Wake Forest the

NOTE Confidence: 0.914125553636364

00:01:26.123 --> 00:01:28.710 faculty Excellence in Research award,

NOTE Confidence: 0.914125553636364

00:01:28.710 --> 00:01:31.040 the Robert Depth and Deborah

NOTE Confidence: 0.914125553636364

00:01:31.040 --> 00:01:32.904 Lee Faculty Fellowship Award,

NOTE Confidence: 0.914125553636364

00:01:32.910 --> 00:01:35.640 and the Eureka Faculty Award of

NOTE Confidence: 0.914125553636364

00:01:35.640 --> 00:01:38.240 Excellence in Mentoring and Research.

NOTE Confidence: 0.914125553636364

00:01:38.240 --> 00:01:40.964 Patricia has published over 60 peer

NOTE Confidence: 0.914125553636364

00:01:40.964 --> 00:01:43.540 reviewed papers and book chapters,

NOTE Confidence: 0.914125553636364

00:01:43.540 --> 00:01:46.823 she's an editor in methods in molecular

NOTE Confidence: 0.914125553636364

00:01:46.823 --> 00:01:49.734 biology and she has had close to

NOTE Confidence: 0.914125553636364

00:01:49.734 --> 00:01:52.176 150 invited talks and peer reviewed

NOTE Confidence: 0.914125553636364

00:01:52.176 --> 00:01:55.000 posters and platform presentations at

NOTE Confidence: 0.914125553636364

00:01:55.000 --> 00:01:57.576 national and international meetings.

NOTE Confidence: 0.914125553636364

00:01:57.580 --> 00:02:01.413 She has been funded by two grants from

NOTE Confidence: 0.914125553636364

00:02:01.413 --> 00:02:04.479 by the National Science Foundation and

NOTE Confidence: 0.914125553636364

00:02:04.479 --> 00:02:07.409 has interdisciplinary research grants

NOTE Confidence: 0.914125553636364

00:02:07.409 --> 00:02:12.053 from the North Carolina Biotechnology Center.

NOTE Confidence: 0.914125553636364

00:02:12.060 --> 00:02:13.866 In addition to her excellent science,

NOTE Confidence: 0.914125553636364

00:02:13.870 --> 00:02:17.070 Patricia is a extremely successful

NOTE Confidence: 0.914125553636364

00:02:17.070 --> 00:02:18.990 teacher and mentor.

NOTE Confidence: 0.914125553636364

00:02:18.990 --> 00:02:21.415 She teaches 6 biochemistry courses

NOTE Confidence: 0.914125553636364

00:02:21.415 --> 00:02:22.870 at Wake Forest.

NOTE Confidence: 0.914125553636364

00:02:22.870 --> 00:02:28.194 She has mentored 20 PhD students

NOTE Confidence: 0.914125553636364

00:02:28.194 --> 00:02:30.567 and honor students.

NOTE Confidence: 0.914125553636364

00:02:30.570 --> 00:02:34.385 She has also mentored 10 postdoc Fellows,

NOTE Confidence: 0.914125553636364

00:02:34.390 --> 00:02:38.632 and she has a fantastic track record

NOTE Confidence: 0.914125553636364

00:02:38.632 --> 00:02:41.420 of mentoring undergraduate students.

NOTE Confidence: 0.914125553636364

00:02:41.420 --> 00:02:43.975 Who do their honour research

NOTE Confidence: 0.914125553636364

00:02:43.975 --> 00:02:46.019 thesis in her lab.

NOTE Confidence: 0.914125553636364

00:02:46.020 --> 00:02:49.835 So she has mentored over 60 of

NOTE Confidence: 0.914125553636364

00:02:49.835 --> 00:02:51.470 these undergraduate students.

NOTE Confidence: 0.914125553636364

00:02:51.470 --> 00:02:53.014 Outside of Wake Forest,

NOTE Confidence: 0.914125553636364

00:02:53.014 --> 00:02:55.640 she is a reviewer on standing

NOTE Confidence: 0.914125553636364

00:02:55.640 --> 00:02:57.800 review panels for NIH,

NOTE Confidence: 0.914125553636364

00:02:57.800 --> 00:02:58.976 National Science Foundation

NOTE Confidence: 0.914125553636364

00:02:58.976 --> 00:03:00.936 and the Department of Energy.

NOTE Confidence: 0.914125553636364

00:03:00.940 --> 00:03:03.670 She has been a session chair at

NOTE Confidence: 0.914125553636364

00:03:03.670 --> 00:03:05.930 Gordon Conferences and a session

NOTE Confidence: 0.914125553636364

00:03:05.930 --> 00:03:07.954 chair at International Conference

NOTE Confidence: 0.914125553636364

00:03:07.954 --> 00:03:09.978 for iron sulfide clusters.

NOTE Confidence: 0.914125553636364

00:03:09.980 --> 00:03:13.641 She's an epoch reviewer for many national

NOTE Confidence: 0.914125553636364

00:03:13.641 --> 00:03:16.000 and international funding agencies.

NOTE Confidence: 0.914125553636364

00:03:16.000 --> 00:03:19.408 Her talk today is entitled The

NOTE Confidence: 0.914125553636364

00:03:19.408 --> 00:03:22.276 Synthesis and Dynamic Landscape of

NOTE Confidence: 0.914125553636364

00:03:22.276 --> 00:03:23.587 Transfer RNA's Epic transcriptome

NOTE Confidence: 0.914125553636364

00:03:23.587 --> 00:03:25.959 and I think we are in for a treat,

NOTE Confidence: 0.914125553636364

00:03:25.960 --> 00:03:28.470 so please welcome Patricia Dossantos.

NOTE Confidence: 0.832084448333333

00:03:33.330 --> 00:03:36.345 Thanks for the kind introduction

NOTE Confidence: 0.832084448333333

00:03:36.345 --> 00:03:38.718 and invitation to come here.

NOTE Confidence: 0.832084448333333

00:03:38.718 --> 00:03:41.370 I had a really great time.

NOTE Confidence: 0.832084448333333

00:03:41.370 --> 00:03:43.410 Today very special meeting and

NOTE Confidence: 0.832084448333333

00:03:43.410 --> 00:03:45.450 talking about women in academia.

NOTE Confidence: 0.832084448333333

00:03:45.450 --> 00:03:47.522 Really enjoyed that with

NOTE Confidence: 0.832084448333333

00:03:47.522 --> 00:03:48.558 department colleagues.

NOTE Confidence: 0.941259797

00:03:50.800 --> 00:03:54.960 OK. So what I want to share with you today,

NOTE Confidence: 0.941259797

00:03:54.960 --> 00:03:58.257 it's my work on T RNA modification.

NOTE Confidence: 0.941259797

00:03:58.260 --> 00:04:01.732 So in changes on T RNA modifications

NOTE Confidence: 0.941259797

00:04:01.732 --> 00:04:04.738 and how that has an impact,

NOTE Confidence: 0.941259797

00:04:04.740 --> 00:04:07.304 but before I do that kind of

NOTE Confidence: 0.941259797

00:04:07.304 --> 00:04:10.760 like very broad, we know that.

NOTE Confidence: 0.941259797

00:04:10.760 --> 00:04:12.110 Several biochemical reactions,

NOTE Confidence: 0.941259797

00:04:12.110 --> 00:04:15.260 they rely on the chemistry afforded by

NOTE Confidence: 0.941259797

00:04:15.332 --> 00:04:18.110 protein cofactors and then the enzymes

NOTE Confidence: 0.941259797

00:04:18.110 --> 00:04:19.962 associated with those cofactors.

NOTE Confidence: 0.941259797

00:04:19.970 --> 00:04:21.758 So among those cofactors,

NOTE Confidence: 0.941259797

00:04:21.758 --> 00:04:23.993 sulfur containing cofactors are widely

NOTE Confidence: 0.941259797

00:04:23.993 --> 00:04:26.586 distributed in nature and then they are

NOTE Confidence: 0.941259797

00:04:26.586 --> 00:04:28.390 actually participate in several lives.

NOTE Confidence: 0.941259797

00:04:28.390 --> 00:04:31.606 Sustaining reactions like photosynthesis,

NOTE Confidence: 0.941259797

00:04:31.606 --> 00:04:34.546 respiration, Nigel fixation will not

NOTE Confidence: 0.941259797

00:04:34.546 --> 00:04:37.750 be here today without those processes.

NOTE Confidence: 0.941259797

00:04:37.750 --> 00:04:41.575 So the main purpose of my lab is really.

NOTE Confidence: 0.941259797

00:04:41.580 --> 00:04:44.370 Trying to understand.

NOTE Confidence: 0.941259797

00:04:44.370 --> 00:04:46.680 Chemical futures for the synthesis

NOTE Confidence: 0.941259797

00:04:46.680 --> 00:04:48.528 of sulfur containing cofactors,

NOTE Confidence: 0.941259797

00:04:48.530 --> 00:04:50.120 which are some of the molecules

NOTE Confidence: 0.941259797

00:04:50.120 --> 00:04:51.610 shown here on this screen,

NOTE Confidence: 0.941259797

00:04:51.610 --> 00:04:53.890 and so scientists and the

NOTE Confidence: 0.941259797

00:04:53.890 --> 00:04:56.170 function of those four factors,

NOTE Confidence: 0.941259797

00:04:56.170 --> 00:04:58.450 so relevant for today's talk,

NOTE Confidence: 0.941259797

00:04:58.450 --> 00:05:03.550 is the synthesis of Taiwan nucleosides.

NOTE Confidence: 0.941259797

00:05:03.550 --> 00:05:04.930 You see them out, yeah.

NOTE Confidence: 0.941259797

00:05:04.930 --> 00:05:06.414 So Tyrone nucleosides that

NOTE Confidence: 0.941259797

00:05:06.414 --> 00:05:08.640 are present on to your RNA.

NOTE Confidence: 0.585111253333333

00:05:10.660 --> 00:05:13.588 So T RNA has, you know,

NOTE Confidence: 0.585111253333333

00:05:13.590 --> 00:05:16.320 very well known function as serving

NOTE Confidence: 0.585111253333333

00:05:16.320 --> 00:05:19.330 as a dactyl in translation.

NOTE Confidence: 0.585111253333333

00:05:19.330 --> 00:05:22.730 Granada reacts with aminoacyl tyranny

NOTE Confidence: 0.585111253333333

00:05:22.730 --> 00:05:26.328 synthetase for the attachment of amino

NOTE Confidence: 0.585111253333333

00:05:26.328 --> 00:05:29.401 acids to their cognate T RNA molecules

NOTE Confidence: 0.585111253333333

00:05:29.401 --> 00:05:32.607 which are then brought to the ribosome

NOTE Confidence: 0.585111253333333

00:05:32.607 --> 00:05:35.798 at the ribosomes tier and a interact

NOTE Confidence: 0.585111253333333

00:05:35.798 --> 00:05:38.412 with the messenger RNA enabling the

NOTE Confidence: 0.585111253333333

00:05:38.412 --> 00:05:40.998 translation of the genetic code and

NOTE Confidence: 0.585111253333333

00:05:40.998 --> 00:05:44.599 the by doing so they promote peptide

NOTE Confidence: 0.585111253333333

00:05:44.599 --> 00:05:46.723 synthesis or protein synthesis.

NOTE Confidence: 0.585111253333333

00:05:46.730 --> 00:05:49.690 What most people don't know is that tyranny.

NOTE Confidence: 0.585111253333333

00:05:49.690 --> 00:05:51.618 One, no canonical role,

NOTE Confidence: 0.585111253333333

00:05:51.618 --> 00:05:54.950 so like several roles in Atable ISM,

NOTE Confidence: 0.585111253333333

00:05:54.950 --> 00:05:56.276 so tyranny molecules,

NOTE Confidence: 0.585111253333333

00:05:56.276 --> 00:05:59.370 they have an impact on gene regulation.

NOTE Confidence: 0.585111253333333

00:05:59.370 --> 00:06:02.210 They are also able to sense nutrient sensing.

NOTE Confidence: 0.585111253333333

00:06:02.210 --> 00:06:04.044 So the relevant to the story that

NOTE Confidence: 0.585111253333333

00:06:04.044 --> 00:06:06.088 I'm going to share with you today,

NOTE Confidence: 0.585111253333333

00:06:06.090 --> 00:06:08.505 they are mediate a seller

NOTE Confidence: 0.585111253333333

00:06:08.505 --> 00:06:09.954 and stress responses.

NOTE Confidence: 0.585111253333333

00:06:09.960 --> 00:06:13.026 They can sense UV radiation and

NOTE Confidence: 0.585111253333333

00:06:13.026 --> 00:06:14.559 modulate translational capacity.

NOTE Confidence: 0.585111253333333

00:06:14.560 --> 00:06:17.806 Under those conditions T RNA is

NOTE Confidence: 0.585111253333333

00:06:17.806 --> 00:06:19.970 important for viral replication.

NOTE Confidence: 0.585111253333333

00:06:19.970 --> 00:06:22.316 So the example here is that

NOTE Confidence: 0.585111253333333

00:06:22.320 --> 00:06:24.770 modified T RNA actually assists

NOTE Confidence: 0.585111253333333

00:06:24.770 --> 00:06:27.220 replication of the HIV virus.

NOTE Confidence: 0.585111253333333

00:06:27.220 --> 00:06:29.375 And they're involved in other

NOTE Confidence: 0.585111253333333

00:06:29.375 --> 00:06:31.530 functions in addition to the

NOTE Confidence: 0.585111253333333

00:06:31.610 --> 00:06:34.140 roles of intact tyranny molecules.

NOTE Confidence: 0.585111253333333

00:06:34.140 --> 00:06:36.359 In all these processes that I described

NOTE Confidence: 0.585111253333333

00:06:36.359 --> 00:06:38.532 to you, fragments of tyranny a,

NOTE Confidence: 0.585111253333333

00:06:38.532 --> 00:06:40.447 there are also equally important

NOTE Confidence: 0.585111253333333

00:06:40.447 --> 00:06:43.000 in metabolism. They are involved.

NOTE Confidence: 0.585111253333333

00:06:43.000 --> 00:06:45.300 They sell proliferation in cancer,

NOTE Confidence: 0.585111253333333

00:06:45.300 --> 00:06:47.452 it hosts defense mechanisms.

NOTE Confidence: 0.585111253333333

00:06:47.452 --> 00:06:51.766 So fragments of that tyranny is not only

NOTE Confidence: 0.585111253333333

00:06:51.766 --> 00:06:54.730 byproducts of degradation of T RNA.

NOTE Confidence: 0.585111253333333

00:06:54.730 --> 00:06:55.685 Uh.

NOTE Confidence: 0.585111253333333

00:06:55.685 --> 00:06:56.640 So.

NOTE Confidence: 0.612182635

00:07:27.670 --> 00:07:28.750 The consequences?

NOTE Confidence: 0.840681864444444

00:07:31.580 --> 00:07:34.982 OK. I'll keep going for those of you there.

NOTE Confidence: 0.6782445425

00:07:38.870 --> 00:07:41.789 Read tyranny modifications

NOTE Confidence: 0.6782445425

00:07:41.789 --> 00:07:45.036 reported into biological TRN's.

NOTE Confidence: 0.6782445425

00:07:45.036 --> 00:07:47.318 So in the human genome there are

NOTE Confidence: 0.6782445425

00:07:47.318 --> 00:07:49.529 many T RNA genes and then we

NOTE Confidence: 0.6782445425

00:07:49.529 --> 00:07:51.866 what we know is that ternative is

NOTE Confidence: 0.6782445425

00:07:51.866 --> 00:07:54.182 found in the cytoplasm and called

NOTE Confidence: 0.6782445425

00:07:54.182 --> 00:07:56.733 by nuclear genomic information.

NOTE Confidence: 0.6782445425

00:07:56.733 --> 00:07:58.896 It's also modified.

NOTE Confidence: 0.6782445425

00:07:58.900 --> 00:08:01.006 So while the structure of tyranny

NOTE Confidence: 0.6782445425

00:08:01.006 --> 00:08:02.818 and then another subset of

NOTE Confidence: 0.6782445425

00:08:02.818 --> 00:08:04.888 modifications are found on T RNA

NOTE Confidence: 0.6782445425

00:08:04.888 --> 00:08:07.068 that is mitochondria encoded to RNA

NOTE Confidence: 0.6782445425

00:08:07.068 --> 00:08:08.873 and those modifications are are.

NOTE Confidence: 0.6782445425

00:08:08.880 --> 00:08:11.184 Important for translation at

NOTE Confidence: 0.6782445425

00:08:11.184 --> 00:08:14.270 the above processes.

NOTE Confidence: 0.6782445425

00:08:14.270 --> 00:08:16.634 So I typically don't talk a

NOTE Confidence: 0.6782445425

00:08:16.634 --> 00:08:18.210 whole lot about pathology,

NOTE Confidence: 0.6782445425

00:08:18.210 --> 00:08:21.059 but I thought this crowd would be

NOTE Confidence: 0.6782445425

00:08:21.059 --> 00:08:24.400 interested to know that a Baron or

NOTE Confidence: 0.6782445425

00:08:24.400 --> 00:08:26.436 altered accumulation of tyranny

NOTE Confidence: 0.6782445425

00:08:26.436 --> 00:08:29.124 modifications are are associated with

NOTE Confidence: 0.6782445425

00:08:29.124 --> 00:08:31.769 a variety of pathological disease.

NOTE Confidence: 0.6782445425

00:08:31.770 --> 00:08:33.870 So we have mitochondrial disease

NOTE Confidence: 0.6782445425

00:08:33.870 --> 00:08:35.970 that are associated with mutations

NOTE Confidence: 0.6782445425

00:08:36.039 --> 00:08:38.230 on enzymes that are involved in the

NOTE Confidence: 0.6782445425

00:08:38.230 --> 00:08:40.387 synthesis of a T RNA modifications

NOTE Confidence: 0.6782445425

00:08:40.387 --> 00:08:42.297 in the mitochondria you have

NOTE Confidence: 0.6782445425

00:08:42.297 --> 00:08:44.448 disease that are affect.

NOTE Confidence: 0.6782445425

00:08:44.448 --> 00:08:46.515 Neurological defects associated

NOTE Confidence: 0.6782445425

00:08:46.515 --> 00:08:49.960 with cancer and even diabetes.

NOTE Confidence: 0.6782445425

00:08:49.960 --> 00:08:52.738 So the slide is really small.

NOTE Confidence: 0.6782445425

00:08:52.740 --> 00:08:54.508 So the intention here is not for you

NOTE Confidence: 0.6782445425

00:08:54.508 --> 00:08:56.556 to read all the disease that are found,

NOTE Confidence: 0.6782445425

00:08:56.560 --> 00:08:58.774 but you can read more about

NOTE Confidence: 0.6782445425

00:08:58.774 --> 00:09:00.810 this in this Suzuki paper.

NOTE Confidence: 0.6782445425

00:09:00.810 --> 00:09:02.646 This is not my my literature,

NOTE Confidence: 0.6782445425

00:09:02.650 --> 00:09:04.876 but it's a paper from a leading

NOTE Confidence: 0.6782445425

00:09:04.876 --> 00:09:06.682 scientist on the ****** tyranny

NOTE Confidence: 0.6782445425

00:09:06.682 --> 00:09:09.356 modification field and you can get a

NOTE Confidence: 0.6782445425

00:09:09.356 --> 00:09:12.627 good idea of the variety of metabolic

NOTE Confidence: 0.6782445425

00:09:12.627 --> 00:09:14.575 consequences associated with this.

NOTE Confidence: 0.6782445425

00:09:14.580 --> 00:09:18.300 Function of T RNA modifications.

NOTE Confidence: 0.6782445425

00:09:18.300 --> 00:09:20.684 So in a recent review did on in

NOTE Confidence: 0.6782445425

00:09:20.684 --> 00:09:22.870 Dagley has stated that dysfunctional

NOTE Confidence: 0.6782445425

00:09:22.870 --> 00:09:25.390 protein synthesis at the level

NOTE Confidence: 0.6782445425

00:09:25.390 --> 00:09:27.260 of translation elongation,

NOTE Confidence: 0.6782445425

00:09:27.260 --> 00:09:30.438 so at point where T RNA modifications

NOTE Confidence: 0.6782445425

00:09:30.438 --> 00:09:33.108 become relevant is now recognized as

NOTE Confidence: 0.6782445425

00:09:33.108 --> 00:09:35.636 a major pathophysiological driver in

NOTE Confidence: 0.6782445425

00:09:35.636 --> 00:09:38.496 many human disease including cancer.

NOTE Confidence: 0.6782445425

00:09:38.500 --> 00:09:41.594 So this topic of research is really

NOTE Confidence: 0.6782445425

00:09:41.594 --> 00:09:43.845 important and and oftentimes

NOTE Confidence: 0.6782445425

00:09:43.845 --> 00:09:46.350 overlooked one understanding.

NOTE Confidence: 0.6782445425

00:09:46.350 --> 00:09:50.598 A disease phenotype and molecular level.

NOTE Confidence: 0.6782445425

00:09:50.600 --> 00:09:52.598 So the modification of interest that

NOTE Confidence: 0.6782445425

00:09:52.598 --> 00:09:55.477 I want to share with you about is a

NOTE Confidence: 0.6782445425

00:09:55.477 --> 00:09:58.108 modification that it's a 2 by your audience.

NOTE Confidence: 0.6782445425

00:09:58.110 --> 00:09:59.710 It's a modification that involves

NOTE Confidence: 0.6782445425

00:09:59.710 --> 00:10:01.653 sulfur and that you know that's

NOTE Confidence: 0.6782445425

00:10:01.653 --> 00:10:03.620 kind of it's fits into the whole

NOTE Confidence: 0.6782445425

00:10:03.620 --> 00:10:05.324 umbrella of my research program

NOTE Confidence: 0.6782445425

00:10:05.324 --> 00:10:07.478 that we will understand how sulfur

NOTE Confidence: 0.6782445425

00:10:07.478 --> 00:10:09.283 containing cofactors are assembled.

NOTE Confidence: 0.6782445425

00:10:09.283 --> 00:10:12.169 So this modification is found at

NOTE Confidence: 0.6782445425

00:10:12.169 --> 00:10:14.858 the wobble position of tyranny,

NOTE Confidence: 0.6782445425

00:10:14.860 --> 00:10:16.756 so interacts with the last space

NOTE Confidence: 0.6782445425

00:10:16.756 --> 00:10:18.973 on the codon and it's phylogenetic

NOTE Confidence: 0.6782445425

00:10:18.973 --> 00:10:20.737 conserved in all three.

NOTE Confidence: 0.6782445425

00:10:20.740 --> 00:10:22.876 Domains of life and it's present

NOTE Confidence: 0.6782445425

00:10:22.876 --> 00:10:24.990 in terminating codes for glutamine,

NOTE Confidence: 0.6782445425

00:10:24.990 --> 00:10:26.547 lysine and glutamate.

NOTE Confidence: 0.6782445425

00:10:26.547 --> 00:10:29.661 And the importance of this modification

NOTE Confidence: 0.6782445425

00:10:29.661 --> 00:10:33.047 is that introduction of a soul for a

NOTE Confidence: 0.6782445425

00:10:33.047 --> 00:10:35.869 two position of uridine ring allows

NOTE Confidence: 0.6782445425

00:10:35.870 --> 00:10:38.455 canonical base pair formation with

NOTE Confidence: 0.6782445425

00:10:38.455 --> 00:10:42.350 adenine for let's say AAA cordon of lysine.

NOTE Confidence: 0.6782445425

00:10:42.350 --> 00:10:44.625 But also taught totalization of

NOTE Confidence: 0.6782445425

00:10:44.625 --> 00:10:47.472 this modification allows for non

NOTE Confidence: 0.6782445425

00:10:47.472 --> 00:10:49.784 canonical base pair formations.

NOTE Confidence: 0.6782445425

00:10:49.790 --> 00:10:51.710 So in this case the you can base.

NOTE Confidence: 0.6782445425

00:10:51.710 --> 00:10:56.110 Pair with the G so lack of those

NOTE Confidence: 0.6782445425

00:10:56.110 --> 00:10:59.096 modifications that causes, you know,

NOTE Confidence: 0.6782445425

00:10:59.096 --> 00:11:00.620 severe metabolic consequences.

NOTE Confidence: 0.6782445425

00:11:00.620 --> 00:11:03.436 What it's what it's known that is inhuman.

NOTE Confidence: 0.6782445425

00:11:03.440 --> 00:11:06.415 This modification is found both in the

NOTE Confidence: 0.6782445425

00:11:06.415 --> 00:11:10.190 cytosolic T RNA is in the mitochondrial DNA.

NOTE Confidence: 0.6782445425

00:11:10.190 --> 00:11:10.790 Interestingly,

NOTE Confidence: 0.6782445425

00:11:10.790 --> 00:11:13.790 the biosynthetic pathway to modify

NOTE Confidence: 0.6782445425

00:11:13.790 --> 00:11:16.469 terminating the cytosol is different

NOTE Confidence: 0.6782445425

00:11:16.469 --> 00:11:19.669 than the one that is used to synthesize

NOTE Confidence: 0.78447247952

00:11:19.748 --> 00:11:22.208 2 thymidine in the mitochondria.

NOTE Confidence: 0.78447247952

00:11:22.210 --> 00:11:24.316 And the mitochondria pathway is similar

NOTE Confidence: 0.78447247952

00:11:24.316 --> 00:11:27.167 to that of what it's found in bacteria

NOTE Confidence: 0.78447247952

00:11:27.167 --> 00:11:29.620 so reinforces the idea that you know,

NOTE Confidence: 0.78447247952

00:11:29.620 --> 00:11:32.000 bacteria was a ancient microorganisms

NOTE Confidence: 0.78447247952

00:11:32.000 --> 00:11:35.855 that had been gold to into ****** cells.

NOTE Confidence: 0.78447247952

00:11:35.855 --> 00:11:38.885 So here's some good examples of

NOTE Confidence: 0.78447247952

00:11:38.885 --> 00:11:41.264 biosynthetic enzymes involved in the

NOTE Confidence: 0.78447247952

00:11:41.264 --> 00:11:43.622 cities of two pyridine and mutations

NOTE Confidence: 0.78447247952

00:11:43.622 --> 00:11:46.239 have been found in those genes

NOTE Confidence: 0.78447247952

00:11:46.239 --> 00:11:48.424 and they are diseased phenotype.

NOTE Confidence: 0.78447247952

00:11:48.430 --> 00:11:49.798 So I'm not really.

NOTE Confidence: 0.5854362895

00:11:52.170 --> 00:11:55.026 A sanitise that studies human disease,

NOTE Confidence: 0.5854362895

00:11:55.030 --> 00:11:57.478 but that's my effort to to connect with

NOTE Confidence: 0.5854362895

00:11:57.478 --> 00:12:00.266 the audience by primary interest is really

NOTE Confidence: 0.5854362895

00:12:00.266 --> 00:12:02.381 trying to understand bacterial metabolism.

NOTE Confidence: 0.5854362895

00:12:02.390 --> 00:12:05.030 And what we know is that in bacteria

NOTE Confidence: 0.5854362895

00:12:05.030 --> 00:12:08.597 lack of two pyridine or mutations in the

NOTE Confidence: 0.5854362895

00:12:08.597 --> 00:12:11.037 the biosynthetic components of tooth

NOTE Confidence: 0.5854362895

00:12:11.037 --> 00:12:13.397 iodine leads to compromise cellular

NOTE Confidence: 0.5854362895

00:12:13.397 --> 00:12:16.682 viability and in some cases including the

NOTE Confidence: 0.5854362895

00:12:16.682 --> 00:12:19.466 organisms that I am interested about,

NOTE Confidence: 0.5854362895

00:12:19.470 --> 00:12:21.430 this pathway is fully essential

NOTE Confidence: 0.5854362895

00:12:21.430 --> 00:12:22.991 for the organization. Survive.

NOTE Confidence: 0.5854362895

00:12:22.991 --> 00:12:25.277 OK, so it's it's an essential

NOTE Confidence: 0.5854362895

00:12:25.277 --> 00:12:26.039 cellular process,

NOTE Confidence: 0.5854362895

00:12:26.040 --> 00:12:29.386 which makes very interesting if you think

NOTE Confidence: 0.5854362895

00:12:29.386 --> 00:12:31.898 about pathogenic bacteria and how you

NOTE Confidence: 0.5854362895

00:12:31.898 --> 00:12:37.418 can discover new metabolic interventions for.

NOTE Confidence: 0.5854362895

00:12:37.420 --> 00:12:39.800 For the treatment of infections

NOTE Confidence: 0.5854362895

00:12:39.800 --> 00:12:42.803 caused by pathogenic so in the

NOTE Confidence: 0.5854362895

00:12:42.803 --> 00:12:44.967 synthesis of new antibiotics.

NOTE Confidence: 0.5854362895

00:12:44.970 --> 00:12:47.772 So that's the story that I

NOTE Confidence: 0.5854362895

00:12:47.772 --> 00:12:50.789 wanted to tell you about how?

NOTE Confidence: 0.5854362895

00:12:50.790 --> 00:12:53.966 My students and I went on this mission

NOTE Confidence: 0.5854362895

00:12:53.966 --> 00:12:56.738 to really understand and identify

NOTE Confidence: 0.5854362895

00:12:56.738 --> 00:12:59.408 the biosynthetic components of two

NOTE Confidence: 0.5854362895

00:12:59.408 --> 00:13:01.790 pyridine and Bacillus subtilis,

NOTE Confidence: 0.5854362895

00:13:01.790 --> 00:13:04.409 and in the work that we have done more

NOTE Confidence: 0.5854362895

00:13:04.409 --> 00:13:06.380 recently to uncover the additional

NOTE Confidence: 0.5854362895

00:13:06.380 --> 00:13:07.992 functions that this modification

NOTE Confidence: 0.5854362895

00:13:07.992 --> 00:13:10.262 may be playing a role in,

NOTE Confidence: 0.5854362895

00:13:10.262 --> 00:13:12.390 in this particular Organism.

NOTE Confidence: 0.5854362895

00:13:12.390 --> 00:13:14.945 So that's the work of two very

NOTE Confidence: 0.5854362895

00:13:14.945 --> 00:13:16.748 talented graduate students in my lab,

NOTE Confidence: 0.5854362895

00:13:16.750 --> 00:13:18.112 I, Catherine Black,

NOTE Confidence: 0.5854362895

00:13:18.112 --> 00:13:20.836 and actually Edwards actually has graduated.

NOTE Confidence: 0.5854362895

00:13:20.840 --> 00:13:22.076 Uh, last month.

NOTE Confidence: 0.5854362895

00:13:22.076 --> 00:13:24.520 So she she's now off to do bigger

NOTE Confidence: 0.5854362895

00:13:24.520 --> 00:13:26.180 and better things in her life,

NOTE Confidence: 0.5854362895

00:13:26.180 --> 00:13:28.052 but I'm grateful for the discoveries

NOTE Confidence: 0.5854362895

00:13:28.052 --> 00:13:29.300 that she made here.

NOTE Confidence: 0.5854362895

00:13:29.300 --> 00:13:31.112 So there are three main points

NOTE Confidence: 0.5854362895

00:13:31.112 --> 00:13:34.003 that I want to convey here on our

NOTE Confidence: 0.5854362895

00:13:34.003 --> 00:13:36.018 study of two pyridine biosynthesis.

NOTE Confidence: 0.5854362895

00:13:36.020 --> 00:13:38.340 It's our experimental approach

NOTE Confidence: 0.5854362895

00:13:38.340 --> 00:13:40.660 to identify biosynthetic enzymes,

NOTE Confidence: 0.5854362895

00:13:40.660 --> 00:13:42.280 the function of two,

NOTE Confidence: 0.5854362895

00:13:42.280 --> 00:13:45.356 two pyridine as a marker or potentially

NOTE Confidence: 0.5854362895

00:13:45.356 --> 00:13:48.698 sensor of so far availability in

NOTE Confidence: 0.5854362895

00:13:48.698 --> 00:13:51.049 Bacillus subtilis and how we.

NOTE Confidence: 0.5854362895

00:13:51.050 --> 00:13:53.406 Understand the biochemical principles

NOTE Confidence: 0.5854362895

00:13:53.406 --> 00:13:56.940 by which those enzymes operate that

NOTE Confidence: 0.5854362895

00:13:57.026 --> 00:13:59.581 restrict and direct their roles

NOTE Confidence: 0.5854362895

00:13:59.581 --> 00:14:01.625 in the sulfur metabolism.

NOTE Confidence: 0.703341018333333

00:14:04.510 --> 00:14:06.406 Before I dive in as that,

NOTE Confidence: 0.703341018333333

00:14:06.410 --> 00:14:08.849 I wanted to kind of like show you some

NOTE Confidence: 0.703341018333333

00:14:08.849 --> 00:14:11.764 key points so you can have an appreciation

NOTE Confidence: 0.703341018333333

00:14:11.764 --> 00:14:14.301 for the complexity of studying those

NOTE Confidence: 0.703341018333333

00:14:14.301 --> 00:14:16.686 systems at the biochemical level.

NOTE Confidence: 0.703341018333333

00:14:16.690 --> 00:14:19.840 So what we know is that in the centers of

NOTE Confidence: 0.703341018333333

00:14:19.926 --> 00:14:22.926 Tyler cofactors and I mentioned before,

NOTE Confidence: 0.703341018333333

00:14:22.930 --> 00:14:25.714 I'm interested in the cities of all the

NOTE Confidence: 0.703341018333333

00:14:25.714 --> 00:14:27.568 biomolecules showing here on this slide.

NOTE Confidence: 0.703341018333333

00:14:27.570 --> 00:14:29.818 What we know is that the first staff

NOTE Confidence: 0.703341018333333

00:14:29.818 --> 00:14:32.277 on super mobilization is catalyzed by

NOTE Confidence: 0.703341018333333

00:14:32.277 --> 00:14:34.567 an enzyme called cysteine disulphide.

NOTE Confidence: 0.703341018333333

00:14:34.570 --> 00:14:38.050 So those enzymes they they use a ping

NOTE Confidence: 0.703341018333333

00:14:38.050 --> 00:14:40.847 pong mechanism to bind sustain and

NOTE Confidence: 0.703341018333333

00:14:40.847 --> 00:14:43.607 convert sustain into alanine and by

NOTE Confidence: 0.703341018333333

00:14:43.694 --> 00:14:47.733 doing so they form a covalent sulfur

NOTE Confidence: 0.703341018333333

00:14:47.733 --> 00:14:49.464 personified enzyme intermediate.

NOTE Confidence: 0.703341018333333

00:14:49.470 --> 00:14:52.398 The sulfur then is transferred to

NOTE Confidence: 0.703341018333333

00:14:52.398 --> 00:14:54.823 downstream pathway components involved in

NOTE Confidence: 0.703341018333333

00:14:54.823 --> 00:14:57.205 the synthesis of iron sulfur clusters,

NOTE Confidence: 0.703341018333333

00:14:57.210 --> 00:15:01.430 tail nucleosides or different vitamins.

NOTE Confidence: 0.703341018333333

00:15:01.430 --> 00:15:04.820 As in the case of tyramine, lipoic acid,

NOTE Confidence: 0.703341018333333

00:15:04.820 --> 00:15:07.850 biotin, so on and so forth.

NOTE Confidence: 0.703341018333333

00:15:07.850 --> 00:15:11.126 But it's a complicated here is that

NOTE Confidence: 0.703341018333333

00:15:11.130 --> 00:15:13.286 if you have at least in humans,

NOTE Confidence: 0.703341018333333

00:15:13.290 --> 00:15:14.890 you have one single enzyme,

NOTE Confidence: 0.703341018333333

00:15:14.890 --> 00:15:17.235 NFS one that is responsible for the

NOTE Confidence: 0.703341018333333

00:15:17.235 --> 00:15:19.340 synthesis of all time nucleosides

NOTE Confidence: 0.703341018333333

00:15:19.340 --> 00:15:20.560 in the human genome.

NOTE Confidence: 0.703341018333333

00:15:20.560 --> 00:15:22.390 So that's that enzyme is found

NOTE Confidence: 0.703341018333333

00:15:22.453 --> 00:15:23.650 in the mitochondria.

NOTE Confidence: 0.703341018333333

00:15:23.650 --> 00:15:26.810 In some study model systems like E coli,

NOTE Confidence: 0.703341018333333

00:15:26.810 --> 00:15:30.642 you also have a primary enzyme and then

NOTE Confidence: 0.703341018333333

00:15:30.642 --> 00:15:34.302 the sulfur transfer pathway here is

NOTE Confidence: 0.703341018333333

00:15:34.302 --> 00:15:36.946 shared across different pathways, right?

NOTE Confidence: 0.703341018333333

00:15:36.946 --> 00:15:38.050 So you have one.

NOTE Confidence: 0.703341018333333

00:15:38.050 --> 00:15:40.210 Primary sulfur donor then and then

NOTE Confidence: 0.703341018333333

00:15:40.210 --> 00:15:42.612 that sulfur is traffic to different

NOTE Confidence: 0.703341018333333

00:15:42.612 --> 00:15:44.852 pathway intermediates and in some

NOTE Confidence: 0.703341018333333

00:15:44.852 --> 00:15:46.589 cases those biosynthetic intermediates

NOTE Confidence: 0.703341018333333

00:15:46.589 --> 00:15:49.487 are shared as in the case of two five

NOTE Confidence: 0.703341018333333

00:15:49.490 --> 00:15:52.964 year adine and moco Biogenesis which

NOTE Confidence: 0.703341018333333

00:15:52.964 --> 00:15:56.889 is also a protein called factor.

NOTE Confidence: 0.703341018333333

00:15:56.890 --> 00:15:59.368 To complicate things a little bit more,

NOTE Confidence: 0.703341018333333

00:15:59.370 --> 00:16:02.798 is that one interest that I had for

NOTE Confidence: 0.703341018333333

00:16:02.798 --> 00:16:04.770 many years and I guess that's where

NOTE Confidence: 0.703341018333333

00:16:04.770 --> 00:16:06.684 most of my publications come from,

NOTE Confidence: 0.703341018333333

00:16:06.690 --> 00:16:08.646 is really trying to understand the

NOTE Confidence: 0.703341018333333

00:16:08.646 --> 00:16:10.752 pathway that leads to the synthesis

NOTE Confidence: 0.703341018333333

00:16:10.752 --> 00:16:12.228 of iron sulfur clusters,

NOTE Confidence: 0.703341018333333

00:16:12.230 --> 00:16:13.818 very essential protein cofactors.

NOTE Confidence: 0.703341018333333

00:16:13.818 --> 00:16:17.339 And then what we want to do is like

NOTE Confidence: 0.703341018333333

00:16:17.339 --> 00:16:19.475 when we try to deconvolute those

NOTE Confidence: 0.703341018333333

00:16:19.475 --> 00:16:21.733 pathways and try to understand

NOTE Confidence: 0.703341018333333

00:16:21.733 --> 00:16:23.565 metabolic defects associated with

NOTE Confidence: 0.703341018333333

00:16:23.565 --> 00:16:26.002 the initial sulfur mobilization step.

NOTE Confidence: 0.703341018333333

00:16:26.002 --> 00:16:29.530 It's quite complex because what we see

NOTE Confidence: 0.703341018333333

00:16:29.610 --> 00:16:32.754 is that there are so iron sulfur enzyme,

NOTE Confidence: 0.703341018333333

00:16:32.760 --> 00:16:35.202 so enzymes that depend on iron

NOTE Confidence: 0.703341018333333

00:16:35.202 --> 00:16:37.837 sulfur cluster for the synthesis of

NOTE Confidence: 0.703341018333333

00:16:37.837 --> 00:16:40.115 other sulfur containing metabolites.

NOTE Confidence: 0.703341018333333

00:16:40.115 --> 00:16:45.033 So when you disrupt the initial steps on

NOTE Confidence: 0.703341018333333

00:16:45.033 --> 00:16:47.998 sulphur mobilization so for instance.

NOTE Confidence: 0.703341018333333

00:16:48.000 --> 00:16:50.090 For the synthesis of tyramine,

NOTE Confidence: 0.703341018333333

00:16:50.090 --> 00:16:52.268 you don't really know if you're

NOTE Confidence: 0.703341018333333

00:16:52.268 --> 00:16:54.593 disrupting the primary route for sulfur

NOTE Confidence: 0.703341018333333

00:16:54.593 --> 00:16:57.023 transfer or if you're inactivating a

NOTE Confidence: 0.703341018333333

00:16:57.023 --> 00:16:58.989 biosynthetic enzyme that requires an

NOTE Confidence: 0.703341018333333

00:16:58.989 --> 00:17:01.167 iron sulfur cluster for its activity.

NOTE Confidence: 0.703341018333333

00:17:01.170 --> 00:17:03.966 So you have this intertwined metabolic

NOTE Confidence: 0.703341018333333

00:17:03.966 --> 00:17:06.397 pathways that you have dependency

NOTE Confidence: 0.703341018333333

00:17:06.397 --> 00:17:09.331 of a super containing cofactor in

NOTE Confidence: 0.703341018333333

00:17:09.331 --> 00:17:12.533 the biosynthesis of another super

NOTE Confidence: 0.703341018333333

00:17:12.533 --> 00:17:16.486 containing cofactor. OK.

NOTE Confidence: 0.703341018333333

00:17:16.486 --> 00:17:23.310 So one primary metabolic.

NOTE Confidence: 0.703341018333333

00:17:23.310 --> 00:17:25.725 A component that we look at it's

NOTE Confidence: 0.703341018333333

00:17:25.725 --> 00:17:28.127 tyranny and how T RNA is modified.

NOTE Confidence: 0.703341018333333

00:17:28.130 --> 00:17:31.154 And this is really great because

NOTE Confidence: 0.703341018333333

00:17:31.154 --> 00:17:35.187 on T RNA modification of a pool you

NOTE Confidence: 0.703341018333333

00:17:35.187 --> 00:17:36.627 can identify pathways,

NOTE Confidence: 0.703341018333333

00:17:36.630 --> 00:17:38.474 enzymes that contain iron,

NOTE Confidence: 0.703341018333333

00:17:38.474 --> 00:17:41.240 sulfur clusters and then they would.

NOTE Confidence: 0.64577314875

00:17:43.700 --> 00:17:46.228 Transfer sulfur to the

NOTE Confidence: 0.64577314875

00:17:46.228 --> 00:17:48.756 cities of this cofactor.

NOTE Confidence: 0.64577314875

00:17:48.760 --> 00:17:50.116 So this is an example here.

NOTE Confidence: 0.64577314875

00:17:50.120 --> 00:17:53.325 The mutations that deplete this

NOTE Confidence: 0.64577314875

00:17:53.325 --> 00:17:55.248 modification causes diabetes,

NOTE Confidence: 0.64577314875

00:17:55.250 --> 00:17:58.029 for instance, so and the enzyme that

NOTE Confidence: 0.64577314875

00:17:58.029 --> 00:18:01.114 does that is an enzyme that contains

NOTE Confidence: 0.64577314875

00:18:01.114 --> 00:18:03.832 an iron sulfur cluster you have.

NOTE Confidence: 0.64577314875

00:18:03.840 --> 00:18:07.070 Sometimes I miss the mouse.

NOTE Confidence: 0.64577314875

00:18:07.070 --> 00:18:09.200 You have pathways like the S2

NOTE Confidence: 0.64577314875

00:18:09.200 --> 00:18:11.508 you pathway that do not require

NOTE Confidence: 0.64577314875

00:18:11.508 --> 00:18:13.944 iron super enzymes and then you

NOTE Confidence: 0.64577314875

00:18:13.944 --> 00:18:16.221 have empathy is not shown here

NOTE Confidence: 0.64577314875

00:18:16.221 --> 00:18:18.620 that do not contain sulfur but it

NOTE Confidence: 0.64577314875

00:18:18.620 --> 00:18:20.170 depends on iron sulfur cluster.

NOTE Confidence: 0.64577314875

00:18:20.170 --> 00:18:22.978 So you can interrogate the cells

NOTE Confidence: 0.64577314875

00:18:22.978 --> 00:18:24.850 under different conditions and

NOTE Confidence: 0.64577314875

00:18:24.934 --> 00:18:27.388 you can extract the that tyranny.

NOTE Confidence: 0.64577314875

00:18:27.390 --> 00:18:29.406 And the primary tool that we use

NOTE Confidence: 0.64577314875

00:18:29.406 --> 00:18:31.948 here is to purify those two RNA

NOTE Confidence: 0.64577314875

00:18:31.948 --> 00:18:34.360 molecules and then analyze the relative

NOTE Confidence: 0.64577314875

00:18:34.431 --> 00:18:37.179 abundance of all those nucleosides using.

NOTE Confidence: 0.64577314875

00:18:37.180 --> 00:18:38.624 High resolution mass spectrometry.

NOTE Confidence: 0.64577314875

00:18:38.624 --> 00:18:40.429 So when we do that,

NOTE Confidence: 0.64577314875

00:18:40.430 --> 00:18:43.174 we not only analyze the analyte of interest

NOTE Confidence: 0.64577314875

00:18:43.174 --> 00:18:46.108 as as to you in this particular case,

NOTE Confidence: 0.64577314875

00:18:46.110 --> 00:18:48.302 but we look at the relative levels of

NOTE Confidence: 0.64577314875

00:18:48.302 --> 00:18:50.310 all those different modifications.

NOTE Confidence: 0.64577314875

00:18:50.310 --> 00:18:52.230 This is important because for

NOTE Confidence: 0.64577314875

00:18:52.230 --> 00:18:55.003 instance in the case of two tire

NOTE Confidence: 0.64577314875

00:18:55.003 --> 00:18:57.987 reading that is in this box here this

NOTE Confidence: 0.64577314875

00:18:57.987 --> 00:19:00.154 modification comes along with additional

NOTE Confidence: 0.64577314875

00:19:00.154 --> 00:19:02.609 modifications on the uridine base.

NOTE Confidence: 0.64577314875

00:19:02.610 --> 00:19:04.986 So if we really want to quantify the effects

NOTE Confidence: 0.64577314875

00:19:04.986 --> 00:19:07.219 on the biosynthesis of two thymidine.

NOTE Confidence: 0.64577314875

00:19:07.220 --> 00:19:09.890 We have to quantify all those

NOTE Confidence: 0.64577314875

00:19:09.890 --> 00:19:11.670 different metabolites and understand

NOTE Confidence: 0.64577314875

00:19:11.741 --> 00:19:13.897 the their relative accumulation.

NOTE Confidence: 0.819992196923077

00:19:16.270 --> 00:19:18.754 Umm. Another point to consider when

NOTE Confidence: 0.819992196923077

00:19:18.754 --> 00:19:21.569 pursuing this analysis is that the levels,

NOTE Confidence: 0.819992196923077

00:19:21.570 --> 00:19:23.270 the relative levels of tyranny,

NOTE Confidence: 0.819992196923077

00:19:23.270 --> 00:19:28.688 modifications, they vary with growth phase,

NOTE Confidence: 0.819992196923077

00:19:28.690 --> 00:19:29.644 growth conditions,

NOTE Confidence: 0.819992196923077

00:19:29.644 --> 00:19:32.983 temperatures and so on and so forth.

NOTE Confidence: 0.819992196923077

00:19:32.990 --> 00:19:35.702 So the notion that TNA is modified and

NOTE Confidence: 0.819992196923077

00:19:35.702 --> 00:19:39.091 now is fully functional to perform roles

NOTE Confidence: 0.819992196923077

00:19:39.091 --> 00:19:41.726 in translation is really misleading.

NOTE Confidence: 0.819992196923077

00:19:41.730 --> 00:19:44.285 What we know is that there are

NOTE Confidence: 0.819992196923077

00:19:44.285 --> 00:19:45.925 degrees of modification that

NOTE Confidence: 0.819992196923077

00:19:45.925 --> 00:19:47.817 confined to the functionality.

NOTE Confidence: 0.819992196923077

00:19:47.820 --> 00:19:50.412 Of that tyranny and therefore fine

NOTE Confidence: 0.819992196923077

00:19:50.412 --> 00:19:53.130 tune the efficiency of translation.

NOTE Confidence: 0.819992196923077

00:19:53.130 --> 00:19:54.636 So for instance,

NOTE Confidence: 0.819992196923077

00:19:54.636 --> 00:19:57.648 if you grow cells and the

NOTE Confidence: 0.819992196923077

00:19:57.648 --> 00:19:58.662 different temperatures,

NOTE Confidence: 0.819992196923077

00:19:58.662 --> 00:20:01.734 you can have a different loading

NOTE Confidence: 0.819992196923077

00:20:01.734 --> 00:20:04.343 of of modification and that's

NOTE Confidence: 0.819992196923077

00:20:04.343 --> 00:20:06.438 interpreted as improving the

NOTE Confidence: 0.819992196923077

00:20:06.438 --> 00:20:09.208 rigidity of that anticodon loop.

NOTE Confidence: 0.819992196923077

00:20:09.210 --> 00:20:11.718 So you can favor base pairing

NOTE Confidence: 0.819992196923077

00:20:11.718 --> 00:20:14.290 information even in a higher temperature

NOTE Confidence: 0.819992196923077

00:20:14.290 --> 00:20:18.870 as in the case of the MSU I6A.

NOTE Confidence: 0.819992196923077

00:20:18.870 --> 00:20:21.330 You can also see a differential

NOTE Confidence: 0.819992196923077

00:20:21.330 --> 00:20:22.970 accumulation of some modifications

NOTE Confidence: 0.819992196923077

00:20:23.040 --> 00:20:25.314 under oxidative stress and this is

NOTE Confidence: 0.819992196923077

00:20:25.314 --> 00:20:27.317 attributed because some of those

NOTE Confidence: 0.819992196923077

00:20:27.317 --> 00:20:28.985 modifications they are dependent

NOTE Confidence: 0.819992196923077

00:20:28.985 --> 00:20:31.070 on enzymes that contain iron

NOTE Confidence: 0.819992196923077

00:20:31.070 --> 00:20:33.610 superclusters and then those clusters

NOTE Confidence: 0.819992196923077

00:20:33.610 --> 00:20:36.150 are susceptible to oxidative damage.

NOTE Confidence: 0.819992196923077

00:20:36.150 --> 00:20:38.142 So you can have a different

NOTE Confidence: 0.819992196923077

00:20:38.142 --> 00:20:40.738 accumulation as a as a readout for

NOTE Confidence: 0.819992196923077

00:20:40.738 --> 00:20:42.728 oxidative stress in those cells.

NOTE Confidence: 0.809869931071428

00:20:45.740 --> 00:20:48.197 So, so when it's studying or trying

NOTE Confidence: 0.809869931071428

00:20:48.197 --> 00:20:51.180 to assign a different pathways in the

NOTE Confidence: 0.809869931071428

00:20:51.180 --> 00:20:54.457 organisms that have not been studied before

NOTE Confidence: 0.809869931071428

00:20:54.457 --> 00:20:57.397 the the standard procedure to do that,

NOTE Confidence: 0.809869931071428

00:20:57.400 --> 00:20:59.521 it's like you take a pathway that

NOTE Confidence: 0.809869931071428

00:20:59.521 --> 00:21:01.464 is well studied and established and

NOTE Confidence: 0.809869931071428

00:21:01.464 --> 00:21:03.718 then you start to blast for that

NOTE Confidence: 0.809869931071428

00:21:03.781 --> 00:21:06.043 gene in that particular Organism and

NOTE Confidence: 0.809869931071428

00:21:06.043 --> 00:21:07.881 then you find equivalent components

NOTE Confidence: 0.809869931071428

00:21:07.881 --> 00:21:10.128 that you can make a good assumption

NOTE Confidence: 0.809869931071428

00:21:10.128 --> 00:21:12.252 based on sequence analysis. So.

NOTE Confidence: 0.809869931071428

00:21:12.252 --> 00:21:15.148 So when we start that that research that's.

NOTE Confidence: 0.809869931071428

00:21:15.150 --> 00:21:18.669 Out of the office workflow to fish out those

NOTE Confidence: 0.809869931071428

00:21:18.669 --> 00:21:22.120 genes and and to do biochemical experiments.

NOTE Confidence: 0.809869931071428

00:21:22.120 --> 00:21:25.060 So but that's not really the case.

NOTE Confidence: 0.809869931071428

00:21:25.060 --> 00:21:27.328 So when we compare the pathway found

NOTE Confidence: 0.809869931071428

00:21:27.328 --> 00:21:30.362 in E coli that is where we study and

NOTE Confidence: 0.809869931071428

00:21:30.362 --> 00:21:32.660 then we're trying to find equivalent

NOTE Confidence: 0.809869931071428

00:21:32.660 --> 00:21:35.354 genes in the basal subtilis genome.

NOTE Confidence: 0.809869931071428

00:21:35.360 --> 00:21:37.782 We do not find a complete pathway

NOTE Confidence: 0.809869931071428

00:21:37.782 --> 00:21:40.984 in terms of all the enzymes are not

NOTE Confidence: 0.809869931071428

00:21:40.984 --> 00:21:43.681 really present in some enzymes are

NOTE Confidence: 0.809869931071428

00:21:43.681 --> 00:21:45.298 missing suggesting that.

NOTE Confidence: 0.809869931071428

00:21:45.300 --> 00:21:48.912 Now you have perhaps an alternate mechanism

NOTE Confidence: 0.809869931071428

00:21:48.912 --> 00:21:51.719 to synthesize that same cofactor.

NOTE Confidence: 0.809869931071428

00:21:51.720 --> 00:21:54.424 And that's the case here for two pyridine.

NOTE Confidence: 0.809869931071428

00:21:54.430 --> 00:21:57.888 So our attempts to search for all

NOTE Confidence: 0.809869931071428

00:21:57.888 --> 00:22:00.910 those enzymes here showing red fail.

NOTE Confidence: 0.809869931071428

00:22:00.910 --> 00:22:03.310 So that means that imbecile subtilis,

NOTE Confidence: 0.809869931071428

00:22:03.310 --> 00:22:05.865 you don't have those pathways like 5

NOTE Confidence: 0.809869931071428

00:22:05.865 --> 00:22:08.210 pathway components are completely missing.

NOTE Confidence: 0.809869931071428

00:22:08.210 --> 00:22:09.462 So how you go,

NOTE Confidence: 0.809869931071428

00:22:09.462 --> 00:22:11.340 how you go from the Sistine,

NOTE Confidence: 0.809869931071428

00:22:11.340 --> 00:22:13.392 the sulfur race to the final

NOTE Confidence: 0.809869931071428

00:22:13.392 --> 00:22:15.674 enzyme in the pathway was the

NOTE Confidence: 0.809869931071428

00:22:15.674 --> 00:22:17.774 question for that particular study.

NOTE Confidence: 0.809869931071428

00:22:17.780 --> 00:22:21.540 OK, So what we know is that in the collide.

NOTE Confidence: 0.809869931071428

00:22:21.540 --> 00:22:23.838 Those pathways are really well studied.

NOTE Confidence: 0.809869931071428

00:22:23.840 --> 00:22:25.736 There's one primary enzyme,

NOTE Confidence: 0.809869931071428

00:22:25.736 --> 00:22:28.106 there's three dominant sulfur receptors,

NOTE Confidence: 0.809869931071428

00:22:28.110 --> 00:22:29.640 and then sulfur receptors showing

NOTE Confidence: 0.809869931071428

00:22:29.640 --> 00:22:31.944 in blue are the ones that Channel

NOTE Confidence: 0.809869931071428

00:22:31.944 --> 00:22:33.724 the sulfur to the biosynthesis.

NOTE Confidence: 0.809869931071428

00:22:33.730 --> 00:22:34.942 So for example,

NOTE Confidence: 0.809869931071428

00:22:34.942 --> 00:22:38.682 if you delete a you get a very distinct

NOTE Confidence: 0.809869931071428

00:22:38.682 --> 00:22:41.154 phenotype that is a deficiency of

NOTE Confidence: 0.809869931071428

00:22:41.154 --> 00:22:43.788 two pyridine and deficiency of MOCO.

NOTE Confidence: 0.809869931071428

00:22:43.790 --> 00:22:45.794 But you don't affect other pathways

NOTE Confidence: 0.809869931071428

00:22:45.794 --> 00:22:47.811 in reality actually affect a little

NOTE Confidence: 0.809869931071428

00:22:47.811 --> 00:22:49.683 bit because you are disrupting the

NOTE Confidence: 0.809869931071428

00:22:49.683 --> 00:22:51.228 equilibrium or so for transfer.

NOTE Confidence: 0.809869931071428

00:22:51.230 --> 00:22:52.178 So you actually.

NOTE Confidence: 0.809869931071428

00:22:52.178 --> 00:22:54.074 That boost on iron sulfur production

NOTE Confidence: 0.809869931071428

00:22:54.074 --> 00:22:55.825 because you don't have that

NOTE Confidence: 0.809869931071428

00:22:55.825 --> 00:22:56.515 competition anymore?

NOTE Confidence: 0.729175663448276

00:22:58.670 --> 00:23:01.246 What we found, you know very early stages

NOTE Confidence: 0.729175663448276

00:23:01.246 --> 00:23:04.738 when I when I joined Wake Forest is that

NOTE Confidence: 0.729175663448276

00:23:04.738 --> 00:23:06.717 Bacillus subtilis doesn't contain one

NOTE Confidence: 0.729175663448276

00:23:06.717 --> 00:23:09.223 Sistine the sulfur is it contains 4.

NOTE Confidence: 0.729175663448276

00:23:09.230 --> 00:23:13.642 So that to us already told that you

NOTE Confidence: 0.729175663448276

00:23:13.642 --> 00:23:15.718 know some of those pathways were

NOTE Confidence: 0.729175663448276

00:23:15.718 --> 00:23:18.205 different and then by looking at the

NOTE Confidence: 0.729175663448276

00:23:18.205 --> 00:23:20.491 genome neighborhood we could get some

NOTE Confidence: 0.729175663448276

00:23:20.491 --> 00:23:22.455 insight about their physiological

NOTE Confidence: 0.729175663448276

00:23:22.455 --> 00:23:24.910 functions in their particular Organism.

NOTE Confidence: 0.729175663448276

00:23:24.910 --> 00:23:27.520 So so far in my lab and also others

NOTE Confidence: 0.729175663448276

00:23:27.520 --> 00:23:28.659 in the field.

NOTE Confidence: 0.729175663448276

00:23:28.660 --> 00:23:32.149 Have been able to demonstrate the

NOTE Confidence: 0.729175663448276

00:23:32.149 --> 00:23:34.065 partnership between assisting the

NOTE Confidence: 0.729175663448276

00:23:34.065 --> 00:23:36.460 Sofras and they're still perceptor

NOTE Confidence: 0.729175663448276

00:23:36.526 --> 00:23:38.521 and validate their proposed roles

NOTE Confidence: 0.729175663448276

00:23:38.521 --> 00:23:41.050 in the centers of tailcoat factor.

NOTE Confidence: 0.729175663448276

00:23:41.050 --> 00:23:43.546 So I have done work in some of

NOTE Confidence: 0.729175663448276

00:23:43.546 --> 00:23:45.429 those all those proteins,

NOTE Confidence: 0.729175663448276

00:23:45.430 --> 00:23:48.386 but what I'm going to concentrate the

NOTE Confidence: 0.729175663448276

00:23:48.386 --> 00:23:52.132 talk it's on wire VO&MA they're they're

NOTE Confidence: 0.729175663448276

00:23:52.132 --> 00:23:55.336 relevant for two though you're adding.

NOTE Confidence: 0.729175663448276

00:23:55.340 --> 00:23:56.428 So as a biochemist,

NOTE Confidence: 0.729175663448276

00:23:56.428 --> 00:23:58.540 the first thing that we do is

NOTE Confidence: 0.729175663448276

00:23:58.540 --> 00:24:00.640 actually isolate the existing the

NOTE Confidence: 0.729175663448276

00:24:00.640 --> 00:24:02.320 Selfridge perform enzyme kinetics.

NOTE Confidence: 0.729175663448276

00:24:02.320 --> 00:24:04.630 And some of those initial studies

NOTE Confidence: 0.729175663448276

00:24:04.630 --> 00:24:07.305 show very clearly that those enzymes

NOTE Confidence: 0.729175663448276

00:24:07.305 --> 00:24:09.960 display very distinct kinetic behaviors.

NOTE Confidence: 0.729175663448276

00:24:09.960 --> 00:24:11.490 What it was really interesting.

NOTE Confidence: 0.729175663448276

00:24:11.490 --> 00:24:14.166 So those initial assays were done

NOTE Confidence: 0.729175663448276

00:24:14.166 --> 00:24:17.163 like most people in the field do.

NOTE Confidence: 0.729175663448276

00:24:17.163 --> 00:24:19.341 So everybody at that point would

NOTE Confidence: 0.729175663448276

00:24:19.341 --> 00:24:21.389 do just have kinetic reactions

NOTE Confidence: 0.729175663448276

00:24:21.389 --> 00:24:24.017 where you react with sustain and

NOTE Confidence: 0.729175663448276

00:24:24.017 --> 00:24:26.228 then you measure the half.

NOTE Confidence: 0.729175663448276

00:24:26.230 --> 00:24:28.273 Reaction rate through

NOTE Confidence: 0.729175663448276

00:24:28.273 --> 00:24:30.316 quantification of sulfide.

NOTE Confidence: 0.805517600625

00:24:32.610 --> 00:24:35.753 What we wanted to do is then

NOTE Confidence: 0.805517600625

00:24:35.753 --> 00:24:38.539 demonstrate that the presence of

NOTE Confidence: 0.805517600625

00:24:38.539 --> 00:24:41.227 the physiological sofa receptor,

NOTE Confidence: 0.805517600625

00:24:41.230 --> 00:24:43.474 so the second service trading this

NOTE Confidence: 0.805517600625

00:24:43.474 --> 00:24:46.510 reaction was a valid SOFA receptor.

NOTE Confidence: 0.805517600625

00:24:46.510 --> 00:24:48.466 And then in this particular case,

NOTE Confidence: 0.805517600625

00:24:48.470 --> 00:24:50.990 the reaction rate in the presence

NOTE Confidence: 0.805517600625

00:24:50.990 --> 00:24:53.258 of the sulfur acceptor enhanced

NOTE Confidence: 0.805517600625

00:24:53.258 --> 00:24:55.298 about over a hundredfold,

NOTE Confidence: 0.805517600625

00:24:55.300 --> 00:24:58.268 so indicating that the sulfur here in

NOTE Confidence: 0.805517600625

00:24:58.268 --> 00:25:01.879 this case was much better in abstracting.

NOTE Confidence: 0.805517600625

00:25:01.880 --> 00:25:04.308 The personal file then

NOTE Confidence: 0.805517600625

00:25:04.308 --> 00:25:06.129 an artificial reductant.

NOTE Confidence: 0.8653921

00:25:08.250 --> 00:25:08.870 Sure.

NOTE Confidence: 0.2021982

00:25:10.980 --> 00:25:11.440 Reaction.

NOTE Confidence: 0.69554375

00:25:15.140 --> 00:25:17.650 Yes, you.

NOTE Confidence: 0.768738014583333

00:25:20.270 --> 00:25:22.662 Yeah. So you may want to think there

NOTE Confidence: 0.768738014583333

00:25:22.662 --> 00:25:25.110 are very high but the intracellular

NOTE Confidence: 0.768738014583333

00:25:25.110 --> 00:25:27.335 level concentration on reduce this

NOTE Confidence: 0.768738014583333

00:25:27.335 --> 00:25:30.602 thing in the cells of his 68 micromolar.

NOTE Confidence: 0.768738014583333

00:25:30.602 --> 00:25:34.690 So actually that's actually quite nice if

NOTE Confidence: 0.768738014583333

00:25:34.795 --> 00:25:38.820 you study kind of like metabolism because

NOTE Confidence: 0.768738014583333

00:25:38.820 --> 00:25:42.527 most enzymes they kind of operate around

NOTE Confidence: 0.768738014583333

00:25:42.527 --> 00:25:45.228 the KM that they they have you know.

NOTE Confidence: 0.768738014583333

00:25:45.230 --> 00:25:48.093 So if the concentration is it OK

NOTE Confidence: 0.768738014583333

00:25:48.093 --> 00:25:50.779 that allows the cells to adjust.

NOTE Confidence: 0.768738014583333

00:25:50.780 --> 00:25:53.167 The velocity of that reaction because they

NOTE Confidence: 0.768738014583333

00:25:53.167 --> 00:25:55.497 are operating around KM and that's the case.

NOTE Confidence: 0.768738014583333

00:25:55.500 --> 00:25:57.390 But one thing that you may,

NOTE Confidence: 0.768738014583333

00:25:57.390 --> 00:26:00.414 you know, kind of notice is that the

NOTE Confidence: 0.768738014583333

00:26:00.414 --> 00:26:03.058 lowest KM here is for a wire VO.

NOTE Confidence: 0.768738014583333

00:26:03.060 --> 00:26:05.052 You know one thing that we may want

NOTE Confidence: 0.768738014583333

00:26:05.052 --> 00:26:06.887 to postulate like because this enzyme

NOTE Confidence: 0.768738014583333

00:26:06.887 --> 00:26:08.813 is so essential in this modification,

NOTE Confidence: 0.768738014583333

00:26:08.820 --> 00:26:11.334 so essential maybe the enzyme has

NOTE Confidence: 0.768738014583333

00:26:11.334 --> 00:26:14.294 evolved to have a really low KM

NOTE Confidence: 0.768738014583333

00:26:14.294 --> 00:26:16.294 to give a preference for,

NOTE Confidence: 0.768738014583333

00:26:16.300 --> 00:26:18.664 so for mobilization on that pathway

NOTE Confidence: 0.768738014583333

00:26:18.664 --> 00:26:20.240 under conditions that sulfur

NOTE Confidence: 0.768738014583333

00:26:20.301 --> 00:26:21.837 is not readily available.

NOTE Confidence: 0.880771825

00:26:25.240 --> 00:26:26.608 No, no, that's great.

NOTE Confidence: 0.5226583

00:26:29.520 --> 00:26:30.010 Guys.

NOTE Confidence: 0.5839956

00:26:32.450 --> 00:26:32.770 Top.

NOTE Confidence: 0.780740590666667

00:26:39.740 --> 00:26:41.168 Not this enzyme.

NOTE Confidence: 0.780740590666667

00:26:41.168 --> 00:26:44.024 The next enzyme on the pathways

NOTE Confidence: 0.780740590666667

00:26:44.024 --> 00:26:46.717 coupled to the hydrolysis of ATP?

NOTE Confidence: 0.780740590666667

00:26:46.720 --> 00:26:50.160 Yeah, not, not this particular.

NOTE Confidence: 0.780740590666667

00:26:50.160 --> 00:26:52.636 Not any assistant sufferers.

NOTE Confidence: 0.780740590666667

00:26:52.636 --> 00:26:57.040 They use POP chemistry to dissolve urate.

NOTE Confidence: 0.780740590666667

00:26:57.040 --> 00:26:59.992 And we have done, I have not included

NOTE Confidence: 0.780740590666667

00:26:59.992 --> 00:27:01.953 here extensive kinetic analysis to

NOTE Confidence: 0.780740590666667

00:27:01.953 --> 00:27:05.105 show this is a ping pong mechanism and

NOTE Confidence: 0.780740590666667

00:27:05.105 --> 00:27:07.475 the formation of the personal fide.

NOTE Confidence: 0.780740590666667

00:27:07.480 --> 00:27:10.500 It's a mandatory staff.

NOTE Confidence: 0.780740590666667

00:27:10.500 --> 00:27:12.068 So as you imagine,

NOTE Confidence: 0.780740590666667

00:27:12.068 --> 00:27:14.420 there's a kinetic burst in the

NOTE Confidence: 0.780740590666667

00:27:14.500 --> 00:27:16.860 absence of the Super receptor

NOTE Confidence: 0.780740590666667

00:27:16.860 --> 00:27:19.700 and then this enzyme actually can

NOTE Confidence: 0.780740590666667

00:27:19.700 --> 00:27:22.100 slowly decay to turn over here,

NOTE Confidence: 0.780740590666667

00:27:22.100 --> 00:27:24.128 but the presence of the software

NOTE Confidence: 0.780740590666667

00:27:24.128 --> 00:27:25.933 sapter enhances over 100 fold

NOTE Confidence: 0.780740590666667

00:27:25.933 --> 00:27:27.497 the overall catalytic cycle.

NOTE Confidence: 0.668682785

00:27:34.510 --> 00:27:39.170 Periodic cells. Similar.

NOTE Confidence: 0.668682785

00:27:39.170 --> 00:27:41.290 Yeah, it could excel.

NOTE Confidence: 0.668682785

00:27:41.290 --> 00:27:44.470 So sisting the cell phrase activity,

NOTE Confidence: 0.668682785

00:27:44.470 --> 00:27:47.310 it's confined to the mitochondria,

NOTE Confidence: 0.668682785

00:27:47.310 --> 00:27:48.770 so there's only one gene.

NOTE Confidence: 0.668682785

00:27:48.770 --> 00:27:51.444 And FS1, the activity of this enzyme

NOTE Confidence: 0.668682785

00:27:51.444 --> 00:27:53.950 is confined to the mitochondria.

NOTE Confidence: 0.668682785

00:27:53.950 --> 00:27:54.766 And interestingly,

NOTE Confidence: 0.668682785

00:27:54.766 --> 00:27:57.622 the reactivity of this enzyme is highly

NOTE Confidence: 0.668682785

00:27:57.622 --> 00:28:00.358 dependent on the presence of the sulfur

NOTE Confidence: 0.668682785

00:28:00.358 --> 00:28:01.870 acceptor and modulating proteins.

NOTE Confidence: 0.668682785

00:28:01.870 --> 00:28:04.770 So there's a sulfur mobilization

NOTE Confidence: 0.668682785

00:28:04.770 --> 00:28:07.440 just coupled to iron metabolism.

NOTE Confidence: 0.668682785

00:28:07.440 --> 00:28:09.300 So there's a protein.

NOTE Confidence: 0.668682785

00:28:09.300 --> 00:28:11.200 It's called for taxing the

NOTE Confidence: 0.668682785

00:28:11.200 --> 00:28:12.720 binds to the sustained,

NOTE Confidence: 0.668682785

00:28:12.720 --> 00:28:15.261 the suffrage and the binding of the

NOTE Confidence: 0.668682785

00:28:15.261 --> 00:28:17.855 frataxin to the assisting the surfaces

NOTE Confidence: 0.668682785

00:28:17.855 --> 00:28:20.705 enhances the rate of sulfur transfer.

NOTE Confidence: 0.668682785

00:28:20.710 --> 00:28:24.598 And then what it's new now is that.

NOTE Confidence: 0.668682785

00:28:24.600 --> 00:28:26.160 This reaction is dependent on

NOTE Confidence: 0.668682785

00:28:26.160 --> 00:28:27.720 the SOFA receptor where iron

NOTE Confidence: 0.668682785

00:28:27.778 --> 00:28:29.338 sulfur clusters you're bound.

NOTE Confidence: 0.668682785

00:28:29.340 --> 00:28:31.800 So relevant for pathological behaviors

NOTE Confidence: 0.668682785

00:28:31.800 --> 00:28:34.879 is there's a disease that's called

NOTE Confidence: 0.668682785

00:28:34.879 --> 00:28:37.055 Fredericks ataxia that's associated

NOTE Confidence: 0.668682785

00:28:37.055 --> 00:28:39.775 with mutations in the FRATAXIN

NOTE Confidence: 0.668682785

00:28:39.852 --> 00:28:42.580 gene and that disrupts not only

NOTE Confidence: 0.668682785

00:28:42.580 --> 00:28:45.010 iron sulfur metabolism but also

NOTE Confidence: 0.668682785

00:28:45.094 --> 00:28:47.858 disrupts iron metabolism overall.

NOTE Confidence: 0.668682785

00:28:47.860 --> 00:28:50.020 So mutation for taxing leads to

NOTE Confidence: 0.668682785

00:28:50.020 --> 00:28:51.825 mitochondrial iron overload at the

NOTE Confidence: 0.668682785

00:28:51.825 --> 00:28:53.960 same time you have all the phenotypes.

NOTE Confidence: 0.668682785

00:28:53.960 --> 00:28:55.884 Associated with iron deficiency

NOTE Confidence: 0.668682785

00:28:55.884 --> 00:28:58.289 because you are not channeling

NOTE Confidence: 0.668682785

00:28:58.289 --> 00:29:00.655 the iron to the proper places.

NOTE Confidence: 0.668682785

00:29:00.655 --> 00:29:03.625 Maybe just deviating, but you know,

NOTE Confidence: 0.668682785

00:29:03.630 --> 00:29:05.840 hopefully that answers your question.

NOTE Confidence: 0.668682785

00:29:05.840 --> 00:29:08.620 Yeah, OK.

NOTE Confidence: 0.668682785

00:29:08.620 --> 00:29:11.098 So what it's quite interesting is

NOTE Confidence: 0.668682785

00:29:11.098 --> 00:29:13.268 that those super receptor molecules

NOTE Confidence: 0.668682785

00:29:13.268 --> 00:29:15.060 are quite as specific,

NOTE Confidence: 0.668682785

00:29:15.060 --> 00:29:15.433 right.

NOTE Confidence: 0.668682785

00:29:15.433 --> 00:29:17.671 So you have this protein here

NOTE Confidence: 0.668682785

00:29:17.671 --> 00:29:19.870 stuff view then we have shown

NOTE Confidence: 0.668682785

00:29:19.870 --> 00:29:21.880 that in the zinc bound form,

NOTE Confidence: 0.668682785

00:29:21.880 --> 00:29:23.440 so tightly bound zinc,

NOTE Confidence: 0.668682785

00:29:23.440 --> 00:29:26.329 so the presence of so few enhances

NOTE Confidence: 0.668682785

00:29:26.329 --> 00:29:29.598 the activity of its partners so fast,

NOTE Confidence: 0.668682785

00:29:29.600 --> 00:29:32.928 but so few is not able to display

NOTE Confidence: 0.668682785

00:29:32.928 --> 00:29:35.258 similar behavior to other systems,

NOTE Confidence: 0.668682785

00:29:35.260 --> 00:29:37.320 the surfaces in Basilius as

NOTE Confidence: 0.668682785

00:29:37.320 --> 00:29:38.556 well as orthologs.

NOTE Confidence: 0.668682785

00:29:38.560 --> 00:29:40.842 Listing to sell for race for him

NOTE Confidence: 0.668682785

00:29:40.842 --> 00:29:43.052 to note here those enzymes are

NOTE Confidence: 0.668682785

00:29:43.052 --> 00:29:45.356 extremely similar so the E coli

NOTE Confidence: 0.668682785

00:29:45.356 --> 00:29:47.669 SUV S and Bacillus sub S they

NOTE Confidence: 0.668682785

00:29:47.669 --> 00:29:50.423 are over 60% identity identical,

NOTE Confidence: 0.668682785

00:29:50.423 --> 00:29:54.689 yet they cannot cross react so.

NOTE Confidence: 0.668682785

00:29:54.690 --> 00:29:57.162 And and that's something that it's

NOTE Confidence: 0.668682785

00:29:57.162 --> 00:29:59.288 an important feature of those

NOTE Confidence: 0.668682785

00:29:59.288 --> 00:30:01.278 enzymes to guarantee that the

NOTE Confidence: 0.668682785

00:30:01.278 --> 00:30:03.842 sulfur is channel to the proper

NOTE Confidence: 0.668682785

00:30:03.842 --> 00:30:06.077 pathway that you were recruiting.

NOTE Confidence: 0.668682785

00:30:06.080 --> 00:30:08.260 Umm.

NOTE Confidence: 0.668682785

00:30:08.260 --> 00:30:10.522 So that's not only a specific

NOTE Confidence: 0.668682785

00:30:10.522 --> 00:30:12.030 feature of self fast.

NOTE Confidence: 0.668682785

00:30:12.030 --> 00:30:14.490 So this wire the operating that

NOTE Confidence: 0.668682785

00:30:14.490 --> 00:30:16.618 we we eventually postulated the

NOTE Confidence: 0.668682785

00:30:16.618 --> 00:30:18.703 dead it's involving 2 pyridine

NOTE Confidence: 0.668682785

00:30:18.703 --> 00:30:21.051 has its activity enhanced by the

NOTE Confidence: 0.668682785

00:30:21.051 --> 00:30:23.186 presence of ATP and then we know

NOTE Confidence: 0.668682785

00:30:23.186 --> 00:30:25.440 that the catalytic competent form

NOTE Confidence: 0.668682785

00:30:25.440 --> 00:30:28.863 of 80 of MDMA that's higher delays

NOTE Confidence: 0.668682785

00:30:28.863 --> 00:30:30.958 is the ATP bound form.

NOTE Confidence: 0.668682785

00:30:30.960 --> 00:30:34.533 So the enzyme has to have ATP bound to

NOTE Confidence: 0.668682785

00:30:34.533 --> 00:30:38.517 be able to receive the sulfur and then.

NOTE Confidence: 0.668682785

00:30:38.520 --> 00:30:42.235 Follow the chemical reaction so we

NOTE Confidence: 0.668682785

00:30:42.235 --> 00:30:44.618 know that this happens out again

NOTE Confidence: 0.668682785

00:30:44.618 --> 00:30:47.234 through formation of a personal fight.

NOTE Confidence: 0.668682785

00:30:47.240 --> 00:30:49.292 Intermedia using those labeling

NOTE Confidence: 0.668682785

00:30:49.292 --> 00:30:51.344 so for 35 assays.

NOTE Confidence: 0.834499641333334

00:30:53.890 --> 00:30:55.778 What we also know is that you know

NOTE Confidence: 0.834499641333334

00:30:55.778 --> 00:30:58.161 what we are doing in vitro reactions is

NOTE Confidence: 0.834499641333334

00:30:58.161 --> 00:31:00.186 important to be mindful and critical

NOTE Confidence: 0.834499641333334

00:31:00.186 --> 00:31:02.376 about the reaction conditions and then

NOTE Confidence: 0.834499641333334

00:31:02.376 --> 00:31:04.745 whether those reaction conditions mimic

NOTE Confidence: 0.834499641333334

00:31:04.745 --> 00:31:07.470 physiological conditions in the cell.

NOTE Confidence: 0.834499641333334

00:31:07.470 --> 00:31:09.274 So like I mentioned,

NOTE Confidence: 0.834499641333334

00:31:09.274 --> 00:31:11.980 the field is populated with publications

NOTE Confidence: 0.834499641333334

00:31:12.063 --> 00:31:14.604 that use DT and that provides a

NOTE Confidence: 0.834499641333334

00:31:14.604 --> 00:31:17.099 means to quantify reaction products.

NOTE Confidence: 0.834499641333334

00:31:17.100 --> 00:31:21.510 So DT is none are available in the cell.

NOTE Confidence: 0.834499641333334

00:31:21.510 --> 00:31:23.190 So most cells use glucose.

NOTE Confidence: 0.834499641333334

00:31:23.190 --> 00:31:25.854 I also the activity of those

NOTE Confidence: 0.834499641333334

00:31:25.854 --> 00:31:28.750 enzymes in the presence of mutation.

NOTE Confidence: 0.834499641333334

00:31:28.750 --> 00:31:30.337 It's very distinct,

NOTE Confidence: 0.834499641333334

00:31:30.337 --> 00:31:34.040 yet you can see an enhancement here.

NOTE Confidence: 0.834499641333334

00:31:34.040 --> 00:31:35.328 Tell us uh so.

NOTE Confidence: 0.834499641333334

00:31:35.328 --> 00:31:36.938 But Tillis doesn't use glutathione,

NOTE Confidence: 0.834499641333334

00:31:36.940 --> 00:31:38.440 doesn't make glutathione instead

NOTE Confidence: 0.834499641333334

00:31:38.440 --> 00:31:40.690 uses basically PIOS or have a

NOTE Confidence: 0.834499641333334

00:31:40.759 --> 00:31:42.759 collaborator in my department that

NOTE Confidence: 0.834499641333334

00:31:42.759 --> 00:31:44.759 synthesize facility file for me

NOTE Confidence: 0.834499641333334

00:31:44.760 --> 00:31:47.852 facility always a very poor reduction

NOTE Confidence: 0.834499641333334

00:31:47.852 --> 00:31:50.736 is even inhibits the reaction in DT.

NOTE Confidence: 0.834499641333334

00:31:50.740 --> 00:31:54.085 But pyridoxine is a quite

NOTE Confidence: 0.834499641333334

00:31:54.085 --> 00:31:56.092 effective personified reductase

NOTE Confidence: 0.834499641333334

00:31:56.092 --> 00:32:00.760 and enhances greatly the rate of a

NOTE Confidence: 0.834499641333334

00:32:00.760 --> 00:32:03.320 personified formation and reduction.

NOTE Confidence: 0.834499641333334

00:32:03.320 --> 00:32:06.380 And this is staff, but not at this is staff.

NOTE Confidence: 0.834499641333334

00:32:06.380 --> 00:32:08.168 So that's what we think it's

NOTE Confidence: 0.834499641333334

00:32:08.168 --> 00:32:09.360 happening in the cell.

NOTE Confidence: 0.834499641333334

00:32:09.360 --> 00:32:13.257 This is not a unique feature of wire VOC

NOTE Confidence: 0.834499641333334

00:32:13.260 --> 00:32:16.316 reactions done with stuff you and so fast.

NOTE Confidence: 0.834499641333334

00:32:16.320 --> 00:32:19.128 Also show that in the kinetic

NOTE Confidence: 0.834499641333334

00:32:19.128 --> 00:32:22.001 profile here indicates that the rate

NOTE Confidence: 0.834499641333334

00:32:22.001 --> 00:32:24.296 of sulfur mobilization is coupled

NOTE Confidence: 0.834499641333334

00:32:24.296 --> 00:32:27.348 with the rate of sulfur reduction

NOTE Confidence: 0.834499641333334

00:32:27.348 --> 00:32:29.460 on those kinetic schemes.

NOTE Confidence: 0.834499641333334

00:32:29.460 --> 00:32:31.692 So next what we wanted to do it's

NOTE Confidence: 0.834499641333334

00:32:31.692 --> 00:32:33.846 kind of replicate what we're seeing

NOTE Confidence: 0.834499641333334

00:32:33.846 --> 00:32:36.364 in vivo or at least what we are

NOTE Confidence: 0.834499641333334

00:32:36.364 --> 00:32:38.660 postulating in in vivo that can we.

NOTE Confidence: 0.834499641333334

00:32:38.660 --> 00:32:41.150 So we know establish that where

NOTE Confidence: 0.834499641333334

00:32:41.150 --> 00:32:43.617 there was assisting the self rays

NOTE Confidence: 0.834499641333334

00:32:43.617 --> 00:32:46.151 and then imma is a sulfa receptor

NOTE Confidence: 0.834499641333334

00:32:46.151 --> 00:32:48.257 here in the ATP bound form.

NOTE Confidence: 0.834499641333334

00:32:48.260 --> 00:32:51.036 So next we wanted to proceed on the

NOTE Confidence: 0.834499641333334

00:32:51.036 --> 00:32:53.355 pathway and validate it and then in

NOTE Confidence: 0.834499641333334

00:32:53.355 --> 00:32:56.064 May it's in fact a tire regulates that

NOTE Confidence: 0.834499641333334

00:32:56.064 --> 00:32:59.983 can pass on the sulfur to the tier and a.

NOTE Confidence: 0.834499641333334

00:32:59.983 --> 00:33:02.725 So the reaction that is proposed here is

NOTE Confidence: 0.834499641333334

00:33:02.725 --> 00:33:05.069 that in the first step of the reaction,

NOTE Confidence: 0.834499641333334

00:33:05.070 --> 00:33:07.828 so in uridine you typically have oxygen

NOTE Confidence: 0.834499641333334

00:33:07.828 --> 00:33:10.949 here which is not a good leaving group.

NOTE Confidence: 0.834499641333334

00:33:10.950 --> 00:33:13.342 So the first step on the reaction is

NOTE Confidence: 0.834499641333334

00:33:13.342 --> 00:33:15.527 that ventilate the uridine acquisition 2.

NOTE Confidence: 0.834499641333334

00:33:15.530 --> 00:33:18.498 So the sulfur can directly attack leading

NOTE Confidence: 0.834499641333334

00:33:18.498 --> 00:33:21.168 to the formation of a tooth iodine.

NOTE Confidence: 0.834499641333334

00:33:21.170 --> 00:33:24.047 So when we have done those experiments,

NOTE Confidence: 0.834499641333334

00:33:24.050 --> 00:33:28.030 yes we can form 2 pyridine in the test tube.

NOTE Confidence: 0.834499641333334

00:33:28.030 --> 00:33:29.980 So validating that this is.

NOTE Confidence: 0.834499641333334

00:33:29.980 --> 00:33:31.404 As A2 pathway component,

NOTE Confidence: 0.834499641333334

00:33:31.404 --> 00:33:33.540 you don't need all the seven

NOTE Confidence: 0.834499641333334

00:33:33.610 --> 00:33:35.746 components that we're seeing in E

NOTE Confidence: 0.834499641333334

00:33:35.746 --> 00:33:38.293 coli in the pathway is reliant on

NOTE Confidence: 0.834499641333334

00:33:38.293 --> 00:33:40.399 the presence of a reducing agent.

NOTE Confidence: 0.834499641333334

00:33:40.400 --> 00:33:43.577 So we don't know what step of it reducing

NOTE Confidence: 0.834499641333334

00:33:43.577 --> 00:33:45.851 agent it's used but we postulated

NOTE Confidence: 0.834499641333334

00:33:45.851 --> 00:33:48.600 it could be a desktop or desktop.

NOTE Confidence: 0.834499641333334

00:33:48.600 --> 00:33:51.057 So you can have personal fight attacking

NOTE Confidence: 0.834499641333334

00:33:51.057 --> 00:33:53.695 the other related or you can have a

NOTE Confidence: 0.834499641333334

00:33:53.695 --> 00:33:55.595 local reduction of that personal fight

NOTE Confidence: 0.834499641333334

00:33:55.595 --> 00:33:58.100 so you have 3 sulfide attacking that.

NOTE Confidence: 0.834499641333334

00:33:58.100 --> 00:33:58.680 Nevertheless,

NOTE Confidence: 0.834499641333334

00:33:58.680 --> 00:34:03.320 so we know and we can validate that

NOTE Confidence: 0.834499641333334

00:34:03.432 --> 00:34:06.807 we can go from you to 2 or you.

NOTE Confidence: 0.834499641333334

00:34:06.810 --> 00:34:10.290 But I also mentioned to you that this

NOTE Confidence: 0.834499641333334

00:34:10.290 --> 00:34:13.506 modification occurs in conjunction

NOTE Confidence: 0.834499641333334

00:34:13.506 --> 00:34:16.330 with a modification at A5 position.

NOTE Confidence: 0.805597788571429

00:34:16.330 --> 00:34:19.844 So in this case M and M5 as as

NOTE Confidence: 0.805597788571429

00:34:19.844 --> 00:34:22.553 to you and in the literature was

NOTE Confidence: 0.805597788571429

00:34:22.553 --> 00:34:25.002 proposed that those two pathways

NOTE Confidence: 0.805597788571429

00:34:25.002 --> 00:34:27.966 were independent one to one another.

NOTE Confidence: 0.805597788571429

00:34:27.970 --> 00:34:29.925 So you could either titillate

NOTE Confidence: 0.805597788571429

00:34:29.925 --> 00:34:32.313 your routine 1st and then you

NOTE Confidence: 0.805597788571429

00:34:32.313 --> 00:34:34.449 can modify the five position or

NOTE Confidence: 0.805597788571429

00:34:34.449 --> 00:34:36.869 you can modify the five position.

NOTE Confidence: 0.805597788571429

00:34:36.870 --> 00:34:38.750 And then thiolate seconds.

NOTE Confidence: 0.805597788571429

00:34:38.750 --> 00:34:43.590 So what we did here is that we use a T RNA,

NOTE Confidence: 0.805597788571429

00:34:43.590 --> 00:34:47.867 a mixture of tyranny a that contain.

NOTE Confidence: 0.805597788571429

00:34:47.870 --> 00:34:51.356 Unmodified you and partially modify you

NOTE Confidence: 0.805597788571429

00:34:51.356 --> 00:34:54.710 and then we incubating the reaction

NOTE Confidence: 0.805597788571429

00:34:54.710 --> 00:34:57.986 and to our surprise we're not able

NOTE Confidence: 0.805597788571429

00:34:57.986 --> 00:35:01.926 to detect the synthesis of the fully

NOTE Confidence: 0.805597788571429

00:35:01.926 --> 00:35:06.290 modified M&M as to you only to thy urity.

NOTE Confidence: 0.805597788571429

00:35:06.290 --> 00:35:08.980 So that initial result suggested

NOTE Confidence: 0.805597788571429

00:35:08.980 --> 00:35:12.568 that maybe the pathways are non

NOTE Confidence: 0.805597788571429

00:35:12.568 --> 00:35:14.989 independent bifurcated pathways,

NOTE Confidence: 0.805597788571429

00:35:14.990 --> 00:35:17.020 maybe there was some sequentiality

NOTE Confidence: 0.805597788571429

00:35:17.020 --> 00:35:18.238 on that pathway.

NOTE Confidence: 0.805597788571429

00:35:18.240 --> 00:35:21.828 Somehow and then they was only

NOTE Confidence: 0.805597788571429

00:35:21.828 --> 00:35:24.220 recognizing the unmodified view.

NOTE Confidence: 0.805597788571429

00:35:24.220 --> 00:35:26.570 Um, we?

NOTE Confidence: 0.805597788571429

00:35:26.570 --> 00:35:29.060 Took advantage that the availability

NOTE Confidence: 0.805597788571429

00:35:29.060 --> 00:35:32.103 of a crystal structure of MMA

NOTE Confidence: 0.805597788571429

00:35:32.103 --> 00:35:34.476 from an ortholog Organism that

NOTE Confidence: 0.805597788571429

00:35:34.476 --> 00:35:36.500 had the tyranny intermediate,

NOTE Confidence: 0.805597788571429

00:35:36.500 --> 00:35:37.430 adenylate intermediate.

NOTE Confidence: 0.805597788571429

00:35:37.430 --> 00:35:40.685 So this is the position of distillation.

NOTE Confidence: 0.805597788571429

00:35:40.690 --> 00:35:43.298 And so we look at the active side

NOTE Confidence: 0.805597788571429

00:35:43.298 --> 00:35:46.640 and what it kind of kind of became

NOTE Confidence: 0.805597788571429

00:35:46.640 --> 00:35:48.380 a structured justification for

NOTE Confidence: 0.805597788571429

00:35:48.458 --> 00:35:51.230 our results is that are in close

NOTE Confidence: 0.805597788571429

00:35:51.230 --> 00:35:53.878 proximity here for this carbon 5

NOTE Confidence: 0.805597788571429

00:35:53.878 --> 00:35:56.794 there was a concern venue alanine.

NOTE Confidence: 0.805597788571429

00:35:56.800 --> 00:35:57.172 Uh,

NOTE Confidence: 0.805597788571429

00:35:57.172 --> 00:35:59.776 that kind of provide a rationale for

NOTE Confidence: 0.805597788571429

00:35:59.776 --> 00:36:02.032 why this partially modified tier and

NOTE Confidence: 0.805597788571429

00:36:02.032 --> 00:36:05.140 a was not reacting to form 2 pyridine.

NOTE Confidence: 0.805597788571429

00:36:05.140 --> 00:36:08.116 So we thought that the phenylalanine

NOTE Confidence: 0.805597788571429

00:36:08.116 --> 00:36:10.496 was provided an historical hindrance

NOTE Confidence: 0.805597788571429

00:36:10.496 --> 00:36:12.849 not restricting the partially modified

NOTE Confidence: 0.805597788571429

00:36:12.849 --> 00:36:14.754 tyranny from entering the active

NOTE Confidence: 0.805597788571429

00:36:14.754 --> 00:36:16.820 side and getting tired related.

NOTE Confidence: 0.805597788571429

00:36:16.820 --> 00:36:18.590 So kind of the obvious experiment

NOTE Confidence: 0.805597788571429

00:36:18.590 --> 00:36:20.654 is to mutate the enzyme and see

NOTE Confidence: 0.805597788571429

00:36:20.654 --> 00:36:22.558 if we open up that active side.

NOTE Confidence: 0.805597788571429

00:36:22.560 --> 00:36:25.262 Now we can feed a bigger substrate

NOTE Confidence: 0.805597788571429

00:36:25.262 --> 00:36:27.284 and that's exactly what we are

NOTE Confidence: 0.805597788571429

00:36:27.284 --> 00:36:28.148 able to demonstrate.

NOTE Confidence: 0.805597788571429

00:36:28.150 --> 00:36:33.802 Is that mutant, so 55155 in Bacillus,

NOTE Confidence: 0.805597788571429

00:36:33.802 --> 00:36:37.308 154 in E coli, but that's the residue.

NOTE Confidence: 0.805597788571429

00:36:37.308 --> 00:36:40.706 So if you open up now we can

NOTE Confidence: 0.805597788571429

00:36:40.706 --> 00:36:45.040 make M&M so the fully modified.

NOTE Confidence: 0.805597788571429

00:36:45.040 --> 00:36:46.820 Modification,

NOTE Confidence: 0.805597788571429

00:36:46.820 --> 00:36:48.600 right?

NOTE Confidence: 0.805597788571429

00:36:48.600 --> 00:36:51.102 Using this variant form so those

NOTE Confidence: 0.805597788571429

00:36:51.102 --> 00:36:53.592 results kind of postulate that at

NOTE Confidence: 0.805597788571429

00:36:53.592 --> 00:36:55.836 least in the source of challenge

NOTE Confidence: 0.805597788571429

00:36:55.836 --> 00:36:57.928 the pathway for modifications is

NOTE Confidence: 0.805597788571429

00:36:57.928 --> 00:37:00.472 sequential where you till late 1st

NOTE Confidence: 0.805597788571429

00:37:00.472 --> 00:37:04.470 and then you modify it A5 position.

NOTE Confidence: 0.805597788571429

00:37:04.470 --> 00:37:07.263 So you know this work on devices

NOTE Confidence: 0.805597788571429

00:37:07.263 --> 00:37:09.438 was very interesting and and

NOTE Confidence: 0.805597788571429

00:37:09.438 --> 00:37:11.693 established that but still subtilis

NOTE Confidence: 0.805597788571429

00:37:11.693 --> 00:37:14.282 uses a dedicated system to Socrates

NOTE Confidence: 0.805597788571429

00:37:14.282 --> 00:37:16.970 and a SOFA receptor to violate a

NOTE Confidence: 0.805597788571429

00:37:16.970 --> 00:37:20.282 tyranna at the U34 position and

NOTE Confidence: 0.805597788571429

00:37:20.282 --> 00:37:23.979 what we thought here was that the.

NOTE Confidence: 0.805597788571429

00:37:23.980 --> 00:37:26.040 This distinctive reactivity provided

NOTE Confidence: 0.805597788571429

00:37:26.040 --> 00:37:29.130 sort of an opportunity for alternate

NOTE Confidence: 0.805597788571429

00:37:29.200 --> 00:37:31.740 regulation of the pathways involved,

NOTE Confidence: 0.805597788571429

00:37:31.740 --> 00:37:33.420 so for mobilization and

NOTE Confidence: 0.805597788571429

00:37:33.420 --> 00:37:34.984 biosynthesis of thiol factors.

NOTE Confidence: 0.805597788571429

00:37:34.984 --> 00:37:37.156 So by meaning is that you

NOTE Confidence: 0.805597788571429

00:37:37.156 --> 00:37:39.270 have a different system,

NOTE Confidence: 0.805597788571429

00:37:39.270 --> 00:37:41.688 the surfaces here showing in yellow

NOTE Confidence: 0.805597788571429

00:37:41.688 --> 00:37:44.282 and perhaps regulating them at a

NOTE Confidence: 0.805597788571429

00:37:44.282 --> 00:37:46.737 different conditions can kind of

NOTE Confidence: 0.805597788571429

00:37:46.737 --> 00:37:48.824 regulate specific pathways and

NOTE Confidence: 0.805597788571429

00:37:48.824 --> 00:37:51.509 scenario that is completely different.

NOTE Confidence: 0.805597788571429

00:37:51.510 --> 00:37:53.214 Than organisms that only have one

NOTE Confidence: 0.805597788571429

00:37:53.214 --> 00:37:54.700 assisting the self race right?

NOTE Confidence: 0.805597788571429

00:37:54.700 --> 00:37:58.774 Like you have to have a different.

NOTE Confidence: 0.805597788571429

00:37:58.780 --> 00:38:00.470 Mechanism to regulate those different

NOTE Confidence: 0.805597788571429

00:38:00.470 --> 00:38:00.808 pathways.

NOTE Confidence: 0.805597788571429

00:38:00.810 --> 00:38:02.112 So the experiment that we set

NOTE Confidence: 0.805597788571429

00:38:02.112 --> 00:38:02.980 ourselves to do it,

NOTE Confidence: 0.805597788571429

00:38:02.980 --> 00:38:06.655 it's is if those are so sulfur

NOTE Confidence: 0.805597788571429

00:38:06.655 --> 00:38:07.180 containing

NOTE Confidence: 0.866105306470588

00:38:07.180 --> 00:38:10.288 pathways, do we see a differential

NOTE Confidence: 0.866105306470588

00:38:10.288 --> 00:38:13.564 regulation if we grow cells under

NOTE Confidence: 0.866105306470588

00:38:13.564 --> 00:38:16.339 low sulfur versus high sulfur?

NOTE Confidence: 0.866105306470588

00:38:16.340 --> 00:38:19.337 So what we did here was that we cultured

NOTE Confidence: 0.866105306470588

00:38:19.337 --> 00:38:22.372 both type associate solar cells under

NOTE Confidence: 0.866105306470588

00:38:22.372 --> 00:38:24.472 various sulfur concentrations and

NOTE Confidence: 0.866105306470588

00:38:24.472 --> 00:38:27.374 then we analyze the relative levels

NOTE Confidence: 0.866105306470588

00:38:27.374 --> 00:38:29.977 of those proteins using Western blot.

NOTE Confidence: 0.866105306470588

00:38:29.977 --> 00:38:32.740 And So what you can see here is the

NOTE Confidence: 0.866105306470588

00:38:32.820 --> 00:38:35.742 relative abundance of wire video is

NOTE Confidence: 0.866105306470588

00:38:35.742 --> 00:38:38.445 greatly enhanced under sulfur replete

NOTE Confidence: 0.866105306470588

00:38:38.445 --> 00:38:43.468 conditions versus sulfur depleted conditions.

NOTE Confidence: 0.866105306470588

00:38:43.470 --> 00:38:48.273 And the same is true for in the MA.

NOTE Confidence: 0.866105306470588

00:38:48.273 --> 00:38:50.859 So what we have observed that

NOTE Confidence: 0.866105306470588

00:38:50.859 --> 00:38:53.309 both components wire VMA,

NOTE Confidence: 0.866105306470588

00:38:53.310 --> 00:38:55.476 they had decrease abundance on on

NOTE Confidence: 0.866105306470588

00:38:55.476 --> 00:38:56.920 their sulfur limiting condition.

NOTE Confidence: 0.866105306470588

00:38:56.920 --> 00:39:00.286 So if that is the case and then the

NOTE Confidence: 0.866105306470588

00:39:00.286 --> 00:39:03.642 other enzymes are not having much

NOTE Confidence: 0.866105306470588

00:39:03.642 --> 00:39:06.060 expression what we thought is that

NOTE Confidence: 0.866105306470588

00:39:06.060 --> 00:39:07.900 under conditions of Christ sulfur

NOTE Confidence: 0.866105306470588

00:39:07.969 --> 00:39:10.164 concentration then this pathway can

NOTE Confidence: 0.866105306470588

00:39:10.164 --> 00:39:12.359 proceed and you get accumulation

NOTE Confidence: 0.866105306470588

00:39:12.428 --> 00:39:13.848 on the fully modified.

NOTE Confidence: 0.866105306470588

00:39:13.850 --> 00:39:16.565 On tyranny and then under

NOTE Confidence: 0.866105306470588

00:39:16.565 --> 00:39:18.194 sulfur depleted conditions,

NOTE Confidence: 0.866105306470588

00:39:18.200 --> 00:39:20.804 then you don't get as much

NOTE Confidence: 0.866105306470588

00:39:20.804 --> 00:39:23.020 as modified to your RNA.

NOTE Confidence: 0.866105306470588

00:39:23.020 --> 00:39:25.358 And that's exactly what we have observed.

NOTE Confidence: 0.866105306470588

00:39:25.360 --> 00:39:28.360 So from South culture under different

NOTE Confidence: 0.866105306470588

00:39:28.360 --> 00:39:31.534 conditions we can analyze the relative

NOTE Confidence: 0.866105306470588

00:39:31.534 --> 00:39:34.254 levels of those modifications using

NOTE Confidence: 0.866105306470588

00:39:34.260 --> 00:39:37.210 high rates in Ms and we can see a nice

NOTE Confidence: 0.866105306470588

00:39:37.289 --> 00:39:40.643 dose dependent effect on the relative

NOTE Confidence: 0.866105306470588

00:39:40.643 --> 00:39:42.879 accumulation of this modification.

NOTE Confidence: 0.866105306470588

00:39:42.880 --> 00:39:46.592 So put into kind of repeat what I said

NOTE Confidence: 0.866105306470588

00:39:46.592 --> 00:39:49.320 before is this is an essential pathway,

NOTE Confidence: 0.866105306470588

00:39:49.320 --> 00:39:50.828 an essential modification but

NOTE Confidence: 0.866105306470588

00:39:50.828 --> 00:39:53.090 you have a cellular contacts that

NOTE Confidence: 0.866105306470588

00:39:53.153 --> 00:39:55.008 you kind of vary in the degree.

NOTE Confidence: 0.866105306470588

00:39:55.010 --> 00:39:55.982 Of modification,

NOTE Confidence: 0.866105306470588

00:39:55.982 --> 00:39:58.898 and presumably you were making the

NOTE Confidence: 0.866105306470588

00:39:58.898 --> 00:40:01.768 tyranny less optimal for translation.

NOTE Confidence: 0.767856469

00:40:04.850 --> 00:40:07.440 So what we know also from the

NOTE Confidence: 0.767856469

00:40:07.440 --> 00:40:09.096 literature that under conditions

NOTE Confidence: 0.767856469

00:40:09.096 --> 00:40:12.393 that tyranny is hyper modified is not

NOTE Confidence: 0.767856469

00:40:12.393 --> 00:40:14.923 fully functional and an offer often

NOTE Confidence: 0.767856469

00:40:14.923 --> 00:40:17.185 hyper modified T RNA's target for

NOTE Confidence: 0.767856469

00:40:17.190 --> 00:40:20.265 degradation and northern blot analysis

NOTE Confidence: 0.767856469

00:40:20.265 --> 00:40:24.100 showed that tyranny that is carried

NOTE Confidence: 0.767856469

00:40:24.100 --> 00:40:27.420 this modification has reduced levels

NOTE Confidence: 0.767856469

00:40:27.420 --> 00:40:29.940 under sulfur depleted accommodations.

NOTE Confidence: 0.767856469

00:40:29.940 --> 00:40:34.105 By analyzing T RNA we can also

NOTE Confidence: 0.767856469

00:40:34.105 --> 00:40:36.750 interrogate the relative levels of

NOTE Confidence: 0.767856469

00:40:36.750 --> 00:40:39.240 modifications that depend on this thing.

NOTE Confidence: 0.767856469

00:40:39.240 --> 00:40:41.823 The software is not a wire video

NOTE Confidence: 0.767856469

00:40:41.823 --> 00:40:43.368 and modifications that presumably

NOTE Confidence: 0.767856469

00:40:43.368 --> 00:40:45.951 depend on on self assess and known

NOTE Confidence: 0.767856469

00:40:45.951 --> 00:40:48.568 to depend on ebz two other sustained.

NOTE Confidence: 0.767856469

00:40:48.570 --> 00:40:50.622 The software is in this Organism

NOTE Confidence: 0.767856469

00:40:50.622 --> 00:40:52.700 remain steady under those conditions.

NOTE Confidence: 0.752974525555555

00:40:55.070 --> 00:40:56.835 Yeah, because my lab has

NOTE Confidence: 0.752974525555555

00:40:56.835 --> 00:40:58.247 an expertise on iris.

NOTE Confidence: 0.752974525555555

00:40:58.250 --> 00:41:00.602 So for Biogenesis we also test the

NOTE Confidence: 0.752974525555555

00:41:00.602 --> 00:41:02.451 activity of three different iron

NOTE Confidence: 0.752974525555555

00:41:02.451 --> 00:41:04.773 sulfur enzymes to see if those

NOTE Confidence: 0.752974525555555

00:41:04.773 --> 00:41:06.868 conditions are affecting iron super

NOTE Confidence: 0.752974525555555

00:41:06.868 --> 00:41:09.364 metabolism and that remains the same.

NOTE Confidence: 0.752974525555555

00:41:09.370 --> 00:41:11.215 Whereas you know likewise enzymes

NOTE Confidence: 0.752974525555555

00:41:11.215 --> 00:41:13.510 that do not depend on iris

NOTE Confidence: 0.752974525555555

00:41:13.510 --> 00:41:15.808 superclusters also is an out there.

NOTE Confidence: 0.752974525555555

00:41:15.810 --> 00:41:18.883 So if it looks like that sulfur

NOTE Confidence: 0.752974525555555

00:41:18.883 --> 00:41:22.045 availability has a targeted effect on

NOTE Confidence: 0.752974525555555

00:41:22.045 --> 00:41:25.555 modulating the pathway involving wire VO.

NOTE Confidence: 0.752974525555555

00:41:25.560 --> 00:41:29.172 And MDMA and is not really

NOTE Confidence: 0.752974525555555

00:41:29.172 --> 00:41:30.978 disrupting other pathways.

NOTE Confidence: 0.752974525555555

00:41:30.980 --> 00:41:32.420 So, you know,

NOTE Confidence: 0.752974525555555

00:41:32.420 --> 00:41:34.820 in this particular study we

NOTE Confidence: 0.752974525555555

00:41:34.820 --> 00:41:36.879 interrogate sulfur availability and

NOTE Confidence: 0.752974525555555

00:41:36.879 --> 00:41:39.909 then this modification is known to

NOTE Confidence: 0.752974525555555

00:41:39.909 --> 00:41:42.273 be affected by other physiological

NOTE Confidence: 0.752974525555555

00:41:42.273 --> 00:41:46.704 conditions and we are now carrying on.

NOTE Confidence: 0.752974525555555

00:41:46.710 --> 00:41:47.766 Modification, you know,

NOTE Confidence: 0.752974525555555

00:41:47.766 --> 00:41:50.230 analysis of the relative levels on the

NOTE Confidence: 0.752974525555555

00:41:50.296 --> 00:41:52.626 different conditions and testing hypoxia,

NOTE Confidence: 0.752974525555555

00:41:52.630 --> 00:41:53.714 UV radiation,

NOTE Confidence: 0.752974525555555

00:41:53.714 --> 00:41:56.966 heat and cold and interrogating the

NOTE Confidence: 0.752974525555555

00:41:56.966 --> 00:41:59.366 whole effect transcriptome TNA epigen

NOTE Confidence: 0.752974525555555

00:41:59.366 --> 00:42:01.686 script home in Bacillus subtilis.

NOTE Confidence: 0.752974525555555

00:42:01.690 --> 00:42:04.362 We do believe that this is not a

NOTE Confidence: 0.752974525555555

00:42:04.362 --> 00:42:06.449 specific phenomenon to Bacillus subtilis,

NOTE Confidence: 0.752974525555555

00:42:06.450 --> 00:42:08.487 but it's also observed in other types

NOTE Confidence: 0.752974525555555

00:42:08.487 --> 00:42:10.260 of bacteria and we have preliminary

NOTE Confidence: 0.752974525555555

00:42:10.260 --> 00:42:12.610 data to show that and it's also known,

NOTE Confidence: 0.752974525555555

00:42:12.610 --> 00:42:16.588 well documented for different types of.

NOTE Confidence: 0.752974525555555

00:42:16.590 --> 00:42:18.726 Product sales and mammals that you

NOTE Confidence: 0.752974525555555

00:42:18.726 --> 00:42:21.179 also have some of the equivalent

NOTE Confidence: 0.752974525555555

00:42:21.180 --> 00:42:22.360 cellular responses.

NOTE Confidence: 0.8659738805

00:42:24.410 --> 00:42:26.370 OK. So the so now it's like

NOTE Confidence: 0.8659738805

00:42:26.370 --> 00:42:28.512 the last bit of story that I

NOTE Confidence: 0.8659738805

00:42:28.512 --> 00:42:30.360 want to tell you about this,

NOTE Confidence: 0.8659738805

00:42:30.360 --> 00:42:32.700 our study on why review MMA.

NOTE Confidence: 0.8659738805

00:42:32.700 --> 00:42:35.500 So we know that those

NOTE Confidence: 0.8659738805

00:42:35.500 --> 00:42:37.740 enzymes are very specific.

NOTE Confidence: 0.8659738805

00:42:37.740 --> 00:42:40.105 The results from the biosynthesis

NOTE Confidence: 0.8659738805

00:42:40.105 --> 00:42:42.470 and also sulfur metabolism project

NOTE Confidence: 0.8659738805

00:42:42.543 --> 00:42:44.593 really informed us that other

NOTE Confidence: 0.8659738805

00:42:44.593 --> 00:42:47.068 assisting the sulfur races in this

NOTE Confidence: 0.8659738805

00:42:47.068 --> 00:42:49.156 Organism cannot pick up the job

NOTE Confidence: 0.8659738805

00:42:49.156 --> 00:42:51.793 offer wire VO and rescue those

NOTE Confidence: 0.8659738805

00:42:51.793 --> 00:42:54.448 phenotypes by meaning that wire.

NOTE Confidence: 0.8659738805

00:42:54.450 --> 00:42:56.450 Video is a dedicated sustained

NOTE Confidence: 0.8659738805

00:42:56.450 --> 00:42:59.257 self race to MMA that plays a

NOTE Confidence: 0.8659738805

00:42:59.257 --> 00:43:01.891 role once you tie your routine and

NOTE Confidence: 0.8659738805

00:43:01.891 --> 00:43:04.537 you know stuff asked for instance

NOTE Confidence: 0.8659738805

00:43:04.537 --> 00:43:07.768 cannot be the sulfur source to MMA,

NOTE Confidence: 0.8659738805

00:43:07.770 --> 00:43:09.595 neither all this other system

NOTE Confidence: 0.8659738805

00:43:09.595 --> 00:43:10.690 the soul phrases.

NOTE Confidence: 0.8659738805

00:43:10.690 --> 00:43:13.672 We also have in vivo and in

NOTE Confidence: 0.8659738805

00:43:13.672 --> 00:43:16.518 vitro data to show that the.

NOTE Confidence: 0.8659738805

00:43:16.520 --> 00:43:18.626 The dedicated role,

NOTE Confidence: 0.8659738805

00:43:18.626 --> 00:43:21.756 it's actually mutual because so

NOTE Confidence: 0.8659738805

00:43:21.756 --> 00:43:23.652 few cannot cross react with our

NOTE Confidence: 0.8659738805

00:43:23.652 --> 00:43:25.778 view and so on and so forth.

NOTE Confidence: 0.8659738805

00:43:25.780 --> 00:43:28.706 So we wanted to understand what are

NOTE Confidence: 0.8659738805

00:43:28.706 --> 00:43:31.107 the structure features on those

NOTE Confidence: 0.8659738805

00:43:31.107 --> 00:43:33.777 enzymes that are really regulating

NOTE Confidence: 0.8659738805

00:43:33.777 --> 00:43:35.379 their physiological functions.

NOTE Confidence: 0.8659738805

00:43:35.380 --> 00:43:38.138 So one way to approach that is

NOTE Confidence: 0.8659738805

00:43:38.138 --> 00:43:40.385 actually to cost compare the

NOTE Confidence: 0.8659738805

00:43:40.385 --> 00:43:43.300 closest ortholog to wire view which

NOTE Confidence: 0.8659738805

00:43:43.300 --> 00:43:47.016 is the E coli ISS, so those two.

NOTE Confidence: 0.8659738805

00:43:47.016 --> 00:43:49.362 Proteins there are about 63%

NOTE Confidence: 0.8659738805

00:43:49.362 --> 00:43:51.170 similar to each other,

NOTE Confidence: 0.8659738805

00:43:51.170 --> 00:43:53.330 but yeah they cannot cross

NOTE Confidence: 0.8659738805

00:43:53.330 --> 00:43:54.626 complement in vivo.

NOTE Confidence: 0.8659738805

00:43:54.630 --> 00:43:57.566 So by meaning that if we transform and

NOTE Confidence: 0.8659738805

00:43:57.566 --> 00:44:00.107 express wire view and an E coli cell,

NOTE Confidence: 0.8659738805

00:44:00.110 --> 00:44:03.400 I cannot rescue the phenotype

NOTE Confidence: 0.8659738805

00:44:03.400 --> 00:44:05.374 associated with ISS.

NOTE Confidence: 0.8659738805

00:44:05.380 --> 00:44:07.700 So this was kind of like part of

NOTE Confidence: 0.8659738805

00:44:07.700 --> 00:44:10.787 a a initial work where we can

NOTE Confidence: 0.8659738805

00:44:10.787 --> 00:44:12.723 do those cross complementation

NOTE Confidence: 0.8659738805

00:44:12.723 --> 00:44:14.722 and expression of wires.

NOTE Confidence: 0.8659738805

00:44:14.722 --> 00:44:17.014 The old the vessel assisting the

NOTE Confidence: 0.8659738805

00:44:17.014 --> 00:44:18.908 sofras cannot react cross react

NOTE Confidence: 0.8659738805

00:44:18.908 --> 00:44:21.274 with us A and rescue their pathway.

NOTE Confidence: 0.8659738805

00:44:21.280 --> 00:44:23.961 But if we Co express both vessels

NOTE Confidence: 0.8659738805

00:44:23.961 --> 00:44:27.299 operating in an ISS knockout of equal life,

NOTE Confidence: 0.8659738805

00:44:27.300 --> 00:44:29.252 we can fully rescue.

NOTE Confidence: 0.8659738805

00:44:29.252 --> 00:44:33.299 The same is true for admission in the MA.

NOTE Confidence: 0.8659738805

00:44:33.299 --> 00:44:35.910 We can only rescue if we express.

NOTE Confidence: 0.8659738805

00:44:35.910 --> 00:44:38.560 This pathway.

NOTE Confidence: 0.8659738805

00:44:38.560 --> 00:44:40.036 At the same time,

NOTE Confidence: 0.8659738805

00:44:40.036 --> 00:44:42.837 so that tells us there's a specific

NOTE Confidence: 0.8659738805

00:44:42.837 --> 00:44:46.358 sulfur transfer from wire video to MMA,

NOTE Confidence: 0.8659738805

00:44:46.360 --> 00:44:49.000 and that sulfur transfer event

NOTE Confidence: 0.8659738805

00:44:49.000 --> 00:44:51.659 cannot happen as prevented somehow

NOTE Confidence: 0.8659738805

00:44:51.659 --> 00:44:54.324 from wire reveal to Tuesday

NOTE Confidence: 0.8659738805

00:44:54.324 --> 00:44:57.229 to rescue that ecoli pathway.

NOTE Confidence: 0.8659738805

00:44:57.230 --> 00:45:00.022 So that kind of provide the premise for

NOTE Confidence: 0.8659738805

00:45:00.022 --> 00:45:02.197 a series of biochemical experiments

NOTE Confidence: 0.8659738805

00:45:02.197 --> 00:45:04.993 where we test the cross reactivity

NOTE Confidence: 0.8659738805

00:45:04.993 --> 00:45:07.788 of those enzymes in the test tube.

NOTE Confidence: 0.8659738805

00:45:07.790 --> 00:45:11.465 So again via video enhances the catalytic

NOTE Confidence: 0.8659738805

00:45:11.465 --> 00:45:15.169 activity of its physiological partner,

NOTE Confidence: 0.8659738805

00:45:15.170 --> 00:45:18.362 but it does not react with the ecoli

NOTE Confidence: 0.8659738805

00:45:18.362 --> 00:45:21.038 ortholog and then the ecoli system.

NOTE Confidence: 0.8659738805

00:45:21.040 --> 00:45:23.224 The suffrage can only have its

NOTE Confidence: 0.8659738805

00:45:23.224 --> 00:45:24.680 activity enhanced in presence

NOTE Confidence: 0.8659738805

00:45:24.749 --> 00:45:26.329 of its geological partner,

NOTE Confidence: 0.8659738805

00:45:26.330 --> 00:45:27.033 the.

NOTE Confidence: 0.8659738805

00:45:27.033 --> 00:45:30.548 Why are video doesn't display

NOTE Confidence: 0.8659738805

00:45:30.550 --> 00:45:31.873 that phenomenon so?

NOTE Confidence: 0.8659738805

00:45:31.873 --> 00:45:34.519 We know those enzymes are catalyzing

NOTE Confidence: 0.8659738805

00:45:34.519 --> 00:45:36.446 the same chemical reaction

NOTE Confidence: 0.8659738805

00:45:36.446 --> 00:45:38.796 which is sulfur transfer from

NOTE Confidence: 0.8659738805

00:45:38.796 --> 00:45:41.139 cysteine to a sulfur receptor.

NOTE Confidence: 0.8659738805

00:45:41.140 --> 00:45:44.213 And then we took advantage of a

NOTE Confidence: 0.8659738805

00:45:44.213 --> 00:45:46.456 crystal structure that was available

NOTE Confidence: 0.8659738805

00:45:46.456 --> 00:45:49.410 in of ecoli ICS in complex where

NOTE Confidence: 0.8659738805

00:45:49.410 --> 00:45:52.111 Texas A and we match the residues

NOTE Confidence: 0.8659738805

00:45:52.111 --> 00:45:56.090 that were at this binding interface.

NOTE Confidence: 0.8659738805

00:45:56.090 --> 00:45:58.555 And we postulated that perhaps

NOTE Confidence: 0.8659738805

00:45:58.555 --> 00:46:01.528 the lack of cross reactivity of

NOTE Confidence: 0.8659738805

00:46:01.528 --> 00:46:03.618 the Bacillus assisting the sulfur

NOTE Confidence: 0.8659738805

00:46:03.618 --> 00:46:06.672 ace in E coli was associated with

NOTE Confidence: 0.8659738805

00:46:06.672 --> 00:46:07.968 a now third

NOTE Confidence: 0.67446936

00:46:07.970 --> 00:46:11.160 binding interface.

NOTE Confidence: 0.67446936

00:46:11.160 --> 00:46:13.128 So what we did here is

NOTE Confidence: 0.67446936

00:46:13.128 --> 00:46:14.440 to guide those analysis.

NOTE Confidence: 0.67446936

00:46:14.440 --> 00:46:17.040 We conducted a multi sequence

NOTE Confidence: 0.67446936

00:46:17.040 --> 00:46:20.040 alignment using several sequences of ice.

NOTE Confidence: 0.67446936

00:46:20.040 --> 00:46:21.475 So this is just an example here.

NOTE Confidence: 0.67446936

00:46:21.480 --> 00:46:23.765 But several sequences of organisms

NOTE Confidence: 0.67446936

00:46:23.765 --> 00:46:26.494 that contain ISS like enzymes and

NOTE Confidence: 0.67446936

00:46:26.494 --> 00:46:29.091 use staff as partners and in several

NOTE Confidence: 0.67446936

00:46:29.091 --> 00:46:31.337 organs that contain wire veal like

NOTE Confidence: 0.67446936

00:46:31.337 --> 00:46:33.851 enzymes and use and then MA as

NOTE Confidence: 0.67446936

00:46:33.851 --> 00:46:35.706 sort of an abbreviated pathway.

NOTE Confidence: 0.67446936

00:46:35.710 --> 00:46:37.718 And then we try to map residues that

NOTE Confidence: 0.67446936

00:46:37.718 --> 00:46:39.579 were shared within those groups but

NOTE Confidence: 0.67446936

00:46:39.579 --> 00:46:41.529 there were distinct between those two.

NOTE Confidence: 0.67446936

00:46:41.530 --> 00:46:44.050 Families of assisting the cell for assist.

NOTE Confidence: 0.67446936

00:46:44.050 --> 00:46:46.450 So although they have a high

NOTE Confidence: 0.67446936

00:46:46.450 --> 00:46:47.650 degree of similarity,

NOTE Confidence: 0.67446936

00:46:47.650 --> 00:46:50.080 there were some key differences in.

NOTE Confidence: 0.67446936

00:46:50.080 --> 00:46:52.328 I want to point here on this table.

NOTE Confidence: 0.67446936

00:46:52.330 --> 00:46:56.187 So what do you see is that?

NOTE Confidence: 0.67446936

00:46:56.190 --> 00:46:58.060 And it's very interesting is

NOTE Confidence: 0.67446936

00:46:58.060 --> 00:47:00.282 that some of the residues that

NOTE Confidence: 0.67446936

00:47:00.282 --> 00:47:02.908 are at the binding interface,

NOTE Confidence: 0.67446936

00:47:02.908 --> 00:47:06.973 we thus say for instance glutamate 48

NOTE Confidence: 0.67446936

00:47:06.973 --> 00:47:10.053 and 49 in ecoli had opposite charge

NOTE Confidence: 0.67446936

00:47:10.053 --> 00:47:13.778 in the wire video sequence and that

NOTE Confidence: 0.67446936

00:47:13.780 --> 00:47:16.402 provide the basis for a proposal

NOTE Confidence: 0.67446936

00:47:16.402 --> 00:47:19.200 that those proteins were not cross

NOTE Confidence: 0.67446936

00:47:19.200 --> 00:47:22.098 reacting because they were not having

NOTE Confidence: 0.67446936

00:47:22.098 --> 00:47:25.336 a complementary charge afforded by that.

NOTE Confidence: 0.67446936

00:47:25.336 --> 00:47:25.854 Surface.

NOTE Confidence: 0.67446936

00:47:25.854 --> 00:47:29.480 Also important to note here is that

NOTE Confidence: 0.67446936

00:47:29.577 --> 00:47:33.002 this binding interface between

NOTE Confidence: 0.67446936

00:47:33.002 --> 00:47:37.656 ISIS and Tus 8/6 as I remote.

NOTE Confidence: 0.67446936

00:47:37.656 --> 00:47:40.349 So the active site is here and you

NOTE Confidence: 0.67446936

00:47:40.349 --> 00:47:42.792 have a loop that swings into the

NOTE Confidence: 0.67446936

00:47:42.792 --> 00:47:45.299 active side and donates the sulfur.

NOTE Confidence: 0.67446936

00:47:45.300 --> 00:47:47.295 So the binding interface between

NOTE Confidence: 0.67446936

00:47:47.295 --> 00:47:49.759 the enzyme and the sulfur receptor

NOTE Confidence: 0.67446936

00:47:49.759 --> 00:47:52.153 occurs at remote site and actually

NOTE Confidence: 0.67446936

00:47:52.153 --> 00:47:54.656 at a different sub unit where

NOTE Confidence: 0.67446936

00:47:54.656 --> 00:47:56.304 the catalytic chemistry is.

NOTE Confidence: 0.67446936

00:47:56.310 --> 00:47:57.540 Company,

NOTE Confidence: 0.67446936

00:47:57.540 --> 00:47:58.770 OK.

NOTE Confidence: 0.67446936

00:47:58.770 --> 00:48:00.630 So the obviously experiment that

NOTE Confidence: 0.67446936

00:48:00.630 --> 00:48:03.618 we set up ourselves to do is like

NOTE Confidence: 0.67446936

00:48:03.618 --> 00:48:05.730 construct a library of mutants and

NOTE Confidence: 0.67446936

00:48:05.730 --> 00:48:08.350 trying to take wire video and convert

NOTE Confidence: 0.67446936

00:48:08.350 --> 00:48:11.290 into ISS like by modifying those

NOTE Confidence: 0.67446936

00:48:11.290 --> 00:48:13.533 select residues into residues that

NOTE Confidence: 0.67446936

00:48:13.533 --> 00:48:16.861 are present in ISS and see if we

NOTE Confidence: 0.67446936

00:48:16.861 --> 00:48:19.849 can expand the reactivity of this

NOTE Confidence: 0.67446936

00:48:19.849 --> 00:48:23.939 enzyme towards equalized so for acceptors.

NOTE Confidence: 0.67446936

00:48:23.940 --> 00:48:26.424 So we first passed the reactivity

NOTE Confidence: 0.67446936

00:48:26.424 --> 00:48:28.482 towards the native effectors and

NOTE Confidence: 0.67446936

00:48:28.482 --> 00:48:30.486 you know some of those residues

NOTE Confidence: 0.67446936

00:48:30.486 --> 00:48:32.940 here they lost the ability to

NOTE Confidence: 0.67446936

00:48:32.940 --> 00:48:35.060 engage with the native acceptor,

NOTE Confidence: 0.67446936

00:48:35.060 --> 00:48:37.910 but most importantly.

NOTE Confidence: 0.67446936

00:48:37.910 --> 00:48:40.826 By doing this music Genesis studies

NOTE Confidence: 0.67446936

00:48:40.826 --> 00:48:44.468 we could screen that some of

NOTE Confidence: 0.67446936

00:48:44.468 --> 00:48:49.203 those mutations so 44, so R44E.

NOTE Confidence: 0.67446936

00:48:49.203 --> 00:48:51.756 Why are VOC?

NOTE Confidence: 0.67446936

00:48:51.760 --> 00:48:54.238 The head contain equivalent mutation here.

NOTE Confidence: 0.67446936

00:48:54.240 --> 00:48:59.200 So when we mutated to look like ISS

NOTE Confidence: 0.67446936

00:48:59.200 --> 00:49:03.640 now we can engage in a reaction with

NOTE Confidence: 0.67446936

00:49:03.640 --> 00:49:06.240 pasta and have these activities

NOTE Confidence: 0.67446936

00:49:06.336 --> 00:49:09.732 stimulation to you know over tenfold

NOTE Confidence: 0.67446936

00:49:09.732 --> 00:49:13.130 on the catalytic turnover rate and

NOTE Confidence: 0.67446936

00:49:13.130 --> 00:49:15.735 this is another super receptor.

NOTE Confidence: 0.67446936

00:49:15.740 --> 00:49:18.071 I that we don't have a crystal

NOTE Confidence: 0.67446936

00:49:18.071 --> 00:49:19.700 structure for the complex,

NOTE Confidence: 0.67446936

00:49:19.700 --> 00:49:22.353 but when we mutate 4 residues at

NOTE Confidence: 0.67446936

00:49:22.353 --> 00:49:24.240 that particular binding interface,

NOTE Confidence: 0.67446936

00:49:24.240 --> 00:49:27.810 we observe a high degree of extenuation,

NOTE Confidence: 0.67446936

00:49:27.810 --> 00:49:31.835 so suggesting that we are kind of.

NOTE Confidence: 0.67446936

00:49:31.840 --> 00:49:33.616 Who were somewhat successful

NOTE Confidence: 0.67446936

00:49:33.616 --> 00:49:35.836 in engineering those enzymes to

NOTE Confidence: 0.67446936

00:49:35.836 --> 00:49:39.036 now adopt in a very intentional

NOTE Confidence: 0.67446936

00:49:39.036 --> 00:49:41.684 mariner expanded reactivity towards

NOTE Confidence: 0.67446936

00:49:41.684 --> 00:49:43.060 selected pathways.

NOTE Confidence: 0.67446936

00:49:43.060 --> 00:49:46.616 So to validate some of those findings,

NOTE Confidence: 0.67446936

00:49:46.620 --> 00:49:50.316 what we did here is that we.

NOTE Confidence: 0.67446936

00:49:50.320 --> 00:49:54.296 We wanted to determine whether or not

NOTE Confidence: 0.67446936

00:49:54.296 --> 00:49:57.815 those variant enzymes were able to

NOTE Confidence: 0.67446936

00:49:57.815 --> 00:50:01.689 partake role on ISS pathways in vivo.

NOTE Confidence: 0.67446936

00:50:01.690 --> 00:50:05.980 So to do that work we use a ISS knockout

NOTE Confidence: 0.8321999435

00:50:06.090 --> 00:50:09.438 strain and we know that this

NOTE Confidence: 0.8321999435

00:50:09.438 --> 00:50:12.454 is spraying is affected in its

NOTE Confidence: 0.8321999435

00:50:12.454 --> 00:50:14.806 ability to make four thought errity

NOTE Confidence: 0.8321999435

00:50:14.806 --> 00:50:17.849 in a pathway that depends on ,

NOTE Confidence: 0.8321999435

00:50:17.850 --> 00:50:20.755 and it's also affected in a pathway.

NOTE Confidence: 0.8321999435

00:50:20.760 --> 00:50:24.310 To make 2 thyroxine in a through

NOTE Confidence: 0.8321999435

00:50:24.310 --> 00:50:27.310 through engagement with us a.

NOTE Confidence: 0.8321999435

00:50:27.310 --> 00:50:29.320 When we express the wall

NOTE Confidence: 0.8321999435

00:50:29.320 --> 00:50:30.928 type of stimulus enzyme,

NOTE Confidence: 0.8321999435

00:50:30.930 --> 00:50:33.366 we don't really rescue those pathways,

NOTE Confidence: 0.8321999435

00:50:33.370 --> 00:50:35.716 so this is relative levels to

NOTE Confidence: 0.8321999435

00:50:35.716 --> 00:50:37.870 the wall type equalized strain.

NOTE Confidence: 0.8321999435

00:50:37.870 --> 00:50:40.235 However, when we take the

NOTE Confidence: 0.8321999435

00:50:40.235 --> 00:50:43.840 single point mutation R44E,

NOTE Confidence: 0.8321999435

00:50:43.840 --> 00:50:47.130 what we're able to achieve is fully

NOTE Confidence: 0.8321999435

00:50:47.130 --> 00:50:49.761 recovery of two pyridine pathway

NOTE Confidence: 0.8321999435

00:50:49.761 --> 00:50:53.485 indicating that it took only one single

NOTE Confidence: 0.8321999435

00:50:53.582 --> 00:50:57.397 amino acid substitution to convert via VOA.

NOTE Confidence: 0.8321999435

00:50:57.400 --> 00:51:01.568 Into an ISS like enzyme in the pathway

NOTE Confidence: 0.8321999435

00:51:01.568 --> 00:51:03.430 requiring to say those results are

NOTE Confidence: 0.8321999435

00:51:03.430 --> 00:51:05.419 kind of in agreement with the system,

NOTE Confidence: 0.8321999435

00:51:05.420 --> 00:51:07.625 the self race because that's the mutant

NOTE Confidence: 0.8321999435

00:51:07.625 --> 00:51:10.178 that we could show activity stimulation.

NOTE Confidence: 0.8321999435

00:51:10.180 --> 00:51:12.955 Likewise this wire deal quadruple

NOTE Confidence: 0.8321999435

00:51:12.955 --> 00:51:16.074 mutant here could engage with I,

NOTE Confidence: 0.8321999435

00:51:16.074 --> 00:51:19.203 I and recovery if not even more

NOTE Confidence: 0.8321999435

00:51:19.203 --> 00:51:20.939 accumulation of 4th iritty.

NOTE Confidence: 0.8321999435

00:51:20.940 --> 00:51:23.940 And that's a pathway that depends on thi.

NOTE Confidence: 0.8321999435

00:51:23.940 --> 00:51:25.970 This mutant again was a mutant that

NOTE Confidence: 0.8321999435

00:51:25.970 --> 00:51:28.519 showed a 20 fold activity stimulation.

NOTE Confidence: 0.8321999435

00:51:28.520 --> 00:51:32.838 So we're really pleased with this and

NOTE Confidence: 0.8321999435

00:51:32.838 --> 00:51:35.688 kind of struck by the results that

NOTE Confidence: 0.8321999435

00:51:35.688 --> 00:51:38.397 you know it takes only one change

NOTE Confidence: 0.8321999435

00:51:38.480 --> 00:51:40.958 for for a gain of functionality.

NOTE Confidence: 0.8321999435

00:51:40.960 --> 00:51:45.060 We also look at in terms of

NOTE Confidence: 0.8321999435

00:51:45.060 --> 00:51:45.740 growth phenotypes.

NOTE Confidence: 0.8321999435

00:51:45.740 --> 00:51:49.142 So ISS is involved with so

NOTE Confidence: 0.8321999435

00:51:49.142 --> 00:51:50.843 many cellular processes.

NOTE Confidence: 0.8321999435

00:51:50.850 --> 00:51:53.518 Inactivation of ISS causes

NOTE Confidence: 0.8321999435

00:51:53.518 --> 00:51:56.186 a severe growth phenotype.

NOTE Confidence: 0.8321999435

00:51:56.190 --> 00:51:57.990 If we express the wall type,

NOTE Confidence: 0.8321999435

00:51:57.990 --> 00:51:59.538 it doesn't really help,

NOTE Confidence: 0.8321999435

00:51:59.538 --> 00:52:01.086 it actually makes worse.

NOTE Confidence: 0.8321999435

00:52:01.090 --> 00:52:04.360 But expression of that single

NOTE Confidence: 0.8321999435

00:52:04.360 --> 00:52:06.976 mutant partially recovers ISS.

NOTE Confidence: 0.8321999435

00:52:06.980 --> 00:52:09.055 We didn't observe full recovery

NOTE Confidence: 0.8321999435

00:52:09.055 --> 00:52:12.323 in relation to the wild type and

NOTE Confidence: 0.8321999435

00:52:12.323 --> 00:52:14.555 that's actually expected because

NOTE Confidence: 0.8321999435

00:52:14.555 --> 00:52:17.245 we're selectively recovering one of

NOTE Confidence: 0.8321999435

00:52:17.245 --> 00:52:19.446 the pathways that ICS participate.

NOTE Confidence: 0.8321999435

00:52:19.446 --> 00:52:22.920 So in the end, you know my background,

NOTE Confidence: 0.8321999435

00:52:22.920 --> 00:52:24.460 other pathways involving ISS,

NOTE Confidence: 0.8321999435

00:52:24.460 --> 00:52:27.780 they still depleted and contributing

NOTE Confidence: 0.8321999435

00:52:27.780 --> 00:52:29.344 to growth,

NOTE Confidence: 0.8321999435

00:52:29.344 --> 00:52:34.036 growth rates in this particular Organism.

NOTE Confidence: 0.8321999435

00:52:34.040 --> 00:52:34.382 OK.

NOTE Confidence: 0.8321999435

00:52:34.382 --> 00:52:35.408 So with that,

NOTE Confidence: 0.8321999435

00:52:35.408 --> 00:52:38.320 I don't know how I'm doing with time,

NOTE Confidence: 0.8321999435

00:52:38.320 --> 00:52:40.952 but the main take away points that

NOTE Confidence: 0.8321999435

00:52:40.952 --> 00:52:43.758 I want you to kind of remember

NOTE Confidence: 0.8321999435

00:52:43.760 --> 00:52:46.736 from from this talk is that T RNA

NOTE Confidence: 0.8321999435

00:52:46.736 --> 00:52:48.539 performs multiple roles besides

NOTE Confidence: 0.8321999435

00:52:48.539 --> 00:52:51.473 translation and those roles are really

NOTE Confidence: 0.8321999435

00:52:51.473 --> 00:52:53.920 important that defects on enzymes,

NOTE Confidence: 0.8321999435

00:52:53.920 --> 00:52:56.335 they modify T RNA and like some

NOTE Confidence: 0.8321999435

00:52:56.335 --> 00:52:58.729 some folks in the field they

NOTE Confidence: 0.8321999435

00:52:58.729 --> 00:53:00.437 call riders TNA writers,

NOTE Confidence: 0.8321999435

00:53:00.440 --> 00:53:02.840 they are associated with multiple

NOTE Confidence: 0.8321999435

00:53:02.840 --> 00:53:04.760 pathologies and cellular viability.

NOTE Confidence: 0.8321999435

00:53:04.760 --> 00:53:07.270 That the abundance of those

NOTE Confidence: 0.8321999435

00:53:07.270 --> 00:53:09.278 modifications are impacted by

NOTE Confidence: 0.8321999435

00:53:09.280 --> 00:53:10.716 nutrient availability and then

NOTE Confidence: 0.8321999435

00:53:10.716 --> 00:53:12.870 I showed you the example about

NOTE Confidence: 0.8321999435

00:53:12.930 --> 00:53:15.210 sulfur concentration but also their

NOTE Confidence: 0.8321999435

00:53:15.210 --> 00:53:17.110 environmental factors that fine-tuned

NOTE Confidence: 0.8321999435

00:53:17.110 --> 00:53:19.760 the functionality of transfer RNA.

NOTE Confidence: 0.8321999435

00:53:19.760 --> 00:53:22.440 Then in Bacillus subtilis at

NOTE Confidence: 0.8321999435

00:53:22.440 --> 00:53:24.711 least those modifications they

NOTE Confidence: 0.8321999435

00:53:24.711 --> 00:53:27.596 involve dedicated enzymes and the

NOTE Confidence: 0.8321999435

00:53:27.596 --> 00:53:29.790 interaction between the assisting

NOTE Confidence: 0.8321999435

00:53:29.790 --> 00:53:32.676 the surprises and they are sulfur

NOTE Confidence: 0.8321999435

00:53:32.676 --> 00:53:35.118 receptor partners is a very specific.

NOTE Confidence: 0.8321999435

00:53:35.120 --> 00:53:38.726 Event that directs sulfur to the

NOTE Confidence: 0.8321999435

00:53:38.726 --> 00:53:40.529 pathways they're participating.

NOTE Confidence: 0.8321999435

00:53:40.530 --> 00:53:41.850 And then with that,

NOTE Confidence: 0.8321999435

00:53:41.850 --> 00:53:44.594 I want to thank the people that have

NOTE Confidence: 0.8321999435

00:53:44.594 --> 00:53:47.610 done the work. I have a very young lab.

NOTE Confidence: 0.8321999435

00:53:47.610 --> 00:53:50.368 You may recognize the last name here.

NOTE Confidence: 0.8321999435

00:53:50.370 --> 00:53:53.910 So nick?

NOTE Confidence: 0.8321999435

00:53:53.910 --> 00:53:55.902 It was a member of my lab, he graduated.

NOTE Confidence: 0.8321999435

00:53:55.902 --> 00:53:58.830 But I I'm very thankful for all the

NOTE Confidence: 0.809717455833333

00:53:58.904 --> 00:54:01.156 students that, graduate and

NOTE Confidence: 0.809717455833333

00:54:01.156 --> 00:54:03.568 undergraduate students that and

NOTE Confidence: 0.809717455833333

00:54:03.570 --> 00:54:05.726 are in the lab doing hard work,

NOTE Confidence: 0.809717455833333

00:54:05.730 --> 00:54:08.530 and also my collaborators that.

NOTE Confidence: 0.909748937142857

00:54:10.870 --> 00:54:12.724 Very important for other projects that

NOTE Confidence: 0.909748937142857

00:54:12.724 --> 00:54:14.909 I have not talked to you about it.

NOTE Confidence: 0.909748937142857

00:54:14.910 --> 00:54:17.460 I'm also thankful for the National

NOTE Confidence: 0.909748937142857

00:54:17.460 --> 00:54:20.020 Science Foundation that has been mainly

NOTE Confidence: 0.909748937142857

00:54:20.020 --> 00:54:22.134 funded this this project and other

NOTE Confidence: 0.909748937142857

00:54:22.134 --> 00:54:24.630 projects in my lab since they started

NOTE Confidence: 0.909748937142857

00:54:24.630 --> 00:54:26.310 and then thank you for your attention.

NOTE Confidence: 0.38838714

00:54:31.300 --> 00:54:32.530 It's time for a public question.

NOTE Confidence: 0.4727253

00:54:36.090 --> 00:54:36.840 Chat.

NOTE Confidence: 0.8725853

00:54:42.420 --> 00:54:43.150 Yeah.

NOTE Confidence: 0.733557336

00:54:47.340 --> 00:54:50.010 Oh, I'm sorry. So so

NOTE Confidence: 0.7732843

00:54:50.960 --> 00:54:55.505 how do I close? You know the first point.

NOTE Confidence: 0.7732843

00:54:55.505 --> 00:54:56.772 The modification was carried

NOTE Confidence: 0.7732843

00:54:56.772 --> 00:54:58.340 in the non canonical function.

NOTE Confidence: 0.1721715

00:55:00.760 --> 00:55:01.430 Umm.

NOTE Confidence: 0.692440166

00:55:04.110 --> 00:55:09.008 OK. So let's do that. Uh.

NOTE Confidence: 0.692440166

00:55:09.008 --> 00:55:11.150 There we go. OK. Sorry.

NOTE Confidence: 0.07768679

00:55:13.890 --> 00:55:14.480 Curated.

NOTE Confidence: 0.47206411

00:55:17.250 --> 00:55:20.860 Partner talk. Are the modifications to the

NOTE Confidence: 0.47206411

00:55:20.860 --> 00:55:23.345 modifications of the tyranny that dictate the

NOTE Confidence: 0.660914215714286

00:55:23.360 --> 00:55:25.824 other the other problems like in viral?

NOTE Confidence: 0.6988261

00:55:27.540 --> 00:55:32.430 Yeah. Directs the.

NOTE Confidence: 0.6988261

00:55:32.430 --> 00:55:34.817 So you know that's a really great

NOTE Confidence: 0.6988261

00:55:34.817 --> 00:55:36.732 one because for example tyranny

NOTE Confidence: 0.6988261

00:55:36.732 --> 00:55:39.192 lysine and it's modified form is

NOTE Confidence: 0.6988261

00:55:39.192 --> 00:55:41.970 actually a primer for HIV replication.

NOTE Confidence: 0.6988261

00:55:41.970 --> 00:55:45.048 So that modification is really important.

NOTE Confidence: 0.6988261

00:55:45.050 --> 00:55:47.586 I think the work that I just showed

NOTE Confidence: 0.6988261

00:55:47.586 --> 00:55:49.814 you in its modified form and then the

NOTE Confidence: 0.6988261

00:55:49.814 --> 00:55:51.994 work that I kind of show you here

NOTE Confidence: 0.6988261

00:55:51.994 --> 00:55:54.588 also kind of sides to that because the

NOTE Confidence: 0.6988261

00:55:54.588 --> 00:55:57.048 unmodified form is targeted for degradation.

NOTE Confidence: 0.6988261

00:55:57.050 --> 00:55:59.866 So I think you know for you guys

NOTE Confidence: 0.6988261

00:55:59.866 --> 00:56:02.638 that you know the pathology and.

NOTE Confidence: 0.6988261

00:56:02.640 --> 00:56:04.383 You know, I think there's a great

NOTE Confidence: 0.6988261

00:56:04.383 --> 00:56:06.242 deal of appreciation on, you know,

NOTE Confidence: 0.6988261

00:56:06.242 --> 00:56:09.008 let's run next gene sequencing transcriptome

NOTE Confidence: 0.6988261

00:56:09.008 --> 00:56:12.057 and then getting a proteome analysis.

NOTE Confidence: 0.90287343

00:56:14.180 --> 00:56:15.540 I think would be great.

NOTE Confidence: 0.90287343

00:56:15.540 --> 00:56:17.871 You also have the eppi tyranny transcriptome

NOTE Confidence: 0.90287343

00:56:17.871 --> 00:56:20.819 in some of those disease phenotypes right?

NOTE Confidence: 0.90287343

00:56:20.820 --> 00:56:24.250 Like I bet you will be altered.

NOTE Confidence: 0.90287343

00:56:24.250 --> 00:56:26.162 There are different modifications

NOTE Confidence: 0.90287343

00:56:26.162 --> 00:56:29.572 like cuisine is one that it's highly

NOTE Confidence: 0.90287343

00:56:29.572 --> 00:56:31.887 evolved on nutritional status and

NOTE Confidence: 0.90287343

00:56:31.887 --> 00:56:34.904 in associated with a whole slew

NOTE Confidence: 0.90287343

00:56:34.904 --> 00:56:37.080 of different disease phenotypes.

NOTE Confidence: 0.90287343

00:56:37.080 --> 00:56:44.784 So. How they do so? One way is.

NOTE Confidence: 0.90287343

00:56:44.790 --> 00:56:48.350 Depending on the seller response.

NOTE Confidence: 0.90287343

00:56:48.350 --> 00:56:51.050 T RNA is playing a role

NOTE Confidence: 0.90287343

00:56:51.050 --> 00:56:52.850 because expression of genes,

NOTE Confidence: 0.90287343

00:56:52.850 --> 00:56:54.914 for example stress response.

NOTE Confidence: 0.90287343

00:56:54.914 --> 00:56:58.548 It is known that genes involved in

NOTE Confidence: 0.90287343

00:56:58.548 --> 00:57:01.705 stress response they have a codon bias,

NOTE Confidence: 0.90287343

00:57:01.710 --> 00:57:05.455 so codons that require TNA that is

NOTE Confidence: 0.90287343

00:57:05.455 --> 00:57:08.282 modified are necessary for translation

NOTE Confidence: 0.90287343

00:57:08.282 --> 00:57:12.290 of those of those proteins and evolving

NOTE Confidence: 0.90287343

00:57:12.290 --> 00:57:15.170 in stress response for diabetes,

NOTE Confidence: 0.90287343

00:57:15.170 --> 00:57:18.541 for instance the MS2I6A.

NOTE Confidence: 0.90287343

00:57:18.541 --> 00:57:21.296 What was known is that

NOTE Confidence: 0.90287343

00:57:21.296 --> 00:57:22.949 for insulin translation.

NOTE Confidence: 0.90287343

00:57:22.950 --> 00:57:25.734 You require you have a codon bias towards

NOTE Confidence: 0.90287343

00:57:25.734 --> 00:57:28.807 T RNA that carries that modification.

NOTE Confidence: 0.90287343

00:57:28.810 --> 00:57:31.554 So if you don't have the modification,

NOTE Confidence: 0.90287343

00:57:31.560 --> 00:57:35.130 then you're compromising translation of

NOTE Confidence: 0.90287343

00:57:35.130 --> 00:57:38.210 of the proteins that depend on that.

NOTE Confidence: 0.90287343

00:57:38.210 --> 00:57:40.258 Does that make sense?

NOTE Confidence: 0.90287343

00:57:40.258 --> 00:57:41.480 Yeah, good question.

NOTE Confidence: 0.39195618

00:57:47.920 --> 00:57:50.074 See any of the benefits

NOTE Confidence: 0.39195618

00:57:50.074 --> 00:57:51.958 that you described utilized

NOTE Confidence: 0.39195618

00:57:51.958 --> 00:57:54.338 development for material, yeah.

NOTE Confidence: 0.39195618

00:57:54.338 --> 00:57:56.774 So there there's a good understanding

NOTE Confidence: 0.39195618

00:57:56.774 --> 00:57:59.020 much more on the operatic front.

NOTE Confidence: 0.39195618

00:57:59.020 --> 00:58:00.016 But for a bacteria,

NOTE Confidence: 0.39195618

00:58:00.016 --> 00:58:02.040 I think there has been some attempts,

NOTE Confidence: 0.39195618

00:58:02.040 --> 00:58:04.608 especially for modifications that

NOTE Confidence: 0.39195618

00:58:04.608 --> 00:58:07.818 are essential to target the.

NOTE Confidence: 0.39195618

00:58:07.820 --> 00:58:10.196 To target those writers,

NOTE Confidence: 0.39195618

00:58:10.196 --> 00:58:11.978 like tyranny writers,

NOTE Confidence: 0.39195618

00:58:11.980 --> 00:58:13.790 as a mechanism to hold.

NOTE Confidence: 0.468091815

00:58:15.930 --> 00:58:20.242 So viability but that is

NOTE Confidence: 0.468091815

00:58:20.242 --> 00:58:22.666 still kind of in its infancy.

NOTE Confidence: 0.468091815

00:58:22.670 --> 00:58:24.926 There's a great deal of interest

NOTE Confidence: 0.468091815

00:58:24.926 --> 00:58:27.421 more recent one up maybe targeting

NOTE Confidence: 0.468091815

00:58:27.421 --> 00:58:30.163 the system itself races because they

NOTE Confidence: 0.468091815

00:58:30.163 --> 00:58:32.780 have they are so specific right.

NOTE Confidence: 0.468091815

00:58:32.780 --> 00:58:35.147 So if you can just drop the function of

NOTE Confidence: 0.468091815

00:58:35.147 --> 00:58:37.456 those sustained itself races and that's

NOTE Confidence: 0.468091815

00:58:37.456 --> 00:58:39.951 specific super transfer event then you

NOTE Confidence: 0.468091815

00:58:39.951 --> 00:58:41.727 selectively inhibit those enzymes.

NOTE Confidence: 0.468091815

00:58:41.730 --> 00:58:43.626 So I don't really do drug

NOTE Confidence: 0.468091815

00:58:43.626 --> 00:58:45.540 development you know my research.

NOTE Confidence: 0.468091815

00:58:45.540 --> 00:58:48.606 Like as you can tell is more

NOTE Confidence: 0.468091815

00:58:48.610 --> 00:58:51.020 kind of fundamental basic science

NOTE Confidence: 0.468091815

00:58:51.020 --> 00:58:52.466 understanding biochemical pathways.

NOTE Confidence: 0.468091815

00:58:52.470 --> 00:58:55.536 But hopefully you know they're being

NOTE Confidence: 0.468091815

00:58:55.536 --> 00:58:57.580 interested from pharmaceutical companies

NOTE Confidence: 0.468091815

00:58:57.650 --> 00:58:59.858 on talking about let's trying to

NOTE Confidence: 0.468091815

00:58:59.858 --> 00:59:01.604 find an inhibitor especially liking

NOTE Confidence: 0.468091815

00:59:01.604 --> 00:59:03.823 but still is and other gram positive

NOTE Confidence: 0.468091815

00:59:03.823 --> 00:59:05.671 because you have multiple enzymes and

NOTE Confidence: 0.468091815

00:59:05.671 --> 00:59:07.770 then they have very specific phenotypes.

NOTE Confidence: 0.468091815

00:59:07.770 --> 00:59:10.682 Can we find any inhibitor that binds to

NOTE Confidence: 0.468091815

00:59:10.682 --> 00:59:13.730 like only so fast that is found in Gram

NOTE Confidence: 0.468091815

00:59:13.730 --> 00:59:16.229 positive as a specialized drug development.

NOTE Confidence: 0.468091815

00:59:16.229 --> 00:59:18.794 So antibiotic that targets only

NOTE Confidence: 0.468091815

00:59:18.794 --> 00:59:21.130 grandparent grand positive pathogens.

NOTE Confidence: 0.468091815

00:59:21.130 --> 00:59:21.700 Yeah.

NOTE Confidence: 0.82425005

00:59:26.550 --> 00:59:29.000 Good, OK.