WEBVTT

NOTE duration:"01:04:58"

NOTE recognizability:0.362

NOTE language:en-us

NOTE Confidence: 0.37744993

00:00:00.000 --> 00:00:02.284 OK. Good afternoon, everyone.

NOTE Confidence: 0.37744993

00:00:02.284 --> 00:00:05.108 It's almost 12:30, so we'll get started.

NOTE Confidence: 0.37744993

00:00:05.108 --> 00:00:06.770 It's my great honor to introduce

NOTE Confidence: 0.37744993

00:00:06.829 --> 00:00:09.464 my good friend, Doctor Bo Yi Gan

NOTE Confidence: 0.37744993

00:00:09.464 --> 00:00:11.794 from MD Anderson Cancer Center.

NOTE Confidence: 0.37744993

00:00:11.800 --> 00:00:16.200 Bo Yi currently is Ng and Hannon T

NOTE Confidence: 0.37744993

00:00:16.200 --> 00:00:18.782 Hawkins Distinguished professor of

NOTE Confidence: 0.37744993

00:00:18.782 --> 00:00:22.200 Cancer Research and also so as the

NOTE Confidence: 0.37744993

00:00:22.200 --> 00:00:24.240 director of radiation and cancer

NOTE Confidence: 0.37744993

00:00:24.320 --> 00:00:27.062 metabolism research program at

NOTE Confidence: 0.37744993

00:00:27.062 --> 00:00:29.390 the radiation oncology division.

NOTE Confidence: 0.37744993

00:00:29.390 --> 00:00:33.056 Actually I know boy since high

NOTE Confidence: 0.37744993

00:00:33.056 --> 00:00:35.812 school we we went to the same high

NOTE Confidence: 0.37744993

00:00:35.812 --> 00:00:37.438 school and then we we connected

NOTE Confidence: 0.37744993

00:00:37.438 --> 00:00:39.390 that when we were doing a post doc.

NOTE Confidence: 0.37744993

00:00:39.390 --> 00:00:41.360 I identify the Cancer Institute

NOTE Confidence: 0.37744993

00:00:41.360 --> 00:00:44.652 and where he did his post doc with

NOTE Confidence: 0.37744993

00:00:44.652 --> 00:00:47.942 Ron Dipino's lab and he studied his

NOTE Confidence: 0.37744993

00:00:47.942 --> 00:00:51.106 NAB laboratory in 2011 I I think

NOTE Confidence: 0.37744993

00:00:51.106 --> 00:00:53.560 and then rose through the ranks

NOTE Confidence: 0.37744993

00:00:53.654 --> 00:00:57.930 became full professor in 2021.

NOTE Confidence: 0.37744993

00:00:57.930 --> 00:01:00.410 He has done an auto

NOTE Confidence: 0.32533148

00:01:05.570 --> 00:01:09.656 very nice work on cancer metabolism

NOTE Confidence: 0.32533148

00:01:09.656 --> 00:01:13.005 and cell deaths specifically for

NOTE Confidence: 0.32533148

00:01:13.005 --> 00:01:16.102 pertosis and the new cell death

NOTE Confidence: 0.32533148

00:01:16.102 --> 00:01:18.206 mechanism called the disulfidipotosis.

NOTE Confidence: 0.32533148

00:01:18.210 --> 00:01:23.650 It's difficult to pronounce,

NOTE Confidence: 0.32533148

00:01:23.650 --> 00:01:26.267 has published you very well with

NOTE Confidence: 0.32533148

00:01:26.267 --> 00:01:27.809 many papers in Nature and Nature,

NOTE Confidence: 0.32533148

00:01:27.810 --> 00:01:30.914 Cell Biology and I I think he will

NOTE Confidence: 0.32533148

00:01:30.914 --> 00:01:33.850 tell you more about those findings

NOTE Confidence: 0.32533148

00:01:33.850 --> 00:01:37.330 today without further ado for you.

NOTE Confidence: 0.5409583

00:01:43.890 --> 00:01:46.734 So really want to thank you for the for

NOTE Confidence: 0.5409583

00:01:46.734 --> 00:01:49.707 the invitation and kind of introduction

NOTE Confidence: 0.5409583

00:01:49.710 --> 00:01:51.845 and it's really my great pleasure to

NOTE Confidence: 0.5409583

00:01:51.845 --> 00:01:53.828 visit Yale and have the opportunity

NOTE Confidence: 0.5409583

00:01:53.828 --> 00:01:56.173 to you know talk about our research

NOTE Confidence: 0.5409583

00:01:56.235 --> 00:01:58.269 at the pathology and grand rounds.

NOTE Confidence: 0.5409583

00:01:58.270 --> 00:02:01.070 So this so my presentation,

NOTE Confidence: 0.5409583

00:02:01.070 --> 00:02:03.406 so yeah, so this is my title and

NOTE Confidence: 0.5409583

00:02:03.406 --> 00:02:05.669 this is the disclosure slides.

NOTE Confidence: 0.5409583

00:02:05.670 --> 00:02:07.511 But just to give you a little

NOTE Confidence: 0.5409583

00:02:07.511 --> 00:02:08.667 bit introduction about our

NOTE Confidence: 0.5409583

00:02:08.667 --> 00:02:10.227 overview of our research program.

NOTE Confidence: 0.5409583

00:02:10.230 --> 00:02:13.030 So as changes to alluded that we are

NOTE Confidence: 0.5409583

00:02:13.030 --> 00:02:14.780 interested in studying cosmetabolism

NOTE Confidence: 0.5409583

00:02:14.780 --> 00:02:17.930 and the survival cell test and we're

NOTE Confidence: 0.5409583

00:02:17.930 --> 00:02:19.695 interested in the question basically

NOTE Confidence: 0.5409583

00:02:19.695 --> 00:02:22.592 how cells survive or die you know very,

NOTE Confidence: 0.5409583

00:02:22.592 --> 00:02:23.996 very fundamental question and

NOTE Confidence: 0.5409583

00:02:23.996 --> 00:02:25.761 particularly how cell die survival

NOTE Confidence: 0.5409583

00:02:25.761 --> 00:02:27.579 by on the metabolic stress condition

NOTE Confidence: 0.5409583

00:02:27.579 --> 00:02:29.566 and that we are also interested

NOTE Confidence: 0.5409583

00:02:29.566 --> 00:02:31.084 in targeting those metabolic

NOTE Confidence: 0.5409583

00:02:31.084 --> 00:02:33.169 vulnerability for kind of therapy.

NOTE Confidence: 0.5409583

00:02:33.170 --> 00:02:35.890 Now as Ching just mentioned that we are

NOTE Confidence: 0.5409583

00:02:35.890 --> 00:02:38.490 studying two types of cell deaths right now.

NOTE Confidence: 0.5409583

00:02:38.490 --> 00:02:41.654 The first is cell deaths called for

NOTE Confidence: 0.5409583

00:02:41.654 --> 00:02:44.790 pulses and the second form of cell

NOTE Confidence: 0.5409583

00:02:44.790 --> 00:02:46.690 deaths actually was discovered by

NOTE Confidence: 0.5409583

00:02:46.690 --> 00:02:49.222 us recently called disulfide tosis.

NOTE Confidence: 0.5409583

00:02:49.222 --> 00:02:51.790 So I think quite some people

NOTE Confidence: 0.5409583

00:02:51.790 --> 00:02:52.990 ask me how to pronounce it.

NOTE Confidence: 0.5409583

00:02:52.990 --> 00:02:56.270 So basically this the the D here is

NOTE Confidence: 0.5409583

00:02:56.270 --> 00:02:58.935 not pronounced so so yeah so you see

NOTE Confidence: 0.5409583

00:02:58.935 --> 00:03:01.169 the so this D is not pronounced so

NOTE Confidence: 0.5409583

00:03:01.169 --> 00:03:03.083 it's disulfide toss about you know in

NOTE Confidence: 0.5409583

00:03:03.083 --> 00:03:05.127 rich respect I I should make it the

NOTE Confidence: 0.5409583

00:03:05.127 --> 00:03:06.943 name a little bit easier for us to

NOTE Confidence: 0.5409583

00:03:06.950 --> 00:03:09.582 pronounce it but basically I refers to

NOTE Confidence: 0.5409583

00:03:09.582 --> 00:03:12.060 the disulfide stress induced cell deaths.

NOTE Confidence: 0.5409583

00:03:12.060 --> 00:03:13.873 So I'm going to also talk about

NOTE Confidence: 0.5409583

00:03:13.873 --> 00:03:16.282 this new form of cell death in the

NOTE Confidence: 0.5409583

00:03:16.282 --> 00:03:18.337 second part of my presentation.

NOTE Confidence: 0.5409583

00:03:18.340 --> 00:03:19.660 Now for the first part So

NOTE Confidence: 0.5409583

00:03:19.660 --> 00:03:20.540 what is perposes right.

NOTE Confidence: 0.5409583

00:03:20.540 --> 00:03:23.558 So you know think for the either the

NOTE Confidence: 0.5409583

00:03:23.558 --> 00:03:25.292 research fellow here or any clinician

NOTE Confidence: 0.5409583

00:03:25.292 --> 00:03:27.368 here you probably know apoptosis right.

NOTE Confidence: 0.5409583

00:03:27.368 --> 00:03:30.126 So this is the widening most widely

NOTE Confidence: 0.5409583

00:03:30.126 --> 00:03:33.040 studied form of cell death for process

NOTE Confidence: 0.5409583

00:03:33.040 --> 00:03:37.153 was discovered now I think 11 years ago by

NOTE Confidence: 0.5409583

00:03:37.153 --> 00:03:39.418 brand Stockwell at Columbia University.

NOTE Confidence: 0.5409583

00:03:39.420 --> 00:03:41.700 But basically refers to the the

NOTE Confidence: 0.5409583

00:03:41.700 --> 00:03:44.284 cellular states when the cells are

NOTE Confidence: 0.5409583

00:03:44.284 --> 00:03:46.759 overwhelmed with the lipid approximation.

NOTE Confidence: 0.5409583

00:03:46.760 --> 00:03:49.952 So this is 1 type of osteo damage

NOTE Confidence: 0.5409583

00:03:49.952 --> 00:03:51.560 on cellular membranes.

NOTE Confidence: 0.5409583

00:03:51.560 --> 00:03:53.583 Now you can think about this as

NOTE Confidence: 0.5409583

00:03:53.583 --> 00:03:55.460 basically in your cells those

NOTE Confidence: 0.5409583

00:03:55.460 --> 00:03:56.876 normal metabolic activities,

NOTE Confidence: 0.5409583

00:03:56.880 --> 00:03:59.432 they can generate all kinds of you know

NOTE Confidence: 0.5409583

00:03:59.432 --> 00:04:02.142 error on and also one type of fatty

NOTE Confidence: 0.5409583

00:04:02.142 --> 00:04:04.830 acids called polyunsaturated acids.

NOTE Confidence: 0.5409583

00:04:04.830 --> 00:04:07.479 And there are also enormous body

NOTE Confidence: 0.5409583

00:04:07.479 --> 00:04:08.826 activity from mitochondria.

NOTE Confidence: 0.5409583

00:04:08.826 --> 00:04:11.520 So all those normal metabolic activity

NOTE Confidence: 0.5409583

00:04:11.592 --> 00:04:14.189 they can generate leave the proxies okay.

NOTE Confidence: 0.5409583

00:04:14.190 --> 00:04:16.134 So this leave the proxy basically

NOTE Confidence: 0.5409583

00:04:16.134 --> 00:04:18.370 as a byproduct of normal metabolic

NOTE Confidence: 0.5409583

00:04:18.370 --> 00:04:20.110 activities in our cells.

NOTE Confidence: 0.5409583

00:04:20.110 --> 00:04:23.148 But then then we also have this

NOTE Confidence: 0.5409583

00:04:23.148 --> 00:04:25.003 antioxidant defence system which

NOTE Confidence: 0.5409583

00:04:25.003 --> 00:04:27.835 basically are designed to quench to

NOTE Confidence: 0.5409583

00:04:27.835 --> 00:04:30.620 counteract those LEAP deproxides, OK.

NOTE Confidence: 0.5409583

00:04:30.620 --> 00:04:32.970 So basically the ferposis reflects

NOTE Confidence: 0.5409583

00:04:32.970 --> 00:04:36.298 a similar state in which this the

NOTE Confidence: 0.5409583

00:04:36.298 --> 00:04:38.668 metabolic activity which drives LEAP,

NOTE Confidence: 0.5409583

00:04:38.670 --> 00:04:39.167 deprox,

NOTE Confidence: 0.5409583

00:04:39.167 --> 00:04:42.149 the park station far overwhelms those

NOTE Confidence: 0.5409583

00:04:42.149 --> 00:04:44.949 the the antioxidant defense systems.

NOTE Confidence: 0.5409583

00:04:44.950 --> 00:04:47.827 OK, now this occurs when for example,

NOTE Confidence: 0.5409583

00:04:47.830 --> 00:04:50.206 those antioxidant oxidant defense

NOTE Confidence: 0.5409583

00:04:50.206 --> 00:04:51.988 system is inactivity.

NOTE Confidence: 0.5409583

00:04:51.990 --> 00:04:54.055 So I'm going to mention a little

NOTE Confidence: 0.5409583

00:04:54.055 --> 00:04:54.940 bit about what

NOTE Confidence: 0.7253315

00:04:55.010 --> 00:04:57.240 are those our current understanding

NOTE Confidence: 0.7253315

00:04:57.240 --> 00:04:59.470 of this antioxidant defense systems

NOTE Confidence: 0.7253315

00:04:59.540 --> 00:05:01.488 involving for positive defense.

NOTE Confidence: 0.7253315

00:05:01.490 --> 00:05:03.639 So this part is the most important

NOTE Confidence: 0.7253315

00:05:03.639 --> 00:05:05.210 defense system in our cells.

NOTE Confidence: 0.7253315

00:05:05.210 --> 00:05:07.622 This involved this key enzyme called

NOTE Confidence: 0.7253315

00:05:07.622 --> 00:05:10.048 the glute cyan proxies 4 or GPX 4.

NOTE Confidence: 0.7253315

00:05:10.050 --> 00:05:13.106 So this is the enzyme which basically use

NOTE Confidence: 0.7253315

00:05:13.106 --> 00:05:15.967 glute cyan as its cofactor to directly

NOTE Confidence: 0.7253315

00:05:15.967 --> 00:05:18.800 you know quench those lipid peroxides.

NOTE Confidence: 0.7253315

00:05:18.800 --> 00:05:20.640 This also touch on another

NOTE Confidence: 0.7253315

00:05:20.640 --> 00:05:22.770 transport of protein called SRC 711.

NOTE Confidence: 0.7253315

00:05:22.770 --> 00:05:24.720 So this is a cystine transport.

NOTE Confidence: 0.7253315

00:05:24.720 --> 00:05:26.118 As you know we have many,

NOTE Confidence: 0.7253315

00:05:26.120 --> 00:05:27.926 you know our cells contain many

NOTE Confidence: 0.7253315

00:05:27.926 --> 00:05:29.762 amino acid transported can import all

NOTE Confidence: 0.7253315

00:05:29.762 --> 00:05:31.478 kinds of nutrients or amino acid.

NOTE Confidence: 0.7253315

00:05:31.480 --> 00:05:35.010 But this guy is specifically transport cyst.

NOTE Confidence: 0.7253315

00:05:35.010 --> 00:05:38.640 OK, cystine and cystine was important,

NOTE Confidence: 0.7253315

00:05:38.640 --> 00:05:40.596 the cells were reduced to cystine.

NOTE Confidence: 0.7253315

00:05:40.600 --> 00:05:43.440 So I will get get back to this part at

NOTE Confidence: 0.7253315

00:05:43.519 --> 00:05:45.799 the the second part of my presentation.

NOTE Confidence: 0.7253315

00:05:45.799 --> 00:05:49.071 But now just to know that the system

NOTE Confidence: 0.7253315

00:05:49.071 --> 00:05:51.904 provides the key precursor for glucing

NOTE Confidence: 0.7253315

00:05:51.904 --> 00:05:53.788 biosynthesis and therefore provide

NOTE Confidence: 0.7253315

00:05:53.788 --> 00:05:56.657 the key resource for the antioxidant

NOTE Confidence: 0.7253315

00:05:56.657 --> 00:05:58.774 defense system regulated by GPX 4.

NOTE Confidence: 0.7253315

00:05:58.774 --> 00:06:01.466 So this pathway is the most important one

NOTE Confidence: 0.7253315

00:06:01.466 --> 00:06:04.004 and if you inactivity this antioxidant

NOTE Confidence: 0.7253315

00:06:04.004 --> 00:06:06.585 defense system and then that can use

NOTE Confidence: 0.7253315

00:06:06.585 --> 00:06:09.170 to the overwhelming need to peroxation.

NOTE Confidence: 0.7253315

00:06:09.170 --> 00:06:11.088 So the quick and accumulating the cells,

NOTE Confidence: 0.7253315

00:06:11.090 --> 00:06:12.786 they eventually kill the

NOTE Confidence: 0.7253315

00:06:12.786 --> 00:06:14.290 cells through for process.

NOTE Confidence: 0.7253315

00:06:14.290 --> 00:06:16.090 So those compounds are some

NOTE Confidence: 0.7253315

00:06:16.090 --> 00:06:18.169 of them are summarized here.

NOTE Confidence: 0.7253315

00:06:18.170 --> 00:06:20.424 So they are basically those are the

NOTE Confidence: 0.7253315

00:06:20.430 --> 00:06:22.770 so-called for process inducers of fins.

NOTE Confidence: 0.7253315

00:06:22.770 --> 00:06:25.647 So they're actually the inhibitors of those

NOTE Confidence: 0.7253315

00:06:25.650 --> 00:06:28.806 proteins involving anti for process defense.

NOTE Confidence: 0.7253315

00:06:28.810 --> 00:06:31.260 So for example this you're asking why

NOTE Confidence: 0.7253315

00:06:31.260 --> 00:06:33.864 did they use in the research actually

NOTE Confidence: 0.7253315

00:06:33.864 --> 00:06:36.468 inhibits the system transport right And

NOTE Confidence: 0.7253315

00:06:36.468 --> 00:06:39.590 the RSS three are the GPS 4 inhibitors.

NOTE Confidence: 0.7253315

00:06:39.590 --> 00:06:41.403 So those are the compounds which are

NOTE Confidence: 0.7253315

00:06:41.403 --> 00:06:43.507 widely used in the field is for process,

NOTE Confidence: 0.7253315

00:06:43.510 --> 00:06:46.270 inducer to to study for process.

NOTE Confidence: 0.7253315

00:06:46.270 --> 00:06:48.835 Now on the flip side we also have for

NOTE Confidence: 0.7253315

00:06:48.835 --> 00:06:50.895 process inhibitor so Zynca block for

NOTE Confidence: 0.7253315

00:06:50.895 --> 00:06:53.067 process mainly act as the radical

NOTE Confidence: 0.7253315

00:06:53.067 --> 00:06:55.839 trapping and oxidant to broad for process.

NOTE Confidence: 0.7253315

00:06:55.840 --> 00:06:57.952 Now those compounds right yeah for

NOTE Confidence: 0.7253315

00:06:57.952 --> 00:06:59.815 process inducer for process inhibitors

NOTE Confidence: 0.7253315

00:06:59.815 --> 00:07:02.113 the not only provide important you

NOTE Confidence: 0.7253315

00:07:02.113 --> 00:07:04.618 know tools plus to study to understand

NOTE Confidence: 0.7253315

00:07:04.618 --> 00:07:07.201 the the mechanism of process but also

NOTE Confidence: 0.7253315

00:07:07.201 --> 00:07:09.394 really provide potential targets or

NOTE Confidence: 0.7253315

00:07:09.394 --> 00:07:12.090 the the approach or you know tools to

NOTE Confidence: 0.7253315

00:07:12.169 --> 00:07:14.829 to to as a for therapeutic attacking

NOTE Confidence: 0.7253315

00:07:14.829 --> 00:07:17.358 of for processing disease like we

NOTE Confidence: 0.7253315

00:07:17.358 --> 00:07:19.553 talk about for processing disease.

NOTE Confidence: 0.7253315

00:07:19.560 --> 00:07:21.870 So you know particularly for any

NOTE Confidence: 0.7253315

00:07:21.870 --> 00:07:24.490 clinician here there are two you know

NOTE Confidence: 0.7253315

00:07:24.490 --> 00:07:27.610 ways to target for process in disease.

NOTE Confidence: 0.7253315

00:07:27.610 --> 00:07:30.334 So on one side many disease have now

NOTE Confidence: 0.7253315

00:07:30.334 --> 00:07:32.020 have been shown to be associated

NOTE Confidence: 0.7253315

00:07:32.081 --> 00:07:33.489 with excessive for process.

NOTE Confidence: 0.7253315

00:07:33.490 --> 00:07:35.037 So you have too much for process

NOTE Confidence: 0.7253315

00:07:35.037 --> 00:07:36.130 that can cause disease.

NOTE Confidence: 0.7253315

00:07:36.130 --> 00:07:38.321 I think it's a relatively easy to

NOTE Confidence: 0.7253315

00:07:38.321 --> 00:07:40.370 understand this So if you have too

NOTE Confidence: 0.7253315

00:07:40.370 --> 00:07:42.379 much cell that's 'cause that's bad for

NOTE Confidence: 0.7253315

00:07:42.379 --> 00:07:44.638 you know for example for the the the,

NOTE Confidence: 0.7253315

00:07:44.638 --> 00:07:47.046 you know the high cost neuron degenerate

NOTE Confidence: 0.7253315

00:07:47.046 --> 00:07:48.957 disease can cause acute kidney injury

NOTE Confidence: 0.7253315

00:07:48.957 --> 00:07:51.201 and so on is similar profusion induced

NOTE Confidence: 0.7253315

00:07:51.201 --> 00:07:53.546 organ damage and so on so forth.

NOTE Confidence: 0.7253315

00:07:53.550 --> 00:07:55.536 So so that's you know certainly

NOTE Confidence: 0.7253315

00:07:55.536 --> 00:07:56.860 you know a pulses

NOTE Confidence: 0.2917919

00:07:56.927 --> 00:07:58.991 has been implicated in many of

NOTE Confidence: 0.2917919

00:07:58.991 --> 00:08:01.679 this disease and now there is the

NOTE Confidence: 0.2917919

00:08:01.679 --> 00:08:03.744 increase in appreciation for pulses.

NOTE Confidence: 0.2917919

00:08:03.750 --> 00:08:05.618 Excessive for pulses can

NOTE Confidence: 0.2917919

00:08:05.618 --> 00:08:07.486 also 'cause this diseases,

NOTE Confidence: 0.2917919

00:08:07.490 --> 00:08:09.602 So in those for those diseases

NOTE Confidence: 0.2917919

00:08:09.602 --> 00:08:11.813 has had there have been expensive

NOTE Confidence: 0.2917919

00:08:11.813 --> 00:08:14.471 preclinical models to support to use

NOTE Confidence: 0.2917919

00:08:14.471 --> 00:08:16.817 for process inhibitors to block for

NOTE Confidence: 0.2917919

00:08:16.817 --> 00:08:19.022 process and therefore can be used to

NOTE Confidence: 0.2917919

00:08:19.088 --> 00:08:21.208 potentially treat those diseases.

NOTE Confidence: 0.2917919

00:08:21.210 --> 00:08:23.306 Now I'm going to focus on is the

NOTE Confidence: 0.2917919

00:08:23.306 --> 00:08:25.384 other side is the cancer which has

NOTE Confidence: 0.2917919

00:08:25.384 --> 00:08:27.430 also been shown to be associated

NOTE Confidence: 0.2917919

00:08:27.503 --> 00:08:29.179 with impaired for sources.

NOTE Confidence: 0.2917919

00:08:29.180 --> 00:08:31.076 So that means the for process

NOTE Confidence: 0.2917919

00:08:31.076 --> 00:08:32.827 like apoptosis actually is a

NOTE Confidence: 0.2917919

00:08:32.827 --> 00:08:34.099 tumor suppression mechanism.

NOTE Confidence: 0.2917919

00:08:34.100 --> 00:08:35.969 It normally find you to as a

NOTE Confidence: 0.2917919

00:08:35.969 --> 00:08:37.465 tumor suppression as a barrier

NOTE Confidence: 0.2917919

00:08:37.465 --> 00:08:38.737 to for tumor development.

NOTE Confidence: 0.2917919

00:08:38.740 --> 00:08:41.554 So therefore if this for process

NOTE Confidence: 0.2917919

00:08:41.554 --> 00:08:43.996 mechanism is inactivity so that

NOTE Confidence: 0.2917919

00:08:43.996 --> 00:08:46.858 can leads to tumor formation and

NOTE Confidence: 0.2917919

00:08:46.858 --> 00:08:48.672 the consequently many studies

NOTE Confidence: 0.2917919

00:08:48.672 --> 00:08:50.600 including our study I've shown

NOTE Confidence: 0.2917919

00:08:50.600 --> 00:08:52.550 that you use for process inducers.

NOTE Confidence: 0.2917919

00:08:52.550 --> 00:08:54.895 So in this case is to induce

NOTE Confidence: 0.2917919

00:08:54.895 --> 00:08:56.364 vertosis for treating cancers.

NOTE Confidence: 0.2917919

00:08:56.364 --> 00:08:58.632 So that would be the focus

NOTE Confidence: 0.2917919

00:08:58.632 --> 00:09:00.270 of my presentation.

NOTE Confidence: 0.2917919

00:09:00.270 --> 00:09:00.494 Now.

NOTE Confidence: 0.2917919

00:09:00.494 --> 00:09:02.286 So first in order to target the ferposis

NOTE Confidence: 0.2917919

00:09:02.286 --> 00:09:04.263 in cancer we need to 1st understand the

NOTE Confidence: 0.2917919

00:09:04.263 --> 00:09:06.069 what's the rule of ferposis in cancer,

NOTE Confidence: 0.2917919

00:09:06.070 --> 00:09:06.438 right.

NOTE Confidence: 0.2917919

00:09:06.438 --> 00:09:08.646 So the way for process inactivation

NOTE Confidence: 0.2917919

00:09:08.646 --> 00:09:10.865 can use to tumor development

NOTE Confidence: 0.2917919

00:09:10.865 --> 00:09:13.266 progression with the sarsis is

NOTE Confidence: 0.2917919

00:09:13.266 --> 00:09:14.846 through different mechanism as I

NOTE Confidence: 0.2917919

00:09:14.846 --> 00:09:16.695 just alluded at beginning of my

NOTE Confidence: 0.2917919

00:09:16.695 --> 00:09:18.550 presentation in the ferposis kind of as.

NOTE Confidence: 0.2917919

00:09:18.550 --> 00:09:21.376 A it's an imbalance between the

NOTE Confidence: 0.2917919

00:09:21.380 --> 00:09:23.858 error metabolism that you know the

NOTE Confidence: 0.2917919

00:09:23.858 --> 00:09:25.510 metabolic activity just mentioned

NOTE Confidence: 0.2917919

00:09:25.579 --> 00:09:27.739 which drive the peroxation including

NOTE Confidence: 0.2917919

00:09:27.739 --> 00:09:29.899 error metabolism or the metabolism

NOTE Confidence: 0.2917919

00:09:29.900 --> 00:09:32.378 versus the other side you have this

NOTE Confidence: 0.2917919

00:09:32.380 --> 00:09:35.218 the anti for process defence systems.

NOTE Confidence: 0.2917919

00:09:35.220 --> 00:09:36.420 So think about this right.

NOTE Confidence: 0.2917919

00:09:36.420 --> 00:09:39.400 So if you have too much the activities

NOTE Confidence: 0.2917919

00:09:39.400 --> 00:09:41.980 which push the lipid peroxation that

NOTE Confidence: 0.2917919

00:09:41.980 --> 00:09:44.420 can promote for process so cancer,

NOTE Confidence: 0.2917919

00:09:44.420 --> 00:09:46.808 they find a way to inactivate

NOTE Confidence: 0.2917919

00:09:46.810 --> 00:09:48.330 those metabolic activity right,

NOTE Confidence: 0.2917919

00:09:48.330 --> 00:09:50.610 which normally pushed you to proxy.

NOTE Confidence: 0.2917919

00:09:50.610 --> 00:09:52.842 For example they can limit the

NOTE Confidence: 0.2917919

00:09:52.842 --> 00:09:54.904 profile for containing false belief

NOTE Confidence: 0.2917919

00:09:54.904 --> 00:09:57.330 synthesis or prostation or can

NOTE Confidence: 0.2917919

00:09:57.330 --> 00:09:59.338 restrict the bare arrival ability.

NOTE Confidence: 0.2917919

00:09:59.338 --> 00:10:02.025 So those kind serves to inactive the

NOTE Confidence: 0.2917919

00:10:02.025 --> 00:10:04.328 first process and therefore to a few

NOTE Confidence: 0.2917919

00:10:04.330 --> 00:10:06.610 tumor progression and that's classes.

NOTE Confidence: 0.2917919

00:10:06.610 --> 00:10:08.675 But perhaps the most important

NOTE Confidence: 0.2917919

00:10:08.675 --> 00:10:10.890 mechanism is the third part actually

NOTE Confidence: 0.2917919

00:10:10.890 --> 00:10:13.302 by up regulating the the antioxidant,

NOTE Confidence: 0.2917919

00:10:13.302 --> 00:10:16.218 the defence system against per process

NOTE Confidence: 0.2917919

00:10:16.218 --> 00:10:18.722 caust in stressing the antifeptosis

NOTE Confidence: 0.2917919

00:10:18.722 --> 00:10:21.740 mechanism so that can also inactivity

NOTE Confidence: 0.2917919

00:10:21.820 --> 00:10:24.260 pertosis and therefore to promote

NOTE Confidence: 0.2917919

00:10:24.260 --> 00:10:25.982 tumor growth and also metastasis.

NOTE Confidence: 0.2917919

00:10:25.982 --> 00:10:28.597 So the third part is I'm going to

NOTE Confidence: 0.2917919

00:10:28.597 --> 00:10:30.697 mention one example that's from our

NOTE Confidence: 0.2917919

00:10:30.697 --> 00:10:32.349 previous study that's actually how

NOTE Confidence: 0.2917919

00:10:32.349 --> 00:10:34.659 we get into this field is when we

NOTE Confidence: 0.2917919

00:10:34.659 --> 00:10:36.720 at a time we were studying a team of

NOTE Confidence: 0.2917919

00:10:36.787 --> 00:10:38.785 scarcity gene called called BOP 1.

NOTE Confidence: 0.2917919

00:10:38.790 --> 00:10:39.243 So,

NOTE Confidence: 0.2917919

00:10:39.243 --> 00:10:41.902 so actually BOP one is directly

NOTE Confidence: 0.2917919

00:10:41.902 --> 00:10:43.470 to involving IP genetics.

NOTE Confidence: 0.2917919

00:10:43.470 --> 00:10:44.883 So you said,

NOTE Confidence: 0.2917919

00:10:44.883 --> 00:10:48.000 but in this case is to regulate

NOTE Confidence: 0.2917919

00:10:48.000 --> 00:10:49.700 the ubiquitination on histone.

NOTE Confidence: 0.2917919

00:10:49.700 --> 00:10:51.260 As you know histone can be

NOTE Confidence: 0.2917919

00:10:51.260 --> 00:10:52.300 regulated through different post

NOTE Confidence: 0.2917919

00:10:52.351 --> 00:10:54.000 transmission modification, right,

NOTE Confidence: 0.2917919

00:10:54.000 --> 00:10:55.500 such as estimation.

NOTE Confidence: 0.2917919

00:10:55.500 --> 00:10:57.736 But histone ubiquitination can also

NOTE Confidence: 0.2917919

00:10:57.736 --> 00:10:59.796 play important role in genetic

NOTE Confidence: 0.2917919

00:10:59.796 --> 00:11:01.839 regulation of gene transcription.

NOTE Confidence: 0.2917919

00:11:01.840 --> 00:11:05.200 In this case the BOP one is to

NOTE Confidence: 0.2917919

00:11:05.200 --> 00:11:06.680 remove ubiquity on the

NOTE Confidence: 0.2812378

00:11:06.680 --> 00:11:08.444 on the keystone H2A and therefore

NOTE Confidence: 0.2812378

00:11:08.444 --> 00:11:10.440 to modulate the gene transcription.

NOTE Confidence: 0.2812378

00:11:10.440 --> 00:11:12.416 So in this case we we did the

NOTE Confidence: 0.2812378

00:11:12.416 --> 00:11:13.758 genetic the you know RSC,

NOTE Confidence: 0.2812378

00:11:13.760 --> 00:11:16.604 TC analysis and we identified this

NOTE Confidence: 0.2812378

00:11:16.604 --> 00:11:18.880 gene ICS 711 as I just alluded

NOTE Confidence: 0.2812378

00:11:18.880 --> 00:11:20.920 earlier as the system transporter.

NOTE Confidence: 0.2812378

00:11:20.920 --> 00:11:23.953 So this is a key targets of BOP 1.

NOTE Confidence: 0.2812378

00:11:23.960 --> 00:11:26.520 So basically BOP one for him to remove

NOTE Confidence: 0.2812378

00:11:26.520 --> 00:11:28.623 the ubiquity from H2A and therefore

NOTE Confidence: 0.2812378

00:11:28.623 --> 00:11:30.856 surprise the expression of this transporter.

NOTE Confidence: 0.2812378

00:11:30.856 --> 00:11:33.028 Now that is to the decrease

NOTE Confidence: 0.2812378

00:11:33.028 --> 00:11:34.930 the import of the system,

NOTE Confidence: 0.2812378

00:11:34.930 --> 00:11:37.440 decrease bio biosynthesis since sinuses

NOTE Confidence: 0.2812378

00:11:37.440 --> 00:11:40.357 of glucion and therefore the cells

NOTE Confidence: 0.2812378

00:11:40.357 --> 00:11:43.138 the can are more sensitive to for

NOTE Confidence: 0.2812378

00:11:43.138 --> 00:11:45.890 process when there is a wild type AP1.

NOTE Confidence: 0.2812378

00:11:45.890 --> 00:11:47.570 Now POP one is the tumes part of the gene,

NOTE Confidence: 0.2812378

00:11:47.570 --> 00:11:50.279 so it's lost in some of you know kidney

NOTE Confidence: 0.2812378

00:11:50.279 --> 00:11:52.286 cancer and other form of tumors.

NOTE Confidence: 0.2812378

00:11:52.290 --> 00:11:54.558 So in the tumors in those cancers

NOTE Confidence: 0.2812378

00:11:54.558 --> 00:11:56.469 the loss of the POP one.

NOTE Confidence: 0.2812378

00:11:56.470 --> 00:11:58.246 So as she mentioned other people

NOTE Confidence: 0.2812378

00:11:58.246 --> 00:12:00.492 I was assume that PBS three can

NOTE Confidence: 0.2812378

00:12:00.492 --> 00:12:02.152 also regulates this the expression

NOTE Confidence: 0.2812378

00:12:02.152 --> 00:12:03.590 of SSSC development.

NOTE Confidence: 0.2812378

00:12:03.590 --> 00:12:06.230 So loss of BAA point or PBS three

NOTE Confidence: 0.2812378

00:12:06.230 --> 00:12:08.423 that needs to the key repression

NOTE Confidence: 0.2812378

00:12:08.423 --> 00:12:10.470 of this SSC 711 transcription.

NOTE Confidence: 0.2812378

00:12:10.470 --> 00:12:13.060 So that in other in other word is

NOTE Confidence: 0.2812378

00:12:13.060 --> 00:12:14.899 that this expression is now up

NOTE Confidence: 0.2812378

00:12:14.899 --> 00:12:16.819 regulated So those tumor cell with

NOTE Confidence: 0.2812378

00:12:16.819 --> 00:12:18.714 deficiency of BAAA consequently are

NOTE Confidence: 0.2812378

00:12:18.714 --> 00:12:20.960 more resistant for ******* and the

NOTE Confidence: 0.2812378

00:12:20.960 --> 00:12:22.585 consequently is to tumor formation.

NOTE Confidence: 0.2812378

00:12:22.590 --> 00:12:24.536 So that basically is the the study

NOTE Confidence: 0.2812378

00:12:24.536 --> 00:12:26.744 we show that the PowerPoint division

NOTE Confidence: 0.2812378

00:12:26.744 --> 00:12:29.139 promoting the growth and it's the

NOTE Confidence: 0.2812378

00:12:29.139 --> 00:12:30.954 partners through up regulating this

NOTE Confidence: 0.2812378

00:12:30.954 --> 00:12:32.808 transport immediate for process defense.

NOTE Confidence: 0.2812378

00:12:32.810 --> 00:12:34.544 So as you mentioned this was

NOTE Confidence: 0.2812378

00:12:34.544 --> 00:12:36.540 previous work by a previous trainee

NOTE Confidence: 0.2812378

00:12:36.540 --> 00:12:39.170 by Ellie from our lab.

NOTE Confidence: 0.2812378

00:12:39.170 --> 00:12:41.850 So this and odd work are really established

NOTE Confidence: 0.2812378

00:12:41.850 --> 00:12:45.056 for process just like apoptosis as a

NOTE Confidence: 0.2812378

00:12:45.056 --> 00:12:49.078 as a key to suppression mechanism.

NOTE Confidence: 0.2812378

00:12:49.080 --> 00:12:51.120 So now I'm going to talk about the

NOTE Confidence: 0.2812378

00:12:51.120 --> 00:12:52.840 our current understanding how in terms

NOTE Confidence: 0.2812378

00:12:52.840 --> 00:12:55.147 of how we can target this type of

NOTE Confidence: 0.2812378

00:12:55.147 --> 00:12:56.960 cell that's in in kind of therapy.

NOTE Confidence: 0.2812378

00:12:56.960 --> 00:12:59.156 So one way you can do this is to

NOTE Confidence: 0.2812378

00:12:59.160 --> 00:13:01.206 basically some tumors we know they

NOTE Confidence: 0.2812378

00:13:01.206 --> 00:13:03.399 are resistant to to for process.

NOTE Confidence: 0.2812378

00:13:03.400 --> 00:13:06.557 So therefore you can design strategy to

NOTE Confidence: 0.2812378

00:13:06.557 --> 00:13:09.120 resize those resistant tumors to process.

NOTE Confidence: 0.2812378

00:13:09.120 --> 00:13:13.440 So I just use one slide one key data

NOTE Confidence: 0.2812378

00:13:13.547 --> 00:13:15.776 to to to to illustrate this point.

NOTE Confidence: 0.2812378

00:13:15.776 --> 00:13:18.180 So again this was done by Eli.

NOTE Confidence: 0.2812378

00:13:18.180 --> 00:13:20.042 So in this study we showed that

NOTE Confidence: 0.2812378

00:13:20.042 --> 00:13:22.361 M2 or plus we actually can also

NOTE Confidence: 0.2812378

00:13:22.361 --> 00:13:23.817 regulate the for process.

NOTE Confidence: 0.2812378

00:13:23.820 --> 00:13:26.130 So basically the M2 hyperactivation makes

NOTE Confidence: 0.2812378

00:13:26.130 --> 00:13:28.459 them more resistant to for process.

NOTE Confidence: 0.2812378

00:13:28.460 --> 00:13:30.863 So I don't have time to to get into

NOTE Confidence: 0.2812378

00:13:30.863 --> 00:13:33.412 the detail that in terms of mechanism

NOTE Confidence: 0.2812378

00:13:33.412 --> 00:13:36.247 but this has suggest a way to use

NOTE Confidence: 0.2812378

00:13:36.247 --> 00:13:38.173 combine M2 inhibitor with with for

NOTE Confidence: 0.2812378

00:13:38.180 --> 00:13:40.050 process inducers as a combination

NOTE Confidence: 0.2812378

00:13:40.050 --> 00:13:42.655 therapy to recently ties some of those

NOTE Confidence: 0.2812378

00:13:42.655 --> 00:13:44.986 tumors to for process as a therapeutic

NOTE Confidence: 0.2812378

00:13:44.986 --> 00:13:46.749 strategy what kind of treatment.

NOTE Confidence: 0.2812378

00:13:46.750 --> 00:13:49.222 So one example is shown here when we

NOTE Confidence: 0.2812378

00:13:49.222 --> 00:13:51.606 combine this drug called Ike which is

NOTE Confidence: 0.2812378

00:13:51.606 --> 00:13:53.860 a proposes inducer which can block

NOTE Confidence: 0.2812378

00:13:53.860 --> 00:13:55.910 the system and transport activity.

NOTE Confidence: 0.2812378

00:13:55.910 --> 00:13:58.185 When we combine Ike with ample inhibitor,

NOTE Confidence: 0.2812378

00:13:58.190 --> 00:14:00.842 I will see a more you know the

NOTE Confidence: 0.2812378

00:14:00.842 --> 00:14:02.306 combination therapy effects in

NOTE Confidence: 0.2812378

00:14:02.306 --> 00:14:03.770 this PDX models to

NOTE Confidence: 0.33917716

00:14:03.839 --> 00:14:05.228 surprise tumor growth.

NOTE Confidence: 0.33917716

00:14:05.230 --> 00:14:08.010 Now the second point,

NOTE Confidence: 0.33917716

00:14:08.010 --> 00:14:10.310 second strategy is to basically

NOTE Confidence: 0.33917716

00:14:10.310 --> 00:14:12.689 combine those for process inducer

NOTE Confidence: 0.33917716

00:14:12.690 --> 00:14:14.994 with some of the conventional kind

NOTE Confidence: 0.33917716

00:14:14.994 --> 00:14:16.530 of therapy including radiotherapy,

NOTE Confidence: 0.33917716

00:14:16.530 --> 00:14:18.075 chemotherapy and immunotherapy.

NOTE Confidence: 0.33917716

00:14:18.075 --> 00:14:21.165 We now appreciate that those therapies

NOTE Confidence: 0.33917716

00:14:21.165 --> 00:14:24.087 they can also induce for process right.

NOTE Confidence: 0.33917716

00:14:24.090 --> 00:14:26.386 So therefore make sense to combine for

NOTE Confidence: 0.33917716

00:14:26.386 --> 00:14:28.210 process inducers with those therapeutic

NOTE Confidence: 0.33917716

00:14:28.210 --> 00:14:30.544 strategy therefore to further boost the

NOTE Confidence: 0.33917716

00:14:30.544 --> 00:14:32.713 induction for process as a therapeutic

NOTE Confidence: 0.33917716

00:14:32.713 --> 00:14:34.383 strategy in kind of treatment.

NOTE Confidence: 0.33917716

00:14:34.390 --> 00:14:36.455 So again I'm going to use one

NOTE Confidence: 0.33917716

00:14:36.455 --> 00:14:37.990 example from our research.

NOTE Confidence: 0.33917716

00:14:37.990 --> 00:14:40.023 So this was done by Guan

NOTE Confidence: 0.33917716

00:14:40.023 --> 00:14:41.388 a student in the lab.

NOTE Confidence: 0.33917716

00:14:41.390 --> 00:14:43.938 So he discovered that the the airlines

NOTE Confidence: 0.33917716

00:14:43.938 --> 00:14:45.947 radiation right which is used the

NOTE Confidence: 0.33917716

00:14:45.947 --> 00:14:47.942 commonly used to treat cancers as a

NOTE Confidence: 0.33917716

00:14:48.005 --> 00:14:50.189 part of the radiotherapy can induce.

NOTE Confidence: 0.33917716

00:14:50.190 --> 00:14:52.409 So I'm going to use this cartoon

NOTE Confidence: 0.33917716

00:14:52.409 --> 00:14:53.950 to summarize his finding.

NOTE Confidence: 0.33917716

00:14:53.950 --> 00:14:55.774 So he found the airlines radiation

NOTE Confidence: 0.33917716

00:14:55.774 --> 00:14:57.938 can use lipid prox station and this

NOTE Confidence: 0.33917716

00:14:57.938 --> 00:14:59.928 can kill cells through for process.

NOTE Confidence: 0.33917716

00:14:59.928 --> 00:15:02.996 But more importantly is we know that many

NOTE Confidence: 0.33917716

00:15:02.996 --> 00:15:05.636 tumors are resistant to radiotherapy right?

NOTE Confidence: 0.33917716

00:15:05.640 --> 00:15:07.980 So they have radio resistance and the

NOTE Confidence: 0.33917716

00:15:07.980 --> 00:15:09.980 part of the reason why some tumors are

NOTE Confidence: 0.33917716

00:15:10.042 --> 00:15:12.002 resistant to radiotherapy is because

NOTE Confidence: 0.33917716

00:15:12.002 --> 00:15:13.962 they have certain mutations because

NOTE Confidence: 0.33917716

00:15:14.022 --> 00:15:15.817 those tumors are more intrinsically

NOTE Confidence: 0.33917716

00:15:15.817 --> 00:15:18.140 resistant to radiation such as when the,

NOTE Confidence: 0.33917716

00:15:18.140 --> 00:15:20.220 you know in some of the lung cancers

NOTE Confidence: 0.33917716

00:15:20.278 --> 00:15:22.217 they have key point mutation and they

NOTE Confidence: 0.33917716

00:15:22.217 --> 00:15:24.190 will get to this why those tumors

NOTE Confidence: 0.33917716

00:15:24.190 --> 00:15:26.180 will be resistant to for a process.

NOTE Confidence: 0.33917716

00:15:26.180 --> 00:15:28.700 But when the key point is mutated,

NOTE Confidence: 0.33917716

00:15:28.700 --> 00:15:31.339 the lung cancer cells are generally more

NOTE Confidence: 0.33917716

00:15:31.339 --> 00:15:33.670 resistant to to for a process because

NOTE Confidence: 0.33917716

00:15:33.670 --> 00:15:36.328 they have up regulation of some of the

NOTE Confidence: 0.33917716

00:15:36.328 --> 00:15:38.380 genes involving for a process defense,

NOTE Confidence: 0.33917716

00:15:38.380 --> 00:15:38.846 right.

NOTE Confidence: 0.33917716

00:15:38.846 --> 00:15:42.046 This including GPS 4 and SLC 711.

NOTE Confidence: 0.33917716

00:15:42.046 --> 00:15:45.469 So we found that reason why those tumor

NOTE Confidence: 0.33917716

00:15:45.469 --> 00:15:47.803 cells are radio resistant is because

NOTE Confidence: 0.33917716

00:15:47.803 --> 00:15:50.398 they actually are resistant to airline

NOTE Confidence: 0.33917716

00:15:50.398 --> 00:15:52.609 radiation induced the the lipid peroxation.

NOTE Confidence: 0.33917716

00:15:52.609 --> 00:15:54.590 So as showing this cartoon kind of

NOTE Confidence: 0.33917716

00:15:54.648 --> 00:15:56.226 like those soldiers you can see

NOTE Confidence: 0.33917716

00:15:56.226 --> 00:15:57.839 they have the shells there too.

NOTE Confidence: 0.33917716

00:15:57.840 --> 00:16:00.120 So therefore they can defend against

NOTE Confidence: 0.33917716

00:16:00.120 --> 00:16:03.480 this lipid peroxation batch.

NOTE Confidence: 0.33917716

00:16:03.480 --> 00:16:05.586 Now therefore based on this finding

NOTE Confidence: 0.33917716

00:16:05.586 --> 00:16:08.357 we propose to use those for process

NOTE Confidence: 0.33917716

00:16:08.357 --> 00:16:10.570 inducers as a way to basically

NOTE Confidence: 0.33917716

00:16:10.570 --> 00:16:12.350 re sanitize those radio resistant

NOTE Confidence: 0.33917716

00:16:12.415 --> 00:16:13.708 tumors to radiation.

NOTE Confidence: 0.33917716

00:16:13.710 --> 00:16:15.670 So if the effect of those radios,

NOTE Confidence: 0.33917716

00:16:15.670 --> 00:16:17.506 the ferptosis user here it's kind

NOTE Confidence: 0.33917716

00:16:17.506 --> 00:16:19.450 of like you basically disrupted the

NOTE Confidence: 0.33917716

00:16:19.450 --> 00:16:21.746 shells here right used by the soldiers.

NOTE Confidence: 0.33917716

00:16:21.750 --> 00:16:24.228 So then those soldiers now will be

NOTE Confidence: 0.33917716

00:16:24.228 --> 00:16:26.692 directly exposed to the lipid peroxides

NOTE Confidence: 0.33917716

00:16:26.692 --> 00:16:28.907 triggered by the allies radiation.

NOTE Confidence: 0.33917716

00:16:28.910 --> 00:16:32.536 So they're killed by those lipid peroxides.

NOTE Confidence: 0.33917716

00:16:32.540 --> 00:16:34.416 So the so the approach here is

NOTE Confidence: 0.33917716

00:16:34.416 --> 00:16:36.248 basically again is to use proposed

NOTE Confidence: 0.33917716

00:16:36.248 --> 00:16:37.858 inducer as a radio synthetizer.

NOTE Confidence: 0.33917716

00:16:37.860 --> 00:16:40.676 And as one example again we use the

NOTE Confidence: 0.33917716

00:16:40.676 --> 00:16:42.744 keypoint mutants noncat PDX model and

NOTE Confidence: 0.33917716

00:16:42.744 --> 00:16:45.320 here we use a different for process

NOTE Confidence: 0.33917716

00:16:45.320 --> 00:16:47.540 inducer called the sulfasalazine.

NOTE Confidence: 0.33917716

00:16:47.540 --> 00:16:49.692 This is FDA approved the drug and again

NOTE Confidence: 0.33917716

00:16:49.692 --> 00:16:51.646 is the first process inducer which

NOTE Confidence: 0.33917716

00:16:51.646 --> 00:16:54.350 have been shown to block SLS system

NOTE Confidence: 0.33917716

00:16:54.350 --> 00:16:57.380 11 induced immediate the system transport.

NOTE Confidence: 0.33917716

00:16:57.380 --> 00:16:59.812 So as as you can see the subzalasine

NOTE Confidence: 0.33917716

00:16:59.812 --> 00:17:01.931 treatment allow doesn't have much effect

NOTE Confidence: 0.33917716

00:17:01.931 --> 00:17:04.103 but we can dramatic can significantly

NOTE Confidence: 0.33917716

00:17:04.171 --> 00:17:06.216 synthetize the tumors to radiation.

NOTE Confidence: 0.37253195

00:17:06.220 --> 00:17:08.824 So therefore we combine it has more

NOTE Confidence: 0.37253195

00:17:08.824 --> 00:17:12.460 dramatic effect to suppress tumor growth.

NOTE Confidence: 0.37253195

00:17:12.460 --> 00:17:14.683 So this and other studies oh I just want

NOTE Confidence: 0.37253195

00:17:14.683 --> 00:17:17.309 to mention that I want to talk a little bit

NOTE Confidence: 0.37253195

00:17:17.309 --> 00:17:19.640 more about this keep one mechanism here.

NOTE Confidence: 0.37253195

00:17:19.640 --> 00:17:21.984 So key point is some of you might

NOTE Confidence: 0.37253195

00:17:21.984 --> 00:17:23.468 know it's basically is a part of

NOTE Confidence: 0.37253195

00:17:23.468 --> 00:17:24.839 the you looking like it's complex.

NOTE Confidence: 0.37253195

00:17:24.840 --> 00:17:27.444 It's normal function is to degrade a

NOTE Confidence: 0.37253195

00:17:27.444 --> 00:17:29.199 transcription factor called nerve two.

NOTE Confidence: 0.37253195

00:17:29.200 --> 00:17:31.904 OK now nerve two is a master transcription

NOTE Confidence: 0.37253195

00:17:31.904 --> 00:17:33.846 factor involved in antioxidant defense

NOTE Confidence: 0.37253195

00:17:33.846 --> 00:17:36.258 can regulate many chains involved in

NOTE Confidence: 0.37253195

00:17:36.258 --> 00:17:37.900 defending against the antioxidant

NOTE Confidence: 0.37253195

00:17:37.900 --> 00:17:39.865 stress including for a pulses.

NOTE Confidence: 0.37253195

00:17:39.870 --> 00:17:41.604 So for example this assistant transport

NOTE Confidence: 0.37253195

00:17:41.604 --> 00:17:44.266 s s 711 is the one of the transcription

NOTE Confidence: 0.37253195

00:17:44.266 --> 00:17:46.533 target of nerve 2 and involve also

NOTE Confidence: 0.37253195

00:17:46.533 --> 00:17:48.819 other genes involving glute sign of

NOTE Confidence: 0.37253195

00:17:48.819 --> 00:17:51.270 biosynthesis also regulated by nerve two.

NOTE Confidence: 0.37253195

00:17:51.270 --> 00:17:54.619 Now when keep Y is mutated in non

NOTE Confidence: 0.37253195

00:17:54.619 --> 00:17:57.774 casters so that means to the nerve 2

NOTE Confidence: 0.37253195

00:17:57.774 --> 00:18:00.134 stabilization so the upper regulation

NOTE Confidence: 0.37253195

00:18:00.134 --> 00:18:03.018 of SSS 11 and other genes so that

NOTE Confidence: 0.37253195

00:18:03.018 --> 00:18:05.655 kind of promotes the GPS 4 pathway

NOTE Confidence: 0.37253195

00:18:05.655 --> 00:18:07.565 right in for process defense.

NOTE Confidence: 0.37253195

00:18:07.570 --> 00:18:10.209 So that explains why the keep mutant

NOTE Confidence: 0.37253195

00:18:10.209 --> 00:18:12.870 cancers are resistant to for process.

NOTE Confidence: 0.37253195

00:18:12.870 --> 00:18:16.441 Now we further show that this analysis

NOTE Confidence: 0.37253195

00:18:16.441 --> 00:18:19.606 gene involving for process defense.

NOTE Confidence: 0.37253195

00:18:19.610 --> 00:18:22.136 So this was discovered by others,

NOTE Confidence: 0.37253195

00:18:22.140 --> 00:18:23.859 just to put a little bit of context here,

NOTE Confidence: 0.37253195

00:18:23.860 --> 00:18:27.340 initially people believe the GPS 4,

NOTE Confidence: 0.37253195

00:18:27.340 --> 00:18:28.336 you know, a few years ago.

NOTE Confidence: 0.37253195

00:18:28.340 --> 00:18:28.652 Yeah.

NOTE Confidence: 0.37253195

00:18:28.652 --> 00:18:30.824 So the field at the time people

NOTE Confidence: 0.37253195

00:18:30.824 --> 00:18:32.980 believe the GPS four is the only

NOTE Confidence: 0.37253195

00:18:33.053 --> 00:18:34.985 protein or this is the only pass

NOTE Confidence: 0.37253195

00:18:34.985 --> 00:18:36.831 we will be for process defense.

NOTE Confidence: 0.37253195

00:18:36.831 --> 00:18:39.821 But we now know that there are additional

NOTE Confidence: 0.37253195

00:18:39.821 --> 00:18:42.045 so-called process independent mechanism

NOTE Confidence: 0.37253195

00:18:42.045 --> 00:18:44.825 involving for process defense and

NOTE Confidence: 0.37253195

00:18:44.895 --> 00:18:47.445 this FSP one its full name is for

NOTE Confidence: 0.37253195

00:18:47.445 --> 00:18:49.666 process surprise of protein one is

NOTE Confidence: 0.37253195

00:18:49.666 --> 00:18:52.410 one of the major mechanism which is

NOTE Confidence: 0.37253195

00:18:52.410 --> 00:18:54.208 operate independent of GPS pathway

NOTE Confidence: 0.37253195

00:18:54.210 --> 00:18:56.610 to defend against per process.

NOTE Confidence: 0.37253195

00:18:56.610 --> 00:18:58.930 Now mechanistically this is the

NOTE Confidence: 0.37253195

00:18:58.930 --> 00:19:01.898 OXY reductase which acts to reduce

NOTE Confidence: 0.37253195

00:19:01.898 --> 00:19:04.490 this metabolite called COOQ.

NOTE Confidence: 0.37253195

00:19:04.490 --> 00:19:07.325 So another name of COOQ is Ubiquinol.

NOTE Confidence: 0.37253195

00:19:07.330 --> 00:19:07.765 OK.

NOTE Confidence: 0.37253195

00:19:07.765 --> 00:19:10.375 And two is reduced form called

NOTE Confidence: 0.37253195

00:19:10.375 --> 00:19:12.030 ubiquinol or Coq H2.

NOTE Confidence: 0.37253195

00:19:12.030 --> 00:19:13.950 Now I will get back to this nature

NOTE Confidence: 0.37253195

00:19:13.950 --> 00:19:15.950 and this probably is commonly known

NOTE Confidence: 0.37253195

00:19:15.950 --> 00:19:17.910 involving the electron transport chain,

NOTE Confidence: 0.37253195

00:19:17.910 --> 00:19:18.184 right.

NOTE Confidence: 0.37253195

00:19:18.184 --> 00:19:20.766 So if you are you know the read the

NOTE Confidence: 0.37253195

00:19:20.766 --> 00:19:22.950 back hamstring textbook you would know this.

NOTE Confidence: 0.37253195

00:19:22.950 --> 00:19:25.870 But the Coq H2 actually has another role.

NOTE Confidence: 0.37253195

00:19:25.870 --> 00:19:28.530 It actually can also act as a

NOTE Confidence: 0.37253195

00:19:28.530 --> 00:19:29.670 radical trapping antioxidant.

NOTE Confidence: 0.37253195

00:19:29.670 --> 00:19:31.990 It's kind of similar to some of the

NOTE Confidence: 0.37253195

00:19:31.990 --> 00:19:34.025 first process in use of inhibitors

NOTE Confidence: 0.37253195

00:19:34.025 --> 00:19:35.066 I mentioned earlier.

NOTE Confidence: 0.37253195

00:19:35.070 --> 00:19:37.534 So you can directly and also can

NOTE Confidence: 0.37253195

00:19:37.534 --> 00:19:40.576 inhibit to those can block those if the

NOTE Confidence: 0.37253195

00:19:40.576 --> 00:19:43.000 peroxides and thereby surprise for a process.

NOTE Confidence: 0.37253195

00:19:43.000 --> 00:19:44.400 So this would now appreciate.

NOTE Confidence: 0.37253195

00:19:44.400 --> 00:19:46.465 This protein is also important

NOTE Confidence: 0.37253195

00:19:46.465 --> 00:19:48.117 in for pulses suppression.

NOTE Confidence: 0.37253195

00:19:48.120 --> 00:19:51.410 So we found that we also discovered

NOTE Confidence: 0.37253195

00:19:51.410 --> 00:19:53.710 this FSP one is also another

NOTE Confidence: 0.37253195

00:19:53.710 --> 00:19:55.975 transmission target of nerve two and

NOTE Confidence: 0.37253195

00:19:55.975 --> 00:19:57.775 therefore not only under directly

NOTE Confidence: 0.37253195

00:19:57.775 --> 00:20:00.592 to this branch to to in for process

NOTE Confidence: 0.37253195

00:20:00.592 --> 00:20:02.843 defense but also operate the FSP 1.

NOTE Confidence: 0.37253195

00:20:02.843 --> 00:20:04.541 So there are two branches major

NOTE Confidence: 0.37253195

00:20:04.541 --> 00:20:06.140 branches in for process defense

NOTE Confidence: 0.37253195

00:20:06.140 --> 00:20:07.875 are regulated by nerve two.

NOTE Confidence: 0.37253195

00:20:07.880 --> 00:20:10.160 So one of the key data here I just show

NOTE Confidence: 0.33782867

00:20:10.221 --> 00:20:12.204 one data here. So if you with no call

NOTE Confidence: 0.33782867

00:20:12.204 --> 00:20:14.093 keep one in non kind of cell lines

NOTE Confidence: 0.33782867

00:20:14.093 --> 00:20:15.683 and you can see the stabilization

NOTE Confidence: 0.33782867

00:20:15.741 --> 00:20:17.344 of nerve two and this also needs

NOTE Confidence: 0.33782867

00:20:17.344 --> 00:20:19.396 to the upper regulation of FSP

NOTE Confidence: 0.33782867

00:20:19.396 --> 00:20:22.560 one in those non kind of cells.

NOTE Confidence: 0.33782867

00:20:22.560 --> 00:20:24.492 So we're further sure that we

NOTE Confidence: 0.33782867

00:20:24.492 --> 00:20:26.280 can also targeted this pathway

NOTE Confidence: 0.33782867

00:20:26.280 --> 00:20:29.120 for for for radiation therapy.

NOTE Confidence: 0.33782867

00:20:29.120 --> 00:20:31.520 Now so this was done by prime of a student,

NOTE Confidence: 0.33782867

00:20:31.520 --> 00:20:33.560 previous students with one together.

NOTE Confidence: 0.33782867

00:20:33.560 --> 00:20:37.160 So we can use either FSP 1 inhibitors.

NOTE Confidence: 0.33782867

00:20:37.160 --> 00:20:38.324 So as I mentioned,

NOTE Confidence: 0.33782867

00:20:38.324 --> 00:20:41.200 this is the Ox to Ox to reductase.

NOTE Confidence: 0.33782867

00:20:41.200 --> 00:20:42.684 So it's a enzyme,

NOTE Confidence: 0.33782867

00:20:42.684 --> 00:20:45.652 so there's a inhibitor available or we can

NOTE Confidence: 0.33782867

00:20:45.652 --> 00:20:48.004 target off stream the Coq biosynthesis.

NOTE Confidence: 0.33782867

00:20:48.004 --> 00:20:51.627 So example can use 4 CBA to block

NOTE Confidence: 0.33782867

00:20:51.627 --> 00:20:53.816 the Coq biosynthesis and when we

NOTE Confidence: 0.33782867

00:20:53.816 --> 00:20:56.310 either use the FSP inhibitor of four

NOTE Confidence: 0.33782867

00:20:56.310 --> 00:20:58.338 CBA and then we can resynthesize.

NOTE Confidence: 0.33782867

00:20:58.340 --> 00:21:00.188 So here as you can see the green

NOTE Confidence: 0.33782867

00:21:00.188 --> 00:21:02.108 line here you we lock out TP1

NOTE Confidence: 0.33782867

00:21:02.108 --> 00:21:03.508 makes them more radio resistant

NOTE Confidence: 0.33782867

00:21:03.571 --> 00:21:05.515 and that we can resynthetize those

NOTE Confidence: 0.33782867

00:21:05.515 --> 00:21:08.094 radio resistant the cell lines by

NOTE Confidence: 0.33782867

00:21:08.094 --> 00:21:11.279 treating those cells with with

NOTE Confidence: 0.33782867

00:21:11.279 --> 00:21:14.550 either FSPN inhibitor or four CBA.

NOTE Confidence: 0.33782867

00:21:14.550 --> 00:21:16.279 In wave world we can also combine

NOTE Confidence: 0.33782867

00:21:16.279 --> 00:21:18.010 force EA with radiation and we can

NOTE Confidence: 0.33782867

00:21:18.010 --> 00:21:19.470 see a very dramatic suppression

NOTE Confidence: 0.33782867

00:21:19.470 --> 00:21:22.136 of the tumor growth in this keep

NOTE Confidence: 0.33782867

00:21:22.136 --> 00:21:26.310 one mutants non cancer PDX models.

NOTE Confidence: 0.33782867

00:21:26.310 --> 00:21:28.254 So this data really suggests that

NOTE Confidence: 0.33782867

00:21:28.254 --> 00:21:29.903 you know again different approaches

NOTE Confidence: 0.33782867

00:21:29.903 --> 00:21:32.790 we can target a user SSS 711 or

NOTE Confidence: 0.33782867

00:21:32.790 --> 00:21:35.190 targeted different you know components

NOTE Confidence: 0.33782867

00:21:35.190 --> 00:21:39.143 such as FS21 pathway to to to

NOTE Confidence: 0.33782867

00:21:39.143 --> 00:21:40.787 synthesize tumors to radiation.

NOTE Confidence: 0.33782867

00:21:40.790 --> 00:21:43.758 Now this data and others allow us to

NOTE Confidence: 0.33782867

00:21:43.760 --> 00:21:45.944 proposed the strategy you know to

NOTE Confidence: 0.33782867

00:21:45.944 --> 00:21:48.277 form this so-called a crowd resistant

NOTE Confidence: 0.33782867

00:21:48.277 --> 00:21:51.105 to therapy and the error center or

NOTE Confidence: 0.33782867

00:21:51.105 --> 00:21:53.376 articenter you know institution and

NOTE Confidence: 0.33782867

00:21:53.376 --> 00:21:55.626 fortunately this was supported by

NOTE Confidence: 0.33782867

00:21:55.626 --> 00:21:59.240 alternate UV 4 centigrade from ACI.

NOTE Confidence: 0.33782867

00:21:59.240 --> 00:22:01.502 The overarching theme of our center

NOTE Confidence: 0.33782867

00:22:01.502 --> 00:22:04.020 is to basically identify the strategy

NOTE Confidence: 0.33782867

00:22:04.020 --> 00:22:06.780 to induce process as a therapeutic

NOTE Confidence: 0.33782867

00:22:06.780 --> 00:22:08.880 strategy to to overcome a crowd

NOTE Confidence: 0.33782867

00:22:08.880 --> 00:22:11.340 radio resistance as well as other

NOTE Confidence: 0.33782867

00:22:11.340 --> 00:22:12.160 therapy resistance.

NOTE Confidence: 0.33782867

00:22:12.160 --> 00:22:12.626 So,

NOTE Confidence: 0.33782867

00:22:12.626 --> 00:22:15.888 so we're really work on this theme

NOTE Confidence: 0.33782867

00:22:15.888 --> 00:22:18.552 and together with with either other

NOTE Confidence: 0.33782867

00:22:18.552 --> 00:22:21.520 groups in the Indiana and also other

NOTE Confidence: 0.33782867

00:22:21.602 --> 00:22:24.800 PIS from the alternate network to

NOTE Confidence: 0.33782867

00:22:24.800 --> 00:22:28.160 tackle this important question.

NOTE Confidence: 0.33782867

00:22:28.160 --> 00:22:28.614 So OK,

NOTE Confidence: 0.33782867

00:22:28.614 --> 00:22:30.430 so now I'll get back to to the

NOTE Confidence: 0.33782867

00:22:30.496 --> 00:22:31.748 original slides, right.

NOTE Confidence: 0.33782867

00:22:31.748 --> 00:22:33.892 I'm going to you know I was talking

NOTE Confidence: 0.33782867

00:22:33.892 --> 00:22:35.557 about the different strategies to

NOTE Confidence: 0.33782867

00:22:35.557 --> 00:22:37.567 to target it for processing kind

NOTE Confidence: 0.33782867

00:22:37.624 --> 00:22:39.430 of therapy and I just mentioned

NOTE Confidence: 0.33782867

00:22:39.430 --> 00:22:40.938 to combine for process inducer

NOTE Confidence: 0.33782867

00:22:40.938 --> 00:22:41.534 with radiotherapy.

NOTE Confidence: 0.33782867

00:22:41.534 --> 00:22:43.024 I'm not going to talk

NOTE Confidence: 0.33782867

00:22:43.024 --> 00:22:44.400 about the immunotherapy.

NOTE Confidence: 0.33782867

00:22:44.400 --> 00:22:45.600 I think this is again very,

NOTE Confidence: 0.33782867

00:22:45.600 --> 00:22:46.869 very interesting topic.

NOTE Confidence: 0.33782867

00:22:46.869 --> 00:22:49.830 But this was also have been demonstrated

NOTE Confidence: 0.33782867

00:22:49.898 --> 00:22:52.076 by other researchers in the field

NOTE Confidence: 0.33782867

00:22:52.080 --> 00:22:55.146 but they are the third strategy is

NOTE Confidence: 0.33782867

00:22:55.146 --> 00:22:57.876 to really exploit the for process

NOTE Confidence: 0.33782867

00:22:57.876 --> 00:23:00.566 as a vulnerability in cancer.

NOTE Confidence: 0.33782867

00:23:00.570 --> 00:23:02.181 So what I mean here is that it turns

NOTE Confidence: 0.33782867

00:23:02.181 --> 00:23:03.841 out that even though for a process

NOTE Confidence: 0.33782867

00:23:03.841 --> 00:23:05.290 is a tumor suppression mechanism.

NOTE Confidence: 0.33782867

00:23:05.290 --> 00:23:07.020 So therefore many tumors the

NOTE Confidence: 0.33782867

00:23:07.020 --> 00:23:09.100 for example keep the keep mutant

NOTE Confidence: 0.33782867

00:23:09.100 --> 00:23:11.170 cancer or BOP Y mutant cancer,

NOTE Confidence: 0.33782867

00:23:11.170 --> 00:23:14.124 they are more resistant to for process.

NOTE Confidence: 0.33782867

00:23:14.130 --> 00:23:16.266 But in some other cases those

NOTE Confidence: 0.33782867

00:23:16.266 --> 00:23:17.690 tumors actually are vulnerable.

NOTE Confidence: 0.27602023

00:23:17.690 --> 00:23:20.406 They actually are more sensitive to for

NOTE Confidence: 0.27602023

00:23:20.406 --> 00:23:22.500 process inducers compared with these other

NOTE Confidence: 0.27602023

00:23:22.500 --> 00:23:24.930 kind of cell lines or or normal cells.

NOTE Confidence: 0.27602023

00:23:24.930 --> 00:23:27.233 And there are different reasons why some

NOTE Confidence: 0.27602023

00:23:27.233 --> 00:23:29.080 tumors are vulnerable to for process.

NOTE Confidence: 0.27602023

00:23:29.080 --> 00:23:31.546 So for example some tumors because

NOTE Confidence: 0.27602023

00:23:31.546 --> 00:23:33.574 of the metabolic reprogramming the

NOTE Confidence: 0.27602023

00:23:33.574 --> 00:23:36.175 for example they have a high levels

NOTE Confidence: 0.27602023

00:23:36.175 --> 00:23:37.955 of profile polyunsaturated acids,

NOTE Confidence: 0.27602023

00:23:37.960 --> 00:23:39.928 so therefore they are more resistant

NOTE Confidence: 0.27602023

00:23:39.928 --> 00:23:40.912 to fur pulses.

NOTE Confidence: 0.27602023

00:23:40.920 --> 00:23:42.528 They may also have increased in

NOTE Confidence: 0.27602023

00:23:42.528 --> 00:23:44.456 the bare iron levels and you know

NOTE Confidence: 0.27602023

00:23:44.456 --> 00:23:46.064 in those tumors therefore they are

NOTE Confidence: 0.27602023

00:23:46.064 --> 00:23:47.929 also more vulnerable to fur pulses.

NOTE Confidence: 0.27602023

00:23:47.930 --> 00:23:50.114 Another strategy is the some of the

NOTE Confidence: 0.27602023

00:23:50.114 --> 00:23:52.390 mutations such as the mutation in the

NOTE Confidence: 0.27602023

00:23:52.390 --> 00:23:54.790 HIPAA pathway so they can regulate a

NOTE Confidence: 0.27602023

00:23:54.790 --> 00:23:56.490 certain genes involving Fertausis.

NOTE Confidence: 0.27602023

00:23:56.490 --> 00:23:59.314 So when the when those two in the

NOTE Confidence: 0.27602023

00:23:59.314 --> 00:24:01.188 HIPAA pathway was mutated that

NOTE Confidence: 0.27602023

00:24:01.188 --> 00:24:03.970 needs to also the high increase

NOTE Confidence: 0.27602023

00:24:03.970 --> 00:24:07.930 the sensitivity to for a process.

NOTE Confidence: 0.27602023

00:24:07.930 --> 00:24:10.499 But the third strategy here is the

NOTE Confidence: 0.27602023

00:24:10.499 --> 00:24:12.170 imbalances in Fertausis defence.

NOTE Confidence: 0.27602023

00:24:12.170 --> 00:24:14.403 So you can think about the Fera

NOTE Confidence: 0.27602023

00:24:14.403 --> 00:24:16.272 process defense as the the basically

NOTE Confidence: 0.27602023

00:24:16.272 --> 00:24:17.913 there are two arms, right?

NOTE Confidence: 0.27602023

00:24:17.913 --> 00:24:19.578 So Y is GPS 4,

NOTE Confidence: 0.27602023

00:24:19.580 --> 00:24:21.859 so GPS four is the most important guy, right?

NOTE Confidence: 0.27602023

00:24:21.859 --> 00:24:22.936 Infer process defense.

NOTE Confidence: 0.27602023

00:24:22.936 --> 00:24:25.620 Then there are also other backup systems,

NOTE Confidence: 0.27602023

00:24:25.620 --> 00:24:28.735 right? Those are collectively called GPS 4.

NOTE Confidence: 0.27602023

00:24:28.740 --> 00:24:30.402 Independence mechanisms to

NOTE Confidence: 0.27602023

00:24:30.402 --> 00:24:32.618 to defend against purposes.

NOTE Confidence: 0.27602023

00:24:32.620 --> 00:24:34.630 I just mentioned FSP one is

NOTE Confidence: 0.27602023

00:24:34.630 --> 00:24:35.648 one such proteins.

NOTE Confidence: 0.27602023

00:24:35.648 --> 00:24:37.388 Then there are others I'm

NOTE Confidence: 0.27602023

00:24:37.388 --> 00:24:39.104 going to mention later Now.

NOTE Confidence: 0.27602023

00:24:39.104 --> 00:24:41.048 So you have two arms here

NOTE Confidence: 0.27602023

00:24:41.048 --> 00:24:42.700 to defend against purposes.

NOTE Confidence: 0.27602023

00:24:42.700 --> 00:24:44.972 So if one arm is defective then the

NOTE Confidence: 0.27602023

00:24:44.972 --> 00:24:47.152 cells have to be more dependent on

NOTE Confidence: 0.27602023

00:24:47.152 --> 00:24:49.478 the other arm for fratosis defense and

NOTE Confidence: 0.27602023

00:24:49.478 --> 00:24:51.626 therefore that make those tumor cells

NOTE Confidence: 0.27602023

00:24:51.626 --> 00:24:54.222 are more sensitive to the fratosis

NOTE Confidence: 0.27602023

00:24:54.222 --> 00:24:57.030 inducers which targeted the other arm,

NOTE Confidence: 0.27602023

00:24:57.030 --> 00:24:57.318 right.

NOTE Confidence: 0.27602023

00:24:57.318 --> 00:24:59.334 So one way to help you understand

NOTE Confidence: 0.27602023

00:24:59.334 --> 00:25:01.384 this is you know as many of you

NOTE Confidence: 0.27602023

00:25:01.384 --> 00:25:03.229 know to use the POP inhibitor,

NOTE Confidence: 0.27602023

00:25:03.230 --> 00:25:05.066 the treated BRC one division cancer.

NOTE Confidence: 0.27602023

00:25:05.070 --> 00:25:06.970 The rationale here is that that

NOTE Confidence: 0.27602023

00:25:06.970 --> 00:25:08.510 there are different ways to repel it.

NOTE Confidence: 0.27602023

00:25:08.510 --> 00:25:11.429 In A1 require you know PRC one,

NOTE Confidence: 0.27602023

00:25:11.430 --> 00:25:12.486 the other require top.

NOTE Confidence: 0.27602023

00:25:12.486 --> 00:25:14.727 So then in the PRC one mutant kind

NOTE Confidence: 0.27602023

00:25:14.727 --> 00:25:16.820 of cells they have to be more

NOTE Confidence: 0.27602023

00:25:16.820 --> 00:25:18.469 dependent on POP foot in repair,

NOTE Confidence: 0.27602023

00:25:18.470 --> 00:25:20.710 so therefore more sensitive to POP inhibitor.

NOTE Confidence: 0.27602023

00:25:20.710 --> 00:25:24.030 So this is kind of similar concept here.

NOTE Confidence: 0.27602023

00:25:24.030 --> 00:25:27.054 So to one one example to illustrate

NOTE Confidence: 0.27602023

00:25:27.054 --> 00:25:30.325 this strategy is from our recent study

NOTE Confidence: 0.27602023

00:25:30.325 --> 00:25:33.163 in which we discovered this protein

NOTE Confidence: 0.27602023

00:25:33.252 --> 00:25:36.214 called THUDHE MOB inferosis defense.

NOTE Confidence: 0.27602023

00:25:36.214 --> 00:25:38.260 So THUDH is an enzyme involved

NOTE Confidence: 0.27602023

00:25:38.260 --> 00:25:40.406 in in pure medium biosynthesis.

NOTE Confidence: 0.27602023

00:25:40.406 --> 00:25:40.870 OK,

NOTE Confidence: 0.27602023

00:25:40.870 --> 00:25:42.652 but it's interesting in that because

NOTE Confidence: 0.27602023

00:25:42.652 --> 00:25:44.270 this is the protein localized

NOTE Confidence: 0.27602023

00:25:44.270 --> 00:25:46.430 on like chondra in the membrane,

NOTE Confidence: 0.27602023

00:25:46.430 --> 00:25:48.650 so you converse this option

NOTE Confidence: 0.27602023

00:25:48.650 --> 00:25:50.870 metabolite called THO to OA.

NOTE Confidence: 0.27602023

00:25:50.870 --> 00:25:53.270 So both are involved in pyramid

NOTE Confidence: 0.27602023

00:25:53.270 --> 00:25:55.134 biosynthesis but this is reduction,

NOTE Confidence: 0.27602023

00:25:55.134 --> 00:25:57.330 this is the oxidation reaction right

NOTE Confidence: 0.27602023

00:25:57.398 --> 00:25:59.505 from conversion from the THO to OA

NOTE Confidence: 0.27602023

00:25:59.510 --> 00:26:02.102 and this needs to be coupled with a

NOTE Confidence: 0.27602023

00:26:02.102 --> 00:26:03.794 reduction reaction and which is a

NOTE Confidence: 0.27602023

00:26:03.794 --> 00:26:05.750 conversion from Co Q to Co QH two.

NOTE Confidence: 0.27602023

00:26:05.750 --> 00:26:06.854 As I alluded earlier,

NOTE Confidence: 0.27602023

00:26:06.854 --> 00:26:09.278 Co QH two is involving in this case

NOTE Confidence: 0.27602023

00:26:09.278 --> 00:26:11.742 is involved in the electron transport chain.

NOTE Confidence: 0.27602023

00:26:11.750 --> 00:26:13.798 So the Co QH two then you try

NOTE Confidence: 0.27602023

00:26:13.798 --> 00:26:14.310 to convert

NOTE Confidence: 0.273399107272727

00:26:14.383 --> 00:26:16.315 it will be be delivered to complex

NOTE Confidence: 0.273399107272727

00:26:16.315 --> 00:26:18.430 3 or the electron transport.

NOTE Confidence: 0.273399107272727

00:26:18.430 --> 00:26:19.660 But as I've just mentioned the

NOTE Confidence: 0.273399107272727

00:26:19.660 --> 00:26:21.069 quick H2 extra has another rule.

NOTE Confidence: 0.273399107272727

00:26:21.070 --> 00:26:24.530 You can also act as radical tracking and

NOTE Confidence: 0.273399107272727

00:26:24.530 --> 00:26:28.910 and oxidant to detoxify lipid peroxides.

NOTE Confidence: 0.273399107272727

00:26:28.910 --> 00:26:31.633 So we show that the GOGHD besides

NOTE Confidence: 0.273399107272727

00:26:31.633 --> 00:26:33.780 its canonical rule involved in

NOTE Confidence: 0.273399107272727

00:26:33.780 --> 00:26:36.025 the the pure medium biosenses,

NOTE Confidence: 0.273399107272727

00:26:36.030 --> 00:26:38.814 it can also can actually also

NOTE Confidence: 0.273399107272727

00:26:38.814 --> 00:26:41.258 suppress for process in mitochondria

NOTE Confidence: 0.273399107272727

00:26:41.258 --> 00:26:44.198 by generating Co QH two.

NOTE Confidence: 0.273399107272727

00:26:44.200 --> 00:26:46.120 So now I just mentioned as

NOTE Confidence: 0.273399107272727

00:26:46.120 --> 00:26:48.039 a protein right as FSP one,

NOTE Confidence: 0.273399107272727

00:26:48.040 --> 00:26:50.224 it has a somewhat similar function

NOTE Confidence: 0.273399107272727

00:26:50.224 --> 00:26:51.680 right because biochemical it

NOTE Confidence: 0.273399107272727

00:26:51.741 --> 00:26:53.356 also generate the Cocker H2.

NOTE Confidence: 0.273399107272727

00:26:53.360 --> 00:26:55.560 But the difference difference between

NOTE Confidence: 0.273399107272727

00:26:55.560 --> 00:26:57.760 this protein is their localization.

NOTE Confidence: 0.273399107272727

00:26:57.760 --> 00:27:01.072 So DHUDH localize in mitochondria in

NOTE Confidence: 0.273399107272727

00:27:01.072 --> 00:27:04.092 the membrane versus FSPN plasm membrane

NOTE Confidence: 0.273399107272727

00:27:04.092 --> 00:27:06.141 and other non mitochondria compartment.

NOTE Confidence: 0.273399107272727

00:27:06.141 --> 00:27:08.667 So these two proteins they can

NOTE Confidence: 0.273399107272727

00:27:08.667 --> 00:27:11.043 also depend against for process

NOTE Confidence: 0.273399107272727

00:27:11.043 --> 00:27:12.606 at different localizations.

NOTE Confidence: 0.273399107272727

00:27:12.610 --> 00:27:14.200 And also interestingly this other

NOTE Confidence: 0.273399107272727

00:27:14.200 --> 00:27:16.456 protein called the GPS four as I

NOTE Confidence: 0.273399107272727

00:27:16.456 --> 00:27:17.971 mentioned is the most important

NOTE Confidence: 0.273399107272727

00:27:17.971 --> 00:27:19.770 protein involving for process defense.

NOTE Confidence: 0.273399107272727

00:27:19.770 --> 00:27:21.810 You have different ice forms,

NOTE Confidence: 0.273399107272727

00:27:21.810 --> 00:27:23.334 so one neuchalizing cytosol,

NOTE Confidence: 0.273399107272727

00:27:23.334 --> 00:27:24.858 the other neuchalizing mitochondria

NOTE Confidence: 0.273399107272727

00:27:24.858 --> 00:27:27.080 together you can think about a picture

NOTE Confidence: 0.273399107272727

00:27:27.080 --> 00:27:28.490 here is the different proteins,

NOTE Confidence: 0.273399107272727

00:27:28.490 --> 00:27:30.410 the neuchalizing different compartment

NOTE Confidence: 0.273399107272727

00:27:30.410 --> 00:27:32.942 to defend against the for process.

NOTE Confidence: 0.273399107272727

00:27:32.942 --> 00:27:35.084 OK. So that's the bottom line here,

NOTE Confidence: 0.273399107272727

00:27:35.090 --> 00:27:37.568 but utilize this finding we think

NOTE Confidence: 0.273399107272727

00:27:37.568 --> 00:27:39.974 about OK maybe in the cells with

NOTE Confidence: 0.273399107272727

00:27:39.974 --> 00:27:42.356 if you have this GPS four,

NOTE Confidence: 0.273399107272727

00:27:42.356 --> 00:27:44.974 let me use this next slide,

NOTE Confidence: 0.273399107272727

00:27:44.974 --> 00:27:46.484 I'll ask you this point.

NOTE Confidence: 0.273399107272727

00:27:46.490 --> 00:27:49.660 So in this tumors with if you

NOTE Confidence: 0.273399107272727

00:27:49.660 --> 00:27:51.490 have low or high GPS 4,

NOTE Confidence: 0.273399107272727

00:27:51.490 --> 00:27:53.206 if you have low GPS four,

NOTE Confidence: 0.273399107272727

00:27:53.210 --> 00:27:54.890 then those tumor cells they have

NOTE Confidence: 0.273399107272727

00:27:54.890 --> 00:27:56.708 to be more dependent on other

NOTE Confidence: 0.273399107272727

00:27:56.708 --> 00:27:58.298 GPS for independent mechanism to

NOTE Confidence: 0.273399107272727

00:27:58.298 --> 00:28:00.002 depend against for process, right.

NOTE Confidence: 0.273399107272727

00:28:00.002 --> 00:28:01.906 So have to be more dependent on

NOTE Confidence: 0.273399107272727

00:28:01.906 --> 00:28:03.785 for example THUTH and therefore

NOTE Confidence: 0.273399107272727

00:28:03.785 --> 00:28:06.010 those tumors now becomes more

NOTE Confidence: 0.273399107272727

00:28:06.010 --> 00:28:07.450 sensitive to DHUDH inhibitors.

NOTE Confidence: 0.273399107272727

00:28:07.450 --> 00:28:09.375 So we've done a number of experiment,

NOTE Confidence: 0.273399107272727

00:28:09.380 --> 00:28:11.300 one experiment is used the

NOTE Confidence: 0.273399107272727

00:28:11.300 --> 00:28:12.365 the preclinograph model.

NOTE Confidence: 0.273399107272727

00:28:12.365 --> 00:28:14.936 You can see in this in this

NOTE Confidence: 0.273399107272727

00:28:14.936 --> 00:28:17.116 particular Xenophra model the GPS

NOTE Confidence: 0.273399107272727

00:28:17.116 --> 00:28:19.710 4 expression is low and therefore

NOTE Confidence: 0.273399107272727

00:28:19.710 --> 00:28:22.398 when we treat the tumors with the

NOTE Confidence: 0.273399107272727

00:28:22.398 --> 00:28:24.272 PQR which is DHUDH inhibitors,

NOTE Confidence: 0.273399107272727

00:28:24.272 --> 00:28:26.824 you can see a more obvious

NOTE Confidence: 0.273399107272727

00:28:26.824 --> 00:28:29.134 suppression effect on tumor growth.

NOTE Confidence: 0.273399107272727

00:28:29.140 --> 00:28:31.144 They suppress the tumor growth can

NOTE Confidence: 0.273399107272727

00:28:31.144 --> 00:28:33.770 be restored by lead prostate as you

NOTE Confidence: 0.273399107272727

00:28:33.770 --> 00:28:35.986 mentioned this is for a process inhibitor.

NOTE Confidence: 0.273399107272727

00:28:35.986 --> 00:28:38.395 So we should use this to show that the

NOTE Confidence: 0.273399107272727

00:28:38.395 --> 00:28:40.290 suppression of the tumor growth was

NOTE Confidence: 0.273399107272727

00:28:40.290 --> 00:28:43.510 really caused by the induction of process.

NOTE Confidence: 0.273399107272727

00:28:43.510 --> 00:28:45.652 So the bottom line is if you

NOTE Confidence: 0.273399107272727

00:28:45.652 --> 00:28:48.222 tumor have low expression GPS 4,

NOTE Confidence: 0.273399107272727

00:28:48.222 --> 00:28:50.210 the DHUDH works better than in

NOTE Confidence: 0.273399107272727

00:28:50.210 --> 00:28:52.333 the tumors with high GPS for the

NOTE Confidence: 0.273399107272727

00:28:52.333 --> 00:28:54.307 reason is because in the GPS high

NOTE Confidence: 0.273399107272727

00:28:54.307 --> 00:28:56.056 tumors we just inactivity DHUDH.

NOTE Confidence: 0.273399107272727

00:28:56.056 --> 00:28:58.478 The GPS four is there to continue

NOTE Confidence: 0.273399107272727

00:28:58.478 --> 00:29:00.350 to defend against process.

NOTE Confidence: 0.273399107272727

00:29:00.350 --> 00:29:03.500 So that explains why the DHU,

NOTE Confidence: 0.273399107272727

00:29:03.500 --> 00:29:04.588 the PQR,

NOTE Confidence: 0.273399107272727

00:29:04.588 --> 00:29:08.348 the DHUDH inhibitor fails to have much

NOTE Confidence: 0.273399107272727

00:29:08.348 --> 00:29:11.540 obvious effect to surprise tumor growth.

NOTE Confidence: 0.273399107272727

00:29:11.540 --> 00:29:13.388 So the bottom line is we propose to

NOTE Confidence: 0.273399107272727

00:29:13.388 --> 00:29:15.504 use DHUDH inhibitor to specifically

NOTE Confidence: 0.273399107272727

00:29:15.504 --> 00:29:17.859 induce for process for therapy

NOTE Confidence: 0.273399107272727

00:29:17.859 --> 00:29:19.779 in GPS for low tumors.

NOTE Confidence: 0.273399107272727

00:29:19.780 --> 00:29:20.916 So here Oh yeah,

NOTE Confidence: 0.273399107272727

00:29:20.916 --> 00:29:22.620 here I just want to mention

NOTE Confidence: 0.273399107272727

00:29:22.691 --> 00:29:24.047 another point of this

NOTE Confidence: 0.3642967

00:29:24.050 --> 00:29:26.465 this finding is that DHUDH as just

NOTE Confidence: 0.3642967

00:29:26.465 --> 00:29:29.040 mentioned is the protein localized the in

NOTE Confidence: 0.3642967

00:29:29.040 --> 00:29:31.036 the mitochondrial in the membrane, right.

NOTE Confidence: 0.3642967

00:29:31.036 --> 00:29:34.339 But there is an issue with this pathway.

NOTE Confidence: 0.3642967

00:29:34.339 --> 00:29:37.477 So this pathway is pyramid biosynthesis

NOTE Confidence: 0.3642967

00:29:37.477 --> 00:29:39.569 involves 3 lines called CAD,

NOTE Confidence: 0.3642967

00:29:39.570 --> 00:29:41.814 DHUDH and the umps.

NOTE Confidence: 0.3642967

00:29:41.814 --> 00:29:46.626 Now the CAD and umps nucleus in cytosol

NOTE Confidence: 0.3642967

00:29:46.626 --> 00:29:48.930 versus DHUDH leuclide in mitochondria,

NOTE Confidence: 0.3642967

00:29:48.930 --> 00:29:50.570 mitochondria in the membrane.

NOTE Confidence: 0.3642967

00:29:50.570 --> 00:29:52.950 So they're separated by this

NOTE Confidence: 0.3642967

00:29:52.950 --> 00:29:54.378 mitochondrial auto membrane.

NOTE Confidence: 0.3642967

00:29:54.380 --> 00:29:56.558 Now as you might know that

NOTE Confidence: 0.3642967

00:29:56.558 --> 00:29:58.374 many enzymes involved in the

NOTE Confidence: 0.3642967

00:29:58.374 --> 00:30:00.320 meta in the metabolic pathway,

NOTE Confidence: 0.3642967

00:30:00.320 --> 00:30:01.980 they actually formed this

NOTE Confidence: 0.3642967

00:30:01.980 --> 00:30:03.880 metabolic market enzyme complexes.

NOTE Confidence: 0.3642967

00:30:03.880 --> 00:30:06.673 So they can form complexes so-called,

NOTE Confidence: 0.3642967

00:30:06.673 --> 00:30:09.151 so, so therefore the metabolite can

NOTE Confidence: 0.3642967

00:30:09.151 --> 00:30:11.499 directly channel the from the upstream

NOTE Confidence: 0.3642967

00:30:11.500 --> 00:30:13.158 enzyme to the next one, right.

NOTE Confidence: 0.3642967

00:30:13.158 --> 00:30:15.448 So that kind of facilitates

NOTE Confidence: 0.3642967

00:30:15.448 --> 00:30:17.280 so-called the substrate channeling.

NOTE Confidence: 0.3642967

00:30:17.280 --> 00:30:19.050 So that's very common for example

NOTE Confidence: 0.3642967

00:30:19.050 --> 00:30:20.786 in the electron transport chain all

NOTE Confidence: 0.3642967

00:30:20.786 --> 00:30:22.410 those complex that form a so-called

NOTE Confidence: 0.3642967

00:30:22.410 --> 00:30:24.630 super complex to really promote the

NOTE Confidence: 0.3642967

00:30:24.630 --> 00:30:26.919 efficiency of the electron transport.

NOTE Confidence: 0.3642967

00:30:26.920 --> 00:30:28.984 But in this case this all all these

NOTE Confidence: 0.3642967

00:30:28.984 --> 00:30:30.755 airlines look as a different compartment

NOTE Confidence: 0.3642967

00:30:30.755 --> 00:30:33.189 which is kind of puzzling wide the cells

NOTE Confidence: 0.3642967

00:30:33.189 --> 00:30:34.923 were designed like this way right.

NOTE Confidence: 0.3642967

00:30:34.930 --> 00:30:36.640 So you really doesn't make sense

NOTE Confidence: 0.3642967

00:30:36.640 --> 00:30:38.552 in terms of the increase the

NOTE Confidence: 0.3642967

00:30:38.552 --> 00:30:40.688 maintain the efficiency of the the,

NOTE Confidence: 0.3642967

00:30:40.690 --> 00:30:41.629 the subject channeling.

NOTE Confidence: 0.3642967

00:30:41.629 --> 00:30:44.138 But so I just want to mention this

NOTE Confidence: 0.3642967

00:30:44.138 --> 00:30:46.170 is not this study was not from our

NOTE Confidence: 0.3642967

00:30:46.170 --> 00:30:48.316 lab but this figure the cartoon was

NOTE Confidence: 0.3642967

00:30:48.320 --> 00:30:50.678 John from a commentary I mentioned

NOTE Confidence: 0.3642967

00:30:50.678 --> 00:30:52.782 I discovered I introduced this

NOTE Confidence: 0.3642967

00:30:52.782 --> 00:30:54.159 study this publication.

NOTE Confidence: 0.3642967

00:30:54.160 --> 00:30:55.798 But what they discovered is actually

NOTE Confidence: 0.3642967

00:30:55.798 --> 00:30:57.549 these three enzymes they can form also

NOTE Confidence: 0.3642967

00:30:57.549 --> 00:30:59.294 form a complex but in this case even

NOTE Confidence: 0.3642967

00:30:59.294 --> 00:31:00.729 though they leukalize in different

NOTE Confidence: 0.3642967

00:31:00.729 --> 00:31:02.872 compartments as they can use this

NOTE Confidence: 0.3642967

00:31:02.872 --> 00:31:04.856 transmembrane protein leukalize on

NOTE Confidence: 0.3642967

00:31:04.856 --> 00:31:07.182 the mitochondria auto membrane called

NOTE Confidence: 0.3642967

00:31:07.182 --> 00:31:09.540 VDS 3 to collect all them together

NOTE Confidence: 0.3642967

00:31:09.540 --> 00:31:12.223 as they're able to facilitate the the

NOTE Confidence: 0.3642967

00:31:12.223 --> 00:31:14.203 the the substance challenging between

NOTE Confidence: 0.3642967

00:31:14.203 --> 00:31:16.249 this this enzymes and therefore

NOTE Confidence: 0.3642967

00:31:16.249 --> 00:31:18.625 to not only promote peer meeting

NOTE Confidence: 0.3642967

00:31:18.625 --> 00:31:21.212 biosynthesis but also to increase the

NOTE Confidence: 0.3642967

00:31:21.212 --> 00:31:23.452 efficiency in for process defence.

NOTE Confidence: 0.3642967

00:31:23.460 --> 00:31:26.411 So they call this complex as peer

NOTE Confidence: 0.3642967

00:31:26.411 --> 00:31:29.477 peer meeting or some with basically

NOTE Confidence: 0.3642967

00:31:29.477 --> 00:31:32.388 used to the proposed this complex

NOTE Confidence: 0.3642967

00:31:32.388 --> 00:31:35.220 can promote the for process defence.

NOTE Confidence: 0.3642967

00:31:35.220 --> 00:31:35.435 OK.

NOTE Confidence: 0.3642967

00:31:35.435 --> 00:31:37.370 So I want to give a brief summary for

NOTE Confidence: 0.3642967

00:31:37.431 --> 00:31:39.219 the first part of my presentation.

NOTE Confidence: 0.3642967

00:31:39.220 --> 00:31:41.376 So I introduced the concept of process.

NOTE Confidence: 0.3642967

00:31:41.380 --> 00:31:43.666 I mentioned the different ways to

NOTE Confidence: 0.3642967

00:31:43.666 --> 00:31:46.036 target this cell that's in treating

NOTE Confidence: 0.3642967

00:31:46.036 --> 00:31:48.151 different diseases right and also

NOTE Confidence: 0.3642967

00:31:48.151 --> 00:31:50.620 mentioned the in cancer in in

NOTE Confidence: 0.3642967

00:31:50.620 --> 00:31:52.368 in tumor development for pulses.

NOTE Confidence: 0.3642967

00:31:52.368 --> 00:31:54.222 In power for pulses can drive

NOTE Confidence: 0.3642967

00:31:54.222 --> 00:31:55.817 tumor development progression and

NOTE Confidence: 0.3642967

00:31:55.817 --> 00:31:57.665 metastasis with different mechanisms.

NOTE Confidence: 0.3642967

00:31:57.670 --> 00:31:59.285 I mentioned the briefly mentioned

NOTE Confidence: 0.3642967

00:31:59.285 --> 00:32:01.670 that you know by Mimi team profile

NOTE Confidence: 0.3642967

00:32:01.670 --> 00:32:03.518 synthesis or restricting liberal

NOTE Confidence: 0.3642967

00:32:03.518 --> 00:32:05.828 availability but also more important

NOTE Confidence: 0.3642967

00:32:05.828 --> 00:32:08.632 than perhaps is to up regulate the

NOTE Confidence: 0.3642967

00:32:08.632 --> 00:32:10.909 cellular defence system against for pulses.

NOTE Confidence: 0.3642967

00:32:10.910 --> 00:32:12.734 One example is in the case

NOTE Confidence: 0.3642967

00:32:12.734 --> 00:32:13.950 of PowerPoint mutant cancer,

NOTE Confidence: 0.3642967

00:32:13.950 --> 00:32:16.990 the upper regulation of AT s s 711.

NOTE Confidence: 0.3642967

00:32:16.990 --> 00:32:17.302 Well,

NOTE Confidence: 0.3642967

00:32:17.302 --> 00:32:19.486 I then talk about how to target

NOTE Confidence: 0.3642967

00:32:19.486 --> 00:32:20.950 for processing cancer right.

NOTE Confidence: 0.3642967

00:32:20.950 --> 00:32:22.550 I talk about different strategies.

NOTE Confidence: 0.3642967

00:32:22.550 --> 00:32:24.454 The 1st is to reason the highest

NOTE Confidence: 0.3642967

00:32:24.454 --> 00:32:26.501 resistant tumor to for process such as

NOTE Confidence: 0.3642967

00:32:26.501 --> 00:32:28.259 by combining and to inhibit through

NOTE Confidence: 0.27588323

00:32:28.321 --> 00:32:29.549 is for process inducer.

NOTE Confidence: 0.27588323

00:32:29.550 --> 00:32:31.998 The 2nd is combined for process

NOTE Confidence: 0.27588323

00:32:31.998 --> 00:32:33.630 inducer with others conventional

NOTE Confidence: 0.27588323

00:32:33.694 --> 00:32:35.670 therapies such as radiotherapy.

NOTE Confidence: 0.27588323

00:32:35.670 --> 00:32:38.430 And the third is to explore for

NOTE Confidence: 0.27588323

00:32:38.430 --> 00:32:40.430 process vulnerability in cancer.

NOTE Confidence: 0.27588323

00:32:40.430 --> 00:32:42.470 And I also mentioned different mechanisms.

NOTE Confidence: 0.27588323

00:32:42.470 --> 00:32:45.942 One is to use the imbalances in

NOTE Confidence: 0.27588323

00:32:45.942 --> 00:32:48.610 feroptosis defense such as targeting

NOTE Confidence: 0.27588323

00:32:48.610 --> 00:32:50.968 DHUDH in GPS for low tumors.

NOTE Confidence: 0.27588323

00:32:50.970 --> 00:32:53.266 OK. So now I want to switch the

NOTE Confidence: 0.27588323

00:32:53.266 --> 00:32:55.804 gear a little bit here to the

NOTE Confidence: 0.27588323

00:32:55.804 --> 00:32:57.689 second part of my presentation.

NOTE Confidence: 0.27588323

00:32:57.690 --> 00:33:00.090 Now actually the the bisulfi pulses

NOTE Confidence: 0.27588323

00:33:00.090 --> 00:33:03.810 I'm going to just to to to to talk

NOTE Confidence: 0.27588323

00:33:03.810 --> 00:33:05.850 about actually relates to feroptosis.

NOTE Confidence: 0.27588323

00:33:05.850 --> 00:33:08.482 It's actually how we get into this

NOTE Confidence: 0.27588323

00:33:08.482 --> 00:33:10.886 new formal cell that just to kind

NOTE Confidence: 0.27588323

00:33:10.886 --> 00:33:13.332 of mentioned a little more here is

NOTE Confidence: 0.27588323

00:33:13.332 --> 00:33:15.510 this for a process that mentioned

NOTE Confidence: 0.27588323

00:33:15.510 --> 00:33:18.198 the can be defended by the GPS 4

NOTE Confidence: 0.27588323

00:33:18.272 --> 00:33:20.990 pathway which use uses Glusayan right.

NOTE Confidence: 0.27588323

00:33:20.990 --> 00:33:22.574 But glusayan as you know is

NOTE Confidence: 0.27588323

00:33:22.574 --> 00:33:23.630 a trip peptide right.

NOTE Confidence: 0.27588323

00:33:23.630 --> 00:33:25.334 It derives from glycine,

NOTE Confidence: 0.27588323

00:33:25.334 --> 00:33:27.890 cysteine and the glutamate among which

NOTE Confidence: 0.27588323

00:33:27.965 --> 00:33:30.929 the cysteine is the written limiting

NOTE Confidence: 0.27588323

00:33:30.929 --> 00:33:32.905 precursor for Glusayan biosynthesis.

NOTE Confidence: 0.27588323

00:33:32.910 --> 00:33:34.650 So basically cell needs

NOTE Confidence: 0.27588323

00:33:34.650 --> 00:33:36.825 cysteine to build up glusayan.

NOTE Confidence: 0.27588323

00:33:36.830 --> 00:33:38.846 Now the cysteine is like many

NOTE Confidence: 0.27588323

00:33:38.846 --> 00:33:40.950 other amino acid or nutrients,

NOTE Confidence: 0.27588323

00:33:40.950 --> 00:33:43.785 the cell have the transporter to import

NOTE Confidence: 0.27588323

00:33:43.785 --> 00:33:46.550 the system from extracellular space.

NOTE Confidence: 0.27588323

00:33:46.550 --> 00:33:49.310 But they have a problem here and the

NOTE Confidence: 0.27588323

00:33:49.310 --> 00:33:51.831 reason is because this is released

NOTE Confidence: 0.27588323

00:33:51.831 --> 00:33:54.430 to the different redox environments

NOTE Confidence: 0.27588323

00:33:54.430 --> 00:33:58.270 between the outside versus inside cells.

NOTE Confidence: 0.27588323

00:33:58.270 --> 00:34:01.186 Outside cells, the actual cellular space,

NOTE Confidence: 0.27588323

00:34:01.190 --> 00:34:03.018 they have oxidizing environment

NOTE Confidence: 0.27588323

00:34:03.018 --> 00:34:04.389 versus inside cell.

NOTE Confidence: 0.27588323

00:34:04.390 --> 00:34:07.060 In the cytosol we have the

NOTE Confidence: 0.27588323

00:34:07.060 --> 00:34:08.395 reducing micro environment.

NOTE Confidence: 0.27588323

00:34:08.400 --> 00:34:11.004 So in the in the extracellular space

NOTE Confidence: 0.27588323

00:34:11.004 --> 00:34:13.799 because of the oxidizing environment,

NOTE Confidence: 0.27588323

00:34:13.800 --> 00:34:16.804 the cysteine is very unstable, right.

NOTE Confidence: 0.27588323

00:34:16.804 --> 00:34:20.676 So it rapidly oxidized it to a system.

NOTE Confidence: 0.27588323

00:34:20.680 --> 00:34:22.276 So as the structure in shown here,

NOTE Confidence: 0.27588323

00:34:22.280 --> 00:34:24.806 basically the system is the is the

NOTE Confidence: 0.27588323

00:34:24.806 --> 00:34:27.584 oxidized by America form of cysteine

NOTE Confidence: 0.27588323

00:34:27.584 --> 00:34:31.309 linked by a by sulfide bar is shown here.

NOTE Confidence: 0.27588323

00:34:31.310 --> 00:34:32.885 So in the actual center space if

NOTE Confidence: 0.27588323

00:34:32.885 --> 00:34:34.710 you just add for example in medium,

NOTE Confidence: 0.27588323

00:34:34.710 --> 00:34:37.262 if you add the system in the system

NOTE Confidence: 0.27588323

00:34:37.262 --> 00:34:39.230 were quickly oxidized to system.

NOTE Confidence: 0.27588323

00:34:39.230 --> 00:34:41.130 So consequently the system concentration

NOTE Confidence: 0.27588323

00:34:41.130 --> 00:34:43.030 is much higher than system.

NOTE Confidence: 0.27588323

00:34:43.030 --> 00:34:43.414 OK,

NOTE Confidence: 0.27588323

00:34:43.414 --> 00:34:45.718 but even though CR needs system

NOTE Confidence: 0.27588323

00:34:45.718 --> 00:34:46.870 for growth biosynthesis,

NOTE Confidence: 0.27588323

00:34:46.870 --> 00:34:49.070 but what they can get most from from

NOTE Confidence: 0.27588323

00:34:49.070 --> 00:34:51.229 the outside of the cells is the system.

NOTE Confidence: 0.27588323

00:34:51.230 --> 00:34:53.685 So therefore the cells actually

NOTE Confidence: 0.27588323

00:34:53.685 --> 00:34:55.070 use this transport.

NOTE Confidence: 0.27588323

00:34:55.070 --> 00:34:57.070 I just mentioned the earlier,

NOTE Confidence: 0.27588323

00:34:57.070 --> 00:34:58.670 it's called SRC 711.

NOTE Confidence: 0.27588323

00:34:58.670 --> 00:35:01.846 The other name is XCT to import system.

NOTE Confidence: 0.27588323

00:35:01.846 --> 00:35:04.590 OK, but then the system within cells,

NOTE Confidence: 0.27588323

00:35:04.590 --> 00:35:06.702 the system is then it's reduced

NOTE Confidence: 0.27588323

00:35:06.702 --> 00:35:08.970 to system and system is then

NOTE Confidence: 0.27588323

00:35:08.970 --> 00:35:10.550 used to synthesize gluosam.

NOTE Confidence: 0.27588323

00:35:10.550 --> 00:35:12.416 So this is some of the

NOTE Confidence: 0.27588323

00:35:12.416 --> 00:35:13.349 background knowledge here.

NOTE Confidence: 0.27588323

00:35:13.350 --> 00:35:14.604 But this system,

NOTE Confidence: 0.27588323

00:35:14.604 --> 00:35:17.112 commercial system is a reduction reaction

NOTE Confidence: 0.27588323

00:35:17.112 --> 00:35:19.790 across the reducing power called in ADPH.

NOTE Confidence: 0.27588323

00:35:19.790 --> 00:35:20.198 OK,

NOTE Confidence: 0.27588323

00:35:20.198 --> 00:35:23.054 so it turns out that this reduction

NOTE Confidence: 0.27588323

00:35:23.054 --> 00:35:25.351 reaction actually has a very

NOTE Confidence: 0.27588323

00:35:25.351 --> 00:35:27.227 important role in maintaining

NOTE Confidence: 0.27588323

00:35:27.227 --> 00:35:28.424 redox chromostasis particularly

NOTE Confidence: 0.27588323

00:35:28.424 --> 00:35:30.202 in those kind of cells with high

NOTE Confidence: 0.27588323

00:35:30.202 --> 00:35:31.410 expression of this transport.

NOTE Confidence: 0.27588323

00:35:31.410 --> 00:35:33.475 I just I should mention that this

NOTE Confidence: 0.27588323

00:35:33.475 --> 00:35:34.724 transport is highly expressed

NOTE Confidence: 0.27588323

00:35:34.724 --> 00:35:36.266 in your number of cancers.

NOTE Confidence: 0.27588323

00:35:36.266 --> 00:35:38.618 You know for example Q1 mutant non

NOTE Confidence: 0.27588323

00:35:38.618 --> 00:35:40.572 cancer or pop one mutant cancers.

NOTE Confidence: 0.27588323

00:35:40.572 --> 00:35:43.470 So so but it turns out this has a

NOTE Confidence: 0.386867

00:35:43.547 --> 00:35:45.770 very interesting consequence.

NOTE Confidence: 0.386867

00:35:45.770 --> 00:35:47.863 This is because it turns out the

NOTE Confidence: 0.386867

00:35:47.863 --> 00:35:50.450 system is one of the is very insoluble.

NOTE Confidence: 0.386867

00:35:50.450 --> 00:35:54.362 OK, so one of the needs to soluble

NOTE Confidence: 0.386867

00:35:54.362 --> 00:35:56.268 amino acids, this also is here.

NOTE Confidence: 0.386867

00:35:56.268 --> 00:35:57.860 Yeah, the solability is very low,

NOTE Confidence: 0.386867

00:35:57.860 --> 00:35:59.332 yeah, it's actually the.

NOTE Confidence: 0.386867

00:35:59.332 --> 00:36:01.540 So then because of the instability,

NOTE Confidence: 0.386867

00:36:01.540 --> 00:36:03.385 the system, the high accumulation

NOTE Confidence: 0.386867

00:36:03.385 --> 00:36:05.700 of system in cells is toxic.

NOTE Confidence: 0.386867

00:36:05.700 --> 00:36:07.505 OK. The cells cannot tolerate

NOTE Confidence: 0.386867

00:36:07.505 --> 00:36:10.220 to have a high levels of system

NOTE Confidence: 0.386867

00:36:10.220 --> 00:36:12.295 inside inside the inside cells.

NOTE Confidence: 0.386867

00:36:12.300 --> 00:36:14.260 So therefore they have to the system

NOTE Confidence: 0.386867

00:36:14.260 --> 00:36:16.450 has to be quickly reduced to cystine

NOTE Confidence: 0.386867

00:36:16.450 --> 00:36:19.060 and the cystine as you can see it is.

NOTE Confidence: 0.386867

00:36:19.060 --> 00:36:20.710 So ability can be improved

NOTE Confidence: 0.386867

00:36:20.710 --> 00:36:22.474 by more than 1000 fold.

NOTE Confidence: 0.386867

00:36:22.474 --> 00:36:24.796 Now this as I just mentioned,

NOTE Confidence: 0.386867

00:36:24.800 --> 00:36:26.180 this reduction reaction reports

NOTE Confidence: 0.386867

00:36:26.180 --> 00:36:29.075 NDPH and we know that NDPH is mainly

NOTE Confidence: 0.386867

00:36:29.075 --> 00:36:30.980 supplied from glucose through the

NOTE Confidence: 0.386867

00:36:30.980 --> 00:36:32.720 pentons of phosphate possible.

NOTE Confidence: 0.386867

00:36:32.720 --> 00:36:34.880 OK. So then based on this,

NOTE Confidence: 0.386867

00:36:34.880 --> 00:36:37.504 it turns out this the tumor cells with

NOTE Confidence: 0.386867

00:36:37.504 --> 00:36:39.132 high expression of this transporter,

NOTE Confidence: 0.386867

00:36:39.132 --> 00:36:41.395 they need to import a lot of

NOTE Confidence: 0.386867

00:36:41.395 --> 00:36:42.439 system in the cells.

NOTE Confidence: 0.386867

00:36:42.440 --> 00:36:42.766 Therefore,

NOTE Confidence: 0.386867

00:36:42.766 --> 00:36:45.374 they also need a lot of NDPH to

NOTE Confidence: 0.386867

00:36:45.374 --> 00:36:47.435 support this conversion from system

NOTE Confidence: 0.386867

00:36:47.435 --> 00:36:49.520 to system and consequently that

NOTE Confidence: 0.386867

00:36:49.520 --> 00:36:52.017 make those cells more dependent on

NOTE Confidence: 0.386867

00:36:52.017 --> 00:36:55.540 glucose to support this conversion.

NOTE Confidence: 0.386867

00:36:55.540 --> 00:36:57.206 On the normal condition this is fine

NOTE Confidence: 0.386867

00:36:57.206 --> 00:36:59.179 because for your cultural cells for example,

NOTE Confidence: 0.386867

00:36:59.180 --> 00:37:00.896 you know those cells are culturally

NOTE Confidence: 0.386867

00:37:00.896 --> 00:37:02.903 in the medium with plenty of glucose

NOTE Confidence: 0.386867

00:37:02.903 --> 00:37:04.793 or even in the MAVO condition the

NOTE Confidence: 0.386867

00:37:04.847 --> 00:37:06.855 glucose we have you know a high level,

NOTE Confidence: 0.386867

00:37:06.860 --> 00:37:08.500 relatively high level of glucose.

NOTE Confidence: 0.386867

00:37:08.500 --> 00:37:09.580 So normally this is fine.

NOTE Confidence: 0.386867

00:37:09.580 --> 00:37:11.236 Even the tumor cells they have

NOTE Confidence: 0.386867

00:37:11.236 --> 00:37:12.340 high experience is transported

NOTE Confidence: 0.386867

00:37:12.391 --> 00:37:14.026 don't have any issue because there

NOTE Confidence: 0.386867

00:37:14.026 --> 00:37:15.856 is sufficient supply of glucose.

NOTE Confidence: 0.386867

00:37:15.860 --> 00:37:18.632 However if this glucose supply is

NOTE Confidence: 0.386867

00:37:18.632 --> 00:37:20.959 limited somehow then those this

NOTE Confidence: 0.386867

00:37:20.959 --> 00:37:23.317 cells now run into trouble and

NOTE Confidence: 0.386867

00:37:23.317 --> 00:37:25.490 this is because the so because

NOTE Confidence: 0.386867

00:37:25.490 --> 00:37:27.470 this glucose is limited so there

NOTE Confidence: 0.386867

00:37:27.470 --> 00:37:30.210 is NADPH supply is limited and this

NOTE Confidence: 0.386867

00:37:30.210 --> 00:37:32.826 conversion they don't have any pH to

NOTE Confidence: 0.386867

00:37:32.826 --> 00:37:34.806 you know to mediate this conversion

NOTE Confidence: 0.386867

00:37:34.806 --> 00:37:36.157 from cistine to cystine.

NOTE Confidence: 0.386867

00:37:36.157 --> 00:37:38.530 So that means to the high accumulation

NOTE Confidence: 0.386867

00:37:38.594 --> 00:37:40.710 of cistine in the cells with high

NOTE Confidence: 0.386867

00:37:40.710 --> 00:37:41.934 expression of this transporter.

NOTE Confidence: 0.386867

00:37:41.940 --> 00:37:43.916 And I can use a couple of data

NOTE Confidence: 0.386867

00:37:43.916 --> 00:37:45.258 to illustrate to this model.

NOTE Confidence: 0.386867

00:37:45.260 --> 00:37:46.988 So you can see in the tumor cell

NOTE Confidence: 0.386867

00:37:46.988 --> 00:37:48.633 with over expression of this

NOTE Confidence: 0.386867

00:37:48.633 --> 00:37:50.710 transporter and when we measure the

NOTE Confidence: 0.386867

00:37:50.710 --> 00:37:52.062 system concentration inside cells

NOTE Confidence: 0.386867

00:37:52.062 --> 00:37:54.066 and you don't see much difference

NOTE Confidence: 0.386867

00:37:54.066 --> 00:37:56.113 between you know the control servers

NOTE Confidence: 0.386867

00:37:56.113 --> 00:37:57.998 is over expression right again

NOTE Confidence: 0.386867

00:37:57.998 --> 00:37:59.506 this transport import system.

NOTE Confidence: 0.386867

00:37:59.510 --> 00:38:01.862 But if you measure system you don't see

NOTE Confidence: 0.386867

00:38:01.862 --> 00:38:03.774 much difference and this because the

NOTE Confidence: 0.386867

00:38:03.774 --> 00:38:05.670 system quickly is converted to system.

NOTE Confidence: 0.386867

00:38:05.670 --> 00:38:06.750 So if we measure system,

NOTE Confidence: 0.386867

00:38:06.750 --> 00:38:08.638 I don't show the data here you will

NOTE Confidence: 0.386867

00:38:08.638 --> 00:38:11.079 see a huge increase in the sales with

NOTE Confidence: 0.386867

00:38:11.079 --> 00:38:12.990 over expression of this transport.

NOTE Confidence: 0.386867

00:38:12.990 --> 00:38:14.684 However if you cut your cells in

NOTE Confidence: 0.386867

00:38:14.684 --> 00:38:16.396 the glucose free media and always

NOTE Confidence: 0.386867

00:38:16.396 --> 00:38:18.262 see a massive increase of system

NOTE Confidence: 0.386867

00:38:18.262 --> 00:38:19.888 concentration in the cells with

NOTE Confidence: 0.386867

00:38:19.888 --> 00:38:21.148 over experience this transporter,

NOTE Confidence: 0.386867

00:38:21.150 --> 00:38:23.300 this is complicated with dramatic

NOTE Confidence: 0.386867

00:38:23.300 --> 00:38:24.590 depletion of NDPH.

NOTE Confidence: 0.386867

00:38:24.590 --> 00:38:27.867 So shown here is the NDP plus to NDPH ratio.

NOTE Confidence: 0.386867

00:38:27.867 --> 00:38:29.820 So you see it reverse the ways

NOTE Confidence: 0.386867

00:38:29.883 --> 00:38:31.307 as a dramatic increase.

NOTE Confidence: 0.35725307

00:38:31.310 --> 00:38:33.767 So by this reflects A dramatic reduction

NOTE Confidence: 0.35725307

00:38:33.767 --> 00:38:36.738 of the NDPH reserves in the cells and

NOTE Confidence: 0.35725307

00:38:36.738 --> 00:38:39.949 then the cells now wrapped in your eyes.

NOTE Confidence: 0.35725307

00:38:39.950 --> 00:38:41.936 You can see there's massive cell

NOTE Confidence: 0.35725307

00:38:41.936 --> 00:38:44.118 deaths in the s s 711 over expression

NOTE Confidence: 0.35725307

00:38:44.118 --> 00:38:46.150 cells on the glucose starvation.

NOTE Confidence: 0.35725307

00:38:46.150 --> 00:38:48.502 Like she mentioned that this is the

NOTE Confidence: 0.35725307

00:38:48.502 --> 00:38:50.165 first observation actually were made

NOTE Confidence: 0.35725307

00:38:50.165 --> 00:38:51.655 actually this was initially made

NOTE Confidence: 0.35725307

00:38:51.655 --> 00:38:53.910 by a student in the lab primarily.

NOTE Confidence: 0.35725307

00:38:53.910 --> 00:38:57.351 So when she they actually she

NOTE Confidence: 0.35725307

00:38:57.351 --> 00:38:58.899 accidentally captured these cells

NOTE Confidence: 0.35725307

00:38:58.899 --> 00:39:00.829 on the glucose free medium.

NOTE Confidence: 0.35725307

00:39:00.830 --> 00:39:02.454 So she showed me the data and

NOTE Confidence: 0.35725307

00:39:02.454 --> 00:39:03.790 initially I didn't believe her,

NOTE Confidence: 0.35725307

00:39:03.790 --> 00:39:05.386 right, because if you think about it,

NOTE Confidence: 0.35725307

00:39:05.390 --> 00:39:06.590 it doesn't make sense right?

NOTE Confidence: 0.35725307

00:39:06.590 --> 00:39:10.046 Because it is very established that

NOTE Confidence: 0.35725307

00:39:10.046 --> 00:39:12.379 this transporter actually have a

NOTE Confidence: 0.35725307

00:39:12.379 --> 00:39:14.344 very established the the antioxidant

NOTE Confidence: 0.35725307

00:39:14.344 --> 00:39:16.318 role right pro survival rule.

NOTE Confidence: 0.35725307

00:39:16.320 --> 00:39:18.553 So you can protect it from protect

NOTE Confidence: 0.35725307

00:39:18.553 --> 00:39:20.862 cell from for process protect cell

NOTE Confidence: 0.35725307

00:39:20.862 --> 00:39:23.418 from other optic stress or genotoxic

NOTE Confidence: 0.35725307

00:39:23.418 --> 00:39:25.830 stress because it promotes are the

NOTE Confidence: 0.35725307

00:39:25.830 --> 00:39:27.455 synthesis of glue scion right.

NOTE Confidence: 0.35725307

00:39:27.460 --> 00:39:29.026 So I saw initially this doesn't

NOTE Confidence: 0.35725307

00:39:29.026 --> 00:39:31.175 make sense so she did a number of

NOTE Confidence: 0.35725307

00:39:31.175 --> 00:39:32.741 experiments to convince me so and

NOTE Confidence: 0.35725307

00:39:32.802 --> 00:39:35.018 other people repeat it so this is very

NOTE Confidence: 0.35725307

00:39:35.018 --> 00:39:36.704 very dramatic phenotype and turns out

NOTE Confidence: 0.35725307

00:39:36.704 --> 00:39:38.738 that and we didn't figure out the

NOTE Confidence: 0.35725307

00:39:38.738 --> 00:39:40.733 reason together with Xiaobo in the lab.

NOTE Confidence: 0.35725307

00:39:40.740 --> 00:39:43.028 So we now know this is because the

NOTE Confidence: 0.35725307

00:39:43.028 --> 00:39:44.602 increase the bisulfide molecules

NOTE Confidence: 0.35725307

00:39:44.602 --> 00:39:46.478 including system molecules in

NOTE Confidence: 0.35725307

00:39:46.478 --> 00:39:48.780 these conditions that chaos cells.

NOTE Confidence: 0.35725307

00:39:48.780 --> 00:39:50.700 So the way to improve prove this is

NOTE Confidence: 0.35725307

00:39:50.700 --> 00:39:53.037 to I'm going to I'm going to show the

NOTE Confidence: 0.35725307

00:39:53.037 --> 00:39:55.007 data later you can Add all kinds of

NOTE Confidence: 0.35725307

00:39:55.010 --> 00:39:57.308 compounds which as a reducing reagent

NOTE Confidence: 0.35725307

00:39:57.308 --> 00:39:59.998 and you can convert this system back

NOTE Confidence: 0.35725307

00:39:59.998 --> 00:40:02.176 to cysteine and that can rescue

NOTE Confidence: 0.35725307

00:40:02.176 --> 00:40:04.688 fully rescue this type of cell death.

NOTE Confidence: 0.35725307

00:40:04.690 --> 00:40:06.559 But here the question is right we

NOTE Confidence: 0.35725307

00:40:06.559 --> 00:40:09.076 need to sort OK we see this cell

NOTE Confidence: 0.35725307

00:40:09.076 --> 00:40:10.731 that's induced by bisulfite molecules

NOTE Confidence: 0.35725307

00:40:10.792 --> 00:40:12.670 but really what is the mechanistic

NOTE Confidence: 0.35725307

00:40:12.670 --> 00:40:14.756 basis right of this specified stress

NOTE Confidence: 0.35725307

00:40:14.756 --> 00:40:16.408 induced this cell deaths.

NOTE Confidence: 0.35725307

00:40:16.410 --> 00:40:17.596 So we first want to see, OK,

NOTE Confidence: 0.35725307

00:40:17.596 --> 00:40:19.458 this does this cell death belongs to

NOTE Confidence: 0.35725307

00:40:19.458 --> 00:40:21.676 any known cell death mechanism, right?

NOTE Confidence: 0.35725307

00:40:21.676 --> 00:40:23.700 A pulses or pulses?

NOTE Confidence: 0.35725307

00:40:23.700 --> 00:40:26.256 Like you know necroposis so on and so forth.

NOTE Confidence: 0.35725307

00:40:26.260 --> 00:40:28.700 So we can do this very easily in the lab.

NOTE Confidence: 0.35725307

00:40:28.700 --> 00:40:30.564 You can add just you can use those

NOTE Confidence: 0.35725307

00:40:30.564 --> 00:40:32.306 cell death inhibitor to see whether

NOTE Confidence: 0.35725307

00:40:32.306 --> 00:40:33.218 they can rescue.

NOTE Confidence: 0.35725307

00:40:33.220 --> 00:40:34.949 You can also know how the genes

NOTE Confidence: 0.35725307

00:40:34.949 --> 00:40:36.620 such as you know backspack,

NOTE Confidence: 0.35725307

00:40:36.620 --> 00:40:37.958 you can see whether that was

NOTE Confidence: 0.35725307

00:40:37.958 --> 00:40:39.220 also rescue the cell deaths.

NOTE Confidence: 0.35725307

00:40:39.220 --> 00:40:40.380 But as far we can,

NOTE Confidence: 0.35725307

00:40:40.380 --> 00:40:43.036 as we can tell none of those cell

NOTE Confidence: 0.35725307

00:40:43.036 --> 00:40:45.314 death inhibitor or you know compounds

NOTE Confidence: 0.35725307

00:40:45.314 --> 00:40:47.244 or genetic approach can rescue

NOTE Confidence: 0.35725307

00:40:47.244 --> 00:40:49.144 this cell death so soon.

NOTE Confidence: 0.35725307

00:40:49.144 --> 00:40:51.054 Here is a few examples.

NOTE Confidence: 0.35725307

00:40:51.060 --> 00:40:53.108 You can see the the the cell desk

NOTE Confidence: 0.35725307

00:40:53.108 --> 00:40:55.462 can be rescued by NAC but cannot be

NOTE Confidence: 0.35725307

00:40:55.462 --> 00:40:57.506 rescued by any of those inhibitors

NOTE Confidence: 0.35725307

00:40:57.506 --> 00:40:59.822 we have tested and furthermore it

NOTE Confidence: 0.35725307

00:40:59.822 --> 00:41:02.066 doesn't issue cleave the CASP 3

NOTE Confidence: 0.35725307

00:41:02.066 --> 00:41:04.348 or any other cell desk hallmarks

NOTE Confidence: 0.35725307

00:41:04.348 --> 00:41:06.820 now as a port positive control.

NOTE Confidence: 0.35725307

00:41:06.820 --> 00:41:09.676 Here I show you a few bisulf by

NOTE Confidence: 0.35725307

00:41:09.676 --> 00:41:12.434 reducing agents such as DTT by me so

NOTE Confidence: 0.35725307

00:41:12.434 --> 00:41:14.959 those can fully rescue this cell desk.

NOTE Confidence: 0.35725307

00:41:14.960 --> 00:41:16.958 So based on this finding and the other data,

NOTE Confidence: 0.58112645

00:41:16.960 --> 00:41:20.502 we then propose this as we call

NOTE Confidence: 0.58112645

00:41:20.502 --> 00:41:23.208 the term disulfide process to

NOTE Confidence: 0.58112645

00:41:23.208 --> 00:41:25.416 describe this type of cell death.

NOTE Confidence: 0.58112645

00:41:25.420 --> 00:41:26.860 But then the question is right,

NOTE Confidence: 0.58112645

00:41:26.860 --> 00:41:28.415 what what what's the what

NOTE Confidence: 0.58112645

00:41:28.415 --> 00:41:29.659 is the mechanism right?

NOTE Confidence: 0.58112645

00:41:29.660 --> 00:41:31.700 Is any different components involving

NOTE Confidence: 0.58112645

00:41:31.700 --> 00:41:33.740 the cell diets or different

NOTE Confidence: 0.58112645

00:41:33.740 --> 00:41:35.105 biology biochemical pathways.

NOTE Confidence: 0.58112645

00:41:35.105 --> 00:41:37.380 So we took two approaches,

NOTE Confidence: 0.58112645

00:41:37.380 --> 00:41:39.180 one is the proteomic approach.

NOTE Confidence: 0.58112645

00:41:39.180 --> 00:41:41.700 So we're basically want to look at whether

NOTE Confidence: 0.58112645

00:41:41.700 --> 00:41:43.576 this disulfide accumulation needs to

NOTE Confidence: 0.58112645

00:41:43.576 --> 00:41:45.940 that disulfide bounding the anti proteins.

NOTE Confidence: 0.58112645

00:41:45.940 --> 00:41:49.228 We did a proteinomic analysis to a surprise.

NOTE Confidence: 0.58112645

00:41:49.228 --> 00:41:51.293 The major proteins which undergo

NOTE Confidence: 0.58112645

00:41:51.293 --> 00:41:52.937 disulfide bounding under the

NOTE Confidence: 0.58112645

00:41:52.937 --> 00:41:55.590 conditions during the TYSOP courses.

NOTE Confidence: 0.58112645

00:41:55.590 --> 00:41:57.398 Actually those cytoskeleton

NOTE Confidence: 0.58112645

00:41:57.398 --> 00:41:59.270 acting cytoskeleton proteins.

NOTE Confidence: 0.58112645

00:41:59.270 --> 00:42:00.986 So this is surprising to us.

NOTE Confidence: 0.58112645

00:42:00.990 --> 00:42:02.740 And here I want to mention a

NOTE Confidence: 0.58112645

00:42:02.740 --> 00:42:04.149 few proteins with many dated.

NOTE Confidence: 0.58112645

00:42:04.150 --> 00:42:06.038 So for example phenomi,

NOTE Confidence: 0.58112645

00:42:06.038 --> 00:42:06.510 myosin,

NOTE Confidence: 0.58112645

00:42:06.510 --> 00:42:08.310 painting and even acting self.

NOTE Confidence: 0.58112645

00:42:08.310 --> 00:42:10.320 The way we do this is we can run the

NOTE Confidence: 0.58112645

00:42:10.379 --> 00:42:11.938 chair on the non reducing condition.

NOTE Confidence: 0.58112645

00:42:11.938 --> 00:42:14.341 So for any of the training here must

NOTE Confidence: 0.58112645

00:42:14.341 --> 00:42:16.224 have done western blot right and you

NOTE Confidence: 0.58112645

00:42:16.224 --> 00:42:18.295 know you have to add a better ME or

NOTE Confidence: 0.58112645

00:42:18.295 --> 00:42:20.370 TTT right in the in the in the buffer.

NOTE Confidence: 0.58112645

00:42:20.370 --> 00:42:21.650 So you run it,

NOTE Confidence: 0.58112645

00:42:21.650 --> 00:42:23.250 you're on the reducing condition.

NOTE Confidence: 0.58112645

00:42:23.250 --> 00:42:24.566 So when you do the western blot,

NOTE Confidence: 0.58112645

00:42:24.570 --> 00:42:26.634 you always run the western blot

NOTE Confidence: 0.58112645

00:42:26.634 --> 00:42:28.010 on the reducing conditions.

NOTE Confidence: 0.58112645

00:42:28.010 --> 00:42:30.883 But if we do this experiment now

NOTE Confidence: 0.58112645

00:42:30.883 --> 00:42:31.948 on the non reducing condition,

NOTE Confidence: 0.58112645

00:42:31.950 --> 00:42:33.714 you're going to see all this span

NOTE Confidence: 0.58112645

00:42:33.714 --> 00:42:35.802 shift and this is because they form

NOTE Confidence: 0.58112645

00:42:35.802 --> 00:42:37.402 this specify bounding and therefore

NOTE Confidence: 0.58112645

00:42:37.402 --> 00:42:39.509 show the migration retardations right.

NOTE Confidence: 0.58112645

00:42:39.510 --> 00:42:41.092 So this is not because post relation

NOTE Confidence: 0.58112645

00:42:41.092 --> 00:42:42.444 or any other post transmission

NOTE Confidence: 0.58112645

00:42:42.444 --> 00:42:43.684 modification because we have

NOTE Confidence: 0.58112645

00:42:43.684 --> 00:42:45.509 control here we have the reducing

NOTE Confidence: 0.58112645

00:42:45.509 --> 00:42:47.903 gel here on the reducing condition

NOTE Confidence: 0.58112645

00:42:47.903 --> 00:42:50.693 and you can see those Spanish shift

NOTE Confidence: 0.58112645

00:42:50.693 --> 00:42:52.588 now is totally is gone.

NOTE Confidence: 0.58112645

00:42:52.590 --> 00:42:55.430 Now this span ships there's

NOTE Confidence: 0.58112645

00:42:55.430 --> 00:42:57.428 you know those reduce the the,

NOTE Confidence: 0.58112645

00:42:57.430 --> 00:42:58.330 the protein,

NOTE Confidence: 0.58112645

00:42:58.330 --> 00:43:00.580 the disulfide bounding those proteins,

NOTE Confidence: 0.58112645

00:43:00.580 --> 00:43:03.593 it can be fully rescued by the

NOTE Confidence: 0.58112645

00:43:03.593 --> 00:43:06.058 XCT or SS711 knockout right.

NOTE Confidence: 0.58112645

00:43:06.060 --> 00:43:08.111 So again showing here this is really

NOTE Confidence: 0.58112645

00:43:08.111 --> 00:43:10.778 caused by this assistant uptake in the cells.

NOTE Confidence: 0.58112645

00:43:10.780 --> 00:43:13.420 So you can not call this key transporter.

NOTE Confidence: 0.58112645

00:43:13.420 --> 00:43:15.737 You can fully abolish this that by

NOTE Confidence: 0.58112645

00:43:15.737 --> 00:43:17.721 sweat bonding those proteins and this

NOTE Confidence: 0.58112645

00:43:17.721 --> 00:43:20.327 also can be shown and other ways to

NOTE Confidence: 0.58112645

00:43:20.327 --> 00:43:22.250 do the cytoskeleton staining, acting,

NOTE Confidence: 0.58112645

00:43:22.250 --> 00:43:23.300 cytoskeleton staining staining.

NOTE Confidence: 0.58112645

00:43:23.300 --> 00:43:25.852 You can see the normally the cell

NOTE Confidence: 0.58112645

00:43:25.852 --> 00:43:28.156 show this very nice stress fiber

NOTE Confidence: 0.58112645

00:43:28.156 --> 00:43:30.296 and also the the acting standing

NOTE Confidence: 0.58112645

00:43:30.296 --> 00:43:32.528 under this similar cortex but then

NOTE Confidence: 0.58112645

00:43:32.528 --> 00:43:35.016 the structure is very much disrupted

NOTE Confidence: 0.58112645

00:43:35.020 --> 00:43:37.415 in this glucose star glucose

NOTE Confidence: 0.58112645

00:43:37.415 --> 00:43:39.810 starvation conditions and again if

NOTE Confidence: 0.58112645

00:43:39.894 --> 00:43:42.450 we knock out this transporter that

NOTE Confidence: 0.58112645

00:43:42.450 --> 00:43:45.430 we can totally rescue this this

NOTE Confidence: 0.58112645

00:43:45.430 --> 00:43:48.100 cytoskeleton disruption phenotype.

NOTE Confidence: 0.58112645

00:43:48.100 --> 00:43:50.088 So OK so this shows the somehow

NOTE Confidence: 0.58112645

00:43:50.088 --> 00:43:51.988 this cell does have something to

NOTE Confidence: 0.58112645

00:43:51.988 --> 00:43:53.950 do with cytoskeleton but you know

NOTE Confidence: 0.58112645

00:43:53.950 --> 00:43:56.136 I mean you know pathways right.

NOTE Confidence: 0.58112645

00:43:56.140 --> 00:43:58.732 So we did another approach we did is

NOTE Confidence: 0.58112645

00:43:58.732 --> 00:44:00.708 to use the CRISPR screening, right.

NOTE Confidence: 0.58112645

00:44:00.708 --> 00:44:03.128 So you can easily do the CRISPR

NOTE Confidence: 0.58112645

00:44:03.128 --> 00:44:05.268 screening to identify the proteins

NOTE Confidence: 0.58112645

00:44:05.268 --> 00:44:06.980 or genes somehow differentially

NOTE Confidence: 0.58112645

00:44:07.040 --> 00:44:09.290 accumulated it on the two conditions

NOTE Confidence: 0.58112645

00:44:09.290 --> 00:44:10.790 that glucose containing and

NOTE Confidence: 0.58112645

00:44:10.852 --> 00:44:12.259 glucose free conditions.

NOTE Confidence: 0.58112645

00:44:12.260 --> 00:44:14.852 And here I'm going to focus on here this,

NOTE Confidence: 0.58112645

00:44:14.860 --> 00:44:15.472 this part.

NOTE Confidence: 0.58112645

00:44:15.472 --> 00:44:17.614 So this is the ranking of this

NOTE Confidence: 0.30218259

00:44:17.620 --> 00:44:20.820 case involved in the the the cell test.

NOTE Confidence: 0.30218259

00:44:20.820 --> 00:44:22.220 But this part is so-called

NOTE Confidence: 0.30218259

00:44:22.220 --> 00:44:23.060 the suppressor case.

NOTE Confidence: 0.30218259

00:44:23.060 --> 00:44:24.970 So suppressor case means if

NOTE Confidence: 0.30218259

00:44:24.970 --> 00:44:26.498 you suppress this suppression,

NOTE Confidence: 0.30218259

00:44:26.500 --> 00:44:29.307 it can it can make cells more.

NOTE Confidence: 0.30218259

00:44:29.310 --> 00:44:31.914 So basically the when the protein are

NOTE Confidence: 0.30218259

00:44:31.914 --> 00:44:34.030 suppressed makes cells more resistant.

NOTE Confidence: 0.30218259

00:44:34.030 --> 00:44:36.334 So the SO. So another way to think

NOTE Confidence: 0.30218259

00:44:36.334 --> 00:44:38.604 about this is the genes which are

NOTE Confidence: 0.30218259

00:44:38.604 --> 00:44:40.750 important to induce the cell deaths.

NOTE Confidence: 0.30218259

00:44:40.750 --> 00:44:43.110 OK, so that's what we're interested in here.

NOTE Confidence: 0.30218259

00:44:43.110 --> 00:44:45.063 Now you can see the number one hit here.

NOTE Confidence: 0.30218259

00:44:45.070 --> 00:44:47.625 Number one hit is SSN 711 itself.

NOTE Confidence: 0.30218259

00:44:47.630 --> 00:44:50.374 The second hit is a protein called SSS 382.

NOTE Confidence: 0.30218259

00:44:50.374 --> 00:44:52.550 So as shown here the 382 is a

NOTE Confidence: 0.30218259

00:44:52.625 --> 00:44:55.044 Chevron protein for SSS 711 function.

NOTE Confidence: 0.30218259

00:44:55.044 --> 00:44:57.457 So we identify these two protein as

NOTE Confidence: 0.30218259

00:44:57.457 --> 00:44:59.437 the top is actually really validated

NOTE Confidence: 0.30218259

00:44:59.437 --> 00:45:02.231 from you know in fact from the GNL

NOTE Confidence: 0.30218259

00:45:02.231 --> 00:45:03.971 wider screening really validate our

NOTE Confidence: 0.30218259

00:45:03.980 --> 00:45:05.550 screening right because this cell

NOTE Confidence: 0.30218259

00:45:05.550 --> 00:45:07.487 does is indeed actually induced by

NOTE Confidence: 0.30218259

00:45:07.487 --> 00:45:09.057 high expression of this transporter.

NOTE Confidence: 0.30218259

00:45:09.060 --> 00:45:11.100 So that make perfect sense.

NOTE Confidence: 0.30218259

00:45:11.100 --> 00:45:12.774 But we're more interesting in can

NOTE Confidence: 0.30218259

00:45:12.774 --> 00:45:14.420 we identify any new proteins.

NOTE Confidence: 0.30218259

00:45:14.420 --> 00:45:16.716 So the next one is a protein

NOTE Confidence: 0.30218259

00:45:16.716 --> 00:45:18.100 called NCP AP one.

NOTE Confidence: 0.30218259

00:45:18.100 --> 00:45:20.361 This protein is a part of this

NOTE Confidence: 0.30218259

00:45:20.361 --> 00:45:22.300 so-called we've regulatory complex.

NOTE Confidence: 0.30218259

00:45:22.300 --> 00:45:26.170 So this complex is function to

NOTE Confidence: 0.30218259

00:45:26.170 --> 00:45:28.179 to to regulate the up to three

NOTE Confidence: 0.30218259

00:45:28.179 --> 00:45:29.507 mediate the acting primerization

NOTE Confidence: 0.30218259

00:45:29.507 --> 00:45:31.901 and the function bouncing of this

NOTE Confidence: 0.30218259

00:45:31.901 --> 00:45:33.689 multi protein called the rack.

NOTE Confidence: 0.30218259

00:45:33.690 --> 00:45:35.970 So basically rack activates this

NOTE Confidence: 0.30218259

00:45:35.970 --> 00:45:39.250 wave record complex to promote up to

NOTE Confidence: 0.30218259

00:45:39.250 --> 00:45:41.250 three mediate effect implementation.

NOTE Confidence: 0.30218259

00:45:41.250 --> 00:45:43.716 Eventually this needs to the laminipodia

NOTE Confidence: 0.30218259

00:45:43.716 --> 00:45:46.216 formation as you know laminipodia from

NOTE Confidence: 0.30218259

00:45:46.216 --> 00:45:48.953 this web like you know structure right

NOTE Confidence: 0.30218259

00:45:48.953 --> 00:45:51.230 for the actions to really mediate.

NOTE Confidence: 0.30218259

00:45:51.230 --> 00:45:54.430 So for example the cell migration and so on.

NOTE Confidence: 0.30218259

00:45:54.430 --> 00:45:57.470 So we just to I want to validate the results.

NOTE Confidence: 0.30218259

00:45:57.470 --> 00:45:59.006 We've not called the gene didn't

NOTE Confidence: 0.30218259

00:45:59.006 --> 00:46:00.030 make cell more resistance.

NOTE Confidence: 0.30218259

00:46:00.030 --> 00:46:02.658 I just want to point out that the phenotype

NOTE Confidence: 0.30218259

00:46:02.658 --> 00:46:05.694 is not as dramatic as we knock out SSC 11.

NOTE Confidence: 0.30218259

00:46:05.694 --> 00:46:08.510 I'm going to come back to this point

NOTE Confidence: 0.30218259

00:46:08.590 --> 00:46:10.649 later but the other way to show this

NOTE Confidence: 0.30218259

00:46:10.649 --> 00:46:12.981 is if we over express this constitute

NOTE Confidence: 0.30218259

00:46:12.981 --> 00:46:15.697 active rack to promote this pathway we

NOTE Confidence: 0.30218259

00:46:15.697 --> 00:46:17.888 can also promote cell deaths and this

NOTE Confidence: 0.30218259

00:46:17.888 --> 00:46:20.051 cell death again can be rescued by

NOTE Confidence: 0.30218259

00:46:20.051 --> 00:46:22.310 the specify the the reducing regions

NOTE Confidence: 0.30218259

00:46:22.310 --> 00:46:24.874 and again the cell death does not

NOTE Confidence: 0.30218259

00:46:24.874 --> 00:46:27.023 occur in the NCK one local cells.

NOTE Confidence: 0.30218259

00:46:27.030 --> 00:46:29.004 So therefore the rack effect on

NOTE Confidence: 0.30218259

00:46:29.004 --> 00:46:31.293 the cell death is really dependent

NOTE Confidence: 0.30218259

00:46:31.293 --> 00:46:33.548 on this wave recordly complex.

NOTE Confidence: 0.30218259

00:46:33.550 --> 00:46:36.259 So all this study and other data

NOTE Confidence: 0.30218259

00:46:36.259 --> 00:46:38.409 show that basically the activation

NOTE Confidence: 0.30218259

00:46:38.409 --> 00:46:41.133 of this password rack we've somehow

NOTE Confidence: 0.30218259

00:46:41.133 --> 00:46:43.389 to promote this cell deaths,

NOTE Confidence: 0.30218259

00:46:43.390 --> 00:46:46.495 but not at the level of the SSSM 11

NOTE Confidence: 0.30218259

00:46:46.495 --> 00:46:48.830 or system uptake or NEPHI don't.

NOTE Confidence: 0.30218259

00:46:48.830 --> 00:46:50.150 I don't show the data here,

NOTE Confidence: 0.30218259

00:46:50.150 --> 00:46:53.108 but it's really to regulate the

NOTE Confidence: 0.30218259

00:46:53.108 --> 00:46:55.080 cytoskeleton structure and therefore

NOTE Confidence: 0.30218259

00:46:55.160 --> 00:46:56.828 to promote cell deaths.

NOTE Confidence: 0.30218259

00:46:56.830 --> 00:46:58.643 So I'm going to discuss a little

NOTE Confidence: 0.30218259

00:46:58.643 --> 00:47:00.927 bit how we can interpret this data.

NOTE Confidence: 0.30218259

00:47:00.930 --> 00:47:01.291 OK.

NOTE Confidence: 0.30218259

00:47:01.291 --> 00:47:03.457 But this really shows that this

NOTE Confidence: 0.30218259

00:47:03.457 --> 00:47:05.861 rack and we've rec it complex play

NOTE Confidence: 0.30218259

00:47:05.861 --> 00:47:07.874 a role in this cell deaths.

NOTE Confidence: 0.30218259

00:47:07.874 --> 00:47:08.566 So OK,

NOTE Confidence: 0.30218259

00:47:08.570 --> 00:47:10.234 so I'm going to also we kind of

NOTE Confidence: 0.30218259

00:47:10.234 --> 00:47:12.033 want to think about how we can

NOTE Confidence: 0.30218259

00:47:12.033 --> 00:47:13.363 target this cell deaths in,

NOTE Confidence: 0.29294682

00:47:13.370 --> 00:47:14.647 in, in kind of therapy, right.

NOTE Confidence: 0.29294682

00:47:14.647 --> 00:47:16.586 So the way we study this cell

NOTE Confidence: 0.29294682

00:47:16.586 --> 00:47:18.524 deaths is to culture cells in

NOTE Confidence: 0.29294682

00:47:18.524 --> 00:47:20.066 the glucose free medium, right.

NOTE Confidence: 0.29294682

00:47:20.066 --> 00:47:21.578 The other way we can do this

NOTE Confidence: 0.29294682

00:47:21.578 --> 00:47:23.170 is to use glute inhibitors,

NOTE Confidence: 0.29294682

00:47:23.170 --> 00:47:25.825 So glute glute glucose transport

NOTE Confidence: 0.29294682

00:47:25.825 --> 00:47:28.890 inhibitors to block the glucose transport

NOTE Confidence: 0.29294682

00:47:28.890 --> 00:47:31.340 and therefore mimic glucose starvation.

NOTE Confidence: 0.29294682

00:47:31.340 --> 00:47:34.284 So hopefully that can also make those cells

NOTE Confidence: 0.29294682

00:47:34.284 --> 00:47:36.854 more sensitive to to to the best of pulses.

NOTE Confidence: 0.29294682

00:47:36.860 --> 00:47:39.280 And this is indeed what we found in the cells

NOTE Confidence: 0.29294682

00:47:39.334 --> 00:47:41.536 with high expression of this transporter.

NOTE Confidence: 0.29294682

00:47:41.540 --> 00:47:43.451 And you can see with different glute

NOTE Confidence: 0.29294682

00:47:43.451 --> 00:47:45.233 inhibitors we can make cells more

NOTE Confidence: 0.29294682

00:47:45.233 --> 00:47:47.051 sensitive compared with those cells with

NOTE Confidence: 0.29294682

00:47:47.051 --> 00:47:48.979 low expression of this transporter.

NOTE Confidence: 0.29294682

00:47:48.980 --> 00:47:49.357 Conversely,

NOTE Confidence: 0.29294682

00:47:49.357 --> 00:47:51.996 if we over expressed this transporter in

NOTE Confidence: 0.29294682

00:47:51.996 --> 00:47:54.500 the in the in the low expression cell line,

NOTE Confidence: 0.29294682

00:47:54.500 --> 00:47:57.048 we can also since it has those

NOTE Confidence: 0.29294682

00:47:57.048 --> 00:47:59.525 cells increased the cell that's in

NOTE Confidence: 0.29294682

00:47:59.525 --> 00:48:01.710 response to the glute inhibitors.

NOTE Confidence: 0.29294682

00:48:01.710 --> 00:48:03.467 Furthermore, we have found this in vivo.

NOTE Confidence: 0.29294682

00:48:03.470 --> 00:48:06.386 So this was done by Xiao Wang and so

NOTE Confidence: 0.29294682

00:48:06.390 --> 00:48:08.406 we tested the PDX model with is a low

NOTE Confidence: 0.29294682

00:48:08.406 --> 00:48:10.586 or high expression of this transport.

NOTE Confidence: 0.29294682

00:48:10.590 --> 00:48:13.140 And again the glute inhibitors

NOTE Confidence: 0.29294682

00:48:13.140 --> 00:48:14.670 are more sensitive,

NOTE Confidence: 0.29294682

00:48:14.670 --> 00:48:16.651 works better in the in the PDX

NOTE Confidence: 0.29294682

00:48:16.651 --> 00:48:18.310 model with high expressions.

NOTE Confidence: 0.29294682

00:48:18.310 --> 00:48:20.380 So Randy suggested we can use

NOTE Confidence: 0.29294682

00:48:20.380 --> 00:48:23.230 glute in which to target this this

NOTE Confidence: 0.29294682

00:48:23.230 --> 00:48:25.605 tumors with high expression of

NOTE Confidence: 0.29294682

00:48:25.605 --> 00:48:27.784 this transporter as a therapeutic

NOTE Confidence: 0.29294682

00:48:27.784 --> 00:48:29.980 strategy to induce specs of pulses.

NOTE Confidence: 0.29294682

00:48:29.980 --> 00:48:32.074 And we further prove those glutin

NOTE Confidence: 0.29294682

00:48:32.074 --> 00:48:33.859 inhibitors indeed induce this type

NOTE Confidence: 0.29294682

00:48:33.859 --> 00:48:36.327 of cell diets because as a you

NOTE Confidence: 0.29294682

00:48:36.327 --> 00:48:38.181 know for example it doesn't use

NOTE Confidence: 0.29294682

00:48:38.181 --> 00:48:40.479 other cell diets induce the best

NOTE Confidence: 0.29294682

00:48:40.479 --> 00:48:42.916 by bonding and also disruption of

NOTE Confidence: 0.29294682

00:48:42.916 --> 00:48:45.156 cytoskeleton structures in the cells.

NOTE Confidence: 0.29294682

00:48:45.160 --> 00:48:47.500 So here I want to just give you a summary

NOTE Confidence: 0.29294682

00:48:47.566 --> 00:48:49.799 for the second part of my presentation.

NOTE Confidence: 0.29294682

00:48:49.800 --> 00:48:51.928 So what we found here is that in

NOTE Confidence: 0.29294682

00:48:51.928 --> 00:48:53.981 the first part of my presentation

NOTE Confidence: 0.29294682

00:48:53.981 --> 00:48:56.153 I mentioned that is transport the

NOTE Confidence: 0.29294682

00:48:56.219 --> 00:48:58.284 SSC significant important system to

NOTE Confidence: 0.29294682

00:48:58.284 --> 00:49:00.731 protect cell from for process and

NOTE Confidence: 0.29294682

00:49:00.731 --> 00:49:03.398 that benefit kind of cells because by

NOTE Confidence: 0.29294682

00:49:03.398 --> 00:49:05.649 surprise for process you can clean

NOTE Confidence: 0.29294682

00:49:05.649 --> 00:49:08.182 ability to to to to induce tumor

NOTE Confidence: 0.29294682

00:49:08.182 --> 00:49:10.870 progression metastasis so on and so forth.

NOTE Confidence: 0.29294682

00:49:10.870 --> 00:49:11.268 However,

NOTE Confidence: 0.29294682

00:49:11.268 --> 00:49:14.013 what I'm going to see for the second

NOTE Confidence: 0.29294682

00:49:14.013 --> 00:49:15.770 part of my presentation I want to

NOTE Confidence: 0.29294682

00:49:15.827 --> 00:49:17.659 say is that that comes with a cost.

NOTE Confidence: 0.29294682

00:49:17.660 --> 00:49:19.200 So many things have right have two

NOTE Confidence: 0.29294682

00:49:19.200 --> 00:49:21.070 sides where I have to you know the coin

NOTE Confidence: 0.29294682

00:49:21.070 --> 00:49:22.900 has two sides so you benefit something,

NOTE Confidence: 0.29294682

00:49:22.900 --> 00:49:24.260 you have to lose something.

NOTE Confidence: 0.29294682

00:49:24.260 --> 00:49:27.268 So the cost here is that this high

NOTE Confidence: 0.29294682

00:49:27.268 --> 00:49:28.992 expression of SS7 ivine because

NOTE Confidence: 0.29294682

00:49:28.992 --> 00:49:31.260 import a lot of system that can

NOTE Confidence: 0.29294682

00:49:31.329 --> 00:49:33.214 induce bisulfide stress and this

NOTE Confidence: 0.29294682

00:49:33.214 --> 00:49:35.537 is the mainly because of bisulfide

NOTE Confidence: 0.29294682

00:49:35.537 --> 00:49:38.760 such as system are you know toxic to

NOTE Confidence: 0.29294682

00:49:38.760 --> 00:49:40.918 the cells And under the conditions

NOTE Confidence: 0.29294682

00:49:40.918 --> 00:49:43.661 with any pH depletion such as on the

NOTE Confidence: 0.29294682

00:49:43.661 --> 00:49:45.536 glucose deprivation condition that can

NOTE Confidence: 0.29294682

00:49:45.536 --> 00:49:48.065 induce rapid cell deaths but a very

NOTE Confidence: 0.29294682

00:49:48.065 --> 00:49:49.735 different cell deaths mechanism and

NOTE Confidence: 0.29294682

00:49:49.735 --> 00:49:54.109 we can't we we termed by soft tosses.

NOTE Confidence: 0.29294682

00:49:54.110 --> 00:49:56.365 Now mechanistically we propose that

NOTE Confidence: 0.29294682

00:49:56.365 --> 00:49:58.620 this high accumulation of diazol

NOTE Confidence: 0.29294682

00:49:58.690 --> 00:50:00.958 molecules can induce a parent of

NOTE Confidence: 0.29294682

00:50:00.958 --> 00:50:02.925 diazepam bounding in the acting

NOTE Confidence: 0.29294682

00:50:02.925 --> 00:50:05.235 cytoscondin protein that can use to

NOTE Confidence: 0.29294682

00:50:05.235 --> 00:50:07.986 the collapse of the acting network

NOTE Confidence: 0.29294682

00:50:07.986 --> 00:50:10.114 and eventually this contribute

NOTE Confidence: 0.3404071

00:50:10.120 --> 00:50:12.521 to bisulfi tosis and the reason why

NOTE Confidence: 0.3404071

00:50:12.521 --> 00:50:14.886 this can contribute to that that's of

NOTE Confidence: 0.3404071

00:50:14.886 --> 00:50:17.233 tosses perhaps because those as I just

NOTE Confidence: 0.3404071

00:50:17.233 --> 00:50:19.477 mentioned that this involve this rack

NOTE Confidence: 0.3404071

00:50:19.480 --> 00:50:23.400 WRC pathway and to active up to three

NOTE Confidence: 0.3404071

00:50:23.400 --> 00:50:25.080 complex to immediate the namely protea.

NOTE Confidence: 0.3404071

00:50:25.080 --> 00:50:27.920 So namely protea form this web like you

NOTE Confidence: 0.3404071

00:50:27.920 --> 00:50:30.496 know acting structure so that perhaps

NOTE Confidence: 0.3404071

00:50:30.496 --> 00:50:32.666 can facilitated the bisulfi bounding

NOTE Confidence: 0.3404071

00:50:32.666 --> 00:50:35.144 in those status skeleton network so

NOTE Confidence: 0.3404071

00:50:35.144 --> 00:50:38.778 therefore can promote the cell deaths.

NOTE Confidence: 0.3404071

00:50:38.780 --> 00:50:41.486 So we further propose this this Oh yeah

NOTE Confidence: 0.3404071

00:50:41.486 --> 00:50:43.390 so it's just point that I just mentioned

NOTE Confidence: 0.3404071

00:50:43.390 --> 00:50:45.448 and we further propose that this can

NOTE Confidence: 0.3404071

00:50:45.448 --> 00:50:47.585 perhaps we can use this as a strategic

NOTE Confidence: 0.3404071

00:50:47.585 --> 00:50:49.654 strategy for kind of therapy you know

NOTE Confidence: 0.3404071

00:50:49.654 --> 00:50:52.160 and it's the particularly in the tumors

NOTE Confidence: 0.3404071

00:50:52.228 --> 00:50:54.979 with high expression of this SRC simulator.

NOTE Confidence: 0.3404071

00:50:54.980 --> 00:50:57.339 So one quick question for us is,

NOTE Confidence: 0.3404071

00:50:57.340 --> 00:50:59.815 so if you follow my presentation, right,

NOTE Confidence: 0.3404071

00:50:59.815 --> 00:51:02.975 so we define what is that's of course

NOTE Confidence: 0.3404071

00:51:02.975 --> 00:51:05.202 basically is glucose starvation induced

NOTE Confidence: 0.3404071

00:51:05.202 --> 00:51:08.585 cell deaths in the cell lines or in cells

NOTE Confidence: 0.3404071

00:51:08.585 --> 00:51:10.960 with high expression of s s similar,

NOTE Confidence: 0.3404071

00:51:10.960 --> 00:51:11.245 right.

NOTE Confidence: 0.3404071

00:51:11.245 --> 00:51:13.529 So this is a very specific scenario, right.

NOTE Confidence: 0.3404071

00:51:13.529 --> 00:51:15.841 But we want to see whether you know

NOTE Confidence: 0.3404071

00:51:15.841 --> 00:51:18.355 this can be broadened to other contacts,

NOTE Confidence: 0.3404071

00:51:18.360 --> 00:51:18.688 right?

NOTE Confidence: 0.3404071

00:51:18.688 --> 00:51:20.656 Because the essence of this cell

NOTE Confidence: 0.3404071

00:51:20.656 --> 00:51:22.859 that's actually is by so far stress

NOTE Confidence: 0.3404071

00:51:22.859 --> 00:51:24.593 is the high accumulation of system

NOTE Confidence: 0.3404071

00:51:24.650 --> 00:51:26.178 or other dysfile molecules.

NOTE Confidence: 0.3404071

00:51:26.180 --> 00:51:27.874 So we want to see whether we

NOTE Confidence: 0.3404071

00:51:27.874 --> 00:51:28.940 can also induce more,

NOTE Confidence: 0.3404071

00:51:28.940 --> 00:51:30.844 you know the apparent accumulation of this

NOTE Confidence: 0.3404071

00:51:30.844 --> 00:51:32.580 disulfide molecules on any other conditions,

NOTE Confidence: 0.3404071

00:51:32.580 --> 00:51:32.993 right.

NOTE Confidence: 0.3404071

00:51:32.993 --> 00:51:35.058 So we started this recently.

NOTE Confidence: 0.3404071

00:51:35.060 --> 00:51:37.352 We tested this idea in the

NOTE Confidence: 0.3404071

00:51:37.352 --> 00:51:38.498 hydrogen peroxide induced.

NOTE Confidence: 0.3404071

00:51:38.500 --> 00:51:40.418 The reason we do this is because

NOTE Confidence: 0.3404071

00:51:40.418 --> 00:51:42.012 hydrogen peroxide is also conditioned

NOTE Confidence: 0.3404071

00:51:42.012 --> 00:51:44.060 to induce oxygen stress.

NOTE Confidence: 0.3404071

00:51:44.060 --> 00:51:46.846 And so as shown here the action

NOTE Confidence: 0.3404071

00:51:46.846 --> 00:51:48.904 hydrogen peroxide can be detoxified

NOTE Confidence: 0.3404071

00:51:48.904 --> 00:51:51.268 in the cells by gluteus ion.

NOTE Confidence: 0.3404071

00:51:51.270 --> 00:51:53.818 So this converts it to the oxides

NOTE Confidence: 0.3404071

00:51:53.818 --> 00:51:56.086 of glucion and oxide Glucion

NOTE Confidence: 0.3404071

00:51:56.086 --> 00:51:59.158 called GSSG will be commonly packed

NOTE Confidence: 0.3404071

00:51:59.158 --> 00:52:01.498 glucion which consumes any pH.

NOTE Confidence: 0.3404071

00:52:01.498 --> 00:52:05.255 So we think this might have something to

NOTE Confidence: 0.3404071

00:52:05.255 --> 00:52:08.410 do with this any pH depletion which is

NOTE Confidence: 0.3404071

00:52:08.410 --> 00:52:10.910 required for the tacit pauses induction.

NOTE Confidence: 0.3404071

00:52:10.910 --> 00:52:11.240 However,

NOTE Confidence: 0.3404071

00:52:11.240 --> 00:52:13.550 the issue here is that this transporter

NOTE Confidence: 0.3404071

00:52:13.550 --> 00:52:15.274 also can generate the glucion

NOTE Confidence: 0.3404071

00:52:15.274 --> 00:52:17.284 but so therefore to protect cell

NOTE Confidence: 0.3404071

00:52:17.284 --> 00:52:19.277 from protected cell from hydrogen

NOTE Confidence: 0.3404071

00:52:19.277 --> 00:52:20.869 peroxide into cell that's.

NOTE Confidence: 0.3404071

00:52:20.870 --> 00:52:23.638 But on the other hand you actually promote

NOTE Confidence: 0.3404071

00:52:23.638 --> 00:52:25.630 because the system right conversion

NOTE Confidence: 0.3404071

00:52:25.630 --> 00:52:28.102 of assisting also consumes any pH.

NOTE Confidence: 0.3404071

00:52:28.110 --> 00:52:30.477 So this has a kind of has a opposing

NOTE Confidence: 0.3404071

00:52:30.477 --> 00:52:32.985 role potentially on the dice of pulses.

NOTE Confidence: 0.3404071

00:52:32.990 --> 00:52:34.952 So we think perhaps it's expression

NOTE Confidence: 0.3404071

00:52:34.952 --> 00:52:37.005 level depending how high the expression

NOTE Confidence: 0.3404071

00:52:37.005 --> 00:52:39.063 level of this transporter maybe have

NOTE Confidence: 0.3404071

00:52:39.063 --> 00:52:41.164 a different role in regulating the

NOTE Confidence: 0.3404071

00:52:41.164 --> 00:52:43.054 hydrogen peroxide induced to sell

NOTE Confidence: 0.3404071

00:52:43.054 --> 00:52:45.942 this that is the when there's moderate

NOTE Confidence: 0.3404071

00:52:45.942 --> 00:52:47.594 expression of this transporter.

NOTE Confidence: 0.3404071

00:52:47.600 --> 00:52:49.862 So this transporter might have a

NOTE Confidence: 0.3404071

00:52:49.862 --> 00:52:51.767 beneficial role right because in

NOTE Confidence: 0.3404071

00:52:51.767 --> 00:52:53.741 this condition the major effect here

NOTE Confidence: 0.3404071

00:52:53.741 --> 00:52:56.153 is to generate more glucose ion and

NOTE Confidence: 0.3404071

00:52:56.153 --> 00:52:58.199 then can protect cell from hydrogen

NOTE Confidence: 0.3404071

00:52:58.200 --> 00:53:01.203 peroxide induced the cell deaths and

NOTE Confidence: 0.3404071

00:53:01.203 --> 00:53:03.787 we know the cell deaths many are at

NOTE Confidence: 0.3404071

00:53:03.787 --> 00:53:06.080 pauses however in the cells with very

NOTE Confidence: 0.3404071

00:53:06.080 --> 00:53:07.480 high expression of this transporter.

NOTE Confidence: 0.3404071

00:53:07.480 --> 00:53:10.528 So the cells are overwhelmed with

NOTE Confidence: 0.3404071

00:53:10.528 --> 00:53:12.560 those assistant molecules when

NOTE Confidence: 0.2755118

00:53:12.560 --> 00:53:15.584 when the cells are captured in the

NOTE Confidence: 0.2755118

00:53:15.584 --> 00:53:17.744 hydrogen peroxide condition because now

NOTE Confidence: 0.2755118

00:53:17.744 --> 00:53:20.126 the GSSG also consumes the conversion

NOTE Confidence: 0.2755118

00:53:20.126 --> 00:53:23.359 back to GSH also consumes a lot of any pH.

NOTE Confidence: 0.2755118

00:53:23.360 --> 00:53:25.957 So under this condition the there is

NOTE Confidence: 0.2755118

00:53:25.957 --> 00:53:27.943 massive condition system so that can

NOTE Confidence: 0.2755118

00:53:27.943 --> 00:53:29.640 kill cells through by soft tosses.

NOTE Confidence: 0.2755118

00:53:29.640 --> 00:53:31.909 So I'm going to show you a couple

NOTE Confidence: 0.2755118

00:53:31.909 --> 00:53:33.743 of data to illustrate our model.

NOTE Confidence: 0.2755118

00:53:33.743 --> 00:53:37.540 So first is to see the system concentration.

NOTE Confidence: 0.2755118

00:53:37.540 --> 00:53:39.588 Recall Ernie I show you that in glucose

NOTE Confidence: 0.2755118

00:53:39.588 --> 00:53:41.271 dye vision condition there's increased

NOTE Confidence: 0.2755118

00:53:41.271 --> 00:53:43.491 the disify system concentration in the

NOTE Confidence: 0.2755118

00:53:43.491 --> 00:53:45.227 cells with over expression transport.

NOTE Confidence: 0.2755118

00:53:45.227 --> 00:53:47.523 So here we have three sets of cell

NOTE Confidence: 0.2755118

00:53:47.523 --> 00:53:49.349 lines relatively low or relatively

NOTE Confidence: 0.2755118

00:53:49.349 --> 00:53:50.459 moderate or high.

NOTE Confidence: 0.2755118

00:53:50.460 --> 00:53:52.796 So the definition here it will be a

NOTE Confidence: 0.2755118

00:53:52.796 --> 00:53:54.501 moderate will be probably increase

NOTE Confidence: 0.2755118

00:53:54.501 --> 00:53:56.613 the system uptake by fivefold and

NOTE Confidence: 0.2755118

00:53:56.613 --> 00:53:58.578 high will be more than tenfold.

NOTE Confidence: 0.2755118

00:53:58.580 --> 00:54:00.420 So we see it under the moderate condition,

NOTE Confidence: 0.2755118

00:54:00.420 --> 00:54:02.564 we don't see much system accumulation

NOTE Confidence: 0.2755118

00:54:02.564 --> 00:54:04.552 but really when you have very high

NOTE Confidence: 0.2755118

00:54:04.552 --> 00:54:06.507 expression now you'll see a massive

NOTE Confidence: 0.2755118

00:54:06.507 --> 00:54:07.839 accumulation of system concentration.

NOTE Confidence: 0.2755118

00:54:07.840 --> 00:54:09.376 Now the cell death is interesting

NOTE Confidence: 0.2755118

00:54:09.376 --> 00:54:11.464 if you capture this cells on the

NOTE Confidence: 0.2755118

00:54:11.464 --> 00:54:12.478 glucose starvation condition,

NOTE Confidence: 0.2755118

00:54:12.480 --> 00:54:15.088 you can see in regarding this is moderate

NOTE Confidence: 0.2755118

00:54:15.088 --> 00:54:17.877 or high expression of this transporter,

NOTE Confidence: 0.2755118

00:54:17.880 --> 00:54:19.825 it's always promotes this glucose

NOTE Confidence: 0.2755118

00:54:19.825 --> 00:54:22.824 starvation use the cell death which is best

NOTE Confidence: 0.2755118

00:54:22.824 --> 00:54:25.120 of process and we have high expression.

NOTE Confidence: 0.2755118

00:54:25.120 --> 00:54:26.830 I have more cell deaths now.

NOTE Confidence: 0.2755118

00:54:26.830 --> 00:54:28.741 However the patent changed a lot when

NOTE Confidence: 0.2755118

00:54:28.741 --> 00:54:31.202 we studied on the culture of the cells

NOTE Confidence: 0.2755118

00:54:31.202 --> 00:54:32.782 on the hydrogen proxide condition.

NOTE Confidence: 0.2755118

00:54:32.790 --> 00:54:34.566 So with modern over expression you

NOTE Confidence: 0.2755118

00:54:34.566 --> 00:54:36.309 can actually can protect the cells.

NOTE Confidence: 0.2755118

00:54:36.310 --> 00:54:39.194 So this is what I illustrated here because

NOTE Confidence: 0.2755118

00:54:39.194 --> 00:54:41.534 you can increase glucion biosynthesis

NOTE Confidence: 0.2755118

00:54:41.534 --> 00:54:44.063 so therefore can surprise the hydrogen

NOTE Confidence: 0.2755118

00:54:44.063 --> 00:54:46.349 peroxide and use the cell toxicity.

NOTE Confidence: 0.2755118

00:54:46.350 --> 00:54:46.657 However,

NOTE Confidence: 0.2755118

00:54:46.657 --> 00:54:48.499 the cell that you just drastically

NOTE Confidence: 0.2755118

00:54:48.499 --> 00:54:50.456 increased when you have very high

NOTE Confidence: 0.2755118

00:54:50.456 --> 00:54:51.764 expressions this transporter and

NOTE Confidence: 0.2755118

00:54:51.764 --> 00:54:53.452 that's because the best of tosses

NOTE Confidence: 0.2755118

00:54:53.452 --> 00:54:55.375 because we can show this by a number

NOTE Confidence: 0.2755118

00:54:55.375 --> 00:54:57.745 of other approaches to prove this

NOTE Confidence: 0.2755118

00:54:57.745 --> 00:55:01.138 is indeed caused by Dysol 5 bonding.

NOTE Confidence: 0.2755118

00:55:01.140 --> 00:55:02.676 So I want to end my talk by

NOTE Confidence: 0.2755118

00:55:02.676 --> 00:55:04.260 presenting a couple of key questions.

NOTE Confidence: 0.2755118

00:55:04.260 --> 00:55:06.094 I think because this is a new

NOTE Confidence: 0.2755118

00:55:06.100 --> 00:55:06.748 formal cell dies,

NOTE Confidence: 0.2755118

00:55:06.748 --> 00:55:08.745 I think that there are a number of new

NOTE Confidence: 0.2755118

00:55:08.745 --> 00:55:10.257 customers we can start in the future.

NOTE Confidence: 0.2755118

00:55:10.260 --> 00:55:10.900 For example,

NOTE Confidence: 0.2755118

00:55:10.900 --> 00:55:12.820 want to study if there's any

NOTE Confidence: 0.2755118

00:55:12.820 --> 00:55:13.980 other bouncing factors.

NOTE Confidence: 0.2755118

00:55:13.980 --> 00:55:16.230 I should only mention that AC key AP one or

NOTE Confidence: 0.2755118

00:55:16.286 --> 00:55:18.536 cause the phenotype is relatively moderate.

NOTE Confidence: 0.2755118

00:55:18.540 --> 00:55:20.955 So we think there must be other downstream

NOTE Confidence: 0.2755118

00:55:20.955 --> 00:55:23.580 effectors mediating this type of cell test.

NOTE Confidence: 0.2755118

00:55:23.580 --> 00:55:25.736 So we're very interested in starting that.

NOTE Confidence: 0.2755118

00:55:25.740 --> 00:55:28.340 And there's any performing proteins.

NOTE Confidence: 0.2755118

00:55:28.340 --> 00:55:30.092 So people study,

NOTE Confidence: 0.2755118

00:55:30.092 --> 00:55:31.260 for example,

NOTE Confidence: 0.2755118

00:55:31.260 --> 00:55:32.436 parapaulsis or necropaulsis,

NOTE Confidence: 0.2755118

00:55:32.436 --> 00:55:35.180 know that the performing protein are very,

NOTE Confidence: 0.2755118

00:55:35.180 --> 00:55:35.930 very important.

NOTE Confidence: 0.2755118

00:55:35.930 --> 00:55:38.180 So we'll want to know whether

NOTE Confidence: 0.2755118

00:55:38.180 --> 00:55:39.758 those proteins play a similar role

NOTE Confidence: 0.2755118

00:55:39.758 --> 00:55:41.980 in this type of cell test and we

NOTE Confidence: 0.2755118

00:55:41.980 --> 00:55:43.900 want to see what is threshold.

NOTE Confidence: 0.2755118

00:55:43.900 --> 00:55:46.996 So we'll talk about you know highest system

NOTE Confidence: 0.2755118

00:55:46.996 --> 00:55:49.638 Commission but really is how high is high,

NOTE Confidence: 0.2755118

00:55:49.640 --> 00:55:49.900 right.

NOTE Confidence: 0.2755118

00:55:49.900 --> 00:55:51.980 So we want to see really what is

NOTE Confidence: 0.2755118

00:55:51.980 --> 00:55:54.000 the stretch code for the Tysabad

NOTE Confidence: 0.2755118

00:55:54.000 --> 00:55:56.000 stress required for this CL test

NOTE Confidence: 0.2755118

00:55:56.000 --> 00:55:58.200 and what about the Ocneos,

NOTE Confidence: 0.26234633

00:55:58.200 --> 00:56:00.240 any other signal pathways cross talk

NOTE Confidence: 0.26234633

00:56:00.240 --> 00:56:03.152 with type of CL test, so on and so

NOTE Confidence: 0.26234633

00:56:03.152 --> 00:56:06.780 forth but not really is the what is,

NOTE Confidence: 0.26234633

00:56:06.780 --> 00:56:09.580 is the unique marker for this cell test.

NOTE Confidence: 0.26234633

00:56:09.580 --> 00:56:11.692 So we don't have a unique marker to

NOTE Confidence: 0.26234633

00:56:11.692 --> 00:56:13.656 measure this type of cell test so far.

NOTE Confidence: 0.26234633

00:56:13.660 --> 00:56:15.280 So that's really A1 important question

NOTE Confidence: 0.26234633

00:56:15.280 --> 00:56:17.378 for us to address in the future study,

NOTE Confidence: 0.26234633

00:56:17.380 --> 00:56:19.865 particularly if we want to explore this

NOTE Confidence: 0.26234633

00:56:19.865 --> 00:56:22.132 type of cell test for any therapy,

NOTE Confidence: 0.26234633

00:56:22.132 --> 00:56:23.380 you know disease treatment.

NOTE Confidence: 0.26234633

00:56:23.380 --> 00:56:26.899 So the bear market will be important for us.

NOTE Confidence: 0.26234633

00:56:26.900 --> 00:56:29.366 So with that I'm going to in my talk,

NOTE Confidence: 0.26234633

00:56:29.366 --> 00:56:30.458 I'm going to thank my name,

NOTE Confidence: 0.26234633

00:56:30.460 --> 00:56:32.702 I think I mentioned them during my

NOTE Confidence: 0.26234633

00:56:32.702 --> 00:56:34.538 presentation and some of them already

NOTE Confidence: 0.26234633

00:56:34.538 --> 00:56:36.902 left lab established their lab and also

NOTE Confidence: 0.26234633

00:56:36.902 --> 00:56:39.090 thank our collaborators and the funding,

NOTE Confidence: 0.26234633

00:56:39.090 --> 00:56:39.520 resource funding.

NOTE Confidence: 0.26234633

00:56:39.520 --> 00:56:41.025 I want to thank you for your

NOTE Confidence: 0.26234633

00:56:41.025 --> 00:56:42.192 attention and I would like to

NOTE Confidence: 0.26234633

00:56:42.192 --> 00:56:43.330 address any question if you have.

NOTE Confidence: 0.26234633

00:56:43.330 --> 00:56:43.730 Thank you.

NOTE Confidence: 0.26234633

00:56:43.730 --> 00:56:44.130 Good questions.

NOTE Confidence: 0.5557587

00:56:55.930 --> 00:56:56.290 Yes,

NOTE Confidence: 0.66361624

00:57:14.070 --> 00:57:14.430 right,

NOTE Confidence: 0.41648257

00:57:32.130 --> 00:57:32.754 right, right, right.

NOTE Confidence: 0.41648257

00:57:32.754 --> 00:57:34.210 So yeah that's a very good question.

NOTE Confidence: 0.41648257

00:57:34.210 --> 00:57:37.210 I think we haven't the systematic study this.

NOTE Confidence: 0.41648257

00:57:37.210 --> 00:57:39.858 I think there are a number of bioinformatic

NOTE Confidence: 0.41648257

00:57:39.858 --> 00:57:42.152 papers or you know genomics papers

NOTE Confidence: 0.41648257

00:57:42.152 --> 00:57:45.164 have we have done such analysis.

NOTE Confidence: 0.41648257

00:57:45.170 --> 00:57:46.983 I think I think it's not very

NOTE Confidence: 0.41648257

00:57:46.983 --> 00:57:49.720 clear for GPS for about 4-4 s s

NOTE Confidence: 0.41648257

00:57:49.720 --> 00:57:52.512 711 it is over expressed in many

NOTE Confidence: 0.41648257

00:57:52.512 --> 00:57:54.138 cancers such As for example keep

NOTE Confidence: 0.41648257

00:57:54.138 --> 00:57:55.850 one that's very good coronation.

NOTE Confidence: 0.41648257

00:57:55.850 --> 00:57:58.125 So the key prime mutant lung cancer.

NOTE Confidence: 0.41648257

00:57:58.130 --> 00:58:00.290 I think we have also done this yeah you

NOTE Confidence: 0.41648257

00:58:00.290 --> 00:58:02.382 want for papers so if you look at the

NOTE Confidence: 0.41648257

00:58:02.382 --> 00:58:04.850 TCG data set the keep one mutant non

NOTE Confidence: 0.41648257

00:58:04.850 --> 00:58:07.689 kind of cells have higher expression of

NOTE Confidence: 0.41648257

00:58:07.690 --> 00:58:10.530 SSS 711 compared with keep my wild type.

NOTE Confidence: 0.41648257

00:58:10.530 --> 00:58:12.570 Other people have shown that also

NOTE Confidence: 0.41648257

00:58:12.570 --> 00:58:14.456 over expressed in other kind of

NOTE Confidence: 0.41648257

00:58:14.456 --> 00:58:16.849 types such as P DAG and you know

NOTE Confidence: 0.41648257

00:58:16.849 --> 00:58:19.327 certainly the kidney kinds of example.

NOTE Confidence: 0.41648257

00:58:19.330 --> 00:58:22.726 So, so definitely SSS 711 has been

NOTE Confidence: 0.41648257

00:58:22.726 --> 00:58:25.291 had studied a lot and also you as you

NOTE Confidence: 0.41648257

00:58:25.291 --> 00:58:27.468 mentioned the s s 711 also undergo

NOTE Confidence: 0.41648257

00:58:27.468 --> 00:58:29.260 this transcription regulation by a

NOTE Confidence: 0.41648257

00:58:29.260 --> 00:58:30.740 number of transcription factors.

NOTE Confidence: 0.41648257

00:58:30.740 --> 00:58:33.785 So that explains why is you know

NOTE Confidence: 0.41648257

00:58:33.785 --> 00:58:35.033 should the the,

NOTE Confidence: 0.41648257

00:58:35.033 --> 00:58:36.898 the the differential expression consists.

NOTE Confidence: 0.41648257

00:58:36.900 --> 00:58:37.188 Yeah,

NOTE Confidence: 0.41648257

00:58:37.188 --> 00:58:39.204 I think the GPS 4 probably is

NOTE Confidence: 0.41648257

00:58:39.204 --> 00:58:40.815 nice understood and certainly we

NOTE Confidence: 0.41648257

00:58:40.815 --> 00:58:43.284 should do that more thoroughly.

NOTE Confidence: 0.41648257

00:58:43.284 --> 00:58:43.820 Yeah.

NOTE Confidence: 0.41648257

00:58:43.820 --> 00:58:44.300 Yes,

NOTE Confidence: 0.34843826

00:58:48.420 --> 00:58:48.820 yeah,

NOTE Confidence: 0.28463373

00:58:52.150 --> 00:58:52.430 right,

NOTE Confidence: 0.28463373

00:59:00.830 --> 00:59:01.470 right, right, right, right.

NOTE Confidence: 0.28463373

00:59:06.590 --> 00:59:07.950 Oh yeah, yeah, it's a very good question.

NOTE Confidence: 0.28463373

00:59:07.950 --> 00:59:10.309 So the question is the keep one

NOTE Confidence: 0.28463373

00:59:10.310 --> 00:59:12.263 is the loss in the non conscious

NOTE Confidence: 0.28463373

00:59:12.263 --> 00:59:13.590 union switched with RKP one.

NOTE Confidence: 0.28463373

00:59:13.590 --> 00:59:15.552 So whether the phenotype we described

NOTE Confidence: 0.28463373

00:59:15.552 --> 00:59:17.829 here has anything to do with RKP one.

NOTE Confidence: 0.28463373

00:59:17.830 --> 00:59:19.918 So in this case we have done the

NOTE Confidence: 0.28463373

00:59:19.918 --> 00:59:21.774 experiment for example in the we have

NOTE Confidence: 0.28463373

00:59:21.774 --> 00:59:23.256 done the genetic experiment in the

NOTE Confidence: 0.28463373

00:59:23.256 --> 00:59:25.077 keep 10 sorry in keep on what type

NOTE Confidence: 0.28463373

00:59:25.077 --> 00:59:26.871 not kind of cell we know called keep

NOTE Confidence: 0.28463373

00:59:26.871 --> 00:59:28.400 one and then we shoot the phenotype.

NOTE Confidence: 0.28463373

00:59:28.400 --> 00:59:30.614 So the phenotype is so therefore

NOTE Confidence: 0.28463373

00:59:30.614 --> 00:59:32.679 it's not associated with LTB one.

NOTE Confidence: 0.28463373

00:59:32.680 --> 00:59:35.296 Now she mentioned that the LTB one also

NOTE Confidence: 0.28463373

00:59:35.296 --> 00:59:38.274 has also played a role in in for a pulses.

NOTE Confidence: 0.28463373

00:59:38.280 --> 00:59:40.870 I did I don't have time to talk about here

NOTE Confidence: 0.28463373

00:59:40.938 --> 00:59:43.714 that's because LTB one can also regulate MPK.

NOTE Confidence: 0.28463373

00:59:43.720 --> 00:59:47.185 We prove to show that MPK function

NOTE Confidence: 0.28463373

00:59:47.185 --> 00:59:49.770 to to surprise for a pulses.

NOTE Confidence: 0.28463373

00:59:49.770 --> 00:59:52.240 So the air QP one and no cost the you

NOTE Confidence: 0.28463373

00:59:52.307 --> 00:59:54.547 know for example the air QP one no

NOTE Confidence: 0.28463373

00:59:54.547 --> 00:59:56.993 cost or deficient non kind of cells

NOTE Confidence: 0.28463373

00:59:56.993 --> 00:59:59.344 are more sensitive to to from process.

NOTE Confidence: 0.28463373

00:59:59.344 --> 01:00:01.890 So that has been published by other groups.

NOTE Confidence: 0.28463373

01:00:01.890 --> 01:00:03.892 So you see that there's the difference

NOTE Confidence: 0.28463373

01:00:03.892 --> 01:00:06.434 rather keep one and mute non non kind of

NOTE Confidence: 0.28463373

01:00:06.434 --> 01:00:08.730 cells are more resistant versus air QP

NOTE Confidence: 0.28463373

01:00:08.798 --> 01:00:11.486 one and no cost cells are more sensitive.

NOTE Confidence: 0.28463373

01:00:11.490 --> 01:00:13.849 Yeah so that it's not coordinated here.

NOTE Confidence: 0.28463373

01:00:13.850 --> 01:00:14.124 Yeah,

NOTE Confidence: 0.28463373

01:00:14.124 --> 01:00:16.316 even though the I don't understand the air

NOTE Confidence: 0.28463373

01:00:16.316 --> 01:00:18.900 QP 1 mutation and the keep one mutation open.

NOTE Confidence: 0.28463373

01:00:18.900 --> 01:00:20.416 Commutated, right. So, yeah,

NOTE Confidence: 0.28463373

01:00:20.416 --> 01:00:23.260 but in terms of functioning for process,

NOTE Confidence: 0.28463373

01:00:23.260 --> 01:00:24.976 I think it's kind of opposite.

NOTE Confidence: 0.28463373

01:00:24.980 --> 01:00:27.060 Yeah.

NOTE Confidence: 0.28463373

01:00:27.060 --> 01:00:27.580 Yes.

NOTE Confidence: 0.54428625

01:00:34.860 --> 01:00:35.180 Yeah,

NOTE Confidence: 0.54428625

01:00:42.700 --> 01:00:42.980 Right,

NOTE Confidence: 0.26025218

01:01:00.930 --> 01:01:04.448 right. Yeah. So whether,

NOTE Confidence: 0.26025218

01:01:12.050 --> 01:01:14.050 yeah, yeah. So that's a very good question.

NOTE Confidence: 0.26025218

01:01:14.050 --> 01:01:17.045 So I think as in one of my slides I

NOTE Confidence: 0.26025218

01:01:17.045 --> 01:01:18.618 mentioned rather two sides, right.

NOTE Confidence: 0.26025218

01:01:18.618 --> 01:01:20.914 So you use either use for process

NOTE Confidence: 0.26025218

01:01:20.914 --> 01:01:22.908 inhibitor or for process inducer

NOTE Confidence: 0.26025218

01:01:22.908 --> 01:01:24.604 to treat different diseases.

NOTE Confidence: 0.26025218

01:01:24.610 --> 01:01:26.521 So for cancer we use for process

NOTE Confidence: 0.26025218

01:01:26.521 --> 01:01:28.421 inducer but for many other diseases

NOTE Confidence: 0.26025218

01:01:28.421 --> 01:01:30.126 Nash you know kidney injury,

NOTE Confidence: 0.26025218

01:01:30.130 --> 01:01:32.250 urine to general disease to

NOTE Confidence: 0.26025218

01:01:32.250 --> 01:01:34.370 issue use for process inhibitor.

NOTE Confidence: 0.26025218

01:01:34.370 --> 01:01:36.467 So the question the you know if you use

NOTE Confidence: 0.26025218

01:01:36.467 --> 01:01:38.639 one actually you can actually can maybe

NOTE Confidence: 0.26025218

01:01:38.639 --> 01:01:40.930 induce the open damage on the other side.

NOTE Confidence: 0.26025218

01:01:40.930 --> 01:01:43.289 So that indeed is why important question

NOTE Confidence: 0.26025218

01:01:43.289 --> 01:01:45.840 I think requires more rigorous test in

NOTE Confidence: 0.26025218

01:01:45.840 --> 01:01:49.170 the in the in many curriculum models.

NOTE Confidence: 0.26025218

01:01:49.170 --> 01:01:53.210 Now generally the for process

NOTE Confidence: 0.26025218

01:01:53.210 --> 01:01:56.010 inhibits or for process inducer.

NOTE Confidence: 0.26025218

01:01:56.010 --> 01:01:58.285 So for example for process

NOTE Confidence: 0.26025218

01:01:58.285 --> 01:02:01.141 inhibits we tested in annual model

NOTE Confidence: 0.26025218

01:02:01.141 --> 01:02:03.490 itself doesn't have much effect.

NOTE Confidence: 0.26025218

01:02:03.490 --> 01:02:06.010 I think that the basal because the

NOTE Confidence: 0.26025218

01:02:06.010 --> 01:02:08.757 basal level for process in tissues are

NOTE Confidence: 0.26025218

01:02:08.757 --> 01:02:10.980 relatively low so therefore you just

NOTE Confidence: 0.26025218

01:02:10.980 --> 01:02:12.780 inhibit those are the antioxidants.

NOTE Confidence: 0.26025218

01:02:12.780 --> 01:02:13.740 So it doesn't have much.

NOTE Confidence: 0.26025218

01:02:13.740 --> 01:02:16.060 It needs to be based on the tissue,

NOTE Confidence: 0.26025218

01:02:16.060 --> 01:02:18.634 I mean the the the you know past

NOTE Confidence: 0.26025218

01:02:18.634 --> 01:02:20.720 logic analysis or based on the animal

NOTE Confidence: 0.26025218

01:02:20.786 --> 01:02:22.658 weight we don't see much effect.

NOTE Confidence: 0.26025218

01:02:22.660 --> 01:02:25.817 The for process inducer might be a

NOTE Confidence: 0.26025218

01:02:25.817 --> 01:02:28.864 concern because induce might induce for

NOTE Confidence: 0.26025218

01:02:28.864 --> 01:02:31.200 processing tumors than the normal tissues.

NOTE Confidence: 0.26025218

01:02:31.200 --> 01:02:32.775 So that's always the issue.

NOTE Confidence: 0.26025218

01:02:32.780 --> 01:02:34.698 If you think about for example chemotherapy,

NOTE Confidence: 0.26025218

01:02:34.700 --> 01:02:35.432 radiotherapy, right,

NOTE Confidence: 0.26025218

01:02:35.432 --> 01:02:37.994 you can kill cells in tumors as

NOTE Confidence: 0.26025218

01:02:37.994 --> 01:02:40.092 well as in normal tissues, right.

NOTE Confidence: 0.26025218

01:02:40.092 --> 01:02:41.964 That's why they also have all

NOTE Confidence: 0.26025218

01:02:41.964 --> 01:02:42.900 this side effect.

NOTE Confidence: 0.26025218

01:02:42.900 --> 01:02:45.180 So I think that indeed is a concern.

NOTE Confidence: 0.26025218

01:02:45.180 --> 01:02:47.707 So that's why we think the identified

NOTE Confidence: 0.26025218

01:02:47.707 --> 01:02:49.591 the specific context which tumors

NOTE Confidence: 0.26025218

01:02:49.591 --> 01:02:51.426 are more more vulnerable to

NOTE Confidence: 0.26025218

01:02:51.426 --> 01:02:53.220 fructoses might be important.

NOTE Confidence: 0.26025218

01:02:53.220 --> 01:02:54.484 So in this case,

NOTE Confidence: 0.26025218

01:02:54.484 --> 01:02:56.380 if the tumors are more vulnerable

NOTE Confidence: 0.26025218

01:02:56.445 --> 01:02:58.290 to for ******* the normal tissue,

NOTE Confidence: 0.26025218

01:02:58.290 --> 01:03:00.738 then we can use this sorry fructose

NOTE Confidence: 0.26025218

01:03:00.738 --> 01:03:02.858 inducer to selectively kill tumor

NOTE Confidence: 0.26025218

01:03:02.858 --> 01:03:05.130 cells with aspiring normal tissues.

NOTE Confidence: 0.26025218

01:03:05.130 --> 01:03:06.122 So that's the idea.

NOTE Confidence: 0.26025218

01:03:06.122 --> 01:03:06.370 Yeah,

NOTE Confidence: 0.30661964

01:03:21.290 --> 01:03:22.490 right. Yeah,

NOTE Confidence: 0.42499304

01:03:27.020 --> 01:03:28.460 Yeah. So, yeah,

NOTE Confidence: 0.42499304

01:03:28.460 --> 01:03:30.860 some audience asked this question.

NOTE Confidence: 0.42499304

01:03:30.860 --> 01:03:32.967 I think in Weibo probably would be

NOTE Confidence: 0.42499304

01:03:32.967 --> 01:03:34.626 difficult to mimic this glucose

NOTE Confidence: 0.42499304

01:03:34.626 --> 01:03:37.055 starvation because you are expert on this.

NOTE Confidence: 0.42499304

01:03:37.060 --> 01:03:40.456 The glucose homostasis is tightly regulated.

NOTE Confidence: 0.42499304

01:03:40.460 --> 01:03:43.436 So it's really difficult to see a dramatic

NOTE Confidence: 0.42499304

01:03:43.436 --> 01:03:46.012 decrease of glucose supply right to the,

NOTE Confidence: 0.42499304

01:03:46.020 --> 01:03:48.816 I mean in the systemic level.

NOTE Confidence: 0.42499304

01:03:48.820 --> 01:03:51.700 But what we can propose here is use

NOTE Confidence: 0.42499304

01:03:51.700 --> 01:03:54.470 the glute glute inhibitors to block

NOTE Confidence: 0.42499304

01:03:54.470 --> 01:03:57.620 the glucose optic in the into tumors

NOTE Confidence: 0.42499304

01:03:57.620 --> 01:03:59.717 because glute glutes expression

NOTE Confidence: 0.42499304

01:03:59.717 --> 01:04:03.047 is typically tumors that have high

NOTE Confidence: 0.42499304

01:04:03.047 --> 01:04:04.806 expression glute glucose transporter.

NOTE Confidence: 0.42499304

01:04:04.806 --> 01:04:06.744 So that's why people use FDG

NOTE Confidence: 0.42499304

01:04:06.744 --> 01:04:08.200 pad to image tumors.

NOTE Confidence: 0.42499304

01:04:08.200 --> 01:04:10.085 So that probably is more

NOTE Confidence: 0.42499304

01:04:10.085 --> 01:04:12.013 feasible than I don't know.

NOTE Confidence: 0.42499304

01:04:12.013 --> 01:04:14.359 They use fasting to decrease glucose

NOTE Confidence: 0.42499304

01:04:14.360 --> 01:04:16.232 the the level in the in the blood

NOTE Confidence: 0.42499304

01:04:16.232 --> 01:04:18.101 that probably is more tricky I think

NOTE Confidence: 0.42499304

01:04:18.101 --> 01:04:19.446 right because of the tightening

NOTE Confidence: 0.42499304

01:04:19.502 --> 01:04:21.198 regulated the glucose chromostasis

NOTE Confidence: 0.2988537

01:04:27.380 --> 01:04:28.860 that could be. Yeah. Yeah. Yeah.

NOTE Confidence: 0.2988537

01:04:31.700 --> 01:04:32.480 Right, right, right.

NOTE Confidence: 0.2988537

01:04:32.480 --> 01:04:34.164 We can probably test that. Yeah.

NOTE Confidence: 0.2988537

01:04:34.164 --> 01:04:35.700 Yeah. Probably more challenging.

NOTE Confidence: 0.2988537

01:04:35.700 --> 01:04:37.494 Yeah. I think even fasting itself

NOTE Confidence: 0.2988537

01:04:37.494 --> 01:04:39.317 people have proposed use fasting to

NOTE Confidence: 0.2988537

01:04:39.317 --> 01:04:41.045 as A1 therapeutic strategy but never

NOTE Confidence: 0.2988537

01:04:41.045 --> 01:04:43.020 has been moved to the clinical yet.

NOTE Confidence: 0.2988537

01:04:43.020 --> 01:04:46.457 Yeah, because of many other you know

NOTE Confidence: 0.2988537

01:04:46.460 --> 01:04:49.762 practical challenges couple minutes over.

NOTE Confidence: 0.2988537

01:04:49.762 --> 01:04:53.800 So I would like to thank.

NOTE Confidence: 0.2988537

01:04:53.800 --> 01:04:55.120 OK, thank you. Thank you.