WEBVTT

00:00:00.000 --> 00:00:02.490 Support for Yale Cancer Answers

NOTE Confidence: 0.8570802

00:00:02.490 --> 00:00:04.980 comes from AstraZeneca, dedicated

NOTE Confidence: 0.8570802

00:00:05.057 --> 00:00:07.432 to advancing options and providing

NOTE Confidence: 0.8570802

00:00:07.432 --> 00:00:10.420 hope for people living with cancer.

NOTE Confidence: 0.8570802

00:00:10.420 --> 00:00:13.968 More information at astrazeneca-us.com.

NOTE Confidence: 0.8570802

00:00:13.970 --> 00:00:15.950 Welcome to Yale Cancer Answers with

NOTE Confidence: 0.8570802

00:00:15.950 --> 00:00:18.482 your host doctor Anees Chagpar.

NOTE Confidence: 0.8570802

00:00:18.482 --> 00:00:20.402 Yale Cancer Answers features the

NOTE Confidence: 0.8570802

00:00:20.402 --> 00:00:22.742 latest information on cancer care by

NOTE Confidence: 0.8570802

00:00:22.742 --> 00:00:24.254 welcoming oncologists and specialists

NOTE Confidence: 0.8570802

00:00:24.254 --> 00:00:26.820 who are on the forefront of the

NOTE Confidence: 0.8570802

00:00:26.820 --> 00:00:29.060 battle to fight cancer. This week,

NOTE Confidence: 0.8570802

00:00:29.060 --> 00:00:31.214 it's a conversation about pancreatic cancer

NOTE Confidence: 0.8570802

00:00:31.214 --> 00:00:33.110 research with Doctor Luisa Escobar-Hoyos,

NOTE Confidence: 0.8570802

00:00:33.110 --> 00:00:35.462 Doctor Escobar-Hoyos is an

NOTE Confidence: 0.8570802

00:00:35.462 --> 00:00:37.030 assistant professor of therapeutic

NOTE Confidence: 0.8570802

00:00:37.094 --> 00:00:39.122 radiology at the Yale School of

NOTE Confidence: 0.8570802

00:00:39.122 --> 00:00:41.255 Medicine where Doctor Chagpar is

NOTE Confidence: 0.8570802

00:00:41.255 --> 00:00:43.035 a professor of surgical oncology.

NOTE Confidence: 0.8832874

00:00:44.300 --> 00:00:47.372 Luisa maybe we can take a step back

NOTE Confidence: 0.8832874

00:00:47.372 --> 00:00:50.724 first and just tell us a little bit more

NOTE Confidence: 0.8832874

00:00:50.730 --> 00:00:52.986 about yourself and what you do.

NOTE Confidence: 0.8832874

00:00:52.990 --> 00:00:55.636 Sure, I am a cancer scientist.

NOTE Confidence: 0.8832874

00:00:55.640 --> 00:00:57.530 I basically try to understand

NOTE Confidence: 0.8832874

00:00:57.530 --> 00:00:59.420 at the molecular cell level,

NOTE Confidence: 0.8832874

00:00:59.420 --> 00:01:01.310 how do cancer cells work?

NOTE Confidence: 0.8832874

00:01:01.310 --> 00:01:04.326 I am originally born and raised in Columbia,

NOTE Confidence: 0.8832874

00:01:04.330 --> 00:01:06.948 South America, but I always had a

NOTE Confidence: 0.8832874

00:01:06.948 --> 00:01:10.018 passion to come to the US to train

NOTE Confidence: 0.8832874

00:01:10.018 --> 00:01:11.888 in cancer biology and therapy.

NOTE Confidence: 0.8832874

00:01:11.890 --> 00:01:14.332 And this was based on an

NOTE Confidence: 0.8832874

00:01:14.332 --> 00:01:15.892 inspiration because my mom is

NOTE Confidence: 0.8832874

00:01:15.892 --> 00:01:18.489 also a cancer scientist and she

NOTE Confidence: 0.8832874

00:01:18.489 --> 00:01:20.957 inspired me from a young

NOTE Confidence: 0.8832874

00:01:20.957 --> 00:01:23.198 age to become a cancer scientist.

NOTE Confidence: 0.8832874

00:01:23.200 --> 00:01:25.258 So Fast forward a few years I

NOTE Confidence: 0.8832874

00:01:25.258 --> 00:01:27.610 came here 10 years ago with this

NOTE Confidence: 0.8832874

00:01:27.610 --> 00:01:29.710 big dream to make a difference

NOTE Confidence: 0.8832874

00:01:29.780 --> 00:01:32.132 for cancer and especially for

NOTE Confidence: 0.8832874

00:01:32.132 --> 00:01:34.034 the patients and their families.

NOTE Confidence: 0.8832874

00:01:34.034 --> 00:01:36.706 And recently a year ago I started my

NOTE Confidence: 0.8832874

00:01:36.706 --> 00:01:39.397 own lab here at Yale and in my lab we

NOTE Confidence: 0.8832874

00:01:39.397 --> 00:01:41.511 have different individuals that

NOTE Confidence: 0.8832874

00:01:41.511 --> 00:01:44.550 are training in research.

NOTE Confidence: 0.8832874

00:01:44.550 --> 00:01:46.650 So at this level we have

00:01:47.432 --> 00:01:48.214 graduate students and

NOTE Confidence: 0.8832874

00:01:49.000 --> 00:01:51.688 Master students and pH D students and

3

00:01:51.688 --> 00:01:54.637 we also have postdocs that come to

00:01:54.637 --> 00:01:57.217 train after their PhD level before

00:01:57.296 --> 00:01:59.600 they can launch their own lab.

00:01:59.600 --> 00:02:02.456 So my job as a mentor and as

00:02:02.460 --> 00:02:05.228 a leader is to manage all the

00:02:05.228 --> 00:02:07.396 research activity and programs that

00:02:07.396 --> 00:02:10.210 are being funded by different institutions,

00:02:10.210 --> 00:02:12.350 government or private

00:02:12.350 --> 00:02:15.331 institutions and it's all with the hope

00:02:15.331 --> 00:02:17.641 that we can cure pancreatic cancer

00:02:17.641 --> 00:02:20.409 and change the course of this disease.

00:02:21.540 --> 00:02:24.888 Tell us more about that.

00:02:24.890 --> 00:02:27.938 It sounds like a lofty goal to

00:02:27.938 --> 00:02:31.640 find a cure for pancreatic cancer, and

00:02:31.640 --> 00:02:35.240 change the course of this disease. But how

00:02:35.240 --> 00:02:37.490 exactly are you doing that?

NOTE Confidence: 0.8774481

00:02:37.490 --> 00:02:40.004 We try to understand this disease

NOTE Confidence: 0.8774481

00:02:40.004 --> 00:02:42.440 by using as many

NOTE Confidence: 0.8774481

00:02:42.440 --> 00:02:44.690 biological systems that we can,

NOTE Confidence: 0.8774481

00:02:44.690 --> 00:02:47.192 so we start by first understanding

NOTE Confidence: 0.8774481

00:02:47.192 --> 00:02:49.640 the tumors from the patients.

NOTE Confidence: 0.8774481

00:02:49.640 --> 00:02:51.440 So to do this,

NOTE Confidence: 0.8774481

00:02:51.440 --> 00:02:54.140 we dive into doing DNA sequencing,

NOTE Confidence: 0.8774481

00:02:54.140 --> 00:02:55.619 RNA sequencing proteomics

NOTE Confidence: 0.8774481

00:02:55.619 --> 00:02:57.098 to really understand

NOTE Confidence: 0.8774481

00:02:57.100 --> 00:02:59.220 the building blocks of these

NOTE Confidence: 0.8774481

00:02:59.220 --> 00:03:01.340 cells and from those analysis

NOTE Confidence: 0.8774481

00:03:01.415 --> 00:03:03.869 that we generate from the tumors,

NOTE Confidence: 0.8774481

00:03:03.870 --> 00:03:05.895 but also with clear understanding

NOTE Confidence: 0.8774481

00:03:05.895 --> 00:03:08.436 of the clinical need to develop

NOTE Confidence: 0.8774481

00:03:08.436 --> 00:03:11.058 new therapies to diagnose it early,

NOTE Confidence: 0.8774481

00:03:11.060 --> 00:03:13.170 that's when we start combining

NOTE Confidence: 0.8774481

00:03:13.170 --> 00:03:16.050 how can we use the data that we're

NOTE Confidence: 0.8774481

00:03:16.050 --> 00:03:18.675 receiving from the patients to answer

NOTE Confidence: 0.8774481

00:03:18.675 --> 00:03:20.955 these questions that the clinical

NOTE Confidence: 0.8774481

00:03:20.955 --> 00:03:23.329 field is being challenged with.

NOTE Confidence: 0.8774481

00:03:23.330 --> 00:03:26.354 Then we go and we start engineering

NOTE Confidence: 0.8774481

00:03:26.354 --> 00:03:27.650 different model systems

NOTE Confidence: 0.8774481

00:03:27.650 --> 00:03:30.068 where we tightly control the variables.

NOTE Confidence: 0.8774481

00:03:30.070 --> 00:03:31.279 So for example,

NOTE Confidence: 0.8774481

00:03:31.279 --> 00:03:33.697 in cells we can manipulate the

NOTE Confidence: 0.8774481

00:03:33.697 --> 00:03:35.730 expression of genes and proteins,

NOTE Confidence: 0.8774481

00:03:35.730 --> 00:03:38.628 or in mice we can actually introduce

NOTE Confidence: 0.8774481

00:03:38.628 --> 00:03:40.764 mutations to the mice in their pancreata

NOTE Confidence: 0.8774481

00:03:40.764 --> 00:03:43.606 and lead them

NOTE Confidence: 0.8774481

00:03:43.606 --> 00:03:45.972 to form tumors that

NOTE Confidence: 0.8774481

00:03:45.972 --> 00:03:47.847 later we can use

NOTE Confidence: 0.8774481

00:03:47.850 --> 00:03:50.508 all these models combined to test

NOTE Confidence: 0.8774481

00:03:50.508 --> 00:03:52.681 different hypothesis related to the

NOTE Confidence: 0.8774481

00:03:52.681 --> 00:03:54.956 basic biology of the cancer cell or

NOTE Confidence: 0.8774481

00:03:54.956 --> 00:03:58.038 to test novel therapies that

NOTE Confidence: 0.8774481

00:03:58.040 --> 00:04:00.026 either we generated or a pharmaceutical

NOTE Confidence: 0.8774481

00:04:00.026 --> 00:04:02.354 company comes to us because they are

NOTE Confidence: 0.8774481

00:04:02.354 --> 00:04:04.552 interested in testing it in our models.

NOTE Confidence: 0.8774481

00:04:04.560 --> 00:04:07.161 So I guess what I'm trying to say is

NOTE Confidence: 0.8774481

00:04:07.161 --> 00:04:09.661 every time you're going to learn such

NOTE Confidence: 0.8774481

00:04:09.661 --> 00:04:12.060 a complex disease as cancer,

NOTE Confidence: 0.8774481

00:04:12.060 --> 00:04:14.076 you need to take advantage and

NOTE Confidence: 0.8774481

00:04:14.076 --> 00:04:16.074 generate as many model systems to

NOTE Confidence: 0.8774481

00:04:16.074 --> 00:04:18.573 interrogate the hypothesis that is behind it.

NOTE Confidence: 0.8774481

00:04:18.580 --> 00:04:21.505 So we do this in a team based effort.

NOTE Confidence: 0.8774481

00:04:21.510 --> 00:04:23.994 In my group we not only have people

NOTE Confidence: 0.8774481

00:04:23.994 --> 00:04:26.396 that are interested in basic science,

NOTE Confidence: 0.8774481

00:04:26.400 --> 00:04:28.528 but we also have clinicians or

NOTE Confidence: 0.8774481

00:04:28.528 --> 00:04:30.709 individuals who are in clinical training.

NOTE Confidence: 0.8774481

00:04:30.710 --> 00:04:33.142 So we can bring all of these areas

NOTE Confidence: 0.8774481

00:04:33.142 --> 00:04:35.528 of thought into these questions and

NOTE Confidence: 0.8774481

00:04:35.528 --> 00:04:38.084 these experimental designs that we do.

NOTE Confidence: 0.8774481

00:04:38.090 --> 00:04:39.940 We also bring computational scientists.

NOTE Confidence: 0.8774481

00:04:39.940 --> 00:04:40.518 For example,

NOTE Confidence: 0.8774481

00:04:40.518 --> 00:04:42.830 there is a lot of data out there

NOTE Confidence: 0.8774481

00:04:42.896 --> 00:04:45.320 that has been derived from multiple

NOTE Confidence: 0.8774481

00:04:45.320 --> 00:04:47.834 institutions and across the world of

NOTE Confidence: 0.8774481

00:04:47.834 --> 00:04:49.899 sequencing from the patient samples.

NOTE Confidence: 0.8774481

00:04:49.900 --> 00:04:52.042 And sometimes we can build those

NOTE Confidence: 0.8774481

00:04:52.042 --> 00:04:53.960 databases in house,

NOTE Confidence: 0.8774481

00:04:53.960 --> 00:04:56.536 but we also take advantage of all of

NOTE Confidence: 0.8774481

00:04:56.536 --> 00:04:58.906 this data that is being deposited

NOTE Confidence: 0.8774481

00:04:58.906 --> 00:05:01.384 out there from other scientists too.

00:05:02.671 --> 00:05:05.660 So as a community we can actually

NOTE Confidence: 0.8774481

00:05:05.737 --> 00:05:08.557 develop and better

NOTE Confidence: 0.8774481

00:05:08.557 --> 00:05:10.437 understand these tumors

NOTE Confidence: 0.8774481

00:05:10.519 --> 00:05:12.039 and also come up with

NOTE Confidence: 0.8464524

00:05:12.040 --> 00:05:14.140 better ways to treat them.

NOTE Confidence: 0.8464524

00:05:14.140 --> 00:05:16.745 And so by sequencing you mean

NOTE Confidence: 0.8464524

00:05:16.745 --> 00:05:18.860 sequencing the genes of the

NOTE Confidence: 0.8464524

00:05:18.860 --> 00:05:20.084 tumor itself?

NOTE Confidence: 0.8464524

00:05:20.084 --> 00:05:23.472 Yes, so what we do is we sequencebthe

NOTE Confidence: 0.8464524

00:05:23.472 --> 00:05:26.100 whole genome of that tumor cell.

NOTE Confidence: 0.8464524

00:05:26.100 --> 00:05:28.722 So we're looking at more than

NOTE Confidence: 0.8464524

00:05:28.722 --> 00:05:31.459 95,000 genes at the same time.

NOTE Confidence: 0.8464524

00:05:31.460 --> 00:05:34.040 And we are interrogating,

NOTE Confidence: 0.8464524

00:05:34.040 --> 00:05:36.620 are there mutations on these genes?

NOTE Confidence: 0.8464524

00:05:36.620 --> 00:05:39.665 How differently is a gene being turned

NOTE Confidence: 0.8464524

00:05:39.665 --> 00:05:42.838 on or turned off between normal cells and

NOTE Confidence: 0.8464524

00:05:42.838 --> 00:05:45.983 cancer cells and when we turn them

NOTE Confidence: 0.8464524

00:05:45.983 --> 00:05:48.734 on do they produce a single protein

NOTE Confidence: 0.8464524

00:05:48.734 --> 00:05:51.388 or do they produce multiple proteins

NOTE Confidence: 0.8464524

00:05:51.388 --> 00:05:54.644 from that same template of the DNA?

NOTE Confidence: 0.8464524

00:05:54.644 --> 00:05:57.255 And so that level of complexity and

NOTE Confidence: 0.8464524

00:05:57.260 --> 00:05:58.980 imagine all of this,

NOTE Confidence: 0.8464524

00:05:58.980 --> 00:06:01.130 all these 95,000 genes mutations,

NOTE Confidence: 0.8464524

00:06:01.130 --> 00:06:02.674 expressions on and off

NOTE Confidence: 0.8464524

00:06:02.674 --> 00:06:06.309 times the number of cells in a tumor and

NOTE Confidence: 0.8464524

00:06:06.310 --> 00:06:08.165 all the patients that are

NOTE Confidence: 0.8464524

00:06:08.165 --> 00:06:10.020 coming for us to analyze.

NOTE Confidence: 0.8464524

00:06:10.020 --> 00:06:12.533 So there is a lot of data

NOTE Confidence: 0.8464524

00:06:12.533 --> 00:06:14.100 analysis that goes on here.

NOTE Confidence: 0.8464524

00:06:14.100 --> 00:06:16.522 But really what's driving this

NOTE Confidence: 0.8464524

00:06:16.522 --> 00:06:18.798 analysis is the biological and clinical

NOTE Confidence: 0.8464524

00:06:18.798 --> 00:06:21.144 questions that we want to answer.

NOTE Confidence: 0.85006595

00:06:22.220 --> 00:06:25.180 And so as you look at

NOTE Confidence: 0.85006595

00:06:25.180 --> 00:06:27.966 all of this data, and you're

NOTE Confidence: 0.85006595

00:06:27.966 --> 00:06:29.718 sequencing the genomes

NOTE Confidence: 0.85006595

00:06:29.718 --> 00:06:31.923 of these cancers and figuring

NOTE Confidence: 0.85006595

00:06:31.923 --> 00:06:34.173 out which genes are turned on

NOTE Confidence: 0.85006595

00:06:34.173 --> 00:06:36.428 and which ones are turned off.

NOTE Confidence: 0.85006595

00:06:36.430 --> 00:06:38.054 What's the next step?

NOTE Confidence: 0.85006595

00:06:38.054 --> 00:06:41.705 I mean, what people really want to know is,

NOTE Confidence: 0.85006595

00:06:41.710 --> 00:06:44.005 can you prevent pancreatic cancer

NOTE Confidence: 0.85006595

00:06:44.005 --> 00:06:46.704 either by causing aberrant genes that

NOTE Confidence: 0.85006595

00:06:46.704 --> 00:06:49.014 should not be turned on to stay,

NOTE Confidence: 0.85006595

00:06:49.020 --> 00:06:52.625 not turned on, or turn them off

NOTE Confidence: 0.85006595

00:06:52.630 --> 00:06:54.194 once they're already there,

NOTE Confidence: 0.85006595

00:06:54.194 --> 00:06:57.140 so can you prevent cancers from forming?

NOTE Confidence: 0.85006595

00:06:57.140 --> 00:06:59.916 Or can you use some of what you're

NOTE Confidence: 0.85006595

00:06:59.916 --> 00:07:02.575 learning in terms of the sequencing

NOTE Confidence: 0.85006595

00:07:02.575 --> 00:07:04.925 to actually treat these cancers?

NOTE Confidence: 0.85006595

00:07:04.930 --> 00:07:08.018 So how do you kind of get from

NOTE Confidence: 0.85006595

00:07:08.018 --> 00:07:10.036 understanding what genes are turned

NOTE Confidence: 0.85006595

00:07:10.036 --> 00:07:13.286 on and what genes are turned off to

NOTE Confidence: 0.85006595

00:07:13.286 --> 00:07:15.586 really having something that has

NOTE Confidence: 0.85219145

00:07:15.590 --> 00:07:16.410 clinical impact?

NOTE Confidence: 0.85219145

00:07:16.410 --> 00:07:18.460 That's a very good question.

NOTE Confidence: 0.85219145

00:07:18.460 --> 00:07:20.148 So in the pancreatic cancer

NOTE Confidence: 0.85219145

00:07:20.148 --> 00:07:22.258 field there are two points of research

00:07:24.426 --> 00:07:26.420 that we're trying to tackle.

NOTE Confidence: 0.85219145

00:07:26.420 --> 00:07:28.968 The first one is early diagnosis and

NOTE Confidence: 0.85219145

00:07:28.968 --> 00:07:31.329 then the second one is treatment.

NOTE Confidence: 0.85219145

00:07:31.330 --> 00:07:32.830 My lab in particular

NOTE Confidence: 0.85219145

00:07:32.830 --> 00:07:35.490 is focused more on the treatment side,

NOTE Confidence: 0.85219145

00:07:35.490 --> 00:07:37.800 so when we start looking for what

NOTE Confidence: 0.85219145

00:07:37.800 --> 00:07:40.267 are we going to learn from all

NOTE Confidence: 0.85219145

00:07:40.267 --> 00:07:42.373 of these sequencing in terms to

NOTE Confidence: 0.85219145

00:07:42.452 --> 00:07:45.511 really come up with novel ways for

NOTE Confidence: 0.85219145

00:07:45.511 --> 00:07:47.208 therapeutic approaches for these

NOTE Confidence: 0.85219145

00:07:47.208 --> 00:07:48.720 patients that desperately need it,

NOTE Confidence: 0.85219145

00:07:48.720 --> 00:07:51.275 we take an approach where we start

NOTE Confidence: 0.85219145

00:07:51.275 --> 00:07:53.709 comparing the tumors from patients that

00:07:54.108 --> 00:07:55.700 we're very aggressive versus

NOTE Confidence: 0.85219145

00:07:55.700 --> 00:07:57.690 those tumors from other patients

NOTE Confidence: 0.85219145

00:07:57.749 --> 00:07:59.633 that were maybe a little bit

NOTE Confidence: 0.85219145

00:07:59.633 --> 00:08:00.889 more responsive to therapy,

NOTE Confidence: 0.85219145

00:08:00.890 --> 00:08:03.690 and we try to understand how are these

NOTE Confidence: 0.85219145

00:08:03.690 --> 00:08:05.920 tumors different at the molecular level.

NOTE Confidence: 0.85219145

00:08:05.920 --> 00:08:08.692 The reason why we want to understand

NOTE Confidence: 0.85219145

00:08:08.692 --> 00:08:10.617 differences is because we don't

NOTE Confidence: 0.85219145

00:08:10.617 --> 00:08:12.962 think that there is a single therapy

NOTE Confidence: 0.85219145

00:08:12.962 --> 00:08:15.249 that works for all of the tumors.

NOTE Confidence: 0.85219145

00:08:15.250 --> 00:08:17.674 We know that the mutations that the tumors

NOTE Confidence: 0.85219145

00:08:17.674 --> 00:08:19.920 carry makes them biologically different.

NOTE Confidence: 0.85219145

00:08:19.920 --> 00:08:22.426 So what I'm trying to say is,

NOTE Confidence: 0.85219145

00:08:22.430 --> 00:08:25.174 although they may have the same diagnosis,

NOTE Confidence: 0.85219145

00:08:25.180 --> 00:08:26.568 at the molecular level,

NOTE Confidence: 0.85219145

00:08:26.568 --> 00:08:29.130 they're almost kind of oranges and apples,

NOTE Confidence: 0.85219145

00:08:29.130 --> 00:08:31.954 and so we're trying to dissect out the

NOTE Confidence: 0.85219145

00:08:31.954 --> 00:08:34.464 therapy that goes for the oranges and

NOTE Confidence: 0.85219145

00:08:34.464 --> 00:08:37.030 the therapy that goes for the apples.

NOTE Confidence: 0.85219145

00:08:37.030 --> 00:08:39.508 What my lab is doing differently

NOTE Confidence: 0.85219145

00:08:39.508 --> 00:08:42.273 from what other labs have done is

NOTE Confidence: 0.85219145

00:08:42.273 --> 00:08:44.674 we look at the level of turning

NOTE Confidence: 0.85219145

00:08:44.756 --> 00:08:47.188 on or turning off genes at a

NOTE Confidence: 0.85219145

00:08:47.188 --> 00:08:49.168 level that it's almost imagine

NOTE Confidence: 0.85219145

00:08:49.168 --> 00:08:51.220 10 times deeper than what other

NOTE Confidence: 0.85219145

00:08:51.285 --> 00:08:53.180 scientists have covered so far.

NOTE Confidence: 0.85219145

00:08:53.180 --> 00:08:55.672 So let me tell you a little

NOTE Confidence: 0.85219145

00:08:55.672 --> 00:08:58.429 bit of how the genome works.

NOTE Confidence: 0.85219145

00:08:58.430 --> 00:09:01.318 We used to think that a gene would

NOTE Confidence: 0.85219145

00:09:01.318 --> 00:09:03.277 get transcribed into this MRNA

NOTE Confidence: 0.85219145

00:09:03.277 --> 00:09:05.827 and then the MRNA would form a

NOTE Confidence: 0.85219145

00:09:05.827 --> 00:09:07.672 single protein, and the proteins

NOTE Confidence: 0.85219145

00:09:07.672 --> 00:09:10.274 to remind everyone are

NOTE Confidence: 0.85219145

00:09:10.274 --> 00:09:13.262 the functional units of the cell.

NOTE Confidence: 0.85219145

00:09:13.270 --> 00:09:16.196 There is a pathway by which the

NOTE Confidence: 0.85219145

00:09:16.196 --> 00:09:18.689 cells actually form a single gene.

NOTE Confidence: 0.85219145

00:09:18.690 --> 00:09:22.434 They can produce up to 7 different MRNA's,

NOTE Confidence: 0.85219145

00:09:22.440 --> 00:09:25.248 and each one of these MRNA's can

NOTE Confidence: 0.85219145

15

00:09:25.248 --> 00:09:27.449 produce seven different proteins.

NOTE Confidence: 0.85219145

00:09:27.450 --> 00:09:30.594 So most of the time the scientists

NOTE Confidence: 0.85219145

00:09:30.594 --> 00:09:34.288 focus on just one of the forms of

NOTE Confidence: 0.85219145

00:09:34.288 --> 00:09:37.039 those proteins from that single gene,

NOTE Confidence: 0.85219145

00:09:37.040 --> 00:09:39.959 because probably it is the more abundant one.

NOTE Confidence: 0.85219145

00:09:39.960 --> 00:09:42.522 But it's not until you start

NOTE Confidence: 0.85219145

00:09:42.522 --> 00:09:43.803 doing these analysis,

NOTE Confidence: 0.85219145

00:09:43.810 --> 00:09:46.450 that we do at the MRNA sequencing

NOTE Confidence: 0.85219145

00:09:46.450 --> 00:09:48.508 level that you start understanding

NOTE Confidence: 0.85219145

00:09:48.508 --> 00:09:51.148 that they're not only genes that

NOTE Confidence: 0.85219145

00:09:51.148 --> 00:09:53.869 are being turned on or turned off,

NOTE Confidence: 0.85219145

00:09:53.870 --> 00:09:56.228 but that when some gene is

NOTE Confidence: 0.85219145

00:09:56.228 --> 00:09:58.130 turned is being turned on,

NOTE Confidence: 0.85219145

00:09:58.130 --> 00:10:01.386 maybe it's producing protein A and maybe in

NOTE Confidence: 0.85219145

00:10:01.386 --> 00:10:04.315 other tumors the gene is still turned on,

NOTE Confidence: 0.85219145

00:10:04.320 --> 00:10:05.868 but is producing protein B.

NOTE Confidence: 0.85219145

00:10:05.868 --> 00:10:07.416 A&B are so different,

NOTE Confidence: 0.85219145

00:10:07.802 --> 00:10:11.670 and this is what my lab tries to dissect out.

00:10:12.876 --> 00:10:14.484 A&B are

NOTE Confidence: 0.85219145

00:10:14.490 --> 00:10:16.935 protein isoforms, and these protein

NOTE Confidence: 0.85219145

00:10:16.935 --> 00:10:19.380 isoforms as I was mentioning,

NOTE Confidence: 0.85219145

00:10:19.380 --> 00:10:21.692 may have different functions,

NOTE Confidence: 0.85219145

00:10:21.692 --> 00:10:24.004 and because previously the

NOTE Confidence: 0.85219145

00:10:24.004 --> 00:10:26.963 technology or the methods that we

NOTE Confidence: 0.85219145

00:10:26.963 --> 00:10:29.537 had available could only tell us

NOTE Confidence: 0.85219145

00:10:29.627 --> 00:10:31.607 is the gene on or not,

NOTE Confidence: 0.823728

00:10:31.610 --> 00:10:35.166 now we have the analytical tools in

NOTE Confidence: 0.823728

00:10:35.166 --> 00:10:38.450 their technology to say it's been on,

NOTE Confidence: 0.823728

00:10:38.450 --> 00:10:41.100 but then it's preferentially expressing

NOTE Confidence: 0.823728

00:10:41.100 --> 00:10:45.000 the protein isoform A or the isoform B.

NOTE Confidence: 0.823728

00:10:45.000 --> 00:10:47.766 And that uncovers a very new

NOTE Confidence: 0.823728

00:10:47.766 --> 00:10:49.610 biology about cancer cells,

NOTE Confidence: 0.823728

00:10:49.610 --> 00:10:54.634 but something that had not been seen before.

NOTE Confidence: 0.823728

00:10:54.640 --> 00:10:56.236 Why is this important?

NOTE Confidence: 0.823728

00:10:56.236 --> 00:10:59.333 It turns out that if we can

NOTE Confidence: 0.823728

00:10:59.333 --> 00:11:01.765 dissect this complexity and

NOTE Confidence: 0.823728

00:11:01.765 --> 00:11:04.197 diversity in pancreatic cancer,

NOTE Confidence: 0.823728

00:11:04.200 --> 00:11:06.710 potentially this can lead us

NOTE Confidence: 0.823728

00:11:06.710 --> 00:11:08.216 to new therapies.

NOTE Confidence: 0.823728

00:11:08.220 --> 00:11:11.244 Actually, last year my

NOTE Confidence: 0.823728

00:11:11.244 --> 00:11:13.669 work group published that pancreatic

NOTE Confidence: 0.823728

00:11:13.669 --> 00:11:16.279 cancer is highly susceptible to

NOTE Confidence: 0.823728

00:11:16.279 --> 00:11:19.003 any therapy that perturbs this

NOTE Confidence: 0.823728

00:11:19.003 --> 00:11:21.693 system of producing protein isoform

NOTE Confidence: 0.823728

00:11:21.693 --> 00:11:24.310 A versus protein isoform B,

NOTE Confidence: 0.823728

00:11:24.310 --> 00:11:25.310 suggesting that

NOTE Confidence: 0.823728

00:11:25.310 --> 00:11:27.810 there is potentially a therapeutic

NOTE Confidence: 0.823728

00:11:27.810 --> 00:11:29.924 opportunity to understand more of

NOTE Confidence: 0.823728

00:11:29.924 --> 00:11:32.234 these tumors at the protein isoform

NOTE Confidence: 0.823728

00:11:32.307 --> 00:11:34.707 level and to generate particular

NOTE Confidence: 0.823728

00:11:34.707 --> 00:11:36.627 therapies for these different

NOTE Confidence: 0.823728

00:11:36.627 --> 00:11:38.910 proteins that are being expressed.

NOTE Confidence: 0.82090443

00:11:39.900 --> 00:11:42.576 Let me make sure

NOTE Confidence: 0.82090443

00:11:42.576 --> 00:11:44.360 I've got this straight.

NOTE Confidence: 0.82090443

00:11:44.360 --> 00:11:47.482 So you've kind of discovered that

NOTE Confidence: 0.82090443

00:11:47.482 --> 00:11:50.473 various genes can, when turned on,

NOTE Confidence: 0.82090443

00:11:50.473 --> 00:11:52.677 will make different isoforms.

NOTE Confidence: 0.82090443

00:11:52.680 --> 00:11:56.925 And that these isoforms will

NOTE Confidence: 0.82090443

00:11:56.925 --> 00:11:58.705 respond differently to therapy.

NOTE Confidence: 0.82090443

00:11:58.710 --> 00:12:00.930 So then the question is,

NOTE Confidence: 0.82090443

00:12:00.930 --> 00:12:03.160 at the clinic level,

NOTE Confidence: 0.82090443

00:12:03.160 --> 00:12:05.385 is it possible to distinguish

NOTE Confidence: 0.82090443

00:12:05.385 --> 00:12:06.720 which are which?

NOTE Confidence: 0.82090443

00:12:06.720 --> 00:12:08.019 In other words,

NOTE Confidence: 0.82090443

00:12:08.019 --> 00:12:11.050 if there is a particular therapy that

NOTE Confidence: 0.82090443

00:12:11.134 --> 00:12:14.726 works better for protein isoform A versus B,

NOTE Confidence: 0.82090443

00:12:14.730 --> 00:12:18.234 is there a way to know whether a

NOTE Confidence: 0.82090443

00:12:18.234 --> 00:12:20.079 particular patient is producing

NOTE Confidence: 0.82090443

00:12:20.079 --> 00:12:22.284 protein isoform A or B?

NOTE Confidence: 0.83065695

00:12:23.880 --> 00:12:27.024 Yes, so basically we're trying to

NOTE Confidence: 0.83065695

00:12:27.024 --> 00:12:31.220 get at the point where we develop

NOTE Confidence: 0.83065695

00:12:31.220 --> 00:12:34.307 an isoform specific therapy and

NOTE Confidence: 0.83065695

00:12:34.307 --> 00:12:37.500 this will drive personalized therapy.

NOTE Confidence: 0.83065695

00:12:37.500 --> 00:12:41.620 We have developed in my lab a novel

NOTE Confidence: 0.83065695

00:12:41.620 --> 00:12:45.360 therapeutic mechanism to be able to switch

NOTE Confidence: 0.83065695

00:12:45.360 --> 00:12:47.980 and correct these isoform expression.

NOTE Confidence: 0.83065695

00:12:47.980 --> 00:12:51.088 Let's say that isoform B is

NOTE Confidence: 0.83065695

00:12:51.088 --> 00:12:53.890 the most

NOTE Confidence: 0.83065695

00:12:53.890 --> 00:12:54.674 aggressive one,

NOTE Confidence: 0.83065695

00:12:54.674 --> 00:12:57.418 and it's the most tumorigenic we can

NOTE Confidence: 0.83065695

00:12:57.418 --> 00:12:59.456 actually correct that isoform and

NOTE Confidence: 0.83065695

00:12:59.456 --> 00:13:02.463 switch it to the form which

NOTE Confidence: 0.83065695

00:13:02.463 --> 00:13:04.509 is actually the less aggressive form

NOTE Confidence: 0.83065695

00:13:04.510 --> 00:13:06.730 and this can drastically impact the

NOTE Confidence: 0.83065695

00:13:06.730 --> 00:13:09.110 biology and the growth of the tumor.

NOTE Confidence: 0.83065695

00:13:09.110 --> 00:13:11.790 So we're excited to see what was going

NOTE Confidence: 0.83065695

00:13:11.790 --> 00:13:14.069 to happen with this new therapy

NOTE Confidence: 0.83065695

00:13:14.070 --> 00:13:16.894 as we start moving it into clinical trials.

00:13:17.960 --> 00:13:20.095 We're going to have to take a short

NOTE Confidence: 0.8658893

00:13:20.095 --> 00:13:22.210 break for a medical minute,

NOTE Confidence: 0.8658893

00:13:22.210 --> 00:13:24.968 but we'll get back into that conversation

NOTE Confidence: 0.8658893

00:13:24.970 --> 00:13:27.820 right after this with my guest

NOTE Confidence: 0.8658893

00:13:27.820 --> 00:13:29.720 doctor Luisa Escobar-Hoyos.

NOTE Confidence: 0.82040554

00:13:29.720 --> 00:13:32.305 Support for Yale Cancer Answers

NOTE Confidence: 0.82040554

00:13:32.305 --> 00:13:35.393 comes from AstraZeneca, working to

NOTE Confidence: 0.82040554

00:13:35.393 --> 00:13:38.270 eliminate cancer as a cause of death.

NOTE Confidence: 0.82040554

00:13:38.270 --> 00:13:41.978 Learn more at astrazeneca-us.com.

NOTE Confidence: 0.82040554

00:13:41.980 --> 00:13:44.015 This is a medical minute

NOTE Confidence: 0.82040554

00:13:44.015 --> 00:13:45.236 about pancreatic cancer,

NOTE Confidence: 0.82040554

00:13:45.240 --> 00:13:48.187 which represents about 3% of all cancers

NOTE Confidence: 0.82040554

00:13:48.187 --> 00:13:51.636 in the US and about 7% of cancer deaths.

NOTE Confidence: 0.82040554

00:13:51.636 --> 00:13:53.446 Clinical trials are currently being

NOTE Confidence: 0.82040554

00:13:53.446 --> 00:13:55.127 offered at federally designated

NOTE Confidence: 0.82040554

00:13:55.127 --> 00:13:56.915 comprehensive Cancer Centers for

NOTE Confidence: 0.82040554

00:13:56.915 --> 00:13:59.571 the treatment of advanced stage and

NOTE Confidence: 0.82040554

00:13:59.571 --> 00:14:01.179 metastatic pancreatic cancer using

NOTE Confidence: 0.82040554

00:14:01.179 --> 00:14:03.212 chemotherapy and other novel therapies.

NOTE Confidence: 0.82040554

00:14:03.212 --> 00:14:06.166 Folfirinox, a combination of five

NOTE Confidence: 0.82040554

00:14:06.166 --> 00:14:08.176 different chemotherapies is the latest

NOTE Confidence: 0.82040554

00:14:08.176 --> 00:14:10.390 advance in the treatment of metastatic

NOTE Confidence: 0.82040554

00:14:10.390 --> 00:14:12.577 pancreatic cancer and research continues

NOTE Confidence: 0.82040554

00:14:12.580 --> 00:14:14.740 at centers around the world

NOTE Confidence: 0.82040554

00:14:14.740 --> 00:14:16.468 looking into targeted therapies.

NOTE Confidence: 0.82040554

00:14:16.470 --> 00:14:18.565 And a recently discovered marker

NOTE Confidence: 0.82040554

00:14:18.565 --> 00:14:21.515 HENT one. This has been a medical

NOTE Confidence: 0.82040554

00:14:21.515 --> 00:14:24.231 minute brought to you as a public

NOTE Confidence: 0.82040554

00:14:24.231 --> 00:14:26.379 service by Yale Cancer Center.

NOTE Confidence: 0.82040554

00:14:26.380 --> 00:14:28.505 More information is available at

NOTE Confidence: 0.82040554

00:14:28.505 --> 00:14:29.780 yalecancercenter.org you're listening

NOTE Confidence: 0.82040554

00:14:29.780 --> 00:14:31.339 to Connecticut Public Radio.

NOTE Confidence: 0.8025475

00:14:33.650 --> 00:14:36.280 Welcome back to Yale Cancer Answers.

NOTE Confidence: 0.8025475

00:14:36.280 --> 00:14:38.954 This is doctor Anees Chagpar

NOTE Confidence: 0.8025475

00:14:38.954 --> 00:14:42.188 and I'm joined tonight by my guest

NOTE Confidence: 0.8025475

00:14:42.188 --> 00:14:44.184 doctor Luisa Escobar-Hoyos.

NOTE Confidence: 0.8025475

00:14:44.190 --> 00:14:47.238 We're talking about her recent research

NOTE Confidence: 0.8025475

00:14:47.238 --> 00:14:49.705 looking at pancreatic cancers and

NOTE Confidence: 0.8025475

00:14:49.705 --> 00:14:51.865 before the break she was telling

NOTE Confidence: 0.8025475

00:14:51.865 --> 00:14:54.279 us about how she's looking at

NOTE Confidence: 0.8025475

00:14:54.280 --> 00:14:57.584 the genome of these cancers,

NOTE Confidence: 0.8025475

00:14:57.590 --> 00:15:00.691 finding out that it's not just about

NOTE Confidence: 0.8025475

00:15:00.691 --> 00:15:03.560 genes being turned on and turned off,

NOTE Confidence: 0.8025475

00:15:03.560 --> 00:15:05.984 but what protein isoforms those genes

NOTE Confidence: 0.8025475

00:15:05.984 --> 00:15:08.690 that are turned on actually make?

NOTE Confidence: 0.8025475

00:15:08.690 --> 00:15:11.679 And some of those may be more

NOTE Confidence: 0.8025475

00:15:11.679 --> 00:15:12.960 aggressive than others.

NOTE Confidence: 0.8025475

00:15:12.960 --> 00:15:15.781 Luisa, before we dig more into

NOTE Confidence: 0.8025475

00:15:15.781 --> 00:15:18.627 your research and the idea that

NOTE Confidence: 0.8025475

00:15:18.627 --> 00:15:20.567 you could actually switch from

NOTE Confidence: 0.8025475

00:15:20.567 --> 00:15:23.399 a protein isoform that is more

NOTE Confidence: 0.8025475

00:15:23.399 --> 00:15:25.764 aggressive to a protein isoform,

NOTE Confidence: 0.8025475

00:15:25.770 --> 00:15:26.853 that's less aggressive.

NOTE Confidence: 0.8025475

00:15:26.853 --> 00:15:29.743 Maybe we can take a step back and

NOTE Confidence: 0.8025475

00:15:29.743 --> 00:15:32.087 you can tell us a little bit more

NOTE Confidence: 0.8025475

00:15:32.087 --> 00:15:34.614 about why you decided to look at

NOTE Confidence: 0.8025475

00:15:34.614 --> 00:15:36.377 pancreatic cancer to begin with.

NOTE Confidence: 0.8025475

00:15:36.377 --> 00:15:38.279 It's certainly one of the most

NOTE Confidence: 0.8025475

00:15:38.279 --> 00:15:38.913 lethal cancers,

NOTE Confidence: 0.8025475

00:15:38.920 --> 00:15:42.760 but talk a little bit more about that.

NOTE Confidence: 0.86888814

00:15:42.760 --> 00:15:45.777 Yes, so it's actually a personal journey.

NOTE Confidence: 0.86888814

00:15:45.780 --> 00:15:48.360 When I was a PhD student,

NOTE Confidence: 0.86888814

00:15:48.360 --> 00:15:50.946 I used to study cervical cancer,

NOTE Confidence: 0.86888814

00:15:50.950 --> 00:15:53.536 and cervical cancer, as we all know,

NOTE Confidence: 0.86888814

00:15:53.540 --> 00:15:56.772 is now not as lethal because we have

NOTE Confidence: 0.86888814

00:15:56.772 --> 00:15:59.101 it controlled because we screened

NOTE Confidence: 0.86888814

00:15:59.101 --> 00:16:01.486 for this disease and there's

NOTE Confidence: 0.86888814

00:16:01.486 --> 00:16:04.308 less cases that appear in the US.

NOTE Confidence: 0.86888814

00:16:04.310 --> 00:16:05.990 But after my PhD,

NOTE Confidence: 0.86888814

00:16:05.990 --> 00:16:09.476 I started thinking that I wanted to put

NOTE Confidence: 0.86888814

00:16:09.476 --> 00:16:12.549 all my effort to understanding a cancer

NOTE Confidence: 0.86888814

00:16:12.550 --> 00:16:14.710 that really needed our attention,

NOTE Confidence: 0.86888814

00:16:14.710 --> 00:16:16.430 and that's when pancreatic

NOTE Confidence: 0.86888814

00:16:16.430 --> 00:16:18.580 cancer came to my mind.

NOTE Confidence: 0.86888814

00:16:18.580 --> 00:16:21.856 Several reasons there is a clinical need

NOTE Confidence: 0.86888814

00:16:21.856 --> 00:16:25.904 that we need to meet in the last 40 years.

NOTE Confidence: 0.86888814

00:16:25.910 --> 00:16:28.808 We have not changed the five year

NOTE Confidence: 0.86888814

00:16:28.808 --> 00:16:30.650 survival of pancreatic cancer,

NOTE Confidence: 0.86888814

00:16:30.650 --> 00:16:33.709 although we have made big progress

NOTE Confidence: 0.86888814

00:16:33.709 --> 00:16:35.823 in understanding the genetics and

NOTE Confidence: 0.86888814

00:16:35.823 --> 00:16:38.695 also I wanted to be sure to bring

NOTE Confidence: 0.86888814

00:16:38.778 --> 00:16:41.778 whatever I had learned from my

NOTE Confidence: 0.86888814

00:16:41.778 --> 00:16:43.778 understanding of cervical cancer

NOTE Confidence: 0.86888814

00:16:43.780 --> 00:16:46.420 and apply it into understanding

26

NOTE Confidence: 0.86888814

00:16:46.420 --> 00:16:48.532 this more aggressive disease.

NOTE Confidence: 0.86888814

00:16:48.540 --> 00:16:51.354 And that's when I started training

NOTE Confidence: 0.86888814

00:16:51.354 --> 00:16:53.952 in pancreatic cancer at Memorial

NOTE Confidence: 0.86888814

00:16:53.952 --> 00:16:56.480 Sloan Kettering Cancer Center,

NOTE Confidence: 0.86888814

00:16:56.480 --> 00:16:59.648 under the mentorship of Stephen Leach

00:17:00.178 --> 00:17:02.818 a world renowned pancreatic cancer scientist,

NOTE Confidence: 0.86888814

00:17:02.820 --> 00:17:05.860 so we both kind of wanted to study

NOTE Confidence: 0.86888814

00:17:05.860 --> 00:17:08.925 a different level of gene expression

NOTE Confidence: 0.86888814

00:17:08.925 --> 00:17:11.141 by understanding isoform switching

NOTE Confidence: 0.86888814

00:17:11.141 --> 00:17:13.771 by more specifically understanding

NOTE Confidence: 0.86888814

00:17:13.771 --> 00:17:16.639 the RNA splicing pathway

NOTE Confidence: 0.86888814

00:17:16.640 --> 00:17:17.969 in these cancer

NOTE Confidence: 0.82109797

00:17:17.970 --> 00:17:20.630 cells so you had talked a

NOTE Confidence: 0.82109797

00:17:20.630 --> 00:17:23.467 little bit before the break about

NOTE Confidence: 0.82109797

00:17:23.467 --> 00:17:25.968 this isoform switching, but you

NOTE Confidence: 0.82109797

00:17:25.968 --> 00:17:29.520 just introduced a new term, RNA splicing.

NOTE Confidence: 0.82109797

00:17:29.520 --> 00:17:33.507 What exactly is that and how does that play

NOTE Confidence: 0.82109797

00:17:33.510 --> 00:17:35.286 into this whole story?

NOTE Confidence: 0.82109797

00:17:35.286 --> 00:17:38.034 Yes, so RNA splicing is this pathway

NOTE Confidence: 0.82109797

00:17:38.034 --> 00:17:41.175 by which the cells decide to produce

NOTE Confidence: 0.82109797

00:17:41.175 --> 00:17:43.720 one protein isoform versus another,

NOTE Confidence: 0.82109797

00:17:43.720 --> 00:17:46.402 and this is what allows the

NOTE Confidence: 0.82109797

00:17:46.402 --> 00:17:48.930 cell to diversify the podium.

NOTE Confidence: 0.82109797

00:17:48.930 --> 00:17:50.738 So previously we were

NOTE Confidence: 0.82109797

00:17:50.738 --> 00:17:52.546 talking about 95,000 genes,

NOTE Confidence: 0.82109797

00:17:52.550 --> 00:17:55.168 and if we can now multiply that

NOTE Confidence: 0.82109797

00:17:55.168 --> 00:17:57.661 each one of those genes is

NOTE Confidence: 0.82109797

00:17:57.661 --> 00:18:00.223 going to produce at least five

NOTE Confidence: 0.82109797

00:18:00.223 --> 00:18:02.970 or seven different proteins.

NOTE Confidence: 0.82109797

00:18:02.970 --> 00:18:05.105 Imagine how large and versatile

NOTE Confidence: 0.82109797

00:18:05.105 --> 00:18:07.960 the proteome of a cell becomes.

NOTE Confidence: 0.85616624

00:18:10.170 --> 00:18:12.630 Why we wanted to study this pathway

NOTE Confidence: 0.85616624

00:18:12.630 --> 00:18:15.878 or why it came to our attentio,.

NOTE Confidence: 0.85616624

00:18:15.880 --> 00:18:19.400 it was actually from patient derived data in

NOTE Confidence: 0.85616624

00:18:19.400 --> 00:18:22.896 2016 when I decided to study this cancer.

NOTE Confidence: 0.85616624

00:18:22.900 --> 00:18:25.054 There were many groups that were

NOTE Confidence: 0.85616624

00:18:25.054 --> 00:18:27.075 coming up with this hypothesis

NOTE Confidence: 0.85616624

00:18:27.075 --> 00:18:29.630 that pancreatic cancer comes into

NOTE Confidence: 0.85616624

00:18:29.630 --> 00:18:31.674 these two molecular subtypes.

NOTE Confidence: 0.85616624

00:18:31.680 --> 00:18:34.672 And there is one subtype that is more

NOTE Confidence: 0.85616624

00:18:34.672 --> 00:18:37.587 lethal that different authors coined the

NOTE Confidence: 0.85616624

00:18:37.587 --> 00:18:40.719 term either basal or squamous subtype.

NOTE Confidence: 0.85616624

00:18:40.720 --> 00:18:43.709 And then the less lethal form which

NOTE Confidence: 0.85616624

00:18:43.709 --> 00:18:46.371 the authors called it classical when

NOTE Confidence: 0.85616624

00:18:46.371 --> 00:18:49.409 we look back into the more aggressive

NOTE Confidence: 0.85616624

00:18:49.497 --> 00:18:51.947 form this basal squamous molecular

NOTE Confidence: 0.85616624

00:18:51.947 --> 00:18:54.836 subtype we were seeing that these

29

NOTE Confidence: 0.85616624

00:18:54.836 --> 00:18:58.324 tumors have a high expression of all of

NOTE Confidence: 0.85616624

00:18:58.324 --> 00:19:01.768 these genes that are going to encode

NOTE Confidence: 0.85616624

00:19:01.768 --> 00:19:05.086 for the splicing machinery

NOTE Confidence: 0.85616624

00:19:05.086 --> 00:19:08.075 that actually allows the cells to

NOTE Confidence: 0.85616624

00:19:08.080 --> 00:19:10.750 produce the protein isoforms.

NOTE Confidence: 0.85616624

00:19:10.750 --> 00:19:13.543 And we started wondering if the reason

NOTE Confidence: 0.85616624

00:19:13.543 --> 00:19:16.041 why these tumors are so aggressive

NOTE Confidence: 0.85616624

00:19:16.041 --> 00:19:18.483 is probably because could they be

NOTE Confidence: 0.85616624

00:19:18.483 --> 00:19:20.739 more versatile in switching from

NOTE Confidence: 0.85616624

00:19:20.739 --> 00:19:22.959 one isoform to another one,

NOTE Confidence: 0.85616624

00:19:22.960 --> 00:19:24.940 depending on whatever therapy we

NOTE Confidence: 0.85616624

00:19:24.940 --> 00:19:27.590 provide to the patient

NOTE Confidence: 0.85616624

00:19:27.590 --> 00:19:30.537 that they're lancing to the tumor.

NOTE Confidence: 0.85616624

00:19:30.540 --> 00:19:33.011 Is this why previously we had not

NOTE Confidence: 0.85616624

00:19:33.011 --> 00:19:35.966 been able to target the right protein

NOTE Confidence: 0.85616624

00:19:35.966 --> 00:19:38.684 isoforms because we had until this

NOTE Confidence: 0.85616624

00:19:38.767 --> 00:19:41.147 point ignored the importance of

NOTE Confidence: 0.85616624

00:19:41.150 --> 00:19:43.070 isoforms in this disease.

NOTE Confidence: 0.85878503

00:19:43.070 --> 00:19:46.416 That's an interesting concept,

NOTE Confidence: 0.85878503

00:19:46.420 --> 00:19:49.492 that certain cancer cells may

NOTE Confidence: 0.85878503

00:19:49.492 --> 00:19:52.069 have this splicing ability that

NOTE Confidence: 0.85878503

00:19:52.069 --> 00:19:55.191 helps them to switch from a given

NOTE Confidence: 0.85878503

00:19:55.191 --> 00:19:57.551 protein isoform to another protein

NOTE Confidence: 0.85878503

00:19:57.551 --> 00:20:00.323 isoform that may be more resistant

NOTE Confidence: 0.85878503

00:20:00.323 --> 00:20:03.658 to therapy when you look at these.

NOTE Confidence: 0.85878503

00:20:03.660 --> 00:20:06.156 two different subtypes, are they different

NOTE Confidence: 0.85878503

00:20:06.156 --> 00:20:08.930 in terms of their aggressiveness?

NOTE Confidence: 0.85878503

00:20:08.930 --> 00:20:11.002 Even before the therapy?

NOTE Confidence: 0.85878503

00:20:11.002 --> 00:20:12.556 In other words,

NOTE Confidence: 0.85878503

00:20:12.560 --> 00:20:15.864 is it that these protein isoforms actually

NOTE Confidence: 0.85878503

00:20:15.864 --> 00:20:19.160 cause differences in the biology of the

NOTE Confidence: 0.85878503

00:20:19.160 --> 00:20:21.410 aggressiveness of the tumor itself,

NOTE Confidence: 0.85878503

00:20:21.410 --> 00:20:24.434 or is it really this ability to react

NOTE Confidence: 0.85878503

00:20:24.434 --> 00:20:27.497 to the treatment with a different

NOTE Confidence: 0.85878503

00:20:27.497 --> 00:20:30.267 isoform that is more resistant?

NOTE Confidence: 0.85878503

00:20:30.270 --> 00:20:31.200 We think

NOTE Confidence: 0.86011857

00:20:31.200 --> 00:20:32.529 it's actually both.

NOTE Confidence: 0.86011857

00:20:32.529 --> 00:20:34.301 We think that this

NOTE Confidence: 0.86011857

00:20:34.301 --> 00:20:36.320 capability of being plastic,

NOTE Confidence: 0.86011857

00:20:36.320 --> 00:20:38.650 it appears in naive tumors,

NOTE Confidence: 0.86011857

00:20:38.650 --> 00:20:41.848 so meaning before any treatment.

NOTE Confidence: 0.86011857

00:20:41.850 --> 00:20:45.002 But it also gets used once you challenge

NOTE Confidence: 0.86011857

00:20:45.002 --> 00:20:47.838 the tumor with different therapies,

NOTE Confidence: 0.86011857

00:20:47.840 --> 00:20:51.064 so we think that this is kind

NOTE Confidence: 0.86011857

00:20:51.064 --> 00:20:53.363 of an active pathway

NOTE Confidence: 0.86011857

00:20:53.363 --> 00:20:56.646 that it allows the cells to transform

NOTE Confidence: 0.86011857

00:20:56.731 --> 00:20:59.689 and to become cancer cells during

NOTE Confidence: 0.86011857

00:20:59.689 --> 00:21:02.132 the pathogenesis and after the

NOTE Confidence: 0.86011857

00:21:02.132 --> 00:21:04.440 pathogenesis during treatment time.

NOTE Confidence: 0.85592186

00:21:04.440 --> 00:21:06.540 You were mentioning that you've

NOTE Confidence: 0.85592186

00:21:06.540 --> 00:21:10.274 come up with a way to block

NOTE Confidence: 0.85592186

00:21:10.274 --> 00:21:12.849 that splicing, block that switching.

NOTE Confidence: 0.85592186

00:21:12.850 --> 00:21:14.914 So that if you prevent the

NOTE Confidence: 0.85592186

00:21:14.914 --> 00:21:16.290 cancer cell from actually

NOTE Confidence: 0.85592186

00:21:16.357 --> 00:21:18.537 switching to a different isoform,

NOTE Confidence: 0.85592186

00:21:18.540 --> 00:21:20.790 then potentially that cell is going

NOTE Confidence: 0.85592186

00:21:20.790 --> 00:21:23.080 to be more responsive to therapy,

NOTE Confidence: 0.85592186

00:21:23.080 --> 00:21:25.520 or at least would not be able to

NOTE Confidence: 0.85592186

00:21:25.520 --> 00:21:27.593 produce a protein isoform that

NOTE Confidence: 0.85592186

00:21:27.593 --> 00:21:30.280 would be resistant to therapy. Is

NOTE Confidence: 0.83769935

00:21:30.280 --> 00:21:32.180 that right?

NOTE Confidence: 0.83769935

00:21:32.180 --> 00:21:34.490 Yes, what we have learned

NOTE Confidence: 0.83769935

00:21:34.490 --> 00:21:36.730 so far from these therapies,

NOTE Confidence: 0.83769935

00:21:36.730 --> 00:21:38.640 that is actually very potent

NOTE Confidence: 0.83769935

00:21:38.640 --> 00:21:40.900 that these cancer cells do not,

NOTE Confidence: 0.83769935

00:21:40.900 --> 00:21:43.260 whenever you correct a splicing

NOTE Confidence: 0.83769935

00:21:43.260 --> 00:21:46.740 defect that they have in that they need

NOTE Confidence: 0.83769935

00:21:46.740 --> 00:21:49.874 to survive as soon as you corrected

NOTE Confidence: 0.83769935

00:21:49.874 --> 00:21:52.660 the cells become more sensitive

NOTE Confidence: 0.83769935

00:21:52.660 --> 00:21:55.270 to chemotherapeutic agents and or

NOTE Confidence: 0.83769935

00:21:55.270 --> 00:21:58.908 they just die on their own because

NOTE Confidence: 0.83769935

00:21:58.908 --> 00:22:01.488 they cannot tolerate losing that

NOTE Confidence: 0.83769935

00:22:01.488 --> 00:22:04.800 expression of a particular isoforms.

NOTE Confidence: 0.8746222

00:22:04.800 --> 00:22:06.830 The next question obviously

NOTE Confidence: 0.8746222

00:22:06.830 --> 00:22:09.460 is how exactly does that happen?

NOTE Confidence: 0.8746222

00:22:09.460 --> 00:22:11.735 I mean, because this splicing

NOTE Confidence: 0.8746222

00:22:11.735 --> 00:22:13.555 mechanism is presumably something

NOTE Confidence: 0.8746222

00:22:13.555 --> 00:22:16.220 that is intrinsic to that tumor cell.

NOTE Confidence: 0.8746222

00:22:16.220 --> 00:22:18.758 So in order to stop it,

NOTE Confidence: 0.8746222

00:22:18.760 --> 00:22:21.301 you would need to get something into

NOTE Confidence: 0.8746222

00:22:21.301 --> 00:22:23.932 that tumor cell that actually stops

NOTE Confidence: 0.8746222

00:22:23.932 --> 00:22:26.377 something that it intrinsically has.

NOTE Confidence: 0.8746222

00:22:26.380 --> 00:22:28.490 How do you do that?

NOTE Confidence: 0.8746222

00:22:28.490 --> 00:22:31.028 And has that been tested in

NOTE Confidence: 0.8746222

00:22:31.030 --> 00:22:34.446 humans?

NOTE Confidence: 0.8746222

00:22:34.450 --> 00:22:37.187 The cell in order to switch from

NOTE Confidence: 0.8746222

00:22:37.187 --> 00:22:39.450 one isoform to another one,

NOTE Confidence: 0.8746222

00:22:39.450 --> 00:22:42.288 the MRNA's have different sequences

NOTE Confidence: 0.8746222

00:22:42.288 --> 00:22:44.615 or different signals that

NOTE Confidence: 0.8746222

00:22:44.615 --> 00:22:47.072 is going to tell a cell produce

NOTE Confidence: 0.8746222

00:22:47.072 --> 00:22:49.459 isoform A or produce isoform B.

NOTE Confidence: 0.8746222

00:22:49.460 --> 00:22:51.545 Once we have identified which

NOTE Confidence: 0.8746222

00:22:51.545 --> 00:22:53.630 isoform we want to target.

NOTE Confidence: 0.8746222

00:22:53.630 --> 00:22:56.549 What we do is we introduce these

NOTE Confidence: 0.8746222

00:22:56.550 --> 00:22:59.070 small pieces of RNA into

NOTE Confidence: 0.8746222

00:22:59.070 --> 00:23:02.074 a cell and what we're going to

NOTE Confidence: 0.8746222

00:23:02.074 --> 00:23:04.528 do is we're going to block

NOTE Confidence: 0.8746222

00:23:04.530 --> 00:23:06.430 signals that usually the

NOTE Confidence: 0.8746222

00:23:06.430 --> 00:23:08.870 cancer cell would read to produce

NOTE Confidence: 0.8746222

00:23:08.870 --> 00:23:10.710 the most lethal isoform,

NOTE Confidence: 0.8746222

00:23:10.710 --> 00:23:13.531 and we're going to fool it to

NOTE Confidence: 0.8746222

00:23:13.531 --> 00:23:16.479 make sure that it doesn't see it.

NOTE Confidence: 0.8746222

00:23:16.480 --> 00:23:19.070 To mask these sites and

NOTE Confidence: 0.8746222

00:23:19.070 --> 00:23:22.044 force it to produce the other form and

NOTE Confidence: 0.8746222

00:23:22.044 --> 00:23:25.181 this therapy because of the way that

NOTE Confidence: 0.8746222

00:23:25.181 --> 00:23:28.428 it works, we called it SHOT.

NOTE Confidence: 0.8746222

00:23:28.430 --> 00:23:31.088 Actually giving SHOT to the

NOTE Confidence: 0.8746222

00:23:31.088 --> 00:23:34.048 cancer cells and shot stands for

NOTE Confidence: 0.8746222

00:23:34.048 --> 00:23:36.240 Splicing-Hit Oligonucleotide Therapy.

00:23:36.240 --> 00:23:40.480 So far we have not tested it in humans.

00:23:40.480 --> 00:23:43.448 All of our data comes so far

00:23:43.448 --> 00:23:44.720 from patient cells.

00:23:44.720 --> 00:23:46.416 Tumor patient tumor cells

00:23:46.416 --> 00:23:48.960 that we grow in the lab.

00:23:48.960 --> 00:23:52.040 We also have tested this in our

00:23:52.040 --> 00:23:53.852 genetically engineered mouse models

00:23:53.852 --> 00:23:56.318 and all of that has produced

00:23:56.318 --> 00:23:58.289 the preliminary data to start.

00:23:58.290 --> 00:24:00.345 Hopefully launching a clinical trial

00:24:00.345 --> 00:24:03.380 in the short future in the patients.

00:24:03.800 --> 00:24:06.845 So the next question is when you

00:24:06.850 --> 00:24:09.664 have this mechanism, this shot that

00:24:09.664 --> 00:24:12.430 can block this splicing mechanism,

00:24:12.430 --> 00:24:15.466 presumably you're giving it

00:24:15.470 --> 00:24:19.019 whether it's IV or orally,

NOTE Confidence: 0.86429554

00:24:19.020 --> 00:24:21.304 somehow you're trying to

NOTE Confidence: 0.86429554

00:24:21.304 --> 00:24:24.159 get this into tumor cells.

NOTE Confidence: 0.86429554

00:24:24.160 --> 00:24:26.536 Does it get into normal cells

NOTE Confidence: 0.86429554

00:24:26.536 --> 00:24:28.600 and does it have any effect

NOTE Confidence: 0.86429554

00:24:28.600 --> 00:24:30.976 on the normal cells as well?

NOTE Confidence: 0.86429554

00:24:30.980 --> 00:24:33.386 Or do normal cells not have

NOTE Confidence: 0.86429554

00:24:33.386 --> 00:24:34.589 this splicing mechanism?

NOTE Confidence: 0.86429554

00:24:34.590 --> 00:24:36.590 That's a very important question,

NOTE Confidence: 0.8587167

00:24:36.590 --> 00:24:39.821 so far the therapy that we

NOTE Confidence: 0.8587167

00:24:39.821 --> 00:24:43.007 like, the first phase of this therapy,

NOTE Confidence: 0.8587167

00:24:43.010 --> 00:24:45.355 we know that it's a specific for

NOTE Confidence: 0.8587167

00:24:45.355 --> 00:24:47.812 cancer cells because it's only

NOTE Confidence: 0.8587167

00:24:47.812 --> 00:24:50.107 going to correct splicing defect

NOTE Confidence: 0.8587167

00:24:50.107 --> 00:24:52.628 that appears only on cancer cells.

NOTE Confidence: 0.8587167

00:24:52.630 --> 00:24:56.150 It still gets into the normal cells.

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NOTE Confidence: 0.8587167

00:24:56.150 --> 00:24:58.430 But it's not active there.

00:25:00.154 --> 00:25:03.430 because the splicing defect is not present.

NOTE Confidence: 0.8587167

00:25:03.430 --> 00:25:06.552 So far we have managed to introduce

NOTE Confidence: 0.8587167

00:25:06.552 --> 00:25:09.936 the therapy into the cancer cells by

NOTE Confidence: 0.8587167

00:25:09.936 --> 00:25:12.381 directly injecting into the tumors

NOTE Confidence: 0.8587167

00:25:12.381 --> 00:25:15.431 of mice what we are excited right

NOTE Confidence: 0.8587167

00:25:15.431 --> 00:25:18.490 now is that we're going to start

NOTE Confidence: 0.8587167

00:25:18.490 --> 00:25:21.310 coupling SHOT with another therapy

NOTE Confidence: 0.8587167

00:25:21.310 --> 00:25:23.493 delivery technology that has been

NOTE Confidence: 0.8587167

00:25:23.493 --> 00:25:26.710 developed here at Yale and is actually

NOTE Confidence: 0.8587167

00:25:26.710 --> 00:25:28.720 currently under clinical trial testing

NOTE Confidence: 0.8587167

00:25:28.720 --> 00:25:31.901 called FLIP and FLIP is almost like a

NOTE Confidence: 0.8587167

00:25:31.901 --> 00:25:35.062 bio syringe that is going to carry shot

NOTE Confidence: 0.8587167

00:25:35.062 --> 00:25:38.030 and once said it lands into the tumor

NOTE Confidence: 0.8587167

00:25:38.030 --> 00:25:40.816 that has this particularly low pH,

NOTE Confidence: 0.8587167

00:25:40.820 --> 00:25:44.438 at that time it will convert into a syringe.

NOTE Confidence: 0.8587167

00:25:44.440 --> 00:25:46.678 It will introduce shot into the

NOTE Confidence: 0.8587167

00:25:46.678 --> 00:25:49.568 cells that are in that

NOTE Confidence: 0.8587167

00:25:49.568 --> 00:25:50.885 tumor microenvironment.

NOTE Confidence: 0.8587167

00:25:50.890 --> 00:25:53.065 So in that tumor microenvironment

NOTE Confidence: 0.8587167

00:25:53.065 --> 00:25:55.717 you have cancer cells and you

NOTE Confidence: 0.8587167

00:25:55.717 --> 00:25:58.117 have cells that are non cancerous.

NOTE Confidence: 0.8587167

00:25:58.120 --> 00:26:00.442 But the specificity comes that shot

NOTE Confidence: 0.8587167

00:26:00.442 --> 00:26:03.264 would only be able to correct splicing

NOTE Confidence: 0.8587167

00:26:03.264 --> 00:26:05.652 defects in cells that have it,

NOTE Confidence: 0.8587167

00:26:05.660 --> 00:26:07.645 and those splicing defects are

NOTE Confidence: 0.8587167

00:26:07.645 --> 00:26:09.630 only present in cancer cells.

NOTE Confidence: 0.8587167

00:26:09.630 --> 00:26:12.213 So I think the combination of flip and shot

NOTE Confidence: 0.8587167

00:26:12.213 --> 00:26:15.359 is going to be highly specific

NOTE Confidence: 0.8587167

00:26:15.359 --> 00:26:18.636 for tumor cells is going to be highly

NOTE Confidence: 0.8587167

00:26:18.636 --> 00:26:20.706 specific for splicing defects that

NOTE Confidence: 0.8587167

00:26:20.706 --> 00:26:23.445 we know are important for these cells

NOTE Confidence: 0.8587167

00:26:23.445 --> 00:26:26.268 and is going to decrease the amount

NOTE Confidence: 0.8587167

00:26:26.268 --> 00:26:28.806 of side effects because this therapy

NOTE Confidence: 0.8587167

00:26:28.810 --> 00:26:30.618 is so specific.

NOTE Confidence: 0.8339394

00:26:30.620 --> 00:26:33.308 One question is, if shot

NOTE Confidence: 0.8339394

00:26:33.308 --> 00:26:36.537 is so specific based on the fact

NOTE Confidence: 0.8339394

00:26:36.537 --> 00:26:38.525 that this slicing mechanism

NOTE Confidence: 0.8339394

00:26:38.525 --> 00:26:41.008 only exists in cancer cells,

NOTE Confidence: 0.8339394

00:26:41.010 --> 00:26:44.174 then I guess the next question is,

NOTE Confidence: 0.8339394

00:26:44.180 --> 00:26:47.508 do you really need flip to kind of

NOTE Confidence: 0.8339394

00:26:47.508 --> 00:26:51.409 take it to where the cancer cells are,

NOTE Confidence: 0.8339394

00:26:51.410 --> 00:26:54.116 which is a low pH area?

NOTE Confidence: 0.8339394

00:26:54.120 --> 00:26:56.952 Or can you just inject shot

NOTE Confidence: 0.8339394

00:26:56.952 --> 00:26:58.840 systemically and know that

NOTE Confidence: 0.8339394

00:26:58.840 --> 00:27:01.360 even if it were to circulate around,

NOTE Confidence: 0.8339394

00:27:01.360 --> 00:27:03.887 and get absorbed by other cells that

NOTE Confidence: 0.8339394

00:27:03.887 --> 00:27:06.039 it really wouldn't cause any harm,

NOTE Confidence: 0.8339394

00:27:06.040 --> 00:27:08.086 the only harm it would cause

NOTE Confidence: 0.8339394

00:27:08.086 --> 00:27:10.000 is in the tumor cells,

NOTE Confidence: 0.8339394

00:27:10.000 --> 00:27:12.485 or is the idea behind flip that

NOTE Confidence: 0.8339394

00:27:12.485 --> 00:27:14.602 you would decrease the amount of

NOTE Confidence: 0.8339394

00:27:14.602 --> 00:27:16.884 shot that you would need so that

NOTE Confidence: 0.8339394

00:27:16.963 --> 00:27:18.878 you could more accurately target

NOTE Confidence: 0.8339394

00:27:18.878 --> 00:27:21.520 it to where the tumor actually is.

NOTE Confidence: 0.886036099999999

00:27:21.520 --> 00:27:22.936 It's actually the latter.

NOTE Confidence: 0.886036099999999

00:27:22.936 --> 00:27:26.150 This is the way that we can increase the

NOTE Confidence: 0.886036099999999

00:27:26.150 --> 00:27:28.990 amount of dose of shot that is going

NOTE Confidence: 0.886036099999999

00:27:28.990 --> 00:27:31.706 to go directly into the cancer cells.

NOTE Confidence: 0.886036099999999

00:27:31.710 --> 00:27:33.936 Because if we just put shot systemically

NOTE Confidence: 0.886036099999999

00:27:33.936 --> 00:27:35.540 without a delivery technology,

NOTE Confidence: 0.886036099999999

00:27:35.540 --> 00:27:38.291 it will start getting word out and

NOTE Confidence: 0.886036099999999

00:27:38.291 --> 00:27:40.486 the concentration is going to drop

NOTE Confidence: 0.886036099999999

00:27:40.486 --> 00:27:43.083 and by the time the little bit that

NOTE Confidence: 0.886036099999999

00:27:43.083 --> 00:27:45.651 reaches the tumor it might be too low

NOTE Confidence: 0.886036099999999

00:27:45.651 --> 00:27:47.720 to have a biological impact.

NOTE Confidence: 0.87575865

00:27:47.720 --> 00:27:49.748 And so has this

NOTE Confidence: 0.87575865

00:27:49.748 --> 00:27:51.550 combination of flip and shot

NOTE Confidence: 0.87575865

00:27:51.550 --> 00:27:53.740 been tried in mouse models?

NOTE Confidence: 0.87575865

00:27:53.740 --> 00:27:56.070 Were actually testing it and this is part

NOTE Confidence: 0.87575865

00:27:56.070 --> 00:27:59.240 of the one of the reasons why I wanted to

NOTE Confidence: 0.87575865

00:27:59.324 --> 00:28:02.500 come to Yale because I wanted to combine

NOTE Confidence: 0.87575865

00:28:02.500 --> 00:28:05.914 a very exciting therapy with other

NOTE Confidence: 0.87575865

00:28:05.914 --> 00:28:08.914 delivery technologies that were being

NOTE Confidence: 0.87575865

00:28:08.914 --> 00:28:11.458 developed here specifically for

NOTE Confidence: 0.87575865

00:28:11.460 --> 00:28:13.580 these therapies that

NOTE Confidence: 0.87575865

00:28:13.580 --> 00:28:16.227 modify the way that the cells

NOTE Confidence: 0.87575865

00:28:16.227 --> 00:28:18.915 express proteins and turn on genes,

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NOTE Confidence: 0.87575865

00:28:18.920 --> 00:28:22.216 and so we are hoping that now that

NOTE Confidence: 0.87575865

00:28:22.216 --> 00:28:24.958 the research is ramping up after

NOTE Confidence: 0.87575865

00:28:24.958 --> 00:28:27.694 COVID that we can start testing,

NOTE Confidence: 0.87575865

00:28:27.700 --> 00:28:30.214 we cannot wait to collaborate and

NOTE Confidence: 0.87575865

00:28:30.214 --> 00:28:32.426 we're already starting to synthesize

NOTE Confidence: 0.87575865

00:28:32.426 --> 00:28:35.168 the shot in combination with flip.

NOTE Confidence: 0.86357164

00:28:35.850 --> 00:28:38.286 Doctor Luisa Escobar-Hoyos is an

NOTE Confidence: 0.86357164

00:28:38.286 --> 00:28:39.910 assistant professor of therapeutic

NOTE Confidence: 0.86357164

00:28:39.977 --> 00:28:42.427 radiology at the Yale School of Medicine.

NOTE Confidence: 0.86357164

00:28:42.430 --> 00:28:43.982 If you have questions,

NOTE Confidence: 0.86357164

00:28:43.982 --> 00:28:45.534 the address is canceranswers@yale.edu

NOTE Confidence: 0.86357164

00:28:45.534 --> 00:28:47.677 and past editions of the program

NOTE Confidence: 0.86357164

00:28:47.677 --> 00:28:49.633 are available in audio and written

NOTE Confidence: 0.86357164

00:28:49.696 --> 00:28:51.328 form at yalecancercenter.org.

NOTE Confidence: 0.86357164

00:28:51.330 --> 00:28:54.226 We hope you'll join us next week to

NOTE Confidence: 0.86357164

00:28:54.226 --> 00:28:57.048 learn more about the fight against

NOTE Confidence: 0.86357164

00:28:57.048 --> 00:29:00.072 cancer here on Connecticut Public Radio.