WEBVTT

NOTE duration:"00:55:48"

NOTE recognizability:0.812

NOTE language:en-us

NOTE Confidence: 0.52924847

00:00:00.000 --> 00:00:03.800 You can see it. Fred.

NOTE Confidence: 0.52924847

00:00:03.800 --> 00:00:06.020 So with no further ado on

NOTE Confidence: 0.52924847

00:00:06.020 --> 00:00:07.500 behalf of Doctor Nita,

NOTE Confidence: 0.52924847

00:00:07.500 --> 00:00:09.680 Hoosier Interim Cancer Center director,

NOTE Confidence: 0.52924847

00:00:09.680 --> 00:00:12.200 and actually this time next week,

NOTE Confidence: 0.52924847

00:00:12.200 --> 00:00:13.850 your good friend Doctor Eric

NOTE Confidence: 0.52924847

00:00:13.850 --> 00:00:15.981 Wyner will be sitting in that

NOTE Confidence: 0.52924847

00:00:15.981 --> 00:00:18.056 position as our permanent director.

NOTE Confidence: 0.52924847

00:00:18.060 --> 00:00:21.077 We're really excited to have you here,

NOTE Confidence: 0.52924847

00:00:21.080 --> 00:00:22.538 even though it's not in person,

NOTE Confidence: 0.52924847

00:00:22.540 --> 00:00:24.815 as the Julia Patricia Kingsbury

NOTE Confidence: 0.52924847

00:00:24.815 --> 00:00:26.635 Memorial lecturer and lectureship

NOTE Confidence: 0.52924847

00:00:26.635 --> 00:00:28.358 that's been sponsored for.

NOTE Confidence: 0.52924847

00:00:28.360 --> 00:00:30.957 You know well over 2 decades by

NOTE Confidence: 0.52924847

00:00:30.957 --> 00:00:32.712 their family for me to introduce.

NOTE Confidence: 0.52924847

00:00:32.712 --> 00:00:33.724 Doctor Norton is like.

NOTE Confidence: 0.52924847

00:00:33.730 --> 00:00:34.957 Introducing a Rockstar.

NOTE Confidence: 0.52924847

00:00:34.957 --> 00:00:37.411 Obviously he's a senior vice president

NOTE Confidence: 0.52924847

00:00:37.411 --> 00:00:39.647 in the office of the President,

NOTE Confidence: 0.52924847

00:00:39.650 --> 00:00:40.838 Memorial Sloan Kettering,

NOTE Confidence: 0.52924847

00:00:40.838 --> 00:00:42.818 the medical director of the

NOTE Confidence: 0.52924847

00:00:42.818 --> 00:00:44.612 Evelyn Lauder Breast Center.

NOTE Confidence: 0.52924847

00:00:44.612 --> 00:00:47.618 I think you're also the founding

NOTE Confidence: 0.52924847

00:00:47.618 --> 00:00:50.218 and incumbent N Norna Serafin

NOTE Confidence: 0.52924847

00:00:50.218 --> 00:00:52.234 clinical chair in oncology.

NOTE Confidence: 0.52924847

00:00:52.240 --> 00:00:53.062 Career started,

NOTE Confidence: 0.52924847

00:00:53.062 --> 00:00:53.884 you know,

NOTE Confidence: 0.52924847

00:00:53.884 --> 00:00:55.939 undergraduate and undergraduate at Rochester,

NOTE Confidence: 0.52924847

00:00:55.940 --> 00:00:58.383 then went on to Columbia for medical

NOTE Confidence: 0.52924847

00:00:58.383 --> 00:01:00.762 school in Albert Einstein and the NCI

NOTE Confidence: 0.52924847

00:01:00.762 --> 00:01:03.020 for Training and Medicine and Oncology.

NOTE Confidence: 0.52924847

00:01:03.020 --> 00:01:03.600 And really,

NOTE Confidence: 0.52924847

00:01:03.600 --> 00:01:06.357 you know the first time I was I was

NOTE Confidence: 0.52924847

00:01:06.357 --> 00:01:08.172 privileged to meet Doctor Norton

NOTE Confidence: 0.52924847

00:01:08.172 --> 00:01:10.580 was in 2002 at the old CLG or

NOTE Confidence: 0.52924847

00:01:10.580 --> 00:01:12.249 the cancer and Leukemia Group B.

NOTE Confidence: 0.52924847

00:01:12.250 --> 00:01:14.206 And you know that committee which

NOTE Confidence: 0.52924847

00:01:14.206 --> 00:01:16.547 you chaired for such a long time and

NOTE Confidence: 0.52924847

00:01:16.547 --> 00:01:19.814 then passed on to doctor Doctor Weiner again.

NOTE Confidence: 0.52924847

00:01:19.820 --> 00:01:21.585 Our incoming director and Doctor

NOTE Confidence: 0.52924847

00:01:21.585 --> 00:01:24.210 Hudis just to see how masterfully.

NOTE Confidence: 0.52924847

00:01:24.210 --> 00:01:24.850 The research,

NOTE Confidence: 0.52924847

00:01:24.850 --> 00:01:25.490 the work,

NOTE Confidence: 0.52924847

00:01:25.490 --> 00:01:28.070 the care of your patients over the years,

NOTE Confidence: 0.52924847

00:01:28.070 --> 00:01:30.142 and then you know more recently in the

NOTE Confidence: 0.52924847

00:01:30.142 --> 00:01:32.450 last decade you know being involved with

NOTE Confidence: 0.52924847

00:01:32.450 --> 00:01:34.185 the breast Cancer Research Foundation,

NOTE Confidence: 0.52924847

00:01:34.190 --> 00:01:36.730 which you and Evelyn Lauder,

NOTE Confidence: 0.52924847

00:01:36.730 --> 00:01:38.258 the late Evelyn Lauder,

NOTE Confidence: 0.52924847

00:01:38.258 --> 00:01:39.450 and Leonard Lauder,

NOTE Confidence: 0.52924847

00:01:39.450 --> 00:01:40.260 you know,

NOTE Confidence: 0.52924847

00:01:40.260 --> 00:01:42.690 put together really bringing over 200,

NOTE Confidence: 0.52924847

00:01:42.690 --> 00:01:43.268 I think,

NOTE Confidence: 0.52924847

00:01:43.268 --> 00:01:45.002 probably close to 300 of the

NOTE Confidence: 0.52924847

00:01:45.002 --> 00:01:46.081 world's leading investigators

NOTE Confidence: 0.52924847

00:01:46.081 --> 00:01:47.869 and breast Cancer Research.

NOTE Confidence: 0.52924847

00:01:47.870 --> 00:01:49.530 Really, for the cure,

NOTE Confidence: 0.52924847

00:01:49.530 --> 00:01:51.605 as defined as the founding

NOTE Confidence: 0.52924847

00:01:51.605 --> 00:01:52.730 scientific director.

NOTE Confidence: 0.52924847

00:01:52.730 --> 00:01:53.074 Gosh,

NOTE Confidence: 0.52924847

00:01:53.074 --> 00:01:54.450 this is such a.

NOTE Confidence: 0.52924847

00:01:54.450 --> 00:01:56.880 A great day for for a Yale and I

NOTE Confidence: 0.52924847

00:01:56.880 --> 00:01:58.915 know everyone is really excited

NOTE Confidence: 0.52924847

00:01:58.915 --> 00:02:00.740 to hear your thoughts on the

NOTE Confidence: 0.52924847

00:02:00.740 --> 00:02:01.860 nature of breast neoplasia.

NOTE Confidence: 0.52924847

00:02:01.860 --> 00:02:03.145 So thank you Doctor Norton

NOTE Confidence: 0.52924847

00:02:03.145 --> 00:02:04.173 for making the time.

NOTE Confidence: 0.837315272857143

00:02:04.360 --> 00:02:06.054 OK, thank you. Thank you very much.

NOTE Confidence: 0.837315272857143

00:02:06.060 --> 00:02:08.067 I hope everybody can hear me and thank you

NOTE Confidence: 0.837315272857143

00:02:08.067 --> 00:02:10.239 for that really very gracious introduction.

NOTE Confidence: 0.837315272857143

00:02:10.240 --> 00:02:12.864 You know it's a it's it's totally shame.

NOTE Confidence: 0.837315272857143

00:02:12.870 --> 00:02:14.274 In the old days when you give a lecture

NOTE Confidence: 0.837315272857143

00:02:14.274 --> 00:02:15.624 ship like this, you'd come in person.

NOTE Confidence: 0.837315272857143

00:02:15.624 --> 00:02:17.192 You'd have a dinner you'd meet with a

NOTE Confidence: 0.837315272857143

00:02:17.192 --> 00:02:19.222 lot of people, one on one, and so many

NOTE Confidence: 0.837315272857143

00:02:19.222 --> 00:02:21.111 of my great interactions in my career

NOTE Confidence: 0.837315272857143

00:02:21.111 --> 00:02:22.940 started really by those kinds of events.

NOTE Confidence: 0.837315272857143

00:02:22.940 --> 00:02:24.712 And so it's a. It's a shame that

NOTE Confidence: 0.837315272857143

00:02:24.712 --> 00:02:26.050 we have to do this electronically.

NOTE Confidence: 0.837315272857143

00:02:26.050 --> 00:02:28.227 But it's a great pleasure to be

NOTE Confidence: 0.837315272857143

00:02:28.227 --> 00:02:30.258 here and and speak with you.

NOTE Confidence: 0.837315272857143

00:02:30.258 --> 00:02:31.092 I'm, you know,

NOTE Confidence: 0.837315272857143

00:02:31.092 --> 00:02:33.020 my neighbors in the Northeast about some of

NOTE Confidence: 0.837315272857143

00:02:33.065 --> 00:02:35.017 the things that that I've been thinking of.

NOTE Confidence: 0.837315272857143

00:02:35.020 --> 00:02:36.712 What I've been doing,

NOTE Confidence: 0.837315272857143

00:02:36.712 --> 00:02:38.404 it's called mathematical insights,

NOTE Confidence: 0.837315272857143

00:02:38.410 --> 00:02:40.363 but for those of you who are math phobic,

NOTE Confidence: 0.837315272857143

00:02:40.370 --> 00:02:43.010 please don't don't run away screaming.

NOTE Confidence: 0.837315272857143

00:02:43.010 --> 00:02:44.190 You know it's a.

NOTE Confidence: 0.837315272857143

00:02:44.190 --> 00:02:46.650 I'm only going to show one equation,

NOTE Confidence: 0.837315272857143

00:02:46.650 --> 00:02:48.170 and it's not important really for the talk.

NOTE Confidence: 0.837315272857143

00:02:48.170 --> 00:02:49.790 Basically, it is mathematical thinking

NOTE Confidence: 0.837315272857143

00:02:49.790 --> 00:02:52.368 and a lot of people don't know math.

NOTE Confidence: 0.837315272857143

00:02:52.370 --> 00:02:53.875 Don't realize that what math

NOTE Confidence: 0.837315272857143

00:02:53.875 --> 00:02:56.120 is is is not the equations.

NOTE Confidence: 0.837315272857143

00:02:56.120 --> 00:02:58.005 The equivalency would be sheet

NOTE Confidence: 0.837315272857143

00:02:58.005 --> 00:02:59.136 music for music.

NOTE Confidence: 0.837315272857143

00:02:59.140 --> 00:03:00.400 The sheet music is not the music,

NOTE Confidence: 0.837315272857143

00:03:00.400 --> 00:03:01.516 it's the sound.

NOTE Confidence: 0.837315272857143

00:03:01.516 --> 00:03:03.748 And and with mathematics it's it's

NOTE Confidence: 0.837315272857143

00:03:03.748 --> 00:03:05.416 the the insights that you gain which

NOTE Confidence: 0.837315272857143

00:03:05.416 --> 00:03:06.939 you know in terms of how things.

NOTE Confidence: 0.837315272857143

00:03:06.940 --> 00:03:07.960 In this case, how they grow,

NOTE Confidence: 0.837315272857143

00:03:07.960 --> 00:03:08.629 how they shrink,

NOTE Confidence: 0.837315272857143

00:03:08.629 --> 00:03:10.718 why they grow that way and and and so on,

NOTE Confidence: 0.837315272857143

00:03:10.720 --> 00:03:12.418 how we take advantage of that.

NOTE Confidence: 0.837315272857143

00:03:12.420 --> 00:03:15.290 The the equations are not really the

NOTE Confidence: 0.837315272857143

00:03:15.290 --> 00:03:17.116 mathematics for many years when I was

NOTE Confidence: 0.837315272857143

00:03:17.116 --> 00:03:19.063 giving this talk I I skipped over a

NOTE Confidence: 0.837315272857143

00:03:19.063 --> 00:03:20.860 lot of the early stuff that I did,

NOTE Confidence: 0.837315272857143

00:03:20.860 --> 00:03:22.740 but then I realized a few years back

NOTE Confidence: 0.837315272857143

00:03:22.740 --> 00:03:24.666 that a lot of the younger people

NOTE Confidence: 0.837315272857143

00:03:24.666 --> 00:03:26.450 are unaware of that early stuff.

NOTE Confidence: 0.837315272857143

00:03:26.450 --> 00:03:27.962 And that really stuff is really

NOTE Confidence: 0.837315272857143

00:03:27.962 --> 00:03:28.970 very important for understanding

NOTE Confidence: 0.837315272857143

00:03:29.011 --> 00:03:30.349 the later things that we're doing.

NOTE Confidence: 0.837315272857143

00:03:30.350 --> 00:03:32.818 So I am going to be talking about it.

NOTE Confidence: 0.837315272857143

00:03:32.818 --> 00:03:33.310 I mean,

NOTE Confidence: 0.837315272857143

00:03:33.310 --> 00:03:35.318 it really happened to me a bunch of

NOTE Confidence: 0.837315272857143

00:03:35.318 --> 00:03:37.104 years already that I was a visiting

NOTE Confidence: 0.837315272857143

00:03:37.104 --> 00:03:38.889 professor and somebody presented a

NOTE Confidence: 0.837315272857143

00:03:38.889 --> 00:03:41.447 case and and said this patient dose.

NOTE Confidence: 0.837315272857143

00:03:41.450 --> 00:03:45.323 Dense chemotherapy with AC and Taxol, Dr.

NOTE Confidence: 0.837315272857143

00:03:45.323 --> 00:03:47.188 Ordinary familiar with that regimen.

NOTE Confidence: 0.837315272857143

00:03:47.190 --> 00:03:48.858 And that's when I realized that

NOTE Confidence: 0.837315272857143

00:03:48.858 --> 00:03:50.540 that perhaps I should really cover

NOTE Confidence: 0.837315272857143

00:03:50.540 --> 00:03:52.339 some of the early things that I

NOTE Confidence: 0.837315272857143

00:03:52.339 --> 00:03:54.227 that that I've done and and how it

NOTE Confidence: 0.837315272857143

00:03:54.227 --> 00:03:55.750 relates to to the bigger picture.

NOTE Confidence: 0.837315272857143

00:03:55.750 --> 00:03:57.150 So I'm going to talk.

NOTE Confidence: 0.837315272857143

00:03:57.150 --> 00:03:58.595 About growth models and of

NOTE Confidence: 0.837315272857143

00:03:58.595 --> 00:04:00.040 course the the premier growth

NOTE Confidence: 0.837315272857143

00:04:00.096 --> 00:04:01.746 model being from Howard skipper,

NOTE Confidence: 0.837315272857143

00:04:01.750 --> 00:04:04.606 I'll talk about the work that I did

NOTE Confidence: 0.837315272857143

00:04:04.606 --> 00:04:07.557 in the 70s interpreting that growth

NOTE Confidence: 0.837315272857143

00:04:07.557 --> 00:04:10.773 model in with the appreciation for

NOTE Confidence: 0.837315272857143

00:04:10.780 --> 00:04:12.450 understanding a different pattern of

NOTE Confidence: 0.837315272857143

00:04:12.450 --> 00:04:15.065 the way that cancers grow than how it

NOTE Confidence: 0.837315272857143

00:04:15.065 --> 00:04:16.829 skipper and and colleagues had shown.

NOTE Confidence: 0.837315272857143

00:04:16.830 --> 00:04:18.998 How it led to the concept of dose

NOTE Confidence: 0.837315272857143

00:04:18.998 --> 00:04:20.381 dense sequential therapy and what

NOTE Confidence: 0.837315272857143

00:04:20.381 --> 00:04:22.201 are the results of that that we

NOTE Confidence: 0.837315272857143

00:04:22.263 --> 00:04:23.898 just fairly recently summarized

NOTE Confidence: 0.837315272857143

00:04:23.898 --> 00:04:26.090 by the Oxford overview?

NOTE Confidence: 0.837315272857143

00:04:26.090 --> 00:04:27.806 And then talk about self seating

NOTE Confidence: 0.837315272857143

00:04:27.806 --> 00:04:30.160 theory and how it relates to all of

NOTE Confidence: 0.837315272857143

00:04:30.160 --> 00:04:31.876 that previous work and that will

NOTE Confidence: 0.889571411428571

00:04:31.943 --> 00:04:34.407 bring me into the area of fractal geometry,

NOTE Confidence: 0.889571411428571

00:04:34.410 --> 00:04:36.510 which is where where another topic

NOTE Confidence: 0.889571411428571

00:04:36.510 --> 00:04:40.582 in math comes in and how our that's

NOTE Confidence: 0.889571411428571

00:04:40.582 --> 00:04:44.943 informing our current work on the tumor,

NOTE Confidence: 0.889571411428571

00:04:44.943 --> 00:04:45.649 infiltrating leukocytes,

NOTE Confidence: 0.889571411428571

00:04:45.649 --> 00:04:47.767 and the interpretation of their firm.

NOTE Confidence: 0.889571411428571

00:04:47.770 --> 00:04:49.730 And I don't know if David Rim is,

NOTE Confidence: 0.889571411428571

00:04:49.730 --> 00:04:52.264 you know, here among us today, but,

NOTE Confidence: 0.889571411428571

00:04:52.264 --> 00:04:54.322 but we've had a number of early

NOTE Confidence: 0.889571411428571

00:04:54.322 --> 00:04:56.159 conversations a few years back about.

NOTE Confidence: 0.889571411428571

00:04:56.160 --> 00:04:57.980 The importance of fractal geometry

NOTE Confidence: 0.889571411428571

00:04:57.980 --> 00:04:59.436 and understanding biology from

NOTE Confidence: 0.889571411428571

00:04:59.436 --> 00:05:01.160 a pathology point of view,

NOTE Confidence: 0.889571411428571

00:05:01.160 --> 00:05:04.107 and then how that relates to concepts

NOTE Confidence: 0.889571411428571

00:05:04.107 --> 00:05:07.660 of drug resistance and and the use of

NOTE Confidence: 0.889571411428571

00:05:07.660 --> 00:05:09.875 immunotherapeutic agents and and lately.

NOTE Confidence: 0.889571411428571

00:05:09.880 --> 00:05:11.630 Our work that we're doing on antibody

NOTE Confidence: 0.889571411428571

00:05:11.630 --> 00:05:12.960 drug conjugates in that regard,

NOTE Confidence: 0.889571411428571

00:05:12.960 --> 00:05:16.296 but all informed by mathematical thinking.

NOTE Confidence: 0.889571411428571

00:05:16.300 --> 00:05:18.376 Let's just start back with Hippocrates,

NOTE Confidence: 0.889571411428571

00:05:18.380 --> 00:05:20.110 the father of us all.

NOTE Confidence: 0.889571411428571

00:05:20.110 --> 00:05:22.566 The parent of us all in, in in,

NOTE Confidence: 0.889571411428571

00:05:22.566 --> 00:05:23.850 in, in medicine.

NOTE Confidence: 0.889571411428571

00:05:23.850 --> 00:05:25.390 The actual quote translated from

NOTE Confidence: 0.889571411428571

00:05:25.390 --> 00:05:27.435 the Greek is an illness is once

NOTE Confidence: 0.889571411428571

00:05:27.435 --> 00:05:29.235 you keep two things in mind to be

NOTE Confidence: 0.889571411428571

00:05:29.295 --> 00:05:31.107 useful rather than cause no harm.

NOTE Confidence: 0.889571411428571

00:05:31.110 --> 00:05:31.986 That's frequently misquoted,

NOTE Confidence: 0.889571411428571

00:05:31.986 --> 00:05:34.170 as as first of all, do no harm.

NOTE Confidence: 0.889571411428571

00:05:34.170 --> 00:05:35.610 That's not quite what he said.

NOTE Confidence: 0.889571411428571

00:05:35.610 --> 00:05:37.367 What he said is don't be neutral,

NOTE Confidence: 0.889571411428571

00:05:37.370 --> 00:05:39.530 but but, but, but be useful,

NOTE Confidence: 0.889571411428571

00:05:39.530 --> 00:05:41.798 and that is,

NOTE Confidence: 0.889571411428571

00:05:41.798 --> 00:05:44.602 is is a very important quote

NOTE Confidence: 0.889571411428571

00:05:44.602 --> 00:05:45.894 because it relates very.

NOTE Confidence: 0.889571411428571

00:05:45.900 --> 00:05:47.924 Very directly to one of our major topics

NOTE Confidence: 0.889571411428571

00:05:47.924 --> 00:05:50.135 that we have to deal with in clinical

NOTE Confidence: 0.889571411428571

00:05:50.135 --> 00:05:51.720 oncology all the time, which is OK.

NOTE Confidence: 0.889571411428571

00:05:51.720 --> 00:05:52.680 I have a drug that works.

NOTE Confidence: 0.889571411428571

00:05:52.680 --> 00:05:54.728 How should I use it and dose level of

NOTE Confidence: 0.889571411428571

00:05:54.728 --> 00:05:56.396 course is a mix between the efficacy

NOTE Confidence: 0.889571411428571

00:05:56.396 --> 00:05:58.612 of the drug that you're giving and the

NOTE Confidence: 0.889571411428571

00:05:58.612 --> 00:06:00.328 toxicity that you're causing from it.

NOTE Confidence: 0.889571411428571

00:06:00.330 --> 00:06:02.282 And I spent almost all of my youth

NOTE Confidence: 0.889571411428571

00:06:02.282 --> 00:06:03.903 learning to be a medical oncologist

NOTE Confidence: 0.889571411428571

00:06:03.903 --> 00:06:05.840 learning how to to avoid or manage

NOTE Confidence: 0.889571411428571

00:06:05.840 --> 00:06:07.653 toxicity of of the agents and pick

NOTE Confidence: 0.889571411428571

00:06:07.653 --> 00:06:09.280 out the right dose level quotes

NOTE Confidence: 0.889571411428571

00:06:09.280 --> 00:06:10.930 in the modern world has gotten

NOTE Confidence: 0.889571411428571

00:06:10.981 --> 00:06:12.606 much more complicated than that.

NOTE Confidence: 0.889571411428571

00:06:12.610 --> 00:06:13.933 We have to not only look at

NOTE Confidence: 0.889571411428571

00:06:13.933 --> 00:06:15.328 at the at the dose level,

NOTE Confidence: 0.889571411428571

00:06:15.330 --> 00:06:16.930 but also the schedule.

NOTE Confidence: 0.889571411428571

00:06:16.930 --> 00:06:19.816 The duration of Therapy will give it

NOTE Confidence: 0.889571411428571

00:06:19.816 --> 00:06:22.258 impulses and that leads to various

NOTE Confidence: 0.889571411428571

00:06:22.258 --> 00:06:24.490 changes in efficacy and toxicity.

NOTE Confidence: 0.889571411428571

00:06:24.490 --> 00:06:26.350 Toxicity is not just acute toxicity,

NOTE Confidence: 0.889571411428571

00:06:26.350 --> 00:06:28.310 but late toxicities chronic

NOTE Confidence: 0.889571411428571

00:06:28.310 --> 00:06:30.270 toxicities that may arise.

NOTE Confidence: 0.889571411428571

00:06:30.270 --> 00:06:32.478 The personal cost to the patient and the

NOTE Confidence: 0.889571411428571

00:06:32.478 --> 00:06:34.389 personal goals for the patient have been

NOTE Confidence: 0.889571411428571

00:06:34.389 --> 00:06:36.349 taken into account and and in planning,

NOTE Confidence: 0.889571411428571

00:06:36.350 --> 00:06:39.242 dosing and scheduling as but also

NOTE Confidence: 0.889571411428571

00:06:39.242 --> 00:06:40.963 societal cost that everything that

NOTE Confidence: 0.889571411428571

00:06:40.963 --> 00:06:42.720 we do is going to have implications

NOTE Confidence: 0.889571411428571

00:06:42.772 --> 00:06:44.206 basically to all of our society.

NOTE Confidence: 0.889571411428571

00:06:44.210 --> 00:06:46.786 All of our patients and society in general.

NOTE Confidence: 0.889571411428571

00:06:46.790 --> 00:06:48.842 And how does all of this relate to a

NOTE Confidence: 0.889571411428571

00:06:48.842 --> 00:06:50.295 very rapidly evolving therapeutical

NOTE Confidence: 0.889571411428571

00:06:50.295 --> 00:06:52.629 landscape so so dosing is scheduling

NOTE Confidence: 0.889571411428571

00:06:52.629 --> 00:06:54.496 is actually a very germane topic

NOTE Confidence: 0.889571411428571

00:06:54.496 --> 00:06:55.911 in in the modern era,

NOTE Confidence: 0.889571411428571

00:06:55.920 --> 00:06:57.020 even when we're talking about

NOTE Confidence: 0.889571411428571

00:06:57.020 --> 00:06:58.120 some of the newer agents.

NOTE Confidence: 0.889571411428571

00:06:58.120 --> 00:06:59.470 And and what we've learned in

NOTE Confidence: 0.889571411428571

00:06:59.470 --> 00:07:01.061 looking at the older agents, IE.

NOTE Confidence: 0.889571411428571

00:07:01.061 --> 00:07:02.987 Chemotherapy is directly related to how

NOTE Confidence: 0.889571411428571

00:07:02.987 --> 00:07:05.617 we're going to be applying our newer agents,

NOTE Confidence: 0.889571411428571

00:07:05.620 --> 00:07:06.838 and as I close the talk,

NOTE Confidence: 0.889571411428571

00:07:06.840 --> 00:07:09.060 I hope I'll be addressing some

NOTE Confidence: 0.889571411428571

00:07:09.060 --> 00:07:10.170 of these points.

NOTE Confidence: 0.889571411428571

00:07:10.170 --> 00:07:13.370 But the central dogma that led most of us in

NOTE Confidence: 0.858240378235294

00:07:13.452 --> 00:07:16.364 our careers in medical oncology is this.

NOTE Confidence: 0.858240378235294

00:07:16.370 --> 00:07:17.866 If you want to kill more cancer cells,

NOTE Confidence: 0.858240378235294

00:07:17.870 --> 00:07:19.270 you have to use higher dose levels.

NOTE Confidence: 0.858240378235294

00:07:19.270 --> 00:07:21.583 So you want to use the highest possible dose

NOTE Confidence: 0.858240378235294

00:07:21.583 --> 00:07:23.648 level you can to kill more cancer cells.

NOTE Confidence: 0.858240378235294

00:07:23.650 --> 00:07:24.698 Because the more cancer

NOTE Confidence: 0.858240378235294

00:07:24.698 --> 00:07:26.008 more cancer cells you kill,

NOTE Confidence: 0.858240378235294

00:07:26.010 --> 00:07:28.026 the more benefit to the patient

NOTE Confidence: 0.858240378235294

00:07:28.026 --> 00:07:29.370 either eradicating the cancer.

NOTE Confidence: 0.858240378235294

00:07:29.370 --> 00:07:31.730 If if if that should actually be possible,

NOTE Confidence: 0.858240378235294

00:07:31.730 --> 00:07:34.050 or just buying time 'cause we have smaller.

NOTE Confidence: 0.858240378235294

00:07:34.050 --> 00:07:35.794 Buying more tumors can take longer to regrow,

NOTE Confidence: 0.858240378235294

00:07:35.800 --> 00:07:38.040 and that's going to be translated into

NOTE Confidence: 0.858240378235294

00:07:38.040 --> 00:07:40.650 into improvement in duration of Disease

NOTE Confidence: 0.858240378235294

00:07:40.650 --> 00:07:43.452 Control for the patient and hence our

NOTE Confidence: 0.858240378235294

00:07:43.452 --> 00:07:45.576 training was all about determining and

NOTE Confidence: 0.858240378235294

00:07:45.576 --> 00:07:47.509 treating at maximum tolerated dose.

NOTE Confidence: 0.864022766666667

00:07:49.960 --> 00:07:52.852 I'm going back to another great

NOTE Confidence: 0.864022766666667

00:07:52.852 --> 00:07:54.840 teacher of medicine, William Ostler.

NOTE Confidence: 0.864022766666667

00:07:54.840 --> 00:07:55.920 The greater their ignorance,

NOTE Confidence: 0.864022766666667

00:07:55.920 --> 00:07:57.028 the greater the dogmatism,

NOTE Confidence: 0.864022766666667

00:07:57.028 --> 00:07:59.000 and I believe that this this this.

NOTE Confidence: 0.864022766666667

00:07:59.000 --> 00:08:00.530 This dogmatism is really dominating

NOTE Confidence: 0.864022766666667

00:08:00.530 --> 00:08:02.407 us even to the present day

NOTE Confidence: 0.864022766666667

00:08:02.407 --> 00:08:03.857 when we have targeted agents,

NOTE Confidence: 0.864022766666667

00:08:03.860 --> 00:08:05.480 and yet we're still trying to

NOTE Confidence: 0.864022766666667

00:08:05.480 --> 00:08:06.560 achieve maximum tolerated dose.

NOTE Confidence: 0.864022766666667

00:08:06.560 --> 00:08:07.760 Thinking that we're going to be

NOTE Confidence: 0.864022766666667

00:08:07.760 --> 00:08:08.919 benefiting the patient by doing so,

NOTE Confidence: 0.864022766666667

00:08:08.920 --> 00:08:11.092 and I'd like to really question

NOTE Confidence: 0.864022766666667

00:08:11.092 --> 00:08:12.960 that this this concept really came

NOTE Confidence: 0.864022766666667

00:08:12.960 --> 00:08:14.980 from the work of Howard skipper,

NOTE Confidence: 0.864022766666667

00:08:14.980 --> 00:08:16.810 Franckesche Bold and Griswald and others

NOTE Confidence: 0.864022766666667

00:08:16.810 --> 00:08:19.089 at at at Southern Research Institute.

NOTE Confidence: 0.864022766666667

00:08:19.090 --> 00:08:21.826 It was an extremely important part of my

NOTE Confidence: 0.864022766666667

00:08:21.826 --> 00:08:24.210 education in in in medicine and oncology,

NOTE Confidence: 0.864022766666667

00:08:24.210 --> 00:08:26.010 in in in the 60s.

NOTE Confidence: 0.864022766666667

00:08:26.010 --> 00:08:28.068 The concept was based on mooring,

NOTE Confidence: 0.864022766666667

00:08:28.070 --> 00:08:30.040 leukemia and Howard skipper made

NOTE Confidence: 0.864022766666667

00:08:30.040 --> 00:08:32.702 the observation that if you if you

NOTE Confidence: 0.864022766666667

00:08:32.702 --> 00:08:34.865 inject a certain number of cells and

NOTE Confidence: 0.864022766666667

00:08:34.865 --> 00:08:37.150 the mouse died at a certain time,

NOTE Confidence: 0.864022766666667

00:08:37.150 --> 00:08:38.850 that could tell you basically

NOTE Confidence: 0.864022766666667

00:08:38.850 --> 00:08:40.550 how many cells you injected.

NOTE Confidence: 0.864022766666667

00:08:40.550 --> 00:08:41.942 'cause it took a certain very

NOTE Confidence: 0.864022766666667

00:08:41.942 --> 00:08:43.327 reproducible amount of time for those

NOTE Confidence: 0.864022766666667

00:08:43.327 --> 00:08:44.575 cells to reach a lethal number.

NOTE Confidence: 0.864022766666667

00:08:44.580 --> 00:08:46.516 So all of his work was not really

NOTE Confidence: 0.864022766666667

00:08:46.516 --> 00:08:47.680 measuring cancer cell numbers,

NOTE Confidence: 0.864022766666667

00:08:47.680 --> 00:08:49.210 it was actually measuring animal.

NOTE Confidence: 0.864022766666667

00:08:49.210 --> 00:08:50.562 Death and extrapolating back

NOTE Confidence: 0.864022766666667

00:08:50.562 --> 00:08:51.914 to cancer cell members.

NOTE Confidence: 0.864022766666667

00:08:51.920 --> 00:08:53.225 And that's common,

NOTE Confidence: 0.864022766666667

00:08:53.225 --> 00:08:55.204 not commonly appreciated is is

NOTE Confidence: 0.864022766666667

00:08:55.204 --> 00:08:56.889 that it was all extrapolation,

NOTE Confidence: 0.864022766666667

00:08:56.890 --> 00:08:58.726 but the the fundamental observation that

NOTE Confidence: 0.864022766666667

00:08:58.726 --> 00:09:01.369 he made is that if you kill cancer cells,

NOTE Confidence: 0.864022766666667

00:09:01.370 --> 00:09:03.806 you can extend lifespan and the

NOTE Confidence: 0.864022766666667

00:09:03.806 --> 00:09:05.650 extension of lifespan was a.

NOTE Confidence: 0.864022766666667

00:09:05.650 --> 00:09:07.180 Basically it took time for lethal

NOTE Confidence: 0.864022766666667

00:09:07.180 --> 00:09:09.272 number of cells to arrive and you can

NOTE Confidence: 0.864022766666667

00:09:09.272 --> 00:09:11.089 go back and extrapolate from that in

NOTE Confidence: 0.864022766666667

00:09:11.089 --> 00:09:12.734 terms of how many cells you killed

NOTE Confidence: 0.864022766666667

00:09:12.734 --> 00:09:14.382 because it would take that certain

NOTE Confidence: 0.864022766666667

00:09:14.382 --> 00:09:16.478 number of cells that were left or

NOTE Confidence: 0.864022766666667

00:09:16.478 --> 00:09:18.452 residual to lead to eventual or lethal

NOTE Confidence: 0.864022766666667

00:09:18.452 --> 00:09:20.538 number and and the death of the mouse.

NOTE Confidence: 0.864022766666667

00:09:20.540 --> 00:09:23.901 This led to a concept that is shown

NOTE Confidence: 0.864022766666667

00:09:23.901 --> 00:09:27.110 here by one of the one of the.

NOTE Confidence: 0.864022766666667

00:09:27.110 --> 00:09:29.665 Very very often in in my youth,

NOTE Confidence: 0.864022766666667

00:09:29.670 --> 00:09:30.958 especially reproduce figures is

NOTE Confidence: 0.864022766666667

00:09:30.958 --> 00:09:33.454 that if you start off with a large

NOTE Confidence: 0.864022766666667

00:09:33.454 --> 00:09:34.954 number of cancer cells and you

NOTE Confidence: 0.864022766666667

00:09:34.954 --> 00:09:36.850 give a certain dose of therapy,

NOTE Confidence: 0.864022766666667

00:09:36.850 --> 00:09:38.634 you kill and will go back over this

NOTE Confidence: 0.864022766666667

00:09:38.634 --> 00:09:40.178 a constant fraction of the cells

NOTE Confidence: 0.864022766666667

00:09:40.178 --> 00:09:41.750 that are present with each dose.

NOTE Confidence: 0.864022766666667

00:09:41.750 --> 00:09:42.930 Each chemotherapy core skills,

NOTE Confidence: 0.864022766666667

00:09:42.930 --> 00:09:43.815 in this case,

NOTE Confidence: 0.864022766666667

00:09:43.820 --> 00:09:47.195 2 logs of gotta get rid of this pop

NOTE Confidence: 0.864022766666667

00:09:47.195 --> 00:09:50.447 up two logs of kill means means you're

NOTE Confidence: 0.864022766666667

00:09:50.447 --> 00:09:52.374 you're killing 99% of the cells,

NOTE Confidence: 0.864022766666667

00:09:52.374 --> 00:09:53.890 90% is 1 log killed,

NOTE Confidence: 0.864022766666667

00:09:53.890 --> 00:09:55.775 99% is a two log kill and you

NOTE Confidence: 0.864022766666667

00:09:55.775 --> 00:09:57.831 could drive to cure unless you get

NOTE Confidence: 0.864022766666667

00:09:57.831 --> 00:09:59.486 the emergence of drug resistance.

NOTE Confidence: 0.864022766666667

00:09:59.490 --> 00:09:59.984 Of course,

NOTE Confidence: 0.864022766666667

00:09:59.984 --> 00:10:01.713 if you stop treating when the cancer

NOTE Confidence: 0.864022766666667

00:10:01.713 --> 00:10:03.627 is disappeared, that's not enough,

NOTE Confidence: 0.864022766666667

00:10:03.627 --> 00:10:05.322 because because there's plenty of

NOTE Confidence: 0.864022766666667

00:10:05.322 --> 00:10:06.968 cancers left and they can grow

NOTE Confidence: 0.864022766666667

00:10:06.968 --> 00:10:08.700 back and and the concept of roses

NOTE Confidence: 0.864022766666667

00:10:08.700 --> 00:10:10.787 that if you start a small of tumor

NOTE Confidence: 0.864022766666667

00:10:10.787 --> 00:10:12.669 size that you can actually get rid

NOTE Confidence: 0.864022766666667

00:10:12.669 --> 00:10:14.403 of the cancer cells before this

NOTE Confidence: 0.864022766666667

00:10:14.403 --> 00:10:16.004 emergence of drug resistance arises

NOTE Confidence: 0.864022766666667

00:10:16.004 --> 00:10:18.573 and hence the concept of Azure and

NOTE Confidence: 0.864022766666667

00:10:18.573 --> 00:10:20.290 chemotherapy came from this Vince

NOTE Confidence: 0.864022766666667

00:10:20.290 --> 00:10:21.900 Davida long associated with Yale

NOTE Confidence: 0.864022766666667

00:10:21.900 --> 00:10:23.692 was my great teacher and still

NOTE Confidence: 0.864022766666667

00:10:23.692 --> 00:10:25.102 is my great teacher and

NOTE Confidence: 0.841825336190476

00:10:25.110 --> 00:10:26.958 in oncology took these concepts and use

NOTE Confidence: 0.841825336190476

00:10:26.958 --> 00:10:28.575 them to develop the MOP chemotherapy

NOTE Confidence: 0.841825336190476

00:10:28.575 --> 00:10:30.630 regimen and those of you who have not.

NOTE Confidence: 0.841825336190476

00:10:30.630 --> 00:10:33.699 Read Vince on his book of the Death of

NOTE Confidence: 0.841825336190476

00:10:33.699 --> 00:10:36.855 Cancer about the early days where this

NOTE Confidence: 0.841825336190476

00:10:36.855 --> 00:10:39.392 figure was extrapolated into the cure

NOTE Confidence: 0.841825336190476

00:10:39.392 --> 00:10:41.192 of a solid tumor Hodgkin's disease.

NOTE Confidence: 0.841825336190476

00:10:41.192 --> 00:10:43.054 You really should read it because it's

NOTE Confidence: 0.841825336190476

00:10:43.054 --> 00:10:44.862 it's an excellent book and it really

NOTE Confidence: 0.841825336190476

00:10:44.862 --> 00:10:46.383 captures the excitement of those early

NOTE Confidence: 0.841825336190476

00:10:46.383 --> 00:10:47.823 days in oncology and the application

NOTE Confidence: 0.841825336190476

00:10:47.823 --> 00:10:49.810 of this mathematical model to the

NOTE Confidence: 0.841825336190476

00:10:49.810 --> 00:10:51.685 development of a curative regimen.

NOTE Confidence: 0.841825336190476

00:10:51.690 --> 00:10:54.480 Well, this was led in the in in in the

NOTE Confidence: 0.841825336190476

00:10:54.557 --> 00:10:57.350 60s to the concept of dose escalation.

NOTE Confidence: 0.841825336190476

00:10:57.350 --> 00:10:59.690 This way if you have no therapy and you

NOTE Confidence: 0.841825336190476

00:10:59.690 --> 00:11:02.147 have simple exponential growth like this,

NOTE Confidence: 0.841825336190476

00:11:02.150 --> 00:11:03.198 you give one drug.

NOTE Confidence: 0.841825336190476

00:11:03.198 --> 00:11:05.170 You get certain log kill two drugs.

NOTE Confidence: 0.841825336190476

00:11:05.170 --> 00:11:06.270 You get you double that.

NOTE Confidence: 0.841825336190476

00:11:06.270 --> 00:11:08.166 If this causes one log kill and this

NOTE Confidence: 0.841825336190476

00:11:08.166 --> 00:11:09.906 causes one log kill then you get 2

NOTE Confidence: 0.841825336190476

00:11:09.906 --> 00:11:12.110 log kill 90% sale killing here and 90%

NOTE Confidence: 0.841825336190476

00:11:12.110 --> 00:11:14.514 sale killing here since 99% sale of

NOTE Confidence: 0.841825336190476

00:11:14.514 --> 00:11:16.566 killing three drugs should be should

NOTE Confidence: 0.841825336190476

00:11:16.566 --> 00:11:18.510 should cause disease eradication.

NOTE Confidence: 0.841825336190476

00:11:18.510 --> 00:11:18.855 Therefore,

NOTE Confidence: 0.841825336190476

00:11:18.855 --> 00:11:20.580 four drugs should certainly cause

NOTE Confidence: 0.841825336190476

00:11:20.580 --> 00:11:22.470 disease eradication, which was very.

NOTE Confidence: 0.841825336190476

00:11:22.470 --> 00:11:22.870 Influential,

NOTE Confidence: 0.841825336190476

00:11:22.870 --> 00:11:24.870 they're thinking about Rob chemotherapy,

NOTE Confidence: 0.841825336190476

00:11:24.870 --> 00:11:26.946 but it also applies to doses.

NOTE Confidence: 0.841825336190476

00:11:26.950 --> 00:11:29.590 1 dose, 2 doses, 3 doses,

NOTE Confidence: 0.841825336190476

00:11:29.590 --> 00:11:31.702 all increased cell killin,

NOTE Confidence: 0.841825336190476

00:11:31.702 --> 00:11:33.286 causing DC radication.

NOTE Confidence: 0.841825336190476

00:11:33.290 --> 00:11:36.210 So the 70s was a decade of enthusiasm.

NOTE Confidence: 0.841825336190476

00:11:36.210 --> 00:11:38.149 Fueled by this confidence in the skipper.

NOTE Confidence: 0.841825336190476

00:11:38.150 --> 00:11:39.254 In the skippers model,

NOTE Confidence: 0.841825336190476

00:11:39.254 --> 00:11:41.280 there are many drugs that came along,

NOTE Confidence: 0.841825336190476

00:11:41.280 --> 00:11:42.724 such as the Cyclones,

NOTE Confidence: 0.841825336190476

00:11:42.724 --> 00:11:43.807 the platinum agents,

NOTE Confidence: 0.841825336190476

00:11:43.810 --> 00:11:45.480 the concept of combination chemotherapy

NOTE Confidence: 0.841825336190476

00:11:45.480 --> 00:11:47.400 as I've just demonstrated to you,

NOTE Confidence: 0.841825336190476

00:11:47.400 --> 00:11:48.868 arose from these thinking.

NOTE Confidence: 0.841825336190476

00:11:48.868 --> 00:11:50.703 And indeed we're getting successes.

NOTE Confidence: 0.841825336190476

00:11:50.710 --> 00:11:51.988 Cure simply nysm.

NOTE Confidence: 0.841825336190476

00:11:51.988 --> 00:11:53.692 And and leukemia is

NOTE Confidence: 0.841825336190476

00:11:53.692 --> 00:11:54.970 infamous testicular cancer,

NOTE Confidence: 0.841825336190476

00:11:54.970 --> 00:11:56.332 it really looked like we were

NOTE Confidence: 0.841825336190476

00:11:56.332 --> 00:11:57.760 moving in the right direction.

NOTE Confidence: 0.841825336190476

00:11:57.760 --> 00:11:59.524 Getting high response rates and many

NOTE Confidence: 0.841825336190476

00:11:59.524 --> 00:12:01.060 other tumors including breast cancer.

NOTE Confidence: 0.841825336190476

00:12:01.060 --> 00:12:03.100 The field that I eventually specialized

NOTE Confidence: 0.841825336190476

00:12:03.100 --> 00:12:05.140 in the concept of postoperative attribute

NOTE Confidence: 0.841825336190476

00:12:05.140 --> 00:12:06.840 chemotherapy rose from that period.

NOTE Confidence: 0.841825336190476

00:12:06.840 --> 00:12:09.633 Based on that on that mathematical idea

NOTE Confidence: 0.841825336190476

00:12:09.633 --> 00:12:12.300 and an enthusiasm for those those level

NOTE Confidence: 0.841825336190476

00:12:12.300 --> 00:12:15.256 escalation which we led to a lot of

NOTE Confidence: 0.841825336190476

00:12:15.256 --> 00:12:17.614 enthusiasm for a mega dose escalation,

NOTE Confidence: 0.841825336190476

00:12:17.620 --> 00:12:19.560 which is bone marrow transplantation.

NOTE Confidence: 0.841825336190476

00:12:19.560 --> 00:12:22.530 This enthusiasm was so was so.

NOTE Confidence: 0.841825336190476

00:12:22.530 --> 00:12:25.518 Pronounced that a mentor, not Vince,

NOTE Confidence: 0.841825336190476

00:12:25.520 --> 00:12:28.648 is another mentor in 1976 cents Me Larry,

NOTE Confidence: 0.841825336190476

00:12:28.650 --> 00:12:29.810 you still got a chance.

NOTE Confidence: 0.841825336190476

00:12:29.810 --> 00:12:30.910 You're young enough to change

NOTE Confidence: 0.841825336190476

00:12:30.910 --> 00:12:31.570 your career path,

NOTE Confidence: 0.841825336190476

00:12:31.570 --> 00:12:32.038 you're not.

NOTE Confidence: 0.841825336190476

00:12:32.038 --> 00:12:33.442 There's not gonna be any field

NOTE Confidence: 0.841825336190476

00:12:33.442 --> 00:12:34.607 of oncology in a few years.

NOTE Confidence: 0.841825336190476

00:12:34.610 --> 00:12:35.282 All these combinations.

NOTE Confidence: 0.841825336190476

00:12:35.282 --> 00:12:36.626 All these agents are just going

NOTE Confidence: 0.841825336190476

00:12:36.626 --> 00:12:37.911 to come together and cancer will

NOTE Confidence: 0.841825336190476

00:12:37.911 --> 00:12:39.210 be disappeared in a few years.

NOTE Confidence: 0.841825336190476

00:12:39.210 --> 00:12:40.290 You better think about training

NOTE Confidence: 0.841825336190476

00:12:40.290 --> 00:12:40.938 and something else.

NOTE Confidence: 0.854357669090909

00:12:42.980 --> 00:12:44.785 Well, I persisted against that

NOTE Confidence: 0.854357669090909

00:12:44.785 --> 00:12:47.100 advice and kept working on cancer.

NOTE Confidence: 0.854357669090909

00:12:47.100 --> 00:12:49.116 And as you know it hasn't been that easy

NOTE Confidence: 0.854357669090909

00:12:49.116 --> 00:12:51.044 and a lot of that enthusiasm is still

NOTE Confidence: 0.854357669090909

00:12:51.044 --> 00:12:53.178 there and we definitely making progress.

NOTE Confidence: 0.854357669090909

00:12:53.180 --> 00:12:54.288 No question about it,

NOTE Confidence: 0.854357669090909

00:12:54.288 --> 00:12:55.950 but the rate of progress really

NOTE Confidence: 0.854357669090909

00:12:56.011 --> 00:12:57.553 has has slowed even with the

NOTE Confidence: 0.854357669090909

00:12:57.553 --> 00:12:59.000 addition of of newer agents.

NOTE Confidence: 0.854357669090909

00:12:59.000 --> 00:13:01.058 And we're not getting cures of

NOTE Confidence: 0.854357669090909

00:13:01.058 --> 00:13:02.430 metastatic colon cancers and

NOTE Confidence: 0.854357669090909

00:13:02.491 --> 00:13:04.116 and and and stomach cancers.

NOTE Confidence: 0.854357669090909

00:13:04.120 --> 00:13:05.704 And and and and and many

NOTE Confidence: 0.854357669090909

00:13:05.704 --> 00:13:07.000 lung cancers and so on.

NOTE Confidence: 0.854357669090909

00:13:07.000 --> 00:13:08.505 But certainly breast cancer as

NOTE Confidence: 0.854357669090909

00:13:08.505 --> 00:13:10.400 readily as we would have hoped.

NOTE Confidence: 0.854357669090909

00:13:10.400 --> 00:13:13.368 Metastatic disease is still a big problem.

NOTE Confidence: 0.854357669090909

00:13:13.370 --> 00:13:14.374 So what went wrong?

NOTE Confidence: 0.854357669090909

00:13:14.374 --> 00:13:16.197 And this is my number one favorite

NOTE Confidence: 0.854357669090909

00:13:16.197 --> 00:13:18.510 quote and kind of a kind of you know,

NOTE Confidence: 0.854357669090909

00:13:18.510 --> 00:13:19.174 model for my life.

NOTE Confidence: 0.854357669090909

00:13:19.174 --> 00:13:20.170 It's not what you don't know

NOTE Confidence: 0.854357669090909

00:13:20.206 --> 00:13:21.086 that gets you in trouble.

NOTE Confidence: 0.854357669090909

00:13:21.090 --> 00:13:23.575 It's what you know that for sure

NOTE Confidence: 0.854357669090909

00:13:23.575 --> 00:13:25.860 that turns out not to be true.

NOTE Confidence: 0.854357669090909

00:13:25.860 --> 00:13:27.596 And the thing that we knew for sure

NOTE Confidence: 0.854357669090909

00:13:27.596 --> 00:13:29.573 was that the skipper model worked

NOTE Confidence: 0.854357669090909

00:13:29.573 --> 00:13:31.057 because cancers grow exponentially,

NOTE Confidence: 0.854357669090909

00:13:31.060 --> 00:13:33.060 but they don't grow exponentially,

NOTE Confidence: 0.854357669090909

00:13:33.060 --> 00:13:35.174 nor do they grow in a strictly

NOTE Confidence: 0.854357669090909

00:13:35.174 --> 00:13:35.778 linear fashion.

NOTE Confidence: 0.854357669090909

00:13:35.780 --> 00:13:36.615 And we know this because

NOTE Confidence: 0.854357669090909

00:13:36.615 --> 00:13:37.450 if that were the case,

NOTE Confidence: 0.854357669090909

00:13:37.450 --> 00:13:39.613 from the time of initial diagnosis to

NOTE Confidence: 0.854357669090909

00:13:39.613 --> 00:13:41.912 the time that that the cancer would

NOTE Confidence: 0.854357669090909

00:13:41.912 --> 00:13:43.874 cause problem would be too long.

NOTE Confidence: 0.854357669090909

00:13:43.880 --> 00:13:45.040 Exponential growth also doesn't

NOTE Confidence: 0.854357669090909

00:13:45.040 --> 00:13:46.490 make sense because for the

NOTE Confidence: 0.854357669090909

00:13:46.490 --> 00:13:47.798 time of initial diagnosis,

NOTE Confidence: 0.854357669090909

00:13:47.800 --> 00:13:50.136 the time of lethality would be too short.

NOTE Confidence: 0.854357669090909

00:13:50.140 --> 00:13:51.780 It's got to be somewhere

NOTE Confidence: 0.854357669090909

00:13:51.780 --> 00:13:53.760 in between and indeed,

NOTE Confidence: 0.854357669090909

00:13:53.760 --> 00:13:56.196 Benjamin Gompertz in 1825.

NOTE Confidence: 0.854357669090909

00:13:56.196 --> 00:13:59.388 Then invented a curve of human mortality,

NOTE Confidence: 0.854357669090909

00:13:59.390 --> 00:14:01.028 which we call the Gompertz curve is

NOTE Confidence: 0.854357669090909

00:14:01.028 --> 00:14:02.878 and kind of sigmoid curve sigmoid.

NOTE Confidence: 0.854357669090909

00:14:02.880 --> 00:14:04.872 Because you see as as as shape and

NOTE Confidence: 0.854357669090909

00:14:04.872 --> 00:14:06.742 and others had shown that that

NOTE Confidence: 0.854357669090909

00:14:06.742 --> 00:14:08.377 Gompertz curves actually applied to

NOTE Confidence: 0.854357669090909

00:14:08.377 --> 00:14:10.429 the growth of experimental tumors.

NOTE Confidence: 0.854357669090909

00:14:10.430 --> 00:14:13.165 I got into this in the mid 70s and

NOTE Confidence: 0.854357669090909

00:14:13.165 --> 00:14:16.350 this early paper I wrote in nature.

NOTE Confidence: 0.854357669090909

00:14:16.350 --> 00:14:19.206 In 1976 these are two rat tumors.

NOTE Confidence: 0.854357669090909

00:14:19.210 --> 00:14:21.130 This is a mouse tumor and what we

NOTE Confidence: 0.854357669090909

00:14:21.130 --> 00:14:22.746 found are working with Richard Simon

NOTE Confidence: 0.854357669090909

00:14:22.746 --> 00:14:25.238 is that if you have a few early

NOTE Confidence: 0.854357669090909

00:14:25.238 --> 00:14:26.574 measurements that it actually fits

NOTE Confidence: 0.854357669090909

00:14:26.574 --> 00:14:27.960 a pattern and you could predict

NOTE Confidence: 0.854357669090909

00:14:28.005 --> 00:14:29.269 later measurements that gone.

NOTE Confidence: 0.854357669090909

00:14:29.270 --> 00:14:31.466 Protein growth was really very predictable.

NOTE Confidence: 0.854357669090909

00:14:31.470 --> 00:14:32.710 This is really an important

NOTE Confidence: 0.854357669090909

00:14:32.710 --> 00:14:34.205 observation that just sort of sat

NOTE Confidence: 0.854357669090909

00:14:34.205 --> 00:14:35.689 there and up until the present day,

NOTE Confidence: 0.854357669090909

00:14:35.690 --> 00:14:36.990 but it actually is rather

NOTE Confidence: 0.854357669090909

00:14:36.990 --> 00:14:37.770 meaningful but nest.

NOTE Confidence: 0.854357669090909

00:14:37.770 --> 00:14:38.832 But but indeed,

NOTE Confidence: 0.854357669090909

00:14:38.832 --> 00:14:40.248 Gompertz equations are applied

NOTE Confidence: 0.854357669090909

00:14:40.248 --> 00:14:42.090 and then not exponential,

NOTE Confidence: 0.854357669090909

00:14:42.090 --> 00:14:44.078 and so my my work was basically

NOTE Confidence: 0.854357669090909

00:14:44.078 --> 00:14:46.710 to see how do we apply the

NOTE Confidence: 0.854357669090909

00:14:46.710 --> 00:14:47.988 skipper Schaible principles.

NOTE Confidence: 0.854357669090909

00:14:47.990 --> 00:14:49.930 To the.

NOTE Confidence: 0.854357669090909

00:14:49.930 --> 00:14:52.222 How do we apply skipper Schaible

NOTE Confidence: 0.854357669090909

00:14:52.222 --> 00:14:54.150 principles to gum persien curves

NOTE Confidence: 0.854357669090909

00:14:54.150 --> 00:14:56.568 and papers in the early days about

NOTE Confidence: 0.854357669090909

00:14:56.568 --> 00:14:58.706 this and they eventually led to

NOTE Confidence: 0.854357669090909

00:14:58.706 --> 00:15:00.411 the concept of sequential therapy

NOTE Confidence: 0.854357669090909

00:15:00.411 --> 00:15:02.390 and then dose dense therapy?

NOTE Confidence: 0.854357669090909

00:15:02.390 --> 00:15:04.598 And this was the work in the 70s

NOTE Confidence: 0.854357669090909

00:15:04.598 --> 00:15:06.971 and and again Vince DeVito was

NOTE Confidence: 0.854357669090909

00:15:06.971 --> 00:15:09.151 was working closely with Johnny

NOTE Confidence: 0.854357669090909

00:15:09.151 --> 00:15:11.211 Bonadona in those days and and

NOTE Confidence: 0.854357669090909

00:15:11.211 --> 00:15:13.214 some of these ideas got translated

NOTE Confidence: 0.854357669090909

00:15:13.214 --> 00:15:15.878 and indeed this was actually a

NOTE Confidence: 0.854357669090909

00:15:15.878 --> 00:15:18.325 competition in the adjutant setting

NOTE Confidence: 0.854357669090909

00:15:18.325 --> 00:15:20.397 between a other modelers.

NOTE Confidence: 0.854357669090909

00:15:20.400 --> 00:15:21.865 Called Goldie and Coldman and

NOTE Confidence: 0.854357669090909

00:15:21.865 --> 00:15:23.330 and myself and and Richard

NOTE Confidence: 0.774361399333333

00:15:23.391 --> 00:15:25.372 Simon that they predicted that if you

NOTE Confidence: 0.774361399333333

00:15:25.372 --> 00:15:27.063 have agents like doxorubicin and see

NOTE Confidence: 0.774361399333333

00:15:27.063 --> 00:15:29.248 at math you should use them in an

NOTE Confidence: 0.774361399333333

00:15:29.248 --> 00:15:30.988 alternating fashion because that would

NOTE Confidence: 0.774361399333333

00:15:30.988 --> 00:15:34.003 get this drug in these all the drugs in

NOTE Confidence: 0.774361399333333

00:15:34.003 --> 00:15:36.382 sooner to limit the emergence of drug

NOTE Confidence: 0.774361399333333

00:15:36.382 --> 00:15:38.650 resistance by random mutation whereas my

NOTE Confidence: 0.774361399333333

00:15:38.650 --> 00:15:40.436 modeling which I'll show you in a second,

NOTE Confidence: 0.774361399333333

00:15:40.440 --> 00:15:41.960 suggested that it would be

NOTE Confidence: 0.774361399333333

00:15:41.960 --> 00:15:43.480 better to use them sequentially.

NOTE Confidence: 0.774361399333333

00:15:43.480 --> 00:15:45.853 So we'll go over that modeling because

NOTE Confidence: 0.774361399333333

00:15:45.853 --> 00:15:48.139 this is buried in ancient literature

NOTE Confidence: 0.774361399333333

00:15:48.139 --> 00:15:49.938 and was published before many of you

NOTE Confidence: 0.774361399333333

00:15:49.938 --> 00:15:51.709 who are listening to this lecture were.

NOTE Confidence: 0.774361399333333

00:15:51.710 --> 00:15:53.654 Warren, so you're not aware of

NOTE Confidence: 0.774361399333333

00:15:53.654 --> 00:15:55.490 this work is that, of course,

NOTE Confidence: 0.774361399333333

00:15:55.490 --> 00:15:57.110 it's always better if you've got

NOTE Confidence: 0.774361399333333

00:15:57.110 --> 00:15:58.709 two agents or two combinations,

NOTE Confidence: 0.774361399333333

00:15:58.710 --> 00:16:00.806 you gonna use them simultaneously if you can,

NOTE Confidence: 0.774361399333333

00:16:00.810 --> 00:16:03.090 that's going to give you maximum cell kill,

NOTE Confidence: 0.774361399333333

00:16:03.090 --> 00:16:05.386 but you can't really do this in most

NOTE Confidence: 0.774361399333333

00:16:05.386 --> 00:16:07.117 situations without such toxicity that you

NOTE Confidence: 0.774361399333333

00:16:07.117 --> 00:16:09.509 have to reduce the dose levels of the drugs.

NOTE Confidence: 0.774361399333333

00:16:09.510 --> 00:16:10.610 And by reducing the drugs,

NOTE Confidence: 0.774361399333333

00:16:10.610 --> 00:16:11.770 dose levels of the drugs,

NOTE Confidence: 0.774361399333333

00:16:11.770 --> 00:16:13.184 you're not going to get the maximum

NOTE Confidence: 0.774361399333333

00:16:13.184 --> 00:16:14.328 efficacy from any of the drugs.

NOTE Confidence: 0.774361399333333

00:16:14.330 --> 00:16:15.234 So the question is,

NOTE Confidence: 0.774361399333333

00:16:15.234 --> 00:16:17.357 what can you do if you can't give

NOTE Confidence: 0.774361399333333

00:16:17.357 --> 00:16:19.127 them in a simultaneous combination?

NOTE Confidence: 0.774361399333333

00:16:19.130 --> 00:16:20.750 The Goldie Coleman idea

NOTE Confidence: 0.774361399333333

00:16:20.750 --> 00:16:22.370 is you alternate them.

NOTE Confidence: 0.774361399333333

00:16:22.370 --> 00:16:24.122 And by the Norton Simon modeling

NOTE Confidence: 0.774361399333333

00:16:24.122 --> 00:16:26.070 when we did it, we found well,

NOTE Confidence: 0.774361399333333

00:16:26.070 --> 00:16:27.630 we got a very inferior cell

NOTE Confidence: 0.774361399333333

00:16:27.630 --> 00:16:29.007 killed than if we did them.

NOTE Confidence: 0.774361399333333

00:16:29.010 --> 00:16:30.670 Obviously by simultaneous therapy.

NOTE Confidence: 0.774361399333333

00:16:30.670 --> 00:16:33.160 But if you give them in

NOTE Confidence: 0.774361399333333

00:16:33.241 --> 00:16:34.888 an alternating fashion.

NOTE Confidence: 0.774361399333333

00:16:34.890 --> 00:16:36.606 You can actually get cell killed.

NOTE Confidence: 0.774361399333333

00:16:36.610 --> 00:16:38.311 That's better than you can get by

NOTE Confidence: 0.774361399333333

00:16:38.311 --> 00:16:40.129 giving him an alternating fashion,

NOTE Confidence: 0.774361399333333

00:16:40.130 --> 00:16:41.760 so the bonadona experiment which

NOTE Confidence: 0.774361399333333

00:16:41.760 --> 00:16:44.506 started in the mid 80s was a was

NOTE Confidence: 0.774361399333333

00:16:44.506 --> 00:16:45.906 basically a competition between

NOTE Confidence: 0.774361399333333

00:16:45.906 --> 00:16:47.849 this approach and this approach.

NOTE Confidence: 0.774361399333333

00:16:47.850 --> 00:16:50.028 And of course this approach one.

NOTE Confidence: 0.774361399333333

00:16:50.030 --> 00:16:51.830 Then, with the advent of grants,

NOTE Confidence: 0.774361399333333

00:16:51.830 --> 00:16:53.394 iconic stimulating factor where

NOTE Confidence: 0.774361399333333

00:16:53.394 --> 00:16:55.349 you can actually squeeze the

NOTE Confidence: 0.774361399333333

00:16:55.349 --> 00:16:57.290 doses of drugs closer together,

NOTE Confidence: 0.774361399333333

00:16:57.290 --> 00:16:58.748 you can actually get maximum self

NOTE Confidence: 0.774361399333333

00:16:58.748 --> 00:17:00.618 kill and even a better cell kill.

NOTE Confidence: 0.774361399333333

00:17:00.620 --> 00:17:03.280 Then you can just with the simultaneous

NOTE Confidence: 0.774361399333333

00:17:03.280 --> 00:17:06.306 combination by by the application of GCSF.

NOTE Confidence: 0.774361399333333

00:17:06.310 --> 00:17:08.284 So you can make a through cycle,

NOTE Confidence: 0.774361399333333

00:17:08.290 --> 00:17:10.467 for example into a two week cycle.

NOTE Confidence: 0.774361399333333

00:17:10.470 --> 00:17:12.180 Tax oil can be given even

NOTE Confidence: 0.774361399333333

00:17:12.180 --> 00:17:14.389 without GCSF in a one week cycle,

NOTE Confidence: 0.774361399333333

00:17:14.390 --> 00:17:16.214 and that's also a dose dental

NOTE Confidence: 0.774361399333333

00:17:16.214 --> 00:17:17.126 regimen as well.

NOTE Confidence: 0.774361399333333

00:17:17.130 --> 00:17:19.307 So that's the understanding of dose density,

NOTE Confidence: 0.774361399333333

00:17:19.310 --> 00:17:20.468 which is kind of lost in

NOTE Confidence: 0.774361399333333

00:17:20.468 --> 00:17:21.240 history a little bit.

NOTE Confidence: 0.774361399333333

00:17:21.240 --> 00:17:22.563 And a lot of people don't appreciate

NOTE Confidence: 0.774361399333333

00:17:22.563 --> 00:17:23.539 really where it came from.

NOTE Confidence: 0.774361399333333

00:17:23.540 --> 00:17:25.499 Water million means.

NOTE Confidence: 0.774361399333333

00:17:25.500 --> 00:17:28.300 Hence we designed this regimen

NOTE Confidence: 0.774361399333333

00:17:28.300 --> 00:17:29.980 which basically started.

NOTE Confidence: 0.774361399333333

00:17:29.980 --> 00:17:35.615 In 1997, nineteen 9741 with Mark Citron,

NOTE Confidence: 0.774361399333333

00:17:35.620 --> 00:17:37.636 who we just lost very recently

NOTE Confidence: 0.774361399333333

00:17:37.636 --> 00:17:39.839 from a from from a neoplasm.

NOTE Confidence: 0.774361399333333

00:17:39.840 --> 00:17:41.488 A great great Lawson,

NOTE Confidence: 0.774361399333333

00:17:41.488 --> 00:17:43.960 and really a great clinician and

NOTE Confidence: 0.774361399333333

00:17:44.038 --> 00:17:46.708 and and a great clinical scientist.

NOTE Confidence: 0.774361399333333

00:17:46.710 --> 00:17:48.705 And this was A and the regimen

NOTE Confidence: 0.774361399333333

00:17:48.705 --> 00:17:50.639 was a two by two design,

NOTE Confidence: 0.774361399333333

00:17:50.640 --> 00:17:52.047 and you'll notice those of you who

NOTE Confidence: 0.774361399333333

00:17:52.047 --> 00:17:53.199 are doing cooperative group studies.

NOTE Confidence: 0.774361399333333

00:17:53.200 --> 00:17:54.964 We don't do two by two designs

NOTE Confidence: 0.774361399333333

00:17:54.964 --> 00:17:55.720 very much anymore,

NOTE Confidence: 0.774361399333333

00:17:55.720 --> 00:17:57.323 and I really wish we did because

NOTE Confidence: 0.774361399333333

00:17:57.323 --> 00:17:59.077 it would answer a whole lot of

NOTE Confidence: 0.774361399333333

00:17:59.077 --> 00:18:00.595 questions faster than doing doing just

NOTE Confidence: 0.849236412666667

00:18:00.650 --> 00:18:02.000 some of the some of the

NOTE Confidence: 0.849236412666667

00:18:02.000 --> 00:18:03.185 regimens that we're now doing,

NOTE Confidence: 0.849236412666667

00:18:03.185 --> 00:18:04.895 which is comparing 2 treatments or

NOTE Confidence: 0.849236412666667

00:18:04.895 --> 00:18:07.148 now even not comparing it at all, but

NOTE Confidence: 0.849236412666667

00:18:07.148 --> 00:18:08.876 basically comparing it to historical data.

NOTE Confidence: 0.849236412666667

00:18:08.880 --> 00:18:14.610 Which is, you know, Noninferiority designs.

NOTE Confidence: 0.849236412666667

00:18:14.610 --> 00:18:16.626 For the topic about the the wisdom of that,

NOTE Confidence: 0.849236412666667

00:18:16.630 --> 00:18:18.352 but, but certainly certainly these two

NOTE Confidence: 0.849236412666667

00:18:18.352 --> 00:18:20.619 by two designs get a lot of information,

NOTE Confidence: 0.849236412666667

00:18:20.620 --> 00:18:25.220 and we gave a. We gave adriamycin and

NOTE Confidence: 0.849236412666667

00:18:25.220 --> 00:18:27.286 cyclophosphamide AC with paclitaxel.

NOTE Confidence: 0.849236412666667

00:18:27.286 --> 00:18:31.888 Either all the drugs in in in in a Q3

NOTE Confidence: 0.849236412666667

00:18:31.888 --> 00:18:34.230 week regimen, in a sequential fashion,

NOTE Confidence: 0.849236412666667

00:18:34.230 --> 00:18:37.465 or the AC together 'cause you can do

NOTE Confidence: 0.849236412666667

00:18:37.465 --> 00:18:39.745 that without having dose modifications.

NOTE Confidence: 0.849236412666667

00:18:39.750 --> 00:18:41.647 That's why it makes sense in a

NOTE Confidence: 0.849236412666667

00:18:41.647 --> 00:18:43.800 three week Red room or squeeze these

NOTE Confidence: 0.849236412666667

00:18:43.800 --> 00:18:45.714 together in a two week regimen.

NOTE Confidence: 0.849236412666667

00:18:45.720 --> 00:18:47.520 In a sequential way and squeeze

NOTE Confidence: 0.849236412666667

00:18:47.520 --> 00:18:48.720 these together and this.

NOTE Confidence: 0.849236412666667

00:18:48.720 --> 00:18:50.622 This of course became the standard

NOTE Confidence: 0.849236412666667

00:18:50.622 --> 00:18:53.056 because the the AC from axle 2 weeks

NOTE Confidence: 0.849236412666667

00:18:53.056 --> 00:18:55.395 was better than AC for Taxol 3 weeks

NOTE Confidence: 0.849236412666667

00:18:55.395 --> 00:18:57.261 I would just emphasize that this

NOTE Confidence: 0.849236412666667

00:18:57.261 --> 00:18:58.786 regimen and this regimen really came

NOTE Confidence: 0.849236412666667

00:18:58.786 --> 00:19:00.747 out the same and so they were pulled

NOTE Confidence: 0.849236412666667

00:19:00.747 --> 00:19:02.627 together for the analysis and and if

NOTE Confidence: 0.849236412666667

00:19:02.627 --> 00:19:03.872 you can't give the cyclophosphamide

NOTE Confidence: 0.849236412666667

00:19:03.872 --> 00:19:05.341 with the age of my son together

NOTE Confidence: 0.849236412666667

00:19:05.341 --> 00:19:06.680 and if you give it the end,

NOTE Confidence: 0.849236412666667

00:19:06.680 --> 00:19:08.096 it would be just as effective.

NOTE Confidence: 0.849236412666667

00:19:08.100 --> 00:19:10.204 I have done this in certain situations with

NOTE Confidence: 0.849236412666667

00:19:10.204 --> 00:19:11.919 patients we're running into into issues.

NOTE Confidence: 0.849236412666667

00:19:11.920 --> 00:19:12.548 For example.

NOTE Confidence: 0.849236412666667

00:19:12.548 --> 00:19:14.746 The other thing that I've done is

NOTE Confidence: 0.849236412666667

00:19:14.746 --> 00:19:16.908 basically substitute Murph for adriamycin.

NOTE Confidence: 0.849236412666667

00:19:16.910 --> 00:19:18.102 In in this regimen,

NOTE Confidence: 0.849236412666667

00:19:18.102 --> 00:19:19.592 if there's issues related to

NOTE Confidence: 0.849236412666667

00:19:19.592 --> 00:19:20.430 cardiac toxicity,

NOTE Confidence: 0.849236412666667

00:19:20.430 --> 00:19:22.230 'cause we know that CMF and

NOTE Confidence: 0.849236412666667

00:19:22.230 --> 00:19:23.830 AC really are the same.

NOTE Confidence: 0.849236412666667

00:19:23.830 --> 00:19:25.405 In terms of efficacy in

NOTE Confidence: 0.849236412666667

00:19:25.405 --> 00:19:26.665 in the action setting,

NOTE Confidence: 0.849236412666667

00:19:26.670 --> 00:19:29.040 and retrospectively I'll say I think

NOTE Confidence: 0.849236412666667

00:19:29.040 --> 00:19:32.590 it was a shame that we did not do a

NOTE Confidence: 0.849236412666667

00:19:32.590 --> 00:19:35.074 comparison between AC dose, dense AC.

NOTE Confidence: 0.849236412666667

00:19:35.074 --> 00:19:37.684 Those dents followed by Taxol.

NOTE Confidence: 0.849236412666667

00:19:37.690 --> 00:19:39.930 Those stands compared to CMF.

NOTE Confidence: 0.849236412666667

00:19:39.930 --> 00:19:41.175 Those tents followed by Taxol

NOTE Confidence: 0.849236412666667

00:19:41.175 --> 00:19:42.926 'cause I bet you they come out

NOTE Confidence: 0.849236412666667

00:19:42.926 --> 00:19:44.501 the same and we wouldn't have all

NOTE Confidence: 0.849236412666667

00:19:44.501 --> 00:19:46.517 the drama about the potential for

NOTE Confidence: 0.849236412666667

00:19:46.517 --> 00:19:47.909 cardiac toxicity with anticyclone.

NOTE Confidence: 0.849236412666667

00:19:47.910 --> 00:19:49.848 Sorry I fear that we're throwing

NOTE Confidence: 0.849236412666667

00:19:49.848 --> 00:19:51.916 the baby out with the bathwater

NOTE Confidence: 0.849236412666667

00:19:51.916 --> 00:19:54.046 often when we're not using AC.

NOTE Confidence: 0.849236412666667

00:19:54.050 --> 00:19:54.404 Taxol,

NOTE Confidence: 0.849236412666667

00:19:54.404 --> 00:19:56.528 because we're afraid of cardiac toxicity

NOTE Confidence: 0.849236412666667

00:19:56.528 --> 00:19:58.543 and using other regimens that avoid

NOTE Confidence: 0.849236412666667

00:19:58.543 --> 00:20:00.629 the anti cycling and in doing so,

NOTE Confidence: 0.849236412666667

00:20:00.630 --> 00:20:02.490 we're also leaving out those density.

NOTE Confidence: 0.849236412666667

00:20:02.490 --> 00:20:05.690 I think that's a mistake and I'll show you

NOTE Confidence: 0.849236412666667

00:20:05.690 --> 00:20:08.260 why I think that's a mistake in a second.

NOTE Confidence: 0.849236412666667

00:20:08.260 --> 00:20:09.352 I just also want to emphasize and

NOTE Confidence: 0.849236412666667

00:20:09.352 --> 00:20:10.578 I just wanna mention this quickly.

NOTE Confidence: 0.849236412666667

00:20:10.580 --> 00:20:12.239 Is that the doses of the drugs

NOTE Confidence: 0.849236412666667

00:20:12.239 --> 00:20:14.287 we use did not come from nowhere?

NOTE Confidence: 0.849236412666667

00:20:14.290 --> 00:20:16.180 We actually studied the doses and

NOTE Confidence: 0.849236412666667

00:20:16.180 --> 00:20:18.662 we found out that moderate levels of

NOTE Confidence: 0.849236412666667

00:20:18.662 --> 00:20:20.582 the CF combination was equivalent

NOTE Confidence: 0.849236412666667

00:20:20.582 --> 00:20:22.835 to higher levels that going higher

NOTE Confidence: 0.849236412666667

00:20:22.835 --> 00:20:24.259 doses was not better.

NOTE Confidence: 0.849236412666667

00:20:24.260 --> 00:20:25.804 Half doses were inferior.

NOTE Confidence: 0.849236412666667

00:20:25.804 --> 00:20:28.120 This network that Dan Budman did,

NOTE Confidence: 0.849236412666667

00:20:28.120 --> 00:20:30.976 and in this in the cancer Community,

NOTE Confidence: 0.849236412666667

00:20:30.980 --> 00:20:31.526 Group B,

NOTE Confidence: 0.849236412666667

00:20:31.526 --> 00:20:33.710 and so the whole idea of going higher

NOTE Confidence: 0.849236412666667

00:20:33.775 --> 00:20:35.644 with doses to get more so killed

NOTE Confidence: 0.849236412666667

00:20:35.644 --> 00:20:37.816 was just not borne out by the data.

NOTE Confidence: 0.849236412666667

00:20:37.820 --> 00:20:39.580 The same thing was done

NOTE Confidence: 0.849236412666667

00:20:39.580 --> 00:20:40.284 with cyclophosphamide.

NOTE Confidence: 0.849236412666667

00:20:40.290 --> 00:20:42.068 And with Bernie Fisher in the NSA,

NOTE Confidence: 0.849236412666667

00:20:42.070 --> 00:20:42.432 BP,

NOTE Confidence: 0.849236412666667

00:20:42.432 --> 00:20:44.242 where they looked at higher

NOTE Confidence: 0.849236412666667

00:20:44.242 --> 00:20:45.690 and higher doses of

NOTE Confidence: 0.862027931904762

00:20:45.761 --> 00:20:47.781 cyclophosphamide in the CF combination

NOTE Confidence: 0.862027931904762

00:20:47.781 --> 00:20:51.995 and and it did not add in in the in in

NOTE Confidence: 0.862027931904762

00:20:51.995 --> 00:20:55.226 the in in the various regimens they

NOTE Confidence: 0.862027931904762

00:20:55.226 --> 00:20:58.394 went to higher and higher doses and they

NOTE Confidence: 0.862027931904762

00:20:58.394 --> 00:21:01.461 did not add so that and and Eric which

NOTE Confidence: 0.862027931904762

00:21:01.461 --> 00:21:03.323 I he told me he'd be listening today

NOTE Confidence: 0.862027931904762

00:21:03.323 --> 00:21:05.058 did the same thing with paclitaxel,

NOTE Confidence: 0.862027931904762

00:21:05.060 --> 00:21:07.124 going to higher dose of the 175 not

NOTE Confidence: 0.862027931904762

00:21:07.124 --> 00:21:08.986 showing any advantage in a study.

NOTE Confidence: 0.862027931904762

00:21:08.986 --> 00:21:10.642 So this notion that just going

NOTE Confidence: 0.862027931904762

00:21:10.642 --> 00:21:11.470 higher and higher?

NOTE Confidence: 0.862027931904762

00:21:11.470 --> 00:21:12.870 Doses you can get more cell kill.

NOTE Confidence: 0.862027931904762

00:21:12.870 --> 00:21:14.480 It's just not borne out

NOTE Confidence: 0.862027931904762

00:21:14.480 --> 00:21:15.446 by empirical evidence,

NOTE Confidence: 0.862027931904762

00:21:15.450 --> 00:21:17.349 and we have to keep that in mind as

NOTE Confidence: 0.862027931904762

00:21:17.349 --> 00:21:18.945 we question the original dogma that

NOTE Confidence: 0.862027931904762

00:21:18.945 --> 00:21:21.353 led to a lot of what we're still

NOTE Confidence: 0.862027931904762

00:21:21.353 --> 00:21:23.387 currently doing in in our application.

NOTE Confidence: 0.862027931904762

00:21:23.390 --> 00:21:25.310 Medicinal chemistry to the treatment

NOTE Confidence: 0.862027931904762

00:21:25.310 --> 00:21:27.550 of cancer of the present day.

NOTE Confidence: 0.862027931904762

00:21:27.550 --> 00:21:31.575 Well, this led to 26 randomized trials

NOTE Confidence: 0.862027931904762

00:21:31.575 --> 00:21:33.554 over 37,000 randomized patients looking

NOTE Confidence: 0.862027931904762

00:21:33.554 --> 00:21:36.170 at various permutations at dose and schedule,

NOTE Confidence: 0.862027931904762

00:21:36.170 --> 00:21:37.829 and this was published in The Lancet.

NOTE Confidence: 0.862027931904762

00:21:37.830 --> 00:21:41.160 I'm just summarizing all this work is that if

NOTE Confidence: 0.862027931904762

00:21:41.160 --> 00:21:43.910 you use and they talk about intensity here,

NOTE Confidence: 0.862027931904762

00:21:43.910 --> 00:21:45.950 but there's a very big choice of terms,

NOTE Confidence: 0.862027931904762

00:21:45.950 --> 00:21:47.465 but nevertheless that was the

NOTE Confidence: 0.862027931904762

00:21:47.465 --> 00:21:49.310 consensus that we use the term.

NOTE Confidence: 0.862027931904762

00:21:49.310 --> 00:21:50.990 It's really dose density,

NOTE Confidence: 0.862027931904762

00:21:50.990 --> 00:21:52.670 standard schedule rather than

NOTE Confidence: 0.862027931904762

00:21:52.670 --> 00:21:54.909 using a dose dense schedule,

NOTE Confidence: 0.862027931904762

00:21:54.910 --> 00:21:56.071 you get recurrences,

NOTE Confidence: 0.862027931904762

00:21:56.071 --> 00:21:57.619 reduced breast cancer mortality.

NOTE Confidence: 0.862027931904762

00:21:57.620 --> 00:21:59.295 Reduced and this is over 37,000

NOTE Confidence: 0.862027931904762

00:21:59.295 --> 00:22:01.640 randomized patients, so this is hard data,

NOTE Confidence: 0.862027931904762

00:22:01.640 --> 00:22:01.949 no.

NOTE Confidence: 0.862027931904762

00:22:01.949 --> 00:22:03.494 No increase in death without

NOTE Confidence: 0.862027931904762

00:22:03.494 --> 00:22:05.412 recurrence and there is no incremental

NOTE Confidence: 0.862027931904762

00:22:05.412 --> 00:22:06.957 toxicity from our agents by

NOTE Confidence: 0.862027931904762

00:22:06.957 --> 00:22:08.999 using them in dose dense fashion,

NOTE Confidence: 0.862027931904762

00:22:09.000 --> 00:22:11.045 and indeed all 'cause mortality

NOTE Confidence: 0.862027931904762

00:22:11.045 --> 00:22:13.090 is reduced because reducing cancer

NOTE Confidence: 0.862027931904762

00:22:13.153 --> 00:22:15.597 specific mortality as you see here so

NOTE Confidence: 0.862027931904762

00:22:15.597 --> 00:22:17.619 clearly it's shown that the concepts

NOTE Confidence: 0.862027931904762

00:22:17.619 --> 00:22:20.103 of those 10s therapy work and are

NOTE Confidence: 0.862027931904762

00:22:20.103 --> 00:22:22.203 applicable and the reason why I'm

NOTE Confidence: 0.862027931904762

00:22:22.276 --> 00:22:24.420 saying this is oh and by the way,

NOTE Confidence: 0.862027931904762

00:22:24.420 --> 00:22:28.356 is that and paclitaxel 80 weekly is superior.

NOTE Confidence: 0.862027931904762

00:22:28.360 --> 00:22:30.352 75 and it's a dose 10 schedule and

NOTE Confidence: 0.862027931904762

00:22:30.352 --> 00:22:31.746 the sideman showed this because

NOTE Confidence: 0.862027931904762

00:22:31.746 --> 00:22:32.976 it's being given every week.

NOTE Confidence: 0.862027931904762

00:22:32.980 --> 00:22:34.888 Rather than reading every three weeks

NOTE Confidence: 0.862027931904762

00:22:34.888 --> 00:22:36.605 and the dose response relationship

NOTE Confidence: 0.862027931904762

00:22:36.605 --> 00:22:38.915 for paclitaxel as Eric Weiner showed,

NOTE Confidence: 0.862027931904762

00:22:38.920 --> 00:22:42.722 is not is not steep and that you are

NOTE Confidence: 0.862027931904762

00:22:42.722 --> 00:22:44.738 accomplishing at least 1/3 as much

NOTE Confidence: 0.862027931904762

00:22:44.738 --> 00:22:46.850 efficacy with 80 as you are with 175.

NOTE Confidence: 0.849411774411765

00:22:49.000 --> 00:22:51.780 So the reason why I show all this most first

NOTE Confidence: 0.849411774411765

00:22:51.848 --> 00:22:54.200 of all is to catch some historical facts.

NOTE Confidence: 0.849411774411765

00:22:54.200 --> 00:22:55.800 For those of you who are not familiar

NOTE Confidence: 0.849411774411765

00:22:55.800 --> 00:22:57.280 with them but also make this point,

NOTE Confidence: 0.849411774411765

00:22:57.280 --> 00:22:59.870 it's gone pretty and growth is true.

NOTE Confidence: 0.849411774411765

00:22:59.870 --> 00:23:01.809 And you can use growth gun purchasing

NOTE Confidence: 0.849411774411765

00:23:01.809 --> 00:23:03.829 growth kinetics to improve cancer therapy,

NOTE Confidence: 0.849411774411765

00:23:03.830 --> 00:23:05.636 which leads us with the big question

NOTE Confidence: 0.849411774411765

00:23:05.636 --> 00:23:07.329 what is the etiology of gun?

NOTE Confidence: 0.849411774411765

00:23:07.330 --> 00:23:08.125 Pretty and growth?

NOTE Confidence: 0.849411774411765

00:23:08.125 --> 00:23:09.980 I was at something called the Ideas

NOTE Confidence: 0.849411774411765

00:23:10.038 --> 00:23:12.046 Festival in Aspen one year and I was

NOTE Confidence: 0.849411774411765

00:23:12.046 --> 00:23:14.105 having trouble parking my car so I was

NOTE Confidence: 0.849411774411765

00:23:14.105 --> 00:23:15.598 blocking somebody else from getting out

NOTE Confidence: 0.849411774411765

00:23:15.598 --> 00:23:17.550 of her parking spot and she got really

NOTE Confidence: 0.849411774411765

00:23:17.607 --> 00:23:19.367 angry and she came running up to me.

NOTE Confidence: 0.849411774411765

00:23:19.370 --> 00:23:20.768 With her hands on her hips,

NOTE Confidence: 0.849411774411765

00:23:20.770 --> 00:23:22.750 and I pulled down my window and she and she.

NOTE Confidence: 0.849411774411765

00:23:22.750 --> 00:23:24.183 And she was really angry, said,

NOTE Confidence: 0.849411774411765

00:23:24.183 --> 00:23:25.581 what's your problem and I said

NOTE Confidence: 0.849411774411765

00:23:25.581 --> 00:23:27.463 my problem is the etiology of gun

NOTE Confidence: 0.849411774411765

00:23:27.463 --> 00:23:28.883 protein growth what's your problem?

NOTE Confidence: 0.849411774411765

00:23:28.890 --> 00:23:30.717 She obviously thought I was a lunatic,

NOTE Confidence: 0.849411774411765

00:23:30.720 --> 00:23:31.806 which I probably am and she

NOTE Confidence: 0.849411774411765

00:23:31.806 --> 00:23:32.530 walked away from me.

NOTE Confidence: 0.849411774411765

00:23:32.530 --> 00:23:34.126 But this has been my preoccupation.

NOTE Confidence: 0.849411774411765

00:23:34.130 --> 00:23:36.368 For many years is understanding what

NOTE Confidence: 0.849411774411765

00:23:36.368 --> 00:23:39.149 is the etiology of compresion growth.

NOTE Confidence: 0.849411774411765

00:23:39.150 --> 00:23:39.832 And so,

NOTE Confidence: 0.849411774411765

00:23:39.832 --> 00:23:41.878 thinking about this in the early

NOTE Confidence: 0.849411774411765

00:23:41.878 --> 00:23:44.671 2000s I I got a phone call from a

NOTE Confidence: 0.849411774411765

00:23:44.671 --> 00:23:46.710 Jean massage my great collaborator

NOTE Confidence: 0.849411774411765

00:23:46.710 --> 00:23:48.890 here at Morrison Kettering.

NOTE Confidence: 0.849411774411765

00:23:48.890 --> 00:23:50.336 He had just published his paper

NOTE Confidence: 0.849411774411765

00:23:50.336 --> 00:23:51.059 by Andy Mineo,

NOTE Confidence: 0.849411774411765

00:23:51.060 --> 00:23:53.580 was about to publish his paper by Andy Min,

NOTE Confidence: 0.849411774411765

00:23:53.580 --> 00:23:55.610 where they were looking at the etiology,

NOTE Confidence: 0.849411774411765

00:23:55.610 --> 00:23:57.610 molecular etiology and metastasis,

NOTE Confidence: 0.849411774411765

00:23:57.610 --> 00:23:59.610 and found this tumor.

NOTE Confidence: 0.849411774411765

00:23:59.610 --> 00:24:00.054 You know,

NOTE Confidence: 0.849411774411765

00:24:00.054 --> 00:24:00.720 which is an

NOTE Confidence: 0.662351875714286

00:24:03.530 --> 00:24:07.100 MMDA MB 231. Sometimes is rushing ahead,

NOTE Confidence: 0.662351875714286

00:24:07.100 --> 00:24:08.620 which had a certain gene

NOTE Confidence: 0.662351875714286

00:24:08.620 --> 00:24:09.228 expression profiling.

NOTE Confidence: 0.662351875714286

00:24:09.230 --> 00:24:10.590 Machines being locked, these genes

NOTE Confidence: 0.662351875714286

00:24:10.590 --> 00:24:12.569 being on and the tumor sticks here.

NOTE Confidence: 0.662351875714286

00:24:12.570 --> 00:24:14.663 But occasionally you get along with tax

NOTE Confidence: 0.662351875714286

00:24:14.663 --> 00:24:17.040 assist and if you get a long metastasis

NOTE Confidence: 0.662351875714286

00:24:17.040 --> 00:24:18.984 and you take the cells out of the lung,

NOTE Confidence: 0.662351875714286

00:24:18.990 --> 00:24:20.838 wash them and put them back into

NOTE Confidence: 0.662351875714286

00:24:20.838 --> 00:24:22.699 the memory fat pad several times,

NOTE Confidence: 0.662351875714286

00:24:22.700 --> 00:24:25.700 you can develop a cell line 4175,

NOTE Confidence: 0.662351875714286

00:24:25.700 --> 00:24:28.100 now called the lung metastasis signature,

NOTE Confidence: 0.662351875714286

00:24:28.100 --> 00:24:30.455 which has a signature which

NOTE Confidence: 0.662351875714286

00:24:30.455 --> 00:24:32.339 predicts lung metastasis because

NOTE Confidence: 0.662351875714286

00:24:32.339 --> 00:24:34.226 the mouse develops long itassis.

NOTE Confidence: 0.662351875714286

00:24:34.226 --> 00:24:35.836 He's done this for other

NOTE Confidence: 0.662351875714286

00:24:35.836 --> 00:24:36.970 other organs as well.

NOTE Confidence: 0.662351875714286

00:24:36.970 --> 00:24:38.895 Well in this paper they they had

NOTE Confidence: 0.662351875714286

00:24:38.895 --> 00:24:40.130 this very interesting figure.

NOTE Confidence: 0.662351875714286

00:24:40.130 --> 00:24:42.083 It showed that the tumor that goes

NOTE Confidence: 0.662351875714286

00:24:42.083 --> 00:24:44.464 to the lung more readily that has

NOTE Confidence: 0.662351875714286

00:24:44.464 --> 00:24:46.314 this gene expression profile also

NOTE Confidence: 0.662351875714286

00:24:46.314 --> 00:24:48.566 grows faster in the mammary fat pad.

NOTE Confidence: 0.662351875714286

00:24:48.570 --> 00:24:49.866 The one that doesn't go to

NOTE Confidence: 0.662351875714286

00:24:49.866 --> 00:24:51.139 the lung doesn't grow as fast,

NOTE Confidence: 0.662351875714286

00:24:51.140 --> 00:24:53.996 and the intermediate steps

NOTE Confidence: 0.662351875714286

00:24:53.996 --> 00:24:56.138 have an intermediate.

NOTE Confidence: 0.662351875714286

00:24:56.140 --> 00:24:58.499 Intermediate growth rate in terms of memory,

NOTE Confidence: 0.662351875714286

00:24:58.500 --> 00:24:59.214 fat pad.

NOTE Confidence: 0.662351875714286

00:24:59.214 --> 00:25:01.356 So the question that I was

NOTE Confidence: 0.662351875714286

00:25:01.356 --> 00:25:03.696 asked in on a phone call is.

NOTE Confidence: 0.662351875714286

00:25:03.700 --> 00:25:04.810 Number one, is it true?

NOTE Confidence: 0.662351875714286

00:25:04.810 --> 00:25:06.441 As a clinician that cancers that are

NOTE Confidence: 0.662351875714286

00:25:06.441 --> 00:25:07.948 metastatic tend to be faster growing?

NOTE Confidence: 0.662351875714286

00:25:07.950 --> 00:25:09.930 And I said that's true and he said Larry,

NOTE Confidence: 0.662351875714286

00:25:09.930 --> 00:25:11.918 can you figure out why and the

NOTE Confidence: 0.662351875714286

00:25:11.918 --> 00:25:13.720 answer was really rather obvious.

NOTE Confidence: 0.662351875714286

00:25:13.720 --> 00:25:14.734 Is that yes,

NOTE Confidence: 0.662351875714286

00:25:14.734 --> 00:25:16.762 they're getting metastatic to distant sites.

NOTE Confidence: 0.662351875714286

00:25:16.770 --> 00:25:17.143 Why?

NOTE Confidence: 0.662351875714286

00:25:17.143 --> 00:25:19.754 Why were they stop them from getting

NOTE Confidence: 0.662351875714286

00:25:19.754 --> 00:25:21.949 metastatic back to the original site?

NOTE Confidence: 0.662351875714286

00:25:21.950 --> 00:25:23.950 And he and the so the query was

NOTE Confidence: 0.662351875714286

00:25:23.950 --> 00:25:26.056 but the S phase fraction the KS

NOTE Confidence: 0.662351875714286

00:25:26.056 --> 00:25:28.244 67 was not different and I said

NOTE Confidence: 0.662351875714286

00:25:28.244 --> 00:25:30.288 that's makes a whole lot of sense,

NOTE Confidence: 0.662351875714286

00:25:30.290 --> 00:25:32.225 because basically if the tumor

NOTE Confidence: 0.662351875714286

00:25:32.225 --> 00:25:33.386 that goes metastatic,

NOTE Confidence: 0.662351875714286

00:25:33.390 --> 00:25:34.570 let's say to the lung,

NOTE Confidence: 0.662351875714286

00:25:34.570 --> 00:25:37.810 also gets meta meta static back to itself,

NOTE Confidence: 0.662351875714286

00:25:37.810 --> 00:25:39.738 then in this case we have like 3

NOTE Confidence: 0.662351875714286

00:25:39.738 --> 00:25:41.244 lumps that are growing independently

NOTE Confidence: 0.662351875714286

00:25:41.244 --> 00:25:43.484 and each of them growing at 5%.

NOTE Confidence: 0.662351875714286

00:25:43.490 --> 00:25:45.008 Let's say you're still going to

NOTE Confidence: 0.662351875714286

00:25:45.008 --> 00:25:46.349 have a growth fraction of 5%,

NOTE Confidence: 0.662351875714286

00:25:46.350 --> 00:25:48.350 but you're going to grow three times faster.

NOTE Confidence: 0.662351875714286

00:25:48.350 --> 00:25:49.800 'cause three things going at

NOTE Confidence: 0.662351875714286

00:25:49.800 --> 00:25:51.602 5% each is going to grow faster

NOTE Confidence: 0.662351875714286

00:25:51.602 --> 00:25:52.959 than one thing growing at 5%.

NOTE Confidence: 0.662351875714286

00:25:52.960 --> 00:25:54.766 And so therefore it makes sense that

NOTE Confidence: 0.662351875714286

00:25:54.766 --> 00:25:56.777 they carry 67 would not be different,

NOTE Confidence: 0.662351875714286

00:25:56.780 --> 00:25:58.698 and yet you would get faster growth.

NOTE Confidence: 0.662351875714286

00:25:58.700 --> 00:26:00.320 And because it's being metastatic

NOTE Confidence: 0.662351875714286

00:26:00.320 --> 00:26:01.940 back to back to itself,

NOTE Confidence: 0.662351875714286

00:26:01.940 --> 00:26:04.190 so Jean message and I labeled

NOTE Confidence: 0.662351875714286

00:26:04.190 --> 00:26:06.550 this self seating and and did

NOTE Confidence: 0.662351875714286

00:26:06.550 --> 00:26:08.118 subsequent work in this.

NOTE Confidence: 0.662351875714286

00:26:08.120 --> 00:26:10.878 This was a hypothesis me on Kim.

NOTE Confidence: 0.662351875714286

00:26:10.880 --> 00:26:12.840 Did this work published in 2009?

NOTE Confidence: 0.662351875714286

00:26:12.840 --> 00:26:14.590 And this was just a brilliant experiment

NOTE Confidence: 0.662351875714286

00:26:14.590 --> 00:26:16.200 of the exact same tumor implanted

NOTE Confidence: 0.662351875714286

00:26:16.200 --> 00:26:18.185 in two different fat pads but with

NOTE Confidence: 0.662351875714286

00:26:18.185 --> 00:26:19.915 different fluorescent proteins in them.

NOTE Confidence: 0.662351875714286

00:26:19.920 --> 00:26:21.460 So they're different colors.

NOTE Confidence: 0.662351875714286

00:26:21.460 --> 00:26:23.000 And indeed they exchange.

NOTE Confidence: 0.662351875714286

00:26:23.000 --> 00:26:23.820 And this would be this.

NOTE Confidence: 0.662351875714286

00:26:23.820 --> 00:26:24.980 The left side of tumor.

NOTE Confidence: 0.662351875714286

00:26:24.980 --> 00:26:26.220 This would be the right side of tumor.

NOTE Confidence: 0.662351875714286

00:26:26.220 --> 00:26:28.516 This started green and and then turn

NOTE Confidence: 0.662351875714286

00:26:28.516 --> 00:26:30.638 red because red cells moved over.

NOTE Confidence: 0.662351875714286

00:26:30.640 --> 00:26:32.236 This started red and moved and

NOTE Confidence: 0.662351875714286

00:26:32.236 --> 00:26:33.034 and developed green.

NOTE Confidence: 0.662351875714286

00:26:33.040 --> 00:26:34.280 'cause green cells moved over

NOTE Confidence: 0.662351875714286

00:26:34.280 --> 00:26:35.815 and there's an exchange of cells

NOTE Confidence: 0.662351875714286

00:26:35.815 --> 00:26:37.070 between the two tumor sites.

NOTE Confidence: 0.662351875714286

00:26:37.070 --> 00:26:39.670 On much more work was in this paper.

NOTE Confidence: 0.8556101385

00:26:39.670 --> 00:26:41.986 Obviously if you inject a non

NOTE Confidence: 0.8556101385

00:26:41.986 --> 00:26:44.318 seeding tumor here and then inject

NOTE Confidence: 0.8556101385

00:26:44.318 --> 00:26:47.166 the LM 2 seating tumor to the heart,

NOTE Confidence: 0.8556101385

00:26:47.170 --> 00:26:48.830 it will see that tumor.

NOTE Confidence: 0.8556101385

00:26:48.830 --> 00:26:50.105 Here's an interesting observation which

NOTE Confidence: 0.8556101385

00:26:50.105 --> 00:26:51.930 I still think is very provocative.

NOTE Confidence: 0.8556101385

00:26:51.930 --> 00:26:53.550 When you inject the tumor cells,

NOTE Confidence: 0.8556101385

00:26:53.550 --> 00:26:55.430 they they light up the whole body obviously,

NOTE Confidence: 0.8556101385

00:26:55.430 --> 00:26:57.798 but then over a period of 42 days

NOTE Confidence: 0.8556101385

00:26:57.798 --> 00:27:00.048 they grow in the implanted tumor.

NOTE Confidence: 0.8556101385

00:27:00.050 --> 00:27:02.678 That's not metastatic on this side.

NOTE Confidence: 0.8556101385

00:27:02.680 --> 00:27:04.188 Why is this interesting?

NOTE Confidence: 0.8556101385

00:27:04.188 --> 00:27:05.696 Because you're not developing

NOTE Confidence: 0.8556101385

00:27:05.696 --> 00:27:06.450 lung metastases.

NOTE Confidence: 0.8556101385

00:27:06.450 --> 00:27:07.356 In other words,

NOTE Confidence: 0.8556101385

00:27:07.356 --> 00:27:09.168 the tumor is citing the the

NOTE Confidence: 0.8556101385

00:27:09.168 --> 00:27:10.899 cells that you're injecting,

NOTE Confidence: 0.8556101385

00:27:10.900 --> 00:27:12.946 which were developed to siedlung are

NOTE Confidence: 0.8556101385

00:27:12.946 --> 00:27:15.607 not going to the lung 'cause they

NOTE Confidence: 0.8556101385

00:27:15.607 --> 00:27:17.657 preferentially going to the tumor,

NOTE Confidence: 0.8556101385

00:27:17.660 --> 00:27:20.018 and indeed to follow this out.

NOTE Confidence: 0.8556101385

00:27:20.020 --> 00:27:22.108 If you give the tumor cells into a

NOTE Confidence: 0.8556101385

00:27:22.108 --> 00:27:24.212 tail vein injection and get lung

NOTE Confidence: 0.8556101385

00:27:24.212 --> 00:27:26.112 metastases first and then implanted

NOTE Confidence: 0.8556101385

00:27:26.112 --> 00:27:27.784 tumor that implanted tumor will

NOTE Confidence: 0.8556101385

00:27:27.784 --> 00:27:29.872 then suck cells out of the lungs.

NOTE Confidence: 0.8556101385

00:27:29.872 --> 00:27:30.800 As you can see,

NOTE Confidence: 0.8556101385

00:27:30.800 --> 00:27:32.280 the recipient tumor of the

NOTE Confidence: 0.8556101385

00:27:32.280 --> 00:27:33.464 cells will grow at.

NOTE Confidence: 0.8556101385

00:27:33.470 --> 00:27:35.054 Here 'cause it's sucking sells out

NOTE Confidence: 0.8556101385

00:27:35.054 --> 00:27:37.019 a lung and these mice can actually

NOTE Confidence: 0.8556101385

00:27:37.019 --> 00:27:38.729 live longer because they you can

NOTE Confidence: 0.8556101385

00:27:38.729 --> 00:27:40.411 live longer with a subcutaneous tumor

NOTE Confidence: 0.8556101385

00:27:40.411 --> 00:27:42.960 than you can with a long list full

NOTE Confidence: 0.8556101385

00:27:42.960 --> 00:27:45.384 of metastases and and these these

NOTE Confidence: 0.8556101385

00:27:45.384 --> 00:27:47.414 these have really profound implications.

NOTE Confidence: 0.8556101385

00:27:47.420 --> 00:27:49.355 We think not all of which we followed up

NOTE Confidence: 0.8556101385

00:27:49.355 --> 00:27:51.470 on in terms of therapeutic implications,

NOTE Confidence: 0.8556101385

00:27:51.470 --> 00:27:52.646 but perhaps if we have time we

NOTE Confidence: 0.8556101385

00:27:52.646 --> 00:27:53.380 can talk about them.

NOTE Confidence: 0.914196397142857

00:27:56.040 --> 00:27:58.172 What I want to focus in on, however,

NOTE Confidence: 0.914196397142857

00:27:58.172 --> 00:28:00.566 is that if cancers are growing at

NOTE Confidence: 0.914196397142857

00:28:00.566 --> 00:28:02.493 least partially by cells that are

NOTE Confidence: 0.914196397142857

00:28:02.493 --> 00:28:04.647 spreading and coming back to the tumor

NOTE Confidence: 0.914196397142857

00:28:04.647 --> 00:28:06.915 mass from the outside in rather than

NOTE Confidence: 0.914196397142857

00:28:06.915 --> 00:28:08.726 just growing from the inside out,

NOTE Confidence: 0.914196397142857

00:28:08.726 --> 00:28:10.171 as we always anticipated that

NOTE Confidence: 0.914196397142857

00:28:10.171 --> 00:28:12.428 they would grow, it would grow in

NOTE Confidence: 0.914196397142857

00:28:12.428 --> 00:28:14.088 this fashion like a snowflake,

NOTE Confidence: 0.914196397142857

00:28:14.090 --> 00:28:15.470 and this is this.

NOTE Confidence: 0.914196397142857

00:28:15.470 --> 00:28:18.002 This pattern of growth is with the

NOTE Confidence: 0.914196397142857

00:28:18.002 --> 00:28:19.844 skinny Franz is reminiscent of

NOTE Confidence: 0.914196397142857

00:28:19.844 --> 00:28:21.634 what the physics physicists called

NOTE Confidence: 0.914196397142857

00:28:21.634 --> 00:28:23.020 Diffusion limited aggregation,

NOTE Confidence: 0.914196397142857

00:28:23.020 --> 00:28:25.138 and it's because a water molecule.

NOTE Confidence: 0.914196397142857

00:28:25.140 --> 00:28:27.060 Or sell coming here is more likely to

NOTE Confidence: 0.914196397142857

00:28:27.060 --> 00:28:29.284 stick here than work its way into the middle.

NOTE Confidence: 0.914196397142857

00:28:29.290 --> 00:28:30.910 And if you do that,

NOTE Confidence: 0.914196397142857

00:28:30.910 --> 00:28:32.730 you actually get a pattern of growth.

NOTE Confidence: 0.914196397142857

00:28:32.730 --> 00:28:34.638 That's from Purtian because

NOTE Confidence: 0.914196397142857

00:28:34.638 --> 00:28:36.546 as objects get larger.

NOTE Confidence: 0.914196397142857

00:28:36.550 --> 00:28:38.713 The ratio of their surface to their

NOTE Confidence: 0.914196397142857

00:28:38.713 --> 00:28:40.677 volume decreases and we're going to talk

NOTE Confidence: 0.914196397142857

00:28:40.677 --> 00:28:42.969 more about that in in in a few minutes,

NOTE Confidence: 0.914196397142857

00:28:42.970 --> 00:28:43.870 and you could actually.

NOTE Confidence: 0.914196397142857

00:28:43.870 --> 00:28:44.770 Here's my only equation.

NOTE Confidence: 0.914196397142857

00:28:44.770 --> 00:28:46.142 I'm going to show you you could

NOTE Confidence: 0.914196397142857

00:28:46.142 --> 00:28:47.290 actually write an equation that's

NOTE Confidence: 0.914196397142857

00:28:47.290 --> 00:28:48.850 called the Norton mass gay equation,

NOTE Confidence: 0.914196397142857

00:28:48.850 --> 00:28:50.174 which basically summarizes that,

NOTE Confidence: 0.914196397142857

00:28:50.174 --> 00:28:52.160 and it's been much more subsequent

NOTE Confidence: 0.914196397142857

00:28:52.217 --> 00:28:53.947 mathematical work on this equation.

NOTE Confidence: 0.914196397142857

00:28:53.950 --> 00:28:55.610 And really what it means.

NOTE Confidence: 0.914196397142857

00:28:55.610 --> 00:28:57.466 But what it really means to me now,

NOTE Confidence: 0.914196397142857

00:28:57.470 --> 00:28:59.318 and I want to get into this topic.

NOTE Confidence: 0.914196397142857

00:28:59.320 --> 00:28:59.890 You know,

NOTE Confidence: 0.914196397142857

00:28:59.890 --> 00:29:01.885 with the limited time that we have,

NOTE Confidence: 0.914196397142857

00:29:01.890 --> 00:29:04.440 is that that this pattern of

NOTE Confidence: 0.914196397142857

00:29:04.440 --> 00:29:06.480 growth explains a lot of.

NOTE Confidence: 0.914196397142857

00:29:06.480 --> 00:29:07.956 Things that we know already about

NOTE Confidence: 0.914196397142857

00:29:07.956 --> 00:29:09.392 clinical medicine and not the least

NOTE Confidence: 0.914196397142857

00:29:09.392 --> 00:29:10.820 of which is the pattern of growth.

NOTE Confidence: 0.914196397142857

00:29:10.820 --> 00:29:13.860 For example, take a look at this MRI.

NOTE Confidence: 0.914196397142857

00:29:13.860 --> 00:29:15.659 This is a breast cancer MRI we

NOTE Confidence: 0.914196397142857

00:29:15.659 --> 00:29:18.161 we see this all the time and we

NOTE Confidence: 0.914196397142857

00:29:18.161 --> 00:29:19.493 call these satellite lesions.

NOTE Confidence: 0.914196397142857

00:29:19.500 --> 00:29:21.660 But frankly, it's all satellite lesions.

NOTE Confidence: 0.914196397142857

00:29:21.660 --> 00:29:22.540 This is a lesion.

NOTE Confidence: 0.914196397142857

00:29:22.540 --> 00:29:24.072 This is a delusion, this illusion.

NOTE Confidence: 0.914196397142857

00:29:24.072 --> 00:29:24.724 This illusion.

NOTE Confidence: 0.914196397142857

00:29:24.724 --> 00:29:26.354 It's got long skinny tendrils

NOTE Confidence: 0.914196397142857

00:29:26.354 --> 00:29:27.740 sticking out like a snowflake.

NOTE Confidence: 0.914196397142857

00:29:27.740 --> 00:29:29.315 It's the pattern of growth of what

NOTE Confidence: 0.914196397142857

00:29:29.315 --> 00:29:31.169 you'd see if the cells are coming in

NOTE Confidence: 0.914196397142857

00:29:31.169 --> 00:29:32.866 from the outside and so self seeding

NOTE Confidence: 0.914196397142857

00:29:32.866 --> 00:29:34.420 actually explains a lot about what

NOTE Confidence: 0.914196397142857

00:29:34.420 --> 00:29:36.980 we see in in the anatomy of cancers.

NOTE Confidence: 0.914196397142857

00:29:36.980 --> 00:29:38.180 At least the gross anatomy.

NOTE Confidence: 0.914196397142857

00:29:38.180 --> 00:29:39.785 And we'll get into the

NOTE Confidence: 0.914196397142857

00:29:39.785 --> 00:29:41.390 microscopic anatomy in a second,

NOTE Confidence: 0.914196397142857

00:29:41.390 --> 00:29:43.545 because this pattern of growth

NOTE Confidence: 0.914196397142857

00:29:43.545 --> 00:29:45.269 is called a fractal,

NOTE Confidence: 0.914196397142857

00:29:45.270 --> 00:29:47.976 and a fractal is repeated patterns

NOTE Confidence: 0.914196397142857

00:29:47.976 --> 00:29:50.100 at different scales and fractals

NOTE Confidence: 0.914196397142857

00:29:50.100 --> 00:29:52.025 have what's called a dimension.

NOTE Confidence: 0.914196397142857

00:29:52.030 --> 00:29:53.866 So now I'm going to go to a discussion

NOTE Confidence: 0.914196397142857

00:29:53.866 --> 00:29:55.360 of dimensionality because I think

NOTE Confidence: 0.914196397142857

00:29:55.360 --> 00:29:57.508 this is very important for some of

NOTE Confidence: 0.914196397142857

00:29:57.508 --> 00:29:59.209 the work that we're doing right now,

NOTE Confidence: 0.914196397142857

00:29:59.210 --> 00:30:01.562 and is implications particularly

NOTE Confidence: 0.914196397142857

00:30:01.562 --> 00:30:03.326 tumor infiltrating leukocytes.

NOTE Confidence: 0.914196397142857

00:30:03.330 --> 00:30:05.398 Now in Euclidean geometry.

NOTE Confidence: 0.914196397142857

00:30:05.398 --> 00:30:06.949 Dimensions are simple.

NOTE Confidence: 0.914196397142857

00:30:06.950 --> 00:30:08.550 A point has no dimension.

NOTE Confidence: 0.914196397142857

00:30:08.550 --> 00:30:10.806 A straight line only has length as one

NOTE Confidence: 0.914196397142857

00:30:10.806 --> 00:30:12.947 dimension a a sheet has two dimensions,

NOTE Confidence: 0.914196397142857

00:30:12.950 --> 00:30:14.972 length and and and and and

NOTE Confidence: 0.914196397142857

00:30:14.972 --> 00:30:16.790 and height and a cube.

NOTE Confidence: 0.914196397142857

00:30:16.790 --> 00:30:18.428 A solid cube has three dimensions.

NOTE Confidence: 0.914196397142857

00:30:18.430 --> 00:30:20.050 You're adding you're adding the depth.

NOTE Confidence: 0.914196397142857

00:30:20.050 --> 00:30:21.823 That's simple dimensionality

NOTE Confidence: 0.914196397142857

00:30:21.823 --> 00:30:23.596 in Euclidean space.

NOTE Confidence: 0.914196397142857

00:30:23.600 --> 00:30:25.435 In fractals it's a little

NOTE Confidence: 0.914196397142857

00:30:25.435 --> 00:30:26.536 bit more complicated.

NOTE Confidence: 0.914196397142857

00:30:26.540 --> 00:30:28.190 Let's just take one of our

NOTE Confidence: 0.914196397142857

00:30:28.190 --> 00:30:29.979 sheets that we had before that

NOTE Confidence: 0.914196397142857

00:30:29.979 --> 00:30:31.857 had a civil dimension of two,

NOTE Confidence: 0.914196397142857

00:30:31.860 --> 00:30:33.740 and let's look on it and cross section.

NOTE Confidence: 0.9064683075

00:30:33.740 --> 00:30:35.380 Well, if you start to crumble it up,

NOTE Confidence: 0.9064683075

00:30:35.380 --> 00:30:36.916 if you if you crumple up the sheet,

NOTE Confidence: 0.9064683075

00:30:36.920 --> 00:30:39.152 it's going to be a little bit more than

NOTE Confidence: 0.9064683075

00:30:39.152 --> 00:30:41.256 just a flat sheet and dimensionality.

NOTE Confidence: 0.9064683075

00:30:41.260 --> 00:30:42.838 Here is actually 2.1 number of

NOTE Confidence: 0.9064683075

00:30:42.838 --> 00:30:44.920 flat sheet is a dimension of two.

NOTE Confidence: 0.9064683075

00:30:44.920 --> 00:30:46.733 If you crumple it some more it

NOTE Confidence: 0.9064683075

00:30:46.733 --> 00:30:48.456 gets a higher dimension. 2.3.

NOTE Confidence: 0.9064683075

00:30:48.456 --> 00:30:50.528 Now let's say that it's really getting

NOTE Confidence: 0.9064683075

00:30:50.528 --> 00:30:52.498 more and more crumpled overtime.

NOTE Confidence: 0.9064683075

00:30:52.500 --> 00:30:54.705 Well, it starts to. Have the appearance

NOTE Confidence: 0.9064683075

00:30:54.705 --> 00:30:56.130 of something that's thicker.

NOTE Confidence: 0.9064683075

00:30:56.130 --> 00:30:58.042 This is a dimension of 2.6.

NOTE Confidence: 0.9064683075

00:30:58.042 --> 00:31:00.113 This is dimension of 2.8.

NOTE Confidence: 0.9064683075

00:31:00.113 --> 00:31:02.171 A dimension 3 would mean you're

NOTE Confidence: 0.9064683075

00:31:02.171 --> 00:31:04.384 prompted so much that it's now just

NOTE Confidence: 0.9064683075

00:31:04.384 --> 00:31:06.710 a solid mass of of sheet material,

NOTE Confidence: 0.9064683075

00:31:06.710 --> 00:31:08.654 but it's in a solid mass, so now it's a.

NOTE Confidence: 0.9064683075

00:31:08.654 --> 00:31:09.659 It's a it's it's got.

NOTE Confidence: 0.9064683075

00:31:09.660 --> 00:31:10.844 It's got the dimensionality

NOTE Confidence: 0.9064683075

00:31:10.844 --> 00:31:12.620 of a 3 dimensional object or

NOTE Confidence: 0.9064683075

00:31:12.678 --> 00:31:14.318 having dimensionality of three.

NOTE Confidence: 0.9064683075

00:31:14.320 --> 00:31:16.516 So these are things to keep in mind and

NOTE Confidence: 0.9064683075

00:31:16.516 --> 00:31:18.878 and it's a big difference between a 2.6

NOTE Confidence: 0.9064683075

00:31:18.878 --> 00:31:21.002 and and and a 2.8 dimensionality you

NOTE Confidence: 0.9064683075

00:31:21.002 --> 00:31:23.627 can see in terms of the thickness well.

NOTE Confidence: 0.9064683075

00:31:23.627 --> 00:31:26.126 Fractals occur in nature all the time.

NOTE Confidence: 0.9064683075

00:31:26.130 --> 00:31:27.410 These are artificial fractals

NOTE Confidence: 0.9064683075

00:31:27.410 --> 00:31:29.010 on top of various sorts.

NOTE Confidence: 0.9064683075

00:31:29.010 --> 00:31:30.492 These are the kinds of fractals

NOTE Confidence: 0.9064683075

00:31:30.492 --> 00:31:32.150 that occur in nature all the time.

NOTE Confidence: 0.9064683075

00:31:32.150 --> 00:31:34.120 Plants and animals and and

NOTE Confidence: 0.9064683075

00:31:34.120 --> 00:31:36.090 and and diffusion in in.

NOTE Confidence: 0.9064683075

00:31:36.090 --> 00:31:40.010 In substances like like ice or plastic,

NOTE Confidence: 0.9064683075

00:31:40.010 --> 00:31:41.654 these these the fractals

NOTE Confidence: 0.9064683075

00:31:41.654 --> 00:31:43.709 are just common in nature.

NOTE Confidence: 0.9064683075

00:31:43.710 --> 00:31:44.865 Mandelbrot was discovered,

NOTE Confidence: 0.9064683075

00:31:44.865 --> 00:31:46.405 there's been more Mandelbrot

NOTE Confidence: 0.9064683075

00:31:46.405 --> 00:31:47.910 and written extensively about,

NOTE Confidence: 0.9064683075

00:31:47.910 --> 00:31:48.910 and there's been an extensive

NOTE Confidence: 0.9064683075

00:31:48.910 --> 00:31:49.910 explosion of literature in this.

NOTE Confidence: 0.9064683075

00:31:49.910 --> 00:31:51.590 Written this in this regard.

NOTE Confidence: 0.9064683075

00:31:51.590 --> 00:31:53.880 So what we've done is.

NOTE Confidence: 0.9064683075

00:31:53.880 --> 00:31:56.360 We we've looked at this in the context

NOTE Confidence: 0.9064683075

00:31:56.360 --> 00:31:59.156 of self seating and the context of

NOTE Confidence: 0.9064683075

00:31:59.156 --> 00:32:01.153 leukocytes and why leukocytes because

NOTE Confidence: 0.9064683075

00:32:01.153 --> 00:32:03.657 as me and Kim showed in this paper,

NOTE Confidence: 0.9064683075

00:32:03.660 --> 00:32:06.964 we join mask and colleagues is an

NOTE Confidence: 0.9064683075

00:32:06.964 --> 00:32:09.380 unseated state compared to a seated state.

NOTE Confidence: 0.9064683075

00:32:09.380 --> 00:32:11.620 This would be an unseated tumor and

NOTE Confidence: 0.9064683075

00:32:11.620 --> 00:32:14.218 this would be a tumor that's received.

NOTE Confidence: 0.9064683075

00:32:14.220 --> 00:32:15.710 Received cells that have come

NOTE Confidence: 0.9064683075

00:32:15.710 --> 00:32:16.604 from the outside,

NOTE Confidence: 0.9064683075

00:32:16.610 --> 00:32:16.984 Ellen,

NOTE Confidence: 0.9064683075

00:32:16.984 --> 00:32:19.228 two cells in the blood vessels

NOTE Confidence: 0.9064683075

00:32:19.228 --> 00:32:21.861 are brought in with the seeds and

NOTE Confidence: 0.9064683075

00:32:21.861 --> 00:32:23.966 they're mostly bone marrow derived

NOTE Confidence: 0.9064683075

00:32:23.966 --> 00:32:25.650 endothelial cell precursors that

NOTE Confidence: 0.9064683075

00:32:25.712 --> 00:32:27.668 close that blood level of growth.

NOTE Confidence: 0.9064683075

00:32:27.670 --> 00:32:29.320 But I was particularly fascinated

NOTE Confidence: 0.9064683075

00:32:29.320 --> 00:32:31.866 by the fact that that that when you

NOTE Confidence: 0.9064683075

00:32:31.866 --> 00:32:34.242 get seating and this is is these are

NOTE Confidence: 0.9064683075

00:32:34.242 --> 00:32:36.510 seated cells that they're staying green,

NOTE Confidence: 0.9064683075

00:32:36.510 --> 00:32:38.420 the green for some protein.

NOTE Confidence: 0.9064683075

00:32:38.420 --> 00:32:40.540 Not they have for some protein not staying,

NOTE Confidence: 0.9064683075

00:32:40.540 --> 00:32:42.508 but they're obvious here in this

NOTE Confidence: 0.9064683075

00:32:42.508 --> 00:32:43.820 particular setting they bring

NOTE Confidence: 0.9064683075

00:32:43.876 --> 00:32:45.196 white cells in with them.

NOTE Confidence: 0.9064683075

00:32:45.200 --> 00:32:46.406 CD 45 cells in with them,

NOTE Confidence: 0.9064683075

00:32:46.410 --> 00:32:48.696 and so the seating process bringing

NOTE Confidence: 0.9064683075

00:32:48.696 --> 00:32:51.069 bringing brings white cells in with them.

NOTE Confidence: 0.9064683075

00:32:51.070 --> 00:32:51.319 Well,

NOTE Confidence: 0.9064683075

00:32:51.319 --> 00:32:52.813 if it's bringing white cells in

NOTE Confidence: 0.9064683075

00:32:52.813 --> 00:32:54.190 with them from the outside,

NOTE Confidence: 0.9064683075

00:32:54.190 --> 00:32:56.080 perhaps the growth the pattern of

NOTE Confidence: 0.9064683075

00:32:56.080 --> 00:32:58.079 white cells that we're going to see

NOTE Confidence: 0.9064683075

00:32:58.079 --> 00:33:00.110 in a tumor is also going to follow,

NOTE Confidence: 0.9064683075

00:33:00.110 --> 00:33:01.982 or fractal geometric pattern,

NOTE Confidence: 0.9064683075

00:33:01.982 --> 00:33:04.503 and so with, with Matthew, Hannah,

NOTE Confidence: 0.9064683075

00:33:04.503 --> 00:33:07.052 and and and and, and George Reese,

NOTE Confidence: 0.9064683075

00:33:07.052 --> 00:33:08.468 Philo, Hannah when Ebro,

NOTE Confidence: 0.9064683075

00:33:08.470 --> 00:33:12.740 G and and and and others we've looked at

NOTE Confidence: 0.9064683075

00:33:12.740 --> 00:33:15.276 this by actually looking at at tumors.

NOTE Confidence: 0.9064683075

00:33:15.276 --> 00:33:16.082 Conventional tumors.

NOTE Confidence: 0.9064683075

00:33:16.082 --> 00:33:18.500 These are triple negative breast cancers

NOTE Confidence: 0.763816441111111

00:33:18.557 --> 00:33:21.013 and using image analysis in this acute pack.

NOTE Confidence: 0.763816441111111

00:33:21.020 --> 00:33:22.620 Roughly available image analysis

NOTE Confidence: 0.763816441111111

00:33:22.620 --> 00:33:24.620 program visual image analysis program

NOTE Confidence: 0.763816441111111

00:33:24.620 --> 00:33:26.613 to actually segment the white cells

NOTE Confidence: 0.763816441111111

00:33:26.613 --> 00:33:29.040 from the tumor cells so that we can

NOTE Confidence: 0.763816441111111

00:33:29.040 --> 00:33:30.714 actually measure the number of cells

NOTE Confidence: 0.763816441111111

00:33:30.714 --> 00:33:33.052 in each region of interest and then

NOTE Confidence: 0.763816441111111

00:33:33.052 --> 00:33:34.420 using various mathematical techniques,

NOTE Confidence: 0.763816441111111

00:33:34.420 --> 00:33:36.190 mathematical tricks that we've developed.

NOTE Confidence: 0.763816441111111

00:33:36.190 --> 00:33:38.248 We can then calculate the fractal dimension

NOTE Confidence: 0.763816441111111

00:33:38.248 --> 00:33:40.472 of those white cells and what we found

NOTE Confidence: 0.763816441111111

00:33:40.472 --> 00:33:42.274 in this is preliminary work and much

NOTE Confidence: 0.763816441111111

00:33:42.274 --> 00:33:44.098 more work is going on in this topic,

NOTE Confidence: 0.763816441111111

00:33:44.100 --> 00:33:45.748 so this is not a take home message

NOTE Confidence: 0.763816441111111

00:33:45.748 --> 00:33:47.734 just to show you that we've done it is.

NOTE Confidence: 0.763816441111111

00:33:47.740 --> 00:33:48.628 We looked at.

NOTE Confidence: 0.763816441111111

00:33:48.628 --> 00:33:50.404 This is the very first experiment

NOTE Confidence: 0.763816441111111

00:33:50.404 --> 00:33:52.020 that we did three cases of.

NOTE Confidence: 0.763816441111111

00:33:52.020 --> 00:33:53.852 Triple negative breast cancer

NOTE Confidence: 0.763816441111111

00:33:53.852 --> 00:33:55.226 and not neoadjuvant.

NOTE Confidence: 0.763816441111111

00:33:55.230 --> 00:33:56.070 These are patients treating

NOTE Confidence: 0.763816441111111

00:33:56.070 --> 00:33:56.700 the agent setting.

NOTE Confidence: 0.763816441111111

00:33:56.700 --> 00:33:58.430 They're small tumors versus non

NOTE Confidence: 0.763816441111111

00:33:58.430 --> 00:34:00.160 cases without recurrence at the

NOTE Confidence: 0.763816441111111

00:34:00.218 --> 00:34:01.666 fractal dimensions are different

NOTE Confidence: 0.763816441111111

00:34:01.666 --> 00:34:03.838 and in fact the fractal dimension

NOTE Confidence: 0.763816441111111

00:34:03.901 --> 00:34:05.829 of the of the white cells in the

NOTE Confidence: 0.763816441111111

00:34:05.829 --> 00:34:08.124 cancer that that that that recurred

NOTE Confidence: 0.763816441111111

00:34:08.124 --> 00:34:10.645 or that became metastatic was 2.77

NOTE Confidence: 0.763816441111111

00:34:10.645 --> 00:34:12.514 on the average and it was 2.65.

NOTE Confidence: 0.763816441111111

00:34:12.514 --> 00:34:14.706 So it's like 2.8 verse 2.6 like I

NOTE Confidence: 0.763816441111111

00:34:14.706 --> 00:34:16.918 showed you in previous diagram and

NOTE Confidence: 0.763816441111111

00:34:16.918 --> 00:34:18.793 a statistically significant P tire.

NOTE Confidence: 0.763816441111111

00:34:18.800 --> 00:34:20.492 Much more work is going on in this direction,

NOTE Confidence: 0.763816441111111

00:34:20.500 --> 00:34:21.907 but I think this is a very.

NOTE Confidence: 0.763816441111111

00:34:21.910 --> 00:34:23.989 Interesting area for us to think about

NOTE Confidence: 0.763816441111111

00:34:23.989 --> 00:34:25.769 the application of fractal geometry

NOTE Confidence: 0.763816441111111

00:34:25.770 --> 00:34:27.492 motivated by the concept of self

NOTE Confidence: 0.763816441111111

00:34:27.492 --> 00:34:29.590 seeding in terms of analyzing tills,

NOTE Confidence: 0.763816441111111

00:34:29.590 --> 00:34:31.302 and of course we're doing much more work

NOTE Confidence: 0.763816441111111

00:34:31.302 --> 00:34:32.799 in terms of characterizing those cells

NOTE Confidence: 0.763816441111111

00:34:32.799 --> 00:34:34.809 and and and other aspects of this work,

NOTE Confidence: 0.763816441111111

00:34:34.810 --> 00:34:36.028 that would be a separate talk.

NOTE Confidence: 0.763816441111111

00:34:36.030 --> 00:34:38.330 Hopefully at another time.

NOTE Confidence: 0.763816441111111

00:34:38.330 --> 00:34:40.674 What are those white cells doing in there?

NOTE Confidence: 0.763816441111111

00:34:40.680 --> 00:34:41.133 Well,

NOTE Confidence: 0.763816441111111

00:34:41.133 --> 00:34:44.304 previous work again from John Massage shop.

NOTE Confidence: 0.763816441111111

00:34:44.310 --> 00:34:45.482 In this one area,

NOTE Confidence: 0.763816441111111

00:34:45.482 --> 00:34:46.068 Korea published.

NOTE Confidence: 0.763816441111111

00:34:46.070 --> 00:34:48.126 This shows one of the things that they're

NOTE Confidence: 0.763816441111111

00:34:48.126 --> 00:34:50.526 doing is that they can actually provide

NOTE Confidence: 0.763816441111111

00:34:50.526 --> 00:34:52.506 resistance to chemotherapy the white cell,

NOTE Confidence: 0.763816441111111

00:34:52.506 --> 00:34:54.550 and this is work that's published here

NOTE Confidence: 0.763816441111111

00:34:54.608 --> 00:34:58.228 in cell in 2012 under stress of any sort

NOTE Confidence: 0.763816441111111

00:34:58.228 --> 00:35:01.969 releases a substance that causes TNF alpha.

NOTE Confidence: 0.763816441111111

00:35:01.970 --> 00:35:05.260 This pop up just driving me crazy.

NOTE Confidence: 0.763816441111111

00:35:05.260 --> 00:35:05.755 Right,

NOTE Confidence: 0.763816441111111

00:35:05.755 --> 00:35:06.250 right?

NOTE Confidence: 0.763816441111111

00:35:06.250 --> 00:35:08.437 So I'm gonna now gonna go move with the

NOTE Confidence: 0.763816441111111

00:35:08.437 --> 00:35:09.752 lightning speed and custom stuff out.

NOTE Confidence: 0.763816441111111

00:35:09.752 --> 00:35:11.490 I have no idea why that happened,

NOTE Confidence: 0.763816441111111

00:35:11.490 --> 00:35:13.611 but nevertheless here we are is that

NOTE Confidence: 0.763816441111111

00:35:13.611 --> 00:35:16.439 when you do when when we when I showed

NOTE Confidence: 0.763816441111111

00:35:16.439 --> 00:35:18.394 you about self seeding and when you

NOTE Confidence: 0.763816441111111

00:35:18.394 --> 00:35:20.060 have self seeding white cells come in.

NOTE Confidence: 0.763816441111111

00:35:20.060 --> 00:35:21.936 So we hypothesize that the white cells

NOTE Confidence: 0.763816441111111

00:35:21.936 --> 00:35:23.998 that come in the CD 45 positive cells

NOTE Confidence: 0.763816441111111

00:35:23.998 --> 00:35:26.111 here are coming in as a reflection of

NOTE Confidence: 0.763816441111111

00:35:26.111 --> 00:35:28.092 the seating process and we can uncover

NOTE Confidence: 0.763816441111111

00:35:28.100 --> 00:35:30.494 that by looking at their fractal geometry.

NOTE Confidence: 0.763816441111111

00:35:30.500 --> 00:35:31.710 And indeed we've looked at

NOTE Confidence: 0.763816441111111

00:35:31.710 --> 00:35:32.920 this is work with Matthew,

NOTE Confidence: 0.763816441111111

00:35:32.920 --> 00:35:33.919 Hannah and colleagues.

NOTE Confidence: 0.763816441111111

00:35:33.919 --> 00:35:35.917 We've we've done this with a.

NOTE Confidence: 0.763816441111111

00:35:35.920 --> 00:35:37.184 Two paths you know,

NOTE Confidence: 0.763816441111111

00:35:37.184 --> 00:35:38.764 method for being for segmenting

NOTE Confidence: 0.763816441111111

00:35:38.764 --> 00:35:40.697 between white cells and cancer cells.

NOTE Confidence: 0.763816441111111

00:35:40.700 --> 00:35:42.744 And indeed it is indeed fractal and

NOTE Confidence: 0.763816441111111

00:35:42.744 --> 00:35:44.306 the fractal dimension is different

NOTE Confidence: 0.763816441111111

00:35:44.306 --> 00:35:45.891 in triple negative breast cancers

NOTE Confidence: 0.763816441111111

00:35:45.891 --> 00:35:47.602 that recur then triple negative

NOTE Confidence: 0.763816441111111

00:35:47.602 --> 00:35:49.357 breast cancers that don't recur.

NOTE Confidence: 0.763816441111111

00:35:49.360 --> 00:35:51.313 Much more work is going on in this direction,

NOTE Confidence: 0.801118103

00:35:51.320 --> 00:35:52.470 and I discussed I described

NOTE Confidence: 0.801118103

00:35:52.470 --> 00:35:53.620 it a few minutes ago,

NOTE Confidence: 0.801118103

00:35:53.620 --> 00:35:54.924 but I can't go back over it now.

NOTE Confidence: 0.801118103

00:35:54.930 --> 00:35:56.616 We'll have to do another lecture

NOTE Confidence: 0.801118103

00:35:56.616 --> 00:35:57.740 on this particular topic.

NOTE Confidence: 0.801118103

00:35:57.740 --> 00:35:59.476 One of those white cells doing one

NOTE Confidence: 0.801118103

00:35:59.476 --> 00:36:01.338 of the things that they're doing

NOTE Confidence: 0.801118103

00:36:01.338 --> 00:36:02.754 is providing drug resistance.

NOTE Confidence: 0.801118103

00:36:02.760 --> 00:36:04.356 His work of sworn ally Acarya,

NOTE Confidence: 0.801118103

00:36:04.360 --> 00:36:06.260 and John Messages Laboratory.

NOTE Confidence: 0.801118103

00:36:06.260 --> 00:36:09.110 If you stress the cancer cells.

NOTE Confidence: 0.801118103

00:36:09.110 --> 00:36:12.890 And with anything chemotherapy or radiation,

NOTE Confidence: 0.801118103

00:36:12.890 --> 00:36:14.154 or or even heat,

NOTE Confidence: 0.801118103

00:36:14.154 --> 00:36:16.830 you can get the secretion of TNF alpha,

NOTE Confidence: 0.801118103

00:36:16.830 --> 00:36:19.336 which causes the secretion of CXCL one

NOTE Confidence: 0.801118103

00:36:19.336 --> 00:36:21.988 which goes through receptor on white cells,

NOTE Confidence: 0.801118103

00:36:21.990 --> 00:36:24.230 which causes the release of S 100

NOTE Confidence: 0.801118103

00:36:24.230 --> 00:36:26.670 proteins and can save the cancer cell

NOTE Confidence: 0.801118103

00:36:26.670 --> 00:36:28.782 as a mechanism of drug resistance.

NOTE Confidence: 0.801118103

00:36:28.790 --> 00:36:31.436 We showed this by actually showing that

NOTE Confidence: 0.801118103

00:36:31.436 --> 00:36:33.989 the inhibited by itself does nothing,

NOTE Confidence: 0.801118103

00:36:33.990 --> 00:36:35.754 but that if you give a stress

NOTE Confidence: 0.801118103

00:36:35.754 --> 00:36:37.470 in this case a chemotherapy,

NOTE Confidence: 0.801118103

00:36:37.470 --> 00:36:39.216 you can up regulate the loop.

NOTE Confidence: 0.801118103

00:36:39.220 --> 00:36:40.220 And kill cancer cells,

NOTE Confidence: 0.801118103

00:36:40.220 --> 00:36:42.280 but some are being saved by this loop.

NOTE Confidence: 0.801118103

00:36:42.280 --> 00:36:43.896 And by Ablating that loop we can get

NOTE Confidence: 0.801118103

00:36:43.896 --> 00:36:45.620 a much higher degree of cell kill.

NOTE Confidence: 0.801118103

00:36:45.620 --> 00:36:48.042 So one of the things that those

NOTE Confidence: 0.801118103

00:36:48.042 --> 00:36:50.241 infiltrating white cells is doing is

NOTE Confidence: 0.801118103

00:36:50.241 --> 00:36:52.425 providing a mechanism of drug resistance.

NOTE Confidence: 0.801118103

00:36:52.430 --> 00:36:55.544 We've also and I I told I I gave

NOTE Confidence: 0.801118103

00:36:55.544 --> 00:36:58.688 you a a wonderful anecdote here.

NOTE Confidence: 0.801118103

00:36:58.690 --> 00:37:01.889 That was a that that is lost.

NOTE Confidence: 0.801118103

00:37:01.890 --> 00:37:03.480 Now for very history about how

NOTE Confidence: 0.801118103

00:37:03.480 --> 00:37:04.890 why we did this work.

NOTE Confidence: 0.801118103

00:37:04.890 --> 00:37:06.807 But we looked at the at at those white

NOTE Confidence: 0.801118103

00:37:06.807 --> 00:37:08.818 cells that are infiltrating human cancers.

NOTE Confidence: 0.801118103

00:37:08.820 --> 00:37:10.829 And we found that very often indeed,

NOTE Confidence: 0.801118103

00:37:10.830 --> 00:37:13.218 in most cases they have leukemia

NOTE Confidence: 0.801118103

00:37:13.218 --> 00:37:14.810 genetic mutations in them.

NOTE Confidence: 0.801118103

00:37:14.810 --> 00:37:16.181 Tumor infiltrating leukocytes

NOTE Confidence: 0.801118103

00:37:16.181 --> 00:37:18.009 are not genetically normal,

NOTE Confidence: 0.801118103

00:37:18.010 --> 00:37:18.670 they are mutant,

NOTE Confidence: 0.801118103

00:37:18.670 --> 00:37:19.110 and they,

NOTE Confidence: 0.801118103

00:37:19.110 --> 00:37:20.434 however known leukemia Jennifer

NOTE Confidence: 0.801118103

00:37:20.434 --> 00:37:22.089 mutations and not only that,

NOTE Confidence: 0.801118103

00:37:22.090 --> 00:37:23.506 but if the patient is followed.

NOTE Confidence: 0.801118103

00:37:23.510 --> 00:37:24.938 In developing secondary leukemia

NOTE Confidence: 0.801118103

00:37:24.938 --> 00:37:26.723 much later in the future,

NOTE Confidence: 0.801118103

00:37:26.730 --> 00:37:28.355 those secondary leukemias have have

NOTE Confidence: 0.801118103

00:37:28.355 --> 00:37:30.770 the same mutations that you found in

NOTE Confidence: 0.801118103

00:37:30.770 --> 00:37:32.246 the tumor infiltrating leukocytes.

NOTE Confidence: 0.801118103

00:37:32.250 --> 00:37:34.368 In many cases many years earlier,

NOTE Confidence: 0.801118103

00:37:34.370 --> 00:37:35.990 there's something else that we're

NOTE Confidence: 0.801118103

00:37:35.990 --> 00:37:38.179 exploring and and doing work on on

NOTE Confidence: 0.801118103

00:37:38.179 --> 00:37:39.971 what role mutant white cells may be

NOTE Confidence: 0.801118103

00:37:39.971 --> 00:37:42.008 playing and actually and actually growth.

NOTE Confidence: 0.801118103

00:37:42.010 --> 00:37:43.414 Promotion of the cancer,

NOTE Confidence: 0.801118103

00:37:43.414 --> 00:37:45.520 as well as providing a potential

NOTE Confidence: 0.801118103

00:37:45.582 --> 00:37:47.430 mechanism for drug resistance.

NOTE Confidence: 0.801118103

00:37:47.430 --> 00:37:48.718 The last point I made in this

NOTE Confidence: 0.801118103

00:37:48.718 --> 00:37:49.868 regard or second to last point,

NOTE Confidence: 0.801118103

00:37:49.870 --> 00:37:52.334 I made this regard that you missed

NOTE Confidence: 0.801118103

00:37:52.334 --> 00:37:55.533 is that the that all of this could

NOTE Confidence: 0.801118103

00:37:55.533 --> 00:37:57.114 be exploited because circulating

NOTE Confidence: 0.801118103

00:37:57.114 --> 00:37:58.834 cancer cells in self seeding

NOTE Confidence: 0.801118103

00:37:58.834 --> 00:38:00.909 can only return to the cancer.

NOTE Confidence: 0.801118103

00:38:00.910 --> 00:38:02.604 But you can have circulating cancer cells

NOTE Confidence: 0.801118103

00:38:02.604 --> 00:38:04.548 going from one metastatic site to another,

NOTE Confidence: 0.801118103

00:38:04.550 --> 00:38:07.420 and it's been shown in both xenografts

NOTE Confidence: 0.801118103

00:38:07.420 --> 00:38:09.352 by Jonathan Weissman and also

NOTE Confidence: 0.801118103

00:38:09.352 --> 00:38:11.564 been shown in in in lung cancer.

NOTE Confidence: 0.801118103

00:38:11.570 --> 00:38:13.185 Clinical lung cancer specimens as

NOTE Confidence: 0.801118103

00:38:13.185 --> 00:38:15.225 well as some breast cancer specimens

NOTE Confidence: 0.801118103

00:38:15.225 --> 00:38:17.397 obviously can't read the details now.

NOTE Confidence: 0.801118103

00:38:17.400 --> 00:38:19.542 But this could all be exploited by

NOTE Confidence: 0.801118103

00:38:19.542 --> 00:38:21.995 giving some form of local therapy to a

NOTE Confidence: 0.801118103

00:38:21.995 --> 00:38:24.070 tumor to cause secretion of antigens,

NOTE Confidence: 0.801118103

00:38:24.070 --> 00:38:26.518 which then you can use checkpoint

NOTE Confidence: 0.801118103

00:38:26.518 --> 00:38:28.150 inhibitors and checkpoint inhibitors

NOTE Confidence: 0.801118103

00:38:28.214 --> 00:38:29.994 to get stimulation and and

NOTE Confidence: 0.801118103

00:38:29.994 --> 00:38:31.774 theoretically in this concept kill

NOTE Confidence: 0.801118103

00:38:31.833 --> 00:38:33.668 circulating cancer cells that are

NOTE Confidence: 0.801118103

00:38:33.668 --> 00:38:35.853 self seeding being drawn back to

NOTE Confidence: 0.801118103

00:38:35.853 --> 00:38:37.568 the area of inflammation that's

NOTE Confidence: 0.801118103

00:38:37.568 --> 00:38:38.940 caused by this particular

NOTE Confidence: 0.892513605454546

00:38:38.998 --> 00:38:41.292 procedure. We did this with with Becky

NOTE Confidence: 0.892513605454546

00:38:41.292 --> 00:38:43.939 Weights did this with Jim Allison when Jim

NOTE Confidence: 0.892513605454546

00:38:43.939 --> 00:38:46.087 Allison was at Memorial Sloan Kettering,

NOTE Confidence: 0.892513605454546

00:38:46.090 --> 00:38:47.728 where we looked at an animal.

NOTE Confidence: 0.892513605454546

00:38:47.730 --> 00:38:48.990 Model, in this case,

NOTE Confidence: 0.892513605454546

00:38:48.990 --> 00:38:51.330 the one that's growing in in green.

NOTE Confidence: 0.892513605454546

00:38:51.330 --> 00:38:53.269 If you just give anti CTA forward,

NOTE Confidence: 0.892513605454546

00:38:53.270 --> 00:38:53.794 nothing happens.

NOTE Confidence: 0.892513605454546

00:38:53.794 --> 00:38:55.104 If you just a BLT,

NOTE Confidence: 0.892513605454546

00:38:55.110 --> 00:38:57.610 a contralateral tumor, nothing happens,

NOTE Confidence: 0.892513605454546

00:38:57.610 --> 00:39:00.364 but the combination of ablation and

NOTE Confidence: 0.892513605454546

00:39:00.364 --> 00:39:04.074 and anti CTA 4 gets a 90% cell kill,

NOTE Confidence: 0.892513605454546

00:39:04.074 --> 00:39:05.370 and Heather MacArthur,

NOTE Confidence: 0.892513605454546

00:39:05.370 --> 00:39:07.596 who's now in Dallas has been exploiting

NOTE Confidence: 0.892513605454546

00:39:07.596 --> 00:39:10.568 this in a number of interesting studies.

NOTE Confidence: 0.892513605454546

00:39:10.570 --> 00:39:12.551 This is a work that she did

NOTE Confidence: 0.892513605454546

00:39:12.551 --> 00:39:14.100 at Memorial Sloan Kettering,

NOTE Confidence: 0.892513605454546

00:39:14.100 --> 00:39:16.480 where a primary breast tumor was ablated

NOTE Confidence: 0.892513605454546

00:39:16.480 --> 00:39:18.948 with crir ablation and the remaining tumor.

NOTE Confidence: 0.892513605454546

00:39:18.950 --> 00:39:20.600 Inside the two is profoundly

NOTE Confidence: 0.892513605454546

00:39:20.600 --> 00:39:22.694 Immunogen IK and we showed and

NOTE Confidence: 0.892513605454546

00:39:22.694 --> 00:39:24.230 published in several papers.

NOTE Confidence: 0.892513605454546

00:39:24.230 --> 00:39:26.084 Now in a new paper coming out of Elizabeth,

NOTE Confidence: 0.892513605454546

00:39:26.090 --> 00:39:29.468 Coleman has just a first authored

NOTE Confidence: 0.892513605454546

00:39:29.470 --> 00:39:31.522 that that you can increase the

NOTE Confidence: 0.892513605454546

00:39:31.522 --> 00:39:33.355 immunogenicity of that residual tumor

NOTE Confidence: 0.892513605454546

00:39:33.355 --> 00:39:35.380 by giving immune checkpoint inhibitors

NOTE Confidence: 0.892513605454546

00:39:35.380 --> 00:39:37.170 and indeed combinations work better.

NOTE Confidence: 0.892513605454546

00:39:37.170 --> 00:39:38.578 And this is now being looked at in

NOTE Confidence: 0.892513605454546

00:39:38.578 --> 00:39:39.999 terms of therapeutic implications.

NOTE Confidence: 0.778110919444444

00:39:42.350 --> 00:39:43.946 Coming and this could be done with

NOTE Confidence: 0.778110919444444

00:39:43.946 --> 00:39:45.889 radiation as well as with prior ablation

NOTE Confidence: 0.778110919444444

00:39:45.889 --> 00:39:47.097 which we're currently exploring.

NOTE Confidence: 0.778110919444444

00:39:47.100 --> 00:39:49.060 Combinations of immune checkpoint

NOTE Confidence: 0.778110919444444

00:39:49.060 --> 00:39:51.020 inhibitors and other thoughts

NOTE Confidence: 0.778110919444444

00:39:51.020 --> 00:39:53.280 related to educated T cells in

NOTE Confidence: 0.778110919444444

00:39:53.280 --> 00:39:55.478 terms of car T cells, for example,

NOTE Confidence: 0.778110919444444

00:39:55.478 --> 00:39:57.886 as well as inducing trans genes that

NOTE Confidence: 0.778110919444444

00:39:57.886 --> 00:40:00.284 actually may make the the the inflammation

NOTE Confidence: 0.778110919444444

00:40:00.284 --> 00:40:02.150 that were causing even greater.

NOTE Confidence: 0.778110919444444

00:40:02.150 --> 00:40:04.150 So, so this is where I left off

NOTE Confidence: 0.778110919444444

00:40:04.150 --> 00:40:06.792 and I just want to give you one

NOTE Confidence: 0.778110919444444

00:40:06.792 --> 00:40:08.850 other quick thought about geometry.

NOTE Confidence: 0.778110919444444

00:40:08.850 --> 00:40:11.070 You all remember that a sphere,

NOTE Confidence: 0.778110919444444

00:40:11.070 --> 00:40:12.768 something I mentioned to you earlier,

NOTE Confidence: 0.778110919444444

00:40:12.770 --> 00:40:14.709 is that the surface area is related

NOTE Confidence: 0.778110919444444

00:40:14.709 --> 00:40:16.390 to the square of the radius,

NOTE Confidence: 0.778110919444444

00:40:16.390 --> 00:40:18.007 whereas the volume is related to Cuba.

NOTE Confidence: 0.778110919444444

00:40:18.010 --> 00:40:18.666 The radius.

NOTE Confidence: 0.778110919444444

00:40:18.666 --> 00:40:20.634 This explains why mice are furry

NOTE Confidence: 0.778110919444444

00:40:20.634 --> 00:40:22.639 because they're very small and so they

NOTE Confidence: 0.778110919444444

00:40:22.639 --> 00:40:24.609 have a very high surface area related

NOTE Confidence: 0.778110919444444

00:40:24.609 --> 00:40:26.481 to their volume and therefore they

NOTE Confidence: 0.778110919444444

00:40:26.481 --> 00:40:28.478 lose heat easily and they need to be

NOTE Confidence: 0.778110919444444

00:40:28.478 --> 00:40:30.149 very furry to hold their heat in.

NOTE Confidence: 0.778110919444444

00:40:30.150 --> 00:40:32.274 You get to a large animal like an elephant.

NOTE Confidence: 0.778110919444444

00:40:32.280 --> 00:40:34.506 Is bald and doesn't need for her

NOTE Confidence: 0.778110919444444

00:40:34.506 --> 00:40:36.423 because its surface area is very

NOTE Confidence: 0.778110919444444

00:40:36.423 --> 00:40:37.913 low related to its volume.

NOTE Confidence: 0.778110919444444

00:40:37.920 --> 00:40:39.719 Its problem is getting rid of heat,

NOTE Confidence: 0.778110919444444

00:40:39.720 --> 00:40:41.232 which is why orphans Jen tend not to

NOTE Confidence: 0.778110919444444

00:40:41.232 --> 00:40:43.081 want to run very very quickly because

NOTE Confidence: 0.778110919444444

00:40:43.081 --> 00:40:44.217 generating heat is uncomfortable

NOTE Confidence: 0.778110919444444

00:40:44.217 --> 00:40:45.792 for them 'cause they don't get rid

NOTE Confidence: 0.778110919444444

00:40:45.792 --> 00:40:47.342 of heat very very very readily,

NOTE Confidence: 0.778110919444444

00:40:47.342 --> 00:40:49.869 and that is something else that we

NOTE Confidence: 0.778110919444444

00:40:49.869 --> 00:40:51.614 can exploit therapeutically because

NOTE Confidence: 0.778110919444444

00:40:51.614 --> 00:40:54.673 the fact is that as tumors grow

NOTE Confidence: 0.778110919444444

00:40:54.680 --> 00:40:56.200 just 'cause they're getting bigger,

NOTE Confidence: 0.778110919444444

00:40:56.200 --> 00:40:58.256 the ratio of their surface area is there,

NOTE Confidence: 0.778110919444444

00:40:58.260 --> 00:40:59.880 volume drops comes down.

NOTE Confidence: 0.778110919444444

00:40:59.880 --> 00:41:02.310 So you're converting basically a mouse.

NOTE Confidence: 0.778110919444444

00:41:02.310 --> 00:41:03.441 Into an elephant,

NOTE Confidence: 0.778110919444444

00:41:03.441 --> 00:41:05.703 it comes down faster for well

NOTE Confidence: 0.778110919444444

00:41:05.703 --> 00:41:07.578 differentiated cancers than for

NOTE Confidence: 0.778110919444444

00:41:07.578 --> 00:41:09.009 poorly differentiated cancers,

NOTE Confidence: 0.778110919444444

00:41:09.010 --> 00:41:11.747 and this is because of fractal geometry.

NOTE Confidence: 0.778110919444444

00:41:11.750 --> 00:41:13.094 You know if they're interested in that,

NOTE Confidence: 0.778110919444444

00:41:13.100 --> 00:41:14.367 we could talk about the reasons why,

NOTE Confidence: 0.778110919444444

00:41:14.370 --> 00:41:16.040 but that's the reason why.

NOTE Confidence: 0.778110919444444

00:41:16.040 --> 00:41:17.138 So that actually,

NOTE Confidence: 0.778110919444444

00:41:17.138 --> 00:41:19.700 if you have a tumor that's growing

NOTE Confidence: 0.778110919444444

00:41:19.700 --> 00:41:22.668 and you do A and the surface area

NOTE Confidence: 0.778110919444444

00:41:22.668 --> 00:41:24.598 decreases related to the volume

NOTE Confidence: 0.778110919444444

00:41:24.598 --> 00:41:26.824 while it's growing and then shrink

NOTE Confidence: 0.778110919444444

00:41:26.824 --> 00:41:28.580 it with chemotherapy.

NOTE Confidence: 0.778110919444444

00:41:28.580 --> 00:41:30.296 That the surface area to volume

NOTE Confidence: 0.778110919444444

00:41:30.296 --> 00:41:31.800 ratio is going to rise,

NOTE Confidence: 0.778110919444444

00:41:31.800 --> 00:41:34.380 and since we when when we're

NOTE Confidence: 0.778110919444444

00:41:34.380 --> 00:41:36.100 talking about immuno immunotherapy,

NOTE Confidence: 0.778110919444444

00:41:36.100 --> 00:41:37.455 we're talking about a relationship

NOTE Confidence: 0.778110919444444

00:41:37.455 --> 00:41:39.305 between the surface of the cancer and

NOTE Confidence: 0.778110919444444

00:41:39.305 --> 00:41:40.859 white cells that are trying to kill

NOTE Confidence: 0.778110919444444

00:41:40.859 --> 00:41:42.870 the cancer is that is that the best

NOTE Confidence: 0.778110919444444

00:41:42.870 --> 00:41:44.967 time to use this kind of ablation

NOTE Confidence: 0.778110919444444

00:41:44.967 --> 00:41:47.079 would be after an initial induction.

NOTE Confidence: 0.778110919444444

00:41:47.080 --> 00:41:49.131 And to take this idea and exploit

NOTE Confidence: 0.778110919444444

00:41:49.131 --> 00:41:51.180 it by inducing small tumor first,

NOTE Confidence: 0.778110919444444

00:41:51.180 --> 00:41:53.436 increasing the surface area to volume

NOTE Confidence: 0.778110919444444

00:41:53.436 --> 00:41:56.119 ratio and then coming in with your

NOTE Confidence: 0.778110919444444

00:41:56.119 --> 00:41:58.709 oblated therapy and then combining that with.

NOTE Confidence: 0.778110919444444

00:41:58.710 --> 00:42:02.358 Combining that with your.

NOTE Confidence: 0.778110919444444

00:42:02.360 --> 00:42:04.904 Your immune checkpoint inhibition.

NOTE Confidence: 0.778110919444444

00:42:04.904 --> 00:42:05.540 Now,

NOTE Confidence: 0.778110919444444

00:42:05.540 --> 00:42:08.965 the same concept can apply to in

NOTE Confidence: 0.778110919444444

00:42:08.965 --> 00:42:10.960 to one of the really most exciting

NOTE Confidence: 0.778110919444444

00:42:10.960 --> 00:42:13.077 areas in terms I think most exciting

NOTE Confidence: 0.778110919444444

00:42:13.077 --> 00:42:15.619 areas in terms of of modern medicinal

NOTE Confidence: 0.778110919444444

00:42:15.620 --> 00:42:16.613 therapy of cancer,

NOTE Confidence: 0.778110919444444

00:42:16.613 --> 00:42:18.599 which is the antibody drug conjugates,

NOTE Confidence: 0.778110919444444

00:42:18.600 --> 00:42:19.480 as we all know,

NOTE Confidence: 0.778110919444444

00:42:19.480 --> 00:42:21.340 they attacked a target antigen in the cancer,

NOTE Confidence: 0.778110919444444

00:42:21.340 --> 00:42:23.980 so they have increased payload delivery,

NOTE Confidence: 0.778110919444444

00:42:23.980 --> 00:42:25.455 but their penetration could be

NOTE Confidence: 0.778110919444444

00:42:25.455 --> 00:42:26.930 poor and this is something

NOTE Confidence: 0.896994353333333

00:42:26.991 --> 00:42:28.827 that has to be exploited when

NOTE Confidence: 0.896994353333333

00:42:28.827 --> 00:42:30.404 they're internalized that the the

NOTE Confidence: 0.896994353333333

00:42:30.404 --> 00:42:32.332 payload is reduced, it is is is

NOTE Confidence: 0.896994353333333

00:42:32.332 --> 00:42:33.880 released in 'cause the cancer cell.

NOTE Confidence: 0.896994353333333

00:42:33.880 --> 00:42:35.028 But more than that.

NOTE Confidence: 0.896994353333333

00:42:35.028 --> 00:42:37.186 In terms of the activity of these

NOTE Confidence: 0.896994353333333

00:42:37.186 --> 00:42:39.388 payloads on killing the cancer cell,

NOTE Confidence: 0.896994353333333

00:42:39.390 --> 00:42:41.646 they often leak out and they can kill

NOTE Confidence: 0.896994353333333

00:42:41.646 --> 00:42:43.449 adjacent cells that don't necessarily

NOTE Confidence: 0.896994353333333

00:42:43.449 --> 00:42:45.029 have that particular target.

NOTE Confidence: 0.896994353333333

00:42:45.030 --> 00:42:47.424 This or this work of Josh Drago.

NOTE Confidence: 0.896994353333333

00:42:47.430 --> 00:42:49.638 Well, this can be exploited by the same

NOTE Confidence: 0.896994353333333

00:42:49.638 --> 00:42:52.522 way is that when you if you used your

NOTE Confidence: 0.896994353333333

00:42:52.522 --> 00:42:54.579 antibody drug conjugate to a large tumor,

NOTE Confidence: 0.896994353333333

00:42:54.580 --> 00:42:57.149 you get down regulation of the target,

NOTE Confidence: 0.896994353333333

00:42:57.150 --> 00:42:58.980 and that's not not what you

NOTE Confidence: 0.896994353333333

00:42:58.980 --> 00:43:00.710 want to optimize the effect.

NOTE Confidence: 0.896994353333333

00:43:00.710 --> 00:43:02.348 So one of the things we're exploring,

NOTE Confidence: 0.896994353333333

00:43:02.350 --> 00:43:03.526 and this is not in the clinic yet.

NOTE Confidence: 0.896994353333333

00:43:03.530 --> 00:43:05.114 This is just an experiment experiment

NOTE Confidence: 0.896994353333333

00:43:05.114 --> 00:43:06.390 that we're doing right now,

NOTE Confidence: 0.896994353333333

00:43:06.390 --> 00:43:08.445 preclinical in preparation for clinical

NOTE Confidence: 0.896994353333333

00:43:08.445 --> 00:43:11.710 experiment is by giving a non ADC induction.

NOTE Confidence: 0.896994353333333

00:43:11.710 --> 00:43:13.485 First we can increase the

NOTE Confidence: 0.896994353333333

00:43:13.485 --> 00:43:15.260 surface area to volume ratio.

NOTE Confidence: 0.896994353333333

00:43:15.260 --> 00:43:17.195 And then come in with the ADC as a

NOTE Confidence: 0.896994353333333

00:43:17.195 --> 00:43:18.493 late intensification and therefore

NOTE Confidence: 0.896994353333333

00:43:18.493 --> 00:43:21.274 it should be even more active in this

NOTE Confidence: 0.896994353333333

00:43:21.274 --> 00:43:23.260 area to get tumor volume eradication.

NOTE Confidence: 0.896994353333333

00:43:23.260 --> 00:43:24.940 And if the animal experiments work,

NOTE Confidence: 0.896994353333333

00:43:24.940 --> 00:43:26.554 I think there's something else that

NOTE Confidence: 0.896994353333333

00:43:26.554 --> 00:43:27.866 could be exploited extremely easily

NOTE Confidence: 0.896994353333333

00:43:27.866 --> 00:43:29.346 in the clinic 'cause we have a lot

NOTE Confidence: 0.896994353333333

00:43:29.346 --> 00:43:31.120 of drugs in breast cancer that can

NOTE Confidence: 0.896994353333333

00:43:31.120 --> 00:43:32.427 cause tumor volume regression that

NOTE Confidence: 0.896994353333333

00:43:32.427 --> 00:43:34.366 are not Adcs and then instead of

NOTE Confidence: 0.896994353333333

00:43:34.366 --> 00:43:36.285 waiting for the tumor to grow and

NOTE Confidence: 0.896994353333333

00:43:36.285 --> 00:43:38.312 using using your Adcs in as a salvage

NOTE Confidence: 0.896994353333333

00:43:38.312 --> 00:43:40.203 if you use them at time of maximum

NOTE Confidence: 0.896994353333333

00:43:40.203 --> 00:43:41.918 tumor volume regression and this,

NOTE Confidence: 0.896994353333333

00:43:41.920 --> 00:43:42.553 by the way,

NOTE Confidence: 0.896994353333333

00:43:42.553 --> 00:43:44.030 could be determined not just by actually

NOTE Confidence: 0.896994353333333

00:43:44.074 --> 00:43:45.700 watching the cancer shrink with imaging.

NOTE Confidence: 0.896994353333333

00:43:45.700 --> 00:43:48.402 But also by by the burden of

NOTE Confidence: 0.896994353333333

00:43:48.402 --> 00:43:50.260 of circulating cancer and DNA,

NOTE Confidence: 0.896994353333333

00:43:50.260 --> 00:43:51.676 which would be another way of

NOTE Confidence: 0.896994353333333

00:43:51.676 --> 00:43:52.620 actually when that plateaus,

NOTE Confidence: 0.896994353333333

00:43:52.620 --> 00:43:54.504 you know you've achieved your maximum

NOTE Confidence: 0.896994353333333

00:43:54.504 --> 00:43:56.227 volume regression would be the best

NOTE Confidence: 0.896994353333333

00:43:56.227 --> 00:43:59.400 time to come in with your ABC's.

NOTE Confidence: 0.896994353333333

00:43:59.400 --> 00:44:00.696 Last slide and I'm not going

NOTE Confidence: 0.896994353333333

00:44:00.696 --> 00:44:01.925 to talk about this, obviously,

NOTE Confidence: 0.896994353333333

00:44:01.925 --> 00:44:03.750 is that we're exploiting exploiting

NOTE Confidence: 0.896994353333333

00:44:03.750 --> 00:44:06.705 all of this in much more sophisticated

NOTE Confidence: 0.896994353333333

00:44:06.705 --> 00:44:09.095 mathematics with a number of

NOTE Confidence: 0.896994353333333

00:44:09.095 --> 00:44:10.051 mathematical collaborators.

NOTE Confidence: 0.896994353333333

00:44:10.060 --> 00:44:13.119 I don't album and Jodeci in particular.

NOTE Confidence: 0.896994353333333

00:44:13.120 --> 00:44:15.130 Arena Elkin and jungle in terms

NOTE Confidence: 0.896994353333333

00:44:15.130 --> 00:44:17.351 of actually looking at this same

NOTE Confidence: 0.896994353333333

00:44:17.351 --> 00:44:19.805 mathematical concepts in terms of gene

NOTE Confidence: 0.896994353333333

00:44:19.805 --> 00:44:21.870 gene interactions and their networks.

NOTE Confidence: 0.896994353333333

00:44:21.870 --> 00:44:23.422 The same thing that works at the cell

NOTE Confidence: 0.896994353333333

00:44:23.422 --> 00:44:24.883 level and the the tumor of brain

NOTE Confidence: 0.896994353333333

00:44:24.883 --> 00:44:26.578 leukocyte level may work at the gene level.

NOTE Confidence: 0.896994353333333

00:44:26.580 --> 00:44:28.068 This would have a different fractal

NOTE Confidence: 0.896994353333333

00:44:28.068 --> 00:44:29.260 dimension than this, for example.

NOTE Confidence: 0.896994353333333

00:44:29.260 --> 00:44:30.800 'cause we have a lower fractal dimension.

NOTE Confidence: 0.896994353333333

00:44:30.800 --> 00:44:32.515 This would have a higher fractal dimension.

NOTE Confidence: 0.896994353333333

00:44:32.520 --> 00:44:34.368 You can look at gene networks in

NOTE Confidence: 0.896994353333333

00:44:34.368 --> 00:44:36.561 the same way as another term for

NOTE Confidence: 0.896994353333333

00:44:36.561 --> 00:44:37.566 this cord curvature.

NOTE Confidence: 0.896994353333333

00:44:37.570 --> 00:44:39.310 Obviously I can't get into it,

NOTE Confidence: 0.896994353333333

00:44:39.310 --> 00:44:41.109 but this is giving us some great

NOTE Confidence: 0.896994353333333

00:44:41.109 --> 00:44:42.990 insights and we recently published a

NOTE Confidence: 0.896994353333333

00:44:42.990 --> 00:44:45.084 paper in ovarian cancer that actually

NOTE Confidence: 0.896994353333333

00:44:45.084 --> 00:44:47.392 showed that the the structure of the

NOTE Confidence: 0.896994353333333

00:44:47.392 --> 00:44:49.027 gene gene interaction network has

NOTE Confidence: 0.896994353333333

00:44:49.027 --> 00:44:51.229 predicted values in terms of response

NOTE Confidence: 0.896994353333333

00:44:51.229 --> 00:44:53.040 to immune checkpoint inhibition.

NOTE Confidence: 0.896994353333333

00:44:53.040 --> 00:44:54.120 In this situation and,

NOTE Confidence: 0.896994353333333

00:44:54.120 --> 00:44:55.740 and indeed that you can actually

NOTE Confidence: 0.896994353333333

00:44:55.791 --> 00:44:57.411 predict which patients with ovarian

NOTE Confidence: 0.896994353333333

00:44:57.411 --> 00:44:59.031 cancer there's not supposed to

NOTE Confidence: 0.8251976656

00:44:59.083 --> 00:45:00.948 respond to immune checkpoint ambition.

NOTE Confidence: 0.8251976656

00:45:00.950 --> 00:45:04.302 Will respond on the basis of the the

NOTE Confidence: 0.8251976656

00:45:04.302 --> 00:45:06.088 mathematical analysis of of their.

NOTE Confidence: 0.8251976656

00:45:06.090 --> 00:45:07.698 Gene Gene interactive networks.

NOTE Confidence: 0.8251976656

00:45:07.698 --> 00:45:10.400 So what I've been able to do,

NOTE Confidence: 0.8251976656

00:45:10.400 --> 00:45:12.392 I hope in this lightning talk made even

NOTE Confidence: 0.8251976656

00:45:12.392 --> 00:45:14.235 more lightning by the loss of the Internet.

NOTE Confidence: 0.8877959

00:45:16.500 --> 00:45:19.348 It's just described where this all came from.

NOTE Confidence: 0.8877959

00:45:19.350 --> 00:45:22.476 Skippers model being modified to the

NOTE Confidence: 0.8877959

00:45:22.476 --> 00:45:25.574 compression growth model and leading to

NOTE Confidence: 0.8877959

00:45:25.574 --> 00:45:28.766 a clinical advance and then why tumors

NOTE Confidence: 0.8877959

00:45:28.766 --> 00:45:31.460 grow in that kind protein fashion.

NOTE Confidence: 0.8877959

00:45:31.460 --> 00:45:33.294 The whole self seating concept which led

NOTE Confidence: 0.8877959

00:45:33.294 --> 00:45:35.548 us into the concept of fractal geometry,

NOTE Confidence: 0.8877959

00:45:35.550 --> 00:45:38.214 which is now one of my most active areas.

NOTE Confidence: 0.8877959

00:45:38.220 --> 00:45:38.860 Investigation how,

NOTE Confidence: 0.8877959

00:45:38.860 --> 00:45:41.100 how can we actually quantify tills and

NOTE Confidence: 0.8877959

00:45:41.100 --> 00:45:42.900 what is the prognostic significance

NOTE Confidence: 0.8877959

00:45:42.900 --> 00:45:44.680 of them using fractal geometry?

NOTE Confidence: 0.8877959

00:45:44.680 --> 00:45:46.222 How does all of this relate

NOTE Confidence: 0.8877959

00:45:46.222 --> 00:45:46.993 to drug resistance?

NOTE Confidence: 0.8877959

00:45:47.000 --> 00:45:49.075 And optimizing immunotherapy and optimizing

NOTE Confidence: 0.8877959

00:45:49.075 --> 00:45:52.150 new agents such as antibody drug conjugates.

NOTE Confidence: 0.8877959

00:45:52.150 --> 00:45:53.770 Forgive me for speaking too fast,

NOTE Confidence: 0.8877959

00:45:53.770 --> 00:45:55.340 but I I know we have to end on time

NOTE Confidence: 0.8877959

00:45:55.390 --> 00:45:56.830 and thank you all for listening.

NOTE Confidence: 0.8877959

00:45:56.830 --> 00:45:58.475 I apologize that we lost the Internet.

NOTE Confidence: 0.6354031325

00:45:59.770 --> 00:46:00.778 Thank you Larry. That

NOTE Confidence: 0.77946363368421

00:46:00.790 --> 00:46:02.482 was if we have a couple of minutes let

NOTE Confidence: 0.77946363368421

00:46:02.482 --> 00:46:04.285 you know if I can do a couple of talks.

NOTE Confidence: 0.77946363368421

00:46:04.290 --> 00:46:05.658 I can stay later if people want to

NOTE Confidence: 0.6598767775

00:46:05.670 --> 00:46:08.270 stay late. We have a couple of questions.

NOTE Confidence: 0.6598767775

00:46:08.270 --> 00:46:10.476 First of all, thank you so much for you.

NOTE Confidence: 0.6598767775

00:46:10.476 --> 00:46:13.256 Know it just to me. It's amazing for

NOTE Confidence: 0.6598767775

00:46:13.256 --> 00:46:15.914 a Conservatory trained musician to be

NOTE Confidence: 0.6598767775

00:46:15.914 --> 00:46:17.960 such mathematician at the same time,

NOTE Confidence: 0.6598767775

00:46:17.960 --> 00:46:20.057 I don't know how both sides of the border

NOTE Confidence: 0.797828341666667

00:46:20.070 --> 00:46:21.379 link they get. They link together music

NOTE Confidence: 0.797828341666667

00:46:21.379 --> 00:46:23.094 and math is the same, the same the same.

NOTE Confidence: 0.797828341666667

00:46:23.094 --> 00:46:24.420 You know part of the brain. So

NOTE Confidence: 0.726744671428571

00:46:25.440 --> 00:46:27.575 we have some questions from Pat Larussa

NOTE Confidence: 0.726744671428571

00:46:27.575 --> 00:46:29.697 and David Rim to start with there.

NOTE Confidence: 0.726744671428571

00:46:29.700 --> 00:46:31.800 Kind of on the same pattern on

NOTE Confidence: 0.726744671428571

00:46:31.800 --> 00:46:33.240 the fractal pattern differences

NOTE Confidence: 0.726744671428571

00:46:33.240 --> 00:46:35.160 between hormone receptor positive

NOTE Confidence: 0.726744671428571

00:46:35.160 --> 00:46:37.560 and triple negative breast cancer.

NOTE Confidence: 0.726744671428571

00:46:37.560 --> 00:46:38.970 Are there differences that you see

NOTE Confidence: 0.726744671428571

00:46:38.970 --> 00:46:41.107 not only for the tumor, but the tills?

NOTE Confidence: 0.726744671428571

00:46:41.107 --> 00:46:42.841 And then does that work in

NOTE Confidence: 0.726744671428571

00:46:42.841 --> 00:46:44.308 terms of the agency used

NOTE Confidence: 0.81089918

00:46:44.920 --> 00:46:45.185 colleagues?

NOTE Confidence: 0.81089918

00:46:45.185 --> 00:46:46.775 That's what we work in progress,

NOTE Confidence: 0.81089918

00:46:46.780 --> 00:46:48.730 but but the answer is almost

NOTE Confidence: 0.81089918

00:46:48.730 --> 00:46:50.400 certainly so because you know,

NOTE Confidence: 0.81089918

00:46:50.400 --> 00:46:51.990 I'm not doing anything with the

NOTE Confidence: 0.81089918

00:46:51.990 --> 00:46:53.660 fractal geometry that the pathologist,

NOTE Confidence: 0.81089918

00:46:53.660 --> 00:46:55.265 they scope pathologist is doing

NOTE Confidence: 0.81089918

00:46:55.265 --> 00:46:56.706 with their eyes. You know,

NOTE Confidence: 0.81089918

00:46:56.706 --> 00:46:58.134 a skilled pathologist looking and says,

NOTE Confidence: 0.81089918

00:46:58.140 --> 00:46:59.300 hey, this is well differentiated.

NOTE Confidence: 0.81089918

00:46:59.300 --> 00:47:01.100 This poor differentiated differentiation.

NOTE Confidence: 0.81089918

00:47:01.100 --> 00:47:02.900 Is poor differentiated means

NOTE Confidence: 0.81089918

00:47:02.900 --> 00:47:04.910 a high fractal dimension,

NOTE Confidence: 0.81089918

00:47:04.910 --> 00:47:06.394 whereas a well differentiated

NOTE Confidence: 0.81089918

00:47:06.394 --> 00:47:08.249 means a low fractal dimension?

NOTE Confidence: 0.81089918

00:47:08.250 --> 00:47:10.125 And so basically I'm just

NOTE Confidence: 0.81089918

00:47:10.125 --> 00:47:11.250 basically just quantifying.

NOTE Confidence: 0.81089918

00:47:11.250 --> 00:47:13.266 I'm quantifying something that that the eyes

NOTE Confidence: 0.81089918

00:47:13.266 --> 00:47:15.426 of the beholder have seen is seen already.

NOTE Confidence: 0.81089918

00:47:15.430 --> 00:47:17.260 So clearly we're gonna see this.

NOTE Confidence: 0.81089918

00:47:17.260 --> 00:47:18.616 But you're talking here about fractional

NOTE Confidence: 0.81089918

00:47:18.616 --> 00:47:19.770 dimension of the cancer cells,

NOTE Confidence: 0.81089918

00:47:19.770 --> 00:47:21.858 which is obviously something we're exploring.

NOTE Confidence: 0.81089918

00:47:21.860 --> 00:47:23.145 I was talking about fractal

NOTE Confidence: 0.81089918

00:47:23.145 --> 00:47:24.790 dimension of of of the tills,

NOTE Confidence: 0.81089918

00:47:24.790 --> 00:47:27.445 but it all relates together and and I think

NOTE Confidence: 0.81089918

00:47:27.445 --> 00:47:29.830 what makes it really intriguing to me.

NOTE Confidence: 0.81089918

00:47:29.830 --> 00:47:30.462 Just personally,

NOTE Confidence: 0.81089918

00:47:30.462 --> 00:47:32.049 maybe nobody else, but to me.

NOTE Confidence: 0.81089918

00:47:32.049 --> 00:47:33.327 Is that it relates to this

NOTE Confidence: 0.81089918

00:47:33.327 --> 00:47:34.687 concept of a pattern of growth?

NOTE Confidence: 0.81089918

00:47:34.690 --> 00:47:36.538 This self seeding pattern of growth?

NOTE Confidence: 0.81089918

00:47:36.540 --> 00:47:39.015 One thing you gotta know about math is that

NOTE Confidence: 0.81089918

00:47:39.015 --> 00:47:41.687 you know even if self seeding didn't happen.

NOTE Confidence: 0.81089918

00:47:41.690 --> 00:47:44.406 If if things anatomically look the way

NOTE Confidence: 0.81089918

00:47:44.406 --> 00:47:46.890 they would happen were it to happen,

NOTE Confidence: 0.81089918

00:47:46.890 --> 00:47:49.420 it still is biologically significant.

NOTE Confidence: 0.81089918

00:47:49.420 --> 00:47:50.842 That's that's the way that's the

NOTE Confidence: 0.81089918

00:47:50.842 --> 00:47:52.160 way math mathematics works alright.

NOTE Confidence: 0.81089918

00:47:52.160 --> 00:47:53.396 You don't have to have the

NOTE Confidence: 0.81089918

00:47:53.396 --> 00:47:54.619 the example you know the the.

NOTE Confidence: 0.81089918

00:47:54.620 --> 00:47:56.550 The same mathematics works for

NOTE Confidence: 0.81089918

00:47:56.550 --> 00:47:58.094 gravity and for magnetism,

NOTE Confidence: 0.81089918

00:47:58.100 --> 00:48:00.038 even though the mechanisms are different,

NOTE Confidence: 0.81089918

00:48:00.040 --> 00:48:01.200 we don't understand the mechanisms,

NOTE Confidence: 0.81089918

00:48:01.200 --> 00:48:02.696 but we know they're different at the same,

NOTE Confidence: 0.81089918

00:48:02.700 --> 00:48:03.660 the same, the same.

NOTE Confidence: 0.81089918

00:48:03.660 --> 00:48:04.140 The same.

NOTE Confidence: 0.81089918

00:48:04.140 --> 00:48:05.260 You know the same mathematics

NOTE Confidence: 0.81089918

00:48:05.260 --> 00:48:07.010 you know works for the theory of

NOTE Confidence: 0.81089918

00:48:07.010 --> 00:48:08.460 universal gravitation works the same.

NOTE Confidence: 0.81089918

00:48:08.460 --> 00:48:10.164 So so once we actually understand

NOTE Confidence: 0.81089918

00:48:10.164 --> 00:48:11.016 the mathematical principles,

NOTE Confidence: 0.81089918

00:48:11.020 --> 00:48:12.352 they can generalize even if the

NOTE Confidence: 0.81089918

00:48:12.352 --> 00:48:14.355 thing that got us into that which is

NOTE Confidence: 0.81089918

00:48:14.355 --> 00:48:15.690 substituting concept is not valid.

NOTE Confidence: 0.81089918

00:48:15.690 --> 00:48:17.944 But I really do think the self

NOTE Confidence: 0.81089918

00:48:17.944 --> 00:48:19.390 seeding thing is valid.

NOTE Confidence: 0.81089918

00:48:19.390 --> 00:48:20.776 But based on the on the accumulating

NOTE Confidence: 0.81089918

00:48:20.776 --> 00:48:22.090 body of evidence that we're seeing,

NOTE Confidence: 0.81089918

00:48:22.090 --> 00:48:23.155 so I'm just basically trying

NOTE Confidence: 0.81089918

00:48:23.155 --> 00:48:23.794 to quantify that.

NOTE Confidence: 0.879511855652174

00:48:24.960 --> 00:48:26.820 Thank you we have another question

NOTE Confidence: 0.879511855652174

00:48:26.820 --> 00:48:28.792 on the implications of Gumpertz and

NOTE Confidence: 0.879511855652174

00:48:28.792 --> 00:48:30.814 growth for the rate of survival

NOTE Confidence: 0.879511855652174

00:48:30.814 --> 00:48:32.419 and proliferation of cancer cells.

NOTE Confidence: 0.879511855652174

00:48:32.420 --> 00:48:34.592 What are there implications and then

NOTE Confidence: 0.879511855652174

00:48:34.592 --> 00:48:37.430 does it imply that proliferation slows?

NOTE Confidence: 0.879511855652174

00:48:37.430 --> 00:48:39.866 And if so, why are the clinical

NOTE Confidence: 0.879511855652174

00:48:39.866 --> 00:48:41.920 implications of that slowed growth?

NOTE Confidence: 0.879511855652174

00:48:41.920 --> 00:48:42.070 All

NOTE Confidence: 0.641229542166667

00:48:42.080 --> 00:48:43.742 right? You know, you're asking for

NOTE Confidence: 0.641229542166667

00:48:43.742 --> 00:48:45.400 treatise and a little bit comma,

NOTE Confidence: 0.641229542166667

00:48:45.400 --> 00:48:47.311 and I wrote a really nice review

NOTE Confidence: 0.641229542166667

00:48:47.311 --> 00:48:48.878 article about the clinical implications

NOTE Confidence: 0.641229542166667

00:48:48.878 --> 00:48:51.300 of cancer self seating so you know,

NOTE Confidence: 0.641229542166667

00:48:51.300 --> 00:48:51.852 COMEN and Norton.

NOTE Confidence: 0.641229542166667

00:48:51.852 --> 00:48:53.619 You can Google it and go with that paper.

NOTE Confidence: 0.641229542166667

00:48:53.620 --> 00:48:55.260 Really, really, really very quickly.

NOTE Confidence: 0.641229542166667

00:48:55.260 --> 00:48:56.970 When we go into all that in great depth,

NOTE Confidence: 0.641229542166667

00:48:56.970 --> 00:48:57.654 first of all,

NOTE Confidence: 0.641229542166667

00:48:57.654 --> 00:48:59.022 gun person growth has to happen.

NOTE Confidence: 0.641229542166667

00:48:59.030 --> 00:49:00.892 'cause if it didn't happen we we

NOTE Confidence: 0.641229542166667

00:49:00.892 --> 00:49:03.008 would have no chance against cancer

NOTE Confidence: 0.641229542166667

00:49:03.008 --> 00:49:04.610 because with exponential growth I

NOTE Confidence: 0.641229542166667

00:49:04.610 --> 00:49:06.380 mean from the time of diagnosis,

NOTE Confidence: 0.641229542166667

00:49:06.380 --> 00:49:08.800 time of death would be a matter of of of

NOTE Confidence: 0.641229542166667

00:49:08.866 --> 00:49:11.226 of weeks at even even for solid tumors.

NOTE Confidence: 0.641229542166667

00:49:11.230 --> 00:49:12.878 So we know there's gotta be a tailing

NOTE Confidence: 0.641229542166667

00:49:12.878 --> 00:49:14.764 off of growth rates and it really

NOTE Confidence: 0.641229542166667

00:49:14.764 --> 00:49:15.904 has great profound implications

NOTE Confidence: 0.641229542166667

00:49:15.904 --> 00:49:17.509 in terms of our understanding,

NOTE Confidence: 0.641229542166667

00:49:17.510 --> 00:49:20.478 growth and and and planning for therapy.

NOTE Confidence: 0.641229542166667

00:49:20.480 --> 00:49:22.181 I I think it's a shame that we haven't

NOTE Confidence: 0.641229542166667

00:49:22.181 --> 00:49:23.617 used those dense sequential therapy

NOTE Confidence: 0.641229542166667

00:49:23.617 --> 00:49:25.411 for more tumors beside breast cancer.

NOTE Confidence: 0.641229542166667

00:49:25.420 --> 00:49:26.792 There's been a little bit of work

NOTE Confidence: 0.641229542166667

00:49:26.792 --> 00:49:27.900 in lymphomas in this regard.

NOTE Confidence: 0.641229542166667

00:49:27.900 --> 00:49:29.108 A little bit of work in other tumors,

NOTE Confidence: 0.641229542166667

00:49:29.110 --> 00:49:31.036 but we haven't optimally exploited it,

NOTE Confidence: 0.641229542166667

00:49:31.040 --> 00:49:32.321 and I think that we could actually

NOTE Confidence: 0.641229542166667

00:49:32.321 --> 00:49:33.461 do better even with existing agents

NOTE Confidence: 0.641229542166667

00:49:33.461 --> 00:49:35.231 if we were able to take some of the

NOTE Confidence: 0.641229542166667

00:49:35.231 --> 00:49:36.575 principles we learned with breast cancer,

NOTE Confidence: 0.641229542166667

00:49:36.580 --> 00:49:38.260 move them into that setting.

NOTE Confidence: 0.641229542166667

00:49:38.260 --> 00:49:40.018 But right now where I'm focusing

NOTE Confidence: 0.641229542166667

00:49:40.018 --> 00:49:40.897 in on instead,

NOTE Confidence: 0.641229542166667

00:49:40.900 --> 00:49:42.930 is how do we use some of the newer agents,

NOTE Confidence: 0.641229542166667

00:49:42.930 --> 00:49:43.624 particularly Adcs,

NOTE Confidence: 0.641229542166667

00:49:43.624 --> 00:49:46.053 and apply some of the things we've

NOTE Confidence: 0.641229542166667

00:49:46.053 --> 00:49:47.785 learned from chemotherapy to it

NOTE Confidence: 0.641229542166667

00:49:47.785 --> 00:49:49.765 using gun protein growth and using

NOTE Confidence: 0.641229542166667

00:49:49.829 --> 00:49:51.709 our concepts with tumor geometry.

NOTE Confidence: 0.870274622

00:49:53.370 --> 00:49:57.390 And maybe the last question is from

NOTE Confidence: 0.870274622

00:49:57.390 --> 00:49:59.150 Doctor Bafan. Thoracic surgery?

NOTE Confidence: 0.870274622

00:49:59.150 --> 00:50:01.691 Is the self seating limited to cancer

NOTE Confidence: 0.870274622

00:50:01.691 --> 00:50:04.832 cells or do other employee put in stem

NOTE Confidence: 0.870274622

00:50:04.832 --> 00:50:07.270 cells from normal cellular turnover,

NOTE Confidence: 0.870274622

00:50:07.270 --> 00:50:09.310 preferentially land and tumors,

NOTE Confidence: 0.870274622

00:50:09.310 --> 00:50:13.986 for example to gastro intestinal stem cells?

NOTE Confidence: 0.870274622

00:50:13.990 --> 00:50:16.474 Go on to blood, still some lines and other.

NOTE Confidence: 0.707112316

00:50:16.580 --> 00:50:17.550 Yeah, it's a great question.

NOTE Confidence: 0.707112316

00:50:17.550 --> 00:50:19.182 It's a great question because it's

NOTE Confidence: 0.707112316

00:50:19.182 --> 00:50:21.100 something that that that we are on verbal.

NOTE Confidence: 0.707112316

00:50:21.100 --> 00:50:22.647 Yeah, stem cells and seeds I think

NOTE Confidence: 0.707112316

00:50:22.647 --> 00:50:23.939 is the same thing. Basically,

NOTE Confidence: 0.707112316

00:50:23.939 --> 00:50:26.251 I think that's the capacity of stem cells

NOTE Confidence: 0.707112316

00:50:26.251 --> 00:50:28.384 is being able to move around and and.

NOTE Confidence: 0.707112316

00:50:28.390 --> 00:50:29.685 And frankly it's not such a stretch.

NOTE Confidence: 0.707112316

00:50:29.690 --> 00:50:31.286 'cause that's what happens in Embryology.

NOTE Confidence: 0.707112316

00:50:31.290 --> 00:50:32.490 I mean, that's that's how

NOTE Confidence: 0.707112316

00:50:32.490 --> 00:50:33.450 the embryo forms is,

NOTE Confidence: 0.707112316

00:50:33.450 --> 00:50:35.130 that is that the the stem cells move

NOTE Confidence: 0.707112316

00:50:35.130 --> 00:50:36.809 from one spot to another in a very,

NOTE Confidence: 0.707112316

00:50:36.810 --> 00:50:38.970 very logical kind of fashion.

NOTE Confidence: 0.707112316

00:50:38.970 --> 00:50:40.035 It isn't that and people

NOTE Confidence: 0.707112316

00:50:40.035 --> 00:50:41.100 always ask that you know,

NOTE Confidence: 0.707112316

00:50:41.100 --> 00:50:43.089 you know what draws them self to that site.

NOTE Confidence: 0.707112316

00:50:43.090 --> 00:50:44.530 It isn't drawn to that site.

NOTE Confidence: 0.707112316

00:50:44.530 --> 00:50:46.123 We know this from this from the self seeding

NOTE Confidence: 0.707112316

00:50:46.123 --> 00:50:47.608 work that's been done in the laboratory.

NOTE Confidence: 0.707112316

00:50:47.610 --> 00:50:49.532 The cells go all over, it's just

NOTE Confidence: 0.707112316

00:50:49.532 --> 00:50:51.008 where they stick that really matters.

NOTE Confidence: 0.707112316

00:50:51.010 --> 00:50:52.490 So it looks like it's drawn to that

NOTE Confidence: 0.707112316

00:50:52.490 --> 00:50:54.054 site only 'cause they stuck there and

NOTE Confidence: 0.707112316

00:50:54.054 --> 00:50:55.490 and it's that sticking their stickiness

NOTE Confidence: 0.707112316

00:50:55.490 --> 00:50:57.156 that I think is something that that

NOTE Confidence: 0.707112316

00:50:57.156 --> 00:50:59.380 that that's being scored by a number

NOTE Confidence: 0.707112316

00:50:59.380 --> 00:51:02.370 of by a number of investigators.

NOTE Confidence: 0.707112316

00:51:02.370 --> 00:51:04.550 You know that particular phenomenon,

NOTE Confidence: 0.707112316

00:51:04.550 --> 00:51:05.985 but I'm sure this happens in general.

NOTE Confidence: 0.707112316

00:51:05.990 --> 00:51:06.858 Look at wound healing.

NOTE Confidence: 0.707112316

00:51:06.858 --> 00:51:07.726 I mean wound healing.

NOTE Confidence: 0.707112316

00:51:07.730 --> 00:51:08.810 You know you heal your wound,

NOTE Confidence: 0.707112316

00:51:08.810 --> 00:51:09.212 your surgeons,

NOTE Confidence: 0.707112316

00:51:09.212 --> 00:51:10.820 you don't heal your wound because of the

NOTE Confidence: 0.707112316

00:51:10.861 --> 00:51:12.508 cells that are right there where you cut you.

NOTE Confidence: 0.707112316

00:51:12.510 --> 00:51:13.650 The cells are brought in there,

NOTE Confidence: 0.707112316

00:51:13.650 --> 00:51:13.992 you know,

NOTE Confidence: 0.707112316

00:51:13.992 --> 00:51:15.018 married to rod cells are brought

NOTE Confidence: 0.707112316

00:51:15.018 --> 00:51:16.169 in there and that's what allows.

NOTE Confidence: 0.707112316

00:51:16.170 --> 00:51:17.980 The wound to heal so that so that I I

NOTE Confidence: 0.707112316

00:51:18.031 --> 00:51:19.705 think seating is a general biological

NOTE Confidence: 0.707112316

00:51:19.705 --> 00:51:21.847 phenomena and a lot of things that we're

NOTE Confidence: 0.707112316

00:51:21.847 --> 00:51:23.762 doing in cancer may relate to other things,

NOTE Confidence: 0.707112316

00:51:23.762 --> 00:51:25.364 such As for instance, wound healing.

NOTE Confidence: 0.707112316

00:51:25.364 --> 00:51:26.078 Uhm, uh,

NOTE Confidence: 0.707112316

00:51:26.078 --> 00:51:28.850 that that we're starting to think you know,

NOTE Confidence: 0.707112316

00:51:28.850 --> 00:51:30.848 you know about the cytokine release

NOTE Confidence: 0.707112316

00:51:30.848 --> 00:51:32.989 syndrome that we're seeing with COVID-19,

NOTE Confidence: 0.707112316

00:51:32.990 --> 00:51:34.398 and how that relates to the mobility of

NOTE Confidence: 0.707112316

00:51:34.398 --> 00:51:36.168 of of white cells in that regard as well.

NOTE Confidence: 0.707112316

00:51:36.170 --> 00:51:37.118 In response to inflammation.

NOTE Confidence: 0.707112316

00:51:37.118 --> 00:51:38.968 So so it may be a much

NOTE Confidence: 0.707112316

00:51:38.968 --> 00:51:40.090 more general phenomenon.

NOTE Confidence: 0.707112316

00:51:40.090 --> 00:51:41.280 The cool thing for me,

NOTE Confidence: 0.707112316

00:51:41.280 --> 00:51:41.596 and again,

NOTE Confidence: 0.707112316

00:51:41.596 --> 00:51:42.386 I'm just speaking for me,

NOTE Confidence: 0.707112316

00:51:42.390 --> 00:51:43.515 is that the mathematics we

NOTE Confidence: 0.707112316

00:51:43.515 --> 00:51:44.913 workout in one area may relate

NOTE Confidence: 0.707112316

00:51:44.913 --> 00:51:46.488 to all these other areas as well.

NOTE Confidence: 0.707112316

00:51:46.490 --> 00:51:47.680 And that once we understand,

NOTE Confidence: 0.707112316

00:51:47.680 --> 00:51:48.984 developed these mathematical principles,

NOTE Confidence: 0.707112316

00:51:48.984 --> 00:51:51.621 that we can actually use them to generalize

NOTE Confidence: 0.707112316

00:51:51.621 --> 00:51:53.186 beyond cancer into heart disease.

NOTE Confidence: 0.707112316

00:51:53.190 --> 00:51:55.647 We know that colonial meta polices cells

NOTE Confidence: 0.707112316

00:51:55.647 --> 00:51:57.402 are are important in arteriosclerotic

NOTE Confidence: 0.707112316

00:51:57.402 --> 00:51:59.962 heart disease as well as as as we

NOTE Confidence: 0.707112316

00:52:00.031 --> 00:52:02.149 just discussed with cancer as well,

NOTE Confidence: 0.707112316

00:52:02.150 --> 00:52:03.866 so that these principles may generalize

NOTE Confidence: 0.707112316

00:52:03.866 --> 00:52:06.300 and and and have much more replicability.

NOTE Confidence: 0.669345702166667

00:52:06.770 --> 00:52:08.450 Can we squeeze one more question.

NOTE Confidence: 0.669345702166667

00:52:08.450 --> 00:52:10.500 This is from an Chang former

NOTE Confidence: 0.669345702166667

00:52:10.500 --> 00:52:12.250 memorial colleague who are now

NOTE Confidence: 0.669345702166667

00:52:12.250 --> 00:52:13.650 our Chief Network Officer.

NOTE Confidence: 0.669345702166667

00:52:13.650 --> 00:52:15.966 She's asked, can we exploit Atascosa

NOTE Confidence: 0.669345702166667

00:52:15.966 --> 00:52:18.534 specific or other gene processes in

NOTE Confidence: 0.669345702166667

00:52:18.534 --> 00:52:20.919 the tumor microenvironment to prevent?

NOTE Confidence: 0.669345702166667

00:52:20.920 --> 00:52:22.810 Self seating in the niche of growth.

NOTE Confidence: 0.797651765

00:52:23.220 --> 00:52:25.140 Yeah yeah, great another great question.

NOTE Confidence: 0.797651765

00:52:25.140 --> 00:52:26.188 Another great hot topic.

NOTE Confidence: 0.797651765

00:52:26.188 --> 00:52:27.900 You know something that Joe and I,

NOTE Confidence: 0.797651765

00:52:27.900 --> 00:52:28.542 Joe and Megan.

NOTE Confidence: 0.797651765

00:52:28.542 --> 00:52:30.332 I thought a very early days when we

NOTE Confidence: 0.797651765

00:52:30.332 --> 00:52:31.778 started doing this when we started

NOTE Confidence: 0.797651765

00:52:31.778 --> 00:52:33.507 doing this work and I remember that

NOTE Confidence: 0.797651765

00:52:33.507 --> 00:52:34.905 we published the paper with 2009,

NOTE Confidence: 0.797651765

00:52:34.905 --> 00:52:36.545 so it's been a lot of time this

NOTE Confidence: 0.797651765

00:52:36.545 --> 00:52:38.017 past and and and and you know,

NOTE Confidence: 0.797651765

00:52:38.020 --> 00:52:40.008 we know that that that cytokines in

NOTE Confidence: 0.797651765

00:52:40.008 --> 00:52:41.212 flammatory cytokines are important

NOTE Confidence: 0.797651765

00:52:41.212 --> 00:52:43.030 for the process and that's already

NOTE Confidence: 0.797651765

00:52:43.030 --> 00:52:44.518 that's already been demonstrated and

NOTE Confidence: 0.797651765

00:52:44.518 --> 00:52:46.373 that may be why inflammation is is

NOTE Confidence: 0.797651765

00:52:46.373 --> 00:52:47.996 such a problem is related to cancer.

NOTE Confidence: 0.797651765

00:52:48.000 --> 00:52:49.528 But I want to get the things that

NOTE Confidence: 0.797651765

00:52:49.528 --> 00:52:50.909 are more targetable than that.

NOTE Confidence: 0.797651765

00:52:50.910 --> 00:52:52.618 And so that's one of the reasons

NOTE Confidence: 0.797651765

00:52:52.618 --> 00:52:54.750 why that very last slide that I

NOTE Confidence: 0.797651765

00:52:54.750 --> 00:52:56.425 showed you that very complicated

NOTE Confidence: 0.797651765

00:52:56.425 --> 00:52:57.929 mathematical slide is is is we we,

NOTE Confidence: 0.797651765

00:52:57.930 --> 00:53:00.274 we are right now doing a number of

NOTE Confidence: 0.797651765

00:53:00.274 --> 00:53:02.110 different studies looking at gene

NOTE Confidence: 0.797651765

00:53:02.110 --> 00:53:03.690 interactive networks using the

NOTE Confidence: 0.797651765

00:53:03.690 --> 00:53:05.560 same basic mathematical principles.

NOTE Confidence: 0.797651765

00:53:05.560 --> 00:53:06.130 In fact,

NOTE Confidence: 0.797651765

00:53:06.130 --> 00:53:08.125 trying to see what are the gene

NOTE Confidence: 0.797651765

00:53:08.125 --> 00:53:10.036 interactions that may may underlie that

NOTE Confidence: 0.797651765

00:53:10.036 --> 00:53:11.946 process, because that will tell us what,

NOTE Confidence: 0.797651765

00:53:11.950 --> 00:53:12.326 what,

NOTE Confidence: 0.797651765

00:53:12.326 --> 00:53:14.206 what genes we maybe have

NOTE Confidence: 0.797651765

00:53:14.206 --> 00:53:15.334 development chemicals to,

NOTE Confidence: 0.797651765

00:53:15.340 --> 00:53:17.030 medicines to to be able to be able to target,

NOTE Confidence: 0.797651765

00:53:17.030 --> 00:53:18.186 to interfere with this,

NOTE Confidence: 0.797651765

00:53:18.186 --> 00:53:19.920 the just there's something in that

NOTE Confidence: 0.797651765

00:53:19.974 --> 00:53:21.864 regard I think is is really important.

NOTE Confidence: 0.797651765

00:53:21.870 --> 00:53:22.328 Is that?

NOTE Confidence: 0.797651765

00:53:22.328 --> 00:53:24.160 We focused on so much of our energy

NOTE Confidence: 0.797651765

00:53:24.212 --> 00:53:26.018 in terms of medicinal chemistry on

NOTE Confidence: 0.797651765

00:53:26.018 --> 00:53:27.750 targeting genes or gene products,

NOTE Confidence: 0.797651765

00:53:27.750 --> 00:53:29.478 and one of the things we're learning by

NOTE Confidence: 0.797651765

00:53:29.478 --> 00:53:31.041 using that mathematics and looking at

NOTE Confidence: 0.797651765

00:53:31.041 --> 00:53:32.890 gene interaction networks is this is yes,

NOTE Confidence: 0.797651765

00:53:32.890 --> 00:53:35.305 indeed is the action of individual genes,

NOTE Confidence: 0.797651765

00:53:35.310 --> 00:53:36.594 but it's not the action of

NOTE Confidence: 0.797651765

00:53:36.594 --> 00:53:37.450 individual genes by themselves.

NOTE Confidence: 0.797651765

00:53:37.450 --> 00:53:39.208 They're all interacting with each other,

NOTE Confidence: 0.797651765

00:53:39.210 --> 00:53:41.100 and it's the whole network of

NOTE Confidence: 0.797651765

00:53:41.100 --> 00:53:43.112 genes that actually forms a a

NOTE Confidence: 0.797651765

00:53:43.112 --> 00:53:44.488 meaningful biological entity and

NOTE Confidence: 0.797651765

00:53:44.488 --> 00:53:46.270 not just the individual genes.

NOTE Confidence: 0.797651765

00:53:46.270 --> 00:53:48.167 So we're going to have to target

NOTE Confidence: 0.797651765

00:53:48.170 --> 00:53:49.642 target those interactions rather

NOTE Confidence: 0.797651765

00:53:49.642 --> 00:53:51.482 than target the genes themselves,

NOTE Confidence: 0.797651765

00:53:51.490 --> 00:53:53.275 and that's not something that we commonly.

NOTE Confidence: 0.797651765

00:53:53.280 --> 00:53:53.834 Do you?

NOTE Confidence: 0.797651765

00:53:53.834 --> 00:53:55.496 Although we we probably do it,

NOTE Confidence: 0.797651765

00:53:55.500 --> 00:53:57.166 we don't realize we do it with

NOTE Confidence: 0.797651765

00:53:57.166 --> 00:53:57.880 with with therapy.

NOTE Confidence: 0.797651765

00:53:57.880 --> 00:53:59.644 When you give steroids to a patient

NOTE Confidence: 0.797651765

00:53:59.644 --> 00:54:01.657 for all the reasons that we give

NOTE Confidence: 0.797651765

00:54:01.657 --> 00:54:03.457 Google Corticoids for a patient you

NOTE Confidence: 0.797651765

00:54:03.517 --> 00:54:05.287 you're attaching to Google Corticoid

NOTE Confidence: 0.797651765

00:54:05.287 --> 00:54:07.057 receptors all over the place,

NOTE Confidence: 0.797651765

00:54:07.060 --> 00:54:08.620 not just in a particular place,

NOTE Confidence: 0.797651765

00:54:08.620 --> 00:54:09.824 and you're basically affecting

NOTE Confidence: 0.797651765

00:54:09.824 --> 00:54:11.329 cell cell interactions all over

NOTE Confidence: 0.797651765

00:54:11.329 --> 00:54:12.863 the place and you're affecting

NOTE Confidence: 0.797651765

00:54:12.863 --> 00:54:14.343 gene interaction networks all over

NOTE Confidence: 0.797651765

00:54:14.343 --> 00:54:16.084 the place by using some of the

NOTE Confidence: 0.797651765

00:54:16.084 --> 00:54:17.822 most powerful drugs that we have

NOTE Confidence: 0.797651765

00:54:17.822 --> 00:54:19.827 actually are not targeted therapy,

NOTE Confidence: 0.797651765

00:54:19.830 --> 00:54:21.720 it's starting to question the notion of

NOTE Confidence: 0.797651765

00:54:21.720 --> 00:54:23.928 are we really better off using targeted

NOTE Confidence: 0.797651765

00:54:23.928 --> 00:54:25.944 therapy when we're dealing with complex?

NOTE Confidence: 0.797651765

00:54:25.950 --> 00:54:28.778 Processes or should we be able to

NOTE Confidence: 0.797651765

00:54:28.778 --> 00:54:30.968 target the complexity itself so so

NOTE Confidence: 0.797651765

00:54:30.968 --> 00:54:32.571 that's one of the things that we're

NOTE Confidence: 0.797651765

00:54:32.571 --> 00:54:34.308 zeroing in on on that particular thing.

NOTE Confidence: 0.797651765

00:54:34.310 --> 00:54:34.547 Now,

NOTE Confidence: 0.797651765

00:54:34.547 --> 00:54:37.092 how do we find those drugs is is that?

NOTE Confidence: 0.797651765

00:54:37.092 --> 00:54:37.466 Basically,

NOTE Confidence: 0.797651765

00:54:37.466 --> 00:54:40.310 if you understand the networks and you can,

NOTE Confidence: 0.797651765

00:54:40.310 --> 00:54:42.081 you could then screen a lot of

NOTE Confidence: 0.797651765

00:54:42.081 --> 00:54:43.572 different drugs and see how it

NOTE Confidence: 0.797651765

00:54:43.572 --> 00:54:45.161 affects the network and so you can

NOTE Confidence: 0.863095656666667

00:54:45.219 --> 00:54:47.060 actually as as possible that even old

NOTE Confidence: 0.863095656666667

00:54:47.060 --> 00:54:48.742 drugs could be repurposed for this reason.

NOTE Confidence: 0.863095656666667

00:54:48.742 --> 00:54:50.764 And you may not be able to put your

NOTE Confidence: 0.863095656666667

00:54:50.764 --> 00:54:52.042 finger on exactly why they work,

NOTE Confidence: 0.863095656666667

00:54:52.050 --> 00:54:53.160 but you could just show that

NOTE Confidence: 0.863095656666667

00:54:53.160 --> 00:54:54.290 they are working in the show.

NOTE Confidence: 0.863095656666667

00:54:54.290 --> 00:54:55.574 They have clinical utility.

NOTE Confidence: 0.863095656666667

00:54:55.574 --> 00:54:57.500 And and and that's that's really

NOTE Confidence: 0.863095656666667

00:54:57.559 --> 00:54:59.659 kind of a very different way of

NOTE Confidence: 0.863095656666667

00:54:59.659 --> 00:55:01.150 thinking about medicinal chemistry.

NOTE Confidence: 0.863095656666667

00:55:01.150 --> 00:55:02.326 Rather than saying I,

NOTE Confidence: 0.863095656666667

00:55:02.326 --> 00:55:04.090 I'm gonna go after the specific

NOTE Confidence: 0.863095656666667

00:55:04.153 --> 00:55:06.003 target to actually go after

NOTE Confidence: 0.863095656666667

00:55:06.003 --> 00:55:07.483 basically the biological effect.

NOTE Confidence: 0.863095656666667

00:55:07.490 --> 00:55:08.069 Or you know,

NOTE Confidence: 0.863095656666667

00:55:08.069 --> 00:55:09.227 in in general with your agents

NOTE Confidence: 0.863095656666667

00:55:09.227 --> 00:55:10.646 and then and then move them into

NOTE Confidence: 0.863095656666667

00:55:10.646 --> 00:55:11.850 clinic on that kind of basis.

NOTE Confidence: 0.863095656666667

00:55:11.850 --> 00:55:13.050 So those are some of the things that

NOTE Confidence: 0.863095656666667

00:55:13.050 --> 00:55:13.858 we're thinking about right now.

NOTE Confidence: 0.841433167142857

00:55:14.800 --> 00:55:15.457 Thank you Larry.

NOTE Confidence: 0.841433167142857

00:55:15.457 --> 00:55:16.771 This is been really great and

NOTE Confidence: 0.841433167142857

00:55:16.771 --> 00:55:18.300 we really appreciate your time.

NOTE Confidence: 0.841433167142857

00:55:18.300 --> 00:55:20.442 I know next year Eric will want

NOTE Confidence: 0.841433167142857

00:55:20.442 --> 00:55:22.658 to have you here in person again

NOTE Confidence: 0.841433167142857

00:55:22.658 --> 00:55:25.563 to talk to us and this was really

NOTE Confidence: 0.841433167142857

00:55:25.563 --> 00:55:27.057 just phenomenal lecture.

NOTE Confidence: 0.841433167142857

00:55:27.060 --> 00:55:27.884 Even though you dropped

NOTE Confidence: 0.841433167142857

00:55:27.884 --> 00:55:28.914 off for a few minutes,

NOTE Confidence: 0.841433167142857

00:55:28.920 --> 00:55:30.584 if you were able to bring everything back

NOTE Confidence: 0.796250152857143

00:55:30.850 --> 00:55:32.194 and and and please thank thank

NOTE Confidence: 0.796250152857143

00:55:32.194 --> 00:55:33.448 the person who actually called me

NOTE Confidence: 0.796250152857143

00:55:33.448 --> 00:55:35.176 on my cell phone so that I they

NOTE Confidence: 0.796250152857143

00:55:35.180 --> 00:55:36.647 got to me so I was able to come

NOTE Confidence: 0.796250152857143

00:55:36.647 --> 00:55:37.819 back in I I appreciate it.

NOTE Confidence: 0.796250152857143

00:55:37.820 --> 00:55:38.828 Thank you all very much for

NOTE Confidence: 0.8540798

00:55:38.840 --> 00:55:40.288 listening. Thank you Larry.