You can see it. Fred.

So with no further ado on behalf of Doctor Nita, Hoosier Interim Cancer Center director, and actually this time next week, your good friend Doctor Eric Wyner will be sitting in that position as our permanent director. We're really excited to have you here, even though it's not in person, as the Julia Patricia Kingsbury Memorial lecturer and lectureship that's been sponsored for.
You know well over 2 decades by their family for me to introduce. Doctor Norton is like. Introducing a Rockstar. Obviously he’s a senior vice president in the office of the President, Memorial Sloan Kettering, the medical director of the Evelyn Lauder Breast Center. I think you’re also the founding and incumbent N Norna Serafin and incumbent N Norna Serafin. Career started, you know, undergraduate and undergraduate at Rochester, 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,
and then you know more recently in the last decade you know being involved with the breast Cancer Research Foundation, which you and Evelyn Lauder, the late Evelyn Lauder, and Leonard Lauder, you know, put together really bringing over 200, probably close to 300 of the world’s leading investigators and breast Cancer Research. Really, for the cure, as defined as the founding scientific director. Gosh,
00:01:53.074 --> 00:01:54.450 this is such a.
00:01:54.450 --> 00:01:56.880 A great day for for a Yale and I
00:01:56.880 --> 00:01:58.915 know everyone is really excited
00:02:00.740 --> 00:02:01.860 to hear your thoughts on the
00:02:00.740 --> 00:02:01.860 nature of breast neoplasia.
00:02:01.860 --> 00:02:04.173 So thank you Doctor Norton
00:02:03.145 --> 00:02:04.173 for making the time.
00:02:04.360 --> 00:02:06.054 OK, thank you. Thank you very much.
00:02:06.060 --> 00:02:08.067 I hope everybody can hear me and thank you
00:02:08.067 --> 00:02:10.239 for that really very gracious introduction.
00:02:10.240 --> 00:02:12.864 You know it’s a it’s totally shame.
00:02:12.870 --> 00:02:14.274 In the old days when you give a lecture
00:02:14.274 --> 00:02:15.624 ship like this, you’d come in person.
00:02:15.624 --> 00:02:17.192 You’d have a dinner you’d meet with a
00:02:17.192 --> 00:02:19.222 lot of people, one on one, and so many
of my great interactions in my career

started really by those kinds of events.

And so it’s a. It’s a shame that

we have to do this electronically.

But it’s a great pleasure to be

here and and speak with you.

I’m, you know,

my neighbors in the Northeast about some of

the things that that I’ve been thinking of.

What I’ve been doing,

it’s called mathematical insights,

but for those of you who are math phobic,

please don’t don’t run away screaming.

You know it’s a.

I’m only going to show one equation,

and it’s not important really for the talk.
Basically, it is mathematical thinking and a lot of people don’t know math. Don’t realize that what math is not the equations. The equivalency would be sheet music for music. The sheet music is not the music, it’s the sound. And and with mathematics it’s the insights that you gain which you know in terms of how things. In this case, how they grow, how they shrink, why they grow that way and and so on, how we take advantage of that.
The equations are not really the mathematics for many years when I was giving this talk I skipped over a lot of the early stuff that I did, but then I realized a few years back that really stuff is really very important for understanding the later things that we're doing. That really stuff is really very important for understanding the later things that we're doing. So I am going to be talking about it. It really happened to me a bunch of years already that I was a visiting professor and somebody presented a case and said this patient dose.
Dense chemotherapy with AC and Taxol, Dr. Ordinary familiar with that regimen. And that’s when I realized that perhaps I should really cover some of the early things that I’ve done and how it relates to the bigger picture. So I’m going to talk. About growth models and the premier growth model being from Howard skipper, I’ll talk about the work that I did in the 70s interpreting that growth model with the appreciation for understanding a different pattern of
the way that cancers grow than how it
skipper and colleagues had shown.
How it led to the concept of dose
by the Oxford overview?
And then talk about self seating
theory and how it relates to all of
that previous work and that will
bring me into the area of fractal geometry,
which is where another topic
in math comes in and how our that’s
informing our current work on the tumor,
infiltrating leukocytes,
and the interpretation of their firm.
And I don’t know if David Rim is, you know, here among us today, but we’ve had a number of early conversations a few years back about. The importance of fractal geometry and understanding biology from a pathology point of view, and then how that relates to concepts of drug resistance and the use of immunotherapeutic agents and lately. Our work that we’re doing on antibody drug conjugates in that regard, but all informed by mathematical thinking. Let’s just start back with Hippocrates, the father of us all.
The parent of us all in medicine.

The actual quote translated from the Greek is an illness is once you keep two things in mind to be useful rather than cause no harm. That's frequently misquoted, as first of all, do no harm. That's not quite what he said. What he said is don't be neutral, but but, but, but be useful, and that is, is a very important quote because it relates very. Very directly to one of our major topics that we have to deal with in clinical
oncology all the time, which is OK.

I have a drug that works.

How should I use it and dose level of course is a mix between the efficacy

And I spent almost all of my youth learning to be a medical oncologist learning how to to avoid or manage toxicity of of the agents and pick out the right dose level quotes in the modern world has gotten much more complicated than that. We have to not only look at the dose level,
but also the schedule. The duration of Therapy will give it impulses and that leads to various changes in efficacy and toxicity. Toxicity is not just acute toxicity, but late toxicities chronic toxicities that may arise. The personal cost to the patient and the personal goals for the patient have been taken into account and in planning, dosing and scheduling as but also societal cost that everything that we do is going to have implications basically to all of our society. All of our patients and society in general. And how does all of this relate to a
very rapidly evolving therapeutical landscape so so dosing is scheduling is actually a very germane topic in the modern era, even when we're talking about some of the newer agents. And what we’ve learned in looking at the older agents, IE. Chemotherapy is directly related to how we’re going to be applying our newer agents, and as I close the talk, I hope I’ll be addressing some of these points. But the central dogma that led most of us in our careers in medical oncology is this.
If you want to kill more cancer cells, you have to use higher dose levels. So you want to use the highest possible dose level you can to kill more cancer cells. Because the more cancer cells you kill, the more benefit to the patient either eradicating the cancer. If that should actually be possible, or just buying time 'cause we have smaller. Buying more tumors can take longer to regrow, and that's going to be translated into improvement in duration of Disease Control for the patient and hence our training was all about determining and treating at maximum tolerated dose.
I’m going back to another great teacher of medicine, William Ostler. The greater their ignorance, the greater the dogmatism, and I believe that this dogmatism is really dominating us even to the present day when we have targeted agents, thinking that we’re going to benefit the patient by doing so, and I’d like to really question that this concept really came from the work of Howard Skipper.
Franckesche Bold and Griswald and others at Southern Research Institute. It was an extremely important part of my education in medicine and oncology, the concept was based on mooring, leukemia and Howard skipper made the observation that if you inject a certain number of cells and the mouse died at a certain time, that could tell you basically how many cells you injected. 'cause it took a certain very reproducible amount of time for those cells to reach a lethal number. So all of his work was not really
measuring cancer cell numbers, it was actually measuring animal. Death and extrapolating back to cancer cell members. And that's common, not commonly appreciated is that it was all extrapolation, but the fundamental observation that he made is that if you kill cancer cells, you can extend lifespan and the extension of lifespan was a. Basically it took time for lethal number of cells to arrive and you can go back and extrapolate from that in terms of how many cells you killed.
because it would take that certain number of cells that were left or residual to lead to eventual or lethal number and the death of the mouse. This led to a concept that is shown here by one of the of the. Very very often in my youth, especially reproduce figures is that if you start off with a large number of cancer cells and you give a certain dose of therapy, you kill and will go back over this a constant fraction of the cells that are present with each dose. Each chemotherapy core skills, in this case,
2 logs of gotta get rid of this pop

up two logs of kill means means you’re killing 99% of the cells,

90% is 1 log killed,

99% is a two log kill and you could drive to cure unless you get the emergence of drug resistance.

Of course, if you stop treating when the cancer is disappeared, that’s not enough, because there’s plenty of cancers left and they can grow back and and the concept of roses that if you start a small of tumor size that you can actually get rid
of the cancer cells before this emergence of drug resistance arises and hence the concept of Azure and chemotherapy came from this Vince Davida long associated with Yale was my great teacher and still is my great teacher and in oncology took these concepts and use them to develop the MOP chemotherapy regimen and those of you who have not. You really should read it because it’s an excellent book and it really read Vince on his book of the Death of Cancer about the early days where this figure was extrapolated into the cure of a solid tumor Hodgkin’s disease.
00:10:44.862 --> 00:10:46.383 captures the excitement of those early days in oncology and the application of this mathematical model to the development of a curative regimen.

00:10:49.810 --> 00:10:51.685 Well, this was led in the 60s to the concept of dose escalation. This way if you have no therapy and you have simple exponential growth like this, you give one drug.

00:10:54.557 --> 00:10:57.350 You get certain log kill two drugs.

00:10:57.350 --> 00:10:59.690 If this causes one log kill and this causes one log kill then you get 2 log kill 90% sale killing here and 90% sale killing here since 99% sale of
killing three drugs should be should cause disease eradication. Therefore, four drugs should certainly cause disease eradication, which was very influential, they’re thinking about Rob chemotherapy, but it also applies to doses. 1 dose, 2 doses, 3 doses, all increased cell killing, causing DC eradication. So the 70s was a decade of enthusiasm. Fueled by this confidence in the skipper. In the skippers model, there are many drugs that came along, such as the Cyclones,
the platinum agents, the concept of combination chemotherapy as I’ve just demonstrated to you, arose from these thinking. And indeed we’re getting successes. Cure simply nysm. And and leukemia is infamous testicular cancer, it really looked like we were moving in the right direction. Getting high response rates and many other tumors including breast cancer. The field that I eventually specialized in the concept of postoperative attribute chemotherapy rose from that period.
Based on that mathematical idea and an enthusiasm for those level escalation which we led to a lot of enthusiasm for a mega dose escalation, which is bone marrow transplantation. This enthusiasm was so pronounced that a mentor, not Vince, is another mentor in 1976 cents Me Larry, you still got a chance. You’re young enough to change your career path, you’re not. There’s not gonna be any field of oncology in a few years. All these combinations. All these agents are just going
00:12:36.626 --> 00:12:37.911 to come together and cancer will
be disappeared in a few years.

00:12:37.911 --> 00:12:39.210 You better think about training
and something else.

00:12:42.980 --> 00:12:44.785 Well, I persisted against that
advice and kept working on cancer.

00:12:44.785 --> 00:12:47.100 And as you know it hasn’t been that easy
and a lot of that enthusiasm is still
there and we definitely making progress.

00:12:47.100 --> 00:12:49.116 No question about it,
but the rate of progress really
has slowed even with the
addition of newer agents.

00:12:53.180 --> 00:12:55.950 And we’re not getting cures of
metastatic colon cancers and
and stomach cancers.

And and and and many lung cancers and so on.

But certainly breast cancer as readily as we would have hoped.

Metastatic disease is still a big problem.

So what went wrong?

And this is my number one favorite quote and kind of a kind of you know, model for my life.

It’s not what you don’t know that gets you in trouble.

It’s what you know that for sure turns out not to be true.

And the thing that we knew for sure was that the skipper model worked.
because cancers grow exponentially,

but they don’t grow exponentially,

nor do they grow in a strictly linear fashion.

And we know this because if that were the case,

from the time of initial diagnosis to the time of lethality would be too short.

Exponential growth also doesn’t make sense because for the time of initial diagnosis,

the time of lethality would be too short.

It’s got to be somewhere in between and indeed,
Benjamin Gompertz in 1825. Then invented a curve of human mortality, which we call the Gompertz curve and kind of sigmoid curve. Because you see as a shape and others had shown that Gompertz curves actually applied to the growth of experimental tumors. In 1976 these are two rat tumors. This is a mouse tumor and what we found are working with Richard Simon. Is that if you have a few early measurements that it actually fits a pattern and you could predict.
later measurements that gone.

Protein growth was really very predictable.

This is really an important observation that just sort of sat there and up until the present day, but it actually is rather meaningful but nest.

But but indeed, Gompertz equations are applied and then not exponential, and so my my work was basically to see how do we apply the skipper Schaible principles.

How do we apply skipper Schaible
principles to gum persien curves

and papers in the early days about

this and they eventually led to

the concept of sequential therapy

And this was the work in the 70s

And again Vince DeVito was

was working closely with Johnny

Bonadona in those days and and

some of these ideas got translated

and indeed this was actually a

competition in the adjutant setting

between a other modelers.

Called Goldie and Coldman and

and myself and and Richard

that they predicted that if you
have agents like doxorubicin and see
at math you should use them in an alternating fashion because that would get this drug in these all the drugs in sooner to limit the emergence of drug resistance by random mutation whereas my modeling which I’ll show you in a second, suggested that it would be better to use them sequentially. So we’ll go over that modeling because this is buried in ancient literature and was published before many of you who are listening to this lecture were. Warren, so you’re not aware of this work is that, of course,
it’s always better if you’ve got two agents or two combinations, you gonna use them simultaneously if you can, that’s going to give you maximum cell kill, but you can’t really do this in most situations without such toxicity that you have to reduce the dose levels of the drugs. And by reducing the drugs, dose levels of the drugs, you’re not going to get the maximum efficacy from any of the drugs. So the question is, what can you do if you can’t give them in a simultaneous combination? The Goldie Coleman idea is you alternate them.
And by the Norton Simon modeling when we did it, we found well, we got a very inferior cell than if we did them. Obviously by simultaneous therapy. But if you give them in an alternating fashion, you can actually get cell killed. That’s better than you can get by giving him an alternating fashion, so the bonadona experiment which started in the mid 80s was a was basically a competition between this approach and this approach. And of course this approach one.
Then, with the advent of grants, iconic stimulating factor where you can actually squeeze the doses of drugs closer together, you can actually get maximum self kill and even a better cell kill. Then you can just with the simultaneous combination by the application of GCSF. So you can make a through cycle, for example into a two week cycle. Tax oil can be given even without GCSF in a one week cycle, and that’s also a dose dental regimen as well. So that’s the understanding of dose density, which is kind of lost in
history a little bit. And a lot of people don’t appreciate really where it came from. Water million means. Hence we designed this regimen which basically started. In 1997, nineteen 9741 with Mark Citron, who we just lost very recently from a neoplasm. A great great Lawson, who we just lost very recently from a neoplasm. A great great Lawson, and really a great clinician and and a great clinical scientist. And this was A and the regimen was a two by two design, and you’ll notice those of you who
are doing cooperative group studies.

We don’t do two by two designs very much anymore, and I really wish we did because it would answer a whole lot of questions faster than doing just some of the regimens that we’re now doing, which is comparing 2 treatments or now even not comparing it at all, but basically comparing it to historical data. Which is, you know, Noninferiority designs. For the topic about the the wisdom of that, but certainly these two by two designs get a lot of information, and we gave adriamycin and
cyclophosphamide AC with paclitaxel.

Either all the drugs in a Q3 week regimen, in a sequential fashion, or the AC together 'cause you can do that without having dose modifications. That's why it makes sense in a three week Red room or squeeze these together in a two week regimen. In a sequential way and squeeze these together and this. This of course became the standard because the the AC from axle 2 weeks was better than AC for Taxol 3 weeks. I would just emphasize that this regimen and this regimen really came
out the same and so they were pulled together for the analysis and and if you can’t give the cyclophosphamide with the age of my son together and if you give it the end, it would be just as effective. I have done this in certain situations with patients we’re running into into issues. For example. The other thing that I’ve done is basically substitute Murph for adriamycin. In this regimen, if there’s issues related to cardiac toxicity, ’cause we know that CMF and AC really are the same.
In terms of efficacy in the action setting, and retrospectively I'll say I think it was a shame that we did not do a comparison between AC dose, dense AC. Those dents followed by Taxol. Those stands compared to CMF. Those tents followed by Taxol 'cause I bet you they come out the same and we wouldn’t have all the drama about the potential for cardiac toxicity with anticyclone. Sorry I fear that we’re throwing the baby out with the bathwater often when we’re not using AC.
Taxol, because we’re afraid of cardiac toxicity and using other regimens that avoid the anti cycling and in doing so, we’re also leaving out those density. I think that’s a mistake and I’ll show you why I think that’s a mistake in a second. I just also want to emphasize and I just wanna mention this quickly. Is that the doses of the drugs we use did not come from nowhere? We actually studied the doses and we found out that moderate levels of the CF combination was equivalent to higher levels that going higher doses was not better.
Half doses were inferior.

This network that Dan Budman did, and in this in the cancer Community, and so the whole idea of going higher with doses to get more so killed was just not borne out by the data. The same thing was done with cyclophosphamide. And with Bernie Fisher in the NSA, where they looked at higher and higher doses of cyclophosphamide in the CF combination and it did not add in the in in...
the in the various regimens they went to higher and higher doses and they did not add so that and and Eric which he told me he’d be listening today did the same thing with paclitaxel, going to higher dose of the 175 not showing any advantage in a study. So this notion that just going higher and higher? Doses you can get more cell kill. It’s just not borne out by empirical evidence, and we have to keep that in mind as we question the original dogma that led to a lot of what we’re still currently doing in in our application.
Medicinal chemistry to the treatment of cancer of the present day. Well, this led to 26 randomized trials over 37,000 randomized patients looking at various permutations at dose and schedule, and this was published in The Lancet. I’m just summarizing all this work is that if you use and they talk about intensity here, but there’s a very big choice of terms, but nevertheless that was the consensus that we use the term. It’s really dose density, standard schedule rather than using a dose dense schedule, you get recurrences.
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.
75 and it's a dose 10 schedule and
the sideman showed this because
it's being given every week.
Rather than reading every three weeks
and the dose response relationship
for paclitaxel as Eric Weiner showed,
is not steep and that you are
accomplishing at least 1/3 as much
efficacy with 80 as you are with 175.
So the reason why I show all this most first
of all is to catch some historical facts.
or those of you who are not familiar
of all is to catch some historical facts.
For those of you who are not familiar
with them but also make this point,
it's gone pretty and growth is true.
growth kinetics to improve cancer therapy,
which leads us with the big question
what is the etiology of gun?
I was at something called the Ideas Festival in Aspen one year and I was having trouble parking my car so I was blocking somebody else from getting out of her parking spot and she got really angry and she came running up to me. With her hands on her hips, I pulled down my window and she said, And she was really angry, said, what’s your problem and I said my problem is the etiology of gun protein growth what’s your problem?
She obviously thought I was a lunatic, which I probably am and she walked away from me. But this has been my preoccupation. For many years is understanding what is the etiology of compression growth. And so, thinking about this in the early 2000s I got a phone call from Jean massage my great collaborator here at Morrison Kettering. He had just published his paper by Andy Mineo, we were looking at the etiology.
molecular etiology and metastasis, and found this tumor. You know, which is an MMDA MB 231. Sometimes is rushing ahead, which had a certain gene expression profiling. Machines being locked, these genes being on and the tumor sticks here. But occasionally you get along with tax assist and if you get a long metastasis and you take the cells out of the lung, wash them and put them back into the memory fat pad several times, the lung metastasis signature,
which has a signature which predicts lung metastasis because the mouse develops long itasis. He’s done this for other other organs as well. Well in this paper they had this very interesting figure. It showed that the tumor that goes to the lung more readily that has this gene expression profile also grows faster in the mammary fat pad. The one that doesn’t go to the lung doesn’t grow as fast, and the intermediate steps have an intermediate.
Intermediate growth rate in terms of memory, fat pad.

So the question that I was asked in on a phone call is.

Number one, is it true? As a clinician that cancers that are metastatic tend to be faster growing? Is that yes, they’re getting metastatic to distant sites. Why were they stop them from getting metastatic back to the original site?
but the S phase fraction the KS was not different and I said that’s makes a whole lot of sense, because basically if the tumor that goes metastatic, let’s say to the lung, also gets meta meta static back to itself, then in this case we have like 3 lumps that are growing independently and each of them growing at 5%.

Let’s say you’re still going to have a growth fraction of 5%, but you’re going to grow three times faster. ’cause three things going at 5% each is going to grow faster.
than one thing growing at 5%.
And so therefore it makes sense that
they carry 67 would not be different,
and yet you would get faster growth.
And because it’s being metastatic
Jean message and I labeled
this self seating and did
subsequent work in this.
This was a hypothesis me on Kim.
so Jean message and I labeled
this self seating and and did
subsequent work in this.
This was a hypothesis me on Kim.
Did this work published in 2009?
And this was just a brilliant experiment
of the exact same tumor implanted
in two different fat pads but with
different fluorescent proteins in them.
So they’re different colors.
And indeed they exchange.

And this would be this.

The left side of tumor.

This would be the right side of tumor.

This started green and and then turn

This started red and moved and

red because red cells moved over.

This started red and moved and

d and developed green.

’cause green cells moved over

and there’s an exchange of cells

between the two tumor sites.

On much more work was in this paper.

Obviously if you inject a non

seeding tumor here and then inject

the LM 2 seating tumor to the heart,
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 --> 00:26:55.430 When you inject the tumor cells,
NOTE Confidence: 0.8556101385

00:26:55.430 --> 00:26:57.798 they light up the whole body obviously,
NOTE Confidence: 0.8556101385

00:26:57.798 --> 00:27:00.048 but then over a period of 42 days
NOTE Confidence: 0.8556101385

00:27:00.050 --> 00:27:02.678 they grow in the implanted tumor.
NOTE Confidence: 0.8556101385

00:27:02.680 --> 00:27:04.188 That’s not metastatic on this side.
NOTE Confidence: 0.8556101385

00:27:04.188 --> 00:27:05.696 Why is this interesting?
NOTE Confidence: 0.8556101385

00:27:05.696 --> 00:27:06.450 Because you’re not developing
NOTE Confidence: 0.8556101385

00:27:06.450 --> 00:27:07.356 lung metastases.
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
tail vein injection and get lung
NOTE Confidence: 0.8556101385
00:27:22.108 --> 00:27:24.212 metastases first and then implanted
NOTE Confidence: 0.8556101385
00:27:24.212 --> 00:27:26.112 tumor that implanted tumor will
NOTE Confidence: 0.8556101385
00:27:26.112 --> 00:27:27.784 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 live longer with a subcutaneous tumor
NOTE Confidence: 0.8556101385
00:27:42.960 --> 00:27:45.384 of metastases 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 --> 00:28:00.566 What I want to focus in on, however,
NOTE Confidence: 0.914196397142857
00:28:00.566 --> 00:28:02.493 is that if cancers are growing at
NOTE Confidence: 0.914196397142857
00:28:02.493 --> 00:28:04.647 least partially by cells that are
NOTE Confidence: 0.914196397142857
00:28:04.647 --> 00:28:06.915 spreading and coming back to the tumor
NOTE Confidence: 0.914196397142857
00:28:06.915 --> 00:28:10.171 mass from the outside in rather than
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.
This pattern of growth is with the skinny Franz is reminiscent of what the physics physicists called Diffusion limited aggregation, and it's because a water molecule. Or sell coming here is more likely to stick here than work its way into the middle. And if you do that, you actually get a pattern of growth. That's from Puritan because as objects get larger. The ratio of their surface to their volume decreases and we're going to talk more about that in a few minutes, and you could actually.
Here's my only equation.

I'm going to show you you could actually write an equation that's called the Norton mass gay equation, which basically summarizes that, and it's been much more subsequent mathematical work on this equation.

But what it really means to me now, and I want to get into this topic. You know, with the limited time that we have, is that this pattern of growth explains a lot of things that we know already about clinical medicine and not the least.
00:29:09.392 --> 00:29:10.820 of which is the pattern of growth.
00:29:10.820 --> 00:29:13.860 For example, take a look at this MRI.
00:29:13.860 --> 00:29:15.659 This is a breast cancer MRI we
00:29:15.659 --> 00:29:18.161 we see this all the time and we
00:29:18.161 --> 00:29:19.493 call these satellite lesions.
00:29:19.500 --> 00:29:21.660 But frankly, it’s all satellite lesions.
00:29:21.660 --> 00:29:22.540 This is a lesion.
00:29:22.540 --> 00:29:24.072 This is a delusion, this illusion.
00:29:24.072 --> 00:29:26.354 It’s got long skinny tendrils
00:29:26.354 --> 00:29:29.315 sticking out like a snowflake.
00:29:29.315 --> 00:29:31.169 It’s the pattern of growth of what
00:29:31.169 --> 00:29:32.866 you’d see if the cells are coming in
00:29:32.866 --> 00:29:34.420 from the outside and so self seeding
00:29:34.420 actually explains a lot about what
00:29:34.420
we see in the anatomy of cancers.

At least the gross anatomy.

And we’ll get into the microscopic anatomy in a second, because this pattern of growth is called a fractal, and a fractal is repeated patterns at different scales and fractals have what’s called a dimension.

So now I’m going to go to a discussion of dimensionality because I think this is very important for some of the work that we’re doing right now, and is implications particularly tumor infiltrating leukocytes.

Now in Euclidean geometry.
Dimensions are simple.

A point has no dimension.

A straight line only has length as one dimension. A sheet has two dimensions, length and height. A cube has three dimensions.

You're adding the depth. That's simple dimensionality. In Euclidean space. In fractals it's a little more complicated.

Let's just take one of our sheets that we had before that had a civil dimension of two.
and let's look on it and cross section. Well, if you start to crumble it up, if you crumple up the sheet, it's going to be a little bit more than just a flat sheet and dimensionality. Here is actually 2.1 number of flat sheet is a dimension of two. If you crumple it some more it gets a higher dimension. 2.3. Now let's say that it's really getting more and more crumpled overtime. It starts to. Have the appearance of something that's thicker. This is a dimension of 2.6. This is dimension of 2.8. A dimension 3 would mean you're
prompted so much that it’s now just a solid mass of sheet material, but it’s in a solid mass, so now it’s a.

It’s got the dimensionality of a 3-dimensional object or having dimensionality of three.

So these are things to keep in mind and it’s a big difference between a 2.6 and and a 2.8 dimensionality you can see in terms of the thickness well.

Fractals occur in nature all the time. These are artificial fractals on top of various sorts. These are the kinds of fractals.
that occur in nature all the time.

Plants and animals and and diffusion in in.

In substances like like ice or plastic, these the fractals are just common in nature.

Mandelbrot was discovered, there’s been more Mandelbrot and written extensively about, and there’s been an extensive explosion of literature in this.

So what we’ve done is. We’ve looked at this in the context of self seating and the context of leukocytes and why leukocytes because
as me and Kim showed in this paper, we join mask and colleagues is an unseated state compared to a seated state. This would be an unseated tumor and this would be a tumor that’s received. Received cells that have come from the outside, two cells in the blood vessels are brought in with the seeds and they’re mostly bone marrow derived. endothelial cell precursors that close that blood level of growth. But I was particularly fascinated by the fact that that when you
get seating and this is these are seated cells that they’re staying green, the green for some protein. Not they have for some protein not staying, but they’re obvious here in this particular setting they bring white cells in with them. CD 45 cells in with them, bringing brings white cells in with them. if it’s bringing white cells in, with them from the outside, perhaps the growth the pattern of white cells that we’re going to see in a tumor is also going to follow,
or fractal geometric pattern, and so with, with Matthew, Hannah, and George Reese, Philo, Hannah when Ebro, and others we’ve looked at this by actually looking at at tumors.

These are triple negative breast cancers and using image analysis in this acute pack. Roughly available image analysis to actually segment the white cells from the tumor cells so that we can actually measure the number of cells in each region of interest and then.
using various mathematical techniques, mathematical tricks that we’ve developed.

We can then calculate the fractal dimension of those white cells and what we found in this is preliminary work and much more work is going on in this topic, so this is not a take home message just to show you that we’ve done it is.

This is the very first experiment that we did three cases of.

Triple negative breast cancer and not neoadjuvant.

These are patients treating the agent setting.

They’re small tumors versus non
00:33:58.430 --> 00:34:00.160 cases without recurrence at the

00:34:00.218 --> 00:34:01.666 fractal dimensions are different

00:34:01.666 --> 00:34:03.838 and in fact the fractal dimension

00:34:03.901 --> 00:34:05.829 of the white cells in the

00:34:05.829 --> 00:34:08.124 cancer that that that that recurred

00:34:08.124 --> 00:34:10.645 or that became metastatic was 2.77

00:34:10.645 --> 00:34:12.514 on the average and it was 2.65.

00:34:12.514 --> 00:34:14.706 So it’s like 2.8 verse 2.6 like I

00:34:14.706 --> 00:34:16.918 showed you in previous diagram and

00:34:16.918 --> 00:34:18.793 a statistically significant P tire.

00:34:18.800 --> 00:34:20.492 Much more work is going on in this direction,

00:34:20.500 --> 00:34:21.907 but I think this is a very.

00:34:21.910 --> 00:34:23.989 Interesting area for us to think about

00:34:23.989 --> 00:34:25.769 the application of fractal geometry

00:34:25.770 --> 00:34:27.492 motivated by the concept of self
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 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 Previous work again from John Massage shop.
NOTE Confidence: 0.763816441111111
00:34:41.133 --> 00:34:44.304 In this one area,
NOTE Confidence: 0.763816441111111
00:34:44.310 --> 00:34:46.070 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
00:34:58.228 --> 00:35:01.969 releases a substance that causes TNF alpha.

00:35:01.970 --> 00:35:05.260 This pop up just driving me crazy.

00:35:05.260 --> 00:35:05.755 Right,

00:35:05.755 --> 00:35:06.250 right?

00:35:08.437 --> 00:35:08.437 So I’m gonna now gonna go move with the

00:35:08.437 --> 00:35:09.752 lightning speed and custom stuff out.

00:35:09.752 --> 00:35:11.490 I have no idea why that happened,

00:35:11.490 --> 00:35:13.611 but nevertheless here we are is that

00:35:13.611 --> 00:35:16.439 when you do when when we when I showed

00:35:16.439 --> 00:35:18.394 you about self seeding and when you

00:35:18.394 --> 00:35:20.060 have self seeding white cells come in.

00:35:20.060 --> 00:35:21.936 So we hypothesize that the white cells

00:35:21.936 --> 00:35:23.998 that come in the CD 45 positive cells

00:35:23.998 --> 00:35:26.111 here are coming in as a reflection of

00:35:26.111 --> 00:35:28.092 the seating process and we can uncover

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that by looking at their fractal geometry.
And indeed we've looked at this work with Matthew,
Hannah and colleagues. We've done this with two paths you know,
two methods for being for segmenting between white cells and cancer cells.
And indeed it is indeed fractal and the fractal dimension is different in triple negative breast cancers
that recur then triple negative breast cancers that don't recur.
Much more work is going on in this direction,
but I can’t go back over it now.

We’ll have to do another lecture on this particular topic.

One of those white cells doing one of the things that they’re doing is providing drug resistance.

His work of sworn ally Acarya, and John Messages Laboratory.

If you stress the cancer cells.

And with anything chemotherapy or radiation, or even heat,

can get the secretion of TNF alpha,

which causes the secretion of CXCL one which goes through receptor on white cells,

which causes the release of S 100
proteins and can save the cancer cell as a mechanism of drug resistance. We showed this by actually showing that the inhibited by itself does nothing, but that if you give a stress you can up regulate the loop. And kill cancer cells, but some are being saved by this loop. And by Ablating that loop we can get a much higher degree of cell kill. So one of the things that those infiltrating white cells is doing is providing a mechanism of drug resistance. We’ve also and I I told I I gave you a a wonderful anecdote here.
That was a that that is lost.

Now for very history about how why we did this work.

But we looked at the at those white cells that are infiltrating human cancers.

And we found that very often indeed, in most cases they have leukemia.

Tumor infiltrating leukocytes are not genetically normal, however known leukemia.

Mutations and not only that, but if the patient is followed.
In developing secondary leukemia much later in the future, those secondary leukemias have have the same mutations that you found in the tumor infiltrating leukocytes. In many cases many years earlier, there’s something else that we’re exploring and doing work on on what role mutant white cells may be playing and actually growth. Promotion of the cancer, as well as providing a potential mechanism for drug resistance. The last point I made in this regard or second to last point, I made this regard that you missed.
is that all of this could be exploited because circulating cancer cells in self seeding can only return to the cancer. But you can have circulating cancer cells going from one metastatic site to another, and it’s been shown in both xenografts by Jonathan Weissman and also been shown in lung cancer. Clinical lung cancer specimens as well as some breast cancer specimens obviously can’t read the details now. But this could all be exploited by giving some form of local therapy to a tumor to cause secretion of antigens,
which then you can use checkpoint inhibitors and checkpoint inhibitors to get stimulation and theoretically in this concept kill circulating cancer cells that are self seeding being drawn back to the area of inflammation that’s caused by this particular procedure. We did this with Becky and Jim Allison when Jim Allison was at Memorial Sloan Kettering, where we looked at an animal. Model, in this case, the one that’s growing in green. If you just give anti CTA forward, nothing happens.
If you just a BLT, a contralateral tumor, nothing happens, but the combination of ablation and anti CT A 4 gets a 90% cell kill, who’s now in Dallas has been exploiting this in a number of interesting studies. This is a work that she did at Memorial Sloan Kettering, where a primary breast tumor was ablated with crir ablation and the remaining tumor. Inside the two is profoundly Immunogen IK and we showed and published in several papers. Now in a new paper coming out of Elizabeth,
Coleman has just a first authored
NOTE Confidence: 0.892513605454546
that that you can increase the
NOTE Confidence: 0.892513605454546
immunogenicity of that residual tumor
NOTE Confidence: 0.892513605454546
by giving immune checkpoint inhibitors
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and indeed combinations work better.
NOTE Confidence: 0.892513605454546
And this is now being looked at in
NOTE Confidence: 0.892513605454546
terms of therapeutic implications.
NOTE Confidence: 0.778110919444444
Coming and this could be done with
NOTE Confidence: 0.778110919444444
radiation as well as with prior ablation
NOTE Confidence: 0.778110919444444
which we’re currently exploring.
NOTE Confidence: 0.778110919444444
Combinations of immune checkpoint
NOTE Confidence: 0.778110919444444
inhibitors and other thoughts
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related to educated T cells in
NOTE Confidence: 0.778110919444444
terms of car T cells, for example,
NOTE Confidence: 0.778110919444444
as well as inducing trans genes that
NOTE Confidence: 0.778110919444444
actually may make the the inflammation
that were causing even greater.
So, so this is where I left off and I just want to give you one other quick thought about geometry. You all remember that a sphere, something I mentioned to you earlier, is that the surface area is related to the square of the radius, whereas the volume is related to the cube of the radius. This explains why mice are furry because they’re very small and so they have a very high surface area related to their volume and therefore they lose heat easily and they need to be
very furry to hold their heat in.

You get to a large animal like an elephant.

Is bald and doesn’t need for her.

because its surface area is very low related to its volume.

Its problem is getting rid of heat, which is why orphans Jen tend not to want to run very very quickly because generating heat is uncomfortable for them ‘cause they don’t get rid of heat very very very readily, and that is something else that we can exploit therapeutically because the fact is that as tumors grow just ‘cause they’re getting bigger, the ratio of their surface area is there,
00:40:58.260 --> 00:40:59.880 volume drops comes down.
00:40:59.880 --> 00:41:02.310 So you’re converting basically a mouse.
00:41:02.310 --> 00:41:03.441 Into an elephant,
00:41:03.441 --> 00:41:05.703 it comes down faster for well
00:41:05.703 --> 00:41:07.578 differentiated cancers than for
00:41:07.578 --> 00:41:09.009 poorly differentiated cancers,
00:41:09.010 --> 00:41:11.747 and this is because of fractal geometry.
00:41:11.750 --> 00:41:13.094 You know if they’re interested in that,
00:41:13.100 --> 00:41:14.367 we could talk about the reasons why,
00:41:14.370 --> 00:41:16.040 but that’s the reason why.
00:41:16.040 --> 00:41:17.138 So that actually,
00:41:17.138 --> 00:41:19.700 if you have a tumor that’s growing
00:41:19.700 --> 00:41:22.668 and you do A and the surface area
00:41:22.668 --> 00:41:24.598 decreases related to the volume
00:41:24.598 --> 00:41:26.824 while it’s growing and then shrink
it with chemotherapy.

That the surface area to volume ratio is going to rise,

and since we when when we’re talking about immuno immunotherapy,

we’re talking about a relationship between the surface of the cancer and white cells that are trying to kill the cancer is that is that the best time to use this kind of ablation would be after an initial induction. And to take this idea and exploit it by inducing small tumor first, increasing the surface area to volume ratio and then coming in with your oblated therapy and then combining that with.
Combining that with your immune checkpoint inhibition. Now, the same concept can apply to one of the really most exciting areas in terms of modern medicinal therapy of cancer, which is the antibody drug conjugates, as we all know, they attacked a target antigen in the cancer, so they have increased payload delivery, but their penetration could be poor and this is something that has to be exploited when
they’re internalized that the the payload is reduced, it is released in ’cause the cancer cell.

But more than that. In terms of the activity of these payloads on killing the cancer cell, they often leak out and they can kill adjacent cells that don’t necessarily have that particular target. This or this work of Josh Drago. Well, this can be exploited by the same way is that when you used your antibody drug conjugate to a large tumor, you get down regulation of the target, and that’s not what you want to optimize the effect.
So one of the things we're exploring, and this is not in the clinic yet. This is just an experiment that we're doing right now, preclinical in preparation for clinical experiment is by giving a non ADC induction. First we can increase the surface area to volume ratio. And then come in with the ADC as a late intensification and therefore it should be even more active in this area to get tumor volume eradication. And if the animal experiments work, I think there's something else that could be exploited extremely easily.
in the clinic 'cause we have a lot of drugs in breast cancer that can cause tumor volume regression that are not Adcs and then instead of waiting for the tumor to grow and using your Adcs in as a salvage if you use them at time of maximum tumor volume regression and this, could be determined not just by actually watching the cancer shrink with imaging, but also by the burden of circulating cancer and DNA, which would be another way of actually when that plateaus, 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
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

91
leukocyte level may work at the gene level. This would have a different fractal dimension than this, for example. 'cause we have a lower fractal dimension. This would have a higher fractal dimension. You can look at gene networks in the same way as another term for this cord curvature. Obviously I can't get into it, but this is giving us some great insights and we recently published a paper in ovarian cancer that actually showed that the the structure of the gene gene interaction network has predicted values in terms of response to immune checkpoint inhibition.
00:44:53.040 --> 00:44:54.120 In this situation and,
00:44:54.120 --> 00:44:55.740 and indeed that you can actually
00:44:55.791 --> 00:44:57.411 predict which patients with ovarian
00:44:57.411 --> 00:44:59.031 cancer there’s not supposed to
00:44:59.083 --> 00:45:00.948 respond to immune checkpoint ambition.
00:45:00.950 --> 00:45:06.088 Will respond on the basis of the the
00:45:04.302 --> 00:45:06.088 mathematical analysis of of their.
00:45:06.090 --> 00:45:07.698 Gene Gene interactive networks.
00:45:07.698 --> 00:45:10.400 So what I’ve been able to do,
00:45:10.400 --> 00:45:12.392 I hope in this lightning talk made even
00:45:06.090 --> 00:45:07.698 Gene Gene interactive networks.
00:45:07.698 --> 00:45:10.400 So what I’ve been able to do,
00:45:10.400 --> 00:45:12.392 I hope in this lightning talk made even
00:45:12.392 --> 00:45:14.235 more lightning by the loss of the Internet.
00:45:16.500 --> 00:45:19.348 It’s just described where this all came from.
00:45:12.392 --> 00:45:14.235 more lightning by the loss of the Internet.
00:45:14.235 --> 00:45:28.766 a clinical advance and then why tumors
00:45:14.235 --> 00:45:28.766 a clinical advance and then why tumors
grow in that kind protein fashion.

The whole self seating concept which led us into the concept of fractal geometry, which is now one of my most active areas. Investigation how, how can we actually quantify tills and what is the prognostic significance of them using fractal geometry? How does all of this relate to drug resistance? And optimizing immunotherapy and optimizing new agents such as antibody drug conjugates. Forgive me for speaking too fast, but I know we have to end on time and thank you all for listening. I apologize that we lost the Internet.
Thank you Larry. That was if we have a couple of minutes let you know if I can do a couple of talks. I can stay later if people want to stay late. We have a couple of questions. First of all, thank you so much for know it just to me. It’s amazing for a Conservatory trained musician to be such mathematician at the same time, I don’t know how both sides of the border link they get. They link together music and math is the same, the same the same. You know part of the brain. So we have some questions from Pat Larussa and David Rim to start with there.
Kind of on the same pattern on the fractal pattern differences between hormone receptor positive and triple negative breast cancer. Are there differences that you see not only for the tumor, but the tills? And then does that work in terms of the agency used? That’s what we work in progress, but the answer is almost certainly so because you know, I’m not doing anything with the fractal geometry that the pathologist, they scope pathologist is doing with their eyes. You know,
a skilled pathologist looking and says, "hey, this is well differentiated."

This poor differentiated differentiation. Is poor differentiated means a high fractal dimension, whereas a well differentiated means a low fractal dimension?

And so basically I’m just quantifying. I’m quantifying something that the eyes of the beholder have seen is seen already.

But you’re talking here about fractional dimension of the cancer cells, which is obviously something we’re exploring.
I was talking about fractal dimension of the tills, but it all relates together and I think what makes it really intriguing to me. Just personally, maybe nobody else, but to me. Is that it relates to this concept of a pattern of growth? One thing you gotta know about math is that even if self seeding didn’t happen, if things anatomically look the way they would happen were it to happen, it still is biologically significant. That’s that’s the way that’s the way math mathematics works alright.
You don’t have to have the example you know the the. The same mathematics works for gravity and for magnetism, even though the mechanisms are different, but we know they’re different at the same, the same. You know the same mathematics you know works for the theory of universal gravitation works the same. So so once we actually understand the mathematical principles, they can generalize even if the
thing that got us into that which is substituting concept is not valid.
But I really do think the self seeding thing is valid.
But based on the accumulating body of evidence that we’re seeing,
so I’m just basically trying to quantify that.
Thank you we have another question on the implications of Gumpertz and growth for the rate of survival and proliferation of cancer cells. What are there implications and then does it imply that proliferation slows? And if so, why are the clinical implications of that slowed growth?
All right? You know, you’re asking for a treatise and a little bit comma, and I wrote a really nice review article about the clinical implications of cancer self seating so you know, COMEN and Norton. You can Google it and go with that paper. Really, really, really very quickly. When we go into all that in great depth, first of all, gun person growth has to happen. ’cause if it didn’t happen we we would have no chance against cancer because with exponential growth I
mean from the time of diagnosis,

time of death would be a matter of weeks at even for solid tumors.

So we know there’s gotta be a tailing off of growth rates and it really has great profound implications in terms of our understanding,

growth and planning for therapy.

I think it’s a shame that we haven’t used those dense sequential therapy for more tumors beside breast cancer.

There’s been a little bit of work in lymphomas in this regard.

A little bit of work in other tumors,

but we haven’t optimally exploited it,
00:49:32.321 --> 00:49:33.461 do better even with existing agents

00:49:33.461 --> 00:49:35.231 if we were able to take some of the

00:49:35.231 --> 00:49:36.575 principles we learned with breast cancer,

00:49:36.580 --> 00:49:38.260 move them into that setting.

00:49:38.260 --> 00:49:40.018 But right now where I’m focusing

00:49:40.018 --> 00:49:40.897 in on instead,

00:49:40.900 --> 00:49:42.930 is how do we use some of the newer agents,

00:49:42.930 --> 00:49:43.624 particularly Adcs,

00:49:43.624 --> 00:49:46.053 and apply some of the things we’ve

00:49:46.053 --> 00:49:47.785 learned from chemotherapy to it

00:49:47.785 --> 00:49:49.765 using gun protein growth and using

00:49:49.829 --> 00:49:51.709 our concepts with tumor geometry.

00:49:53.370 --> 00:49:57.390 And maybe the last question is from

00:49:57.390 --> 00:49:59.150 Doctor Bafan. Thoracic surgery?

00:49:59.150 --> 00:50:01.691 Is the self seating limited to cancer
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 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,
that the stem cells move from one spot to another in a very logical kind of fashion. It isn’t that and people always ask that you know, you know what draws them self to that site. We know this from this from the self seeding work that’s been done in the laboratory. The cells go all over, it’s just where they stick that really matters. So it looks like it’s drawn to that site only ’cause they stuck there and it’s that sticking their stickiness that I think is something that that
that’s being scored by a number of investigators.

You know that particular phenomenon, but I’m sure this happens in general. Look at wound healing.

You know you heal your wound, your surgeons, married to rod cells are brought in there and that’s what allows.

The wound to heal so that so that I I 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 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,
that the mathematics we workout in one area may relate to all these other areas as well. And that once we understand, developed these mathematical principles, that we can actually use them to generalize beyond cancer into heart disease. We know that colonial meta polices cells are important in arteriosclerotic heart disease as well as as we just discussed with cancer as well, so that these principles may generalize and have much more replicability. Can we squeeze one more question. This is from an Chang former memorial colleague who are now
our Chief Network Officer.

She’s asked, can we exploit Atascosa specific or other gene processes in the tumor microenvironment to prevent? Self seating in the niche of growth.

Yeah yeah, great another great question. You know something that Joe and I, Joe and Megan. I thought a very early days when we started doing this when we started started doing this when we started doing this work and I remember that we published the paper with 2009, so it’s been a lot of time this past and and and you know,
we know that cytokines in
flammatory cytokines are important
for the process and that’s already
that may be why inflammation is
such a problem is related to cancer.
But I want to get the things that
are more targetable than that.
And so that’s one of the reasons
why that very last slide that I
showed you was very complicated
mathematical slide is we are right now doing a number of
different studies looking at gene
interactive networks using the
same basic mathematical principles.
In fact, trying to see what are the gene interactions that may underlie that process, because that will tell us what, what genes we maybe have development chemicals to, medicines to to be able to target, medicines to to be able to be able to target, to interfere with this, the just there’s something in that regard I think is is really important. Is that? We focused on so much of our energy in terms of medicinal chemistry on targeting genes or gene products,
and one of the things we’re learning by using that mathematics and looking at gene interaction networks is this is yes, indeed is the action of individual genes, but it’s not the action of individual genes by themselves. They’re all interacting with each other, and it’s the whole network of genes that actually forms a meaningful biological entity and not just the individual genes. So we’re going to have to target those interactions rather than target the genes themselves, and that’s not something that we commonly.
Although we probably do it, we don’t realize we do it with therapy.

When you give steroids to a patient for all the reasons that we give Google Corticoids for a patient you’re attaching to Google Corticoid receptors all over the place, and you’re basically affecting gene interaction networks all over the place by using some of the most powerful drugs that we have.
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 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
drugs could be repurposed for this reason. And you may not be able to put your finger on exactly why they work, but you could just show that they are working in the show. They have clinical utility. And that’s a very different way of thinking about medicinal chemistry. Rather than saying I’m gonna go after the specific target to actually go after basically the biological effect. Or you know, in general with your agents.
and then move them into clinic on that kind of basis. So those are some of the things that we're thinking about right now. Thank you Larry. This is been really great and we really appreciate your time. I know next year Eric will want to have you here in person again to talk to us and this was really just phenomenal lecture. Even though you dropped off for a few minutes, if you were able to bring everything back and please thank the person who actually called me.
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.