TRANSCRIPT: ASK A SCIENTIST
Tuesday, September 13, 2005
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Speaker: Dr. Martin McMahon; Efim Guzik Distinguished Professor of Cancer Biology, UCSF
Topic: The War on Cancer—Where We Are Now and Hopes for the Future
Host: Juliana Gallin

Juliana Gallin: Hi everyone, thanks for coming to Ask a Scientist tonight, here at the Bazaar Café. Tonight our speaker is Martin McMahon, the Efim Guzik Distinguished Professor of Cancer Biology at UCSF. He's going to be talking to us about the War on Cancer. Welcome, Martin! *[Applause]*

Martin McMahon: Well I want to start off by thanking Juliana for the invitation. It's always a fun thing to do, to come and tell people about the different sorts of research that we do. Juliana's success with Ask a Scientist is such an important thing because there's such a growing sophistication of science, and it's so important that scientists who do this stuff communicate with you, the taxpayers who fund it, what it means, what its importance is, and what impact it may have on people's lives. And certainly in the phase of cancer research that we're in right now, we are on the cusp of breakthroughs and discoveries that will help us treat patients with cancer, prevent cancer more effectively, and diagnose it and prognose it, and understand the whole process much more thoroughly than we ever have. And before I actually get into the main part of my talk, I want to emphasize that this is totally informal, and that I'd love you all to ask questions as we go along. Interrupt me if I say something that you don't understand, or if my impenetrable Scottish accent becomes impossible to listen to. *[Laughter]* I can also do scenes from *So I Married an Axe Murderer. [More laughter]*

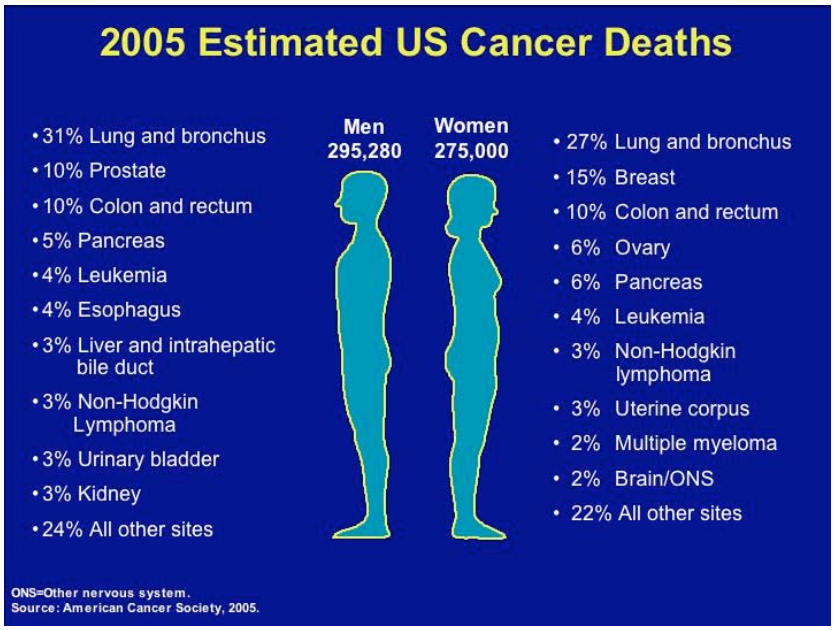
So the topic today is *The War on Cancer,* where we are now and what hope we have for cancer prevention, diagnosis, and therapy. Unfortunately, almost every talk on cancer, really, has to emphasize initially the rather grim statistics of cancer incidence and cancer mortality in the United States, or in the western world generally. A quarter of all U.S. citizens will be afflicted with cancer in their lifetimes and by virtue of the fact that we all have relatives or friends or loved ones or even ourselves, we will all come into contact with cancer at some point in our lives. And in 1993 there were roughly 1.2 million new diagnoses of cancer in the United States and of those roughly a half million cancer deaths in that same year. Roughly 20% of all U.S. citizens will die of cancer, so it's a pretty sobering thought, the incidence of this disease in our society.

Attendee: What are the statistics like world wide?

McMahon: Cancer, because of the way it develops is a disease of older people, and so in those societies where there are more immediate health concerns, like healthcare early on in life, infectious disease and so on, those societites tend to have lesser incidence of cancer because people don't actually live long enough to develop the disease. But as India and China, for instance, are developing, and the longevity statistics in those societies are rising because infectious diseases are being dealt with more thoroughly, cancer will become a major problem in those countries. And in fact China is a case in point. There is a smoking epidemic in China which is unlike anything we've ever seen anywhere in the world. The same is true in India to some extent. The incidence of lung cancer in China is going to go through the roof in about 10, 15 years' time unless major public health measures are taken in China to try and educate people to the dangers of smoking. The same will be true for Africa and other countries as the deaths from preventable, communicable diseases, and issues of healthcare and water supply are resolved.

Attendee: So the slide shows that 25% of Americans will get cancer, and 20% will die from it? Is that the current success rate?

McMahon: As we understand it right now, that is the current success rate, yes. Now bear in mind, 20% of U.S. citizens will die of cancer, but they might die of cancer 10 or 15 or 20 years after their diagnosis. And in fact, if 15 or 16 or 17 of those years turn out to be quality years in which their disease is under control, then you can actually say that we've made something of an impact even though those people might ultimately die of cancer. So if you get a cancer diagnosis and you're 65, and your therapy allows you to live to 85, and then you finally succumb to lung cancer or whatever it is at 85, you can imagine that the healthcare has actually done something good for you even though it didn't actually eradicate the cancer. And in fact in some ways we're starting to think about cancer in a way that we think about managing patients with HIV. HIV as a disease is impossible to cure—we don't know how to eradicate the virus from someone who has become infected—but what we do know something about is how to manage patients with HIV so they can live a full and complete life. And even though they may succumb to the virus later in their older years, we can actually provide people with a significant quality of life that they would not have had otherwise. And that's one of the ways that cancer is now being addressed in society. We may not be able to cure it, but we may be able to forestall its effects to the point where you'll actually be able to live a full life.



You'll notice here that the number one cancer for both men and women is lung cancer, and that tells us that immediately that the number one cancer in our society is entirely preventable, because the vast majority of lung cancer deaths are directly attributable to smoking. In men, obviously, prostate cancer is quite common and in women breast cancer is common, and you can see the rest of this here and get a sense of the prevalence of the various types of cancer. Some cancers have got excellent prognoses. If you're diagnosed with early stage breast cancer your prognosis for a complete cure is very good. By contrast if you're diagnosed with pancreatic cancer, the vast majority, sadly, are dead within six months. So there are great disparities in terms of our ability to treat the various different types of cancer, and I'll be more than happy to discuss where those differences lie.

So the War on Cancer has been ongoing now for just over 30 years. It was initiated by Richard Nixon when he was the president and he established the National Cancer Institute in 1974, with the goal of eradicating cancer. In 2005, after 30 years of cancer research and many tens of billions of dollars, I'm sorry to have to say that we haven't made enormous inroads into the statistics of cancer mortality or even cancer incidence. But what we have achieved, at the basic science level, is a complete and revolutionary understanding about where cancer comes from, what the nature of the disease is, and armed with that information, to begin the steps to developing therapies and ways of treating patients with cancer and thinking about ways in which we can prevent people from getting cancer in the first place.

Attendee: Do you think, historically, in the Middle Ages and before, that cancer was as prevalent then?

McMahon: Well lung cancer certainly wasn't, because people didn't smoke in the Middle Ages. So I think that there were cancers, but again one has to be careful, in the Middle Ages people died of small pox, cholera, and so on. And so one would have to go back with really accurate medical records and do an age-adjusted, population-adjusted analysis, and we just simply can't do that. I guess the question you're driving at is, is cancer more prevalent now in our society because of environmental toxins, and because of the way we live our lives?

Attendee: I'm thinking of hydrocarbons, and plastics, and that sort of thing.

McMahon: To the best of my knowledge, there is no specific link between plastics, for instance, and cancer. But nonetheless there are potentially more mutagens in our environment, and by the way in which we manage our food, for instance, it's conceivable that there could be toxins in plastic, but I don't think there's really any strong evidence to support that. If anything, the way we handle our food these days has cut down the incidence of cancer. Something as simple as refrigeration probably has made enormous inroads into the incidence of gastric cancer. And the reason is that aflatoxin, which comes about as a consequence of microorganisms in your food, can propagate when you don't keep food refrigerated. And aflatoxins have a capacity to cause liver cancer and gastric cancer. And so when you refrigerate your meat, and food, you actually minimize the growth of things that can make toxins that could, in principle, promote cancer.

Attendee: So can you attribute that knowledge of those connections to the research from the last 30 years, or did we know that even longer?

McMahon: No, I think a lot of that has come about in recent years.

Attendee: Is there a particular danger from the consumption of red meat, as opposed to a vegetarian diet?

McMahon: There seems to be a clear connection between rates of gastrointestinal, and especially colon, cancer and the consumption of red meat. And so I would say that the consumption of red meat in large amounts probably is a risk factor for colon cancer. I'm not aware of any published studies that say that consumption of tofu in large amounts is potentially a risk factor for cancer, but to be honest with you I'm not an epidemiologist and I'm not sure if anyone's ever done that study. But undoubtedly there is a connection between the consumption of red meat and the susceptibility to colon cancer.

Attendee: You say that lung cancer is linked to smoking, but in some third world countries where women cook indoors I think there's a high level of cancer. Can you comment on that?

McMahon: I really can't comment directly. I can certainly comment on the fact that the products of combustion can contain carcinogens, which if you are in an enclosed environment and inhaling those products of combustion on a daily basis, undoubtedly that could be a risk factor for cancer. But when you think about it, when you light up a cigarette and you suck cigarette smoke into your lungs, you are sucking in the most incredible mixture of cancer promoters, cancer initiators, and substances that will promote the growth of cancer in your lungs. And so I think in that situation there's a clear and direct association, but nonetheless there are definitely other risk factors for cancer of the lung. For instance asbestos exposure, you may be aware of the fact that people who are exposed to asbestos have a propensity for a disease called *mesothelioma*. It's a different type of lung cancer from the one you get with smoking, but nonetheless is definitely a separate risk factor for a different type of lung cancer. And

as far as the combustion from whatever they come from—whether it be cooking or whatever—could definitely be a risk factor.

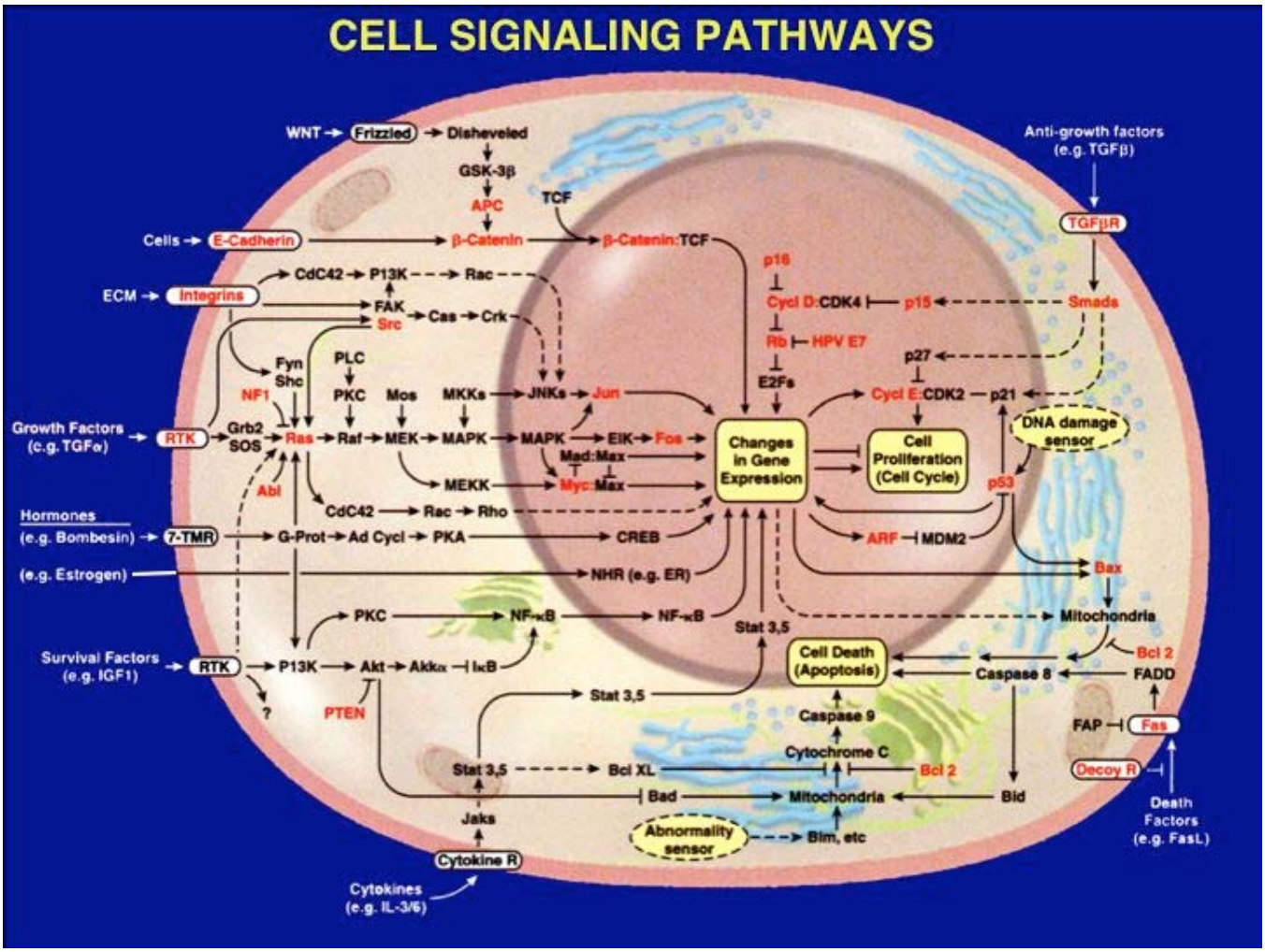
Attendee: Can you go back one slide and talk about that sentence for just a minute?

McMahon: That's actually going to be the main part of my discussion. What we're able to understand through thirty years of research is that there are genes in our bodies, in all of our cells, that are normally involved in the control of normal cell division. And that's the way that we go from being a single cell, a single fertilized oocyte, which we refer to as "the ultimate stem cell"—how a fertilized egg can give rise, from a single cell, to a human being with some 10 to 100 trillion cells. So that one single cell, by a process of many, many rounds of cell division, gives rise to all the cells in the human body. And they go from being a single stem cell with no particular differentiated characteristics to being cells, for instance, from the liver, or the lung, or the heart, or the bone marrow, or the skin, or any one of the things that you recognize as being specialized organs. So the potential for all of our development exists within our chromosomes, which contain all the DNA that programs the way that we develop as human beings.

Our DNA has two copies of every gene—and I'll come back to what a gene is in just a minute—and the DNA in a human cell comprises roughly 3 billion base pairs of information. Those are arranged in 46 chromosomes—and many of you have seen pictures of what the human chromosome look like—and in total there are about 25,000 to 30,000 human genes. That's actually kind of a remarkably low number, because if you sequence the DNA of a simple nematode worm—just a little worm that may be a few millimeters in size—nematode worms have about 16,000 genes. And so when the human genome was about to be sequenced there was a wonderful prediction that we had to be at least ten times more complicated than a worm. Well it turns out, at least in terms of sheer gene number, we're not. We're only about two times more complicated. The likelihood is that we just do more complicated things with combinations of genes.

So, as I said, a typical adult consists of 10 to 100 trillion cells. There are many highly specialized cells, but we do retain adult stem cells. There are cells in our bone marrow and in our muscles and in our brains which have stem cell characteristics, which give rise to the self-renewal capacity when you have to make more cells under certain circumstances.

Now, that process whereby a single cell becomes 10 or 100 trillion cells is exquisitely regulated at the biochemical level. This is a schematic diagram of what a mammalian cell looks like *[see next page]*. This is the outer cell membrane, the exterior of the cell. This is the cell nucleus, where the DNA is contained. And all the instructions for what the cell needs to do come from the interpretation of the instructions in the nucleus. So when a cell receives a signal to grow, which is often a soluble factor floating along in the extracellular milieu, it will bind to a specific receptor on the surface of that cell, and by binding to that receptor, will activate a series of signaling pathways inside the cell to do a number of specific biological processes. If there are any electrical engineers here, you may recognize that some of the details of signal transduction systems in mammalian cells are actually not unlike the way electrical circuits are wired. There are rheostats and switches, there are nodes for signaling, and the way in which a mammalian cell is put together is like an extraordinarily and exquisitely complicated electrical circuit. And the overall response of that cell is coordinated by what the cell sees, in its extracellular milieu, telling it to either divide, or to move, or to become a special cell, or to die in some cases—cells undergo programmed cell death. And that is normally controlled by what we call "cell signaling pathways."

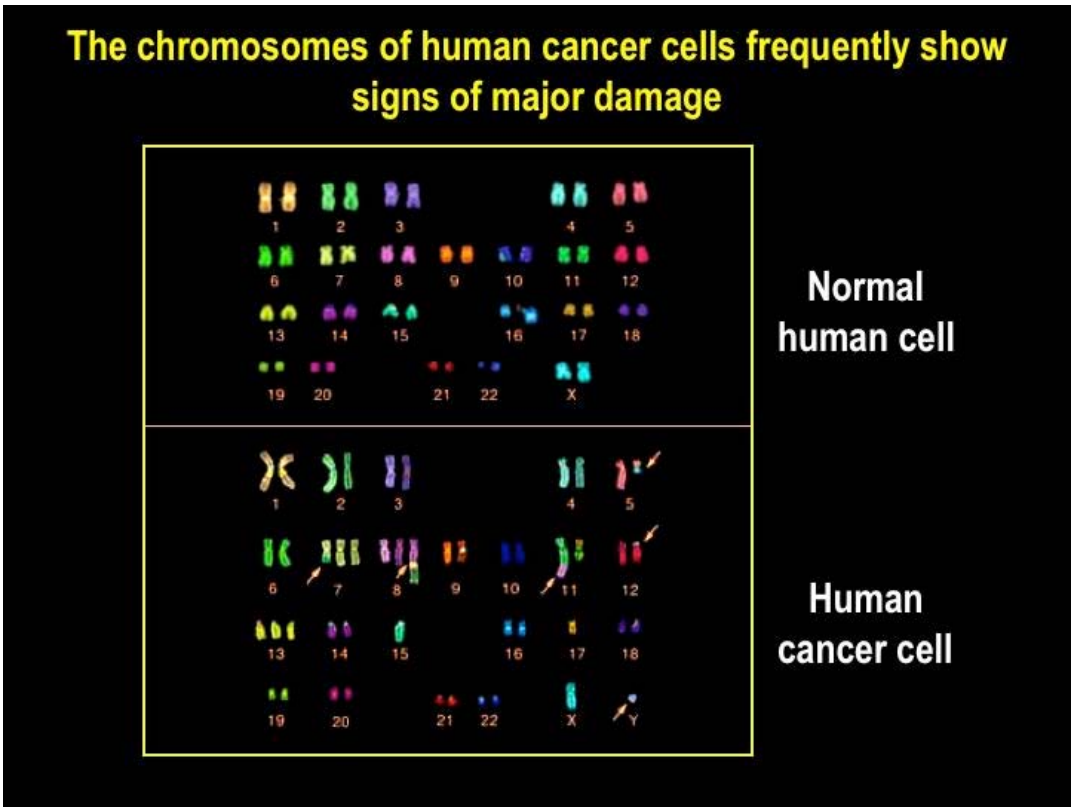


To go into this in some more detail I need to give you just a little bit of background about what we think of as the central paradigm about the genetic information flow in the way mammalian cells work. So, I told we have about 25 or 30,000 genes in our genome. And each one of those genes makes a single protein, which is comprised of amino acids. And to get from the DNA in the chromosome to a protein that goes about in the cell like a little catalyst, making things happen in the cell, there's an intermediate step where you transcribe the DNA into a messenger RNA copy and then there's a machinery in the cell that reads the code and converts the sequence of nucleic acid into a sequence of a protein. An average gene may be comprised of, perhaps, 400 to 500 amino acids—those are the single building blocks of a protein. And those 400 to 500 building blocks are in turn, made up, of a code that comprises 1200 to 1500 bases, because the bases are read by the translation machinery in triplicate. And when this all goes well, a normal gene makes a normal messenger RNA and that will make a normal protein. But in the immortal words of Elvis Costello, "Accidents will happen." *[Laughter]* And through bad luck, defects or mistakes in DNA repair processes, exposure to chemicals, ultraviolet light, second-hand smoke, and so on, one can sometimes get mistakes in the DNA—changes in the sequence of the DNA that changes the ultimate function of the protein that is made by that gene.

Just for an example, imagine there's a sequence of a gene, and it makes a normal protein. We change a single base, that "C" gets changed to a "G," and by that single mutation, what that leads to is perhaps the change of a single amino acid out of 400. And that's exemplified by that little red dot, that one amino acid is no different. But as a consequence of changing that one amino acid the protein now works in a different way. It is no longer regulated in a way that it should be regulated. That's the process of one of

the processes of mutation that drives the process of cancer. In a second I'm going to tell you how that works.

Another process that drives mutation is a process that leads to wholesale changes in chromosomes. That one little point mutation I showed you wouldn't be detectable if you were to simply look down the microscope at a cell because it's such a small tiny change, we don't have microscopes with sufficient resolution. But there are types of genetic abnormalities which occur, which cause wholesale genetic damage.



So this is the composition of human chromosomes in a normal human cell. Anyone want to tell me what gender the person was, who gave this cell?

Attendee: Female.

McMahon: Two X chromosomes, well spotted. And the chromosomes are arranged in pairs, and in this really elegant type of analysis we can use what's called chromosome painting to actually give the individual chromosomes specific colors. These are false colors, that allow you to see each of the individual chromosome components. However, in a cancer cell, you can see here that the normal organization of chromosomes has become completely screwed up. They no longer have the right number of chromosomes, which is normally 46, and they no longer have the right numbers in the right balance, as in two copies of each chromosome. In addition what you can sometimes see, for instance here in this particular case, a piece of a green chromosome has been inadvertently fused to a piece of one of the purple chromosomes. And there are other examples of that sort of thing happening here. Again, that sort of wholesale genetic damage can cause alterations in the cellular signaling pathways that make a normal cell go and become a cancer cell.

Attendee: If you got a bunch of different cells from the same tumor, would you see different patterns or would they all look the same way?

McMahon: That's a really good question, it's actually technologically quite a sophisticated question to answer in the sense that it just depends on what type of cancer you look at. There are some cancers that actually look very like normal human chromosomes. There are some cancers which, if you were to take individual cells, each cell might look a little bit different. But generally speaking, as you'll see in a minute, we believe that there's a selection for specific clones of cells that have a particular ability to divide and proliferate, so there tends to be a dominant population.

Now I've got to define two essential terms: *oncogenes* and *tumor suppressor genes.* So what is an oncogene? We don't have in us genes that are dedicated solely to cancer. Oncogenes are genes that normally make proteins involved in normal cell division—involved in that process of going from one cell to 10 or 100 trillion cells. But oncogenes are genes that if they sustain some sort of genetic damage, they then have the capacity to drive a cell into proliferation in an entirely unrestrained way. What you can think about as an analogy might be like the accelerator on a car. You can apply the gas under normal circumstances and take your foot off the gas to make the car go faster or slower. But imagine you slam a brick on the accelerator and now the car has the capacity for unrestrained movement. And so the genetic damage that occurs in cancer cells can be in oncogenes, which effectively puts the brick on the accelerator. Now if you're fortunate, though, you might have a really good break. So even if you've got a brick on the accelerator, the breaking mechanism might still be sufficient to restrain the car from further movement. And in fact, there are a class of genes in our cells called *tumor suppressor genes*. These are genes whose normal function is to stop cells from growing. And they normally function to make cells come out of the cell division cycle and to stop their proliferative process. And a tumor suppressor gene is a gene that, when it is altered, is like taking your foot off the break. And so the types of genetic damage that occur in these cancer cells are alterations that make the oncogenes work in a sustained and "always on" fashion. They remove the activity of the tumor suppressor genes. And by that combination of the gain of an oncogene, or oncogenes, and the loss of tumor suppressor genes, you then end up with a cell that can proliferate in an unrestrained fashion.

They key point is that oncogenes and tumor suppressor genes have a normal role to play. They play an essential and important role in the normal process of cell division. It's when they are altered by mutations that they end up taking on the activity of genes that play an essential role in cancer development.

Attendee: So are we now trying to come to grips with this and control it at this level?

McMahon: Yep, that's the point.

So what we think happens in cancer is actually a microcosm of cellular evolution. Imagine you have a cell—let's just imagine it's a cell in the colon. Colon cells turn over really quickly, they're constantly being sloughed off and removed, and then they replenish themselves. These cells have a normal cell lifespan. Their lifespan might be limited by being sloughed off, but they also have a process called *programmed cell death* that makes them die when they're no longer of any use. If you imagine that that cell sustains a mutation in an oncogene, and that mutation gives that cell an initial proliferative capacity—it may not be particularly strong and it certainly wouldn't be a cancer—but it might be just enough that that cell can squeeze out a few more cell divisions. Or even that it could somehow avoid the process of being sloughed off, and just hangs out a lot longer. Imagine then, that *that* cell sustains another mutation in a tumor suppressor gene. Now you've got two mutations in that cell. And that tumor suppressor gene mutation combined with the first oncogene mutation gives that cell even further of a proliferative capacity. And this can continue on constantly. And what happens is because there's a powerful selection for cells that grow faster and faster and faster, as the cell accumulates more and more genetic damage, it gives rise to clonal variants that then have a natural selective advantage in our bodies. And that's where we think cancer comes from.

And the reason that cancer is a disease of older people for the most part, is because it takes quite a bit of time for this whole process to occur. In some cases, 5, 10, 15, maybe 20 years from the single mutation that gave rise to that cell until you have enough cells that you would actually then end up in a doctor's office with a cancer diagnosis.

Attendee: Then if you reach that point where you go to the doctor with a tumor, certain cancers grow very quickly in months, and sometimes it takes decades?

McMahon: Sometimes it can. Some cancers are very indolent. It's been suggested that all men over the age of about 75 have prostate cancer. It's just that they have a prostate cancer that is so benignly growing that it's not a threat to their life. And in fact they'll die of natural causes, heart disease, or even lung cancer—and yet they'll die with prostate cancer. And so the rate of growth is obviously a major factor in determining whether that cancer will grow to be life threatening or not.

With lung cancer, one of the powers of cigarette smoking to promote lung cancer is that it contains within it not just substances that make mutations in DNA happen, but substances that can actually make the cancer cell grow even more rapidly than it would do normally. So different cancers might have different growth rates depending on their specific types of mutations, the specific cell type that was initiated, and other environmental factors that can have an influence.

So this is what we think happens in the context of colon cancer. The initial idea is that you might get a mutation that would cause just something like a benign polyp, a small growth that might not even be visible in an endoscope. As that polyp grows in size it then may sustain mutations in other oncogenes. And gradually there is a selection for cells that grow more and more rapidly until such times as the colon cancer then may be clinically obvious by some sort of obstructive process , or alternatively, if you go to your doctor and you have an examination that might detect the presence of polyps in your colon.

However, even up to this stage, when the polyp is still relatively benign and has not begun the process of invasion and metastasis, it's relatively readily curable—because you can actually resect the colon, remove a chunk of it, and as long as the disease has not metastasized to outside of its normal site, generally speaking you can effect a fairly good cure rate for people with colon cancer. The complication is when cells start to invade out of the colon, and they start to invade into the basement membrane and the structures underneath the colon and start to go to places like the liver, and the lungs, brain, and kidneys. Then the disease becomes life-threatening. So this is a pitch for those of you who are over 45, to think about having a colonoscopy. It's not the most pleasant experience in the world, but nonetheless, it could save your life.

Attendee: Do you know how likely it is, say if you get to the third stage [of colon cancer] that you're going to go to the fourth stage, and so on?

McMahon: That's a really complicated question to answer for colon cancer because if you were to look at someone and you found Stage 3, you'd cut it out right away, you'd never wait to find out if it could possibly go forward. The best place that we know this from, is in skin cancer. There are types of lesions called *benign melanocytic nevi,* some of you may even have these things. Often if you go out in the sun and get a withering dose of UV, sometimes you'll get little melanocytic nevi, little dark spots on your skin. You might get several of them. And these are, we think, potentially precursors to melanoma. We already have mutations in genes we know play a role in melanoma. However, we know, also, that someone with 100 or 200 or 300 of those little lesions on their skin, only one of them might progress to the next stage in melanoma development. So there clearly is random chance involved in whether a disease like cancer will progress from Stage 1 to Stage 2 to Stage 3 to Stage 4. And some of the underlying genetic mechanisms that give rise to these mutations can have an impact on whether it will progress or not.

Attendee: Having a lot of meat, for example, does that set up the colon to not slough off as much as it should? Because to me it sounded like you were talking about *[inaudible].*

McMahon: I think the connection between meat and colon cancer is likely due to the presence of mutagens in the meat when you cook it.

Attendee: So it's just something within the meat itself?

McMahon: Yeah, it's not necessarily a physical thing. For instance when you cook—especially if you barbecue, which I love to do—you make a substance called *benzopyrene*. And benzopyrene is a noted mutagen. And it may be that in meat you make a particularly high concentration of it. Fortunately for us we have these exquisite mechanisms of DNA repair, so the vast majority of DNA damage that occurs in any of your cells at any time is fixed, by an elaborate process called *DNA repair* that involves hundreds of different types of enzymes, always monitoring the integrity of your DNA.

I think with meat—although I'm not even sure that it's really completely understood—when you cook meat you can generate mutagens that could then influence the colon cells to then become mutated for a specific one of these oncogenes or tumor suppressor genes.

Attendee: So should we all be eating pre-frozen tartare? *[Laughter]*

McMahon: Everything in moderation—including moderation itself. *[Laughter]*

Attendee: You're suggesting mutations followed by other mutations followed by more. I thought that mutations were rather rare. Is that just because we have *so many* cells?

McMahon: That's a really good point. Mutations are for the most part, relatively rare, in part because we have elaborate mechanisms to fix the damage. The problem is that when you get a mutation in an oncogene or a loss of a tumor suppressor gene, if that is not fixed properly then that cell has a selective advantage. Going back to my slide on this sort of natural selection process, when that cell has sustained a mutation and now gained something that allows it to expand its numbers. And once it's expanded its numbers, then the template, the numbers of cells for which you could get another mutation, the odds ratio goes down. In other words the chance of getting a mutation in one cell is maybe one in a million. If you've got a million cells like that then you're almost guaranteed that you'll get a second mutation.

Question: Aren't mutations usually fatal to the mutating—

McMahon: Again, that's an excellent question. In many cases the mutations would be fatal to the protein or even fatal to the cell. So when you get that rare mutation in an oncogene that is not fatal to the cell, and actually makes the cell grow in an unrestrained fashion, then that cell is powerfully selected for because it them outgrow its neighbors.

Attendee: So you overcome the rarity by having huge, huge numbers?

McMahon: Yep. A good example of this: if you go out in to the sun, and if you've got Scottish skin like I have, and you get a really good dose of UV, and your skin flakes off. The reason it flakes off is because the *keratinocytes,* which are the cells that make up the layers of skin, are dying through a process of programmed cell death. They've recognized they've gotten a lot of damage, they can't fix the damage, and they deliberately commit suicide because it's better that they die and get replaced by new cells that are undamaged then for them to try and fix the damage and continue. And so in that case you get rid of most of the damaged cells because they die. However, if you're unlucky, you might happen to get a mutation in a gene that stops the cell from dying, Now you have in your skin—maybe just one

cell—with one mutation in one gene. But if that cell hangs around and it expands, then it could be subject to another mutation, which would then allow a potential skin cancer to develop.

Cancer cells are very different from their normal counterparts because of these mutations in oncogenes and tumor suppressor genes. And there are six ways that we think cancer cells differ from normal cells. First of all, they are immortal. They grow forever. There's a cell line called *HeLa cells,* that were derived from a woman with cervical cancer some time, I think, in the 1940s. And that cell line has been in culture continuously now for over 65 years, and would have consumed the entire biomass of the planet had we not stopped growing it in culture. By contrast, if I took normal skin cells from…YOU *[pointing]*, they would grow for fifty population doublings in the culture dish and then they would stop growing. And that's because normal human cells are designed to grow for a period of time, and then they stop. Cancer cells evade that process and become immortal.

Cancer cells undergo unscheduled cell division, in other words they grow and they divide in an unrestrained way. They also become remarkably resistant to cell death. That could be cell death that could be induced by normal environmental cues, but also cell death that might be induced if you were to give someone a chemotherapeutic drug designed to kill the cell. They tend to be more resistant.

They're also very resistant to normal antigrowth signals. In our bodies we make factors that can stop cells from growing. However, cancer cells become resistant to these factors and they proliferate even in the face of molecules that would make their normal cell counterparts stop growing.

And then two really important features of the cancer cell are firstly, they can recruit their own blood supply. A tumor could not get bigger than about a cubic millimeter, which is a really tiny and non-threatening disease, unless it recruits for itself a blood supply. Because cancer cells, like any other cells, need oxygen and nutrients to grow. And so the key thing for tumors early in their development is to recruit themselves a blood supply to provide them with the nutrients and take away the waste products of their metabolism.

And then finally, and most importantly, cancer cells have the capacity to pack their bags and pick up from one site, move through the blood or the lymph, and take up residence in a completely new site. *That* is the feature of cancer that makes it most lethal. Generally speaking, most primary tumors could be excised by surgical techniques, and if they didn't metastasize chances are cancer would not necessarily be a major disease, a major killer. However, cancer cells have the remarkable capacity to pack up from one environment, move through a completely hostile and alien environment in the blood, and then go to a tissue or an organ where they would never normally live, and to establish a colony of cells in that site. *That's* the feature of cancer that makes it so lethal.

Attendee: Do you know why cancer metastasizes to certain tissues?

McMahon: Excellent question. So for instance prostate cancer goes to the bone, breast cancer will go either to the lungs or the bone—we really don't have a full understanding of how this works. However there are now sophisticated technologies called *microarrays* that are beginning to make a sort of snapshot of what the cancer cell looks like, to relate that to its biological behavior, and then to try to understand what genes drive a cell to want to go to one site but not in another location. But it's very much a major research question right now. And there were papers in the past two months or so trying to identify signatures of cancer cells that'll tell you where the cell is liable to go and in what site it's liable to take up residence.

So coming back to this *[indicating slide not shown here]*, cancer is a multi-stage disease. It takes many mutations to turn a normal cell into a cancer cell, and it takes time for those mutations to occur and to be selected for. And that's why it may 5, 10, or 15 years or more for a single cell that's been initiated—has that first mutation—to turn into something that is potentially life-threatening. This just simply shows you the notion that you can acquire these mutations at different rates. But the ultimate readout is a cancer cell that has these six biological properties that can be acquired to give rise to that cell's behavior.

Attendee: There are pediatric cancers that hit much younger, though.

McMahon: I knew you were going to ask that. *[Laughter]* So in pediatric cancers the mechanisms are fundamentally rather similar, but for reasons that we don't understand, pediatric leukemias and lymphomas appear to require many less mutations to convert their cells to a leukemic phenotype. And it may reflect the fact that in the process of embriogenesis and development of the immune system, there are particular points in the process where if you get a mutation in a gene, you end up with a leukemia or a lymphoma in children. And that they don't require the sustained and long-term process.

Attendee: It seems like there are a lot of similarities between cancer cells and stem cells.

McMahon: I'm going to come to that right at the very end. That's a great question, a really important question.

Attendee: How does a cell in a benign tumor compare to a malignant tumor vs. a normal cell? Is it similar to a cancer cell in some way?

McMahon: It's kind of halfway between the two. In other words, cells in a benign tumor have, clearly, some enhanced capacity for proliferation. But benign tumors tend not to be very invasive or metastatic. A benign tumor tends to be resident and localized in one spot—often quite well organized if you do histology and pathology sections—and if you look at it you can see that they look abnormal, but they don't look like full-blown metastatic cancer cells.

Attendee: So there could still be something wrong with the oncogenes?

McMahon: Oh yeah, undoubtedly that's the case but it could be that they've not sustained the full list of genetic alterations that make them a fully metastatic cell. They may have gotten two mutations, but they still haven't gotten that key mutation that makes it become metastatic.

Okay, so remember that slide of cell signaling systems. It turns out that oncogenes and tumor suppressor genes are all key components of these signaling nodes. Perhaps that's not surprising given what I've told you. And these molecules work throughout the cell, their normal role is to control normal cell division. But when they're mutated then they tell the cell, "You should be dividing all the time, you should be resistant to death and do all the other things that cancer cells do." The thirty years of cancer research has led us to the understanding that key signaling molecules that normally play a role in normal division are mutated and altered and contribute to cancer cell proliferation. And that observation led to the award of the Nobel Prize to Jay Michael Bishop and Harold Varmus, two UCSF professors in 1989—they were the first UCSF Nobel Prize recipients—because they were the folks that made the understanding in the 1970s that oncogenes are normal genes in our normal genomes that can be altered and subverted by mutation, and turn into genes that can drive a cancer cell's proliferation. And this is a picture *[indicating slide not shown here]* taken in October 1989, right before the Giants beat the Cubs to

get to the World Series *[laughter]* approximately, I believe, ten days before the Loma Prieta earthquake. I can tell you some more stories about this later on if you want. *[Laughter]*

So that's the background. Here's the cancer challenge: thirty years of basic science, tens of billions of dollars of money gone into trying to understand what cancer is all about. How can we take the knowledge of the cancer cell and turn it into better strategies to either prevent, diagnose, or treat cancer? And I think what I'll do is go for five more minutes, and I'll stop and give you guys a break and a chance to get a beer or whatever and we'll pick up again in the next stage.

Let me tell you about cancer drug discovery and how drug discovery works. Imagine you identify, in some particular cancer type, some specific oncogene that you think is driving that cancer cell to grow in an unrestrained way. One potential way to target that cancer cell is to develop an inhibitor that specifically blocked that oncogene, and it could get in there—a spanner in the works—somehow gumming up its mechanism. You could use a high-throughput screening to identify a target inhibitor and then use medicinal chemistry to turn that initial small molecule hit—the druglike molecule—into something that looks like you could actually give it to the patient. You'd have to test that drug in experimental model systems—we use tissue culture systems, we use mouse model systems, a variety of different types of model systems to see if your idea might work. You then have to do what's called pre-clinical evaluation of drug safety—basically you have to administer the drug to a number of different animal system to make sure the drug is not super toxic because of some unexpected side effect or cross-reactivity you didn't know about.

At that point you then have an agent that looks quite promising, and what you then do is file an Investigational New Drug Application with the FDA, which says, "We have a drug, it looks promising in certain model systems, and we would like permission now to go into Phase 1 clinical trials, where you start to administer that drug to human beings." And that's a big jump. You have to be *sure* that you're willing to go down that route, the drug looks promising, that it's safe, and it's not going to give toxicity. When the FDA looks at all your data and they say, yes, we think this looks good, they will then approve you to do a Phase 1 clinical trial. A Phase 1 clinical trial is a trial that is designed to work out how to give the drug, at what dose, and in what regimen. How often should you give the drug, how much of it should you give, at what point do you reach a dose-limiting toxicity where you can't give any more of the drug without killing, or giving major side effects, to the patients.

Phase 1 clinical trials are normally done on the sickest patients. Those are the folks for whom they've done almost every possible therapy, all therapies have failed, and they're willing to take on the burden, if you like, or the opportunity, of being a research subject in a clinical trial. I have to say—where we are in clinical medicine, for treating patients with cancer is on the backs of millions of cancer patients who agreed to be subjects in Phase 1 clinical trials. It's a testament to their bravery to take on with that sort of thing, because often, while the agents won't kill them on their own, nonetheless the benefit is often minimal for those patients. Occasionally there's a home run, but it's rare.

Attendee: So given what you've just said, the benefit is not necessarily to cure the disease, but rather to assess the *[inaudible]*.

McMahon: In a perfect world you might get a cure, and I'm going to give you a very specific example of one situation where that happened. But generally speaking, Phase 1 clinical trials are often done to evaluate the safety of an agent in a patient population who have failed all other conventional forms of therapy.

Attendee: So they're not expecting to be healed.

McMahon: In fact when they go into these trials they're counseled about the fact that the Phase 1 clinical trial is an experimental agent and that there is absolutely no guarantee of any clinical benefit whatsoever. It's a process called *informed consent.*

So your drug looks safe in Phase 1 and you've worked out a regimen where you think you can give the drug, and now you start to target specific diseases, and you do what's called a Phase 2 clinical trial. These are a small number of patients, but they usually have a very specific type of cancer. Imagine you've developed a drug that you think might work specifically in some type of leukemia. Then what you might try to do is register small numbers of patients and test your drug in that patient population. At this point, the doctor giving the drug *and* the patient getting the drug, know they're getting the drug. So it's not in any way double blind or placebo-controlled. Everyone knows what's going on. And based on the results of the Phase 2 clinical trials, if the drug continues to look successful, you do what's called a Phase 3 clinical trial. At this point you now register large numbers of patients so you can do really hardcore statistical analysis of the data. It's double blind, which means the doctor giving the drug doesn't know he's giving the drug vs. the placebo, and the patient receiving the drug doesn't know either. And these are conducted on large numbers of patients, usually In multiple different clinical centers in the U.S. so it's not just one hospital. And at the end of that analysis the trials are unblinded and you can then look at the data and conduct a statistical test to ask if the patients that got the drug did statistically better than the patients that got the placebo.

Attendee: In Phase 2, in round figures, what's illustrative of the number of patients who participate in that trial vs. in Phase 3?

McMahon: I'd say in Phase 2, between maybe a minimum of 15 or 20 patients up to maybe 150 patients. So it could be a sizeable number. A lot depends on how good you think your drug is going to be. So imagine you have a drug you think might cure 10% of patients. You have to power your clinical trial with enough patients in the Phase 3 to show a 10% effect, which might mean you'll need 2,000 patients. Whereas if you think your drug might have an effect in 90% of patients, then the numbers of patients you need—

Attendee: So if you need 2,000 patients for every new drug, and there are —

McMahon: You don't always need 2,000 patients, it just depends on how efficacious you think the drug is going to be. So the Phase 2 clinical trials might tell you that you don't need 2,000 patients. But basically in this game the more patients you do, the more robust your statistics will be, so if you see a difference between the drug and the placebo control you can be sure that it's a real effect and not just a statistical anomaly that is not related to the mechanism of action of the drug.

Attendee: And a smaller variation will be detectable.

McMahon: Right. Classically, in this business, people developing anti-allergy drugs—you take a hundred patients with seasonal allergies and you give them a placebo, and you give another hundred patients Claritin or othert real bona fide anti-allergy drug, 25% of the patients who got the placebo control will say they felt better. And the reason they felt better is that they got "something" that made them feel better, even though it didn't have an effect.

Attendee: But in the case of these trials, are the placebos designed in such a way that they would give the same side effects as the real drug?

McMahon: No, no you can't. So in those circumstances sometimes the doctors and patients will know who's actually on the drug because there are certain side effects. But generally speaking, when you give these agents you've already known from your Phase 1 and Phase 2 clinical trials, what the dose toxicity is, so you're trying to work at a level where there are not major side effects. But it's certainly true that people can know who's getting the drug. And that's why the FDA does a major statistical review of all the data at the end of the clinical trial, to make sure that what's really going on is an effect of the drug, and not a statistical anomaly that's based on observer bias.

And if the FDA is satisfied that you really have an effect, then they will approve your drug for prescription to patients with specific diseases.

Attendee: What about drugs that are tested outside the U.S.? Like in Canada or Mexico?

McMahon: One has to be very careful about therapies that are offered in cowboy clinics in Mexico that have absolutely no scientific validity whatsoever. Shark cartilage would be a good example, or coral calcium. There are no scientific studies that support the use of those agents in clinical trials or in clinical support of cancer patients. There was even this claim that sharks don't get cancer, which is actually not true—sharks do indeed get cancer. So I think one has to be extraordinarily careful about things that are offered outside of the U.S. system. But the vast majority of cancer drugs that I'm aware of—that work—would be equally approvable in the U.S. and in Canada and in Western Europe.

And then finally, once your drug's been approved, it's not necessarily the end of the story. Companies will often try to expand the use of their drugs into different diseases than the one in which they conducted the Phase 3 clinical trial. And they will often do what's called Phase 4 clinical trials, where they will then say, "Ok, we have this drug, it's approved for skin cancer, but we have an idea that maybe it will also work for kidney cancer. We will now enroll and do another clinical trial to see if we can prove statistically with the same rigor as the Phase 3 clinical trial, that this drug works for kidney cancer." The time from beginning to end is somewhere between 10 and 15 years. And the amount of money required to develop that varies a lot, but it can be somewhere between 250 million to a billion dollars in terms of the actual amount of the money required for the drug development process. So it's time consuming and it's heinously expensive.

Attendee: How many fail?

McMahon: One in ten drugs that goes into Phase 1 clinical trial will be approved by the FDA. One in ten.

Attendee: Do you think we should ease up on this, to get the drugs faster?

McMahon: No, I don't think so. What we'll end up with then is bad drugs that don't work. This is an extraordinarily rigorous process that, at the end of the day, if the FDA says, "We think this drug work has a mechanism of action that helps patients with this disease," you can pretty much take that information to the bank. There's a statistical validity and reality to that analysis. If you ease up on it, the danger is you'll get things that go through the process really quickly that won't necessarily work as well as they're expected to. And I should also say, in the example I'll give you in a few minutes, after the break, the FDA can be responsive, fast, when agents look really promising. And that's the next topic, once we've had a break.

Attendee: Is that process with the FDA driven by venture capitalists, by grants, or by government funding?

McMahon: All of the above. Generally speaking, the early stuff is done in both the public sector in University type research and in small biotech companies that would often be funded by venture capital. A lot of the later stuff is done by large pharmaceutical companies because only they have the financial wherewithal to develop the drug through those clinical trials. There is not sufficient money in the university system, nor within the National Cancer Institute, to do this on a routine basis. There are occasional examples of drugs the National Cancer Institute have picked up because the large pharma company didn't want to develop it for whatever reason, and they've been developed through the NCI. But the vast majority of this stuff is done through a public-private sector partnership, whereby the drug companies do the development of the agents, and they will then come to the clinical cancers like UCSF and other places and say, "We have a new drug to treat brain cancer, and we would like to run a clinical trial, to enroll patients through your center," and then it's done in partnership.

Attendee: Can you compare socialist countries, or the Soviet Union to capitalism *[laughter]*, and which has a better track record in curing disease?

McMahon: Let me say that the U.S. is, without a doubt, preeminent in the world in terms of where we've gotten to in terms of cancer research. Western Europe has also made an enormous contribution to what we understand. And the vast majority of all this basic information I've described to you, came from research conducted in our research universities, funded by the U.S. federal government with the dollars you guys paid in taxes, that were then allocated to the NIH and the National Cancer Institute. So the basic science stuff is actually best done in the public sector. The drug discovery stuff, though, is a completely different kettle of fish, best done by the pharma companies because they have the wherewithal and resources to do the sorts of complex medicinal chemistry in drug development that universities are simply not in the business of doing.

And with that, a break.

Gallin: We need to give this guy a break! *[Applause]* Stick around, we'll pick up where we left off in about 15 minutes.

----------BREAK----------

McMahon: I'm drinking Guinness now, so if I start to slur my speech, let me know. *[Laughter]*

So, we ended up with the process of drug discovery, and what I'm going to do is give you an example of one specific situation where the drug discovery process led to a real revolution in the treatment of one specific type of cancer. We think it might be a paradigm for the development of new drugs. There's a disease called *chronic myelogenous leukemia*, that's a blood borne disease, where you get an expansion of cells of the myeloid lineage—these are cells that are normally involved in fighting off infectious agents from the outside. But if they grow in an inappropriate fashion it can become a leukemia. They correspond to about 15 to 20% of all leukemias, and about 10 to 15,000 patients per year. In drug company terms that's actually a rather small number of patients. Nonetheless, as you'll see, the drug that we're going to talk about had a big impact on this disease, and ultimately, a big impact for Novartis, the company that developed it.

Chronic myelogenous leukemia is a progressive and fatal disease. The average age of onset is 50 years. It starts off in what we call the *chronic phase,* and it has a median duration of about 5 to 6 years. And then for reasons we don't entirely understand, but probably related to that alteration of oncogenes and tumor suppressor genes, the disease can progress to what's called an *accelerated phase,* where the cells are growing more rapidly and causing more physiological problems for the patients. And then they

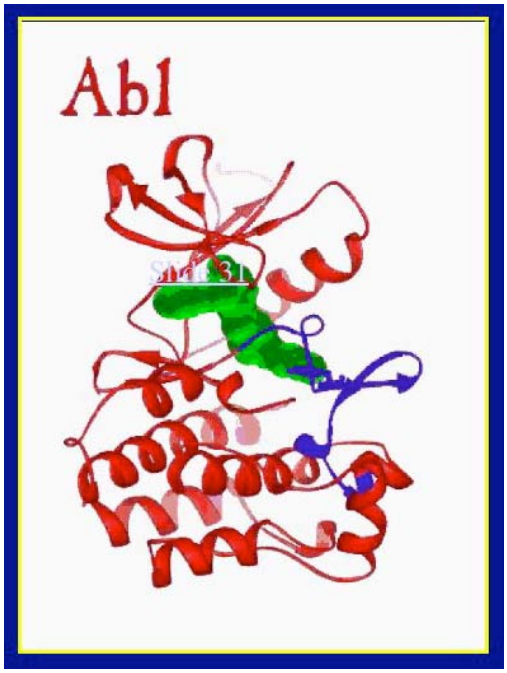
undergo a process called *blast crisis,* where there is some particular clone of cells that grows out of the leukemia that is extraordinarily aggressive, that can invade and metastasize into many organs, and which will actively kill a patient who suffers from the disease.

Over many, many years of research, starting back in the 1960s, through the research funded by the NCI and the NIH and other cancer charities and organizations, the molecular description of what goes on in this disease came to be revealed. It was revealed because when we looked at the chromosomes of the cancer cells they had a very characteristic abnormality. You probably can't see it on here *[indicating slide not shown here]* but a little piece of chromosome 22 was fused onto chromosome 9, and reciprocally, a piece of chromosome 9 was fused onto chromosome 22. This is known as the *Philadelphia chromosome* because it was first glimpsed by Peter Nowell's group in Philadelphia. The consequence of that chromosome alteration is that an oncogene called *ABL* gets fused to another protein called *BCR,* to give rise to the protein called *BCR-ABL,* which is now able to drive these myeloid cells to uncontrolled proliferation. That is the initiating event in the genesis of this disease—that generation of the Philadelphia chromosome that one can see in karyotypic analysis.

Attendee: What organ does that happen in, would that be the marrow?

McMahon: In the bone marrow, yep. These cells arise in the bone marrow and once they've proliferated they then come out into the bloodstream, so you can actually take a little blood smear from a patient and you'll see it in a minute You can tell immediately by looking down the microscope that they've got many, many more white cells than they should have.

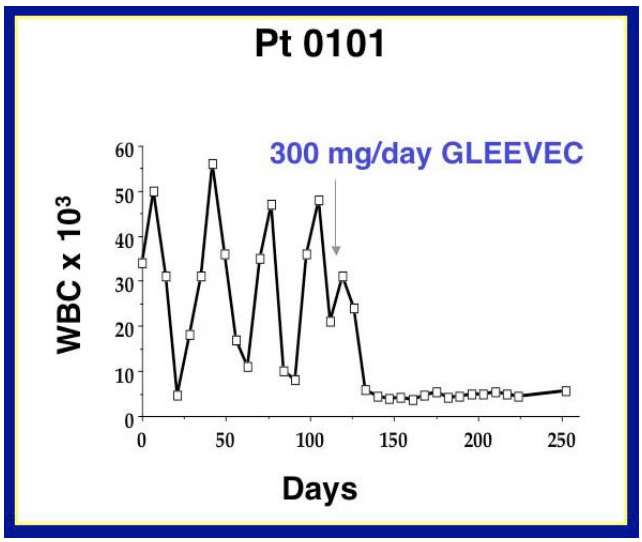
So what is BCR-ABL? BCR-ABL encodes an enzyme that has catalytic function. A little factory that allows one biochemical process to happen very, very efficiently. And what it does is it takes a molecule of ATP, which is an energy generating substrate in our cells, and it transfers one of the phosphate groups onto a whole bunch of other proteins. And they specifically transfer them onto an amino acid called *tyrosine*. It's a process called *tyrosine phosphorylation.* When these target proteins get phosphorylated on tyrosine, it, in turn, changes their function and makes them more active. And the consequence of that process is the activation of all those signaling cascades, that I showed you earlier on, that drive the cell into cell division and uncontrolled proliferation.



The idea was very simple. If one could develop an inhibitor molecule, that bound in the site where ATP normally binds, it could basically be a spanner in the works that would gum up the enzyme and prevent it from working. So the question is, could that be done? Ciba-Geigy, which was then merged with another company to become Novartis, conducted a drug screening procedure where they used a high-throughput assay system for that enzyme, looking for small molecules, pharmacalogic agents, that could bind to the enzyme and block its activity. And they identified a molecule which was originally called STI571—it's now known by its name, Gleevec—which binds to that BCR-ABL molecule in a way that I'll show you in a minute. This is what it looks like if you get the drug from your pharmacy, and these little caplets contains 100 mg of Gleevec. Generally speaking, patients on this drug take 6 to 8 of these a day.

On the next slide *[to left]* is actually the intricate molecular details of what this interaction looks like. The red ribbon

structure shows the structure of the BCR-ABL protein. And the protein folds up into all manner of interesting shapes. These are helical regions, these are sheet regions, and the way that molecule folds up is what makes it a catalyst, that gives its capacity to take phosphate from ATP and put it onto target proteins. And the green thing that you're looking at here is one molecule of the Gleevec inhibitor, bound into the active site of the ABL protein kinase. See how it fits in there really nicely? What it does is it binds into the region of the molecule that would normally bind to ATP and by blocking its normal substrates, Gleevec, which is not a substrate, prevents that molecule from being active.



So the question then became, could one test this in clinical trials and actually see if this has a benefit to patients with, in this particular case, chronic myelogenous leukemia. So here I'm showing you the very first patient in the Phase 1 clinical trial. As I told you, Phase 1 is about dose toxicity, and in most circumstances one rarely sees a clinical benefit for patients. What this shows you is a patient with a diagnosis of chronic myelogenous leukemia, and at the point where he came into the clinic he had way too many white cells in his bloodstream. This initial phase shows him on what was the conventional chemotherapy before Gleevec was put into the clinic, which was a combination of a drug called *interferon* and another drug called *hydroxyurea*. And what you can see here is that the drug would work, and his blood cell counts would drop back to normal, then he would go off the drug because you can't take it all the time—it's a bit toxic—his blood cell counts would come back up again, he'd go back on the drug, they'd come back down, and so on. Then at this point he went on 300mg a day of Gleevec, and you can see for yourself that with continuous taking of this drug his blood cell counts returned to normal in a way that was entirely unexpected. I would think the clinicians who were doing these clinical trials really couldn't believe their eyes. In fact, one patient could just be an anomaly. But as they expanded the numbers of patients from these clinical trials, what they found was a remarkable response rate, even in the Phase 1 clinical trials. The vast majority of patients were showing responses where the cancer cells in their blood were, largely speaking, disappearing, and their blood cell counts were returning to normal. This again shows you a slightly higher dose, 500mg, of Gleevec. But you can see here how all these patients are showing a decrease of their white blood cells, their cancer cells specifically, back down to levels which are almost undetectable.

Using, in some cases, an extraordinarily sensitive test called a *polymerase chain reaction*, you can actually do a molecular analysis for the presence of cancer cells in these people and in many cases what it appeared like was that you couldn't even detect the cancer cells in the patients' blood or bone marrow. But, they were still there. And the reason that they knew they were still there was that sometimes if you give the patient a little bit too much Gleevec, the patient showed differential sensitivities. They get a phenomenon called *myelosuppression*. That's basically a reduction in the numbers of the normal cells that you really need to fight infection in your blood. And so, generally speaking, if the patient shows myelosuppression you either take them off the drug or you reduce the dose of the drug. And in those patients who got removed from Gleevec, within one or two months, the cancer had come back. Even though, with the most sensitive tests we had available to us, we couldn't detect it at the point of the therapy. And that says that there must be some special niche in the body—the bone marrow somewhere, who knows where—where the cancer cells are still hanging around. You can't detect them, but they are there. But at the same time, as long as you remain on the drug, you appear to have fairly long-term and

stable remission of the disease. And in fact, this is an example of clinical trials that went extraordinarily well and have a very *[inaudible]* the FDA to a new drug that looked extraordinarily promising.

So in 1998, the Phase 1 clinical trials on patients who had all failed conventional therapy—so bear in mind that the people who started these trials had already been through multiple cycles of interferon, or hydroxyurea or whatever—of the first 54 patients that were tested, 53 showed a response. That's entirely unprecedented and really quite remarkable.

Now, I told you though, there is an advanced stage of CML where the disease progresses to what's called a blast crisis. And so the drug was also tested in Phase 1 clinical trials on more advanced patients. And again almost all the Phase 1 studies on the blast crisis patients also showed a great response, but the vast majority of those patients relapsed with resistance to the drug within 4 to 8 weeks. And so even the stage of the disease has a big impact. If you can get the patients at the chronic phase, you can get very long-term and sustained remissions. But once the patients have got to the more advanced phase, the cells have the capacity to become remarkably resistant, very quickly. But, nonetheless, these Phase 2 clinical trials led to the approval of Gleevec within two years of its initial introduction into the clinics. And that is the fastest time ever for the approval of a drug from the initiation of clinical trials to an approved agent.

This drug is now the number one therapy for a patient with CML. If you're diagnosed with CML, your doctor will put you on Gleevec almost immediately. Thankfully, the drug is remarkably well tolerated, has relatively minimal side effects, and in those patients who show signs of myelosuppression they can reduce the dose to a level that you're more comfortable with and still achieve a good cancer remission.

Attendee: This is a question about cost to the patient. On a daily basis, would those medicines—what should we be aware that it costs?

McMahon: I actually don't know how much it costs. I think that a year's course of Gleevec probably is somewhere between 10 and 20,000 dollars. But I actually don't know the specifics.

So, it got better for Gleevec, in some regards, because there's a disease called *gastrointestinal stromal tumors*, which is every bit as bad as it sounds. These are solid tumors that tend to occur in and around the stomach, and are the consequence of really large growths of cells in the gastrointestinal tract. They don't have an alteration in ABL, but they have an alteration in another kinase, another enzyme called *KIT*. And it just so happens that KIT is one of the other five enzymes that Gleevec is also able to hit. Gastrointestinal stromal tumors are really pretty rare, there's only a few hundred patients a year, but for that group of patients, when you put them on Gleevec, it works fantastically well. And I've seen these CT scans of patients before and after Gleevec therapy, where they have this massive solid tumor in their GI tract that just melts away. Now I should also say that there are resistance mutations occurring in those patients as well, but nonetheless, GIST was an entirely untreatable disease, and Gleevec at least provides some hope for future therapy, at least for short-term remissions.

These two diseases, *polycythemia vera* and *hypereosinophilic syndrome* are pre-leukemias. They're not full-blown leukemias, but they are diseases that can give rise to abnormal proliferation of cells in the blood, and if left unchecked they can progress to full-blown leukemias. And it turns out that Gleevec is also useful for treating these diseases.

And then in one that I really like myself, and it remains entirely unexplained, patients on Gleevec have shown repigmentation of gray hair. *[Laughter]* It turns out that melanocytes, the cells that make pigment for our skin and our hair, are controlled by this enzyme, KIT. And we don't quite know what it means about blocking KIT in the melanocytes, but something about inhibiting KIT appears to reactivate the

pigmentation process. So this happens in a certain percentage of patients, where all of a sudden they start to make pigment in their melanocytes again, and their hair starts to be dark.

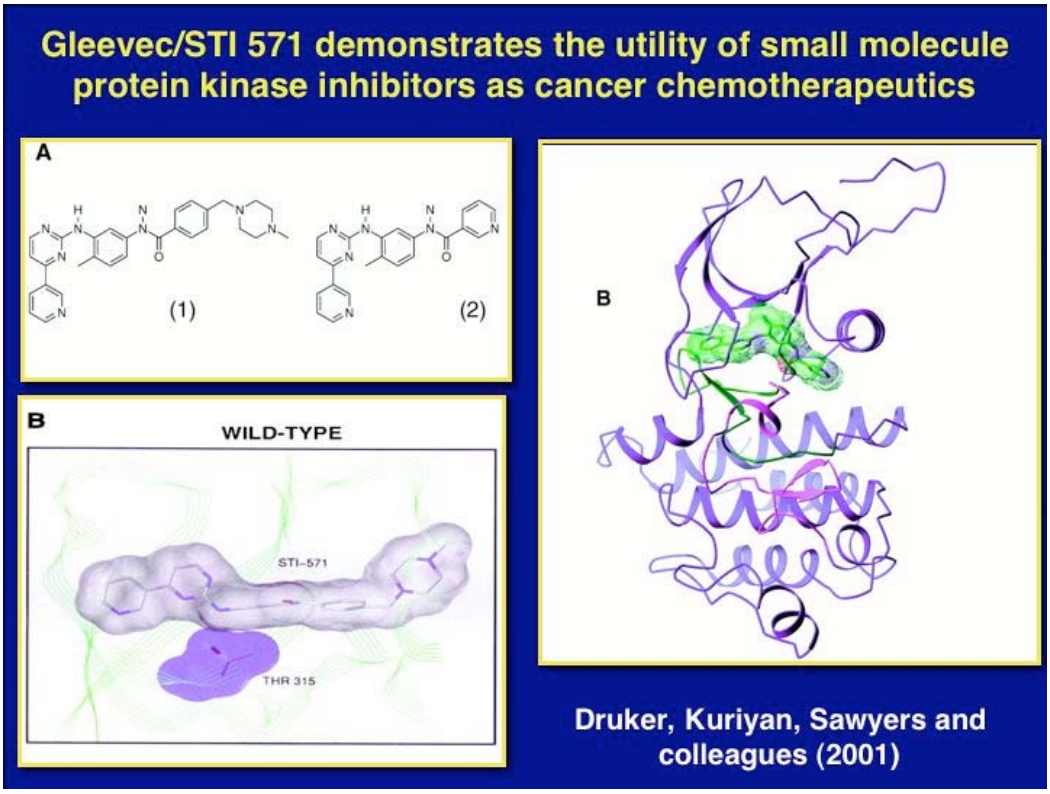
Attendee: So is there a commercial expectation of that? *[Laughter]*

McMahon: No, because it's one of those things—gray hair's not regarded as a life-threatening situation *[laughter]* so you wouldn't give someone a drug that could, in principle, cause their immune system not to work.

Attendee: Well, they would get their money back. *[Laughter]*

McMahon: *[Laughing]* So, but there's bad news as well. So I already told you that patients in blast crisis became rapidly resistant to the drug, and resistance is a feature that occurs in many cancer types in response to all sorts of chemotherapies. And that is also true for Gleevec, it just so happens that we actually know something about the mechanisms. So there are several ways that you can actually cause resistance. Firstly, you can get a process called *gene amplification.* The starting cells have got one copy of the BCR-ABL gene. But you can make much more of the BCR-ABL protein if you amplify the numbers of the copies of that gene. You can go from one copy of the gene, in some cases, to a hundred copies of the gene. And what happens is you then have so much BCR-ABL protein in target cell that you can't dose the patient with enough drug to block the enzyme from being active.

There are also mechanisms of *drug efflux*, where cancer cells will pump the drugs out more quickly, and that also appears to give rise to resistance to Gleevec.



But then one thing I'm going to show you is that you can get genetic mutations in the BCR-ABL gene—single changes in one amino acid that can make the drug unable to bind to the target protein. So here again is a slightly different view of the BCR-ABL gene with Gleevec bound. That's the Gleevec in green and now the BCR-ABL kinase is in purple. And this is kind of a zoomed-in view of Gleevec in the kind of light lilac color—the greenish ribbon in the background is the backbone of the enzyme. And that shows just one amino acid, an amino acid called *threonine*, at position 315. You can see here that the Gleevec drug snuggles up against the threonine really quite closely. What happens is in patients who develop resistance to Gleevec, they do so, often because that threonine gets changed to an *isoleucine*. A very similar amino acid, but as you'll see

it's slightly bigger in its side chain size, and that close interaction that was kind of snuggly is now actually so close that the Gleevec is no longer able to bind, because that isoleucine residue blocks the access to the site that Gleevec binds. See, there's that nice association, but when you get a mutation that changes that threonine to isoleucine, now the Gleevec doesn't bind so well because it's being blocked by that mutation. So this is one of the very common mechanisms of drug resistance for Gleevec, but also for other molecules like Gleevec that target other signaling pathways.

Now there is some good news in this as well, because another company—Bristol-Myers Squibb—have developed a molecule that looks a bit like Gleevec, but which still retains the capacity to bind to this mutated form of the BCR-ABL molecule. And so you can actually play with medicinal chemistry to change the shape of your molecules to take advantage of the fact that even when you get resistance mutations that make you resistant to Gleevec, you can come in with a second drug that will still bind into the active site and block the enzyme from being functional.

Attendee: When you talk about playing with the chemistry to change that, what would you actually—how would that work?

McMahon: Here we go *[indicating slide shown above],* this is the structure of Gleevec here. And you can actually relate the structure of all those rings on this 2-dimensional thing to this 3-dimensional representation. So by medicinal chemistry you can do all sorts of stuff to this molecule. You can build groups on here or here or here, or take stuff off here or here, or knock this group off here—it's amazing what you can do with medicinal chemistry.

Attendee: By adding drops of things?

McMahon Yeah, by just simply changing the chemical synthesis, by adding other compounds in—organic chemistry is the most remarkable discipline. Because using organic chemistry you can synthesize *so many* complex molecules. And you can take a molecule you already have and you can change it *so many* hundreds or thousands of different ways. Even just to change a single hydrogen atom—right there—you can do that, you can add a methyl group, which would be slightly bigger, or an ethylene group, slightly bigger again. Medicinal chemistry is just extraordinarily powerful once you've got a sense of what it is you want to achieve.

So in this particular case you can see here that this ring structure we're looking at is here, and this is it down here, so in principle you could change this oxygen and make a molecule that might bind more efficiently in that site—change the oxygen to a smaller atom like a hydrogen. And that's what drug companies are fantastically good at because they've got medicinal chemists that know molecules, and can change them around and do all manner of interesting and clever things with these molecules, to make them into better drugs.

Attendee: Sounds like they have a lot of supercomputers to do a lot of 3-D imaging of these molecules.

McMahon: Yep, right. So this structure here is actually done by a process called *x-ray crystallography,* where you make a crystal of your enzyme and you fire x-rays at it. And the way in which the x-rays get scattered onto detectors allow you to go back and work out the ribbon structure where every single atom in that protein can be worked out exactly where it's located.

Attendee: *[Inaudible]*

McMahon: Right. So that's a very insightful question. So you're absolutely right, when you make a crystal of a molecule it doesn't always retain precisely the same conformation. But in many cases it does, and enzymes like protein kinases appear to be pretty good. The other technique that people use is a technique called *NMR, nuclear magnetic resonance,* where you actually solve the structure in solution. And then you see the molecule with all the water molecules attached to it. So there's a variety of different techniques that you can use to get a sort of molecular, atom-by-atom picture of your enzyme with the inhibitor bound in the site here.

Okay, so I'm going to shift gears now. I've just spent the past 10 or 15 minutes talking about a success story. I'll tell you about two more success stories that are slightly different approaches to the problem of cancer. So if this is Gleevec as a molecule *[indicating slide not shown here]*, it's a small molecule, its molecular weight is less than 600—it's a technical thing, but simply means that the molecule can gain free access into the cell. It can diffuse across the cell membrane. The types of molecules I'm going to talk about next are much, much bigger. These are antibody molecules, about 250 times bigger. These molecules can not gain access to the inside of the cell because they're too big, but they can be used to target surfaces on the cell that are presented to the outside environment. I'm going to talk about two drugs—one is called *Herceptin,* which is used in breast cancer, and the other one is called *Avastin*, which is used in colon cancer. And both of these drugs were developed by folks at Genentech. So this is one of the big avenues of research in cancer, which is the development of antibody therapeutics to target diseases.

In a certain population of breast cancer patients, roughly about 20% of all breast cancer patients, they have a protein on the surface of the cell called *erbB2*. And erbB2 is a signaling molecule, it's one of these oncogenes that presses the gas to make the cell divide more rapidly. And when the erbB2 is on the surface of the cell it stimulates the cells to undergo proliferation, to give an enhanced survival and enhanced invasion and migration. And what the folks at Genentech did was to develop an antibody molecule that bound specifically, and only, to Herceptin on the outside of the cell. And when the Herceptin binds to the erbB2 molecule on the outside of the cell, it forces the cell to internalize the erbB2 from the membrane. And it turns out that once erbB2 goes inside of a cell, in this internalization process, it is no longer able to send the signals for proliferation, survival, and invasion.

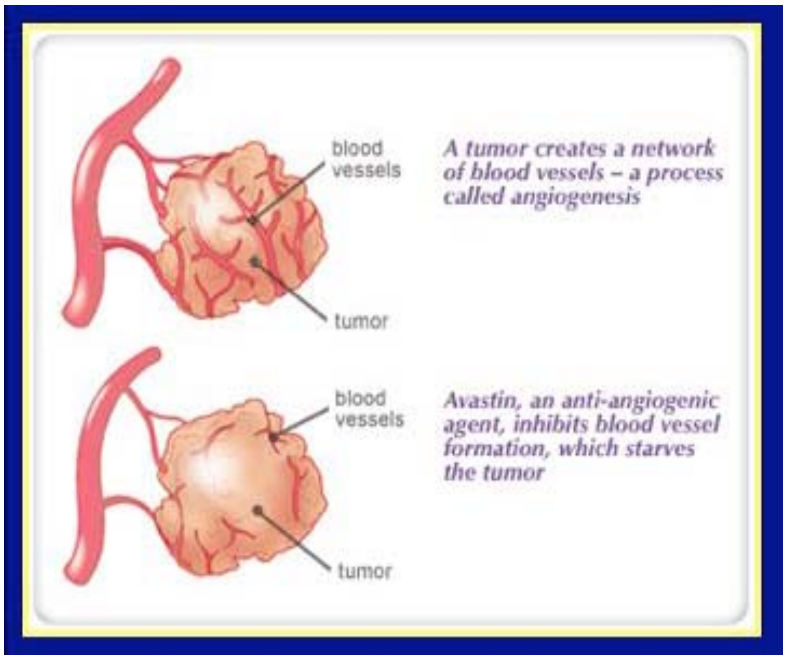
The use of that antibody, then, allows, in a certain subpopulation of patients, to give you down-regulation of the signaling from this guy *[indicating slide not shown here]* and slowing, or inhibition of the proliferation of the cancer cell. Now I should say this is an example where combination chemotherapy was key, because it turned out that Herceptin on its own doesn't work particularly good. But if you combine Herceptin with a drug called *Taxol,* which I'm sure many of you may have heard about—Taxol plus Herceptin appears to give you a much better clinical benefit than either Taxol alone or Herceptin alone. And so combination chemotherapy is definitely one of the ways in which we are beginning to move forward in terms of what we think about as *targeted* or *rational* drug design, combining it with agents like Taxol that have more cytotoxic—that have more toxic compounds.

Now, we still don't really know how best to use this drug. As I said, 20% of women have erbB2 on the surface of their cells, 80% don't. And in those folks that don't have it there's no point in giving them Herceptin. It doesn't work. Even in the 20% that *do* have the erbB2 on the surface of their cell, only 50% or so of those patients will actually respond. And we don't know why that is. It could be something to do with the Herceptin, or it could be something to do with the combination of the Taxol—it's a research question that's currently being investigated.

When this molecule, Herceptin, was originally approved, it was approved for patients with late stage breast cancer that had already metastasized. However, Genentech recently completed a major clinical

trial in a large number of breast cancer patients, where early stage breast cancer patients were then streamed into two groups. They either got Herceptin or didn't get Herceptin, to ask if you gave the drug even earlier could you have a clinical benefit. And there was a clear cut statistical benefit of early treatment of breast cancer patients that have erbB2, with Herceptin. And the drug is now being approved more generally, for earlier stage intervention.

The second antibody I want to talk about is a thing called *Avastin,* and this is something that doesn't even target the cancer cells. This is a molecule that targets the supporting endothelial cells that give rise to the blood vessels. As I mentioned early on, cancer cannot grow beyond a very small size unless it is able to recruit blood vessels. And a very astute scientist and clinician, Judah Folkman, who works at Harvard, proposed the idea that if you could develop drugs that blocked the cancer's blood vessel supply, that you might then be able to prevent cancer cells from growing. And this is the concept here—this is a cancer having recruited a blood supply allowing it to get oxygen and nutrients and to take away the waste products of metabolism. And the idea was, if you could block that process, the tumors would have much less vasculature and therefore that would create a toxic environment that would either kill the tumor cells or even might promote chemotherapy-induced killing.



And the way this works, we think, is that the tumor cells—in order to recruit a blood supply—release molecules called *angiogenic factors.* There's just simply growth factors that endothelial cells like. And endothelial cells are the cells that line the blood vessels. What they do is they make a particular molecule, in many cases, called *vascular endothelial growth factor.* Just simply a factor that endothelial cells like. When they see it they grow, and when they see it coming from a specific source they will grow towards that specific source. So you can see how a tumor cell making VEGF, which is what everyone calls it, will then recruit blood vessels into the local microenvironment and promote the growth of the blood supply. And again, the folks at Genentech, particularly a fellow by the name of Napoleon Ferrara, developed an antibody which would recognize VEGF. So this is VEGF *[indicating slide not shown here]* now on its endothelial cell. It has a receptor that would instruct the endothelial cell to grow. So VEGF binds to its receptor and says to the endothelial cells, "Hey, start to divide and come over here."

Genentech made an antibody called Avastin that will now bind to VEGF and prevent it from binding to its receptor. And by doing that it prevents this recruitment of blood vessels into the tumors. The initial studies that were done in this situation were done in breast cancer and in colon cancer. But the breast cancer trial was a complete bust. There was no benefit of Avastin in that setting because it turns out that breast cancer cells don't use this molecule to recruit a blood supply, they use a completely different molecule called FGF. But in the colon cancer trials, the Avastin had a significant impact on the survival of patients with metastatic colon cancer in the liver. So again, tailoring the drugs to specific diseases is also really important. If we go back to Gleevec—the super successful drug for CML—if you try it in melanoma, for instance, it doesn't work at all. You need to know about the cancer cell and what its

particular pathways are, so that you can apply the drugs that you need, or you use, in a rational and scientifically based way. And that was also true for this Avastin and VEGF.

Attendee: *[Inaudible]*

McMahon: So, they clearly show enhanced survival. And these were patients that were already pretty sick. The increase in survival was about five months in the clinical trials that were conducted. The next question then, is if you start to use Avastin in earlier stage disease, to what extent could you even further extend the lifespan of the patients. And moreover, what would happen if you combined Avastin with a conventional chemotherapeutic? If you target the cancer cell *and* the endothelial cell, maybe you'll get an even better benefit. And again, all these drugs that have been approved, the reality is that a drug approval is not the end of the story. There is still an enormous amount of additional research that goes on in how to optimize the drugs, how to use them in combination chemotherapy—and even when you've got dosing schedules, sometimes changing the dosing schedule, in a different experimental paradigm, in a different disease, can change the way the outcome of the disease goes.

So we're getting close to the end. This is now my, sort of, prognostications for what we think is going to happen in the future. There are three really big areas. The first one is cancer prevention. The second one is early detection, diagnosis, and prognosis. And then new and better treatments.

Prevention. Clearly, what's the old adage, "An ounce of prevention is worth a pound of cure." And if we knew all the things in our environment and in our lifestyle that cause cancer, we could—that's the best way, by far the best way. And there are some really obvious ones. Smoking cessation is the number one. As I told you, lung cancer is the most prevalent disease in our society—90% of all lung cancers are caused by smoking, and if smoking goes away, lung cancer will, largely speaking, become a less prevalent disease. The other one we've talked a little bit about is to limit sun, or UV, exposure. The main cause of melanoma, and the main cause of most skin cancers, is excessive exposure to UV light. There are major environmental issues here because of the fact that the depletion of the ozone layer means that we're all seeing more UV than we ever used to see. And if you are a light-skinned Scottish person and then you move to Australia or New Zealand, you're going to be subjected to major doses of UV. And so sun protection, covering up, and so on are all really important aspects. And again since we live in San Francisco we don't have to worry too much about too much summer sun, right? *[Laughter]*

One thing I also want to emphasize is that although viruses, generally speaking, don't cause cancer, viruses can create inflammatory processes that can promote cancer. And the three best examples here are probably hepatitis B virus, hepatitis C virus, and human papiloma virus. Hepatitis B and hepatitis C cause lots and lots of liver inflammation, because of the ongoing viral replication. And that sets up a microenvironment where cancer cells can be selected for. There are now vaccines for HPV, there's a vaccine in development for hepatitis C virus, and those are going to make a big impact, I think, on the prevalence of *hepatocellular carcinoma*, liver cancer.

Now if there is one virus that might cause cancer, it's human papiloma virus. Two particular forms of this virus, HPV 16 and 18, are directly linked to cervical cancer in women. And what's really exciting for this is that two companies—Glaxo Smith Kline and Novartis—are now working on vaccines for papiloma virus that look *fantastic* as preventatives, to prevent infection with papiloma virus in the first place. And again, this is a fantastic example of the public-private collaboration. Much of the work on the vaccine development was actually conducted at the National Cancer Institute, by colleagues of mine who've done a spectacular job in devising the vaccines. And they have now licensed these vaccines to companies who are actually now doing—in Costa Rica is the main clinical trial—looking at the ability of the vaccine to prevent infection in young women, and then ultimately looking for outcomes to see if

it prevents cervical cancer. And I strongly predict that in the next 15 years, or maybe less, that there will be a vaccine that will, largely speaking, prevent papiloma-induced cervical cancer. It may not do it for all of them, but it will do it for the vast majority of them. And it will become routine, I suspect, the papiloma virus vaccination.

We need to identify and minimize our dietary and environmental factors. We've talked about red meat, for instance—I think we all know that eating too much red meat is not such a great thing. I wouldn't say you should cut red meat out of your diet—I certainly wouldn't tend to—but again, moderation is probably a good thing. But this is such a political hot-button issue, in the sense that we really don't know what the dietary and environmental factors are. And there's a whole lot of research going on to try to identify what those factors might be, what are the sources of these factors and how can we minimize our exposure to such factors.

One of the other things that's clear cut is that we can have intrinsic genetic resistance or susceptibility to cancer, so everyone's probably got a lucky Uncle Harry or a lucky Auntie Jane who smoked 40 unfiltered cigarettes [per day] all of her life and got run down by a double-decker bus when she was 80. Right? *[Laughter]* Had no lung cancer. And it's undoubtedly clear from studies in mice, and also from humans, that some people can smoke and will not get lung cancer—even though the vast majority who smoke will be very strongly at risk for lung cancer. We don't know anything about that process. However, it turns out this genetic resistance can be studied in mice. It turns out that some strains of mice are extraordinarily resistant to cancer, and some strains of mice are extraordinarily susceptible to cancer. And if you make crosses of those mice you can identify genes that are involved in the resistance or susceptibility process. Since those mouse genes will have counterparts in human beings, by studying the process in the mouse we might be able to identify human susceptibility and resistance loci, such that in 20 years' time you might go to a doctor and he'll say, "I've looked at all your risk factors for cancer, and here's what we think you might have a risk for." And then give you an opportunity to think about ways in which you can monitor your health, especially for something like pancreatic cancer, where the biggest problem is knowing when to look for it and how to find it.

And then the final thing is this thing called *chemoprevention*. This is a very new idea, but it's already at play in medicine. There are a number of women in high-risk breast cancer families—for whatever reason, often genetic mutations are transmitted in the germ line, from mother to daughter, and they're at extraordinarily high risk for breast cancer. And it's known in that group, based on clinical trials, that if those young women initiate Tamoxifen therapy who are at risk for breast cancer, that taking Tamoxifen can actually prevent them from developing breast cancer. And so if we could identify mechanisms of chemoprevention for other types of cancer, it could be that one could take a relatively innocuous substance, in a fashion that would protect you from a cancer that you know you're at risk for. It's an extraordinarily complicated issue, and it may not be for everyone, but if you, for instance, came from a family where you knew prostate cancer ran in the family, and there was a chemopreventitive agent that could actually prevent prostate cancer cells from growing, you might consider taking it. But it would be your prerogative to decide.

Attendee: Why would you not take a drug like that?

McMahon Well, I mean someone people just don't like taking even an aspirin. So these are things that are entirely up to each individual. Some people are very suspicious of the motivations of the drug companies and might feel they're being manipulated. And there's all manner of reasons why people might or might not take a given drug. There are people who won't give their kids a blood transfusion, and all sorts of stuff like that.

Attendee: On the last slide, you were talking about how inflammation can cause cancer—

McMahon: It can promote cancer—

Attendee: Or promote cancer—would you already have to have had a mutated cell there?

McMahon: Sometimes localized inflammation can actually generate reactive chemicals that can cause mutations. So for instance there's an enzyme called *COX 2, or cyclooxygenase 2*, which is the target for Vioxx, Celebrex, and all of these more modern pain killers. And the reason that the heart connection in Vioxx was found was because Merck was doing a clinical trial to ask if taking Vioxx, which blocks inflammation, could prevent colon cancer. And they noticed in their colon cancer clinical trials that there was a much higher incidence of adverse heart events in the patients that were taking the Vioxx compared to the placebo control.

So what is undoubtedly clear is that if you have chronic rheumatoid arthritis, that Vioxx and its relatives are fantastically good drugs. However, there is clearly an increased risk for heart disease. But there's also evidence that the same enzyme that's involved in—that's a target for this drug—is also involved in creating a local inflammatory environment in the colon that can promote colon cancer. There are very elegant studies done in mice that directly identify that same enzyme as being required and responsible for certain aspects of colon cancer development. So the reason Merck was doing that was they were hoping that Vioxx might be a chemopreventitive for colon cancer. And that process is being played out in other types of cancers where inflammatory processes might be important, especially very early on in the disease.

Okay, so better detection, diagnosis and prognosis. For many of the major internal organ cancers, if you could diagnose it earlier, you could do a much better job clinically. Best example here is pancreas cancer. Pancreas cancer is almost uniformly fatal. Reason is, is that most folks don't show up in the clinic until they have a late stage disease. And the reason for that is because the symptoms of pancreas cancer are really nebulous: lower back pain, maybe a little bit of jaundice, maybe unexplained weight loss, a variety of things you can readily dismiss—even your clinician might dismiss as being just the products of getting a little bit older. And so if we had better tools to diagnose pancreas cancer earlier, we could do a better job surgically and probably do a better job with therapy, like chemotherapy.

There are some incredible things coming down the pike. So these nanotechnology sensors—any of you guys ever see the film *Fantastic Voyage*, where they shrank the submarine and it goes into this guy to cure the brain cancer? That's definitely science fiction, but there are tools being developed for nanosensors that you could literally inject into your body and it could monitor specific types of cancer—either the presence or absence of cancer, or the response to therapy. Is your cancer dying when you give a patient a specific drug. And these are very much cutting edge research questions, but definitely the sorts of things that are happening and will happen over the course of the next ten years.

This process of microarrays, which is a high-throughput way of taking signatures of cancers—that I'll tell you about in a second—is also being used to profile individual cancers. In other words, if I have a prostate cancer and you have a prostate cancer, to what extent are they similar, and to what extent would analyzing that prostate cancer tell us about how I would respond to a particular drug and how someone else would respond to that drug. And I'll come to that right at the very end.

And then, microarray technology to identify cancers that need more radical intervention—what we call *bad actors*. You take a hundred Stage I breast cancer patients, and you resect the tumor, 80% of those patients will do just fine after their follow-up. Five years from then they will have no signs of breast

cancer and it will not recur. 20% of those patients, however, *will* recur and they will come back into the clinic within five years and they will have metastatic breast cancer that will have gone to the lungs or the bone or somewhere else. And right now we can't tell the difference between those hundred women as to who are likely to be the ones that are going to relapse, and who are the ones that are likely to be ok. So these high-throughput expression signature techniques are allowing us to take those hundred women, assess on a tumor-by-tumor basis the signature of that tumor, and relate the signature for the outcome. So that when the next hundred women come along you can analyze their tumors and say, "You've got a signature of a good disease, you've got a signature of a bad disease, and because of that we'll now give you a somewhat more aggressive chemotherapy regimen to try and prevent this relapse process from happening five years from now. And that's, again, very much a technique that's going on, and that's in the area of prognosis.

And then finally, better treatments. I've already told you about Gleevec and some other agents that have looked very promising and looked really good. There's a whole bunch of new things coming down the pike. Will they all work? No. Certainly not. Will some of them be like Gleevec? We certainly hope so. But there's undoubtedly going to be a whole lot of molecules which I think will have an impact in cancer treatment.

One of the other areas of excitement, which has not yet borne any fruit, is a cancer vaccine. If you could identify the target molecules to which you could raise an immune response, it's possible that if you show up in the clinic with an early stage prostate cancer we'd actually administer a prostate cancer vaccine that would basically freeze the cancer cells, or even kill them, in such a fashion that you could then prevent the prostate cancer from progressing. And this is being explored for prostate cancer, breast cancer, melanoma, and many other cancer types. One particular agent that's in the most advanced stage and looks most promising is a thing called *Provenge,* which is a prostate cancer vaccine. And there's a whole bunch of other ones that are being worked on right now.

Oncolytic viruses. There are viruses that are engineered specifically to get into cancer cells and kill them. They don't kill normal cells, they kill cancer cells. It's a very experimental idea, but these have already been tested in the clinic and have shown some initial promise. And there's a whole bunch of different small companies and university labs that are developing this whole concept of making a virus that will only get into the cancer cell and take advantage of the genetics to kill that cell.

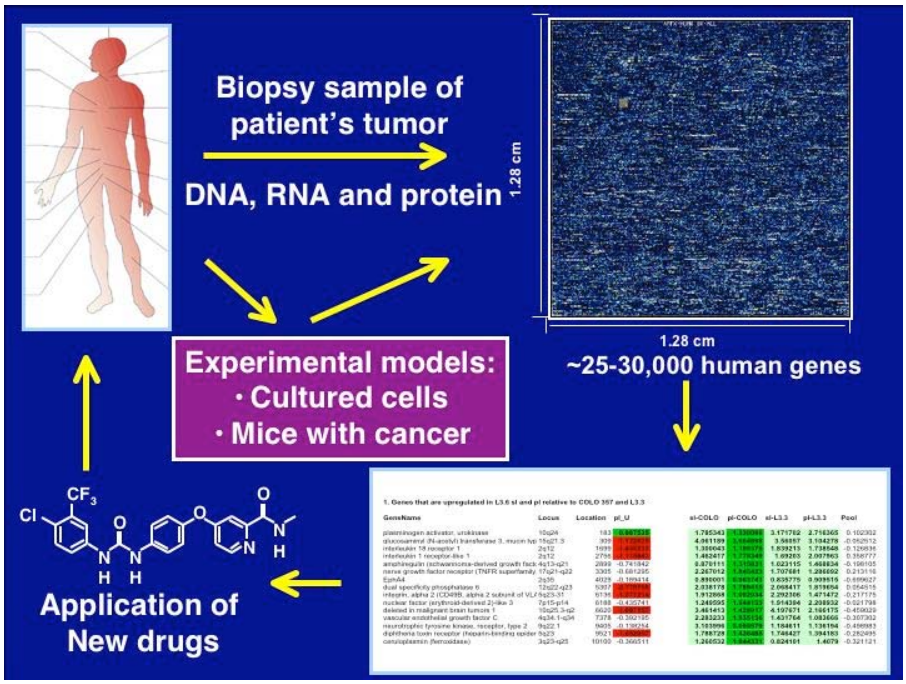
There's room for complimentary and alternative medicine, either directly in cancer chemotherapy, or in things like "quality of life" issues. And undoubtedly there are ways in which this type of approach could have an influence.

And then finally, someone asked me earlier on about stem cells. This is one of the big things that's happening right now in cancer, is the recognition that maybe cancer is a disease not just of genetics and DNA but also specifically of cancer stem cells. And here is what we think might be going on—and again, it's far from proven, so I'm giving you this idea as it's one that currently consuming a lot of time and effort. Imagine that you have a cancer, and that within that cancer there's a cancer stem cell population. And that from that stem cell population you can always renew the cancer, such that if you treat the disease with drugs that kill the tumor cells but don't target the cancer stem cells, you might get an initial response to therapy, but because the cancer stem cells are still around, once you go off the therapy the cancer stem cells can then proliferate and give rise to a brand new cancer. And in fact this is what many of the conventional chemotherapeutics seem to do. Even Gleevec, which is remarkably successful in myelogenous leukemia, appears not to be able to target the cancer stem cell population that gives rise to the tumor. And I already told you that if you take patients off of Gleevec the tumors will

come back pretty quickly. We believe that somewhere in the body there's a cancer stem cell that is not blocked by Gleevec, which can entirely give you cancer again.

So if we knew more about these cells, it's conceivable that if we had drugs that specifically targeted the cancer stem cell, we could knock these cells off and kill them in such a fashion that even though we don't kill the other cells these guys are just going to run their normal course and just die out. And it's because the cancer stem cell is constantly priming the pump, that the tumor has a continuous capacity to grow.

Now I'll be honest with you, this is still somewhat of a controversial idea. There is some evidence to support this idea, but there's also evidence that maybe says it's not true. And so I think there's a lot of basic research that will be done to actually try and identify if this is case or not. But it definitely opens up a new avenue of research, not just for treatments that extend life but for things that might actually cure people and actually get rid of the cancer.



So this is what I think cancer therapy may look like in five years' time. A patient will come into the clinic with any one of a number of different types of cancers. A biopsy sample of that patient's tumor will be removed and then subjected to what we call *microarray analysis.* So this is an example of a microarray, millions of little tiny elements that can profile each individual gene in that cell. That will then give rise to a molecular signature that will be unique for that person's cancer—different from any other cancer, even cancers of the same type from a different patient. And that analysis will give rise to a signature. It will say, "This oncogene is on, this tumor suppressor gene is off." Or, "These three oncogenes are on, these three tumor suppressor genes are off." And based on that combination, we predict from prior analysis that if you give Drug X, you ought to be able to get some clinical response. And that what you'll end up with, in principle, is highly personalized cancer medication. Not a "one size fits all" type of approach, but an approach where the drugs are directly tailored to the cancer patient in a fashion where you should be able to effect a more efficient cancer remission and control. In the meantime, this is all being worked out with experimental model systems in the context of lab-based research that's going on both in the university system and in the private sector. And the reality is that the success in managing or conquering cancer will end up being a public-private sector collaboration. The drug companies can't do the basic research that we can do at the universities, and the universities can't do the types of drug development stuff that the biotech companies and pharma companies are expert at.

Attendee: What about genetic testing, will that be more important ahead of time, for the susceptibility to cancer?

McMahon: Yeah, so that's a good question. There is already genetic testing available for certain genes, especially for families where there's a known history of particular types of cancer. So I think if we had really good identifiers, where you knew that a particular gene was a high probability of causing a specific cancer, then there's a strong justification for having such a test. There are really big issues associated with that, for instance the information has to be entirely confidential because you wouldn't want insurance companies taking that information and then changing your premiums on your life insurance. It's also very important, your genetic information is private information that only you should have. And so I think, from a scientific standpoint, I have no doubt that tests will be developed. The question is how best to use the tests—should everyone have all the tests or should you tailor them to specific individuals with specific known risk factors? And how do you identify what those risk factors are?

Attendee: So if someone takes a genetic test and they're armed, personally, with that information—because there are companies now that provide this, confidentially—what would someone do? Is there even a mechanism in place to accept a person with that information?

McMahon: Well so, generally speaking, if you're going to get genetic tests, I would say you should probably not be going directly to a company to ask for a genetic test. If a genetic test is being done it should be in the context of a consultation with either your primary care physician or, if you know you're in a family that has a high risk of some particular type of cancer, with an oncologist who can give you specific advice. Because when someone just gives you the information, you don't know what to do with it. But your oncologist or your physician should be able to help you make decisions. So for instance, in patients who have identified mutations in the BRCA1 or BRCA2 genes, there are a variety of options that offered, the most radical of which are prophylactic mastectomy and removal of ovaries. And that will pretty much guarantee that you won't get breast cancer or ovarian cancer, but that's a fairly major intervention that one would not want to take on lightly. Alternatively, the simpler intervention is Tamoxifen. Every patient has to decide what they think is the most important way of managing their disease. And until we have much more information about how much of a risk a specific gene alteration has—so there are some diseases where if you've got the BRCA1 mutation you're almost guaranteed of getting breast cancer; however, there are other genetic alterations where if you've got the gene alteration you maybe have a 20% increased risk of cancer. And is that 20% increased risk something that you can manage? Or is it something you need to do some sort of surgical intervention? And there are some sort of surgical interventions that just don't work. I mean, you can't take all your skin off. If you've got a melanoma susceptibility gene, clearly in that case you're forced to deal with the fact that you're going to have to monitor your skin and keep an eye out for unusual lesions.

So then in the final slide, if this will work—which I don't think it's going to work—this is the one little piece of data from my lab that I wanted to show, and I'm not sure it's going to work. But let's see if it will. It's a time-lapsed video microscopy of cells growing in culture. And the big problem in cancer is cancer cells—*[looking at video]* there we go! Okay so, nothing's going to happen in this video for quite some time, but when it starts to happen, you'll see it. The big problem in cancer is invasion and metastasis. As I told you, if you could just get primary cancers all you'd need to deal with would be cutting out and removing the residual cancer, we wouldn't have to worry about the process of invasion and metastasis. But, cancer cells have a remarkable capacity to pick up and move. And what you're going to see here is an experiment that was done by a summer student in my lab, where he watched a bunch of normal cells in culture, that had been seeded specifically with cancer cells, and you're going to watch these guys coming in from here. The cancer cells—see how motile they are? And how static the normal cells are? So that's the issue. And then what you can see here is that the cancer cells start to pretty much destroy everything around them. And by the end of the video, what you'll see is that pretty

much the cancer cells have come to dominate the culture and the normal cells have all been either destroyed or they have picked up and packed their little suitcases and got the hell out of there.

[Sorry, video not available here.]

This is a process that we need to understand more about. It's the process that we know the least about in cancer, but there's an enormous amount of effort going in now to trying to identify how these cells can pick up from one site—even in a petri dish—and move from one site to another site. And by this process we can maybe think about ways to stop invasion and metastasis.

Attendee: What kind of cells are these?

McMahon: These are actually fibroblastic cells. Cells of mesangial origins, like connective tissue. Could be found in muscle—almost any tissue whatsoever. It's an experimental model system that we use in the lab.

Attendee: What is the time frame?

McMahon: It's down here—so we started off at zero and we're now at 86 hours. And you can see how these cells—I mean, so now they've just taken over the culture dish.

Attendee: It's like a horror movie!

Attendee: Of course I know cancer isn't contagious, but could there be danger for people in the lab to be handling cancer cells?

McMahon: If you're handling human cancer cells, we take precautions about how they are used. So one would be cautious about if—you wouldn't want to spill them on yourself. You couldn't ingest them through your nose or your mouth or whatever because your body's immune system and your mucosal surfaces will prevent those cells from gaining access. If you were to cut yourself and drop cancer cells on the surface of the cut, it's conceivable that they could gain access to your body. And if the cancer cell was not particularly immunogenic, even though it came from a completely different person, it could take up residence. However, the truth of the matter is I'm not aware of any incidents, I don't think, of any researcher having become contaminated with cancer cells that they were working with, and that led to them having a major health problem. Unlike virus work, where you could infect yourself with hepatitis or HIV or any one of a number of viruses that could then replicate. I'm not aware of anyone ever having had that problem.

Attendee: So once the cell's infected by an oncogene, it's not like they're viral *[inaudible]* DNA could transfer to a different cell in a different organism *[inaudible]?*

McMahon: No, these cells are not infected. So one example is the human papiloma virus, which has in it its own oncogenes. In that case it brings in oncogenes from the outside. But in the vast majority of human cancers, once the mutation happens in the cancer cell, that mutation cannot be picked up and moved to a completely normal cell. Basically, it resides in that cancer cell and will expand with the cell, but it doesn't jump from one cell to another like a virus or a bacterium could do. You can't catch cancer from anyone else.

Attendee: So with papiloma—

McMahon: Papiloma's a very special example, but an important one because the papiloma virus—I said that most viruses don't cause cancer—but there's no doubt that papiloma viruses contain, within their DNA, oncogenes. And they're pretty unusual in that regard, and it's clear that the oncogenes of papiloma virus are involved in making the cells of the cervix grow in an abnormal way. So when you get infected with HPV 16 or 18, the oncogenes in the virus make the cells of the cervix that get infected, proliferate in an abnormal way. It's not enough for a full-blown cancer, but it definitely appears to be enough to initiate the process.

Attendee: Once again, the Herceptin and the Avastin, sounds like those are drugs that once you start to take them you have to take them for the rest of your life?

McMahon: I suspect that's the case, though it's too early to say with Avastin yet. But I believe that if you're on Herceptin, that may be a constant administration. But you do it in cycles. I think it's usually maybe one week on, three weeks off. So it's not as if you're taking it all the time. And there are some side effects associated with herceptin, for instance, breast cancer patients who've got a prior history of heart disease can not take Herceptin because it turns out the very same molecule that's important in breast cancer is also important in normal cardiac function. And if you block it in the heart, in some patients with prior heart disease, you can actually precipitate a second or third cardiac event. So there's a variety of contraindications in certain situations like that.

[So sorry readers, tape cuts off about ten minutes before the end of the talk.]

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