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While she's writing that up, I also wanted to clarify a point that was raised by a TA last time at the end of last lecture. Some of you might have thought about this fact, and it's important to clarify at least as best we can.

I told you last time that people who inherit a defective copy of the RB, retinoblastoma tumor susceptibility gene are highly predisposed to the development of retinoblastoma, a tumor of the eye. Actually, these patients end up getting bilateral retinoblastoma, affecting both eyes, and typically have about a dozen tumors, independent tumors.

And, if you recall, those tumors arise through the loss of the normal copy of the RB gene in the cells that give rise to these tumors. And I also told you that the RB gene is a critical regulator of cell cycle progression. And so you might have wondered why don't these people get all sorts of tumors? Why are they predisposed only to retinoblastomas?

Why not breast cancer, lung cancer, pancreatic cancer and so on? We don't actually know in complete detail why that is, but we suspect that there's a fundamental difference between retinal cells and other cells with respect to their requirement for RB gene function. So I told you previously that RB is a regulator of the cell cycle. Specifically it regulates the entry of cells from the G1 phase of the cell cycle into S phase. It blocks. And it has to, itself, be inactivated for tumor development.

Or rather for normal cell cycle progression. And we think that in retinal cells this is the key regulator of S phase progression, of S cell cycle entry, so that if you get rid of it you now have deregulated cell cycle control and tumor development. And we suspect that in other cells where RB is almost certainly important --

-- there are probably other factors, let's call them X, which can also regulate cell cycle progression. So that even if the cell were to lose RB, there are other factors that can, in a sense, back it up. And in these cells, in most of your cells, although RB loss might contribute to tumor formation, it's not sufficient. In these cells other events must be necessary to inactivate, one way or another, these X functions. OK? So hopefully that helps clarify.

Now, I told you last time, the last two times that we now think of cancer as a clonal progression from normal cells to tumor cells. The acquisition of mutations in cellular genes, oncogenes, tumor suppressor genes, and collectively these

give rise to cells that are malignant and potentially life-threatening. This is interesting information from a scientific point of view, but is it useful? Why do we want to understand these cancer-associated genes?

Why do we want to understand these mutations? Well, there are a variety of reasons why. We're going to focus today on therapy which is directed against the mutations that arise in cancers. But there are other purposes that I just want to mention to you.

Early detection. Cancer is most easily treated when caught early. If we know somebody has cancer, before the cancer has spread, they have a much better chance of curing that individual.

And so it's desirable to have tests for early detection. And increasingly there are PCR-based tests looking for cancer cells in bodily fluids. Sometimes the blood, urine or other tissues. PCR-based tests looking for mutations in the cancer-associated genes, looking for cells that have a Ras mutation or have a p53 mutation or have an RB gene mutation and so on.

So this is not commonplace, but there are now tests, commercially available tests that are based on PCR looking for such mutations. There are also blood tests for what we call cancer markers.

You've probably heard of the PSA test for prostate cancer. There are certain other tests for other types of cancer. These are blood tests that detect inappropriate levels of something, often something produced by the cancer. And, again, increasingly, as we understand what happens in cancer cells, we'll have more and more precise cancer makers that will be detectable in the blood in a very simple screening test so that you can go to the doctor every year, go through one of these tests and know whether or not you have an early form of one or another type of cancer.

That's not, again, happening today, at least in a widespread way, but it will happen in the years to come. And when it does, we will be in a position to do what we call cancer prevention. Rather than waiting until somebody has a full-blown tumor and trying to treat it, which is difficult, we will hopefully detect those tumors at a very early stage and then prevent their progression.

So this is not treating cancer really, but treating the hyperplasias I told you about.

Or early lesions, benign lesions before they progress to true cancer. And we think that this will be easier to do because those cancer cells will have acquired fewer mutations. And, therefore, it will be easier to design very specific agents that will effectively limit their proliferation or possibly even kill them.

OK. Today we're going to focus on the use of this information for better therapies, ways to design more effective, more specific anti-cancer agents. And I'll come towards the end to using this information and related information to do better diagnosis to try to distinguish two people who have clinically similar tumors.

But those tumors might actually be quite different at the molecular level, and we'd like to understand that. OK. Before we get into sort of the New Age cancer treatments, I thought I should at least mention to you conventional therapies.

Right now, if you have to have cancer treatment, you might get one of the drugs that I'm going to tell you about later in the lecture, but more likely you're going to get what we call a conventional anti-cancer treatment. And these anti-cancer treatments have actually been around for quite some time, and they do work. They do work, but they don't work as well as we need them to work. Radiation is a very common anti-cancer agent, as you probably are aware.

And there are a variety of drugs that we list along with radiation like Adriamycin, Cisplatin. And there are a variety of other chemical agents, which together are grouped because they cause DNA damage. These are DNA damaging agents, and they're also effective anti-cancer agents.

There's another category of anti-cancer agents which is exemplified by a drug called Taxol, and there is a series of Taxol-related compounds. And these are microtubule inhibitors. Microtubule inhibitors. And these therefore, microtubules are important in mitosis, if you'll remember the mitotic spindle. So these are anti-mitotic drugs.

And these drugs do work. And we think that they work in part because cancer cells are rapidly dividing cells compared to most normal cells in your body. And, therefore, if you damage their DNA or you block their ability to divide you'll more effectively block cancer growth compared to normal cell growth.

Now, overall, in the context of cancer, what we're looking for, and actually in the context of other diseases as well is something called a therapeutic window. A therapeutic window is defined as a difference in the concentration of a drug necessary to kill the cell of interest versus normal cells in the body. These drugs, anti-mitotics and DNA damaging agents will kill normal cells.

So if you look at a graph of percent killing versus drug concentration, normal cells will eventually die. The hope is that cancer cells will die sooner. And this difference is defined as the therapeutic window.

And that does exist for many of these drugs for many different types of cancer. And so these agents will, in fact, give initial responses. Unfortunately, they tend not to be, tend not be durable. That is patients tend to relapse. Not always but

tend to relapse in response to these agents. This slide just makes the same point that many of the drugs that we know about affect the cell cycle either in S phase during DNA synthesis or in M phase during mitosis.

And this also points out that many of these agents cause the death of cancer cells by inducing apoptosis, inducing the death of cells. In contrast to most, but not all, most normal cells in the body, which in response to that same concentration of drug, will not die. And instead those cells will arrest at some point in the cell cycle and repair the damage.

And the difference, what makes up the therapeutic window in many cases, is that the cancer cells are dying at a given concentration, the normal cells are staying alive and simply arresting. However, there are other cells in the body that in response to the same drug at the same concentration will undergo apoptosis. And you actually know what those cells are if you've thought about cancer chemotherapy before. It's the cells that support the hair follicles.

Those cells die in response to these drugs. And that's why cancer patients lose their hair. It is cells in the blood, in the bone marrow which will die in response to these concentrations. And that's why cancer patients get anemic. And in cells of the lining of the stomach and intestine which will die in response to these drugs. And that's why cancer patients feel sick, feel nauseous. So there are side effects in response to these drugs.

And that's because many cells, some cells in your body will also die by apoptosis. Now, we've learned, actually my lab has participated in this process, that the p53 tumor suppressor gene that I've told you about is actually quite important in guiding the responsive cells to these drugs. Many normal cells turn on p53 in response to this damage and arrest. Those other cells that I just told you about will turn on p53 and die.

And cancer cells, likewise, if they have a functional p53 gene will turn it on. And this will induce apoptosis. And it's the difference between cancer cells turning on p53 and dying compared to normal cells turning on p53 and resting, it gives the therapeutic window. Unfortunately, as I've mentioned to you, about 50% of human cancers carry p53 mutations. And given that p53 is important in this response, if you don't have p53 then you won't die, or won't die as effectively, and that limits the therapeutic window.

And this is one of the reasons why cancer therapy is not as good as it should be and why cancer cells will sometimes come back, because they're now no longer responsive to the drug, at least especially responsive to the drug. So we'd like to do better, and we think we can do better by taking advantage of the information that we've gained over the last 30 years about cancer-associated mutations.

And I'm going to review for you in detail the first three of these new agents, all three FDA approved in the last five years or so for the treatment of one or another type of cancer. And I'll also mention anti-Ras therapies, although we don't have an FDA approved drug for those. If there's time I'll mention inhibitors of an enzyme called telomerase, as well as anti-angiogenesis. There are other therapies, not drug-based therapies but other therapies that are under consideration, and in some places in use.

Gene therapy, replacing cancer mutation genes. Immunotherapy, trying to convince your immune system to attack your cancer. And also cancer prevention strategies, which I mentioned actually last time, trying to make vaccines against viruses that are associated with certain types of cancer including human papillomavirus and cervical cancer. So Ras is the first one that I'd like to mention to you.

And it's an example of where we haven't done enough. We don't know enough. Even though we know that Ras is mutated in 30% of human tumors, 30%, 90% of pancreatic cancers carry Ras mutations. Pancreatic cancer is one of the worst killers in the cancer category. If you get pancreatic cancer, of a particular type at least, it's a very, very, very serious disease. We know that these tumors carry mutations in the Ras gene but we cannot do anything about it at the moment.

So, as I've told you, Ras proteins are involved in signaling proliferation. And this takes place through kinase cascades, phosphorylating enzymes that phosphorylate other enzymes in a cascade. When you have a mutation in Ras, it turns the protein on in a constitutive fashion leading to increased signaling down these pathways and increased proliferation.

We know some of these enzymes. I've told you about Raf and MEK and MAP kinase. And so many drug companies are now trying to find inhibitors that might block those enzymes, small molecule inhibitors, drugs.

And because these are kinases, the approach is to try to find ATP analogs. Drugs that look like ATP, can get into the active site of the enzyme and compete for ATP, and thereby block enzyme function. Some of these drugs work, at least in cells in culture.

There's a bit of a fear that these pathways are so commonly used in normal cells that the drugs might be highly toxic and therefore not tolerated. And, importantly, we don't understand what these arrows mean well enough. We have some basic ideas, but we don't have enough detail to know exactly which kinase to inhibit in exactly which type of tumor. So this is in progress but it's not quite there yet. I'll come back to another couple of stories related to ATP analogs that do work and are now in use in cancer treatment.

Before I do, I want to mention another class of inhibitors, and these are antibodies.

Antibody-directed therapy. Cancer cells often up-regulate proteins on their surface. I mentioned one last time in the context of breast cancer.

It's a protein called HER2. I mentioned the fact that 30% of breast cancers have an amplification of the HER2 gene and, therefore, make more of this HER2 receptor on their cell surface. So, in contrast to normal cells which will have a certain concentration of this receptor on their surface, cancer cells, breast cancer cells that carry this amplification will have a much higher density.

Maybe ten times or a hundred times the level of this receptor on their surface. And they are using that increased level of receptor to increase the signal downstream of that receptor to promote proliferation. Now, the receptor is responding to ligands as it would normally do. And therapy is based on the fact that the ligand has to bind to the receptor in order to activate it.

And so what was done by a company called Genentech out in California was to make antibodies that block to the receptor, that bind to the receptor and block the binding of the ligand to the receptor. So these are anti-HER2 antibodies. And this drug, which is now approved by the FDA, is called Herceptin.

And it works. For those breast cancer patients who have amplification, too much of this receptor on their surface, Herceptin works and can give them months, sometimes years of symptom-free survival. It's not curative, unfortunately, but it does extend life. And it's therefore an extremely important drug. This is just a blocking antibody. There's nothing attached to the antibody. It's just blocking the binding of the receptor to its ligand and thereby blocking the function of the receptor.

But antibodies can also be linked to toxins or radionuclides, and thereby deliver bad stuff to the tumor cell, either a toxin or something that will irradiate this cell. And these are being tested currently. There are no FDA approved versions of this, but I suspect that will change in the years to come.

So Herceptin is an effective antibody-based therapy. There are a couple more now, but it was the first. And this is actually from the Genentech website which gives you a little bit of information about Herceptin and shows you a bottle of Herceptin as you would see in the pharmacy. And this diagram is just a reiteration of what I've told you already. Normal cells have low levels of the receptor on their surface, cancer cells have higher concentrations of the receptor on their surface, and the antibody binds to the receptor thereby blocking its function.

OK? So this is a clear example. We learned that Herceptin was over-expressed in cancer, breast cancer and ovarian cancer. The company made an antibody and it works.

Another story, my favorite story relates to a disease called chronic myelogenous leukemia --

-- or CML. CML is a disease that affects young adults, adults and children. Child patient shown here.

It is leukemia so it's a disease of the blood. It affects both the blood, as well as the bone marrow. And we've learned a lot about this disease over the years. It's not a very common disease. It only affects about 4,000 or 5,000 people in this country per year. And it falls in stages. Initially the person is diagnosed with CML based on relatively low concentrations of, low levels of white blood cells in their circulation.

And then they progress with that phase in what's called the chronic phase where there are still relatively low levels of white blood cells, higher than normal but lower than are dangerous. However, this can progress over time through an accelerated phase where there's even higher levels of white blood cells in the blood to the final phase which is called blast crisis where the levels of white blood cells really shoot up. And this is lethal.

And these patients invariably progress through these stages and eventually died. So what have we done? This is a picture of what the blood cells look like in a normal individual. This is a white blood cell you could see in a CML patient. There are higher levels, and they can be even higher than this. This disease has been studied for a very long time.

And we now know that there's a signature mutation, a mutation that takes place in almost all CML cases. It's a translocation that rearranges two genes called BCR and ABL and places them together on a translocated chromosome. There's a swapping of genetic information from chromosomes 9 and 22 such that there's production of a new gene called BCR-ABL that results in a new protein, a fusion protein that has a little bit of this BCR protein and a little bit of this ABL protein.

And you can see in the karyotypes of these individuals that they have an abnormal chromosome 9 which is a little shorter, sorry, a little longer than it should be, and an abnormal chromosome 22 which is a little shorter than it should be. And when you look at cancer cells of CML patients you always find that translocation. It's called the Philadelphia translocation because it was discovered by researchers in Philadelphia.

And it's sometimes referred to as the Philadelphia chromosome. And, again, it's a translocation involving chromosome 9 which has a gene called ABL which is a tyrosine kinase.

And so it's a signaling protein. And chromosome 22 which has a separate gene called BCR. And, in the development of CML, breaks take place on these two chromosomes leading to a translocation and the formation of a new chromosome that has a fusion gene composed of both BCR and ABL.

And this gives rise to a fusion protein with a piece of BCR and the kinase domain of ABL. And this leads to increased proliferation, as well as increased survival of the cells that carry that translocation, more cells in the blood and eventually leukemia. And the hope is, the hope was, as this was being worked out, actually important experiments done at MIT in the early 1980s here.

As this was being worked out that maybe, because it's such a common mutation in this disease, if you could find an inhibitor --

-- maybe you could block the proliferation of these cells or perhaps induce their death. This just gives you a little a bit, a sort of cartoon version of BCR-ABL signaling. I don't want you to literally pay great attention to this.

Suffice it to say BCR-ABL as a signaling protein stimulates many of the pathways that you've learned about already in this class and causes cells to proliferate, as well as to survive better. So, again, can you find an inhibitor that blocks the activity of this enzyme and thereby blocks the proliferation of these cancer cells? This was undertaken by probably many drug companies in the world, but a drug company now called Novartis, which has its research headquarters here in Cambridge, succeeded.

They generated this drug which goes by the name Gleevec. It has a trade name, the name of which I can never remember, but everybody called it Gleevec when it was being developed. It was also called STI571 but Gleevec is the common name. They found this drug through a screen looking for small molecules that look a little bit like ATP, although it doesn't look much like ATP anymore, that can specifically bind to and block the kinase activity of this particular kinase.

And this drug is successful. It does bind to the kinase and blocks its kinase activity. And importantly in cell lines, as well as in mouse models, it was found to be effective in killing CML cells. It was then used in treatment of CML patients and found to be effective there, too. So the number of white blood cells in these patients dropped dramatically and the number of Philadelphia chromosome positive cells likewise.

So if you were to plot the number of white blood cells in a normal patient it would be low. In a CML patient, in the early phase of the disease it would be down

here, and then it would go up in the accelerated phase and then it would go up still further in blast crisis.

And, as I said, this could take years, several years to progress. And at this stage, late-stage disease, this person might have hundreds of thousands of white blood cells per mill.

But when treated with Gleevec the white blood cell counts dropped to mere normal. And amazingly the drug is extremely well-tolerated. So even though all of your cells have this same ABL kinase, not fused to BCR but the same ABL kinase unfused, and it's probably doing stuff in your cells, those cells don't need it.

But the cancer cells, in the context of this BCR-ABL fusion, are totally dependent on it. And if you inhibit it now the cells will not proliferate anymore. And, indeed, as you can see how precipitous this fall is, the cells will actually die, undergo apoptosis. So the drug is extremely effective. As I said, clinical tests were done. Sorry. This just illustrates a cartoon version of what we've been talking about. Here's the BCR-ABL protein.

Here it's in its normal state binding to ATP and transferring a phosphate to some substrate protein in the context of signaling. And what Gleevec does is binds to the ATP pocket and blocks the access of ATP to the enzyme and, therefore, blocks the kinase activity. And this is actual clinical data provided by Novartis in this case. And what you're looking at here is the number of Philadelphia chromosome positive cells in the blood.

And what percentage reduction you're seeing, either somewhat or completely, looking at the accepted therapy before Gleevec came along, which was not very effective, only 12% of patients showed any response, or rather a major response, and only 3% showed a complete response. That is when you looked in their blood by PCR you could find no more Philadelphia chromosome positive cells.

But now with Gleevec, 75% of patients showed a major response. And 54% of patients showed a complete response, you could not find Philadelphia chromosome positive cells by PCR in the blood of these patients. So it really worked extremely well.

It gave what we call clinical remissions. Clinical remissions. And these patients survived, had, you know, dramatically extended lifetimes. This would go on for in some cases as little as a half a year, in other cases up to ten years increased survival, especially if the patients were treated early in the disease. But unfortunately for all the patients the numbers went back up.

Clinical relapse. An all too familiar problem in cancer therapy. You might see initial treatments, they might even last a while, but too many patients undergo

relapses where their disease comes back. So what's going on here? These patients are continuing to receive Gleevec throughout this course, and yet the tumors are returning.

Why? What might be going on? Remember that cancer cells acquire mutations? Cancer cells are always acquiring mutations. So what kind of mutation might be taking place in these cells that would lead them to be Gleevec resistant? Well, maybe they're acquiring mutations within the BCR-ABL gene, that fusion gene, which blocks their ability to bind the drug.

So Charles Sawyers, investigator at UCLA, took the cancer cells from these relapsed patients, PCR-ed up the BCR-ABL gene, sequenced it, and lo and behold he found a bunch of mutations. Individual tumors had one or another of these point mutations within the ABL kinase.

And the consequence of those mutations was that the drug Gleevec could no longer bind. And that's illustrated here. So this is, again, a cutaway view of the BCR-ABL kinase. Here's Gleevec where it normally sits, but that red dot is a mutation that sticks an amino acid side chain right in the way of where Gleevec binds.

So now it cannot bind anymore. The drug cannot bind, it cannot be effective, cancer cells come back. OK? So that's a problem. What are you going to do about it? What can be done? What would you do?

Maybe we could find a drug that will bind even if there is a mutation there. And that actually works and that's why this Gleevec fits nicely into that pocket and blocks the activity. So this enzyme is inhibited. The problem is that apparently invariably mutant BCR-ABLs arise which are Gleevec resistant.

So you can have Gleevec around, but it cannot get in there, the enzyme still functions, it still causes proliferation. But working with a different drug company, Charles Sawyers screened new drugs. And he found a drug which has a similar but slightly different shape than Gleevec, and it's able to bind to the mutant BCR-ABLs.

This drug is called BMS-354825 produced by Bristol-Myers Squibb. And just in December of this past year Charles Sawyers reported the first clinical trial with this drug in patients who had failed Gleevec therapy who had relapsed. And 31 out of 36 responded.

And to my knowledge they are still in remission. And the five who didn't respond had a particular kind of mutation that actually also blocked the binding of this drug. But the majority of mutations, even though there are several mutations that will affect Gleevec resistance, the majority of them are still sensitive to this new drug. So this is smart and smart again.

Smart, understanding how cells can be sensitive. Then smart again, finding out how they become resistance. And then smart for a third time, finding new drugs that will bind even in the presence of those resistance mutations. And this, I suspect, is the future of cancer treatments. Understanding the molecular signature mutations, finding specific drugs, and then being prepared to find second-generation drugs that will still work even if resistance arises.

A very similar story, which I'll have to tell you quickly, comes from the world of lung cancer. In this case, several drug companies were trying to find drugs that would block a different tyrosine kinase. This time a receptor tyrosine kinase by the name of epidermal growth factor receptor, EGF receptor.

They were motivated to do so because this receptor is over-expressed, there is too much of it in many types of cancer, including lung cancer.

And so different companies made different drugs. One of them is called Iressa which goes by the trade name Gefitinib. Another made by Genentech is called Tarceva. And these do function as EGF inhibitors, anti-EGF receptor inhibitors. They work. They work in the test-tube. However, when tested in clinical trials they were a spectacular failure. Even for patients who had high levels of EGF receptor on the surface of their cancer cells, the drug didn't do anything.

And they were almost not going to be FDA approved for that purpose, except that a very small number of lung cancer patients responded extremely well to the drug. about 10% of lung cancer patients showed responses like the one I'm showing you here, where this, and outlined in red, is a lung tumor where the tumor is basically filling the entire lobe of the lung.

Six weeks after treatment with this drug Iressa, you can see massive resolution of the tumor. The tumor is almost all gone, and that white stuff is probably just fibrotic tissue. The tumor cells are practically gone. A dramatic response. What's going on? Why do those 10% of patients respond so well? Well, it turns out that those 10% of patients carry a mutation in the EGF receptor gene.

In those 10% of patients, one of the ways the cancer cells are growing and surviving is that they have a mutation that activates this gene making those tumor cells highly dependent on that particular protein in the same way that these cancers are highly dependent on BCR-ABL. And if you deprive those cancer cells of that activity by using these drugs, the cells will die. So this is a good example of what will come in the future of individualized medicine.

If you're a lung cancer patient, you shouldn't just indiscriminately take Iressa because 95% of the time it won't do anything for you. But if you're one of those 10% who has a mutation in this gene, you would benefit dramatically from having it. And that will happen more and more in cancer and other diseases. Your

tumor will be molecularly typed to find out exactly what mutations it has to find out which of a collection of targeted therapies you should be taking.

These patients, just so you know, tend to be women, non-smokers, and tend to be Asians for reasons that we don't understand. Any of those three we don't understand, but the percentage of EGFR mutant lung cancer patients are higher in those categories of people. And so they have a greater likelihood of being responsive. But, in fact, nowadays if you have lung cancer you get your EGFR gene sequenced. And if it has a mutation you take this drug.

And it will work. It will resolve your tumor. Unfortunately, your tumor will come back. The same story but faster. These patients tend only to get three months, six months, maybe a year, two years, three years extra survival, and then their tumors come back. Same story, the receptors that are now insensitive to the drug carry a new mutation that blocks access of the drug to the receptor.

Fortunately, just last month there was a paper that described a new drug that will still work even if the receptor carries such a resistance mutation. So there's hope that we'll see a story similar to this one emerging for lung cancer. Now, I've told you three of, just a handful of molecularly targeted agents for therapy in cancer.

There are more to come. Telomerase is an enzyme that cancer cells need, that normal cells or at least most normal cells don't need. We won't go into the details of that, but suffice to say this is a promising area for therapy as well. Angiogenesis, I've mentioned to you before. Tumors, solid tumors need a new blood supply. If you can block the ability of the tumor to recruit a blood supply, you might be able to block the development of the tumor.

And there has recently, Genentech once again, been an FDA approved anti-angiogenesis drug that blocks, that prevents progression of colon cancer, and also they just reported breast cancer. So anti-angiogenesis is a viable therapy strategy as well. Gene therapy, putting lost genes back. Cancer cells have mutations in tumor suppressor genes, p53, RB I've told you about, and others.

Perhaps you could just put the gene back in, the gene that got lost. Make a virus that expresses that gene and put it back. This is being tried. I'm not super enthusiastic about whether it will work because I don't know that we can get the virus carrying the good gene into all the cancer cells. But, nevertheless, it's something to consider. Immunotherapy is also a promising area. It's possible that we can convince your immune system to detect the abnormal proteins that cancer cells make by virtue of the mutations that they carry.

You can make antibodies or T cells that eliminate those, and that's underway. And I've mentioned already the cancer prevention approaches with vaccines. I want to draw your attention to the fact that the Cancer Center here at MIT will have a symposium in June. Many of you will have gone home for the summer,

but some of you may not have. June 24th. This is free to MIT students, and actually features many alums of MIT. Two of these people were undergraduates here at MIT, including Dan Heber, the guy who did the EGF lung cancer story that I just showed you.

This is a very great group of people who will be telling you the latest and greatest about the new science of cancer therapy, an extension of what I've told you about today. All right. Before we finish I want to just briefly mention that in addition to tracking mutations in cancer-associated genes, we can also track the expression patterns, the levels of expression of all the genes in a cancer cell.

And this is done using a technology called array technology where all of the genes of a cell, the 30,000 genes of a cell can be assessed based on how much RNA is being produced in those cells at any given time or at any given sample. This is called a GeneChip or a gene expression array. And increasingly it's being used to diagnose cancers. Cancer is typically diagnosed by histopathology.

You look at the tumor, or the pathologist looks at the tumor in a histological section and says it's a this or it's a that. The problem is that many cancers look very similar to the histologist or the pathologist, but in the underlying molecular level they might be quite different. Some of them might be fairly benign. Others might be really dangerous. And maybe you cannot tell that apart by looking at the cells, but looking at the activity of the different genes inside those cells you may be able to get to that.

So this is done by comparing, on a glass slide, the levels of expression of all the genes from the cancer cell compared to some reference RNA, let's say the normal cell of that tissue. And then the signal that you read out by looking at labeled RNAs, the cancer cell being labeled red, for example, the normal RNA being labeled green, the signal that you read out from each of those spots using a laser and a CCD camera to detect the signal coming off of the chip, the signal that you see can be quantified.

And a red signal would mean there's more RNA in sample one for that particular gene, a green signal more RNA for sample two, and a yellow signal roughly equal. And the pattern that you get from these chips can then give you information about the state of those cells, and that information might be extremely important clinically. And in the last two minutes I'll just tell you a brief story about how it is being used.

This is a collection of 75 breast cancer specimens, early stage breast cancers, node negative, lymph node negative breast cancers. These patients, before this technology, all would undergo removal of the tumor and then chemotherapy. But it turns out that only some of them will actually go on to progress. These patients were followed for ten years after that sample was taken. And it was known that

some of them progressed, and those fall over here, progressed in the sense that they developed metastatic tumors.

And others didn't progress. And so what was done was is to take RNA from these samples at this early stage, RNA from these samples and do one of these GeneChips and ask, is the pattern of expression of genes correlative to the outcome, the eventual outcome? It might take some years for it to happen. And what they found was that indeed --

And you can probably see it from where you're sitting, that this collection of genes in red over here is highly expressed in the guys who actually do pretty well and is relatively lower expressed in the guys that don't do well. And this collection of genes is highly expressed in the ones who don't do well compared to the ones who do. And so now there's a clinical test. You can have your early-stage breast cancer typed by this analysis and it will tell you with some degree of certainty, not complete, whether your tumor will eventually, maybe five year down the road progress into a metastatic tumor.

If you get the signal, if you get the answer yes, then you have it removed and you undergo therapy. If you get the answer no, you have a choice. Perhaps you get the tumor removed, but you don't undergo what is in fact quite difficult and sometimes damaging therapy. So this is an example of, again, stuff to come, molecule medicine, specific patient-oriented medicine.