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PROFESSOR: Last time I told you about oncogenes. Oncogenes-- we discussed the fact that these were gain of function mutations that occur in cancer cells-- that occur in normal cells as they develop into cancer cells, and then occur in cancer cells. And we discussed the fact that these are dominant mutations. And this was exemplified by the Weinberg experiment in which he transferred a dominant oncogene into a "normal cell' and caused that cell to become transformed despite the fact that it had normal copies of the same gene in its genome-- definition of a dominant mutation.

We also talked about tumor suppressor genes. And tumor suppressor genes importantly, carry within them loss of function mutations in the context of cancer. Loss of function mutations, as such, these mutations are recessive mutations at the cellular level. It's necessary to inactivate both copies of a tumor suppressor gene in order to give rise to a cell that's lacking that function altogether. And that's a cell that is on its way to becoming a cancer cell. And these loss of function mutations can be various. You might find nonsense mutations in a tumor suppressor gene-- blocks the production of the protein.

You might find a deletion. It takes out the entire gene, or a big portion of the gene. You might find a frame shift mutation-- again, that blocks the ability to make any protein, or much protein. And I also told you about chromosome loss events. The loss of the chromosome that carries the normal copy of the tumor suppressor gene as a frequent second event to lose the remaining wild type copy of the gene.

OK, so this is just a little bit of review. Now, I framed the discussion about oncogenes and tumor suppressor genes from the point of view of cell division control and the production of more cells through the action of these mutations. And indeed, cancer is a product of inappropriate cell division. And the two genes that we discussed in some detail regulate this process.

The RAS gene and the product oncogene stimulate cell division. The RB tumor suppressor gene inhibits cell division. When we consider the kinds of mutations that we have in these genes that regulate the cell division process-- in the case of the RAS gene, we find activating mutations. And in the case of the tumor suppressor gene RB, we find inactivating mutations. RAS is in oncogene. RB is a tumor suppressor gene. Activating mutations in the oncogene.

Inactivating mutations in the tumor suppressor gene.

But cancer isn't only about cell division. It's really about cell number-- inappropriate cell number. And there's another important process to remember in this context. Apoptosis-- program cell death, which I've referred to many times in many different contexts. Apoptosis, which results in dead cells. And failure to undergo apoptosis properly will likewise result in too many cells, which again can be cancer causing. We have genes that regulate this process. For example, the P53 gene, which we'll discuss in some more detail, positively regulates apoptosis. And another gene called BCL-2, which negatively regulates apoptosis.

Is P53 an oncogene or a tumor suppressor gene? Oncogene? Tumor suppressor gene? Good.

P53 is a very important tumor suppressor gene. It is inactivated in the context of cancer because you want to get rid of apoptosis as you are developing cancer cell. Is BCL-2 an oncogene or a tumor suppressor gene? It's an oncogene. We find gain of function mutations in BCL-2, producing more of this inhibitor of apoptosis in the context of cancer to block apoptosis leading to an increased number of developing cancer cells.

OK, so oncogenes and tumor suppressor genes can regulate these two processes differently. As you can see, inhibitors in this case, stimulator's in this case, in the context of tumor suppressor genes. All right, a little bit more about P53, which is probably the most important cancer gene of all. It's mutated in at least 50% of all human tumors. And P53 is known to function as a molecular policeman of sorts.

It's sensitive to various perturbations within the cell. For example, DNA damage. DNA damage will feed into the P53 regulated pathway, as will a fascinating process, which is still incompletely understood, where the cell can recognize that it's dividing inappropriately. Abnormal proliferation-- cells dividing when it shouldn't. This gets detected, and this, too, can feed into the P53 pathway. And this leads to an increase in the levels of the P53 protein.

P53 is a transcription factor. It regulates the expression of other genes. And the genes that it regulates fall into two broad categories, some of which cause the cell to undergo cell cycle arrest. When the P53 pathway is activated under certain circumstances, the cells are instructed to arrest. During which time, whatever the damage is can be fixed before the cell continues to cycle. If there's DNA damage, the cell might arrest, fix the damage, and then continue on.

In addition, P53 regulates apoptosis, as I mentioned a few moments ago, causing the cells to die. Causing the damaged cells to die-- and that's good because dead cells make no tumors. This is a sacrifice by the individual cell who has been damaged, basically saying, I'm in trouble, killing itself, and allowing the organism to survive. OK, and this is a very important process in cancer prevention we now know. And I'll tell you some examples of how we know that momentarily.

OK, so I've introduced you to a couple of different oncogenes and a couple of different tumor suppressor genes. I want to focus a little bit more on the tumor suppressor genes in one respect. We touched on this last time, but very briefly.

Tumor suppressor genes is sporadically occurring cancers. And sporadic means that the individual has no family history of that particular cancer type-- sort of a chance event. And tumor suppressor genes in sporadic cancers require two mutational events. And I described these as hits. And we typically do describe them as hits in the context of tumor suppressor gene inactivation.

Sometimes it's mutations. Sometimes it's mutations coupled with chromosome loss as the second hit. But regardless, two mutations are necessary to get rid of both copies of the tumor suppressor gene. And I also briefly introduced you to the fact that tumor suppressor genes are often-- not always-- but for the most part, familial cancer syndromes, where the individuals have a predisposition to developing a particular type of cancer are caused by inherited mutations in tumor suppressor genes.

So one of the hits, one of the mutations, is inherited from one parent. Meaning that every cell in that person's body carries one of the mutations already. Meaning that only one hit, one mutation, is required somatically. That is in the individual's own cells in their body. And this is why these individuals are cancer prone, because they're one step away from lacking the tumor suppressor gene altogether, whereas in most people two mutational events are necessary, and it's rare-- not never, but rare-- to get those two mutations.

And I showed you briefly this pedigree, which is a pedigree of familial retinoblastoma, where the individuals inherit a defective copy of the RB gene, and as such are predisposed to the development of this tumor of the eye. And in fact, they will develop the tumor typically in both the eyes, and typically multiple foci of tumor. So they inherit a defective copy of the gene from

one parent and they go on to develop the disease at high frequency.

When you look at this pedigree, remembering back to your lessons in disease genetics, this looks like an autosomal dominant disease. If you inherit the disease allele, you have a very high likelihood of developing the disease regardless of who your other parent was. It looks like an autosomal dominant disease with actually incomplete penetrance, as we can see here. And we'll talk more about this in a second.

An autosomal dominate disease, but interestingly, we've been talking about the fact that the mutations are actually recessive. So this seems confusing. So who can explain it? How do we have a recessive mutation at the cellular level causing what appears to be an autosomal dominant disease? Who can answer that question? Yeah?

AUDIENCE: Predisposition is the dominant. It only needs one mutation.

PROFESSOR: Exactly. Exactly. You are predisposed.

And there's a very high likelihood that in some or in fact, many of your cells, this second event will occur. It's almost guaranteed. And since it's almost guaranteed, if you inherit just one mutation, you will develop the disease, and therefore it appears to be at the organismal level-- autosomal dominant-- because your predisposition nearly always guarantees that you will develop the disease even though the mutations at the cellular level are recessive.

And so with that in mind, as we consider a pedigree similar to the one I just showed you, where one parent is heterozygous for the mutation-- the loss of function mutation-- passes that onto the next generation and beyond, in this individual, as well as the other ones shown with the dark symbols where a tumor did develop, what is a necessary second event? The loss of the wild type of allele, either by a second mutation, or a chromosome loss event. And that happens at very high frequency. In the case of retinoblastoma, it typically happens in a dozen cells in the developing retina-- leading to an average of a dozen independent tumors in those kids.

OK, but now let's think about this individual here who did inherit the defective allele because he actually passed it on to his three sons, but he himself did not develop retinoblastoma. How can we explain that? Why was he spared?

Well, there are two general explanations. First, he was incredibly lucky. Although it's highly likely that some cell or cells in the developing retina will mutate the normal copy of the gene. In

him, it just didn't happen. He got lucky. None of his cells mutated the normal copy of the gene.

His eyes developed normally. And after that point, actually, the cells are much less sensitive to mutation, and therefore after about three or five years of age, you typically wouldn't develop the tumor. So he might be incredibly lucky. Or it might be that in him, because of some other inherited allele of some other gene, even if he were to lose the wild type alleled of RB gene it wouldn't matter, because he's got some other gene that's functioning maybe in the place of the RB gene, leading to him to be protected. And these two possibilities exist, and we have examples of how both can be important.

OK, final question on this slide-- what would happen if an individual inherited a mutation from both parents and was therefore homozygous for a mutation in a tumor suppressor gene. What do you think would happen? The answer was they would be stillborn or they wouldn't make it out of embryogenesis. And that's usually the case. And we know that not so much from the study of people who are homozygous for these mutations, because it's actually quite rare to find people who are heterozygous who have children-- so the number of such examples is few-- but we know it from knock-out mice.

All of these tumor suppressor genes exist within the mouse genome as well. And my group and others have made mice with mutations in these genes. And actually we know that, in fact, for many of the tumor suppressor genes that we care about, like the RB tumor suppressor gene, if one creates a homozygous mutant mouse, or the APC tumor suppressor gene, which is important in colon cancer prevention, or the BRCA1 tumor suppressor gene, which is important in breast and ovarian cancer prevention-- in all of these cases, the embryos don't survive. And they die at different points along the way of embryogenesis.

And it's actually not because they develop lots of cancer as embryos. Although, you might have thought that was true. They die because these genes are actually important in normal development. They're not there just to protect against cancer. They're there because they play a role in regulating normal cell division processes, normal cell death processes, normal physiology, such that when they're missing, the embryo can't survive. There's actually one exception to this. Well, I shouldn't say it that way. There are a few exceptions to this-- but one notable exception to this.

And that happens to be the P53 tumor suppressor gene that I've introduced you to. My group and others have made animals that are mutant for P53 either heterozygous for the mutation.

What would you expect the phenotype of these mice to be? Are they going to be totally normal mice, do you think?

They are, in fact, cancer prone. They look like those people with inherited predisposition to cancer. They carry one mutant copy of a tumor suppressor gene. And they're one mutational event away from lacking the tumor suppressor gene altogether. And that happens at some frequency in their cells. And the mice will go on to develop cancer and die early for that reason.

We cross these mice together with an expectation that again, they would not survive embryogenesis. But in fact to our surprise, you can make a fully P53 null mouse. And what do you think the phenotype of that mouse is? It's very cancer prone. Because this is a mouse, that in all of its cells, this very important tumor suppressor gene is lacking.

Normal mice will live about 2 and 1/2 to three years. These mice will live about 1 and 1/2 years and die from cancer as a consequence. These mice will live about four to six months and die from cancer. So P53 is actually not important in normal development.

It is a true tumor suppressor gene. It probably evolved to protect cells against the kind of damage that is inflicted on cells in an individual's lifetime. And if that damage is sufficiently great, the cells are eliminated or arrest permanently so they will not develop into cancer cells. It's a true tumor suppressor gene in that case.

OK, so I've told you about oncogene and tumor suppressor genes. We are now entering an era over the last couple of years really, where many, many more cancer genes are being discovered through the application of genomic sequencing in the context of cancer. Cancer genomics is all the rage, including here at MIT, for example in the Broad Institute.

And there are many papers appearing in the literature like these looking at the complexity of the genome of individual cancers, like this study out of the Broad on prostate cancer, and this study out of the Sanger Institute in England on small cell lung cancer. All the genes or the entire genomes of lots of different cancers are being sequenced and compared to the normal DNA of the same individual to catalog all of the mutations that are present within an individual tumor.

And although there are differences depending on the cancer type, the average cancer genome actually has 100's and sometimes thousands of mutations. Small cell lung cancer, for

example, has tens of thousands of mutations compared to normal cells of the lung. Why? Because they arise following years of exposure to cigarette smoke, which carries mutagens that bathe the DNA in mutation causing chemicals leading to mutations.

Now, not all of the mutations that you find in a cancer cell are relevant to the cancer phenotype. In fact, we think that there's only amongst all those mutations that are found that there's only about 5 to 20 or so mutations in oncogenes or tumor suppressor genes. And we call these mutations driver mutations.

Driver mutations, meaning, they actually are participating in the development of the tumor, causing some aspect of the cancer phenotype. And the remainder, we call passenger mutations. Silent mutations-- mutations that actually don't do anything to the cancer cell, but they just happened to occur at the same time, or in the lifetime of the cancer cell when another important mutation took place. So that clone of cells that develops carries those mutations too, but they're not actually contributing to the cancer phenotype.

So among the hundreds and thousands of mutations, some of them really matter, and some of them are just going along for the ride. It makes the analysis of the cancer genome much more complicated, actually, because it's hard to tell what's a passenger, and what's a driver. But increasingly recognizing what are the important ones and focusing our attention on them.

OK, that's all I'm going to tell you about cancer genetics. And I want to now turn my attention for the last 25 minutes-- and I may run over a little bit, so I ask for your patience if I run over a little bit, because I do want to finish this-- to talk about cancer therapy. Before I make the switch to cancer therapy, I want to first introduce the concept of cancer prevention.

A lot of us work on cancer genes and cancer genetics to understand how to treat cancer better. But in the future, hopefully we'll have many fewer cancers to treat, because we'll be able to prevent them. If people would stop smoking, we'd have 80% fewer lung cancers to treat. If you use sunblock and stay out of the sun, we'll have fewer skin cancers to treat and so forth. Better diet and excess exercise will prevent a lot of other types of cancers. So there are lifestyle things that can lower the number of cancers in the context of cancer prevention.

There's also ways to prevent agents from producing cancer in your body. And the best example of that is Gardasil. Gardasil is an example of cancer prevention involving a particular virus-- human papillomavirus-- and specifically, human papillomaviruses, which are described as the high risk type. Human papillomaviruses or HPV of the high risk type can cause cervical

cancer. They are the main reason that women develop cervical cancer. And they're responsible for other types of cancers as well, including in men.

And what we know is that in a normal cell of the cervix, when infected by the human papilloma virus, will at some frequency, and after a period of time, develop into cervical cancer. This suggests that the virus-- some genes of the virus-- are changing the cells behavior in such a way that it develops into cancer. Yes?

AUDIENCE: I don't know if you're talking about our class or something else, but it's very rude to talk. It makes so much noise during the lecture.

PROFESSOR: Thank you. So something in the virus is causing the cells to divide abnormally into a tumor. And this has been studied at length. And we now know that there are two genes, which are responsible for causing cervical cells to become cancer cells-- two genes of the virus called E6 and E7. And it's been learned that these genes in fact encode proteins that inhibit cellular proteins that we're actually quite familiar with. And we now believe we understand why the virus causes cancer. E6 inhibits P53. And E7 inhibits RB.

So the virus for its own reasons of viral replication, takes out these two tumor suppressor genes. And as such, the cells are lacking these two critical tumor suppressor genes, and they're well on their way to becoming uncontrolled cancer cells. OK, so that's how HPV high risk types cause cancer. And what was developed in the context of Gardasil is an HPV vaccine so that individuals cannot be infected productively with this class of viruses, specifically it's a component vaccine made of recombinant proteins that are present in the high risk types of HPV. As a component vaccine, this vaccine does not produce a replicating virus. It's just pieces of the virus. So there's no risk of a viral infection here.

But an potent antibody response can be elicited, including neutralizing antibodies that will prevent an individual from being infected by the real thing at a future time. OK, so that's an example of cancer prevention, eliminating an ideological agent that is responsible. There aren't many examples of virus caused cancers in humans. So this is kind of a special case. But HBV-- hepatitis B virus induced liver cancer will be another one before too long.

OK, so now let's talk about cancer therapy. I'm going to talk to you in a few minutes about some new cancer therapies that are based on our improved knowledge of the genes in cancer cells. I'm going to tell you more about anti HER-2 antibodies. I'm going to talk to you more about a small molecule inhibitor of this kinase. There are actually many theorems that are

based on mutations that we know occur in cancer cells.

There are processes that I've mentioned to you, like angiogenesis, the recruitment of new blood vessels. These two have led to new therapies for cancer to block that process and inhibit cancer development. In the case of tumor suppressor genes, individuals are trying to develop gene therapy to put the genes back. If the gene is lost in a cancer cell, perhaps you can restore its function by gene therapy, and normalize the growth of the cancer cells. And although I won't talk about it, there's a lot of promise for immunitherapy for cancer.

Cancer cells acquire a lot of mutations. As such, they produce a lot of antigens. In theory, your immune system should recognize those as foreign and eliminate the cancer. But in general, the cancer wins, the immune system fails. And we think that there's ways the cancer actually inhibits the immune system from functioning properly. But that's being figured out now, so it's possible that we'll be able to develop new cancer therapeutics based on the immune system.

All right, but before I get into the cool new stuff, let me tell you just a little bit about cancer therapy more generally-- what we would consider to be conventional cancer therapy. The most effective form of cancer therapy is surgery. If you can get to the tumor early before it has spread, you cut it out, the person is generally cured. Another very effective form of cancer therapy is radiation therapy. And this is good because you can focus the radiation beam directly on the cancer cells and eliminate them by causing a lot of damage to those cells.

And the third is chemotherapy. And chemotherapy is used when you think that the cancer has spread, so radiation can't work because the cancer cells are somewhere else-- and you need a drug that can diffuse throughout the body and hopefully kill the cancer cells. Radiation and many chemotherapies act in the same general way. Adriamycin, which you will have heard of, cisplatin, which you will have heard of-- these are well used cancer therapeutics-- and many more function by inducing in the cancer cell DNA damage. And the damage can be sufficiently severe that the cell will die. And these therapies can be effective.

There's another class of cancer drugs for which Taxol is the best known, which are described as mitosis inhibitors. These drugs actually bind to microtubules, block the formation of the microtubular spindle, and that way prevent cells from dividing. And since cancer cells divide a lot and you want to inhibit their division, these drugs are used and can be effective. In fact, they're used because they were tested and shown to be effective first in cell-based studies, where one looks at the growth or survival of cells in a Petri dish, scoring the number of cells or

the percentage of cells that are alive at any given time, or in any given dose of drug when the concentration of drug is increasing in this experiment.

What we find is that for certain normal cells, they will survive to a certain concentration of drug and then start to die off. And for certain cancer cells, the concentration required to kill them is lower. And this difference is called the therapeutic window.

In theory, this looks good, because it suggests that the cancer cells are more sensitive to the drug than are normal cells. And that's why some cancer therapeutics work for some cancers. But there are problems.

Some normal cells in your body, unlike these normal cells, are very sensitive to the drug at low concentrations-- the DNA damaging agents, for example. This results in side effects. And I suspect you are all familiar with the side effects of cancer chemotherapy. Your hair falls out. You get nauseous. You get anemic.

This is because cells in your hair follicles, or your intestines, or your blood system are dying at low concentrations of the drug. They're actually dying by apoptosis. They're actually dying by P53 dependent apoptosis. So that's why cancer drugs cause many bad side effects, because some cells in your body are very sensitive and will kill themselves in response to low concentrations of the drug.

The second problem is that some, in fact not a small percentage, are very resistant to the concentrations of the drug-- even high concentrations of the drug. And one reason for that is that many cancer cells are lacking P53. I told you that P53 is mutated in about 50% or more of human cancers. I also told you that P53 was required for cells to respond to DNA damage and die. And these cells lack that protein. And therefore, are very resistant to dying.

So many therapeutics don't work, because this important machinery is lacking. So we have problems with standard therapies based on both kinds of issues. So the goal then, is to find drugs that don't cause these kinds of side effects and can work even in a P53 deficient cell, which leads us to developing new types of therapy.

OK, so I want to introduce you specifically to two. And they are probably the best known and highly effective actually, great examples of molecularly targeted anti-cancer agents. The first is in the context of breast cancer. And the gene in question here is a gene called HER-2. In a normal breast cell, there are two copies of this HER-2 gene, as there are in virtually all of your

cells. And those produce amounts of RNA that produce amounts of protein that lead to the decoration on the surface of these cells-- the certain number of receptor molecules called HER-2, which are a growth factor receptors. They bind to specific growth factors.

And when they are engaged with their growth factors, they send a signal into the cell. And the product of that signal is for the cell to proliferate. And this is necessary in normal development and in other times. So this is normal regulation, normal signaling in response to a growth factor in the normal levels of a growth factor receptor. 30% of breast cancers carry a mutation that results in amplification of the HER-2 gene. So we don't have two copies anymore, we've got 10, or 20, or 50, or 100 amplification.

This is a mechanism by which all good genes get activated. Too many genes, too many proteins. This cell now has way too much of that growth factor receptor on its surface. And in the presence of the same concentration of the growth factor itself, we get a much stronger signal-- much higher levels of proliferation. This also affects the ability of the cells to survive. It keeps them alive at times when they shouldn't be. Too much proliferation, too much survival.

Given this situation, a logical therapeutic would be something that blocks the function of this growth factor receptor. And what a company called Genentech discovered was that they could make an antibody. An anti-HER-2 antibody. And that led to a drug called Herceptin, which binds to the growth factor receptor and prevents it from functioning. And in women who have this alteration, and only in them, the drug is actually highly effective.

In the metastatic setting, it will lead to multiple additional years of life. But it is actually not curative in that setting. Recently, individuals are being typed for this mutation at a much earlier stage in their disease course. And when women are given the drug then, it's leading to some cures. So this is a targeted agent which is highly effective in the context of a specific mutation. And actually only then-- other breast cancer patients given the same drug have no benefit whatsoever.

So this is what it looks like. This is actually the drug package. And this is what I just described to you-- normal cells, cancer cells, Herceptin antibody binding to and blocking the function of this abnormal number of growth factor receptors. OK, let me now turn to the second classic example. And this comes in the context of chronic myelogenous leukemia, which is a leukemia-- a blood cell tumor. It's a particular type of blood cell-- the myeloid lineage type of white blood cell. You can diagnose this disease by looking at blood smears and you can see

that this is the normal blood smear with a single of these myeloid cells. And here is a cancer situation where we've got too many of these white blood cells circulating.

This is a disease that's been studied for a very long time. And it's been discovered that in the vast majority of this type of cancer, there is a specific chromosomal event-- a specific mutation caused by a particular translocation. And that translocation was actually identified a long time ago in the city of Philadelphia. And as such, it's called the Philadelphia chromosome. It's the product of a specific translocation-- chromosome 9, which has a gene on it called ABL, which encodes a protein that is a kinase involved in phosphoralating other proteins.

And chromosome 22, which has another gene called BCR-- chromosome break events occur here. Chromosome break events occur here. And a translocation results, which produces a new chromosome-- the Philadelphia chromosome, which has the BCR gene and ABL gene inappropriately fused to each other. This produces a fusion gene, which encodes a fusion protein. And that fusion protein is referred to as BCR ABL. And it was discovered that the BCR ABL form had increased kinase activity.

And this resulted in increased proliferation within the cells that carried that translocation. And so the question was, could one develop an inhibitor? An inhibitor that blocked the kinase? And this resulted in the development of a drug called Gleevec. Gleevec, which is highly, highly effective.

This is the idea, here's the BCR ABL fusion protein. It binds to ATP, which it needs to transfer the phosphate group onto a substrate protein in this signaling cascade. The idea is that one could make a small molecule drug that could fit into the ATP binding site very specifically, and block access of ATP, therefore shutting off the kinase. And if that were possible, then the cancer cells would be deprived of this signal, and may stop proliferating, or even die. That was the idea. In fact, they were successful in making a small molecule drug.

And that may surprise you, because you might think there are a lot of kinases in this cell. They all bind to ATP. How could you ever find one that was specific to this kinase? But in fact, it was possible. You can make kinase inhibitors, because not all the ATP binding pockets look the same. And you can therefore get some specificity.

And when this drug was used in patients, it showed remarkable activity. If we looked at white blood cell number, normal individuals would have a certain low level. And in case of CML, the level would be high. And actually, it goes higher still as the disease progresses through a

phase called blast crisis, where additional alterations take place and the cells begin to divide even more abnormally.

In this context, however, if you give the drug Gleevec, in the vast majority of patients, the numbers drop precipitously. And the drug is extremely well tolerated-- has almost no side effects. The patients take the pill with their orange juice in the morning every day, keeping their cancer cells at bay, leading to what is called clinical remission. Clinical remission-- the disease has gone into remission. And it can stay in remission for a very long time. And it's sometimes curative.

But sometimes the disease cells come back. And this is a phase we call relapse. And even though the drug is present throughout this disease course, the tumor cells are dividing again. Can anybody tell me why? Mutation.

The cancer cells have acquired additional mutations, specifically within DCR ABL. If we imagine DCR ABL, it can bind to Gleevec, and be shut off. At some frequency, however, mutations can occur, which change the active site in such a way that Gleevec can no longer bind. And this is still an active kinase. So now the cells begin to divide again.

So the question now is what can you do about it? And the answer is, you can make a new drug. And this has actually been done successfully. A new drug that can bind specifically to the mutant form of ABL kinase. And there's a drug called SPRYCEL, which is now also FDA approved for the treatment of drug resistant forms of CML.

So before you run away, this is what I've just told you, here's ABL kinase. This is where the drug binds. This is the structure of the drug. But at some frequency, mutations occur within that ATP binding site. And different mutations will do this, as shown down here. And those mutations will block the access of the drug. And the good news is that one could make new drugs that will overcome that form of resistance. So this is a good news, bad news, good news story. We'll stop there.