

How Scientific Teams Develop New Anti-Cancer Drugs English mp4

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[00:00:20.09] KRISTINA MASSON: Welcome to our lesson on drug development and cancer. My name is Kristina, and I work here at the Broad Institute. Today you're going to be following drug development in different cancer treatments. And first, let's take a look at two different patients and how they're different treatments are affecting them.

[00:00:34.91] LISA CUCOLO: Here you see a patient who has cancer for which there is no targeted therapy. She has been undergoing standard chemotherapy and radiation therapy. These have harsh side effects including fatigue, nausea, hair loss that prevent her from attending work.

[00:00:49.09] On the other hand, this person is a cancer patient for which there is a targeted therapy. With this medicine, his has far fewer side effects and is able to continue with normal daily activities, such as attending work.

[00:01:01.89] One goal of the Broad cancer program is to try to find targeted therapy like this for each type of cancer. My name is Lisa, and I work here at the Broad cancer program on a project with this goal in mind. And I will be your narrator for this lesson.

[00:01:15.55] KRISTINA MASSON: You've just seen how two different types of treatments affect patients. Now please take a moment to discuss with your neighbor how cancer's impacted people around you. I'll see you when you're done.

[00:01:37.79] DR DAVID THOMAS: Hello. My name is David. I'm a cancer doctor at Dana-Farber Cancer Institute and a researcher here at the Broad Institute. There's been a remarkable revolution in the treatment of cancer. And to understand that a little better, we should take a look at the history of cancer treatment.

[00:01:52.34] One of the very first therapies for cancer was actually surgery. And it was developed in 3000 BC. And it was thought that by removing the tumor, you could treat the cancer. And that's true for certain number of diseases, but it often comes back.

[00:02:08.01] One of the very earliest chemotherapies that was ever developed was actually a poison, arsenic. And it was used for the treatment of leukemia, or a cancer blood cells called CML.

[00:02:18.63] Around that same time in the late 1800s also we found out that you could use x-rays or radiation to also treat cancer. And it wasn't until the mid-1900s that we started to refine our treatments of cancer using hormonal therapy as well as less toxic chemotherapies.

[00:02:38.49] However, the real revolution started in the 1970s when we first found out bits of DNA could make a normal cell turn into a cancer cell. And again, this was found in Chronic Myelogenous Leukemia, or CML. It took another 30 years for us to understand what the actual genes were in that bit of DNA that was found.

[00:02:59.09] And with that new target, we could discover a specific drug to treat that particular cancer and improve, not only the outcomes, but also the toxicity that was associated with that new target. It wasn't until 2001 that that drug actually became FDA approved and is now marketed across the world for the treatment of CML.

[00:03:21.81] To better understand how the impact of this new targeted therapy works, we should look at how it affects patients and their survival. This is a simple survival curve called a Kaplan-Meier curve. On the y-axis, we have survival. On the x-axis, we have time.

[00:03:42.22] Patients with CML, before targeted therapy, tended to have a survival curve that looked like this, really poor outcomes. But after the introduction of targeted therapy and this oral drug, it made a dramatic difference in their survival, such that somewhere about 70% of patients responded to this drug. And the difference was really tremendous.

[00:04:05.83] Not every cancer has this kind of dramatic finding or result. But actually, the revolution in DNA sequencing accomplished a lot here at the Broad. It's actually making a huge difference in finding new targets for many different types of cancer therapies.

[00:04:20.05] To take a look at this a little bit more specifically for CML, we're now going to have an activity where you can look at the DNA or the chromosomes of normal cells and cells from CML and see if you can tell the

difference between the two. You can take a look at these things and discuss it with your class now.

[00:04:50.92] KRISTINA MASSON: Welcome back. My name is Kristina, and I'm an experimental biologist at the Broad. You just looked images from normal cells and cancer cells. And you might have an idea of what's going on and what the difference is. Before we reveal that to you, we're going to go through some basic principles of DNA structure and function.

[00:05:07.75] LISA CUCOLO: Here in this image, you see a cell with its nucleus. Inside the nucleus, you can see its chromosomes. The chromosomes contain tightly wound DNA. DNA is a double-stranded helix. It has bases A, T, G, C. A and T bind together, and G and C bind together.

[00:05:27.98] Mutations can occur in DNA that can lead to cancer. One example of such mutation is a translocation. Here you can see a translocation.

[00:05:37.20] One example of a translocation that causes cancer is in CML. In CML pieces of chromosomes 9 and 22 break off and swap places. If you look back at the pictures of the chromosomes from the activity you just did, one set of chromosomes is from non-cancer cells and the others from a CML patient. There you can see the translocation between 9 and 22.

[00:06:00.98] KRISTINA MASSON: We've gone through some principles of DNA structure and function. And here's your new assignment. Here are images of Bcr and Abl before the translocation, and we'd like you draw the product after the translocation. Please take a moment to do this with your classmates.

[00:06:32.68] LISA CUCOLO: Welcome back to translocation that occurs in CML causes the genome Bcr and the gene of Abl to fuse. This results in the fusion protein seen here, where the Bcr protein is joined to the Abl protein.

[00:06:45.96] Once we know the genetic change that leads to cancer, how do we go about finding a new treatment targeted to that cancer? Let's look at how this works at the Broad.

[00:06:54.73] The scientific process of the collaboration between a lot of people. Here you see the Broad lobby, where you can find people working in many different careers.

[00:07:02.75] For instance, here you see a doctor, a synthetic chemist, a computational biologist, an experimental biologist, a medicinal chemist, and a scientific writer. All of these people come together at the Broad to discover new cancer treatments. This starts with a chemical screen, a process in which 300,000 chemicals are all tested to see which one kills cancer cells.

[00:07:24.09] JEN BEAUDOIN: Hi. I'm Jen. I'm a chemist of the Broad, and I make the chemicals that are used to target cells and proteins. And this is what is called chemical screening. Biologists use this information and tell us what is interesting of the chemicals that we've made.

[00:07:40.83] LISA CUCOLO: Scientists use machines, like these robots you see here, to speed up the process and keep the experiment as precise and consistent as possible. In these experiments, we use plastic plates containing hundreds of wells, or tiny tubes. We put a different chemical into each well of the dish. We then add the protein we want to target into every well of the plate.

[00:08:00.24] For example, if you're looking for a chemical that might be good treatment for leukemia CML, we would want the chemical to inhibit the activity of Bcr-Abl fusion protein. Let's meet some of the people at the Broad involved in this chemical screening process.

[00:08:14.72] AARON BRANDES: Hi. I'm Aaron. I'm a computational biologist here at the Broad. And what I do is I take data that's produced, like the experiments that you just saw with 300,000 chemicals, and then I talk to biologists to understand the questions that they're trying to answer.

[00:08:37.46] And then I write computer programs to analyze the data and to create graphs so that they can more easily understand what I've found. So this would be an example of the kind of output that would make sense to a biologist.

[00:08:55.97] KRISTINA MASSON: So we just heard Aaron describe how to analyze a lot of data points. Now, what one data point really mean? Here, I'm looking at cells grown in plates like this. And they're growing in the regular growth media, which looks red.

[00:09:10.60] And I'm looking under the microscope to see which cells are dead or alive after a treatment with a particular compound. Now, if we have a lot of data points, we can use robotic microscopes for this.

[00:09:21.58] Take a look at these images of living cells stained. And the assignment is to discuss the purpose of positive and negative controls in an assay like this. And also discuss with your classmates what a good potent drug would look like in the assay on these cells.

[00:09:54.78] LISA CUCOLO: Welcome back. Hopefully you saw in the last activity how chemicals that are interesting potential cancer treatments would result in the cancer cells growing in a dish to be killed by those chemicals. Now that we've found a promising chemical from a very large experiment, let's take a look back at the flowchart to see where we go next in this process.

[00:10:13.87] At this point, the process returns to the chemistry lab, where we will see Jen again, and meet her colleague Chris.

[00:10:20.18] JEN BEAUDOIN: When biologists just find something of interest, I synthesize more of this compound in a large batch. Then I hand it off to Chris.

[00:10:33.72] CHRIS DOCKENDORFF: Thank you, Jen. My name is Chris. I'm a medicinal chemist here the Broad Institute. And it's my job to take some of the material that Jen has kindly provided and to make analogs of the original hit compound. And basically, this is an iterative process where we made different changes to the molecule in order to find compounds that are hopefully more potent and have better properties.

[00:10:55.12] So for example, this is a project that we've recently published here at the Broad Institute. And you can see, we've made some changes to the original lead compound. You can see in the first case we've reversed the position of the nitrogen and oxygen atoms. We've shorten the molecule to make it smaller. We've added a nitrogen atom to improve its properties. And one of the main things we're concerned with is coming up with compounds that have improved potencies.

[00:11:18.98] So finally in this example, we've added a chlorine atom to the molecule. And by doing so, we had a new compound that was much more potent than the original lead. So finally, to determine if the compounds are more potent, we will examine a dose response curve of the compound after it's been given to the biologist and undergone further testing.

[00:11:41.01] And a dose response curve is simply a measurement of a particular activity in an assay. It could be a cellular assay or a biochemical assay of some kind. And so we have an example here for you. This is, for example, an assay against a cancer cell line. And we're looking to see which compounds provide the best inhibition of growth, for example, of a group of cells.

[00:12:06.39] So we'll pause here. And you can take a look at these dose response curves and answer a few questions about the potency of the compounds.

[00:12:30.01] DR DAVID THOMAS: Welcome back. You've just taken a look at dose response curves for compounds in the drug discovery process. Let's remind ourselves where we are in the flowchart. We've gone through basic science to discovery of new potential drugs. Now let's take a look at the actual structure of the most promising candidate for CML.

[00:12:47.69] How do we convert a compound like this to an actual drug? And that's through clinical trials and actual human patients. The first phase is actually to test safety. And that's done in healthy volunteers, a few number, maybe 10 to 20 patients.

[00:13:05.15] If it passes safety measures there, it's then moved on into phase two clinical trials that looks at its effectiveness. They might be creating a few hundred actual patients with a drug.

[00:13:17.30] After it passes that phase, it moves on to phase three, which is really optimization of the protocol for the treatment using that drug in a few thousand patients. Once it passes this assessment, and we make graphs like survival curves to show and demonstrate what the efficacy actually is, the FDA would approve a drug at that phase.

[00:13:39.86] After that point, we still continue to analyze how the drug is working. And that's done in the phase four part of clinical trials. Haley will talk to you a little bit more about that in just a moment.

[00:13:51.36] HALEY BRIDGER: Hi, my name is Haley. And I'm science writer at the Broad Institute. My job at the Broad is to help communicate about the science happening within the Institute to the greater world.

[00:14:01.45] So in the segment that you just saw, you saw what happens during a clinical trial. You may be wondering what happens after that? How

are the discoveries that scientists are making shared with the rest of the world?

[00:14:12.69] Scientists share information like that with each other through journals, like Nature. They publish journal articles, and other scientists can read and understand what they've learned through such trials.

[00:14:24.96] We also, at the Broad, communicate stories on our website. And we'll sit down with scientists to learn about what's important from their work, and what might be interesting most to people outside of the scientists here. So we'll put articles on the Broad's website, we write entries for the BroadMinded blog, and we share other stories via Twitter and Google+ and social media platforms.

[00:14:50.43] In this next segment you're going to be taking a break, and then your teacher is going to be leading you through an activity.

[00:15:06.63] KRISTINA MASSON: Welcome back. I hope you enjoyed putting the sequence of careers in science together. We've reached the end of our lesson, which brings us to one last point, which is the natural changes that occur in cancer, in all types of cancer.

[00:15:19.42] Take a look at this image, for example. We've develop a drug that targets a particular protein. It happens in nature that this protein is altered, and then the drug no longer binds and is effective. Then we have a cancer where the drug no longer works, and we need to develop a new drug. This brings us back to the beginning of our lesson, and really illustrates how cancer research is a cyclical process.

[00:15:43.12] Thank you very much. I hope you've enjoyed this lesson, learning about cancer research here at the Broad.

[00:16:01.50] MEGAN ROKOP: Hi. Thank you for considering using our lesson on cancer research made here at the Broad Institute, and in collaboration between the researchers in the cancer program and the Educational Outreach Program. Our lesson is focused on finding out how scientists develop new cancer treatments that are targeted toward specific kinds of cancers. My name's Megan Rokop, and I'm the director of the Education Outreach Program here at the Broad, and I'll be telling you a little bit about this lesson.

[00:16:27.63] The learning objectives for the lesson are to show students the progression of how cancer treatments have progressed over time, from nonspecific treatments, such as radiation, surgery, and chemotherapy, to more specific targeted treatments. The example shown in this lesson is CMO, one kind of leukemia.

[00:16:47.79] There is little prerequisite knowledge required for using this lesson, although it is helpful if students know that DNA is the genetic material, basic principles of central dogma, and structure of DNA. There is no necessary supplies for this lesson other than the ability to visualize our slides and to print out the handouts.

[00:17:09.46] I'll now go through an outline of this lesson, the different segments, and what the activities are in between those segments. In segment one, the concept of nonspecific treatments versus targeted treatments are introduced. And it is discussed and shown how patients taking nonspecific treatments often have side effects, while patients who are taking targeted treatments are typically much healthier and able to, for instance, go to work.

[00:17:35.93] The activity after that segment is for the students to turn to their classmates and discuss how cancer has impacted people that they know around them.

[00:17:46.78] When we come back to segment two, we have a physician here at the Broad, an oncologist, who briefly goes over the timeline of cancer therapy and talks about how survival curves are used to show that targeted therapies are often much more effective in treating cancers than nonspecific therapies.

[00:18:07.24] The activity after that segment is that students are shown the DNA, the chromosomes, of a non-cancerous cell and a cell from a CML cancer patient. The students are asked just to look at the pictures of the chromosomes and try to figure out what might be different between the DNA of a CML cancer cell and the DNA of a normal cell.

[00:18:28.96] When we come back in segment three, we go over the basic principles of DNA and how mutations can lead to cancer. And the specific example of the mutation we show is the mutation that does, in fact, exist in the CML patients, which is a translocation between chromosomes 9 and 22.

[00:18:48.89] At the end of this segment, the activity that the students do is to see what the proteins that are encoded by those genes at the junctions of translocation, i.e., a gene on chromosome 9 and a gene on chromosome 22-- those genes are called Bcr and Abl-- how the proteins coded by those genes are fused together into a fusion protein, which is the mutant protein that leads to CML.

[00:19:16.19] When we come back into segment four, we begin to talk about the process of actually going through step-by-step through all the different scientists at the Broad who would be involved in the process for finding a treatment for a specific kind of cancer like CML. In this specific segment, we talk about the large, high-throughput experiments that we do in chemical screening at the Broad, where we screen through hundreds of thousands of chemicals looking for the one, for instance, that may affect the activity of the Bcr-Abl fusion protein. In this segment, the students meet chemist at the Broad who synthesize these molecules and see the robots that actually do these screening experiments for us.

[00:19:58.17] At the end of this segment, the activity is that the students see images of cells that are treated with chemicals that may be promising cancer drugs. And the students see how, through image analysis, you can observe which chemicals kill the cancer cells and therefore may be promising new drugs.

[00:20:16.77] In segment five, we return again to the chemistry lab to go through the next steps of the process, which is to take the one or few compounds that are interesting that come out of the chemical screen, make large batches of them, and then use those core compounds to synthesize many different analogs. Chemists then test those different analogs to see which ones are most potent, i.e., which ones give the best response in dose response curves.

[00:20:43.13] The activity after this segment is that the students examine a dose response curve for an original compound and two analogs and determine which of the analogs is most potent.

[00:20:54.29] When we return in segment six, our oncologist, our cancer doctor at the Broad, returns to discuss how the most promising analog would then be tested in a clinical trial. He goes through the stages of the clinical trial and shows examples of Kaplan-Meier curves, or survival curves, that are generated during the clinical trial process.

[00:21:17.35] We then turn into a science writer who talks about how the science is communicated once a discovery like a new treatment is made. For instance, she talks about how scientists will communicate these results through journals or conferences to other scientists, but also how people like her as a science writer would communicate these results to the general public.

[00:21:41.65] The end of this activity is that the students will break into groups of 10, and each student in the group will receive a strip of paper. Every strip of paper has a career of the person involved in the process from start to finish of developing a new cancer treatment. The students in the group then read their strip of paper, and they have to determine, based on their career description, what the title of their job would be, where they might work, for instance, a hospital, or a lab, or at a computer. And then they have to go around to each member of the group and order those strips of paper to end up with a sequence of all the different careers involved in this process and how they fit together.

[00:22:23.08] This activity allows them to collaborate with each other, but also to integrate all of the different stages we learned in the lesson and work as a team together, just as the scientists at the Broad do when developing new cancer treatments.

[00:22:37.17] When we return to segment eight, we wrap up by explaining that this process of developing new treatments is continually occurring. And this is for two reasons. One is that every time a drug is discovered, it is possible that the cancer will then acquire resistance to that drug. In which case, we can go back to the beginning of the process and look for a chemical that will work in a mutated form of the target that's become resistant to the original drug. This process is also continuous because there are many, many different kinds of cancer, and we would go through this process to find a specific targeted treatment for each different, unique kind of cancer.

[00:23:17.74] At the end of this activity, we do have an optional extension activity where we have a handout describing a career project, where each student can select one of the careers that they heard about in this lesson and either prepare an oral presentation or a one- or two-page report about that career. In this optional extension activity, there are a series of questions about that career that the students research, and recommendations of what to put in their presentation.

[00:23:48.45] We hope you enjoyed this preview into a lesson, and that you enjoy using it with your students. Thank you.