GLEEVEC

Adapted from and courtesy: National Center for Case Study Teaching in Science

http://sciencecases.lib.buffalo.edu/cs/collection/detail.asp?case_id=819&id=819

Just a routine checkup?

Oliver Casey, age 53, was visiting his doctor, Ariana Kagan, for his annual physical. Aside from feeling a little more tired than usual, which he attributed to increased responsibilities at work, Oliver thought he was in good health. However, during the physical examination, Dr. Kagan noted that Oliver had an enlarged spleen.

“I’m going to order some blood work to see if we can figure out why your spleen is enlarged. You may have an infection; it’s probably nothing serious,” Dr. Kagan told Oliver.

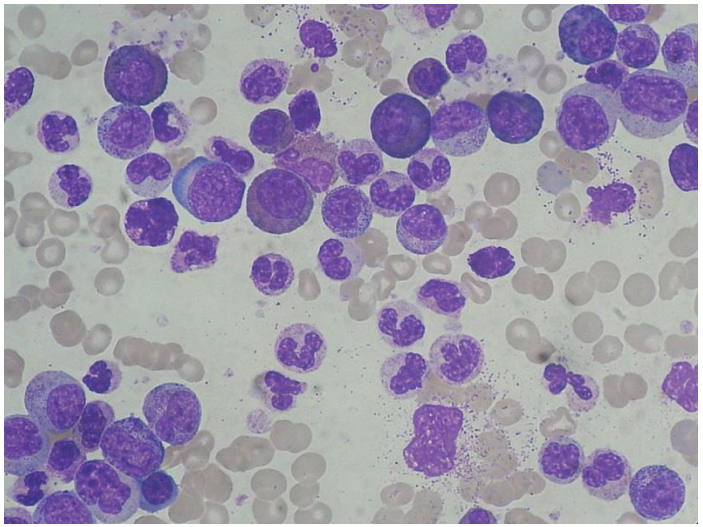
Oliver left the doctor’s office that day feeling a little unsettled, but hopeful that his enlarged spleen was caused by nothing more than a virus.

The results

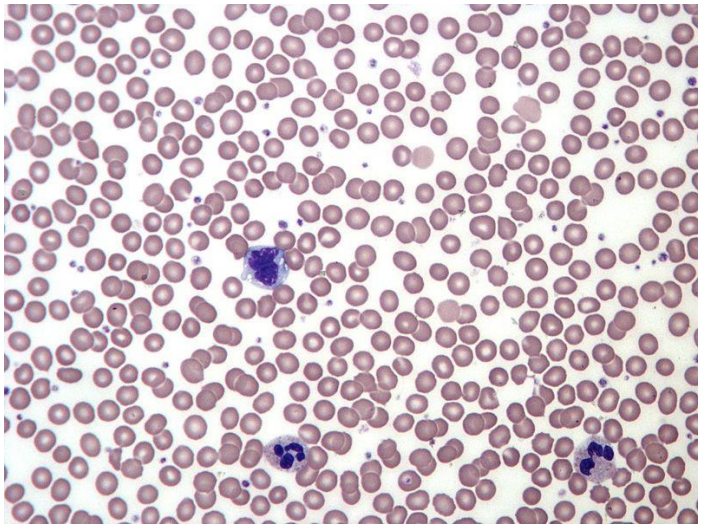
Oliver's palms were sweaty and his heart was racing as he sat across from Dr. Kagan in her office. He knew it couldn't be good news that he had been called in to discuss his blood test results in person. Here are some of the findings:

Oliver's white blood cell count	225 x 10^9 cells/L
Normal white blood cell count range	4.5 - 10 x 10^9 cells/L

Oliver's Blood Smear



Normal Blood Smear



The results, continued

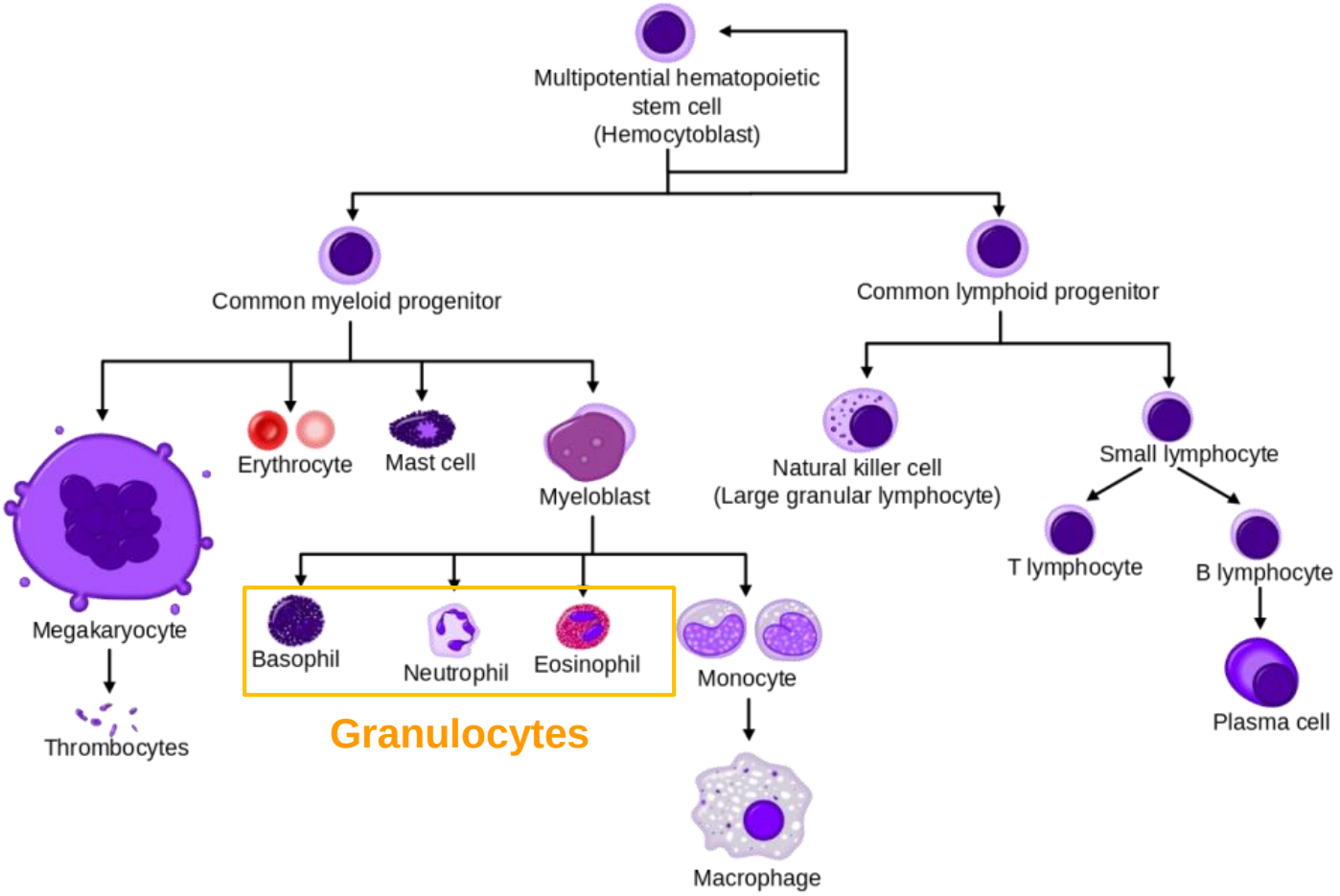
Oliver sat in stunned silence while Dr. Kagan reviewed his blood test results. “Your very high white blood cell count and enlarged spleen prompted me to perform some additional testing on your blood cells, and I’m afraid the results are not very good. The results reveal that your blood cells contain a mutation that has caused you to develop a blood disease called Chronic Myeloid Leukemia, or CML. This is a slowly progressing cancer of the blood cells. I am going to refer you to a doctor called a hematologist, who specializes in blood diseases, who will discuss your treatment options.”

“Chronic what?” replied Oliver, snapping out of his silent state.

Dr. Kagan explained to Oliver a little more about what CML is, and what causes the disease.

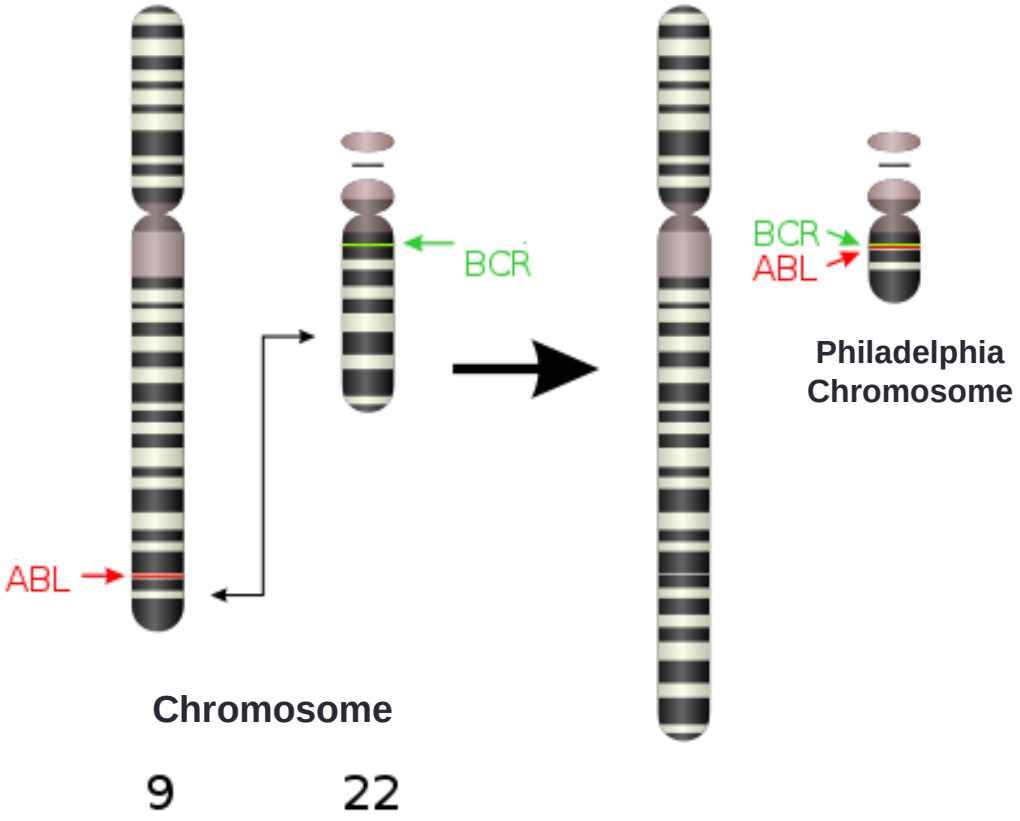
Genetics of CML

- CML is characterized by an overproduction of a particular type of white blood cell called the ***granulocyte***



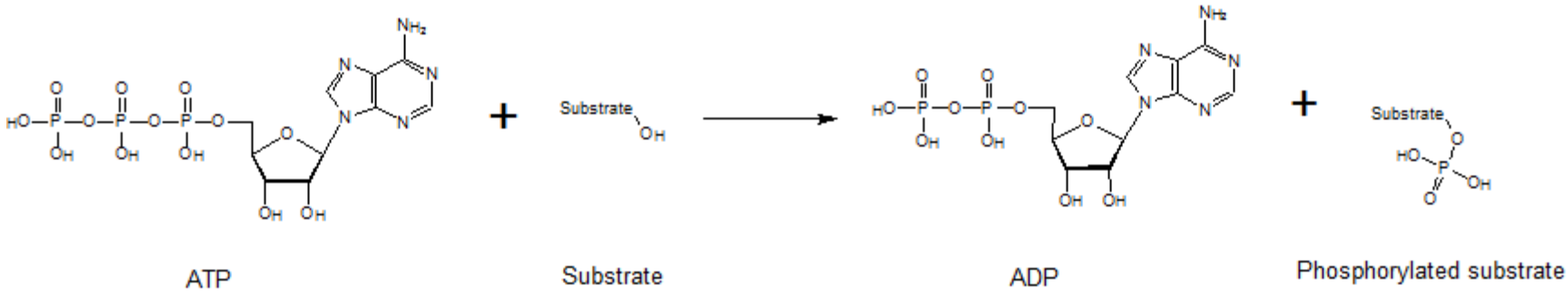
Genetics of CML

- The vast majority of cases of CML are caused by a chromosomal translocation, a specific type of mutation in which two different chromosomes swap their DNA
  - Generates the ***Philadelphia chromosome***, containing the BCR-ABL fusion protein



What is a kinase?

- BCR-ABL is a mutated version of the ABL protein, a ***tyrosine kinase***
- A kinase is an ***enzyme*** that catalyzes ***phosphorylation*** reactions
  - Transfers a phosphate group from ATP to the substrate



- Therefore, a kinase must be able to bind both **ATP** and its **substrate**

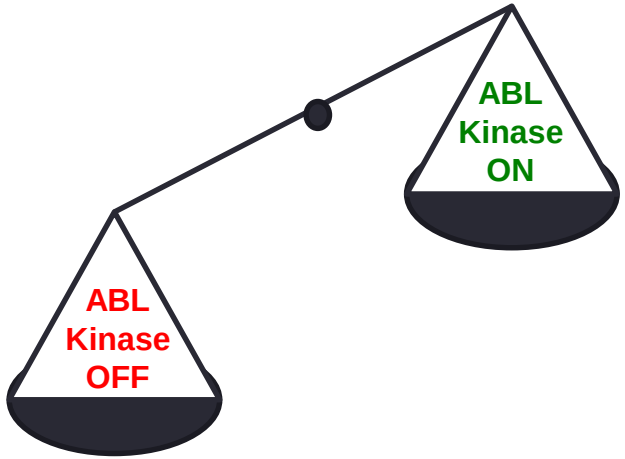
Biology of CML

Normal Granulocytes

- ABL kinase is regulated
- Granulocyte proliferation is regulated

Cancerous Granulocytes

- BCR-ABL mutant kinase is ***constitutively active***
- Granulocyte proliferation is unregulated



A visit to the specialist

Oliver's meeting with the hematologist, Dr. Clement, went well. The doctor was optimistic about Oliver's treatment options, particularly since they had caught the cancer at a relatively early stage.

"We will start you on a drug called **imatinib, more commonly known as Gleevec,** and we will monitor your white blood cell count to see how you respond to the drug," Dr. Clement advised Oliver. "Please see the receptionist to schedule a follow-up appointment, and call the office if you experience any negative side effects."

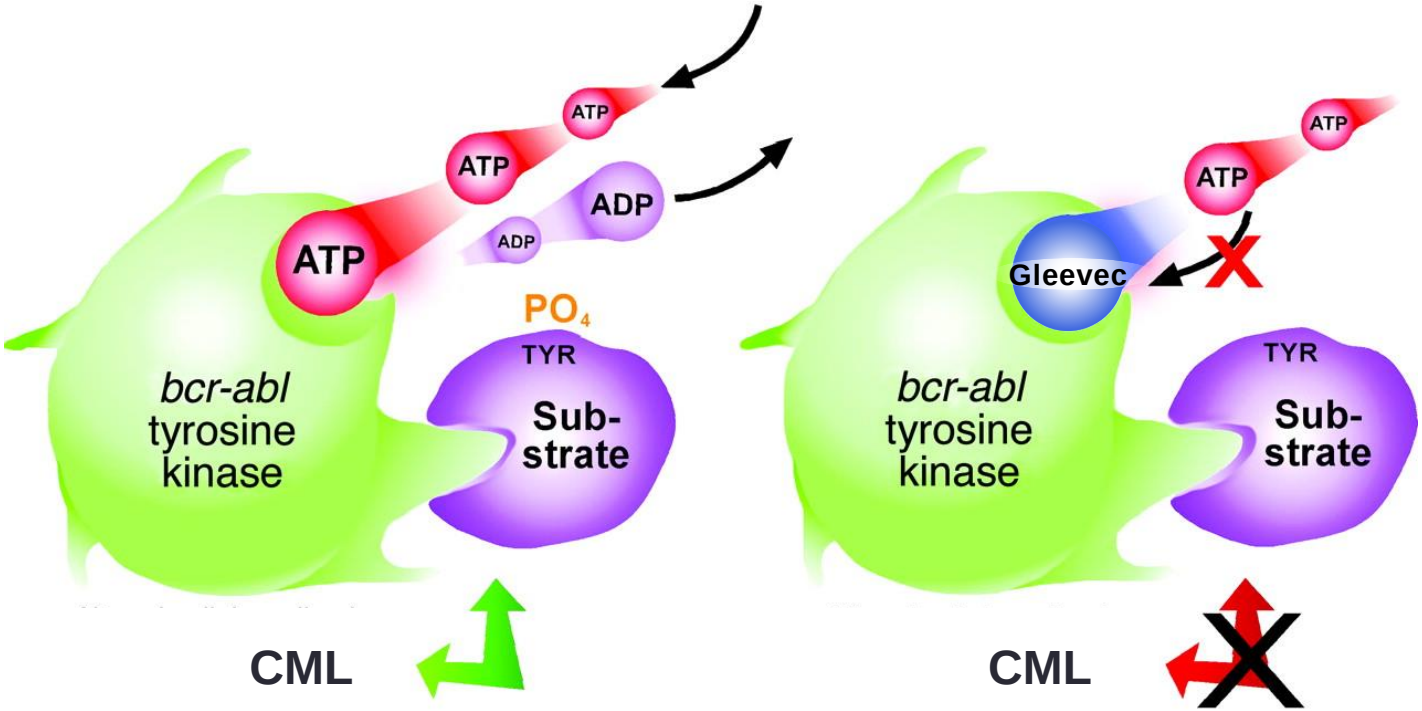
Oliver left the office and picked up his prescription for Gleevec.

How does imatinib work?

- Video: Gleevec® mechanism of action
  https://youtu.be/alsAk4pyWIE

Gleevec is a competitive inhibitor of BCR-ABL

- Competes with ATP for binding site
- Blocks ATP from binding to enzyme

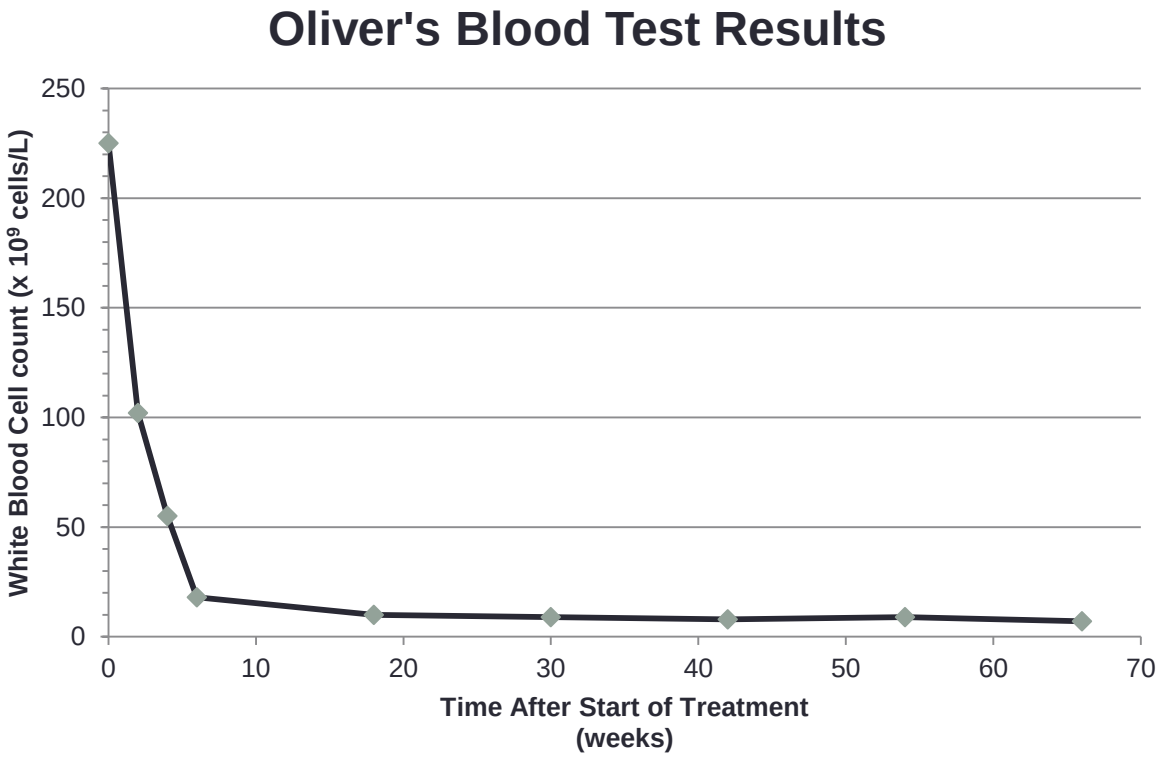


Blood tests, blood tests, and more blood tests!

Oliver had to admit it; he was getting used to the needle stick. Eighteen months ago, Dr. Clement had warned Oliver that it would be crucial to routinely monitor Oliver's blood to determine if the Gleevec was effectively fighting his cancer. And Dr. Clement was right! There sure were a lot of blood tests! And each time Oliver went to the phlebotomy lab, he hoped that his test results would reveal good news.

Refer to the graph below, charting some of Oliver's blood test results over the past 18 months. Based on this graph, is Oliver's treatment working?

a. Yes
b. No
c. Not Sure



Feeling good

Oliver was pleased. It had been about 18 months since his initial diagnosis of CML, and it appeared that the Gleevec was working. His white blood cell counts were back to within normal range, and Dr. Clement indicated that other testing revealed that the BCR-ABL mutation was no longer detectable in his blood cells.

He would continue to have his blood tested every three months, and was scheduled for a checkup with Dr. Clement in 6 months, provided everything continued to look good.

Troubling Results

Dr. Benjamin Clement frowned as he looked at the latest blood test results on his patient, Oliver Casey. Oliver had been taking imatinib for a little over 21 months now, and had responded beautifully. But the most recent blood work showed Oliver's white blood cell count was very high again. And genetic analysis revealed the presence of the BCR-ABL mutant kinase in his cells again. It was time to call Oliver in for a discussion.

What happened?

In groups of 2-3, discuss what could be the possible causes of Oliver's relapse. Be prepared to share at least one possible cause of Oliver's relapse with the rest of the class.

Resistance!

Dr. Clement shared the bad news with his patient. “I’m sorry, Oliver, but it appears that the Gleevec you have been taking is no longer working against your cancer, and your white blood cells are growing out of control again. We’ll do some genetic testing to confirm, but the most likely cause of this relapse is that the BCR-ABL gene has mutated once again, and that mutation has rendered the protein resistant to the Gleevec you have been taking.”

Video: mechanism of resistance to Gleevec

https://youtu.be/Jns9IiMrbeo

And what does the future hold for Oliver?

- The development and use of tyrosine kinase inhibitors that specifically block the function of BCR-ABL has revolutionized the treatment of CML
  - Mortality has dropped from 10-20% per year to 1-2% per year
  - Treated as a chronic disease rather than life-threatening cancer
- Tyrosine kinase inhibitors are a lifelong treatment
  - Stopping therapy often results in relapse
- Resistance mutations are always a threat; new tyrosine kinase inhibitors that are effective against known resistance mutations are currently in Clinical Trials
- Allogeneic bone marrow transplantation is the only truly “curative” treatment available, though this is often not an option due to patient age, other health issues, and lack of a suitable donor

References

Jabbour, E. & Kantarjian, H. (2012). Chronic myeloid leukemia: 2012 update on diagnosis, monitoring, and management. *American Journal of Hematology,* 87 (11), 1037-45.

National Cancer Institute. (May 23, 2014). *Chronic Myelogenous Leukemia Treatment (PDQ) Health Professional Version.* Retrieved from http://www.cancer.gov/cancertopics/pdq/treatment/CML/HealthProfessional.

National Cancer Institute. (June 27, 2014). *Chronic Myelogenous Leukemia Treatment (PDQ) Patient Version.* Retrieved from http://www.cancer.gov/cancertopics/pdq/treatment/CML/HealthProfessional

United States Food and Drug Administration. (August 26, 2013). *Gleevec (Imatinib Mesylate) Questions and Answers.* Retrieved from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110505.htm

Image Credits

Description: Chronic myeloid leukemia (CML): marked leucocytosis with granulocyte left shift.
Author: Paulo Henrique Orlandi Mourao
Source: http://commons.wikimedia.org/wiki/File:Chronic_Myeloid_Leukemia_smear_2009-04-09.JPG
Clearance: This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.
Description: Blood smear from a normal healthy adult. Stained with Giemsa. Note the uniform staining and size of cells.
Author: Keith Chambers
Source: http://commons.wikimedia.org/wiki/File:Normal_Adult_Blood_Smear.JPG
Clearance:This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.
Description: This diagram shows the hematopoiesis as it occurs in humans.
Author: A. Rad
Source: http://commons.wikimedia.org/wiki/File:Hematopoiesis_%28human%29_diagram.png
Clearance: GFDL-self. This image is released under the GFDL-self license and is considered freely distributable. This image or any reproductions/customizations thereof (or any reproductions/customizations of its reproductions/customizations, and so forth) may NOT be sold without my explicit consent.
Description: Philadelphia Chromosome Translocation
Author: A Obeidat
Source: http://commons.wikimedia.org/wiki/File:Philadelphia_chromosome.jpg
Clearance: This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.
Description: Basic Phosphorylation reaction
Author: Boc13
Source: http://commons.wikimedia.org/wiki/File:Basic_phosphorylation_reaction.png
Clearance: This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.
Adapted from : Mauro M J , and Druker B J. STI-571: Targeting BCR-ABL as therapy for CML. The Oncologist 2001;6:233-238

Video Credits

- Video clips adapted from:
  - http://www.hhmi.org/biointeractive/gleevec-inhibits-cancer-causing-kinase-bcr-abl
  - http://www.hhmi.org/biointeractive/gleevec-resistant-form-kinase-bcr-abl

PRACTICAL 1
WORKFLOW

https://www.learner.org/courses/biology/casestudy/cancer.html

CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

Overview

The development of a drug begins with basic research on a disease, which can take decades. (CML was first described in 1900.) Once the cause is defined, a pharmaceutical company must invest its research and development dollars into a treatment. While a drug is being planned and tested, companies say that it is "in the pipeline." The general steps, which we'll follow for Gleevec, are shown in the "Drug Development Pipeline" below. As we proceed, it will give us an idea of the time and cost for a drug to go "down the pipeline."

Because the first step is to learn as much as possible about the disease, let's start by learning about CML.

MENU OF STEPS IN THIS CASE STUDY:

1. Focus on a disease.
2. Identify the cause of a disease.
3. Identify a drug target.
4. Screen to find a lead compound.
5. Modify and retest the lead compound.
6. Lab and animal testing.
7. Human clinical trials (Phases I, II and III).
8. New drug approval.
9. Post-marketing surveillance (Phase IV).

INSTRUCTIONS:

Click the CONTINUE button to begin the investigation.

Or, if you'd like to skip to a specific step, select from the MENU.

CONTINUE ▶

■ CLOSE | MENU ■ | ◀ BACK | NEXT ▶

Drug Development Pipeline

Focus on a disease

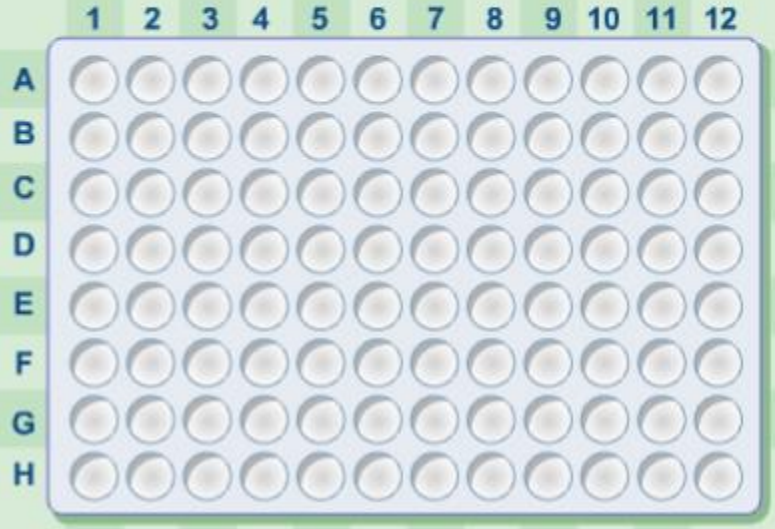
Identifying lead compound

CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

Random Screening

Finding an inhibitor of the Bcr-Abl kinase begins with a process that sounds contrary to drug "design": screening hundreds of chemical compounds for inhibitors. The screened compounds are selected because they have properties that might be expected of the desired drug, based on what is known about the target. However, a screen is required to find the ones that are most promising. The "microtiter dish" on the right allows us to screen 96 compounds at once. Each well in the dish contains tyrosine kinase and a substrate that turns color if the enzyme is active. A different candidate compound is added to each well. Any that inhibit tyrosine kinases prevent the substrate from turning color.



INSTRUCTIONS:

Click START SCREENING to add the candidate compounds to the tyrosine kinase samples and begin the screening.

After the test is complete, select the two most promising inhibitors. These will be our "lead compounds."

START SCREENING ▶

■ CLOSE | MENU ■ ◀ BACK | NEXT ▶

Drug Development Pipeline

Screening to Find a Lead Compound

For every 10,000 compounds screened to find a lead compound about 1,000 pass standards of efficacy & lack of toxicity — only 1 makes it to market.

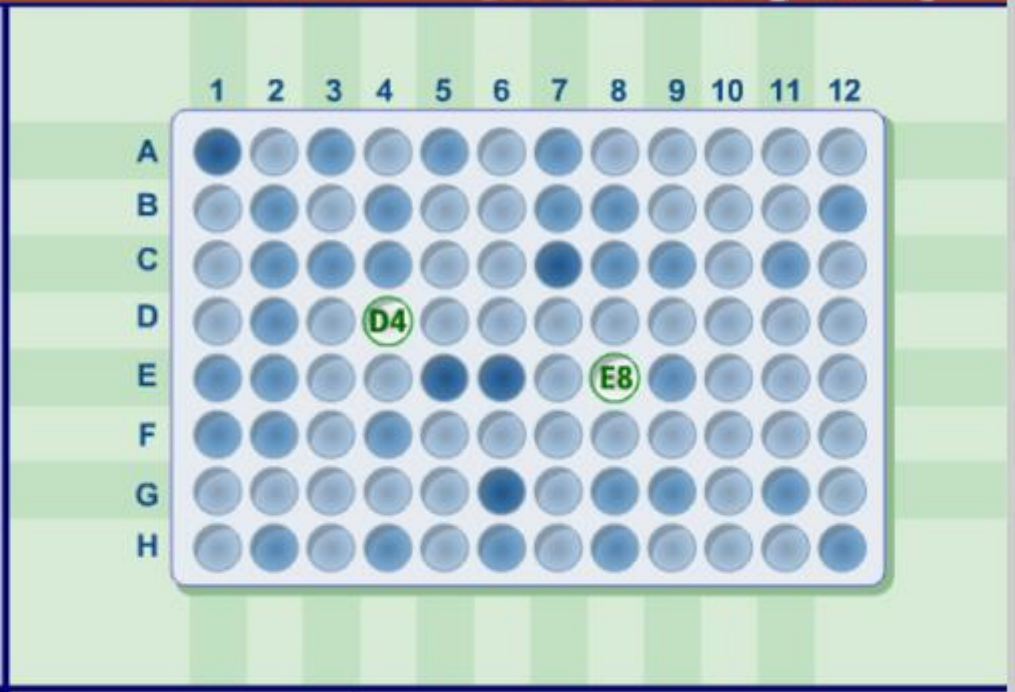
Identifying lead compound

CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

Random Screening

Finding an inhibitor of the Bcr-Abl kinase begins with a process that sounds contrary to drug "design": screening hundreds of chemical compounds for inhibitors. The screened compounds are selected because they have properties that might be expected of the desired drug, based on what is known about the target. However, a screen is required to find the ones that are most promising. The "microtiter dish" on the right allows us to screen 96 compounds at once. Each well in the dish contains tyrosine kinase and a substrate that turns color if the enzyme is active. A different candidate compound is added to each well. Any that inhibit tyrosine kinases prevent the substrate from turning color.



INSTRUCTIONS:

Click START SCREENING to add the candidate compounds to the tyrosine kinase samples and begin the screening.

After the test is complete, select the two most promising inhibitors. These will be our "lead compounds."

Click on the 2 most promising inhibitors.

You correctly identified our two lead compounds, located in wells D4 and E8.

Click NEXT to examine their characteristics.

■ CLOSE | MENU ■ | ◀ BACK | NEXT ▶

Drug Development Pipeline

Screening to Find a Lead Compound

For every 10,000 compounds screened to find a lead compound about 1,000 pass standards of efficacy & lack of toxicity — only 1 makes it to market.

An effective drug?

CASE STUDY

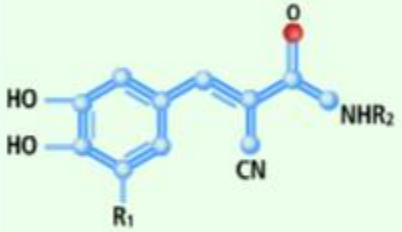
Designing Cancer Drugs: Development of Gleevec™

Characteristics of Drugs

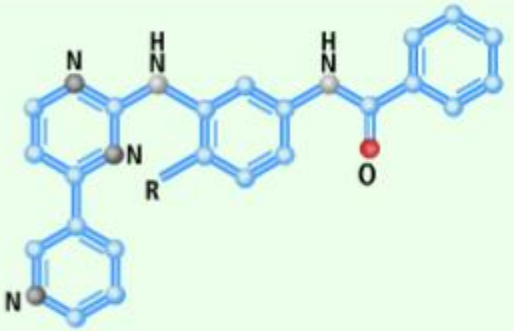
Our screen found two promising tyrosine kinase inhibitors, whose structures are shown here. These "lead compounds" will go through many rounds of modification and retesting in the quest to develop a highly specific, non-toxic, clinically effective Bcr-Abl inhibitor. Before we begin this process, let's consider our goals. What characteristics make an effective drug?

Lead Compounds

Lead Compound 1



Lead Compound 2



Source: Lead compound 1 adapted from Levitski A. (2002), S11. Figure 1
Source: Lead compound 2 adapted from Manley, PW et al. (2002), S19, Figure 3

Note: In the lead compound 1, R_1 stands for one of several small chemical groups.

INSTRUCTIONS:

In this activity, you will be given a series of drug characteristics. For each, choose the option that you feel will make the most effective drug.
Click START ACTIVITY to begin.

START ACTIVITY ▶

Answer questions here after clicking 'Start activity'

■ CLOSE | MENU ■ | ◀ BACK | NEXT ▶

Drug Development Pipeline

Screening to Find a Lead Compound

The lag between learning the molecular cause of a disease and having a treatment based on that knowledge is 25-30 years.

CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

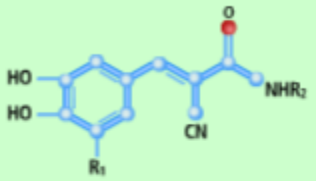
Comparing Lead Compounds and Substrates

Now that we know the qualities we want in a drug, let's consider our lead compounds.

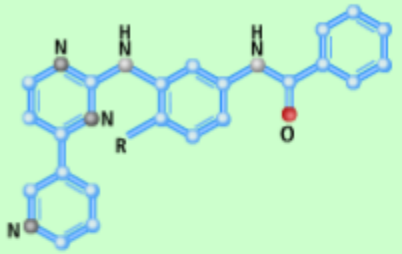
Many drugs are classic "competitive inhibitors" that compete with the normal substrates for an enzyme's attention. They often mimic the structure of the normal substrates. In this case, Bcr-Abl's substrates are a tyrosine amino acid that will be phosphorylated, and ATP, which will provide the phosphate. A compound that mimics either tyrosine or ATP might be a good candidate for a specific Bcr-Abl inhibitor.

The structures of our two lead compounds

Lead Compound 1

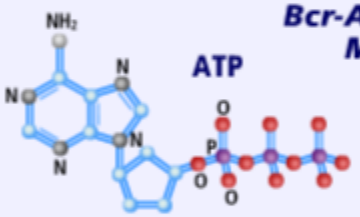


Lead Compound 2

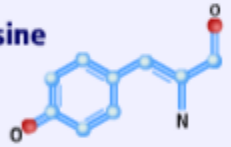


Bcr-Abl Substrate Molecules

ATP



tyrosine



INSTRUCTIONS:

Classify each lead compound by dragging the ATP and tyrosine molecules until their common structures are aligned with one of the two lead compounds.

CASE STUDY

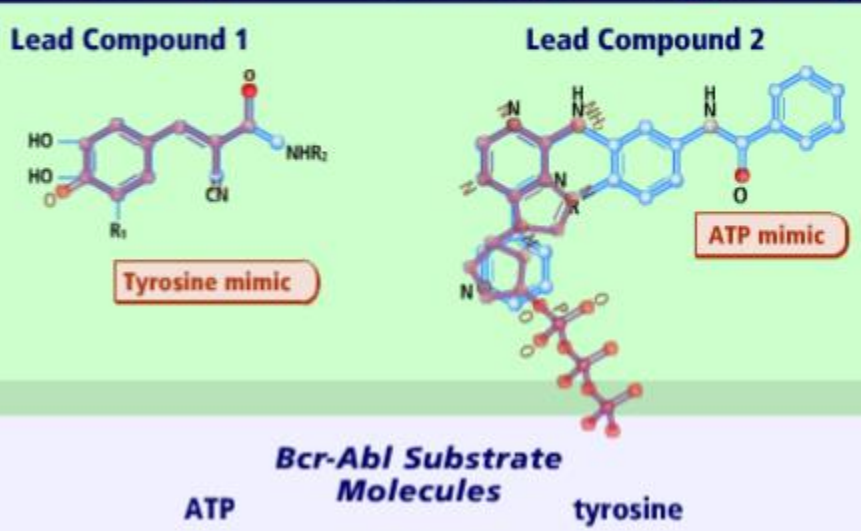
Designing Cancer Drugs: Development of Gleevec™

Comparing Lead Compounds and Substrates

Now that we know the qualities we want in a drug, let's consider our lead compounds.

Many drugs are classic "competitive inhibitors" that compete with the normal substrates for an enzyme's attention. They often mimic the structure of the normal substrates. In this case, Bcr-Abl's substrates are a tyrosine amino acid that will be phosphorylated, and ATP, which will provide the phosphate. A compound that mimics either tyrosine or ATP might be a good candidate for a specific Bcr-Abl inhibitor.

The structures of our two lead compounds



Do both steps

INSTRUCTIONS:

Classify each lead compound by dragging the ATP and tyrosine molecules until their common structures are aligned with one of the two lead compounds.

Now that you've classified the two lead compounds, choose which compound you'd like to pursue.

- Pursue the development of the tyrosine mimic.
- Pursue the development of the ATP mimic.

CLOSE | MENU | BACK | NEXT

Drug Development Pipeline

Screening to Find a Lead Compound

The lead compounds for the tyrosine kinase inhibitors were identified in the 1980s.

Lead Discovery

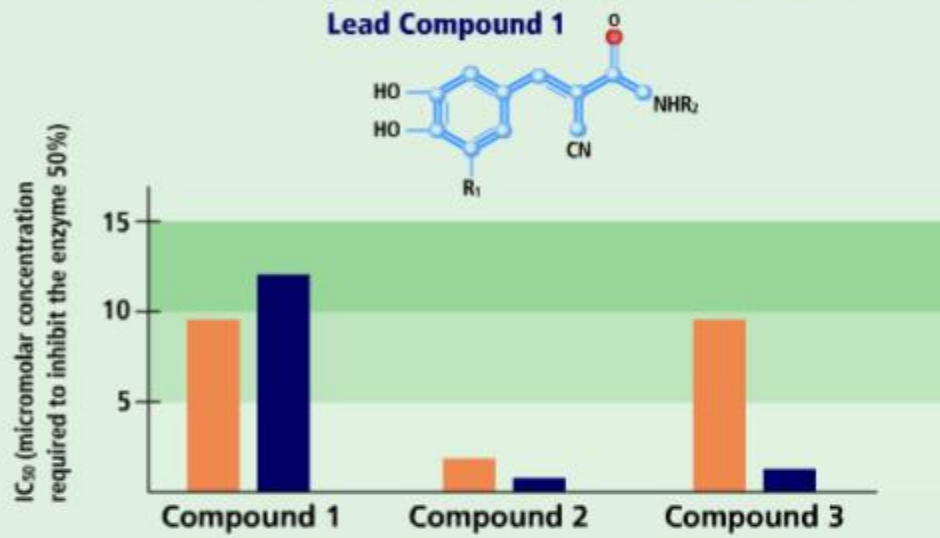
CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

Testing Mimics: In Vitro Kinase Inhibition

The next step is to make small modifications to the lead compounds and retest them for Bcr-Abl inhibition. We'll also test the effect on a normal Abl enzyme, because a drug that affects a normal, as well as a mutant, enzyme might cause side effects.

Three compounds (A, B, and C) were generated by small changes to the tyrosine mimic lead. Each was tested for its ability to inhibit the cancer-causing Bcr-Abl tyrosine kinase in vitro, and its effect on the normal Abl kinase. Results are given as IC_{50}, the concentration that inhibits enzyme activity by 50 percent.



Source: Graph adapted from Anafi M et al., 267:4518, Table 1

INSTRUCTIONS:

Examine the data for the experiment and select the compound that shows the most promise for drug development.

Which compound shows the most promise?

Compound 1 ▸ Compound 2 ▸ Compound 3 ▸

Click one by one and choose right option

■ CLOSE MENU ■ ◂ BACK NEXT ▸

Drug Development Pipeline

Modify and Re-test the Lead Compound

Tyrosine mimics were modified and tested through the early 1990s. These data were published in 1992.

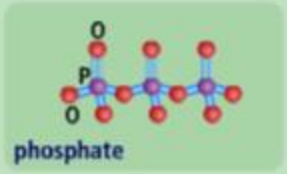
CASE STUDY

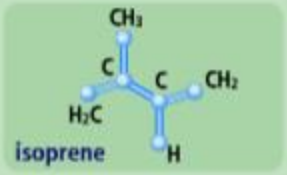
Designing Cancer Drugs: Development of Gleevec™

Refinement of ATP Mimics

After finding lead compounds, the next step in drug development is many rounds of modifying and retesting to improve characteristics like stability and specificity. Another consideration in the refinement process is to keep the potential drug hydrophilic enough to be soluble in water, yet hydrophobic enough to pass through the cell membranes.

The ATP mimic that was a lead compound for Gleevec is shown here. One of the modifications was the addition of a group where the arrow indicates. What group would you add to meet all the criteria necessary for a drug that is specific and soluble but also membrane-permeable?





INSTRUCTIONS:

Roll over each of the chemical groups to read more about its properties. Then select one of the groups to add to the lead compound.

Choose a group:

- Phosphate
- Methylpiperizine
- Isoprene

Click these and choose right option

■ CLOSE | MENU ■ | ◀ BACK | NEXT ▶

Drug Development Pipeline

Modify and Re-test the Lead Compound

Over 300 compounds were synthesized and tested between the lead compound and Gleevec.

Lead Optimization

CASE STUDY

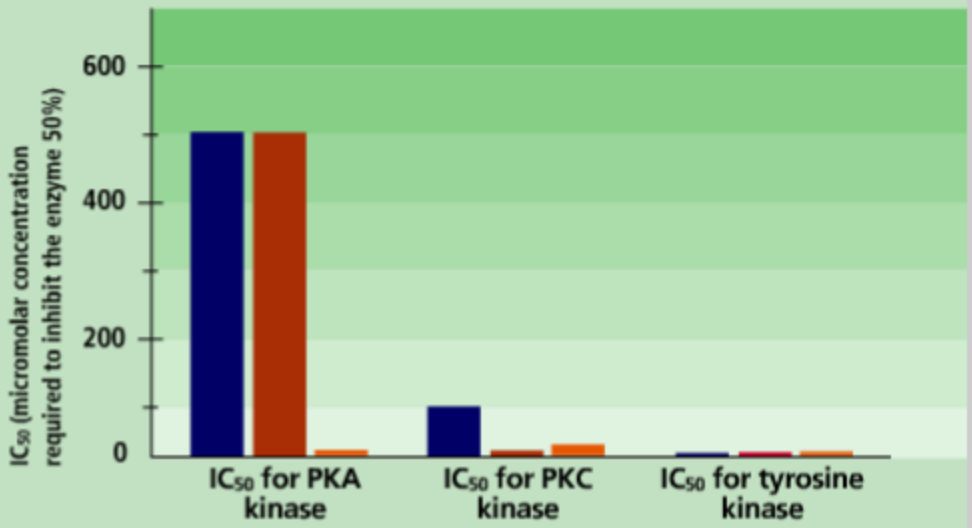
Designing Cancer Drugs: Development of Gleevec™

without adding charges that prevent passage through membranes.

After modification, the potential drug is retested for inhibition and specificity. In tests similar to those done with the tyrosine mimic, researchers demonstrated that our compound inhibits mutant Bcr-Abl, but not the normal Abl enzyme.

But what about the cell's other kinases? This experiment tests ATP mimics 1, 2, and 3 (one is our modified lead compound) against three different kinases. We want inhibition of tyrosine kinases at low concentration, without affecting protein kinases PKA or PKC. Results are given as IC_{50} (concentration that inhibits enzyme activity by 50 percent).

Is compound 1, 2, or 3 the most effective?



Source: Graph adapted from Zimmerman et al. (1997), 7:187, Table 2

INSTRUCTIONS:

An effective drug works at low concentrations (has a low "IC_{50}") and is specific for its target. Choose the compound that is the most likely to be effective against Bcr-Abl, without causing side effects.

Which compound shows the most promise?

Compound 1 ▶ Compound 2 ▶ Compound 3 ▶

choose target compound

■ CLOSE MENU ■ ◀ BACK NEXT ▶

Drug Development Pipeline

Modify and Re-test the Lead Compound

These data were published in 1997.

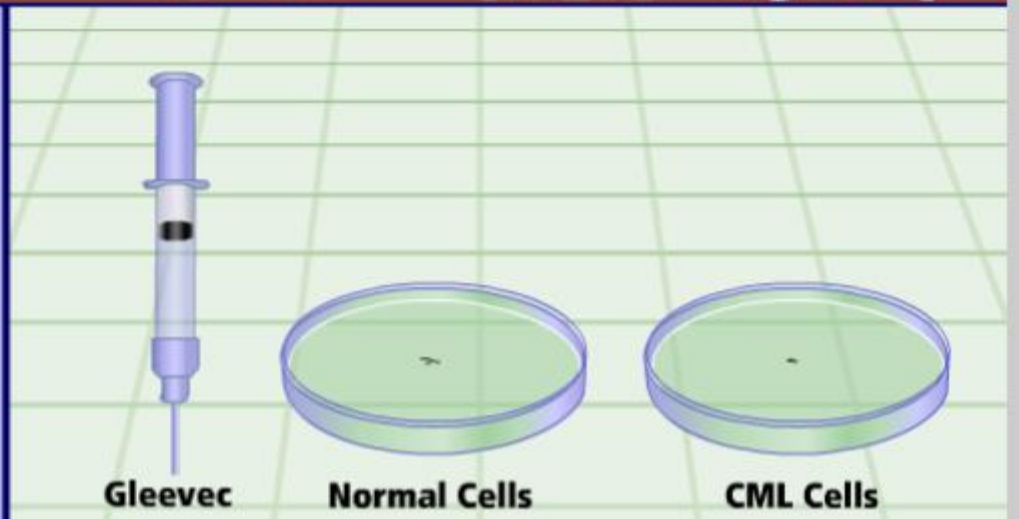
CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

Testing Gleevec: Cultured Cells Data

Gleevec was tested extensively against purified kinases in a test tube. The next step in drug development is to test the activity against cultured cells. To be effective, Gleevec must suppress the proliferation of cultured chronic myelogenous leukemia (CML) cells. To cause minimal side effects, it must be specific enough to inhibit CML cells that have the unregulated Bcr-Abl tyrosine kinase, but allow the growth of normal cells that have properly regulated kinases.

In this experiment, cultured CML cells and cultured normal cells were treated with Gleevec. Does Gleevec inhibit cancerous CML cells without inhibiting normal cells?



Source: Graphic adapted from Druker BJ et al. (1996), 2:561, Figure 5.

INSTRUCTIONS:

Click ADD GLEEVEC to see the results of treating cultured CML cells and cultured normal cells with Gleevec.

ADD GLEEVEC ▶

■ CLOSE | MENU ■ | ◀ BACK | NEXT ▶

Drug Development Pipeline

Lab and Animal Testing

The first data from testing Gleevec in vitro and against cultured cells were published in the mid-1990s.

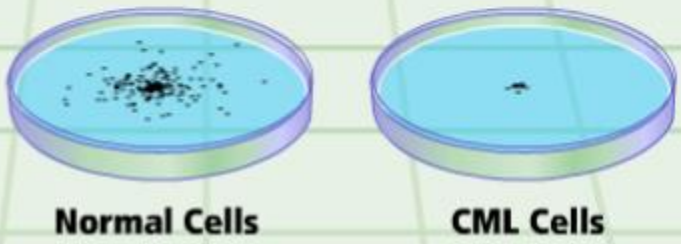
CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

Testing Gleevec: Cultured Cells Data

Gleevec was tested extensively against purified kinases in a test tube. The next step in drug development is to test the activity against cultured cells. To be effective, Gleevec must suppress the proliferation of cultured chronic myelogenous leukemia (CML) cells. To cause minimal side effects, it must be specific enough to inhibit CML cells that have the unregulated Bcr-Abl tyrosine kinase, but allow the growth of normal cells that have properly regulated kinases.

In this experiment, cultured CML cells and cultured normal cells were treated with Gleevec. Does Gleevec inhibit cancerous CML cells without inhibiting normal cells?



Source: Graphic adapted from Druker BJ et al. (1996), 2:561, Figure 5.

INSTRUCTIONS:

Click ADD GLEEVEC to see the results of treating cultured CML cells and cultured normal cells with Gleevec.

Gleevec inhibited the growth of leukemic cells from a CML patient by 60-80%. Furthermore, when the cells that were able to grow were tested for Bcr-Abl, only 20% of them were positive. This suggests that Gleevec selectively inhibits Bcr-Abl positive cells, while allowing the growth of any normal cells the patient has. The next step in the process is to begin testing Gleevec in animals and humans.

Click NEXT to continue.

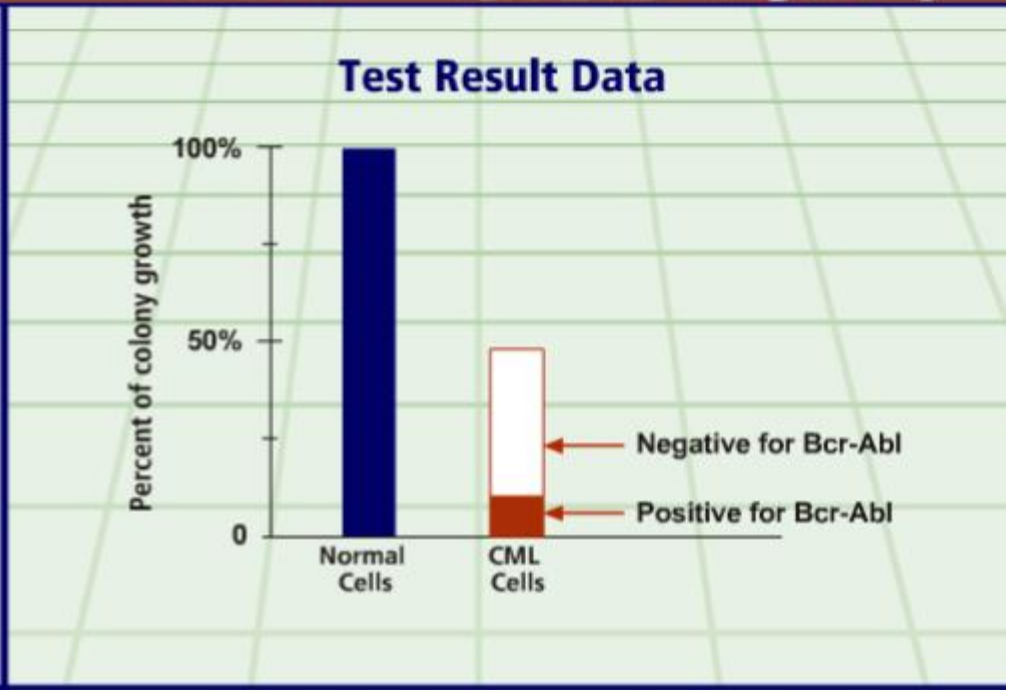
CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

Testing Gleevec: Cultured Cells Data

Gleevec was tested extensively against purified kinases in a test tube. The next step in drug development is to test the activity against cultured cells. To be effective, Gleevec must suppress the proliferation of cultured chronic myelogenous leukemia (CML) cells. To cause minimal side effects, it must be specific enough to inhibit CML cells that have the unregulated Bcr-Abl tyrosine kinase, but allow the growth of normal cells that have properly regulated kinases.

In this experiment, cultured CML cells and cultured normal cells were treated with Gleevec. Does Gleevec inhibit cancerous CML cells without inhibiting normal cells?



INSTRUCTIONS:

Click ADD GLEEVEC to see the results of treating cultured CML cells and cultured normal cells with Gleevec.

Gleevec inhibited the growth of leukemic cells from a CML patient by 60-80%. Furthermore, when the cells that were able to grow were tested for Bcr-Abl, only 20% of them were positive. This suggests that Gleevec selectively inhibits Bcr-Abl positive cells, while allowing the growth of any normal cells the patient has. The next step in the process is to begin testing Gleevec in animals and humans.

Click NEXT to continue.

Clinical trials

CASE STUDY

Designing Cancer Drugs: Development of Gleevec™

Testing Gleevec: Clinical Testing

After positive results in vitro and in cultured cells, researchers started Gleevec studies in animals and humans. The results were astonishing: one study showed leukemia blood cell counts returning to normal in 90 percent of 54 patients. This success, along with lobbying by CML patients, convinced the drug company Novartis to begin large-scale manufacture of the drug, even though the market is small.

But are we done? Have we designed the perfect anti-CML drug?

INSTRUCTIONS:

Click NEXT to continue.

Drug resistance

Designing Cancer Drugs: Development of Gleevec™

Conclusion

We've just had a look at the long process of drug design — and for Gleevec, it's not over. Research continues because Gleevec shows promise against glioblastomas and gastrointestinal tumors caused by uncontrolled tyrosine kinases. Combining Gleevec with other drugs may increase effectiveness against resistant cells. (Resistance is often fought by treatment with several drugs. This strategy, which relies on the decreased chance of simultaneous resistance to multiple drugs, is used to treat HIV infection.)

Drugs are also being designed against other diseases. According to Julian Adams at Millennium Pharmaceutical in Cambridge, Massachusetts, "There are hundreds of enzymes that are [targets]...Not all of [them] will turn out like Gleevec, but I've got to believe that there are several dozen great targets..."

QUIT ✕ PLAY AGAIN ▸ VIEW SOURCES ■

MENU ■ ◂ BACK