Landmark Lesson Plan:

Discovery of Ivermectin: Preventing Blindness and Heartworm

Grades: 9-12
Subject areas: Chemistry, medicine, and history.
Based on the "Discovery of Ivermectin" National Historic Chemical Landmark
Principal author: Erica K. Jacobsen

The following inquiry-based student activities are designed for use in high school lesson planning. The handout and activities will help students learn about the history of ivermectin as a groundbreaking medical treatment, including its current and future use in eliminating river blindness and treating heartworm and other parasites in pets and livestock, understand its chemical structures, and describe its various impacts.

The activities are designed as a ready-to-go lesson, easily implemented by a teacher or substitute to supplement a unit of study. In chemistry, the activities relate to chemical structures and how they can be represented. In medicine, the activities relate to how small changes to a molecule can have a large impact on its effectiveness as a drug and the multiple areas of impact of ivermectin. In history, the activities highlight the people and organizations involved in developing and using ivermectin, and also the past, present, and future of the drug.

All resources are available online at
https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/lesson-plans.html.

While these activities are thematically linked, each is designed to stand alone as an accompaniment for the reading on pages three to five. Teachers may choose activities based on curricular needs and time considerations.

- Take a few minutes to introduce the lesson with a few conversation starters. Ask students to consider whether they would consider taking the same medication as a pet or livestock. What do they know about how medications are discovered and developed?
- Have students read the reading, **Discovery of Ivermectin: Preventing Blindness and Heartworm**.
- Distribute the **Activities** selected for the class.
- After class use the **Answer Guide** for student feedback and discussion.
- Show the ACS Reactions video, "What Is Ringworm and How Do You Get Rid of It?" (4 min., 19 sec.). Compare and contrast ringworm to river blindness. Despite having "worm" in its name, it is a fungal rather than parasitic infection. Both infections have skin-related symptoms. In both, the typical treatment doesn't kill the fungus or the parasites, but stops the fungus from growing and the parasites from releasing larvae.

Student Activities with Objectives

History Exercise: Chronology of Ivermectin (15–20 min.)
- Using the handout, students describe major events before and after the discovery of ivermectin, including plans for the future.

Ivermectin: People and Places (15–20 min.)
- Students note that ivermectin's history extends across the globe and involves a combination of individual researchers, companies and organizations, and the people receiving it as a treatment.

Ivermectin: Chemical Structures (10–15 min.)
- Students practice using bond line notation with structures related to ivermectin's precursor. They also look for small changes to molecules that resulted in an even more successful drug.

Ivermectin Impacts (10–15 min.)

- Students describe the wide-ranging health benefits of ivermectin, along with its economic impacts. They also imagine the effect on their own activities and mental health if they were affected by river blindness.

Discovery of Ivermectin: Preventing Blindness and Heartworm

The story is so improbable it defies belief: A soil sample from Japan prevents suffering in Africa. It starts when a scientist discovers a lowly bacterium in soil near a golf course outside Tokyo. A team of scientists in the U.S. finds that the bacterium produces compounds that interfere with the activity of nematode worms. It is developed into a drug that wards off parasites in countless pets and farm animals, averting billions of dollars in losses worldwide. Extraordinarily, the drug also prevents or treats human parasitic diseases that would otherwise cause blindness and other severe symptoms in hundreds of millions of people in many of the poorest countries on Earth.

International partnership

The tale depends on an international cast of thousands of scientists, medical practitioners and other dedicated participants. It also involves a company and research institute willing to give a drug away for free to rid the developing world of debilitating diseases. Yet none of this would have happened without that soil dug up in Japan—and a healthy dose of serendipity.

In the late 1960s and early 1970s, Satoshi Ōmura, a microbiologist and bioorganic chemist at Tokyo's Kitasato Institute, was hunting for new sources of pharmaceuticals. He knew that some existing drugs, including antibiotics, had been derived from compounds found in nature. So he developed screening methods to identify medicinally promising compounds from soil. His team collected thousands of soil samples from around Japan, cultured bacteria from them, and screened each culture for medicinal potential.

In 1971, Ōmura took a sabbatical in the laboratory of Max Tishler, an eminent professor of chemistry at Wesleyan University in Connecticut. A year earlier, Tishler had retired from an illustrious research career at the pharmaceutical company Merck. Before Ōmura returned to Japan in 1973, he arranged a pioneering agreement between the company and the research institute. Kitasato would continue to collect samples and screen them, and then send the most promising ones to Merck Research Laboratories in Rahway, New Jersey, for testing and development. The institute would receive royalties from any products that were commercialized through the partnership.

At Merck Research Labs, a team led by parasitology specialist William C. Campbell began testing the samples as potential treatments for parasitic worms. A veterinary scientist and zoologist by training, Campbell identified compounds that could be effectively developed as drugs for livestock and other animals.

An effective culture

To test potential treatments, the Merck researchers first infected mice with nematodes and then fed each mouse a different culture sample supplied by Ōmura's team. They found that one culture was extraordinarily effective at ridding mice of worm infestations.

This culture was derived from soil collected near a golf course in Kawana, about 80 miles southwest of Tokyo. Ōmura identified the bacterium in that culture as a new strain, which was ultimately christened *Streptomyces avermectinius*. The Merck team isolated the active component produced by the bacterium and named it "avermectin." They found that

Olivier Asselin

A boy leads a man impacted by river blindness in Sierra Leone. The disease is among the leading causes of preventable blindness in the world. Ivermectin was approved for human use against river blindness in 1987.

Glossary

Antibiotic: A substance that kills bacteria or prevents their growth. They can be used to fight bacterial infections. Some antibiotics are derived from mold or bacteria, while others are produced through chemical synthesis.

Bacterial culture: A population of bacterial cells intentionally cultivated in a growth medium in a lab.

Bioorganic chemistry: The use of chemistry tools to study processes that occur in living organisms.

Biosynthesis: A living organism's transformation of one or more chemical compounds into one or more new compounds.

Cellular channel: A natural passageway through the membrane that surrounds a cell. When activated, ion channels let charged molecules pass into and out of the cell.

Enzyme: A protein that helps chemical reactions take place in living organisms. Proteins are made of amino acids linked together according to instructions encoded in genes.

Heartworm: A parasite that, in the adult phase, forms long, skinny worms in the heart, lungs and blood vessels of pets and other animals. If not treated, the infestation can cause severe disease or death.

Larvae: An immature stage of insects before they turn into adults.

Microbiology: The study of microscopic organisms.

Nematode: A type of roundworm. Some species are parasitic.

Parasite: An organism that lives off another organism, often harming that host organism.

Zoology: The study of animals.

avermectin is actually a combination of eight closely related compounds. The researchers began chemically modifying the compounds, tweaking their molecular structures to see if they could make avermectin more potent against parasites and safer for the animals being treated.

By synthesizing thousands of similar compounds, Merck scientists found that, with slight chemical modification, some of the avermectin compounds displayed enhanced activity as well as safety. They dubbed the resulting pair of avermectin derivatives "ivermectin." The mixture was 25 times more potent than existing treatments for parasitic worms.

Further testing at Merck showed that ivermectin could also fight infestations by mites, ticks and botfly parasites that cause huge economic losses in the livestock industry. It was effective against parasites in horses, cattle, pigs, sheep and dogs, and was nontoxic to these animals.

These results led Merck to commercialize ivermectin as a veterinary treatment beginning in 1981. Starting in 1987, the drug was also marketed to the public under the brand name Heartgard® (now sold by the animal-health company Merial) to prevent heartworms in dogs. These products quickly became the top-selling veterinary medicines in the world, with sales topping $1 billion annually.

The cycle of parasitic disease often begins with a bug bite. Mosquitoes carry the larvae of worms that cause heartworm. And blackflies, which breed in fast-flowing rivers, carry the larvae of the worm that causes onchocerciasis (also known as river blindness) in humans. When an infected fly bites a person, the fly deposits worm larvae on the person's skin. The parasites enter the body through the bite wound, where they mature into adult worms that live and breed. Female worms release thousands of microscopic larvae that move throughout the body, including to the eyes, where they cause scarring that leads to blindness. The parasite also causes intense itching and disfiguring skin conditions. The disease occurs primarily in Africa, but also exists in Yemen and several Latin American countries. It is one of the leading causes of preventable blindness in the world.

Treatment for river blindness

At Campbell's urging, his colleagues studied ivermectin as a potential treatment for river blindness. Ivermectin is a particularly attractive treatment because it has no antibacterial or antiviral activity, and has few serious side effects. That's because these drugs act primarily on cellular channels of the targeted parasites that are not accessible in people, pets or livestock. In young worms, the drug alters the function of these channels in nerve and muscle

Further reading

- The Nobel Prize in Physiology or Medicine, 2015 (NobelPrize.org)
- Mectizan Donation Program: History (Mectizan Donation Program)
- The Ivermectin Story (Satoshi Ōmura)
- River Blindness (Carter Center)

cells, leading to paralysis. In addition, the drug makes these immature worms more vulnerable to the human immune response, and stops adult female worms from releasing larvae. This combined effect helps end the parasite infestation.

In its drug development efforts, Merck worked with the World Health Organization to design and implement human clinical trials with ivermectin for river blindness in Senegal in 1981. The results with single doses of the pill proved the effectiveness of the drug against river blindness, and ivermectin was approved for human use in 1987 under the name Mectizan®.

Mectizan Donation Program

Most patients who would benefit from Mectizan® live in developing nations. Recognizing that these patients would not be able to afford the drug at any price and no donors were willing to pay for it, Merck CEO P. Roy Vagelos in 1987 announced the company's commitment to donate "as much as needed, for as long as needed," with the goal to help eliminate river blindness. To reach this goal, Merck established the Mectizan Donation Program (MDP), a ground-breaking public-private partnership.

Mectizan® is also administered with albendazole—a drug that GlaxoSmithKline donates—as part of a massive campaign to eliminate lymphatic filariasis (also known as elephantiasis), another tropical disease that disrupts the immune system and is common among people living in under-resourced settings in about 80 countries.

Today, the MDP program reaches more than 250 million people, with more than 2 billion treatments donated since it was established. With this support, health authorities hope to eliminate these diseases within the next decade.

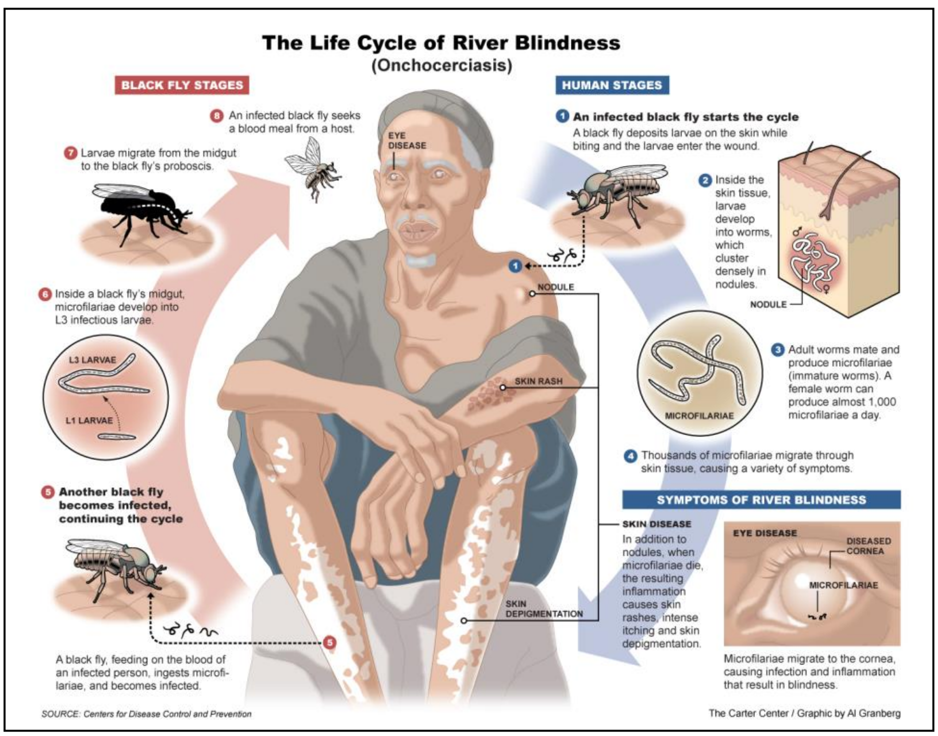
Further Developments

Additional uses for ivermectin and other avermectin derivatives continue to be found, including the treatment of infestations by other worms and by head lice, as well as scabies and strongyloidiasis.

Even after ivermectin went on the market, research continued on the bacterium that started it all. In 1999, Ōmura's team announced that it had identified the genes that control biosynthesis of the avermectin compounds in *S. avermectinius*. In all, the organism relies on 17 genes to produce the enzymes required for the dozens of steps in this biochemical pathway.

Ōmura and Campbell's contributions were honored with the 2015 Nobel Prize in Physiology or Medicine. They shared the prize with Tu Youyou of the China Academy of Traditional Chinese Medicine, who has had a similarly outsized impact on the developing world by discovering a treatment for malaria. In conferring the award, the Nobel Assembly noted that the consequences of these researchers' discoveries in terms of improved human health and reduced suffering are immeasurable.

The odds against finding avermectin and recognizing its potential were astronomical. It could so easily have been missed, and the life-altering pharmaceutical that Merck derived from it might never have been discovered.



The Carter Center/Graphic by Al Granberg

Student Name: ______________________________ Date: _____________ Period: __________

History Exercise: Chronology of Ivermectin

Ivermectin has been a successful treatment against parasites in humans as well as pets and farm animals for several decades. It continues to be used as a tool in the fight to eliminate river blindness in Africa and other locations.

1. Using the reading provided, briefly describe the major events before and after the discovery of ivermectin during each of the time periods listed below.

Time Period	**Event(s)**
Late 1960s–early 1970s	
1971	
1973	
1974–1975	*Bacterium from soil sample collected in Kawana is sent to Merck. Active component from bacterium is later chemically modified to produce a treatment named ivermectin.*
1981	
1987	

Student Name: ______________________________ Date: _____________ Period: __________

1999	
2015	

2. One dose of ivermectin is effective for an entire year against the worms that cause river blindness. Adult female worms have a typical life span of 14 years, so ivermectin is usually prescribed for 16 to 18 years. What would happen after 16 to 18 years of annual doses in a human population? Explain your answer.

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3. In 1987 Merck committed to donate ivermectin doses “as much as needed, for as long as needed” to help eliminate river blindness. Describe the current state of progress toward that goal.

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Student Name: _____________________________ Date: ____________ Period: _________

Ivermectin: People and Places

The history of ivermectin is an international one. It began with a soil sample from Japan, and continued with testing and development ion the U.S. As a treatment, it has spread to locations across the globe.

1. Using the reading provided, list the location for each person or organization and briefly describe their roles in ivermectin's history.

Person/Organization	Location(s)	Role in Ivermectin's History
Satoshi Ōmura		
Max Tishler		
William C. Campbell		
Merck Research Laboratories		
World Health Organization	Worldwide	
Populations treated for river blindness	Nearly 3 dozen countries in Africa, South Asia, and Central and South America	

Student Name: ______________________________ Date: ____________ Period: _________

2. Describe how GlaxoSmithKline, another pharmaceutical company, is connected to ivermectin's treatment to prevent river blindness.

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3. Using other sources or your own knowledge, draw small circles on the map for each of the locations you listed in the table for question 1. Then, draw larger circles on the general areas of treated populations (see final row of table).

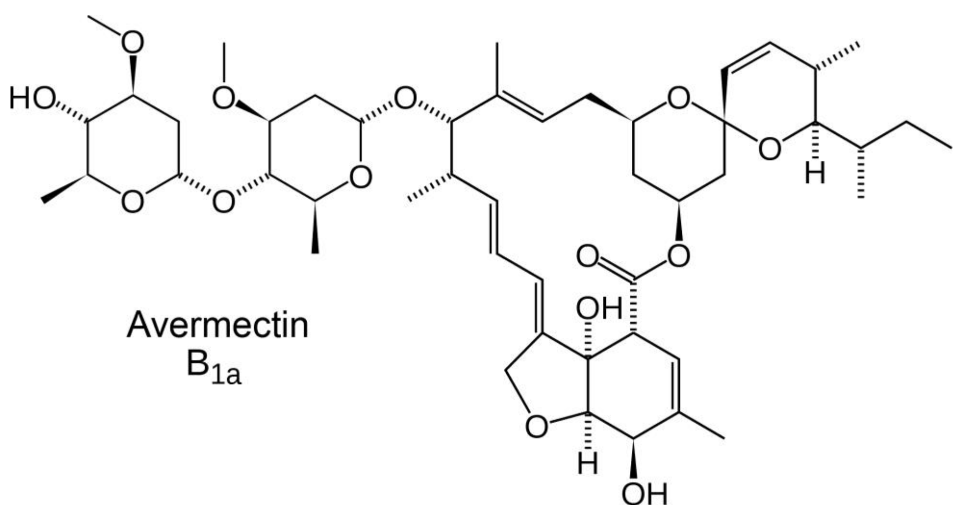
Student Name: ______________________________ Date: _____________ Period: __________

Ivermectin: Chemical Structures

The active component produced by the soil sample bacterium found by Ōmura's team was eventually named avermectin. It was discovered to be a combination of eight similar compounds.

1. The structure of one of avermectin's eight compounds is below. The drawing uses one line to show a single bond. Some show direction into or out of the page using a dotted or bolded line. A double bond is shown by adding a second line next to a single bond line. Carbon atoms are at places where two lines join and at ends of lines. The drawing does not show all of the hydrogen atoms or carbon–hydrogen bonds.

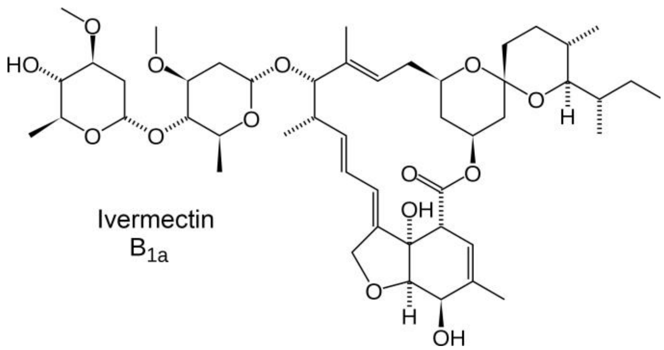
- Draw a mark at each carbon atom location.
- How many carbon atoms are in the structure? _______



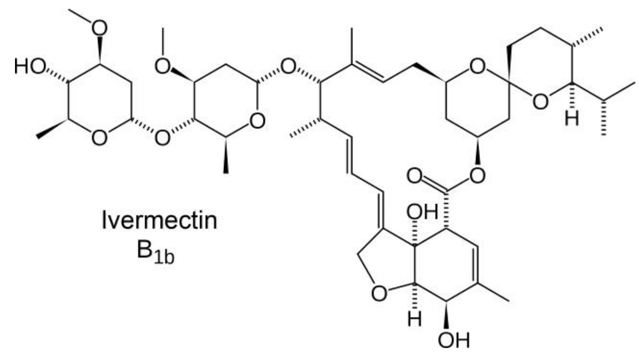
2. Researchers made small structural modifications to avermectin's compounds to try to make the components more potent as a treatment while increasing its safety. They succeeded with the changes shown below; the resulting pair of compounds was called ivermectin.

- Compare each structure to the avermectin structure above. Circle any changes.

Student Name: ______________________________ Date: _____________ Period: __________



Ivermectin B_{1a}



Ivermectin B_{1b}

3. Ivermectin is an effective treatment for parasites in a range of organisms, such as humans, livestock, and pets, with few serious side effects. Describe how ivermectin's method of action makes this possible.

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4. The graphic on the last page of the reading shows the life cycle of river blindness. In which stages of the life cycle does ivermectin work?

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Student Name: ______________________________ Date: _____________ Period: __________

Ivermectin Impacts

When using a medicine, one might only think about curing a certain condition or helping to reduce symptoms associated with it. Ivermectin's impacts reach beyond this, with not only health benefits, but also economic and social benefits.

1. Ivermectin was initially identified as a very effective treatment for parasitic worms in animals. What did further testing reveal about its potential uses for animal health?

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2. Later, the use of ivermectin was expanded to human health applications. Using the reading, describe the process that led up to ivermectin being approved for human use in 1987.

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3. Before ivermectin, one way of dealing with river blindness had been people moving away from fertile farmland to avoid areas where infected blackflies lived. Discuss the economic impact of using this method of prevention.

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Student Name: ______________________________ Date: _____________ Period: __________

4. Individuals with untreated river blindness typically have symptoms of severe itching, rashes, muscle pain, and weakness. Imagine your own daily life and picture yourself with these symptoms. Discuss how they would affect your activities and mental health.

History Exercise: Chronology of Ivermectin

Ivermectin has been a successful treatment against parasites in humans as well as pets and farm animals for several decades. It continues to be used as a tool in the fight to eliminate river blindness in Africa and other locations.

1. Using the reading provided, briefly describe the major events before and after the discovery of ivermectin during each of the time periods listed below.

Time Period	Event(s)
Late 1960s–early 1970s	**Ōmura looks for new sources of pharmaceuticals from bacteria in soil.**
1971	**Ōmura takes a sabbatical in Tishler's laboratory in the U.S.**
1973	**Ōmura arranges a pioneering agreement between pharmaceutical company Merck and Kitasato Institute.**
1974–1975	*Bacterium from soil sample collected in Kawana is sent to Merck. Active component from bacterium is later chemically modified to produce a treatment named ivermectin.*
1981	**Merck commercializes ivermectin as a veterinary treatment.**
	Merck works with World Health Organization for human clinical trials with ivermectin for river blindness in Senegal.
1987	**Ivermectin marketed to public under brand name Heartgard®.**
	Ivermectin approved for human use under the name Mectizan®.
	Merck commits to donating ivermectin to help eliminate river blindness.
1999	**Ōmura's team announces that it had identified the genes that control biosynthesis of the avermectin compounds in *S. avermectinius*.**

2015	**Ōmura and Campbell win 2015 Nobel Prize in Physiology or Medicine, shared with Tu Youyou for her discovery of a treatment for malaria.**

2. One dose of ivermectin is effective for an entire year against the worms that cause river blindness. Adult female worms have a typical life span of 14 years, so ivermectin is usually prescribed for 16 to 18 years. What would happen after 16 to 18 years of annual doses in a human population? Explain your answer.

Each annual dose stops adult female worms from releasing larvae, preventing them from adding new parasites to the human body. Taking 16 to 18 years of doses would outlast the entire life span of the original adult female worms, ending the parasitic infestation.

3. In 1987 Merck committed to donate ivermectin doses “as much as needed, for as long as needed” to help eliminate river blindness. Describe the current state of progress toward that goal.

More than 2 billion treatments have been donated since the establishment of the Mectizan Donation Program. Health authorities hope to eliminate river blindness and also lymphatic filariasis within the next decade.

Ivermectin: People and Places

The history of ivermectin is an international one. It began with a soil sample from Japan, and continued with testing and development in the U.S. As a treatment, it has spread to locations across the globe.

1. Using the reading provided, list the location for each person or organization and briefly describe their roles in ivermectin's history.

Person/Organization	Location(s)	Role in Ivermectin's History
Satoshi Ōmura	**Kitasato Institute, Tokyo, Japan**	**Collected soil samples in Japan as potential sources for medical treatments. Arranged an agreement between Merck and Kitasato to test and develop compounds from samples.**
Max Tishler	**Wesleyan University, Connecticut & Merck Research Laboratories (U.S.)**	**Hosted a sabbatical for Ōmura in his laboratory at Wesleyan.**
William C. Campbell	**Merck Research Laboratories, New Jersey, U.S.**	**Tested culture samples as potential treatments for parasitic worms.**
Merck Research Laboratories	**New Jersey, U.S.**	**Commercialized ivermectin as a veterinary treatment in 1981 and for human use in 1987. Committed to donate drug to eliminate river blindness.**
World Health Organization	Worldwide	**Worked with Merck on human clinical trials for river blindness.**

Populations treated for river blindness	Nearly 3 dozen countries in Africa, South Asia, and Central and South America	**Received donated doses of ivermectin to assist in eliminating river blindness.**

2. Describe how GlaxoSmithKline, another pharmaceutical company, is connected to ivermectin's treatment to prevent river blindness.

GlaxoSmithKline has donated albendazole to be administered with ivermectin as part of a campaign to eliminate elephantiasis, another tropical disease.

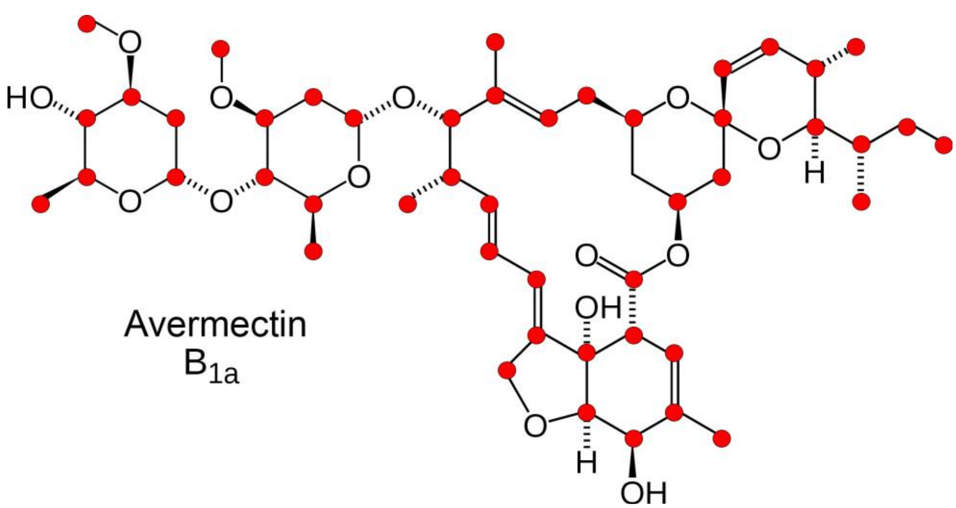
3. Using other sources or your own knowledge, draw small circles on the map for each of the locations you listed in the table for question 1. Then, draw larger circles on the general areas of treated populations (see final row of table).

Ivermectin: Chemical Structures

The active component produced by the soil sample bacterium found by Ōmura's team was eventually named avermectin. It was discovered to be a combination of eight similar compounds.

1. The structure of one of avermectin's eight compounds is below. The drawing uses one line to show a single bond. Some show direction into or out of the page using a dotted or bolded line. A double bond is shown by adding a second line next to a single bond line. Carbon atoms are at places where two lines join and at ends of lines. The drawing does not show all of the hydrogen atoms or carbon–hydrogen bonds.

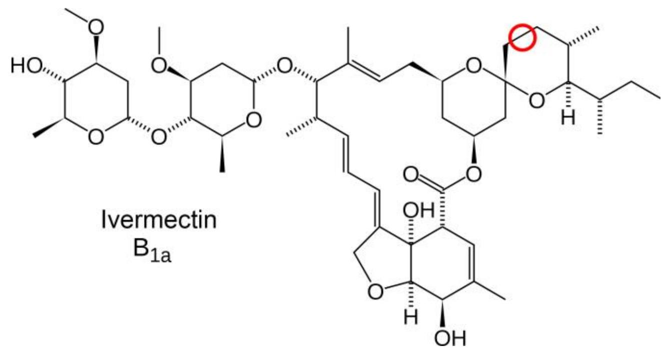
- Draw a mark at each carbon atom location.
- How many carbon atoms are in the structure? **47**

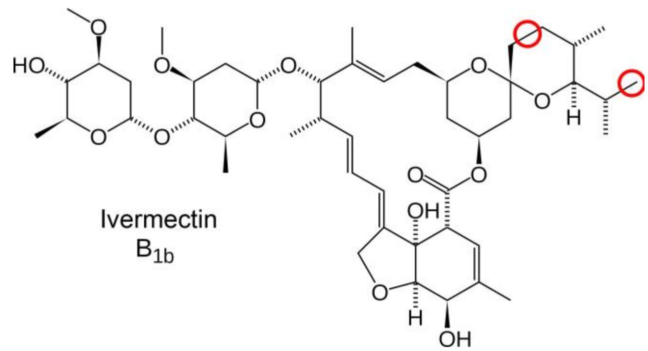


Avermectin B_{1a}

2. Researchers made small structural modifications to avermectin's compounds to try to make the components more potent as a treatment while increasing its safety. They succeeded with the changes shown below; the resulting pair of compounds was called ivermectin.

- Compare each structure to the avermectin structure above. Circle any changes.





3. Ivermectin is an effective treatment for parasites in a range of organisms, such as humans, livestock, and pets, with few serious side effects. Describe how ivermectin's method of action makes this possible.

It acts primarily on cellular channels of the targeted parasites that are not accessible in people, pets or livestock.

4. The graphic on the last page of the reading shows the life cycle of river blindness. In which stages of the life cycle does ivermectin work?

During human stages 2 and 3

Ivermectin Impacts

When using a medicine, one might only think about curing a certain condition or helping to reduce symptoms associated with it. Ivermectin's impacts reach beyond this, with not only health benefits, but also economic and social benefits.

1. Ivermectin was initially identified as a very effective treatment for parasitic worms in animals. What did further testing reveal about its potential uses for animal health?

> **Further testing showed it could also fight infestations by mites, ticks and botfly parasites. It was also effective against parasites in horses, cattle, pigs, sheep and dogs.**

2. Later, the use of ivermectin was expanded to human health applications. Using the reading, describe the process that led up to ivermectin being approved for human use in 1987.

> **Merck worked with the World Health Organization to design and implement human clinical trials with ivermectin for river blindness in Senegal in 1981. The results showed the effectiveness of the drug against river blindness.**

3. Before ivermectin, one way of dealing with river blindness had been people moving away from fertile farmland to avoid areas where infected blackflies lived. Discuss the economic impact of using this method of prevention.

> **Less suitable farmland would be available for growing crops. This would result in less food being grown to use or sell.**

4. Individuals with untreated river blindness typically have symptoms of severe itching, rashes, muscle pain, and weakness. Imagine your own daily life and picture yourself with these symptoms. Discuss how they would affect your activities and mental health.

> **Answers will vary. It would be difficult to concentrate on work or other activities and to physically participate in certain activities like sports or sitting/walking comfortably all day. Mental health would be affected negatively.**