

## Structure-Based Drug Design: From the Computer to the Clinic

In 1981, doctors recognized a strange new disease in the United States. The first handful of patients suffered from unusual cancers and pneumonias. As the disease spread, scientists discovered its cause—a virus that attacks human immune cells. Now a major killer worldwide, the disease is best known by its acronym, AIDS.

Formally called acquired immunodeficiency syndrome, AIDS is caused by the human immunodeficiency virus, or HIV.

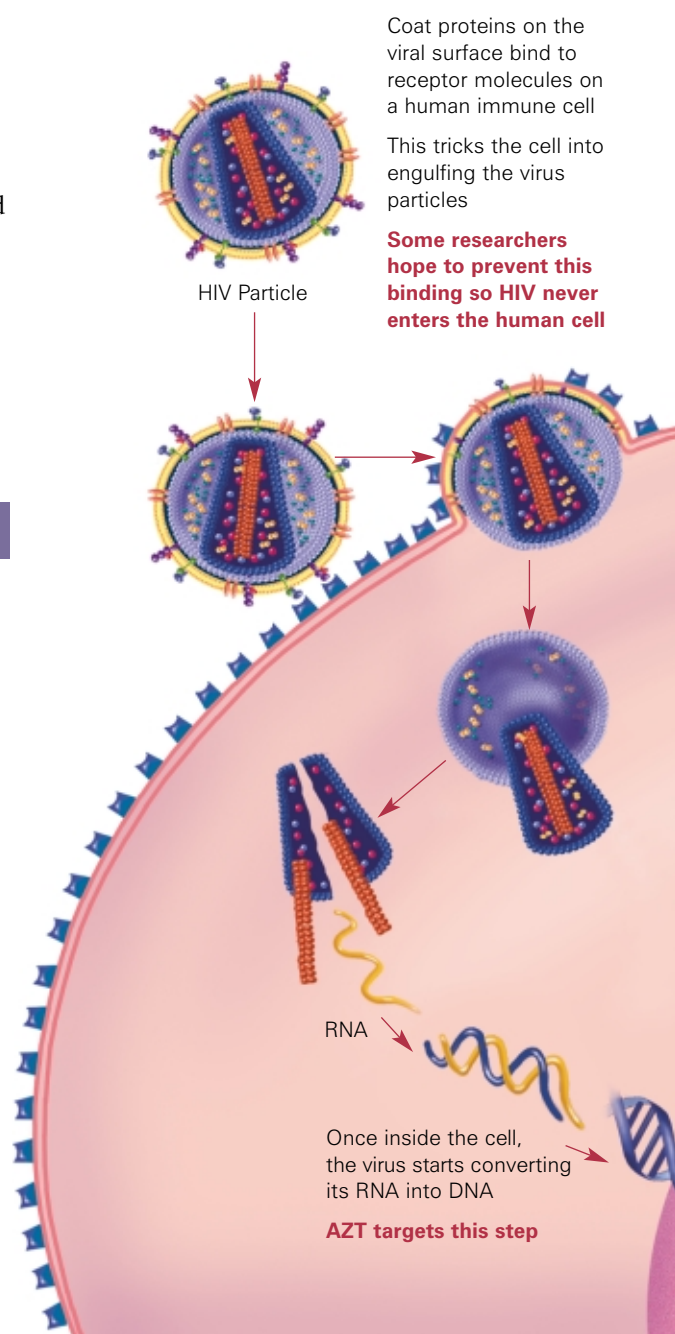
Although researchers have not found a cure for AIDS, structural biology has greatly enhanced their understanding of HIV and has played a key role in the development of drugs to treat this deadly disease.

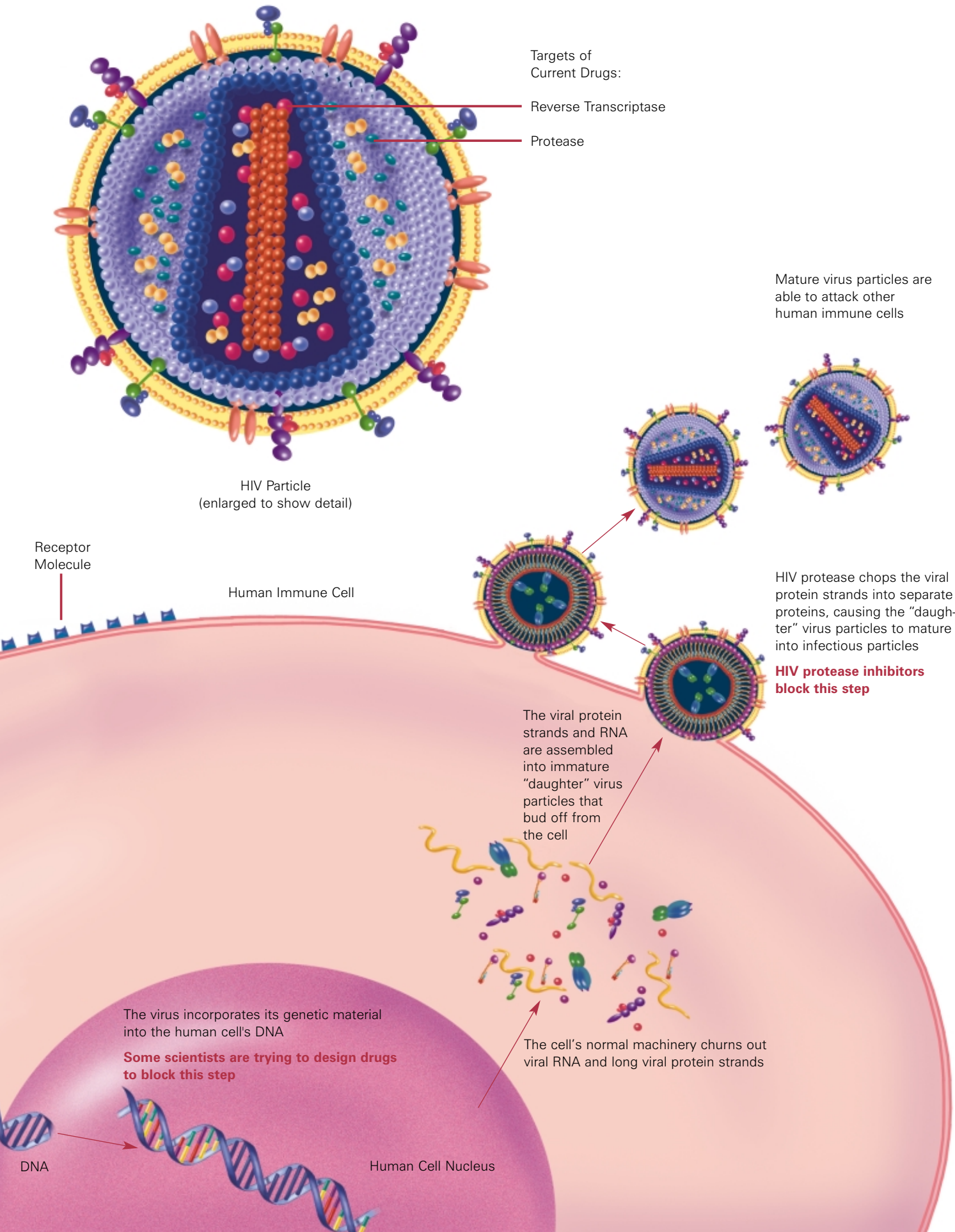
### The Life of an AIDS Virus

HIV was quickly recognized as a retrovirus, a type of virus that carries its genetic material not as DNA, as do most other organisms on the planet, but as RNA that the virus then “reverse transcribes” into DNA.

Long before anyone had heard of HIV, researchers in labs all over the world studied retroviruses, some of which were known to cause cancers in animals. These scientists traced out the life cycle of retroviruses and identified the key proteins and enzymes the viruses use to infect cells.

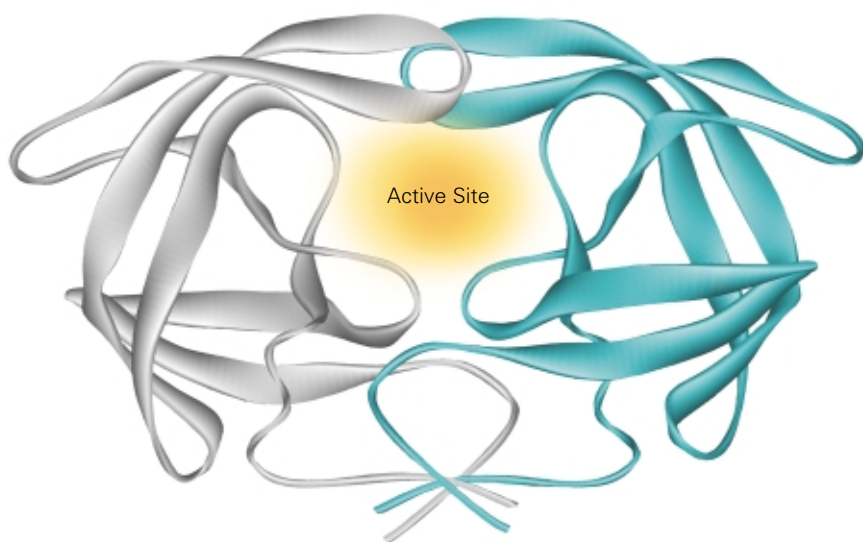
When HIV was identified as a retrovirus, the work of these scientists gave AIDS researchers an immediate jump-start. The viral proteins they had already identified became initial drug targets.





### Revealing the Target

Our story begins in 1989, when scientists determined the X-ray crystallographic structure of HIV protease, a viral enzyme critical in HIV's life cycle. Pharmaceutical scientists hoped that by blocking this enzyme, they could prevent the virus from spreading in the body.



- ▲ HIV protease is a symmetrical molecule with two equal halves and an active site near its center.

Molecular models of HIV protease in this chapter were generated by Alisa Zapp Machalek

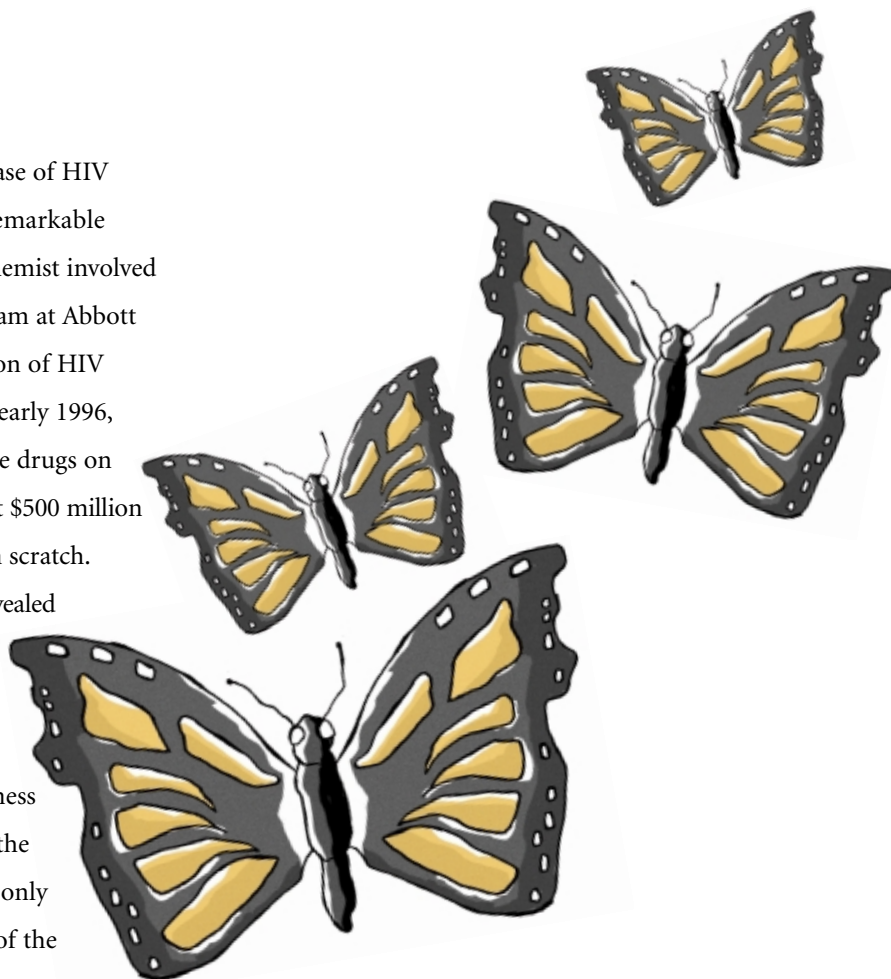
With the structure of HIV protease at their fingertips, researchers were no longer working blindly. They could finally see their target enzyme—in exhilarating, color-coded detail. By feeding the structural information into a computer modeling program, they could spin a model of the enzyme around, zoom in on specific atoms, analyze its chemical properties, and even strip away or alter parts of it.

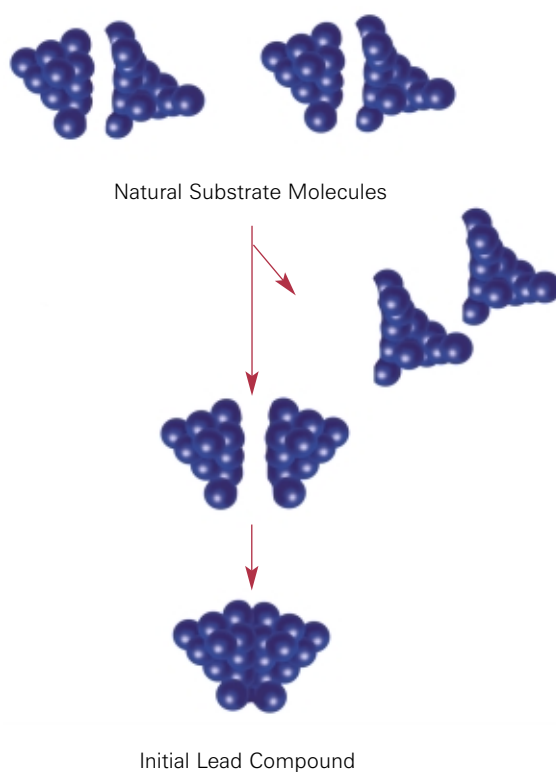
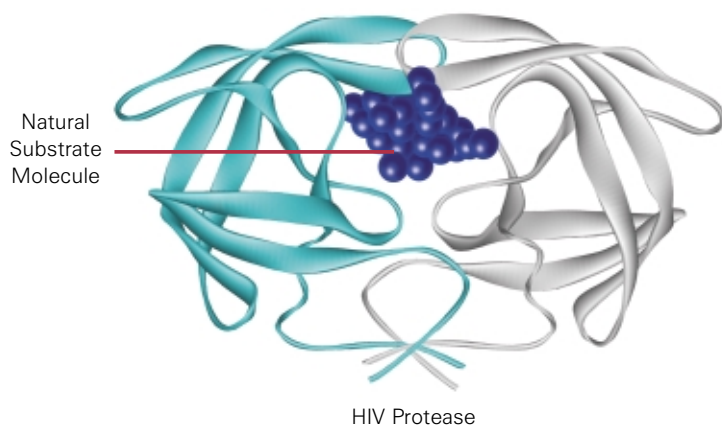
Most importantly, they could use the computerized structure as a reference to determine the types of molecules that might block the enzyme. These molecules can be retrieved from chemical libraries or can be designed on a computer screen and then synthesized in a laboratory. Such structure-based drug design strategies have the potential to shave off years and millions of dollars from the traditional trial-and-error drug development process.

These strategies worked in the case of HIV protease inhibitors. “I think it’s a remarkable success story,” says Dale Kempf, a chemist involved in the HIV protease inhibitor program at Abbott Laboratories. “From the identification of HIV protease as a drug target in 1988 to early 1996, it took less than 8 years to have three drugs on the market.” Typically, it takes at least \$500 million and 15 years to develop a drug from scratch.

The structure of HIV protease revealed a crucial fact—like a butterfly, the enzyme is made up of two equal halves. For most such symmetrical molecules, both halves have a “business area,” or active site, that carries out the enzyme’s job. But HIV protease has only one such active site—in the center of the molecule where the two halves meet.

Pharmaceutical scientists knew they could take advantage of this feature. If they could plug this single active site with a small molecule, they could shut down the whole enzyme—and theoretically stop the virus’ spread in the body.





- ▲ Knowing that HIV protease has two symmetrical halves, pharmaceutical researchers initially attempted to block the enzyme with symmetrical small molecules. They made these by chopping in half molecules of the natural substrate, then making a new molecule by fusing together two identical halves of the natural substrate.

Several pharmaceutical companies started out by using the enzyme's shape as a guide. "We designed drug candidate molecules that had the same two-fold symmetry as HIV protease," says Kempf. "Conceptually, we took some of the enzyme's natural substrate [the molecules it acts upon], chopped these molecules in half, rotated them 180 degrees, and glued two identical halves together."

To the researchers' delight, the first such molecule they synthesized fit perfectly into the active site of the enzyme. It was also an excellent inhibitor—it prevented HIV protease from functioning normally. But it wasn't water-soluble, meaning it couldn't be absorbed by the body and would never be effective as a drug.

Abbott scientists continued to tweak the structure of the molecule to improve its properties. They eventually ended up with a nonsymmetrical molecule they called Norvir® (ritonavir).



- ▲ A drug candidate molecule must pass many hurdles to earn the description "good medicine." It must have the best possible activity, solubility, bioavailability, half-life, and metabolic profile. Attempting to improve one of these factors often affects other factors. For example, if you structurally alter a lead compound to improve its activity, you may also decrease its solubility or shorten its half-life. The final result must always be the best possible compromise.

## Structure-Based Drug Design: Blocking the Lock

Traditionally, scientists identify new drugs either by fiddling with existing drugs or by testing thousands of compounds in a laboratory. If you think of the target molecule—HIV protease in this case—as a lock, this approach is rather like trying to design a key perfectly shaped to the lock if you're given an armload of tiny metal scraps, glue, and wire cutters.

Using a structure-based strategy, researchers have an initial advantage. With molecular modeling software, they can make a “mold” of the lock and of the natural molecule, called a substrate, that fits into the lock and opens the door to viral replication. The goal is to plug the lock by finding a small molecule that fits inside HIV protease and prevents the natural substrate from entering.

Knowing the exact three-dimensional shape of the lock, scientists can discard any of the metal scraps (small molecules) that are not the right size or shape to fit the lock. They might even be able to design a small molecule to fit the lock precisely. Such a molecule may be a starting point—a lead compound—for pharmaceutical researchers who are designing a drug to treat HIV infection.

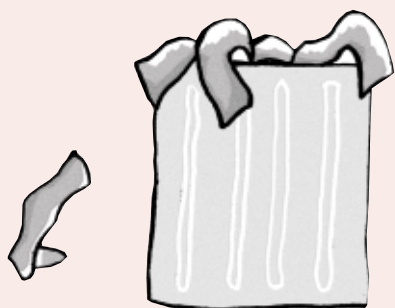
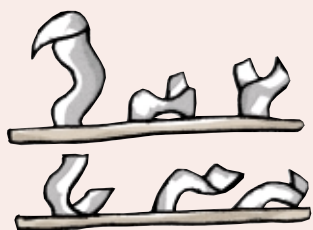
Of course, biological molecules are much more complex than locks and keys, and human bodies can react in unpredictable ways to drug molecules, so the road from the computer screen to pharmacy shelves remains long and bumpy.

► Traditional drug design often requires random testing of thousands—if not hundreds of thousands—of compounds (shown here as metal scraps)

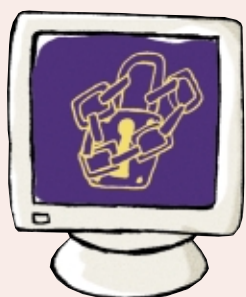


► By knowing the shape and chemical properties of the target molecule, scientists using structure-based drug design strategies can approach the job more “rationally.” They can discard the drug candidate molecules that have the wrong shape or properties.





Clinical Trials: Testing on humans is still one of the most time-consuming parts of drug development and one that is not accelerated by structural approaches



### A Hope for the Future

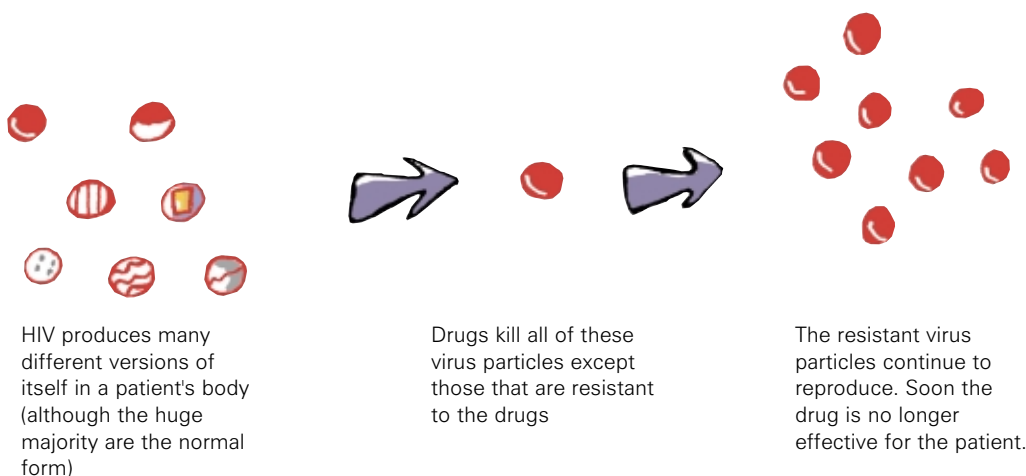
Between December 1995 and March 1996, the Food and Drug Administration approved the first three HIV protease inhibitors—Hoffman-La Roche’s Invirase™ (saquinavir), Abbott’s Norvir™ (ritonavir), and Merck and Co., Inc.’s Crixivan® (indinavir). Initially, these drugs were hailed as the first real hope in 15 years for people with AIDS. Newspaper headlines predicted that AIDS might even be cured.

Although HIV protease inhibitors did not become the miracle cure many had hoped for, they represent a triumph for antiviral therapy. Antibiotics that treat bacterial diseases abound (although they are becoming less effective as bacteria develop resistance), but doctors have very few drugs to treat viral infections.

Protease inhibitors are also noteworthy because they are a classic example of how structural biology can enhance traditional drug development. “They show that with some ideas about structure and rational drug design, combined with traditional medicinal chemistry, you can come up with potent drugs that function the way they’re predicted to,” says Kempf.

“That doesn’t mean we have all the problems solved yet,” he continues. “But clearly these compounds have made a profound impact on society.” The death rate from AIDS went down dramatically after these drugs became available. Now protease inhibitors are often prescribed with other anti-HIV drugs to create a “combination cocktail” that is more effective at squelching the virus than are any of the drugs individually.

### How HIV Resistance Arises

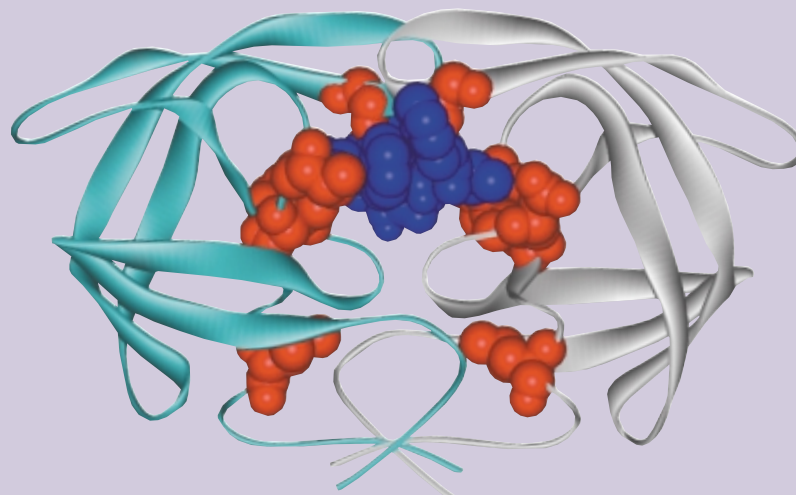


## Homing in on Resistance

HIV is a moving target. When it reproduces inside the body, instead of generating exact replicas of itself, it churns out a variety of slightly altered daughter virus particles. Some of these mutants are able to evade, or “resist,” the effects of a drug—and can pass that resistance on to their own daughter particles. While most virus particles initially succumb to the drug, these resistant mutants survive and multiply. Eventually, the drug loses its anti-HIV activity, because most of the virus particles in the infected person are resistant to it.

Some researchers now are working on new generations of HIV protease inhibitors that are designed to combat specific drug-resistant viral strains.

Detailed, computer-modeled pictures of HIV protease from these strains reveal how even amino acid substitutions far away from the enzyme’s active site can produce drug resistance. Some research groups are trying to beat the enzyme at its own game by designing drugs that bind specifically to these mutant amino acids. Others are designing mole-



▲ Scientists have identified dozens of mutations (shown in red) that allow HIV protease to escape the effects of drugs. The protease molecules in some drug-resistant HIV strains have two or three such mutations. To outwit the enzyme’s mastery of mutation, researchers are designing drugs that interact specifically with amino acids in the enzyme that are critical for the enzyme’s function. This approach cuts off the enzyme’s escape routes. As a result, the enzyme—and thus the entire virus—is forced to succumb to the drug.

cules that latch onto the enzyme’s Achilles’ heels—the aspartic acids in the active site and other amino acids that, if altered, would render the enzyme useless. Still others are trying to discover inhibitors that are more potent, more convenient to take, have fewer side effects, or are better able to combat mutant strains of the virus.

**STUDENT SNAPSHOT**

## *The Fascination of Infection*

“I really like to study retroviruses,” says Kristi Pullen, who majored in biochemistry at the University of Maryland, Baltimore County (UMBC). “I also like highly infectious agents, like Ebola. The more virulent something is, the less it’s worked on, so it opens up all sorts of fascinating questions. I couldn’t help but be interested.”

In addition to her UMBC classwork, Pullen helped determine the structure of retroviruses in the NMR spectroscopy laboratory of Michael Summers. This research focuses on how retroviruses package “RNA warheads” that enable them to spread in the body. Eventually, the work may reveal a new drug target for retroviral diseases, including AIDS.



Kelly Burns Photography, Columbia, Maryland

“Working in Dr. Summers’ lab and other labs teaches you that research can be fun. It’s not just a whole lot of people in white coats. We went biking and skiing together. All the people were great to work with.”

Kristi Pullen  
Graduate Student  
University of California, Berkeley

Until her senior year in high school, Pullen wanted to be an orthopedic surgeon. But after her first experience working in a lab, she recognized “there’s more to science than medicine.” Then, after taking some science courses, she realized she had an inner yearning to learn science and to work in a lab.

Pullen is now a graduate student at the University of California, Berkeley in the Department of Molecular and Cell Biology. She plans to continue

studying structural biology, to earn a Ph.D., and possibly also to earn an M.D.

She also has some longer-term goals.

“Ultimately what I want to do way, way, way down the line is head the NIH [National Institutes of Health] or CDC [Centers for Disease Control and Prevention] and in that way affect the health of a large number of people—the whole country.”

## Gripping Arthritis With “Super Aspirin”

While the HIV protease inhibitors are classic examples of structure-based drug design, they are also somewhat unusual—at least for now. Although many pharmaceutical companies have entire divisions devoted to structural biology,

most use it as a complementary approach, in partnership with other, more traditional, means of drug discovery. In many cases, the structure of a target molecule is determined after traditional screening, or even after a drug is on the market.

This was the case for Celebrex®, a drug marketed by the Searle pharmaceutical company. Celebrex® was initially designed to treat osteoarthritis and adult rheumatoid arthritis, but it is now the first drug approved to treat a rare condition called FAP, for familial adenomatous polyposis, that leads to colon cancer.

Normally, the pain and swelling of arthritis are treated with drugs like aspirin or Advil® (ibuprofen), the so-called NSAIDs, or non-steroidal anti-inflammatory drugs. But these medications can cause damage to gastrointestinal organs, including bleeding ulcers. In fact, a recent study found that such side effects result in more than 100,000 hospitalizations and 16,500 deaths every year. According to another study, if these side effects were included in tables listing mortality data, they would rank as the 15th most common cause of death in the United States.



National Institutes of Health

▲ Rheumatoid arthritis is an immune system disorder that affects more than 2 million Americans, causing pain, stiffness, and swelling in the joints. It can cripple hands, wrists, feet, knees, ankles, shoulders, and

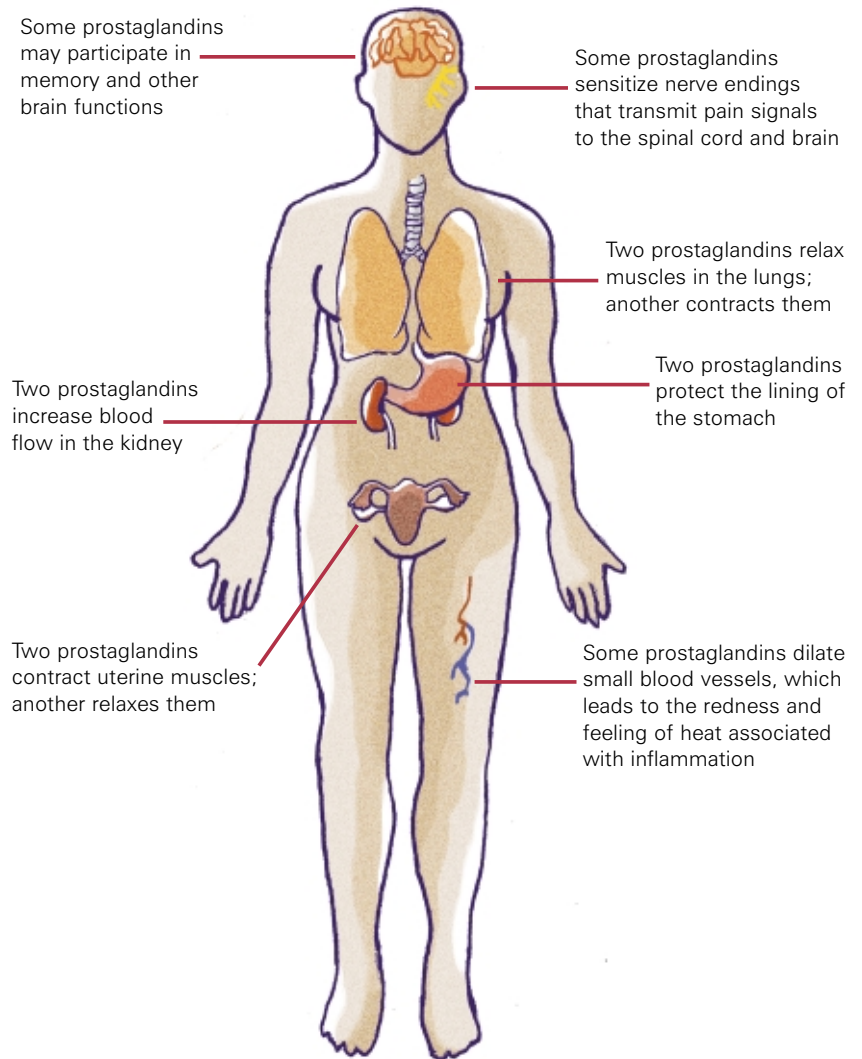
elbows. It also causes inflammation in internal organs and can lead to permanent disability. Osteoarthritis has some of the same symptoms, but it develops more slowly and only affects certain joints.

A fortunate discovery enabled scientists to design drugs that retain the anti-inflammatory properties of NSAIDs without the ulcer-causing side effects.

By studying the drugs at the molecular level, researchers learned that NSAIDs block the action of two closely related enzymes called cyclooxygenases. These enzymes are abbreviated COX-1 and COX-2.

Although the enzymes share some of the same functions, they also differ in important ways. COX-2 is produced in response to injury or infection and activates molecules that trigger inflammation and an immune response. By blocking COX-2, NSAIDs reduce inflammation and pain caused by arthritis, headaches, and sprains.

In contrast, COX-1 produces molecules, called prostaglandins, that protect the lining of the stomach from digestive acids. When NSAIDs block this function, they foster ulcers.



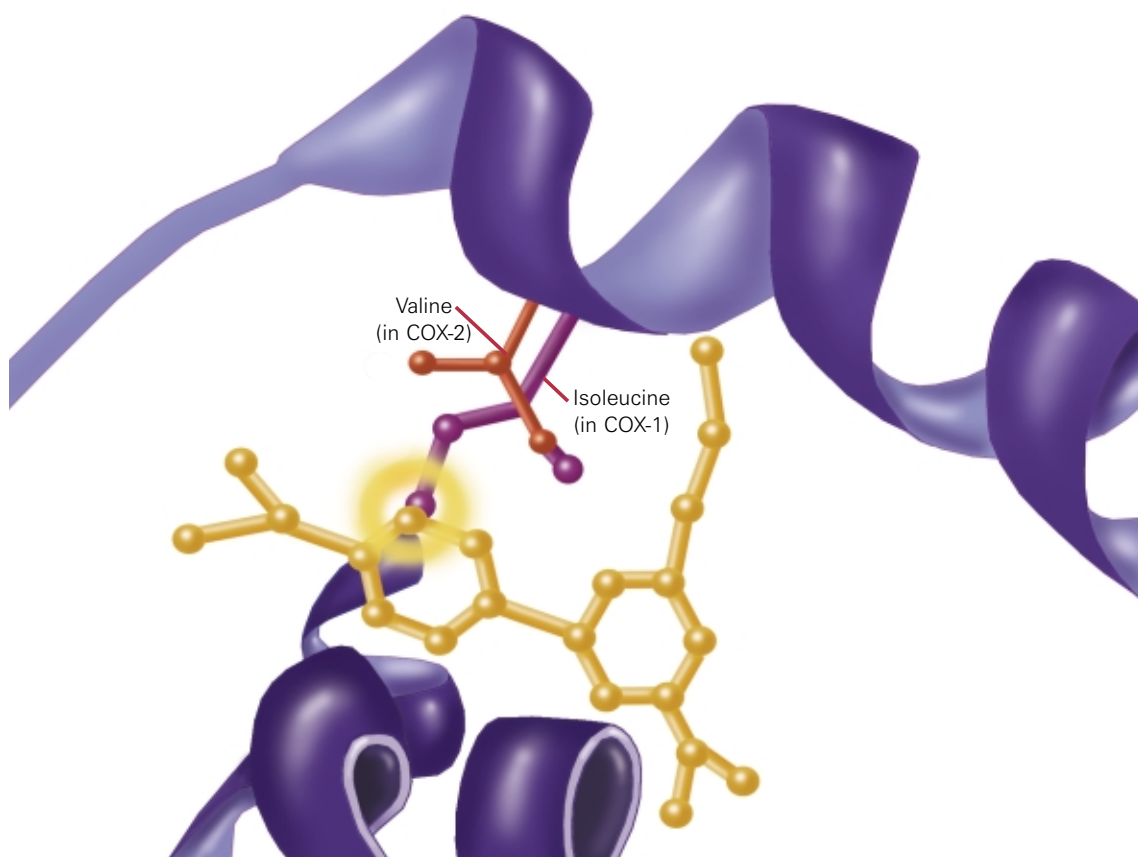
▲ Both COX-1 and COX-2 produce prostaglandins, which have a variety of different—and sometimes opposite—roles in the body. Some of these roles are shown here.

To create an effective painkiller that doesn't cause ulcers, scientists realized they needed to develop new medicines that shut down COX-2 but not COX-1. Such a compound was discovered using standard medicinal chemistry. Searle marketed it under the name Celebrex®, and it quickly became the fastest selling drug in U.S. history,

generating more prescriptions in its first year than the next two leading drugs combined.

At the same time, scientists were working out the molecular structure of the COX enzymes. Through structural biology, they could see exactly why Celebrex®—and other so-called “super aspirin” drugs—plug up COX-2 but not COX-1.

The three-dimensional structures of COX-2 and COX-1 are almost identical. But there is one



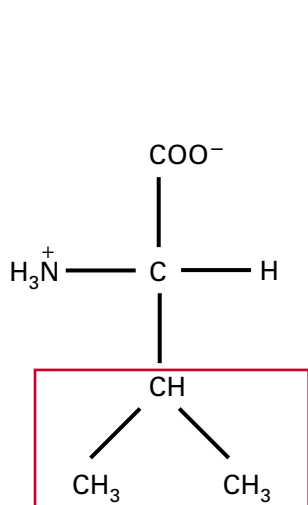
▲ The overall structures of COX-1 and COX-2 (ribbons) are nearly identical, but a close-up of the active site reveals why Celebrex® and similar molecules can bind to COX-2 but not to COX-1. A single amino acid substitution makes all the difference. At this one position, COX-2 contains valine, a small amino acid, while COX-1 contains isoleucine. The valine in COX-2

creates a pocket into which the “super aspirin” drugs (in yellow) can bind. The isoleucine in COX-1 elbows out the drugs. Because Celebrex® and other “super aspirin” drugs bind only to COX-2 and not to COX-1, they control pain and inflammation without causing stomach ulcers.

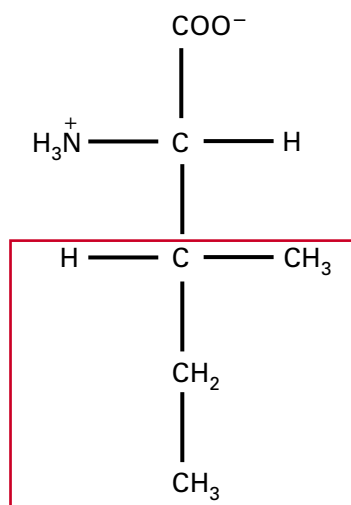
amino acid change in the active site of COX-2 that creates an extra binding pocket. It is this extra pocket into which Celebrex® binds.

In addition to showing researchers in atom-by-atom detail how the drug binds to its target, the structures are also greatly aiding the design of new, second- and third-generation drugs that

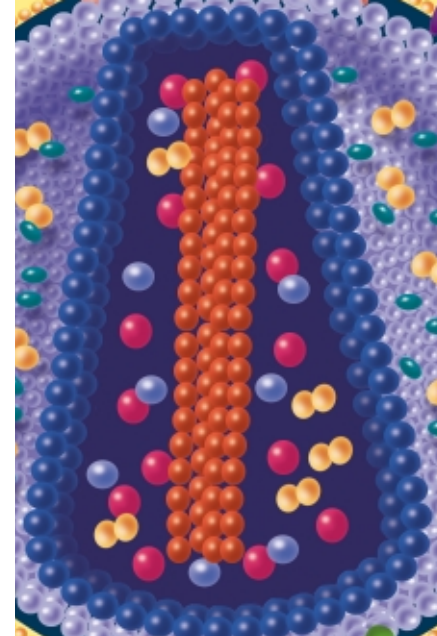
have different properties than Celebrex® or work better for certain people. And of course the structure of the COX enzymes will continue to provide basic researchers with insight into how these molecules work in the body.



Valine



Isoleucine



### Got It?

What is structure-based drug design?

How was structure-based drug design used to develop an HIV protease inhibitor?

How is the structural difference between COX-1 and COX-2 responsible for the effectiveness of Celebrex®?

How do viruses become resistant to drugs?

# Glossary

**Acquired immunodeficiency syndrome (AIDS)** | A viral disease caused by the human immunodeficiency virus (HIV).

**Active site** | The region of an enzyme to which a substrate binds and at which a chemical reaction occurs.

**AIDS** | Acquired immunodeficiency syndrome—an infectious disease that is a major killer worldwide.

**Alpha helix** | A short, spiral-shaped section within a protein structure.

**Amino acid** | A chemical building block of proteins. There are 20 standard amino acids. A protein consists of a specific sequence of amino acids.

**Angstrom** | A unit of length used for measuring atomic dimensions. One angstrom equals  $10^{-10}$  meters.

**Antibiotic-resistant bacteria** | A strain of bacteria with slight alterations (mutations) in some of their molecules that enable the bacteria to survive drugs designed to kill them.

**Atom** | A fundamental unit of matter. It consists of a nucleus and electrons.

**AZT (azido-deoxythymidine)** | A drug used to treat HIV. It targets the reverse transcriptase enzyme.

**Bacterium (*pl.* bacteria)** | A primitive, one-celled microorganism without a nucleus. Bacteria live almost everywhere in the environment. Some bacteria may infect humans, plants, or animals. They may be harmless or they may cause disease.

**Base** | A chemical component (the fundamental information unit) of DNA or RNA. There are four bases in DNA: adenine (A), thymine (T), cytosine (C), and guanine (G). RNA also contains four bases, but instead of thymine, RNA contains uracil (U).

**Beta sheet** | A pleated section within a protein structure.

**Chaperones** | Proteins that help other proteins fold or escort other proteins throughout the cell.

**Chemical shift** | An atomic property that varies depending on the chemical and magnetic properties of an atom and its arrangement within a molecule. Chemical shifts are measured by NMR spectroscopists to identify the types of atoms in their samples.

**COX-1 (cyclooxygenase-1)** | An enzyme made continually in the stomach, blood vessels, platelet cells, and parts of the kidney. It produces prostaglandins that, among other things, protect the lining of the stomach from digestive acids. Because NSAIDs block COX-1, they foster ulcers.

**COX-2 (cyclooxygenase-2)** | An enzyme found in only a few places, such as the brain and parts of the kidney. It is made only in response to injury or infection. It produces prostaglandins involved in inflammation and the immune response. NSAIDs act by blocking COX-2. Because elevated levels of COX-2 in the body have been linked to cancer, scientists are investigating whether blocking COX-2 may prevent or treat some cancers.

**Cyclooxygenases** | Enzymes that are responsible for producing prostaglandins and other molecules in the body.

**Deoxyribose** | The type of sugar in DNA.

**DNA (deoxyribonucleic acid)** | The substance of heredity. A long, usually double-stranded chain of nucleotides that carries genetic information necessary for all cellular functions, including the building of proteins. DNA is composed of the sugar deoxyribose, phosphate groups, and the bases adenine, thymine, guanine, and cytosine.

**Drug target** | See *target molecule*.

**Electromagnetic radiation** | Energy radiated in the form of a wave. It includes all kinds of radiation, including, in order of increasing energy, radio waves, microwaves, infrared radiation (heat), visible light, ultraviolet radiation, X-rays, and gamma radiation.

**Enzyme** | A substance, usually a protein, that speeds up, or catalyzes, a specific chemical reaction without being permanently altered or consumed. Some RNA molecules can also act as enzymes.

**Gauss** | A unit of magnetic field strength (also called magnetic flux density). The Earth's magnetic field at its surface is approximately 0.5 gauss. A good loudspeaker coil is on the order of 10,000 gauss, or 1 tesla.

**Gene** | A unit of heredity. A segment of DNA that contains the code for a specific protein or protein subunit.

**Genetic code** | The set of triplet letters in DNA (or mRNA) that code for specific amino acids.

**HIV protease** | An HIV enzyme that is required during the life cycle of the virus. It is required for HIV virus particles to mature into fully infectious particles.

**Human immunodeficiency virus (HIV)** | The virus that causes AIDS.

**Inhibitor** | A molecule that “inhibits,” or blocks, the biological action of another molecule.

**Isotope** | A form of a chemical element that contains the same number of protons but a different number of neutrons than other forms of the element. Isotopes are often used to trace atoms or molecules in a metabolic pathway. In NMR, only one isotope of each element contains the correct magnetic properties to be useful.

**Kilodalton** | A unit of mass equal to 1,000 daltons. A dalton is a unit used to measure the mass of atoms and molecules. One dalton equals the atomic weight of a hydrogen atom ( $1.66 \times 10^{-24}$  grams).

**Lead compound** | A molecule, usually a small one, that pharmaceutical researchers use as the basis for a drug. Often, the lead compound shows some of the desired biological activity, but it must be chemically altered to enhance this activity and to make the molecule safe and effective for delivery as a drug.

**MAD** | See *multi-wavelength anomalous diffraction*.

**Megahertz** | A unit of measurement equal to 1,000,000 hertz. A hertz is defined as one event or cycle per second and is used to measure the frequency of radio waves and other forms of electromagnetic radiation. The strength of NMR magnets is often reported in megahertz, with most NMR magnets ranging from 500 to 800 megahertz.

**Messenger RNA (mRNA)** | An RNA molecule that serves as an intermediate in the synthesis of protein. Messenger RNA is complementary to DNA and carries genetic information to the ribosome.

**Molecule** | The smallest unit of matter that retains all of the physical and chemical properties of that substance. It consists of one or more identical atoms or a group of different atoms bonded together.

**mRNA** | Messenger RNA.

**Multi-dimensional NMR** | A technique used to solve complex NMR problems.

**Multi-wavelength anomalous diffraction (MAD)** | A technique used in X-ray crystallography that accelerates the determination of protein structures. It uses X-rays of different wavelengths, relieving crystallographers from having to make several different metal-containing crystals.

**NMR** | Nuclear magnetic resonance.

**NMR-active atom** | An atom that has the correct magnetic properties to be useful for NMR. For some atoms, the NMR-active form is a rare isotope, such as  $^{13}\text{C}$  or  $^{15}\text{N}$ .

**NOESY** | Nuclear Overhauser effect spectroscopy.

**Non-steroidal anti-inflammatory drugs** | A class of medicines used to treat pain and inflammation. Examples include aspirin and ibuprofen. They work by blocking the action of the COX-2 enzyme. Because they also block the COX-1 enzyme, they can cause side effects such as stomach ulcers.

**NSAIDs** | Non-steroidal anti-inflammatory drugs such as aspirin or ibuprofen.

**Nuclear magnetic resonance (NMR) spectroscopy** | A technique used to determine the detailed, three-dimensional structure of molecules and, more broadly, to study the physical, chemical, and biological properties of matter. It uses a strong magnet that interacts with the natural magnetic properties in atomic nuclei.

**Nuclear Overhauser effect spectroscopy (NOESY)** | An NMR technique used to help determine protein structures. It reveals how close different protons (hydrogen nuclei) are to each other in space.

**Nucleotide** | A subunit of DNA or RNA that includes one base, one phosphate molecule, and one sugar molecule (deoxyribose in DNA, ribose in RNA). Thousands of nucleotides join end-to-end to create a molecule of DNA or RNA. See *base*, *phosphate group*.

**Nucleus (pl. nuclei)** | 1. The membrane-bounded center of a cell, which contains genetic material. 2. The center of an atom, made up of protons and neutrons.

**Phosphate group** | A chemical group found in DNA and RNA, and often attached to proteins and other biological molecules. It is composed of one phosphorous atom bound to four oxygen atoms.

**Photosynthesis** | The chemical process by which green plants, algae, and some bacteria use the Sun's energy to synthesize organic compounds (initially carbohydrates).

**Prostaglandins** | A hormone-like group of molecules involved in a variety of functions in the body, including inflammation, blood flow in the kidney, protection of the stomach lining, blood clotting, and relaxation or contraction of muscles in the lungs, uterus, and blood vessels. The formation of prostaglandins is blocked by NSAIDs.

**Protein** | A large biological molecule composed of amino acids arranged in a specific order determined by the genetic code and folded into a specific three-dimensional shape. Proteins are essential for all life processes.

**Receptor protein** | Specific proteins found on the cell surface to which hormones or other molecules bind, triggering a specific reaction within the cell. Receptor proteins are responsible for initiating reactions as diverse as nerve impulses, changes in cell metabolism, and hormone release.

**Resistance** | See *antibiotic-resistant bacteria*.

Viruses can also develop resistance to antiviral drugs.

**Retrovirus** | A type of virus that carries its genetic material as single-stranded RNA, rather than as DNA. Upon infecting a cell, the virus generates a DNA replica of its RNA using the enzyme reverse transcriptase.

**Reverse transcriptase** | An enzyme found in retroviruses that copies the virus' genetic material from single-stranded RNA into double-stranded DNA.

**Ribose** | The type of sugar found in RNA.

**Ribosomal RNA** | RNA found in the ribosome.

**RNA (ribonucleic acid)** | A long, usually single-stranded chain of nucleotides that has structural, genetic, and enzymatic roles. There are three major types of RNA, which are all involved in making proteins: messenger RNA (mRNA), transfer RNA (tRNA), and ribosomal RNA (rRNA). RNA is composed of the sugar ribose, phosphate groups, and the bases adenine, uracil, guanine, and cytosine. Certain viruses contain RNA, instead of DNA, as their genetic material.

**Side chain** | The part of an amino acid that confers its identity. Side chains range from a single hydrogen atom (for glycine) to a group of 15 or more atoms.

**Signal transduction** | The process by which chemical, electrical, or biological signals are transmitted into and within a cell.

**Structural biology** | A field of study dedicated to determining the detailed, three-dimensional structures of biological molecules to better understand the function of these molecules.

**Structural genomics** | A field of study that seeks to determine a large inventory of protein structures based on gene sequences. The eventual goal is to be able to produce approximate structural models of any protein based on its gene sequence. From these structures and models, scientists hope to learn more about the biological function of proteins.

**Structure-based drug design** | An approach to developing medicines that takes advantage of the detailed, three-dimensional structure of target molecules.

**Substrate** | A molecule that binds to an enzyme and undergoes a chemical change during the ensuing enzymatic reaction.

**Synchrotron** | A large machine that accelerates electrically charged particles to nearly the speed of light and maintains them in circular orbits. Originally designed for use by high-energy physicists, synchrotrons are now heavily used by structural biologists as a source of very intense X-rays.

**Target molecule (or target protein)** | The molecule on which pharmaceutical researchers focus when designing a drug. Often, the target molecule is from a virus or bacterium, or is

an abnormal human protein. In these cases, the researchers usually seek to design a small molecule—a drug—to bind to the target molecule and block its action.

**Tesla** | A unit of magnetic field strength (also called magnetic flux density). A field of 1 tesla is quite strong; the largest NMR magnets are approximately 20 teslas. One tesla equals 10,000 gauss.

**Transcription** | The first major step in protein synthesis, in which the information coded in DNA is copied (transcribed) into mRNA.

**Translation** | The second major step in protein synthesis, in which the information encoded in mRNA is deciphered (translated) into sequences of amino acids. This process occurs at the ribosome.

**Virus** | An infectious microbe that requires a host cell (plant, animal, human, or bacterial) in which to reproduce. It is composed of proteins and genetic material (either DNA or RNA).

**Virus particle** | A single member of a viral strain, including all requisite proteins and genetic material.

**X-ray crystallography** | A technique used to determine the detailed, three-dimensional structure of molecules. It is based on the scattering of X-rays through a crystal of the molecule under study.