BREAKTHROUGH

Scientists combined elements of two proteins to create DRACO, a superprotein with broad-spectrum antiviral capabilities.

O. KINKEL/SCANPIX

1928

ALEXANDER FLEMING

discovers penicillin, the first truly effective treatment against infectious diseases.

BACTERIA

2011

TODD RIDER

and colleagues create DRACO, a super-protein that may eradicate viral diseases.

VIRUSES

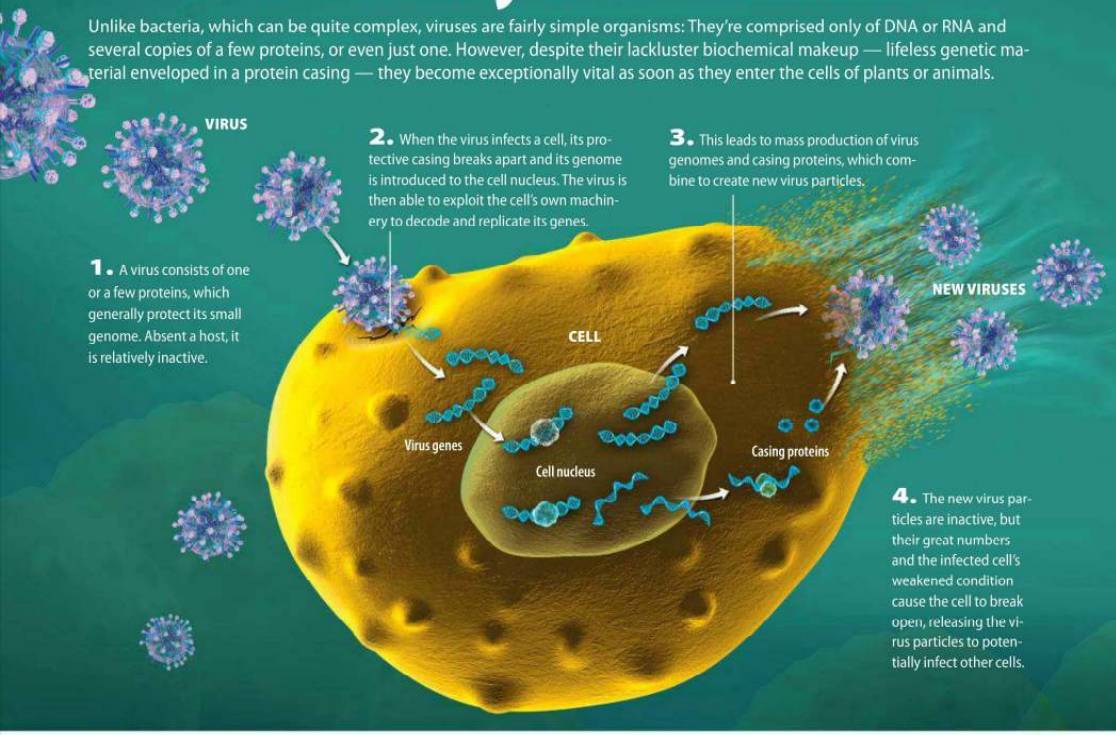
DRACO

the ultimate virus killer?

Scientists have long dreamed of finding a universal antiviral drug — a dream that may soon be within reach, thanks to a newly created superprotein that uses a cell's own suicide mechanism against an invading virus. Have we finally found a way to stop viral infections before they even start?

Viruses destroy cells from within

Unlike bacteria, which can be quite complex, viruses are fairly simple organisms: They're comprised only of DNA or RNA and several copies of a few proteins, or even just one. However, despite their lackluster biochemical makeup — lifeless genetic material enveloped in a protein casing — they become exceptionally vital as soon as they enter the cells of plants or animals.



Vaccines have greatly reduced the number of polio cases worldwide.
CORBIS/POLFOTO

Limited weapons in a deadly war

We have two weapons against viruses: vaccines and antiviral therapy. Vaccines stimulate the immune system to create antibodies against viruses, but because they only recognize viruses by specific proteins, they have no effect on mutating viruses. Antivirals interrupt the virus' life cycle to keep it from spreading, but rarely eliminate it.

	VACCINE	ANTIVIRAL THERAPY	DRACO
TIME OF PRESCRIPTION	Preventive treatment	Acute treatment in case of infection	Acute treatment in case of infection; preventive for high-risk individuals
DURATION	Several years or lifelong	Hours or days	Days to years
COMBATS VIRUS BEFORE REPLICATION	In some cases	No	Yes
ACTIVE AGAINST	Specific viruses or virus strains	A group of viruses	Virtually all viruses
EFFECT	Kills the virus or the infected cell	Delays the virus' life cycle	Forces the infected cell to commit suicide
COST	Inexpensive	Expensive	Expensive

The deadliest viruses

It's difficult to pinpoint which virus is the world's worst; viruses can be vicious in a variety of ways. Some are relatively harmless with timely intervention but sure to be fatal without treatment. Others can be mild in certain individuals, but kill on a large scale due to the sheer number of people they infect.

HIV
Annual deaths: 1.8 million
Infection: Spreads through blood and other bodily fluids such as sperm.
Vaccine: None. Treatment relieves symptoms.

INFLUENZA
Annual deaths: 500,000
Infection: Spreads through the air or via direct contact.
Vaccine: Must be re-engineered and administered on an annual basis.

RABIES
Annual deaths: 55,000
Infection: Spreads via bites from dogs, bats and other carriers.
Vaccine: Given when infection is suspected.

EBOLA
Annual deaths: fewer than 100
Infection: Spreads between humans via bodily fluids; may be transmitted from animals to humans via consumption of infected meat.
Vaccine: None.

SMALLPOX — Success story
Annual deaths: None. The disease has been completely eradicated in the wild, although it used to kill some 2 million people a year.
Infection: Spreads through the air or via direct contact.
Vaccine: Successfully eliminated the disease.

Ever since Alexander Fleming discovered penicillin in 1928, doctors have had a potent weapon for effectively treating virtually every type of disease-causing bacteria. This is because penicillin, as well as the many other types of antibiotics that have since been developed, are broad spectrum, meaning that they can attack characteristics that are shared by many bacteria species. But there is no equivalent universal drug to combat viral infections; viruses often can only be treated individually, with drugs customized for a particular strain of a virus. Since many viruses mutate very quickly, scientists have struggled to produce effective, reliable long-term therapies against those viral diseases that can sometimes be deadly.

For several decades, scientists have been searching for a characteristic that is shared among many different viruses that could serve as a universal target of a new treatment. Such a trait would need to be essential to viruses across the spectrum, so that no virus could afford to change it by mutation, and it would also need to be unique to viruses, so that the therapy would act only against the virus. To date, most treatments have targeted the specific proteins that viruses use to construct their protective casing or to decode and copy their genetic material. However, these strategies have not been particularly effective or long-lived, because many viruses are able to easily make their proteins unrecognizable to treatment through even slight mutations.

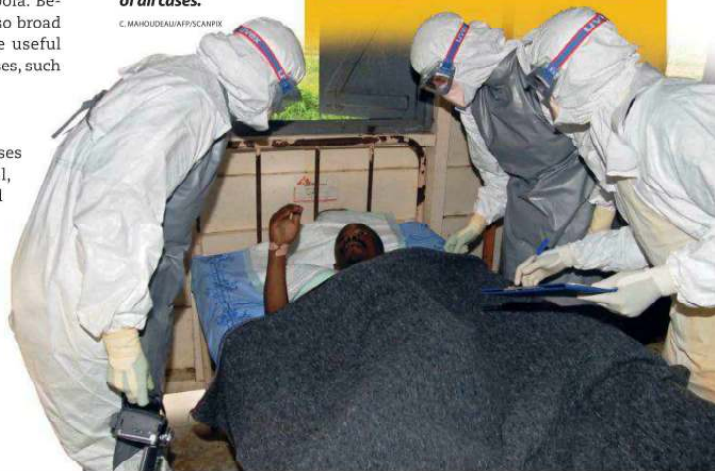
This conundrum inspired a team of scientists from the Massachusetts Institute of Technology (MIT) to try a different approach. Under the leadership of biomedical scientist Todd Rider, the team decided to focus not on a single feature, but to attack a process that takes place in the virus' genetic material. Last year, they published the first results from tests of the new treatment they developed, which they named DRACO (Double-stranded RNA [dsRNA] Activated Caspase Oligomerizer).

So far, the drug shows great promise in treating a broad spectrum of viruses. In lab experiments, DRACO protected cells against at least 15 different viruses that cause diseases ranging from influenza to dengue and hemorrhagic fevers. DRACO has also been tested on mice, in which it completely cured those infected with the H1N1 influenza virus. As a result, Rider is confident that he and his colleagues are on the right track to develop a true superprotein, telling reporters, "DRACO has the potential to revolutionize the treatment and prevention of virtually all viral diseases, including everything from the common cold to Ebola. Because the antiviral activity of DRACO is so broad spectrum, we hope that it may even be useful against outbreaks of new or mutated viruses, such as the 2003 SARS outbreak."

Targeting viruses' genetic structure

DRACO takes advantage of the way viruses store and utilize their genetic material, which is different from how humans and animals do. Human genes are located on chromosomes as double-stranded DNA (dsDNA); when a gene must be decoded, it is translated into single-stranded RNA (ssRNA). In many viruses, the genome consists of long, double-stranded RNA (dsRNA) molecules. But in humans, ▶

During a 2007 outbreak in Uganda, doctors examine a man possibly infected with Ebola, which is deadly in 90 percent of all cases.
C. MAHOUDEAU/AFP/SCANPIX



> ***DRACO has the potential to revolutionize the treatment and prevention of virtually all viral diseases, from the common cold to Ebola.***
>
> — Todd Rider, MIT

this type of genetic material is comprised of short sequences of some 23 base pairs, whereas in a virus like the diarrhea-causing rotavirus, the genetic material is typically made up of molecules consisting of several thousand base pairs. Other viruses, such as herpes, store their genetic material in DNA, but when they enter a cell and start replicating, the DNA is briefly converted to an intermediate state of double-stranded RNA. These long chains of double-stranded RNA are consequently a unique characteristic of virtually all of the viruses that we would like to protect ourselves against. Since they rely on this type of genetic material in order to carry out their life cycle, it is difficult for them to resist a drug targeted at it.

However, it is not enough for a drug to be able to recognize a virus; it also must be able to eliminate it. Thus, Rider conjectured that the ideal virus fighter would need to be made up of two parts: a tracking system that would recognize the virus by its double-stranded RNA and a killing mechanism that would eliminate the virus before it could grow into a full-fledged — and potentially fatal — infection.

Nature has already developed several such targeted weapons. Humans produce many different virus-combating proteins in which one half is able to recognize the long chains of double-stranded RNA characteristic of viruses while the other half is programmed to destroy the virus, either by preventing it from replicating or by triggering an alarm that activates the body's defense mechanisms. However, many viruses have successfully mutated over many years in order to avoid these defenses, so they are not affected and can go on replicating in the cell. Rider and his colleagues wondered if it would be more efficient to aim the weapons at the infected cell instead of at the virus.

Destroying the virus' production plant

Viruses are generally not considered living creatures; they are parasitic in nature and depend entirely on the cells of their host to multiply and spread. Consequently, viruses must use their hosts' cells to replicate. In the process, the affected cells break open, which destroys them and releases the virus to infect the surrounding cells. But if a cell dies immediately after being infected, the virus cannot use it to make a copy of itself, and the infection will be stopped before it can gain a foothold in the host's body. Therefore, a sick cell can conceivably save its neighboring cells if it "commits suicide" very quickly. This is actually a fundamental mechanism that the body uses to protect itself against the threat of an infection at a cellular level: Cells are programmed to commit suicide as soon as they recognize that something is wrong with them.

The cell's suicide triggers a chain reaction in which many different proteins activate each other, one by one, in a domino effect. Normally, such a reaction starts at one end of the chain, but a protein located somewhere else on the chain can also set off the process if it is activated directly, just as the central domino in a row will knock down its neighbor as it tips over. This means that there are many proteins involved in the cell's programmed death that can be used as switches to trigger the suicide mechanism. Viruses, however, tend to latch onto this suicide mechanism and shut it down.

Rider and the MIT team capitalized on this by selecting several different tracking systems and buttons in the cell's suicide mechanism, which they combined in several different ways. This customized compound is essentially a superprotein, one half of which was able to recognize the double-stranded RNA in a virus-infected cell, while the other half was then able to activate the switch that forced the cell to kill itself.

Using this process, the MIT scientists constructed several DRACO variants and tested them on laboratory-grown cells from humans, monkeys and mice by injecting the virus-free cells with the different DRACOs. Nothing happened. The component of the superprotein that was intended to bring about the cell's suicide had no effect, provided that no virus — and thus no double-stranded RNA — was present. But when Rider injected long chains of synthetic double-stranded RNA into the same cells, they started to commit suicide almost immediately. This indicated that DRACO worked exactly as intended: The tracking system in one half recognized the double-stranded RNA and the suicide mechanism in the other half was activated, resulting in the cell's timely destruction.

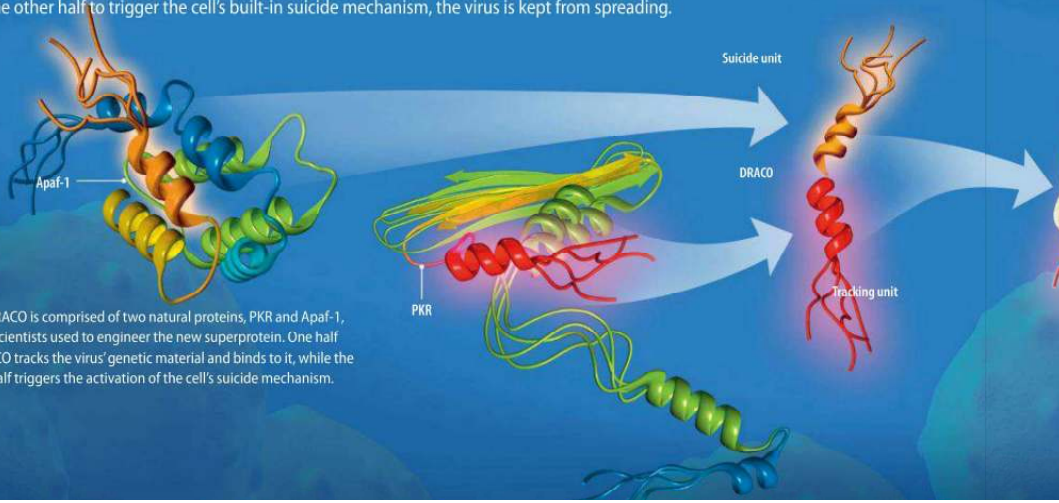
Defeating a broad spectrum of viruses

The next step was to test DRACO's ability to recognize a naturally occurring virus — in this case, the ordinary cold virus (rhinovirus) — and force any infected cells to commit suicide. When laboratory-grown human lung cells that had not been treated with DRACO were subjected to the rhinovirus, they were immediately infected. The infection spread so quickly that nearly all of the cells in the culture had been used by the virus to replicate after only four days. However, the outcome was completely different in cells treated with DRACO in advance. Although the cold virus uses single-stranded RNA in its genome — and thus would not be recognized immediately by DRACO's tracking system — the infected cells quickly committed suicide anyway. This is due to the fact that the virus' life cycle requires it to briefly convert its genetic material into double-stranded RNA, which enabled DRACO to detect it almost immediately. As a result, a very few lung cells sacrificed themselves to protect the other cells against the invader.

The experiment also showed that DRACO could both prevent infection and eliminate an infection that was already established. The treatment ▶

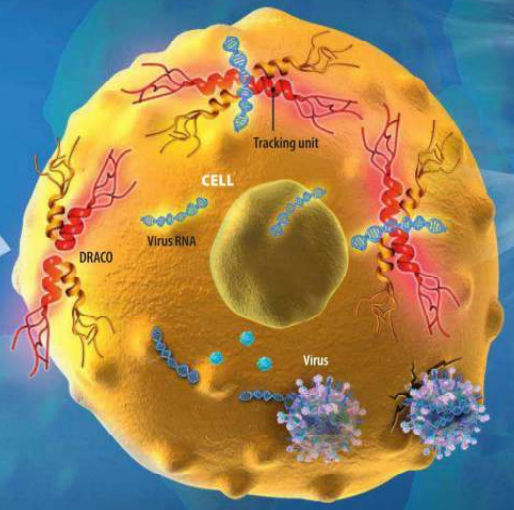
Cells' sacrifice stops the virus

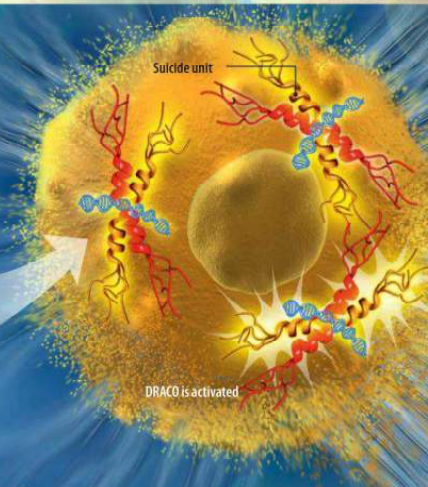
The DRACO superprotein targets the virus' genetic material. Unlike humans, at some point every virus stores its genome as long chains of double-stranded RNA. By using half of the DRACO protein to track the virus' RNA and the other half to trigger the cell's built-in suicide mechanism, the virus is kept from spreading.



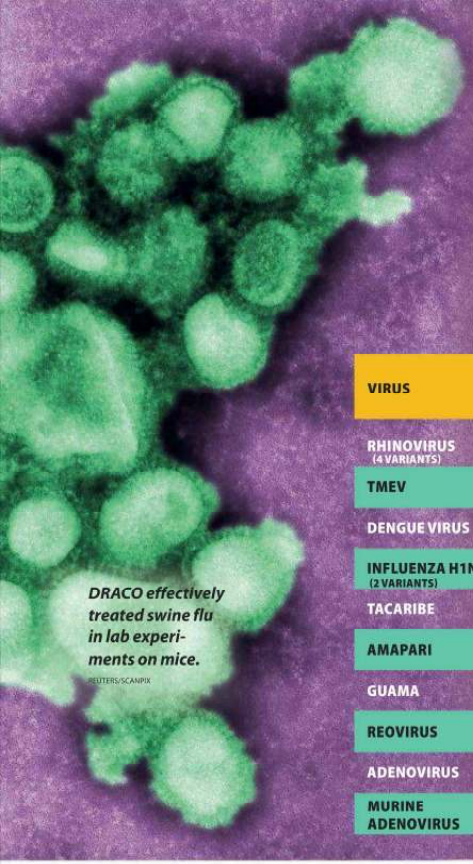
1. DRACO is comprised of two natural proteins, PKR and Apaf-1, which scientists used to engineer the new superprotein. One half of DRACO tracks the virus' genetic material and binds to it, while the other half triggers the activation of the cell's suicide mechanism.

2. Once it enters a virus-infected cell, DRACO uses the PKR tracking unit to find the virus' double-stranded RNA and binds to it.





3. After DRACO binds to the virus' double-stranded RNA, the Apaf-1 suicide unit is activated, forcing the cell to kill itself. Once the cell is dead, it cannot produce any more virus particles.



DRACO effectively treated swine flu in lab experiments on mice.

REUTERS/SCANPIX

No virus is safe

Most antiviral drugs have a significant limitation: They target a specific trait of the virus they are developed to fight, which is found only in a given strain of that virus. But DRACO does not have this limitation, because its revolutionary structure targets the double-stranded RNA that virtually every virus must use at some point during its life cycle, whether its genome consists of single-stranded RNA (ssRNA), double-stranded RNA (dsRNA) or double-stranded DNA (dsDNA). Because the virus' life cycle is dependent on this type of RNA, it cannot avoid being detected — and thwarted — by DRACO.

VIRUS	DISEASE	GENOME	NATURAL HOST	GENOME PROTECTED BY FATTY MEMBRANE CASING	CARRIES OUT ITS LIFE CYCLE IN THE CELL'S
RHINOVIRUS (4 VARIANTS)	Cold	ssRNA	Humans	No	Cytoplasm
TMEV	Paralysis	ssRNA	Mice	No	Cytoplasm
DENGUE VIRUS	Dengue fever	ssRNA	Humans	Yes	Cytoplasm
INFLUENZA H1N1 (2 VARIANTS)	Swine flu	ssRNA	Humans	Yes	Nucleus
TACARIBE	Hemorrhagic fever	ssRNA	Bats	Yes	Cytoplasm
AMAPARI	Hemorrhagic fever	ssRNA	Rodents	Yes	Cytoplasm
GUAMA	Hemorrhagic fever	ssRNA	Rodents	Yes	Cytoplasm
REOVIRUS	Diarrhea	dsRNA	Humans	No	Cytoplasm
ADENOVIRUS	Respiratory infections	dsDNA	Humans	No	Nucleus
MURINE ADENOVIRUS	Infection of internal organs	dsDNA	Mice	No	Nucleus

UNCOLN LABORATORY/M.I.T.

DRACO has been tested on 15 different viruses that cause diseases ranging from influenza to dengue fever. In every case, it effectively protected cells from widespread viral infection, as shown by these images from an experiment with rhinovirus.

A universal cure for viruses may be on the horizon

Experiments have shown that DRACO is remarkably effective against viruses that commonly infect humans, but it will likely take at least 10 years for the treatment to hit the market. But when it does, it may fight an array of viral diseases, from the flu to AIDS.

Today: Scientists have engineered the DRACO superprotein, which has proved harmless to healthy, laboratory-grown human and animal cells, but deadly to cells infected by 15 different viruses.

2013: Scientists develop new versions of DRACO with improved tracking and suicide mechanisms that can eliminate more viruses more effectively.

2014: Scientists discover how DRACO spreads in the bodies of mice and how long the superprotein remains active.

2016: Large-scale experiments show that DRACO is effective against viral infection of animals living under natural conditions.

2017: Initial clinical tests demonstrate that DRACO is harmless to healthy humans.

2020: Large-scale clinical trials determine that DRACO can combat a series of viral infections in humans living under natural conditions.

2022: Health authorities approve DRACO, which subsequently goes on the market.

TODAY — 2022

proved to be equally effective whether it was carried out six days before the infection began or four hours after the virus had started its attack. (The scientists were actually able to wait until three days after infection to start the DRACO treatment, but by that time the cells' protection was far less robust.)

The scientists repeated the experiments by subjecting several other cell types to a variety of viruses, including influenza, meningitis, dengue fever, hemorrhagic fevers (such as Ebola) and respiratory infections. Not only do these viruses cause different diseases, but they are also fundamentally distinct, biologically speaking. Some use single-stranded RNA as their genetic material, whereas others use double-stranded RNA or DNA, and their natural hosts can be anything — humans, bats, mice or another animal.

While DRACO is very effective at combating severe and even life-threatening viral infections, its greater strength is that it can be used to treat virtually every type of virus.

In spite of these differences, the DRACO superprotein was highly effective in all cases, consistently managing to fight off viral attacks. The effect was unmistakable: The untreated cells burst open and disappeared from the culture after only a few days, whereas most of the DRACO-treated cells stayed safe and sound, uncompromised by virus.

To ensure that they had created a true superprotein, the researchers thoroughly tested the different DRACOs to find the optimal combination of tracking and suicide mechanisms. All were effective to some degree, but the results did show some stark contrasts: One of the DRACOs containing a tracking system of the RNaseL type saved significantly fewer cells from the rhinovirus, while an adenovirus was able to gain a foothold in the cells protected by one of the suicide mechanisms of the FADD type.

One of the most successful variants was a combination of the PKR tracking system and Apaf-1 suicide mechanism. PKR recognizes double-stranded RNA molecules that make up chains of at least 30 to 50 base pairs. In its natural incarnation, it is one half of a defense in which the other half weakens the virus' ability to decode its genetic material into proteins. Apaf-1 is a particularly important "button" in the cells' suicide mechanism, because it is found in all animals, from roundworms to humans.

Saving lives in the laboratory and beyond

Once the scientists were able to establish DRACO's exceptional efficiency in preventing viral infections from spreading in laboratory-grown cell cultures, they tested its effect on a living organism. The team injected the superprotein into the stomachs of mice, from which it spread to the lungs, kidneys and liver without causing any harm to the animals.

The scientists also infected the mice via the nasal route with influenza virus A (H1N1), better known as the swine flu that quickly became a global epidemic in 2009. The results were dramatic. In nine days, the virus killed roughly 80 percent of the untreated mice, but the DRACO-treated mice fared significantly better: Nearly all were saved.

While DRACO is very effective at combating severe and even life-threatening viral infections, its greater strength is that it can be used to treat virtually every type of virus. As Rider explained to reporters, "We have demonstrated that DRACOs are effective against viruses with DNA, dsRNA, positive-sense ssRNA, and negative-sense ssRNA genomes; enveloped and nonenveloped viruses; viruses that replicate in the cytoplasm and viruses that replicate in the nucleus; human, bat and rodent viruses; and viruses that use a variety of cellular receptors."

The successful experiments with cell cultures and mice lend hope that DRACO will ultimately be an effective weapon against viral infections in humans. Clinical testing will determine whether it is completely harmless to people and will force only infected cells to commit suicide. Such tests will also reveal whether DRACO will be able to quickly trigger the suicide response in all infected cells in the body and if it can be delivered effectively before a viral infection takes a firm hold and becomes more difficult, or impossible, to defeat.

It will probably be at least 10 years before we can expect to find DRACO on drugstore shelves. But should this superprotein live up to its early billing, we may be in for the greatest revolution since penicillin: a universal antiviral drug that may be able to save millions of human lives every year. SCI