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Cool Jobs: Finding new uses for nature's poisons

If poison dart frogs are what they eat, then the colorful amphibians are definitely poison.

A toxin is a poisonous substance produced by a living thing. Certain species of plants, fungi and animals may produce toxins. So can bacteria. (When a toxin is injected, through a bite, sting or other means, it is called *venom*.) Poison dart frogs absorb toxins from the ants, millipedes, beetles and mites that they eat. The frogs then secrete those toxins from their skin. That protects them from getting eaten. Some of these rainforest frogs are so toxic that just touching them can bring death.

Other organisms have evolved different types of poisons. Many of these chemicals attack microbes, fungi, insects and other threats in ways that make it unlikely they will become resistant to the poisons.

Scientists are finding ways to adapt compounds that frogs and other animals rely on for protection against threats in their environment. These compounds can be put to use fighting pests that threaten human health, the environment and the food supply. Frog poisons, for instance, can be used to fight insects such as the mosquito. Already, some of these natural compounds are being enlisted to guard human health and safety.

Throughout nature, one organism's defense can become another's offense — and vice versa. Here we meet some scientists who look at poisons not as a source of fear but as a raw material for drugs and other useful chemicals. They're investigating how to harness toxins — Mother Nature's chemical weapons — for the good of people and the environment.

Turning microbes into Swiss cheese

For decades, people have used drugs called antibiotics to kill bacteria that cause disease. Many bacteria, though, have become resistant to antibiotics. As a result, these infections are becoming much more difficult to treat. But natural compounds, including toxins, are providing a new way to fight these microbes.

Michael Zasloff discovered one of these beneficial toxins by accident. It was the late 1980s, and Zasloff was a medical scientist at the National Institutes of Health (NIH) in Bethesda, Md. (He now works at Georgetown University in Washington, D.C.) At NIH, he used ovaries from African clawed frogs for genetic studies. After surgery to remove the ovaries, he placed the frogs in a tank to recover. One day it dawned on him: Almost all of the frogs healed without infection. And it happened even though their water teemed with germs.

The skin of these African clawed frogs contains germ-killing chemicals that help them heal, even when their water is not sterile.

Zasloff examined the frogs closely. He discovered their skin contained a group of compounds that attacked bacteria. He named them magainins (Muh-GAYN-inz). The name comes from the Hebrew word for shield.

Peptides are short strings of amino acids that are similar to (but usually far smaller than) proteins. Magainins turned out to be one class of peptides with *antimicrobial* — germ-killing — properties. All types of life produce these peptides. They form one of the most basic defenses against *pathogens*, or disease-causing microbes.

Antimicrobial peptides kill bacteria by poking holes in their cell membrane. This is the soft outer wall surrounding each cell. These holes break down the bacterial cell's ability to function. Even better: Antimicrobial peptides can also attack protozoa, fungi and viruses.

But with bacteria, the peptides attack in a way that is very different from antibiotic drugs. "Conventional antibiotics are like keys in a lock," explains Zasloff. The antibiotics fit into specific proteins — or locks — and block their function. Depending on the antibiotic, those target proteins can be located inside a germ or on its surface. But all it takes is a slight change in the shape of that protein "lock" for the "key" to stop working, he says. That's what makes it so easy for bacteria to evolve resistance to antibiotics.

In contrast, magainins burrow through a microbe's cell membrane. The peptides effectively turn that membrane into Swiss cheese. To evolve resistance, a microbe would have to alter the structure of its membrane. That type of change would be too difficult for the microbe to easily make, says Zasloff.

Promising as it is, this new class of antibiotics is not yet ready for use in people. That's because some of these compounds can be very costly and too toxic.

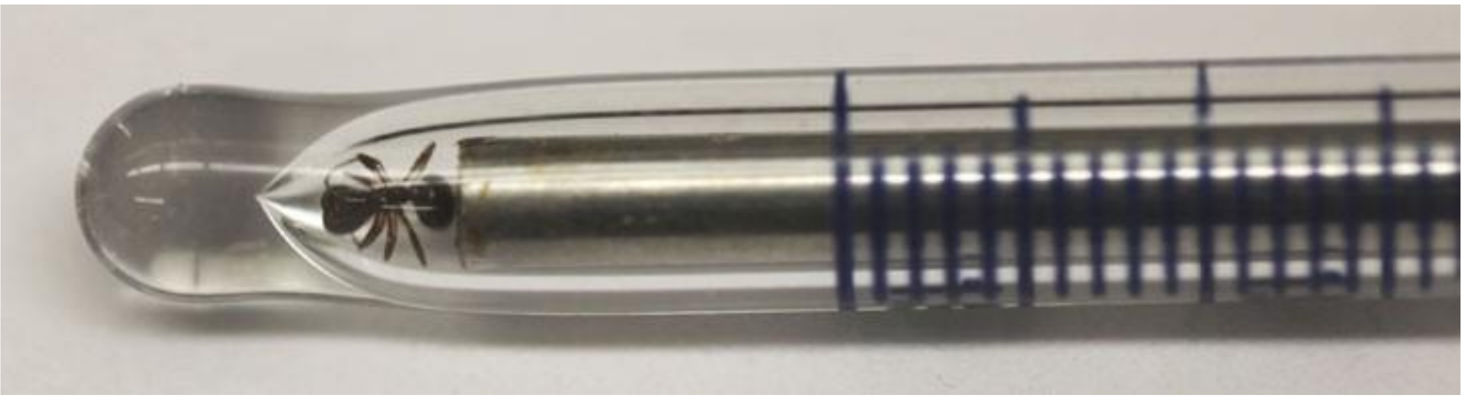
Still, the power of antimicrobial peptides already benefits many people. Consider nisin (NY-sin). Bacteria called *Lactococcus lactis* (LAK-tow-KOK-uss LAK-tiss) make it. This toxin is not harmful to people. Indeed, some manufacturers use it to make buttermilk and cheese. The bacteria make nisin as a poisonous defense against other bacteria, including those that cause two potentially deadly foodborne illnesses in people: botulism and listeria.

Today, scientists grow large batches of *L. lactis*. Then they extract nisin, which food companies often add to foods (such as processed cheese) and to food packaging. Listed on labels as E234, nisin keeps potentially deadly germs from growing on foods.

Fighting pests with frogs and mites

Antimicrobial peptides have been found in a wide variety of organisms, including people. They act as the first line of defense against invading microbes. That’s why these natural germ killers are common on the skin. More than 300 of these peptides have been found on frog skins alone.

The skin of some frogs also contains compounds called *alkaloids* (AL-kuh-loidz). These are the poisons in poison dart frogs. Those alkaloids can protect a frog from predators and kill germs.



A fire ant is trapped in a glass tube by a plunger coated with poison dart frog alkaloid.

Bob Vander Meer/USDA

You can’t see the toxic alkaloids on a frog's skin. Fortunately, a frog usually advertises — with a colorful skin sporting bold patterns — when those poisons are present. That coloring makes them easy to spot and avoid.

In fact, many animals that bear such colorful warnings are toxic in some way. For some, it can be a venomous bite or sting. For others, it’s enough to taste bad if eaten. Maybe you have seen a dog pick up a toad in its mouth and spit it out again. If so, you’ve probably seen alkaloids in action. Along with frogs and toads, other animals that use bright colors to advertise their toxicity include wasps, butterflies and even some birds.

The deadly alkaloids lurking on the skin of poison dart frogs keep them safe. At just 2.5 centimeters (about 1 inch) in length, the frogs would make a perfect snack for many birds, fish or mammals. But forget taking a taste. Even touching one of these frogs can prove deadly. Scientists have identified some 900 alkaloids in the skin of poison dart frogs.

Robert Vander Meer wanted to learn whether these alkaloids might also protect the frogs from insect predators. As a chemical ecologist with the U.S. Department of Agriculture (USDA) in Gainesville, Fla., Vander Meer studies the role of chemicals in plants, animals and their environment. He focuses on red imported fire ants.

The species first entered the United States in the 1930s. It likely stowed away on ships headed for the southern United States from Argentina. Today, this ant is one of the world's worst *invasive species*. (Lacking natural predators in its new home, an invasive species tends to spread rapidly, often harming its ecosystem.) Red imported fire ants are aggressive. People who live where these ants are found face a 1-in-3 chance every year of being stung, says Vander Meer. And their stings don't just hurt. The ant's venom actually kills insects, turtles, snakes — even young birds. Finding ways to control the ants is one of Vander Meer's goals.

A fire ant experiences convulsions following exposure to poison dart frog alkaloids. The alkaloid this ant was exposed to originally came from mites.
Bob Vander Meer/USDA

For a recent study, he selected 20 alkaloids from poison dart frogs. One species lives in areas of Central America that also are home to fire ants. The alkaloids had been isolated earlier by other scientists. This allowed Vander Meer to select only the ones he desired.

Vander Meer and his colleagues then brought local fire ants into the lab. There they used a *bioassay* to determine whether any of the alkaloids affected the ants. A bioassay looks for the effect of compounds, such as toxins, vitamins or hormones, on animals. (If you have ever had an allergy test, you have taken part in a bioassay.)

Here is how that test worked. First, the experts removed the plunger from a syringe (like the one used to spritz flu vaccine into your nose) and coated its end with one of the alkaloids. When the plunger was dry, the researchers placed a single ant inside a glass tube that had been sealed at one end. Then they inserted the plunger into the tube until it touched the ant's body (usually its abdomen). The plunger fit snuggly against the walls of the tube,. That prevented the ant's escape.

After three minutes of contact, the ant was released into a *Petri dish*. There, the experts centered the ant on a piece of paper marked like a target. The circles on the target were 2 centimeters (0.8 inch) apart. This allowed the researchers to measure how far the ant could move in a short period. The team also repeated the test using untreated plungers. This means that some of the tests didn't expose the ants to any of the alkaloids. That helped scientists learn whether it was an alkaloid, and not the cramped conditions, that caused a specific response.

Not all alkaloids affected the ants. For instance, toxins that the frogs originally obtained by eating fire ants had no effect. And that makes sense, explains Vander Meer. After all, fire ants have to be resistant to their own poisons. But some other alkaloids reduced the ability of the ants to walk for a time. Still others provoked convulsions and ultimately killed the insects. Those alkaloids had come from frogs that had dined on small relatives of spiders, known as mites. Now that the scientists know the source of those compounds, future studies may not require them to use frogs. They can go straight to the mites.

The alkaloids won't be useful in the fight against red imported fire ants, notes Vander Meer. The reason: They act too quickly. Effective control requires slow-acting poisons. Such poisons, whether natural or not, can be mixed in with ant food. Foraging ants then take the bait back to their nest. There, they will share the toxic meal with thousands of unseen workers. In time, the whole colony can die.

But the alkaloids could play an important role against another pest — mosquitoes — and the tropical diseases that they carry, notes Vander Meer. Some of these blood-sucking insects carry yellow fever, chikungunya, malaria and other diseases. Fabric sheets treated with alkaloids could be hung on the walls of homes to kill mosquitoes and protect against devastating diseases.

The trick, Vander Meer points out, is to modify the alkaloids. He and others are working to do that. Without changes, the alkaloids not only are toxic to mosquitoes but also to people. Even slight changes, though, might greatly alter how alkaloids work, he notes. And that may permit scientists to develop a version safe for people but still deadly to insect pests.

Safe for people and the environment

Although alkaloids can be hazardous to people, some peptides derived from toxins can control pests and disease without harming us. Spider venom is one source of such peptides, notes Natalie Saez. This molecular pharmacologist works at the University of Queensland in Brisbane, Australia. A molecular pharmacologist studies the interaction between drugs and the structures found on and inside of cells.

The venom of this Trinidad chevron tarantula contains peptides that might be useful to fight malaria.

Michael Minter/Flickr (CC-BY-NC 2.0)

Collectively, spider venoms may contain more than 10 million different peptides, says Saez. Some paralyze prey. Others kill microbes. Together, the peptides help keep spiders healthy by killing off infectious germs they encounter as they slurp down meals. But those same peptides also show the potential to boost human health. And scientists have just begun the work of identifying them all.

One interesting group of them blocks pain signals. One day, medicine might turn to these as the basis of new painkillers, Saez says. Others might help maintain a steady heartbeat in patients with irregular heart rhythms.

Large numbers of germ-killing peptides might even be harnessed to fight bacteria, fungi and other microbes. Among them is a peptide in the venom of a spider called the Trinidad chevron tarantula.

Malaria is caused by a *protozoan* parasite known as *Plasmodium* (Plaz-MOE-dee-um). It can enter the body through a mosquito bite. It then moves into red blood cells, where it reproduces. When the cells break open, huge numbers of new infectious parasites spew out. Malaria's victims now experience prolonged fevers as the body tries to fight off the parasite invasion.

Mosquitoes can carry deadly diseases such as dengue fever and malaria. But toxins from frogs and other organisms may one day be used to fight these disease-spreading bugs.
Muhammad Mahdi Karim/Wikimedia Commons

But *Plasmodium* needs a specific enzyme to enter a red blood cell. And the tarantula peptide blocks this enzyme. As a medicine, that peptide could stop the infection from spreading, Saez says. Further tests are still needed, she notes. But it appears the peptide may be safe enough that it could be given to malaria patients, possibly even in pill form.

Other spider-venom peptides show promise as insecticides. They one day might protect farm crops from pests, such as caterpillars, locusts or grasshoppers. In fact, the first pesticide based on venom peptides recently won approval for use from the U.S. Environmental Protection Agency. It comes from Australian funnel-web spiders. Called Versitude, this pesticide is safe not only for people, but also for the environment, says John Sorenson, who helped develop the insecticide. He heads the Vestaron Corp. in Kalamazoo, Mich.

Unlike many existing pesticides, the newly approved one doesn't harm mammals, Sorenson says. It also breaks down quickly in the environment. He says that means it shouldn't cause prolonged — and unintentional — damage. Sorenson expects this to be the first of many such natural pesticides.

So far, scientists have identified only about 1,000 spider venom peptides, Saez points out. That means there is still much to learn about these compounds and how they might be exploited to help people.

If alkaloids, peptides and other natural compounds measure up to their potential, these compounds could start replacing existing antibiotics and pesticides. Though born from compounds that harm and sometimes kill, these products could end up helping people and even saving lives. That's why a whole cadre of scientists are now looking to turn such poisons into life savers.

Power Words

(for more about Power Words, click here)

agriculture The growth of plants, animals or fungi for human needs, including food, fuel, chemicals and medicine.

alkaloid A type of naturally occurring chemical with many nitrogen atoms in its structure. Alkaloids are often produced by plants, and they can have many effects on the body and brain. Examples include drugs such as cocaine and morphine.

allergy The inappropriate reaction by the body's immune system to a normally harmless substance. Untreated, a particularly severe reaction can lead to death.

amino acids Simple molecules that occur naturally in plant and animal tissues and that are the basic constituents of proteins.

amphibians A group of animals that includes frogs, salamanders and caecilians. Amphibians have backbones and can breathe through their skin. Unlike reptiles, birds and mammals, unborn or unhatched amphibians do not develop in a special protective sac called an amniotic sac.

antibiotic A germ-killing substance prescribed as a medicine (or sometimes as a feed additive to promote the growth of livestock). It does not work against viruses.

antimicrobial A substance used to kill or inhibit the growth of microbes. This includes naturally derived chemicals, such as many antibiotic medicines. It also includes synthetic chemical products, such as triclosan and triclocarban. Manufacturers have added some antimicrobials — especially triclosan — to a range of sponges, soaps and other household products to deter the growth of germs.

antimicrobial peptide A short chain of amino acids that attacks the cell membrane of microbes. Antimicrobial peptides are produced by almost all organisms, from bacteria to people.

bioassay A test that measures the potency or the concentration of a substance on living cells or tissue. An allergy test that measures the effect of different allergens is an example.

botulism A potentially lethal paralyzing disease caused by a toxin made by bacteria (usually *Clostridium botulinum*). It is usually triggered by eating food contaminated with the microbe's "botulinum toxin."

cell The smallest structural and functional unit of an organism. Typically too small to see with the naked eye,it consists of watery fluid surrounded by a membrane or wall. Animals are made of anywhere from thousands to trillions of cells, depending on their size.

chemical A substance formed from two or more atoms that unite (become bonded together) in a fixed proportion and structure. For example, water is a chemical made of two hydrogen atoms bonded to one oxygen atom. Its chemical symbol is H2O.

chemical ecology The study of how plants and animals use chemicals and chemical signals in their interactions with each other and their environment. Scientists who work in this field are called chemical ecologists.

colonial Geographical: An area under full or partial control of another country, typically far away. (in biology) Organisms that live as part of a structured and organized community.

compound (often used as a synonym for chemical) A compound is a substance formed from two or more chemical elements united in fixed proportions. For example, water is a compound made of two hydrogen atoms bonded to one oxygen atom. Its chemical symbol is H2O.

Environmental Protection Agency (or EPA) An agency of the federal government charged with helping create a cleaner, safer and healthier environment in the United States. Created on Dec. 2, 1970, it reviews data on the possible toxicity of new chemicals (other than food or drugs, which are regulated by other agencies) before they are approved for sale and use. Where such chemicals may be toxic, it sets rules on how much may be used and where it may be used. It also sets limits on the release of pollution into the air, water or soil.

fire ant A tropical American ant that has a painful and sometimes poisonous sting.

fungus (plural: **fungi**) One of a group of single- or multiple-celled organisms that reproduce via spores and feed on living or decaying organic matter. Examples include mold, yeasts and mushrooms.

genetic Having to do with chromosomes, DNA and the genes contained within DNA. The field of science dealing with these biological instructions is known as *genetics*. People who work in this field are geneticists.

germ Any one-celled microorganism, such as a bacterium, fungal species or virus particle. Some germs cause disease. Others can promote the health of higher-order organisms, including birds and mammals. The health effects of most germs, however, remain unknown.

hormone (in zoology and medicine) A chemical produced in a gland and then carried in the bloodstream to another part of the body. Hormones control many important body activities, such as growth. Hormones act by triggering or regulating chemical reactions in the body. (in botany) A chemical that serves as a signaling compound that tells cells of a plant when and how to develop, or when to grow old and die.

insect A type of arthropod that as an adult will have six segmented legs and three body parts: a head, thorax and abdomen. There are hundreds of thousands of insects, which include bees, beetles, flies and moths.

insecticide A poison applied to kill insects.

invasive species (also known as aliens) A species that is found living, and often thriving, in an ecosystem other than the one in which it evolved. Some invasive species were deliberately introduced to an environment, such as a prized flower, tree or shrub. Some entered an environment unintentionally, such as a fungus whose spores traveled between continents on the winds. Still others may have escaped from a controlled environment, such as an aquarium or laboratory, and begun growing in the wild. What all of these so-called invasives have in common is that their populations are becoming established in a new environment, often in the absence of natural factors that would control their spread. Invasive species can be plants, animals or disease-causing pathogens. Many have the potential to cause harm to wildlife, people or to a region's economy.

listeria The bacteria responsible for a serious foodborne infection known as listeriosis.It's caused by eating food tainted with the toxin produced by the bacterium *Listeria monocytogenes*. This germ is particularly worrisome because it's common and grows well at the temperatures inside a refrigerator.

magainins A family of natural peptides with germ-fighting properties. They tend to be common in the skin and mouths (and sometimes other organs) of many animals.

malaria A disease caused by a parasite that invades the red blood cells. The parasite is transmitted by mosquitoes, largely in tropical and subtropical regions.

mammal A warm-blooded animal distinguished by the possession of hair or fur, the secretion of milk by females for feeding the young, and (typically) the bearing of live young.

membrane A barrier which blocks the passage (or flow through of) some materials depending on their size or other features. Membranes are an integral part of filtration systems. Many serve that function on cells or organs of a body.

microbe Short for microorganism. A living thing that is too small to see with the unaided eye, including bacteria, some fungi and many other organisms such as amoebas. Most consist of a single cell.

millipede Long-bodied invertebrates with many segments. Most body segments have two pairs of legs.

mite An invertebrate belonging to the broad group of animals known as arachnids, which also includespiders and ticks. None of these are insects, although like insects they belong to the larger umbrella group, called arthropods (named for their members' segmented legs).

molecule An electrically neutral group of atoms that represents the smallest possible amount of a chemical compound. Molecules can be made of single types of atoms or of different types. For example, the oxygen in the air is made of two oxygen atoms (O2), but water is made of two hydrogen atoms and one oxygen atom (H2O).

molecular biology The branch of biology that deals with the structure and function of molecules essential to life. Scientists who work in this field are called molecular biologists.

nisin A defensive poison produced by certain *Lactococcus* bacteria to kill certain other microbes in their environment. Food manufacturers have harnessed this natural germ-warfare agent to also kill off certain harmful bacteria that frequently infect foods.

parasite An organism that gets benefits from another species, called a host, but doesn't provide it any benefits. Classic examples of parasites include ticks, fleas and tapeworms.

pathogen An organism that causes disease.

peptide A short chain of amino acids (usually fewer than 100).

pesticide A chemical or mix of compounds used to kill insects, rodents or other organisms harmful to cultivated plants, pet or livestock, or unwanted organisms that infest homes, offices, farm buildings and other protected structures.

pesticide resistance The ability to survive being sprayed or treated with pesticides.

Petri dish A shallow, circular dish used to grow bacteria or other microorganisms.

pharmacology The study of how chemicals work in the body, often as a way to design new drugs to treat disease.

plasmodium A form within the life cycle of some simple organisms such as slime molds, typically consisting of a mass of naked protoplasm containing many nuclei. (in medicine) It also refers to a genus of protozoa that cause the disease malaria. The *Plasmodium* genus includes more than 100 species; just five are responsible for most infections in humans.

predator (adjective: **predatory**) A creature that preys on other animals for most or all of its food.

proteins Compounds made from one or more long chains of amino acids. Proteins are an essential part of all living organisms. They form the basis of living cells, muscle and tissues; they also do the work inside of cells. The hemoglobin in blood and the antibodies that attempt to fight infections are among the better-known, stand-alone proteins.Medicines frequently work by latching onto proteins.

protozoan (plural: **protozoa**) Any of many types of single-celled organisms, most of them too small to be seen with the unaided eye. They include amoebas, parameciums and many others. Some can cause disease in humans and other animals.

rainforest Dense forest rich in biodiversity found in tropical areas with consistent heavy rainfall.

red blood cells Colored red by hemoglobin, these cells move oxygen from the lungs to all tissues of the body.

resistance (as in drug resistance) The reduction in the effectiveness of a drug to cure a disease, usually a microbial infection. (as in disease resistance) The ability of an organism to fight off disease. (as in exercise) A type of rather sedentary exercise that relies on the contraction of muscles to build strength in localized tissues.

secrete (noun: **secretion**) The natural release of some liquid substance — such as hormones, an oil or saliva — often by an organ of the body.

species A group of similar organisms capable of producing offspring that can survive and reproduce.

toxic Poisonous or able to harm or kill cells, tissues or whole organisms. The measure of risk posed by such a poison is its **toxicity.**

toxin A poison produced by living organisms, such as germs, bees, spiders, poison ivy and snakes.

venom A poisonous secretion of an animal, such as a snake, spider or scorpion, usually transmitted by a bite or sting.

virus Tiny infectious particles consisting of RNA or DNA surrounded by protein. Viruses can reproduce only by injecting their genetic material into the cells of living creatures. Although scientists frequently refer to viruses as live or dead, in fact no virus is truly alive. It doesn’t eat like animals do, or make its own food the way plants do. It must hijack the cellular machinery of a living cell in order to survive.

vitamin Any of a group of chemicals that are essential for normal growth and nutrition and are required in small quantities in the diet because they cannot be made by the body.

yellow fever A disease that creates flu-like symptoms that can start with fever, chills, headache, backache and vomiting. Roughly 15 percent of patients may go on to develop more serious disease. This can lead to uncontrolled bleeding, the failure of multiple internal organs — and death.

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USES FOR NATURE'S POISONS

K	Y	M	F	A	W	S	S	H	R	N	O	B	Y	V	P	N	V	A	M
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ABDOMEN	EVOLVE	MOSQUITO	VENOM
ALKALOID	FIRE ANTS	NISIN	WASPS
AMPHIBIAN	FORAGING	PARALYZE	WEAPONS
ANTIBIOTIC	FUNGI	PEPTIDE	
BACTERIA	GLASS	PLUNGER	
BOTULISM	INVASIVE	POISON	
BURROW	LISTERIA	RESISTANCE	
COLORFUL	MAGAININ	RHYTHM	
ECOLOGIST	MALARIA	SPIDER	
ENZYME	MEMBRANE	TARANTULA	