

Viral Voyages





MAVIS AGBANDJE-MCKENNA



DAVID BLANKENSHIP

"I feel like I'm one of the lucky ones."

Mavis Agbandje-McKenna is a structural biologist at the University of Florida in Gainesville. She studies how viruses infect cells.

By Alisa Zapp Machalek

ARURAL FARM IN NIGERIA, 1969—Six-year old Mavis played under the shade of a tree while her grandmother planted crops in the nearby field. Suddenly, her grandmother scooped her up, rushed toward the scraggly bushes, and thrust her underneath. In the distance, Mavis heard rumblings and shouting—soldiers!

Mavis squeezed further under the bush, trembling and silent. Her grandmother hugged her from behind and she could feel both of their hearts pounding.

Eventually, the shouts faded. A sunbird chattered nearby, searching for nectar, then buzzed off in a flash of iridescent green. After what seemed like hours, her grandmother slowly unwrapped herself from the girl and stood up. Moments later, she extended her hand, saying in her native tongue, "It's OK to come out now, Mavis."

Today, Mavis Agbandje-McKenna is half a world away from her war-torn homeland. Now 42 and a scientist, she spends her days solving mysteries about viral diseases in her lab at the University of Florida in Gainesville.

"My life has certainly taken an interesting route so far—from growing up in a small village in Nigeria and hiding from soldiers during the Biafra war, to being an associate professor at an American university," she says.

Her scientific voyage has also been an unusual one. Currently a structural biologist, Agbandje-McKenna started out as a chemist making small molecules designed to fight cancer. Then she learned a technique called X-ray crystallography and used it to reveal the three-dimensional structures of viruses.

Now, she has entered the world of glycobiology, a field that focuses on carbohydrates. These molecules, made up of one or more sugars linked together, are essential for many biological processes, including cell communication, inflammation, and pregnancy.

Carbohydrates are also used by viruses to infect the cells of people and animals, sometimes causing serious disease.

Agbandje-McKenna's research has helped reveal the way harmless viruses can become vicious killers by switching which carbohydrates they latch onto. Her research also sheds light on how viruses can hop from one host to another.

The work is especially timely given worldwide fear that avian influenza, or bird flu, will genetically change into a form that

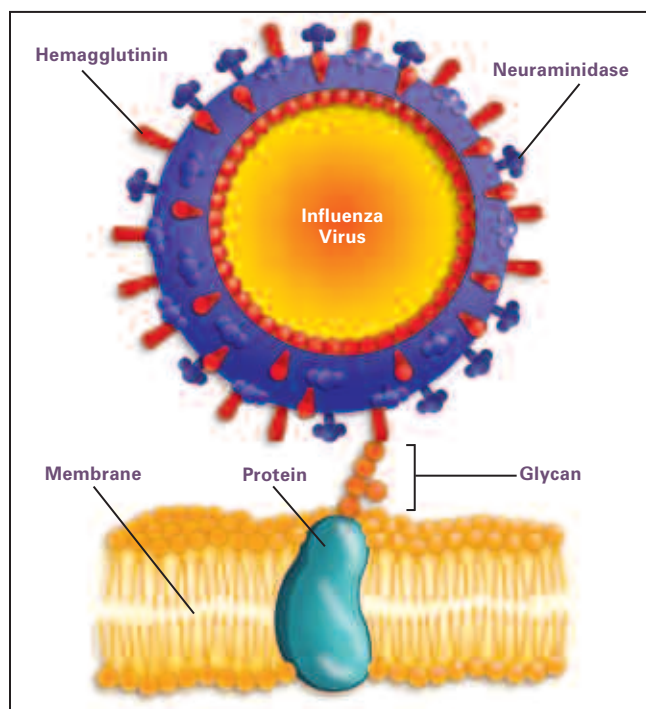
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can infect humans. If that occurs, it could unleash a global pandemic, killing millions (see sidebar, page 13).

Gripping Glycans

Carbohydrate molecules protrude from the outer surfaces of nearly all cells. The molecules serve as specialized receptors that act as docking stations for certain proteins on other cells.

Viruses infect cells by recognizing and latching onto these same carbohydrates. After attaching, a virus enters the cell and takes over its machinery.



Think of carbohydrates, also called glycans, as twigs that are either straight or branched. Like their botanical equivalents, the most interesting parts—the leaves and flowers—are at the tips.

And as plants are characterized by their leaves and flowers, each organ and tissue has its own special glycans. Each strain of virus can only grab onto glycans with a specific set of molecules at their tips. So, the types of glycans that a virus latches onto determine whether the virus will infect the lungs, the intestines, or other tissues.

Influenza A infects a host cell when hemagglutinin grips onto glycans on its surface. Neuraminidase, an enzyme that chews sugars, helps newly made virus particles detach so they can infect other cells.

Incredibly, viruses are even more finely tuned than that to infect specific cells. They can only latch onto glycans whose

sugars are arranged in a particular way. Going back to the plant analogy, it's as if a virus doesn't recognize just any twig with four leaves and a flower—the leaves and flower have to be arranged on the twig in a certain fashion.

This may sound like a level of detail that only a few specialists would care about. But because the arrangement of sugars on glycans is specific for each type of organism, it's relevant for all of us.

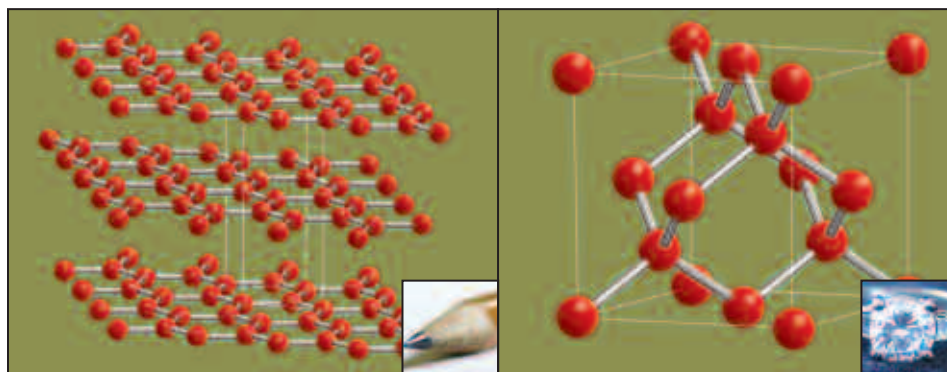
Take the case of influenza A, which infects cells by attaching to certain types of glycans. The glycan arrangement favored by a strain of influenza determines whether the virus will infect birds or people.

Mystery of the Dead Mice

One of Agbandje-McKenna's favorite viruses to study is the minute virus of mice, often abbreviated MVM. This virus usually comes in two strains. One version, called MVMp, produces no symptoms and infects mice in connective tissues like skin, bone, and fat. A more dangerous version, called MVMi, infects blood and lymph cells and can kill mice with weakened immune systems.

At least that's what scientists used to think.

A few years ago, when Agbandje-McKenna was visiting a coworker in Spain, she learned some troubling news.

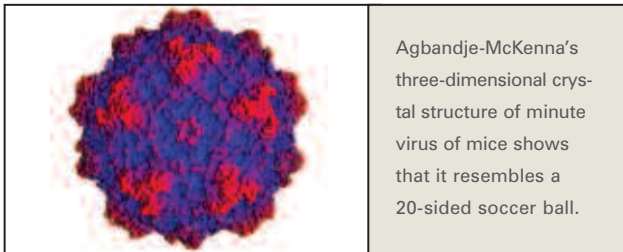


Glycans are made of various combinations of sugar building blocks. The arrangement of identical sugars can make as dramatic a difference as a more well-known example of identical carbon atoms rearranged: dull graphite (left) and sparkly diamonds (right).



According to the scientist's research, mice exposed to the usually mild MVMP strain had suddenly started dropping down dead. Intrigued, the two researchers set out to solve the mystery of how and why the mice died.

MVM works like almost all viruses: It protects its genetic material with an outer shell known as a capsid. In MVM, the capsid shell is made of 60 interlocking copies of a protein that assemble into an icosahedron—a soccer ball-like shape that has 20 faces.



Agbandje-McKenna's three-dimensional crystal structure of minute virus of mice shows that it resembles a 20-sided soccer ball.

Capsid proteins are critical to infection because they are what actually grab glycans. Small changes in the capsid can make a big difference in the infectivity of the virus. For example, MVMP and MVMi have very different impacts on mice, but on the molecular level, they are virtually identical. The only difference between them is an alteration of 14 amino acids out of a total of more than 500 that make up the capsid protein.

Because of their key role in infection, capsid proteins were the prime suspect in the case of the dead mice. Agbandje-McKenna and her coworker guessed that genetic changes in MVMP may have created a mutant version of the capsid protein that made the virus more deadly.

To investigate this theory, the scientists decoded the genetic sequences of viruses from the dead mice. To their surprise, they found not one, but three different mutant versions of MVMP. Each mutant contained a change in just one amino acid in the capsid protein.

You might think that just one change among 587 amino acids wouldn't be a big deal. But, explains Agbandje-McKenna, if the change lies in a critical region of the virus' capsid shell, it could transform a virus that is essentially harmless to its host into one that is invincible. According to Agbandje-McKenna, that's exactly what happened.

The three-dimensional structure of MVM, which Agbandje-McKenna used structural biology techniques to figure out, shows that the viral capsid protein contains a cavity that it uses to recognize and bind glycans.

She discovered that at least two of the changed amino acids sit right inside this cavity. Agbandje-McKenna

suspects that the mutations subtly change the shape of the cavity so that the virus can recognize a different set of glycans than it could originally, boosting its killing powers.

The next step in solving the dead mice mystery was to identify the glycans to which the three mutant viruses could attach. For this, Agbandje-McKenna sought help from a large, international team of researchers that study cell communication by analyzing interactions between proteins and carbohydrates on cell surfaces.

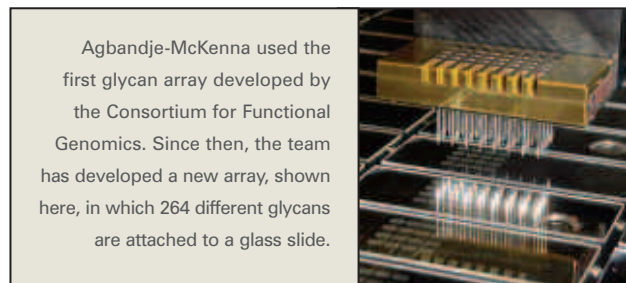
Called the Consortium for Functional Glycomics, the team includes more than 230 scientists in 27 countries. It is one of five special "glue grants" from the National Institute of General Medical Sciences that bring teams like this together to answer some of the biggest biological questions.

Counting Carbs

When Agbandje-McKenna first contacted the Consortium, the group had recently developed a technology called a glycan array, made up of scores of glycans chemically stuck onto tiny wells on a 3- by 5-inch plastic plate.

The array had been designed to screen proteins to find out which glycans they recognize. Agbandje-McKenna wanted to use it to reveal which glycans viruses grab onto.

She applied to join the Consortium team and was accepted. Her research group quickly prepared samples of normal and mutant viral capsid proteins, which she then shipped off to the Consortium's screening center in Oklahoma.



Only a few days later, Agbandje-McKenna had her answer. Both the normal and the mutant capsid proteins stuck to only three of the 189 glycans on the plate. Yet one of the mutants also bound to an additional glycan—one to which the more dangerous MVMi strain routinely attaches.

So, the results of the array experiment supported her theory: A single amino acid change in the mutant capsid protein had changed which glycans the virus could grip, making it more deadly. This is exactly what health officials worldwide hope does *not* happen with bird flu.

The array experiment further revealed that the mutant proteins do something else differently: They don't attach

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to glycans as tightly as do the normal proteins. According to Agbandje-McKenna, this is true of many viruses, including influenza.

But why would more deadly strains of viruses tend to have a looser grip on glycans than do their more mild-mannered relatives? Agbandje-McKenna says scientists don't really know, but they think that if a virus binds to a cell weakly, it can more easily let go and get into the cell to cause disease. If it binds tightly, she explains, the host immune system will engage and attack it before it has a chance to enter the cell.

To delve more deeply into the mystery of the dead mice, Agbandje-McKenna's group is busy solving the three-dimensional structure of MVMp and its mutants while they are attached to various glycans.

Out of Africa

Like many Nigerians, Agbandje-McKenna's parents moved to England for better educational and job opportunities. They left Agbandje-McKenna, then a toddler, in the care of her grandmother.

Two years later, when Agbandje-McKenna was 4 years old, the Biafra civil war broke out. Largely sheltered from the war, which lasted until she was 7, Agbandje-McKenna attended her village's elementary school.

"My grandmother insisted I go, even though it wasn't required," she remembers. It was there that she developed an early interest in science.



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Agbandje-McKenna (bottom right, at age 2) never forgets her "humble beginnings" in a small Nigerian village.

"Originally, I wanted to be a medic, but the sight of blood wasn't pleasant, and I didn't want to deal with people dying," she says. "So, I became a scientist."

At the age of 11, without being able to speak a word of English, Agbandje-McKenna moved to England to rejoin her parents and four younger siblings who had been born there. Another brother was born 5 years later.

Agbandje-McKenna continued her interest in science—"how things work," as she puts it—by studying chemistry and human biology in college. She then earned a Ph.D.

from the University of London, where she met her future husband, Robert McKenna.

"Mavis' background is what makes her who she is," says McKenna. "She always remembers that she used to live in a mud hut." (*"Not exactly a mud hut," Agbandje-McKenna insists, "but a house built from hardened mud. It had a slate roof."*)

"I have a photo of her as a child in her village on my desk, and I look at it for inspiration," McKenna says. "I can get so worked up about issues that are so petty, and she's my reality check. She'll say, 'Two-thirds of the world's population doesn't own any shoes, so why are you so worried about this?'"

In Africa, Agbandje-McKenna learned how to be happy regardless of the circumstances, says McKenna. Now, she spreads her happiness to everyone around her.

"[I think] that's what people like about me," Agbandje-McKenna says. "I'm one of those 'happy people.'"

Yin and Yang

McKenna and Agbandje-McKenna have been married for 17 years and all the while, their lives have been in lockstep. When McKenna accepted a research job in an X-ray crystallography laboratory at Purdue University in West Lafayette, Indiana, Agbandje-McKenna did too. By all accounts, within months, she was running parts of the lab despite having no background in crystallography.

"She's an amazing adapter," said McKenna. "She's jumped [into so many different scientific areas] and succeeded. My career has been much more linear. I don't think I'd be as brave as she is."

Eventually settling in Florida 6 years ago, their lives are still "totally interdigitated," says McKenna. They work together on much of their research and physically share a lab.

Their students see them as essentially interchangeable, which helps them balance work and family issues (they have a son, 15, and a daughter, 12). When one scientist is at a research seminar or needs to drive a child to an activity, the other one is there to answer questions from students.

"A lot of students make comments that our lab is like a family, and we're the Mum and Dad," says McKenna.

"Sometimes, when I have trouble helping one of my students, Mavis comes in and resolves things by seeing the issue from

Work and play go together for Agbandje-McKenna and her husband, with whom she shares a lab.



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a different viewpoint. And I do the same for her. It works out very well.”

“We’re like yin and yang,” says McKenna. “We’re opposite in so many ways. But opposites attract, and we’ve made it work.”

Special Delivery

What will Agbandje-McKenna’s research mean for human health? Not only will her studies shed light on how the flu and other viruses infect cells, but the research may even be relevant for cancer and gene therapy.

Viruses emptied of their genetic material—and thus their ability to cause disease—can be ideal delivery vehicles for carrying medicines or genes into the body.

The trick is getting the cargo to the right tissues. If researchers can fine-tune empty virus shells so that they grab glycans found on cancer cells but not on normal ones, they have a good chance at making this drug delivery strategy work. According to Agbandje-McKenna, other

scientists are learning how to use MVM to deliver genes as medicines.

Agbandje-McKenna would love it if her research found medical application, but her own long-term goals are more fundamental.

“I’m a basic scientist at heart,” she says. “My overall goal is to understand how viruses do it—how they recognize and interact with host cells, and how small differences in the viral capsid can cause such a major disparity in disease outcome.”

“At the end of the day, for us to be able to treat viral disease, we need to understand these things.”

When asked what advice she has for young people considering a career in science, she says, “It doesn’t matter how you get started as long as you work hard and have a lot of support. I had my parents and grandmother, who were keen for me to get a good education.”

Still, she admits her story is a bit unusual. “I feel like I’m one of the lucky ones. I started out very humbly in my village and here I am.” ■

Poultry, People, and a Possible Pandemic

For the past couple of years, news stories have followed the spread of bird flu in Asia. Why all the fuss over a seemingly obscure disease that is killing chickens in a far-off part of the world? Consider a few key facts and you’ll see why.

Pandemic influenza occurs when a new subtype of the flu virus emerges that spreads easily from person to person. Because no one has immunity to it, the new subtype can kill young, healthy people as well as the elderly and sick.

Birds are considered the main repository of influenza and the most likely source of a new subtype. Bird viruses that genetically changed such that they could infect humans contributed to all three of the most recent influenza pandemics: in 1918, 1957, and 1968.

The “H5N1” version of bird flu that has recently infected poultry in Asia has already caused the largest and most lethal epidemic on record. Although H5N1 has never circulated widely among humans, based on the death rate of the more than 150 people who have contracted it, scientists know that it is the deadliest bird flu ever to infect people.

With just one or two minor genetic changes—and influenza is constantly changing—H5N1 could jump the species barrier to spread easily between people. Scientists predict that if that happens, its global spread would be hard to stop. According to the World Health Organization, the virus could reach every continent in less than 3 months and it could kill 2 to 7 million people.

Health officials and policymakers are preparing plans and using modeling data that shows the impact of various interventions.—*A.Z.M.*



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