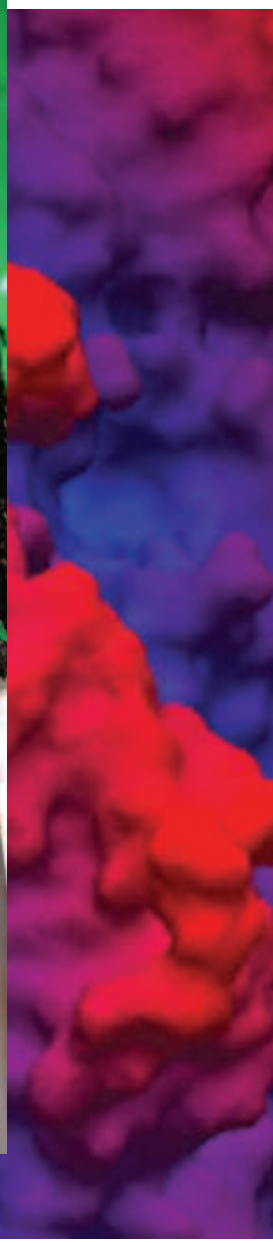
FINDINGS

March 2006



inside

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On the Cover

Photo of Neil Kelleher: *Bill Wiegand*

Photo of Mavis Agbandje-McKenna: *David Blankenship*

Editor's Note

What do Ludwig van Beethoven, dead mice, and the flu have in common?

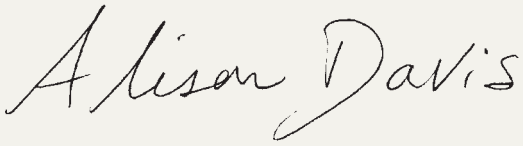
Would you believe…X rays?

Recently, scientist-sleuths solved the mystery of how Beethoven died. Biophysicists took a carefully preserved, 175-year-old fragment of Beethoven's skull and bombarded the sample with X rays. Using this approach, they discovered that large and unhealthy amounts of lead had deposited throughout the legendary composer's skeleton—enough to poison his tissues and ultimately kill him.

Dying mice? The flu?

X rays have become essential resources for modern researchers pursuing countless medical mysteries. On page 9, read how structural biologist Mavis Agbandje-McKenna used X-ray crystallography to track down a crafty virus that suddenly turned deadly from a slight change in its protein coat. Because of this change, the virus—usually quite harmless—had gained the power to kill.

Her detective work is timely because scientists worldwide are frightened that the "bird" flu virus may do the same thing, potentially unleashing a pandemic. Scientific problem solving using X rays and other tools borrowed from physics may provide crucial tools for confronting public health challenges before they turn into emergencies.



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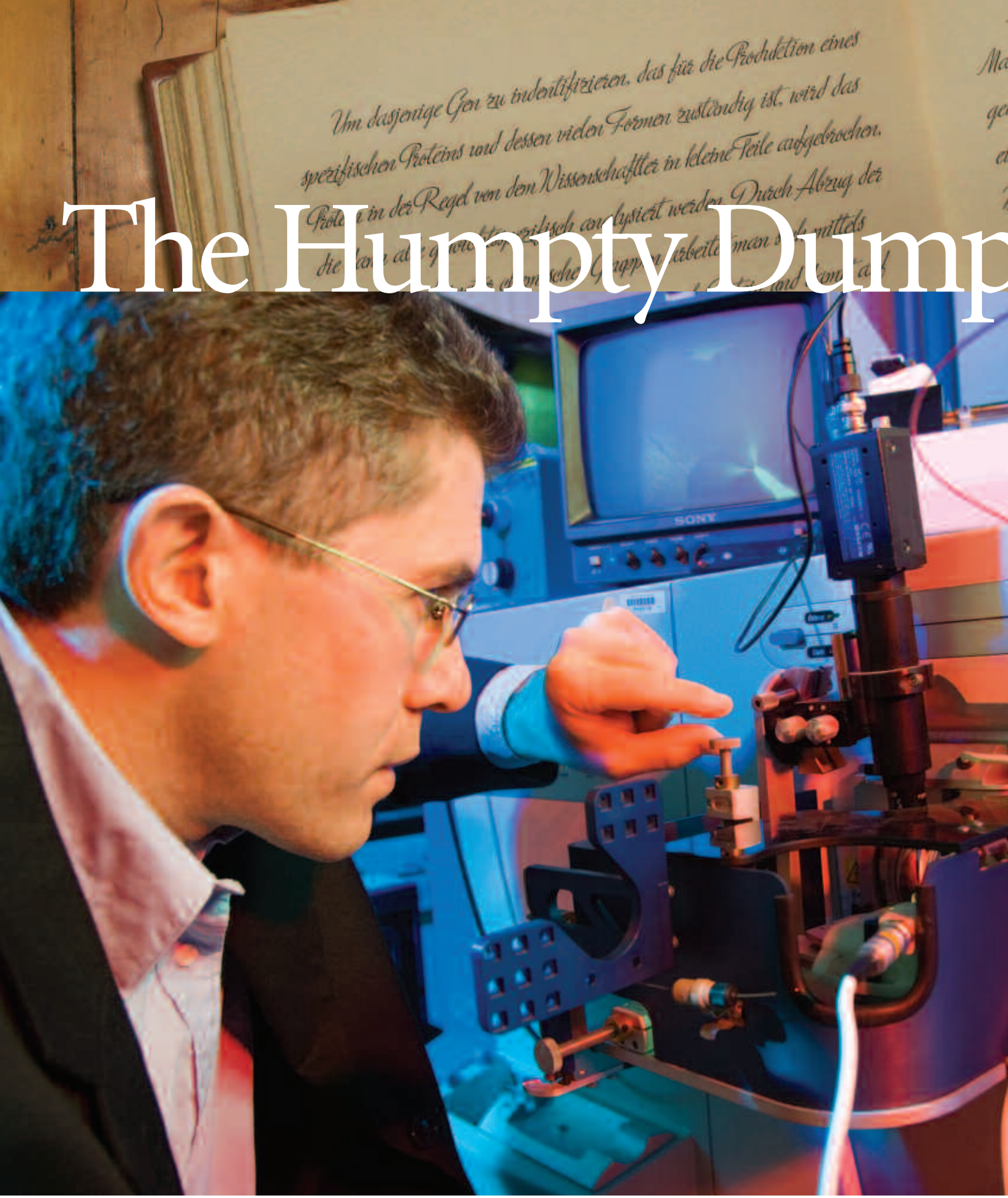
The Humpty Dump



pty Dilemma

BILL WIEGAND

"Like Humpty Dumpty, we generally can't put a protein completely back together again."

Neil Kelleher is a chemical biologist at the University of Illinois at Urbana-Champaign. Kelleher uses "top-down" mass spectrometry to weigh proteins.

By Emily Carlson

Ever dreamed of meeting the President of the United States? Could science be your ticket to the White House?

Neil Kelleher never thought so until last summer, when he found himself in Washington, DC, standing right outside 1600 Pennsylvania Avenue. Having just won a national award for his research on proteins, Kelleher got the prize straight from George W. Bush himself.

"I was sweating bullets," says Kelleher, 35, a chemical biologist at the University of Illinois in Urbana-Champaign. But not from nerves, he says. Mainly, he was suffering the sweltering effects of an early summer heat wave.

"The President came out and said, 'It's hot, let's go into the Oval Office,'" Kelleher recalls.

While most people would probably be intimidated talking to the leader of the United States, Kelleher struck up a conversation with the President.

"Bush said his favorite president was Abraham Lincoln, and I chimed in and said, 'I'm from Illinois!'" (Abraham Lincoln grew up in Springfield, the state capitol of Illinois.)

Kelleher's willingness to speak up served him well that day, but it may also be a secret to his success in general. Many of Kelleher's mentors mention persistent enthusiasm as a main driver of his early scientific achievements.

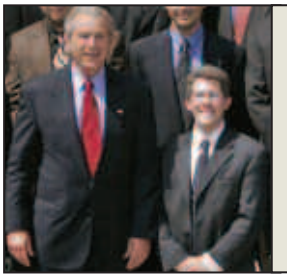
"Neil is the kind of guy we love to have in science," says Fred McLafferty, a retired chemistry professor who advised Kelleher during graduate school. "He's got initiative and loves to try new things."

Kelleher notes, however, that success also has a lot to do with being in the right place, at the right time, with the right people.

"It's good to be good," he says, "but it's better to be fortunate," admitting that a little of both is part of the formula.

Early Decisions

Another key strategy has been making smart choices. Kelleher faced one of his first major decisions in college, when his parents asked him to choose between studying abroad and getting a car.



WHITE HOUSE PHOTO BY PAUL MORSE

Kelleher took a trip to the White House in June 2005 to receive the Presidential Early Career Award for Scientists and Engineers, the highest honor a young scientist or engineer can receive from the United States.

Kelleher, like many young people, wanted a sweet new ride. But his mother thought differently. She advised her son to continue learning German, a subject he had begun in high school.

Because he was also interested in chemistry, Kelleher thought it might be a good idea to spend time in Germany, the country that gave rise to many of the world's chemistry masters. Not too long ago, he explains, chemistry majors needed to know German because a lot of scientific papers were written in the language. The start of organic chemistry, for example, traces back to Germany (see sidebar, page 7).

When Kelleher returned to college in the United States, he completed majors in both German and chemistry. Then, he had to face another important life decision. Should he continue with school or take some time off?

Instead of going straight into a Ph.D. program, Kelleher decided to see for himself what research was all about. He applied for a Fulbright scholarship, a competitive program that pays people to conduct their own research projects in another country.

He won the scholarship and got on another plane to Germany.

There, Kelleher studied organic synthesis, using chemistry techniques to build molecules made naturally by living organisms. He spent nearly all his time in the lab, and before long realized that while he loved research, this kind of chemistry didn't excite him as much as it might have.

One day, Kelleher took a break from the lab to hear a scientific lecture about a completely different area of chemistry.

During the talk, Kelleher listened attentively while McLafferty, who was then a researcher at Cornell University in Ithaca, New York, described a new method for studying proteins. Compared to traditional approaches, McLafferty claimed, this one made it easier for scientists to take a protein and figure out what gene made it.

McLafferty's presentation captivated much of the audience.

"There was dead silence after I finished," says McLafferty, remembering that someone in the back of the room broke the silence and asked a question that spurred a lively scientific discussion.

McLafferty made a special point to meet the questioner. It should come as no surprise to you at this point that it was Kelleher. After talking to McLafferty, the young scientist knew instantly that he wanted to work with him.

Winning Spirit

"Neil has always been one to take the bull by the horns," says McLafferty of his former student. "He loves challenges and throws himself into them."

As with many researchers, Kelleher's energy extends beyond science. Standing just 5 feet tall didn't stop him from playing one of his favorite sports: basketball. Despite being at least a foot shorter than the average team member, Kelleher boasts that he shoots just as well as any other player.

"I'm pretty good," he says, adding that people are usually quite surprised that he can play the game so well.

Another sport Kelleher excelled at was golf, which he played competitively during graduate school. McLafferty remembers jokingly threatening that Kelleher couldn't have his Ph.D. degree until he beat a good golfer among McLafferty's coworkers.

NEIL KELLEHER

Kelleher spent time in Germany (pictured here in Berlin) to learn the language and get a taste for chemistry.

Sure enough, right before his final exam, Kelleher announced victory.

"I beat him!" he told McLafferty.

With both titles in hand, Kelleher soon started his own lab in Illinois, where he now lives with his wife, Jennifer, and their two daughters. There, he spends much of his

time building on the work he began with McLafferty, developing better ways to measure the tiny mass variations between different forms of proteins.

Size Matters

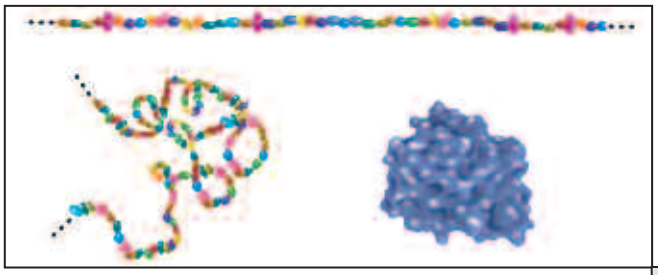
Proteins are central to life. Our bodies build them using cellular machines that read our genetic instructions and then assemble chains of building blocks called amino acids. For a protein to do its job properly, the amino acid chains must fold themselves into exactly the right shape. An error in the genetic instructions can cause a protein to fold incorrectly and malfunction, which can lead to illness.

The gene-to-protein process may sound simple. Indeed, it happens without our thinking about it, every second of every day, inside all living things on the planet.

But there's one little problem that makes it very hard for scientists to unravel the details of the protein-making process: We have thousands more proteins than we have genes that code for them.

How is that possible?

Scientists know that humans have about 25,000 genes, but they also know that each gene can make up to



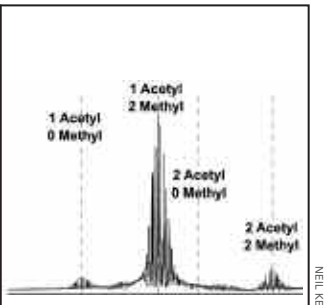
Proteins are made up of amino acids hooked end-to-end like beads on a necklace (top). To become active, proteins must twist and fold (bottom left). A protein's final shape (bottom right) helps it do its job in the body.

50 (or more) different protein forms! Some of the variety comes from chemical changes that alter a protein after its gene has been read, leading to a slightly different version of that protein.

Just like eating too much or too little can affect our weight, these chemical changes to a protein can make it gain or lose mass. For example, the addition of a methyl group—one type of chemical change—adds 14 daltons to the mass of a protein.

A dalton is the unit of mass measurement scientists use to describe proteins. It is the mass of the smallest atom, a hydrogen atom. And it's very, very small: One dalton equals one-trillionth of one-quadrillionth of a pound!

In order to identify the gene that makes a given protein and its many forms, scientists typically break the protein apart into small pieces and then analyze all the pieces by weighing them. By subtracting the masses of attached



A "spectrum," the computer output of a mass spectrometer, reveals the individual parts of a protein. Clusters of spikes in this spectrum show the presence of chemical modifications (acetyl and methyl groups, for example) within a protein molecule.

NEIL KELLEHER

chemical groups, researchers can work their way back to the original protein, and then to its gene.

But getting a protein's mass is much trickier than simply setting it on a scale.

To weigh protein pieces, researchers use machines called mass spectrometers that are billions of times bigger than the molecules they weigh. The instruments can range in size from the microwave in your kitchen to a small bus.

The researchers convert the protein pieces into charged particles called ions. The mass spectrometer then sorts the ions based on their electrical charge and the fragments' molecular weight. A computer takes all the information and creates a chart, or spectrum, that describes the protein and its amino acid parts.

Cruising with the Top Down

But then there's another problem, Kelleher says. Simply adding up the bits of protein doesn't always equal the whole.

"Like Humpty Dumpty, we generally can't put a protein completely back together again," Kelleher explains.

Kelleher realized that to study larger proteins, he and others needed a new way. So, while he was a graduate student, he helped McLafferty's research team develop a new approach for weighing intact proteins and their parts.

They called the method "top down." Instead of rebuilding the protein from its pieces—that is, from the bottom up—the researchers measured the intact protein first, then broke it apart.

According to Kelleher, top-down mass spectrometry requires a special "gas conversion" process that doesn't dismantle the original molecule. This allows researchers

to first collect data on the intact protein, then on its parts. The scientist who invented and used these methods shared the 2002 Nobel Prize in chemistry.

In addition to finding out how much a protein really weighs, Kelleher uses top-down mass spectrometry and custom computer technology to find the protein's gene and identify the chemical changes that help the protein do its job.

Or, in the case of proteins that don't work properly, he can try to figure out what went wrong. Both approaches could lead to new targets for drug development.

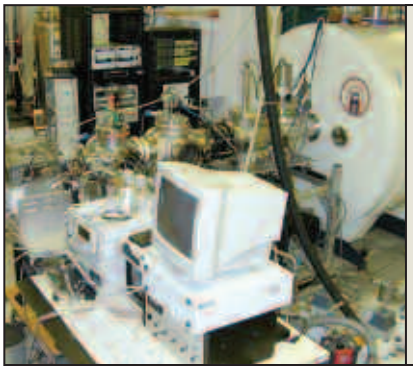
Machine Mechanic

Mass spectrometers are large, expensive machines, and you can't just go to a science supplier and buy one, especially the kind that can perform research tricks like top-down protein measurements.

So, Kelleher has gotten into the business of making them himself.

Don't confuse Kelleher with an inventor. But he's quick to point out that he knows how to find smart people who are.

Just like when he got a hand rebuilding a car engine in high school, Kelleher got help designing his mass spectrometer from an expert: Alan Marshall, a researcher at



NEIL KELLEHER

A very strong magnet (large white cylinder) inside this mass spectrometer helps Kelleher weigh tiny pieces of proteins very accurately.

Florida State University in Tallahassee, who developed the type of instrument Kelleher uses today.

Marshall, whose mass spectrometers hold world records for detail and accuracy, went a step further and even let Kelleher borrow a key item of equipment, a large magnet.

"I knew what I wanted, but I had never built a mass spectrometer this complicated," Kelleher says, acknowledging Marshall's generosity.

It wasn't just any magnet, and certainly not the kind you'd slap on the fridge door. Marshall's magnet pulled 180,000 times stronger than the Earth's magnetic field, weighed 4 tons, and was about as big as a Volkswagen Beetle!

A big, strong magnet is a vital part of a mass spectrometer. Sitting at the core of the machine, it sends charged ions spinning past detectors that collect information about the particles.

After test-driving the magnet, Kelleher bought one for his own lab and worked with Marshall to make a new machine that could perform all the steps of top-down mass spectrometry.

For the cost, Kelleher could have had a couple of new Ferraris.

In his lab, eight computer scientists team with Kelleher to improve the software that helps analyze the data—a task much more complicated and time-consuming than he had originally imagined.

"Neil is innovating all the time," says McLafferty, who occasionally drops in on his former student while visiting family in Illinois.

McLafferty says that Kelleher has made great strides to make top-down mass spectrometry easier for everyone by building better instrumentation and software and taking the science to new levels.

"What he's doing will really shake up the field," McLafferty predicts.

Challenging Course

Today, mass spectrometers are fairly common, but it didn't used to be that way. Back in McLafferty's day, very few academic researchers had their own instruments. While the machines may be more plentiful now, many scientists still use them mainly for the bottom-up approach and for studying small proteins or parts of larger ones.

Kelleher suspects that this will change in the next 5 years, as researchers start acquiring the tools and confidence to analyze larger proteins with mass spectrometry.

"The 2002 Nobel Prize really put mass spectrometry on a collision course with biology," says Kelleher, explaining that scientists from many different fields are now teaming up to use mass spectrometry as a way to explore questions about health and disease.

For example, Kelleher leads a project that brings together chemists, cell biologists, and physicists to better understand how molecules work together in living cells. In addition to mass spectrometry, the researchers use powerful imaging technologies that track individual molecules one by one.

This knowledge will ultimately help researchers learn how to retool molecular reactions to fix disease.

Trained in chemistry, Kelleher is now busy studying cells and human biology. Kelleher knows that he needs to bone

up on these areas in order to answer the questions that drive his intense curiosity.

"I have a lot to learn!" he readily admits.

The need for a little book learning won't stand in Kelleher's way, though. Just like being short didn't keep him from becoming a great basketball player…or from marrying a woman who stands nearly a foot taller than him.

Challenges of any sort have never been an obstacle, and Kelleher says they are actually a very important cog in the gears of progress. He adds that while scientists often only report the things that work, failed experiments are a normal part of discovery. To live in the world of science, you can't be put off by things that don't go your way, he explains, especially when the losses can outnumber the wins.

Similarly, scientists don't usually make a big discovery overnight. As in sports, where athletes only make it to the national level after winning a series of smaller tournaments, many research advances grow from a series of smaller findings made over a long period of time.

"When you see famous scientists talking about all the things they've discovered in 30 years," Kelleher says, "you think, 'WOW! I could never do that.'"

"But you have to remember that 30 years is a *really* long time!"

Still at the early stages of his career, Kelleher has already won a lot of tournaments, so to speak. He credits his wins to great coaches—scientific mentors who helped him make the team.

Now it's time for his own students to get in the game. Kelleher enthusiastically cheers them on from the sidelines and is always looking for great new players. Want to join? ■

"Sprechen Sie Deutsch?"

"Do you speak German?"

Not too long ago, many chemists did!

While most developed countries speak English as the first or second language, you may think it strange that American chemists once had to master German before they could get their degrees.

Why not French or Chinese?

Early chemists worked mostly in metals factories as metallurgists or in apothecary shops as pharmacists. Both jobs were big in Germany, which helped pay for training at technical schools and fostered science in the country.

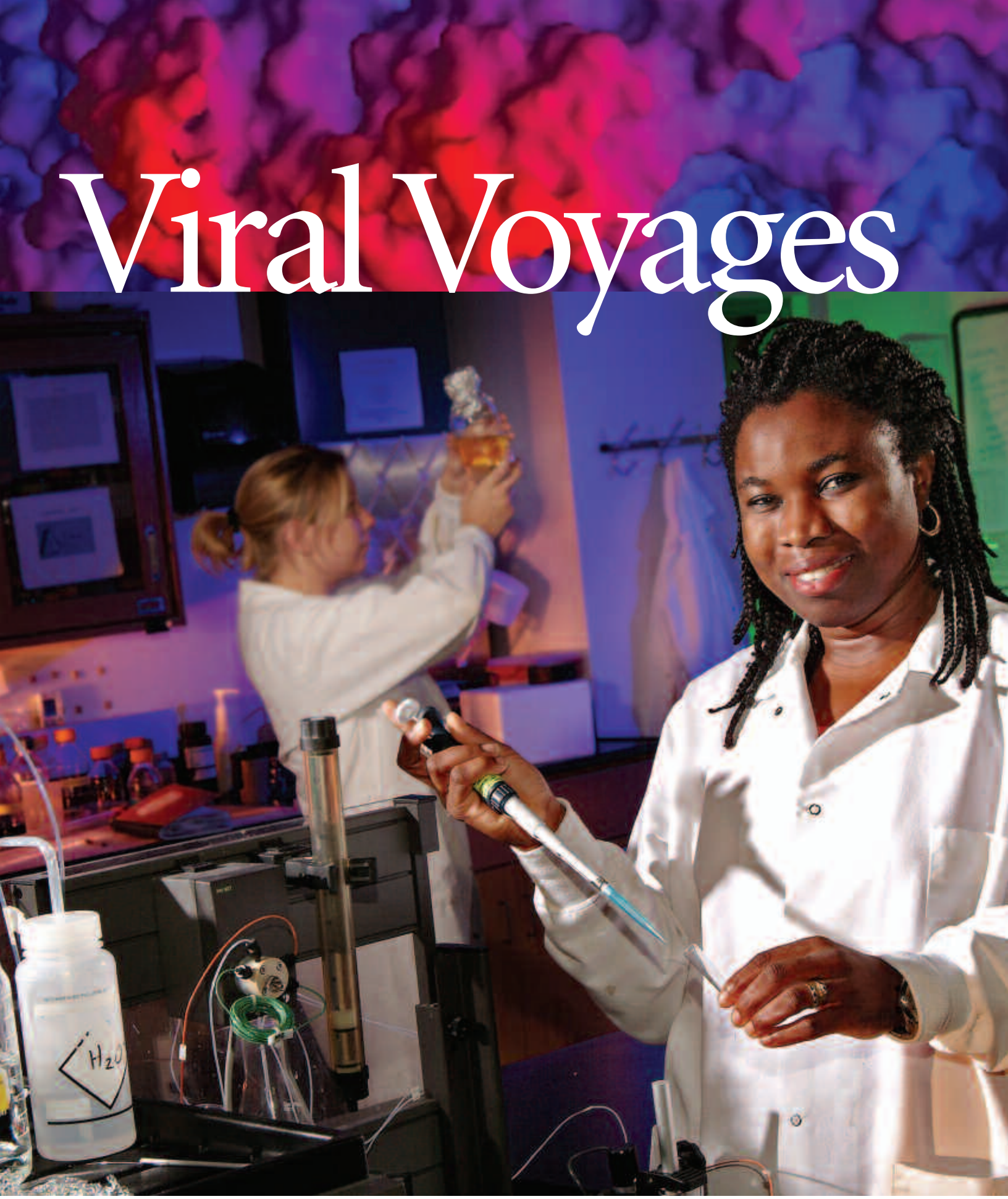
Those who wanted to do more than run the family business went on to a university. Unlike today, when even high school students conduct their own lab experiments, back then, university students usually only got to watch their teachers do all the hands-on work.

All that changed with a young German chemistry scholar, Justus von Liebig, who taught at a German university in 1824. Liebig realized the value of working in the lab as part of scientific training. He offered his students—some of whom traveled from Europe and the United States—the same chance. This sparked a revolution.

Historians credit Liebig for setting up the first real lab course in chemistry, and they call him one of the greatest chemistry teachers of all time. One German chemist who occasionally worked with Liebig was the first to convert an inorganic compound into an organic one. That chemist, Friedrich Wöhler, laid the foundation for what many college science students consider their toughest subject: organic chemistry.

Organic chemistry, in turn, led to another important development: synthetic dyes used to color fabrics and other textiles. Chemists educated by both Liebig and Wöhler dominated this field and helped make Germany a world leader in the dye industry.—*E.C.*

Viral Voyages



National Institute of General Medical Sciences

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

A RURAL 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.

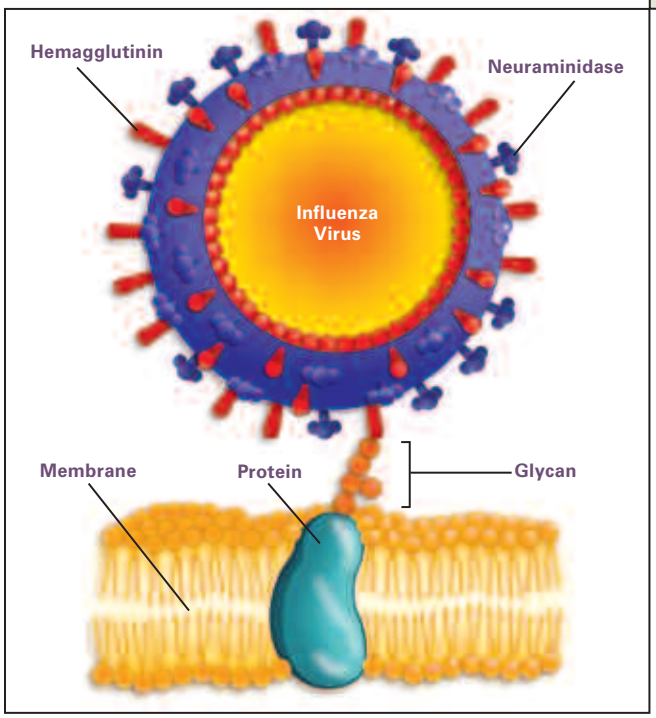
The work is especially timely given worldwide fear that avian influenza, or bird flu, will genetically change into a form that

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.



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.

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.

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.

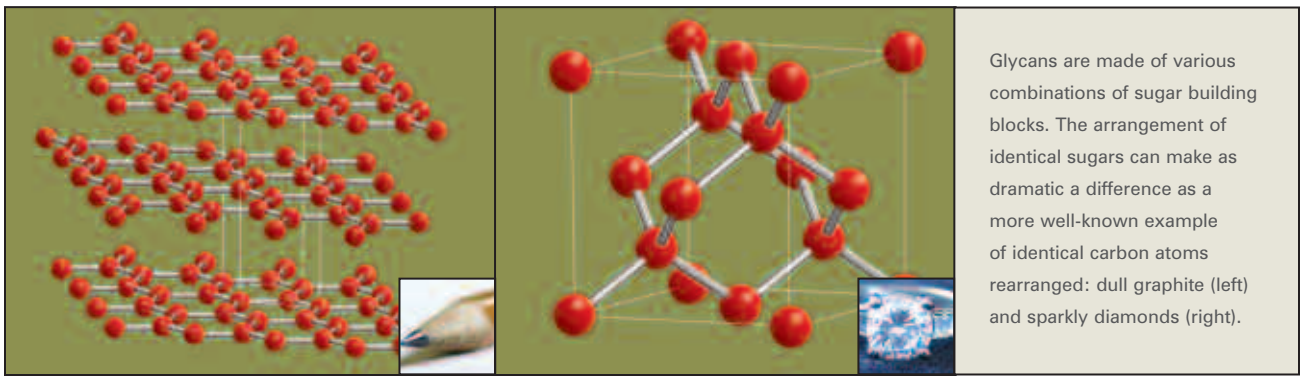
Take the case of influenza A, which infects cells by attaching to certain types of glycans. The glycan arrangement favored by a strain of influenza determines whether the virus will infect birds or people.

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.

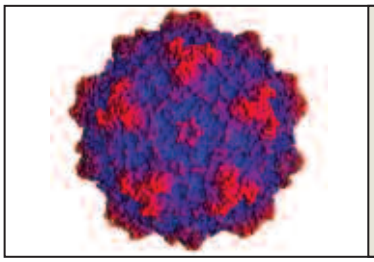
A few years ago, when Agbandje-McKenna was visiting a coworker in Spain, she learned some troubling news.



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.



MAVIS AGBANDJE-MCKENNA

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.

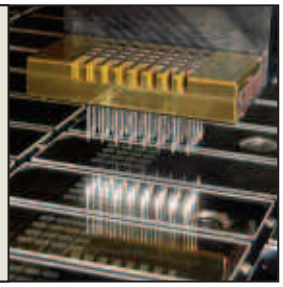
Counting Carbs

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.

Agbandje-McKenna used the first glycan array developed by the Consortium for Functional Genomics. Since then, the team has developed a new array, shown here, in which 264 different glycans are attached to a glass slide.



OLA BLIXT

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

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.

MAVIS AGBANDJE-MCKENNA

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.

DAVID BLANKENSHIP

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

MAVIS AGBANDJE-MCKENNA

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.

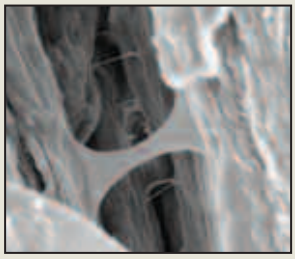
Health officials and policymakers are preparing plans and using modeling data that shows the impact of various interventions.—*A.Z.M.*

Bench to Bedside

Sticky Bones

Bone research dates back many centuries. Galileo, the 16th-century inventor of the telescope, reportedly published some of the first research on bones that explained why elephants need thicker bones than small animals.

Since then, thousands of other scientists have tried to understand the remarkable ability of bone to be both stiff and flexible. For the most part, researchers know that tough protein fibers coated with a thin layer of mineral crystals (mainly calcium and phosphate) make bones stiff.



GEORG FANTNER, PAUL HANSMA

In a surprise finding that may help explain how it can also be flexible, physicist **Paul Hansma** of the University of California, Santa Barbara, has discovered something completely new about bone.

Using a powerful microscope to measure the springiness of a tiny piece of bone sitting in a lab dish, Hansma discovered that a sticky "glue" held the bone together. Hansma thinks that the glue strands stretch like tiny rubber bands to prevent bone cracks.

He now wonders whether the gluey substance may be either missing or defective in some conditions that weaken bone, like osteoporosis.

The finding may also help answer why and how bones weaken with age. Young bones heal fast because they are still growing, but bone mineral density—the most common measure of bone growth—peaks around age 30. Immobilization due to a broken bone in an elderly person can lead to many other associated health problems, like serious infections. Hansma notes that more women die within a year of a hip fracture than after a heart attack.

He plans to continue to study the bone glue and its potential healing properties.—*Alison Davis*

Forget the Surgery?

Despite the fact that general anesthetics have been used since the 1800s, scientists still do not have a clear picture of how these powerful yet complicated drugs work in the brain. Anesthetics are truly multipurpose medicines: They relieve pain, cause loss of consciousness, and induce amnesia (memory loss).

In relatively rare cases, people undergoing surgery experience some but not all of the intended effects of anesthetic medicines. For example, despite being unable to move, some people are still aware of what is happening and may remember parts of the surgery.

Using rats as a research model, anesthesiologist **Michael Alkire** has uncovered new clues about why this happens. He found that the amygdala—a brain region involved in fear, anxiety, and other emotions—helps anesthetics wipe out memories.

In his lab at the University of California, Irvine, Alkire placed two groups of rats, one mildly anesthetized and the other untreated, in a lighted chamber facing a dark tunnel. If the rats entered the dark area, an environment rodents prefer, he gave them a brief electrical shock. The unanesthetized rats remembered this shock until the next day and quickly learned to stay in the safer, lighted environment.

However, those treated with the anesthetic drug sevoflurane behaved differently. Unable to remember the bad experience, these animals continued to enter the tunnel and receive a shock. Alkire then incapacitated the amygdalas of sevoflurane-treated rats and saw that they could remember, and avoid, the shock.

By pinpointing the amygdala's role in memory function during anesthesia, the results may help scientists develop ways to prevent awareness during surgery.
—*Kirstie Saltsman*

Chicken Medicine

Antibodies are the soldiers of our immune system, traveling through blood to defend our bodies against viruses, bacteria, and other germs that can make us sick. Their victory means we stay healthy.

Recognizing the healing power of antibodies, scientists several years ago found a way to make special versions called monoclonal antibodies that zoom in on certain types of unwanted cells.

Just like the antibodies in our body, monoclonal antibodies used as drugs block unhealthy molecular interactions, such as those among cancer cells that form tumors.

Currently, 17 monoclonal antibodies have been approved as drugs for treating cancer, arthritis, multiple sclerosis, and inflammatory bowel disease. Dozens more are on the horizon.

Researchers make these drugs by inserting the genes for antibody proteins into cultured animal cells. But purifying the antibodies from these cells takes a lot of time and money. Now, thanks to an unlikely source—chicken eggs—scientists may have a quicker and cheaper way.

Biologist **Lei Zhu** of Origen Therapeutics in Burlingame, California, inserted into chickens the gene that makes one particular monoclonal antibody. She added extra molecular instructions so that the antibody would only be produced in egg whites.

Extracting the monoclonal antibody from egg whites was simple and provided an abundant supply. What's more, lab tests showed that the chicken-made antibodies were even better at killing cancer cells than were antibodies made with traditional lab methods.

This more efficient approach, made possible by government funding to a small biotechnology company, may lead to less expensive medicine for patients.—*A.D.*

Cancer Drug Fights Early Aging Disease

Most elementary schoolers don't need to worry about wrinkles, brittle bones, stiff joints, and a failing heart. But for some who have a very rare, early aging disorder called progeria, these symptoms begin to appear within a year after birth and usually cause fatal heart attacks and strokes in the teen years.

There is no cure for progeria, which is caused by a genetic error that disfigures the protective covering that envelops a cell's command center, or nucleus. Scientists have suspected that the nucleus becomes misshapen because a molecule called farnesyl sticks to a certain key protein rather than being removed, as happens in healthy cells.

Farnesyl molecules are also found on a protein connected to cancer, and drugs that block farnesyls are currently being tested as treatments for several forms of cancer.

Cell biologist **Susan Michaelis** of the Johns Hopkins University in Baltimore, Maryland, has now discovered that the same drugs, called farnesyl transferase inhibitors, may help treat progeria.

Michaelis added farnesyl transferase inhibitors to lab-grown cells that had the same molecular defect as do the cells of children with progeria. She discovered that the drug treatment returned the nuclei to their normal shape.

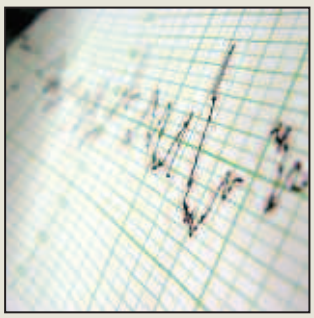
Researchers have observed that farnesyl transferase inhibitors appear to be safe and have no toxic side effects in cancer patients who have taken these drugs in clinical trials. While further studies are needed to confirm that Michaelis' approach works as well in people as it does in lab cells, the findings may offer new hope to children with progeria.—*K.S.*

Heart Alert

After leaving the hospital, heart attack patients and those with a type of chest pain called angina are often prescribed medicines called beta-blockers. These drugs slow pulse and lower blood pressure. Beta-blockers can also correct faulty nerve conduction that causes the heart to beat out of rhythm.

Despite their common use, a new experiment shows that beta-blockers may harm people who have a particular genetic profile.

Howard McLeod of the Washington University School of Medicine in St. Louis, Missouri, looked very closely at the sequence of two genes known to interact with beta-blockers. The clinical pharmacologist and his team read the sequences in more than 700 patients hospitalized for heart attacks or unstable angina.

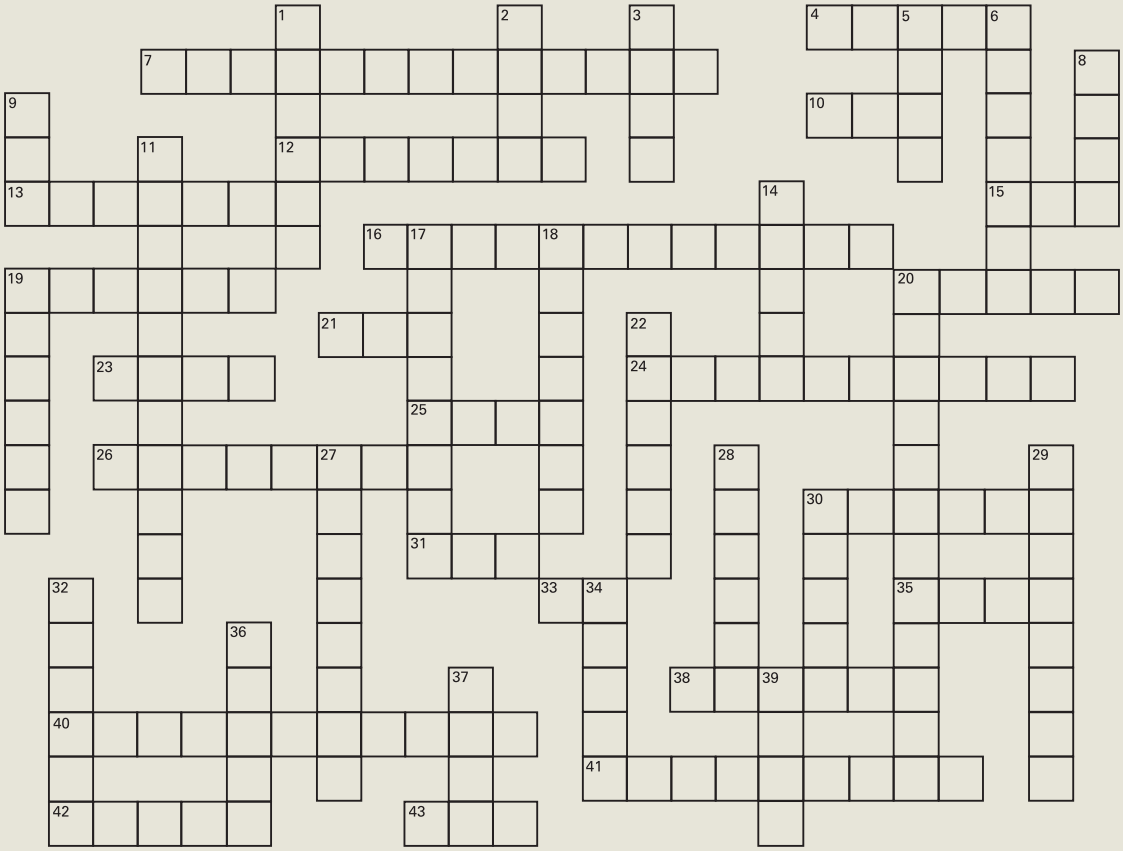


They discovered that people who took beta-blockers and who had a particular variation in one of these genes were about three times more likely to die within 3 years as were those who had other versions of the gene or were not taking beta-blockers.

McLeod and his team plan a larger study of 4,500 heart patients across the country to confirm the findings. If further research generates similar results, doctors may want to find out which version of the gene a person has before prescribing beta-blockers.—*A.D.*

These stories describe NIGMS-funded medical research projects. Although only the lead researchers are named, science is a team sport and it is important to realize that many researchers work together to carry out these studies.

The Last Word



ACROSS

4. warrior's shield
7. teamwork
10. antlered animal
12. molecule maker
13. Mavis' homeland
15. frozen water
16. biological sugar
19. past thought
20. sweet substance
21. purchase
23. sticky stuff
24. medicine before surgery
25. not up
26. early aging disease
30. language for chemists
31. gorilla, for example
33. fam. rm. appliance
35. very small
38. what viruses do
40. heartprotector
41. three-dimensional protein form
42. Halloween visitor
43. virus type, for short

DOWN

1. branched carbohydrate
2. weight, for proteins
3. skeleton part
5. produce
6. wordy pastime
8. lemon cousin
9. charged particle
11. type of anesthesia
14. biologist Agbandje-McKenna
17. brain area for fear and anxiety
18. Wöhler started this chemistry
19. mass spectrometer part
20. protein-weighing machine
22. virus shell
27. protein docking station
28. unit for measuring proteins
29. immune system soldier
30. complain
32. he liked hands-on science
34. master infector
36. big science prize
37. chemist Kelleher
39. home for eyes, nose, and mouth

Puzzle answers can be found at
http://www.nigms.nih.gov/findings/

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