

Um dasjenige Gen zu identifizieren, das für die Produktion eines spezifischen Proteins und dessen vielen Formen zuständig ist, wird das Protein in der Regel von den Wissenschaftler in kleine Teile aufgebrochen, die dann abgesehen, spezifisch analysiert werden. Durch Abzug der die dann abgesehen, spezifisch analysiert werden.

# The Humpty Dump





# Humpty Dilemma

**By Emily Carlson**

**E**ver 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.

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

**“Like Humpty Dumpty, we generally can’t put a protein completely back together again.”**



# The Humpty Dumpty Dilemma



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

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

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



NEIL KELLEHER

remembers jokingly threatening that Kelleher couldn't have his Ph.D. degree until he beat a good golfer among McLafferty's coworkers.

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

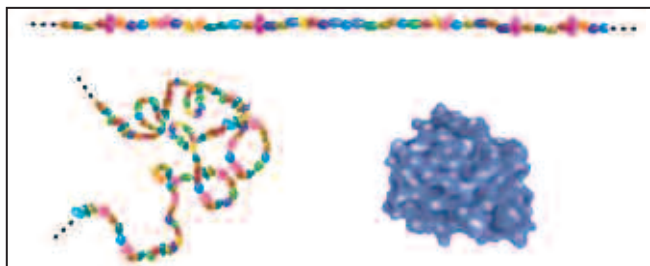
Proteins are central to life. Our bodies build them using cellular machines that read our genetic instructions and then assemble chains of building blocks called amino acids. For a protein to do its job properly, the amino acid chains must fold themselves into exactly the right shape. An error in the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



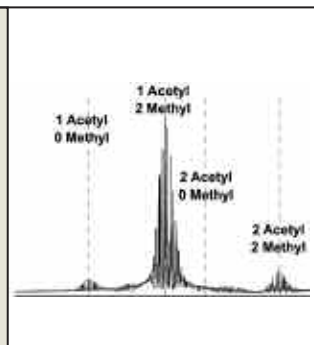
50 (or more) different protein forms! Some of the variety comes from chemical changes that alter a protein after its gene has been read, leading to a slightly different version of that protein.

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.



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.

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.

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

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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

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.

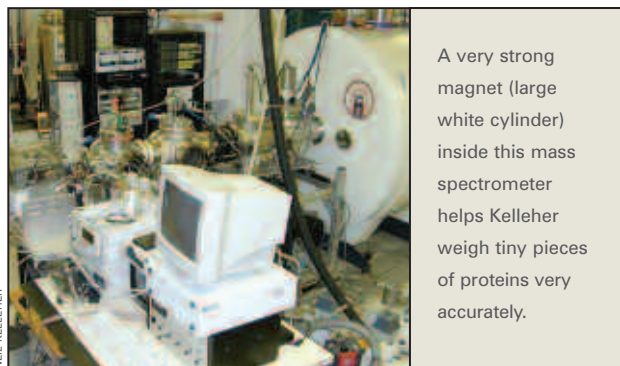
Kelleher suspects that this will change in the next 5 years, as researchers start acquiring the tools and confidence to analyze larger proteins with mass spectrometry.

"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



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!



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.