

Inside Science: Life in the Lab

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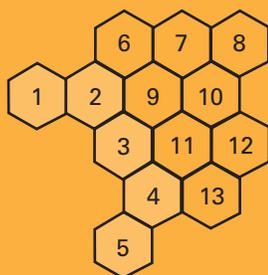
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Up Close With

Marc Zimmer

COMPUTATIONAL CHEMIST

“Chemistry is a bit like a language. The best way to learn it is to immerse yourself and get involved in a research project.”

CAREER ALTERNATIVE

Game warden

BEST ADVENTURE

Hitchhiking across Africa

FUTURE GOAL

Publishing a novel

LIKES TO READ

**Trashy novels,
South African history**

BOB MACDONNELL



Green Light

BY EMILY CARLSON

On a moonless November night, when the water shined brighter than anything in the sky, a group of college students kayaked off the coast of Puerto Rico. As the students scooped their paddles through the water, stringy threads of light appeared beneath their boats.

Shuang Song, one of those students from Connecticut College, pulled her hand through the crystal clear water, leaving a wake of whitish-blue light. Like a shadow, the glow followed the boats across the bay.

The experience left the students in awe—of science. At the heart of this light show was a chemical reaction that caused tiny creatures in the water to flash blue when disturbed by nighttime boaters or swimmers.

The students already knew this. During the months leading up to the excursion, they had taken a chemistry class called “Glow,” where they learned about molecules that light up organisms in a rainbow of colors.

“We learned a lot about dinoflagellates before going on that trip,” says Song. “So it was really cool to see them in person.”

For Marc Zimmer, the students’ chaperone and teacher, the exotic field trip achieved its goal. It showed his students that learning science isn’t just about reading textbooks or listening to lectures—it’s about doing.

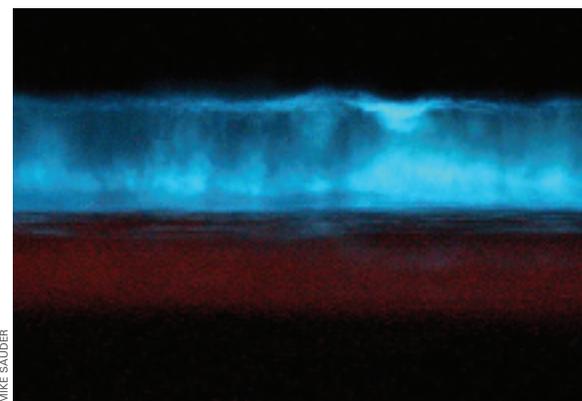
Just Doing It

Unlike his students, Zimmer learned this lesson the hard way.

Growing up in a small, industrial town in South Africa, Zimmer enjoyed hiking into the mountains and seeing rhinos, buffalo and lions. His mother wanted him to become a doctor, but Zimmer had other plans. He wanted to be a game warden.

He imagined spending his days tending to big game—protecting them from the dangers of disease and poaching—and his nights listening to their wails across the wilderness. “There was a freedom associated with being a warden,” he says.

So when Zimmer went to college, he took the first step toward pursuing his dream: He planned to major in biology and get a game warden certificate. But he hit a few snags.

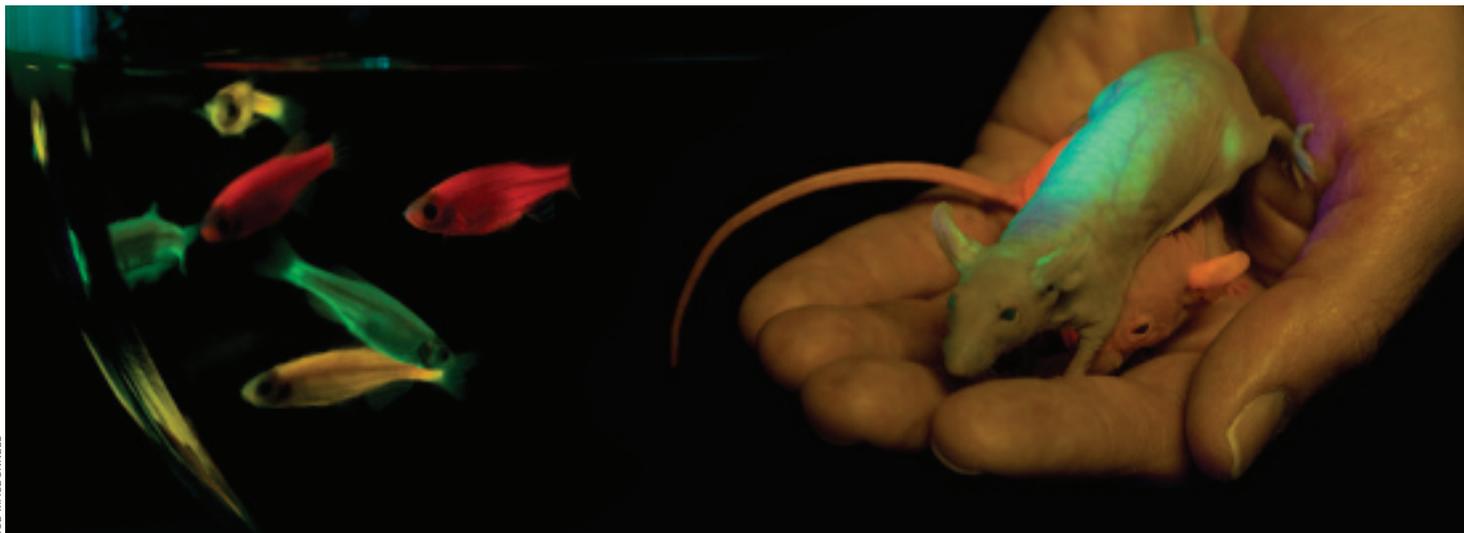


MIKE SAUBER

As waves crash along the shore, tiny creatures called dinoflagellates glow blue in the water.



We can see things on the computer that we can't



BOB MACDONNELL

Zimmer's family pets glow in the dark in response to ultraviolet light.

For starters, he flunked his required botany class because, he says, his teacher was “incredibly boring.” Next, he took a required chemistry course. To his surprise, the course opened up a world of molecules just as vast and magnificent as the African savannah. Zimmer switched majors.

Studying molecules, says Zimmer, offered the same adventure as studying how an infection might spread through a giraffe population. “Both require detective work,” he adds.

But there was still a major difference: location. Instead of learning in the lab—or, as a warden-in-training, in the bush—Zimmer sat in large lecture halls and listened to professors talk about science.

“I was given a lot of material in a pretty dry format and told to learn it,” recalls Zimmer. It wasn't until

he got involved in research projects that he excelled—and realized the importance of hands-on learning.

Now 47, Zimmer uses computers to study the protein molecules that help jellyfish glow in the dark. And he makes sure he gets his students into the act as early as possible.

Recalling his own experience, he says, “I think you have a much better chance of getting students to learn something if they can see the relevance and the excitement and the fun of it.”

That's especially true for students enrolled in Zimmer's 8 a.m. introductory chemistry course.

To keep the students awake, Zimmer performs all sorts of loud and colorful chemistry demonstrations. He blows up hydrogen balloons and makes foam fountains, which he claims were one reason he majored in chemistry.

But the real show-stoppers are his family's pets—two mice and a bowl of zebrafish.

When Zimmer turns off the lights, his show begins. Under an ultraviolet light, the white mice glow green

and red, and the fish go from gray to bright orange or yellow. Geneticists engineered these animals to have fluorescent proteins in their cells, a harmless process that entertains (and educates) students.

Zimmer uses the animals to teach another popular early-morning class, “Glow.”

It Glows

The glowing pet tricks help Zimmer explain his research on bioluminescence, a natural phenomenon in which living organisms convert chemical energy to light energy.

Many species have this capability. Most are marine organisms, but some—like the firefly and the glow-worm—live on land. They fluoresce for many different reasons: to spook predators, lure prey, attract mates and even communicate.

For centuries, fishermen off the west coast of North America noticed that some of the jellyfish gleamed in the water. When researchers took a closer look, they found small organs along the rim of the jellyfish that sparked green pinpricks of light.

According to Zimmer, the scientific story of bioluminescence is just as

FIND MORE

Watch jellyfish glow

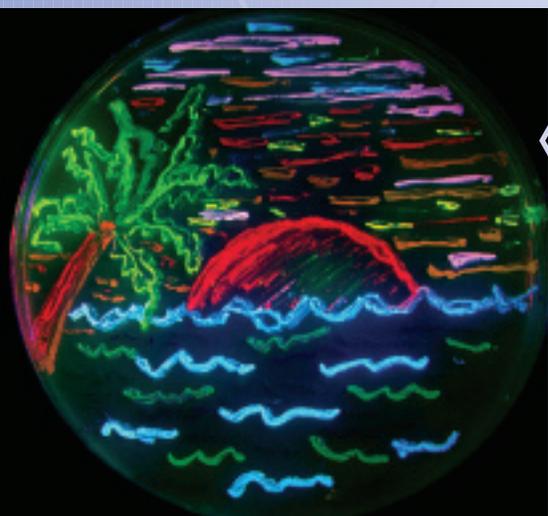
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The Oscars of Chemistry

Like a kid on Christmas morning, Marc Zimmer woke up in sheer excitement on October 8, 2008. Before dawn, he logged onto his computer to watch a live video feed from Stockholm, Sweden, announcing the 2008 Nobel Prize in chemistry.



On that fall morning, the Nobel Foundation broadcast that the chemistry prize would go to Osamu Shimomura, Martin Chalfie and Roger Tsien for “the discovery and development of the green fluorescent protein (GFP).”

Considered the pinnacle of scientific achievement, Nobel Prizes honor discoveries in different fields that have profoundly changed the way we think and live.

Zimmer had a hunch that the 2008 chemistry prize might go to the GFP discovery. Considered an expert on the topic, Zimmer had been contacted by the Nobel Foundation months before the announcement to give the committee details about GFP and groundbreaking research on it.

(Shhh...Zimmer can't share the specifics for 50 years!)

Zimmer was not among the winners (he didn't expect to be), but nonetheless the prize put his field of research in the international spotlight.

And for Zimmer, the news got even better. As a GFP historian and scientist, he was invited to attend the lavish award ceremony in Stockholm. He hob-knobbed with Nobel laureates, met Swedish royalty and ate new foods like reindeer pâté.

In an article he wrote about the trip, Zimmer reports, “The fact that GFP was the basis of a Nobel Prize in chemistry, and that I could be part of the excitement associated with its award, was a dream come true.”—*E.C.*

continued from page 5

Because the discovery of GFP has led to so many potential applications, it was honored with the 2008 Nobel Prize in chemistry (see “The Oscars of Chemistry,” left).

Making Light of Things

Zimmer has spent the last 15 years studying GFP in his computer lab at Connecticut College. He's most interested in the protein's three-dimensional structure.

Shaped like a soda can, GFP is made up of 238 amino acids. Just three of these amino acids come together in the center to form the chromophore—the protein's light source (see image, page 5).

Zimmer wants to know, step-by-step, how this part of GFP helps the protein give off green light. To do this, he uses computers.

“We can see things on the computer that we really can't see in real life because they occur too fast,” he explains.

From start to finish, the chromophore takes its unique shape in about an hour. Compared to other molecular processes, this is pretty slow. But Zimmer says it's still too fast for traditional structure determination methods.

So Zimmer uses information about other fluorescent proteins to calculate each twist and turn of GFP's chromophore formation. This precise sequence, he says, could eventually allow researchers to turn fluorescent proteins on or off whenever needed.

Zimmer is also using this structural information to design brighter proteins, particularly ones that glow red. Unlike other colors, shades of red give off the lowest amount of energy, making these proteins much safer to use in living tissues.

Reds also have the longest wavelength, which means they can

lead to different approaches to problem solving.

penetrate deeper and still be visible. That's why you see only red light when you hold your hand over a flashlight—the colors with shorter wavelengths get absorbed by your flesh.

In addition to improving the properties of fluorescent proteins, Zimmer is studying the structure of a bioluminescent protein found in corals as well as the one that turns fireflies into beacons of light.

Science Club

While many scientists spend their research careers studying just one aspect of fluorescence or one particular protein, Zimmer bounces from project to project. It's partly because he likes to work on many things at once: He's often on the computer, watching TV and listening to music at the same time.

But there's another reason. Zimmer sets up smaller, shorter studies to get students involved in research.

Some of his students work in the lab for class credit during a school semester, while others get paid for it during the summer. Students can make up to \$3,500, but they must work 9 hours a day for 10 weeks. Most of the student projects focus on GFP and other fluorescent proteins.

Zimmer works closely with the students, especially in the beginning, to make sure they're familiar with the basic concepts and equipment. Some students think Zimmer lives on campus, just like them, because they can always find him in class or in his lab or office.

"There has never been a time when I tried approaching Marc and he wasn't there," says sophomore Rabia Nasir. For two and a half hours each week one semester, she downloaded structural details about many different types of fluorescent proteins to compare and modify them.

Senior Luisa Dickson has spent two "intense" summers working in Zimmer's lab, where she calculated specific measurements for more than 1,000 GFP molecules. "Even though this sounds tedious," she says, "I enjoyed every moment."

Her work paid off in other ways, too. The findings contributed to two larger studies on the GFP chromophore structure that were described in scientific journals, making this undergraduate a published author.

And she's not the only one. Of the 56 students who have worked with Zimmer, 34 have co-authored publications and 35 have presented talks or posters at scientific meetings.

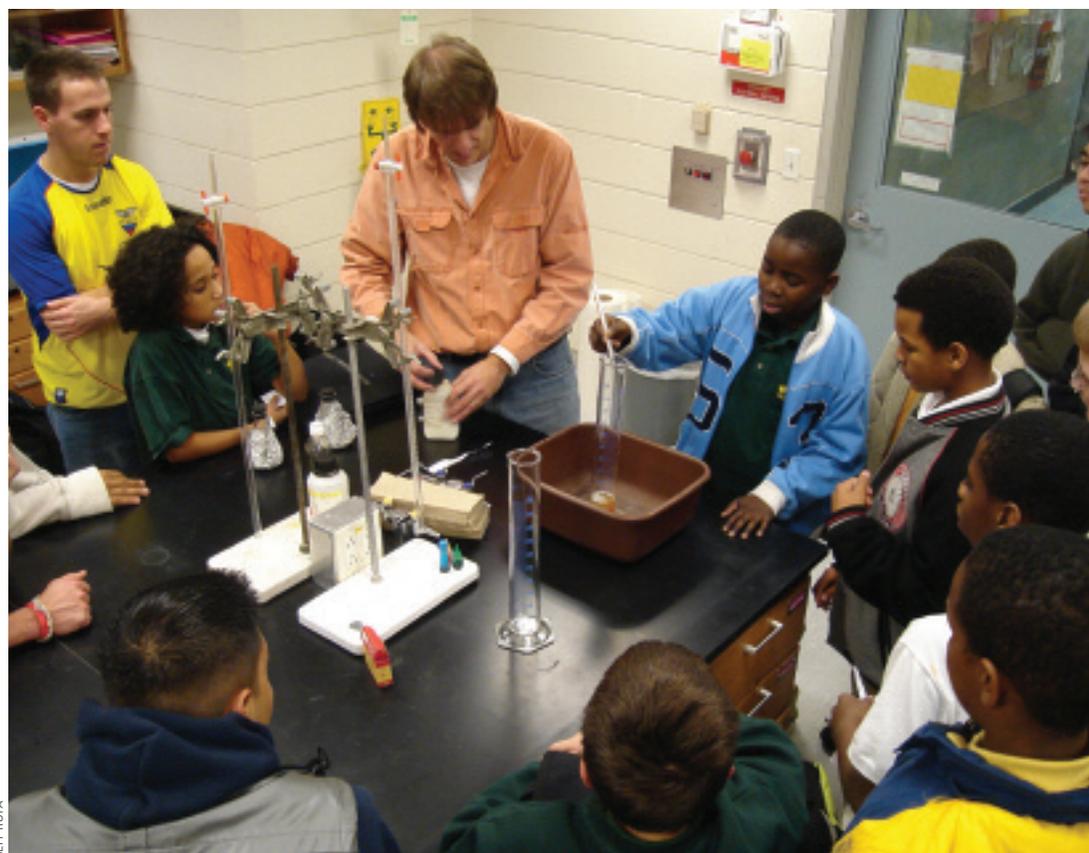
About half of all his students have gone on to medical school or a graduate program in the sciences.

Recruiting Chemists

Zimmer says that students often don't pursue chemistry because they think it will be boring or won't lead to tangible careers, as opposed to fields like nursing or engineering. But chemistry, he counters, offers plenty of job opportunities.

"One of the big challenges for [scientists] is to go out to middle schools

story continues on page 8



JEFF RUTA

Zimmer travels to middle schools and high schools to show students that chemistry can be exciting and fun.

FIND MORE @

Check out Marc Zimmer's article about the GFP Nobel Prize at <http://www.nigms.nih.gov/findings>



Up Close With

Lola Eniola-Adefeso

CHEMICAL ENGINEER

“What I like best about research is that it allows me to solve mysteries.”

SECRET WISH

To live another life as a geographer

FAVORITE MOVIE

The Lord of the Rings: The Return of the King “it shows human courage”

FAVORITE PASTIME

Cooking “I’m famous for my mackerel stew!”

FAVORITE BOOKS

Nancy Drew mysteries

SCOTT GALVIN





SCOTT GALVIN

Special Delivery

BY ALISA ZAPP MACHALEK

Thick bands wrap around your ribs, tightening and squeezing the air from your lungs. Cords coil around your neck and arms, gripping, suffocating. Nausea and dizziness wash over you. Cold beads of sweat wet your forehead. Your vision narrows, then everything goes black.

You have just had a heart attack.

Although more people survive heart attacks today than did years ago, coronary heart disease is still the number-one killer in the United States. Addressing heart disease is also a research focus for Omolola (“Lola”) Eniola-Adefeso, a chemical engineer at the University of Michigan in Ann Arbor.

Eniola-Adefeso (pronounced ah-DAY-feh-so), 32, is developing a way to deliver heart disease medicines right to the places they’re needed—the blood vessels near the heart—and to do so without surgery.

Her strategy relies on an understanding of white blood cells, one of the body’s first lines of defense against illness and infection.

“I am trying to create artificial white blood cells to deliver medicines,” says Eniola-Adefeso. “These drug-filled carriers would navigate through the bloodstream and move into diseased tissues just like white cells do. Then they’d slowly release their drugs.”



Heart disease kills more Americans than any other disease.

Growing Up Early

Eniola-Adefeso’s special interest in heart disease stems in part from the death of her father five years ago from the condition. For as far back as Eniola-Adefeso can remember, he inspired and nurtured her interest in science through storytelling, especially about geography, his favorite topic. He also encouraged what Eniola-Adefeso calls her “profound, sometimes bizarre” questions about the world around her.

Eniola-Adefeso spent her childhood and early teen years with her family in Nigeria, where she describes the educational system as “fabulous, but only through high school.” So, like her two older siblings, she traveled to



Being one of the very first people to observe something—

the United States at the age of 16 to go to college.

The three siblings lived together in Maryland while their parents and two younger siblings remained in Nigeria.

“We grew up early,” she remembers. “We were working, going to school and renting an apartment—it was an adventure!”

The experience shaped not only her own life path, but also the advice she gives to others.

Eniola-Adefeso says she took a “non-glamorous route” with her education. She started out in a community college before attending a four-year college, the University of Maryland, Baltimore County (UMBC).

“By taking a small school path, I learned you can find your way to

anything if you have the desire for it and stay focused,” she says.

Always intensely curious about the human body and driven by a desire to help people, Eniola-Adefeso was drawn to a career in medicine. That was until she took college biology, which drove her nuts.

“[College biology] didn’t have enough numbers [for me],” she remembers.

Soon afterward, Eniola-Adefeso switched her major to chemical engineering. The move satisfied her desire for numerical explanations and harmonized her dual loves of chemistry and math.

“Chemical engineering gave me the tools to answer some of the questions I had growing up—things like ‘Why does heat transfer?’ and ‘How do fluids move?’” she says.

Eniola-Adefeso got hooked on research when she was a junior in college. She was a member of the first class of students at UMBC to participate in the Minority Access to Research Careers (MARC) program (see “Making a MARC,” page 14).

For Eniola-Adefeso, research had an instant appeal. “Being one of the very first people to observe something—it’s very addictive,” she says.

She enjoyed research so much that she decided to apply to graduate school. Knowing she could join a program that would pay her tuition and other expenses only made the choice more appealing.

“When you’re 19 or 20, that’s like, ‘Wow! How cool!’” she says.

Unintended Consequences

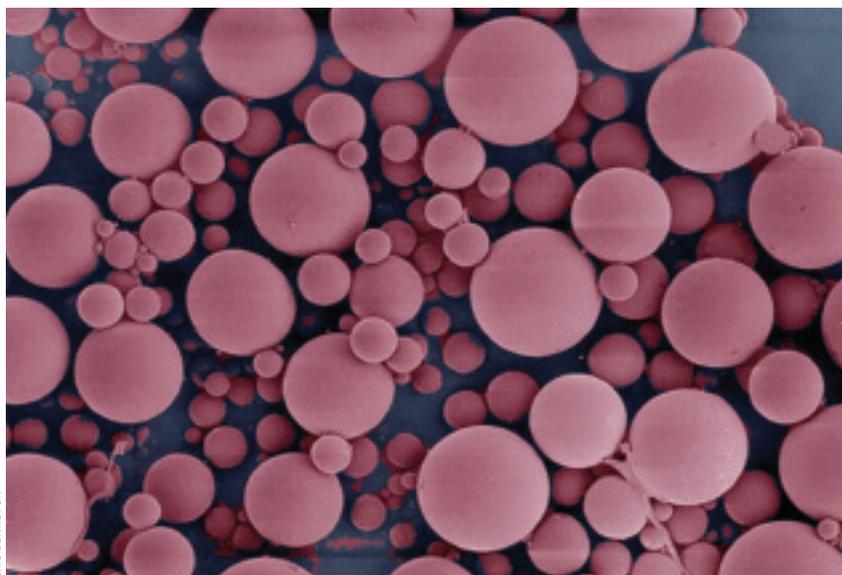
Right now, there are more than 200 different medicines for treating heart disease, and most of them are pills that need to be swallowed. But medicines that enter through the mouth have to navigate the digestive system to get into the bloodstream. Then they have to be ferried throughout the body. During this process, the drugs can leak into the liver, kidneys, fat, muscles and other organs.

Eventually, only a portion of the original dose makes it to the target tissue.

There are two major problems with this, Eniola-Adefeso says.

First, it’s inefficient.

Second, it sometimes causes side effects. When drugs saturate the body, rather than just the problem area, they can have unintended consequences. For example, a notorious side effect of chemotherapy is hair loss. This occurs because cancer drugs affect not only the fast-dividing



ERIC JOHNSTON

Lined up next to each other, 100 of these drug-filled beads would fit within a millimeter.

FIND MORE



Watch an interview with **Lola Eniola-Adefeso**

<http://www.nigms.nih.gov/findings>

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"They always move around, defending our tissues just like the U.S. Coast Guard patrols the nation's shorelines."

When there is an infection or disease in the body, nearby blood vessels send out chemical distress signals. Like superheroes, neutrophils sense the signal and spring into action. They exchange their normal, spherical appearance for an aggressive, action-oriented shape. They manufacture sticky proteins and thrust them through their outer membrane as grappling hooks to connect with specialized molecules on the blood vessel surface.

Grabbing onto vessels slows neutrophils down, enabling them to pull out of the bloodstream. Then the cells slip through tiny holes in the vessel wall and enter the damaged tissue. They confront the threat by surrounding it, spraying it with poison and digesting it.

Eniola-Adefeso is designing her beads to accomplish the same job.

To understand the journey her drug carriers will take, Eniola-Adefeso is carefully studying the human circulatory system.

"Your blood vessels are like rivers," she says. "Some flow smoothly and slowly. Others are fast and turbulent."

In vessels exiting the heart, blood churns rapidly and pulses to the beat of the heart. As vessels get smaller and further from the heart, blood flow becomes smooth and constant, she explains.

Naturally, plastic beads that deliver medicine through a tranquil river blood supply require different properties than those heading for churning rapids.

Making a MARC

What's the best way to solve a complicated problem?

Get a bunch of different people to work on it together.



Research has shown that the diverse ideas, approaches and experiences of a group produce a creative energy and breadth exceeding even that of an expert working on his or her own.

That concept is key to the National Institute of General Medical Sciences' Minority Access to Research Careers (MARC) program. The goal of this program is to increase the number of scientists from groups that are underrepresented in research careers and help the scientific workforce reflect the diversity of the U.S. population.

Lola Eniola-Adefeso (see "Special Delivery," page 10) launched her scientific career as a MARC student at the University of Maryland, Baltimore County. The program there provides two years of research experience, special courses and seminars and lots of academic coaching and career guidance. The program also gives funds for tuition, stipends for living expenses and travel to scientific meetings where students can present their research and meet other scientists.

A number of MARC students go on to Ph.D. programs where tuition, stipends and other fees are also paid by the government.

What made the biggest impression on Eniola-Adefeso was the required MARC course in bioethics. It dealt with issues like whether and when it is acceptable to conduct research on humans or animals.

"It was very useful," she says. "I would not have taken it if it wasn't required for the MARC program, but now it really shapes the way I think about research."—A.Z.M.

artificial white blood cells to deliver medicines.



Also, she adds, targeting different diseases means targeting different vessels.

"If we're going after cancer, we need to look at the sort of vessels that are affected by [cancer] rather than those affected by atherosclerosis," she says. Atherosclerosis, or thickening of the arteries, can begin in early adolescence and is a common cause of heart attacks and sudden death later in life.

Creating Chemistry

In addition to designing drug carriers with particular vessels in mind, Eniola-Adefeso must correctly mimic the chemical connections between neutrophils and a blood vessel wall. To encourage the drug carriers to behave just like neutrophils, Eniola-Adefeso is trying to figure out how to cover them with the same sticky proteins that the white cells display during their superhero stunts.

It's not easy, she says, because the types and combinations of proteins on blood cells and vessel walls differ depending on the medical condition and location in the body.

If Eniola-Adefeso puts the wrong proteins onto these beads, they will misbehave—they could stick too tightly to a vessel wall and never migrate into damaged tissue. Or they might not stick well enough to resist being pulled off by the rush of passing blood.

Eniola-Adefeso is also focused on the material she uses to construct her beads. She aims to combine the properties of plastic and paper.

"Think about plastic grocery bags. They can live in a landfill for decades

before they break down," she says. "In contrast, paper towels start breaking down as soon as they are exposed to water."

"Our bodies are mostly water," she continues, "so we need a material that does not dissolve in water, but that will slowly fall apart to let out the medicine inside."

It's the same theory as timed-release cold capsules. But instead of delivering drugs over a period of 12 or 24 hours, Eniola-Adefeso wants to deliver them at a desired rate for much longer.

"Based on the type of material we use, we can design particles to degrade in days, months or even years," she says.

This would greatly enhance the treatment of long-term conditions like heart disease, cancer or AIDS, to name just a few.

There are lots of materials to choose from, Eniola-Adefeso says. Her favorite is called PLGA, an abbreviation for a long chain made up of repeated units of two chemical building blocks. By altering the relative quantities of each chemical unit, she can control how slowly the material degrades.

Because PLGA is compatible with living tissue and its properties can be tailored, it is already used in a variety of biomedical devices including sutures, skin grafts and bone implants.

Dr. Engineer

Eniola-Adefeso feels lucky that she found a job that allows her to use engineering principles to solve medical questions.

"Engineering is not limited to building pumps, bridges and equipment, but it's applicable to biology," she says,

story continues on page 16



Eniola-Adefeso's medicine-filled beads combine the properties of paper and plastic.



A new genome-reading method scans DNA like words in a book.

Reading DNA Like a Book

You know that DNA “letters” spell out instructions to RNA, which makes proteins. But how do slightly different DNA spellings of genes translate to the differences that makes each of us unique?

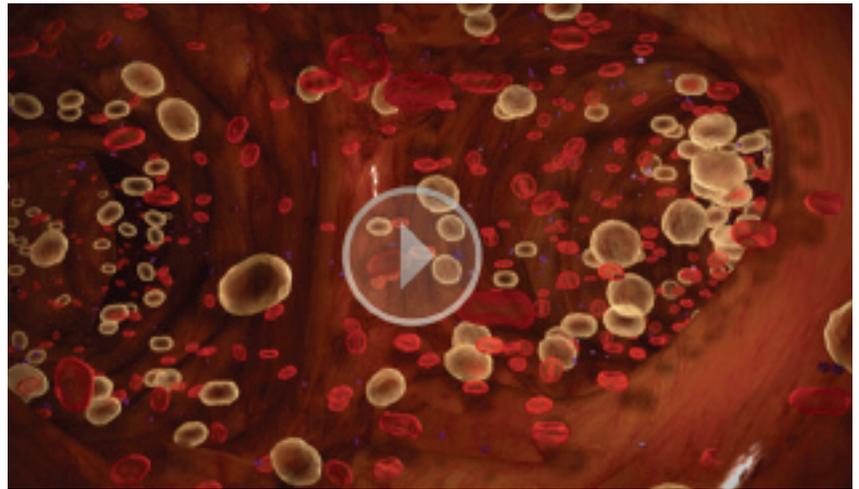
One way researchers are uncovering the meanings in our genes is by comparing human gene sequences to each other or to those of animals, which share a good amount of our DNA sequence.

Now, scientists have tweaked a computerized technique that scans the text in books to scan DNA instead. When all punctuation and spaces are removed from the text of a book, the sequence of alphabetic letters resembles the gene order of a genome.

Chemist **Sung-Hou Kim** of the University of California, Berkeley, used the method to create a dictionary of all adjacent DNA “words” in various genomes. He then counted how often the word features repeated.

When Kim tested his genome-scanning technique on actual online books, he discovered that the method was more successful at identifying related books than other text-scanning methods that searched for the frequency of real words. —A.D.

Blood vessels are like rivers.



Watch blood cells flowing through a vein at <http://www.nigms.nih.gov/findings>.

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“When I finally realized that, I found my own way to be a doctor without being a medical doctor.”

When she’s not working in the lab or spending time with her husband and infant son, Eniola-Adefeso loves to cook.

“I do all sorts of cooking,” she says, adding that she is partial to ethnic cuisines, especially Thai.

She is also particularly fond of seafood.

“Any which way I can make seafood, I go after it,” she says. “I’m a pescetarian—a vegetarian who eats fish.”

Eniola-Adefeso is known for her mackerel stew. “I didn’t realize how good it was until my college roommates showed up with cans of fish and asked me to make it,” she laughs.

She also collects Nancy Drew books and has about 250 of them, including the entire original series.

“I really identify with Nancy,” Eniola-Adefeso says. “She is a smart, powerful character who does good things—solves crimes and brings the bad guys to justice—and has fun.”

She also sees the books as a fictional reflection of her work.

“What I like best about research is that it allows me to solve mysteries,” she says. “I’m a Nancy Drew at heart. In the lab, I’m always trying to solve mysteries.”

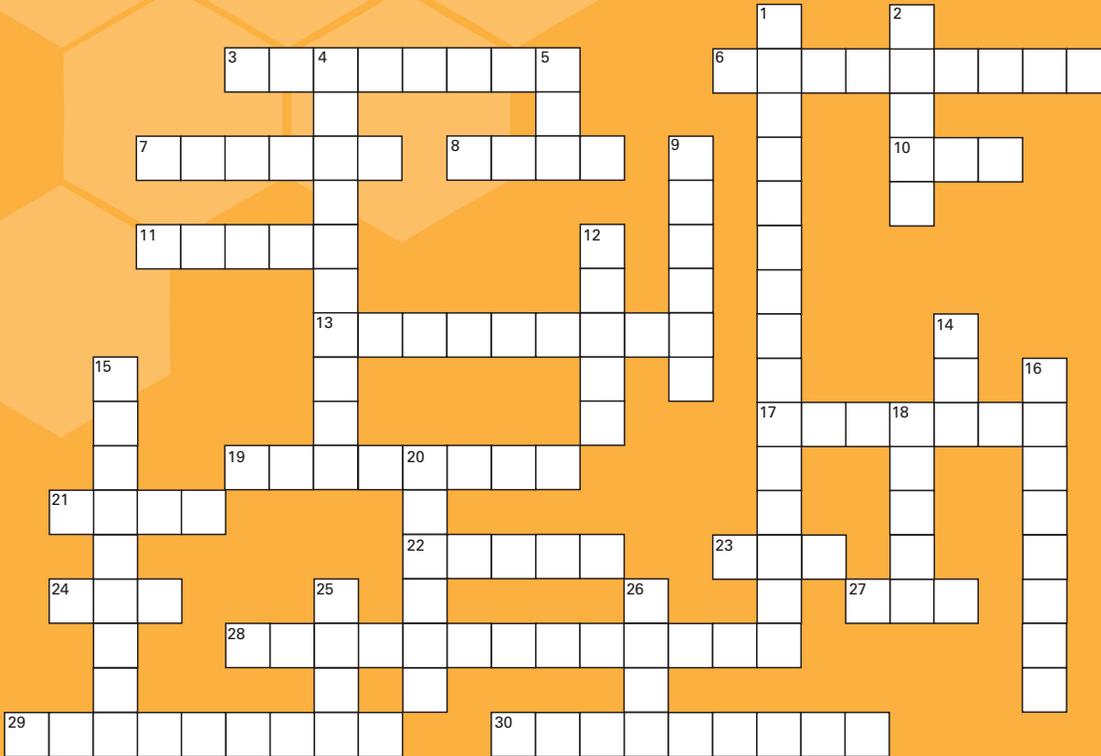
“And the ultimate mystery,” she says, pointing to herself, “is the human body.” ●●●

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Learn about other NIGMS research training programs at <http://www.nigms.nih.gov/Training/Overview>

EXPLORE IT PUZZLE IT FIND IT



ACROSS

3. Fluid flow
6. 24-hour rhythm
7. Cell neighborhood
8. Beach floor
10. Inky pencil
11. Ice, once
13. Throbbing
17. Business end of a nerve cell
19. Gets drug to its target
21. Popular early-morning class
22. Rest
23. Letters of a genome word
24. 238-a.a. protein
27. Buzzer
28. Can be broken down
29. Rotund
30. Nobel city

DOWN

1. Light, naturally
2. Not sad
4. Natural Coast Guard patrol
5. Earth's light
9. Computational chemist Marc
12. Ball's companion
14. Coffee holder
15. GFP source, originally
16. Summer thirst quencher
18. Arsenic cleaner
20. Blood transporter
25. Chemical engineer Eniola-Adefeso
26. NIGMS minority training program

SOLVE IT ONLINE

An interactive version and answers can be found at <http://www.nigms.nih.gov/findings>.

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