

Featuring

- 1 *Up Close With: Alfred Atanda Jr.*
- 2 *Game Changer: Studying Sports Injuries in Kids*
- 6 *The Ins and Outs of Tommy John Surgery*

Spotlights on Hot Science

- 5 *Just Found: Say Cheese*
- 9 *Just Found: Training Cells to Devour Dying Neighbors*
- 10 *On the Trail of Drug-Defying Superbugs*
- 12 *Capitalizing on Cellular Conversations*
- 14 *Spotlight on Videos: The Rise and Fall of Microtubules, Bleach vs. Bacteria*
- 16 *Knowing Networks*

Edited by Alisa Zapp Machalek

Contributing Writers

Carolyn Beans
Elia Ben-Ari
Emily Carlson
Amber Dance
Alisa Zapp Machalek
Joe Piergrossi
Sharon Reynolds

Production Manager

Susan Athey

Online Editor

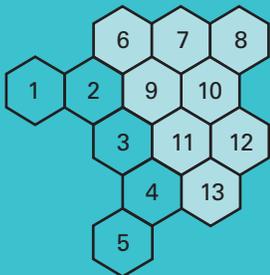
Jilliene Drayton

Produced by the Office of Communications and Public Liaison
National Institute of General Medical Sciences
National Institutes of Health
U.S. Department of Health and Human Services

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

On the Cover

- 1 **Yeast cell frozen in time**, Carolyn Larabell, University of California, San Francisco, and Lawrence Berkeley National Laboratory
- 2 **Vibrio bacteria**, Tina Carvalho, University of Hawaii at Manoa
- 3 **G protein**, RCSB Protein Data Bank
- 4 **Cascade reaction promoted by water**, Tim Jamison, Massachusetts Institute of Technology
- 5 **Mouse fibroblast cells**, Torsten Wittmann, University of California, San Francisco
- 6 **Human neutrophil ingesting MRSA**, National Institute of Allergy and Infectious Diseases, National Institutes of Health
- 7 **Illustration of injured elbow ligament**
- 8 **Bacterial protein**, American Chemistry Council Chlorine Chemistry Division
- 9 **Alfred Atanda Jr.**, Cynthia Brodoway, Nemours/Alfred I. duPont Hospital for Children
- 10 **Cells lining the trachea**, Eva Mutunga and Kate Klein, University of the District of Columbia and National Institute of Standards and Technology
- 11 **School friendships network diagram**, Tarik Crnovrsanin, Robert Faris, Kwan-Liu Ma, University of California, Davis
- 12 **Fat cells and blood vessels**, Daniela Malide, National Heart, Lung, and Blood Institute, National Institutes of Health
- 13 **A healthy cell that has ingested dying cells**, Toru Komatsu, University of Tokyo





Up Close With

Alfred Atanda Jr.

PEDIATRIC ORTHOPEDIC SURGEON

“My goal is to change the culture in sports for young athletes in general.”

FAVORITE SPORT

Soccer

MUSICAL SKILLS

Piano and trumpet

LANGUAGES

**English and Twi,
a language in Ghana**

BLOGS

**as Philly.com’s Sports Doc
at <http://bit.ly/sportsdoc>**

KITCHEN TALENT

**Baking chocolate desserts
for his wife, Nadia Dowshen,
a pediatrician, and their two
young children**

CYNTHIA BRODOWAY, NEMOURS/ALFREED L. DUPONT HOSPITAL FOR CHILDREN



Game Changer

Studying Sports Injuries in Kids

BY JOE PIERGROSSI AND ALISA ZAPP MACHALEK

In addition to an early interest in science and sports, Alfred Atanda always loved to build things and tinker with the inner workings of machines. Growing up, he watched, fascinated, as new houses were built in his neighborhood. He dreamed of being a construction worker or an engineer.

Today, Atanda works on one of the most complex construction projects of all: the human body. Rather than wood or steel, his joists and junctions are living flesh—muscles, bones, ligaments and tendons.

His journey has taken him from playing soccer as a kid in New Jersey to providing medical care to professional athletes in Philadelphia. He is now a pediatric orthopedic surgeon—the type of doctor who repairs damage in bones, joints and muscles—and a researcher in the same field. He focuses on sports medicine and injuries to children.

Atanda has a special passion for helping kids with a particular type of injury—elbow damage in baseball pitchers who overuse their throwing arm. Such injuries have been on the rise, a trend that Atanda sees as alarming. Decades ago, only elite athletes suffered the sort of damage he now sees in children as young as 12 years old. Atanda aims not only to study and treat these injuries, but also to find ways to prevent them, a goal that could have far-reaching effects.

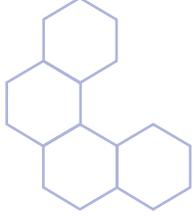
“I want to change the culture of youth baseball pitching,” he says.



Atanda's research focuses on elbow injuries in young baseball pitchers.

CYNTHIA BRODOWAY, NEMOURS/ALFRED I. DUPONT HOSPITAL FOR CHILDREN

JON ZAPP



Kids always just wanted to get better. I liked that.

Working Hard

Growing up as the youngest of seven children of Ghanaian-born parents, Atanda absorbed a tough work ethic.

“You go to work, you sacrifice for your family, and that’s it,” Atanda says of his parents’ attitude toward daily life. “During summers, when a lot of people were going to the beach, I was going to the beach too—to work at my mom’s store.”

There were no family vacations, no fancy clothes, no time for leisure or self-indulgences—only hard work in an effort to better oneself and the family.

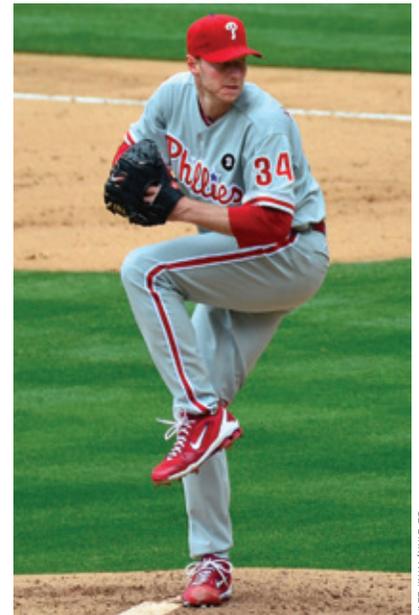
Atanda’s career goal solidified in high school after he watched a documentary film in his anatomy class. The film focused on an orthopedic surgeon who traveled to Central America to provide medical care in underserved communities. Atanda particularly remembers an image of a boy born with a deformed shinbone.

“The surgeon put this thing on the boy’s leg—it just looked like a bunch of pins and wires sticking out—and he adjusted it a millimeter a day until it straightened the boy’s leg out,” Atanda says. “I was completely enamored by that.”

Atanda’s interest in gadgets—and his desire to help others—was piqued.

He spent the next 15 years preparing—4 years in college, 4 in medical school, then 7 of specialized training in orthopedic surgery, pediatric orthopedics and sports medicine. During this time, he found he particularly enjoyed caring for kids.

“I worked with some adults, but they were always complaining about getting injured at work and not wanting to go back to work,” Atanda laughs. “But with kids, they just wanted to get better! Whether they were born with a congenital problem or got injured on the playground, they always just wanted to get better. I liked that.”



SD DIRK, WIKIPEDIA

Atanda’s time with the Philadelphia Phillies, a Major League Baseball team, led him to research on elbow injuries among pitchers.

Pro Elbows

During one of his years of training, Atanda worked alongside the physicians for Philadelphia-area sports teams, including professionals—the Eagles (football), Flyers (ice hockey), Sixers (basketball) and Phillies (baseball)—as well as college and high school leagues.

In his time with the Phillies, he was introduced to research on the elbow injury that would hold his interest for years to come: a tear in the ulnar collateral ligament (UCL). This injury is found in athletes who repeatedly throw or hit overhand—most notably baseball pitchers and javelin throwers, but also volleyball spikers and racquet sports players.

The UCL is the main ligament that stabilizes the elbow, holding the upper arm bone (the humerus) to one of the bones of the forearm (the ulna). The ligament can tear after a single, wrenching action. More commonly, many small tears



CREATIVE COMMONS, WIKIPEDIA

The bone straightening made possible by this sort of device helped inspire Atanda to become an orthopedic surgeon.

accumulate over a long period of repeated use, resulting in pain and decreased pitching accuracy and velocity.

To repair this injury and enable athletes to return to their sports, doctors can reinforce the UCL using a tendon from elsewhere in the body. This is known as Tommy John surgery after the professional baseball player who, in 1974, was the first person to undergo it.

The surgery revolutionized baseball. It allowed John, after extensive rehabilitation, to recover from what would have been a career-ending injury and pitch for another 14 years. Since then, it has been performed on more than a thousand other pitchers. A large percentage—estimates range from 11 percent to 34 percent—of today's professional pitchers have had it done, some more than once.

On average, it takes a year or more to fully recover from the operation, and not all athletes attain their pre-injury level of performance. Others surpass it, which doctors attribute to strengthening exercises and the athletes' improved awareness of safety and proper form.

Early Warning

During his time in Philadelphia, Atanda witnessed the culmination of a multi-year research project on UCL injury. The study investigated whether ultrasound imaging could detect early warning signs—slight anatomical changes in the ligament—before the damage is severe enough to warrant surgery.

“The point is, if you can document that someone is having changes before they actually have an injury, you may be able to do things to prevent it,” Atanda says. “You can modify their pitching habits, their regimen, how much they're pitching, and so forth.”

To examine these early anatomical changes, the researchers used an ultrasound imaging machine. This is the same technology that doctors use to look for damage or disease in soft tissues and internal organs—and to check on the baby developing inside a pregnant woman.

The research team took ultrasound pictures of both elbows of seemingly uninjured Phillies pitchers, then compared the two images to see if there was more wear and tear in the throwing (dominant) elbow than in the nondominant elbow.



Research using cheese rinds sheds light on biofilms and might lead to new treatments for bacterial infections.

Say Cheese

The rinds of aged cheeses are home to complex, highly regulated communities of bacteria and fungi. Researchers study such microbial communities, called biofilms, to understand their many roles in our bodies and the environment.

Studying biofilms can be challenging because many of the environments where they're found are hard to replicate in the lab. According to Rachel Dutton and her colleagues at Harvard University, cheese rinds might serve as a system for understanding how the microbial communities form and function.

By sequencing DNA from the rinds of 137 artisan cheeses collected in 10 countries, Dutton's team identified three general types of biofilms. They then recreated similar microbial communities in the lab by adding representative bacterial and fungal species to a growth medium that included cheese curd. Now they use their lab-grown cheese rinds to examine how microbes compete or cooperate in this environment, what molecules and mechanisms help build biofilms and how the communities change over time.

In addition to answering fundamental questions about microbial ecology, this cheesy research might yield insights that help fight infection-causing biofilms or lead to new antibiotics.

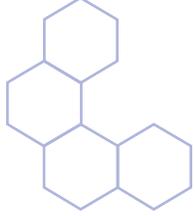
—Elia Ben-Ari



CYNTHIA BRODOWAY, NEWOURS/ALFRED I. DUPONT HOSPITAL FOR CHILDREN

Atanda examines the elbow of a young patient.

Just Found Just Found



Decades ago, only elite athletes suffered the sort of

The scientists visualized the players' elbows both at rest and when under the type of mechanical stress caused by the pitching motion.

"What we saw in these professional athletes is that the UCL—the ligament you have to repair when you do a Tommy John surgery—tends to get thicker over time in the dominant elbow compared to the nondominant elbow," Atanda says. "This suggests that the increase in ligament thickness is a change that happens by prolonged exposure to pitching at a high level."

Atanda and his colleagues also noticed extra space, or gapping, in the throwing elbow when the joint was stressed. The weakened ligament wasn't holding the bones together as tightly as it should.

Such worn-out ligaments are more prone to tear or rupture.

Performance Pressure

When Atanda was hired as a pediatric orthopedic surgeon at Nemours/Alfred I. duPont Hospital for Children in Wilmington, Delaware, he realized that young pitchers—those in Little League through high school—were experiencing the same injuries and undergoing the same surgery as the pros.

The American Sports Medicine Institute calls the rise in injuries requiring Tommy John surgery "epidemic." A position statement from the group gives this explanation: "In previous generations, Major League pitchers grew up competitively pitching only a few

months each year, but nowadays leagues and teams are available for adolescents to play competitive baseball almost all year. Research has shown a strong link between too much competitive pitching and arm injuries."

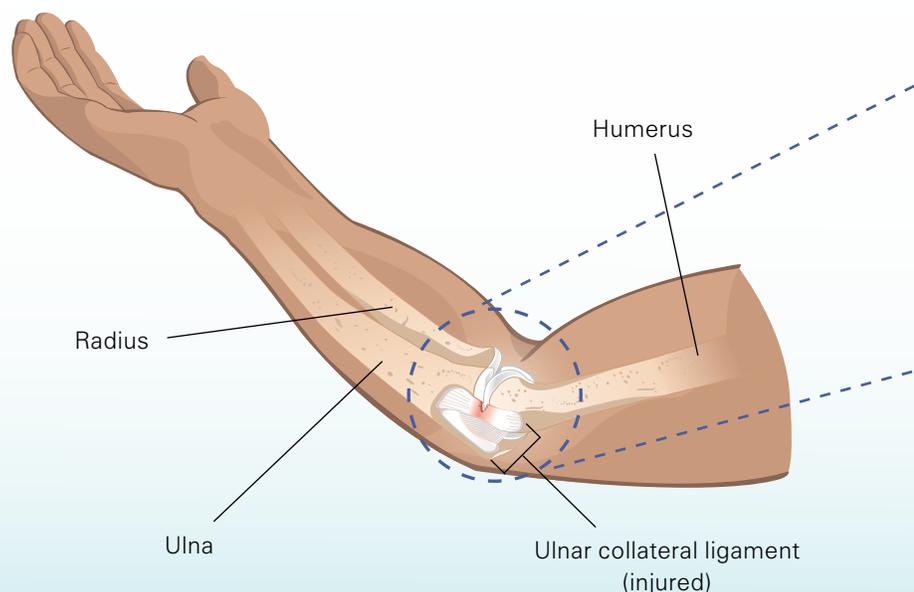
Atanda explains that young pitchers who excel are in high demand, some playing for three or four different teams. "To them, it's a good thing, because they feel important," he says. "But in the long run, it's actually a big problem. They tend to wear themselves out."

The kids might pitch every day with no off days to rest their arm. In the Majors, starting pitchers usually have at least 4 or 5 days rest between games.

The Ins and Outs of Tommy John Surgery

TOMMY JOHN SURGERY has been called a "baseball miracle," allowing pitchers to come back to the game after what would have been career-ending injuries. It is now performed on more than 100 people a year. But like any surgery, it is invasive and carries risks.

Surgeons start the operation somewhere other than the injured elbow. From this site (often the forearm of the same arm), they remove a 6- to 7-inch length of tendon to use as a graft to replace the damaged ligament. Then they make an incision in the elbow, cutting through or pushing aside soft tissue, muscle, nerves and the UCL to expose the bones at the joint.



damage now seen in children as young as 12 years old.

In Atanda's experience, some parents want their children to pitch as much as possible, thinking that more practice will lead to better performance. In addition, he says, teams try to get as many innings as they can out of good pitchers.

A lot of these young athletes "get so overworked when they are 12 that they're done when they're 16," Atanda says.

He also notes that surgery—which in most cases is considered a last resort—is viewed by some in the baseball community as part of the training for aspiring pitchers. This perspective was captured numerically in a 2012 research article titled "Public perceptions of Tommy John surgery." Conducted by scientists at Columbia University's Center for Shoulder, Elbow, and Sports

Medicine, the study showed that half of high school athletes, a quarter of college athletes and a third of coaches and parents believed that Tommy John surgery should be performed on players without elbow injuries to enhance performance.

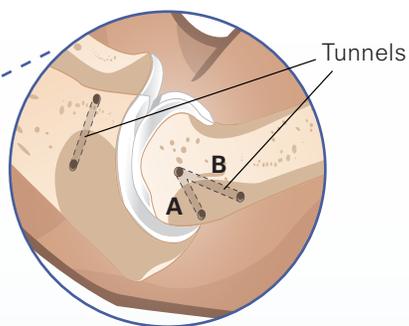
Changing the Culture

One of Atanda's current research projects grows directly from his earlier work with the Phillies. He is using ultrasound imaging and stress-simulating machines to examine the UCL and other elbow structures in pitchers aged 12 to 18 years. Like before, he's comparing the throwing and nonthrowing arms of seemingly uninjured pitchers, looking for evidence of UCL thickening, gapping and weakening.

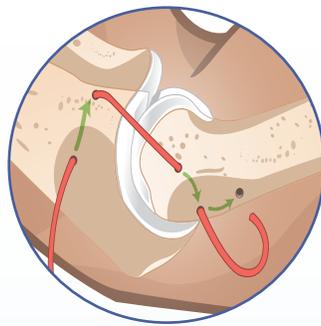
Atanda and his fellow researchers are also asking the young athletes to fill out questionnaires about how many teams they play for, how often and how hard they pitch, and the type of throws they use (curveballs and sliders put more stress on the elbow than do regular fastballs).

"We know kids shouldn't pitch more than 8 months out of the year. They shouldn't pitch more than 100 innings in a calendar year. And they shouldn't pitch and catch in the same game," says Atanda, referring to recommendations from the American Sports Medicine Institute for preventing injuries in young baseball pitchers.

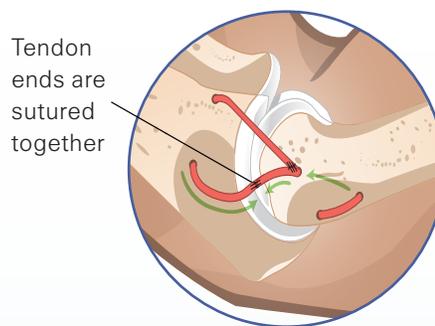
"I'd like to know how pitching activity actually correlates with anatomical changes in the elbow," he continues. "We know that kids



1 Surgeons drill one tunnel through the ulna bone and two tunnels (labeled A and B here) that intersect in a V shape through the humerus.



2 Next, surgeons thread the harvested tendon (shown here in red) through the tunnel in the ulna, then through tunnel A in the humerus.



3 Finally, surgeons thread the tendon back through tunnel B. They then bring together the two ends of the tendon, securing them with sutures.

Over the next year, the muscles, skin and soft tissues knit back together and heal. The patient begins physical therapy and rehabilitation exercises. And the harvested tendon, which used to attach muscle to bone, takes on the role of a ligament, connecting two bones to stabilize a joint.



The focus should be on being active



Little League pitching captured the nation's attention in August 2014 when 13-year-old Mo'ne Davis became the first Little League player—and one of the youngest athletes—to appear on the cover of *Sports Illustrated*.

are more susceptible to elbow injuries the more that they pitch, but we don't know how much the ligament increases in thickness."

By combining the ultrasound measurements with the questionnaire results, Atanda's team is working to answer questions like:

How much does the ligament thicken if you pitch for three teams instead of two? What kind of joint space gapping will you have if you pitch for 100 innings a year versus 50 innings? Are athletes who throw faster pitches more susceptible to anatomical changes in their UCL?

So far, he's examined 55 young athletes.

"We found similar results to what we found with the Phillies," Atanda says, indicating that the UCL in the throwing elbows of young athletes was noticeably thicker—around 5 to 5.5 mm—than the UCL in the nonthrowing elbows, which typically measured around 4 to 4.5 mm.

And these changes worsened over time, he continued: "We saw that these ligaments got thicker as the pitchers got older and had more pitching experience."

Atanda has been conducting this research for about a year and hopes to continue it for another 3 years.

The immediate goal of this project is the same as his earlier work with pros, Atanda says. "We're trying to prevent any kind of overuse elbow injuries and the need for Tommy John surgeries later on."

But when working with kids, he also has longer-term aspirations. "My goal is to change the culture in sports for young athletes in general," he says. "I want to show there are downsides to pitching so much."

Many of the parents Atanda meets hope their child will pitch in college or even in the Majors. (Interestingly, Atanda learned from the Phillies that pro pitchers typically were not Little League pitching stars—many of them played other positions as kids and didn't even pitch until they got to college.)

Instead of grooming kids for future pitching careers, Atanda says "the focus should be on being active, getting good exercise, social interaction, building self-confidence, self-esteem" and having fun.

and having fun.

Supporting Science

Scientists like Atanda need financial support in order to do their research. In his case, some support comes from a National Institutes of Health (NIH) program called the Institutional Development Award (IDeA). The IDeA program builds research capacities in Delaware, where Atanda works, and other states that historically have received low levels of NIH funding.

The type of grant Atanda receives is designed to provide mentoring and professional development opportunities to investigators in the early stages of their careers. The overall goal of the program is to produce independent researchers who receive competitively awarded federal funding for their projects and who publish their work in well-respected scientific journals.

Ultimately, Atanda wants to open an injury prevention center for children in the Mid-Atlantic region. The center would provide treatment and do research. Atanda already envisions a study in which he would tap into state data to identify “hot spots” where a lot of kids are hit by cars. He hopes to identify the reason for the high number of accidents, then find ways to reduce them.

In his medical practice, Atanda helps one child at a time. The community-focused work he dreams of doing would give him the opportunity to prevent injuries to larger numbers of children.

With this sort of project, “I can put myself in a position to help improve kids’ lives,” Atanda says. And that is what makes him feel most fulfilled. ● ● ●

FIND MORE



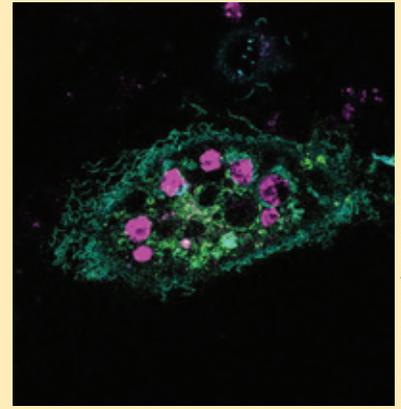
Watch an animated video explaining Tommy John surgery at <http://bit.ly/1rq3ago>

See what the American Sports Medicine Institute says about Tommy John injuries at <http://bit.ly/1uZPXbL>

Read an article in which Atanda talks about knee injuries in athletes at <http://bit.ly/1u8ACHV>

Learn more about the IDeA program that funds Atanda’s research at <http://www.nigms.nih.gov/training/IDeA/pages/COBRE.aspx>

Atanda’s research is funded by the National Institutes of Health through grant P20GM103464.



TORU KOMATSU, UNIVERSITY OF TOKYO

A healthy cell (green) that has ingested dying cells (purple).

Training Cells to Devour Dying Neighbors

In the cellular world, consuming dying comrades (a process called phagocytosis) is crucial to health.

A research team that included Takanari Inoue at Johns Hopkins University and collaborators in Tokyo set out to learn more about phagocytosis. To start, they wondered what it would take to convert laboratory-grown human cells into phagocytotic ones that had the ability to recognize, swallow and digest dying cells.

So far, the scientists have inserted into the ordinary cells two molecules known to play a role in phagocytosis. The resulting engineered cells are able to recognize and surround dying cells, but then they fall short. They don’t digest the cargo.

Now the researchers are looking for a molecular trigger to stimulate cellular digestion, so the engineered cells completely destroy the dying cargo.

Eventually, the scientists aim to use the strategy to help treat diseases. The idea is to program artificial cells to target and destroy abnormal cells, such as those affected by bacteria, cancer, degenerative diseases or other conditions.

—Alisa Zapp Machalek

On The Trail of Drug-Defying Superbugs

By Elia Ben-Ari

Some of the bacteria that cause infections in humans have become resistant to the antibiotics we use to combat them. Antibiotic resistance can turn once-manageable infections into “superbug” diseases that are difficult—and sometimes impossible—to treat. According to the Centers for Disease Control and Prevention, in the United States alone, at least 2 million people each year develop serious infections with drug-resistant bacteria, and about 23,000 die.

Scientists are studying many aspects of antibiotic resistance, including how it spreads. Here are just a few examples of what they’re exploring and how it could aid efforts to curb the emergence of resistance.

Detecting New Sources of Antibiotic Resistance

The most common way that bacteria become invulnerable to antibiotics is through the transfer of resistance genes from other bacteria. Often, these genes are found on small, circular pieces of DNA called plasmids that are readily passed among bacterial species.

David Cummings of Point Loma Nazarene University searches for plasmids bearing resistance genes in sediment samples from several urban wetlands. These habitats provide ideal conditions for bacteria from diverse sources, such as human sewage, animal waste and naturally occurring plant and soil microorganisms, to swap genes and spread antibiotic resistance, he notes.

So far, Cummings has found that during winter rains, the coastal wetlands in San Diego receive runoff containing antibiotic-resistant bacteria and plasmids, which can persist in the wetlands at low levels into the dry summer months. Some of these plasmids contain genes that confer resistance to commonly used antibiotics, including beta-lactam drugs like penicillin and cephalosporins and fluoroquinolones like ciprofloxacin (Cipro).



David Cummings studies the role of urban storm water in spreading genes for antibiotic resistance in natural environments.

MARCUS EMERSON, POINT LOMA NAZARENE UNIVERSITY

By better understanding the nature of drug resistance plasmids in urban wetlands, Cummings hopes to aid future efforts to prevent their potential spread among bacteria that cause human disease. It remains to be seen whether drug-defying bacterial genes that accumulate in the wetlands are likely to move into other species of harmful bacteria and then to us.

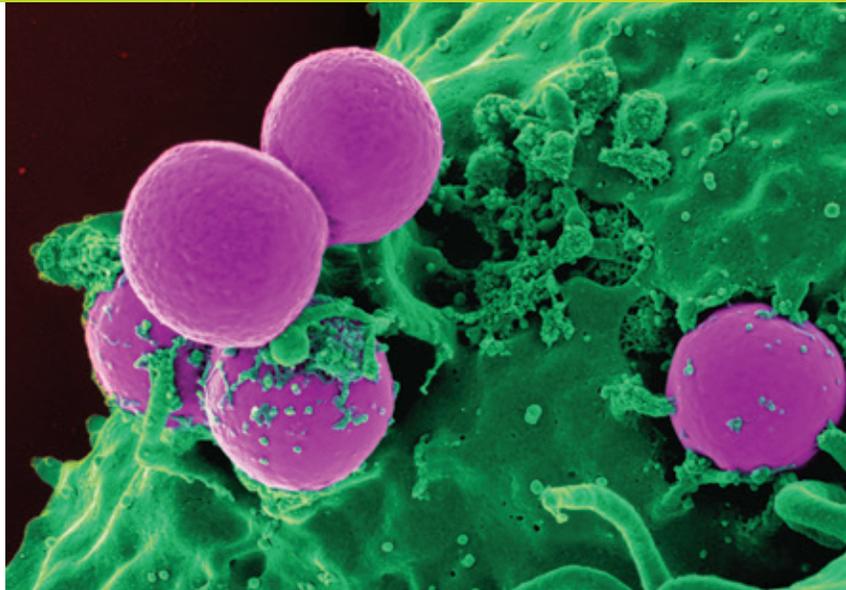
Checking the Gut to Head Off Resistance

Bacteria living in the human body can trade resistance genes, too. Gautam Dantas of Washington University School of Medicine in St. Louis is investigating how resistance develops in and spreads among the bacteria that colonize the human gut during the first 2 years of life.

As soon as babies emerge from the womb, they start picking up microbes from their moms, their other caregivers and the environment. The human intestinal tract, in particular, harbors hundreds of microbial species, many of which are harmless or even beneficial to their hosts.

“The first 2 or 3 years of life are when the real action occurs in terms of setting up the network of microbes in the human gut,” says Dantas. But taking antibiotics can promote the emergence of drug-resistant strains of bacteria by favoring the proliferation of “bugs” that can evade the drugs. And kids from birth to age 5 are given more antibiotics per capita than any other age group, he adds.

Dantas is studying the development of the complete collection of resistance genes in the gut—dubbed the resistome—in healthy sets of twins and in infants with very low birthweights. By cataloging the abundance and diversity of these genes in fecal samples taken from



Antibiotic-resistant strains of *Staphylococcus aureus* bacteria (purple) have become the most common cause of skin infections seen in hospital emergency departments.

infants at regular intervals and looking at how they change over time, he hopes to gain insights on how the gut resistome is affected by antibiotic treatment, genetics and other factors.

“This is a way to detect resistance genes before they [transfer into disease-causing bacteria and] become a problem,” says Dantas. His work also could lead to a more informed strategy for antibiotic use in kids to minimize the risk that bad bugs will survive and multiply.

Modeling the Spread and Control of Resistance

Staphylococcus aureus (staph) bacteria often coexist peaceably with humans, hanging out on body surfaces like the nose or skin without ill effects. Roughly a third of the general population is harmlessly colonized with this form of staph bacteria, and most people don’t develop an active infection.

In the past decade, though, certain virulent, antibiotic-resistant strains of staph, known as methicillin-resistant *Staphylococcus aureus*, or MRSA, have spread rampantly in the general community. These so-called community-associated MRSA (CA-MRSA) infections have become the most common cause of skin infections seen in hospital

emergency departments and can turn deadly if they spread to the bloodstream or internal organs, says Diane Lauderdale of the University of Chicago.

To understand how patterns of contact and behavior among individuals affect the spread of CA-MRSA, Lauderdale and Charles Macal of Argonne National Laboratory developed a computer model representing the real-world interactions of the Chicago metropolitan area population in households, schools, workplaces, gyms, hospitals, prisons and other settings. The scientists fine-tuned the model to simulate retrospectively the actual spread of CA-MRSA that occurred in the city from 2001 to 2011.

The model revealed that more than 90 percent of CA-MRSA infections were due to contact with a colonized, symptom-free individual. It also indicated that households were by far the most common site of infection, followed by schools. These findings, Lauderdale says, point the way to strategies that are most likely to curb the spread of drug-resistant staph in the community, such as disinfectant treatments targeting affected households, which the researchers can then test using their virtual version of the Windy City. ●

Capitalizing on Cellular Conversations

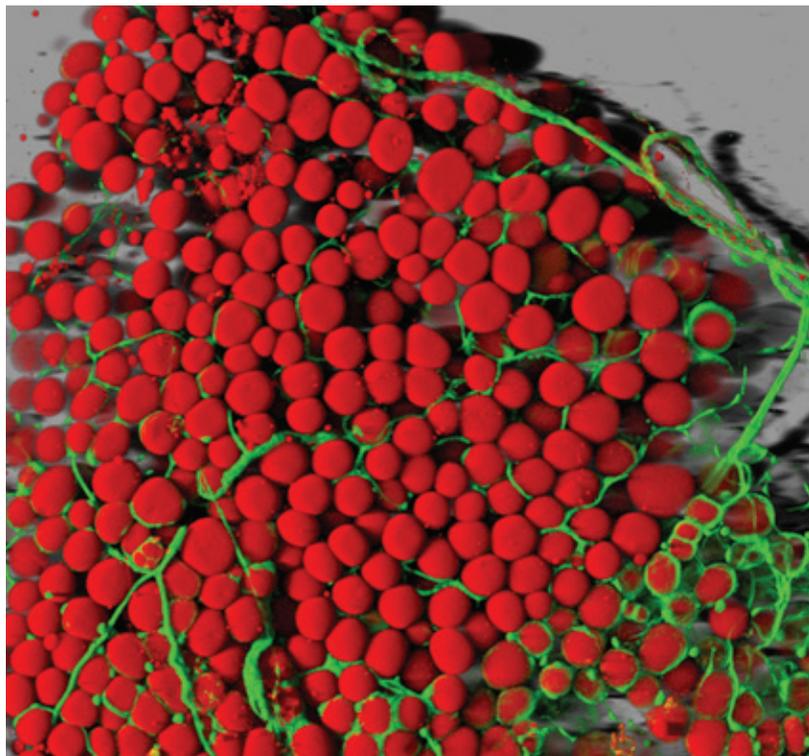
By Amber Dance

Living things are chatty creatures. Even when they're not making actual sounds, organisms constantly communicate using chemical signals that course through their systems.

In multicellular organisms like people, brain cells might call, "I'm in trouble!" signaling others to help mount a protective response. Single-celled organisms like bacteria may broadcast, "We have to stick together to survive!" so they can coordinate certain activities that they can't carry out solo.

In addition to sending out signals, cells have to receive information. To help them do this, they use molecular "ears" called receptors on their surfaces. When a chemical messenger attaches to a receptor, it tells the cell what's going on and causes a response.

Scientists are following the dialogue, learning how cell signals affect health and disease. Researchers are also starting to take part in the cellular conversations, inserting their own comments with the goal of developing therapies that set a diseased system right.



Fat cells such as these listen for incoming signals like FGF21, which tells them to burn more fat.

Signaling a Long, Skinny Life

In cellular conversations, the "words" often take the form of small molecules, or chemicals, released by one cell and received by receptors on another. In multicellular animals, hormones are a common form of chemical message.

For instance, our liver cells release the hormone FGF21 to tell fat cells when it's time to burn off some fat for energy. This signal makes FGF21 of interest to scientists who want to treat obesity and type 2 diabetes.

To investigate the role of the hormone, David Mangelsdorf and Steven Kliewer of the University of Texas Southwestern Medical Center engineered mice to produce extra FGF21. The dramatic result: smaller mice, though they had normal proportions of fat and lean mass. It turns out that the FGF21 signal interrupts other signals involved in growth. Another major change was that the mice lived for up to 4 years, compared to the typical 2.

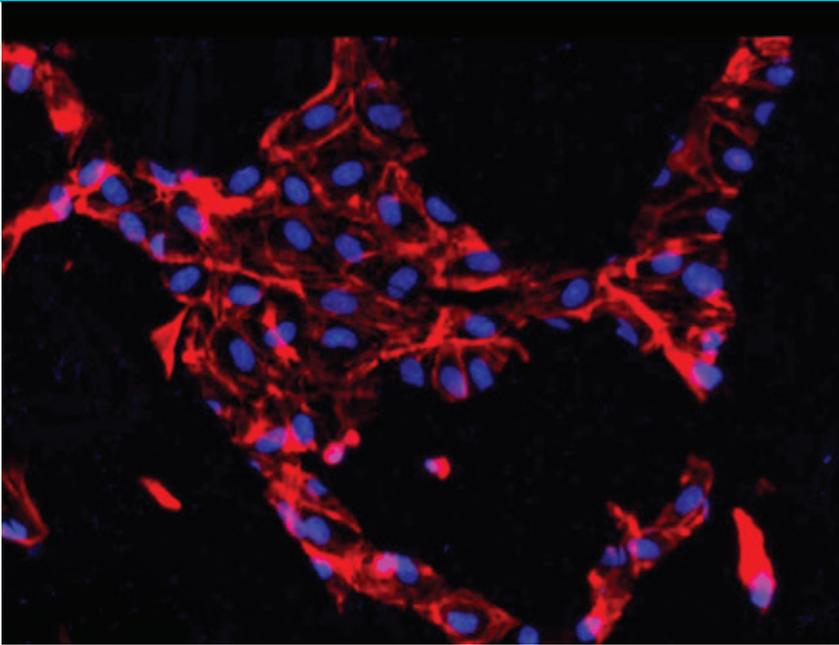
But there were also negative effects. The mice with extra FGF21 had low bone density, as if they were getting osteoporosis. And the female mice couldn't have pups. Mangelsdorf and Kliewer are trying to figure out what other side effects the FGF21 signal might have in different parts of the body.

"Here's a compound that is a potential anti-obesity drug and might also make you live a long time, if the side effects could be overcome," Mangelsdorf says. Now, he and Kliewer are working to better understand exactly how FGF21 creates these positive and negative changes in the body.

Tamping Down Tumors

In the back and forth of cellular communication, endothelial cells are major players. These cells, which

DANIELA MALIDE, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NATIONAL INSTITUTES OF HEALTH



JOSEPH FRANSES, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

This package of healthy endothelial cells (cell skeleton, red; DNA, blue) might someday help control cancer.

line blood vessel walls, are covered in receptors, processing information such as the rate of blood flow. They also send molecular signals that control blood clotting, immune responses and other processes.

In addition, endothelial cells communicate with cancer cells to curb their growth, says Elazer Edelman of the Massachusetts Institute of Technology and Harvard Medical School. But a tumor sends signals of its own, convincing the endothelial cells to send signals that aid cancer growth.

Edelman developed a treatment that might help: a package of healthy endothelial cells, implanted near a tumor, that acts as backup for the body's natural cancer-controlling endothelium. The implanted cells produce complex messages—Edelman has not yet defined all the elements—to keep the cancer in check.

In tests he's done using mice, the implants suppress cancer, but Edelman still has to work out which types of cancers respond best. His collaborators have also tested the implants in healthy people to make sure they're safe before trying them in cancer patients.

Silencing Bacteria

Bacteria communicate with each other using a process called quorum sensing. By sending and listening for "I'm here" signals, they can figure out if they're alone or in a community. Once a number of cells are together—forming a "quorum"—they act differently than if they were alone. They might invade host cells or start to make toxins or biofilms.

If scientists could silence quorum signaling, they could potentially block bacterial damage to cells, reasons Vern Schramm at Albert Einstein College of Medicine of Yeshiva University. His lab works on chemicals that turn off the activity of enzymes, proteins that speed biological reactions.

Bacteria need the MTAN enzyme for quorum sensing. Schramm designed an inhibitor that jams MTAN, like a key stuck in a lock. "This cuts the telegraph wires between the bacteria so they can't communicate," he says.

Schramm's inhibitor has an advantage over antibiotics currently being prescribed. Those drugs kill bacteria, but the bacteria are able

to evolve ways to evade the attack. This leads to antibiotic resistance, which is a serious problem because doctors are running out of drugs that work against some bacteria. But Schramm grew cholera bacteria with MTAN inhibitors for 26 generations, and they never evolved a way to escape the treatment. Schramm is currently looking to develop the inhibitors into what he calls "everlasting antibiotics."

Schramm never thought that would be his goal—he started out just trying to understand enzymes. He points out that this is a good example of how basic research on fundamental processes like cellular communication can lead the way to new medicines. ●



TINA CARVALHO, UNIVERSITY OF HAWAII AT MANOA

Cholera bacteria are among those that use quorum sensing, making them susceptible to Vern Schramm's "everlasting antibiotics."

Spotlight on Videos

Online videos certainly rank high in entertainment value—TV shows and movies, adorable pets, hilarious parodies and more. They're also an incredibly powerful tool for scientists, who use them to better understand their field of interest and share their findings with others.

Researchers who study a biological process—say, cell division—might film the action. Then they can speed it up or slow it down to examine it in detail. Often, researchers will post their videos online as supplementary material to accompany the publication of their research in a scientific journal.

Here, we feature two videos created to investigate the movements of specific molecules, in one case a bacterial protein and in the other, the building blocks of cellular structures called microtubules. Current techniques don't allow scientists to directly film these molecules in action. Instead, the researchers use computational techniques to model what the molecules look like and how they behave.

The Rise and Fall of Microtubules

We might enjoy a day off every so often, but our cellular workers never rest. While we relax, our mitochondria still convert nutrients into cellular power, lysosomes take out molecular trash, ribosomes churn out proteins, and microtubules grow and shrink as needed to accomplish their many tasks in the cell.

Microtubules are strong protein filaments that make up part of the cell's skeleton and serve as tracks for shuttling internal cargo. When cells divide, microtubule fibers physically pull the chromosomes into each daughter cell. And on some cell exteriors, microtubules form long, waving hairs, called cilia, that sweep mucus from the lungs or guide eggs toward the uterus.



Long, hollow fibers called microtubules grow and shrink to get their cellular work done. Watch an animation of the construction and dramatic disassembly of a microtubule at <http://bit.ly/1w7HNCf>.

EVA NOGALES LAB, UNIVERSITY OF CALIFORNIA, BERKELEY

Microtubules are made up of many copies of a protein called tubulin linked together to form a hollow tube. In this animation, tubulin proteins snap into place like LEGO bricks to build a microtubule. When construction ends, the hollow cylinder immediately shortens as it falls to pieces.

Until recently, scientists didn't know exactly what drove microtubules to fall apart. A research team led by Eva Nogales of the Lawrence Berkeley National Laboratory and the University of California, Berkeley, now has an explanation. Using high-powered microscopy, the scientists peered into the structure of a microtubule and found how a chemical reaction puts the stacking tubulin proteins under intense strain. The only thing keeping them from springing apart is the pressure from the addition of more tubulin. So when elongation ends, the microtubule deconstructs.

The team also learned that Taxol, a common cancer drug, relieves the pressure and allows microtubules to remain intact indefinitely. With microtubules frozen in place, a cancer cell cannot multiply and eventually dies.

Because of this research, scientists now better understand both a widely used anticancer agent and one of our hardest working cellular laborers. ●

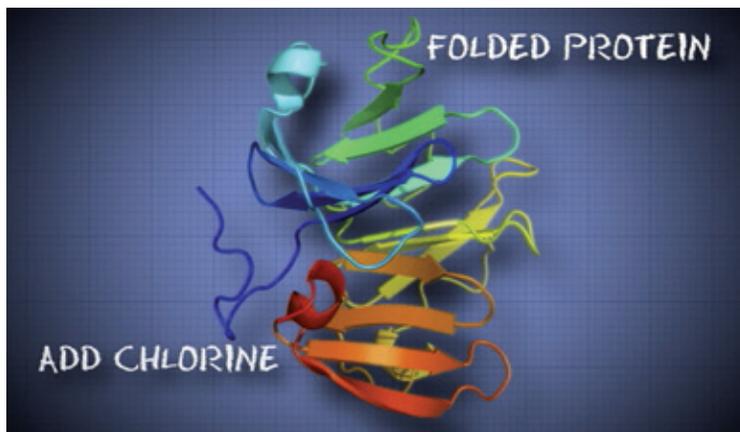
By Carolyn Beans

Bleach vs. Bacteria

People have been using chlorine bleach as a disinfectant for hundreds of years. But our bodies have been using bleach's active component, hypochlorous acid, to help clean house for millennia. As part of our natural response to infection, certain types of immune cells produce hypochlorous acid to help kill invading microbes, including bacteria.

Researchers have made strides in understanding exactly how bleach kills bacteria—and how bacteria's own defenses can protect against the cellular stress caused by bleach. The insights gained may lead to the development of new drugs to breach these microbial defenses, helping our bodies fight disease.

"When we started looking into how bleach actually kills bacteria, there was very little known about it," says Ursula Jakob of the University of Michigan. In a series of experiments, her team showed that hypochlorous acid causes bacterial proteins to unfold and stick to one another, making them nonfunctional and leading to cell death.



AMERICAN CHEMISTRY COUNCIL, CHLORINE CHEMISTRY DIVISION

When exposed to hypochlorous acid—the active ingredient in bleach—the proteins inside bacterial cells unfold and stick to one another, leading to cell death. Watch an animation of the process at <http://bit.ly/1CJgCiW>.

By investigating how bacteria respond to stressful conditions, the Jakob lab has uncovered several ways that bacteria in our bodies—and on our kitchen counters—can survive attack by hypochlorous acid. One such survival mechanism uses a protein called Hsp33, which is a molecular chaperone that helps other proteins fold into and maintain their normal forms. Protection by Hsp33 lets bacteria refold their proteins once a stressful situation has passed, thereby allowing the cells to survive.

The Jakob lab also has discovered several bacterial proteins that sense hypochlorous acid and, in response, activate genes that help the bacteria eliminate toxins produced by exposure to the noxious chemical.

Recently, the team discovered that a simple inorganic molecule called polyphosphate also serves as a molecular chaperone within bacterial cells. Polyphosphate, which likely existed before life arose on Earth and is produced by almost all organisms—from bacteria to humans—may be one of the oldest

molecular chaperones in existence. Bacteria lacking polyphosphate are very sensitive to the cellular stress caused by bleach and are less likely to cause infection.

Together, these results provide insights into how modern-day bacteria defend against immune attack and how early organisms survived environmental challenges. The studies also point to potential targets for antimicrobial drug development. "Many of these protective mechanisms that bacteria use in response to bleach are specific to bacteria," said Jakob, potentially making it possible to target these defenses without harming human cells. She and her team hope to find drugs to exploit this specificity and disarm bacterial defenses against bleach, allowing our immune systems to finish cleaning house. ●

By Sharon Reynolds

Knowing Networks

By Emily Carlson, Sharon Reynolds and Elia Ben-Ari

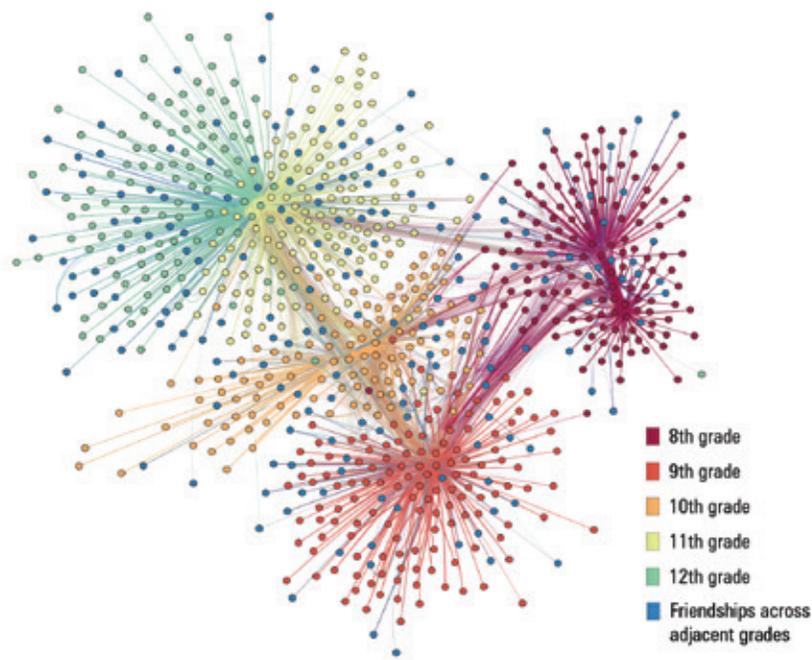
Networks—both real and virtual—are everywhere,

from our social media circles to the power grid that delivers electricity. The interactions of genes, proteins and other molecules in a cell are examples of networks, too. Scientists working in a field called systems biology study and chart these and other living networks to learn how the individual parts work together to make a functioning whole and what happens when these complex, dynamic systems go awry.

Just as you can't understand how a social media post "goes viral" by observing the activity of individual users, scientists can't fully understand the behavior of a cell or other biological system by studying its individual components in isolation. But, by combining data from experiments in living systems with powerful computer modeling techniques, scientists can explore questions that might be difficult or impossible to answer through lab experiments alone—such as what drives a cancer cell to grow into a life-threatening tumor.

According to Aaron Brooks, a biologist at the Institute for Systems Biology (ISB) in Seattle, networks typically are illustrated as diagrams like the one shown here. The circles or dots represent the objects in the network. The lines depict the interactions between those objects.

Network diagrams can yield information that helps us better understand—and potentially



A network diagram showing friendships among students in one school. Students (circles) are color-coded by grade. Lines represent friendships. Similar maps of social networks can be used to help track—and possibly slow—the spread of diseases like the flu.

TARIK CRNOVRSANIN, ROBERT FARIS, KWAN-LIU MA, UNIVERSITY OF CALIFORNIA, DAVIS

influence—complex phenomena that affect our health. Networks showing how drugs interact with each other can help predict harmful combinations of medications. Gene interaction networks can shed light on complex traits like disease susceptibility. And social interaction networks can help predict the spread of an infectious disease and point to ways to contain it.

"Network dynamics fascinate us," says Chris Lausted, a senior research engineer at ISB. "To survive, biological systems need to be very sensitive to some subtle environmental signals while tolerating huge changes in others. Mapping these networks helps us understand which changes cause disease and what can be done to restore health." ●

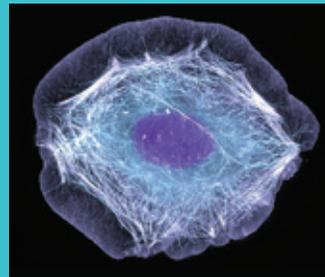
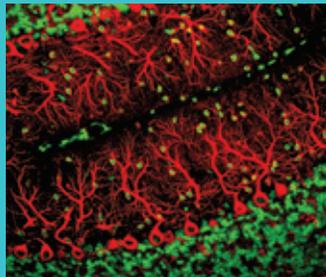
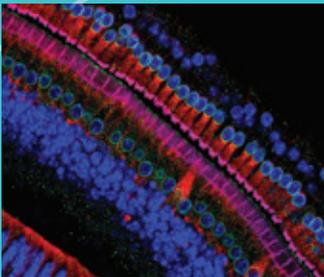
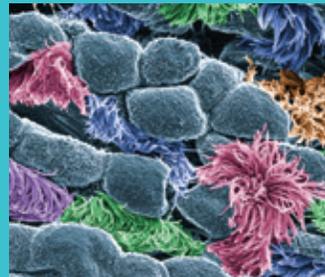
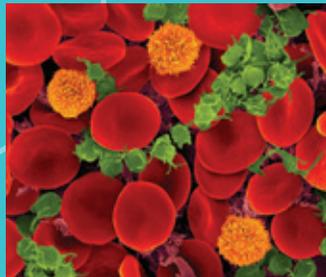
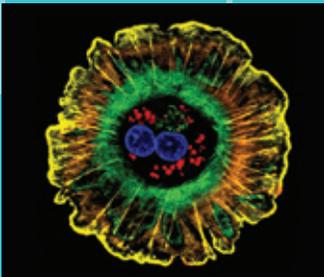
FIND MORE

For more articles about how basic biomedical research lays the foundation for medical advances, see <http://publications.nigms.nih.gov/insidelifescience>

EXPLORE IT MATCH IT FIND IT

Where in the Body?

Each of these images shows a body part magnified with a microscope (the magnifications and microscope types vary). See if you can match each image with its description. Answers are upside down at the bottom of the page.



A. DONNA BEER STOLZ, UNIVERSITY OF PITTSBURGH; B. DENNIS KUNKEL, DENNIS KUNKEL MICROSCOPY, INC.; C. EVA MUTUNGA AND KATE KLEIN, UNIVERSITY OF THE DISTRICT OF COLUMBIA AND NATIONAL INSTITUTE OF STANDARDS AND TECHNOLOGY; D. HENNING HORN, BRIAN BURKE AND COLIN STEWART, INSTITUTE OF MEDICAL BIOLOGY, AGENCY FOR SCIENCE, TECHNOLOGY, AND RESEARCH, SINGAPORE; E. YINGHUA MA AND TIMOTHY VARTANIAN, CORNELL UNIVERSITY; F. TORSTEN WITTMANN, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

- _____ 1. Airways. From our noses to our lungs, a community of cells like the one shown here defends our bodies against inhaled bacteria, allergens, pollutants and debris.
- _____ 2. Liver. Cells called hepatocytes play an important role in building proteins, producing a fat-digesting substance (bile) and chemically processing hormones, toxins, medicines and other substances.
- _____ 3. Skin. The outer layer of our skin is composed mostly of keratinocytes, which provide a protective, waterproof barrier to infection and help maintain our body temperature.
- _____ 4. Bloodstream. Our blood is composed of several cell types, including red blood cells, T cells and platelets.
- _____ 5. Inner ear. Our ability to hear and our sense of balance are made possible by specialized cells known as hair cells (which are completely different from the hair on our heads and bodies).
- _____ 6. Brain. Located in the cerebellum, at the base of our brains, nerve cells known as Purkinje cells have elaborate branching structures that receive signals from other nerve cells.

Discrimination Prohibited

Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the programs of the National Institute of General Medical Sciences must be operated in compliance with these laws and Executive Orders.

Accessibility

This publication can be made available in formats that are more accessible to people with disabilities. To request this material in a different format, contact the NIGMS Office of Communications and Public Liaison at 301-496-7301; send e-mail to info@nigms.nih.gov; or write to the office at the following address: 45 Center Drive MSC 6200, Bethesda, MD 20892-6200. If you have questions or comments about this publication, you can use the same contact information to reach the editor, Alisa Zapp Machalek.

Free Publications

View and download NIGMS publications at <http://publications.nigms.nih.gov/epublications.htm>.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
45 CENTER DR RM 3AN32 MSC 6200
BETHESDA MD 20892-6200

FIRST CLASS PRESORTED
POSTAGE & FEES PAID
NIH/NIGMS
PERMIT NO. G-813

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE \$300



National Institute of
General Medical Sciences

NIH Publication No. 14-4932
Fall 2014
<http://www.nigms.nih.gov>



Printed on 30% recycled paper.

Read, Share, Recycle.