SN
SCIENCE NEWS MAGAZINE
SOCIETY FOR SCIENCE & THE PUBLIC
JUNE 11, 2016

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Pre-Clovis People in Florida

The Missing Mitochondria

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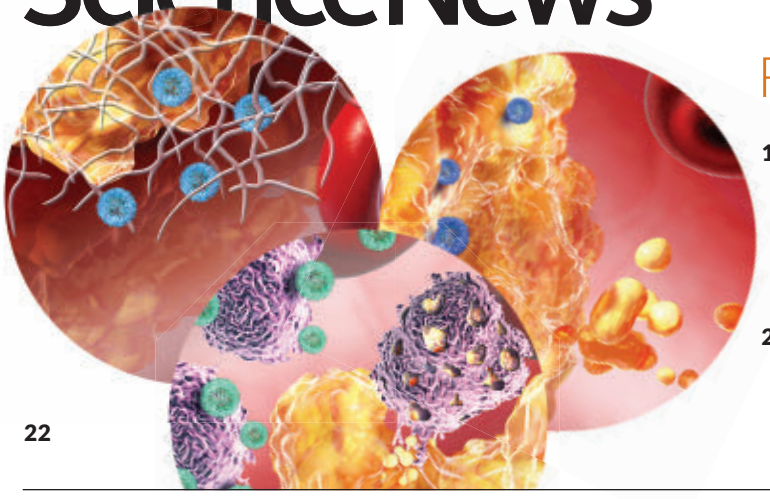

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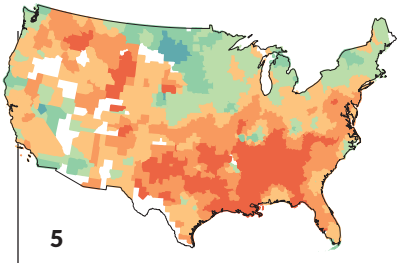

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Departments

COVER With their own take on archaeology, evolutionary biochemists are treating ancient proteins as storytelling fossils. *James Provost*

CLOCKWISE FROM TOP LEFT: NICOLLE RAGER FULLER; P.J. EGAN AND M. MULLIN/*NATURE* 2016; STEFAN MUNDER/FLICKR (CC BY 2.0)

Science fairs offer top students a grand stage

Athletes can aim to win a game — or even the state championship. Actors might try out for the lead in the school play. Budding writers may land their byline in the local newspaper. But what about the kids who explore their world using science? What inspires them not to just think about a question but also to try to answer it, using scientific tools?

Science fairs offer a stage for these students to shine. The biggest such stage for today's high school students is the Intel International Science & Engineering Fair. This competition is run by *Science News*' parent organization, the Society for Science & the Public. Created in 1950 and sponsored by Intel since 1997, this annual competition brings together top student projects from local, regional, state and even national science fairs from all over the world. For one week in May, a dizzying 1,759 science-minded teens from more than 75 countries descended on Phoenix for a chance at big prizes (more than $4 million is awarded to over 400 winners).

Having attended a number of these fairs over the years, it seems to me that the real value goes beyond the scholarships and other awards. It's the experience of being surrounded by hundreds and hundreds of other young people who share a passion for science. It's finding out that there's a world out there in which people recognize and appreciate the value of science. It's being called a scientist, maybe for the first time. It's knowing that awards are doled out based on intellect and hard work. Judges explore how sharply a student crafted his or her questions of nature, designed an experiment, analyzed the results and drew conclusions. Of course, it's also about how well students can tell their stories.

For the second year in a row, Janet Raloff and I gave a talk to attendees on the whys and hows of science communication. Now editor of our free online magazine *Science News for Students*, Raloff has written for *Science News* since 1977. She has a thought or two about how to best write about technical subjects for a wide audience. (A few pointers: Avoid jargon; admit what you don't know; be yourself; say why you wanted to do the project, what you did, what you found and why anyone should care.) After the talk, we gave feedback on students' "elevator pitch" descriptions of their projects. Some had it down. Others got mired in the details of method, while others spent so long on the project's practical implications they never mentioned the actual results. Jargon caught a few in its trap. Shyness held a few others hostage. Language barriers (many of the students are not native English speakers) jammed up some.

Overall, the science communication challenges were not too different from what I've often encountered in talking with adult scientists. Stumbles, but not unfixable. And there was something else these young scientists had in common with their elder peers: excitement. What came through was the thrill and empowerment that comes from not just asking a question, but also actively searching for the answer. And then being noticed for the effort by peers and professionals, like the jocks, theater-types and others who often steal the show in high school. I am always glad to be in that audience.

— Eva Emerson, Editor in Chief

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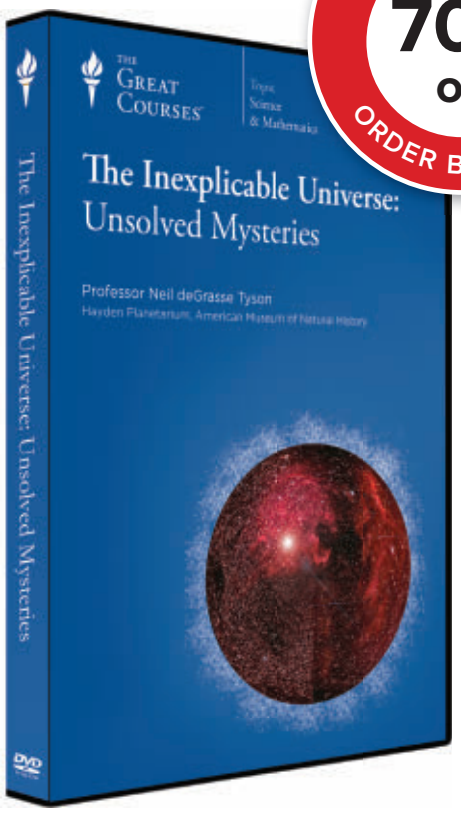

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Excerpt from the June 11, 1966 issue of *Science News*

50 YEARS AGO

3-D Home TV Foreseen

The pace of new developments in the recently revived method of photography known as holography is so fast that three-dimensional television sets portraying life-size scenes could be a reality before 1984, as was predicted in George Orwell's novel.... A hologram is a recording of an interference pattern reflected from an object. From this recording, the object can be reconstructed visually in a three-dimensional form.

UPDATE: Television viewers are still waiting for the 3-D revolution. Although 3-D TVs went on sale in the United States and elsewhere in 2010, they have yet to take off. Most sets require special glasses or have limited viewing angles, and none use holography to create the illusion of depth. Scientists haven't given up, though. Using innovative plastic screens, researchers are projecting small holographic movies in real time (*SN: 12/17/11, p. 18*). The enormous bandwidth and processing power needed to transmit and display the images are still huge barriers to making Orwell's vision a reality.

Kate Rubins will put her years as a molecular biologist and her astronaut training to good use when she rockets to the International Space Station on June 24.

THE SCIENCE LIFE

Space dreams get real

When molecular biologist Kate Rubins blasts off from Kazakhstan on June 24, strapped into the Soyuz spacecraft bound for the International Space Station, the trip will cap off seven years of preparing — and 30 years of hoping.

As a child, Rubins plastered her Napa, Calif., bedroom with pictures of the space shuttle, proudly announcing her intention to be an astronaut. A week at Space Camp in Huntsville, Ala., in seventh grade cemented her vision. But by high school, she concluded that astronaut wasn't "a realistic job," she says.

Flash forward to 2009: Rubins is running a lab at the Whitehead Institute for Biomedical Research in Cambridge, Mass., focusing on virus-host interactions and viral genomics. A friend points out a NASA ad seeking astronaut candidates, and Rubins' long-dormant obsession awakens. Since then, she has learned how to fly a T-38 jet, speak Russian to communicate with her cosmonaut crewmates, conduct a spacewalk, operate the robotic arm on the ISS and even fix the habitable satellite's toilet.

Joining NASA meant leaving her 14-person lab behind. But Rubins gained the rare opportunity to collaborate with dozens of scientists in fields as diverse as cell biology and astrophysics. On the space station, she'll be "their hands, eyes and ears," conducting about 100 experiments over five months.

She will, for instance, probe how heart cells behave when gravity doesn't get in the way. And she'll test a hand-held DNA sequencer, which reads out the genetic information stored in DNA and will be important to future missions looking for signatures of life on Mars.

At times, Rubins will be both experimenter and subject. In one study, she will observe bone cells in a lab dish, comparing their behavior with what happens in a simulated gravity-free environment on the ground. Because astronauts in space are vulnerable to rapid bone loss, CT scanning before and after the mission will also document changes in Rubins' own hip bone.

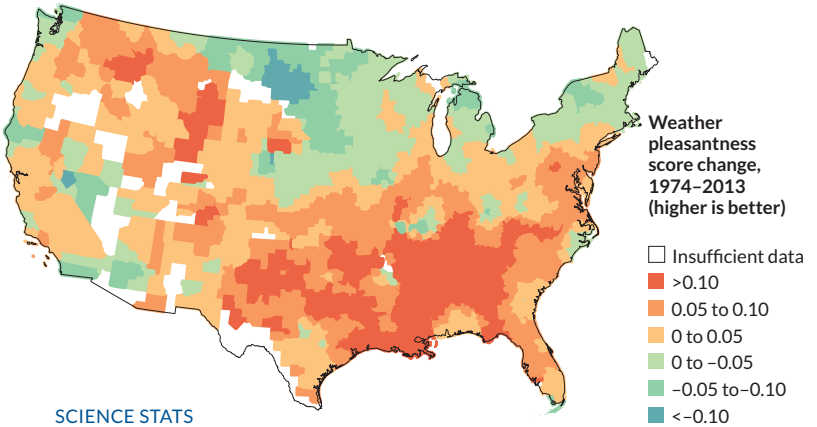
Rubins is particularly eager to examine how liquid behaves in microgravity on a molecular scale. In 2013, Canadian astronaut Chris Hadfield created an Internet sensation when he demonstrated that wringing out a wet washcloth in space caused water to form a bubble that enveloped the cloth and his hands. "It's incredibly bizarre," Rubins says. Understanding how fluids move in test tubes in space will help NASA plan for Mars exploration, among other applications.

Before any of the research can begin, Rubins has to get off the ground. As treacherous as accelerating to 17,500 miles per hour may sound, she's not worried.

"An important part of the training experience is making all the information and skills routine," she says. She predicts that sitting down in the Soyuz spacecraft, pulling out her procedures and getting ready to launch will feel a lot like going into the lab and picking up a pipette — "a normal day at the office."

Until the engines turn on, anyway. "I think it's going to feel different when there's a rocket underneath."

— Siri Carpenter



SCIENCE STATS

Pleasant weather may be history

Americans have climate change to thank for a decades-long spate of milder winters. Around 80 percent of U.S. residents live in counties where the weather has become more pleasant over the last four decades (see map). That trend won't last, however: Researchers predict in the April 21 *Nature* that 88 percent of Americans will experience noticeably worse weather by 2100 than they do today.

The researchers created a weather pleasantness index to rank weather conditions. Hot, humid summers cost points, while mild winters added points. In the contiguous United States, winter warming has outpaced increases in summertime temperature and humidity. But if greenhouse gas emissions continue unabated, summer weather will become less pleasant over the coming decades, potentially sparking increased public interest in combating climate change, the researchers predict. — *Thomas Sumner*

80
percent
Portion of Americans living in counties that experience better weather today than in 1974

88
percent
Portion of today's Americans who live in counties that will have worse weather by 2100

INTRODUCING

Chewbacca is a hairy weevil

In a galaxy far, far away, Chewbacca is a towering Wookiee. On Earth, he's a small furry beetle.

On an island off the coast of Papua New Guinea, researchers discovered four new species of weevil, one of which they named after the *Star Wars* character. *Trigonopterus chewbacca* is a black, flightless beetle about 3 millimeters long that thrives in the tropical forests of New Britain. Although *T. chewbacca* doesn't resemble its namesake in size, the dense hairlike scales covering its head and legs reminded the researchers of Chewbacca's fur.

Before these finds, *Trigonopterus* beetles hadn't been spotted on New Britain. The discovery of *T. chewbacca* and three relatives — *T. obsidianus*, *T. puncticollis* and *T. silaliensis* — suggests that the genus may have colonized the island at least four separate times, the team from Germany and Papua New Guinea reports April 21 in *ZooKeys*.

T. chewbacca joins the ranks of other insects with a *Star Wars* moniker. Among its peers: a furry moth also named after the heroic Wookiee, a wasp named for Yoda and a Darth Vader slime-mold beetle. — *Cassie Martin*

Giant pandas, *Ailuropoda melanoleuca*, are a vocal species, but scientists don't yet know why pandas have such good hearing.

HOW BIZARRE

Pandas' hearing is ultrasonic

Giant pandas have better ears than people — and polar bears. Pandas can hear surprisingly high frequencies, conservation biologist Megan Owen of the San Diego Zoo and colleagues report in the April *Global Ecology and Conservation.*

The scientists played a range of tones for five zoo pandas trained to nose a target in response to sound. Training, which took three to six months for each animal, demanded serious focus and patience, says Owen, who called the effort "a lot to ask of a bear."

Both males and females heard into the range of a "silent" ultrasonic dog whistle. Polar bears, the only other bears scientists have tested, are less sensitive to sounds at or above 14 kilohertz. Researchers still don't know why pandas have ultrasonic hearing. The bears are a vocal bunch, but their chirps and other calls have never been recorded at ultrasonic levels, Owen says. Great hearing may be a holdover from the bears' ancient past. — *Amy McDermott*

CLOCKWISE FROM TOP: P.J. EGAN AND M. MULLIN/*NATURE* 2016; M.H. VAN DAM *ET AL*/*ZOOKEYS* 2016; SAN DIEGO ZOO

BODY & BRAIN

‘Overweight’ may be healthiest BMI

Optimal body mass index on the rise, long-term study finds

BY ESTHER LANDHUIS

Packing on a few pounds may not be such a bad thing.

As a group, overweight people are living the longest nowadays, researchers report in the May 10 *JAMA*. And obese people seem to be at no higher risk of dying than those of normal weight. The new analysis, based on an almost four-decade study in Denmark, fuels ongoing debate about what’s a healthy body mass index — especially in light of rising obesity rates (*SN: 5/14/16, p. 5*), improved heart health treatments and other factors influencing health and longevity.

“This is a very carefully done study,” says Rexford Ahima, a physician who studies endocrine disorders at the Perelman School of Medicine at the University of Pennsylvania. The findings strengthen the notion that “BMI as a number alone may not be sufficient to predict health and risk of death. It has to be taken within context.” Ahima was not involved in the research but has analyzed previous studies urging a rethink of how BMI influences mortality.

Researchers screen for obesity by calculating BMI — a fairly crude measurement of body fat reached by dividing a person’s weight in kilograms by the square of height in meters. People with BMIs between 18.5 and 24.9 are considered normal. A BMI between 25 and 29.9 is “overweight”; 30 and above is “obese.”

Many studies suggest that obese individuals face a higher risk of heart disease, stroke and other ills. But some analyses have found that heavier folks may not be in such dire straits. In one study of people with type 2 diabetes, those with normal weight when diagnosed were more likely to die during the study than those who were overweight or obese (*SN: 9/8/12, p. 13*). And a 2013 meta-analysis of 97 studies found that being overweight was associated with lower risk of death during study periods than having a normal BMI — a surprising finding that echoed a 2005 study by the same researchers.

> “BMI as a number alone may not be sufficient to predict health and risk of death.”
>
> REXFORD AHIMA

In the new analysis, Børge Nordestgaard, a clinical biochemist at Copenhagen University Hospital, and his team studied more than 100,000 adults. Three groups of white Danes, recruited about 15 years apart, reflected the general population in Copenhagen.

From 1976 to 2013, the BMI associated with the lowest risk of death during the study period increased from 23.7 to 27. That falls squarely in the overweight category. What’s more, obese individuals had the same mortality risk as people in the normal range, the analysis finds. That trend held even when researchers took into account potentially confounding factors, including age, sex, smoking status and a history of cardiovascular disease or cancer.

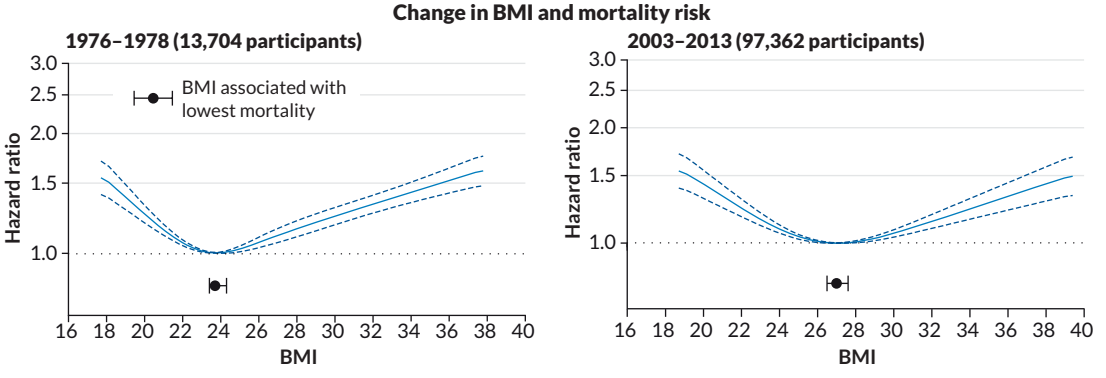
While some might misinterpret the study to mean “you can eat as much as you like,” this is not what the findings suggest, Nordestgaard says. Rather, the results indicate that people who are moderately overweight might not need to worry as much as they had in the past. That might be because better treatments are now available for high blood pressure, high cholesterol and other risk factors for heart disease, Nordestgaard speculates. “So maybe you can be overweight if you have [these conditions] treated.” But the study was not designed to address whether improved health care actually caused “healthy” BMI values to creep up over time.

It’s also unclear whether the results apply to other ethnic groups. A substantial fraction of Asians, for instance, develop type 2 diabetes and heart disease despite having BMIs lower than the existing cutoff point for being overweight.

The findings underscore the idea that a person’s BMI does not tell the whole story. While this measure is good for comparing populations, it is not as useful for evaluating individuals and their risk for disease and death, Ahima says. Interpreting an individual’s BMI depends on many other factors, he says, including “whether you are man or woman, how much muscle you have, how physically fit you are and what diseases you have.” ■

Healthier heavy

A study of adults in Copenhagen shows that, since the 1970s, the BMI with the lowest mortality risk has shifted from 23.7 to 27. The U-shaped curves track the association between BMI and mortality (a hazard ratio of 1 is associated with the lowest mortality risk). SOURCE: S. AFZAL *ET AL*/*JAMA* 2016



E. OTWELL

Present-day tarsiers (one shown) evolved from Asian ancestors that looked much the same tens of millions of years ago, new fossil discoveries suggest.

HUMANS & SOCIETY

Climate shift altered primate evolution

Fossil finds may explain why humans arose in Africa, not Asia

BY BRUCE BOWER

Fossil discoveries in southern China point to an evolutionary crossroads around 34 million years ago that resulted in humans evolving in Africa rather than Asia, scientists say.

The fossil finds date to a period when a sharply cooler and drier climate, combined with upheavals of landmasses that forged the Himalayas and the Tibetan Plateau, destroyed many tropical forests in Asia. Paleontologist Xijun Ni of the Chinese Academy of Sciences in Beijing and his colleagues suggest that those changes sent surviving primates scurrying south. The forerunners of monkeys, apes and humans, also called anthropoids, were then largely replaced in Asia by creatures related to modern lemurs, lorises and tarsiers. The new Chinese discoveries provide the first fossil evidence of this shift, the researchers report in the May 6 *Science*.

"The focal point of anthropoid evolution shifted at some point from Asia to Africa, but we didn't understand when and why the shift occurred until now," says paleontologist and study coauthor K. Christopher Beard of the University of Kansas in Lawrence.

Still, the scarcity of Asian primate fossils from that time relative to those from Africa leaves the matter unsettled. Egyptian sites in particular have yielded numerous primate fossils dating from around 37 million to 30 million years ago.

Excavations from 2008 to 2014 in southern China produced 48 teeth, some still held in jaw fragments, from six new fossil primate species, Beard says. These primates were tree dwellers and had assembled in a region located far enough south to retain forested areas. The new finds provide a rare glimpse of Asian primates that managed to weather the climate shift.

This lower jaw comes from a fossil primate unearthed in China. Climate change some 34 million years ago shrank forests and altered the distribution of primates in Asia.

Fossil teeth of one ancient species look much like those of modern tarsiers. These tiny, bug-eyed primates now live on Southeast Asian islands. "Tarsiers are 'living fossils' that can trace their evolutionary history back tens of millions of years in Asia," Beard says.

Only one of the new Chinese species was an anthropoid, Ni's group concludes. The researchers classify that animal as part of a line of Asian anthropoids previously identified from roughly 40-million-year-old tooth and jaw fragments found in Myanmar, just across China's southwestern border (*SN: 10/16/99, p. 244*).

Ni's team suspects that anthropoids evolved in Asia from earlier primates around 55 million years ago (*SN: 6/29/13, p. 14*). If so, anthropoids must have reached Africa before the 34-million-year-old climate shift devastated forests across Asia. Those intercontinental migrants would then have evolved into present-day monkeys, apes and humans. Investigators already knew that forests in Africa survived the ancient cooldown better than those in Asia.

Only one other Asian site, in Pakistan, has yielded anthropoid fossils of comparable age to the Chinese finds. The Pakistan fossils consist solely of teeth.

Asian anthropoids died out a few million years after the continent's tropical forests began to shrink, Beard suspects.

Too few ancient Asian primate fossils have been found to say whether the southern Chinese discoveries signal a continent-wide survival of lemur and loris ancestors after 34 million years ago, says evolutionary anthropologist Blythe Williams of Duke University. The fossils also could represent an isolated population that went extinct, she says.

The ancestors of modern lemurs and relatives of lorises living in equatorial Africa and Madagascar must have also reached Africa by 34 million years ago, Williams proposes. Not enough Asian forest remained at that time to support a migration of primates discovered by Ni's team to Africa or Madagascar, she suspects. ■

FROM TOP: STEFAN MUNDER/FLICKR (CC BY 2.0); KU NEWS SERVICE/UNIV. OF KANSAS

HUMANS & SOCIETY

Florida inhabited surprisingly early

More evidence puts people in North America before Clovis

BY BRUCE BOWER

Big-game hunters of the Clovis culture have just gotten the biggest blow yet to their reputation as North America's earliest settlers. At least 1,000 years before Clovis people roamed the Great Plains, a group of hunter-gatherers either butchered a mastodon or scavenged its carcass near Florida's Gulf Coast.

Stone tools discovered in an underwater sinkhole in the Aucilla River show that people were present at the once-dry Page-Ladson site about 14,550 years ago. The Clovis people appeared in North America around 13,000 years ago.

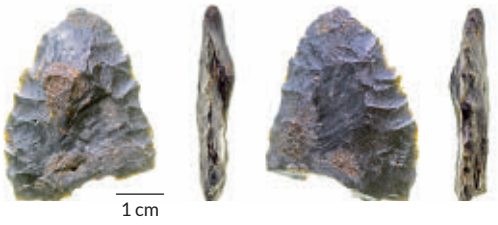
A team led by geoarchaeologists Jessi Halligan of Florida State University in Tallahassee and Michael Waters of Texas A&M University in College Station report the new findings May 13 in *Science Advances*.

Radiocarbon dating of twigs, seeds and plant fragments from submerged sediment layers provides a solid age estimate for six stone artifacts excavated by scuba divers. Five of those finds consist of thin pieces of stone hammered off chunks of rock. Divers also recovered part of a stone instrument for cutting. These artifacts differ substantially from long spearpoints used by Clovis people.

Excavations from 2012 to 2014 uncovered animal bones, too. The bones indicate that Florida's ancient hunter-gatherers lived alongside mastodons, bison and other large creatures for about 2,000 years before the animals died out about 12,600 years ago.

This research shows that the Page-Ladson site "is one of the best cases for pre-Clovis archaeology in the Americas," says geoarchaeologist Vance Holliday of the University of Arizona in Tucson.

A human presence so early in North America's southeastern corner aligns with growing evidence that people reached a land bridge connecting northeastern Asia to what's now Alaska around 23,000 years ago before entering the Americas perhaps 18,000 to 16,000 years ago (*SN: 8/22/15, p. 6*).



Excavation of a submerged archaeological site in Florida produced evidence, including this stone artifact shown from different angles, that people lived there 14,550 years ago.

From 15,000 to 14,000 years ago, humans explored and settled many parts of the Americas. Evidence of hunter-gatherers from that time comes from sites in Oregon (*SN: 8/11/12, p. 15*), Texas (*SN: 4/23/11, p. 12*) and Chile (*SN: 12/26/15, p. 10*). Those discoveries have chipped away at the popular view that the Clovis people were the New World's first inhabitants. But some researchers have questioned whether these sites are as old as reported.

Previous pre-Clovis finds at Page-Ladson have come under fire, too. Underwater investigations of the site from 1983 to 1997 yielded eight stone artifacts and a mastodon tusk displaying parallel grooves possibly made by stone

BODY & BRAIN

Acid reducers may harm blood vessels

Lab study shows how heartburn drugs could cause side effects

BY MEGHAN ROSEN

A popular type of heartburn drug could hasten wear and tear of blood vessels.

Proton pump inhibitors, or PPIs, gunk up cells that typically line the veins and arteries like a slick coat of Teflon, researchers report online May 10 in *Circulation Research*. Excess cellular junk ages the cells, which could make blood vessels work less smoothly.

The results, though controversial, are the first inkling of evidence that might explain why PPIs have recently been linked to so many different health problems, from heart attacks to dementia.

"The authors present a compelling story," says nephrologist Ziyad Al-Aly of the Veterans Affairs St. Louis Health Care System. It begins to outline how using PPIs could spell trouble later on. But, he notes, the study has one big limitation: It was done in cells, not people.

Gastroenterologist Ian Forgacs of King's College Hospital in London agrees. Drawing conclusions about humans from cells grown in the lab requires "a huge leap of faith," he says. So far, scientists have found only correlations between PPIs and their alleged side effects. "We need to know whether these drugs really do cause dementia and coronary disease and renal disease," he says.

In the last few decades, proton pump inhibitors have emerged as a kind of wonder drug for heartburn. The drugs switch off molecular machines that pump acid into the stomach, so less acid surges up to burn the esophagus.

In 2012, nearly 8 percent of U.S. adults were taking prescription PPIs, according to a survey published last year in *JAMA*. (Some PPIs are also available over the counter.) Many people use PPIs for longer than they're supposed to, says study coauthor John Cooke, a cardiologist at Houston Methodist Research Institute in Texas. "These are very powerful drugs — they're not Tums," he says.

Several of the drugs' side effects are still under debate. And if PPIs do increase the risk of dementia, say, or kidney disease, no one knows how.

Cooke and colleagues explored what chronic exposure to the drugs, which travel through the bloodstream, does to cells lining the blood vessels. Human cells treated with a PPI called esomeprazole (sold as Nexium) seemed to age faster than untreated cells. The cells lost

CSFA

implements. An initial radiocarbon date of about 14,400 years for these finds, as well as a proposal that people had butchered the mastodon, drew challenges from several researchers.

New radiocarbon dates and stone tool discoveries identify Page-Ladson as a "slam-dunk pre-Clovis site," Waters says.

In addition, a reexamination of grooves on the mastodon tusk — conducted by paleontologist and study coauthor Daniel Fisher of the University of Michigan in Ann Arbor — finds that tool users probably made those marks while removing the tusk from the animal's skull.

Florida's pre-Clovis people probably had plenty of opportunities to hunt or scavenge the remains of such creatures. High concentrations of *Sporormiella* spores, a dung fungus peculiar to plant-eating animals, turned up in several submerged sediment layers. That evidence indirectly points to mastodons and other now-extinct animals inhabiting Florida at the same time as pre-Clovis humans. No signs of *Sporormiella* appear in sediment dated to about 12,600 years ago, roughly the time when researchers suspect many large North American animals died out. ■

their youthful shape and instead "looked kind of like a fried egg," Cooke says. They also lost the ability to split into new cells, among other signs of aging.

Cooke traced the rapid aging to mishaps in acid-filled cellular chambers called lysosomes. These chambers act as tiny garbage disposals; they get rid of junk such as broken-down proteins. But PPIs, which work so well at shutting down acid production in the stomach, seem to shut down the acidic garbage disposals, too, the researchers find. That causes damaged proteins to pile up.

Mucking with blood vessels' lining could trigger all sorts of problems. For instance, instead of gliding easily through, platelets and white blood cells could get hung up, sticking to vessel walls like Velcro. "That's how hardening of the arteries starts," Cooke says.

The next step is to see if similar damage actually occurs in people. ■

GENES & CELLS

Genes for giraffes' long necks found

Influences on embryonic development may explain length

BY TINA HESMAN SAEY

Giraffes' genes tell a not-so-tall tale about growing necks to great lengths.

Tweaks to genes important for development may account for both the giraffe's stature and turbocharged cardiovascular system, researchers report May 17 in *Nature Communications*.

Researchers compiled the genetic instruction book, or genome, for both the giraffe and the okapi, its short-necked closest living relative. Those two species' most recent common ancestor lived about 11.5 million years ago, says Douglas Cavener, a geneticist at Penn State University. Overall, giraffes and okapis still have very similar genes, with 19.4 percent that are identical.

The researchers compared giraffe, okapi and cattle genomes to see what sets giraffes and okapis apart from other ungulates. About 400 genes differ between those species and cattle.

Additional comparisons revealed 70 genes in which giraffes have DNA differences from all other mammals that have been analyzed. Those uniquely tweaked genes could be responsible for giraffes' unusual height and physiology, the researchers reasoned.

Among the giraffe's most distinctively altered genes are some that are well known to regulate embryo development. For instance, the team found alterations in several genes that govern skeletal development, including the gene *FGFRL1*.

Giraffes' long necks and strong hearts may have resulted from changes to genes that control embryonic development.

D. CAVENER

FGFRL1 encodes a protein that helps regulate the size of body segments. Giraffes have the same number of vertebrae in their necks as okapi and other animals do, but the bones are bigger. The giraffe version of the FGFRL1 protein contains seven amino acids that are different from those found in other mammals. Those amino acid differences may change the way the protein works and allow giraffes' body parts to grow larger than those of other animals.

Some of the same genes that gave the giraffe its long neck — *FGFRL1* included — may also be involved in strengthening the cardiovascular system to pump blood from the heart all the way to the giraffe's brain, the researchers find. Such multifunctional genes would have allowed coordination of giraffes' adaptations, Cavener says.

The researchers "provide some very compelling candidates" for genes that shaped giraffe evolution, says Michael Hiller, an evolutionary genomicist at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, Germany. More research is needed to show that fiddling with those genes really could have turbocharged giraffes' hearts and supersized their bones, Hiller says. He doubts the researchers have found all the genetic secrets to giraffes' many evolutionary innovations.

Although giraffes have a unique appearance, the statuesque leaf eaters don't possess any new genetic tricks, says Cavener. "Giraffes' novelties almost certainly weren't created by new genes or pathways but by modifications of genes and pathways universal to all mammals." ■

ATOM & COSMOS

Aging moon mission still going strong

After 7 years, NASA orbiter continues to discover lunar secrets

BY CHRISTOPHER CROCKETT

Not all cosmic mysteries lie light-years away. Some secrets are being unearthed on our nearest neighbor, about a quarter of a million miles from home.

For almost seven years, NASA's Lunar Reconnaissance Orbiter has been keeping a close eye on the moon. During its tenure, the spacecraft has cataloged craters, pinpointed subsurface deposits of water ice and found evidence of recent volcanic activity. It has even witnessed crashes by three other spacecraft.

"No other mission has orbited the moon for as long as LRO has," says geologist Noah Petro of NASA's Goddard Space Flight Center in Greenbelt, Md. Constant lunar vigilance has "really pushed our understanding of how the moon changes today, over the last billion years and what happened early on." A July 15 special issue of *Icarus* celebrates the mission's many discoveries, which flesh out not only the moon's story, but also reveal how Earth and the other rocky planets have been pummeled by space debris over the last 4 billion or so years.

When LRO launched on June 18, 2009, its goals were more modest. The spacecraft was sent to scout landing sites for future astronaut expeditions, hunt for resources such as water and better understand the radiation hazards that human crews traveling to the moon would face. Since completing its original one-year assignment, the mission has been extended several times. LRO plans to stay busy through September, and the LRO team has asked NASA for two more years.

Water ice turned up in some unexpected places. Other spacecraft had previously seen hints of water, but none could map precisely where it was. Researchers suspected that water lay within permanently shadowed craters at the poles, and LRO did find evidence of ice there. But LRO also found that not all shady spots harbor water, and not all water is found in the shadows — some appears to hide under soil that sits in direct sunlight.

"That was a bit of a surprise," says LRO project scientist John Keller, also at Goddard. Looking at temperature alone, it seems, isn't enough for understanding the history of water on the moon. In the polar shadows, where temperatures hover around –250° Celsius, water ice can endure for billions of years. But elsewhere, water may have been trapped more recently and protected by the terrain. "There's an interplay with time, temperature and topography underlying this water story," Keller says.

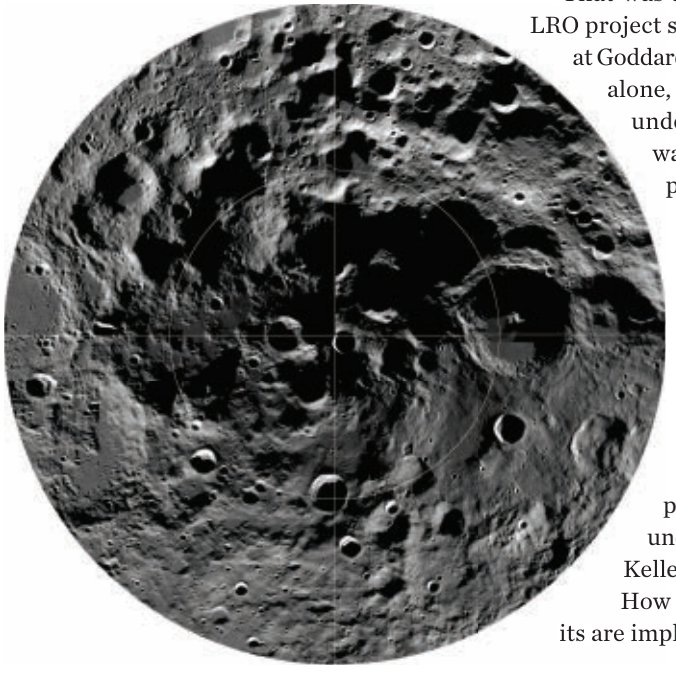
How the various water deposits are implanted and shuffled about is one enduring puzzle. How small subterranean pockets stayed warm for so long after the moon formed is another. Lava oozed on the surface in the last 100 million years, judging by smooth, dark terrains that are sparsely cratered. "This flies in the face with what was known about the moon," Petro says. "We thought lunar volcanism ended about a billion years ago."

Some changes are much more recent. In 2013, Earth-based telescopes detected a flash of light from the moon. LRO checked it out and found a new crater 18 meters across. "What was surprising was how far the ejecta went," Keller says. Debris had been tossed 35 kilometers — much farther than expected from an impact with a space rock estimated to be only about a meter wide.

Understanding what's currently hitting the moon and the traces those objects leave is crucial to interpreting the history of impacts plastered across the lunar surface. Similar impacts also affected Earth, but the signs of most have been erased by weather and geologic forces. "The moon is our way of studying the history of the Earth since the creation of the Earth-moon system," Petro says.

One of the seven instruments that LRO carries is a laser altimeter, a beam of light that scans and maps the surface in exquisite detail. "That's been a game changer," says Simone Marchi, a planetary scientist at the Southwest Research Institute in Boulder, Colo. "We can use the topography data to find old degraded craters that otherwise would not be easily detected in imagery."

Detailed maps reveal craters on top of other craters, laying out a rough sequence of when things hit the moon. Astronauts have brought back samples from some of these terrains, allowing researchers to use radiogenic dating to figure out when craters formed. That in turn supplies a record of what was smacking into other planets and asteroids. "We have a deep understanding of collisions going back to the beginning of the solar system," Marchi says. "That can only be done with the moon." ■



Water ice lurks within permanently shadowed craters at the moon's south pole, seen in this mosaic from the Lunar Reconnaissance Orbiter.

LRO/GSFC/NASA, ARIZONA STATE UNIV.

GENES & CELLS

How a Galápagos bird got tiny wings

Cormorant's flightlessness tied to several genetic changes

BY TINA HESMAN SAEY

Garbled signals from cellular antennas may have grounded the Galápagos cormorant.

Galápagos cormorants (*Phalacrocorax harrisi*) are the only cormorant species with wings too small to lift the birds off the ground. Broken primary cilia — antennas that cells need to receive developmental messages — left the birds with stunted wings, evolutionary biologist Alejandro Burga suggested May 12.

Burga, of UCLA, and colleagues compared DNA of flightless Galápagos cormorants with that of their close relatives, which have large wings and can fly. The researchers found more than 23,000 differences in more than 12,000 genes. Those changes have occurred within the last 2 million years, a short time by evolutionary standards.

The researchers narrowed down which genes might have had the biggest effect on cormorant evolution using a computer program that predicts whether a change in a gene will affect function. Of the genes predicted to have altered function, the researchers selected the 3.3 percent that have changed most drastically.

To determine what these genes do, Burga examined whether any of the human versions of these genes cause problems when they are mutated in people. Eight of the banged-up genes were associated with limb defects caused by faulty primary cilia, hairlike structures that grow from cells. The cilia receive signals important for cell development and functioning (*SN: 11/3/12, p. 16*). In people, genetic mutations that damage primary cilia lead to a variety of diseases, including developmental defects.

Normal versions of those eight genes are necessary for primary cilia to pick up signals sent by an important protein called hedgehog. Three other genes that are mutated in the flightless cormorants affect other aspects of the primary cilia.

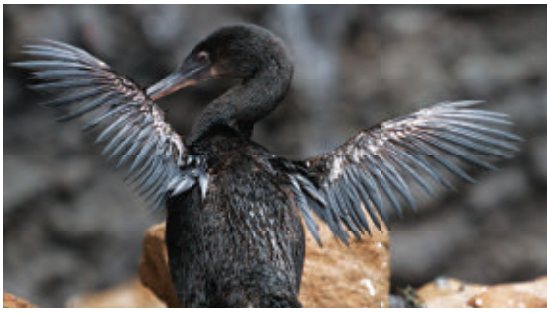
It wasn't clear whether the cilia defects were the primary cause of the birds' flightlessness. So Burga focused on 10 of the altered Galápagos cormorant genes predicted by the computer program to give the biggest functional and evolutionary consequences. Those genes would be the most important wing shrinkers, Burga and colleagues reasoned.

One of those genes is called *CUX1*. The protein it produces helps turn on other genes. Most vertebrates have nearly identical versions of the gene. But in flightless cormorants, four amino acids have been lost from the protein, suggesting that it can no longer do its job or does it poorly. In chickens, a defective form of *CUX1* shrinks wings. Galápagos cormorant's altered form of *CUX1* might also make wings smaller because it fails to turn on limb growth genes.

Many researchers would have left the story at that, says evolutionary biologist Ludovic Orlando of the University of Copenhagen. But "they made an effort to validate their findings."

Burga and colleagues wondered whether *CUX1* and the primary cilia changes were related. The team injected cells used to mimic skeletal development in lab dishes with the normal vertebrate version of *CUX1*. Activity levels of two cilia genes rose by about 50 percent. That is evidence that *CUX1* normally helps to regulate activity of primary cilia genes.

But the Galápagos cormorant version of *CUX1* barely budged activity of the cilia genes. It also was not as good at stimulating growth and development of bone cells as the normal version, the researchers found. Those findings strengthen the case that *CUX1* and primary cilia together were involved in shrinking the flightless fowl's wings. ■



Galápagos cormorants' wings have dwindled so much over the last 2 million years that the birds can no longer fly. New genetic data implicate faulty cellular antennas, called primary cilia, in shrinking the wings.

BRIAN GRATWICKE/FLICKR (CC BY 2.0)

MEETING NOTE

Faulty gene can turn colds deadly for babies, toddlers

A faulty virus-sensing gene can make the common cold or respiratory syncytial virus deadly for babies and toddlers, a new study suggests.

Almost all children catch those viruses by age 2 or 3 years. Most kids quickly clear the viruses, but about one in 1,000 are admitted to the hospital intensive care unit with severe pneumonia. The reason some tykes get really sick is in their genes, Samira Asgari, a computational biologist at the Swiss Federal Institute of Technology in Lausanne, reported May 12.

Asgari and colleagues examined protein-coding DNA of 120 otherwise healthy toddlers and babies who ended up on respirators because of colds or RSV infections. Eight had one of three rare variants in the *IFIH1* gene that cause the gene's protein to be shorter than normal. That affects the protein's ability to detect double-stranded RNA made by some viruses and to turn on virus-fighting defenses. As a result, the viruses replicate better than normal.

Children who carry the variants have a harder time combating a first-time virus infection. If a child survives, the immune system learns to fight the virus by other means, Asgari said. The team also found mutations in other genes that may account for why other children get severely ill from common respiratory viruses. — *Tina Hesman Saey*

ATOM & COSMOS

Kepler doubles its count of exoplanets

Telescope data confirm nine more worlds in 'habitable' zones

BY CHRISTOPHER CROCKETT

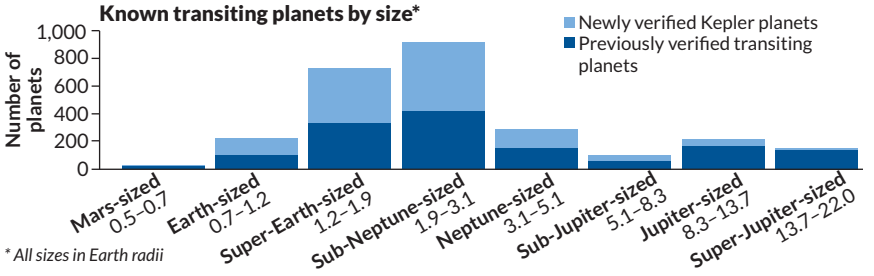
The galaxy is starting to feel a little crowded. Over 1,000 planets have just been added to the roster of worlds known to orbit other stars in the Milky Way, researchers announced May 10 at a news briefing. This is the largest number of exoplanets announced at once.

Most of the 1,284 worlds are larger than Earth but smaller than Neptune. Many of those are probably big balls of gas. But over 100 are smaller than 1.2 times the diameter of Earth. "Those are almost certainly rocky in nature," said Timothy Morton, an astrophysicist at Princeton University. Nine planets also lie within the habitable zone, the distance from a star where liquid water could conceivably collect on a planet's surface. Morton and colleagues detail the findings in the May 10 *Astrophysical Journal*.

This announcement roughly doubles the number of planets discovered by NASA's planet-hunting workhorse, the Kepler space telescope, which has now found 2,325 exoplanets. Kepler spent nearly four years staring at about 150,000 stars in the constellations Cygnus and Lyra, watching for subtle dips in starlight as planets crossed in front of, or transited, their suns. While Kepler has since moved on to other investigations (*SN: 6/28/14, p. 7*), this latest haul comes from those first four years of observing.

The planet bonanza comes courtesy of a new statistical calculation that allows researchers to feel confident that a detection is a real world. Impostors such as companion stars can mimic the signal of a planet. Traditionally, each candidate planet discovery must be followed up with intensive observations from ground-based telescopes. But with over 4,000 candidates in the queue, confirming each one would take a long time. The new calculation takes into account the details of how a passing planet should dim and brighten the starlight along with how common impostors should be and provides a reliability score for each candidate. Planets in this study are those with scores greater than 99 percent. ■

Plenty of planets The Kepler space telescope has added 1,284 planets to its tally. The graph shows the total number of transiting exoplanets discovered as of May 10. SOURCE: W. STENZEL/NASA AMES



* All sizes in Earth radii

MATTER & ENERGY

Physicists smash particle imitators

'Quasiparticle' collider could help devise better materials

BY EMILY CONOVER

Physicists of all stripes have one thing in common: They love smashing things together. This tradition has now been expanded from familiar particles like electrons and protons to quasiparticles, which act like particles but aren't.

A quasiparticle forms when the collective behavior of particles in a material creates a disturbance that behaves like a single particle (*SN: 10/18/14, p. 22*). The first quasiparticle collider, described in the May 12 *Nature*, allows scientists to probe the faux particles' behavior. It's a tool that could lead to improved materials for solar cells and electronic products.

"Colliding particles is really something that has taught us so much," says Peter Hommelhoff, a physicist at the University of Erlangen-Nuremberg in Germany. Colliding quasiparticles "is really interesting and it's really new and pretty fantastic."

Controlling fleeting quasiparticles is challenging, says study coauthor Rupert Huber, a physicist at the University of Regensburg in Germany. But quasiparticles are a useful way to understand how large numbers of particles interact in a solid.

One quasiparticle, called a hole, results from a missing electron that produces a void in a sea of electrons. The hole moves around the material like a positively charged particle. Its apparent movement is the result of many jostling electrons.

The quasiparticle collider slams holes into electrons. Using a short pulse of light, the researchers created pairs of electrons and holes in tungsten diselenide. Then, using an infrared pulse of light to produce an oscillating electric field, the team ripped the electrons and holes apart and then slammed them back together at speeds of thousands of kilometers per second — all within about 10 millionths of a billionth of a second.

The smashup left its imprint in light emitted in the aftermath, which the team analyzed to study the properties of the collision. For example, when holes get together with electrons, they can bind into an atomlike state known as an exciton. The collisions let the team estimate the excitons' binding energy — a measure of the effort required to separate the pair.

Understanding how quasiparticles behave is particularly pertinent for materials in solar cells, Huber says. When sunlight is absorbed in solar cells, it produces pairs of electrons and holes that must be separated and harvested to produce electricity. ■

E. OTWELL

EARTH & ENVIRONMENT

Relics of Earth's birth still linger

Traces of ancient isotope give insight into planet's origin

BY BETH GEIGER

Shaken-but-not-stirred remnants of Earth's earliest years still exist nearly 4.6 billion years later.

Researchers traced the footprints of an isotope that hasn't existed since Earth's early days to much younger lava from the Pacific and Atlantic oceans. That means reservoirs of the ancient mantle may be hidden deep inside the planet, geochemist Hanika Rizo and colleagues report in the May 13 *Science*.

It is spectacular that some of Earth's earliest materials may still be preserved, says Matthias Willbold, a geochemist at the University of Manchester in England. "We may have to revise our view of the Earth's internal structure."

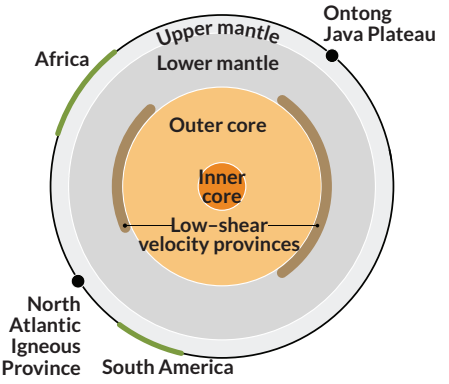
Earth formed about 4.6 billion to 4.5 billion years ago as planetary bodies collided and the debris accreted into a mass like a hot, rocky lint ball. Geologists have assumed that any relics of this beginning were mixed beyond recognition.

But Rizo's team found a surprise: Some modern flood basalts — vast sheets of lava from long-lasting eruptions — have unusually high tungsten-182 concentrations. That's significant because that isotope forms only from radioactive decay of hafnium-182, which existed only during Earth's first 50 million years. "These isotopes had to be created early," says Rizo, of the University of Quebec in Montreal.

Rizo's team measured tungsten-182 in flood basalts from Canada's Baffin Bay (part of the roughly 60-million-year-old North Atlantic Igneous Province) and near the Solomon Islands (part of the roughly 120-million-year-old Ontong Java Plateau in the Pacific). Flood basalt eruptions can tap into the deep mantle, Rizo says.

Tungsten-182 levels in the lavas varied, the team found, suggesting that the deep sources of these younger rocks were different pieces of Earth's oldest material, each with their own isotopic signature and history. The ancient remnants somehow escaped being mixed by convection currents in the mantle.

Two large zones in the deep mantle, called large low–shear velocity provinces, could be candidates for the ancient mantle remnants, Rizo says. ■



Large low–shear velocity provinces at the base of the mantle are possible remnants of ancient Earth, and sources for some lavas found in the North Atlantic Igneous Province and the Ontong Java Plateau.

T. DAHL/*SCIENCE* 2016

BODY & BRAIN

Crohn's genes block microbe messages

Normally, gut bacteria send signals that calm inflammation

BY MEGHAN ROSEN

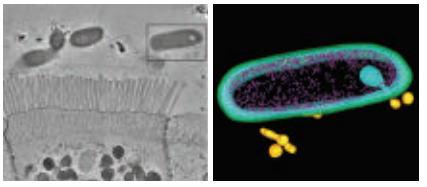
Good gut bacteria might not help people with Crohn's disease.

Protective microbial messages go unread in mice and human immune cells with certain defective genes, researchers report online May 5 in *Science*.

The findings are the first to tie together the roles of genes and beneficial microbes in the inflammatory bowel disease, says microbiologist Brett Finlay of the University of British Columbia in Vancouver, who was not involved in the new work.

"This is a major step forward in this area," he says. Human genes and friendly microbes work together to control inflammation, he says. "And when you muck that up, things can go awry."

In Crohn's disease, the immune system riles up too easily, triggering chronic inflammation. Researchers have linked the disease to glitches in nearly 200 genes, including *ATG16L1* and *NOD2*, which typically help kill bad bacteria.



A microbe (left, boxed) sends signals that calm the immune system in mouse intestinal cells (left, bottom). People with Crohn's disease may not get the messages, which are sent in pouches (right, yellow in microbe reconstruction).

Researchers have also reported that people with Crohn's have a different collection of gut microbes than healthy people do, says study coauthor Sarkis Mazmanian, a Caltech microbiologist. "There's a huge body of literature on the genome and on the microbiome," he says. But "no one knew what the interplay was between the two."

His team explored a potential link using a friendly gut microbe called *Bacteroides fragilis*, which sends out calming molecular messages that tell the immune system to tone down inflammation. Like letters inside envelopes, these messages travel in protective pouches called outer membrane vesicles, or OMVs.

Feeding message-filled OMVs to mice protects them from developing inflamed colons, or colitis — but not in mice lacking the Crohn's-linked genes *ATG16L1* and *NOD2*. When those mice receive a colitis-causing chemical, they succumbed to the disease, even after eating OMVs.

Mice without *ATG16L1* and *NOD2* genes "can't reap the benefits of the beneficial microbiota," Mazmanian says. Immune cells from human patients with defective versions of these genes didn't respond to OMVs either.

Mazmanian says finding ways to deliver *B. fragilis*' messages might help treat patients. Patients' cells dosed with just the contents of the OMVs (and not the protective pouch itself) actually got the message, his team finds. The treatment could have fewer side effects than other therapies, because it doesn't hamper the immune system, he says. ■

LIFE & EVOLUTION

Mitochondria go missing in microbe

Eukaryote breaks fundamental rule of complex life-forms

BY SUSAN MILIUS

A gut microbe collected from chinchilla droppings might be the first complex life-form to lack even a shred of a supposedly universal organelle.

Monocercomonoides, a one-celled gut microbe, apparently has no mitochondria, the organelles known as the cell's power plants. Cataloging DNA in the microbe turns up none of the known genes for mitochondrial proteins. Stealing genetic material from bacteria — which also survive without mitochondria — allowed the microbe to do without them, researchers report in the May 23 *Current Biology*.

Mitochondria are capsules that speckle the insides of all complex cells from pond scum to people, or so textbooks say. Some complex, or eukaryotic, cells look as if they have no mitochondria. So far, though, further searches have eventually detected mitochondrial remnants.

Monocercomonoides appears to have completely done away with mitochondria and the genes to make them, says study coauthor Anna Karnkowska, an evolutionary biologist now at the University of British Columbia in Vancouver.

This discovery marks "the most extreme mitochondrial reduction observed," says study coauthor Vladimír Hampl of Charles University in Prague.

The work also supports the idea that mitochondria lack a single core function. Although often described as cell powerhouses, mitochondria don't have much to do with supplying energy for cells living in low-oxygen or no-oxygen environments, Karnkowska says. For such cells, mitochondria can serve as more of a building studio. One supposedly essential mitochondrial function, scientists have said, is assembling clusters of iron and sulfur that activate useful cell compounds.

Bacteria and other simple, or prokaryotic, cells have their own assembly systems and don't need mitochondria to wall off the construction of iron-sulfur clusters. *Monocercomonoides* carries the genes for an assembly system that looks as if it was taken from bacteria.

The researchers made these discoveries while working out the DNA components that encode instructions for *Monocercomonoides*' proteins. There were no signs of chaperone proteins for conveying other proteins through mitochondrial membranes.

"Pretty amazing story," says Roland Lill of University of Marburg in Germany, who studies iron in cells. "The beauty of biology is that there are always amazing exceptions to basic biological rules." ■

MARK LADINSKY AND GREG DONALDSON/CALTECH

LIFE & EVOLUTION

Male giant water bugs win females by babysitting

There's nothing like a guy doing all the child care to win female favor.

In thumbnail-sized *Appasus* water bugs, females lay eggs on a male's back and leave him to swim around for weeks tending his glued-on load. For an *A. major* water bug, lab tests show an egg burden can have the sweet side effect of attracting more females, researchers in Japan report May 4 in *Royal Society Open Science*. Given a choice of two males, females strongly favored, and laid more eggs on, the male already hauling around 10 eggs rather than the male that researchers had scraped eggless.

Females still favored a well-egged male even when researchers offered two males that a female had already considered, but with their egg-carrying roles switched from the previous encounter. The formerly spurned suitor this time triumphed. "We conclude that sexual selection plays an important role in the maintenance of elaborate paternal care," says study coauthor Shin-ya Ohba of Nagasaki University. — *Susan Milius*

BODY & BRAIN

Mouse studies link Zika virus infection to microcephaly

Three new studies published May 11 further bolster the idea that Zika virus infection in utero causes birth defects.

One study shows that mice engineered to be susceptible to Zika can pass the virus to offspring via the placenta. In these pregnant mice, which have severely crippled immune systems, Zika infection can kill fetuses and developing brain cells, too, researchers at Washington University in St. Louis report in *Cell*. But the researchers can't say for certain whether the virus itself snuffs out cells, or whether damage to the placenta starves cells of oxygen.

Answers might come from two other mouse studies. Injecting Zika virus straight into the brains of fetal mice halts cell growth and kills cells, scientists in China report in *Cell Stem Cell*. Just five days after infection, embryonic mice already have brains smaller than normal.

Even stronger evidence comes from a strain of mice called SJL that were infected with the Brazilian Zika virus — no tinkering with the mice's immune systems required. Infected SJL mice transmitted the virus from placenta to pups, and newborn animals showed signs of microcephaly, an international team of researchers reports in *Nature*. But mice of a genetically different strain, called C57BL/6, resisted Zika's brain-damaging handiwork.

The results suggest that genetic differences could help explain why Zika strikes the babies of some pregnant women but not others, the authors say. — *Meghan Rosen*

BODY & BRAIN

Brain waves in REM sleep help store memories

Brain waves during REM sleep solidify memories in mice, researchers report in the May 13 *Science*.

Scientists suspected that the eye-twitchy, dream-packed slumber known as rapid eye movement sleep was important for memory. But REM sleep's influence on memory has been hard to study, in part because scientists often resort to waking up people or study animals — a stressful experience that might influence memory in different ways.

Richard Boyce of McGill University in Montreal and colleagues interrupted mice's REM sleep in a more delicate way. Using a technique called optogenetics, the team blocked brain oscillations called theta waves in the hippocampus, a brain structure involved in memory, during REM sleep. This light touch meant that mice stayed asleep but had fewer REM-related theta waves in their hippocampi.

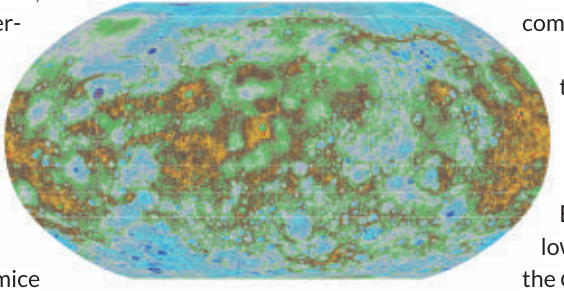
Usually, postlearning sleep helps strengthen memories. But mice with disturbed REM sleep had memory trouble, the researchers found. Curious mice spend more time checking out an object that's been moved to a new spot than an unmoved object. But after the sleep treatment, the mice seemed to not remember objects' earlier positions, spending equal time exploring an unmoved object as one in a new place. These mice also showed fewer signs of fear in a place where they had previously suffered shocks.

Interfering with theta waves during other stages of sleep didn't seem to cause memory trouble, suggesting that something special happens during REM sleep. — *Laura Sanders*

ATOM & COSMOS

Mercury's stunning landscape mapped

Mercury has never looked better. Volcanic plains, craters, mountains and valleys are showcased in the first complete topographic map of the innermost planet, released May 6.



USGS

Mercury's varied terrain is highlighted in this new topographic map. Reds and yellows show elevations that are higher than the global average; bluer colors are lower.

Stitched together from over 100,000 images taken by NASA's now-defunct MESSENGER spacecraft, the global catalog of landscapes provides data that researchers can use to better understand the history and inner workings of the scorched world. Researchers also used X-ray data to map changes in chemical composition from place to place.

Mercury's highest point, in ancient terrain just south of the equator, rises 4.48 kilometers above the planet's average elevation, the data reveal. That's about half of Mount Everest's height above sea level. The lowest point lies on the smooth floor of the double-ringed Rachmaninoff basin, 5.38 kilometers below average — over three times the average depth of the Grand Canyon. — *Christopher Crockett*

PROTEINS of the Past

Reconstructing tiny pieces of history deepens understanding of evolution

By Jennifer Michalowski

The influenza virus is a quick-change artist. In a few decades, its genome can evolve as much as animal genomes can over millions of years. That means that the viral proteins, including those that alert our bodies to an infection, constantly reinvent themselves, threatening our immune systems and frustrating vaccine developers.

For Jesse Bloom, a biologist studying how evolution affects proteins, that relentless change is an opportunity. Thanks to data collected during past flu seasons, Bloom knows the exact genetic makeup of some ancestors of today's influenza viruses. His lab group at the Fred Hutchinson Cancer Research Center in Seattle uses that information to figure out how the viruses made their immunity-dodging transformations.

Bloom and others are part of a growing group of scientists who practice "evolutionary biochemistry." They seek to explain life's tremendous diversity and determine exactly how that diversity emerged. Rather than focusing on how plants or animals adapted to different environments, however, these researchers consider diversity on a much smaller scale: Their work aims to explain how the small set of proteins that powered primitive life-forms evolved into the millions of specialized proteins that drive biological processes today.

Exploiting the genetic records, Bloom can assemble virus proteins that existed in bygone times, then reconstruct how they evolved, one amino acid at a time. Other researchers are analyzing modern species to resurrect the ancestral forms of biological molecules that have evolved over millions of years.

With a historical protein in hand, researchers can test how swapping out a single amino acid — as evolution might have done — changes how the protein flexes or folds and connects (or doesn't) with other molecules. By trying out alternate versions of a protein's history through stepwise amino acid changes, scientists can learn how a protein's physical form has both enabled and constrained its evolution.

Ultimately, this work might answer some long-standing questions: To what extent does evolution depend on chance events? Can evolution reach the same point by traveling different paths? How does biological complexity evolve? Such experiments are also helping researchers who study modern proteins sort out how the order of amino acids relates to biological function.

Form is function

That ordered series of amino acids is spelled out by the gene that holds the blueprint for a protein. Once the proper amino acids are strung together, they origami-fold into tiny structures with nooks and protrusions that determine what the protein does inside a cell. A protein's folded shape lets it grab on to specific bits of DNA or hasten certain chemical reactions. Mutations in a gene can shift the resulting protein's shape or alter subtle aspects of its behavior so that, over time, a protein's function can change. But the possibilities are not endless. New proteins that fall apart, fail to fold or don't perform as needed don't survive the tests of natural selection.

"The physical determinants of folding, stability, solubility, function and specificity are absolutely essential aspects of the evolutionary process," says University of Chicago biologist Joe Thornton. "That has not been widely appreciated or explicitly addressed until pretty recently." Now, Thornton says, it's clear that to understand molecular evolution, it's important to study proteins as functioning, physical objects.

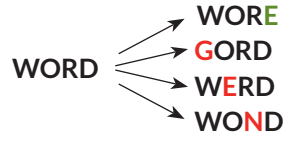
As they reconstruct proteins' pasts, researchers are finding that genetic mutations sometimes remodel a molecule just enough to give a chance to other mutations that would have failed earlier. That creates opportunities for new features and functions to evolve — an idea that biologists have considered for decades but have only just begun to explore in the lab.

Bloom and colleagues, for instance, used an influenza virus protein called nucleoprotein to examine how interactions among mutations have affected the overall evolution of the virus. Understanding the combined effects of several mutations could allow researchers to anticipate the short-term effects of new genetic variation. That knowledge could help improve forecasts of which viral strains are likely to circulate in upcoming flu seasons, important information for designing effective vaccines.

Comparing nucleoprotein genes from strains of the virus isolated in 1968 and 2007, Bloom's team mapped out the most likely steps by which the 1968 protein morphed into its newer form. Though nucleoprotein still plays the same role that it did in 1968 — aiding in the assembly of viral RNA — 33 of its 498 amino acids changed over those four decades, and a few changed more than once, the researchers reported in 2013 in *eLife*.

Bloom's team built the 1968 nucleoprotein, then tested the effects of introducing each historical mutation. Some of the mutations affected parts of the protein that tip off a person's immune cells that an invader is present — they probably helped the flu virus avoid detection. But on their own, some of those changes were bad for the virus: The nucleoprotein could no longer stay properly folded long enough to do its job.

Step by step Evolutionary biologist John Maynard Smith compared protein evolution to a word game: Every sequence of letters created with a single-letter change must be a word. In the word game and in evolution, some changes are tolerated only after other changes are made. SOURCE: L. GONG *ET AL*/*ELIFE* 2013

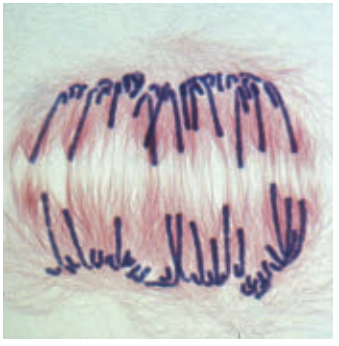


OPPOSITE: JAMES PROVOST

During the course of the nucleoprotein's evolution, some mutations boosted the protein's stability, giving it a bit of a buffer. When later mutations occurred, allowing the virus to buck immune recognition, these earlier changes probably held the structure stable so the protein could still function.

When a mutation's effects depend on other mutations, this interplay is called epistasis. These interactions within individual molecules have been important in shaping evolutionary trajectories, says University of Oregon biophysicist Michael Harms, who is studying how diverse functions evolved in a group of proteins called s100s. He calls epistasis "the common feature in all of evolution."

Codependent interactions don't occur just between pairs of mutations. They can be significantly more complex. Analyzing data from other labs, Harms has found epistatic interactions involving up to six different mutations. Such interplay means that in many cases, if genes had transformed themselves just a bit differently, evolution would have veered onto a different course.



A change in one amino acid transformed a protein that catalyzed reactions to make building blocks of DNA into one that acts as a scaffold during cell division (mitosis shown).

Green light

Scientists call mutations that lay the groundwork for future change "permissive" mutations. Some protein functions came about only after permissive mutations modified an evolving molecule in highly improbable ways.

Thornton uses ancestral protein reconstruction to study how steroid hormones — which control stress responses, growth and sexual developmental in vertebrates — evolved partnerships with their receptors. Receptors are proteins that bind to specific partners to activate responses in the cell. By comparing steroid receptors in different species, Thornton can map the evolutionary relationships between the molecules and infer the likely amino acid sequence of their common ancestor. Then he introduces a DNA molecule that encodes the long-extinct protein into lab-grown cells. Those cells use the genetic instructions to manufacture a tiny piece of the deep past.

Many of Thornton's studies begin with a 450-million-year-old receptor protein that he and colleagues reconstructed in 2006. The protein gave rise to modern receptor molecules that are activated by different hormones. One receptor, the glucocorticoid receptor, responds to the stress hormone cortisol. The other, the mineralocorticoid receptor, controls levels of salt and other electrolytes in response to the hormone aldosterone. Thornton's team found that their reconstructed ancestor could be activated by both cortisol and mineralocorticoids.

A receptor that responded only to cortisol appeared 40 million years after the promiscuous receptor, Thornton showed. His team found a set of amino acid changes that converted the general ancestral receptor into the cortisol-specific one. But the mutations that changed the ancient receptor's preference couldn't have generated a functional receptor by themselves, experiments showed.

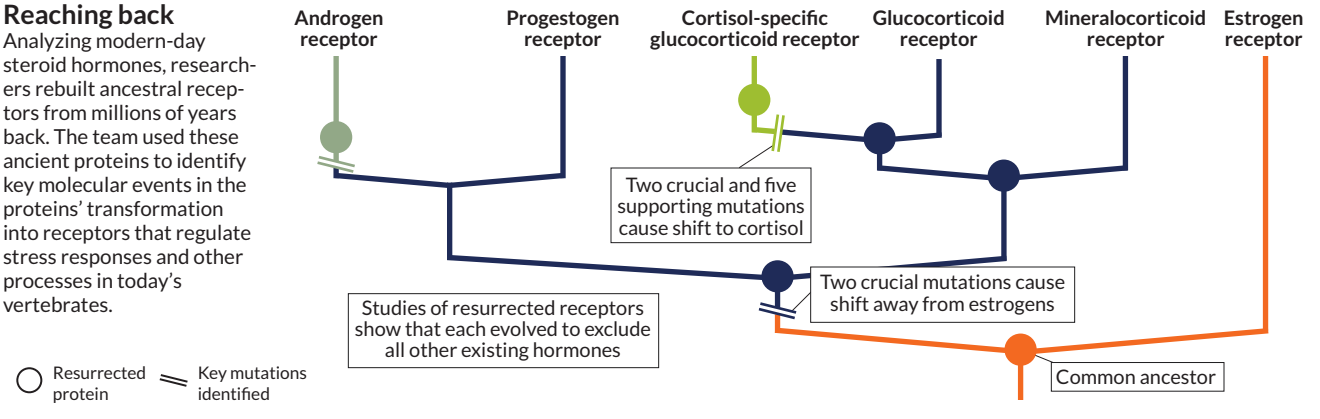
"The function-switching mutations are not tolerated on their own," Thornton says. They destabilize parts of the receptor. Like the flu virus's evolving nucleoprotein, the ancestral receptor's structure had to be buttressed before it could withstand the mutations that would make the receptor choosier.

Two amino acid changes quietly readied the ancient receptor for its transformation, Thornton and colleagues reported in 2009 in *Nature*. Without them, the path to the function-switching mutation would have been inaccessible. "If we were to wind back the clock and set history rolling again, it's very unlikely that those permissive mutations would occur," he says. "We would have ended up with a very different glucocorticoid receptor and a very different endocrine system."

Thornton and Harms, then a postdoctoral researcher in Thornton's lab at University of Oregon in Eugene, explored whether evolution could have taken an alternate route to the same end. Harms created and screened thousands of variants of the ancestral protein, searching for alternative mutations that might have set it up for the same functional switch. He

Reaching back

Analyzing modern-day steroid hormones, researchers rebuilt ancestral receptors from millions of years back. The team used these ancient proteins to identify key molecular events in the proteins' transformation into receptors that regulate stress responses and other processes in today's vertebrates.



FROM TOP: ANDREW S. BAJER/CELL IMAGE LIBRARY; HELEN PEARSON/*NATURE* 2012

found none, the researchers reported in *Nature* in 2014. Evolution, it seems, had acted on a rare opportunity.

Biophysical analyses of variant receptor proteins showed why so few mutations enabled cortisol-specific binding to evolve. Although certain parts need extra support, the receptor also needs to be able to transition between two forms: an inactive conformation when no cortisol is present, and a gene-activating conformation when the hormone binds. Some mutations stabilize the active form of the receptor too much, locking it into an "always-on" configuration. Mutations also had to be compatible with the ancestral protein on their own, before the function-switching mutations were introduced.

"A mutation has to fulfill all these requirements, and that is not easy to do," Thornton says. "That seems to be the explanation for why permissive mutations [for this functional switch] are so rare."

But not every new function is the result of complicated epistatic interactions. In January in *eLife*, Thornton and Ken Prehoda of the University of Oregon described an ancient protein that gained a completely new function by way of a single amino acid change.

The team studied the origins of an animal protein that helps cells orient themselves in space before dividing. Doing so is vital for positioning new cells in the right places within a growing body. Single-celled life-forms had to get this right before multicellular organisms could evolve.

Thornton, Prehoda and colleagues focused on a segment of the protein called GK_{PID} (for GK protein-interaction domain), which orients cells by acting as a scaffold during division. The billion-year-old ancestor of GK_{PID} did nothing of the sort. It was an enzyme predecessor to the modern guanylate kinase, which catalyzes a chemical reaction that cells use to make some of the building blocks of DNA. Amazingly, Thornton says, one mutation was enough to transform the ancestral protein from an enzyme to a working scaffold.

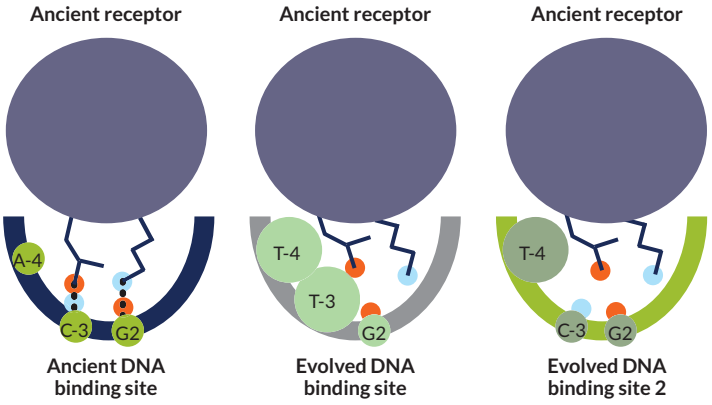
That surprising result is an example of why developing general theories about the physical principles shaping evolution requires a grasp of the evolutionary histories of a broader collection of proteins.

"Every time people take [a protein] apart, they see a new feature," Harms says. Fortunately, he says, thanks to faster computers, better software and a growing number of genomes to reference, research on ancestral protein reconstruction is on the rise.

Roads taken

While chance events can shift the landscape of evolution's possibilities, evolving proteins also have some freedom to explore. They can take more than one path to some functions.

Douglas Theobald, a biochemist at Brandeis University in Waltham, Mass., has seen this in his own investigations of an enzyme that many cells use to produce energy without oxygen. The enzyme, lactate dehydrogenase, evolved from structurally similar enzymes not just once, but at least four



The right fit A reconstructed ancient steroid receptor binds to a DNA site associated with estrogen signaling (left), but not to two others (middle and right) recognized by steroid receptors that evolved later. The receptor can't bind to the others due to physical incompatibilities with parts of the DNA.

times in different groups of organisms. By reconstructing the evolutionary events that transformed a similar enzyme, malate dehydrogenase, into lactate dehydrogenase, Theobald and colleagues found that two groups of single-celled parasites came by the same enzyme in different ways. The researchers reported the findings in *eLife* in 2014 and in *Protein Science* in February.

The work demonstrates that different genetic backgrounds may steer evolution along different paths in different organisms but still lead to similar outcomes, Theobald says. "Even if there is a lot of epistasis, there's still lots of different ways to the same function."

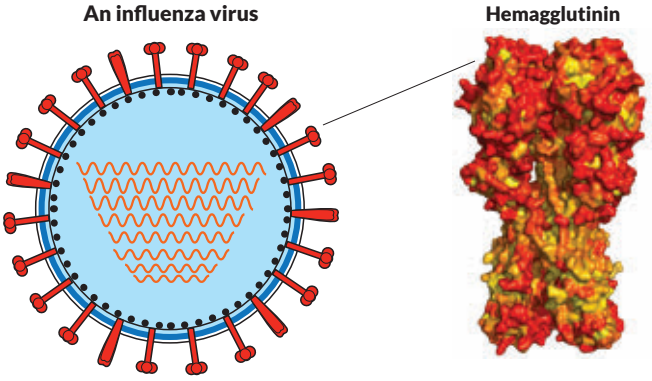
Biochemist Susan Marqusee of the University of California, Berkeley has also found that there's more than one way for a protein to do something new.

Marqusee collaborated with Thornton's team to compare how two bacteria, *Escherichia coli* and the heat-loving *Thermus thermophilus*, evolved enzymes that do the same job at very different temperatures. *T. thermophilus* thrives in hot springs, at temperatures that would cause most proteins to fall apart. Biochemists are eager to borrow from nature's strategies to engineer heat-tolerant proteins but have struggled to find general principles that account for this property. By reconstructing the common ancestor of the RNA-snipping enzyme known as H1 from *E. coli* and *T. thermophilus*, Marqusee's team found out how the bacterial protein takes the heat.

That 3-billion-year-old common ancestor was less stable than the enzyme that *T. thermophilus* uses today, the team reported in 2014 in *PLOS Biology*. As the heat-tolerant protein evolved, its stability steadily increased — not because of any one innovation, but by virtue of distinct biophysical strategies at different points in time.

"The physical chemistry doesn't really matter as long as in the end, they add up to the right phenotype," Marqusee says. Because evolution was able to take advantage of different amino acids to boost stability in a variety of

A.N. MCKEOWN *ET AL*/*CELL* 2014



Designing vaccines Most vaccines against influenza virus (left) aim at segments on the head of the viral protein hemagglutinin (right). The protein's head, recent research finds, is more likely to take on mutations (red means more likely). In contrast, the stalk of the protein is less amenable to mutations (yellow signifies less likely to mutate) and therefore may be a better target for vaccine development.

ways, the enzyme's growing resilience to hot environments didn't depend on the chance occurrence of a particular set of mutations.

Foggy future

Studies of how proteins have evolved in the past are unlikely to spell out how evolution will proceed in the future. "The emerging picture is that the role of chance is so great that long-term predictions of the future evolution of any protein is a very risky enterprise," Thornton says. But recent research does offer insights into how and why today's proteins do what they do.

One example comes from Thornton's work on how the DNA-binding sites on steroid receptors have evolved along with their DNA targets. The hormone-activated receptors act as transcription factors, binding to specific sections of DNA to switch on certain genes. In 2014, Thornton's team reported in *Cell* that a bulky amino acid in an ancestral protein prevented the protein from binding to the stretch of DNA favored by many of today's steroid receptors. The ancestral protein awkwardly bumped up against the DNA, unable to make enough contact to really grab on. The receptor gained its new specificity when mutations ended those obstacles and introduced new clashes that blocked its access to the former binding site.

Researchers often can't tell which differences between two related proteins make them behave differently. But reconstructing evolutionary paths can point them in the right direction.

Using ancestral reconstruction, Theobald and Brandeis colleague Dorothee Kern studied how Abl, a growth-promoting protein linked to chronic myelogenous leukemia, diverged from the related Src protein. The researchers wanted to know why the anticancer drug Gleevec binds to and shuts off Abl without obstructing Src, even though Src has a very similar structure. Theobald, Kern and colleagues identified 15 amino acids in Abl that are crucial for Gleevec binding. The amino acids influence how the protein transitions between two different configurations (that shape-shifting is disrupted in some patients with Gleevec-resistant cancers). The finding, published last year in *Science*, suggests that researchers may be able to develop better drugs by considering these conformational shifts.

Some proteins, or parts of proteins, might even be inherently more able to evolve than others. Certain parts of the fast-evolving viral protein hemagglutinin are unusually tolerant of change, Bloom and Bargavi Thyagarajan, who was a postdoctoral researcher in Bloom's lab, reported in 2014 in *eLife*. Antibodies against hemagglutinin are the immune system's best defense against influenza, but the protein is adept at escaping detection.

The researchers used a relatively new method called deep mutational scanning to build and test hemagglutinin proteins with nearly every possible amino acid change — about 10,000 in all — in viruses grown in the lab. In a host, changes that disguise hemagglutinin from the immune system would be advantageous. Even though there was no immune system to hide from in the lab, viruses still survived more changes to parts of hemagglutinin that would be recognized by an immune system than they did changes to other parts of the protein. Bloom and his graduate student Michael Doud reported a more detailed view of the protein and the areas that are more and less likely to tolerate mutations online on bioRxiv.org in April.

That's good for the virus, but bad for people. Hemagglutinin seems capable of accumulating change in the very sites that vaccine developers would like to remain the same. But the finding also suggests that flu vaccines designed to target less mutation-tolerant regions of hemagglutinin might be more likely to protect against the flu from season to season. That's a strategy some labs are already exploring — targeting the less-evolvable stalk of hemagglutinin's lollipop-shaped structure.

It's not yet clear *why* certain parts of the hemagglutinin protein tolerate change so well; Bloom hopes that studying the mutational tolerance of other proteins will help researchers figure that out.

"We're never going to be able to predict evolution precisely, because it's a highly stochastic process," Bloom says. "But I think we can make better forecasts about many of the evolutionary processes that affect us. These are really challenging problems, but I think we are getting to the point where we can use experiments and molecular understanding to help us think about these processes." ■

Explore more

- Tyler N. Starr and Joseph W. Thornton. "Epistasis in protein evolution." *Protein Science*. February 28, 2016.
- Michael B. Doud and Jesse D. Bloom. "Accurate measurement of the effects of all amino-acid mutations to influenza hemagglutinin." bioRxiv.org. April 7, 2016.

Jennifer Michalowski is a nomadic freelance science journalist.

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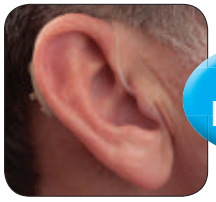

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NANO for the Heart

Scientists are designing tiny 'missiles' to destroy waxy plaques in blood vessels

By Sarah C.P. Williams

Careening through the bloodstream, a single nanoparticle is dwarfed by red blood cells whizzing by that are 100 times larger. But when specially designed nanoparticles bump into an atherosclerotic plaque — a fatty clog narrowing a blood vessel — the tiny particles can play an outsized role. They can cling to the plaque and begin to break it down, clearing the path for those big blood cells to flow more easily and calming the angry inflammation in the vicinity.

By finding and busting apart plaques in the arteries, nanoparticles may offer a new, nonsurgical way to reduce a patient's risk for heart attack and stroke.

Nanoparticles measure less than 100 nanometers across — a thousandth the thickness of a dollar bill. Despite being tiny, they can be engineered to haul a mix of molecules — such as tags that make them stick to a plaque, drugs that block inflammation or dyes that let scientists track their movements. Over the last two decades, scientists have exploited these strategies to fight cancer, designing nanoparticles that deliver drugs (*SN Online: 1/3/14*) or dyes for imaging deep into the core of a tumor. The U.S. Food and Drug Administration has approved a few dozen cancer-focused nanomedicines.

Now researchers have begun engineering nanoparticles to target cardiovascular disease, which kills even more people each year than cancer. Nano-sized compounds have been built that can sweep into clogged arteries to shrink the plaques that threaten to block blood flow. Some nanoparticles home in on the plaques by binding to immune cells in the area, some do so by mimicking natural cholesterol molecules and others search for collagen exposed in damaged vessel walls. Once at the location of a plaque, either the nanoparticles themselves or a piggybacked drug can do the cleanup work.

The aim of all these approaches is to prevent strokes and heart attacks in people with cardiovascular disease, either before surgery becomes necessary or after surgery to prevent a second event. Today, cardiovascular nanoparticles are still far from pharmacy shelves. Most have not reached safety testing in patients. But in mice, rats and pigs, nanodrugs have slowed the growth of the plaques that build up on vessel walls, and in some cases have been able to shrink or clear them.

"I think the effect we can have with these nanoparticles on cardiovascular disease is even more pronounced and direct than what we've seen in cancer," says Prabhas Moghe, a biomedical engineer at Rutgers University in Piscataway, N.J.

Biological blockades

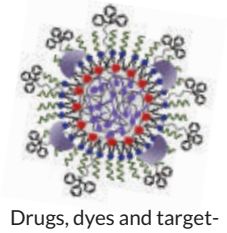
Every minute, more than a gallon of blood pumps through the human heart, pushing through miles of blood vessels to deliver oxygen and nutrients to organs and extremities. In a healthy person, the trip is as smooth as a drive on a freshly paved highway. But in the more than 10 percent of U.S. adults who have cardiovascular disease, the route might be more like a pothole-filled road squeezed by Jersey barriers.

Waxy globs, or plaques, of fat and cholesterol line the blood vessels, thickening and hardening the walls, impeding blood flow. As fat builds up inside the vessels, it also leaks into the vessel walls, swelling them and signaling the body to send immune cells to the area. The congregation of immune cells aggravates the blockage, the way emergency vehicles surrounding the site of a multicar pileup further slow traffic on a highway.

"The inflammation and the accumulation of fat in the walls of the blood vessel sort of feed off each other and exacerbate each other," Moghe says.

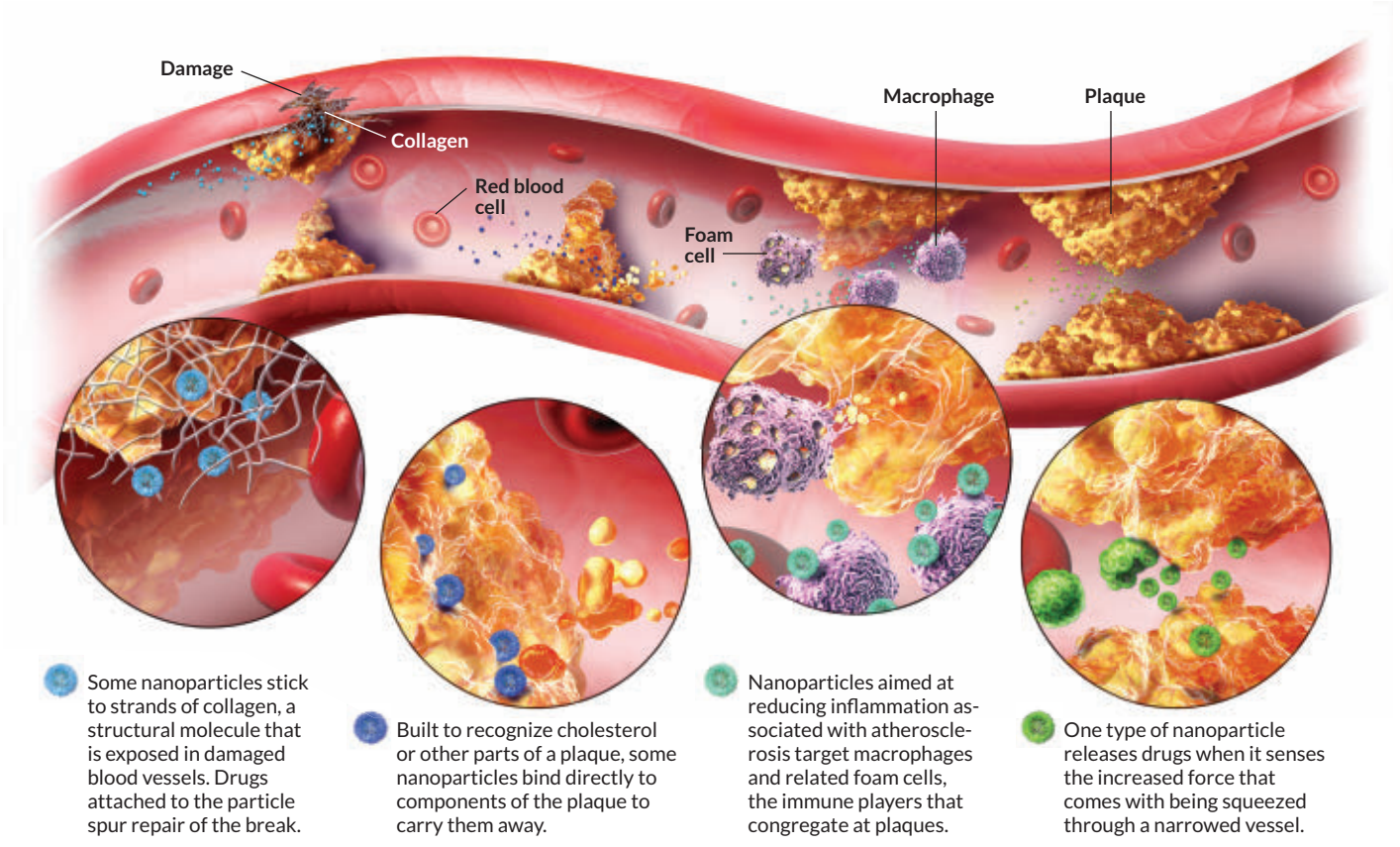
If the plaques grow large enough, or pieces chip off and travel to smaller vessels, they can block a vessel. If oxygen-filled blood can't reach the brain or heart, a stroke or heart attack results.

The drugs most often prescribed to prevent or treat atherosclerosis — plaque buildup on the inner walls of the arteries — are statins (*SN: 5/5/12, p. 30*). This class of drugs, available since 1987, slows the growth of the fatty plaques by lowering the amount of cholesterol circulating in the blood. But taking statins is akin to limiting the number of cars on a damaged road rather than



Drugs, dyes and targeting molecules can be arranged on the perimeter or inside of a nanoparticle (illustration shows one that mimics HDL).

S. MARRACHE AND S. DHAR/*PNAS* 2013



repairing potholes, some argue. And the drugs can boost a person's risk of diabetes and liver damage. In many cases, patients don't begin taking statins until they already have severe atherosclerosis, and the drugs do little to reverse the buildup of plaques that already exist.

"Heart disease is still the number one killer in the U.S.," says endocrinologist and biochemist Ira Tabas of Columbia University Medical Center. "So clearly this approach isn't working." Nanoparticles that can do what statins haven't been able to — shrink existing atherosclerotic plaques and eliminate the accompanying inflammation — could change that, Tabas and others say.

Macrophage magnet

To make nanoparticles congregate at the dangerous plaques, researchers need to identify something that makes the blockage stand out from the rest of the body. The crowds of immune cells near plaques act as a signpost that a plaque exists.

Many of the immune cells involved in atherosclerosis are macrophages, white blood cells that gulp pathogens, dead cells or debris in the body. At the site of a plaque, macrophages become swollen with fats and transform into what are called "foam cells" because of their foamy appearance. As they digest fats, foam cells send out chemical signals to recruit more inflammation-causing cells and molecules to the area. Because they're so intimately involved in the formation of plaques, macrophages and foam cells are a prime target for nanoparticles.

Moghe's group has designed nanoparticles that bind to molecules on the surface of macrophages, preventing them from gobbling fats and becoming foam cells. The researchers made the nanoparticles specifically target a subtype of macrophage that's involved in atherosclerosis, not the macrophages that might respond to other injuries in the body. When nanoparticles were injected into mice with narrowed arteries, the blockages decreased by 37 percent, Moghe's group reported last year in the *Proceedings of the National Academy of Sciences*.

Others are using cholesterol-like molecules as nanoparticle taxis to carry drugs to plaques and subdue the immune reaction. Statins aim to lower the form of cholesterol called low-density lipoprotein, which earned the name "bad cholesterol" for accumulating in plaques. High-density lipoprotein, or "good cholesterol," shuttles LDL away from these clogs to the liver, where it can be broken down. HDL also prevents macrophages from turning into foam cells and producing inflammatory molecules. So Shanta Dhar, a chemist at the University of Georgia in Athens, developed nanoparticles that mimic HDL. She presented the work in March in San Diego at a meeting of the American Chemical Society.

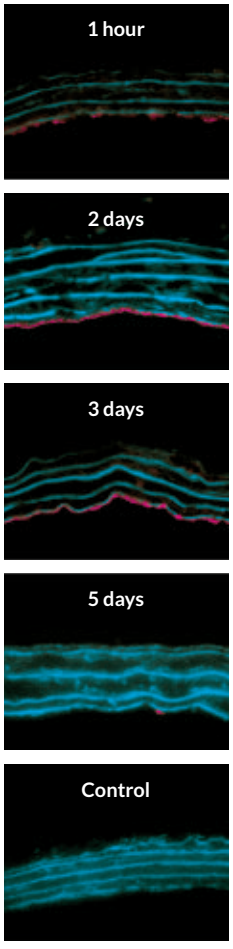
"HDL is our body's natural cholesterol-removing

Going places

To treat atherosclerotic plaques with nanoparticles, researchers have devised a variety of ways to send circulating particles directly to the fatty clogs. In each approach above, a molecule that's part of the nanoparticle binds to a molecule in or near the plaques.

SOURCES: M.E. LOBATTO *ET AL/ NAT. REV. DRUG DISCOV.* 2011; N. KORIN *ET AL/SCIENCE* 2012

NICOLLE RAGER FULLER



After injecting mice with nanofibers designed to bind to injured blood vessels, researchers tracked the location of the nanoparticles (red) and found that they bound to the inner layers of vessels (blue) within an hour and stayed put for three days.

nanomaterial," she says. In animal tests, the HDL-based nanoparticle can bind to free-floating macrophages circulating in the blood, just as HDL does, and follow them to a plaque, she explains. The nanoparticles can also bind to macrophages already glommed on to a plaque, and, mimicking the activities of natural HDL, carry the cells away.

Plaque buster

Willem Mulder, a nanomedicine researcher at the University of Amsterdam and the Icahn School of Medicine at Mount Sinai in New York City, has also designed HDL-mimicking nanoparticles. His particles deliver statins that make a beeline for macrophages and plaques, letting him administer the drug at lower-than-usual doses. He was inspired by earlier studies that showed how extremely high doses of statins, given to mice, could lower LDL levels while also packing anti-inflammatory properties. Of course, in humans, such high doses would probably cause liver or kidney damage. Mulder's solution: tack the statins to a nanoparticle to send them, missile-like, to the plaques. That way, a low dose of the drug could achieve the high concentration needed at the site of the atherosclerosis.

"We're exploiting the inherent targeting properties of HDL," he says. "And it works well with statins, which are small molecules."

In 2014 in *Nature Communications*, Mulder's group reported that plaque-filled arteries in mice given the nanoparticle were 16 percent more open than arteries in mice with no treatment, and 12 percent more open than in mice given a systemic statin. More work is needed to show whether these modest gains would translate to a reduced risk of heart attacks and strokes.

Others are using plaque-targeting nanoparticles to deliver anti-inflammatory drugs similar to methotrexate, which is used as a treatment for rheumatoid arthritis. The side effects of drugs like this, given systemically, are generally severe: vomiting, hair loss and "brain fog," to name a few.

"If someone with rheumatoid arthritis comes into your office completely crippled, it's worth all the side effects to put them on an anti-inflammatory drug," Tabas says. "But imagine someone with some risk factors for heart disease who feels great. They're not going to put up with these side effects."

Tabas thinks certain anti-inflammatories could be perfect candidates to tack on to nanoparticles because they would make possible lower doses with fewer side effects. He's awaiting the results of two large clinical trials testing non–nano-versions of the anti-inflammatory drugs methotrexate and anti-IL1 beta. It remains to be seen whether they're effective at clearing plaques and how severe the side effects are. If the drugs are effective, even with some side effects, Tabas says, it will give weight to his approach: activating the same pathways using targeted nanoparticles.

Tabas attaches his nanoparticles to a small section of a protein called annexin A1, which is involved in the same inflammatory pathway that many anti-inflammatory drugs target. His hope is that delivered only to an atherosclerotic plaque, the drug won't have the host of side effects that other immune blockers have.

Destination: vessel wall

The inflamed vessel wall around an atherosclerotic plaque goes through several changes in addition to the accumulation of belligerent immune molecules. As vessel walls are stretched and inflamed, the structural protein collagen, meant to keep the vessels taut and tubular, becomes exposed the way the threads of a tire begin to appear as it wears down. Scientists are using the exposed collagen to their advantage. Nanoparticles with a tag recognizing the collagen end up at plaques. But it's not as easy as affixing a GPS destination to the particles, says vascular surgeon Melina Kibbe of Northwestern University Feinberg School of Medicine in Chicago.

"It took us over a year of trying to find the right targeting [molecule] that would work," Kibbe says. Her nanoparticle combines a collagen-binding protein with nitric oxide, a molecule that stimulates the growth of new cells at wounds. To maximize the surface area of the drug that contacts the vessel wall, Kibbe's team arranged the molecules in a line, forming a nanofiber, rather than a sphere. As the fiber is swept through the bloodstream, it binds to exposed collagen, anchoring the nitric oxide in place to spur healing of the artery.

Kibbe and colleagues added fluorescent tags to the nanofibers and showed that the fibers congregated at injured spots on mouse arteries within an hour of injection. The tagged particles remained there for three days and the treated vessels ended up 41 percent more open, the researchers reported in the March *Antioxidants & Redox Signaling*.

Tabas also uses a collagen-binding protein, but his is organized in a more spherical shape to get his anti-inflammatory drugs to atherosclerotic plaques. In mice, the particles stayed in the plaques up to five days after treatment, shrinking the plaque by more than a third, his team reported

E.S.M. BAHNSON *ET AL/ANTIOXIDANTS & REDOX SIGNALING* 2016

in *Science Translational Medicine* in 2015. By comparison, some circulating statins last less than a day in the blood.

Rather than targeting proteins or immune cells, scientists at Harvard's Wyss Institute for Biologically Inspired Engineering have designed nanoparticles that are activated by the physical squeeze that comes with being swept through a narrowed artery. When the shear force around them increases, a cue that a plaque is present, the nanoparticles release their payload: a clot-dissolving drug called tissue plasminogen activator. The researchers reported late last year in *Stroke* that the nanoparticle, coupled with a stentlike device placed in the artery, increased the survival rate to more than 80 percent in mice that normally die of a clot entering their lungs.

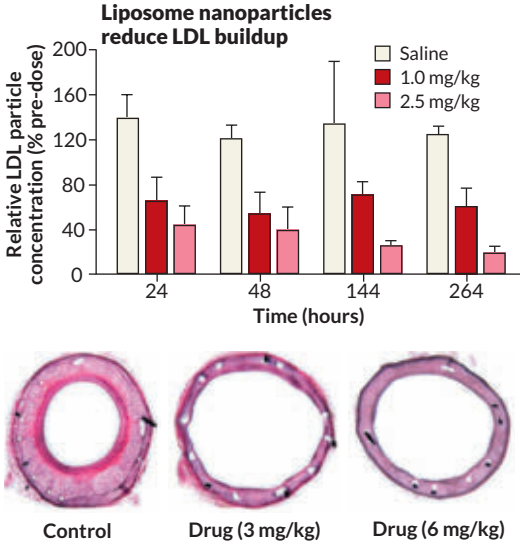
Pathway to patients

Nanoparticles currently in development for cardiovascular disease are still in animal testing. While no one has seen major side effects or toxicity in the animal trials so far, it remains a concern with a class of medicines that is so new.

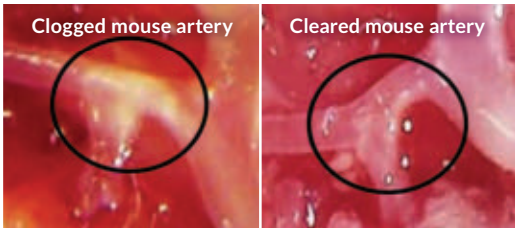
"We sometimes get so wrapped up in exuding only the good stuff about nanomedicine that we forget we also have to look at the side effects," Dhar says.

Another challenge for atherosclerosis drugs is determining who would benefit from treatment.

Clearing vessels Various plaque-targeting nanoparticles have been shown to be effective at lowering the levels of LDL in the blood of nonhuman primates (top graph) and at keeping rabbits' blood vessels open after a stent is inserted (bottom). The approach used in rabbits is now in early patient testing. SOURCE: M.E. LOBATTO *ET AL/NAT. REV. DRUG DISCOV.* 2011



FROM TOP: G. FREDMAN *ET AL/SCI. TRANSL. MED.* 2015; H.D. DANENBERG *ET AL/CIRCULATION* 2003



Mice fed high-fat diets had arteries clogged with yellow, fatty plaques. Animals treated with an anti-inflammatory nanoparticle had more effective plaque clearing (right) than did mice given a version of the nanoparticle without the drug (left).

Kibbe imagines her particles being used first in patients with severe atherosclerosis who receive stents or other invasive procedures to clear their plaques. The procedures are intended to help, she says, "but they actually are so traumatic that they cause injury to the vessel wall." Due in part to this renewed buildup in the arteries, people who have had one heart attack are at higher risk for a second. Even among people who have a permanent stent put in, which is designed to keep part of an artery clear, up to 20 percent become reblocked. Giving these patients nanoparticle-based drugs could keep them healthy, Kibbe says.

Taken to the next level, nanomedicines "certainly might be able to prevent plaques," she adds. Tabas imagines his nanoparticles given as a once-a-month injection, but that's speculation.

Moving to test nanoparticles as a preventive — in the huge percentage of the population at risk for atherosclerosis — is probably a long way off, Mulder says. According to the U.S. Centers for Disease Control and Prevention, around half of all adult Americans have one of the top risk factors for cardiovascular disease.

"I really don't foresee that you would start preventively treating patients who don't have symptoms with nanoparticles," Mulder says. "But to take a person who's hospitalized after a heart attack and stick a needle in their arm and infuse nanoparticles, that's not hard."

Once a few drugs have been validated as working in clinical trials, researchers expect progress to speed up, since the drug cargo on a nanoparticle engineered to target a plaque could easily be switched out for other drugs. Designing the particles, says Moghe, "is almost like building with pieces of Lego." ■

Explore more

- Mark E. Lobatto *et al*. "Perspectives and opportunities for nanomedicine in the management of atherosclerosis." *Nature Reviews Drug Discovery*. November 2011.

Sarah C.P. Williams is a freelance science writer based in San Antonio.

THINK BEYOND

2016 INTEL INTERNATIONAL SCIENCE AND ENGINEERING FAIR WINNERS

Fuel cells that efficiently create electricity, an electronic knee brace and a higher-performance battery are just some of the many incredible inventions and research showcased in May at the 2016 Intel ISEF in Phoenix. More than 1,750 students from over 75 countries, regions and territories participated in this year's fair, making Intel ISEF — a program of Society for Science & the Public — the world's largest international precollege science competition.

"Intel congratulates this year's winners and hopes that their work will inspire other young innovators to apply their curiosity and ingenuity to today's global challenges," said Rosalind Hudnell, president of the Intel Foundation and vice president of Human Resources, director of Corporate Affairs, Intel Corporation.

SPECIAL AWARD ORGANIZATIONS

Over 100 finalists were recognized with scholarships or trips to places such as CERN.

"This gathering represents the most amazing research and ideas in the world," said Maya Ajmera, president & CEO of Society for Science & the Public and publisher of *Science News*, to the participants. "Together, all of you are going to continue to change the world for the better."

Alexis Maria D'Alessandro (left) receives an EPA Special Award from Melissa Anley-Mills.

View the full list of Grand Award and Special Award Organization winners at **student.societyforscience.org/intel-isef**

TOP GRAND AWARD WINNERS

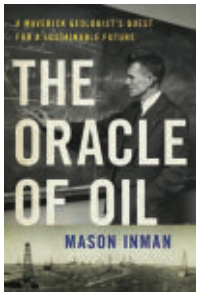
Han Jie (Austin) Wang, 18, of Vancouver received the first place Gordon E. Moore Award and $75,000 for developing microbial fuel cells that more efficiently convert organic waste into electricity.

Syamantak Payra, 15, of Friendswood, Texas, received one of two Intel Foundation Young Scientist Awards of $50,000 for developing a low-cost electronically-aided knee brace that allows an individual with a weakened leg to walk more naturally.

Kathy Liu, 17, of Salt Lake City received the other Intel Foundation Young Scientist Award of $50,000 for developing an alternative battery component that could significantly improve battery performance and safety.

Opposite page, clockwise from top: Top Grand Award winners Kathy Liu, Han Jie Wang and Syamantak Payra; Maya Ajmera, president & CEO of Society for Science & the Public; Camille Miles, Grand Awards: Energy: Chemical, 4th place.

OPPOSITE PAGE: APRIL RIETZE AND LINDA DOANE; THIS PAGE, INSET: CHARLYN VILLEGAS



The Oracle of Oil
Mason Inman
W.W. NORTON & CO., $29.95

BOOKSHELF

Pioneering geophysicist's theory of peak oil still debated

In the 1950s, long before the climate change debate began, geophysicist Marion King Hubbert presented research that made the oil industry queasy. Society needed to quickly wean itself off its dependence on oil, he concluded, or face dire consequences. Hubbert's argument wasn't motivated by the global climate impacts of fossil fuel burning, but rather by a bold prediction that U.S. oil production would soon peak and quickly taper off.

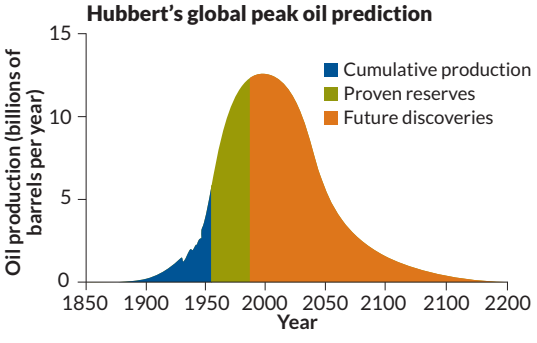
In *The Oracle of Oil*, journalist Mason Inman explores Hubbert's life and legacy as the father of "peak oil." Hubbert's career as an academic, oil industry insider and government scientist was intertwined with the politics and engineering that led to oil becoming the world's dominant energy source. More than a biography of the scientist, the book is also a chronicle of the oil industry.

Hubbert grew up on a Texas farm before selling his cow for train fare and setting off for college in 1923. After transferring to the University of Chicago, he paid for tuition by laboring 13 hours a day with a two-hour round-trip commute. His hard work paid off, however, and his early research provided groundbreaking insights into how geologic forces deform Earth's rocks and how groundwater flows. In 1956, while working for the Royal Dutch Shell oil company, Hubbert calculated that conventional oil production in the continental United States would peak in the late 1960s, with a global peak a few decades later.

That provocative prophecy mired Hubbert's later ideas and career in controversy. His work as a scientist for the U.S. Geological Survey was further complicated by his political views and involvement in the technocracy movement, which argued that technical experts should control governments and industries.

Even today, Hubbert's critics and supporters still debate his oil forecasts. Inman continues his story beyond Hubbert's 1989 death and discusses the recent boom in oil and gas production in the United States. Hubbert's critics contend that this production uptick, thanks in part to technologies such as fracking and horizontal drilling (*SN: 9/8/12, p. 20*), undermines Hubbert's assumption that new techniques wouldn't significantly boost production. Hubbert's supporters, however, warn that oil and gas companies are racking up billions of dollars in debt to squeeze every last extractable drop of oil out of the ground and that production could peak by 2020. "We're setting ourselves up for a major fiasco," Tad Patzek, an earth scientist at the University of Texas at Austin, tells Inman.

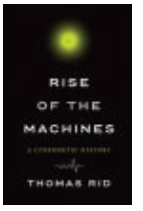
Inman paints a well-researched, well-written portrait of a driven and gifted scientist who stood up to politicians and oil conglomerates alike. *The Oracle of Oil* provides a compelling perspective on what Hubbert might have called society's fossil fuel folly. — *Thomas Sumner*



Oil drop In 1956, Marion King Hubbert predicted world oil production would peak in about 2000. Production has surpassed this forecast, reaching over 30 billion barrels in 2014. SOURCE: M.K. HUBBERT/*DRILLING AND PRODUCTION PRACTICE* 1956

GRAPH: J. HIRSHFELD

BOOKSHELF



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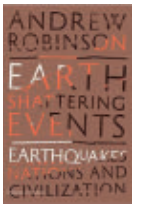

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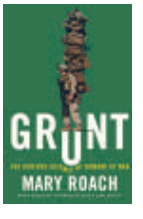

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SOCIAL MEDIA

Fun with frogs

Mimic poison frog tadpoles not only hitch a ride on their dads' backs, they also beg for food by vibrating their tails, reported **Susan Milius** in "Piggybacking tadpoles are epic food beggars" (*SN: 4/16/16, p. 4*). Amused Facebook readers commented on the frog's bright color pattern.

"The Guy Fieri of frogs."
Ryan Reininga

"A frog with 'Flames'... Nice paint job!"
James Patrick Marshall

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Climate commotion

In "Changing Climate: 10 years after An Inconvenient Truth*" (*SN: 4/16/16, p. 22*), **Thomas Sumner** reported on the progress scientists have made revising forecasts of the far-reaching effects of climate change — from extreme temperatures and sea level rise to severe drought and human conflict — in the decade since the Oscar-winning film's release.*

Reader response to the article was overwhelming, with hundreds of online comments. Some people enjoyed the in-depth look at climate change science, while others expressed skepticism about humans' contribution to climate change and a general distrust of climate scientists.

"One of my goals for this article was to highlight that climate change research has itself changed over the last decade," **Sumner** says. Scientists are still working to understand how the consequences of atmospheric warming will play out in the coming centuries. But one big message from the last decade of research is that the fundamentals have held up: Natural variability exists, says **Sumner**, but human activities are largely responsible for the current warming trend.

"The question now is what impact will human contributions have down the line and what should we do to prevent and mitigate those effects," he says.

Plastic feast

***Sarah Schwartz** wrote about the discovery of a microbe,* Ideonella sakaiensis, *that chows down on a hard-to-degrade polymer in "This microbe makes a meal of plastic"* (SN: 4/16/16, p. 5).

Online commenters were amazed by this new plastic-gobbling organism. "This is great news," **Dan** said. "Our world would be doomed if there wasn't a microbe able to do this." **Chuckawobbly** wondered how long it takes *I. sakaiensis* to digest the plastic. And **Jean Harlow** was concerned about the potential by-products of worldwide plastic digestion. "The waste product would be a significant amount ... of what?" she asked.

Researchers observed that *I. sakaiensis* almost completely degraded a thin film of polyethylene terephthalate, or PET, after six weeks in a laboratory. But when extracted from the bacterium, the proteins used to break down plastic begin working in about 18 hours.

I. sakaiensis appears to break PET into smaller molecules, like amino acids and carbon dioxide, says coauthor **Kenji Miyamoto** of Keio University in Yokohama, Japan. But it would probably be hard for the microbe to break down plastic in the outdoors because of its specific growth requirements, he says. **Miyamoto** envisions that it could be possible to use the specialized proteins in a closed environment to break PET down into molecules such as terephthalic acid — one of the plastic's main building blocks, which seems benign in the environment.

Prairie dog predators

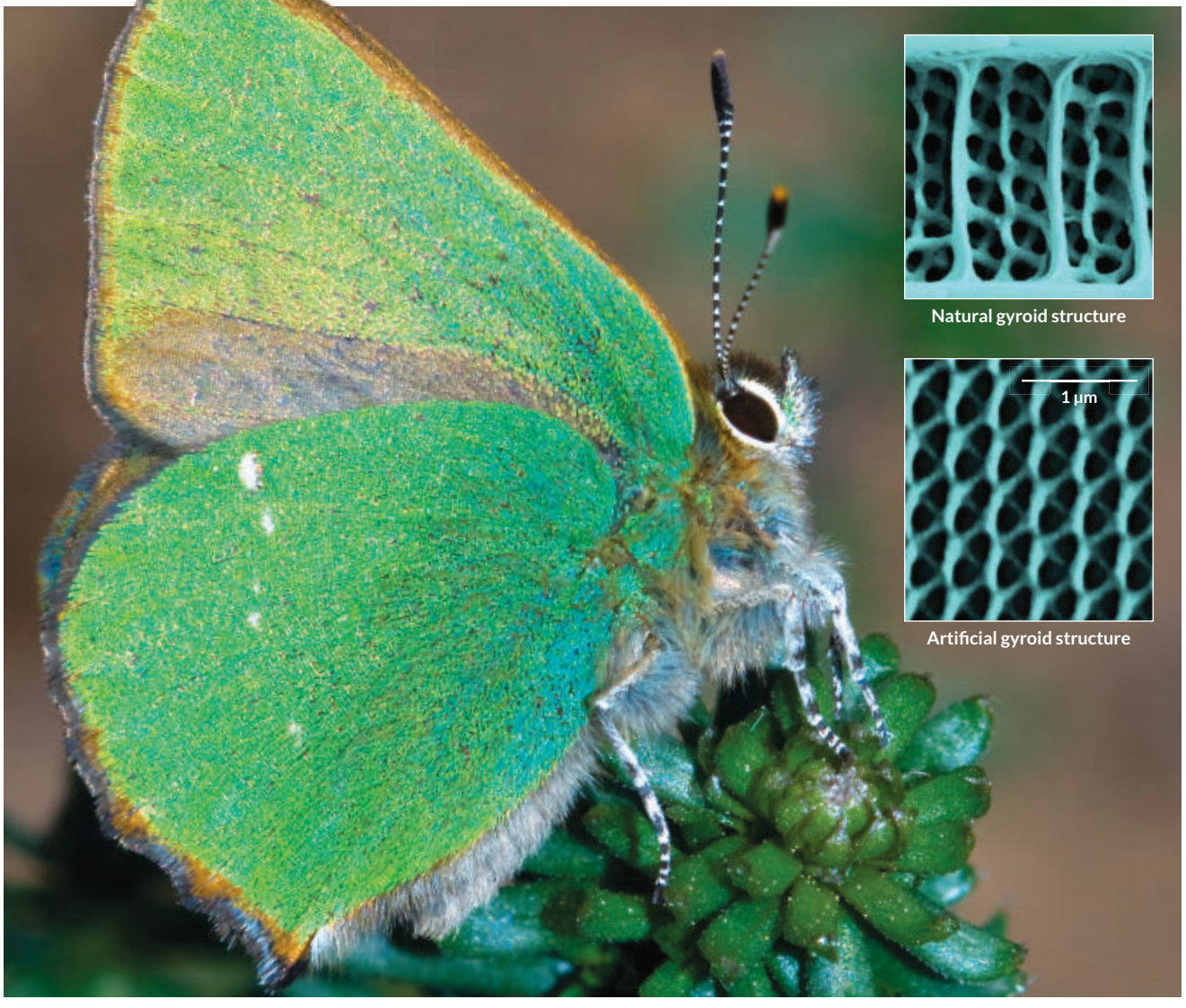
*Herbivorous prairie dog mothers routinely kill baby ground squirrels that encroach on their territories, researchers found. Competition for resources may be a contributing factor to the killings, **Susan Milius** reported in "Killer prairie dogs make good moms"* (SN: 4/16/16, p. 14).

One reader had other ideas. **Audrey Boag** wondered if prairie dog moms kill ground squirrels to protect their pups from predation or from diseases carried by the squirrels. "In either case, minimizing the number of ground squirrels would pay in lifetime biological fitness," she wrote.

"We never observed a ground squirrel kill or injure an adult or juvenile prairie dog," says study coauthor **John Hoogland**. "Perhaps such attacks sometimes occur underground." **Hoogland** notes that the majority of ground squirrels killed by prairie dogs were juveniles, which are too small to be a threat.

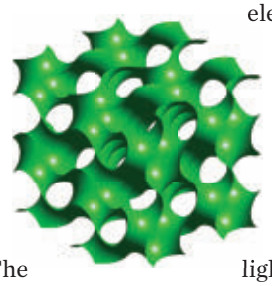
One threat, however, is a species of disease-carrying flea that infests both animals. **Hoogland** found that prairie dog killers and their offspring had fewer fleas than nonkillers and their offspring, "but this trend was not significant," he says.

ADAM STUCKERT



Sorting out a butterfly's bright color, with a twist

The green hairstreak butterfly (*Callophrys rubi*) gets its blue-green hue from complex nanoscale structures on its wings. The structures, called gyroids, are repeating patterns of spiral-shaped curls (computer model below). Light waves bouncing off the patterned surface (top inset above) interfere with one another, amplifying green colors while washing out other shades (*SN: 6/7/08, p. 26*).



Scientists led by Min Gu of the Royal Melbourne Institute of Technology in Australia have now painstakingly re-created the gyroid structure by sculpting the shapes out of a special resin that solidifies when hit with laser light. The technique, called optical two-beam lithography, uses a pair of lasers to set the material in just the right pattern. Afterward, the remaining resin can be washed away, leaving only the gyroid structure. The fabricated version (bottom inset above) repeats its pattern every 360 nanometers, or billionths of a meter.

The gyroid structures determine more than just color. They also divvy up light that is circularly polarized — its electric fields spiral either clockwise or counterclockwise. In the butterfly, this effect is weak because of irregularities in the structure. But the artificial version sorts the light according to polarization, reflecting one type much more than the other, the researchers report May 13 in *Science Advances*.

The ability to control circular polarization of light with structures like these could allow scientists to increase the bandwidth of optical communications, the researchers say. The two polarizations of light could each carry different information, which could then be separated and decoded down the line. — *Emily Conover*

BUTTERFLY: ATOSF/ISTOCKPHOTO; INSETS, TOP: Z. GAN *ET AL*/*SCIENCE ADVANCES* 2016; INSET, BOTTOM: Z. GAN

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