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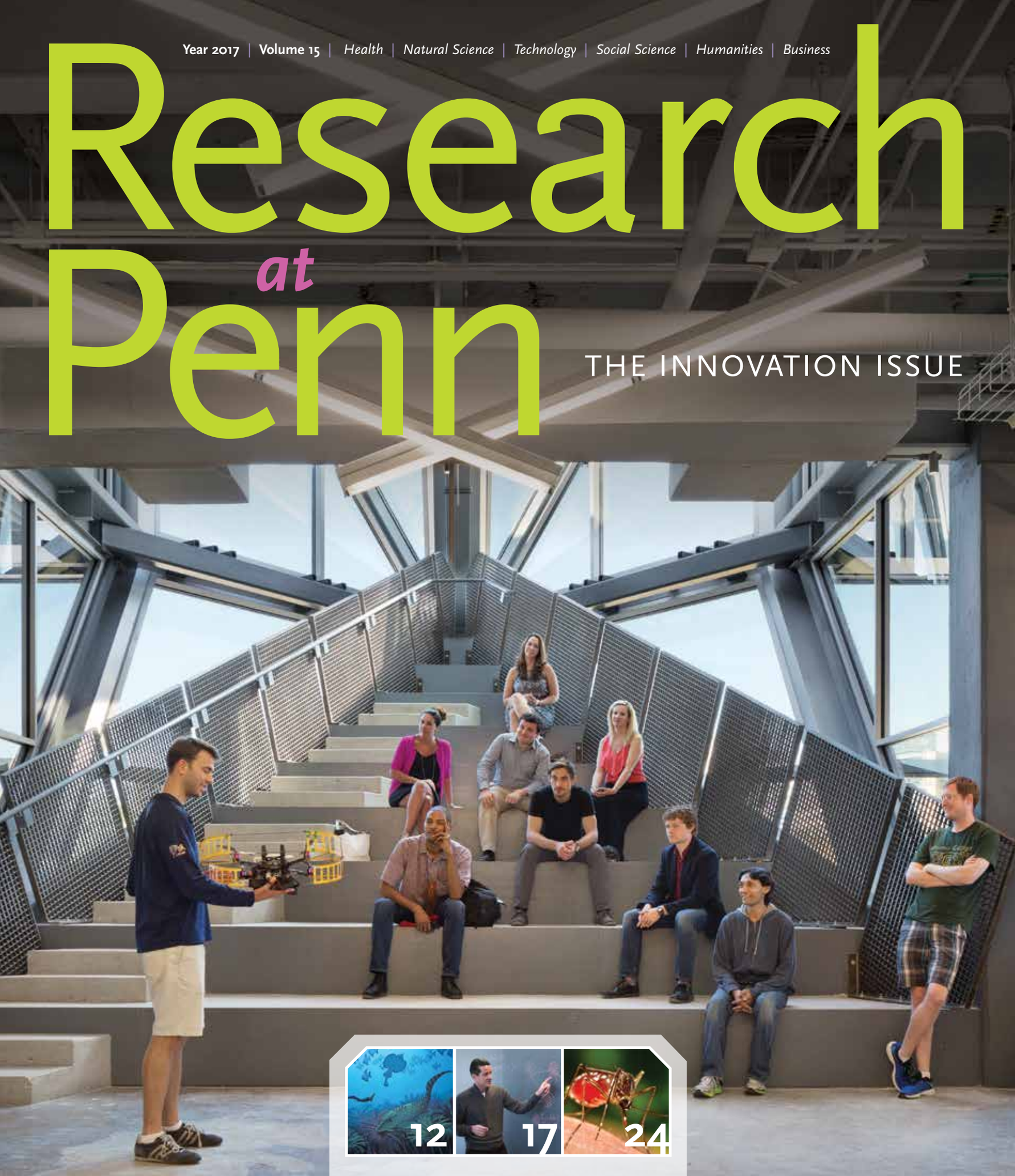
Research at Penn

THE INNOVATION ISSUE



Penn

Research at Penn

Advances in Knowledge from the University of Pennsylvania

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Health | *Natural Science* | *Technology* | *Social Science* | *Humanities* | *Business*

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Penn's Innovative Spirit

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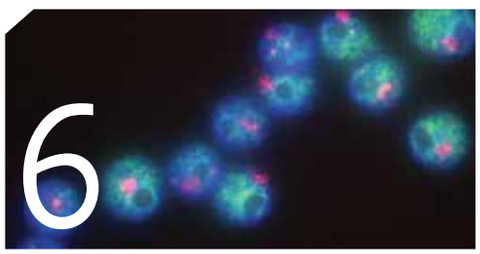
At Penn, there is a tradition of innovation that began with Penn's founder himself, Benjamin Franklin. The philosopher, writer, and Founding Father sought to create an institute of higher learning that was unlike others in the 18th century, where the growing business and governing classes in the American colonies could learn useful and practical subjects, including natural history, geology, geography, and modern languages.

Franklin's innovative idea sparks brighter than ever today. At Penn, researchers cross disciplines and schools, cultivating and improving how we think about and solve the world's greatest needs. Teams are exploring how immunotherapy can treat cancer, asking why more women than men suffer from autoimmune diseases, and studying how a part of the brain associated with negative behaviors also influences kindness. Experts are developing a process to recycle rare-earth magnets, assessing the public's knowledge about the Zika virus, and finding that increasing numbers of Americans are giving up personal data.

The opening of the new Pennovation Center at the Pennovation Works site stands as a testament to the value Penn places on big ideas. It is a place where University scholars, doers, and problem-solvers, including those from the Penn Engineering Research and Collaboration Hub, are working side by side with IT, biotechnology, and robotics startups, *Fortune* 500 companies, and a host of technologists, researchers, and venture capitalists to explore and push new ideas into reality and expand our frontiers of knowledge.

To keep up with all the University's research news, visit Penn's research website: **www.upenn.edu/researchdir.**

26 What's Inside



The reason behind a female bias in autoimmunity diseases lies, quite literally, on the X chromosome.

Penn chemists have pioneered a process that could allow two rare-earth metals to be separated in minutes, easing recycling.

A team created a documentary series about evolution, using different styles to see which is most informative.

The Federal Reserve is very much a human institution with a limited but important role to play.

ON THE COVER: *The Pennovation Center is a 58,000-square-foot anchor for Pennovation Works in Grays Ferry. The building features co-working space, conference rooms, private offices, event space, and wet and dry labs.*

Immunotherapy represents a novel approach to treating cancer, one that harnesses the potency of the immune system to rid the body of malignancies. As such, philanthropist Sean Parker believed the field was worthy of a new model for doing research.

Penn is now a key player in the model that Parker envisioned and brought to life. In 2016, his unprecedented gift of $250 million—the largest ever devoted to immunotherapy—established the Parker Institute for Cancer Immunotherapy. The institute unites Penn with five other leading medical schools and cancer centers in order to break down barriers to collaboration and accelerate the development of breakthroughs in cancer immunotherapy research.

THE NEXT MOONSHOT, LAUNCHED AT PENN

In then-President Barack Obama's final State of the Union address, he charged Vice President Joe Biden with heading up the "moonshot" to find a cure for cancer. And where did Biden choose to launch that effort? Right here at Penn.

Just days after the president's speech, Biden met with Penn experts in breakthrough cancer treatments, including Carl June and Bruce Levine, and toured laboratories that will provide cancer patients with personalized T-cell therapies to help them conquer their disease.

"You're on the cusp of some breakthroughs," Biden said. "In my terms—not your medical terms—we are at an inflection point in the fight against cancer."

Since that visit, Biden appointed Abramson Cancer Center Director Chi Van Dang to the Blue Ribbon Panel that informs the scientific direction of the Cancer Moonshot initiative. That will ensure that the National Institutes of Health allocates resources toward the most promising research to prevent, diagnose, and cure cancer.

A New Research Model for a New Kind of Cancer Therapy

ABOVE, LEFT: *Former Vice President Joe Biden joined Penn President Amy Gutmann and National Institutes of Health Director Francis Collins to kick off the cancer "moonshot" project.*
ABOVE, RIGHT: *Philanthropist Sean Parker donated $250 million to establish the Parker Institute for Cancer Immunotherapy.*

Carl June, the Richard W. Vague Professor in Immunotherapy in the Department of Pathology and Laboratory Medicine of the Perelman School of Medicine and director of the Center for Cellular Immunotherapies in the Abramson Cancer Center, is the director of the Parker Institute at Penn. Robert Vonderheide, the Hanna Wise Professor in Cancer Research and associate director for translational research in the Abramson Cancer Center, and John Wherry, a professor of microbiology and director of Penn's Institute for Immunology, serve as co-directors.

"We're at the dawn of a new age in how we treat cancer," says Vonderheide, "both in the way that we treat it using the patient's own immune system and in the incredible results, remissions, and even cures that we are seeing. And now we have a brand-new way of caring for our patients."

The Parker Institute comprises more than 40 labs and 300 researchers and is already supporting two clinical trials at Penn that aim to bring promising therapies to patients as quickly as possible. One, led by June, is using the cutting-edge tool known as CRISPR to genetically engineer a patient's T cells to go on the attack against myeloma, sarcoma, or melanoma. The other trial, led by Vonderheide, will focus on pancreatic cancer, investigating the effectiveness of a cocktail of two chemotherapy drugs with two immunotherapy drugs.

"By doing this study through the Parker Institute, we've accomplished in three months what might have otherwise taken 30 months," Vonderheide says. "That's the kind of acceleration that is warranted in an age of immunotherapy."

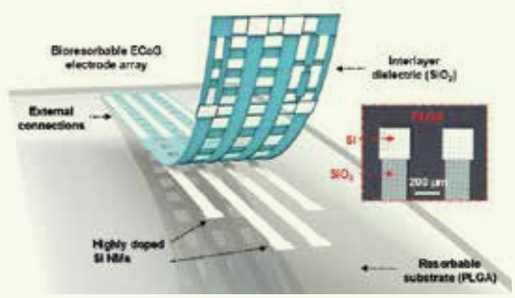
The unique arrangement manages intellectual property in a shared fashion among the six partnering institutions, and it is intended to foster cross-center collaboration and speed the translation of basic research to the clinic.

"Creating this institute was Sean Parker's way of trying to be disruptive in a positive way, breaking down the silos in which we usually work," Wherry says. "We're fortunate that Penn is an unbelievably unique environment to capitalize on translational research and push forward immunotherapy. And now the Parker Institute, in leveraging the strengths here and at the other partnering institutions, is making a package that is more than the sum of its parts." ■

INNOVATION FACT

The unique structure of the Parker Institute, which manages intellectual property in a shared fashion, allows the partnering institutions to act as collaborators instead of competitors in working toward immunotherapy breakthroughs.

BRAIN-MONITORING ELECTRODES THAT MELT AWAY



Advances in neuroscience require increasingly sophisticated ways of monitoring brain activity. Non-invasive methods have provided invaluable insights, but for some research questions, there is no getting around the need to physically probe the delicate organ.

Faced with that daunting prospect, Penn researchers are making progress on a kind of implantable electrode that literally melts away, minimizing the risk of injury associated with such devices.

In a study published in *Nature Materials,* they demonstrated that their device matches or exceeds existing methods for measuring electrical activity in the brains of rats.

It was led by Brian Litt, a professor of neurology and neurosurgery in the Perelman School of Medicine and of bioengineering in the School of Engineering and Applied Science, and John Rogers of the University of Illinois at Urbana-Champaign who has since moved to Northwestern University. Support for the research came from the Defense Advanced Research Projects Agency, the Penn Medicine Neuroscience Center, the National Institutes of Health, the Mirowski Family Foundation, and Neil and Barbara Smit.

"Dissolvable silicon electronics offer an unprecedented opportunity to implant advanced monitoring systems that eliminate the risks, cost, and discomfort associated with surgery to extract current devices used for postoperative monitoring," says Litt.

Penn researchers are making progress on a kind of implantable electrode that literally melts away, minimizing the risk of injury.

The device is made of layers of silicon and molybdenum that dissolve at a rate controlled by its thickness. The researchers tested it in anesthetized rats, recording brain waves, voltage fluctuations between neurons, and other electrical signals.

Chronic measurements were made over a 30-day period, but the researchers believe the device could eventually operate for much longer. This would be a boon for one of the immediate applications for such electrodes: locating the regions of an epilepsy patient's brain where seizures originate.

"Recent evidence suggests that up to three months of intracranial recording may be required to adequately locate seizures before epilepsy surgery or device placement," Litt says.

The team plans to develop more complex devices that can record data beyond electrical activity and to continue to test them in animal models before moving into humans. ■

Nutrition's Growing Role in

Proper nutrition in childhood can positively affect social development and potentially reduce aggressive behavior, according to two studies from Adrian Raine, the Richard Perry University Professor with appointments in the School of Arts & Sciences and Perelman School of Medicine, in collaboration with Jianghong Liu and Therese Richmond of the School of Nursing.

For the first, Liu and Raine analyzed data from 1,795 3-year-olds, focusing on nutrition-related physical health issues like anemia and protein deficiency. They also considered four social development indicators: friendliness, verbalization, active social play, and exploratory behavior.

The researchers noticed a previously undiscovered neurocognitive link between the factors.

"Giving children good nutrition early on will not only enhance cognitive function but, importantly, promote good social behavior," Liu says. Nutrition is essential to brain development and intelligence.

Early Childhood Development

Eight years later, the children with positive social behavior also have higher IQs, Raine adds.

It's a unique take on a field that tends to focus on the negative influences of a poor childhood diet. This viewpoint similarly shaped a second study, about incorporating omega-3s, vitamins, and minerals into diets of children at risk for aggression. Raine and Richmond, the Andrea B. Laporte Professor of Nursing, found that adding such supplements can reduce this behavior in the short term, especially its more impulsive, emotional form.

A randomized clinical trial placed 290 aggressive 11- and 12-year-olds into four groups: One received multivitamins, calcium, and juice containing omega-3 for three months. A second participated in weekly hourlong cognitive behavioral therapy (CBT) sessions. Group three took the supplements and received CBT, and a fourth was given a list of resources targeted at reducing aggressive behavior. Blood samples at the start and finish of treatment measured omega-3 levels.

"Immediately after three months of the nutritional intervention rich in omega-3s, we found a decrease in the children's reporting of their aggressive behavior," Richmond says. Six months later, however, any positive effects had dissipated. What's unknown is whether continued omega-3 use could lead to a long-term reduction in antisocial behavior.

Though both studies answer some questions, they also create new ones, underscoring the complicated relationship between the brain, nutrition, and behavior. ■

INNOVATION FACT

Research on childhood nutrition typically focuses on the negative influences of a poor diet, unlike this work, which flips the methodology on its head, centering on positives.

BIOENGINEERING

HEALTH

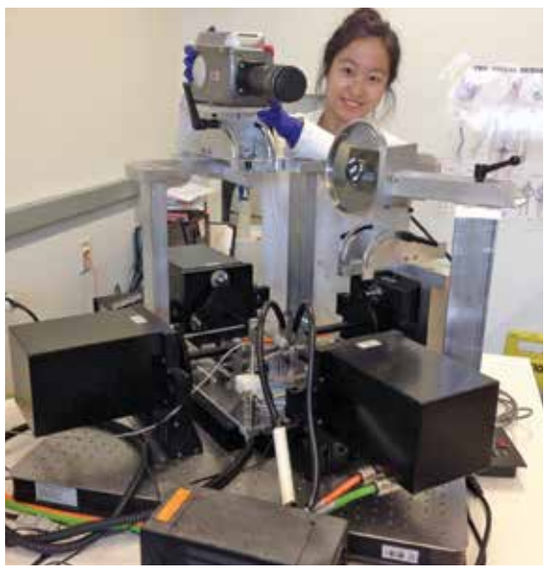
A fully torn ligament shows up on scans, with visible breaks in collagen fibers. But what happens when a ligament doesn't tear all the way or appear on initial screens, yet still causes pain?

These "subfailure" injuries reveal themselves only microscopically, undetected by today's clinical tools. "We're lacking methods to localize where in the tissue the problem occurred," says Beth Winkelstein, professor in the School of Engineering and Applied Science and Perelman School of Medicine. "We'd like to be able to figure that out based on physiology and, ideally, to predict when it's going to happen."

Predicting Ligament Injury Locations

With that goal in mind, Winkelstein, along with fourth-year graduate student Sijia Zhang and Danielle Bassett, the Eduardo D. Glandt Faculty Fellow and an associate professor of bioengineering, turned to network science, a method that analyzes individual elements of a complex system to determine its behavior.

The team hypothesized that cells in what's called the collagen matrix stretch during ligament loading, changing their behavior. Zhang explains, "We set out to see how the matrix reorganized under strain."



Sijia Zhang uses the research team's quantitative polarized light imaging system.

Using ligament samples pulled to their breaking point and viewed through a polarized light imaging system, the researchers learned they could predict where a tear would happen by homing in on areas that showed excessive changes in collagen fiber orientation. The amount of light the fibers let through revealed their alignment; disorganization of the fibers was closely associated with eventual ligament ruptures.

Understanding why tears occur could point to ligament regions prone to failure, as well as lead to improved diagnosis and therapy.

"Network science offers a fundamental explanatory mechanism for subfailure damage, a process that we think may lead to pain," Bassett says. "If a single fiber is turning, a tear is unlikely, as is the activation of pain fibers. But when there is a coordinated change in many fibers, pain and tears may be more likely."

This work, published in the *Journal of the Royal Society Interface,* builds on previous findings from Winkelstein's lab. It also propels the research forward.

"We can now examine those relationships between ligaments and cells, and the grouping of both," Winkelstein says. "We [can] start to actually test how failure happens and what that means on the cellular level." ■

INNOVATION FACT

Axons, the long, tendril-like structures that neurons use to transmit signals to one another, can stretch to 200 percent of their original length without breaking, but only when pulled slowly.

Breakaway Protein Key Factor in Concussions

HEALTH / BIOENGINEERING

From the battlefield to the football field, increasing attention is being paid to the long-term effects of traumatic brain injuries (TBIs). Even in their mildest form—concussions—these injuries can cause irreparable damage to structures in the brain known as microtubules. The structures function like train tracks on which molecular cargo is shipped from one end of a neuron to another; broken tracks mean this cargo piles up undelivered.

To better understand how a TBI breaks these tracks, an interdisciplinary team of Penn researchers refined its computer model of microtubules. In a study published in *Biophysical Journal*, the researchers demonstrated a key aspect of the protein, tau, that binds bundles of microtubules together: It has a way of safely breaking apart, but only under certain conditions.

The study was conducted by Vivek Shenoy, a professor of materials science and engineering in the School of Engineering and Applied Science; Hossein Ahmadzadeh, a member of Shenoy's lab; and Douglas Smith, professor of neurosurgery in the Perelman School of Medicine and director of the Penn Center for Brain Injury and Repair. It was supported by the National Institutes of Health, the National Science Foundation, and the Department of Defense.

Before this study, the team's computer model incorporated tau's viscoelasticity. Like Silly Putty, viscoelastic materials can stretch, but only when strain is slowly applied.

The team's model includes new evidence that shows that the links between microtubules consist of two tau proteins bound together. When slowly strained, the two taus break apart, but then find new partners. This allows the whole bundle to safely stretch, as individual microtubules slide against one another.

But when force is rapidly applied, such as with a crushing tackle or the blast wave of a bomb, that process can't occur.

"When you pull them very fast," Ahmadzadeh says, "that bond doesn't break and the forces get exerted on the microtubule itself. That's what's causing the damage in a traumatic brain injury."

The ability to model this mechanism could provide insights into potential preventive measures and treatments for concussions. ■

BIOMEDICINE / HEALTH

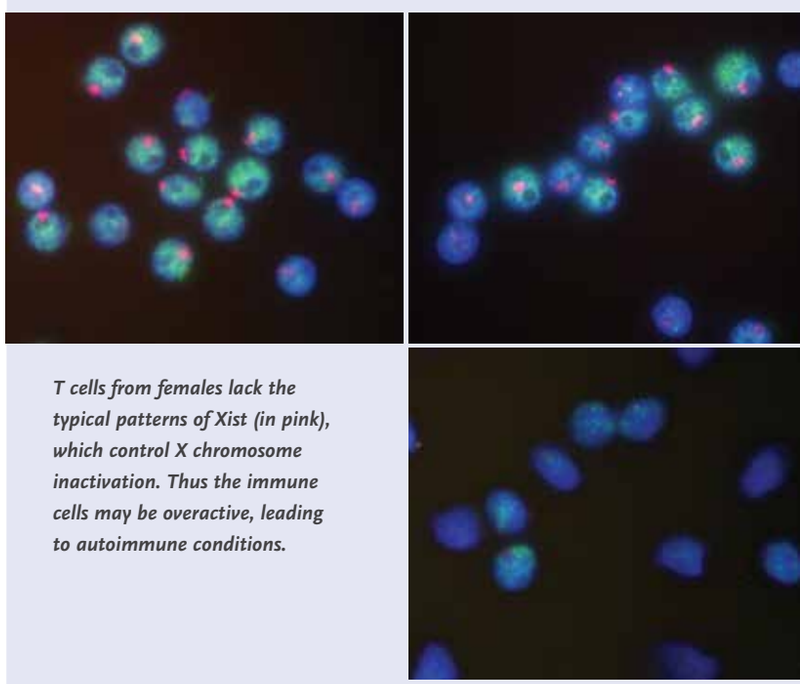
Explaining the Female

Eighty-five percent of lupus patients are female. But why? An investigation by a team from Penn's School of Veterinary Medicine and Perelman School of Medicine found that the answer lies, quite literally, on the second X chromosome.

A process known as X inactivation, which inhibits gene expression on one of a female's two X chromosomes, serves to balance gene dosage between males and females. But in earlier research, Montserrat C. Anguera, an assistant professor in Penn Vet's Department of Biomedical Sciences and the leader of the research team, had seen that the process can go awry, allowing the normally inactive X chromosome to become partially reactivated.

Anguera began considering how this incomplete inactivation related to autoimmune conditions, which disproportionately affect females.

"What caught my attention about autoimmunity and specifically lupus," Anguera says, "was that there were genes on the X chromosome that



T cells from females lack the typical patterns of Xist (in pink), which control X chromosome inactivation. Thus the immune cells may be overactive, leading to autoimmune conditions.

Bias in Autoimmunity

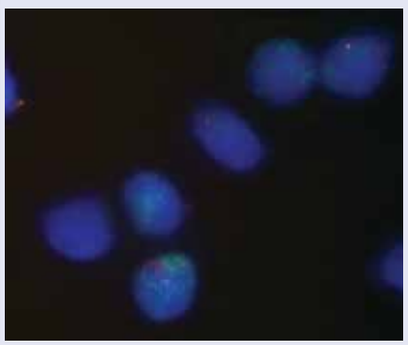
were immunity-related and that had been shown to have higher expression levels in lupus patients."

To see if incomplete X inactivation could be responsible for the autoimmunity bias, the researchers examined lymphocytes, the T cells and B cells of the immune system, from healthy women as well as from female mice. Even in these healthy individuals, Anguera and her colleagues found that lymphocytes lacked the typical patterns of Xist, an RNA molecule essential for X inactivation, as well as other markers of X chromosome inactivation.

Next the team looked at lymphocytes from pediatric lupus patients and found that they also had unique expression patterns of key immunity-related genes and unusual patterns of Xist RNA localization.

Anguera notes that it's possible that all females have a subpopulation of lymphocytes with incomplete X inactivation; in healthy individuals, those lymphocytes stay in the minority, but that subpopulation may take over in patients with autoimmune conditions. The work was reported in *Proceedings of the National Academy of Sciences*.

The researchers are following up their findings in lupus and also pursuing research in another female-biased autoimmune disease, Sjögren's syndrome, to see if similar X inactivation patterns are present. If the findings hold up across diseases, it's possible that the characteristic patterns of Xist localization could be used as a disease biomarker, enabling earlier diagnoses and treatments. ■



A HEALTHY WORKFORCE FOR A HEALTHY WORKPLACE

Four out of five large employers in the United States offer some form of financial incentive for health promotion. The healthier the workforce, the more productive the workplace.

But what's unclear is which incentives actually work. Cue the efforts of Penn researchers Mitesh Patel, David Asch, and Kevin Volpp, all professors in the Perelman School of Medicine and the Wharton School's Health Care Management Department. For years, the trio, along with colleagues outside of Penn, has been studying the most successful approaches to motivate employees to shed some pounds or quit smoking.

"Determining the best ways to deploy incentives in an effective manner can be such a powerful tool to improve the health of the population," says Patel.

The researchers have also been able to point out the common practices in need of restructuring.

For instance, a study in *Health Affairs* found a $550 health insurance premium discount—a relatively common incentive—not effective at all in promoting weight loss. For one year, they tested an immediate and delayed premium adjustment, as well as a daily lottery incentive, all equaling the same amount, and found no statistically significant differences in mean weight change compared to the control group.

"This study indicates that premium adjustments may not be as effective as many employers may have hoped," Patel explains. "Employers should really be looking at how they deliver and design these incentives. For example, we've found more success when incentives are unbundled from premiums, which are virtually hidden in people's paychecks, such as offering cash incentives or a gift card."

INNOVATION FACT

More than 80 percent of large employers use financial incentives for health promotion.

A different study published in *Annals of Internal Medicine* found that financial incentives framed as a loss rather than a gain were more fruitful in achieving physical activity goals. The most successful participants were told that a particular amount of money was allocated up front and would be taken away if their goal wasn't met.

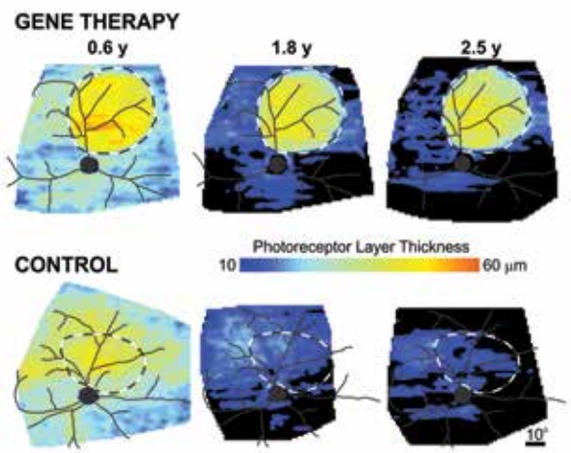
Most recently, the researchers have published a series of corresponding studies looking at the relation of social incentives—being accountable to a team—for weight loss and physical activity.

Patel says: "This work altogether will hopefully give us improved evidence on how to use incentives to better engage individuals to change their health behaviors." ■

Staving off Blindness, No Matter When Treatment Begins

ABOVE: *After treatment, but with the treated eye covered, a dog had trouble navigating the course.*

BELOW: *With the eye uncovered, a treated dog was able to easily navigate the course.*



Treatment with gene therapy markedly preserved photoreceptor cells in dogs.

For years, Penn scientists have studied X-linked retinitis pigmentosa, a disease that leads to progressive vision loss. The disease affects dogs as well as humans, and in 2012, the researchers reported a cure for the canine disease if the gene therapy treatment was started at an early stage.

Now even more encouraging news has been revealed: The Penn team has shown that it can effectively treat the canine disease over the long term, even when treatment is begun later, when half or more of the affected photoreceptor cells have been destroyed.

The 2012 study "was obviously very encouraging," says William A. Beltran, co-lead author and associate professor of ophthalmology at Penn's School of Veterinary Medicine. "But now we've gone further, showing that the treatment is long-lasting and effective even when started at mid- and late-stage disease."

"Because the progression of disease in dogs matches up with the progression in humans," says Artur V. Cideciyan, co-lead author and research professor of ophthalmology in the Scheie Eye Institute at Penn's Perelman School of Medicine, "this gives us a lot of confidence about translating these results to eventually treat humans."

The work, which involved a close collaboration between Penn Vet's Beltran and Gustavo Aguirre, as well as Penn Medicine's Cideciyan and Samuel Jacobson, was published in *Proceedings of the National Academy of Sciences*.

The study used gene therapy to deliver a normal copy of the affected gene, RPGR, to rods and cones, the photoreceptor cells involved in dim-light and bright-light vision, respectively. When the researchers delivered the therapy to dogs at 5, 12, or 26 weeks of age, corresponding to early-, mid-, and late-stage disease, they saw a remarkable and lasting halt in the degeneration of photoreceptor cells in the treated region of the retina. The dogs also had improved performance on a visual behavior test. In the late-stage group, these improvements endured for at least two and a half years.

With such promising results in hand, the researchers are hopeful that the therapy will find success in an eventual human treatment. ■

Repurposing an Alzheimer's Drug to Help Tobacco Smokers Quit

People who attempt to quit smoking often describe mild cognitive deficits—forgetfulness and feeling fuzzy—especially during week one.

"Some smokers report this causes them to relapse," says Heath Schmidt, an assistant professor in the School of Nursing and Perelman School of Medicine.

In search of new smoking cessation options, Schmidt and research assistant psychiatry professor Rebecca Ashare turned to FDA-approved medications called acetylcholinesterase inhibitors (AChEIs) that improve cognitive impairments associated with Alzheimer's disease.

Schmidt began with a rat trial. To model voluntary drug-taking in humans, he allowed rats to self-administer nicotine by pressing a lever for intravenous infusions. Once nicotine intake stabilized, each rat received galantamine or donepezil, two AChEIs.

Both drugs reduced nicotine consumption, but because these compounds often trigger nausea and vomiting in humans, Schmidt had to ensure that malaise didn't cause the decrease. Knowing rats lack a vomit reflex, the researcher offered them kaolin clay, which coats the stomach like an antacid, then compared kaolin intake with and without the AChEIs.

"At the doses shown to reduce nicotine self-administration, the AChEIs did not make our animals sick," Schmidt says.

These findings sparked Ashare's human clinical trial, which to date has studied 53 smokers ages 18 to 60.

People interested in quitting smoking signed on for a three-week study and were assigned to take galantamine or a placebo. The researchers assessed cognitive function three times: once at baseline before the trial, once after 14 days of smoking plus study medication, and, finally, after not smoking for 24 hours. Subjects then underwent a quit attempt during which they tried their best not to smoke for a week straight.

Participants taking the AChEI smoked 2.3 fewer cigarettes daily (about a 12 percent decrease) and felt less satisfied with the cigarettes they did smoke.

"Our goal in investigating these different repurposed medications is not to replace the medications already available," Ashare says. "Our goal is to target different populations of smokers."

The researchers published their findings in *Translational Psychiatry*. ■

How Stem Cell Therapy Can Preserve Bone

CELL BIOLOGY / HEALTH

Stem cell therapies show early promise in treating a number of diseases. It's known, for example, that a mesenchymal stem cell transplant can improve symptoms in an animal model of lupus, an autoimmune disease that can cause fatigue, joint pain, and swelling as well as an increased risk of osteoporosis. But researchers are only beginning to understand the mechanisms by which treatments bring results.

A study led by Songtao Shi, chair and professor of the Department of Anatomy and Cell Biology in Penn's School of Dental Medicine, offers insight into how stem cell infusions may help preserve bone in lupus—a finding that could have implications not only for lupus but also for other diseases.

Shi and his colleagues had previously shown that stem cell therapies could help treat autoimmune diseases in animal models but wanted to know how the treatments worked and why the beneficial effect persisted.

"We found that a one-time injection of stem cells would ameliorate disease for far longer than we would expect," Shi says.

They suspected that the stem cells might be triggering an epigenetic effect in the recipient, one that could alter the way genes are regulated, setting them on a normal course.

Examining a mouse model of lupus, the researchers found that, compared with healthy mice, the lupus mice had a significantly different pattern of DNA methylation, a modification that can alter gene expression. This difference was partially reversed by stem cell therapy, as was the ability of the mice to produce new bone. A series of experiments allowed Shi and colleagues to piece together the pathway by which this occurred, a process that involved the infused stem cells "donating" a healthy version of a protein called Fas, which improved the function of the recipient's bone marrow stem cells. They reported their findings in the journal *Cell Metabolism*.

Shi and colleagues are now exploring the mechanisms by which stem cell therapies reap benefits in other models of disease.

"You can imagine if you can reuse Fas, you might also be able to reuse other stem cell components to target other diseases," Shi says. ■

INNOVATION FACT

Songtao Shi, a dentist and stem cell researcher, discovered a unique population of stem cells from one of his daughter's baby teeth.

INNOVATION FACT

Cystic fibrosis is underdiagnosed in people with African ancestry, likely because it is thought of as a "white" disease. Conversely, sickle-cell anemia is often misdiagnosed in people of European descent, as it is thought of as a "black" disease.

REMOVING RACE FROM BIOLOGICAL RESEARCH

"It's time for biologists to find a better way." This was the call to action by two Penn Integrates Knowledge professors who urged their peers to stop using genetic concepts of race in biological research. Dorothy Roberts, a scholar of race, gender, and the law, with appointments in Penn Law School and in the School of Arts & Sciences' departments of Africana Studies and Sociology, and Sarah Tishkoff, an expert on human genetics, particularly African populations, with appointments in the Perelman School of Medicine and in Arts & Sciences' Biology Department, co-authored a perspective in *Science* on the subject, together with Michael Yudell of Drexel University and Rob DeSalle of the American Museum of Natural History.

The article, which received widespread media attention, noted that countless studies have failed to uphold a biological basis of race and underscored the important distinction between race, a social construction, and ancestry, a description of one's genetic heritage. The authors' appeal aimed to inspire scientists "to strengthen research by thinking more carefully about human genetic diversity." ■

Sarah Tishkoff has created the world's largest database of African diversity derived from genetic samples from more than 9,000 people from 200 distinct ethnic groups.

Stem Cell

During the past decade, a technique for turning adult cells back into stem cells has renewed the promise of regenerative medicine. These induced pluripotent stem cells, or iPS cells, would circumvent the ethical issues of their embryonic counterparts and produce tissue with a patient's own DNA, guaranteeing compatibility.

However, the technique for generating iPS cells is not yet foolproof; after reverting to their pluripotent state, these cells don't always correctly differentiate back into adult cells.

Penn engineers have discovered one of the reasons why. In a study published in *Cell Stem Cell*, they have shown that the reversion process does not always fully replicate the way an embryonic cell's genome is folded up inside its nucleus.

Led by Jennifer Phillips-Cremins, assistant professor in the School of Engineering and Applied Science's Department of Bioengineering, and Jonathan Beagan, a graduate student in her lab, the study was supported by the New York Stem Cell Foundation, the Alfred P. Sloan Foundation, and the National Institutes of Health.

INNOVATION FACT

The maps reported by Jennifer Phillips-Cremins' lab are the highest-resolution maps of genome folding in iPS cells to date.

Success Depends on Proper DNA Folding

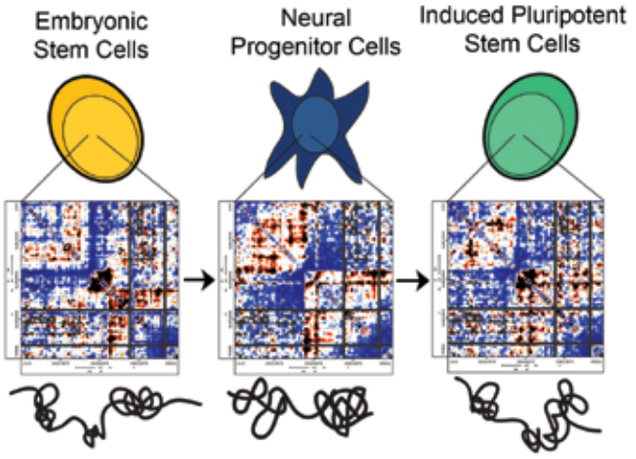
"We know there is a link between the topology of the genome and gene expression," Phillips-Cremins says, "so this motivated us to explore how the genetic material is reconfigured in three dimensions inside the nucleus during the reprogramming of a subclass of brain cells to pluripotency."

Phillips-Cremins' area of research is 3-D epigenetics. Classic epigenetic marks are chemical modifications on top of the DNA sequence, but looking at these marks in a linear fashion does not reveal the whole picture. The way the genome is tightly packed into a cell's nucleus can bring two disparate regions of the DNA into contact.

Her group's method for comparing the folding patterns of adult brain cells, iPS cells derived from them, and embryonic stem cells involved chemically "gluing" DNA such that 3-D folding patterns are preserved prior to sequencing. Computational analysis turned this sequencing data into heat maps, providing a picture of how frequently two DNA segments interact in the 3-D nucleus of stem cells. From there, the researchers could infer the folding configurations of the genome.

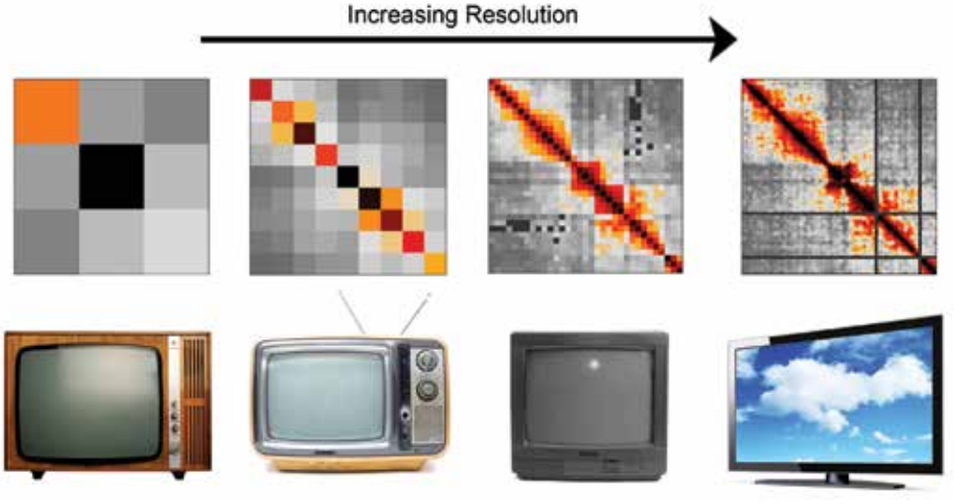
They found that DNA from some iPS cells did not fold in a manner that perfectly resembled traditional embryonic stem cells, but they instead exhibited traces of the 3-D configurations of the brain cells from which they were derived.

"Our observations are important," Beagan says, "because they suggest that, if we can push the 3-D genome conformation of cells that we are turning into iPS cells to be closer to that of embryonic stem cells, then we can possibly generate iPS cells that match gold-standard pluripotent stem cells more rapidly and efficiently." ■

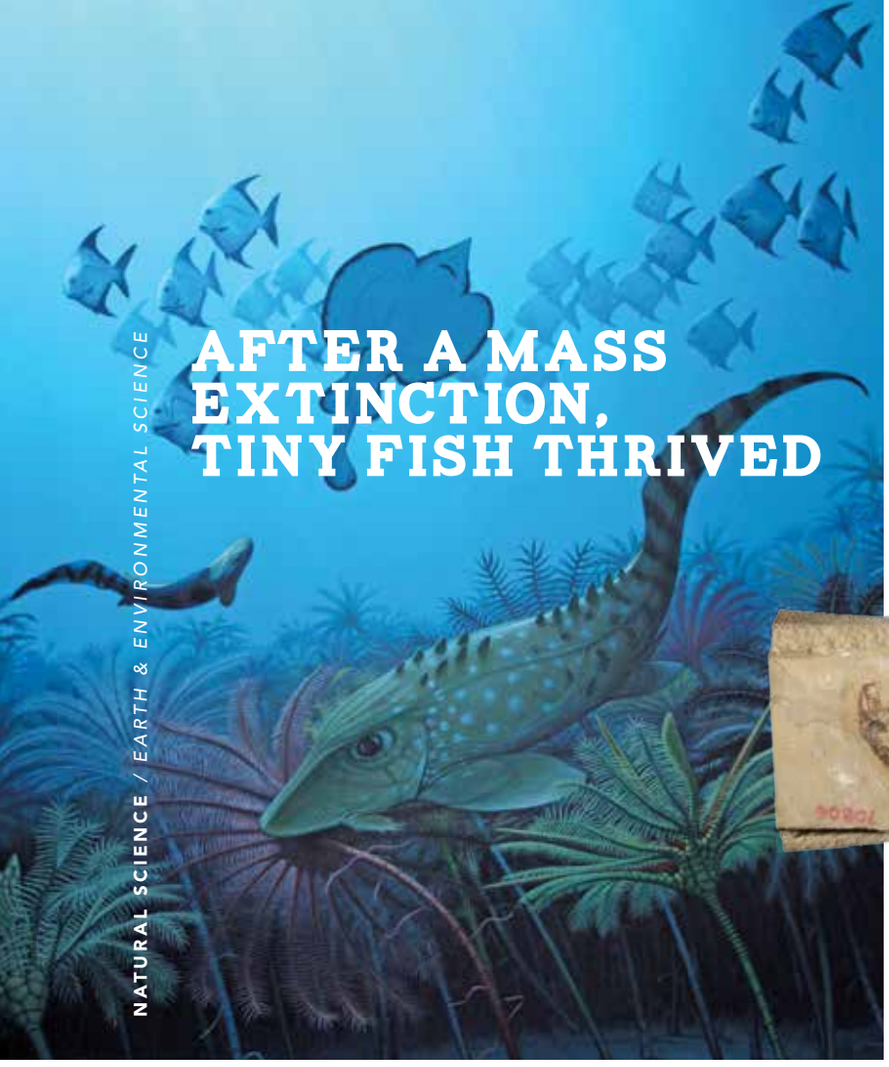


ABOVE: *Using data from their heatmaps, the illustrations represent how the DNA may be folding differently in each cell type.*

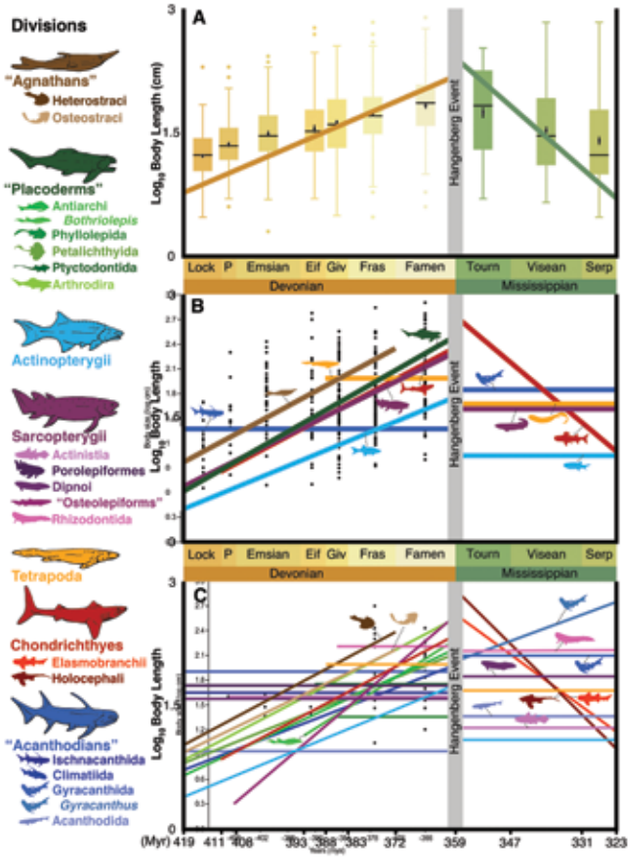
BELOW: *Previous methods provided data analogous to an old television, with large, black-and-white pixels. The team employed methods to create high-resolution maps of genome folding to distinguish detailed topological features and evaluate their similarities and differences.*



AFTER A MASS EXTINCTION, TINY FISH THRIVED



Being small was beneficial for fish following the mass extinction known as the Hangenberg event. Above, two fish from the Mississippian Period post-extinction, are immortalized in a fighting pose.



Bigger isn't always better. A study published in *Science* and led by Penn's Lauren Sallan found that, after a mass extinction 359 million years ago known as the Hangenberg event, large fish were decimated and the oceans became dominated by tiny fish, a paradigm that persisted at least 40 million years.

"Rather than having this thriving ecosystem of large things, you may have one gigantic relict, but otherwise everything is the size of a sardine," says Sallan, an assistant professor in the Department of Earth and Environmental Science in the School of Arts & Sciences.

The finding challenges Cope's rule, an evolutionary theory that states that the body size of a given group of species tends to increase over time. Instead, the new results suggest that in the disturbed, post-extinction environment, being small was an effective survival strategy.

Sallan and her co-author, Andrew K. Galimberti, investigated fish body-size trends by first amassing a data set of 1,120 fish fossils spanning the period from 419 to 323 million years ago.

In line with Cope's rule, fish gradually increased in size during the Devonian Period, from 419 to 359 million years ago. By the end of the Devonian, "the majority of residents in ecosystems, from bottom dweller to apex predator, were a meter or longer," Sallan says.

Then came the Hangenberg event, which wiped out more than 97 percent of the planet's vertebrate species. Sallan and Galimberti found that the mass extinction triggered a decline in body sizes, a trend that continued for much longer than they expected—at least 40 million years.

With some ecologists concerned that the planet is on the brink of a sixth major extinction event, this time caused by humans, Sallan says the results should raise alarm about how long large species, like overfished marine populations, might take to recover.

"These disturbances are shifting natural selection so that smaller, faster reproducing fish are more likely to keep going," she says. "It could take a really long time to get those bigger fish back in any sizable way." ■

INNOVATION FACT

Before Lauren Sallan's analysis, the largest dataset of fish body sizes from the Devonian Period had about 40 specimens. A new approach allowed Sallan to collect more than 1,100.

INNOVATION FACT

This is the first instance of research that links the amygdala, typically associated with fear, to kindness and positive behavior.

NATURAL SCIENCE

Amygdala Influences Kindness and Charitable Behavior, Not Just Fear

The amygdala, a small structure at the front of the brain's temporal lobe, has long been associated with negative behaviors. Research published in *Proceedings of the National Academy of Sciences* from Michael Platt, the James S. Riepe University Professor, shows that this collection of nuclei can also influence positive social functions like kindness. Such a link might help people with autism and schizophrenia, who have trouble connecting with others.

"We're trying to identify and understand the basic brain mechanism that allows us to be kind to each other," says Platt, who has appointments in the School of Arts & Sciences, Perelman School of Medicine, and the Wharton School. "We're also trying to evaluate potential therapies that could improve the function of these neural circuits."

Collaborating with Yale and Duke scientists, Platt turned to rhesus macaques, primates that live in large social groups and form long-term bonds, much like humans do. The researchers used a reward-donation task, teaching one actor monkey that different-colored shapes resulted in juice for him alone, his friend (called the recipient monkey), both, or no one.

Once the researchers determined that the monkeys understood the task, they let the actor choose to keep, share, give away, or dump the juice.

"Generally our actor monkeys preferred to reward the other monkey rather than let it go unclaimed," Platt says. "They were more likely to give to those they're more familiar with, and to subordinate monkeys."

During the test, Platt and colleagues also recorded neural activity in each animal's amygdala; they found it was active in the same way when the actor kept the juice and gave it away. Based on these neural responses, the scientists could accurately predict actors' decisions. Introducing oxytocin, a hormone linked to social bonds, increased the monkeys' willingness to reward others and their attentiveness toward recipients.

This finding could be key for humans—though a deeper understanding requires additional work, Platt says: "When people inhale oxytocin, there is a change in blood flow to the amygdala, which we think might be involved in making people kinder and more receptive." ■

Recycling Rare-Earth Magnets

CHEMISTRY

TECHNOLOGY

Rare-earth metals are, as their name suggests, hard to come by. Mining and purifying them is an expensive, labor-intensive, and ecologically devastating process.

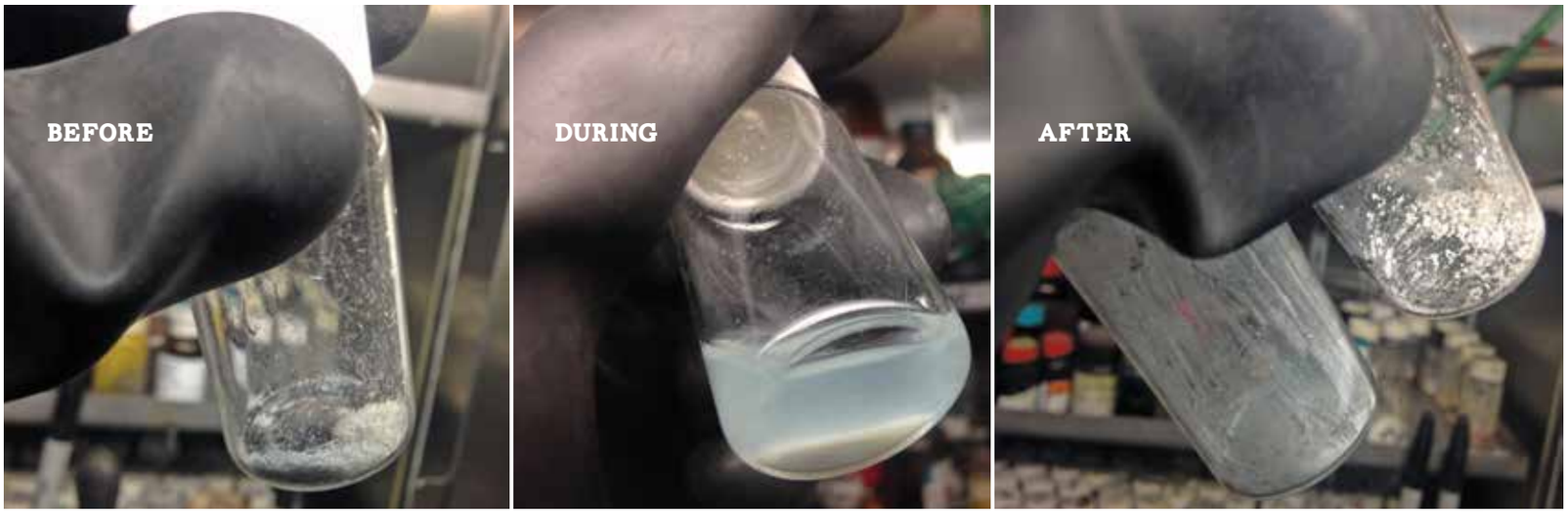
Penn chemists have pioneered a process that could enable the efficient recycling of two of these metals, neodymium and dysprosium. These elements are ubiquitous in the powerful magnets found in many high-tech devices.

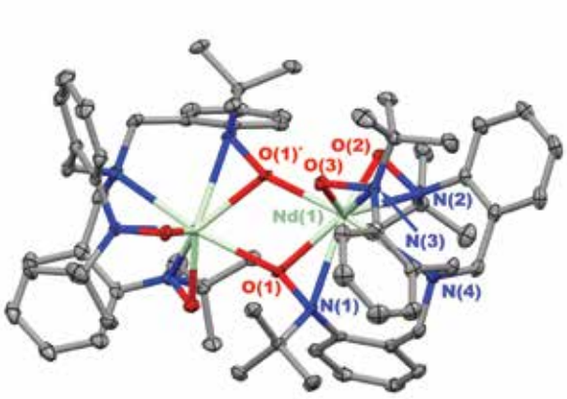
The research was led by Eric J. Schelter, associate professor in the Department of Chemistry in Penn's School of Arts & Sciences, and graduate student Justin Bogart. It was published in *Angewandte Chemie, International Edition*, and supported by the U.S. Department of Energy and the Research Corporation for Science Advancement.

Neodymium magnets are prized for their strength and ability to work at a range of temperatures, but the metal's thermal qualities are achieved by mixing neodymium with dysprosium. Because the ideal ratio depends on a given magnet's intended application, old magnets can't simply be melted down and reused.

INNOVATION FACT

The team's separation method relies on chemically sorting the two types of atoms based on their diameters. A dysprosium atom is about 350 picometers, whereas a neodymium atom is about 20 picometers wider. For comparison, the thickness of a dollar bill is about 100,000,000 picometers.





Rare-earths are naturally found as mixtures in minerals. The technique for first separating them, known as liquid-liquid extraction, involves dissolving the composite material and chemically filtering apart the elements. The energy-intensive process is repeated thousands of times to get useful purities and must be conducted on an industrial scale.

In pursuing a more efficient process, the Penn team focused on a simpler problem: separating just the neodymium and dysprosium.

Reclaiming those metals from smartphone speakers, power tool motors, windmill turbines, and other devices could be much less expensive and polluting than getting them out of the ground.

In the Penn team's method, the two elements begin as a mixed powder to which a metal-binding molecule known as a ligand is applied. The researchers' custom ligand looks like a bird's claw, with three talons that converge on the metal atom. Because of neodymium's slightly larger size, the tips of the talons don't get as close together as they do around dysprosium atoms.

"Because it is more open," Schelter says, "one ligand-neodymium complex can combine with another, and that really changes its solubility."

The combination of two complexes encapsulates the neodymium ions, enabling them to dissolve in solvents like benzene or toluene. Dysprosium complexes can't combine and thus remain as a solid that stays behind when the neodymium solution is poured off. Once separated, an acid bath can strip the ligand off both metals, enabling it to be recycled as well.

"If you have the right ligand, you can do this separation in five minutes," Schelter says, "whereas the liquid-liquid extraction method takes weeks." ■

WHEN SOCIAL MEDIA REINFORCES REAL NEIGHBORHOOD DANGERS

Adolescents from unsafe neighborhoods report avoiding public spaces like parks because of their danger. The teens stay inside, removed from violence or crime. But what happens when the social media they turn to reinforces those same negatives? Their safe haven suddenly turns dangerous, becoming what researcher Robin Stevens, assistant professor in the School of Nursing, has dubbed the "digital hood."

Stevens, who published her findings in the journal *New Media & Society,* knew she'd touched on something after interviews with 60 13- to 24-year-olds from Camden, N.J. Again and again, she heard surprising descriptions of social media as a "ghetto news center" where stories about everything from deaths to parties "get around fast."

"It's a phenomenon going on in communities across the country," Stevens says.

She determined that a negative feedback loop occurs, in which real life and social media imitate one another. "An argument that happens on Facebook turns into a physical fight in real life," she explains. "The fight will be recorded on someone's phone and posted on Facebook." And as with all media, more provocative content often becomes the most popular, commented on, and shared.

Part of the problem is researchers still don't know how such posts shape worldviews for early adolescents. "Let's say 5 percent of the community is involved in some type of this behavior," Stevens says. "All youth in that digital neighborhood are still exposed to it. How does this content influence norms among the younger teens?"

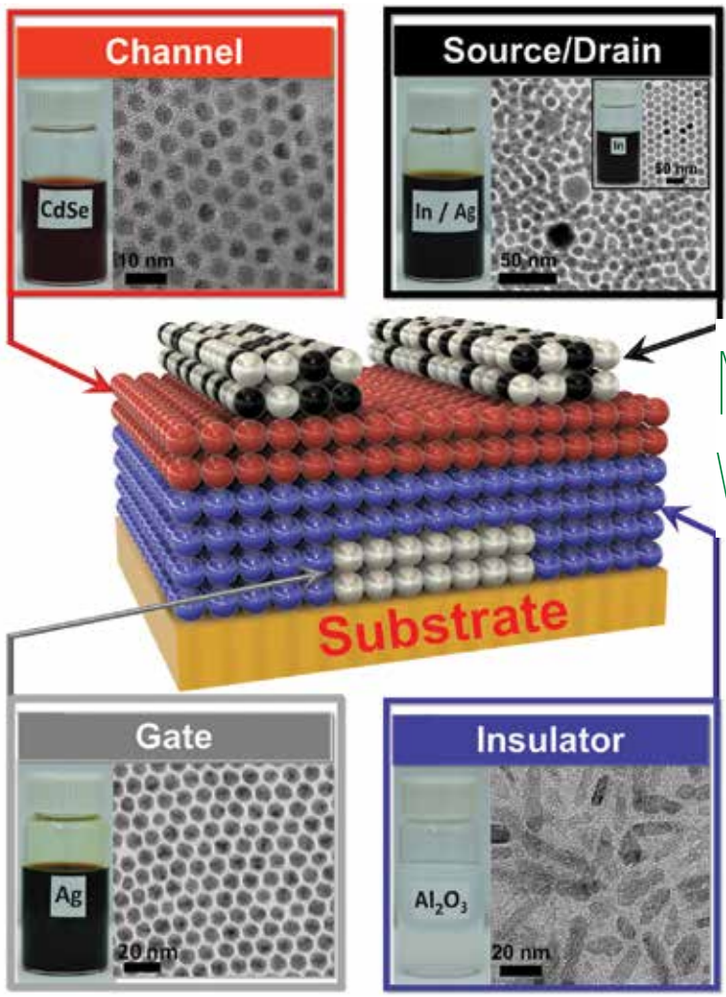
INNOVATION FACT

Robin Stevens' term "digital hood" is the first formal reference to this online phenomenon.

Also, minority and impoverished youth aren't typically part of broad conversations about social media, so there's an information gap about how they use it and how the platforms escalate or amplify already-charged scenarios.

Stevens feels hopeful that this can transform. Teens already think carefully about how they use social media, individually and as activists. Now, she says, the key will be integrating them into the change movement.

"Social media isn't going anywhere," Stevens says. "It may be a different platform in 10 years, but this is the way they communicate, so how do we develop best practices in this space?" ■



Cherie Kagan's group developed four nanocrystal inks that comprise the transistor, then deposited them on a flexible backing.

Making Transistors with Nanocrystal 'Ink'

Transistors are found by the billions on every computer chip, but making them is a complex process that requires high-temperature, high-vacuum equipment.

In a study published in *Science,* Penn engineers have shown a new approach for crafting these devices that has more in common with a summer camp arts-and-crafts activity: spinning a series of special inks over a series of stencils.

What makes these inks special is that they are composed of nanocrystals—tiny particles of carefully selected materials, each providing a different electrical property.

The study was led by Cherie Kagan, the Stephen J. Angello Professor in the School of Engineering and Applied Science, and Ji-Hyuk Choi, then a member of her lab, now a senior researcher at the Korea Institute of Geoscience and Mineral Resources. They collaborated with Christopher Murray, a Penn Integrates Knowledge professor with appointments in the School of Arts & Sciences and Penn Engineering.

Kagan's group developed a library of four inks—a conductor, an insulator, a semiconductor, and a conductor combined with a dopant—and then set out to combine them into full devices.

"Our question was whether you could lay them down on a surface in such a way that they work together to form functional transistors," says Kagan.

That process involved working in sequence, using stencils to mark where that layer of ink should go. In each step, a dollop of ink was deposited, then rapidly spun to draw it out over the stencil. The inks also went through treatment steps to make sure they would stick together without losing their electrical properties.

"The trick to working with solution-based materials is making sure that, when you add the second layer, it doesn't wash off the first, and so on," Kagan says.

Because this ink-based process works at lower temperatures than existing methods, the researchers were able to make their transistors on a flexible plastic backing. This makes the technique particularly promising for wearable applications.

The research was supported by the National Science Foundation, the U.S. Department of Energy, the Office of Naval Research, and Korea's Ministry of Science, ICT, and Future Planning. ■

DIFFERENTIAL PRIVACY FOR SECURITY AND SCIENCE

In the age of big data, removing individuals' identifying information from databases may not be enough to ensure privacy. External data might allow an observer to work out the identity of a member through his or her idiosyncrasies.

With that in mind, Aaron Roth, an associate professor in the Department of Computer and Information Science in Penn's School of Engineering and Applied Science, is one of the leading figures in the development of a concept known as differential privacy.

The "different" in a differentially private algorithm's name refers to the guarantee it makes. Its analyses remain virtually identical when applied to two different data sets: one with and one without the data from any single individual.

Such a guarantee could protect innocents when searching the social networks of people suspected of criminal activity.

Along with Michael Kearns, co-director of the Warren Center and National Center Chair in Engineering, their student Steven Wu, and Warren Center postdoc Grigory Yaroslavtsev, Roth published a study in *Proceedings of the National Academy of Sciences* that outlines differentially private algorithms for this purpose.

Performing network searches through such algorithms would hide results that depend on a single individual as the link between two groups. If there are multiple possible links, no external data could definitively "out" that innocent individual as the connection between the guilty parties.

Roth is also investigating whether this approach could be applied to scientific searches.

When testing a hypothesis on large sets of data, the results also shouldn't rely on the existence of any single member of that set. Such "overfitted" results can't be generalized.

"There's this idea where the more privacy you have, the less useful the data is," Roth says. "There's some truth to that, but it's not quite so simple. Privacy can also increase the usefulness of data by preventing this kind of overfitting."

Roth and colleagues at the research arms of Microsoft, IBM, Google, and Samsung, as well as the University of Toronto, published a study in *Science* that outlines how differential privacy might be used to combat this problem as it applies to adaptive analysis, when multiple hypotheses are tested on the same set in sequence.

The normal check on overfitting in these cases—holding out a portion of the data to test findings generated from the rest—is challenging, as fresh holdouts must be used for each test. When gathering enough data to provide for these holdouts is untenable, differentially private algorithms could be used to generate a reusable holdout.

Roth's research is supported by the National Science Foundation and the Alfred P. Sloan Foundation. ■

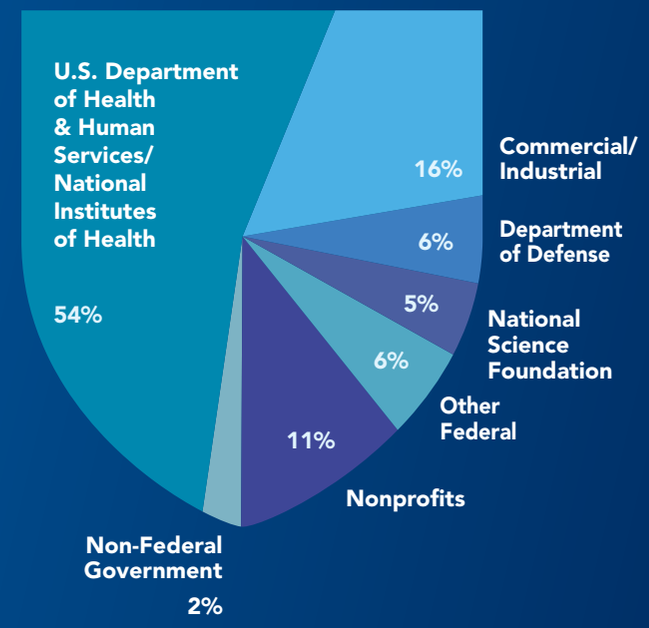
INNOVATION FACT

Apple is now incorporating differentially private algorithms into its products to gather information on user trends without seeing any one user's personal data.

FROM LEFT TO RIGHT: *Steven Wu, Michael Kearns, Aaron Roth, and Grigory Yaroslavtsev*

Penn's Research Enterprise

Research Awards by Sponsor



FY 2016 Total Awards: $1.02 billion

PENNOVATION Center

TECHNOLOGY INNOVATION

The third floor is home to PERCH, the Penn Engineering Research and Collaboration Hub.

An Ecosystem for Entrepreneurs

COSY operates in one of the Pennovation Center's inventor garages.

Many Silicon Valley technology companies got their big breaks after working in garages. Philadelphia-based COSY, one of the first community members in a Pennovation Center "inventor garage," hopes for a similar outcome.

COSY, or Cognitive Operational Systems, which for a year has maintained an office at the Pennovation Works development site, was mostly drawn to the inventor garage for its practicality: It provides easy access for the company's indoor mapping product. The garage's glass door rolls up, and out drive COSY's mobile robots.

"We can put the robots right in the car to go to the retailers," says Jonas Cleveland, who founded COSY as a master's student at Penn's School of Engineering and Applied Science.

The Pennovation Center, a new 58,000-square-foot anchor for Pennovation Works in Grays Ferry, features five additional rentable inventor garages. The rest of the building maintains co-working space for several hundred members, conference rooms, private offices, event space, and wet and dry laboratories equipped with all the basic research necessities. Benjamin's Desk, an innovation network with four existing co-working spaces in Philadelphia, powers the Center's first and second floors.

The second floor's unique laboratory design creates space for up-and-coming biotechnology companies like Liquid Biotech USA, a Penn spinoff looking to develop noninvasive diagnostics tests that allow doctors to safely and effectively discover cancer earlier. Liquid Biotech will be joined by other Penn spinoff companies CytoVas, an in vitro diagnostics company that develops advanced assays for evaluating cardiovascular health, and Blue Pen Biomarkers, a company that quantifies, integrates, and analyzes genomic, proteomic, and other biomarkers.

On the third floor, PERCH, short for Penn Engineering Research and Collaboration Hub, is home to several integrated, multidisciplinary projects with students and faculty from three labs, including the ModLab, under Mark Yim, a professor in the Department of Mechanical Engineering and Applied Mechanics; the Multi-Robot Systems Laboratory, under Vijay Kumar, the Nemirovsky Family Dean of Penn Engineering; and the Kod*lab, under Daniel Koditschek, the Alfred Fitler Moore Professor of Electrical and Systems Engineering.

Koditschek, PERCH's inaugural director, says the third-floor space offers a "unique, open, and flexible area for the sharing of equipment and ideas."

Pennovation Works also houses a large, netted outdoor motion capture arena to test running and flying robots created within PERCH.

"The biggest impact the Pennovation Center has made for us is that it offers these wonderful spaces for interaction and experimentation that would be impossible on the main campus," says Koditschek.

Cleveland, who developed COSY alongside Penn Engineering professor Kostas Daniilidis, through their research in Penn's General Robotics, Automation, Sensing, and Perception (GRASP) Laboratory, is confident about the opportunities presented by simply working in the same building as PERCH.

"Walking through the Center, it's so open, and you're always running into and meeting with people," Cleveland says. "The Center is just so appealing as a hub for collaboration."

Dawn Bonnell, vice provost for research, says the Center is unique in that it's a space "where entrepreneurs and aspiring entrepreneurs interact."

These interactions are encouraged across all disciplines. Hershey Co. was the first company to set up shop in an office on the Center's second floor. The confectionary company is exploring technologies and prototypes that fall outside of its traditional focus. The University's 2016 President's Innovation Prize recipients, XEED and Fever Smart, two biomedical device companies, also have dedicated space.

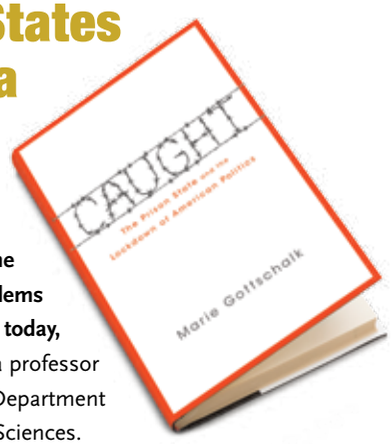
Bonnell says the Center, by design, acts as a physical structure to help all kinds of researchers develop and commercialize discoveries, then use their connections within the space to "take their ideas to the next stage," perhaps by garnering venture capital.

Helping to provide that support network is specifically where the Penn Center for Innovation (PCI) comes into play. Aside from running its Penn I-Corps accelerator and PCI Ventures out of the Center, PCI delivers educational programming for startups, including sessions on how to manage IT issues or how to get investors.

Piccolissimo is the world's smallest self-powered controllable flying vehicle, and is a project from Mark Yim's ModLab.

"The Center is a landing pad for all our activity related to startups and a place to engage external partners like venture capitalists and corporations," says Laurie Actman, PCI's chief operating officer. "This new building is the most symbolic and visible example of the commercialization activities that we've been conducting for a while." ■

The United Carceral States of America



Mass incarceration is one of the most critical problems facing the United States today, says Marie Gottschalk, a professor in the Political Science Department in the School of Arts & Sciences.

"It cuts across so many issues: issues of race, issues of inequality, issues of democracy," she contends. "It's not just about prisons. It's about the direction that the United States is going and how to change that direction."

Gottschalk says writing about criminal justice is a window into the wider pathologies of politics in the United States. In her new book "Caught: The Prison State and the Lockdown of American Politics," she examines the emergence of the carceral state in America and why it continues to intensify and expand.

For many years, talk of mass incarceration focused primarily on the large number of people in U.S. prisons and jails. But today, it is more accurate to talk about a carceral state, according to Gottschalk. For the millions of people who are incarcerated, she says there are millions more who are technically free, but second- or third-class citizens.

"They're on probation, they're on parole, they're people who have a felon record who are not permitted to vote, or to get student loans, or to receive public housing," Gottschalk says.

The carceral state has had a deleterious effect on the quality of American democracy. Even if a person has never been involved in the criminal justice system, Gottschalk says, he or she is still affected by the carceral state. For example, people with criminal records are barred from voting in many states, which has altered the outcomes of elections. Furthermore, many critical demographic surveys and studies do not include the large incarcerated population, leading to misleading findings about key socioeconomic and political indicators, including rates of poverty, unemployment, high school dropouts, and voter participation.

In order to create a successful movement to dismantle the carceral state, Gottschalk contends it must be viewed as a moral issue and issue of equality, and animated by something more than economic concerns about costly prisons and jails.

"If we truly care about ending the carceral state and we truly care about the welfare of people who have been in prison, or about their children, or about their communities," she says, "it's probably going to cost more money rather than less money." ■

THE GOOD NEWS/ BAD NEWS ABOUT AMERICA'S HOMELESSNESS RATE

The homeless rate in America continues to decline as a bipartisan effort has resulted in a 50 percent reduction among military veterans since 2009 and an 11 percent drop overall.

Dennis Culhane, the Dana and Andrew Stone Chair in Social Policy in the School of Social Policy & Practice and director of research at the National Center on Homelessness Among Veterans, says Virginia and Connecticut have ended veteran homelessness altogether, as have several large cities, including Philadelphia, Houston, New Orleans, and Phoenix.

"They've gotten to what they call 'functional zero,' meaning that every veteran has been housed, or they've been identified and there's a housing plan for them, and any newly identified homeless veteran is housed in 30 days," he says.

The most recent data on homelessness in America were reported in the U.S. Department of Housing and Urban Development's "2015 Annual Homeless Assessment Report to Congress," of which Culhane is co-principal investigator. Since 2009, the federal government has increased spending on programs to fight homelessness by more than $1 billion, from $400 million to $1.4 billion. These funds have provided 80,000 housing vouchers for chronically homeless people and emergency housing assistance and relocation funding for 100,000 veterans per year.

While national statistics show a decline, in part due to the drop in veteran homelessness, Culhane says homelessness appears to be increasing in many communities, particularly in coastal cities such as Honolulu, Seattle, Portland Ore., San Francisco, and Los Angeles, which have each announced a homelessness state of emergency.

"By providing health care, providing emergency housing assistance, providing long-term housing assistance for those who need it, we are having a dramatic impact."

Culhane says homelessness is increasing among people in their 20s and 50s, the two age groups most negatively affected by the Great Recession.

"In the case of people in their 50s, they've had very low rates of reemployment," he says. "For people in their 20s, they've had very poor rates of entry into the workforce, in general."

Culhane says interventions used to reduce homelessness among veterans can be used to fight homelessness among the general public, such as permanent housing; providing support for people with disabilities who experience long-term homelessness; the rapid rehousing of people experiencing crisis homelessness; and access to health care for mental health and substance abuse issues.

"By providing health care, providing emergency housing assistance, providing long-term housing assistance for those who need it, we are having a dramatic impact" among veterans, Culhane says. "We could do the same for the non-veteran population." ■

INNOVATION FACT

Social media has played a role in increasing awareness of many protests around the world, including the Arab Spring, the Occupy movement, the Spanish Indignados, and the Umbrella Revolution in Hong Kong.

A Testament to the 'Slacktivists'

In May 2013, a sit-in protest against urban development plans for Istanbul's Taksim Gezi Park quickly escalated into massive antigovernment demonstrations. This was because online networks could circumvent Turkey's heavily controlled mainstream media to rapidly disperse information from the core to the periphery—or from activists on the ground to partakers from afar.

Those peripheral online participants surrounding Gezi Park as well as at other protest events, such as the Occupy Wall Street and Indignados movements, are sometimes dubbed slacktivists. In contrast to those physically at a protest site, their shallow commitment in solely sharing a tweet or clicking "like" on a Facebook post is irrelevant, critics claim.

But a study published in *PLOS ONE* by Sandra González-Bailón, an assistant professor at the Annenberg School for Communication, and colleagues from New York University, found that the role of these so-called feel-good activists generate just as much online content as the core participants.

"The reality is," González-Bailón says, "when all those individual actions are aggregated, that amounts to a lot of activity."

How much of a difference that outside activity makes is significant, too.

"When measuring the impact in terms of audience reach, the protest messages would have much lower influence without the peripheral players," González-Bailón says.

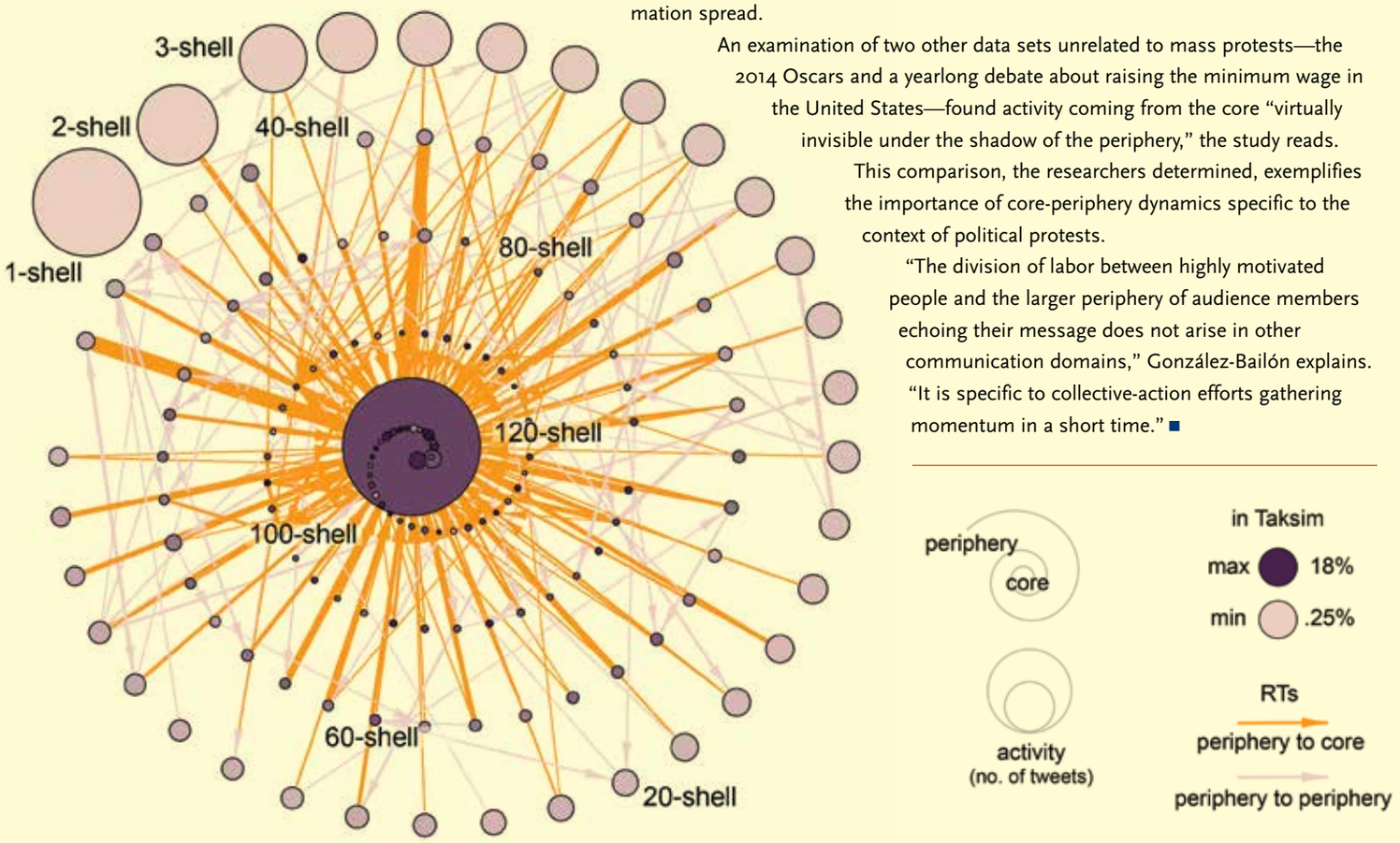
The researchers used location data embedded in tens of millions of tweets to conduct the study, which specifically looked at Twitter activity during the three aforementioned protest events. They also analyzed the Twitter users' networks to determine how information spread.

An examination of two other data sets unrelated to mass protests—the 2014 Oscars and a yearlong debate about raising the minimum wage in the United States—found activity coming from the core "virtually invisible under the shadow of the periphery," the study reads.

This comparison, the researchers determined, exemplifies the importance of core-periphery dynamics specific to the context of political protests.

"The division of labor between highly motivated people and the larger periphery of audience members echoing their message does not arise in other communication domains," González-Bailón explains. "It is specific to collective-action efforts gathering momentum in a short time." ■

Most people who tweeted about protests at Istanbul's Taksim Gezi Park were at the center of the activity, which was also the source of most retweets. In this way, information flowed from the core to the periphery.



Evolution in Action,

How well does the public understand evolution? A 2014 Gallup poll revealed that 40 percent of Americans believe in creationism, the notion that God created life on Earth.

School of Arts & Sciences researchers Michael Weisberg, Department of Philosophy chair, and senior psychology fellow Deena Weisberg, weren't sold on those results. Backed by a National Science Foundation grant, they partnered with the Annenberg Public Policy Center to create a survey with more nuanced questions; suddenly, that number dropped to 25 percent.

Motivated to dig deeper, they began an evidence-based research project that would culminate in a documentary series about evolution. Two undergrads and fifth-year psychology graduate student Emlen Metz interviewed Catholic priests and nuns, Muslim community members, people in retirement homes, and family and friends, and also combed through dozens of nature films. They came away with one overarching conclusion: "A lot of people have no idea what evolution is," Metz says.

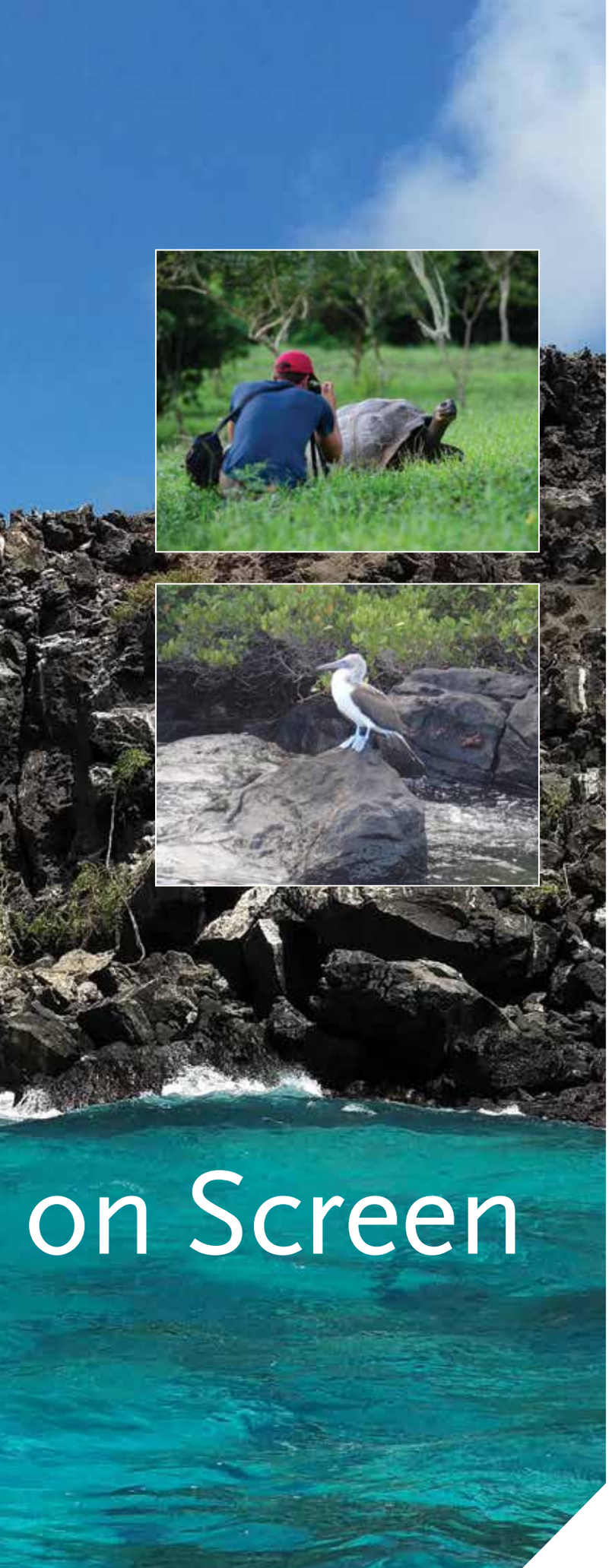
To address that gap, the team created multiple films about adaptation, variation, and natural selection in three different styles: traditional documentary, with voiceover narration and wide shots; cinéma vérité, where the narrator speaks to the camera; and a behind-the-scenes look, prompted by reality television and after-credits reels.

They spent several weeks in December 2015 collecting footage on the Galápagos, 19 islands off Ecuador's coast, one of the places that informed Charles Darwin's "On the Origin of Species."

"The Galápagos Islands are one of those places where you can really show evolution in action," Michael Weisberg says. "It's a place of sparse vegetation, of remarkable animals and plants, remarkable examples of adaptation all around."

The team has finalized the videos and has begun analyzing their effectiveness using tests Metz and Deena Weisberg developed for viewers to take after screenings. The researchers started local, showing the trio of shorts to participants on Penn's campus. They plan to expand to eventually reach a demographically representative sample.

"Whether people say they agree with the scientific consensus or reject the theory of evolution doesn't seem to matter in terms of how well they're able to describe what evolution is," Deena Weisberg says. ■



on Screen

SOCIAL SCIENCE / EDUCATION

Inequity in Higher Education

With each decade, more students from all economic and ethnic backgrounds are enrolling in college. Despite that apparent success, however, inequity in college opportunity and outcomes persists—and some gaps are only widening.

Laura Perna, a professor in the Graduate School of Education and executive director of the Alliance for Higher Education and Democracy, explored this topic in "Indicators of Higher Education Equity in the United States: 2016 Historical Trend Report" with Ph.D. student Roman Ruiz and the Pell Institute for the Study of Opportunity in Higher Education. Their findings illustrate differences in postsecondary enrollment and other outcomes in the United States by family income, race/ethnicity, and family socioeconomic status.

The data show that students from high-income families attain college degrees at far higher rates than students from low-income families. "Not everyone needs a college degree," Perna says, "but the profound and persisting differences in attainment based on students' family income have important negative economic and social consequences for individuals and our society."

She notes that federal grant aid has not kept pace with the growing cost of higher education, and this pattern disproportionately affects students from lower incomes. Disparities in the availability of rigorous coursework and higher education preparation in the K-12 schools that students from different groups attend also affect where students go to college and whether they complete a degree.

"There are considerable differences in the availability of resources along the pipeline in and through college that serve to compound advantage and disadvantage," says Perna.

The report shows that students from lower income families represent considerably smaller shares of first-time, full-time-degree, or certificate-seeking undergraduates at private, nonprofit, four-year schools than at public two-year and for-profit two- and four-year institutions. In addition, low-income students represent just 15 percent of first-time undergraduates at the most competitive schools but 51 percent of students at less competitive institutions.

"Choice" is a misnomer for college destinations of many low-income students, Perna and her colleagues write, because constraints in resources and structural failures restrict the set of college options that are possible.

Perna recently received a grant from Lumina Foundation to help produce the 2017 and 2018 versions of the report, which will include additional data, as well as improved web-based data interfaces.

"A primary goal of this report is to document and make clear the patterns and trends in equity," says Perna. "The findings clearly demonstrate that, despite the many different policies and practices that are now in place, we have substantial and persistent inequalities in our nation's K-12 and higher education systems." ■

Separating Church and State in Early America

The separation of church and state is a pillar of American democracy, but during colonial times, most American colonies had established places of worship that descended from the Church of England.

Sarah Barringer Gordon, the Arlin M. Adams Professor of Constitutional Law and Professor of History, says the American tradition of disestablishment began during the American Revolution. In her forthcoming book "Freedom's Holy Light: Disestablishment in America, 1776-1876," Gordon writes about how and why the church and state separated.

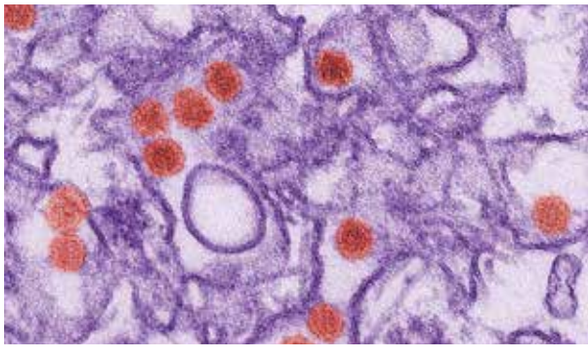
Disestablishment was bold and controversial, Gordon says, as worldwide opinion held that a government without religion could not survive. But in the early United States, separation of church and state spread across political and religious life.

"We have not studied the ways that disestablishment actually worked on the ground," Gordon says. "When we look closely at separation of church and state as it was practiced around the country, we see that it had distinctly conservative as well as liberating elements."

One of the most intense controversies concerning disestablishment was whether clergy should be allowed to address political issues, especially slavery, from the pulpit. Pro-slavery forces saw disestablishment as a way to eliminate religion-based arguments against slavery, and though the attempt to shift debates over slavery out of churches and into legislatures was never completely successful, it did silence many religious voices.

Yet debates over slavery in religious venues grew in the 19th century and caused schisms among prominent denominations by the 1840s. Eventually, slavery became a central focus for both Northern and Southern preachers during the Civil War.

"Freedom's Holy Light" tells this story of religious liberty and the coercion of slavery, and how the two were first separated, then united, as religious groups and the country split in two. Gordon argues that the end of this period marked the end of the formal theory of separation of religion and politics. This theory protected slavery, but gradually it created its own politics, and resistance to the silence imposed on antislavery preaching generated overwhelming countervailing forces. ■



TOP: *A female* Aedes aegypti *mosquito in the process of acquiring a blood meal from her human host.*

BOTTOM: *Transmission electron micrograph of Zika virus, which is a member of the family* Flaviviridae.

INNOVATION FACT

Zika is spread mostly by the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*). These are the same mosquitoes that spread dengue and chikungunya viruses.

Source: Centers for Disease Control and Prevention

Improving the Public's Knowledge of Zika

When a mosquito-borne virus in Latin America was suspected of being linked to birth defects and headed toward the United States, Kathleen Hall Jamieson refused to sit idly by. The Annenberg Public Policy Center (APPC) director recognized the harm that could come if the public wasn't informed about the risks of the disease and how to prevent it.

In February 2016, the APPC launched the Annenberg Science Knowledge survey, which assessed the public's awareness about Zika, a disease that has been linked to microcephaly in babies born to infected mothers. The weekly survey results have been shared with journalists, as well as with the Centers for Disease Control and Prevention and the National Institutes of Health, to help disseminate important Zika-related information.

"We know the conduit through which most people learn is the media," Jamieson explains. "We send reporters these data so they are aware of gaps in public knowledge and can adapt their reporting accordingly."

The policy center quickly found that many in the public lacked understanding of Zika prevention, such as practicing safe sex with anyone who recently visited areas with the disease and effective ways of applying insect repellent. A July 2016 survey, for example, showed that only one in four people took steps in the prior three months to protect themselves from getting Zika.

"It doesn't help you to know it's a problem if you don't know how to prevent one," Jamieson says.

Other survey questions asked whether people would get a Zika vaccine if one were available; whether the Rio Olympics should have been canceled or delayed; and whether Zika-fighting genetically modified mosquitoes should be released in areas with an outbreak.

During the summer of 2016, the APPC released a free, downloadable guide for reporters covering Zika. One tip, Jamieson says, is aimed at television reports: "When there's a backdrop visual on the TV, instead of showing a mosquito, show someone applying repellent or tipping standing water."

Jamieson says her goal is to make sure the communications channels are working "as well as they can to increase the likelihood that pregnant women will avoid infection and, with it, the risk of having a child with microcephaly." ■

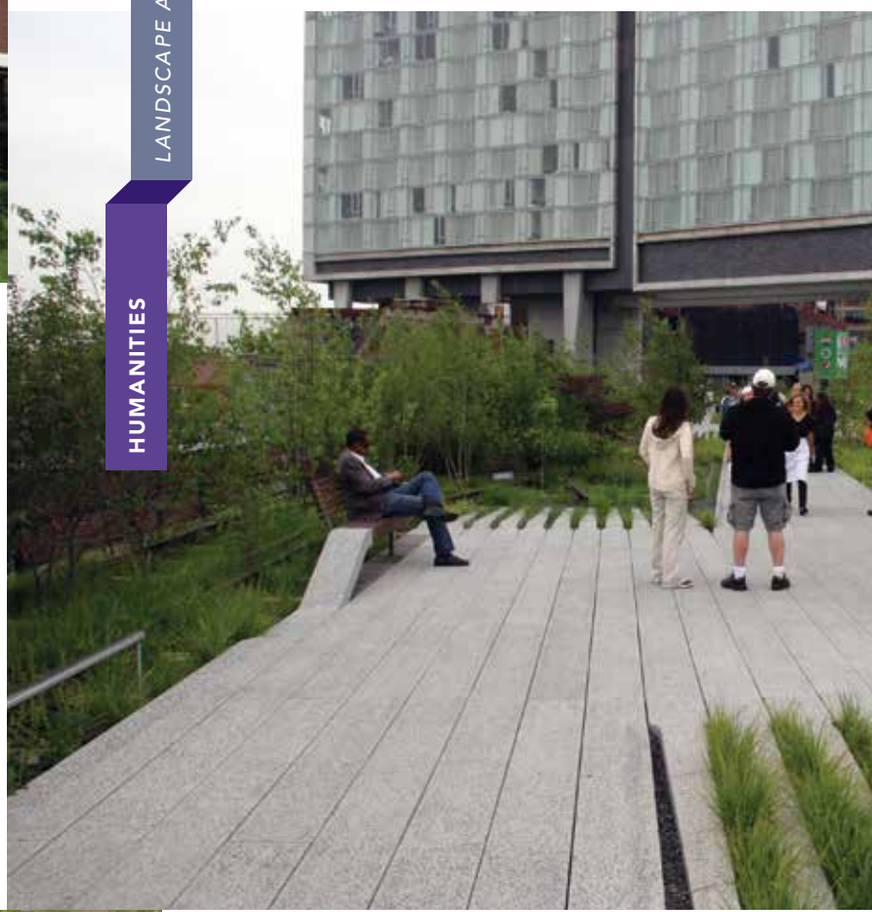
SciCheck: Debunking False Claims

Vanessa Schipani spends her days scouring the news for faulty science-related claims. As the sole writer for SciCheck, the Annenberg Public Policy Center's newest feature of *FactCheck.org*, she has often debunked erroneous statements about the Zika virus.

In February 2016, for instance, Schipani wrote an article discrediting a rumor falsely claiming that genetically modified (GM) mosquitoes caused the Zika outbreak. In fact, she explained, GM mosquitoes may be able to help control the spread of the virus.

SciCheck was founded in January 2015 with a grant from the Stanton Foundation. Ever since, it's taken on hot-button subjects such as Zika, climate change, and vaccinations, to name a few.

"*FactCheck.org* is a resource for the public and holds politicians and others accountable for what they say," explains Eugene Kiely, the website's director. "Having a science focus fits perfectly into that overall picture, since a lot of what is being said these days deals with science-related issues."



INNOVATION FACT

Zero projects of its kind preceded the High Line. Within three years of its completion, 60 projects on six continents cited it as a precedent.

The High Line:
A Visionary Line of Demarcation

The High Line, New York City's derelict railway that was transformed into an urban oasis, has defied categorization since its inception. The unprecedented project was led by PennDesign Professor Emeritus of Landscape Architecture James Corner, whose firm, Field Operations, partnered with Diller Scofidio + Renfro design studio (DS+R) and garden designer Piet Oudolf to create this world-renowned masterpiece.

Variously referred to as a "park in the sky," "aerial greenway," and by Corner himself as a "secret green meadow above," the High Line has become a demarcation line between conventional urban landscape design and a new vision for city living.

Much has been written about the High Line, but nothing from the designers' perspective, so Corner and DS+R felt it was time to share their unique insights with park enthusiasts—and with the many designers and municipalities around the world who were beginning to emulate it.

Expressing the depth and complexity of such an innovative project required an equally innovative book.

The resulting publication, "The High Line," intersperses transcripts of the designers' conversations and initial snapshots with design renderings, photos, drawings, newspaper clippings, and letters that span more than 80 years of the structure's history.

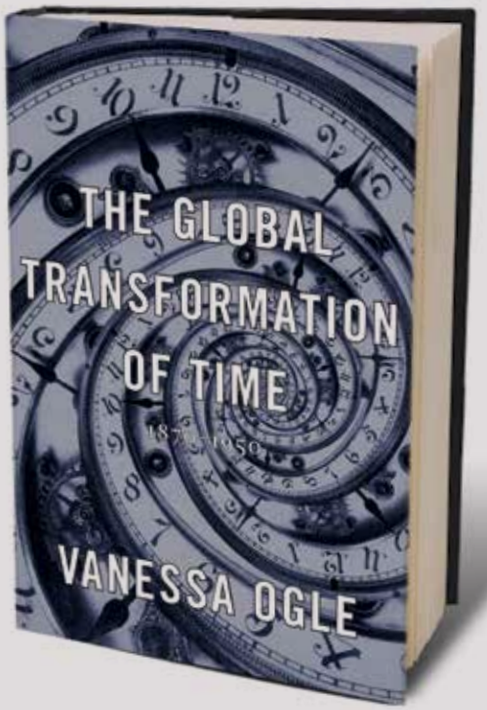
Many pages in the book fold out to reveal an image underneath, making a multidimensional book of layers, folds, voices, and pictures that collectively create a kind of collage. The end result invites readers' personal interpretation of the textual space, much as the High Line invites visitors to interpret the physical space.

This literal level of specificity demonstrates the concrete contributions that urban landscape design makes in shaping the larger idea of how humans live in cities, which is important during a time of rapid urban growth on a global scale.

"What the High Line has shown citizens, governments, and developers around the world is that a thoughtfully considered, well-designed, well-executed public space can be a dynamic heart of a city," says Margaret Jankowsky, director of marketing and business development at Field Operations.

A critical part of that dynamism can be revival, as the economic growth and entrepreneurship stimulated by the High Line has demonstrated.

"The new life and optimism spawned from dereliction and neglect may very well provide a stimulating setting for new forms of interaction," says Corner in one of the book's conversations. "It's this liberating sense of displacement that allows people to see themselves, one another, and the city in new ways." ■



The Complex History of Standardizing Time

"They came to conclude that the world in a way was shrinking, not unlike today's notion of the global village."

The world today is neatly divided into 24 efficient, well-ordered time zones that generally correspond with the 24 hours in a day. If it's 2 p.m. in Philadelphia, it's 11 a.m. in Los Angeles, 7 p.m. in London, 9 p.m. in Tel Aviv, and 4 a.m. tomorrow in Seoul.

Time is uniform, but it wasn't always so. Standardization didn't begin to emerge until the late 19th century.

In her book "The Global Transformation of Time: 1870–1950," Vanessa Ogle, the Julie and Martin Franklin Assistant Professor of History in the School of Arts & Sciences, recounts the nearly century-long effort to homogenize clocks around the world.

Ogle says the initial push for uniformity originated in Europe and the United States in the late 1800s. Onlookers saw a world that we now see as the seeds of 21st-century globalization and spoke of the ways in which time was accelerating and distance was becoming less important in light of new means of communication and transportation, such as the steamship, railway, and telegraph.

"They came to conclude that the world in a way was shrinking, not unlike today's notion of the global village," Ogle says. Advocates for uniformity believed a standardized system of time would act as a "kind of lubricant for this globalizing world, and would facilitate the flow of goods, people, and ideas."

The British Empire foresaw standardized time as a tool to synchronize its vast overseas possessions, ease the spread of information and transportation, and help maintain control.

In the early 1900s, the Empire tried to introduce Greenwich Mean Time in British India but was greeted by a resistance movement. In other parts of the Empire, the British were even less successful.

The movement to standardize time was a failure—up until the Second World War.

Ogle says the standardizing and globalizing impact of World War II, coupled with U.S. occupations in East Asia and other parts of the globe, and the advent of the jet age and increasing military and commercial aviation, ultimately led to the triumph of uniform time. ■

PRESERVING 600 YEARS OF SCHOLARSHIP

Justin McDaniel, professor and chair of the Religious Studies Department in Penn's School of Arts & Sciences, has spent the past two decades researching Lao and Northern Thai manuscripts that date as far back as the 15th century. Largely sequestered in remote mountaintop monasteries, these manuscripts are accessible to few people and vulnerable to the vagaries of weather, insects, and thieves. Most recently, McDaniel was principal investigator for a collaborative project, the Digital Library of Northern Thai Manuscripts (DLNTM), which preserves these texts and makes their rich content freely available to the general public, scholars, and Buddhists around the world.

McDaniel helped secure funding for a group of researchers at Chiang Mai University and the National Library of Laos. These grants—from the Henry Luce and Andrew W. Mellon foundations, the German Federal Foreign Office, Penn Libraries, and the School of Arts & Sciences—enabled his team to collect, scan, digitize, and catalog about 7,000 manuscripts from Northern Thailand.

"The Thai scholars, monks, and nuns we worked with believe the knowledge expressed in these texts can benefit anybody," McDaniel says. "They want to open up dialogue and make connections."

Fostering these connections was, for McDaniel, both the most exciting and the most challenging aspect of the project: "Buddhism in general, and certainly in Southeast Asia, is very decentralized. This creates an open intellectual environment but can also make scholars feel like they're toiling in isolation," he says. "Now the DLNTM gives them a way to see themselves as part of a larger community."

McDaniel and his colleagues tapped their years of research experience to create an innovative—and powerful—digital tool.

"We spent years thinking about the right way to digitize the manuscripts and make them searchable, so it's a really robust, flexible system that we can keep adding texts to," McDaniel explains. "And we made all our technology open-source, so other researchers could adapt it for their own preservation projects."

The fact that two groups have already done so provides an early measure of just how powerful McDaniel's digital research tool is. ■

INNOVATION FACT

Seven thousand Northern Thai manuscripts, reflecting 600 years of scholarship, are now available through a free digital access point.

BUSINESS | MARKETING

Americans Are Resigned to Give Up Their Data in Exchange for Deals

Every day, consumers willingly give stores personal information in exchange for discounts, coupons, and special deals.

Marketers claim that most Americans give up this information as a tradeoff for benefits, says Joe Turow, professor of communication at the Annenberg School for Communication.

But after years of research on privacy and numerous conversations at industry conferences, Turow says he began to suspect that this relationship wasn't that simple. Along with Michael Hennessy of the Annenberg Public Policy Center and Nora Draper from the University of New Hampshire, Turow conducted a survey to understand how feelings of resignation may come into play.

They outlined their findings in a paper, "The Tradeoff Fallacy," which marshals data to show for the first time that a majority of Americans—58 percent—are resigned to give up their data and feel it is futile to manage what and how companies learn about them.

"Don't be so easily persuaded that the reason people give away their data has to do with rational thinking in terms of tradeoff," Turow explains. "Most Americans have much less understanding of what's going on than advertisers would like us to believe. More than believing in rational tradeoffs, they often throw up their hands with respect to what's happening and feel that this is the world and they have to live with it, whether or not they understand it."

By misrepresenting the views of Americans and championing the tradeoff argument, Turow writes, marketers are giving policymakers justifications for allowing the collection and use of all consumer data.

In several national surveys since 1999, Turow and colleagues discovered that large percentages of Americans simply don't understand the ways companies track and mine data from behind their screens. They also overestimate the extent to which the government protects them from discriminatory pricing. Turow says most surprisingly, the more people in the survey knew about information sharing and privacy policies, the more they tended to be resigned.

"It just shows that really knowledgeable people sometimes throw up their hands," he says.

The researchers suggest naming, praising, and shaming companies that are either honest or sneaky about consumer data; convincing regulators to force firms to be clearer about the tracking they carry out; increasing reporting on privacy policies; and demanding full disclosure of consumers' profiles relative to ad personalization and pricing.

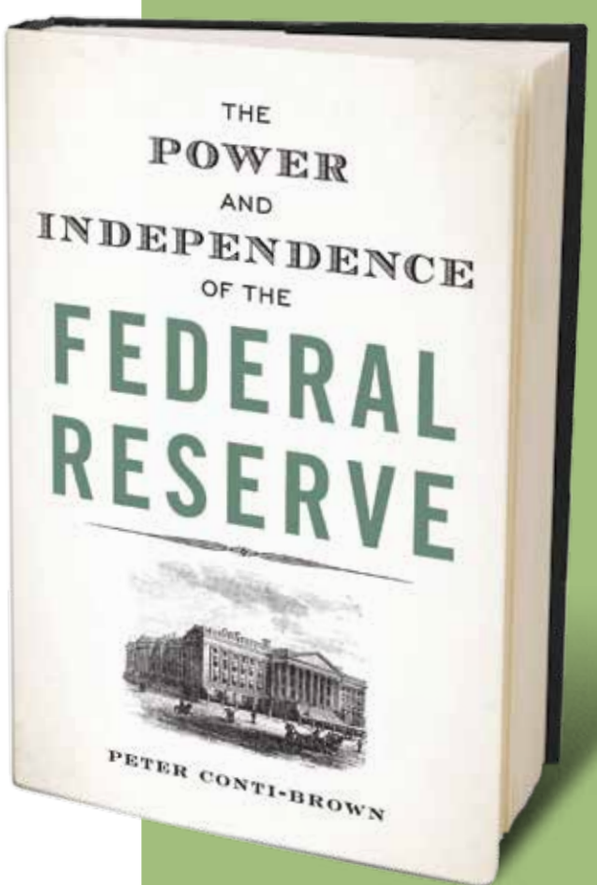
Turow's forthcoming book, "The Aisles Have Eyes," pushes back against marketers who assert there's been little to no harm done with information-sharing.

"Marketers say all they are doing is using data to send people relevant ads and discounts," says Turow. "There's far more to it than that. I try to take a broader perspective, and that is, we have to look at what kind of society we want. Do we want to have a society where there is continual profiling about us taking place without our permission in ways that we don't understand with implications that we really don't know?" ■

INNOVATION FACT

The findings support a new explanation as to why Americans willingly give up their personal information: A majority feel resigned to do so, and this is why many appear to be engaging in tradeoffs.

COINING THE FEDERAL RESERVE'S INDEPENDENCE



In light of the financial crisis of 2008, most people in the United States have an opinion about the Federal Reserve. It's probably a very strong opinion, Peter Conti-Brown says. "They believe either the Fed is horrible, or the Fed is the savior."

What Conti-Brown, an assistant professor at the Wharton School, hopes people do when they read his book, "The Power and Independence of the Federal Reserve," is take those judgments and "put them in their back pockets for a little bit."

"I think the Fed is not horrible. I also don't think the Fed is the last best hope for democracy," says Conti-Brown, who teaches business ethics and legal studies. "I think understanding the Fed and how much of a very human institution it is will help us understand the important but limited role it has to play in our economy and our society."

Conti-Brown maneuvers readers through five major aspects of the central bank's independence. He begins the book discussing the three "foundings," or periods of intense institutional change at the Fed: in 1913, 1935, and 1951. He examines the internal structure of the Fed and its complex relationship to external parties, such as the president, Congress, economists, and bankers. Conti-Brown walks readers through the functions of the Fed and wraps up with proposals to reform the Fed's structure.

"While it's deeply informed by history, it's really more a book about public policy and law," Conti-Brown says. "In that sense, I am trying to develop arguments about legal structures and how they change."

To conduct the research for his book, which was published by Princeton University Press, Conti-Brown spent years scanning memoirs, congressional reports, legislative materials, and numerous newspaper accounts, including every Fed-related article in *Time*, *The New York Times,* and *The Wall Street Journal* since they were founded.

Conti-Brown is now working on another book, under contract with Harvard University Press, titled "The Supreme Court of Finance: The Rise and Rise of the U.S. Federal Reserve." Slated for publication in 2020, the book will provide a comprehensive history told chronologically, aimed at the general reader—a different, but just as essential, take on the Federal Reserve. ■

"I think understanding the Fed and how much of a very human institution it is will help us understand the important but limited role it has to play in our economy and our society."

'SURPRISINGLY ORDINARY' ORIGINAL THINKERS

"Originals: How Non-Conformists Move the World" by Adam Grant, the Class of 1965 Wharton Professor of Management, challenges people's assumptions about original thinkers, encourages people to go against the grain, and provides new insights into how individuals can bring about the change they want to make in the world.

Grant says he was inspired to write the book after conversing with leaders of different organizations, who often asked about driving change and avoiding groupthink, and students who inquired about getting their ideas heard when not in positions of authority.

Featuring non-conformists from the worlds of sports, entertainment, politics, and business, Grant investigates how to nurture originality. Key points include how to make yourself heard, form a base of alliances, overcome doubt, and choose the optimal time to act.

He highlights one idea that was expected to succeed and ultimately failed—the Segway motor scooter—and contrasts it with an idea that was expected to fail and succeeded: the television sitcom "Seinfeld," which networks had very little faith in, save for one executive.

Grant says he was expecting the highly original people to be big risk-takers who were full of confidence.

"I thought they were distinguished by having great ideas and by being the first to take initiative and act," he says. "I was so surprised that most of them actually disliked taking risks. They felt the same doubt and fear that the rest of us do. ... A lot of them were procrastinators and late adopters."

Grant says he hopes the book gives readers confidence and strategies to help them champion their own ideas.

"The people who we admire as highly original thinkers are not as different from the rest of us as we believe," he says. "So often we write ourselves off and say, 'I can't be one of them,' but in reality, a lot of these people are surprisingly ordinary." ■

"The people who we admire as highly original thinkers are not as different from the rest of us as we believe."

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