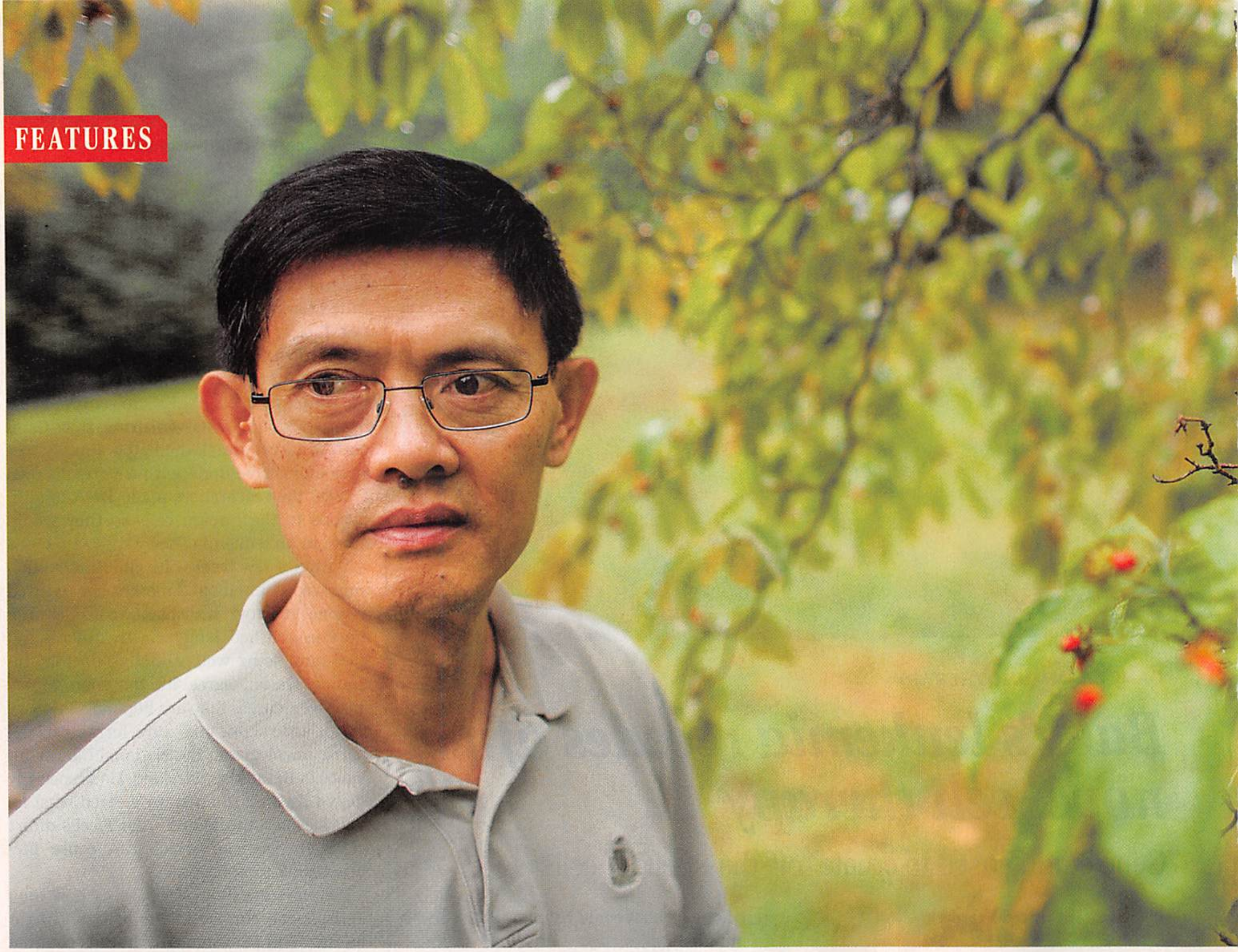


PHOTO: MARK MAKELA FOR THE NEW YORK TIMES

NOT GUILTY AS CHARGED

Several cases have unraveled lately against Chinese-born scientists accused of sharing industrial secrets. Critics smell a witch-hunt

By **Mara Hvistendahl**

Just after dawn on 21 May, physicist Xiaoxing Xi awoke to find a dozen or so armed federal agents swarming his home in the Philadelphia, Pennsylvania, suburbs. When he rushed to open the door, they drew their guns and announced that they had a warrant for his arrest. His wife and daughters—one in middle school and the other in college—watched in horror as agents handcuffed Xi, who was still not fully dressed, and escorted him away.

Then interim chair of the physics department at Temple University in Philadelphia, Xi is a naturalized U.S. citizen who has lived and worked in the United States since 1989. He is among the world's leading experts on superconducting thin films, which carry electricity without resistance at very low temperatures. At the time of his arrest, he was in what he calls a "very productive" phase of his career, overseeing nine research projects, including work for Temple's Energy Frontier Research Center, which is funded by the Department of Energy. But now he stood charged with trying to transfer designs for a proprietary technology to China—a device called a pocket heater, produced by Superconductor Technologies Inc. (STI) of Austin, that makes thin films of the superconductor magnesium diboride—and faced 80 years in prison and a $1 million fine.

Xi was released after putting up his home as bail, but his passport was confiscated and his domestic travel restricted to eastern Pennsylvania. For days, his family avoided the windows in their home as television stations broadcast live from their front yard.

A little girl is doing well after experimental therapy, but it's too soon to say whether she's been cured.

CANCER IMMUNOTHERAPY

Baby's leukemia recedes after novel cell therapy

Gene editing used to create "off-the-shelf" T cells

By **Jennifer Couzin-Frankel**

A London baby with end-stage leukemia has received a remarkable new cancer treatment with apparent success: off-the-shelf T cells with several gene modifications. The little girl's treatment took place in June; it was announced last week by Great Ormond Street Hospital (GOSH) and is being presented at a meeting early next month. "The follow-up is short," says Carl June, an oncologist at the University of Pennsylvania who wasn't involved in the work. "But what we know is, [it] has given this kid a shot."

The announcement, by a team of physicians at GOSH and University College London, advances a frontier in cancer immunotherapy, in which the body's immune system tackles the disease. For the past several years, June and others have been modifying T cells so they can attack blood cancers, but the cells must be painstakingly isolated from the patients themselves and grown for days in a lab (*Science*, 28 June 2013, p. 1514). Drug companies and doctors dream of using off-the-shelf cells to make the therapy more like a regular drug. Now, by harnessing breakthroughs in genome editing to slice and dice genes in donor T cells, researchers have administered one of what could be many such cancer immunotherapies.

The 11-month-old girl had already run through every treatment. Her immune system was barely functioning, and oncologists couldn't collect T cells from her for personalized therapy. Her parents "were being told, 'We haven't really got anything,'" says Waseem Qasim, a consultant in pediatric immunology at GOSH and cell therapy professor at University College London, who led the work. But GOSH's freezers held a potential solution. The hospital was storing genetically modified T cells belonging to a company in Paris called Cellectis. The cells, from a healthy American donor, had DNA added and two genes erased. Final testing was not complete, but the doctors asked that a vial be given to the child. "This was not even a question," says André Choulika, Cellectis's CEO. The company quickly signed off, as did the parents and the requisite ethicists.

The Cellectis cells had been genetically engineered to avoid two major pitfalls. If transplanted intact, the T cells would act like an invading army, attacking the body while the body attacked them right back. In order to block that reaction, scientists used a gene-editing technique called transcription activatorlike effector nucleases (TALENs) to cut out the T cell receptor gene. Without it, the cells can't recognize the recipient's body as foreign. The cells were also designed to survive the intense therapy the girl was receiving: an antibody called Campath, intended to protect the donor T cells from attack by wiping out the child's own immune system. Campath targets an immune-cell marker called *CD52*, so the company used TALENs to remove *CD52* from its donor cells—ensuring that Campath wouldn't attack them, too. Finally, just as doctors have done with a patient's own T cells, the researchers made DNA modifications to the foreign cells so they would home in on leukemia.

Within a few weeks the child's condition improved. After about 3 months she received a bone marrow transplant, considered a more established long-term treatment, and she's now doing well. Although doctors, including Qasim, agree it's too soon to say she's been cured, they are hopeful. "I'm very enthusiastic about this," says Terry Fry, a pediatric oncologist at the National Cancer Institute in Bethesda, Maryland. He's especially excited because the therapy cleared what he describes as "hurdle one"—the T cells didn't attack the patient, which can cause life-threatening complications.

The next question, Fry says, is how long the cells can survive in the body and fight cancer. "The persistence is hurdle two," he says, and it's something he and others are keen to learn more about. June expects that hurdle will be much harder for the cells to overcome. "I think in the end they will get rejected," he says, but an off-the-shelf therapy could still be transformative. "I'm very bullish that they'll be useful in desperate situations like this, where there isn't time," or it's not possible, to use a patient's own T cells. In a trial slated for next year, June and his colleagues hope to offer cells with three genes sliced out via another editing technology, the popular CRISPR, with the leukemia-busting DNA added in.

"You can totally tune up the genome of the T cells to make it a sharp, cancer-killing machine," Choulika says. But with innovation comes uncertainty. "We're going to need better analysis" of these cells with multiple gene edits, says Michael Jensen, a pediatric oncologist at Seattle Children's hospital in Washington, who has run trials of modified T cell therapy. "As we get into more sophisticated engineering, we have to understand the safety parameters." For now, he and others are hoping that one case will open the door to more, for patients with no other options. ■

PHOTO: SHARON LEES

Superconductor physicist Xiaoxing Xi was accused of attempting to share proprietary technology with China—only to watch the investigation against him unravel.

Over the months that followed, they drained their bank accounts to pay legal fees.

Citing a nondisclosure agreement Xi had signed in 2006 in order to conduct research with a pocket heater, the U.S. attorney's office in Philadelphia, Pennsylvania, had charged him with four counts of wire fraud, for four emails sent to contacts in China about establishing labs and a collaboration involving a thin film deposition device. But on 11 September, before a trial date had been set, the U.S. attorney's office abruptly dropped the charges, noting that "additional information came to the attention of the government." A spokesperson for the office declined to comment further on the case.

At issue, Xi's lawyer and scientists familiar with the case assert: a glaring misinterpretation of the science involved. The devices Xi had discussed with Chinese colleagues were not the pocket heater, they say, and the exchanges posed no threat to U.S. interests. "The whole case against Xiaoxing Xi was just completely misconceived," asserts David Larbalestier, a physicist at Florida State University, Tallahassee, who submitted an affidavit for the defense.

The Obama administration names economic espionage and trade secrets theft as among the primary threats facing the United States. Together with cybercrime, economic espionage is now the Federal Bureau of Investigation's (FBI's) No. 3 priority, after terrorism and counterintelligence. According to testimony by Randall Coleman, assistant director of the FBI counterintelligence division, the number of cases overseen by the bureau's dedicated unit grew by 60% from 2009 to 2013.

Many of those cases involve China. In July, the FBI launched an ambitious public awareness campaign around the issue, releasing a dramatic film depicting a Chinese company attempting to steal trade secrets from a U.S. competitor. In September, economic espionage and cyber espionage were forefront at the meeting between President Obama and Chinese President Xi Jinping, with the two leaders vowing in a landmark agreement not to target each other's companies.

Yet a growing number of scientists have been targeted improperly as Department of Justice (DOJ) attorneys have stepped up prosecutions, advocates say. In the past year alone, charges have been dropped against five Chinese-born scientists accused of crimes related to trade secrets theft or economic spying. A sixth defendant, a New York University (NYU) medical imaging researcher accused of passing confidential information about NYU research into magnetic resonance imaging technology to a company in China, pleaded guilty to a single misdemeanor last March. In several instances, critics say, the U.S. government has charged scientists without understanding the science at the heart of its allegations.

Xi's case is emblematic. Court documents state that "the government seized extensive electronic evidence and searched multiple hard drives" in the process of investigating him. But the prosecutors apparently did not consult technical experts before issuing the indictment, says Nelson Dong, a former DOJ official and an attorney with Dorsey & Whitney in Seattle, Washington, who was not involved in Xi's case. "That suggests to me that people really did rush to judgment," Dong says. "They saw red, so to speak."

The prosecutions have spooked many Chinese-American scientists, who fear that any collaboration with Chinese nationals will invite suspicion. Invoking the botched investigation of Los Alamos National Laboratory physicist Wen Ho Lee more than a decade ago, advocacy groups are lobbying the U.S. government for explanations. Last May, following the sudden dismissal of charges against National Weather Service (NWS) hydrologist Xiafen (Sherry) Chen, who was accused of passing information about the nation's dams to a Chinese official, 22 members of Congress signed a letter to U.S. Attorney General Loretta Lynch requesting an investigation into whether federal employees are being racially targeted. The office responded in a letter that "no policy exists of using race or any other civil rights classification" to single out federal employees for arrest or scrutiny. The attorney general's office did not reply to interview requests.

The targeting of innocent scientists is "a constitutional and civil rights problem," said Representative Ted Lieu (D–CA), one of the letter's signatories, in a statement on 14 September. Xi's crime, according to one legal blog: "Emailing while Chinese-American."

THE THEFT OF SCIENTIFIC SECRETS is nearly as old as science itself. Centuries ago, for example, a young United States depended greatly on know-how spirited out of the United Kingdom, showering accolades on those who swiped designs for U.K. textile machinery. Imperial China was a frequent victim as well, with Western powers stealing its methods of porcelain and tea production. But some argue that the past few decades have marked the dawn of a new era, with everything from sensitive military technology to lucrative agricultural secrets now prized spoils.

> *"Get the science right before you put these people through the wringer."*
>
> **Brian Sun**, lawyer at Jones Day

"As the world becomes more advanced, technology just becomes worth more," says Peter Toren, a former federal prosecutor and a litigator with Weisbrod Matteis & Copley in Washington, D.C., who specializes in trade secrets cases. "Developing countries and companies in developing countries can save hundreds of millions of dollars in research costs by stealing new technology."

Developing countries are hardly the only perpetrators. In a secret report leaked by Edward Snowden, the U.S. National Security Agency outlined possible scenarios for cyber operations against foreign research centers, with the aim to capture knowledge that "would be useful to U.S. industry." And as late as the 1990s, Toren says, France and Israel were among the world's most prominent industrial spies.

But the U.S. government now sees China as the major foreign threat. Close to half of

Prosecutors' patchy record

The United States has ramped up prosecutions against Chinese-American scientists for espionage and trade secrets violations. But key cases have fallen apart.

1996 · 1999 · 2006 · 2010 · 2013 · 2014 · 2015

Economic Espionage Act signed
The new law gives the U.S. government another tool for pursuing economic spying and trade secrets cases. Prosecutors continue to try scientists under other statutes as well.

Wen Ho Lee charged
A Los Alamos National Laboratory physicist is charged with stealing secrets connected to the U.S. nuclear arsenal. Lee spends 9 months in solitary confinement before ultimately being cleared of 58 of the 59 charges against him.

Wen Ho Lee civil settlement
Lee is awarded $1.6 million in damages in a lawsuit he brought against the U.S. government and five media organizations, alleging that government leaks violated his privacy.

Dongfan Chung conviction
A former Boeing engineer is sentenced to 16 years for stealing trade secrets connected to the U.S. Space Shuttle program and Delta IV rocket. Federal agents say they found more than 250,000 documents from defense contractors stashed in his house.

Guoqing Cao and Li Shuyu indicted
Two Eli Lilly biologists are accused of passing research into cancer and diabetes treatments to China. After the scientists spend a year in detention, the U.S. attorney drops charges.

Walter Liew sentenced
A businessman is sentenced to 15 years in prison for conspiring to steal trade secrets from DuPont and sell them to state-owned companies in China. Former DuPont engineer Robert Maegerle is convicted of a lesser sentence in the case, which involves the whitener titanium dioxide.

Xiafen Chen indicted
Accused of passing information about the U.S. dam system to a Chinese official, a National Weather Service hydrologist is charged with crimes carrying 25 years in prison and $1 million in fines. Charges are later dropped with little explanation.

Yudong Zhu plea deal
After being charged with bribery and fraud in an eight-count indictment for attempting to pass university-owned research to China, New York University magnetic resonance imaging researcher pleads guilty to a single misdemeanor.

Xiaoxing Xi charged
The Temple University physics department chair is charged with trying to share the pocket heater, a proprietary device used in superconductor research, with collaborators in China. Charges are later dropped after experts submit affidavits.

GRAPHIC: A. CUADRA/SCIENCE

the indictments brought under the Economic Espionage Act since its passage in 1996 have involved China, Toren says.

In some cases, U.S. prosecutors have assembled reams of evidence. In 2010, Boeing engineer Dongfan Chung—a naturalized U.S. citizen who was born in China and grew up in Taiwan—was sentenced to 16 years in prison for stealing trade secrets connected to the U.S. Space Shuttle program and Delta IV rocket on behalf of mainland China. When agents raided Chung's home, they found more than 250,000 sensitive documents from defense contractors, some of them hidden in crawl spaces under the house. The FBI alleged that documents in the stash showed Chung was acting at the direction of China's Civil Aviation Administration.

Another successful prosecution came last year, when entrepreneur Walter Lian-Heen Liew was sentenced to 15 years in prison for conspiring to steal trade secrets related to titanium dioxide production from DuPont and sell them to state-owned companies in China. (Former DuPont engineer Robert Maegerle was also convicted in the case.)

But a startling number of cases have unraveled. Last December, the U.S. government dropped charges against two former Eli Lilly and Company scientists in Indiana. The U.S. attorney's office in Indianapolis had alleged that Guoqing Cao and Shuyu Li, both naturalized U.S. citizens and senior biologists at Eli Lilly, passed research on tailored therapies for cancer and drugs to treat diabetes, obesity, and other metabolic disorders to Jiangsu Hengrui Medicine, a company in Lianyungang, China.

The case invited heated rhetoric, with a government prosecutor labeling the defendants traitors in an early bail hearing and the defense in its filings invoking the 1954 anticommunist Senate hearings convened by then-Senator Joseph McCarthy. From October 2013 to November 2014, the two scientists were variously jailed, locked down in a halfway house, and kept in round-the-clock home detention.

Yet case documents submitted by Cao's attorneys claim that the trade secrets he allegedly stole had all appeared in published papers years earlier, and that the information did not include drug molecules, formulae, or data owned by Eli Lilly. In December 2014, several weeks after a judge agreed to release the researchers, the U.S. attorney's office dropped the charges entirely, citing only its "on-going evaluation and assessment of this case." A spokesperson for the U.S. attorney's office in Indianapolis declined to comment further.

Then, last March, the U.S. government dropped charges against Chen, the NWS hydrologist. Peter Zeidenberg, a partner at Arent Fox in Washington, D.C., who represents both Chen and Xi, says that she merely sent a Chinese official—a former classmate whom she contacted as a favor to her nephew—links to publicly available websites, including www.noaa.gov. The official was tasked with planning repairs for China's reservoirs and had asked Chen how such repairs were funded in the United States. Chen then referred the official to a division head at the Army Corps of Engineers with whom she had worked on projects in the past, Zeidenberg says. "Why would she be giving her contact in China the phone number of her boss and say, 'Call her if you have any further questions?' It was absurd," he says. The National Oceanic and Atmospheric Administration declined to comment on the case, citing an ongoing internal review.

XI, NOW 57, was born in Beijing and came of age during the Cultural Revolution. As a teenager, he was sent to the countryside, where he spent several years working in the fields and shoveling pig manure. After the Cultural Revolution ended in 1976, Xi won admission to Peking University in Beijing. He went on to earn a Ph.D. before leaving for the United States in 1989. In 1995 he joined the faculty at Pennsylvania State University, University Park, where his wife, physicist Qi Li, still teaches.

Before the agents pounded on his door and turned his life upside down, Xi oversaw a team of 10 graduate students, one undergraduate, three postdocs, and two non-tenure-track faculty at Temple and received more than a million dollars a year in research funding. The group had just obtained what Xi calls "breakthrough results" on two topics that they planned to submit to *Science* and *Nature*. Xi "is among the best thin-film physicists around," says physicist Paul Chu of the University of Houston in Texas, who submitted an affidavit in his defense. After the indictment, Temple placed Xi on administrative leave. Xi says university counsel also advised him not to appear on campus. Temple spokesperson Ray Betzner could not immediately confirm whether this was true.

According to affidavits submitted in the case, the allegations center on Xi's collaboration with two institutes in China, the Shanghai Institute of Applied Physics and Peking University. The indictment alleged that Xi "repeatedly reproduced, sold, transferred, distributed, and otherwise shared" the STI pocket heater with these institutions and then pursued "lucrative and prestigious appointments" in exchange for his assistance. Zeidenberg says Xi never profited financially from the interactions highlighted by the U.S. government.

Rather than the pocket heater, say superconductivity researchers who reviewed emails and other case documents, Xi discussed two distinct magnesium diboride heaters—one of which he invented himself and the other based on his invention—that are fundamentally different from the STI device. The labs he offered to help establish, meanwhile, would have focused on an entirely different line of research—oxide thin films—and thus would not have involved research with the pocket heater or another magnesium diboride heater.

The investigation's premise is off base, Larbalestier told *Science*: "The whole idea that there are huge pots of money that anybody is making out of magnesium diboride is just wrong." The compound, he says, is still in development as a superconducting material, and commercialization is "a decade or 2 decades away." And as John Rowell of Arizona State University, Tempe, wrote in an affidavit, the STI pocket heater, itself a modification of an existing technology invented in Germany in 1993, "is in no sense a revolutionary device."

Others say the case was based on a misreading of the scientific partnerships and teaching exchanges that have flowered since China began aggressively investing in research in the 1990s. Xi's offer to help Chinese colleagues build a world-class lab is a common gesture in international collaborations on superconductivity, which is highly developed in China, Chu says. "Ninety percent of scientists involved in this kind of international exchange" could fit the description of Xi's activities in China, he says.

"I am mystified as to why the case was brought," Larbalestier says.

CRITICS of the Justice Department's prosecutions say the government risks repeating the mistakes made in the case against Wen Ho Lee, who was charged with stealing secrets connected to the U.S. nuclear arsenal in 1999. Lee spent 9 months in solitary confinement as the case against him deteriorated. Though he ultimately pleaded guilty to one felony count of mishandling secrets, the U.S. government was never able to prove that he had conducted espionage. James Parker, the judge in the case, apologized to Lee for the "demeaning, unnecessarily punitive conditions" in which he was detained and denounced cabinet officials for having "embarrassed our entire nation and each of us who is a citizen of it."

Protesters demonstrate against the 1999 detention of physicist Wen Ho Lee, who was charged with stealing secrets connected to the U.S. nuclear arsenal.

PHOTO: AP PHOTO/BEN MARGOT

"Yes, America has a legitimate concern about cyber hacking and trade secrets theft," says Brian Sun, a trial lawyer with Jones Day in Los Angeles, California, who represented Lee in a successful civil suit against the U.S. government. "But … do your homework. Get the science right before you put these people through the wringer."

Although the charges were dismissed, Xi says that coming in the U.S. government's cross hairs damaged his career. Before his tribulations began, he had been asked to co-author a chapter for a prestigious handbook on superconductors. After the news broke, he says, several co-authors threatened to pull out if he was kept on the project. Although his team continued its research, with other scientists assuming the principal investigator roles he had held, the lab lost critical time on projects funded by grants due for renewal. Eventually, Xi says, his department arranged for him to talk to senior colleagues via teleconferencing, but because he was forbidden to talk to potential witnesses, he did not communicate with his students. Adrift at home for 4 months, he devoted much of his time to his case.

The string of cases has Chinese-American scientists scrambling to understand how they might avoid being targeted. The Committee of 100, a group of influential Chinese-Americans whose membership includes former NASA astronaut Leroy Chiao and David Ho, scientific director of the Aaron Diamond AIDS Research Center in New York City, has held seminars across the country for scientists outlining the laws governing trade secrets theft and export controls on critical technologies and explaining how to avoid inviting suspicion. Scientists involved in collaborations with China or Chinese colleagues "need to assume that their communications are being scrutinized" and "be clear and precise about what they're communicating," Zeidenberg cautions. "There's an assumption that any collaboration is suspect and potentially problematic."

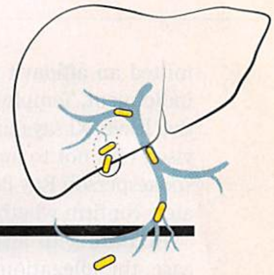
"We need a set of well-defined rules," says Albert Chang, a physicist at Duke University in Durham, North Carolina, and the president of the International Organization of Chinese Physicists and Astronomers. "The indictments have instilled a great deal of uncertainty and anxiety in our community. People are wondering, 'Is this going to happen to me?'" The Committee of 100 and others are pressing the U.S. government for more clarity.

Xi is now back in the lab. On 20 October, Michael Klein, dean of Temple's College of Science and Technology, sent a memo to the physics department welcoming him back as interim chair. But he worries about obtaining research funding, regaining colleagues' trust, and attracting collaborators: "My reputation obviously has been damaged by this," he says. "If this happened to somebody else, I would think that they probably did do some little thing wrong, at least." The ordeal has made him apprehensive about even the most basic of interactions. "I was charged for things that were just normal collaborations," he says. "If all these normal activities could be seen as criminal activities, then the environment is quite frightening." ■

INSIGHTS

Snapshots of charge on the move *p. 740*

A gut-vascular barrier *p. 742* ▸



PERSPECTIVES

EVOLUTION

One era you are in–the next you are out

Evolutionary trends in body size changed during a past mass extinction event

By **Peter J. Wagner**

Trends in body size are a rich source of information for evolutionary studies. This is because body size not only has numerous implications for function and life history but also has necessary limits that differ between groups of organisms. Moreover, there are many evolutionary patterns that might underlie trends, and these patterns need not be constant over time. On page 812 of this issue, Sallan and Galimberti (*1*) show that trends in the body sizes of vertebrates during the Devonian and Mississippian (about 420 to 325 million years ago) not only are markedly different at different times but also likely reflect a variety of different evolutionary mechanisms.

The Devonian shows a distinct trend toward larger vertebrates. This sort of trend often reflects a passive trend (*2*) (see the figure, panel A), where clades beginning near some limit (here, nearly as small as they can be) simply add variation in one direction (here, larger animals). However, Sallan and Galimberti present multiple lines of evidence that this reflects an active trend, where the new condition replaces rather than augments the existing condition (see the figure, panels B to D). In particular, their results suggest that driven trends (*3*), where descendants tend to be larger than their ances-

Department of Paleobiology, National Museum of Natural History, Smithsonian Institution, Washington, DC 20560, USA. E-mail: wagnerpj@si.edu

Ancient sealife. Relatives of modern sharks and reef fishes that lived during the Mississippian (about 360 to 325 million years ago) reached sizes of up to 50 cm.

ILLUSTRATION: BOB NICHOLLS

tors (see the figure, panel B), predominate. Strong active trends toward increasing size are seen not just for all vertebrates but for five of the seven major taxonomic groups; one of the two exceptions (tetrapods) simply started out large.

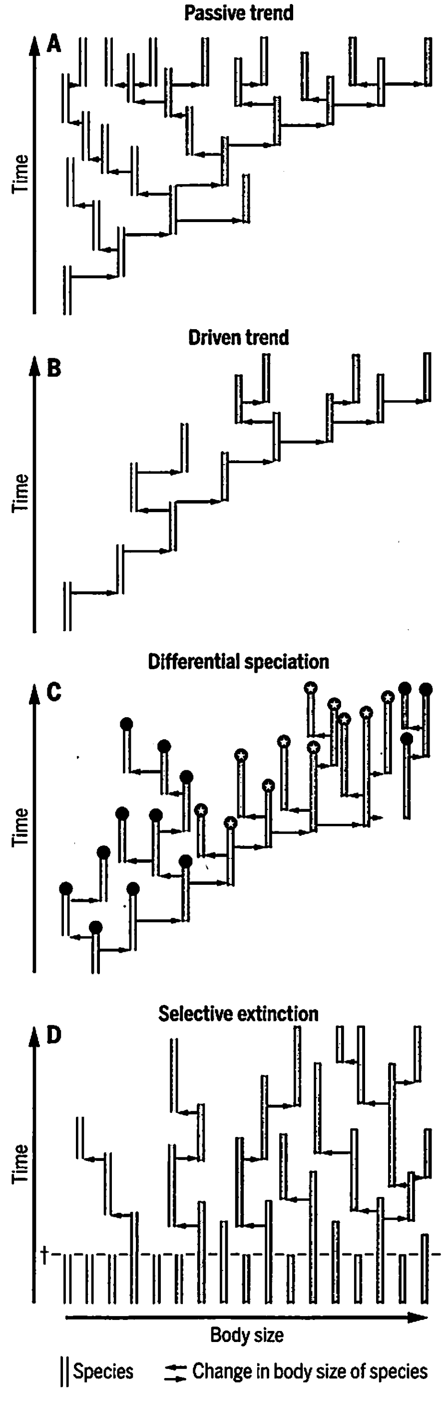
Breaking the trends down into finer taxonomic partitions reveals more heterogeneity. The clades showing no real trend tend to be those that begin fairly large, whereas most clades that start small show increases in size. This "subclade test" strongly suggests driven trends among a wide range of different vertebrates (*3*).

The end-Devonian mass extinction (~375 to 360 million years ago) reverses these trends. Three of the five surviving clades show marked decreases in body size. This indicates that selective extinction, at odds with prior selective forces (*4*), induces a new trend (see the figure, panel D). Devonian trends do not just fail to resume in the Mississippian; they are reversed, with a trend toward smaller size. However, whereas the Devonian trends include many groups, the Mississippian trends reflect two vertebrate groups. Chondrichthyans (elasmobranchs and holocephalans, the precursors of extant sharks and rays) are the only major group that shows evidence of driven trends toward smaller-bodied animals. Moreover, chondrichthyans also diversify in the Mississippian. Actinopterygians (bony fish) also increase greatly in diversity, but, unlike chondrichthyans, they begin small and remain small throughout the Mississippian. Thus, the trend is partially caused by small species leaving more (generally small) descendants rather than descendants typically being smaller than their ancestors. This might reflect higher speciation rates for small species (*5*), or small size "hitchhiking" along with elevated diversification happening for other reasons (*6*). Thus, selective extinction and differential diversification of actinopterygians (see the figure, panels C and D) plus driven trends and differential diversification of chondrichthyans (see the figure, panels B and C) drive the overall trend, with other vertebrates being mere onlookers.

As Sallan and Galimberti stress, there are no obvious correlations with extrinsic variables frequently linked to body size. Long-term trends toward cooler global temperature began after the polyphyletic trend toward increasing size but before that trend ceased. Similarly, there is no obvious association between the trends and atmospheric oxygen levels. Sampling controls (*7*) mean that preservational biases against finding small vertebrates in the Late Devonian or large vertebrates in the Mississippian cannot account for the pattern. Instead, Sallan and Galimberti suggest that size trends reflect trends in life-history traits, such as generation time, that are correlated with size. Thus, the distinction between sorting and selection (*8*) becomes important: The trends we see in a fossilizable trait (size) represent sorting of that trait based on selection for an associated unfossilizable trait (life history). Thus, the true role of size might be akin to the "stars" versus "no stars" in panel C in the figure: a trait that is largely (but not entirely) tied to another trait by functional or developmental association (or even simply because of common ancestry) (*7*) and that "hitchhikes" along the main trend.

In addition to offering a model for different types of trends, Sallan and Galimberti's work offers two important lessons for research concerning extant taxa. The first is the importance of sampling taxa over time. Suppose a time traveler deposited molecular phylogeneticists in the Mississippian and set them with the task of reconstructing the history of body size among (then) extant vertebrates. Shifting trends make reconstructing ancestral conditions extremely difficult without fossil data (*9–11*). Moreover, inferring diversity lost to extinction is generally very difficult given phylogenies of species from just one point in time (*12*). Without fossils, we cannot expect to see indications of when evolutionary parameters themselves changed. Indeed, it goes beyond stating that we need fossils to properly appreciate evolution among extant taxa: We need Devonian fossils to properly appreciate the evolution of subsequent Mississippian taxa.

The second lesson concerns current extinctions. Extinctions in the Late Pleistocene (~126,000 to 12,000 years ago) have preferentially eliminated large mammals (*13*). Large mammals have evolved many times, so it might seem that we should expect them to reevolve in the future. The differences between trends in the Devonian and Mississippian show that we cannot count on the trends of the past being the trends of the future. Thus, if conserving ecological and functional diversity is a priority as well as conserving phylogenetic diversity, then we cannot assume that large animals will quickly reevolve in the future. ■



Evolutionary trends. Different trends might underlie Devonian-Mississippian vertebrate evolution. Light colors denote small and dark colors, large body sizes. **(A)** In a passive trend, small species cannot become much smaller, but they can become much bigger (*2*). (B) In a driven trend, size increases are more common than size decreases (*3*). **(C)** Differential speciation means that large species live longer and/or have higher speciation rates (*4*). The stars/not-stars illustrate a hitchhiking trend in which differential speciation/extinction induces trends in other characters (*6*). **(D)** In the case of selective extinction, an extinction event (dashed line) inducing an immediate trend toward smaller taxa despite signs of the opposite trend before the event (*5*). [Figure adapted from (*6*)]

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ARTIFICIAL PHOTOSYNTHESIS

More efficient together

Hybrid bioinorganic photosynthesis yields a wide range of chemicals

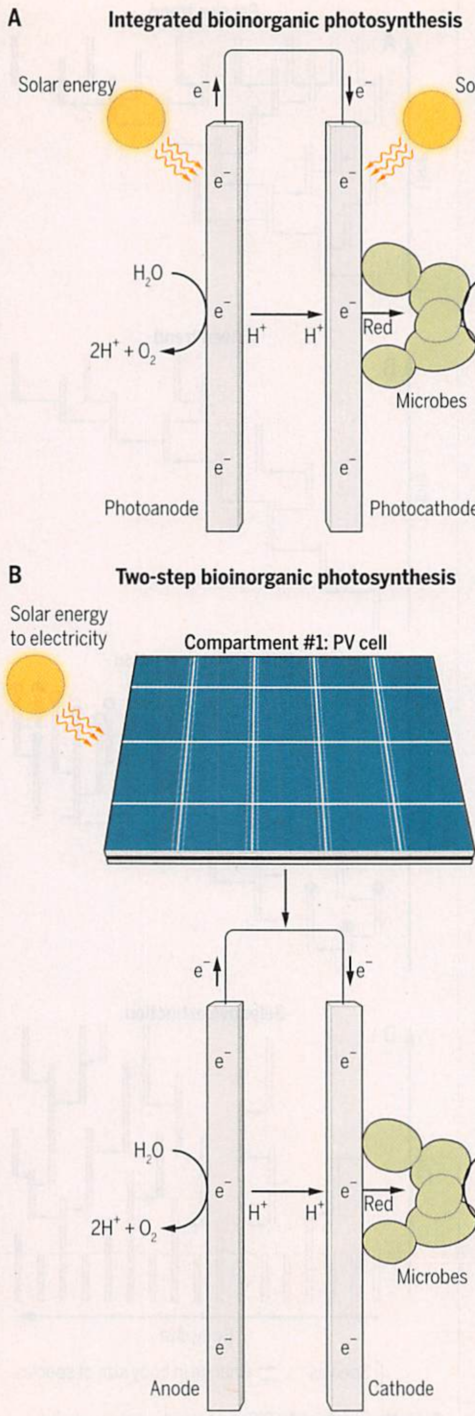
By **Tian Zhang**

The solar-to-biomass conversion efficiency of natural photosynthesis is between 2.9 and 4.3% for most crops (*1*, *2*). Improving the efficiency of photosynthesis could help increase the appeal of biologically derived fuels and chemicals in comparison with traditional petrochemical processes. One approach to make photosynthesis more efficient is to build hybrid systems that combine inorganic and microbial components to produce specific chemicals. Such hybrid bioinorganic systems lead to improved efficiency and specificity and do not require processed vegetable biomass. They thus prevent harmful competition between biotechnology and the food industry and avoid the environmental perturbation caused by intensive agriculture (*3*).

Durable artificial photosynthetic apparatuses that are completely inorganic have been developed for the production of simple chemicals such as carbon monoxide, methane, and methanol (*4*–*6*). Alternatively, the artificial photosynthesis apparatus can be a bioinorganic hybrid that contains a microbial catalyst (see the figure, panel A). Yang and co-workers have recently reported the use of this type of system for the production not only of simple compounds like methane but also of multicarbon chemicals including acetate, *n*-butanol, polyhydroxybutyrate polymer, and isoprenoids (*7*, *8*). This greater repertoire of products is possible because bioinorganic hybrid artificial photosynthesis can take advantage of the opportunities created by synthetic biology and by the metabolic plasticity of microbial cells.

In a bioinorganic artificial photosynthesis apparatus, an inorganic photoanode and photocathode harvest solar energy to split water into molecular oxygen (O_2), protons, and electrons and generate reducing equivalents that will be used by a microbial catalyst to reduce carbon dioxide (CO_2). In the first

Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, 2970 Hørsholm, Denmark. E-mail: zhang@biosustain.dtu.dk



Bioinorganic artificial photosynthesis. (A) Integrated bioinorganic artificial photosynthesis apparatus. A photoanode and photocathode are combined in the same reactor to convert solar energy into reducing equivalents (red) that are used by the microbial catalyst to transform the greenhouse gas CO_2 into useful products. **(B)** PV cell coupled with an MES reactor. PV cell can power an MES reactor for the formation of reducing equivalents that are used by the microbial catalyst for CO_2 reduction.

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of their two studies, Yang and co-workers coupled a TiO_2/Si photoanode with a photocathode in which the acetogen *Sporomusa ovata* was grown directly within a silicone nanowire array (*7*). In this system, *S. ovata* accepts electrons directly from the photocathode (*8*) to reduce CO_2 to acetate. The latter was activated to acetyl-coenzyme A in a second reactor by genetically engineered *Escherichia coli* before being converted into various multicarbon products. In their second study (*9*), they combined a *n*-TiO_2–based photoanode oxidizing water with a *p*-Inp/Pt photocathode to generate H_2 that is then used by the methanogen *Methanosarcina barkerii* for converting CO_2 to methane.

In the apparatus described in (*7*), the conversion efficiency of solar energy to acetate was 0.38% over a period of 200 hours. Because of their relative simplicity compared to natural photosynthesis, artificial photosynthesis systems should be easier to improve. A rational strategy for identifying the best combination of components can readily be established. This would include engineering optimal microbial catalysts, determining the best culture-medium composition and reactor design, and improving photocathode and photoanode for higher conversion efficiency of solar energy into reducing equivalents (*2*).

Bioinorganic artificial photosynthesis can also be achieved by using a photovoltaic (PV) cell to convert solar energy into electricity, which is then used to power a separate microbial electrosynthesis (MES) reactor (*10*) (see the figure, panel B). This approach is different from that described by Yang and co-workers (*7*, *8*) because light harvesting is carried in a compartment separated from the MES reactor where electrons are delivered to the microbial catalyst. This strategy allows the use of PV cells exclusively dedicated to light harvesting, without having to consider their compatibility with living cells.