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A question of balance

The turmoil in the financial markets could lead to severe cost-cutting by governments, but US politicians would do well to note the benefits of continued support for clean energy and climate policies.

As *Nature* went to press, a US$700-billion rescue plan for the collapsing financial sector remained in limbo in the US Congress. Some such deal may yet be passed. If it is, it still may not be enough to stop the global economy from sliding into recession. Faced with the prospect of fresh outlays and declining revenue, the US government may soon be looking for ways to tighten its belt, a situation likely to be echoed in Europe and beyond. For science and technology, this could mean less money for basic research, education and clean energy, and could pose fresh threats to the long-promised climate legislation in the United States.

Those who favour cutbacks — or, in the case of climate regulations, not moving forward — will say such activities cannot be afforded. In some cases, they may well be right; scientists may have to gird themselves for flat budgets into the foreseeable future, and set their priorities accordingly. But there is a danger that the debate will be framed entirely in terms of costs, with no consideration of the benefits. Investment in areas such as research, education and clean energy are part of the foundations for long-term prosperity.

The good news in the United States is that both leading presidential candidates have made this connection, especially in the energy and climate arena. Neither the Republican candidate John McCain nor the Democratic candidate Barack Obama is selling climate regulation as an expensive moral obligation to the environment. Instead, both speak of the benefits of 'green-collar' jobs and energy security.

There are concerns that McCain might succumb to pressure from the far-right of his party and back away from his pledge to curb greenhouse-gas emissions through a cap-and-trade programme. But he has yet to do so. His advisers continue to advocate hybrid vehicles, for instance, as both a cheaper and cleaner alternative to the internal combustion engine and a way to make the United States less dependent on increasingly expensive foreign oil.

Obama has gone further, integrating energy and climate policy with his plan for revitalizing the US economy. He argues that green jobs tend to be domestic jobs, which means energy security goes hand-in-hand with economic development. This might be dismissed as overly optimistic, given that the transition to clean energy won't be cheap, but there is little doubt that new industries will eventually rise in place of the old ones. In last week's first presidential debate, Obama also endorsed solid investments in science and technology generally.

It's refreshing to see that this political realignment has also taken hold in Congress. Efficiency and conservation, frequently played down as feel-good measures in the past, are now seen as critical components of the energy equation. The notion that the government can use its purchasing power to advance the development of clean vehicles has been heralded as a way of increasing energy security while addressing the long-term threat of climate change.

"The fundamental need to create a more sustainable energy infrastructure to power the globe will be as strong as ever, and the market will respond to that opportunity."

Such ideas, if implemented, will drive new investment in the years to come. It will take time for the world's financial institutions to rebuild themselves following the implosion on Wall Street. But the fundamental need to create a more sustainable energy infrastructure to power the globe will be as strong as ever. Eventually the market will respond to that opportunity.

It would be naive to assume that progress on these issues will be easy, even with vigorous leadership. Private investment in new technology has increased significantly in recent years — but so have global greenhouse-gas emissions. This makes it all the more important that Congress and the international community move quickly to establish a solid and predictable climate regulatory framework to carry the world beyond the Kyoto Protocol. The current market turmoil is due in part to a continuing crisis of confidence, so a little regulatory certainty on greenhouse gases might be welcome. It won't solve the financial crisis by itself, but it would help businesses, financial institutions and funding agencies place their bets on the future. ■

Life after Zerhouni

The next NIH director must juggle stagnant budgets, unhappy grantees and investigative lawmakers.

The imminent departure of Elias Zerhouni as director of the US National Institutes of Health (NIH) in Bethesda, Maryland, leaves large shoes to fill. Zerhouni, who announced last week he will quit his post by the end of October (see page 570), managed the agency with a blend of vision, toughness and dedication even as it faced stagnating funding, ethical uproars and an explosion of knowledge in biomedical research. It is to his credit that he leaves the agency with far more friends than enemies, and with a well-earned reputation as a public servant who tirelessly maintained his integrity during the administration of President George W. Bush.

Whoever follows Zerhouni faces unenviable challenges. Stem-cell research remains stymied by an outdated presidential policy. The conflict-of-interest scandal continues as Senator Charles Grassley (Republican, Iowa) has reported troubling instances of extramural NIH researchers failing to report five- and six-figure payments from drug companies that could benefit from their research. And with

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nothing but flat funding for the foreseeable future, NIH-supported labs are being squeezed nationwide. A new generation of academic scientists is being imperilled as many head for jobs in industry or elsewhere rather than face the daunting odds of ever landing an NIH grant.

All of this is occurring in the post-human-genome era with a knowledge base expanding at warp speed. Improved understanding and treatment of diseases have never been so tantalizingly close. So what qualities should the next president seek in a new NIH director? Three are key.

First, despite the fact that some two-thirds of the agency's budget is spent on basic research, the next director should be someone who understands, and is committed to, translating discoveries to the bedside. Zerhouni, a radiologist, did much to advance this agenda, although it was not his idea; the agency's mission statement makes it clear that the NIH is devoted to "science in pursuit of fundamental knowledge … and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability". The agency's next director should not throw money willy-nilly at translational research; accountability is vital as such work goes forward. But taxpayers who invest US$29 billion annually in the NIH deserve to see their lives and health improved because of it.

Second, the next director should be a gifted communicator who can speak with ease to the NIH's scientific constituency, to Congress and to the public. Translating complex research into terms meaningful to the public and to lawmakers is a crucial skill, especially as the NIH seeks its share of an ever-more-constrained federal budget.

Third, the next director should be an able manager willing to make and stick to tough decisions in times of ethical and financial stress. Although the ranks of current and former directors of the agency's 27 component institutes contain many amply qualified candidates for the top job, it may be worth reaching outside NIH circles for a candidate not beholden to long-time peers in Bethesda. Zerhouni, who came from the Johns Hopkins School of Medicine in Baltimore, Maryland, showed that this strategy can work well.

Overall, a director should be chosen with appropriate speed. Allowing the NIH's top post to sit vacant for months or years — as Bush did when he took more than two years to nominate Zerhouni — could do serious damage to the agency at a time when bold leadership is vital. ■

An end to secrecy

China's continuing openness on HIV is a welcome development and a model for other nations.

As part of a special collection of articles on HIV, this week's issue contains a Feature by Linqi Zhang of Tsinghua University in Beijing and his colleagues on the status of HIV in southern China (see page 609). Their conclusions are alarming: HIV prevalence is no longer confined to high-risk groups such as those who inject themselves with drugs, but is now seeping into the general population. Some of the most rapid increases are among men in same-sex relationships. Moreover, the findings confirm what veteran outside-observers of China and those concerned with HIV globally have long suspected: patterns of infection in southern China are similar to those in other developing countries — especially those experiencing large-scale migration from rural areas to cities, which provides men and women with more opportunities for sex.

The good news, however, is that China is doing more to make its AIDS statistics available. Traditionally, China has controlled access to such information very tightly. After the first AIDS cases were reported in the 1980s, for example, it took the Chinese government more than a decade to acknowledge publicly that the epidemic even existed. But during the SARS epidemic of 2002–03, the government's secrecy drew the outrage of Chinese journalists and non-governmental organizations alike; the resulting outcry led to a change in official attitudes.

The work of Zhang and his colleagues illustrates just how radical this change has been. Although the study was led by scientists inside China, the group included a leading US-based researcher, David Ho of the Rockefeller University in New York. The international team had full access to data supplied by government authorities — the results of tests from 3.2 million blood samples. And the authorities apparently made no attempt to control or influence the authors' opinions.

Giving outsiders access to sensitive public health information would have been unthinkable in China even a few years ago — just as it is in many Western countries even now. But then, China is slowly becoming more comfortable with the idea that all of society will benefit by sharing data and knowledge with others. Some of this transparency can be traced back to 1972 and the landmark meeting between US President Richard Nixon and China's Chairman Mao Zedong. As noted by the historian Margaret MacMillan, author of the 2007 book *Nixon and Mao: The Week that Changed the World*, China had a very pragmatic reason for the rapprochement: it needed access to US technology. That opening was greatly expanded by Mao's successor, Deng Xiaoping. Deng accelerated scientific contacts with the rest of the world, sent hundreds of thousands of Chinese students to study in Western universities, and in 1987 hosted a landmark scientific conference in Beijing between China and the international community (see page 598).

"Giving outsiders access to sensitive public health information would have been unthinkable in China even a few years ago."

Of course, opening up on information is not the same as successfully controlling the spread of infection. Much more needs to be done if the government is to meet its self-imposed target of limiting the total number of cases of HIV infection to 1.5 million by 2010. Nonetheless, transparency is an essential first step. There are the many nations — in North Africa and the Middle East, for example — where public discussion of HIV and its causes is still not as open as it could be.

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RESEARCH HIGHLIGHTS

Vampire genes

Naturwissenschaften doi:10.1007/s00114-008-0446-0 (2008)

The evolution of the common vampire bat, *Desmodus rotundus*, included three rounds of duplication of a gene that encodes a salivary enzyme involved in breaking down blood clots. *Desmodus* laps the blood of mammals. The other vampire bats — *Diaemus youngi*, which also feeds from mammals but prefers bird blood, and *Diphylla ecaudata* (pictured), which sticks to birds — have only one copy of a plasminogen activator gene, find David Liberles of the University of Wyoming in Laramie and his colleagues.

Their genetic analysis corroborates established species relationships. DNA sequencing revealed three alternative versions of the gene in *Diaemus* and four in *Diphylla*. The four gene copies that *Desmodus* expresses lack a section called Kringle 2. Its deletion may have aided a dietary switch to mammalian blood.

N. GORDON/OSF/PHOTOLIBRARY

GEOSCIENCES

Carbon crunch

Proc. Natl Acad. Sci. USA doi:10.1073/pnas.0805382105 (2008)

India's smashing into Asia around 50 million years ago brought changes far beyond the creation of the world's highest mountain range: the continental collision is widely thought to have altered global climate.

Dennis Kent of Rutgers University in Piscataway, New Jersey, and Giovanni Muttoni at the University of Milan in Italy offer particular mechanisms for this. The researchers' model predicts that the carbon-rich sediments on the former ocean floor stopped being subducted and producing carbon dioxide when the landmasses touched.

Meanwhile, India's drift into more humid equatorial climes increased the uptake of the greenhouse gas through greater weathering of silicates in the Deccan traps (pictured below). This could have lowered atmospheric carbon dioxide enough to prompt the cooling trend in the Middle to Late Eocene.

DINODIA IMAGES/ALAMY

ECOLOGY

Diatoms downsize

Proc. R. Soc. B doi:10.1098/rspb.2008.1200 (2008)

Global warming is predicted to be bad for diatoms. Hungry and heavy as plankton go, they are expected to find themselves with fewer nutrients and sink more quickly as temperature gradients, and thus density gradients, grow, increasing the energy needed for mixing.

However, the total volume of diatoms in Lake Tahoe, on the California–Nevada border, did not change between 1982 and 2006, despite a warming in average air temperatures in the Tahoe Basin, report Monika Winder and her co-workers at the University of California, Davis. Instead, average diatom sizes fell from 67 micrometres to 35 micrometres, stemming the mean sinking speed and altering energy transfer through the food web.

CANCER BIOLOGY

Ensuring a welcome

Nature Cell Biol. doi:10.1038/ncb1794 (2008)

Before travelling to new organs — or metastasizing — some cancers send chemical signals to prepare the target organ for their arrival.

Yoshiro Maru and his colleagues at the Tokyo Women's Medical University in Japan had previously found that primary tumours in mice secrete growth factors that stimulate lung cells to produce chemoattractant proteins. These recruit white blood cells into the lungs, and the resulting inflammation recruits cancer cells to the site.

The team now reports that the chemoattractants involved induce the synthesis of serum amyloid A3 in lung cells. This protein attracts and activates white blood cells, setting up a state of chronic inflammation that facilitates tumour cell invasion. Antibodies against serum amyloid A3 blocked metastasis.

GEOLOGY

Primitive petrous

Science **321,** 1828–1831 (2008)

A beige outcrop in northern Quebec may be Earth's oldest known crustal rock. Jonathan O'Neil of McGill University in Montreal, Canada, and his colleagues have dated parts of the stone using ratios of neodymium and samarium isotopes, and calculated the oldest section to be 4.28 billion years old. This is 250 million years older than the previous record-holder.

The rocks in question are from the Nuvvuagittuq greenstone belt. This belt had been estimated to be 3.8 billion years old, based on an analysis of zircon crystals. But the stone that O'Neil and his team probed contained no zircons, forcing them to use an alternative method. The outcrop's low levels of neodymium suggest that it formed before Earth's neodymium levels became fixed 4.1 billion years ago.

MECHANICS

Slippery when clean

Phys. Rev. Lett. **101,** 125505 (2008)

Friction is a familiar force in everyday life, but its nanometre-scale details are obscure. This is because the fundamental mechanisms are subtle and sensitive to contamination,

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say André Schirmeisen of the University of Münster, Germany, and his colleagues.

They pushed islands of the element antimony across a graphite surface using the tip of an atomic-force microscope. Some of the particles encountered frictional resistance proportional to their area of contact with the surface; others slid almost friction-free.

The latter state, called superlubricity, has been argued to arise from a mismatch between the atomic-scale corrugations of two surfaces, which, in theory, should be the norm for solids. Schirmeisen and his team conclude that lubricity is undermined by impurities stuck at the interface.

PLANETARY SCIENCE

Mars lander

Icarus **197,** 452–457 (2008)

A curious elongated crater in the northern lowlands of Mars may mark the final resting place of a lost moonlet. A related crater a short distance away and 'butterfly wings' of ejecta to either side show that the crater was formed by the larger of two objects following the same, shallow trajectory.

According to modelling by John Chappelow and Robert Herrick at the University of Alaska Fairbanks, the distance to the secondary crater makes it improbable that this was the impact of an asteroid that split up in the atmosphere. And the alignment of the crater and its secondary makes it unlikely to have been a double asteroid. A small moon brought down by tidal drag and fractured in the atmosphere is, they argue, the most likely source.

ATMOSPHERIC CHEMISTRY

A chemical equator

J. Geophys. Res. doi:10.1029/2008JD009940 (2008)

A narrow atmospheric boundary in the Western Pacific keeps apart the more polluted air of the Northern Hemisphere from the cleaner air of the south. This newfound divide is markedly farther north than the Intertropical Convergence Zone (ITCZ), a tropical low-pressure belt that is thought to separate air masses elsewhere according to their hemispheric origin.

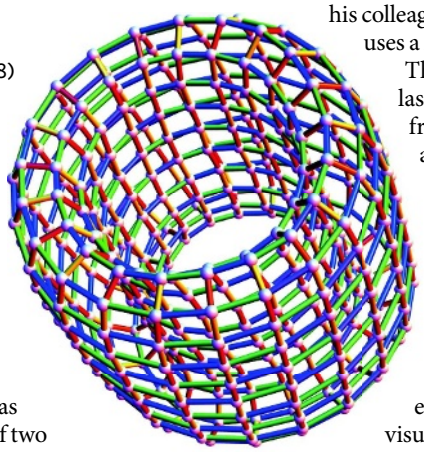
Jacqueline Hamilton of the University of York, UK, and her team found that carbon monoxide pollution from biomass burning in Thailand and Indonesia dropped steeply across the 50-kilometre-wide boundary. They conclude that storms may lift air from the Northern Hemisphere into the upper troposphere — where pollutants remain longer — preventing it from mixing with southern air masses.

THEORETICAL PHYSICS

Computing with rainbows

Phys. Res. Lett. **101,** 130501 (2008)

Schemes for quantum computing abound, but most intend to carry out computations on objects such as atoms. Now Nicolas Menicucci at Princeton University in New Jersey and his colleagues propose a method that uses a rainbow of colours.



N. C. MENICUCCI ET AL./PHYS. REV. LETT.

The group suggests firing lasers of 15 different frequencies into a cavity with a mirror at each end. Inside the cavity, a crystal splits each laser's photons into quantum mechanically 'entangled' pairs. Those pairs, in turn, become entangled with photons from the other lasers. The resulting cobweb of entangled photons could be visualized as a brightly coloured tube (pictured left).

The authors would be able to manipulate their rainbow computer by measuring the entangled photons that escape from the cavity — and the computer could, in theory, perform any computation.

CHEMISTRY

Biofuel acid test

Angew. Chem. Int. Edn doi: 10.1002/anie.200802879 (2008)

Tough, chewy parts of plants and even wood can be tapped for their fuel by dissolving them in an ionic liquid and then passing them over a solid acid catalyst, report Ferdi Schüth and his co-workers at the Max Planck Institute for Coal Research in Mülheim an der Ruhr, Germany. Specifically, a liquid made of an alkylmethylimidazolium salt dissolves woodchips. This allows the cellulose to be selectively hydrolysed when it passes through pores of a resin that contains sulphonic groups, generating sugars and smaller cellulose fragments.

The acidic resins needed to break down the cellulose are already commercially available, making the process easy to apply on a large scale.

JOURNAL CLUB

Roger Buick
University of Washington, Seattle

An astrobiologist considers the implications of microbes' mining abilities.

Microbes have been boring ever since life began on Earth: boring into rocks, that is. But why? Perhaps to avoid competitors or predators, to escape from environmental extremes or simply to secure a site safe from turbulent waters. Or might they be mining minerals for essential nutrients? Although the reason may vary depending on environment and host rock, a recent paper shows that some microbes tunnel towards a particular mineral, suggesting that nutrient mining may be occurring.

Tony Walton of the University of Kansas in Lawrence describes (and illustrates, gloriously) microscopic tubes in submarine glassy basalts from Hawai'i that show all the complex features of microbial borings (A. W. Walton *Geobiology* **6,** 351–364; 2008). The boreholes converge on olivine microcrystals but avoid plagioclase like the plague.

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Two implications arise. First, although hominids have shown an ability to recognize different rocks for almost a million years, this geological aptitude may be more widespread and more ancient among other organisms. And second, as olivine occurs in martian meteorites and on Mars' surface, perhaps future astrobiological space missions should be alert to the possibility that fossils of microbial miners may occur in subaqueously deposited basaltic sands on that planet.

Discuss this paper at **http://blogs.nature.com/nature/journalclub**

say André Schirmeisen of the University of Münster, Germany, and his colleagues.

They pushed islands of the element antimony across a graphite surface using the tip of an atomic-force microscope. Some of the particles encountered frictional resistance proportional to their area of contact with the surface; others slid almost friction-free.

The latter state, called superlubricity, has been argued to arise from a mismatch between the atomic-scale corrugations of two surfaces, which, in theory, should be the norm for solids. Schirmeisen and his team conclude that lubricity is undermined by impurities stuck at the interface.

PLANETARY SCIENCE

Mars lander

Icarus **197,** 452–457 (2008)

A curious elongated crater in the northern lowlands of Mars may mark the final resting place of a lost moonlet. A related crater a short distance away and 'butterfly wings' of ejecta to either side show that the crater was formed by the larger of two objects following the same, shallow trajectory.

According to modelling by John Chappelow and Robert Herrick at the University of Alaska Fairbanks, the distance to the secondary crater makes it improbable that this was the impact of an asteroid that split up in the atmosphere. And the alignment of the crater and its secondary makes it unlikely to have been a double asteroid. A small moon brought down by tidal drag and fractured in the atmosphere is, they argue, the most likely source.

ATMOSPHERIC CHEMISTRY

A chemical equator

J. Geophys. Res. doi:10.1029/2008JD009940 (2008)

A narrow atmospheric boundary in the Western Pacific keeps apart the more polluted air of the Northern Hemisphere from the cleaner air of the south. This newfound divide is markedly farther north than the Intertropical Convergence Zone (ITCZ), a tropical low-pressure belt that is thought to separate air masses elsewhere according to their hemispheric origin.

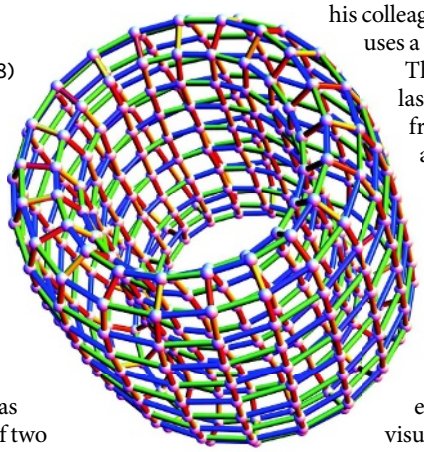
Jacqueline Hamilton of the University of York, UK, and her team found that carbon monoxide pollution from biomass burning in Thailand and Indonesia dropped steeply across the 50-kilometre-wide boundary. They conclude that storms may lift air from the Northern Hemisphere into the upper troposphere — where pollutants remain longer — preventing it from mixing with southern air masses.

THEORETICAL PHYSICS

Computing with rainbows

Phys. Res. Lett. **101,** 130501 (2008)

Schemes for quantum computing abound, but most intend to carry out computations on objects such as atoms. Now Nicolas Menicucci at Princeton University in New Jersey and his colleagues propose a method that uses a rainbow of colours.



N. C. MENICUCCI ET AL./PHYS. REV. LETT.

The group suggests firing lasers of 15 different frequencies into a cavity with a mirror at each end. Inside the cavity, a crystal splits each laser's photons into quantum mechanically 'entangled' pairs. Those pairs, in turn, become entangled with photons from the other lasers. The resulting cobweb of entangled photons could be visualized as a brightly coloured tube (pictured left).

The authors would be able to manipulate their rainbow computer by measuring the entangled photons that escape from the cavity — and the computer could, in theory, perform any computation.

CHEMISTRY

Biofuel acid test

Angew. Chem. Int. Edn doi: 10.1002/anie.200802879 (2008)

Tough, chewy parts of plants and even wood can be tapped for their fuel by dissolving them in an ionic liquid and then passing them over a solid acid catalyst, report Ferdi Schüth and his co-workers at the Max Planck Institute for Coal Research in Mülheim an der Ruhr, Germany. Specifically, a liquid made of an alkylmethylimidazolium salt dissolves woodchips. This allows the cellulose to be selectively hydrolysed when it passes through pores of a resin that contains sulphonic groups, generating sugars and smaller cellulose fragments.

The acidic resins needed to break down the cellulose are already commercially available, making the process easy to apply on a large scale.

JOURNAL CLUB

Roger Buick
University of Washington, Seattle

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NEWS

NIH soon to be leaderless

Plaudits for departing director Elias Zerhouni may be echoing through the US National Institutes of Health (NIH) in Bethesda, Maryland — but underlying them is uncertainty about who will take over, and when. The White House has not yet named an acting director.

After six and a half years at the helm of the NIH, the world's largest biomedical research agency, Zerhouni announced last week that he will leave by the end of October. With this announcement, he sidestepped any notion that his decision is linked to the outcome of the 4 November presidential election. But it ushers in a transition period that will stretch for at least several months. The next US president will not take office until 20 January 2009, and high-level presidential nominations like that of NIH director can be achingly slow to make.

"We are all worried about what is going to happen in the interim and who the next director of NIH will be," says Story Landis, director of the National Institute of Neurological Disorders and Stroke, one of the NIH's 27 institutes and centres.

Zerhouni leaves as the $29-billion agency faces great financial stress. Its budget doubled between 1998 and 2003, but since then its purchasing power has eroded by 10% as slight budget increases have failed to keep up with biomedical inflation. Many say that Zerhouni's work in the face of nearly flat funding has, of necessity, been the defining feature of his directorship (see 'Difficult times to make an impact').

Anthony Fauci, the long-time director of the National Institute of Allergy and Infectious Diseases, remembers advising the newly appointed Zerhouni: "Elias, what happens to you is going to rely very heavily on circumstances that are totally beyond your control." The two men still joke about it.

Elias Zerhouni: leaving this month.

R. L. WOLLENBERG/NEWSCOM

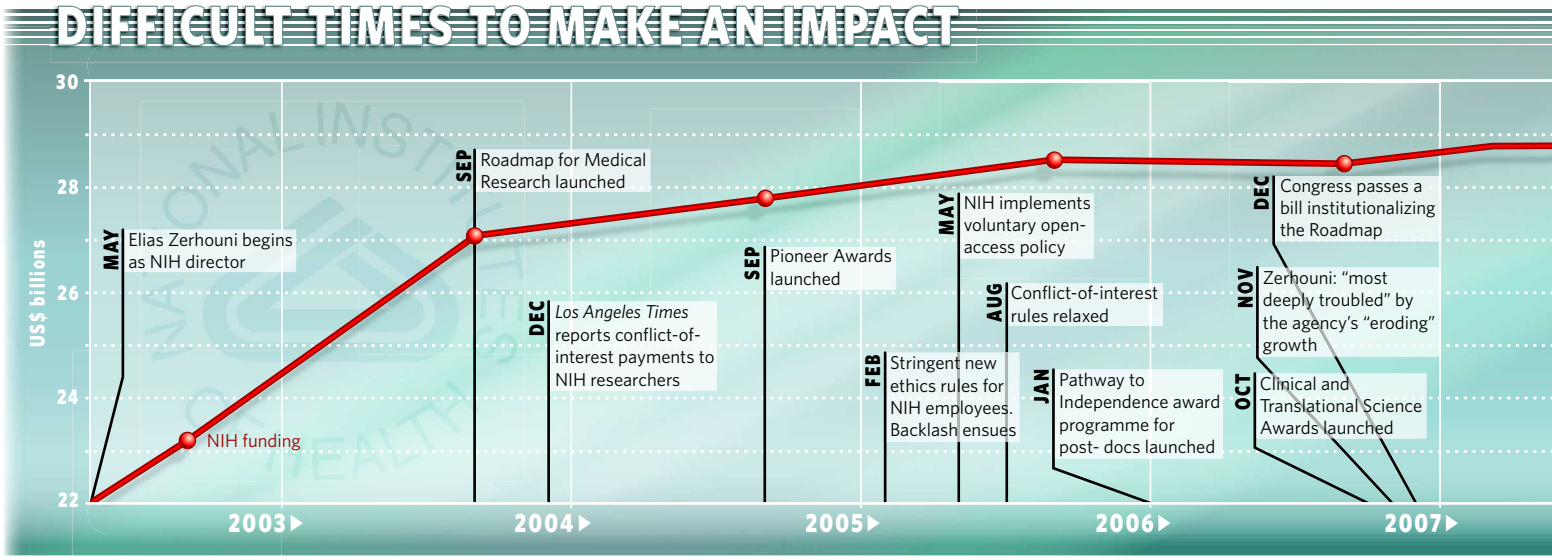
Zerhouni had faced challenges before. As the fifth of seven sons of a homemaker and a maths and physics teacher, he arrived in the United States from his native Algeria at the age of 24 with $369 in his pocket. By the time he was recruited to the NIH in 2002, he was one of the top experts in magnetic resonance imaging (MRI), and, among other things, had pioneered magnetic tagging — an MRI method that can be used to track heart motions in three dimensions. He had also risen to become executive vice-dean and chair of radiology at the Johns Hopkins School of Medicine in Baltimore, Maryland.

But it was soon apparent that the NIH gig wouldn't be a cake walk. "He comes into NIH and almost as soon as he gets there the good old days are over," says Howard Garrison, public-affairs director at the Federation of American Societies for Experimental Biology (FASEB) in Bethesda. As the agency's budget stagnated, success rates for grant applicants — especially first-time grant-seekers — plummeted. Zerhouni responded in 2006 with the 'Pathway to Independence' awards for young scientists, and managed to bring the number of first-time awards back up to 1,600 last year after it had dropped below 1,400 in 2006.

One early and much-criticized initiative was his 'Roadmap for Medical Research', a series of measures promoting trans-institute, high-risk, innovative research. As the budget for this grew from $132 million in 2004 (0.47% of the total NIH budget) to $495 million (1.7% of the total NIH budget) in 2008, it was perceived by some as too costly during a time of scarcity. In April 2006, Andrew Marks, then editor-in-chief of the *Journal of Clinical Investigation*, penned an angry editorial that began by telling Zerhouni: "Obviously you are not a scientist."

To this day, Zerhouni remains unfazed by criticism of the Roadmap. "I needed to do something to recognize that the boundaries of science have changed," he says.

Zerhouni also battled a conflict-of-interest



scandal at the agency, after Congressional examiners uncovered lucrative payments to moonlighting intramural NIH researchers by drug companies with financial stakes in agency recommendations or research. Zerhouni implemented tough new ethics rules for staff scientists — which he softened only a little after an outcry on the Bethesda campus.

"He's had to manage great expectations and stagnant resources," says Tony Mazzaschi, senior director of scientific affairs at the Association of American Medical Colleges in Washington DC. "And in that environment, he was able to add power to the director's role. That's not any mean feat."

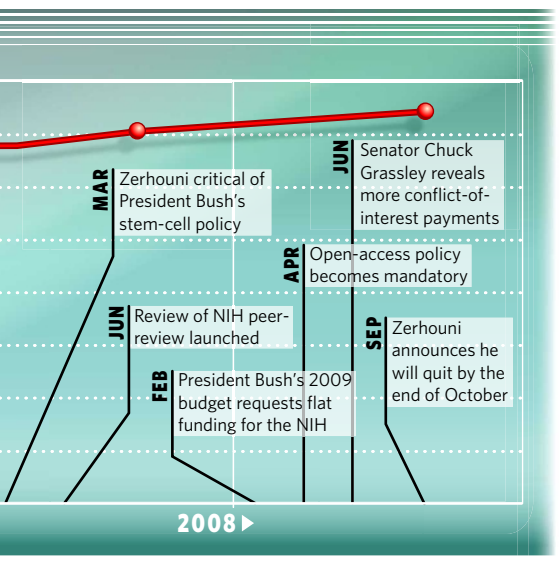
The question is who will come next. Washington is rife with speculation, most of which will turn out to be wrong. "When Elias became director, his name was nowhere on anybody's radar screen," says Fauci. Fauci's own name is inevitably floated whenever the NIH directorship is vacant. And any shortlist could include a stable of current and former institute heads, from heart institute chief Elizabeth Nabel to Francis Collins, who recently departed as director of the genome institute.

One other top medical spot in the Washington area got filled this week. Robert Tjian, a biochemist at the University of California, Berkeley, will take over the presidency of the Howard Hughes Medical Institute in Chevy Chase, Maryland, next spring from departing leader Tom Cech.

Zerhouni's expected choice of acting director in his wake, deputy director Raynard Kington, is said to be a finalist for the chancellorship of the State University of New York. Doubtless the wisest shortlist reads: to be announced. ■

Meredith Wadman

See Editorial, page 565.



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Hwang work granted patent

Australia is to grant a patent for Woo Suk Hwang's cloning method, even though the Korean scientist lied about using it to create human embryonic stem cells. But the patent is unlikely to prevent researchers from carrying out such work.

In 2004 and 2005, while at Seoul National University, South Korea, Hwang published a series of papers in which he claimed to have created a stem-cell line from a cloned embryo. An international patent describing his method was filed in 2004 by the university's patent office. The application was based on an embryonic-stem-cell line that Hwang's team had produced and deposited in an official stem-cell bank in accordance with the Budapest Treaty, which oversees the depositing of biological organisms for patent purposes.

In fact, the stem-cell line had been created not from a cloned embryo, but by a process called parthenogenesis, in which an egg develops into an embryo without being fertilized. Hwang was later charged with fraud, embezzlement and violation of the country's bioethics laws, he was sacked from the university and his high-profile papers were editorially retracted because of their fabricated data. Proceedings against him are ongoing.

In June 2006, six months after Hwang's work was discredited, the university's patent office made applications in eleven countries, most of which were refused. But the patent passed all the requirements of Australia's patent office, IP Australia: it was new, inventive, fully described and adequately defined.

IP Australia does not check for utility — that is, whether the patented procedure can actually produce what it claims. A representative there says there is no way they could test every claim that comes across their desks. Unlike most countries, the Australian patent office does not require authors to sign statements saying that their data are true.

IP Australia announced it was accepting the patent on 12 June, pending its standard 3-month period in which others can oppose it. No one opposed it.

Because of the extraordinary circumstances of this patent, it is now 'on hold'. IP Australia has another 3 months to grant the patent. During that period, the applicant could withdraw or amend it, or some "overriding right to refuse" could deny it. IP Australia is continuing to investigate the matter, but according to the representative, it is likely to be granted.

"There is no statutory basis to refuse to grant a patent on the basis that the scientific data in a patent application is a misrepresentation or fraudulently obtained," wrote David Johnson, acting commissioner of patents at IP Australia, in a statement last week.

But Australia should refuse the patent on other grounds, according to David Earp, chief patent lawyer at Geron, the California company that holds international rights — including Australia — to an earlier patent that covers the cloning technique used to produce Dolly. "Geron retains all rights for use of [the cloning procedure] in human application, including the creation of embryonic stem cells," he says.

"The broad claims of the recently accepted Hwang patent are not distinguishable from the [Dolly cloning] technology, and so the decision by the Australian patent office to grant them appears to have been in error," Earp says.

> "IP Australia is not endorsing the research that underpins the patent."

The patent is unlikely to be a powerful one. It would come into play only if the university's patent office tried to restrict a group in Australia from using the method. But such a group could challenge the patent in court on the grounds of utility, noting that the data were fraudulent and that the cell lines were derived from a parthenote, not a clone.

Johnson points out that even though misrepresentation cannot stop a patent from being granted, it "is grounds for revocation by the Court". He adds that "IP Australia is not endorsing the research that underpins the application".

The university's patent office has applications pending in the United States, Canada, India and China.

Only a few people around the world are currently experimenting with human embryonic cloning. "Until a thorough investigation into the patent and its claims has been completed we cannot make any conclusions about the impact it would have on our project," says Julia Schaft of the firm Sydney IVF, which last month became the first Australian group to receive a licence to attempt the technique. ■

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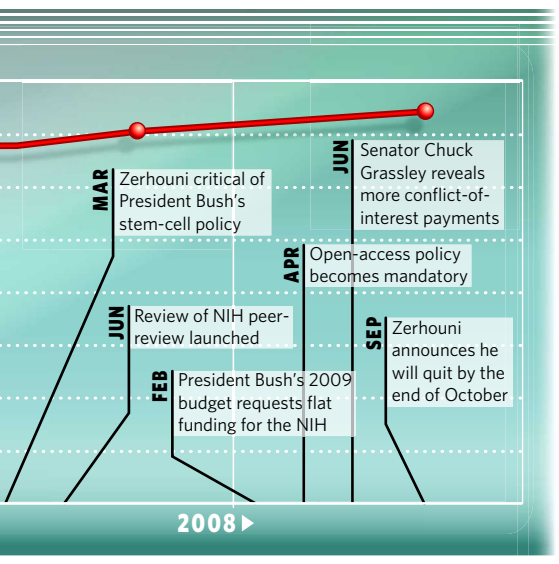

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David Cyranoski

Fears surface over methane leaks

D. VAUGHAN/SCIENCE PHOTO LIBRARY

Preliminary data from two Arctic cruises suggest that rising temperatures are already causing substantial amounts of methane to be released from beneath the ocean floor. But catastrophic gas leaks, like those believed to have occurred 55 million years ago, are unlikely, scientists say.

In the past few weeks, scientists aboard the British research ship *James Clark Ross* have discovered more than 250 plumes of methane bubbling up along the continental margin northwest of Svalbard. The findings add to a similar discovery by a Russian team in August, that reported elevated methane concentrations near the Lena River delta, as part of the International Siberian Shelf Study (ISSS).

The findings have provoked alarmist media reports predicting massive methane bursts that could accelerate global warming. Methane is a far more powerful greenhouse gas than carbon dioxide, although it is present in much lower concentrations in the atmosphere.

But the phenomenon is probably not new. The scientists believe that methane has been released in the region for at least 15,000 years. "What we're now seeing certainly did not start in the last year or so," says geophysicist Graham Westbrook of the University of Birmingham, UK, who led the British team.

"We have observed increased methane concentrations in the Laptev Sea during several expeditions since the mid-1990s," says Igor Semiletov, who oversees the ISSS methane programme aboard the Russian research ship *Jacob Smirnitskyi*. "But the data set is extremely limited. Whether what we're seeing in the region is of any relevance for the global climate is mere speculation."

British researchers found more than 250 plumes of methane bubbling up in the sea northwest of Svalbard.

Semiletov says that the scientists did measure higher concentrations of dissolved methane this summer compared to summer

Credit crunch threatens US wind-energy projects

Wind developers in the United States could be the first among the energy sector to fall victim to the global financial meltdown emanating from Wall Street.

The banking crisis that began with bad loans in the US housing sector has now brought down several commercial banks, one of the world's largest insurance companies and leading investment banks. These last have been particularly important in funding advanced energy technologies (through partnerships with wind developers) and in promoting international carbon markets.

The economic crisis could hit the booming US wind sector first, because the tax incentives designed to promote investment in the technology are meaningless for companies without sufficient profit. Current US law provides wind developers with a tax credit of 2 cents per kilowatt hour. That can add up to millions of dollars annually, but many wind operators do not have enough income to take full advantage of that type of tax credit.

S. PLATT/GETTY

Wall Street's woes may halt the wind-energy boom.

Before declaring itself bankrupt on 15 September, US investment bank Lehman Brothers was one of several major firms that invested in wind projects in exchange for the tax credit, which they used to reduce their federal tax bill. The number of firms making such 'tax equity' investments has dropped from more than a dozen to five or six in recent months, says Ethan Zindler, who heads up North American research for the London-based consultancy firm New Energy Finance. "To use the tax credit, you have to have tax exposure, and to have tax exposure you have to have profits."

Congress is fuelling anxiety; it has so far failed to extend the tax credit, which expires at the end of the year. Companies are on track to secure as much as $8 billion–10 billion in tax-equity deals — up from $5.2 billion in 2007 — assuming they can find the investors. The tax legislation would extend the credit for wind by one year and solar developers would receive an eight-year extension of a separate investment tax credit.

Most expect that the credit will ultimately be extended, even if it is allowed to lapse, but Zindler says that companies are nonetheless rushing to get their deals done now. Forays into carbon markets could become more difficult across the board as banking institutions curb their appetite

sampling in 2003 and 2004 (N. Shakhova and I. Semiletov *J. Mar. Sys.* **66,** 227–243; 2007). At one ice-covered site in the mere 50-metre shelf water, they detected methane bubbling at the surface, indicating that at least some of the gas released at the seabed is escaping into the atmosphere before being consumed by bacteria in the water column.

Geologists think that billions of tonnes of methane lie beneath the sub-sea permafrost in some parts of the shallow Siberian shelf, although estimates vary widely. The hydrocarbon — trapped there either as a gas, or bound in solid ice-like structures called methane hydrates — is a remnant from the last ice age when the sea level was about 100 metres lower. The big fear is that the methane could escape as a result of the permafrost becoming porous, possibly from an increased influx of freshwater from the relatively warm Lena River.

"The risk is real, but there's no reason to panic."

"The risk is real," says Hans-Wolfgang Hubberten, a permafrost expert at the Alfred Wegener Institute of Polar and Marine Research in Potsdam, Germany. "But there's no reason to panic. Claims that gas hydrates are on the brink of dissociating in a big way should be taken with a large pinch of salt."

Thermal modelling suggests that the marine permafrost in the region is relatively stable. However, drillings conducted in 2005 revealed that the permafrost may have slightly warmed and thinned (V. Rachold *et al. Eos* **88,** 149–156; 2007). Even so, says Hubberten, it is likely that the observed emissions come from 'new' methane produced by increased bacterial activity in thawing soil, rather than from degradation of ancient gas hydrates.

Methane, air and water samples taken by both teams will now be sent to isotope labs in the Netherlands and the United Kingdom to help determine the source of the methane. Geochemical analysis should also show how much of the gas escapes to the atmosphere, says Westbrook. "The new findings will be useful in helping us assess the history of climate change in the region, and how the methane reservoirs responded to past temperature changes."

Globally, atmospheric methane concentrations increased by 7.5 parts per billion to nearly 1,800 parts per billion during 2007 after almost zero growth since 1999. The upward trend is likely to continue this year, says Ed Dlugokencky, who oversees the methane database run by the National Oceanographic and Atmospheric Administration (NOAA) in Boulder, Colorado. "Our data suggest increased emissions in the Arctic and the tropics," he says. "Both regions were apparently warmer and wetter than average."

Data collected by NOAA at remote sites are usually at least 6 weeks out of date. And NOAA's measurement network in the Arctic is not dense enough to tell if increased methane emissions come from wetlands, permafrost or from gas hydrates on the continental shelves. ■

Quirin Schiermeier

T. STABLEFORD/GETTY

for risk. In particular, says Abyd Karmali, global head of carbon emissions at Merrill Lynch in London, the development of pilot projects using carbon trading to curb deforestation could get more difficult — at least until an international policy is put in place to guide such investments. Merrill Lynch, which is expected to merge with the Bank of America as a result of the ongoing crisis, is already developing one such project in Indonesia.

Harvard University economist Robert Stavins says that the financial crisis will probably have an impact on the voluntary carbon markets, especially if the economy dives into recession. But regulated markets, such as Europe's carbon trading scheme, will be fine, he says. "Compliance activity by business is immune to business cycles."

Some fear a prolonged economic crisis could make it harder for the United States to enact global-warming legislation owing to concerns about even higher energy prices to come. David Victor, an energy policy expert at Stanford University in Palo Alto, California, says the danger is real: people who are short on cash are less willing to spend money on dealing with distant threats such as global warming.

But Victor believes the fundamental drivers behind the renewed interest in clean energy — high oil prices and concerns about global warming — will remain. "We still have a whole bunch of renewable-energy technologies that are improving their performance," he says. "It's highly likely that people will find capital for these projects." ■

Jeff Tollefson

See Editorial, page 565.

NHPA/A.N.T. PHOTO LIBRARY

STING STORY
Jellyfish's chemical attack bequeathed by bacteria.
www.nature.com/news

Ancient water sites for next rover

The next Mars rover could end up down in the delta if a group of geologists and astrobiologists get their way.

The Mars science community has ranked a landing site called Eberswalde Crater as the most tantalizing destination for the Mars Science Laboratory (MSL), the US$2-billion rover that is due to launch in 2009. The crater seems to contain the remnants of a meandering river that spilled into a lake more than 3 billion years ago and piled up delta sediments — a prime target for MSL's instruments and their search for past or current microbial life. "If you go to any lake bed on Earth, that's where you find fossils," says James Rice, an astrogeologist at Arizona State University in Tempe who is a chief advocate for the site.

Scientists met last week to evaluate seven favoured sites (see 'Experts' shortlist') at a workshop in Monrovia, California. At the end of the meeting 104 paper ballots were cast, based only the scientific potential of each site — graded in 11 categories including the diversity of minerals likely to be present and the potential of the site to preserve evidence of life. At a meeting in November, the engineering team will rate the sites technically, comparing the risks of landing the 900-kilogram rover within 20-by-25-kilometre ellipses and driving it to the most interesting spots within a Martian year — nearly two Earth years — of operation.

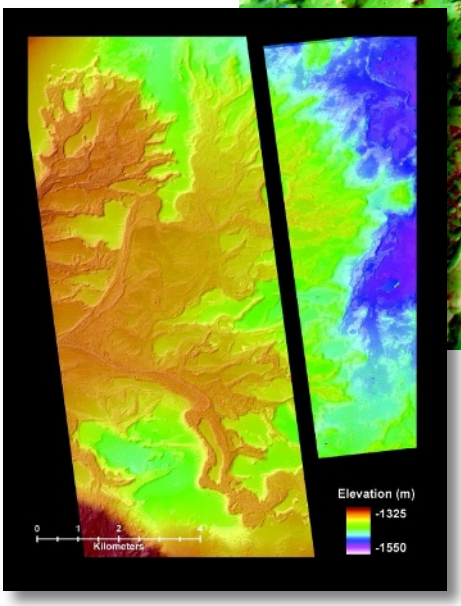
Engineers are worried about Eberswalde and the next most highly ranked site, Holden Crater, because they sit in more southerly latitudes of Mars. The rover will use a lubricant that might not work as well during winter temperatures at those latitudes.

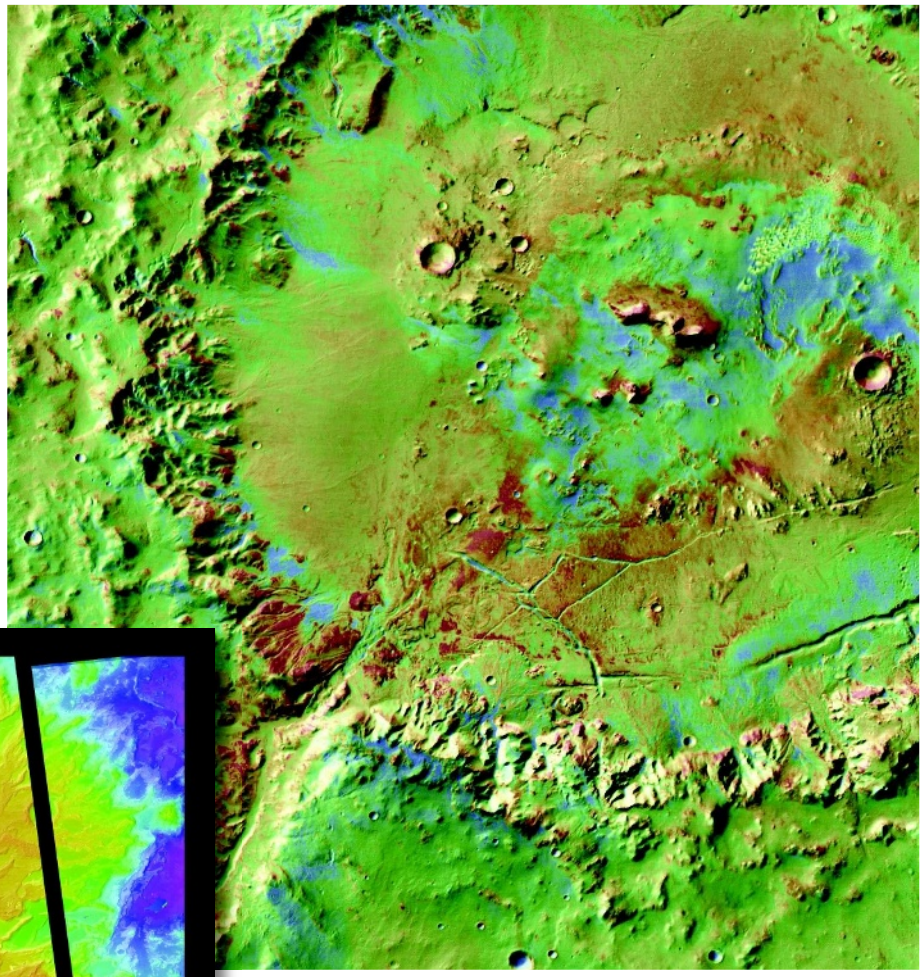
But Rice and others are optimistic about the Eberswalde site's chances — it's made quite a comeback after almost being knocked out of consideration at a workshop last year. Rice says the site shows clear signs of ancient river channels, some 100 metres wide, that emptied into a lake 150 metres deep over a period of perhaps a million years. The Holden Crater site lacks a delta but contains eroded sections of a lake bed that the rover could access more quickly than the delta at Eberswalde, says John Grant, of the Smithsonian Institute in Washington DC, who is co-chair of the landing site steering committee. Grant, an advocate for Holden Crater, says its walls were later breached by a massive flood that added to the volume of the lake.

But one of the two top sites will probably face elimination at the next meeting because of the concerns over their similar southerly latitude, says Grant. After a workshop next April, the committee will present recommendations to NASA science chief Edward Weiler, who will make the final decision on the target for the autumn 2009 launch. ■

Eric Hand

More images at http://tinyurl.com/4vlx98.





K. LEWIS, CALTECH & NASA/JPL/UNIV. ARIZONA

NASA/JPL/ARIZONA STATE UNIV.

The two top-ranked destinations for the next Mars rover are craters thought to contain ancient bodies of water. Eberswalde Crater, left, contains an ancient river delta, and the walls of Holden Crater, above, were breached by a flood that filled a lake in the centre.

Experts' shortlist

1 Eberswalde Crater
2 Holden Crater
3 Gale Crater
4 Mawrth Vallis
5 Nili Fossae Trough
6 South Meridiani Planum
7 Miyamoto Crater

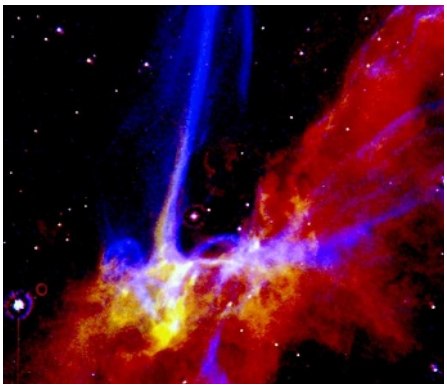
Teams merge for dark-energy mission

A competition between groups hoping to design a space telescope to investigate how the Universe is expanding over time has been scrapped by NASA and the US Department of Energy (DoE).

Instead, the agencies are pursuing a government-built, government-led design for the Joint Dark Energy Mission (JDEM), which may accommodate elements from all three of the teams. "It's a do-over for all of us," says Michael Levi, who is co-principal investigator for the Supernova Acceleration Probe (SNAP), a team that, he says, all of a sudden doesn't really exist any more.

NASA had been giving money to SNAP and two other groups, called the Advanced Dark Energy Physics Telescope (ADEPT) and the Dark Energy Space Telescope (Destiny). Each team was pursuing a proprietary telescope design, emphasizing different methods (see 'The telescope teams') for seeking constraints on the mysterious energy that is thought to be accelerating the expansion of the Universe. The mission is pegged for launch in 2015.

However, on 12 September, NASA and the DoE announced they will develop a common "reference design" that would not preclude any of the three methods. The design will be worked out by a new programme office opened at Goddard Space Flight Center in Greenbelt, Maryland, and a science coordination group of 12–20 people. The membership could be decided by 3 October, according to NASA astrophysics division chief Jon Morse, who says that there were 50 applicants in total, some coming from all three teams. Neil Gehrels, principal investigator for the Swift Gamma Ray Burst Explorer at Goddard, will chair the group.



J. J. HESTER/ARIZONA STATE UNIV./NASA

Supernovae offer clues to the expanding Universe.

The decision took many by surprise. "I'm concerned," says Chuck Bennett, principal investigator for the ADEPT team at Johns Hopkins University in Baltimore, Maryland. "Three teams did a lot of work for a long time. I'm worried that hitting the reset button and starting again is going to set things back."

NASA has removed mention of the competition between the three projects from its websites; just weeks ago, it discussed deciding between the telescopes in 2009.

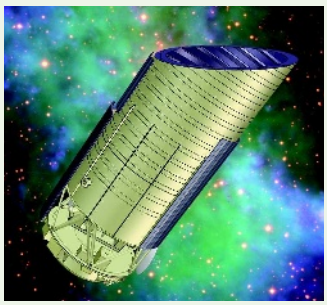
It's not necessarily a bad move by the agencies, says Robert Cahn of Lawrence Berkeley National Laboratory in California, who was part of a task force convened in 2005 to examine the dark-energy question. The JDEM may have become too big and costly to have been managed well by the relatively small teams, but now NASA can adopt the best ideas from each, he says. "In some sense NASA seems to have made up its mind that it wants to do all three methods," he says. "It's certainly not working the way we expected but it might work out well."

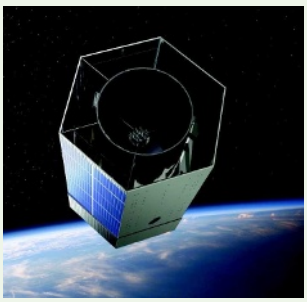
Although the decision eliminates tension between the competing teams — all three presume they will share aspects of their once-secret designs for the science coordination group — there is still tension between what the scientists want to do, and how much NASA and the DoE say they can afford. A 2007 National Academies report that endorsed the JDEM estimated that the three designs would cost more than US$1.3 billion in total. But Morse has said that he can afford only a $600-million mission, not including launch costs. The DoE has said it wants to pay about 25% of the overall costs. Eleven of the academy report's authors complained to NASA and the DoE in May that the science they envisioned the JDEM doing would not be possible at half the cost. "Wishful thinking does not engineer successful spacecraft," they wrote. ■

Eric Hand

The telescope teams

Three main teams designed space telescopes to measure how the Universe's expansion rate has changed over time, by performing surveys of objects from early in its history. Surveys require wide fields of view, and the need to look far back in time means that the telescopes would have to see infrared, the light with which the most distant and early objects glow. Both tasks are difficult from Earth. The teams emphasized different targets and techniques:



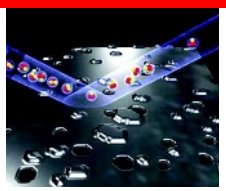


NASA/GSFC

Supernovae
Dark energy was discovered in 1998 by using the assumption that all supernovae in a class shine with the same luminosity, which allows astronomers to calculate their distance from Earth more precisely. It was found that more distant supernovae were receding more quickly than had been expected. The Supernova Acceleration Probe team initially emphasized this technique, although it later adopted all three methods.

Weak gravitational lensing
A high-resolution picture of distant galaxies can reveal tiny distortions in their shapes caused by the 'lensing' of intervening dark matter. The uneven distribution of this matter, and how it changed with cosmological time, would be a proxy for how dark energy influenced the Universe's growth. The Dark Energy Space Telescope team emphasized a blend of lensing and supernovae.

Baryonic acoustic oscillations
Sound waves soon after the Big Bang created ripples in the distribution of galaxies. By comparing the ripples from galaxy clusters in the early Universe with ripples in later clusters, astronomers can deduce the effect of dark energy over time. The Advanced Dark Energy Physics Telescope team emphasized this approach. **E.H.**



ATOM REFLECTIONS
Ultrasmooth mirror could herald birth of a new microscope.
www.nature.com/news

D. BARREDO *ET AL. ADV. MATER.* **20**, 3492–3497 (2008).

SNAPSHOT

How do you like your coffee?

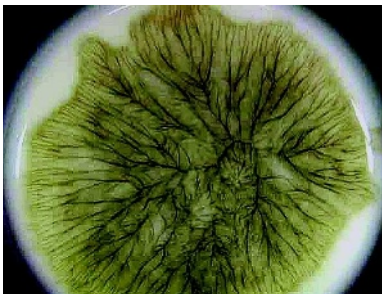
This floating fractal (top, left) is formed 90 seconds after a drop of instant coffee falls into a cup of milk.

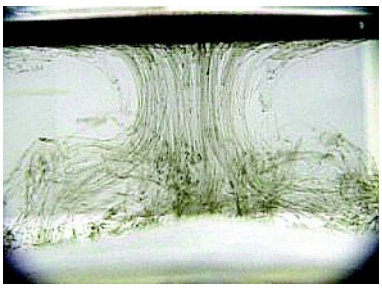
Coffee is heavier than milk and the battle between gravity and surface tension plays out at the boundary between the two liquids. The coffee falls vertically through the milk (bottom, left, with water replacing milk for ease of viewing), and the fractal pattern emerges.

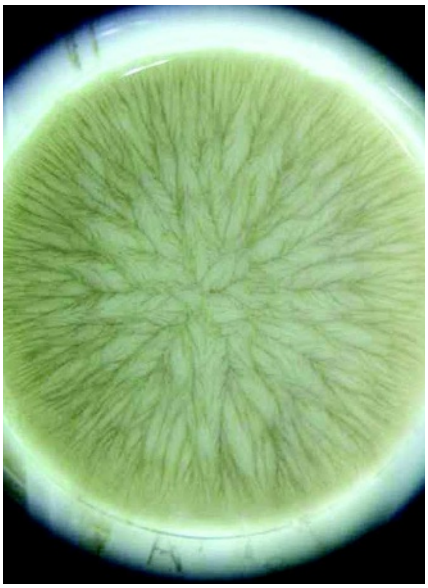
The pattern constantly shifts as parts of it are sucked into the milk, producing a fractal structure with the same dimension as a Sierpiński carpet — formed when a square is cut into nine identical squares; the central square is removed; and the procedure is repeated with the remaining eight squares and so on infinitely.

Michiko Shimokawa and Shonosuke Ohta, fluid scientists at Kyushu University in Fukuoka City, Japan, say that it is the first time this kind of fractal has been shown experimentally (www.arxiv.org/abs/0809.2458), and they managed to recreate the process using a magnetic liquid instead of coffee (far right).

Katharine Sanderson







World nuclear security gets welcome boost

An international initiative to help safeguard nuclear materials worldwide was announced on 30 September. The World Institute for Nuclear Security plans to do for nuclear security what the World Association of Nuclear Operators, created in the aftermath of the 1986 Chernobyl power-plant accident, does for nuclear safety.

The institute will bring together nuclear players, including scientific experts, to share sensitive information. Its goal is to strengthen accounting, control and physical protection of nuclear materials and facilities worldwide. The group, to be based in Vienna, is the brainchild of the Nuclear Threat Initiative group in Washington DC, co-chaired by former senator Sam Nunn and broadcast mogul Ted Turner. Roger Howsley, former director for security at British Nuclear Fuels, will be executive director.

M. GHASEMI, ISNA/AP

Better safeguards are planned for nuclear material.

South Africa replaces its health minister

African National Congress member Barbara Hogan took over last week as South Africa's health minister. She replaces the controversial Manto Tshabalala-Msimang, who had sparked international outrage by proposing that HIV be treated with garlic and beetroot.

AIDS activists welcomed the appointment, made by the government of new president Kgalema Motlanthe. Hogan is on the advisory board of the Amandla AIDS Fund, which provides grants for HIV/AIDS prevention and treatment programmes.

But the South African parliament also quietly passed a law that gives the minister sweeping authority over the approval of new medicines and a remit to regulate traditional medicines alongside conventional pharmaceuticals. The bill created a body — the South African Health Products Regulatory Authority — to oversee the approval of medicines.

Crucially, the agency's chief executive, who will be appointed by the health minister, will be accountable not to a board, as the existing Medicines Control Council is, but only to the minister. Critics of the bill fear that it may lead to conflicts of interest in the public-health system, and that it risks diluting the scientific basis behind making new treatments available.

For a longer version of this story, see http://tinyurl.com/4hh928.

Falcon rocket reaches low-Earth orbit

It was fourth time lucky for Space Exploration Technologies and its Falcon 1 rocket. After a trio of failed flights since 2006, the privately funded rocket soared into low-Earth orbit from Kwajalein atoll on Omelek Island on 28 September.

SpaceX and its founder, Elon Musk, hope that the launch marks the dawn of a new, substantially cheaper era of space flight. The company estimates that each Falcon-1 launch will cost less than US$10 million; existing systems can cost up to four times as much.

Next up are the company's larger heavy-lift rockets. Dubbed Falcon 9 and Falcon 9 Heavy, these rockets could potentially carry

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The first launch for Falcon 9, whose nine engines have been successfully fired on the ground, is slated for next year.

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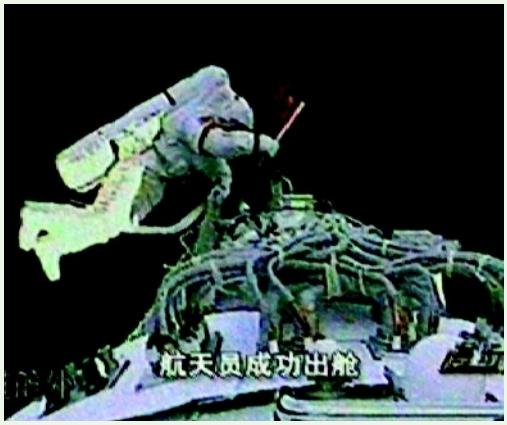
Carbon dioxide emissions rise to record levels

Carbon dioxide emissions from fossil fuels and cement manufacturing are rising faster than the worst-case scenario drawn up by the Intergovernmental Panel on Climate Change (IPCC). According to the latest worldwide carbon budget, released by the Global Carbon Project, CO_2 levels rose by 3.5% a year between 2000 and 2007, compared with 2.7% as calculated by the IPCC. During the 1990s, emissions rose at 0.9% a year.

"For a decade we've been using the [IPCC] middle-ground scenario, while we're actually in a different realm of emissions," says Pep Canadell, the project's executive director.

China is now the biggest emitter of CO_2 and responsible for 21% of the world's emissions — up from 14% in 2002. This knocks the United States into second place, contributing 19% of global emissions. India is fourth, but looks set to take third place from Russia this year.

China's first spacewalk



REUTERS

Zhai Zhigang (pictured), the commander of the three-person Shenzhou VII spacecraft, has become the first Chinese astronaut, or 'taikonaut', to spacewalk. Zhai spent 13 minutes outside the orbital module on 27 September.

A fire alarm went off while he was conducting the spacewalk, but it turned out to be due to a faulty sensor. Zhai retrieved a rack containing lubricant samples from outside the spacecraft.

The mission landed in Mongolia on 28 September.

US Congress approves funding bill for science

Most US science agencies will see their budgets frozen at 2008 levels under a massive $630-billion spending bill that was passed by Congress on 27 September. The 'continuing resolution' keeps the government operating until March 2009, when a new president and new Congress will tackle funding priorities.

A few agencies did get new dollars for 2009. Science and technology funding within the Department of Defense, for instance, rose 7%, and research and development funding at the Department of Homeland Security rose 9%.

The bill also provides NASA with permission to buy flights on Soyuz spacecraft from Russia until 2016, in order to ferry astronauts and cargo to the International Space Station after the space shuttle is retired.

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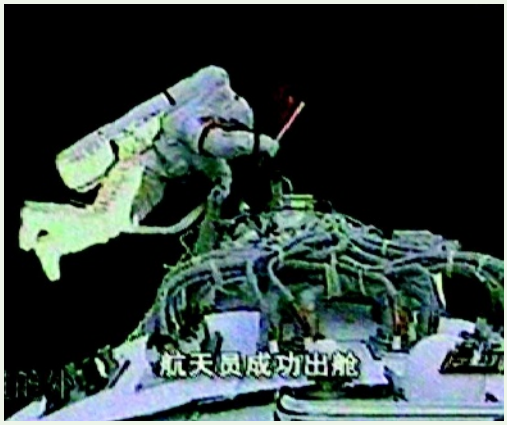

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F. MONTEFORTE/AFP/GETTY IMAGES

The Pentagon's culture wars

What began several years ago as an attempt to recruit social scientists to help the military has sparked a broader debate about militarizing academia. **Sharon Weinberger** reports.

It is a story that repeats with grim monotony: US forces in Iraq detain a suspected insurgent after they find in his home what they think is jihadist literature and an illegal weapon. These detentions — often based on mistaken assumptions or poor intelligence — can easily escalate into major conflicts with the local community.

But in one recent case, researchers helped defuse a potential conflict. Analysts working for a 'human-terrain team' informed a US commander that the 'jihadist' literature discovered in the village of Banat al Hassan, about 30 kilometres northwest of Baghdad, was ordinary religious teaching material, and the weapon — a riflescope — was for a pellet gun that beekeepers in the area use for shooting birds. The suspect was promptly released, and his family ended up helping US forces by revealing the location of a large improvised explosive device.

This upbeat anecdote is "a story about how a little respect, culture and compassion can save human life", says Montgomery McFate, an anthropologist at the Institute for Defense Analyses in Alexandria, Virginia, and senior adviser to the Pentagon's human-terrain programme. But it also underscores some of the complexities and controversies surrounding the Pentagon's quest for 'cultural knowledge'. What if, for example, the literature had indeed been jihadist literature? Would the human-terrain teams, which include civilian social scientists, then be helping the military to target insurgents?

Last year, the Pentagon provided almost $60 million for the Human Terrain System, a Department of Defense programme that represents the latest incarnation of the military's long, troubled relationship with social science (see 'Lessons from the past', overleaf). It includes deployed teams that directly advise military commanders in the field, specialized software for cultural 'mapping' plus personnel based in the United States conducting research. According to official figures provided by the army, there are now sixteen five-person Human Terrain Teams (HTTs) deployed in Iraq and five in Afghanistan, along with about 40 people in 'research reachback cells' in the United States. The teams are supposed to provide deployed military forces with "direct social-science support in the form of ethnographic and social research, cultural information research, and social data analysis".

But the effort is not without its problems; two social scientists have been killed in the field, one in Afghanistan and one in Iraq. And critics fear that this sort of work poses ethical problems, particularly if it's telling the military who is, or isn't, a potential enemy. Last November, the executive board of the American Anthropological Association (AAA) condemned the effort, saying it "creates conditions which are likely to place anthropologists in positions in which their work will be in violation of the AAA code of ethics", as well as endanger other anthropologists by bringing suspicion on their activities. The association is also proposing changes to its rules of ethics that would tighten restrictions on secret research.

Beyond the AAA, a number of researchers

E. LARSEN

in 2007 founded the Network of Concerned Anthropologists, which asks colleagues to sign a pledge committing them to "refrain from directly assisting the US military in combat, be it through torture, interrogation, or tactical advice". Though there hasn't been any known case of that happening with the HTTs, historical precedents exist. During the Second World War, for instance, anthropologists helped raise guerilla armies, passed information used to plan bombing raids and theorized about race-specific bioweapons.

"Why should anthropology be some leftist religion? I mean, it's supposed to be a science."
— Montgomery McFate

Critics say the current work flies in the face of everything anthropology represents, from transparency of research to informed consent (for example, the social scientists on the HTTs do not submit their research to an institutional review board, as would be normally required for human research). "I don't think there's a place for embedded anthropologists with combat missions," says Roberto Gonzalez, an anthropologist at the University of California, Berkeley, who is working on a book about the Human Terrain System. "It runs completely counter to anthropology's ethical framework, something that's come about over a long, bitter period that goes back to the First World War."

Militarizing anthropology?

McFate has emerged as the most public face of the Pentagon's military anthropology work. She got her PhD in anthropology from Yale University, focusing on the British counter-insurgency in Northern Ireland, and by 2005 she had co-authored an article in a military journal outlining a plan for deploying social science advisers with troops (M. McFate and A. Jackson *Military Rev.* July/Aug, 18–21; 2005). For her, the issue is unabashedly about moving anthropology toward an applied discipline that can aid the military. "Why should anthropology be some leftist religion?" she asks. "I mean, it's supposed to be a science; it's not supposed to be a political platform, a substitute for the Peace Corps, or a cult."

The Pentagon, however, has had a hard time recruiting and keeping qualified anthropologists. Of 35 social scientists based in Iraq and Afghanistan, only about half have PhDs, and only seven of those deployed are anthropologists. One social scientist hired to work on a HTT was identified during screening as a convicted criminal (and dismissed prior to deployment), another was found medically unfit, two were let go because of security clearance issues, and two were fired for performance issues. The company responsible for hiring the researchers is BAE Systems, a major Pentagon contractor, and some have criticized its focus on recruiting through intelligence and military-focused websites, as opposed to academic venues.

One of those fired was Zenia Helbig, a PhD candidate in religious studies, who says she was let go by BAE after a joking comment she made over drinks with colleagues about switching sides if the United States attacked Iran. Helbig, who travelled to Iran as a graduate student, had even met Iranian President Mahmoud Ahmadinejad. Now back at the University of Virginia, in Charlottesville, to complete her degree, Helbig describes a programme in disarray, in which social scientists — few of whom have regional or linguistic expertise — sat around for weeks at Fort Leavenworth in Kansas, with little in the way of region-specific training.

Matt Tompkins, Helbig's fiancé and another human-terrain participant, describes other problems. As a PhD student in political science with a military background, he was assigned as a team leader in Baghdad; but the social scientist on his team had no relevant field-research experience, he says, and their de facto translator was a Moroccan who barely spoke English. As for the military commander they were supposed to be supporting, Tomkins says, "I didn't get the inclination that he was particularly interested in what we were doing."

McFate disputes the recruitment problems, although she says some academics have told her they fear being blackballed professionally if they work for the programme. Other supporters note that experiences of different teams have varied widely. Adam Silverman, a political scientist who works on a HTT outside of Baghdad, says he believes such work is valuable. "The programme is new, so it isn't perfect," he says. "It has growing pains."

Working from what he describes as a mix of "unstructured interviews, casual discussions with members of the population, academic sources and the Internet", Silverman has provided advice on everything from local funeral rites to agriculture. Although he is now working on oral histories, he acknowledges that his field research has been difficult to conduct. "We don't interview anyone per se — we do try to talk with anyone who will talk with us," he says. "I've had conversations with fish farmers, brickmakers, government officials and tribal leaders."

However, it is not clear whether academic social scientists are even the key feature in successful human-terrain teams. McFate's story about a team defusing the situation in Banat al Hassan was confirmed by Major Philip Carlson, who led the team in question. But the recommendation to let the man go wasn't from a social scientist; it came from Carlson and an Iraqi–American analyst. There wasn't even a social scientist on that team at the time.

McFate says that "smart, competent, well-trained people on a team" can be successful, as in this case, but that social scientists are needed to achieve the programme's broader goals. But few, if any, definitive numbers exist by which to measure the programme's effectiveness. Earlier this year, Colonel Martin Schweitzer, a military officer working in Afghanistan, testified before Congress that HTTs helped to reduce the number of operations involving military force in his region by 60–70%. Sceptical of those numbers, David Price, an anthropologist at Saint Martin's University in Lacey, Washington, filed a Freedom of Information Act (FOIA) request to look at the report. Price says that what he got back was merely a correspondence stating the numbers; there was no actual report. "When I got my FOIA reply I learned that there was no study out there substantiating any of this," he says.

"Anthropology will thrive more as a discipline if the funding is not directly from the national security state."
— Hugh Gusterson

Even with the doubts surrounding the Human Terrain System, the Pentagon made another foray into the social sciences this April when Defense Secretary Robert Gates announced a broader military initiative. Called Project Minerva, it would fund work at universities that do research ranging from looking at Chinese military technology to Islamic radicalism.

Anthropologists critical of the Human Terrain System didn't welcome Minerva either. In a 28 May letter to the White House's Office of Management and Budget, the president of the AAA outlined a number of concerns,

Lessons from the past

In the 1960s, as the United States faced an array of potential regional conflicts from southeast Asia to Latin America, its army began what seemed to be a modest project to examine the roots and causes of insurgency. Project Camelot, as it was called, would look at "the feasibility of developing a general social-systems model that would make it possible to predict and influence politically significant aspects of social change in the developing nations of the world".

The seemingly innocuous project sparked a firestorm of criticism after researchers associated with Camelot visited Chile, triggering media stories that the work was a prelude to US military involvement in the region. Camelot eventually became the most well known of the Vietnam-era social-science programmes, and has now become synonymous with much of the work from that time.

The Pentagon launched a number of similar social-science projects, setting off a pointed debate among anthropologists, who criticized the military for attempting to subvert social research for its own means and manipulate foreign cultures. Seymour Deitchman, a Pentagon official who spearheaded many of the efforts, describes the rise, fall and backlash against these military social-science programmes in his 1976 book, *The Best-Laid Schemes: A Tale of Social Research and Bureaucracy*.

In one typical case in the late 1960s, a research group contacted an anthropologist about work it wanted to do for the Pentagon in the Congo. "The anthropologist immediately raised a storm," says Deitchman, "writing to the American Anthropological Association and the press that an attempt was being made to enlist him in intelligence activities for the suppression of Congo tribes in the conflict that was then in its final stages there." In fact, the Pentagon had never agreed to fund the work.

Deitchman, who is now retired, sees many of the same frictions echoed in today's efforts by the military to enlist social scientists. Although he does note that Congress and the secretary of defence support the modern studies — unlike in the Vietnam era — the underlying dynamics haven't changed. "The ticking time bomb in government support of social science research is there," he says, "just under the surface, waiting for the trigger." **S.W.**

including the notion that having the Pentagon run such research creates a "potential conflict of interest". Partly in response, the Pentagon forged a relationship with the National Science Foundation (NSF), which culminated earlier this year in the signing of a formal agreement. That, however, created new confusion, as many presumed that the foundation was cooperating on Minerva. Mark Weiss, director of the NSF's behavioural and cognitive sciences division, insists that is not the case. "It is a Memorandum of Understanding that would allow for a number of different interactions that . . . would help enhance the flow of information from the social and behavioural sciences to the Department of Defense," he says.

Shopping for knowledge

One question concerns who would oversee the peer-review process for selecting grantees: the defence department or the NSF. Thomas Mahnken, the deputy assistant secretary of defense for policy planning, says that Minerva is budgeted for approximately $100 million over five years, and that half that money would go through the NSF. The other half would go through the Pentagon, which he insists also has a well-tested peer-review process. "The two paths are complementary," says Mahnken. "NSF certainly gives us access to a different pool of scholars."

Critics of the programme, particularly anthropologists, point to a number of pitfalls associated with Minerva. One social scientist who works with the military warns of 'ScamTechs' — firms that are adept at getting defence department funding, regardless of the subject. And Hugh Gusterson, an anthropologist at George Mason University in Fairfax, Virginia, notes that a government contractor recently contacted several colleagues, "shopping" for an anthropologist so that they could bid on Minerva, which requires university participation.

J. MOORE/GETTY IMAGES

Soldiers of social science? US military meet tribal leaders in Ramadi to discuss Iraq's reconstruction.

Another concern is that the Pentagon's largesse could ultimately shift anthropologists away from their traditional role as advocates for the people and cultures they study. "Anthropologists ought to be involved [in the national security debate], but my fear is what makes anthropology appealing will be undercut and deformed if anthropologists are directly answerable to the Pentagon in that conversation," Gusterson says. "Anthropology will thrive more as a discipline if the funding is not directly from the national security state."

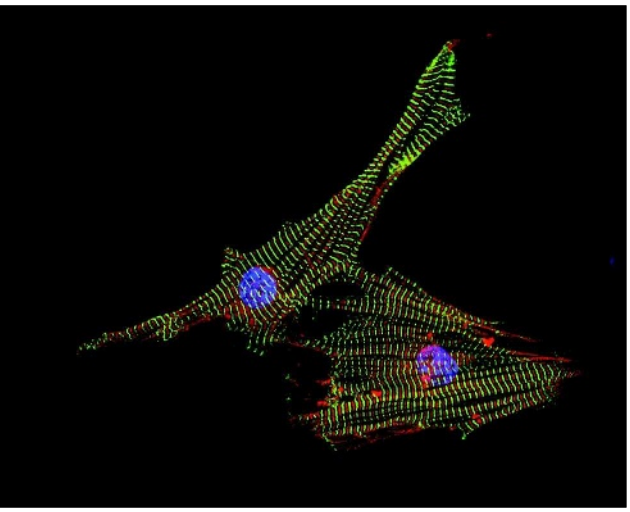
Both the Pentagon and the NSF downplay any concerns that the defence department could flood the field with military funding. Weiss notes that NSF's total annual budget for the behavioural and cognitive division is already about $220 million. The Pentagon money, he says, is "not going to put us into a stratospheric level of funding".

Meanwhile, researchers in other countries are grappling with some of the same issues. Two years ago, Britain's Economic and Social Research Council was criticized for circumventing normal open academic competition by funding counterterrorism studies. Jeremy Keenan, a UK-based anthropologist and North Africa expert, says that the UK Foreign Office gave itself a respectable academic veneer by rerouting money quietly through the council. By contrast, "if one looks at the US military programme, it's been very overt," he says.

Other militaries have not yet developed an exact equivalent to the Human Terrain System, but they do have, on a smaller scale, social scientists providing advice to armed forces — they work in psychological operations units and provide training and education. And McFate says that some NATO allies have also expressed interest in setting up human-terrain-like programmes.

Whether other countries will be engulfed in the same controversy remains to be seen. McFate, for her part, puts the criticism down to a small but vocal group. "It's just a very small segment of the anthropology community," she says of the critics. "We're not going to draft them." ■

Sharon Weinberger is a freelance writer.



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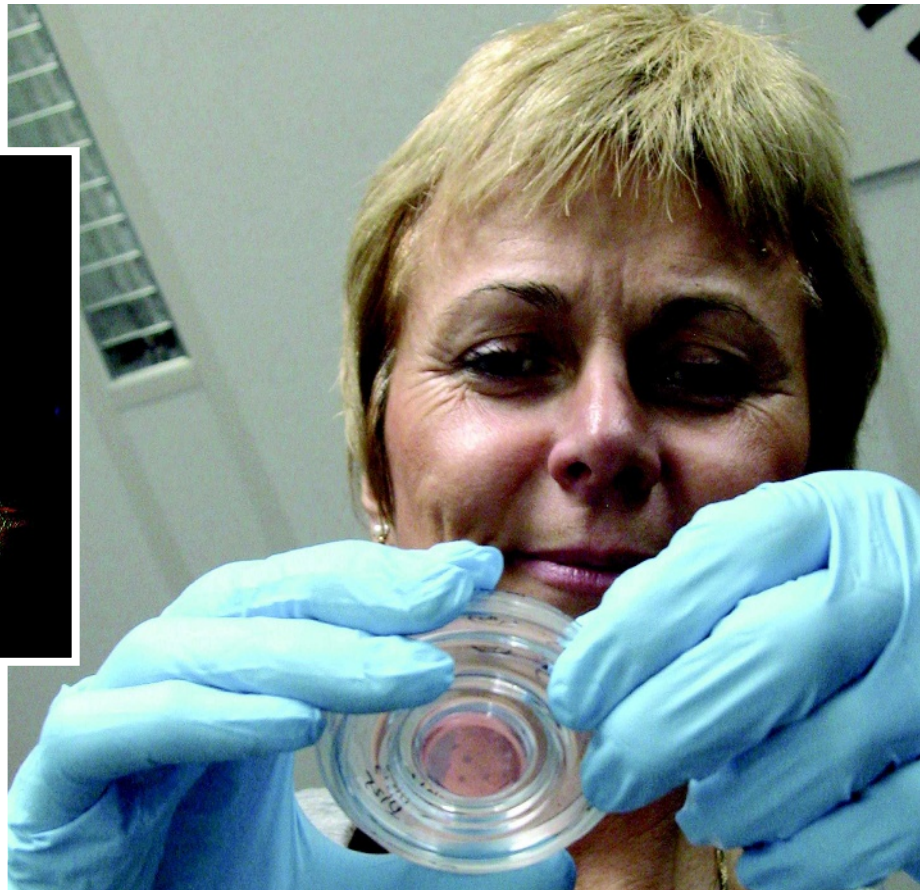


J. LENS

BEING PATIENT

Cell therapies are as much about the patients as they are about the cells. **Monya Baker** meets two stem-cell scientists who have decided to put people first.

The first time Christine Mummery encountered a human heart, she didn't like what she saw. The vessels were brittle with atherosclerosis and the tissue was mottled like a bruise. But the biggest shock was that this diseased heart looked so different from that of a healthy mouse. How could she expect the stem-cell therapy she'd been testing on rodents to work in this alien-looking organ?

This is the type of thinking that led Mummery, a stem-cell scientist, to move to a hospital in May this year. In the six years since she saw the heart, she had become convinced that closer ties to clinicians and better access to human samples would make her research more applicable to patients. So she packed up her lab at the Hubrecht Institute in Utrecht, the Netherlands, and relocated to Leiden University Medical Center. "I thought we'd be better off in a clinical environment," she says. "It's so much easier if you can speak to clinicians over lunch."

Viviane Tabar also talks medicine at the table. A practicing neurosurgeon at Memorial Sloan-Kettering Cancer Center in New York, she spends two to three days a week caring for patients with brain tumours. But she thinks that surgery and the other tools that she has to help them aren't enough, so she is investigating the cells that might make brain therapies of the future. "The patient's perspective is often different from what a scientist might think," Tabar says. "They want to know what a technology can do for them on a very practical basis. So you learn to think much more pragmatically and to ask: would this really be helpful?"

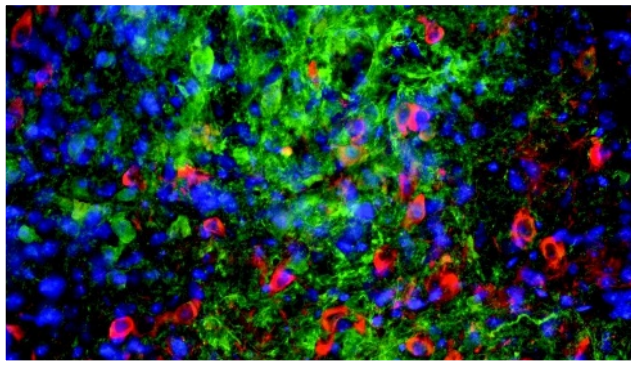
Both Mummery and Tabar have veered from conventional career paths in hopes of making stem cells more useful therapeutically. They work in different countries and on different diseases. Mummery is well-established and Tabar is still early in her career. Yet both believe that the best way to ensure that stem-cell therapies are 'translated' into patients is to be as close as possible to the patients themselves. "Some scientists could really benefit from just one or two days in the clinic," says Tabar.

Patients haven't always been the strongest focus for stem-cell researchers. Getting enough of the right cells to transplant was seen as the biggest stumbling block. That is changing with the derivation of human embryonic stem-cell lines, along with new techniques to make induced pluripotent stem (iPS) cells from patient skin biopsies. Researchers can now generate potentially limitless supplies of cells and use improved methods to grow them into the specialized types they want. The possibilities of human trials are edging nearer, and another problem is moving into focus: healing potential depends not just on the cells going into a patient, but on what they'll encounter inside.

Transplanted cells will be going into diseased bodies, says Marie Csete, scientific director of the California Institute for Regenerative Medicine (CIRM) in San Francisco, and it is the body as much as the cells that needs to be studied if researchers hope to "predict cell behaviour when we put them into a distinctly pathological environment". But few people are well versed with both stem cells and patients. "We've had a crisis in embodying someone who really understands clinical medicine and who really understands basic science in one person," says Csete. There is no question that the field needs more people like Mummery and Tabar to chart a course between an interesting concept and ready-to-test therapy, says Fred Gage, who studies neural stem cells at the Salk Institute for Biological Studies in San Diego, California.

Mummery conveys a sense of purpose. She is tall, sometimes wears her short hair spiked up, and her speech and movements are brisk. She trained as a physicist at the University of Nottingham, UK, and when Mummery later moved into biology she thought that its practitioners should "measure something rather than just look".

Mummery's quantitative approach has shown that, in some cases, stem-cell therapy may not live up to its initial promise even in animals. As a postdoc at the Hubrecht Institute she developed



Christine Mummery (opposite) works with cells for heart repair; Vivian Tabar (above left, with research technician Jayanthi Menon) studies cell therapy in the brain.

R. A. LISAK

V. TABAR *ET AL. NATURE MED.* **14**, 379–381 (2008).

culturing techniques that induce embryonic stem cells to generate plentiful cardiomyocytes, the muscle cells that power the heart. But her later work has highlighted how difficult it could be to use these cells therapeutically.

A common way to track cells transplanted into a mouse, for example, is to engineer them to express a green fluorescent protein and then look for the tell-tale signal. But Mummery discovered that scar tissue within the heart also emits green fluorescence under certain conditions, and posited that at least some transplantation studies were mistaking scar tissue for successful engraftment[1]. She has also shown that cell-therapy results can be frustratingly short-lived. Other researchers showed that one month after derived cardiomyocytes are transfused into injured mouse hearts, the hearts pump significantly more blood[2]. Mummery showed that the effects disappear after three months[3]. "What her work has uncovered is that we need to pay attention to graft survival, appropriate alignment, and integration," says Ken Chien, a cardiologist and stem-cell biologist at Massachusetts General Hospital, Boston, who has collaborated with Mummery.

Around the time she glimpsed her first human heart in 2002, Mummery began to question the relevance of her work to humans. She realized that the way her lab was simulating heart attacks in healthy mice was a poor mimic for the real thing. As soon as a heart attack is diagnosed, heart surgeons work quickly to place stents in blocked vessels, opening them up again to allow oxygenated blood to perfuse the tissue. In mice, Mummery's group tied off blood vessels permanently (partly to comply with animal husbandry laws), making for simpler, cleaner wounds. She recalls her discouragement: "You're already a year and hundreds of mice down the line, and the cardiologist would say 'that's not really it'."

Mummery was also becoming aware that clinicians are less concerned about the heart attack itself, and more about the ensuing heart failure. "I felt we needed to know more about the most relevant clinical problems," she says. She received recruitment offers from various institutions, including Harvard University. But in August 2007, she was offered the position at the hospital in Leiden — and she took it.

Converging paths

Whereas Mummery has gone from basic research to medicine, Tabar has been diverted from medicine to the lab. In 1995, as a third-year neurosurgery resident at Memorial Sloan-Kettering, she found herself intrigued by a talk given by Ron McKay from the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, describing evidence for neural stem cells. "I had been taught that the brain is a post-mitotic organ; that everything dies and nothing regenerates," she says. "And his work was saying 'maybe not.'" Her clinical programme required a year of research, and she went to McKay's lab to study how to coax embryonic stem cells into forming dopaminergic neurons, the kind that die in Parkinson's disease.

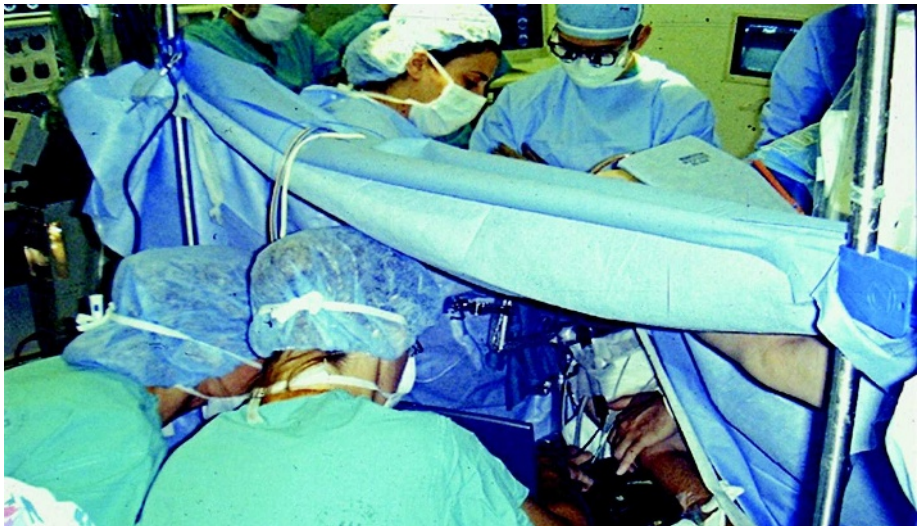
Tabar finished her medical training and in 2002 she joined the medical faculty at Memorial Sloan-Kettering, where she specializes in brain cancers. But while seeing patients, she also took a postdoctoral fellowship in the laboratory of her husband, stem-cell biologist Lorenz Studer. The two had met collaborating on experiments in McKay's lab, and when Tabar went to complete her training, Studer established a lab at Sloan-Kettering studying how embryonic stem cells can create different sorts of neural cells in culture. Tabar wanted to develop animal models to test whether neurons differentiated from embryonic stem cells could restore function, and she wanted her own lab to do so. She established this in 2005.

> **"It's so much easier if you can speak to clinicians over lunch."**
> — Christine Mummery

Researchers sometimes worry that clinicians will rush to act on preliminary results: "Some clinicians want to try an idea tomorrow, rather than the day after," Mummery says. But Tabar says the opposite can be true: being a physician sometimes makes even the best research publications seem less exciting because they will rarely make a concrete difference in a patient's life. McKay recalls visiting Tabar's lab in New York, and her questioning the treatment implications of a recent paper on glioblastoma. "Within five minutes, we were in another room, looking at patient records, talking about specific cases." It is precisely this "ability to dance on both sides of the aisle" that makes people like Tabar able to ferret out the valuable experimental approaches, he says.

Some of Tabar and Studer's most recent work has addressed a pressing question: how closely cell transplants into the brain must be immunologically matched to the recipient. It has not been clear how much tissue rejection and inflammation could present a problem, because brain tissue is better protected from immune attack than that of other organs.

In a paper published this year, Tabar and Studer tackled this question in a mouse model of Parkinson's disease[4]. Drawing on the expertise of colleagues at the RIKEN Center for Developmental Biology in Kobe, Japan, they used therapeutic cloning to create embryonic stem-cell lines from 24 mice, differentiated



Viviane Tabar (facing right, centre of picture) says treating patients helps her to ask research questions that are relevant to therapy.

these into dopamine-producing neurons, and transplanted them back into the animals. Mice that received cell transplants derived from their own cells improved; mice that received cells derived from other mice did not. The foreign transplants seemed to trigger an immune response allowing only a few cells to survive, suggesting that human cell transplants would need to be closely matched immunologically and perhaps even derived from the patients themselves.

The results highlighted the difficulties with such therapies, but it was the paper's success that made headlines: it was the first time that cells made by therapeutic cloning were used to treat exactly the same animal from which they were derived. Tabar says it is difficult to gain recognition for the "unglamorous" work necessary to move from proof-of-principle research to a clinical application. "You could perhaps come up with a paradigm that works beautifully in animals in the lab and that puts together all these biological concepts," she says. "You can get it published, but bringing it to the patient will require a lot of mining through the details."

The hard way

Academia does not tend to reward this type of detailed investigation; recognition is based on experimental 'firsts' and high-profile publications. If a scientist-clinician is not generating a stream of prestigious papers, then pressure increases to see patients, the activity that, after all, generates revenue for a physician's institution. Does Tabar ever consider how much simpler her life would be if she switched to all clinical or all scientific work? "Every day," she responds, laughing. But, she adds, she cannot imagine giving up either pursuit.

Tabar is now studying how cell replacement might help patients whose brains have been damaged by radiation therapy, as they would be after treatment for a brain tumour. Her lab administers various radiation regimes to rats, and then supplies cells — derived from embryonic stem cells — at various stages of differentiation and at various time points, trying to find the best combinations. She insists on measuring any benefits of these treatments using behavioural tests, rather than tissue integrity alone. "It is the clinical problem that I want to address rather than the simple histological or radiographic repair of the brain."

"We've had a crisis finding someone who understands clinical medicine and basic science."
— Marie Csete

Stem-cell researchers are not alone in finding clinical research challenging: scientists in almost every biomedical discipline are struggling to translate basic results into ones that can benefit patients. Stem-cell researchers are under particular pressure though. They must justify the massive investment made in them by funding agencies, philanthropies, and patients, such as the US$3 billion of California taxpayer's money distributed by the CIRM.

Getting cell therapies to patients is also daunting because there is no established path to clinical approval. No treatments based on pluripotent stem cells have been approved for testing in humans, and earlier this year the US Food and Drug Administration halted plans by Californian biotech company Geron for the first trial in human patients of cells derived from embryonic stem cells. The risks for such therapies are almost impossible to assess, but the worry is that even a differentiated cell product could be unpredictable when administered to a patient, and might proliferate or transform into unwanted tissues.

Csete says that the best approach to translational research is funding collaborations or facilitating other practices that bring disease experts, clinicians and cell researchers together. The CIRM plans to announce several large, multi-year grants for such 'disease teams' later this year and has already funded just under two dozen 'planning grants' at around $50,000 apiece to help collaborators at different institutions hammer out proposals.

The collaborative strategy seems to be working for Mummery, whose lab building is adjacent to the hospital at Leiden. There, she has access to fetal and adult human tissue and this has enabled her to try a new line of research: comparing human and mouse cardiac cells. She had good collaborations in hospitals before, she says, but people seem more willing to help colleagues within a hospital than at an unrelated institution. Mummery also benefits from the clinicians' established procedures for gathering informed consent for tissue collection.

Mummery is using the human samples to work out which molecular markers are expressed when and where in developing hearts, and she has already found that rodents can sometimes lead scientists astray. In the mouse embryo, cardiac cells express distinct markers depending on whether they will form the atrial chambers that receive blood or the ventricular chambers that pump it out. But when Mummery's team probed human fetal tissue, they found that human ventricular cells — the type that weaken in heart failure and that cell therapy might replace — actually express the markers used to identify mouse atrial cells. "That made me realize that we are trying to make heart cells from human embryonic stem cells without really knowing what the cells are."

Even as she has moved closer to the clinicians who could do cell transplants, Mummery now feels that the timelines for those transplants are lengthening. She no longer thinks that pursuing cell transplants is the most productive use of her time. Instead, she is using them to screen for drugs that can change how the cells beat *in vitro*, in order to understand the cause and control of cardiac arrhythmias.

The patients are just next door, but Mummery is a bit less intent on putting cells into them. For now, she's decided, there is plenty that the cells can teach her in a dish. ■

Monya Baker is the editor of Nature Reports Stem Cells.

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2. Laflamme, M. A. *et al. Nature Biotechnol.* **25,** 1015–1024 (2007).
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CORRESPONDENCE

Don't release other people's data without their consent

SIR — I am astounded by the audacity of someone photographing the presentation of another researcher and then publishing their data without the presenter's permission ('Physicists aflutter about data photographed at conference' *Nature* **455,** 7; 2008). In what scientific forum, other than apparently the arXiv.org preprint server, is that permissible practice?

The implication in your News story that videorecording conference proceedings somehow justifies this unfortunate incident is misleading. The point is not that data are recorded through a particular medium. We all take notes at meetings in some form, whether physical or mental, and who hasn't had their poster transcribed nearly verbatim? Rather, the issue is whether the information is released in a fair and representative manner.

Although, as you note, videotaping conference proceedings is common in biology, we operate under an implicit, and often explicit, ethic that data presented at meetings are personal communications. As such, publication of personal communications by a second party requires formal approval from the originating researchers. This practice strikes a balance between the public good that arises from collegial sharing of preliminary results and preservation of investigators' rights to ownership of their intellectual work. Therefore, except under exceptional circumstances, scientists ought to obtain permission to cite the unpublished works of others. Sometimes investigators may unfairly withhold data that are so critical that they justify overlooking what is the norm in most academic communities. But any such putatively exceptional case of data release should require unequivocal justification.

Ethics aside, what exactly was the purpose of reporting incompletely vetted, possibly erroneous experimental results? Can the group who released the data provide assurance that the information gleaned during the presentation adequately represents the original data in all its potential complexity? If not, there seems to be little justification for, or value in, usurping the intellectual rights of the group that originally generated and presented the results. And it is doubtful whether all those who contributed to the project received proper credit.

This case violates the spirit of collegiality that most scientists hold as an ideal in our public discourse. We all accept that others may scoop our work. We should not have to worry about being scooped by our own data.

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D. PARKINS

Further reflections on how we interpret the actions of others

SIR — In their Essay 'Behind the looking-glass' (*Nature* **454,** 167–168; 2008), Antonio Damasio and Kaspar Meyer suggest how mirror neurons might work. But they need to reflect on other aspects of the mirror phenomenon to complete the picture.

Mirror neurons are known for their intriguing property of discharging when a particular motor act is either being performed or being observed. Damasio and Meyer describe them as neural ensembles in higher-order association areas called CDZs (for 'convergence–divergence zones') that collect information from specific sensory areas and signal back to those areas. Action understanding (as in the authors' example of hearing a peanut being cracked) depends on activation of this network.

The CDZ model attempts to explain the mechanism underlying action understanding. But it overlooks a fundamental feature of the mirror mechanism: that is, the capacity to transform sensory information into a motor format — why should we have a copy of the actions of others in our motor system?

We can certainly recognize biological actions using sensory information and performing the kind of processing suggested by the CDZ model. But mirror neurons indicate that we must also have another mechanism for understanding another's actions. That mechanism directly maps sensory information on cortical motor neurons, providing the observer with an immediate representation of the motor acts being performed by others. There is no need for a higher-order association, as the CDZ model requires.

This, of course, does not imply that mirror neurons alone 'understand' the actions of others. Such an interpretation of the mirror system would go against all we know about the complexity of cortical organization. The point at issue is the specific contribution of mirror neurons to action understanding. Because of their motor nature, these neurons add a new, personal dimension to our capacity for understanding others that is based on our own motor knowledge and experience.

So, in spite of its heuristic value, the CDZ model underestimates the motor aspect of the mirror mechanism. It was this mechanism that prompted the description of action understanding as "the result of a 'first-person' process where the self feels like an actor, rather than a spectator" (M. Jeannerod *The Cognitive Neuroscience of Action*, Blackwell, 1997).

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Austria: Academy of Sciences states its case

SIR — As president and secretary-general of the Austrian Academy of Sciences, we wish to clarify the academy's position in the investigation into the alleged scientific misconduct associated with the urological clinical trial that you discuss in your Editorial 'Scandalous behaviour' (*Nature* **454,** 917–918; 2008). Contrary to your implications, the academy is committed to help in the resolution of this case.

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"'Social butterflies' and 'open skies' are equally important for the transmission of HIV." Karunesh Tuli, page 594

its investigation, requested by the rector of the Medical University of Innsbruck, on hold following the announcement by the university council that the rector would shortly lose his position (which has since happened). However, the investigations mandated by the rector are still under way, although no externally visible measures have yet been carried out. His withdrawal will not terminate or otherwise influence the investigations.

The academy has declined to make any pronouncement in advance of a verdict by a formal enquiry because the affair's scientific, ethical, legal and political issues must all be taken into consideration. A premature statement would not help to clarify the situation and would encourage accusations that its release was politically motivated.

We consider that it is of the utmost importance for the scientific community in Austria to investigate the case in an impartial and unprejudiced way, which will allow us to draw valid and independent conclusions. Individuals being chosen for the investigation will be completely independent and selected for their high scientific competence and moral integrity.

We therefore strongly reject your implication that the Austrian Academy of Sciences could be directly or indirectly involved in any political moves that might promote scientific misconduct and corrupt the scientific community.

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Science journals have been slow to make themselves audible

SIR — Podcasting has become very popular, mainly as a medium for entertainment. But it also holds huge potential for the visually impaired and others, such as dyslexics, who have reading difficulties. Simultaneously reading and listening to read-aloud news articles and scientific papers, for example, could increase readers' concentration and absorption of information. Such audio files would open a new world for the blind or partially sighted.

Software is available that translates text from digital files or directly from the Internet into a listener-friendly audio file, but it is expensive. Some freeware has built-in 'read out-loud' functions, but the quality is generally inferior.

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Don't forget people and specimens that make the database

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There is also a lack of support for many of those taking time to build up data sets. "I spent lots of time online editing a database" doesn't get you anywhere on a resumé or tenure review, or help an unpaid volunteer make a living.

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Religion and science: a guide for the 'perplexed'

SIR — There is no need for Matthew Cobb and Jerry Coyne (*Nature* **454,** 1049; 2008) to be "perplexed" by your Editorial concerning the funding of science and religion ('Templeton's legacy' *Nature* **454,** 253–254; 2008). As their Correspondence implies, the scientific study of religion is itself an important topic, and the Templeton Foundation gives grants for such work, for example in the field of cognitive psychology and the evolution of religious belief.

There are many reasons why the funding of academic research in this arena should be supported. Far from being in "fundamental conflict", history shows that there has been a constant traffic of ideas between science and religion, which provide complementary accounts of the same reality. In Stephen Hawking's colourful words, religion addresses the question "Why does the Universe go to all the bother of existing?". Boundary disputes arise when science claims too much (as in the philosophy of 'scientism') or when religion encroaches on science (as in so-called intelligent design, or creationism).

One pragmatic reason for supporting good academic science–religion research is that most of the world's taxpayers, who fund science, have religious beliefs. Pitting science against religion in that context is not a smart move for the future of science.

Next year is the bicentenary of Darwin's birth and also marks 150 years since the publication of his *On the Origin of Species*. It would be great if atheists, agnostics and religious believers alike could celebrate Darwin as the brilliant biologist he was, not as the icon of a particular ideology.

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Religion and science: separated by an unbridgeable chasm

SIR — In his Correspondence 'Religion: science is partially based on faith' (*Nature* **455,** 26–27; 2008), Jonathan Cowie argues that science and religion are more similar than often thought, suggesting that experimental application of the scientific method involves faith. However, he is conflating two different meanings of 'faith'.

Cowie's inherent definition of faith pertains to scientists' hopeful expectations that experiments will verify their (rational) hypotheses, whereas the definition relevant to religion is belief without evidence.

Insisting on evidence-based beliefs separates science starkly from religion. Contrary to Cowie's assertion and to the goals of the Templeton Foundation, the chasm between science and religion is fundamentally unbridgeable.

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Readers are welcome to comment at http://tinyurl.com/5rgnuc

"'Social butterflies' and 'open skies' are equally important for the transmission of HIV." Karunesh Tuli, page 594

its investigation, requested by the rector of the Medical University of Innsbruck, on hold following the announcement by the university council that the rector would shortly lose his position (which has since happened). However, the investigations mandated by the rector are still under way, although no externally visible measures have yet been carried out. His withdrawal will not terminate or otherwise influence the investigations.

The academy has declined to make any pronouncement in advance of a verdict by a formal enquiry because the affair's scientific, ethical, legal and political issues must all be taken into consideration. A premature statement would not help to clarify the situation and would encourage accusations that its release was politically motivated.

We consider that it is of the utmost importance for the scientific community in Austria to investigate the case in an impartial and unprejudiced way, which will allow us to draw valid and independent conclusions. Individuals being chosen for the investigation will be completely independent and selected for their high scientific competence and moral integrity.

We therefore strongly reject your implication that the Austrian Academy of Sciences could be directly or indirectly involved in any political moves that might promote scientific misconduct and corrupt the scientific community.

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Austrian Academy of Sciences, Dr Ignaz Seipel-Platz 2, 1010 Vienna, Austria
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Science journals have been slow to make themselves audible

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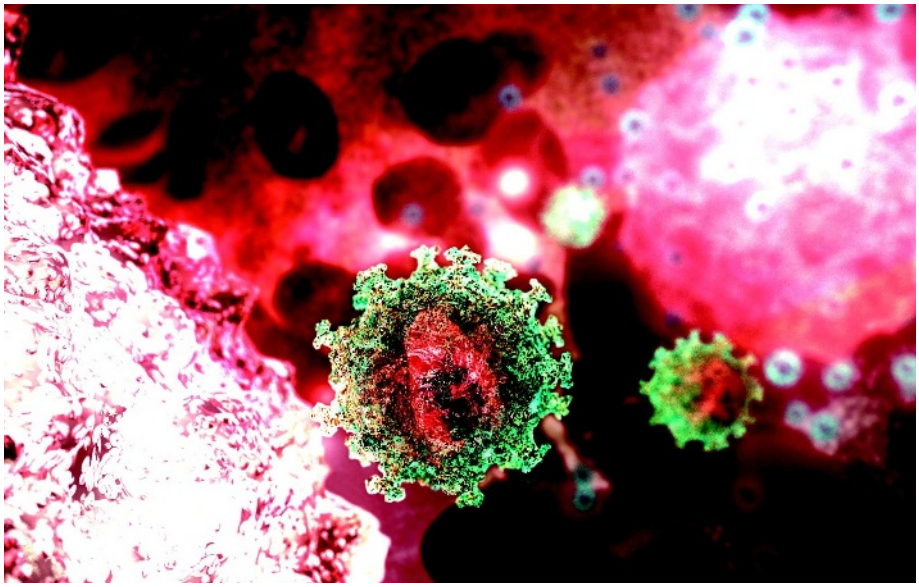
COMMENTARY

HIV immunology needs a new direction

Researchers need to get past the standard model of vaccine development and focus on how immune responses are specifically tailored to retroviruses, argue **Ruslan Medzhitov** and **Dan Littman**.



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Understanding how cells initially sense and recognize HIV could aid vaccine development (computer art).

Recent advances in immunology and failures in HIV-vaccine development suggest that it is time to rethink the current approach to developing an HIV vaccine. Better communication and cooperation is needed between vaccinologists, virologists and the growing number of researchers studying innate immune responses. HIV has evaded the attempts of vaccinologists for 25 years partly because of the unique characteristics of the virus, including its extremely high mutation rate, which enables immune evasion, and its ability to infect and deplete the major orchestrators of the immune response — the $CD4^+$ T cells. But, in our opinion, there are other reasons for failure.

Although vaccination arguably represents biomedical science's greatest triumph over disease, so far the successes can largely be ascribed to empirical findings, scattershot approaches that have yielded great dividends for scourges such as smallpox and polio, but little to speak of for others including HIV and malaria. This reflects our current, clearly limited, level of understanding of the immune system. Specifically, the 'rules' for making a successful vaccine are currently unknown.

If there is any guiding principle to this formidable task, it is that a vaccine should mimic, as much as possible, the immune recognition events that happen during a natural infection with the same pathogen. These would be likely to engage the appropriate mechanisms of immune protection. This is why attenuated pathogens are the most successful vaccines currently available. For HIV, the use of attenuated strains is not an option at present. We therefore need to understand how the virus is normally sensed by the immune system.

> "So far, approaches have been more or less random attempts to see what might work."

Our understanding of early host responses, although incomplete, has improved dramatically in the past decade owing to a focus on the innate immune system, a first responder to pathogens that induces antimicrobial defence mechanisms and activates adaptive immunity. The human immune system has to deal with a variety of pathogens, ranging from RNA viruses to 30-foot-long tapeworms. Naturally, the ways in which these intruders are sensed and handled vary. Indeed several families of microbial sensors have now been identified that detect different classes of pathogens and trigger activation of adaptive immunity by different mechanisms[1,2].

Major gaps remain in the understanding of how HIV and retroviral infection in general is sensed by the innate immune system, and how this initial sensing is translated into the activation of adaptive immunity. In our view, there is currently insufficient effort being devoted to addressing these gaps and this is irreconcilable with the urgent need for a vaccine.

Studying HIV is of course complicated by its human-specific tropism, which precludes many definitive experiments. Although the mouse, as a model system, is often dismissed as irrelevant to HIV infection, there are likely to be common basic principles of retroviral immune recognition that need to be defined. Innate sensors may recognize features of replication that are shared among retroviruses but no other classes of viruses. For example, newly reverse-transcribed retroviral DNA may activate a specialized signalling pathway. Further study of the numerous host factors co-opted by HIV for its replication[3] might provide insight, as these may recruit antiviral innate sensors that limit viral spread.

Approaches currently used in HIV vaccine development are largely based on immunological paradigms wrought from studies using antigen immunizations and infections with several model pathogens. These paradigms may not apply to retroviral infections. In the absence of a basic understanding of how the host immune system responds to retroviral infection, the approaches tried so far have been more or less random, and unsuccessful, attempts to see what might work. Most of the resources devoted to HIV vaccine development have been spent on such efforts, which may remain futile until we gain some understanding of the basic mechanisms of retroviral recognition and induction of adaptive immune responses. ■

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2. Ishii, K.J., Koyama, S., Nakagawa, A., Coban, C. & Akira, S. *Cell Host Microbe* **3,** 352–363 (2008).
3. Brass, A.L. *et al. Science* **319,** 921–926 (2008).

Discuss this Commentary online at http://tinyurl.com/4683h3.

COMMENTARY

UK physics gets a health check

The field is healthy, says **Bill Wakeham**, but scientists need to reclaim the intellectual ownership of research at the margins of the discipline such as medical or atmospheric physics.

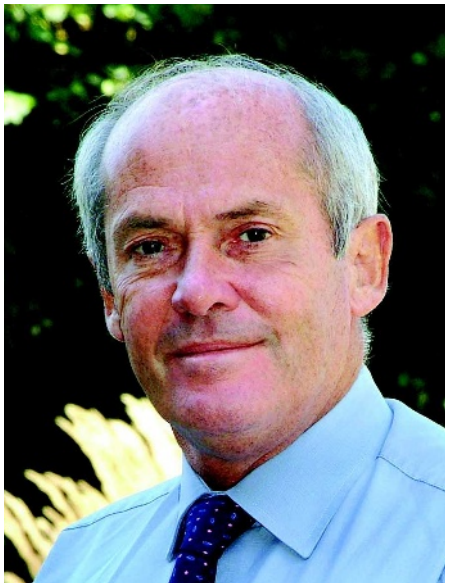
Physics research funding in the United Kingdom has been under the spotlight in the past year. In 2007, a restructuring of the research councils and a government budget settlement were perceived by the community as being unfavourable to the discipline. This prompted a wide review of the health of UK physics, looking at its international status, funding arrangements, university provision, school education, careers and skill supply. I was invited by the research councils to chair the review panel, drawing on expertise across the discipline and from overseas. Our report was published on 1 October.

UK physics is strong but faces important challenges. International reviews conducted in 2000 and 2005 recognized its outputs in terms of publications and citations. An analysis based on ISI citation data from 1998–2008 places the combination of UK physics and space science second only to that of the United States. The study we commissioned from Leiden University in the Netherlands showed that despite having a lower publication volume than Japan, France and Germany, the United Kingdom receives a higher citation rate per publication.

The discipline's impact on the wider economy is also strong. An Institute of Physics study calculated that the economic activity of physics-based sectors in the United Kingdom was £70 billion (US$125 billion) in 2005. These include information technology, construction, transport and aerospace. Physics graduates also find employment in sectors with no obvious connection to the subject, notably finance.

The United Kingdom's academic physics workforce is stable, with around 4,000 academic and postdoctoral researchers. The annual undergraduate intake has increased from 3,415 in 2002/03 to 3,885 in 2006/07, so the appeal of the subject to a core group is clearly robust. Research in the United Kingdom has benefited from an 82% increase in the overall science and research budget in the five years to 2006/07, and physics-research funding has increased by 34% during this period, in line with the growth of UK gross domestic product.

Despite this superficial picture of stability, physics in the United Kingdom has seen significant changes during the past 20 years, with a number of departments closing or merging. Factors driving this change include the expansion of the university sector to embrace the former polytechnics, the increased focus of universities' research strategies driven by the Research Assessment Exercise and the reduction in the unit resource for undergraduate physics teaching.



Bill Wakeham: undoing the merger of research councils would be rash.

Departmental focus on particular areas of physics has had a significant effect. Increasingly, physics departments rely on the core physics programmes of the Engineering and Physical Sciences Research Council and the Science and Technology Facilities Council (STFC); the latter was formed last year through the merger of the Particle Physics and Astronomy Research Council and the Council for the Central Laboratory of the Research Councils. Other British research councils invest in physics — notably the Medical Research Council, the Natural Environment Research Council and the Biotechnology and Biological Sciences Research Council — but 95% of their physics-related funding is spent in non-physics departments.

> "95% of physics-related funding is spent in non-physics departments."

This tells us three things: 1) the dependence on a small number of funding streams makes physics departments vulnerable; 2) physics departments have not fully grasped the opportunities in interdisciplinary research and some subdisciplines; and 3) the intellectual leadership of research at the margins of the discipline is often in other departments. There may be reasons for this at an individual institutional level, but at a national level it militates against the ability of the discipline to work with large sections of industry. Physics departments need to reclaim the intellectual ownership of some parts of their discipline and they need support from the funding agencies to achieve this.

Like many developed countries, the United Kingdom faces a challenge to maintain the supply and recruitment of research scientists. The problem is acute in physics and one that my panel explored at several points of the pipeline. Government intervention may be necessary to solve some of the problems. Physics needs to be taught by those trained in the subject. Too many young people are being taught physics by teachers with little relevant background. Worrying also is the decline in uptake of physics by girls, which has fallen by 16% compared with a 12% fall for boys in the four-year period assessed.

The merger of two research councils to form the STFC was generally welcomed by the research community. It would be precipitate to undo this process rapidly and we are not convinced that significant changes to the remits of individual research councils to unify physics funding or to separate facility and grant spend would be helpful. Nevertheless, the community must be confident that the current remits serve the best interests of UK research and physics and in particular, that commitments to facilities do not have an undesirable impact on the availability of grant funding. We think that government should revisit the current arrangement at a suitable time, guided by the more detailed review of STFC structures that has been commissioned.

The value of physics to the United Kingdom is such that weaknesses in its structures and in the skills pipeline must be addressed. Some aspects of this problem have been recognized, but action now needs to be pursued with greater urgency. ■

Bill Wakeham is chair of the Research Councils UK Review of Physics. He is a member of the Council of the Engineering and Physical Sciences Research Council and vice-chancellor of the University of Southampton, University Road, Southampton SO17 1BJ, UK.
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Discuss this Commentary online at http://tinyurl.com/4hx8zq.

BOOKS & ARTS

A fluid approach to HIV

A readable anthropological account of social networks in South Africa and Uganda explains differences in the spread of sexually transmitted diseases in those countries, finds **Karunesh Tuli**.

Unimagined Community: Sex, Networks, and AIDS in Uganda and South Africa
by Robert J. Thornton
University of California Press: 2008.
282 pp. $60 (hbk), $24.95 (pbk)

B. STIRTON/GETTY IMAGES

Despite safe-sex campaigns, AIDS is harder to prevent in South African communities than in Uganda.

"Abstain," said our hostess as we got off the bus to spend a week in Zwelethemba, a township in Western Cape, South Africa. She added that for her grown-up children, her message is different: "Be wise, condomize." A few days later, our group of students and teachers, visiting the country from the United States to learn about how South Africans handle health problems, was interviewed by some local journalists. After their questions dried up, we asked them what was the biggest problem facing their community. "AIDS," they replied.

Stories about AIDS and violence are often part of the same narrative in South Africa. In *Unimagined Community*, Robert Thornton describes the 2006 rape trial of Jacob Zuma, South Africa's deputy president until 2005. The Johannesburg High Court found him not guilty but the hearings provided Thornton with fertile material for anthropological analysis. Zuma's accuser, a family friend and an AIDS activist, was HIV-positive. Zuma told the court he had unprotected sex with her even though he knew her HIV status; he followed it with a shower to prevent infection.

Unimagined Community is the latest publication in the California Series in Public Anthropology. Robert Borofsky, the series editor, challenges anthropologists to write for a popular audience, inspired by Jared Diamond's much-read *Guns, Germs, and Steel* and Anne Fadiman's *The Spirit Catches You and You Fall Down*. Both writers used anthropological approaches but lack formal training in the field. Thornton reaches out to a general readership with a fresh interpretation of a pressing social problem. With his vigorous and imaginative writing, he succeeds admirably.

Thornton suggests that, in South Africa, sex is more than a personal quest for pleasure. It can be viewed community-wide as an exchange of fluids between males and females, part of a broader flow of objects and services between sexual partners. The men and women are hubs in large sexual networks that are regional and even countrywide. HIV follows the same paths as the flow of sexual fluids.

Traditional healers are reluctant to prescribe condoms. Thornton attended a workshop on HIV/AIDS for healers where the facilitator asked them to recommend condoms to their clients. Yet the attendees assembled a formidable case against the advice, saying, for example, that condoms could lead to illness in the man by causing a backup of semen, or could slip off and disappear inside his partner. Many South Africans believe that damming the flow of fluids disrupts a vital exchange and damages social networks.

Repelling a woman's sexual advances is akin to denying her "human right to sex", as Zuma declared in his defence, claiming his accuser had enticed him. He yielded to help her preserve her sanity and health. His shower may not have warded off HIV, but it was a "ritualistic act of cleansing and strengthening", says Thornton.

Uganda's HIV story offers a more pleasant contrast to South Africa's slow response. South Africa heads global HIV prevalence tables and has little to show in its fight against the virus. Uganda reduced HIV prevalence by two-thirds during the 1990s. Causes continue to be debated. Thornton points to the nature of Ugandan sexual networks. The South African sexual web is similar to information-technology networks with built-in redundancy: when one transmission node in the Internet breaks down, others take over and information continues to flow. The Ugandan network, Thornton believes, is more fragile. Government and community initiatives knocked out key transmission hubs and the whole network collapsed.

Uganda, even with the recent upsurge in infections, can justifiably look back with pride at its track record of HIV management. 'More of the same', with some fine-tuning as the epidemic evolves, is an adequate prescription. South Africa can learn much from Uganda's success.

What should the rest of the world do? Estimates of annual HIV infections have moved dramatically up and down in many countries in recent years, not because of actual changes in the number of new cases, but owing to refinements in the techniques used to measure them. However, the HIV epidemic seems to have peaked years ago in the United States and parts of Asia. The dreaded generalized epidemic of the South African kind has not, and probably will not, come to pass in populous China and India. HIV/AIDS prevention advocates, especially those who work for the Joint United Nations Programme on HIV/AIDS, are being cast as villains who are diverting resources away from other medical problems, such as diarrhoea

and pneumonia, that continue to kill millions. Meanwhile, even if global HIV transmission comes to a complete halt tomorrow, bills for the treatment of those who are currently infected will keep coming in and will need to be paid for decades by governments, donors, family members or patients themselves. Prevention efforts continue to make economic and humanitarian sense: an infection prevented today equals a lifetime of medical costs saved.

Unimagined Community shows how "social butterflies" and "open skies" are equally important for the transmission of HIV. The transmission networks are sustained by highly mobile infected people who change their sexual partners frequently. Thornton makes a strong case for uncovering the social factors that power these networks, and for developing new prevention efforts to counter them. Sex is a social act, not just a behaviour, so it follows that social interventions are necessary to curb the flow of infection.

The failure of ABC messages — "Abstain, Be faithful, use Condoms if you must graze" — to interrupt HIV transmission must be viewed in the light of Thornton's study. Sexual networks need to be understood and targeted alongside individual behaviour change. It is time to recruit anthropologists with the training and experience to carry out a professional analysis. ■

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BUBBLES PHOTOLIBRARY/ALAMY

Patients must have confidence in vaccines to maintain high levels of protection against disease.

Injecting trust into vaccines

Autism's False Prophets: Bad Science, Risky Medicine, and the Search for a Cure
by Paul A. Offit
Columbia University Press: 2008. 328 pp. $24.95, £14.95

Paul Offit's distinguished academic credentials and long-standing advocacy for vaccines in the United States provide the weight behind this forceful book. *Autism's False Prophets* focuses on the people and events in that country that were central to the claimed link between vaccination and autism. Written with passion, authority, bluntness and literary skill, it largely lives up to the back cover's promise of a 'page-turner'.

The text is rich in heroes and villains. The villains include litigious parents, publicity-seeking journalists, politicians, lawyers and environmental activists, lobbyists and expert witnesses. An assortment of quacks, zealots and incompetents, frequently from within the medical or allied professions, complete the roll-call of 'false prophets'. No wonder the public struggles to use good science as the sole arbiter for rational behaviour.

Offit does not underestimate the emotional and financial strains on parents whose children have autism, their compulsion to apportion responsibility for presumed damage, or their rich and positive experiences with their autistic offspring. He is sympathetic to parents who, impatient with the "glacial pace of medical research", all too often succumb to fashionable cures that fail to deliver. He dismisses the 300 or so US physicians who practice alternative and sometimes damaging 'remedies' for autism as "a cottage industry of false hope".

Two chapters cover the measles, mumps and rubella (MMR) vaccine controversy in the United Kingdom. In 1998, physician Andrew Wakefield published a highly flawed study in *The Lancet* proposing a 'link' between the MMR vaccine and autism. At a preceding press conference, he advocated the separation of MMR into three vaccines until the issue of safety was 'resolved'. Offit lays bare the weaknesses of Wakefield's discredited assertions and the questionable ethical practices associated with his work as a physician. Offit also covers the extensive, often uncritical reporting of Wakefield's view by the UK press, which collectively promoted the unwarranted public anxiety still responsible for the dangerously diminished uptake of the MMR vaccine in the United Kingdom.

Later chapters tell the tale of the mercury-containing compound thimerosal, used since the 1940s as an effective, convenient vaccine preservative. By the late 1990s, some vaccine scientists in the United States were calling for the precautionary abandonment of thimerosal. They feared the rare possibility of subtle neurological and psychological effects from the preservative, although evidence is negligible. In 1999, the US vaccine authorities announced the removal of thimerosal from vaccines, using tortuous sentiments to reassure: "The current levels of thimerosal will not hurt children, but reducing those levels will make safe vaccines even safer." In a chapter entitled 'Mercury Rising', Offit vividly describes how such weasel words opened the floodgates of public concern. Here, he misses an opportunity for international comparisons of scientific and public attitudes — thimerosal anxiety was mainly a US fixation, even though the same preservative was used in the United Kingdom and other countries.

Public belief that vaccines cause autism soon escalated, fuelled by environmentalists, lawyers, politicians and opportunistic scientists publishing in journals of mixed repute. The chapter 'Mercury Falling' describes how the accumulating scientific evidence, from more than 200 epidemiological and other analyses, led scientists to refute the notion that thimerosal causes autism. A major factor was that even after the abandonment of thimerosal, rates of autism continued to increase. Over time, the preservative was exonerated to the satisfaction of most critics.

In bemoaning today's withdrawal of trust

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The text is rich in heroes and villains. The villains include litigious parents, publicity-seeking journalists, politicians, lawyers and environmental activists, lobbyists and expert witnesses. An assortment of quacks, zealots and incompetents, frequently from within the medical or allied professions, complete the roll-call of 'false prophets'. No wonder the public struggles to use good science as the sole arbiter for rational behaviour.

Offit does not underestimate the emotional and financial strains on parents whose children have autism, their compulsion to apportion responsibility for presumed damage, or their rich and positive experiences with their autistic offspring. He is sympathetic to parents who, impatient with the "glacial pace of medical research", all too often succumb to fashionable cures that fail to deliver. He dismisses the 300 or so US physicians who practice alternative and sometimes damaging 'remedies' for autism as "a cottage industry of false hope".

Two chapters cover the measles, mumps and rubella (MMR) vaccine controversy in the United Kingdom. In 1998, physician Andrew Wakefield published a highly flawed study in *The Lancet* proposing a 'link' between the MMR vaccine and autism. At a preceding press conference, he advocated the separation of MMR into three vaccines until the issue of safety was 'resolved'. Offit lays bare the weaknesses of Wakefield's discredited assertions and the questionable ethical practices associated with his work as a physician. Offit also covers the extensive, often uncritical reporting of Wakefield's view by the UK press, which collectively promoted the unwarranted public anxiety still responsible for the dangerously diminished uptake of the MMR vaccine in the United Kingdom.

Later chapters tell the tale of the mercury-containing compound thimerosal, used since the 1940s as an effective, convenient vaccine preservative. By the late 1990s, some vaccine scientists in the United States were calling for the precautionary abandonment of thimerosal. They feared the rare possibility of subtle neurological and psychological effects from the preservative, although evidence is negligible. In 1999, the US vaccine authorities announced the removal of thimerosal from vaccines, using tortuous sentiments to reassure: "The current levels of thimerosal will not hurt children, but reducing those levels will make safe vaccines even safer." In a chapter entitled 'Mercury Rising', Offit vividly describes how such weasel words opened the floodgates of public concern. Here, he misses an opportunity for international comparisons of scientific and public attitudes — thimerosal anxiety was mainly a US fixation, even though the same preservative was used in the United Kingdom and other countries.

Public belief that vaccines cause autism soon escalated, fuelled by environmentalists, lawyers, politicians and opportunistic scientists publishing in journals of mixed repute. The chapter 'Mercury Falling' describes how the accumulating scientific evidence, from more than 200 epidemiological and other analyses, led scientists to refute the notion that thimerosal causes autism. A major factor was that even after the abandonment of thimerosal, rates of autism continued to increase. Over time, the preservative was exonerated to the satisfaction of most critics.

In bemoaning today's withdrawal of trust

from medical professionals, Offit risks overegging his case for science. Precaution is sometimes a wise basis for policy-making. Vaccine damage through unforeseen effects does occasionally occur and may be severe. As Offit reminds us, one in every 100,000 patients suffered paralysis as a consequence of the US swine flu vaccination in 1976. Such rare episodes do not detract from the transformational effect of vaccines. But they remind us that not all concerns about vaccines can be dismissed as irrational.

Offit reports the personal testimonies of caring parents to good effect, but despairs in equal measure about their lack of scientific credibility and strong emotional appeal. One celebrity mother of an autistic child said, for example, "My science is Evan, and he's at home." Offit is anxious about patients actively participating in their own medical care using the Internet. For him, scientifically sound information online is drowned by poorly substantiated opinion.

Yet Offit's arguments falter when he uses vaccine controversies as his indicator of the presumed ignorance of science by the public. Communicating risk is notoriously tricky. Vaccine uptake needs to be sufficiently high to ensure protection of the population through 'herd immunity'— a persuasive task made all the more difficult when individual patients are urged to accept responsibility for their health and embrace the principle of choosing a hospital or consultant.

Autism's False Prophets encapsulates the fanciful belief among scientists, not supported by those who research science communication, that understanding the science will inevitably tip the scales of public opinion. This stance was demonstrated earlier this year in a letter to *The Guardian* newspaper from David Salisbury, director of immunization at the UK Department of Health. It draws attention to the ongoing UK public information campaign for adopting a vaccine intended to protect young women from human papilloma virus, the cause of most cervical cancer. The campaign, Salisbury wrote, aims to ensure that "parents and young women have all the information they need to consent to this important vaccine". Absent in such sentiments is a belief in the necessity for dialogue with the public, entirely different in tone and purpose from the mistaken compulsion of some well-intentioned vaccine enthusiasts to inject hard facts into empty vessels. ■

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Dark materials: Karel Nel's art explores the seen and unseen Universe.

ART FIRST, LONDON

Q&A: Creations from the cosmos

Artist **Karel Nel** works with astronomers from COSMOS, the global Cosmic Evolution Survey that is mapping galaxies and dark matter. Now exhibiting his work in London, he tells *Nature* how his view of the Universe has changed.

How did you get involved in astronomy?
Artists and scientists have questioned the nature of reality for centuries. Feeling the need to grasp contemporary scientific paradigms, I had worked for decades at the interface between these disciplines when I met Nick Scoville, leader of the COSMOS project. He invited me to be its resident artist. It was a very steep learning curve: I felt like an ant being taught compound interest by an economist.

What does your work convey?
My art investigates seen and unseen worlds. COSMOS looks back in deep time at patterns of galaxy formation and large-scale structures, and from these, attempts to understand invisible dark energy and dark matter. I use metaphorical means to grasp these abstract ideas, as scientists often do. In my 20 exhibited works, I use mixed media including 540-million-year-old black carboniferous dust and white primordial salts from the oceans to present shimmering images of galaxies that emitted their light millions of years ago.

Have the scientists influenced your ideas?
Yes — representing the Universe is not like painting a traditional landscape; there are invisible as well as visible aspects to convey. Scientists have developed codes to deal with cosmic phenomena, and my work captures the unstable nature of our perceptions of this distant, unknown terrain. In one piece, dotted lines echo the grids found in astronomy textbooks, but also refer to invisible characters, as used in comic books. In another, I evoke the 'blind spots' of telescopes with amorphous dark shapes.

Did you influence the astronomers?
Many of the astronomers focus on incremental, detailed information, so my broad outsider's perception rekindled the extraordinariness of their endeavour.

What was it like, visiting observatories?
At the summit of Mauna Kea, Hawaii, some of the world's most powerful telescopes are trained on the powder-black darkness, looking at complexity and eternity. It is awesome and desolate. Even the scientists fall silent in the face of that. ■

Interview by **Jennifer Rohn**, a researcher at University College London, Gower Street, London WC1E 6BT, UK, and editor of www.lablit.com.
e-mail: jenny@lablit.com

The Brilliance of Darkness
Art First, 9 Cork Street, London W1S 3LL
Until 9 October 2008.

Enhance your life with *Nature* debates

Nature has picked two panels of experts in science, policy and ethics to debate research that is improving mental and physical abilities.

Enhancing the Brain: 13 October 2008
From intelligence to emotional tolerance, sleep requirements and memory power, how are developments in neuroscience affecting the individual and society? Panel: Barbara Sahakian, John Harris and Nick Bostrom.

Enhancing the Body: 10 November 2008
Studies of the human body are focusing on aspects such as speed, strength and healing or the tolerance of pain. But how will this science enhance the human body? Panel: Aubrey de Grey, Andy Miah and Kevin Warwick.

Nature debates will be held at 7pm at Kings Place, 90 York Way, London N1 9AG, UK.
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Beyond the greenhouse

Botanic gardens are using good garden design to attract and educate the public. **Mike Maunder** explains how they can thrive both as businesses and as institutions of learning.

The world's 2,500 botanic gardens are broadening their conservation purpose and embracing their cultural identity. Rallying to help overcome the challenges of the global biodiversity crisis, herbaria and seed banks have been rejuvenated. Meanwhile, an equally profound change has occurred in the public face of the botanic garden.

Botanic gardens retain their core functions of collecting and exhibiting plants for scientific and educational purposes. During the past 30 years, botany research at universities has declined and botanic gardens have become key to documenting plant diversity and promoting plant conservation, many as important players in the United Nations' Global Strategy for Plant Conservation (www.bgci.org/worldwide/gspc). As the extinction spasm accelerates, the skills of such institutions in managing threatened species will be vital. The accumulated plant collections, living and preserved, record what we are losing and offer resources for what we choose to restore. These collections are of immense scientific and cultural value, and their viability presents a financial and political challenge.

Botanic gardens are becoming sophisticated business entities and increasingly depend upon the financial patronage of the public. This is a profound change from the days when many gardens were supported by government funds and visitors were seen as an awkward impediment, coming between curators and horticultural perfection. During the past 20 years, botanic gardens have found a vibrant sense of mission as translators of environmental science to millions of people of all ages. They recognize that their future depends on conveying the importance of their work and establishing strong links with their local community.

Design for delight

This new social role has changed the design of botanic gardens dramatically. Compare the quiet, walled enclaves of the early Italian Renaissance botanic gardens with the space-age domes and invigorating botanical cabaret of the Eden Project in Cornwall, UK. The defining features of old botanic gardens have largely disappeared, such as the awkward opening times, miserable cafes and lack of any institutional interpretation. Gardens are now creating exhibits that inform and inspire: in the words of the philosopher and theologian Thomas Aquinas, "you change people by delight".

P. HYATT/TAYLOR CULLITY LETHLEAN WITH P. THOMPSON

The Royal Botanic Gardens at Cranbourne, Australia, convey the nature of the continent's 'Red Centre'.

This evolution is particularly notable in the latest desert botanic gardens. Here, an appreciation of local floras, declining natural resources and ethnobotanical heritage are influencing both mission and design. The Arizona Sonora Desert Museum was established as an early model of this in 1952 — a mix of botanic garden, zoo and museum, with a clear geographical and ecological identity. It has inspired a new generation of desert gardens. The Royal Botanic Garden near Amman in Jordan showcases the country's natural habitats and wild species; similarly, the new Oman Botanic Garden near Muscat exhibits native plants, ecosystems and ethnobotanical heritage. The Al Ain Wildlife Park in Abu Dhabi, set to open in 2010, will demonstrate the biodiversity and cultures of the world's desert ecosystems and reconnect the people of the United Arab Emirates with their desert heritage. In Australia, the Alice Springs Desert Park interprets the local ecology, culture and landscape. The spectacular new Australian Garden at the Royal Botanic Gardens, Cranborne, near Melbourne, abstracts those same landscapes into a contemporary garden design, acting as envoy for the culture and biology of the 'Red Centre'.

Strong collaboration between scientists and artists coupled with a locally focused mission defines the character of some new gardens. In the late 1990s, Mexican artists Francisco Toledo and Luis Zárate worked with anthropologist Alejandro de Ávila to create dramatic landscapes incorporating pre-Hispanic motifs in the Ethnobotanical Garden of Oaxaca, Mexico, celebrating the natural heritage of Oaxaca state. A similar approach can be seen in the First Nations Garden at the Montreal Botanical Garden, a cultural meeting place where the ethnobotany of Canada's Inuit and Native American cultures is exhibited and interpreted through habitat exhibits and storytelling.

China, with its traditions of academic botany and love of plants, has seen an extraordinary growth in botanic gardens in recent decades. From just 34 in 1960, China now boasts more than 160 gardens, housing some of the world's largest and richest cultivated plant collections. New gardens are being created, including the Shanghai Chenshan Botanical Garden, and existing gardens, such as the Hangzhou Botanical Garden, are being renovated as spectacular venues for the public display of botanical diversity. Similarly, the restored Hengchun Tropical Botanical Gardens in Taiwan reflect the geomorphological, ecological and cultural evolution of Taiwan and celebrate the beauty of the site's tropical-forest habitat.

This new emphasis on gardens as public

spectacles has arisen largely because of the recent interchange of designers between botanic gardens, museums and zoos. Landscape architecture studios — such as Jon Coe in Australia, or Jones and Jones, Field Operations and Portico in the United States — are applying techniques honed in zoos and museums to create innovative botanic-garden exhibits. Landscape architects experienced in designing for private clients are also creating astonishing botanic-garden landscapes; examples include the work of Raymond Jungles and Made Wijaya at the Naples Botanic Garden in Florida and Luis Vallejo's design for the Oman Botanic Garden.

Within the botanic-garden community, there is a palpable sense of confidence. New exhibition spaces showcase their vital scientific work and collections that had historically remained hidden from the visitor. For example, the public galleries of the Millennium Seed Bank at the Royal Botanic Gardens, Kew, UK, convey their role in conserving wild plant resources, and the Pfizer Plant Research Laboratory at the New York Botanic Garden invites visitors to see the workings of a major taxonomic research institute. "Where better than a botanic garden for people to understand the rapidly changing world, to grasp how to change their behaviour and to mobilize action for a sustainable future?" says Stephen Blackmore, regius keeper of the Royal Botanic Gardens in Edinburgh, UK.

Many botanic gardens and their buildings demonstrate sustainable maintenance and construction techniques. The new visitor centre at the Queens Botanical Garden, described as the greenest building in New York City, incorporates the use of solar and geothermal energy, waste-water recycling and composting toilets. As Queens' executive director Susan Lacerte says: "We are an environmental organization; if we are not going to build green, who is?"

B. FOSTER/EDEN PROJECT

The UK Eden Project promotes sustainability.

LIU BI-JIAN

A forest of fossilized and living trees at Shenzhen Fairy Lake Botanical Garden in Guangdong, China.

Crowd pleasing

Amid all this vigour, botanic gardens face a challenge: the temptation to reduce investment in plant collections — a core resource — and emphasize exhibits that generate income. The management of collections and the business of displaying them have historically been separate affairs, so it is encouraging to see important collections now being used in innovative ways. The new Rhizotron and Xstrata Treetop Walkway at the Royal Botanic Garden at Kew have brought life and a story to a traditional arboretum. Plant collections are increasingly packaged as habitats, either generically as desert or rainforest exhibitions, or specifically linked to conservation projects. For instance, the Lin Lougheed Spiny Forest exhibit at Fairchild Tropical Botanic Garden, Florida, is directly linked to supporting field conservation in Madagascar.

Art has always had a place in botanic gardens, and it is being used with gusto for interpretation and marketing. Previously hidden treasures are being given new homes, as with the botanical drawings at the Shirley Sherwood Gallery of Botanical Art at Kew. Some historical collections and landscapes are being given a contemporary interpretation. One example is sculptor Mark Dion's interpretation of botanist William Bartram's explorations of the southern United States in 1773, on show at Bartram's Garden in Philadelphia, Pennsylvania. Environmental degradation is highlighted in the provocative *Hard Rain* exhibit, which is touring various botanic gardens worldwide and combines the lyrics of Bob Dylan with Mark Edwards's apocalyptic photographs. Similarly, in the Garden of Extinction, designed by Willem Boshoff and installed at Kirstenbosch Botanic Garden in South Africa, rows of memorials represent 15,000 threatened or extinct plant species, with disturbing echoes of the First World War cemeteries in Belgium and France.

We have entered the age of blockbuster art in botanic gardens. Roy Lichtenstein's work has been exhibited at Fairchild Tropical Botanic Garden, Niki de St Phalle's art is displayed at Missouri Botanical Garden, St Louis, and Dale Chihuly has exhibited at Kew and the Atlanta Botanical Garden in Georgia. When successful, these shows have a steroidal effect on visitor attendance and membership.

The showman P. T. Barnum said "every crowd has a silver lining", and botanic gardens are using special events to attract new visitors and interpret big environmental issues. Events such as the Chocolate and Mango Festivals at Fairchild, for example, not only generate revenue and membership but also connect the public with the agricultural heritage of the tropics and the challenges of sustainable agriculture.

A deep satisfaction can come from experiencing the diversity and abundance of a good botanic garden, whether it contains tropical orchids and palms, an astonishing prairie reconstruction or a seasonal display of apples or chilli peppers. The challenge is to use that emotional response to change people's behaviour. Botanic gardens need to create landscapes and gardens that are attractive, vibrant and welcoming — otherwise, they will fail as businesses, and thence in their fundamental mission to inform and influence. ■

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More garden images at http://tinyurl.com/5yv2q8.

ESSAY

Beijing 1987: China's coming-out party

Two decades ago, Deng Xiaoping welcomed nations to an international meeting in Beijing. **Mohamed Hassan** recalls how China's leaders set out their plans for the nation to rejoin the world's scientific elite.

The memory is still fresh. On 12 September 1987, I flew into a Beijing airport that comprised a few badly maintained structures, no larger than a small provincial airfield. All around was peeling paint and dim lighting, no signs, no assistance and an anxious wait for luggage.

The drive from the airport was another eye-opener. The road we took was poorly paved. Street lighting was sporadic. A smattering of cars, mainly Japanese-made, had to make room for bicycles, wheelbarrows and the occasional donkey cart. Beijing was a busy, even frenetic place. It was certainly well cared for. But it was impoverished.

The Beijing from the window of my car was the image of China in the West. Yet, over the next five days, the idea of China as a poverty-stricken backwater, unable to harness new ways of learning and ultimately modernity, would be tested and changed forever.

As I and the other delegates were about to discover, China's most prominent officials and scientists all agreed that science and technology would be a key element in the country's plans to re-emerge as a global power. As one of my colleagues, MGK Menon, former chief scientific adviser to India's late prime minister Indira Gandhi, recalls today: "the state of science in China was a welcome surprise but largely because so little was known about it."

Drawn together

I was then starting my career at TWAS, then known as the Third World Academy of Sciences and the brainchild of the Pakistani theoretical physicist Abdus Salam. Salam had lured me to the academy from the University of Khartoum in Sudan, where I was a professor of mathematics, specializing in modelling the formation and the movement of desert dust and sand.

Salam knew China well; his contacts were at the highest levels. He also knew that China's leadership wanted both to open up to the West and to have a leading role for the developing nations of the South. So it was no surprise for me to learn that our second general conference would in effect become China's coming-out party — an opportunity for the country to show itself off to the world (both North and South) and a chance for enterprising scientists and policy-makers from the developing countries to learn from — and do business with — Beijing.

Salam had other reasons for wanting to work with China. He was a candidate for the job of running UNESCO, the United Nations Educational, Scientific and Cultural Organization. As a Nobel prize-winning professor at Imperial College London, Salam had little difficulty accessing the levers of power in the Anglophone world. But to secure the UNESCO post he needed the backing of countries elsewhere. Getting a nod from a permanent member of the UN Security Council, such as China, would certainly help.

China anew

The opening session took place in the Great Hall of the People two days later on 14 September. There were more than 150 participants from 50 countries, joined by an equal number from China. Given that this was a rare example of China putting its science on display, interest from the Western scientific community was high. International organizations represented in Beijing included the then International Council of Scientific Unions (ICSU), headed by Julia Marton-LaFèrre, the International Foundation for Science (IFS), the American Association for the Advancement of Science (AAAS) and the Science Council of Japan.

The Chinese Academy of Sciences, an institution that is key to understanding science in modern China, was our host. Whereas, in Western countries, government ministries, research funding bodies and scientists operate (mostly) independently of each other. In China (as in Russia), all three of these functions are rolled into a single state-run and state-funded academy of sciences. The Chinese academy, which was established just two months after the Communist takeover in 1949, had grown substantially in size and impact over the next two decades. However, the assault on intellectuals during the 10-year Cultural Revolution severely put back the academy's work.

> "The state of science in China was a welcome surprise but largely because so little was known about it."

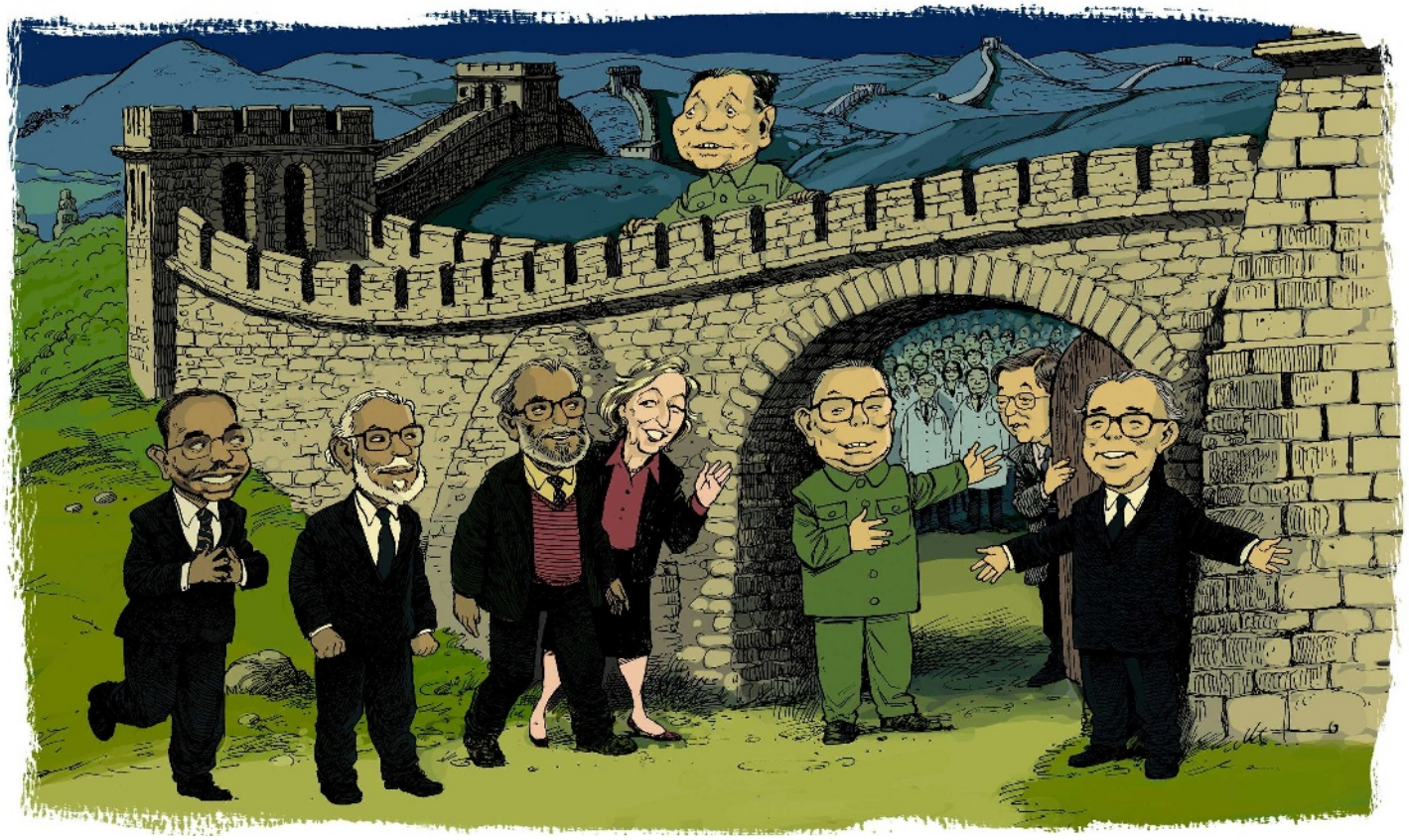
The scars of this period had clearly not yet healed for many of the Chinese speakers at the 1987 conference. In his opening address, Zhou Guangzhao, then president of the Chinese Academy of Sciences, described the Cultural Revolution as a "disaster" for China. Similarly, Zhao Ziyang, general secretary of the Communist Party, said that bullying and humiliation had characterized the Cultural Revolution.

China's leader, Deng Xiaoping, later told Salam that if China did eventually join the ranks of developed nations, it would never forget its history and where it came from: that it would always see itself as a developing country first and foremost. But that said, out of the embers of the Cultural Revolution, it harboured larger ambitions.

Too often, the main message coming out of conferences on science and technology in developing countries was (and still is) one of inadequate salaries, low standards of research and development, poor working conditions and either political apathy or excessive political interference. Beijing 1987 could have been the same. However, our hosts were determined to show that they would not be defined by the past.

We learnt from the opening talks that, in 1949, China, with a population of nearly 550 million, had just 50,000 people recorded as working in science and technology in some 30 scientific institutes. But by 1985, the country had more than 10 million people working in almost all fields of science and technology, including 300,000 active researchers. The Chinese Academy of Sciences alone had 80,000 scientists working in more than 120 research institutes. The academy system was complemented by a rapidly growing system of higher education consisting of 2 million students in more than 1,000 universities.

We also learnt that China's scientists had been busy pushing the envelope in a diverse set of research fields. Among other achievements, they had synthesized bovine insulin, carried out research into low-temperature, high-conducting materials, launched 19 satellites and developed an extensive nationwide remote-sensing system. In agriculture, China had eliminated the wheat-rust fungus and created hybrid rice varieties, allowing improved crop yields. In health care, vaccines had led to significant reductions in the incidence of diseases such as diphtheria, scarlet fever and polio.


D. PARKINS

Listening to the presentations and observing China's scientists, it became clear that this kind of progress was different from that taking place in other Communist countries — especially the Soviet Union. Unlike former Soviet Russia, for example, China had no problems in acknowledging that it would need access to Western science and technology to innovate. At the time of the conference, an estimated 100,000 students from China had studied or worked abroad (mostly in Western countries) and then returned home to help build their nation's infrastructure. This number is now in excess of one million.

Finally, we learnt that China, which had begun to open the door of scientific exchange with both developed and developing countries, was eager to collaborate with partners in a broad range of fields. To facilitate this, Chinese officials announced that they would be hosting a TWAS–China field office inside the Chinese Academy of Sciences.

This was a truly transformational moment. China was telling us that it was no longer alone in science, that it would welcome opportunities to become part of the international scientific community and that it was eager to join with others both to enhance its own capabilities and to help address critical global challenges in both science and society. Biotechnology, materials science, particle physics and space science were about to get a new major partner, and both China and the rest of the world would benefit as a result.

Back to the future

I returned to China in October 2003 to celebrate TWAS's 20th anniversary. My journey began in Trieste and ended at Beijing's international airport, just as it had 15 years earlier. The opening ceremony, just as before, was held in the Great Hall of the People.

I may have followed the same roads to the same places in Beijing, but so much else had changed. The airport was a gleaming new state-of-the-art facility and one of the biggest and busiest airports in the world. The tree-lined avenues that led from the airport to the city centre were jammed with automobiles and taxis, and framed by sleek apartment houses, office buildings and commercial establishments. Enormous holes in the ground, shadowed by large construction cranes overhead, foretold of larger structures to come, including the venues for the 2008 Olympics.

Hu Jintao, China's president, spoke at the opening ceremony in front of 3,000 people. The audience consisted not just of scientists and political leaders from around the world, but also of many young Chinese students who filled the outer reaches of the great hall. Earlier that day, Hu had congratulated China's first astronaut, Yang Liwei, who had just returned home after completing a 21-hour, 14-orbit journey around Earth. The space flight, President Hu observed, constituted "another important step for the Chinese people scaling to the summit of world science and technology".

> "Our hosts were determined to show that they would not be defined by the past."

As I listened to President Hu and peered at the audience beyond the podium, I could not help but think that one of the most important first steps in China's rebirth as an international scientific powerhouse took place in the same hall in 1987. The promise of modern science and technology in China that I had first glimpsed 15 years ago had been fulfilled. ■

Mohamed Hassan is the executive director of TWAS, the academy of sciences for the developing world in Trieste, Italy. He was a participant at the academy's second general conference, held in Beijing from 14–18 September 1987.
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For more Meetings that Changed the World, see www.nature.com/nature/focus/meetings

NEWS & VIEWS

SENSORY ECOLOGY

In sight of speciation

Mark Kirkpatrick and Trevor Price

Adaptation of a fish's eyes to its visual environment can bias females to mate with different males according to their coloration. This sensory preference can contribute to the formation of new species.

How and why do barriers that prevent mating between species evolve? On page 620 of this issue, Seehausen *et al.*[1] present a rich and eclectic data set that suggests a key role for vision in African cichlid fishes. It has been shown in other fish that natural selection tunes eyes to their visual environment, so that individuals can best see not only what they eat and what eats them, but also members of their own species[2–4]. Seehausen *et al.* carry this story a step further with work on fish in which the males are either red or blue (Fig. 1), and which have genetic variation for visual sensitivity to those colours.

In some populations, females with blue-biased vision seem to mate only with blue males, whereas red-biased females mate only with red males. The inference is that natural selection acting on the visual system contributes to reproductive barriers and the formation of new species. In short, what you see determines what you get, and with whom you get it on. More controversially, the authors suggest that these barriers might arise within a population, and do not, as has previously been thought, require a phase in which red and blue populations evolve in geographical isolation.

The biological and ecological setting for this story is dramatic — the cichlid fish in the Great Lakes of Africa. These fish are the most rapidly speciating organisms on Earth, and this explosion of life has produced a panoply of colour, morphology and behaviour, a sampling of which can be seen at your local pet shop. The fish in Lake Victoria, where the present study[1] was done, show a fantastically high rate of speciation. More than 500 species inhabit the lake. They may have originated just a few hundred thousand years ago[5], and possibly went through a period of large-scale interbreeding 20,000 years ago[6].

The lake has diverse visual environments. Starting at the shore and descending along the lake bottom, red becomes increasingly dominant in the ambient visual spectrum. This spectral shift is rapid at some sites and more gradual at others. To study how the fish have adapted to these conditions, Seehausen *et al.* wanted to know what the fish see. They identified genetic variants (alleles) in one of the opsin genes responsible for tuning the fish's visual sensitivity to different colours. By expressing these genes *in vitro* and measuring the absorption properties of the resulting proteins, they found some variants that are red-biased in their sensitivity and others that are blue-biased. The red-biased variant is typically found in fish living at greater depths than the blue-biased one.

The numbers of males with red, blue and intermediate coloration vary between populations. At sites where the spectral shift is neither very rapid nor very gradual, notably Makobe island, blue males are confined to the shallows and red males to greater depths. At this site, the great majority of blue males carry the blue-biased opsin variant, whereas most red males carry the red-biased one. The two colour morphs also show differences in other genetic markers, suggesting that they are nascent species. At sites where the spectral shift is rapid, however, the colour forms interbreed, presumably because they encounter each other frequently.

Is beauty just in the eye of the beholder? In mate-choice experiments using fish from controlled crosses, Seehausen *et al.* find that the opsin variant alone does not strongly determine mating preference. Segregation of the colour morphs by depth in the lake must mean that the fish mainly encounter and hence mate with their own kind. It is not difficult to imagine that fish prefer to spend time in habitats in which they see best — that is, visual tuning could generate a type of habitat preference that

O. SEEHAUSEN & I. VAN DER SLUIJS

Figure 1 | Seeing red doesn't get you blue. These cichlid fish are examples of the colour morphs investigated by Seehausen *et al.*[1] in their study of visually determined mating preference.

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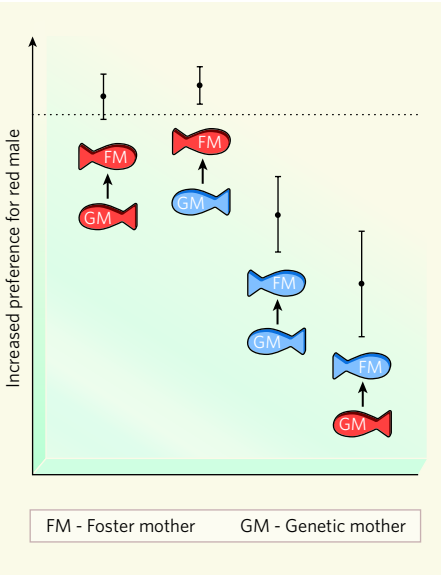

Figure 2 | The mother who raised you determines with whom you mate. In choice tests[7] with mouth-brooding cichlids, female fish raised by foster mothers belonging to different species from their genetic mothers preferred males of that different species. The stylized pictures are of males; females are dull and generally similarly coloured. The preference was measured by the difference in the number of approaches per male display when female fish are given a pairwise choice (with standard errors; dashed line indicates random choice). This evidence suggests that learning at a young age contributes to reproductive isolation in cichlids, in addition to other mechanisms such as the action of natural selection on vision described by Seehausen and colleagues[1]. (Modified from ref. 7.)

contributes to speciation above and beyond its effects on mate choice.

But is even this enough? Other findings point to an additional mechanism that complements reproductive isolation via vision. The females of these remarkable fish brood their eggs in their mouths, then guard the young fry after they hatch. In experiments reported last year, Verzijden and ten Cate[7] swapped eggs between the mouths of red morph and blue morph mothers. Females raised from the experimental broods strongly preferred males from their foster morph over those of their own morph (Fig. 2). As females of the two species look very similar, it is unclear whether the offspring preference is based on colour or some other correlated cue such as odour. Regardless of that, learning at a young age (sexual imprinting) apparently contributes to reproductive isolation in these cichlids, as it does in other groups such as birds[8]. The implication is that assortative mating — the tendency of like to mate with like — can arise whenever male characteristics diverge in response to differences in the environment, which might happen even without divergence in the opsin pigments. It remains to be seen if imprinting, vision and perhaps other mechanisms have been sufficient to generate new species without geographical isolation.

An intriguing observation mentioned by Seehausen *et al.*[1] is that the red- and blue-biased opsin alleles are evolutionarily much older than the species studied here. Red and blue colour morphs are found in other species of cichlid[9], suggesting that the colour polymorphism may also be ancient. Perhaps one key to the spectacular species radiation of African cichlids is that they inherited from distant ancestors a trove of genetic variation for sensory systems and male signals, possibly contributed during the inferred episode of interbreeding 20,000 years ago. This variation is entrained again and again in speciation events. To systematists, these events represent independent nodes on the evolutionary tree. From the fish's point of view, however, they are perhaps more like an evolutionary play that is re-enacted, night after night, with the same genetic cast. ■

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CLIMATE CHANGE

When did the icehouse cometh?

Stephen F. Pekar

The concentration of atmospheric carbon dioxide decreased between 45 million and 25 million years ago, a trend accompanied by glaciation at the poles. Modelling results suggest when and where the ice closed in.

As atmospheric carbon dioxide is predicted to rise to concentrations not seen in perhaps 25 million years (Myr)[1], scientists are working to understand the impact on Earth's climate and ice sheets. This requires a shift in perspective: geologists typically use the present as a key to the past, but in this case the past might well be the key to predicting how climate will change in the future.

The concentration of CO_2 in the atmosphere is predicted to increase to between 500 and 900 parts per million (p.p.m.) by the end of this century. Geochemical proxies indicate that the last time CO_2 levels were that high was about 45 to 25 Myr ago[1]. This was when Earth changed from a generally ice-free 'greenhouse world' to a more heavily glaciated 'icehouse world'[2,3], with atmospheric CO_2 gradually decreasing from more than 1,000 p.p.m. to near pre-industrial levels (280 p.p.m.)[1]. So how did the falling atmospheric CO_2 concentrations affect ice-sheet development during this period? On page 652 of this issue, DeConto *et al.*[4] use numerical modelling to constrain the timing of the initiation of glaciation in relation to decreasing levels of CO_2. Their results not only address a long-standing geological debate, but are also relevant to today's discussion about climate change.

Given the current interest in the effects of CO_2 on climate, it may be surprising to learn that there is a great deal of uncertainty about the extent of ice sheets, and the causal factors in their development, during the last period when atmospheric CO_2 concentrations reached levels as high as those predicted for the end of this century. Some information can be gleaned by studying the remains of shells from foraminifers — single-celled marine organisms — of that period. The ratio of oxygen isotopes in the shells depends on both the temperature and the isotopic composition of the water in which the foraminifers lived. The isotopic composition, in turn, was controlled by the ice volume at the poles, and by the evaporation–precipitation history of the water when it was near the ocean's surface. By contrast, the ratio of magnesium to calcium in the shells is controlled mainly by the seawater temperature alone. By measuring the two ratios, the isotopic composition of sea water can be calculated and used to constrain the polar ice volume for the period in which the foraminifers were alive.

The data suggest[5,6] that the ice volume was much larger than could be reasonably placed on the Antarctic continent. These high ice-volume estimates, combined with evidence of ice-rafted debris off the coast of Greenland, raise the possibility that glaciation in the Northern Hemisphere might have developed about 40 Myr earlier than was previously thought (that is, up to 44 Myr ago, rather than 3 Myr ago).

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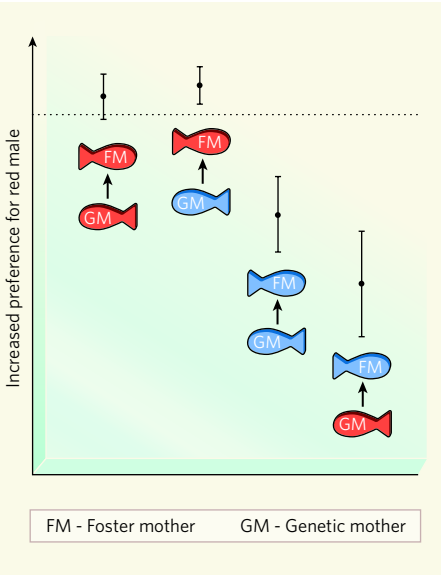

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45 to 25 Myr ago, the oxygen-isotope composition of ancient glacial ice, and the expected effects of these parameters on deep-sea records from foraminifers. Their results show that continental-scale Antarctic glaciation would not have developed until CO_2 concentrations reached about 750 p.p.m. — which occurred in the early Oligocene period, 34 to 32 Myr before present (Fig. 1). However, they also predict that the threshold for significant ice-sheet development in the Northern Hemisphere is much lower (280 p.p.m.), and would have occurred about 25 Myr ago.

The authors' results show that, for glaciation to have occurred in the Northern Hemisphere, the drop in CO_2 at the start of the Oligocene must have resulted in CO_2 concentrations far below those estimated by geochemical proxies. They conclude that a unipolar glacial world developed for the first time about 34 Myr ago, coeval with a decrease in water temperature at the sea bottom that was not registered in previously recorded proxy data. These findings are supported by new data from pristinely preserved foraminiferal shells of that period, which show that significant bottom-water cooling must have occurred at the same time that Antarctic ice sheets grew to near modern-day volumes[7]. The new foraminiferal data are also in good agreement with stratigraphic records of sea-level change from sediments that were deposited on mid- to low-latitude continental margins[8,9].

DeConto and colleagues[4] also show that, at the CO_2 concentrations that occurred during the middle to late Eocene epoch (45 to 34 Myr ago), small, ephemeral ice sheets could have existed on the highlands of Antarctica — even though CO_2 concentrations were up to six times those of pre-industrial levels. Their conclusions are consistent with ice-volume estimates from stratigraphic records from non-polar continental margins[9,10]. Similarly, the authors demonstrate that small, isolated sheets of glacial ice could have formed in the Northern Hemisphere during the cooler intervals of the Eocene and Oligocene, especially during periods when variations in Earth's orbit produced relatively cold northern summers. This could explain why ice-rafted debris existed off the coast of Greenland during the late–middle Eocene (about 44 Myr ago)[6] without having to invoke the presence of massive continental ice sheets. The transient glacial ice in the Northern Hemisphere might have left a sedimentary record, but would have had insufficient volume to be detectable in oxygen-isotope records.

One of DeConto and colleagues' more intriguing conclusions is that, once CO_2 reached near present-day concentrations (about 25 Myr ago), large ice sheets could develop in the Northern Hemisphere during favourable orbits of the Earth. Given that the East Antarctic Ice Sheet is believed to have responded little to changes in climate once it reached near-continental size[11,12], the large variations in ice-volume indicated in isotopic and stratigraphic records[8] younger than 25 Myr old could therefore be explained in part by episodic ice-sheet growth in the Northern Hemisphere. This suggests that substantial ice growth in the Northern Hemisphere might have started up to 20 Myr earlier than previously believed — up to 25 Myr ago, rather than in the Miocene to the Pleiocene epochs 7 to 3 Myr ago. But there is currently scant evidence to suggest that large amounts of glacial ice existed in the Northern Hemisphere before the late Miocene. In addition, the large changes in ice volume suggested by proxy data for the period in which CO_2 reached near-present-day concentrations (less than 25 Myr ago) do not bode well for long-term sea-level changes in the future, as they suggest that small variations in CO_2 might have large effects on ice volume.

With such a paucity of information about the timing of Earth's ice development (especially in the Northern Hemisphere), there is a clear need for data from high-latitude sites in the Northern Hemisphere and around Antarctica to test DeConto and colleagues' conclusions. Fortunately, help is on its way, as several upcoming projects[13–15] will target strata from the greenhouse–icehouse transition in Antarctica, and are expected to provide additional insight into ice-sheet development in the region during this critical time interval. ■

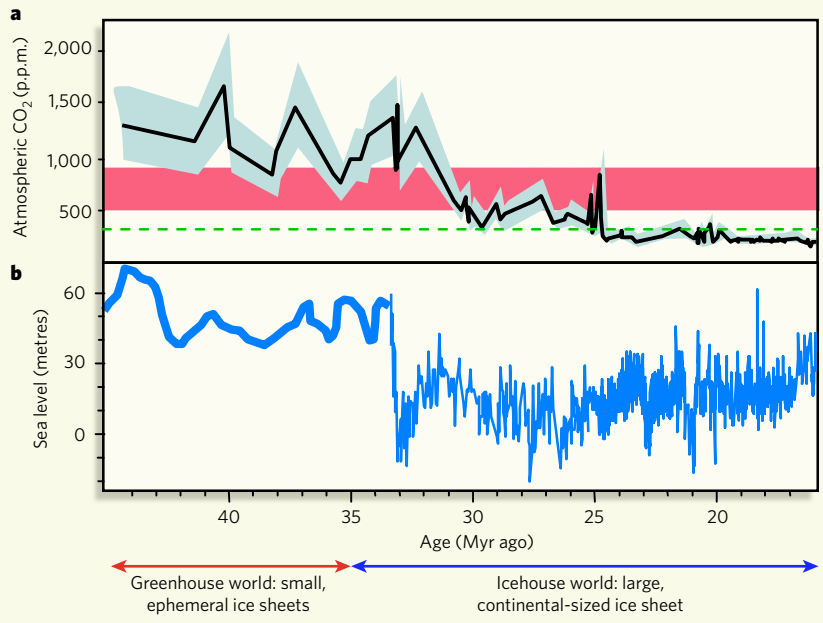

Figure 1 | Atmospheric carbon dioxide at the start of large-scale glaciation. About 34 million years (Myr) ago, Earth changed from a greenhouse world (which was generally ice-free) to an icehouse world (which was heavily glaciated). **a**, The concentration of atmospheric CO_2 during this period declined drastically, reaching pre-industrial levels (280 p.p.m., dashed line) about 25 Myr ago. Grey shaded areas represent the uncertainty in the estimates; the red shading shows the range of CO_2 values predicted for the latter part of this century[16]. Estimates of CO_2 concentrations are taken from ref. 1. **b**, Global sea level shows a downward trend. Zero represents sea level when Antarctica is fully glaciated, and increasing values indicate higher sea level (that is, lower ice volume). DeConto and colleagues' model[4] of global climate and ice-sheet formation suggests that, when Earth was a greenhouse world, short-lived glacial formation could occur at a small scale. But when Earth entered its icehouse phase, a large, continental-sized ice sheet formed, with a correlated lowering of the sea level. Apparent sea-level (ASL) estimates from 45 to 34 Myr ago are modified from ref. 9; ASL estimates from 34 to 16 Myr ago are modified from ref. 8.

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REGENERATIVE MEDICINE

Short cut to cell replacement

Robert Blelloch

To make one differentiated cell type from another, a 'stopover' at an undifferentiated state is often required. An alternative method offering an efficient direct route could have implications for disease treatment.

Regenerative medicine aims to repair diseased or damaged tissues by replacing the affected cells with healthy, functional cells of the same type. The prospects of this discipline have been boosted by the promise of embryonic stem (ES) cells, which are pluripotent — that is, they can differentiate into any cell type — and which can be maintained in culture to 'self-renew' indefinitely. Indeed, recent breakthroughs both in the production of patient-specific ES-like cells and in inducing the differentiation of ES cells into functional adult tissues have provided further hope[1]. Like all promising therapies, however, the use of ES cells has its challenges, among them the difficulties associated with efficiently transplanting and integrating the generated tissue into the physiological framework of the body. On page 627 of this issue, Zhou *et al.*[2] describe an approach whereby differentiated adult cells of one type can be directly and efficiently converted into functional cells of another type within an organism and without the need to first reprogram them into an ES-cell-like state.

As an organism develops, its cells become increasingly specialized, losing their developmental potential (Fig. 1a). This differentiation process involves silencing of gene networks that are no longer needed and activation of other specific networks. These networks are regulated at various levels. First, the RNA and protein composition of a cell drives a specific gene-expression program that is often self-reinforcing. Second, the packaging of DNA — the epigenetic program — affects the access of gene transcription factors to specific genomic regions. Finally, in exceptional cases, the DNA sequence itself can be irreversibly altered. Each of these mechanisms further locks down the developmental potential of the differentiating cell.

For many years, it was presumed that once a cell differentiates, it burns all bridges behind it. But the discovery, first in amphibians and then mammals, that a fully differentiated cell can be manipulated to 'dedifferentiate' (Fig. 1b), and revert to a state resembling that of an early embryonic cell, proved this presumption incorrect. Dedifferentiation can be triggered by either placing the nucleus of a differentiated cell in the cytoplasmic milieu of an egg cell[3] or — as was shown relatively recently[4] — by introducing just four specific transcription factors into the differentiated cell. The latter finding has given a huge boost to the field of regenerative medicine as it indicates that the production of pluripotent cells from many sources, including patients with specific diseases[5,6], can be relatively straightforward. A crucial goal now is to ensure the safety of such induced pluripotent stem cells and to differentiate them into cells that can be used to repair damaged tissue.

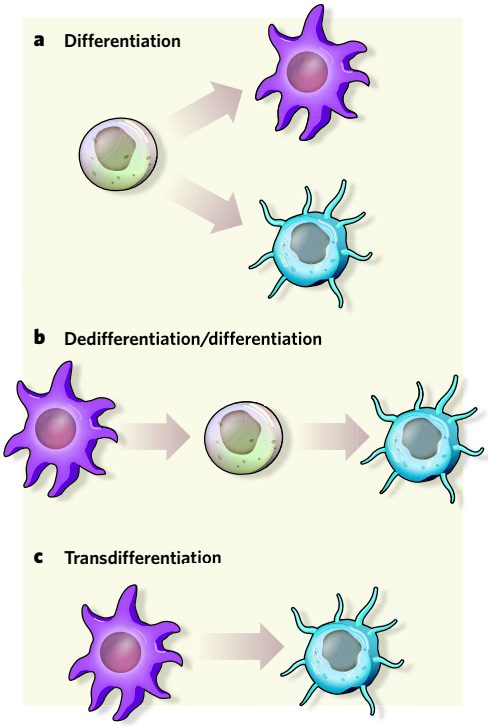

Figure 1 | The regenerative-medicine toolbox. a, During development, non-specialized cells with a broad developmental potential differentiate into various highly specialized cells that have limited developmental potential. **b**, Nonetheless, in the lab, these highly specialized cells can be induced to dedifferentiate — that is, revert back to an earlier stem-cell fate with a broad developmental potential. The cells generated in this way can then be triggered to differentiate into another cell type. **c**, Alternatively, in some circumstances, as Zhou *et al.*[2] show, a highly specialized cell can be induced to transdifferentiate into another specialized cell, bypassing the intermediate step of dedifferentiation.

Transdifferentiation — the direct conversion of one differentiated cell type to another (Fig. 1c) — provides an alternative strategy for repairing damaged tissue. In the early 2000s, this approach received a lot of publicity when several reports suggested that transdifferentiation occurs spontaneously across a wide range of tissues[7]. It was soon realized, however, that what was perceived as spontaneous transdifferentiation was, in fact, the result of cell fusion[7]. Although this realization dampened the general excitement, it did not deter many researchers, who continued to pursue the possibility of inducing transdifferentiation through the introduction of specific 'master regulators' to cells.

In the field of diabetes, for example, efforts were concentrated on generating pancreatic insulin-producing β-islet cells by inducing transdifferentiation of liver cells[8]. In 2003, two groups reported[9,10] that when the gene for either of the transcription factors Pdx1 or NeuroD1 — the latter was used together with the growth factor betacellulin — is directly introduced into the liver of adult mice (using adenoviruses as gene vectors), liver cells transform into long-lived insulin-producing cells. Moreover, these transdifferentiated cells could correct high blood-glucose levels following chemically induced injury of β-islet cells. Nonetheless, the efficiency of this approach was low, and it was unclear which liver-cell type underwent transdifferentiation.

Zhou *et al.*[2] now elegantly marry previous approaches used for inducing transdifferentiation with those that led to the discovery of the four main transcription factors required for dedifferentiation[4]. The outcome is efficient production of β-islet-like cells from a distinct, highly specialized cell type in the pancreas known as exocrine cells.

Using previous data from many labs[11], the authors identified nine genes that are essential to the embryonic development of β-cells. They used adenoviruses to introduce different combinations of these nine genes into the pancreas of adult mice and found that the introduction of a set of three transcription factors (Ngn3, Pdx1 and Mafa) induces transdifferentiation of an impressive 20% of the manipulated exocrine cells into β-islet-like cells. The authors used a combination of cellular markers and lineage-tracing experiments to prove that the cells that underwent transdifferentiation were, indeed, exocrine cells.

Zhou and colleagues' transdifferentiated β-islet cells resemble these cells' natural counterparts in several important aspects, including the proteins they express; their morphology; and their ability to secrete active insulin, which could diminish high blood-glucose levels following chemically induced pancreatic injury. However, unlike their natural counterparts, these cells do not form, or become incorporated into, islets — islands consisting of β-islet cells, other endocrine cells and blood vessels. Nonetheless, they do form intimate contacts with blood vessels, presumably allowing them to sense blood-glucose levels and release insulin into the circulation accordingly.

These exciting results lead to many intriguing questions. For instance, does transdifferentiation involve epigenetic reprogramming or is the nuclear content of exocrine cells already permissive for the activation of the transcriptional program required for β-islet-cell

formation? And how developmentally distant can the cell of origin and the target cell be for this approach to work? Exocrine cells and β-islet cells share a common precursor. When Zhou *et al.* used the same factors to induce transdifferentiation of more distantly related fibroblast cells or muscle cells into the β-islet-like cells, the approach failed. Could it be that the inclusion of other factors allows transdifferentiation of more distantly related cells?

Considering the many problems associated with the use of viral vectors in gene therapy[12], finding alternative ways to induce the expression of the three transcription factors in the exocrine cells of an organism would be especially useful. Can the virus-mediated introduction of genes for Ngn3, Pdx1 and Mafa be substituted with transient introduction of non-DNA elements such as RNAs, recombinant proteins or chemical mimics of these factors, which may be safer? Indeed, the transdifferentiation process that Zhou *et al.* describe occurred rapidly and did not require ongoing expression of the virally introduced genes, suggesting that transient non-DNA-based approaches might succeed. No matter what the answers to these questions are, the authors' findings[2] remind us that the field of regenerative medicine must pursue several strategies to uncover the best therapeutic solutions to degenerative diseases. ■

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Human immunodeficiency virus type 1 (HIV-1) must have been spreading through the human population long before AIDS was first described in 1981, but very few strains from this 'prehistoric' period (pre-1980s) have been characterized. Viral sequences from earlier times can provide insight into the early spread of HIV-1, because the rapid rate of evolution of this virus — up to a million times faster than that of animal DNA — means that substantial amounts of sequence change occur in a matter of decades[1]. On page 661 of this issue, Worobey *et al.*[2] describe the sequences of partial genome fragments of HIV-1 from a lymph-node biopsy collected in 1960 in Léopoldville (now Kinshasa, Democratic Republic of the Congo). They compare these sequences with those of other HIV-1 strains, shedding light on the early evolution and diversification of this virus in Africa.

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DRC60 is not the first 'ancient' HIV-1 sample to be characterized: viral sequences from a blood-plasma sample originally obtained in 1959 — also from Léopoldville — were published 10 years ago[5]. The importance of DRC60 is that it is highly divergent from the 1959 sample (ZR59), which was most closely related to the ancestor of subtype D, thus directly demonstrating that, by 50 years ago, group M HIV-1 strains had already undergone substantial diversification.

The ZR59 and DRC60 sequences differ by about 12%, a value similar to distances now seen between the most divergent strains within subtypes. As the positions of ZR59 and DRC60 within the group M phylogeny indicate that the various subtypes already existed 50 years ago, simple extrapolation suggests that these two viral sequences had a common ancestor at least 50 years before that. For a more robust estimate of the date of the common ancestor of HIV-1 group M strains, Worobey and colleagues used state-of-the-art statistical analyses, allowing a variety of models for the growth of the HIV-1 pandemic and variable rates of evolution. The different analyses gave broadly similar

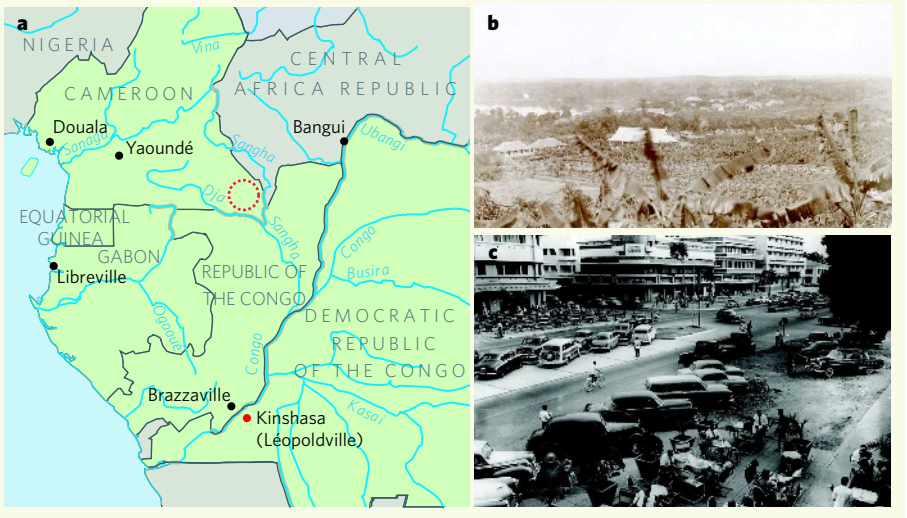

Figure 1 | Origin of pandemic HIV-1. a, Map of west-central Africa showing major rivers, and cities with explosive population growth in the twentieth century. Chimpanzees carrying the SIV strains most closely related to the viruses of HIV-1 group M, such as that described by Worobey *et al.*[2], have been found in southeast Cameroon (red ring). **b**, Léopoldville in 1896 (view from Mount Léopold) and **c**, around 1955 (the commercial centre).(Photos F. L. Michel (**b**) and C. Lamote (**c**), collection of the Royal Museum for Central Africa, Tervuren, Belgium.)

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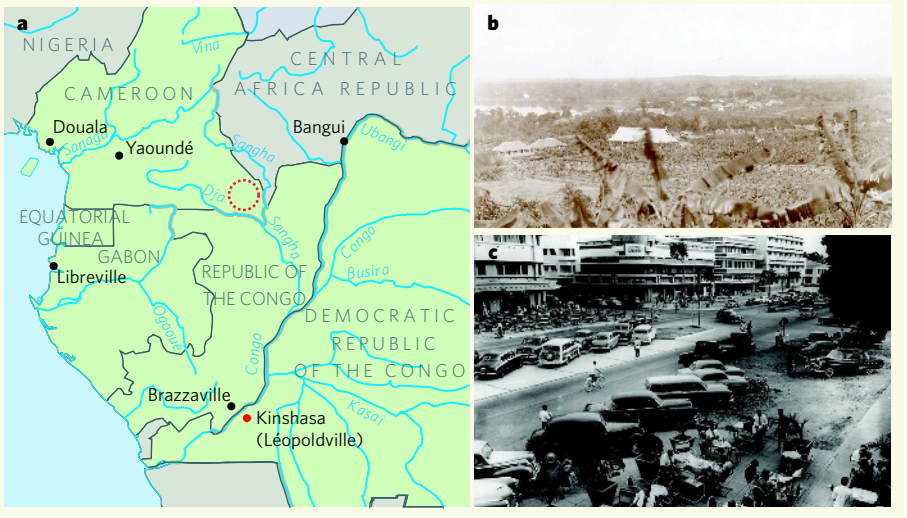

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The interpretation that HIV-1 was spreading among humans for 60–80 years before AIDS was first recognized should not be surprising. If the epidemic grew roughly exponentially from only one or a few infected individuals around 1910 to the more than 55 million estimated to have been infected by 2007, there were probably only a few thousand HIV-infected individuals by 1960, all in central Africa. Given the diverse array of symptoms characteristic of AIDS, and the often-long asymptomatic period following infection, it is easy to imagine how the nascent epidemic went unrecognized. Conversely, such a low prevalence at that time implies that the Congolese co-authors of the paper[2] were very lucky to come across this infected sample, even if most infections were concentrated in the area of Léopoldville. But can we trust these sequences?

In work on ancient DNA, contamination is especially problematic, and the work should, if possible, be replicated in other laboratories. For DRC60, independent analyses were performed at the University of Arizona and Northwestern University, Illinois. The sequences obtained were similar, but not identical, exactly as expected when samples come from the diverse set of related viral sequences that — because of the virus's rapid rate of evolution — arise within an infected individual[6]. Furthermore, the distance along the evolutionary tree from the group M ancestor to the ZR59 or DRC60 sequences is much shorter than those between the ancestor and modern strains, consistent with the earlier dates of isolation of ZR59 and DRC60, and confirming that these viruses are indeed old.

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The answer may be that, for an AIDS epidemic to get kick-started, HIV-1 needs to be seeded in a large population centre. But cities of significant size did not exist in central Africa before 1900. Worobey and colleagues[2] reproduce demographic data showing the rapid growth of cities in west-central Africa during the twentieth century. Léopoldville was not only the largest of these cities, but also a likely destination for a virus escaping from southeast Cameroon. In the early 1900s, the main routes of transportation out of that remote forest region were rivers; those surrounding this area flow south, ultimately draining into the Congo River, and leading to Léopoldville (Fig. 1).

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APPLIED PHYSICS

Virtues of diamond defects

Michael Romalis

A general method for detecting nuclear magnetic resonance signals from a single molecule has so far been elusive. Magnetic sensors that exploit crystal imperfections in diamond might make such a method a reality.

The phenomenon of nuclear magnetic resonance (NMR), which results from the interaction of the spin of an atomic nucleus with an external magnetic field, has successfully been exploited in such disparate techniques as the structural analysis of molecules (NMR spectroscopy) and structural and functional analysis of the human body (NMR imaging), thus spanning length-scales from ångstroms to metres. But these techniques have remained mostly bulk methods, in that they usually require more than a billion spins. Writing in this issue, Maze *et al.*[1] (page 644) and Balasubramanian *et al.*[2] (page 648) describe a new approach to NMR detection that exploits a single spin associated with a crystal imperfection — a 'nitrogen-vacancy centre' — in diamond to achieve unprecedented magnetic-field sensitivity on the nanometre scale. Crucially, the approach works at room temperature, a key requirement for biological applications.

The ideal imaging technique would be passive, applicable to all materials, and have spatial resolution on the atomic scale. In fact, nature provides us with the means for achieving such imaging. Electrons and many nuclei have a finite magnetic moment associated with their spins, and thus create weak magnetic fields around themselves. All one needs, then, is a magnetic sensor with high enough sensitivity to measure these fields.

Several magnetometry techniques have been considered for this purpose, but they mostly fall short of the required sensitivity. The sensitivity of existing magnetic-field sensors improves with their characteristic length-scale (r) approximately to the power 3/2 ($r^{3/2}$). But the magnetic field generated by the magnetic moment of a single electron or proton drops with the third power of the distance from the spin (r^{-3}). Thus, the best hope for detecting magnetic fields from single spins comes from sensors on the nanometre scale.

A milestone in this direction was achieved a few years ago when a cantilever with a magnetic tip was used to detect the magnetic field created by the spin of a single electron[3]. Further improvements to this approach, known as magnetic resonance force microscopy (MRFM), might allow detection of the magnetic field produced by a single nuclear spin, which is a thousand times smaller than that produced by an electron's spin. But MRFM remains a challenging method because it requires a cryogenic environment and prolonged data averaging.

Optical methods involving scattering of light have long been used to study single particles. This is because it is relatively straightforward to detect individual photons. In some atomic systems, the scattering of photons can be made to depend on the direction of the particle's spin, allowing individual spins to be detected. Such methods have been used to detect electron magnetic resonance signals from a single optically active molecule[4,5], but they cannot be used

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in most samples because they lack convenient optical transitions.

To develop a more general method, it is possible to use one spin with optical readout as a detector of the magnetic fields created by the spins in the sample under analysis (Fig. 1). To achieve sufficient sensitivity, the interaction between spins must persist for a relatively long time. This requires both the detector and the sample spins to have long spin-coherence times, so that their direction is only occasionally perturbed by quantum fluctuations. There are many techniques for achieving long spin-coherence times in atomic systems, even for a single spin that is held, for example, in a laser trap. However, it is generally impossible to bring a sample within nanometres of such spin without disrupting the trapping mechanism.

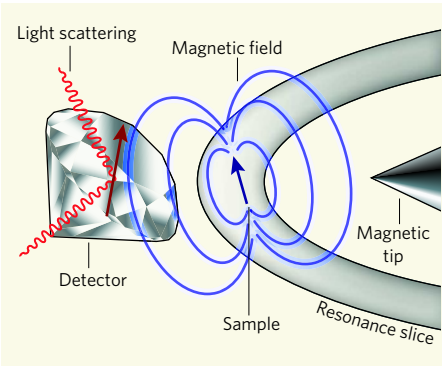
This is where the properties of nitrogen-vacancy centres in diamond become useful. Recent work[6] has shown that a spin-coherence time of the order of a millisecond can be achieved in such a solid-state system. Even in diamond nanocrystals that are tens of nanometres across, the spin-coherence time is not dramatically reduced. Furthermore, initialization and detection of the spin's direction can be achieved at room temperature, so a diamond magnetometer can be placed within tens of nanometres of a biologically active sample.

Such long spin-coherence times can only be achieved by periodically flipping the direction of the spin, a technique known as spin echo, which averages out external fluctuations. With this technique, which was first used in nitrogen-vacancy centres for quantum-computing applications[7], Maze *et al.*[1] describe a magnetometer with a single nitrogen-vacancy centre in both a bulk diamond and a nanocrystal. The magnetometer is sensitive to magnetic fields that oscillate at the frequency of the spin-echo repetition rate, typically in the kilohertz range. After collecting light from the nitrogen-vacancy centre for 100 seconds, Maze and colleagues obtained a magnetic-field sensitivity as low as 3 nanotesla, equal to the magnetic field about 100 nanometres from a single electron, or 10 nanometres from a single proton. This is considerably better than has been achieved with other techniques, such as MRFM, on the nanometre scale.

Balasubramanian *et al.*[2] operate a nitrogen-vacancy diamond magnetometer placed next to a magnetic tip, creating a strong magnetic-field gradient. Because the magnetometer relies on a single, well-localized spin, its magnetic resonance is not broadened by the steep spatial variation of the magnetic field. Such a high gradient could allow magnetic-resonance imaging with sub-nanometre resolution. As a first step in this direction, Balasubramanian and colleagues locate the position of the nitrogen-vacancy centre itself with a spatial resolution of 5 nanometres by measuring its resonance frequency.

A combination of the techniques developed by Maze *et al.*[1] and Balasubramanian *et al.*[2] could lead to the detection and imaging of individual nuclear spins, which would potentially allow the determination of the structure of a single molecule. Crucially, both experiments were performed at room temperature, so biological applications such as the determination of protein structures or detailed imaging of the internal structure of a living cell seem feasible.

Manipulation of spin in diamond is a fast-developing research area, and many avenues remain to be explored. For example, longer spin-coherence times could be achieved using artificial diamond crystals that have a reduced abundance of the carbon-13 isotope, which creates magnetic fields that perturb the sensor. Another point to note is that the NMR signal on very small length-scales is effectively increased because of quantum fluctuations. As the number of spins (N) decreases, their quantum fluctuations, which scale as $N^{1/2}$, become relatively larger[8]. By resolving individual spins, one can obtain NMR signals that correspond to nearly complete spin polarization even in a low magnetic field, alleviating the current need for strong superconducting magnets in NMR detection, which can polarize only 1 spin in 10^4. Although integration of nitrogen-vacancy spin-echo techniques with the conditions necessary for NMR remains to be demonstrated, diamond magnetometers seem to provide a promising route towards single-spin NMR detection. ■



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NEUROSCIENCE

Fragile dopamine

David Weinshenker and Stephen T. Warren

Dopamine dysfunction, which is implicated in Parkinson's disease and drug addiction, seems an unlikely culprit in fragile X syndrome. A surprising set of findings means a rethink is required.

Fragile X syndrome is the commonest inherited form of mental retardation, with the patients often also having autism and attention-deficit hyperactivity disorder[1]. It is usually caused by the absence of the protein FMRP, which is encoded by *FMR1*, a gene on the X chromosome. Although FMRP function is not well understood, most studies concur that it is a selective RNA-binding protein that modulates the translation of its target messenger RNAs[2]. But this deceptively simple description of FMRP function omits any role for the neurotransmitter dopamine, despite the fact that some of the clinical and behavioural features of fragile X syndrome are reminiscent of dysfunction in dopamine-secreting neurons. Writing in *Neuron*, Wang *et al.*[3] elucidate the role of FMRP in modulating dopamine signalling.

Classically, dopamine has been considered an essential mediator of behaviours such as reward-seeking and coordinated movement. Because these brain functions are not always impaired in fragile X syndrome, there has been little reason to link altered dopamine signalling to the aetiology or the manifestation of this disorder. Nevertheless, recent work[4,5] has expanded and refined dopamine's job description in the brain to encompass more cognitively relevant functions, such as involvement in reward-prediction error, motivation, ability to focus on pertinent environmental stimuli and goal-directed behaviours.

To explore a possible connection between

in most samples because they lack convenient optical transitions.

To develop a more general method, it is possible to use one spin with optical readout as a detector of the magnetic fields created by the spins in the sample under analysis (Fig. 1). To achieve sufficient sensitivity, the interaction between spins must persist for a relatively long time. This requires both the detector and the sample spins to have long spin-coherence times, so that their direction is only occasionally perturbed by quantum fluctuations. There are many techniques for achieving long spin-coherence times in atomic systems, even for a single spin that is held, for example, in a laser trap. However, it is generally impossible to bring a sample within nanometres of such spin without disrupting the trapping mechanism.

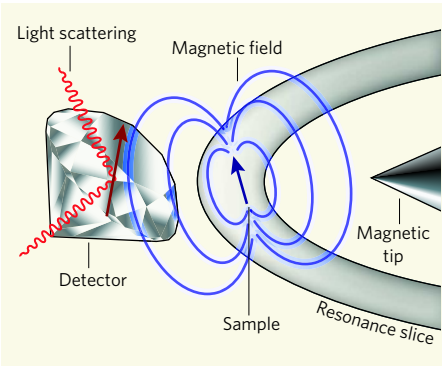
This is where the properties of nitrogen-vacancy centres in diamond become useful. Recent work[6] has shown that a spin-coherence time of the order of a millisecond can be achieved in such a solid-state system. Even in diamond nanocrystals that are tens of nanometres across, the spin-coherence time is not dramatically reduced. Furthermore, initialization and detection of the spin's direction can be achieved at room temperature, so a diamond magnetometer can be placed within tens of nanometres of a biologically active sample.

Such long spin-coherence times can only be achieved by periodically flipping the direction of the spin, a technique known as spin echo, which averages out external fluctuations. With this technique, which was first used in nitrogen-vacancy centres for quantum-computing applications[7], Maze *et al.*[1] describe a magnetometer with a single nitrogen-vacancy centre in both a bulk diamond and a nanocrystal. The magnetometer is sensitive to magnetic fields that oscillate at the frequency of the spin-echo repetition rate, typically in the kilohertz range. After collecting light from the nitrogen-vacancy centre for 100 seconds, Maze and colleagues obtained a magnetic-field sensitivity as low as 3 nanotesla, equal to the magnetic field about 100 nanometres from a single electron, or 10 nanometres from a single proton. This is considerably better than has been achieved with other techniques, such as MRFM, on the nanometre scale.

Balasubramanian *et al.*[2] operate a nitrogen-vacancy diamond magnetometer placed next to a magnetic tip, creating a strong magnetic-field gradient. Because the magnetometer relies on a single, well-localized spin, its magnetic resonance is not broadened by the steep spatial variation of the magnetic field. Such a high gradient could allow magnetic-resonance imaging with sub-nanometre resolution. As a first step in this direction, Balasubramanian and colleagues locate the position of the nitrogen-vacancy centre itself with a spatial resolution of 5 nanometres by measuring its resonance frequency.

A combination of the techniques developed by Maze *et al.*[1] and Balasubramanian *et al.*[2] could lead to the detection and imaging of individual nuclear spins, which would potentially allow the determination of the structure of a single molecule. Crucially, both experiments were performed at room temperature, so biological applications such as the determination of protein structures or detailed imaging of the internal structure of a living cell seem feasible.

Manipulation of spin in diamond is a fast-developing research area, and many avenues remain to be explored. For example, longer spin-coherence times could be achieved using artificial diamond crystals that have a reduced abundance of the carbon-13 isotope, which creates magnetic fields that perturb the sensor. Another point to note is that the NMR signal on very small length-scales is effectively increased because of quantum fluctuations. As the number of spins (N) decreases, their quantum fluctuations, which scale as $N^{1/2}$, become relatively larger[8]. By resolving individual spins, one can obtain NMR signals that correspond to nearly complete spin polarization even in a low magnetic field, alleviating the current need for strong superconducting magnets in NMR detection, which can polarize only 1 spin in 10^4. Although integration of nitrogen-vacancy spin-echo techniques with the conditions necessary for NMR remains to be demonstrated, diamond magnetometers seem to provide a promising route towards single-spin NMR detection. ■



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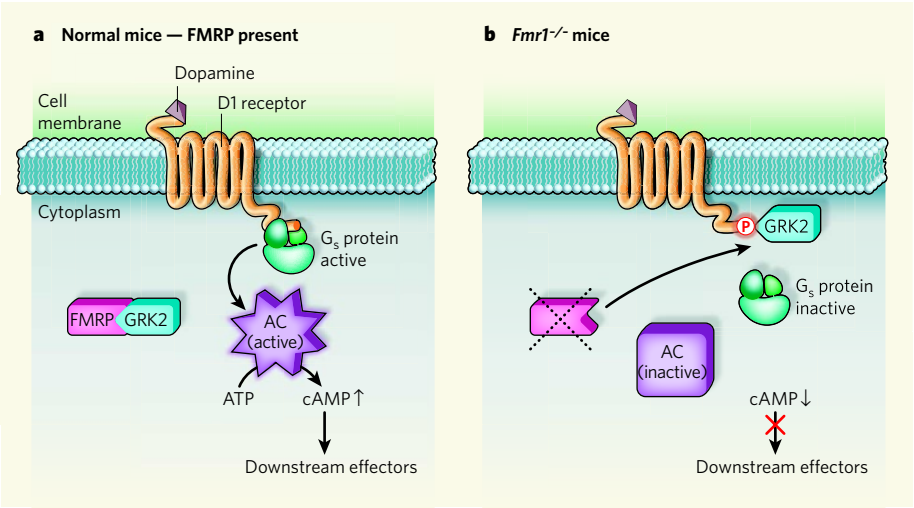

Figure 1 | FMRP-mediated regulation of dopamine signalling. a, Normally, FMRP binds to GRK2 and sequesters it in the cytoplasm, away from D1 dopamine receptors on the cell membrane. On dopamine binding, the D1 receptors couple to and activate G_s, which in turn activates adenylate cyclase (AC). This enzyme then catalyses the formation of cAMP, which acts on various downstream effector molecules. **b**, Wang *et al.*[3] show that, in *Fmr1*$^{-/-}$ mice, which cannot produce FMRP (and presumably in patients with fragile X syndrome), GRK2 is no longer sequestered in the cytoplasm and is free to move to the cell membrane, where it phosphorylates D1 receptors. Consequently, even on dopamine binding, the phosphorylated D1 receptors have reduced affinity for G_s. The signalling cascade stalls, cAMP levels remain low and effector molecules are no longer engaged.

dopamine signalling and FMRP activity, Wang *et al.*[3] studied a common experimental model of fragile X syndrome — mice lacking the *Fmr1* gene (*Fmr1*$^{-/-}$) — and focused on the function of the D1 subtype of dopamine receptor in the brain's prefrontal cortex (PFC). The D1 receptor not only modulates the trafficking of the receptor for another neurotransmitter, glutamate, but also affects long-term potentiation, a form of synaptic plasticity thought to underlie learning and memory. The PFC is crucial for working memory, planning and attention[6,7].

The authors show that, in the culture-grown PFC neurons of *Fmr1*$^{-/-}$ mice, cell-surface expression and phosphorylation of the GluR1 glutamate receptors, processes that are normally mediated by the D1 receptors, are reduced. Normally, D1 receptors are coupled to G_s proteins, which stimulate the production of an intermediary signalling molecule called cyclic AMP by activating the enzyme adenylate cyclase (Fig. 1a). In *Fmr1*$^{-/-}$ mice, the ability of a D1-receptor agonist to raise cAMP levels in PFC neurons was attenuated. However, no deficit in cAMP production was detected in these mice when a direct activator of adenylate cyclase was used. These and other data indicate that FMRP is crucial for the coupling of D1 receptors to G_s proteins.

Kinase enzymes known as GRKs can phosphorylate D1 receptors at several amino-acid residues, diminishing the receptors' ability to couple to G_s. Wang *et al.*[3] show that, in PFC neurons from *Fmr1*$^{-/-}$ mice, the phosphorylation of D1 receptors is abnormally high. Moreover, one specific GRK — GRK2 — was particularly abundant in the cell-membrane fractions of these neurons, where functional D1 receptors are localized. The authors hypothesized that, normally, FMRP interacts with GRK2 and prevents its activity. Hence, in the absence of FMRP in *Fmr1*$^{-/-}$ mice — and possibly in patients with fragile X syndrome — GRK2 is no longer regulated and becomes overactive (Fig. 1b).

Indeed, using imaging and biochemical approaches, the authors show that FMRP and GRK2 interact. Notably, these two proteins seem to associate only in the cytoplasm, suggesting that FMRP normally functions to sequester GRK2. In the absence of FMRP in *Fmr1*$^{-/-}$ mice, GRK2 seems to be free to move to the cell membrane, where it phosphorylates D1 receptors and disrupts their signalling. But what are the functional consequences of these deficits? Assessing the effects of a D1 agonist on long-term potentiation, Wang *et al.* find that, although stimulating D1 receptors enhances this form of plasticity in the PFC of normal mice, it has no effect on the corresponding brain region of *Fmr1*$^{-/-}$ animals.

Intriguing as these findings are, unanswered questions remain about the relevance of impaired dopamine signalling to the manifestation of fragile X syndrome. Wang and colleagues' finding that, following exposure to a D1 agonist cAMP production remains impaired in *Fmr1*$^{-/-}$ mice, is consistent with previous reports[8,9] of reduced cAMP levels and diminished cAMP responses in cells of patients with fragile X syndrome. But unlike the earlier studies, which attributed decreased cAMP levels to reduced adenylate-cyclase activity, Wang *et al.* observe normal cAMP responses to an activator of adenylate cyclase. Instead, they report that D1-receptor–G_s coupling is impaired in *Fmr1*$^{-/-}$ mice. Clearly, these differences must be reconciled. Nonetheless, Wang and colleagues' data will surely spark renewed interest in the role of cAMP in fragile X syndrome.

Another interesting aspect of the results[3] is the implication that the PFC is involved in fragile X syndrome. Patients with this disorder exhibit deficits in executive functions, showing inappropriate behaviours that are usually inhibited, and impairments[10] in working memory, cognitive flexibility and planning — functions attributed to the PFC. Moreover, these patients are often described as 'creatures of habit' by their caregivers and have difficulty adapting to even subtle changes in their daily routines[11]. In agreement with previous work, Wang and colleagues show that D1-receptor-mediated pathways are crucial for long-term potentiation and synaptic plasticity in the corticostriatal neural circuitry, which is believed to be important for learning new goal-directed behaviours and for the formation of habits.

But extended training can override the dopamine-dependence of actions and habits[4]. So one consequence of impaired dopamine signalling in fragile X syndrome could be that, once patients establish a routine reinforced by extended repetition and training, their corticostriatal circuits cannot adapt rapidly to change. Although the authors[3] demonstrate that a D1 agonist efficiently reverses the locomotor hyperactivity behaviour in *Fmr1*$^{-/-}$ mice, it will be crucial to establish whether abbreviated D1-receptor signalling contributes to other cognitively relevant characteristics.

In the 17 years since the identification of *FMR1*, progress towards an understanding of the mechanism behind fragile X syndrome has been swift, with recent attempts at pharmaceutical interventions[12] being particularly noteworthy. But Wang and co-workers' observation that deregulation of GRK2 activity in the absence of FMRP leads to impaired dopamine signalling is a reminder that we still have much to learn about the molecular, cognitive and behavioural manifestations of this disorder. ■

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FEATURE

The changing face of HIV in China

HIV has advanced from high-risk groups such as intravenous drug users to some in the general population, according to comprehensive new data from the south of China. What needs to be done to halt its spread?

Lin Lu, Manhong Jia, Yanling Ma, Li Yang, Zhiwei Chen, David D. Ho, Yan Jiang and Linqi Zhang

The HIV-1/AIDS epidemic in China is at a critical juncture. Historically, HIV-1 infection has been largely confined to certain high-risk populations such as intravenous drug users and former blood and plasma donors in geographically disparate rural areas[1–3]. However, HIV-1 prevalence has now increased rapidly among men who have sex with men and among female sex workers[4,5]. It seems that China is following the path of some of the other Asian countries where HIV-1 infection is no longer confined to high-risk populations[5].

Since the first cases among foreign tourists and local recipients of imported factor VIII in the mid 1980s, HIV-1 has spread to all of mainland China[1,4]. The current epidemic comprises largely of two affected populations: former blood and plasma donors in Henan and neighbouring provinces, and intravenous drug users in Yunnan and along drug-trafficking routes[1,2] (Fig. 1). Both of these populations stemmed from the infection of drug users from Yunnan's Dai and Jingpo ethnic minority groups in Yunnan in the late 1980s[6,7].

Statistics from the Chinese Ministry of Health and UNAIDS have revealed a worrisome trend of the HIV-1 epidemic in China. As of October 2007, an estimated 700,000 infections had occurred[4]. Although the prevalence of infection remains low (0.04–0.07%), the new figure represents an 8% increase since 2006 (refs 4, 5). Remarkably, 38% of the cases were attributed to heterosexual contacts — more than triple the 11% in 2005 (ref. 4). In line with this trend, the proportion of women infected has doubled over the past decade[4]. As 90% of these women are of child-bearing age (15–44), this is likely to translate into more vertical transmission from mother to child[4]. Additionally, the proportion of cases among men who have sex with men increased eight-fold from 0.4% in 2005 to 3.3% in 2007 (ref. 4). These data suggest that the HIV-1 epidemic is expanding, and that more effective preventive measures are urgently needed.

Figure 1 | Pervasive spread. The geographic distribution of cumulative reported HIV-1 infection in mainland China (source: ref. 4).

The epidemic in Yunnan

Located in southwest China, Yunnan has long been regarded as China's Shangri-la for its natural beauty. But now, with all of its 16 prefectures affected, it is a major site of the AIDS epidemic. Yunnan's ethnic diversity is unrivalled in China, with 25 different ethnic minority groups representing one third of the province's population. Of these groups, 13 live along the border with Myanmar, Laos and Vietnam, and cross-border travel and commerce are common. Yunnan has a long history of opium/heroin trade, and the vast majority of illicit drugs in China are trafficked through Yunnan from the 'Golden triangle' of illicit opium production, encompassing Myanmar, Thailand, Laos and Vietnam (Fig. 1)[8,9].

HIV-1 was detected in intravenous drug users inYunnan in 1989 (ref. 10). It then also spread among other populations[11]. Between 1989 and 2006, 3.2 million blood samples were tested in Yunnan. This testing identified 48,951 HIV-1 cases, 3,935 AIDS patients, and 1,768 resultant deaths — representing about 25%, 8% and 13% of the national totals, respectively. Prefectures bordering Myanmar and Vietnam were the first and the most severely affected.

Although the cumulative HIV-1 case load rose gradually from 1989 to 2003, there was a sharp rise in 2004, when 13,486 new cases were seen. This total is comparable to the number identified in the previous 16 years. Identification of these new cases was likely to be due to increased surveillance and testing since the estimated incidence rates remained relative stable over time among the major risk groups. These estimates were determined by re-testing all seropositive samples from the surveillance effort using the BED assay[12] to detect those with low-affinity antibodies to HIV-1. Intravenous drug users had the highest incidence rate throughout the study, varying between 2.2% and 8.0% per year, whereas that for outpatients attending sexually transmitted infection (STI) clinics was 0.3–1.0%

per year and for pregnant women it was about 0.1% per year.

Changing demographics

HIV-1 has hit different Yunnan populations disproportionately. Figure 2 shows provincial average HIV-1 prevalence rates over time among intravenous drug users, female sex workers, STI outpatients, pregnant women and an 'unlinked population' (patients admitted to the hospital who were willing to be tested for HIV-1 anonymously) based on the results from 97 sentinel surveillance sites located through the province. Within these groups, the highest prevalence rate has always been found in the intravenous drug users population. From 1992 to 1995, the average prevalence rate remained around 6%. In 1996, it jumped to about 22%, and then remained near that level. Prevalence rates among female sex workers and STI outpatient groups have been consistently lower, but follow a similar trend. The 'unlinked' and pregnant women populations have also experienced a similar pattern of prevalence increases, although the jumps occurred in 1999 and 2003, respectively. This sequential upsurge of infection among intravenous drug users, female sex workers, STI outpatients, then among the 'unlinked' and finally pregnant women, is reminiscent of what has been seen in other countries, where HIV-1 infection has spread from high-risk groups to some in the general population.

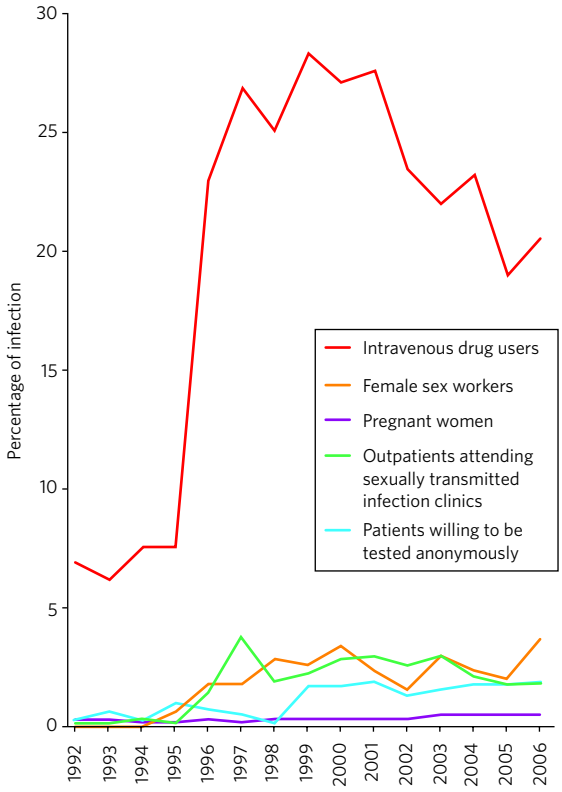

Figure 2 | Changing trends. HIV-1 prevalence among various risk groups in Yunnan between 1992 and 2006.

This trend in transmission mode is further illustrated by the fact that the proportion of cases among intravenous drug users has decreased from 100% in 1989 to 40% in 2006. Concurrently, heterosexual transmission has increased markedly, reaching 37.5% of infections in 2006.

Although most infections were in farmers from 1989 to 1995, more factory workers are now infected, and the number of infections among unemployed persons have come to rival those in farmers. In addition, whereas the Dai and Jingpo minorities were the most affected ethnic groups in 1989–95, Han Chinese overtook these minorities in 1996 and up to 2006 accounted for around 60% of infections.

Changes in age distribution are also evident. Although on average more than 95% of infected individuals have been aged 20–40, HIV-1 prevalence has increased among the 30–59 group and decreased among the 20–29 group. This could be attributed to ageing of infected individuals or to new infections of relatively older age groups over time. Nonetheless, high prevalence in the 20–29 and younger than 20 age groups suggests ongoing infection within the young population.

HIV-1 in Yunnan has also spread to the female population. Before 1996, most infected individuals were male. However, from 1996–2006, the proportion of HIV-1-infected women gradually increased from 7.1% to 35%, and the male to female ratio decreased from 13:1 to 1.9:1.

Virus evolution

With the dramatic changes in disease distribution, HIV-1 genetics in Yunnan have become increasingly complex. The initial HIV-1 epidemic among intravenous drug users in Yunnan in 1989 was caused by a mixture of viruses closely resembling European/North American subtype B and Thai subtype B (B')[13]. But by 1996, the B' subtype began to dominate[13,14]. During the same period, a second epidemic took root among intravenous drug users in Yunnan, with strains genetically related to subtype C viruses from India[15]. Co-existence of multiple subtypes led to the formation of circulating recombinant forms (CRFs) of HIV-1 — CRF07_BC and CRF08_BC among intravenous drug users along drug trafficking routes[16] and CRF01_AE in Chinese sex workers who had worked in Thailand[17]. In the mid-1990s, viruses closely related to CRF01_AE and CRF08_BC in Yunnan were identified among intravenous drug users in Guangxi[18]. Further novel recombinants arose in subsequent years[19].

We compared over 500 nucleotide sequences from Yunnan[6,7] with those from other provinces in China and neighbouring countries. Comparing sequences from the HIV-1 *gag* p17 gene with reference sequences from the HIV-1 Database (www.hiv.lanl.gov/content/index), we identified the three main subtypes of HIV-1 found in Yunnan. These subtypes are those clustering closely with subtype C, CRF07_BC, or CRF08_BC (53.0%); those with CRF01_AE or CRF15_01B (40.5%); and those with subtype B (6.5%). Notably, more than 90% of infected intravenous drug users had C/CRF07_BC/CRF08_BC viruses, whereas 85.4% of CRF01_AE/CRF15_01B infections were acquired through sexual transmission. Furthermore, sequences in the C/CRF07_BC/CRF08_BC group were found throughout Yunnan, while those in the CRF01_AE/CRF15_01B group were largely confined to prefectures bordering Myanmar. Sequences in the subtype B groups have only been identified in the Dehong and Baoshan prefectures in Yunnan.

The dominant C/CRF07_BC/CRF08_BC viruses in Yunnan are related to strains in Guangxi province and distant Xinjiang province, supporting the notion that HIV-1 has spread along known drug-trafficking routes. In contrast, sequences similar to CRF01_AE/CRF15_01B have been largely confined to Yunnan and are closely related to strains from Thailand, Myanmar and Vietnam. Subtype B sequences from Yunnan are genetically similar to those from former blood donors in Henan and adjacent provinces, and can be broadly classified into two major groups: one with sequences similar to those from Thailand and Myanmar, and the other with sequences more similar to those in France and the United States. These results are consistent with the hypothesis that HIV-1 spread from Yunnan to central China, and suggest multiple introductions of HIV-1 from foreign countries to Yunnan[6].

Challenge and opportunity

Over the past 20 years, HIV-1 in Yunnan has overcome preventive measures to spread beyond high-risk populations. The dramatic increase in sexual transmission has changed the demographic profile of those infected. As the epidemic continues to expand, the genetic makeup of HIV-1 subtypes have become increasingly complex, potentially posing greater challenges to our efforts in antiretroviral treatment and vaccine development.

In light of the observed demographic changes, HIV-1 prevention strategies must focus more on stopping sexual transmission of HIV-1 within high-risk groups and halting the spread to the general public. There are urgent needs to scale up and integrate those proven successful prevention programmes such as condom promotion among female sex workers; drug rehabilitation, needle exchange

and methadone maintenance for intravenous drug users ; and free antiretroviral therapy for those infected.

There is an old Chinese saying: "When there is a crisis, there is an opportunity." Indeed, as HIV-1 plagues certain high-risk groups in China, there is still a window of opportunity to prevent further spread to the general population. The time to act is now. ■

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REVIEWS

Challenges in the development of an HIV-1 vaccine

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The development of a safe and effective human immunodeficiency virus (HIV)-1 vaccine is a critically important global health priority. Despite recent advances in our understanding of HIV-1 pathogenesis and immunology, however, major scientific obstacles remain. Prototype HIV-1 vaccine candidates aimed at eliciting humoral and cellular immune responses have so far failed to protect against HIV-1 infection or to reduce viral loads after infection in clinical efficacy studies. A renewed and coordinated commitment to basic discovery research, preclinical studies and clinical trials will therefore be required to overcome the hurdles currently facing the field. Here I review key challenges and future prospects in the quest to develop a prophylactic HIV-1 vaccine.

It has been 25 years since HIV-1 was identified as the causative agent for AIDS[1–5]. More than 60 million people worldwide have been infected with HIV-1, mostly in the developing world, and nearly half of these individuals have died. The development of a safe and effective HIV-1 vaccine would undoubtedly be the best solution for the ultimate control of the worldwide AIDS pandemic[6], but unfortunately HIV-1 vaccine development efforts have not yet proven successful. The extraordinary diversity of HIV-1, the capacity of the virus to evade adaptive immune responses, the inability to induce broadly reactive antibody responses, the early establishment of latent viral reservoirs, and the lack of clear immune correlates of protection represent unprecedented challenges for vaccine development.

The goal of an HIV-1 vaccine would be either to prevent infection or to reduce viral loads and clinical disease progression after infection (Fig. 1). An ideal vaccine would completely block infection and provide sterilizing immunity. Although such a vaccine would be optimal, this degree of protection is not even achieved with most clinically licensed vaccines. In contrast, most licensed viral vaccines seem to function by controlling subclinical viral replication and by preventing clinical disease. It may therefore be more realistic to develop a suboptimal HIV-1 vaccine that fails to prevent infection but that provides partial immune control of viral replication after infection. Such partial control, as exemplified by a reduction in peak and setpoint viral loads after infection, has been demonstrated in certain preclinical studies by vaccines that elicit T lymphocyte responses.

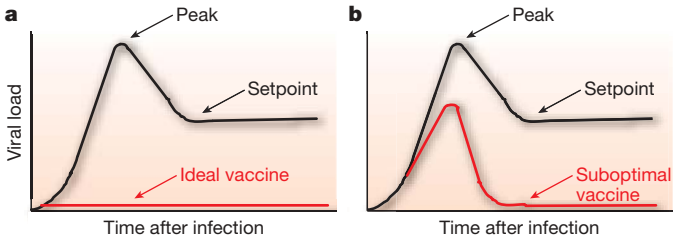

Figure 1 | Goals of an HIV-1 vaccine. After infection, HIV-1 replicates exponentially to a peak level and then is partially controlled to a viral setpoint level (black). **a**, An ideal vaccine would protect against infection and afford sterilizing immunity (red). **b**, A suboptimal vaccine would result in decreased peak and setpoint viral loads after infection (red).

Moreover, because viral loads represent a principal determinant of HIV-1 transmission[7], it is conceivable that such a partially protective vaccine might have substantial impact on a population level.

Despite the urgent need for an HIV-1 vaccine, only two vaccine concepts have completed clinical efficacy studies so far. The first vaccine concept used monomeric HIV-1 Env gp120 protein, and the aim of this strategy was to induce Env-specific humoral immune responses. In early-phase clinical trials, gp120 immunogens elicited type-specific binding antibodies but failed to induce broadly reactive neutralizing antibodies[8,9]. In two phase 3 efficacy trials sponsored by the biotechnology company VaxGen, these vaccine candidates afforded no detectable protective efficacy[10,11], indicating that these type-specific antibody responses were insufficient to protect against HIV-1 infection in humans. Another phase 3 study evaluating the efficacy of a recombinant canarypox vector prime/gp120 protein boost vaccine regimen is currently underway. The second vaccine concept that has completed clinical efficacy studies involved replication-incompetent recombinant adenovirus serotype 5 (rAd5) vectors expressing HIV-1 Gag, Pol and Nef. The aim of this strategy was to elicit HIV-1-specific cellular immune responses. Early-phase clinical trials demonstrated that rAd5 vector-based vaccines elicited cellular immune responses in most subjects, although these responses were partially suppressed in individuals with pre-existing Ad5-specific neutralizing antibodies[12]. Phase 2b efficacy trials sponsored by Merck and the National Institutes of Health (NIH) were unexpectedly terminated when the first planned interim analysis showed that this vaccine failed to protect against infection or to reduce viral loads after infection, and that vaccinees with pre-existing Ad5-specific neutralizing antibodies exhibited an enhanced rate of HIV-1 acquisition[13]. These results have highlighted new scientific challenges and have led to substantial debate regarding the optimal path forward for the HIV-1 vaccine field.

Virologic and immunologic challenges

The challenges in the development of a prophylactic HIV-1 vaccine are unprecedented (Box 1). The extraordinary worldwide diversity of HIV-1 presents perhaps the greatest hurdle[14]. Driven by the error-prone reverse transcriptase, the HIV-1 M group has diversified into nine divergent clades as well as multiple circulating recombinant forms. Amino acid sequences of Env can differ up to 20% within a particular clade and over 35% between clades[14,15]. A vaccine

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Box 1 | Challenges in the development of a prophylactic HIV-1 vaccine

(1) Extensive viral clade and sequence diversity.
(2) Early establishment of latent viral reservoirs.
(3) Immune correlates of protection unclear.
(4) Viral evasion of humoral and cellular immune responses.
(5) Antibody responses typically type-specific.
(6) No method exists to elicit broadly reactive neutralizing antibodies.
(7) Attenuated viruses unsafe for human use.
(8) Lack of a small-animal model.
(9) Little pharmaceutical interest.

immunogen will therefore need to contend with a remarkably high degree of viral diversity, and vaccine protection will necessarily be dependent on the capacity of immune responses to cross-react with highly heterologous viruses. Although cross-reactive humoral and cellular immune responses against conserved regions of the virus have been reported, it is reasonable to assume that protective efficacy will diminish substantially with increasing divergence between vaccine antigens and infecting viruses.

Another key challenge is the lack of clear immune correlates of protection in humans, because HIV-1-infected patients are unable to eradicate the virus. Suggestive evidence regarding immune correlates of protection might be obtained from viral challenge studies in non-human primates and from studies of HIV-1-infected individuals who spontaneously control viral replication to very low levels. However, definitive immune correlates of protection will probably only emerge in the context of successful vaccine efficacy studies in humans.

HIV-1-specific humoral immunity. Virus-specific neutralizing antibody titres represent key immune correlates of protection for most licensed viral vaccines, and thus early studies focused on developing HIV-1 Env subunit immunogens. Advances in our understanding of Env structure and function have begun to elucidate why generating broadly reactive neutralizing antibodies to HIV-1 by vaccination may be so difficult[16]. The HIV-1 Env glycoprotein is a trimer on the virion surface with extensive N-linked glycosylation that effectively shields many conserved epitopes from antibody recognition[17,18]. Highly immunogenic variable loops also elicit type-specific antibodies that may redirect humoral responses away from conserved regions. In addition, key conserved regions, such as the binding site of the chemokine co-receptor, are only formed after Env binds its cellular receptor CD4 and undergoes an extensive conformational change[19]. The development of mutations in N-linked glycans has also been shown to lead to rapid evasion of host neutralizing antibody responses[20,21].

Nevertheless, broadly reactive neutralizing antibody activity has been identified in a small number of HIV-1-infected subjects, and this reactivity seems to be largely directed against conserved regions of the Env glycoprotein such as the CD4-binding site[22]. The broadly reactive monoclonal antibody b12 also binds to the CD4-binding site, suggesting that this region of Env may represent a critical point of vulnerability that is potentially amenable to neutralization[23]. However, the CD4-binding site is recessed and only partially accessible to antibody binding. Another conserved region is the membrane-proximal external region (MPER) of gp41, which represents the target of the broadly reactive monoclonal antibodies 2F5 and 4E10. However, MPER-specific neutralizing antibodies may be difficult to elicit by vaccination for multiple reasons, including tolerance control and immunoregulation[24], sequestration of the epitope in the lipid membrane[25], exposure of the epitope only transiently during viral entry[26], or possibly a combination of multiple factors.

The development of immunogens that induce broadly reactive neutralizing antibodies is perhaps the most important priority for the HIV-1 vaccine field[16]. Proof-of-concept passive transfer studies in non-human primates have shown that administration of high doses of broadly reactive monoclonal antibodies can afford sterilizing protection from infection, thus demonstrating the potential of virus-specific humoral immunity[27,28]. However, it has not been possible to induce such broadly reactive neutralizing antibodies by vaccination so far. Although there has been substantial progress in our understanding of Env structure and function, there are currently no vaccine candidates that are aimed at eliciting broadly reactive Env-specific neutralizing antibodies in clinical trials. It is likely that next-generation Env immunogens will need to be engineered antigens. Strategies that are being pursued include generating biochemically stabilized Env trimers, constraining Env immunogens in structurally defined conformations, scaffolding conserved neutralization epitopes onto foreign proteins, developing methods to circumvent immunoregulation, and designing immunogens to target specific regions such as the CD4-binding site, the MPER region and structurally conserved elements of the V3 loop. The relevance of non-neutralizing antibodies that mediate other effector functions such as antibody-dependent cell-mediated virus inhibition, complement activation and phagocytosis is also being investigated.

HIV-1-specific cellular immunity. Virus-specific T lymphocyte responses are believed to have a critical role in controlling HIV-1 replication and are therefore being actively explored in vaccine development strategies. Early studies showed that virus-specific $CD8^+$ T lymphocyte responses emerge during acute infection coincident with initial control of primary viremia[29–31]. Potent cellular immune responses have also been reported in long-term non-progressors[32], and specific HLA alleles and the breadth of Gag-specific T lymphocyte responses have been correlated with control of viral replication in HIV-1-infected individuals[33,34]. These data indicate the potential importance of cellular immune responses in immune control of HIV-1. Concordant with these observations, experimental depletion of $CD8^+$ lymphocytes has been shown to abrogate immune control of simian immunodeficiency virus (SIV) replication in rhesus monkeys[35,36].

A limitation of virus-specific T lymphocyte responses is the propensity of the virus to accumulate mutations in T lymphocyte epitopes and to evade cellular immune control[37–39]. It is therefore likely that the breadth of epitope-specific T lymphocyte responses will prove critical for an HIV-1 vaccine, not only to maximize immunologic coverage of HIV-1 diversity but also to minimize the potential for viral escape from recognition by T lymphocytes. However, the breadth of vaccine-elicited cellular immune responses may be limited by immunodominance constraints and by the inherent tendency of $CD8^+$ T lymphocyte responses to be highly focused on a limited number of epitopes.

Recent advances in the characterization of T lymphocyte responses by multiparameter flow cytometry have highlighted the functional diversity of virus-specific T lymphocytes in terms of cytokine secretion, degranulation, proliferation and other effector functions in various subpopulations of effector and memory T lymphocytes. It is likely that the complex functionality of T lymphocytes may ultimately prove more relevant than interferon-γ secretion as measured by enzyme-linked immunospot (ELISPOT) assays for the evaluation of vaccine-elicited cellular immune responses. Polyfunctional T lymphocytes capable of performing multiple functions have been reported in long-term non-progressors[40], in recipients of effective vaccines such as vaccinia[41], and in certain preclinical challenge studies[42]. These considerations suggest that the breadth[43] and quality[44] of T lymphocyte responses may prove critical in addition to the magnitude of these responses.

Perhaps the most significant limitation of vaccine-elicited cellular immune responses is that they will probably not protect against acquisition of HIV-1 infection. As a result, vaccine-induced T lymphocyte responses will presumably be unable to prevent lifelong infection, because the virus rapidly establishes latent reservoirs[45,46]. Moreover, it is unclear whether vaccine-elicited T lymphocytes will be able to function rapidly enough given that important immunopathologic events occur within the first few days of acute HIV-1 infection. HIV-1 preferentially infects HIV-1-specific $CD4^+$ T

lymphocytes[47] and rapidly depletes most memory $CD4^+$ T lymphocytes in gut-associated lymphoid tissue within the first 4–10 days of infection[48–50]. This sets the stage for progressive immunodeficiency as well as for chronic immune activation, which probably results at least in part from microbial translocation across damaged gastrointestinal mucosa[51]. Given the time required for vaccine-induced $CD8^+$ T lymphocyte responses to expand after infection, it may be difficult for vaccine-elicited T lymphocytes to prevent these early immunopathologic events completely[52].

Current HIV-1 vaccine strategies

Traditional strategies. Vaccine strategies for HIV-1 can be divided into traditional and novel vaccine approaches (Box 2). Traditional vaccine technologies include live attenuated viruses, whole killed viruses and protein subunits. Although these approaches have proven enormously successful for the development of vaccines against other viruses, they all have substantial limitations in terms of their utility for HIV-1. Live attenuated viruses have afforded substantial protective efficacy against SIV challenges in rhesus monkeys[53,54], but they are unlikely to be used in humans owing to significant safety concerns[55–57]. In contrast, whole killed viruses[58] and protein subunits[10,11] are limited by their inability to induce broadly reactive neutralizing antibody responses as well as by their inability to elicit $CD8^+$ T lymphocyte responses. Recent data, however, suggest that Toll-like receptor adjuvants may increase the utility of protein subunit immunogens[59,60].

Novel strategies. New vaccine strategies include gene-delivery technologies such as plasmid DNA vaccines and live recombinant vectors that are engineered to express HIV-1 antigens. Plasmid DNA vaccines offer considerable promise in terms of simplicity and versatility, but multiple injections of high doses of DNA vaccines are typically required to elicit detectable immune responses in non-human primates and humans[61,62]. Substantial research is therefore focused on the development of adjuvants for DNA vaccines[63,64] and improved delivery technologies such as *in vivo* electroporation[65,66]. Recombinant vectors include attenuated or replication-incompetent viruses, most notably adenoviruses[12,67,68] and poxviruses[69,70]. Viral vectors, administered either alone or in the context of heterologous DNA prime/vector boost regimens, represent most HIV-1 vaccine candidates that are currently in clinical trials. Other viral vectors that are being evaluated include vesicular stomatitis virus, adeno-associated virus, Venezuelan equine encephalitis virus, cytomegalovirus, herpes simplex virus and measles virus. Bacterial and mycobacterial vectors are also being explored, including *Salmonella*, *Listeria* and Bacille Calmette-Guérin (BCG).

The STEP study

Preclinical background. Recombinant Ad5 vectors were selected for development by Merck on the basis of preclinical vector comparison studies that showed that rAd5 vectors were more immunogenic than multiple other vector modalities in rhesus monkeys[67,71]. Moreover, rAd5 vectors expressing SIV Gag afforded marked reductions of viral loads after challenge of rhesus monkeys with the chimaeric simian–human immunodeficiency virus (SHIV)-89.6P (ref. 67). However, it was also observed that the same vaccine afforded minimal to no control of peak or setpoint viral loads after challenge with SIV_{MAC239} (ref. 72), indicating that SIV challenges were considerably more stringent than SHIV-89.6P challenges.

Box 2 | Current HIV vaccine strategies

(1) Traditional strategies
- Live attenuated viruses
- Whole killed viruses
- Protein subunits

(2) Novel strategies
- Plasmid DNA vaccines
- Live recombinant vectors

A DNA prime/rAd5 boost regimen expressing SIV Gag afforded a brief (90 days) and marginal (0.8 log) reduction of peak viral loads after SIV_{MAC239} challenge[72], but this effect was only observed in rhesus monkeys that were selected to express the major histocompatibility complex (MHC) class I molecule Mamu-A*01, which is associated with efficient virologic control[73–75]. A DNA prime/rAd5 boost regimen expressing multiple SIV antigens afforded increased protective efficacy in Mamu-A*01-positive rhesus monkeys[76], indicating that expanding the breadth of cellular immune responses improves protection. However, neither rAd5 alone nor DNA prime/rAd5 boost regimens have been able to reduce setpoint viral loads after SIV challenge of Mamu-A*01-negative rhesus monkeys so far[72,77].

Clinical studies. The Merck HIV-1 vaccine candidate was formulated as a trivalent mixture of rAd5 vectors expressing HIV-1 clade B Gag, Pol and Nef. Phase 1 clinical trials suggested that this vaccine was generally well tolerated and immunogenic in most volunteers[12]. However, as predicted by preclinical studies[61], responses to this vaccine were partially suppressed in individuals with pre-existing neutralizing antibodies against the vaccine vector. Because 30–40% of individuals in the United States and Western Europe and 80–90% of people in sub-Saharan Africa have pre-existing Ad5-specific neutralizing antibodies[78–81], the impact of anti-vector immunity was predicted to be a limitation of rAd5 vectors.

Two phase 2b 'proof-of-concept' efficacy studies were initiated by Merck and the National Institutes of Health to determine whether HIV-1-specific cellular immune responses induced by this vaccine regimen would prevent HIV-1 infection or would reduce viral loads after infection. HIV Vaccine Trials Network (HVTN) 502, also known as the 'STEP' study, was a 3,000-subject study in the Americas, the Caribbean and Australia. HVTN 503, also called 'Phambili' (which means 'to move forward' in Xhosa), was designed as a parallel 3,000-subject study in South Africa.

On 18 September 2007, HVTN 502 was unexpectedly terminated at the first planned interim analysis when the Data and Safety Monitoring Board declared futility in the study achieving its primary end points[13]. Moreover, in subjects with pre-existing Ad5-specific neutralizing antibody titres, a greater number of HIV-1 infections occurred in vaccinees than in placebo recipients (Fig. 2). Although the biological basis for this observation remains unclear, these data suggest that vaccination with rAd5 vectors may be associated with an increased risk of HIV-1 acquisition in this subgroup. Post-hoc multivariate analysis further suggested that the greatest increased risk was in men who had pre-existing Ad5-specific neutralizing antibodies and who were uncircumcised.

It is currently unclear whether the lack of efficacy in the STEP study simply represents the failure of the Merck rAd5-Gag/Pol/Nef vaccine product or whether this might be the harbinger of the failure of the T-cell vaccine concept overall. It is likely that substantial data will emerge from detailed immunologic analyses of vaccinees who subsequently became infected, and it is possible that the rAd5-Gag/Pol/Nef vaccine failed to induce sufficient magnitude, breadth or quality of cellular immune responses[82]. At the present time, therefore, it would seem premature to consider the failure of this single study as the failure of T-cell-based vaccines in general.

The apparent increased risk of HIV-1 acquisition in vaccinees with pre-existing Ad5-specific neutralizing antibodies was unexpected, and this finding highlights our lack of understanding of the parameters that determine susceptibility to HIV-1 infection. The biological basis for this observation remains unclear. One hypothesis is that rAd5 vaccination of individuals with pre-existing Ad5-specific neutralizing antibodies may have resulted in potent anamnestic Ad5-specific $CD4^+$ T lymphocytes that were increased targets for HIV-1 infection. However, early data have suggested that Ad5-specific T lymphocyte responses after rAd5 vaccination are actually lower in individuals with pre-existing Ad5-specific neutralizing antibodies than in those without pre-existing Ad5-specific neutralizing antibodies (J. McElrath,