

# Lupus illuminated

Thanks to a newly identified gatekeeper gene, lupus is now a preventable disease for mice. Humans could be next.

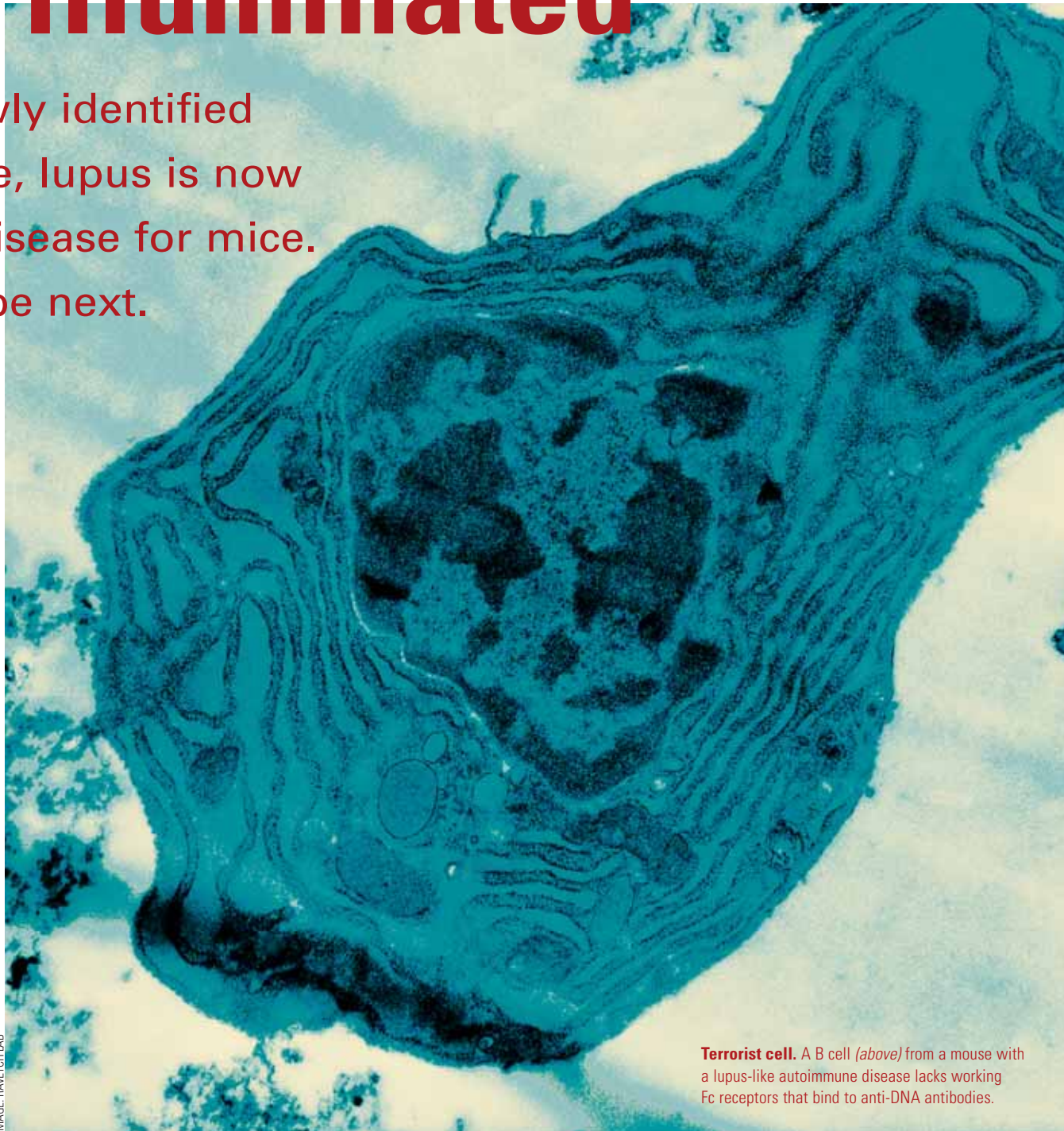
BY LYNN LOVE

Despite the fact that lupus results from a combination of genetic factors that may vary from person to person, Rockefeller scientists have found a common “gatekeeper” gene critical to its prevention — and say that reversing a defect in the gene leads to restored health in animal models.

Lupus, which afflicts some 1.4 million Americans, occurs when auto-antibodies — molecular arrows that trigger the immune system to assault the body's own tissues — accumulate, leading to fatigue, fever, joint pain, anemia and, in some cases, kidney failure, seizures and neurological damage, blood clotting and respiratory inflammation.

But the results of two new studies from **Jeffrey Ravetch's** Rockefeller laboratory suggest that a specific molecule,

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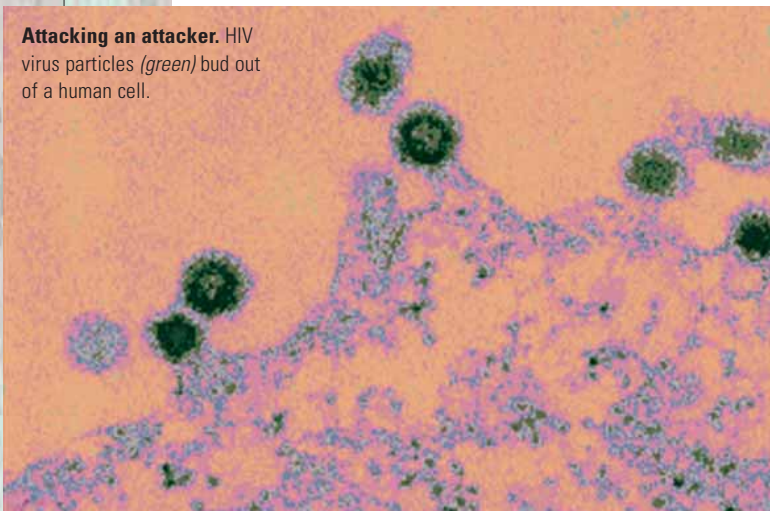


**Terrorist cell.** A B cell (above) from a mouse with a lupus-like autoimmune disease lacks working Fc receptors that bind to anti-DNA antibodies.

## New AIDS vaccine trial launches

*Rockefeller researchers begin testing the 'boost' phase of their 'prime and boost' strategy*

**Attacking an attacker.** HIV virus particles (green) bud out of a human cell.



The second arm of a clinical study to investigate an experimental HIV/AIDS vaccine began at the Rockefeller University Hospital in January, when two volunteers were injected with the ADMVA vaccine. Nine additional volunteers have joined the study to date and a total of 48 healthy men and women will eventually be enrolled in the protocol.

The phase I research study, which is being administered by Rockefeller research associate professor **Sarah Schlesinger**, is designed to evaluate the safety and immune system effects of a new vaccine called ADMVA. Developed by scientists at the Aaron Diamond AIDS Research Center (ADARC), headed by Irene Diamond Professor **David Ho**, the vaccine is a version of Modified Vaccinia Ankara (MVA), a vac-

cine that was used as part of a global smallpox eradication program in the 1970s. The ADMVA vaccine is designed to stimulate immune responses to prevent people who are uninfected with HIV/AIDS from contracting the disease. It is based on the 'C' strain of HIV, which is prevalent in China, India and Sub-Saharan Africa and accounts for more than 50 percent of new HIV infections.

ADMVA represents the second part of what's known as a “prime and boost” vaccine strategy designed to first prime the body's immune system by showing it synthetic, noninfectious parts of the HIV virus's genetic make-up, followed by boosting its ability to stave off HIV. The first arm of the study began in December 2003, when the Rockefeller University

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# Pop science

How Joel Cohen uses math to make sense of a complicated world

BY RENEE TWOMBLY

Inside **Joel Cohen's** head is a 3-D grid of the world, in which 100 million or so interconnected dots pulsate irregularly, sometimes swelling or contracting in slow-mo fashion and then rapidly reversing. To Cohen, who is the university's Abby Rockefeller Mauzé Professor and head of the Laboratory of Populations, each of these dots represents a species and it's his life work to figure out their dynamics and interactions.

Sometimes, Cohen takes on just a bit of this network, as when he modeled the interconnectedness of species found in Dutch farm soil and in a small Wisconsin lake. He has also tackled questions of more immediate concern to most people. In a 532-page book, he laid out what he calls the "choices and constraints" needed to figure out how many people can live well on our planet. Most recently, he has been arguing that modelers like him need to work side by side with bench scientists if biology is to be understood.

Cohen is on the hunt for quantitative theories that explain the behaviors of living populations, no matter what they are.

He admits that while his work may seem scattershot to many, "my mission in science is to understand this network of life that we live in, at both a fine and a worldwide scale of resolution," he says. "What I do for a living is to look for patterns that others have not yet seen. I try to invent better tools for seeing those patterns."

The broad reach of his research has earned Cohen not only entrance into expected societies, such as the U.S. National Academy of Sciences, the American Academy of



what we don't often consider is that the roads that bring energy from humans to other species have increased as well.

"All of our infectious diseases are other species making a living off of us," Cohen says. "Think of the thousands of bacteria in our gut, the fungi on our skin, the insects that suck our blood, and the diseases those insects inject." New microbes and viruses that prey on humans, such as Ebola and HIV, are burgeoning around the world, and old ones continue to thrive. Of particular interest to Cohen is Chagas' disease, caused by an insect-borne parasite similar to the one responsible for African sleeping sickness. Cohen's mathematical model of how the disease spreads has had public health implications for millions of poor Latin Americans. "The network of infectious disease is incredibly dynamic," Cohen says.

## Searching for structure

Within this dynamic, Cohen looks for coherence. He and his lab team use the tools of mathematics to search for patterns in the data and to test ideas. "The role of math in biology is to take a simple idea about how a complicated system works, understand the consequences of that idea, and see how the expected consequences compare with actual observation," he says. The art of Cohen's work is to look for features that seem more persistent within this dynamic web, in order to deduce the rules from which all flux is generated.

A case in point is the relationship between species and biomass. Charted on paper, the populations of different species in an ecosystem resemble a pyramid, called the pyramid of numbers: at the top are a few members of large-sized species; at the bottom are many members of smaller-sized species. Cohen and other ecologists found, however, that the total biomass of each species — the weight of all its members combined — is often relatively consistent, or may be slightly larger for bigger-bodied species. Fish species with a few big individuals at the top of the ecosystem have roughly the same, or slightly more, biomass as single-celled floating plant species with millions or billions of individuals at the bottom of the food web.

Considering the relationships between species based on their biomass leads to new ways of thinking about ecosystems. With former postdoc Tomas Jonsson, Cohen plotted the numbers of organisms in each species on one axis of a chart (logarithmically scaled) and the average body weight on the other axis (also logarithmically scaled), and connected the dots that represent individual species by arrows to show which species are eating which other species. Then, using observations from ecosystems as different as a tiny lake in Michigan's Upper Peninsula and the topsoil of farmlands in the Netherlands, Cohen, Jonsson and colleagues from the University of Wisconsin and the Netherlands found that the dots and arrows fell along a trend line with negative slope near  $-1$ .

In other words, the biomass of different species varied far less than the average body size or the population numbers. With current postdoc Daniel C. Reuman, Cohen also found that this map of a community of species shows how many predator-to-prey steps energy takes to go from the smallest to the largest species.

In 1984, Cohen's collaborator Stephen R. Carpenter and other researchers from the University of Wisconsin catalogued the open-water ecosystem of Michigan's Tuesday Lake, estimating the population of 56 different species that ranged from microscopic phytoplankton to several species of fish. In this environment, the largest species (a fish) was a trillion times the weight of the smallest but was outnumbered by a factor of 10 billion. After graphing each species' average body mass against its abundance (again, on logarithmic scales), Cohen found that nearly all species fell near a straight diagonal line drawn from the rare heavy species to the common light ones.

In 1985, his Wisconsin colleagues replaced the biggest fish with the even larger, and predatory, largemouth bass and, in 1986, again catalogued the lake's ecosystem. Cohen and his colleagues found the ecological pattern remained much the same. It was like a different cast of characters acting out the same play.

More recently, Dutch researchers asked Cohen to collaborate on a study that tested whether soil that was intensively farmed looked ecologically different from soil that was either conventionally or organically farmed. The linear pattern again held across the samples. It was remarkably similar to the overall pattern at Tuesday Lake, Cohen says, but the line sloped downward more steeply in the more intensively farmed plot, compared to organic soil.

"Now we want to understand the connection between the slope and elevation of the line and the physical and chemical management of the farm soil," Cohen says. "The elevation and the slope of the line could be useful summary indicators of the quality of land use, of how people affect a natural system."

## From fish to famines

Understanding populations of lake and farm dwellers is useful, but the big questions Cohen gets asked are often about people. It's often a variation on: How many humans is too many?

We've all heard the dire warnings about shortages of food, wars over water, and epidemics of disease that will befall our planet once we hit a certain number of billions. But Cohen argues that the future cannot be simply plotted as an extension — arithmetically, geometrically or logarithmically — of the past.

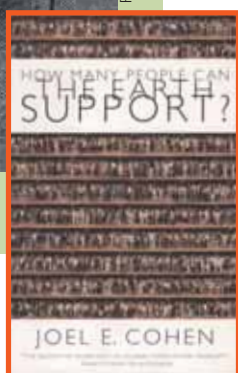
Compared with human history prior to World War II, the world's population growth rate since 1950 has been, and still is, unprecedented, Cohen says. Since 1600, the human population has increased more than tenfold, from about half a billion to well past 6 billion. The increase of 800 million people in the last decade of the 20th century exceeded the total population in 1600. Within the lifetime of some people now alive, world population has tripled, and within the lifetime of everyone older than 40 years old, it has doubled, he says.

Yet his 1995 book on global population, *How Many People Can The Earth Support?*, is neither "an alarmist tract nor a cornucopian lullaby," Cohen says. It is, instead, a study of contingencies. Cohen says that in the process of writing the book, "I came to question the question. 'How many people can the earth support?' is not a question in the same sense as 'How old are you?' It cannot be answered by a



PHOTO: LUBOS STEFANEK

Joel Cohen, above, and his 1995 book.




Arts and Sciences, and the American Philosophical Society, but also onto the worldwide Board of Governors of The Nature Conservancy. In 2002, New York Mayor Michael R. Bloomberg gave Cohen his Award for Excellence in Science and Technology. Cohen also is a professor of populations in the Earth Institute at Columbia University.

In his map of life, the size of each dot is based on the biomass and importance of the species to the rest of the network. The human dot would be huge — like New York City on a U.S. atlas, he says. The roads leading to each dot represent the energy consumed by the species that dot represents.

Because most species rely on other species for their energy, or are consumed by other species in search of energy, the dots are all interconnected. The network formed by the connections between a species and all the other species it eats is known as its food web. Cohen himself has kept logs of the species of food he eats, and over time it comes to about 150 different species of plants and animals. Humans collectively probably consume tens of thousands of other species. "That represents a lot of energy, and a lot of diversity, coming in," he says, with some amusement.

Humans, in fact, have provoked a lot of wobbling in the global food web. "Over the last 10,000 years, the number of humans has increased about 1,000 fold, creating a lot more demand on other species, and providing more available material," Cohen says. It is easy to understand that the roads that bring energy to the human species have multiplied, but



number or even by a range of numbers.”

But that doesn't mean that people have not tried. Estimates of the earth's human carrying capacity range from fewer than 1 billion to more than 1 trillion, he says. Most frequently, estimates fall between 4 billion and 16 billion, with a median estimate of 12 billion. Cohen says this “enormous spread follows from widely varying concepts, methods and assumptions.”

One dramatic example, he says, is the United Nation's prediction that if human populations continued to grow at 1990 rates in each major region, then the population would increase more than 130-fold in 160 years, from about 5.3 billion in 1990 to about 694 billion in 2150. “But those figures are extremely sensitive to the future level of average fertility,” Cohen says. If, hypothetically, couples bore only as many children as needed to replace themselves, world population would level off at about 8.4 billion by 2150.

And while everyone recognizes that the finiteness of the earth guarantees that ceilings on human numbers do exist, Cohen says that human choices, now and in the future, will decide where those limits fall. Questions of wealth, technology, politics, economics, demographics, environment, and, above all, values — what people want from life — can be approached as “population problems” to help quantify what is conditional and probable, Cohen says.

“The earth's capacity to support people is determined partly by the processes that the social and natural sciences have yet to understand, and partly by choices that we and our descendants have yet to make,” says Cohen.

In short, there's no easy answer, and anybody who offers one is probably wrong.

#### Doing math in a cell

Today, Cohen can be found encouraging the use of the mathematical methods he's long applied to groups of organisms to tackle the questions that take place within those organisms.

“Mathematical analysis will ultimately reveal biological processes better than any microscope ever has,” Cohen says. “Coping with the hyper-diversity of life at every scale of spatial and temporal organization will require fundamental conceptual advances in mathematics. Understanding how the cell came together is tremendously exciting, and we ought to really engage mathematics to the fullest extent that we can to help in that quest.”

In an essay published in *Public Library of Science Biology* in December, Cohen suggested applying math to understand how cells work, how the brain is linked to behavior and emotion, how heritable features are transferred between species, and how environmental conditions interact with biochemical processes.

Consider the complex network of gene interactions, proteins and signaling processes within and between cells. “This network is probably incomprehensible without some mathematical structure that has yet to be invented,” Cohen says. Math will not only benefit the study of biology, but working on difficult biological problems will likely stimulate mathematicians to create new math — just as physics and astronomy have in the past.

At Rockefeller, and other institutions, that means educating mathematicians and biologists to be comfortable with each other's thought processes and very different languages. It also means being wrong. The great thing about working with mathematical models, after all, Cohen says, is the opportunity to disprove them.

“I expect to be proved wrong. I announce to my colleagues that I've found a pattern and then lots of them set out to disprove it. In the meantime, though, I have fun pushing the pattern as far as the data will go. I consider my most successful modeling work to be something that looked good enough to push people to go and find out if it was true,” Cohen says.

“What I really hope is that my work stimulates people to find out what actually happens.”

## Where estimation meets litigation

### The unlikely story of Cohen's 22-year involvement in the Johns-Manville asbestos case

BY RENEE TWOMBLY

Leave it to the lawyers to complicate things.

One system that defied Cohen's rational approach to the study of populations is that of the behavior of attorneys. Of course, he couldn't know that in 1982, when he agreed to examine a projection of future asbestos claims.

The projection was the basis of a major bankruptcy filing by the Johns-Manville Corporation, an asbestos manufacturer. “I thought it might be intellectually interesting. It was a chance to test in practice the abstract science I had done on the uncertainty of population projections,” Cohen recalls with a hint of a grin.

Along with researchers from the University of North Carolina, Cohen worked for five years reviewing the epidemiological projection, eventually producing a 500-page report. He decided to examine every uncertainty in each parameter of the Johns-Manville model that projected future asbestos-related injuries and claimants.

Cohen estimated that the claims could be much lower or much higher than the numbers claimed in the bankruptcy filing. “If our higher estimate was true, the company would have to put more money into a trust fund to cover future claims,” Cohen says.

But nobody wanted to hear about uncertainty. The report was promptly buried.

But by 1990, there had already been far more claims of injuries than the Manville bankruptcy filing predicted. In fact, there were about as many claims as the upper extreme calculated in Cohen's buried report, and the trust fund created by Johns-Manville was bankrupt.

So a U.S. Federal District Court Judge in Brooklyn, Jack B. Weinstein, asked Cohen to serve him and the bankruptcy court as a neutral expert. Cohen's job was to refine the projections, give an honest estimate of uncertainty, and bring about a meeting of minds of the contending scientific experts hired by the parties to the bankruptcy legal action. Cohen agreed, with two caveats: he needed original data from Johns-Manville, and he wanted an agreement that the final work could be published.

For the next four years, Cohen worked with Duke researchers Eric Stallard and Kenneth Manton, running dozens of different projections for nine different asbestos-related diseases, based on a huge amount of data no one else had access to. The details of their study were published in October 2004 in a book authored by the three scientists, *Forecasting Product Liability Claims: Epidemiology and Modeling in the Manville Asbestos Case*.

Because it has been a decade since the end of the second court case, Cohen and his colleagues have been able to compare their projections with subsequent observations of an asbestos-related signature disease, mesothelioma, thought to be caused only by asbestos exposure, and of other diseases where the evidence or linkage to asbestos exposure was more ambiguous. The projections of mesothelioma turned out to be right-on. But the number of claims for some other asbestos-related diseases was far higher than Cohen and his colleagues had projected.

“We did the biology correctly, but there were still hundreds of thousands more claims than expected,” Cohen says. As of December 31, 2004, the Manville personal injury settlement trust had 749,288 claims filed against it. Approximately 639,000 have been settled at a cost of about \$3.4 billion. It's more than double the number of Cohen's original estimate and 10 times what Johns-Manville's model suggested.

“We just didn't project the ingenuity of some lawyers,” Cohen says.

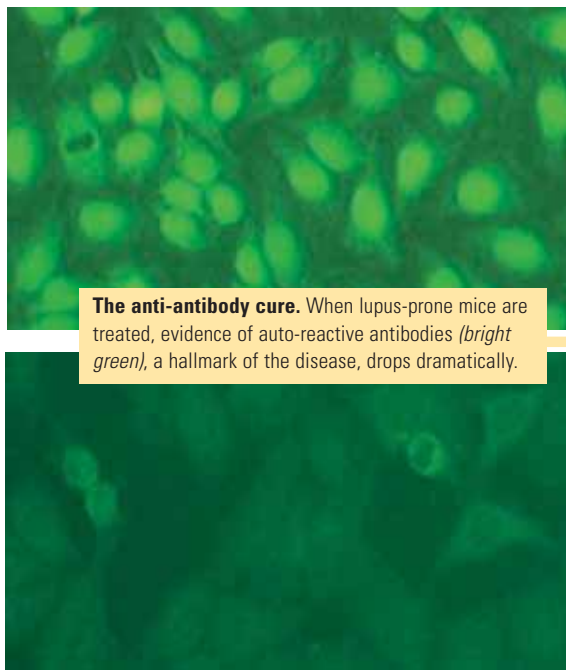
## Lupus illuminated *continued*

which binds to antibodies on the surface of cells, plays a key role in preventing this accumulation.

“Our research makes an important new point in responding to lupus as an autoimmune disease,” says Ravetch, the Theresa and Eugene M. Lang Professor and head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology. “Although the disease itself is a reflection of a cumulative set of factors that work in concert to reach a threshold and then trigger symptoms that are self-enhanced and self-sustaining, we have shown that it may be enough to simply correct a critical ‘gatekeeper’ function and thereby reverse the disease.”

Ravetch, a leader in basic immunology known for his elucidation of an important family of antibody binding molecules called the Fc receptors, and his colleagues have learned that it's a specific Fc receptor, FcγRIIB, that wards off the accumulation of auto-antibodies. The team, which includes post-docs Tracy McGaha, Hidehiro Fukuyama and Falk Nimmerjahn, also have discovered that this receptor is defective in lupus-prone strains of mice.

“Once we determined that this receptor inhibits the culprit immune system cells from becoming activated and limits the production of auto-antibodies, we wondered whether restoring it as the



**The anti-antibody cure.** When lupus-prone mice are treated, evidence of auto-reactive antibodies (bright green), a hallmark of the disease, drops dramatically.

body's last bastion of defense would be enough to prevent autoimmunity,” says Ravetch.

The researchers found that in mice genetically predisposed to lupus-like autoimmunity and with a reduced Fc receptor capacity, they could artificially coax the Fc receptors back into working order. Their modest increases in Fc receptor activity — the equivalent of effective gene therapy in humans — was enough to push the mice back to health.

“The difference between protective immunity and pathological autoimmunity for each individual is quite small,” he added. “We were able to reestablish the Fc receptor's activity by increasing its expression by only about 40 percent, and in only about half the B cells.”

Betty Diamond, a physician-researcher at Columbia University's College of Physicians and Surgeons, is collaborating with Ravetch to take the first steps in determining whether the same progression to lupus, including Fc receptor failure, occurs in humans. “Jeff has laid the groundwork well for understanding this pathway to disease,” says Diamond. “We have hopes of confirming this pathway in humans with lupus.”

What may be even more interesting in the Rockefeller team's findings is that the experiment restored the health of mice with lupus-like symptoms by increasing Fc receptor inhibition of auto-antibody formation. Auto-antibodies that were produced before the therapy persisted in the body, but with no further evidence of disease. These findings suggest that if the human disease is synonymous with the mouse model, a gene therapy approach to restoring Fc receptor activity in lupus patients could cure the disease's aggravating and disabling symptoms.

“The immune system is a balance of excess and inadequacy,” says Ravetch. “We're seeing evidence that the inhibitory Fc receptor on dendritic cells, another immune system cell type, may play a similar role in other illnesses. We may reach a convergence of understanding on immune system-related diseases, where small adjustments to certain checkpoints, like the Fc receptor, may be enough to restore health in multiple diseases.”



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Hospital and ADARC began testing the first part of the vaccine strategy, called ADVAX, in a phase I research study. That study is ongoing for another 6 to 12 months.

Participants in the new study, which are being recruited in New York City and at the University of Rochester Medical Center, must be healthy, HIV-negative, and at low risk of HIV infection. In addition, volunteers must plan not to become pregnant or impregnate a partner during the trial and for four months after the last vaccination. Participants are randomly assigned to receive either the experimental vaccine or placebo. The volunteers then visit the outpatient clinics 12 times over 18 months for follow-up blood work.

This smallpox vaccine on which ADMVA is based was well tolerated by animals when tested, and similar HIV vaccines made from MVA have also been well tolerated in people who received them. The ADMVA vaccine does not contain any material from live HIV, blood or blood products, or materials from individuals who are infected with HIV.

"It is absolutely not possible to get HIV infection from the ADMVA vaccine," says Schlesinger.

A successful vaccine would potentially save millions of lives each year. "With each passing year, the grip of the disease tightens worldwide as the disease makes new inroads into heavily populated regions in Asia," says Ho. "Developing an effective AIDS vaccine is one of the greatest challenges researchers and volunteers have ever faced. But the rewards in terms of lives that could be saved by an effective vaccine are also among the greatest in human history."

If ADMVA proves effective, ADARC and one of the study's funders, the International AIDS Vaccine Initiative (IAVI), are committed to ensuring that it is made available in developing countries at affordable prices.

## New York City rises, again

New Yorkers are rolling up their sleeves again, but not in the way that you might think. We're not showing up unasked to clean up a mountain of rubble and look for the missing and dead as we did in the aftermath of September 11, 2001. And we're not just helping out by assisting in the city's many classrooms or homeless shelters, neighborhood parks, or in the churches, mosques and synagogues of our communities as we consistently do. New Yorkers literally are rolling up their sleeves to receive an injection delivering a new, investigational HIV vaccine and allowing a small group of physician-scientists, including me, to study its effects on their healthy immune systems. New York residents, in unpredicted numbers, are coming forward to be HIV vaccine volunteers. It's humbling to me as a physician to witness this response to the epidemic that we know as HIV and AIDS.

It's been little over one year since we at the Aaron Diamond AIDS Research Center and The Rockefeller University Hospital started recruiting the more than 90 volunteers we will need over two years to test the investigational ADVAX and ADMVA vaccines and determine whether they are safe and promising for preventing infection by HIV. The recruitment effort of identifying 30 healthy individuals in New York City for the first arm of this HIV vaccine clinical trial that we thought last December would take the better part of two years instead took only a few months. We witnessed an immediate, overwhelming response to our call for volunteers. To date, more than 500 people have come forward to fill 30 volunteer research participant positions.

What's more, while we predicted that volunteers would come from communities within New York City that have been, from the epidemic's first days, politically active — such as the gay and lesbian community — and many members of this community have volunteered, we were

not prepared for the tide of response beyond this community. From the African American security guard whose teenage son is HIV+ to the young, not-for-profit sector administrator whose aunt died of AIDS to the Columbia University grad student to the Rockefeller University postdoc, each of their lives have been impacted somehow by the HIV/AIDS epidemic, many in ways that will not be immediately aided by the development of a vaccine. Yet they all say a version of the same thing: "I want to help in the effort to end the HIV/AIDS epidemic in my lifetime."

A vaccine for this viral killer is at the top of the global infectious disease wish list as more than 2 million people per year worldwide die from AIDS and more than 5 million people annually are diagnosed with new HIV infection, adding to the 40 million already infected with HIV. Ours is not the first vaccine to be tested. The early AIDS VAX vaccine, tested in multiple sites in the U.S. and in Bangkok, successfully enrolled a large cohort of healthy volunteers. Though the difficult clinical trial was well executed, sadly the vaccine does not work to prevent HIV infection. There's room for skepticism among the public at large of any new HIV vaccine initiative. Still, AIDS VAX was an important first attempt. There are a number of other HIV vaccine clinical trials in progress.

But one thing distinguishes our New York City HIV vaccine clinical trial from others, and that is a particular kind of fierce commitment to stem an epidemic that has hurt so many and continues to do so in this city. Recruitment for clinical trials is an ongoing challenge for research



PHOTO: ZACH VEILLEUX

physicians. In the majority of experimental treatments, recruitment of patients involves ongoing requests, through advertising, community outreach and physician-patient interaction. We are no different, of course, in our HIV vaccine clinical trial. We are, however, surprised at the large numbers of responses to our calls for research volunteers.

With our second arm of the vaccine, called ADMVA, which began in early 2005, we already have a strong, potential pool of research volunteers in place from the constant stream of willing participants who have contacted us over the past year. Our two-pronged "prime and boost" vaccine strategy using a part of HIV's genetic material may or may not work as a preventive vaccine. And even if it does not ultimately become the much-hoped-for vaccine, the more than 90 volunteers and their time in our clinical study will not go to waste. The data we collect from our participants' immune responses to vaccine is critical to implementing a vaccine strategy, be it this one or any other. We will use the understanding gained in this trial to move forward. And the commitment and enthusiasm of New York City's residents will help carry my colleagues and me through as many versions of a HIV vaccine as needed until we get it right.

## UPDATES UPDATES UPDATES

BY KRISTINE KELLY

### Insects that smell alike

In the battle against insect pests, research from **Leslie Vosshall's** laboratory suggests that it's all about the sense of smell. Last October, Vosshall and colleagues demonstrated

that one gene, Or83b, is essential for the sense of smell in fruit flies — when the Or83b receptor is missing, flies are unable to respond to most odors.

Now, the lab's new findings, reported in the February 22 issue of *Current Biology*, show that Or83b's function appears to be conserved across very different insect species, including the malaria mosquito, that span 250 million years of evolution.

**Shared receptors.** When scientists added the mosquito Or83b gene to fruit flies lacking their own version of Or83b, odor receptor proteins (light purple) worked normally — demonstrating that Or83b's function is conserved across both species.

Fruit flies have 62 odorant receptor proteins, 61 of which are exclusively expressed in specific neurons. But the remaining one, Or83b, is found in almost all olfactory neurons, and serves

a general function in detecting odors.

"We looked at Or83b in medflies and corn earworm moths, which are agricultural pests, and the malaria mosquito, which feeds on humans," says Vosshall. "While they all have very sensitive olfactory systems and very different food preferences, this odorant receptor is highly conserved across all of these different species."

When Vosshall and her colleagues placed Or83b genes from other species into mutant fruit flies that were missing their own Or83b gene, they found the flies' sense of smell was restored. Not only had the flies regained their missing sense, but upon further examination, the researchers found that other odorant receptors — which had been non-functional in the mutants — were now working correctly. This says that the mosquito Or83b could interact with fruit fly odorant receptors — a surprising finding given the different smell preferences of these two insects.

"Although mosquitoes and flies have very different opinions about odors, this receptor from mosquito functionally substitutes in the fly," Vosshall says. "If we could exploit this central function of Or83b-like receptors in insect smell, we might be able to design new insect repellents that would interfere with the function of Or83b to transport odorant receptors. This could in effect make mosquitoes 'blind' to humans. That in turn would be another weapon in the arsenal to interrupt vector-borne disease transmission."

### How bad cholesterol gets worse

Last spring, Kara Maxwell, a biomedical fellow in **Jan Breslow's** Laboratory of Biochemical Genetics and Metabolism, showed that she could increase levels of LDL cholesterol (the "bad" kind) in mice by increasing the expres-

sion of a gene called PCSK9. Now, results from a new paper published in *Proceedings of the National Academy of Sciences* show how that happens.

Maxwell and Breslow experimented on human liver cancer cells, which they engineered to overexpress PCSK9. The extra PCSK9 caused the cells to lose their LDL receptors, which normally serve to soak up LDL cholesterol from the bloodstream. Though normal numbers of LDL receptors were manufactured, the receptor was being destroyed as it made its way to the surface of the cell.

The team's findings complement a recent human population study in which investigators at the University of Texas Southwestern Medical Center found that about 2 percent of African-Americans with low LDL levels have mutations in the PCSK9 gene that disable the protein. Thus a picture has emerged in which too much PCSK9 decreases LDL receptors and raises LDL cholesterol levels, and too little PCSK9 does the opposite. The two papers were cited in *Science* magazine as the Editor's Choice in Biomedicine for the February 11th 2005 issue.

Previous studies of LDL receptor regulation focused on how the receptor's gene was turned on and off. "It is now clear that other genes are capable of regulating LDL receptors by different mechanisms, and LDL cholesterol lowering strategies of the future may target these genes," says Breslow. "For example, an inhibitor of PCSK9 might act to increase liver LDL receptors and lower blood LDL cholesterol levels."

"At this point, we don't know the exact mechanism by which PCSK9 degrades the LDL receptor," says Maxwell. "We are working on understanding whether PCSK9 directly destroys the receptor, or if it destroys another protein essential for the LDL receptor's integrity. We are also developing tools to prevent PCSK9 from destroying the LDL receptor as a way to decrease blood LDL cholesterol levels."

IMAGE: WALTON JONES/VOSSHALL LAB