discovery UPDATE
A Publication of the Lupus Research Institute
Fall 2006

# NIH Director Outlines Vision for Future at LRI Conference

## *Says Lupus Research Institute has 'Focused on What is Key'*

**In beginning** his lively dinner address at the LRI's Annual Scientific Conference, Elias A. Zerhouni, MD, asked the crowd of more than 100 scientists, lupus patients, and Institute supporters how much they think we know—based on what we need to know—to make a difference in the nation's health.

**"Where are we on the curve of science?" he said.**

It's an appropriate question, of course, for the director of the nation's top health laboratory responsible for guiding the research agenda and outlook for the organization's vast enterprise of 27 Institutes and Centers. And it's the kind of paradigm thinking that Dr. Zerhouni has initiated since assuming his post as National Institutes of Health (NIH) director in 2002 after decades of clinical, scientific, and administrative leadership in radiology and other fields of medicine.

The answer, according to the top scientists and 1,600 leaders in cutting edge biotech companies that Dr. Zerhouni previously canvassed, is that we know a mere 10 percent of what we need to know. "At the leading edge of science, we are all ignorant," he explained.

The scientific strategy for the century ahead will largely be shaped by the effort to make that other 90 percent of the trip, he said.

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Elias A. Zerhouni, MD, Director, National Institutes of Health

## LRI Awards 15 More Novel Research Grants

"The class of 2006 is a great mix of new investigators embarking on novel research and established investigators taking new directions."

–Mark Shlomchik, MD, PhD, of Yale University School of Medicine.

See pages 6-7.

## Cautious Optimism on New Drugs for Lupus

### Special Session Features Perspectives from Biotech, Pharma, and Academia

**With the recent surge** in knowledge about what causes and promotes lupus generated by LRI researchers and others, there appear to be—for the first time ever—several candidate drug "targets" for lupus with enough potential to prompt biotechnology and pharmaceutical companies to take a closer a look.

"I think in lupus the most exciting thing is that we are now seeing the possibility of validated targets," said Arthur Kreig, MD, a rheumatologist who started a biotech company. Other panelists at the special panel discussion on *Novel Therapeutics Based on Insights into Disease Pathogenesis,* moderated by Peter Lipsky, MD, largely concurred.

So-called "targets" are molecules or processes in the body that researchers—many of them funded by the LRI—have identified as likely to be involved in lupus. They include B cells, T cells (including regulatory T cells), Toll-like Receptors, dendritic cells, interferons, as well as early "upstream" culprits in activating the immune response pathways in lupus.

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## Forum for Discovery:

# 6th Annual LRI Scientific Conference

### Exciting Advances Reported by 2004 & 2005 Recipients

**More than 40 scientists** from around the country presented and discussed findings on cutting-edge lupus research, viewed posters, and took part in informal discussions among colleagues at the LRI's annual scientific conference at the Yale Club in Manhattan.

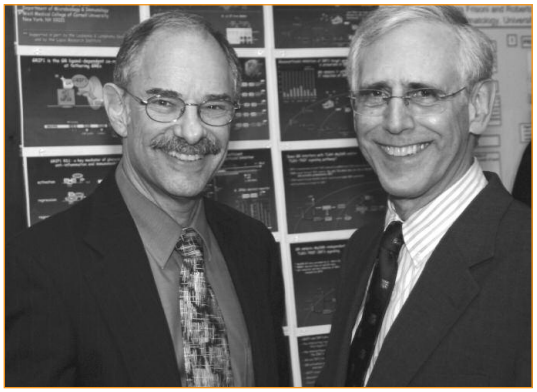
The October 19th and 20th meeting gave grant recipients a unique forum for exchanging ideas and building collaborations—and an invaluable opportunity to witness the intersection of basic science and clinical care.

Formal presentation sessions and lively poster sessions enabled LRI scientists to update their colleagues on findings in biomarkers and hormones, renal disease, cardiovascular complications and disease regulation, and more.

Cornerstone scientific addresses on this year's timely conference theme—innate versus acquired immunity—were given by Ruslan Medzhitov, PhD, of Yale University School of Medicine, Mark Shlomchik, MD, PhD, of Yale University School of Medicine, and Ann Marshak-Rothstein, PhD, Boston University School of Medicine.

Day 1 ended with a dinner address by NIH Director Elias A. Zerhouni, MD (see page 1), followed the next day by an open panel discussion with representatives from academia as well as pharmaceutical and biotechnology companies on the prospects for drug development in the coming years (see story page 1).

At Thursday night's dinner, LRI Novel Research Co-Chair Mark Shlomchik, MD, PhD, introduced the 15 newest LRI grant recipients (see page 6).



Benjamin D. Schwartz, MD, Michael Lockshin, MD

"Meeting other investigators and particularly 'behind the scenes' donors, patients, LRI staff…knowing first-hand what they do, and feeling their compassionate enthusiasm for not only the research but also the patients, made me appreciate further the depth and breadth of the LRI-funded research and reminded me again the ultimate mission of our research—to help patients with lupus."

—LRI researcher Chau-Ching Liu, MD, PhD
University of Pittsburgh School of Medicine

Robert Eisenberg, MD, Thereza Imanishi-Kari, PhD, Mark Shlomchik, MD, PhD

Felipe Andrade, MD, PhD

Greg E. Lemke, PhD

Anne Davidson, MD, Benjamin D. Schwartz, MD, William E. Paul, MD

**Thanks to the following for their generous support of *Forum for Discovery 2006***

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Coley Pharmaceutical Group
FoxKiser
Genentech/biogen idec
Novartis
Vilcek Foundation

# NIH Director Outlines Vision

—Continued from page 1

"The most important concept that I've tried to bring to the NIH is to try to have a conversation in all fields and across all fields of science," he said—part of the NIH Roadmap for Medical Research begun in 2003 to chart the NIH's course for the next several years.

Those conversations among top intramural and extramural scientists and advisors yielded answers. "We have the way to do it," Dr. Zerhouni said of the journey to greater knowledge ahead. "It is to be able to increase the diversity of the science. To multiply the number of scientists that really look—that have a novel way of thinking. We need to change fundamentally the way we conceive of biological experiments."

> "We have to understand not just the content of science but the context of science. That's why I really admired the way the 15 new grants were presented to us because you could really see that in the content of what was being described there was also a context. It's as if there were a neighborhood that the lupus community inhabited."
>
> – Elias A. Zerhouni, MD

## Leveraging Knowledge

With its bold and multidisciplinary approach, an organization like the 6-year-old Lupus Research Institute can play a crucial role in the roadmap, Dr. Zerhouni implied. "I'm so pleased to hear about the Institute and what you've accomplished in a very short time," he said. "And what is really fascinating to me is how you've really been able to focus on what is key."

As with the NIH's unique Pioneer Award Program begun in 2004 on Dr. Zerhouni's watch, the LRI has focused on innovative and potentially high impact—'pioneering'—approaches to scientific inquiry.

To date, the Pioneer Award program has awarded 22 grants. And unlike the normally data-heavy and lengthy applications required for an NIH grant, these competitive awards are only 5 pages long. Their goal is to give scientists a chance to experiment and explore new ideas.

Similar in principle, the independent LRI has, in turn, leveraged much of its novel research into major funding at the NIH. "I was so pleased to come here,", said Dr. Zerhouni, "because you have said that $6 million dollars have attracted $24 million at the NIH!"

"The LRI has amassed a record of accomplishment marked by what most would agree is the gold standard of such success," explained Dr. Paul upon introducing the night's speaker. "That is the ability of their work to attract peer-reviewed funding from the NIH."

## New Strategies for a New Century

"To make change in science," Dr. Zerhouni continued in language evocative of the LRI, "we need to recognize first and foremost that no one knows the answer at the edge of science and you have to be humble. The second is that no one knows the exact pathway or approach by which the next breakthrough is going to occur. You have to be flexible enough to allow the diversity of approaches."

The way to do it is not to pursue known answers, he continued. "What we have to do is to allow people to explore different avenues in the field of science. We need high risk, high impact science."

> "Elias Zerhouni's vision for the future of biomedical science and his efforts to 'herd the scientific cats' will bear fruit for all of us, as citizens, as scientists and as patients."
>
> –William E. Paul, MD
> Chief, Laboratory of Immunology, NIAID, NIH

And good science also starts with one question and always ends up with two questions, he added. "Frankly, I look at immunology or autoimmune diseases like lupus, and I think I started with one question in medical school and ended up with 27. It is really one of the most complex diseases."

New strategies are needed in this era of intense competition for NIH grants and a leveling out of federal funds for scientific investment. "In an environment like this," noted LRI President Margaret Dowd, "the LRI model to risk testing new ideas and then capture expanded funding once the hypothesis proves viable takes on particular appeal."

And it's a model whose power will very likely weather changes that remain hard to anticipate. "It can be argued," said Dr. Paul, "that we stand at a critical transitional moment; the future will not be like the past!"

# Cautious Optimism on New Drugs for Lupus

—Continued from page 1

Having targets is crucial because they give drug developers something to aim for with the goal of preventing, slowing, or halting the disease. The targets are the first step to safer and more effective medicines—and a cure.

"We are living in a very exciting time because over the next few years we will be validating major categories of therapeutics," echoed Flavius Martin, MD. "The likelihood is that by 2011 we may have answers on which of these won't work, at which point the job is to sort out which will work—a much more complex issue, actually."

Dr. Lipsky noted, "it's been 40 years and all we have [approved] for lupus is aspirin, glucocorticoids (such as prednisone), and hydroxychloroquine. That's a rather unique circumstance."

"But we've just had a great two days of science," he added, referring to the numerous scientific sessions in which LRI researchers presented their work, "and we have drug representatives here very involved in research who can talk about what they see for the future."

## A Dose of Provocative Realism

The challenges ahead are formidable but not insurmountable, the panelists agreed. "As we learned from Dr. Zerhouni last night," noted Dr. Lipsky, "we know only 10 percent of what there is to know in biology and science as a whole in order to make progress. But we know even less—possibly just .1 percent—of what we need to know to be successful in preventing and treating lupus."


At podium: Arthur Kreig, MD, Chief Scientific Officer, Coley Pharmaceutical Group
L to R: Jeffrey Browning, PhD, Distinguished Scientist, Biogen Idec; Flavius Martin, MD, Genentech; Peter Lipsky, MD, (moderator) Chief, Autoimmunity Branch of NIAMS Intramural Research Program. Not pictured: Keith Elkon, MD, Head of the Division of Rheumatology, University of Washington; Robert A. Eisenberg, MD, Chief of the Division of Rheumatology, University of Pennsylvania School of Medicine

While several drugs targets in lupus have been identified, for example, it remains to be seen whether they are right for translating into therapies, or whether they can specifically target and block steps in the misguided immune response without damaging other parts of the body.

Cost, risk, and time are all daunting obstacles. For biotechnology and pharmaceutical companies, a new medicine costs an estimated $1 billion to take from research stage to FDA approval.

"It's incredibly expensive," explained Dr. Kreig in an introductory talk on why more companies aren't developing lupus drugs. "A lot of programs fail. Companies are not willing to make the investment unless there is very high confidence they will make their money back."

With a touch of exasperated humor, he added that "if you start a program on drug development, your stock is going to go down 50 percent the next day." And the scenario for lupus drugs is even riskier. According to a recent review of some 450 clinical drug development programs, the probability of success (i.e. FDA approval) when starting a new Phase 1 drug program is a mere 6 percent, but for lupus it is 0 percent, as no new drug as been approved in decades.

Within a company, the view on drug development in lupus also is colored by the size of the company and its capacity to absorb risk, said Jeffrey Browning, PhD. "At a mid- to large pharmaceutical company, you are competing for a pool of money and that pool tends to go towards lower risk things or lifecycle management on existing drugs…[lupus] is trying to eek out an existence on the residue, so you need crisp endpoints."

Validation of a drug target would alter that outlook dramatically, however. "If for lupus one company can validate a target, and show that

they have something that makes a real difference in patient outcomes, all of the companies are going to go after that target. But until the target is validated, the risk of failure is very high," said Dr. Kreig.

## Steep but Surmountable Path

Things are changing for lupus, however. Prospects for a validated lupus drug target improved dramatically with the issuance of the FDA Draft Guidance Document in spring 2005. Overnight, it became much more appealing to pursue lupus drugs, as the document clarifies the pathway for developing one.

To actually get a drug approved, however, more people with lupus will have to participate in the trials that test for safety and efficacy—no easy feat given the often highly variable course of the disease and many disqualifying factors.

## Now Is the Time

Now is the time to prepare for that moment when one of the many lupus targets in the pipeline is validated, Dr. Lipsky and others pointed out. "Or it will all be for naught. We have to start planning now on how to run lupus clinical trials."

The size and flexibility of these trials have to be considered, for example. With the often overwhelming challenge in signing up sufficient participants that fulfill strict trial criteria, "the name of the game is industry rapidly going to small numbers of patients and over a small time frame," said Dr. Browning.

"The ticket to getting more involvement [from industry] is the ability to run extremely focused 'proof of principle' trials with a hard end point," he said,"…to even look at just one snippet of biology and have a key insight and go from there."

"Perhaps smaller trials will give us enough information to further our understanding of the science and biology of the disease before hundreds of millions of dollars are thrown at the subject," explained Robert Eisenberg, MD.

## Working Together

Success in developing new lupus drugs will require more explicit links and good faith interaction between industry and academia, the panelists pointed out. All parties will benefit from conferring on protocol design and strategies for modifying a trial goal even if the study has started—in the event that one outcome isn't showing promise but another is.

Academic researchers can help by developing animal models for quickly testing a new agent, for example. Industry, for its part, can provide resources to support creative ideas in academia.

> "The panel discussion gave a very useful alternative 'real world' perspective on how science can be translated."
>
> – LRI researcher, Theresa Lu, MD, PhD
> Hospital for Special Surgery, NY

"Maybe the whole market concept might need to be tweaked," said Dr. Eisenberg, "so you don't have small companies stick with something they have to and big companies kill things because they can't afford to take risks."

"Perhaps there should be another kind of economic model as to how to develop drugs for difficult diseases like lupus," he added,"…the way that people have suggested new economic models for developing drugs for the third world."

## Reception and Dinner at LRI Scientific Conference Brings Together Donors, Advocates, Patients, and Scientists

Elias A. Zerhouni, MD
Richard K. DeScherer
William E. Paul, MD

Bevra H. Hahn, MD
Benjamin D. Schwartz, MD
Bruce N. Cronstein, MD

Jan Erikson, PhD
Margaret G. Dowd
William E. Paul, MD

Jack Lavery
Kathleen A. Arntsen
Robert J. Ravitz



# Fifteen New LRI Grants in 2006

**Following a rigorous review** of a record number of applications—92 in all—the LRI Novel Research Peer Review Committee selected 15 scientists to receive 3-year, $300,000 grants. As in years past, the selection was based on the novelty and potential of the hypotheses presented and on the promise of the investigators themselves.

The committee is co-chaired by Mark Shlomchik, MD, PhD, of Yale University School of Medicine and Nicholas Chiorazzi, MD, of North Shore/LIJ Health Systems.

The scientists awarded the grants, which were announced at the LRI Annual Scientific Conference in October, are attempting to answer today's most pressing questions about lupus:

## Why is lupus so unpredictable?

In lupus, virtually all organs and tissues are vulnerable to attack at some point. Two studies aim to find ways to better predict the course of this chronic disease.

**Chau-Ching Liu, MD, PhD**
***University of Pittsburgh School of Medicine***

In lupus, T cells are inappropriately "turned on" to attack the body's own cells. Dr. Liu recently developed a test that measures specific proteins on the surface of T cells that may indicate abnormal hyperactivity in these cells. Now she will determine whether the test can help to more accurately diagnosis lupus and predict flares.

**Eric Greidinger, MD**
***University of Miami Miller School of Medicine and VAMC, Miami***

It has long been thought that autoantibodies and T cells dictate which organs are damaged in lupus. But Dr. Greidinger's work in mice suggests that it is actually innate immunity—a primitive defense system that we share with fish, insects, and even plants—that singles out organs for attack and determines the severity of disease. He will test whether this hypothesis holds true in people by studying patients with a range of lupus severity and organs affected. If correct, it may be possible to harness the innate immune system to convert severe disease into milder disease.

## Can the lupus immune system be brought back in line?

Immunotherapies—drugs that modulate the immune system—have the potential to treat lupus with less toxicity. Several grants investigate approaches to restoring normal immune function in lupus.

**Harvey Cantor, MD**
***Dana-Farber Cancer Institute, Boston***

Lupus appears to be caused, in part, by the abnormal production of interferon—blood proteins that "interfere" with viruses. Dr. Cantor has found that a gene implicated in mouse lupus—osteopontin—can make white blood cells release interferon. He will attempt to cement the role of osteopontin in lupus as well as screen for small molecule drugs that might block the gene, and thus interferon.

**Lee Ann Garrett-Sinha, PhD**
***SUNY, Buffalo***

Dr. Garrett-Sinha has found a protein (Ets1) that limits the secretion of antibodies by mouse B cells, including the kind of self-reactive antibodies that cause so much damage in lupus. She will investigate how this protein halts autoantibody production, opening up the possibility of using drugs directed at this protein to lower autoantibody levels in people with lupus.

**Christopher A.J. Roman, PhD**
***SUNY Downstate Medical Center, Brooklyn***

In lupus, white blood cells send out immune-system activating signals—a call to arms—despite there being no infection to fight. The activated immune system then turns on the body. Can this abnormal behavior be controlled? Dr. Roman has discovered two proteins inside white blood cells that trigger a critical immune activating signal (CD154). Using white blood cells from people with lupus, he will examine whether blocking these cell proteins extinguishes the trouble-making activating signal.

**Robert A. Eisenberg, MD**
***University of Pennsylvania School of Medicine, Philadelphia***

B cell-busting drugs such as rituximab have been highly effective in treating B cell leukemias and some autoimmune diseases. Successfully using these drugs in lupus hinges on being able to measure how a patient responds. Dr. Eisenberg will experiment with whole-body scanning techniques to develop (initially in mice) new methods of visualizing B cell loss from the spleen and lymph nodes—the immune system tissues that matter most in lupus.

## Why are women more prone to lupus?

Nine women for every one man are affected by lupus. Two new theories that link sex hormone and autoimmunity are being funded by the LRI.

**Michele M. Kosiewicz, PhD**
***University of Louisville Research Foundation, Kentucky***

Dr. Kosiewicz has found that in female mice with lupus, a type of white blood cell that prevents autoimmune disease—regulatory T cells—is lower than in male mice with lupus. Give the female mice male sex hormone (testosterone), and the levels and activity of these cells increase—and get protection against the disease. By clarifying how regulatory T cells prevent lupus and testosterone enhances their action, Dr. Kosiewicz may unveil strategies for suppressing lupus activity.

**Alessandra B. Pernis, MD**
***Columbia University Medical Center, New York***

Dr. Pernis hypothesizes that the female sex hormone, estrogen, both activates the T cells that push B cells to make autoantibodies and also reigns them in—dual and opposite effects. If true this may explain why most women, despite an abundance of estrogen, don't develop lupus. Having discovered a new estrogen-activated molecule that may fuel this braking mechanism, Dr. Pernis will now test whether it is faulty in women with lupus—and can possibly be fixed.

## What causes nervous system damage in lupus?

Why some people with lupus develop devastating neurologic and psychiatric problems remains unclear. The following may unravel some of the mystery.

**Keith Elkon, MD**
***University of Washington, Seattle***

Autoantibodies can attack and kill brain cells directly, but Dr. Elkon doesn't think this explanation fully accounts for the neurological complications of lupus. He theorizes—and will test—whether damage in lupus is compounded by the build up of dead cells in the brain that together with autoantibodies make neighboring brain cells release interferon, thereby causing significant neurological damage.

## Why and how does the immune system turn against the body?

A primary goal of LRI research is to understand how the immune system that normally attacks invading viruses and bacteria tragically turns against the body in lupus. Five grants examine the role of different white blood cells—the B cells that make autoantibodies and the T cells and dendritic cells that help them—conspire to launch the misdirected attack. A sixth examines whether infection is the initial trigger.

**Chandra Mohan, MD, PhD**
***University of Texas Southwestern, Medical Center, Dallas***

In lupus, restrictions on dangerous B cell behavior break down. Using rapid, cutting-edge genetic technology never before applied to autoimmunity, Dr. Mohan will screen for genes important to this process, and may well find—in a very short time—a whole panel of them for which treatments can be devised to reinstate control over B cell behavior.

**Stephen C. Pelsue, PhD**
***University of Southern Maine, Portland***

In 2005, researchers reported that defects in a previously unknown gene (Ttc7) cause lupus-like disease in mice. Dr. Pelsue, one of the original researchers, will now investigate how the gene controls B cells—work that may reveal a new disease pathway.

**Thereza Imanishi-Kari, PhD**
***Tufts University School of Medicine, Boston***

Most research on the B cells that produce tissue-destroying autoantibodies in lupus has focused on fully developed blood-borne B cells. Dr. Imanishi-Kari will pursue the novel idea that immature B cells—the ones that are still developing in the bone marrow—are in fact the major source of destructive antibodies in lupus. If she's right, researchers working on B cell-directed therapies may need to shift their sights to a new target.

**Jian Zhang, MD**
***University of Chicago***

The T cells of people with lupus produce too much of a molecule called FLIP. Dr Zhang's interest in this molecule intensified when he found that mice that overproduce FLIP develop a lupus-like syndrome. Is FLIP the molecular switch that corrupts lupus T cells? Dr. Zhang will resolve how excess FLIP influences T cells in lupus.

**Jan Erikson, PhD**
***The Wistar Institute, Philadelphia***

The rare and unusual white blood cell, plamsmacytoid dendritic cell (PDC), is suspected of aiding and abetting the immune systems attack on self in lupus. It's been difficult to study PDCs because their numbers are vanishingly small. Dr. Erikson will now clarify the involvement of this prime suspect in lupus by studying mice in which PDCs are genetically engineered to glow fluorescent green.

**Jochen Mattner, MD**
***University of Chicago***

Although never proven, experts have long suspected that bacterial or viral infections elicit strong immune responses that lead to autoimmune diseases such as lupus. Dr. Mattner has preliminary evidence that a common bacterium, Sphingomonas, has a unique ability to induce autoantibodies in mice. If he can prove this bacterium is a culprit in lupus, vaccines to protect people against it—and thus lupus—become a tantalizing possibility.



Candace Baptiste, lupus advocate and patient, is greeted by Valerie Van Buren, chief of staff for Rep. Diane E. Watson (D-CA).

Frances E. Ashe-Goins, RN, MPH, of the Office of Women's Health chats with Martha Nolan of the Society for Women's Health Research.

## Racial Disparities in Lupus Addressed at Congressional Briefing for First Time

LUPUS RESEARCH INSTITUTE National Coalition
The Patient Voice for Lupus Research

Event Presented by the LRI National Coalition and Congresswoman Hilda L. Solis (D-CA)

Rep. Hilda L. Solis (D-CA) and Daniel J. Wallace, MD

**Congressional staff,** lupus advocates, and government representatives gathered on Capitol Hill on October 4th for a briefing to hear about a long-neglected subject: the devastating impact of the autoimmune disease lupus on women of color—who are at increased risk for developing lupus and suffering serious complications.

Leading lupus physicians, NIH staff, private sector advocates and others, including the S.L.E. Lupus Foundation, presented models for grass roots, community-based intervention programs designed to reach minority populations.

## Fifteen LRI-Funded Research Presentations at American College of Rheumatology Meeting

**Once again** a record number of LRI scientists presented findings at this major annual scientific meeting in Washington, D.C. in November. Topics ranged from lupus kidney disease to the discovery of numerous early markers (biomarkers) critical for assessing disease activity, organ damage, and response to therapy. Three investigators funded through the ACR/LRI Lupus Fellowship program—a mentored post-doctoral award designed to encourage careers in lupus research—also presented their work.

"We couldn't be more proud of our scientists," said Margaret Dowd, president of the LRI. "Their highly original hypotheses are yielding results heard at a conference attended by thousands and reported to thousands more."

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