discovery UPDATE
A Publication of the Lupus Research Institute
Fall 2007

Lupus Research Institute Discoveries Blaze New Paths to Understanding and Treating Lupus

Results Ripple through Field, Transform Research Outlook

In frustration over the glacial pace of discoveries in lupus, families and scientists formed the Lupus Research Institute with the conviction that being open to the most brilliant ideas would finally shake up the field, spur innovation, and generate new understanding of why and how the lupus immune system attacks the body that it should be defending.

Now a professional assessment of the Institute-funded work completed to date reports striking successes for this pioneering approach.

In funding ideas that others wouldn't risk—85 new ideas explored over 3 years each—the LRI has energized and advanced immune system research in lupus. "The speed with which the Institute has changed the outlook for lupus research is remarkable," said William Paul, MD, Chief, Laboratory of Immunology, NIAID-NIH, and chairman of the Lupus Research Institute's scientific advisory board.

Key Discoveries Documented Within Just 7 Years of Launching Bold, Novel Research Strategy

- **Genes** that Increase Susceptibility to Lupus
- How Lupus Damages **Organs—Kidneys, Heart, Brain, Skin**
- **Pathways** that Enable Misguided Antibodies to Attack
- **Molecules** that Determine Control of the Immune System
- Targets for **New Treatments**
- 20+ New **Biomarkers** for Diagnosing, Monitoring & Treating Lupus

Several areas of discovery are particularly striking.

Discoveries: Genes that Increase Susceptibility to Lupus

LRI scientists have identified two genes that make lupus-prone mice susceptible to lupus—fresh insight into how the disease develops. Scientists are now examining if the same genes are defective in people with lupus. .

Discoveries: How Lupus Damages Organs—Kidneys, Heart, Brain, Skin

Institute-funded researchers have shown that five novel explanations for how lupus damages vital organs such as the kidneys, brain, and heart, are correct. Now moving ahead: methods to stop this damage.

Discoveries: Pathways that Enable Misguided Antibodies to Attack

Institute-funded investigators have found four pathways involved in auto-antibody production that highlight new ways to prevent lupus.

Discoveries: Molecules of Immune System Control

Institute-funded scientists have described four molecules that act as critical control points for the immune system. These molecules are potential targets for new drugs for lupus and other autoimmune diseases.

Discoveries: Targets for New Treatments

The rapid and highly promising results of the Institute's cutting-

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LRI Strategy Turns $9 Million Investment into $30 Million in Federal Funding for Lupus

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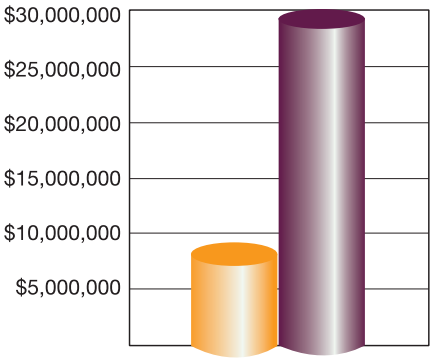
The LRI strategy of backing innovative but high-risk investigations into lupus has yielded an unprecedented figure—$30 million—in large-scale funding from the National Institutes of Health and other sources, an independent progress report has determined.

Delivered by the LRI Research Classes of 2001 through 2004, in whom the LRI invested $9 million for $300,000 awards over 3 years, the large-scale funding was won by the 61 percent who were successful in confirming their innovative hypotheses on why and how lupus happens and what can be done to prevent and treat it.

"These leverage numbers are remarkable and inspire such hope, especially in this era of budget austerity for biomedical research," said LRI Board of Directors Co-Chair, Robert J. Ravitz. "By supporting brilliant but untested ideas in lupus, we are ensuring that exploration into this devastating illness continues."

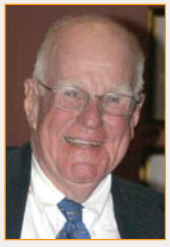
"The LRI has been the leader in seeking and funding unproven but promising scientific hypotheses in lupus," adds Mark Shlomchik, MD, PhD, professor of Laboratory Medicine and Immunology at Yale University School of Medicine and a member of the LRI Scientific Advisory Board. "It's because the LRI supported these innovative ideas in the first place that successful competition for scarce federal funding was possible."

Since its inception 7 years ago, the Institute has invested $22 million overall in cutting-edge lupus research, and subsequent classes, still at work on their investigations, are poised to capture similar large-scale awards.



Strategy Propels Novel Lupus Research to New Levels Despite Federal Budget Tightening

LRI Remembers John A. Luke, Sr.



The Board of Directors and staff of the Lupus Research Institute mark the passing of a beloved founding board member and remarkable person. Mr. Luke passed away in May from complications following a brief illness.

His daughter, Jane Luke Murphy, died from complications of lupus in 2003.

Mr. Luke graced the LRI mission and its work with his wisdom, unceasing commitment, and unwavering certitude that the battle to conquer and cure the devastating disease that is lupus can and will be won.

LRI-Funded Discoveries

—Continued from page 1

edge model for funding new ideas in lupus research is enticing pharmaceutical companies to investigate potential new drugs for lupus for the first time in decades.

Discoveries: 20+ New Biomarkers for Diagnosing, Monitoring & Treating Lupus

Biomarkers are crucial among other things for monitoring, managing, and determining treatment efficacy in lupus. Six of the more than 20 identified by LRI investigators are now being tested in human tissue and people with lupus. Already confirmed: the biomarker, pro-inflammatory HDL (piHDL), as an abnormal plaque-promoting molecule in the blood that signals early atherosclerosis in people with lupus.

Research Spreads Bright Lights of Discovery

LRI discoveries have appeared in such rigorous and widely read journals as *Science, Journal of Immunology, New England Journal of Medicine, Annals of Internal Medicine,* and *Immunity.*

Sixteen papers were published in the past year alone, and at least 25 more are in the pipeline.

Because of this wealth of findings, scientists flicking on their laboratory lights every morning—hundreds of thousands of immunologists, cardiologists, nephrologists, from Los Angeles to Chicago, New York, and beyond—now have a deeper, more nuanced grasp of where to look for answers in lupus.

"The quality and quantity of these studies, and the high number of times that other scientists cite them," said Nicholas Chiorazzi, MD," shows what a dramatic impact the Institute is having on finding solutions to lupus."

LRI Advocacy Victory

New NIH Plan, Initiated by LRI Clarion Call, Brightens Horizon for Lupus Research

Request: June 2004, LRI Advocates meet with House Appropriations Committee Chairman, Bill Young (R-Fla), to describe the need for a 5-year research plan for lupus across all relevant Institutes of the NIH.

Action: Fiscal 2005 House Appropriations Committee Report asks the NIH to develop a lupus strategy to "cover the full spectrum of lupus research." NIAMS meeting shapes and formulates scientific plan. **"Because lupus is a multifaceted disease, the Committee encourages the Director to ensure that all relevant institutes work closely and collaboratively to maximize the output of our national investment in lupus research."**

Result: In August 2007: A Strategic Plan: ***Future Directions for Lupus Research*** – is published to guide the nation's investment in lupus.

Read the plan on www.niams.nih.gov or through the LRI website, LupusResearchInstitute.org.

Thank you, Congressman Young!

Pictured with Rep. Bill Young [center] in June 2004, L to R: LRI President and CEO, Margaret G. Dowd, Lupus Foundation of Mid & NNY's President, Kathleen Arntsen, Secretary Sandi Frear, and Treasurer Sarah Eastup

October 2, 2007

The Honorable C.W. Bill Young
2407 Rayburn House Office Building
Washington, D.C. 20515

Dear Congressman Young,

Little could we have imagined in June 2004 that our meeting with you in your Capitol Hill appropriations office, as advocates from the Lupus Research Institute, would make such a difference in the lives of the more than 1.5 million Americans with lupus.

Your empathy, care and responsiveness on that day, and your subsequent action through the appropriations process to invigorate the research community, has now led to concrete strategies for unlocking the mysteries of this devastating illness.

I am pleased to inform you that two years after you wrote language in the Fiscal 2005 House Appropriations Committee Report mandating development of a plan to cover the full spectrum of lupus research, a new five-year trans-NIH research plan for lupus has come to fruition.

Thanks to you and the leadership of Dr. Steve Katz at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, The Future Directions of Lupus Research—the plan to guide the nation's investment in lupus research—was published August 5.

We, and millions who live with lupus every day, thank you for your vision in understanding the critical need to stimulate the cross-disciplinary research that this complex, destructive and baffling disease requires.

As the only national organization devoted exclusively to funding novel research in lupus, The Lupus Research Institute is now ready to take the next step in its leadership, to work with federal and non federal partners to see that the plan becomes a truly living document and is implemented as envisioned across the powerful Institutes of the NIH.

With sincere appreciation and very best regards,

Margaret G. Dowd
President and CEO
Lupus Research Institute

Thank Congressman Young Yourself!

Write your own letter of appreciation, and encourage Congressman Young and his colleagues to keep up the good work!

Let him know how important the commitment to lupus research is to you.

Send your letters to the LRI and we'll deliver them directly to Congressman Young's office in Washington, DC.

Email letters to lstegmaier@lupusny.org or mail to:
Thank You Congressman Young!
c/o Lupus Research Institute

Deadline for submission: December 15, 2007

2007-2012– *Across the powerful Institutes of the NIH, work to prevent, treat, and cure lupus gets underway. Things are happening in lupus research!*

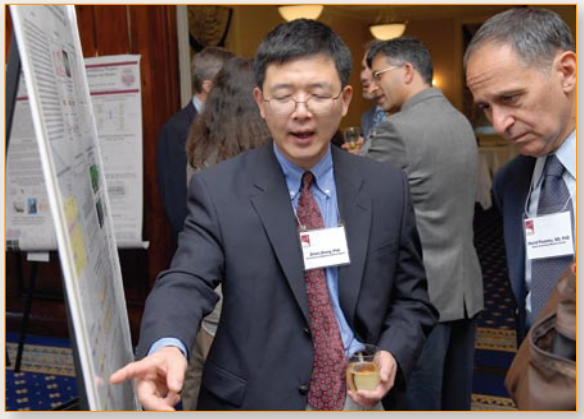
7th Annual LRI Scientific Conference— September 24-25th 2007

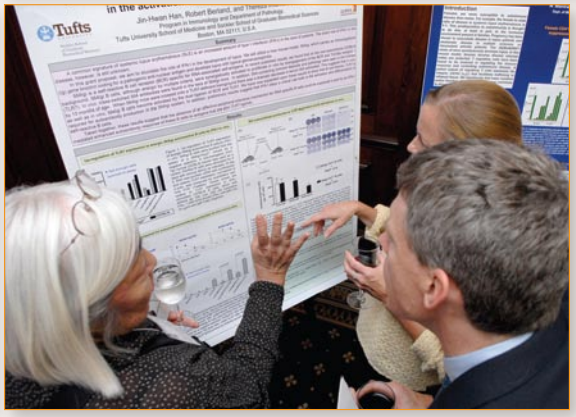
CHALLENGES IN TRANSLATION

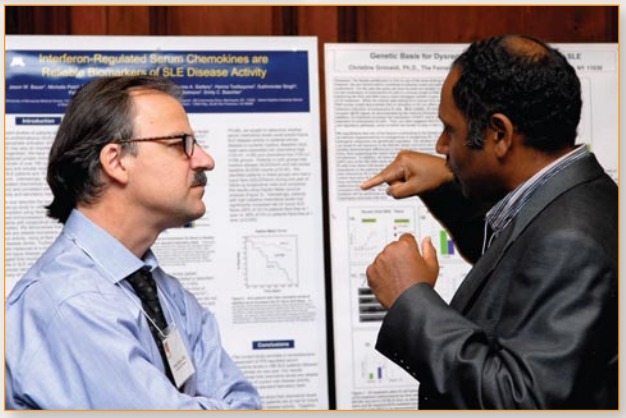
From Innovation to Clinical Development

Panels, Posters, and Presentations Foster Idea Exchange and Collaboration at 2-Day New York Meeting

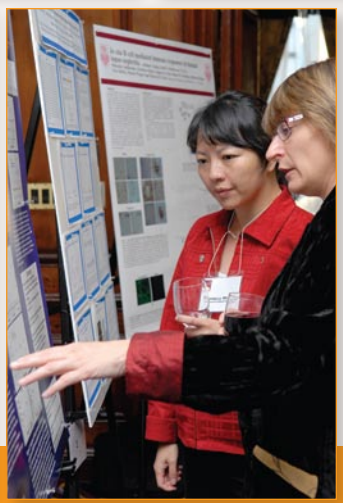






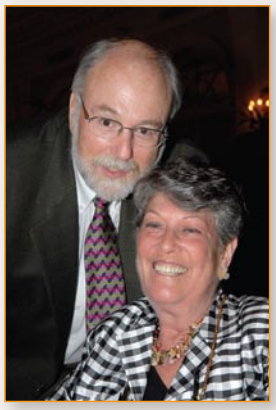





"The key note speaker at dinner and interfacing with pharmaceutical reps at the panel discussion firmly plants our basic science research in the pipeline for drug discovery. It's critical that basic scientists better understand how it all works."

—LRI Class of 2005 Grant Recipient, Marko A. Radic, PhD
University of Tennessee, Memphis, TN

Special Dinner Speaker, FDA Deputy Director, Janet Woodcock, MD, explores the challenges in bringing lupus medicines to market.



Special Industry Panel
Moderator, Mary Crow, MD. Participants: Jeff Browning, PhD, of Biogen Idec, Anthony Coyle, PhD, of Medimmune, Rainer Fuchs, PhD, of Biogen Idec, Arthur Krieg, MD, of Coley Pharmaceutical Group and, (shown at left) Paul Brunetta, MD, of Genentech and Robert Zivin, PhD, of Johnson & Johnson.

Above, far left: Susan Golick, founder of the S.L.E. Lupus Foundation, and husband, Allen Wasserman, DDS.

Left to right: Former LRI Taskforce Co-Chairman and NIAMS Chief, Autoimmunity Branch, Peter Lipsky, MD; LRI Scientific Advisory Board Member and Associate Clinical Professor of Medicine at Harvard Medical School, Lee S. Simon, MD; Betsey Selkowitz; and LRI Board Member, Arthur Selkowitz.

"This is especially important for investigators that are new to the lupus research field, like I am. It has educated me in thinking about all areas of lupus biology and provided me with a better prepared mind to recognize when new discoveries, perhaps in other seemingly unrelated areas, may have relevance to lupus."

—LRI Class of 2006 Grant Recipient Christopher A.J. Roman, PhD
State University of New York Downstate Medical Center, Brooklyn

New Round of Lupus Research Institute Awards

Recipients of the latest round of highly competitive, 3-year $300,000 grants will be working at the laboratory bench as well as through clinical studies to pursue their unique and powerful hypotheses on why, in lupus, the immune system so tragically turns against the body it is designed to defend. The 12 were selected following a rigorous review by the LRI Novel Research Peer Review Committee led by top lupus scientists from around the country and co-chaired by Mark Shlomchik, MD, PhD, of Yale University School of Medicine, and David Pisetsky, MD, PhD, of Duke University Medical Center.

Genetics of Lupus

It's clear now that the genes a person inherits can make him or her more susceptible to lupus. Identifying these genes and figuring out how they cause disease is a major challenge in lupus research today.

Nir Hacohen, PhD

Massachusetts General Hospital

Dr. Hacohen will individually switch off thousands of genes of the mouse and human genomes using a powerful cutting-edge technology—RNA interference—to reveal which control the response to DNA complexes that exacerbate the destructive lupus immune system. Knowledge of these critical genes could also provide new lupus drug targets.

Marianthi Kiriakidou, MD

University of Pennsylvania

Recently discovered MicroRNAs (miRNAs) are small RNA molecules that control the activity of one third of all our genes—and may well play a pivotal part in regulating the immune system. So far, their role in autoimmune diseases such as lupus has not been investigated. By analyzing which miRNAs operate in lupus, Dr. Kiriakidou may well offer evidence for their use as new biomarkers or therapies.

Gender Matters in Lupus

While females are much more likely than males to get lupus—nine women for every one male is affected—illness that does develop in males tends to be particularly severe. One LRI-funded researcher is aiming to identify the genes that underpin male lupus.

Betty Tsao, PhD

University of California, LA

Based in part on several reported cases in which males with lupus carried an extra copy of the X chromosome, Dr. Tsao hypothesizes that X chromosome genetic defects are critical in male lupus. She will now look to see if certain X chromosome genes that already have been implicated in lupus are altered (duplicated, for example) in males with the illness. Her findings may aid in developing genetic tests for susceptibility to lupus.

The Skin's Role in Lupus

Much about the role of the skin in lupus is poorly understood, from why sunlight exposure is a trigger to what causes the skin response to stimulate a broader system-wide (systemic) lupus in some people and not in others. An LRI-funded researcher has a novel idea on what may be happening.

Vicki Kelley, PhD

Brigham and Women's Hospital Boston

Dr. Kelley has early evidence that ultraviolet light (UVB) stimulates the skin to produce a "factor" that recruits white blood cells. Using specially developed mouse models, Dr. Kelley will examine whether UVB-induced production of this factor in the skin leads to both skin and systemic lupus.

Why the Lupus Immune System Reacts to its Own DNA

The blueprint for what makes us each unique—DNA and RNA—is carried inside the nucleus of each of our cells. Normally, our immune systems deftly distinguish our own DNA and RNA from that of foreign invaders such as viruses and bacteria. But in people with lupus, the immune system reacts to its own DNA and RNA as if these blueprint "chips" were the enemy that required extermination. What prompts these cases of misidentification? Tantalizing research indicates that proteins called Toll-Like Receptors (TLRs), which normally recognize DNA and RNA only from infectious pathogens such as viruses, may be to blame. Three LRI investigators will dig deeper.

Yorgo Modis, PhD

Yale University

By creating highly detailed three-dimensional models of TLR proteins bound to DNA and RNA, Dr. Modis will be able to observe how the receptors transmit their "on" signals to the immune system. These intricate models also offer possible ways to design drugs that interfere with, and stop, the alert signals that trigger such devastation in lupus.

Gregory Barton, PhD

University of California, Berkeley

Dr. Barton has found that the level of TLR7 and TLR9 in cells—the TLRs

Brings Promise of More Breakthroughs

implicated in lupus so far—is tightly controlled by a specialized protein disposal system. He suspects that if this disposal system breaks down, cells will have too much TLR7 and TLR9 and will, as a result, be more likely to erroneously respond to the immune system's own DNA and RNA. To test this, he will tinker with the disposal system and see if lupus ensues.

▶ ***Matthias Wabl, PhD***
University of California, SF

The body's DNA carries remnants of ancient viruses that once infected our ancestors, but then became an integral part of the human genome. Dr. Wabl hypothesizes that these viral relics are what that the lupus immune system mistakes for virus DNA, thus triggering the attack on the body's own DNA. Using mice, he will test whether destroying these virus-derived sections of DNA prevents the autoimmune attack.

Immune System Function—Signaling

At some point in lupus, messages are sent among cells that lead the immune system to malfunction. Two 2007 grants aim to understand and interrupt this flawed communication.

▶ ***Tracy McGaha, PhD***
Temple University, Philadelphia

Specialized "scavenger" cells in the spleen called macrophages recognize and remove dead cells from the blood. Dr. McGaha will investigate what happens when

"These 2007 novel research grants are of exceptional interest and quality, and will likely lead to important advances in lupus."

—David S. Pisetsky, MD, PhD, 2007 LRI Novel Research Task Force co-chair
Chief, Division of Rheumatology and Immunology at Duke University

the macrophages don't work properly and the cellular debris is allowed to build up—a scenario known to lead to lupus in mice. She will examine not only how macrophages prevent disease, but how the interaction of macrophages with debris from blood influences their behavior.

▶ **Anne M. Stevens, MD, PhD**
Children's Hospital and Regional Medical Center, Seattle

When the immune system is healthy, it can prevent unwanted, damaging responses by turning itself off, thanks to 'off switches' found on surface of white blood cells. Dr. Stevens has found that one of these critical switches, a molecule known as PD-L1, is missing on the cells of children with active lupus. Interestingly, the molecule re-appears when the lupus subsides and goes into remission. Her aim: to identify what controls the production of PD-L1 in these children.

Immune System Function—B Cells

The body's B cells, or B lymphocytes, mature in the bone marrow. When stimulated by an antigen, they develop into cells that make antibodies. And over the past few years, evidence that they play a central role in the cause and development of lupus—by making antibodies to the body's own DNA—has been growing.

▶ **Thomas Rothstein, MD, PhD**
The Feinstein Institute for Medical Research, NY

Dr. Rothstein aims to discover what triggers B lymphocytes to produce autoantibodies (self-directed antibodies) in lupus. Having recently found that activated B cells make the hormone-like molecule osteopontin, he suspects this may be what instigates or maintains the destructive production of autoantibodies in lupus. If correct, he will have identified a brand new pathway for the development of lupus, and opened the door to the development of targeted new therapies.

▶ ***Jennifer Anolik, MD, PhD***
University of Rochester, NY

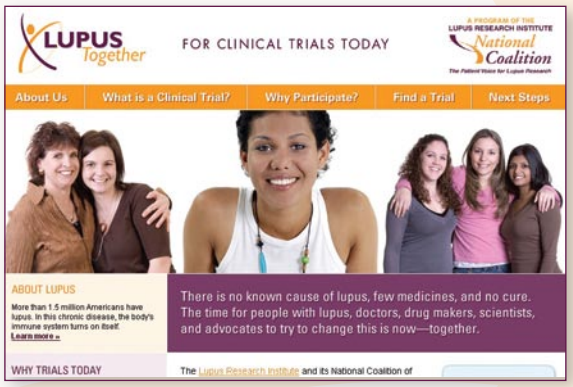
Therapies that eliminate B cells are currently in clinical trials in people with lupus. Dr. Anolik will develop a mouse model to study the why depleting B cells like this successfully counters lupus in some people. With this greater understanding may come more effective treatment strategies.

▶ ***Loren Erickson, PhD***
University of Virginia

Mice with lupus carry a gene that makes B cells produce autoantibodies. But while they know roughly where to find the gene on the "map," they haven't identified it yet and don't know how it causes B cells to turn and attack the body. In this novel study, Dr. Erikson aims to find out.

Since its inception 7 years ago, the LRI has awarded 85 grants for novel research in lupus at 51 academic and medical centers across the nation—a total of $22 million—making it the source of the largest and widest range of privately funded research investigations in lupus.

LupusTrials.org



Over 15,000 visitors have logged on to the official clinical trials campaign website, LupusTrials.org, since it launched in May.

The Lupus Research Institute and its National Coalition of state and local lupus organizations developed the patient-friendly site as part of an initiative to educate the more than 1.5 million Americans with lupus about the importance of participating in lupus clinical trials.

The timing is critical, as promising new research findings spur drug developers to initiate clinical research in lupus for the first time in decades. Visitors to the site learn about the clinical trial process, how to sign up, and can read first-hand accounts of others who participate in trials.

"Our hope is that the next 10 years will be the Golden Age for the development of new lupus drugs. Science is ready. But for success, the lupus community must band together. We have the experts to conduct the trials. We have the Institute and others to get the word out. But to get results, we need lupus patients to show interest. This is for them. They need to do their part."

– Richard Furie, MD. North Shore-Long Island Jewish Health System

LUPUS Together
FOR CLINICAL TRIALS TODAY

PLEASE CONSIDER....

an LRI Research Grant in the Name of a Loved One

For many people, this approach gives tangible meaning to a gift, linking the love that you have for someone with lupus to the discovery of new ways to prevent, treat, and cure this very difficult illness.

For additional information, please contact our Development staff at 212-812-9881 or email Dorey Neilinger at dneilinger@lupusny.org.

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