discovery UPDATE

A Publication of the Lupus Research Institute

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Lupus Research Institute Launches Novel Studies in Human Lupus

Innovative research in human tissue to drive discovery of new therapies

Science is ready. Answers are needed. People will benefit.

The Lupus Research Institute (LRI) is inviting scientists with innovative ideas about what goes wrong in human lupus and ways to fix it to apply for grant funding to mount novel investigations in Human Lupus Biology.

Novel research conducted directly in human tissue will close an existing knowledge gap, extend the horizons of lupus research, and advance the development of more effective and less toxic treatments for people who suffer with this complex and difficult illness.

Rapid discovery and technological advances make new direction possible

Fast-paced scientific discovery in lupus is producing a multitude of insights into the mechanisms at play in animal models of the lupus immune system gone awry.

Now the relevance of these findings needs to be established in human disease.

"What works in the mouse with lupus just doesn't always work in the person with lupus—including what may first appear to be promising drug treatments," said Michel Nussenzweig, MD, PhD, of Rockefeller University in New York and a member of the LRI's Scientific Advisory Board and Novel Research Task Force. "We are therefore enthusiastic about supporting research in patients."

Today the technology exists to take important animal model findings to the next level and open windows of discovery in human lupus—a critical step to developing successful new therapies. Often, only a small amount of human material is needed to supply key information.

"The real need in lupus research is creative work in human lupus biology," said Peter E. Lipsky, MD, chief of the Autoimmunity Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. "This is one of the most important areas to pursue. And now, for the first time, we have the tools to ask incisive questions and make new insights directly in the human lupus immune system."

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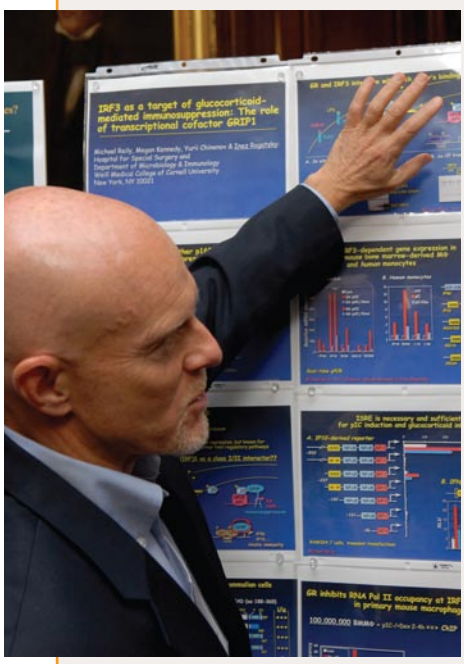
Steady Flow of Discoveries Continues from Novel Research Grants



Greg Lemke, PhD

- Profound Immune System Discovery Opens Door to Halting Destruction of Lupus
- Biomarkers of lupus kidney damage
- Infection's role in confusing immune system
- Behavior of body's infection-fighters misunderstood
- Potential new drug target

(see inside)

Profound Immune System Discovery Opens Door to Halting Destruction of Lupus

"Without the LRI, this project would have stopped—and a fundamental discovery in immunology would not have happened." Greg Lemke, PhD

Molecular biologist Greg Lemke, PhD, at the Salk Institute in La Jolla has discovered an entirely new and powerful molecular switch that controls the inflammatory response of the immune system. The major finding, reported in the prestigious journal *Cell* in December, means that new methods can now be pursued to shut down uncontrolled inflammation, restore immune system regulation, and treat chronic autoimmune disorders such as lupus.

In the *Cell* article, Lemke illustrates how a delicate "TAM" receptor signaling network normally keeps the immune system orderly as well as relatively tranquil. But in people with lupus and certain other autoimmune illnesses, this network may be missing the switch to inhibit inflammation—thereby resulting in immune system pandemonium.

Lemke, who had never previously worked in lupus, and was awarded the Novel Research Grant in 2005, now has a $1 million NIH grant to pursue this landmark work.

Dr. Imanishi-Kari at 2007 LRI Scientific Conference

Discovery

Behavior of body's infection-fighters misunderstood

Thereza Imanishi-Kari, PhD, at the Tufts University School of Medicine in Boston has made a discovery that turns long-held dogma on infection-fighting B cell behavior on its head, and offers a startling new direction for research into lupus and autoimmunity.

Imanishi-Kari discovered that early mutation of undeveloped B cells may prevent them from becoming a source of tissue-destroying antibodies and leading to an early immune system error—a mistake in tolerance—that causes autoimmune diseases such as lupus. This contradicts scientific thinking that only "mature" B cells can mutate their antibody genes, and may explain why the lupus immune system fails to recognize its real enemies and mistakenly turns on healthy tissue—a core error in the autoimmune process.

"Our findings show that the immune system can influence adaptive autoimmunity much earlier than had been previously thought," Imanishi-Kari said. She is now looking at the role of the protein, interferon, in forming these immature B cells.

– **Novel Research Grant in 2006.**

– **Discovery published in September's *Immunity*.**

LUPUS RESEARCH INSTITUTE

Novel Research Grants explore brilliant but untested novel hypotheses.

– **$23 million invested in new ideas since 2001**

– **85 investigations nationwide at 51 academic medical centers in 20 states**

– **$35 million to date in new lupus research at the NIH and other agencies**

Founded by families, shaped by scientists

Discovery

Infection's role in confusing immune system

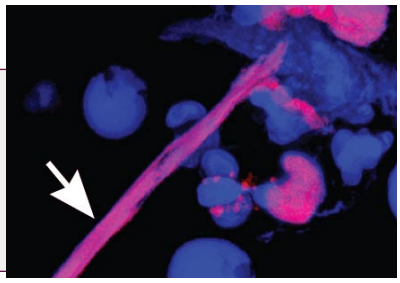
"The LRI support was critical for this study, even from the inception of the idea. It encouraged us to explore novel ideas, which normally one shrinks back from if applying to the National Institutes of Health."

Marko Z. Radic, PhD, at the University of Tennessee in Memphis, has made an important discovery that helps to explain why people with autoimmune disease so often have a bacterial or viral infection just before their symptoms flare—and what might be done about it.

Radic showed that in autoimmune disease, chemical modifications to proteins on immune system cells happen in such a way that the modified proteins (in this case, histones) assume a different structure. This modified structure may explain why the immune response targets these proteins as if they were foreign.

A modified protein normally found inside cells is released by activated white blood cells (neutrophils) and can be 'seen' as foreign by the immune system, triggering an autoimmune attack.

Arrow points to a strand of DNA and modified protein that normally would stay tucked inside cells—and undetectable to the immune system



Courtesy of Dr. Marko Radic

– Novel Research Grant in 2005.

– Discovery published in February's ***Journal of Immunology.***

– Ongoing funding awarded to Radic and others to further explore this discovery: $600,000.

Discovery

Biomarkers of lupus kidney damage

Anne Davidson, MD, at the Feinstein Institute for Medical Research, has discovered that active lupus nephritis is associated with activation of a particular subset of white blood cells (macrophages and dendritic cells) and that these are lost from the kidney upon induction of remission. The implication, reinforced by direct experience with patients, is that these cells are involved in damaging the kidneys in lupus.

Davidson also identified potential biomarkers—six genes—that might be used to detect kidney involvement at its earliest stages in lupus, when it can be more effectively treated. The biomarkers also have promise for measuring responses to new therapies being tested in clinical trials.

–Novel Research Grant in 2004.

–Discovery published in February's ***Journal of Immunology***.

–Ongoing funding awarded to further explore this discovery: $235,000.

Discovery

Potential new drug target

David Pisetsky, MD, PhD, at the Duke University Medical Center in Durham has identified and described in detail a potential new target for the treatment of lupus: the protein HMGB1 (high mobility group 1 protein)—an instigator of inflammatory responses throughout the body.

"With LRI funding, we have shown the range of molecules that can cause the release of this key protein and the types of cells that make it. Now we will work to develop new, more specific and less toxic approaches to suppressing the abnormal immune reaction in lupus—and anti-HMGB1 treatment may represent such an approach."

– Novel Research Grant in 2004.

– Discovery published (co-authored) in October's ***Journal of Leukocyte Biology.***

– Ongoing funding awarded to further explore this discovery: $425,000.

Los Angeles – Chicago – New York

Resolved to fight, strengthening the bonds nationwide

The Lupus Research Institute welcomes families committed to prevent, treat, and cure lupus to its national board.

LOS ANGELES

Debra and Roger Cowan's daughter and second child, Amanda, now a 22-year-old UCLA student, was diagnosed with systemic lupus in 2005. Both Los Angeles natives and Stanford University graduates, the Cowans own and operate a real estate and investment firm in the LA area. Since Amanda's diagnosis, they have learned all they can about lupus and its effects on young women. They also have committed themselves to raising awareness of the disease, bringing leadership to the cause, and supporting the bold and innovative science needed to find answers for Amanda and all others who struggle with lupus.

CHICAGO

John A. and Kathleen A. Buck's daughter, Darby, was diagnosed with lupus at age 24, after struggling with its mysterious symptoms from the age of 18. Speaking to friends and associates at the launch of the Institute's Chicago division in 2006, Kathleen noted that "like many people, I would have drawn a blank on hearing the word lupus if this devastating illness had not touched my family." But it did, and its effects have exacted a steep toll on their daughter. Kathleen as well as John, who runs one of the Midwest's largest real estate management and leasing companies, are providing the crucial leadership needed to advance field-changing, pioneering research in lupus.

NEW YORK

Hope Luke Hetherington's sister, the gentle and courageous Jane Luke Murphy, died in 2003 at age 50 after a long struggle with the complications of lupus. The Luke family, under the leadership of the late John A. Luke, Sr., a founding member of the LRI Board of Directors, has brought almost two decades of dedication and outstanding support to the lupus cause. John's daughter, Hope, now joins the LRI Board with courage and enthusiastic determination to champion the innovative research that will finally conquer this disease.

Shady Ladies™

Signature Event Draws Celebrities and Crowds in Palm Beach

Thanks to presenting sponsor IBM Corporation, as well as Diane's Precious Jewels, Coach, William Grant & Sons, Eyes of Wellington, Hunt Ltd., Shady Day, Inc., Nicole Paxson Cosmetics, and Carol's Daughter.

Shading oneself from the sun's damaging rays is an invaluable goal for the many people with lupus who are sensitive to sunlight.

Sunglasses once worn by such stars as Beyonce, Tommy Lee Jones and Bruce Springsteen were auctioned off at the Winter Equestrian Festival on February 10th, raising over $110,000 for innovative science at the Lupus Research Institute. Michael J. Fox, Regis Philbin, Jay-Z, Lou Dobbs, Michael Kors, and Tracey Ullman also donated shades.

Success of the event is largely attributed to the work and contributions of honorary chairs and fashion designers Mark Badgley and James Mischka, chairperson Jenny Oz LeRoy of Tavern on the Green in Wellington (also in New York's Central Park), and vice chairs Toni and Jean Goutal, Angie and Chris Paradysz, and Teri and John Wood.

In addition to the silent auction, live auctioneers Nona Garson, an equestrian, and John Wood sold off numerous sunglasses. The highest bid went to Arnold Schwarzenegger's original aviators from *Terminator II*.

Jessie has this amazing life ahead of her, and while lupus hasn't stopped her, it's tried to slow her down.

We want her to remember—to really know—what life without lupus is like.

We're convinced that the LRI is heading, racing, towards that day for Jessie and others with this relentless illness.

Why We Give to the LRI

The LRI only works because of the contributions it gets, large and small, from donors around the country and the world. In this ongoing column, we get glimpses of this committed community.

Jessie Russell—Star Athlete, Stellar Student—Has Lupus.

Her siblings tell her story…

Our little sister Jessie couldn't have been more tightly woven into the fabric of our family of seven, our community here in suburban Boston, or the three varsity sports teams she captained when she got the diagnosis in March 2005.

She was just a junior in high school, waiting for college acceptance letters and with a dizzying schedule of sports, friends, school. So when she said she felt exhausted we weren't surprised—we would too, we said, if we did all that she did!

Jessie was always on the go, and excelled at it all. But there were other signs that something wasn't right. Her face was puffy. She was getting migraine headaches and waking up at night from horrible pains in her joints.

After weeks of testing and hospitalizations, we finally learned that Jessie had full-blown kidney disease—caused by systemic lupus.

We couldn't believe it. Just a month earlier, Jessie was scoring her 1,000th point on the basketball court! And now she was lying in a hospital bed, hearing news that would change her life.

Since that day, Jessie's been hospitalized dozens of times. She's taken over 11,500 pills—about 170 weekly—and is constantly napping to ward off exhaustion. She's faced a challenge unlike any she's dealt with in a school book or on a sports field—which says quite a bit, since she's in her second year at Harvard University.

Racing for Jessie

Not being able to take the lupus away from Jessie—that's been so hard for us. So when we found the LRI, **we knew there was something we could really do for her**. Here was a place that channeled money straight to researchers with the best, the most brilliant ideas on why lupus happens and what can be done to stop it.

Older sister Becky started running the Boston Marathon to raise money for the LRI. Brother Josh challenged his college professors to match donations that his classmates pulled together. Teachers in our town of West Bridgewater sent letters home asking for donations.

The police department, where Jessie's brother-in-law is an officer, pooled funds. Neighbors mailed Becky's marathon letter out to their own circle of friends.

We'll get there.

Talking to Congress, Telling the Story

National Coalition Gathers in D.C. to Speak for People with Lupus on Capitol Hill

Your Voice for Lupus Research—Coast to Coast

The LRI National Coalition spread across Capitol Hill in early March to meet and speak with members of the House and Senate.

Their message, delivered for you:

– Be aware of lupus and the damage it can inflict on young women in particular

– Vote for increased funding for research on the causes and potential treatments for lupus

– Encourage implementation of the 5-year Trans-Institute plan for lupus research at the National Institutes of Health

– Recognize and help us do something about the notably high number of black, Hispanic, Native American, and Asian Americans who develop lupus.

California Delegation Brings the Lupus Message to the U.S. Senate

Representing southern California, San Diego, LA, the San Francisco Bay Area, and northern California.

With U.S. Senators Dianne Feinstein (D-CA) and Barbara Boxer (D-CA).

Innovative Research in Human Tissue to Drive Discovery

Science is ready. Answers are needed. People will benefit.

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Powerful pooling of talent and technology

Because the most productive research in human lupus requires basic scientists with cutting edge ideas and experimental techniques, clinicians with access to large patient cohorts, plus key technology components, the LRI will consider consortia applications for this Human Lupus Biology initiative.

Up to three investigators at one or more institutions can now request up to $900,000 over three years to pursue novel human lupus studies. Consortia represent the ability to generate diverse skilled groups—our best scientists and best clinicians regardless of institutional affiliation—coming together to move the field forward.

Pioneering discovery

Since initiating its program of novel research and ambitious inquiry in lupus eight years ago, the LRI has been at the forefront of the field—supporting innovation and risk, and producing dramatic scientific results and novel insights. Why? The LRI only works because of the contributions it gets, large and small, from donors around the country and the world. In this ongoing column, we get glimpses of this committed community.

With the addition of the **Human Lupus Biology** initiative to its ongoing Novel Research Program, the LRI further propels the field of lupus inquiry, discovery, and results, bringing tangible hope for better treatments and a cure for this disease.

With Your Will, A Cure
Help Secure the Future through Intelligent Planned Giving

Remember the Lupus Research Institute in your Will—contact Andrea O'Neill at 212-812-9881 or email aoneill@lupusny.org

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