

discovery UPDATE

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Research Results Stream In

Stress Hormone Enables Lupus Antibodies to Alter Behavior, Damage Cognition



Betty Diamond, M.D.

A major breakthrough in lupus research—one that changes thinking on how the disease affects behavior and cognition—was reported in

the January 17, 2006 *Proceedings of the National Academy of Sciences (PNAS)*. Entitled *Immunity and behavior: Antibodies alter emotion*, the research builds upon a framework of findings supported by Lupus Research Institute funds from 2001 to 2004.

The LRI awarded Betty Diamond, M.D., Chief of the Division of Rheumatology at Columbia University College of Physicians and Surgeons, and colleagues the grant that enabled her to first explore the channels responsible for brain damage in lupus.

Now Dr. Diamond and colleagues report that high levels of a hormone produced by the adrenal glands in reaction to stress—the “stress hormone” epinephrine (adrenalin)—allow for the penetration of toxic antibodies into the brain that likely lead not just to thinking problems, but also to changes in behavior.

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Lupus Artery-Hardening Cholesterol Identified



Bevra H. Hahn, M.D.

A certain form of the normally “good” high density lipoprotein (HDL) cholesterol linked to cardiovascular health plays a counter-productive role in

people with lupus and rheumatoid arthritis, promoting atherosclerosis (hardening of the arteries) and heart disease in many of these individuals. That was the groundbreaking finding of LRI-funded research reported at the 2005 annual meeting of the American College of Rheumatology in San Diego.

The menacing HDL form is pro-inflammatory HDL (piHDL), report Bevra H. Hahn, M.D., Chief of the Division of Rheumatology, Maureen McMahan, M.D., and colleagues at UCLA’s David Geffen School of Medicine, and it can easily be measured and, most importantly, treated. Women with lupus are about 7 to 10 times more likely than women without the disease to suffer a heart attack or stroke.

“Traditional risk factors for atherosclerosis have proved ineffective for predicting atherosclerosis in SLE patients,” said Dr. Hahn.

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LRI Critical as Federal Research Funding Slows

The National Institutes of Health has had its overall budget for research cut for the first time in nearly 40 years, reversing decades of rising funding and casting a dark cloud over research support for countless diseases.

“The reductions in NIH funding are particularly unfortunate for lupus, since they occur during the most exciting time in lupus research,” notes Robert Eisenberg, M.D. at the University of Pennsylvania. “Novel compounds are being tested in the private sector, which is great news for lupus patients. But it is the NIH that has been the largest source of funding for lupus research.”

“The LRI primes the pump, spurring important research and raising the level of proof that ultimately leads to NIH funding. That’s a good investment of research dollars that must continue, especially now.”

— Marcus R. Clark, M.D.
University of Chicago



Results Are What Matter

A person with lupus lives with staggering unknowns. Will I have a heart attack? Will the disease attack my brain? Will my kidneys stop working? Will I stop hurting—ever?

When the Lupus Research Institute was founded six years ago, it was with the steely drive to find answers, and quickly, to these kinds of questions. In this issue of *Discovery Update*, the results of the LRI's unique strategy to back only novel ideas in lupus are stunningly apparent.

The LRI's Novel Research Task Force—a sterling peer review group that holds grant proposals to the most rigorous of scientific standards—saw the genius in Dr. Betty Diamond's hypothesis of how lupus attacks the brain and produces cognitive damage. They recognized the untested potential in Dr. Bevra Hahn's ideas on how lupus prematurely hardens heart vessels. So far, they have seen the spark in more than 55 research ideas that are high-risk yet rich with potential for success and new treatment development.

"I am convinced that without LRI funding," says Dr. Diamond, "our research would not have gotten off the ground." But it did, and the results of her innovative research and that of dozens of other LRI scientists are now streaming in, with promise for tangible tests and treatments in their wake.

For the more than 1.5 million Americans living with lupus and its countless unknowns, these are the results that matter.

Best regards,

Margaret G. Dowd
President and CEO

And More Research Results, Just In...

- A team from the University of Minnesota led by LRI-funded investigator, Timothy W. Behrens, M.D., has linked the development of lupus to the presence of a single variation of a gene associated with the protein interferon. This tantalizing link not only gives clues to the origin of lupus, but could well advance testing for it.
- With the help of LRI funds, Mariana Kaplan, M.D. and colleagues at the University of Michigan have found evidence that lupus worsens when the very cells employed to mop up dying cells in the body—specialized scavenger cells called macrophages—fail to get disposed of properly. The finding opens the door to possible strategies for helping to slow disease in lupus patients.

For more on these and other research findings, or to get a Novel Research grant application, visit www.LupusResearchInstitute.org.

Brain Damage – Continued from page 1

Increased levels of epinephrine can raise blood flow to the brain and cause leaks in the normally well-sealed barriers to this precious organ. Dr. Diamond reports that epinephrine permits the disease's anti-DNA antibodies to leak into the amygdala, a brain region that governs fear and emotional responses, and cause damage there.

These findings start to unravel the mystery as to why behavioral and cognition issues sometimes develop in people with lupus, especially if there is no actual inflammation in the brain—a grave but relatively uncommon complication.

A number of people with lupus experience subtle but insidious changes in behavior (affect), such as unusual feelings of fear (or lack of fear) and loss of interest or curiosity. And an estimated 8 in 10 at some point have progressive cognitive impairment with such signs and symptoms as confusion, fatigue, memory loss, difficulty expressing thoughts, and (occasionally) seizures or strokes.

In her earlier work using mice and focusing on cognition, Dr. Diamond had concluded that lupus antibodies can destroy nerve cells in the brain, causing serious cognitive impairment. The investigators had also found that infection can pave the way for these damaging antibodies to penetrate into the brain, which is normally protected from various antibodies by a "wall" called the blood-brain barrier. In addition, she identified the Alzheimer's medicine, memantine, as a potential drug model for inhibiting lupus brain damage.

"It is truly exciting—and I couldn't be happier—that it was our research funding that allowed Dr. Diamond's novel hypothesis to become a proven hypothesis! Keep making such great selections. We're going to beat this disease yet!"

– Terese Celine Payne
LRI Donor
Mill Valley, California

Cholesterol in Lupus – Continued from page 1

Dr. Hahn's team analyzed blood from 154 women with lupus, 73 age-matched controls, and 50 women with rheumatoid arthritis. The piHDL was found in almost 50 percent of those with lupus, versus approximately 4 percent of controls and 20 percent of rheumatoid arthritis patients. It was also found in 8 of

the 10 individuals with lupus determined to have actual atherosclerosis, and was similarly high in 6 of the 12 individuals with lupus who had suffered a stroke.

"We can clearly see from these results that HDL function fails to protect against cardiovascular disease in

many lupus and rheumatoid arthritis patients," Dr. Hahn concluded. "This discovery may lead to an effective test to identify those at increased risk for blockage of the coronary arteries so that we can start them on preventive treatments like cholesterol-lowering statins."

Joint LRI/ACR Fellows Advance Lupus Science

To encourage qualified physicians without significant prior research experience to develop a career in lupus, the LRI joins with the American College of Rheumatology Research and Education Foundation (ACR REF) in annually awarding a three-year fellowship grant for research training among lupus investigators working in a clinical unit involved in patient care.

2003 Fellow Contributes to Groundbreaking Cholesterol Research

Maureen McMahan, M.D., who reported on the pro-inflammatory HDL findings with UCLA's Dr. Bevra Hahn (see story, page 1 and above), was the first of four scientists to participate in this mentored post-doctoral fellowship program begun in 2003.



Maureen McMahan, M.D.
Fellow 2003

David Geffen School of Medicine at UCLA in Los Angeles

Dr. McMahan, who just completed her fellowship work on the "Role of Abnormal Protective HDL in SLE,"

plans to continue her examination of accelerated atherosclerosis in women with lupus. In an ongoing LRI-funded study with Dr. Bevra Hahn, she will attempt to determine if pro-inflammatory HDL is associated with plaque in the carotid arteries.

"The practice of constant questioning that is central to research also has allowed me to approach patient care from a different perspective, and has encouraged me to think of new ways to help my patients," says Dr. McMahan. "I strongly encourage other physicians to engage in research."



Joyce Hsu, M.D.
Fellow 2004

Stanford University Medical Center in Palo Alto, California

Research focus: Dr. Hsu will explore racial and ethnic group differences in the childhood manifestations of lupus, both at the time of diagnosis and in the first two years of disease. "Our hypothesis is that children of Asian American and Hispanic descent have more severe lupus and have more

renal disease than non-Hispanic Caucasians," explains Dr. Hsu. "By understanding which subgroups are at higher risk, we can target more aggressive treatment towards that group and avoid therapy-related complications in lower risk groups."



Sonwoo Lee, M.D.
Fellow 2005

David Geffen School of Medicine at UCLA in Los Angeles

Research focus: Dr. Lee aims to shed light on the effects of the powerful immune-modulating recombinant galectin-1 in lupus. Greater understanding of this agent as a preventative or treatment therapy in mice may serve as an initial step toward its use in humans with lupus. "As a physician, I will continue my commitment and dedication to disease-oriented basic science research," says Dr. Lee. "And I would like to devote my research life to studying lupus."

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Joint LRI/ACR Fellows

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Ingrid B. Avalos, M.D.
Fellow 2006

*Vanderbilt University Medical Center
in Nashville, TN*

Dr. Avalos, the newest Fellow, will pursue her interest in aspirin resistance in rheumatic disease. “We know that patients with SLE (lupus) are at increased risk of accelerated atherosclerosis and cardiovascular events (like myocardial infarction and stroke) and this means that a majority of them will be treated with low-dose aspirin for primary and secondary prophylaxis (prevention),” explains Dr. Avalos. “What we do not know is how effective this therapy is for the prevention and treatment of cardiovascular events in this specific patient population.”

Read more about LRI/ACR REF Fellows at www.LupusResearchInstitute.org.



Celebrity Sunglasses Add Horse Power to First “Shady Ladies Luncheon”

The 34th Winter Equestrian Festival in Wellington, Florida provided a charming setting for the inaugural “Shady Ladies Luncheon” on March 4th to benefit the Lupus Research Institute. More than 120 guests gathered in “The Shady Ladies Chalet,” a pavilion in the Palm Beach Polo Equestrian Club adjacent to the festival’s grand prix field. It offered a great vantage point for watching the prestigious horse show’s young jumpers and joining in the fun of the luncheon’s celebrity sunglasses auction.

The theme of the “Shady Ladies Luncheon” reflects a common symptom of lupus: extreme sensitivity to the sun. Doctors advise people with lupus to stay in the shade, use sun block, and wear hats and sunglasses.

The auction featured autographed celebrity sunglasses from Paul Newman, Joanne Woodward, Tommy Lee Jones, Carole King, Tom Selleck, Steven Spielberg, Kate Capshaw, Christine Lahti, Eve, Badgley Mischka, *Law & Order* stars Richard Belzer and Mariska Hargitay, among others.

While the event was clearly a hit within the adult equestrian community, junior riders Katie Dinan, as well as Allie and Dani Paradysz, created their own spontaneous fundraiser by securing prize winnings from fellow riders in the pony hunter division. Through that weekend, they raised over \$1,000 and, in an extremely poignant moment, presented the donation to LRI President, Margaret Dowd.

Clearly, the “Shady Ladies Luncheon” is poised to become a yearly festival highlight.



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