

discovery UPDATE

A Publication of the Lupus Research Institute

Fall 2005

High-tech Gene Screens May Speed Lupus Diagnosis and Treatment

Exciting Advances in Functional Genomics Presented at LRI Scientific Conference

Functional genomics is a sophisticated new research approach that analyzes the expression of a person's genes—the actual blueprint for development inherited from one's parents—and links this information to the way that cells, tissues, and organs function. With innovative thinking spurred by nimble organizations such as the LRI, this white-hot research area is poised to revolutionize the diagnosis and treatment of systemic lupus erythematosus (lupus) and other serious diseases.

"I foresee that a whole host of new opportunities for drug discovery, development and new therapies will come online in the next five to 10 years, as we understand the mechanisms through which lupus is mediated in so much greater detail than we have in the past," said William E. Paul, MD, chief of the laboratory of immunology at the National Institute of Allergy and Infectious Diseases (NIAID).

Dr. Paul moderated the special October 7 morning session on functional genomics at the LRI's *Forum for Discovery* in Manhattan. Keynote speakers, Nir Hacohen, PhD, an assistant professor of medicine at Massachusetts General Hospital and Harvard University, and Louis M. Staudt, MD, PhD, related this exciting research area

to breakthroughs in understanding the immune system and lupus, among other diseases.

They pointed out that with help from a new tool for analyzing gene expression called DNA microarray technology, specialists in functional genomics do much more than simply identify genes. They are able to

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Nir Hacohen, PhD, Assistant Professor of Medicine at Harvard University and Massachusetts General Hospital

LRI Awards \$4.5 Million to Advance Lupus Science

Innovative Studies Hold Potential for Key Breakthroughs

Fifteen scientists with highly promising novel research studies in lupus have been awarded 3-year, \$300,000 grants, bringing the total number of researchers funded since the nonprofit LRI started 5 years ago to 56, and the financial support to lupus investigation to \$14.5 million. The LRI Novel Research Peer Review Committee rigorously reviewed a record number of applications (81 in all) to select the recipients, who hail from institutions around the country and offer expertise in research areas from basic immunology to nephrology, neurology and cardiology. A remarkable number—nearly half—are bringing their sci-

"The LRI is willing to take a gamble on ideas that have the potential to really cut new ground."

—William E. Paul, MD

entific talents to the study of lupus for the first time.

While often high-risk (9 of the grants qualify as such), many of the 15 studies have already shown the potential for "high-reward," or the capacity to surge ahead in understanding lupus and identifying prevention and treatment strategies. Nearly half (seven) of the recipients will be conducting

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Forum for Discovery:

5th Annual LRI Scientific Conference, October 6 & 7 2005

Extraordinary Progress Reported by 2003 & 2004 Grant Recipients

"We're counting on you," said LRI Co-Chairman Robert J. Ravitz to the more than 50 researchers and physicians gathered at the Yale Club in Manhattan for the LRI annual



V. Michael Holers, MD



Theresa Lu, MD, PhD (back L),
Joan Von Feldt, MD (foreground L),
Robert Caricchio, MD (foreground R)



Robert Eisenberg, MD

conference, *Forum for Discovery*. The following two days of scientific discussions, poster sessions, and impromptu exchange of findings and ideas indicated that Mr. Ravitz had good reason to place pressure on—and feel upbeat about—the advances that LRI scientists are rapidly making in decoding the enigma that is lupus.

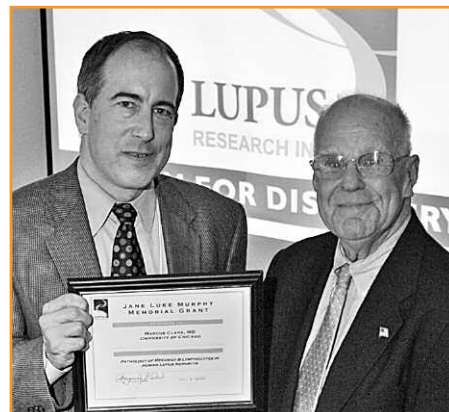
After LRI Novel Research Co-Chair Mark Shlomchik, MD, PhD, laid out the agenda for the meeting (thematic scientific sessions interspersed with poster sessions), and addressed the state of lupus research in general, he introduced the first special speaker, Michel Nussenzweig, MD, PhD, the Sherman Fairchild Professor and Senior Physician at Rockefeller University. Dr Nussenzweig delved into recent findings on immune system function and related them to discoveries on errors in specificity, diversity, and memory that appear to occur with autoimmune diseases such as lupus.

Scientific Sessions Show LRI Science Out Ahead of the Curve

Variouly moderated by LRI Novel Research Co-Chairs Dr. Shlomchik and Nicholas Chiorazzi, MD, as well as scientists V. Michael Holers, MD, Anne Davidson, MD, and Mary Crow, MD, the 23 presentations at 5 sessions gave LRI scientists an opportunity to report on findings in basic science and lupus-related fields such as biomarkers, genetics, and clinical manifestations such as nephritis and atherosclerosis.

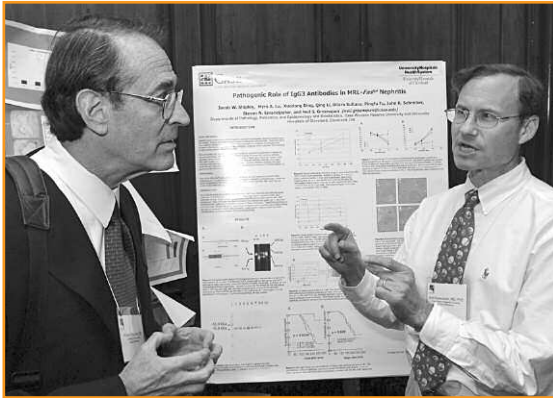
Evening Event Showcases Year 2005 LRI Grant Recipients and Special Speaker

The newest round of LRI grant recipients—15 in all—were introduced after a reception and shortly before presentation of the 2005 Jane Luke Murphy Memorial Grant (see photo below) and a dinner address in which Brian Kotzin, MD, made a case for industry as the key player in spurring new lupus therapeutics (see story page 5). Details on the new grant recipients begin on page 1; reception photos are on page 8.



LRI Treasurer, John A. Luke (R), presents the award named after his late daughter, Jane Luke Murphy, to 2005 LRI grant recipient Marcus Clark, MD (L), from the University of Chicago.

Dr. Clark is researching the role of B lymphocytes in lupus nephritis—a condition from which the Luke's daughter Jane suffered. "I'm a basic scientist," said Dr. Clark, "but I'm also a rheumatologist. Funding by the LRI will help us gain new understanding of how to really attack the disease and go after it as physicians."

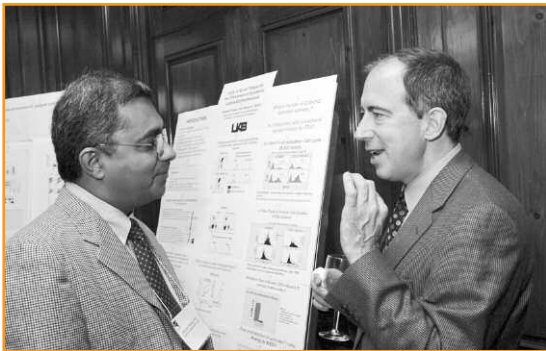


Robert A. Eisenberg, MD and
Neil S. Greenspan, MD, PhD

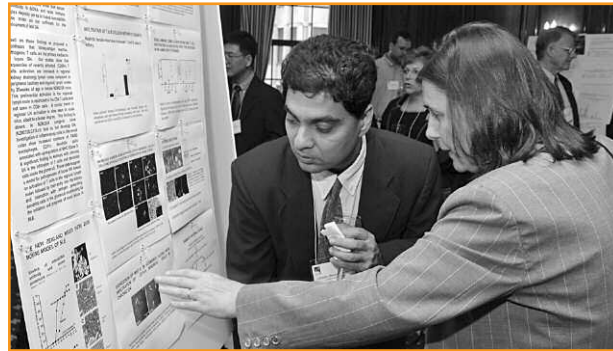


Theresa Lu, MD, PhD

Poster Presentations by 2003 and 2004 grantees spark lively discussions and lay the groundwork for invaluable collaboration between researchers and physicians who treat people with lupus.



Chander Raman, PhD and Marcus Clark, MD



Umesh Deshmukh, PhD and Luminita Pricop, MD



An extended session on functional genomics—a rapidly developing scientific approach that holds hope for providing invaluable insight into lupus—was moderated by William E. Paul, MD (R), and featured Louis M. Staudt, MD, PhD (2nd from L) as one of two keynote speakers. Also pictured here are Greg Lemke, PhD (L) and Neil S. Greenspan, MD, PhD (2nd from R).

Thanks to the following for their generous support of the 2005 *Forum for Discovery*

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The Vilcek Foundation

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High-tech Gene Screens

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actually sift through and analyze the genes, thereby shedding light on what changes they prompt in the human body—quite a feat when it comes to mapping out a complex disease such as lupus.

Immune System Clues

Dr. Nir Hacohen described how first-responder cells designed to alert the body to intruders—dendritic cells—present foreign material to other immune system cells. With microarray technology, he has been able to show, for the first time, that the response of dendritic cells to intruders shifts and changes depending on the stimuli (whether bacteria, virus, or other foreign substance). A key finding for autoimmune diseases like lupus is that these dendritic cells fail to stop alerting the immune system to react—a tragic flaw.

Microarray technology also shows that blood from certain people with lupus (about 1 in 10) carries a strong interferon (IFN) signature that portends serious complications such as central nervous system damage, kidney failure, and blood problems. “The field of developmental biology,” he said later, “is constantly being broken open using genomics

approaches, and this should be possible to do for immunology and immunological diseases.”

Lymphoma Research Lays Groundwork

Dr. Louis Staudt described pioneering work in using microarray analysis to diagnose lymphoma tumors at the molecular level. He noted the power of the new technology to “open up the black box of human disease” and reveal the unique circuitry of diseases that currently present as one ailment but are in fact many—which is a possibility with lupus.

Among the exciting aspects of the technology is that it gives a molecular diagnosis, which “yields molecular targets, and many pharmaceutical companies have [in the pipeline] drugs that can target specific forms of the disease.” Targeted medicines have the potential to be not only more effective but less toxic—a very high priority for people with lupus.

RNAi screening is another important functional genomics tool, as it enables researchers to dissect complex biological processes by switching genes off one at a time and watching what happens. One of the mysteries unraveled in this way is how certain genes direct cells to proliferate, survive, or die—thus revealing which genes participate in the processes which may lead to particular diseases.

Seeing Into the Future

Functional genomics—and microarray analysis especially—provides something of a crystal ball for how a disease will play out, Dr. Staudt

noted. “We can tell from the gene expression profile what will happen years later—whether it [the lymphoma] will be cured by chemotherapy and how fast the disease will progress and whether or not it will spread.”

Some day soon, that same model for prediction may well apply to diseases such as lupus. “The disease would declare itself at diagnosis, and we could tell what type of lupus that you would have,” Dr. Staudt said.

In introducing what became a lively concluding panel discussion following the talks, Dr. Paul noted that “the speakers illustrate the great opportunity that lies ahead. And they challenge all of us to think about how to use these tools in complex diseases such as lupus.”



(L TO R) Nir Hacohen, PhD and Mark Shlomchik, MD, PhD

Industry News

HGS Plans for Phase III Lymphostat-B Testing Despite Mixed Results

Eagerly awaited results from Phase II clinical trials on LymphoStat-B (belimumab), a drug developed by Human Genome Sciences Inc. (HGS), were reported in early October. The drug, an antibody designed to inhibit the activity of B-lymphocyte stimulator and which the FDA has approved for “fast-track” lupus testing, did not fulfill its overall primary endpoints, but showed notable promise nonetheless. It did not reduce lupus signs and symptoms after 24 weeks of treatment nor extend the time to a disease flare over 52-weeks. But it did significantly reduce signs and symptoms in the substantial subgroup—75 percent of the 449 people enrolled in the multi-center trial—who had lupus antibodies in their blood. Study par-

Industry Holds Keys to Spurring New Lupus Therapeutics

Optimism mixed with sober analysis in Brian L. Kotzin, MD's, evening presentation to a crowd of scientific colleagues and lupus advocates in Manhattan on October 6. The intensive labor, immense time demands, and enormous cost in developing new lupus drugs, he explained, pose hurdles that require not only the talent of academia and the nimble approach of organizations such as the LRI, but the weighty resources of industry.

"I used to think that the universities could do it," Dr. Kotzin explained. "But I have had a rude awakening. Now I realize this is definitely too difficult a process." Dr. Kotzin, now the vice-president of global clinical

participants were randomly assigned to one of three doses of LymphoStat-B or a placebo intravenously, along with usual medications. A larger Phase III round of testing involving detailed collection of safety and effectiveness data is being planned, a company spokesperson said.

MedImmune Pursues New Lupus Drug

The biotechnology companies MedImmune, Inc. and Medarex, Inc. applied to the FDA in October for an "investigational new drug application" to explore the ability of a monoclonal antibody, MEDI-545, to prevent and treat lupus flares. Testing in humans is expected to start in 2006. Data collected so far indicate that this fully human monoclonal antibody may suppress certain abnormal immune activity that appears to be elevated in many people with active lupus.

development at the biotechnology company, Amgen, Inc., worked in academic medicine for 25 years on lupus pathogenesis, genetics, and immunology. He is a member of the LRI Scientific Advisory Board.

Task #1: Examine Success

To illustrate the scope of challenges ahead in lupus therapeutics, Dr. Kotzin turned to dramatic advances in a different disease: rheumatoid arthritis (RA). For decades, scant treatment options were available for this crippling condition. That dry spell ended with the development of drugs like etanercept, which transformed the playing field for RA therapeutics largely because it blazed a path to drug approval—a critical feat.

"What happened with RA and etanercept is an example of what success looks like, and all the goodies that come of that," Dr. Kotzin said. Normally the complex and timely journey from concept to safe and effective therapeutic takes an average of 14 years.

With the route to drug approval so daunting, it's little surprise that most proposed therapeutics flounder and fail at some point. Which is just one reason, Dr. Kotzin added, that "I'm not sure that anyone but industry should do it," adding that, "It takes teams of very skilled people to go through the steps in a very high quality way."

A Positive Outlook

"We're really doing well – we've got a lot of things moving forward, finally," he explained as he projected a slide with lupus therapeutics in (or close to) clinical trials.



Brian L. Kotzin, MD

Key developments include the FDA's draft lupus guidance document, the introduction and characterization of instruments to measure changes in overall disease activity, the commitment of multiple companies to develop lupus therapeutics, and cooperation among clinical trial centers. "Only 5 years ago this was not the way it was," Dr. Kotzin emphasized.

Looking forward, there need to be many "shots on goal," Dr. Kotzin asserted—successful attempts to create new treatments. "We need a continuous pipeline of novel targets that have incredibly strong rationale," he continued. "And since it's unlikely we're going to have one drug that cures lupus...we have to have many drugs tested."

Flexible and fast-paced organizations such as the LRI are crucial given the more risk-adverse grant review process at the NIH. Finally, collaboration with industry is vital because it has the deep pockets to fund the staggering cost—\$800 million to \$1 billion—of bringing a novel therapeutic to market. That's key as NIH research funding dwindles. "It's a long road ahead to new lupus drugs," Dr. Kotzin concluded, "but we'll get there."



LRI Awards \$4.5 Million to Advance New Science in Lupus —Continued from page 1

research in humans—a powerful sign of progress and hope in lupus investigation. The scientists awarded the \$300,000 grants are working in the following key areas:

Biomarkers

The LRI funds the largest number of private sector studies seeking predictors of disease activity. While several 2005 grant recipients will conduct research that may generate these biomarkers, one with a specific focus is:

Timothy W. Behrens, MD
University of Minnesota Medical School, Minneapolis

The blood of lupus patients contains certain proteins at unusual levels. Dr. Behrens, an established lupus investigator, will use sophisticated technology to test approximately 1,500 blood samples from 300 people with carefully documented lupus. The goal is to track shifts in protein levels (the biomarkers) that correlate with lupus disease activity—even before a flare or remission becomes apparent.

Genetics

The genes a person inherits may make him or her more susceptible to lupus. The LRI funds research that explores this association, so that measures can be taken to anticipate or modify it.

Christine M. Grimaldi, PhD
Columbia University, New York

Substantial data indicate that the female sex hormone, estrogen, plays a role in making lupus far more prevalent in women than men. Dr. Grimaldi will study the genetic basis for estrogen response by looking first at the genes in mice that encode the estrogen receptors. This knowl-

edge should give possible clues as to how estrogen responses in humans are genetically regulated. Hormone-based lupus therapies become a possibility if a subset of people with lupus do have estrogen-exacerbated lupus.

Marko A. Radic, PhD
University of Tennessee, Memphis

In this highly promising novel research study, Dr. Radic will use advanced imaging technology (confocal microscopy) along with a sophisticated analytical technique (mass spectrometry) to analyze programmed cell death (apoptosis) in a human T cell line. He will explore what happens to the DNA and histones (proteins that fold nuclear DNA and participate in gene regulation) during apoptosis, and test the idea that the histones become modified and more likely to stimulate immune system reactions.

Immune System Function

In lupus, the immune system goes awry. The LRI funds research that explores the mechanisms at play in jump-starting and fueling this faulty autoimmune response.

Daniel H. Kaplan, MD, PhD
Yale University School of Medicine, New Haven

Dr. Kaplan plans to engineer a lupus-prone strain of mice that lacks a recently identified cell (the Plasmacytoid Dendritic cell) that is the primary source of interferon alpha early in infection, and that has recently been implicated in the development and promotion of lupus. By developing a strain of mice that lacks this cell type and observing whether the development of lupus is attenuated, this investigator's project could lead to more refined lupus treatments.

Greg E. Lemke, PhD
The Salk Institute for Biologic Studies, La Jolla

Dr. Lemke will study the role of certain enzymes called TAM receptors in regulating the lupus immune response to apoptotic cells. This new and unexpected area of investigation is particularly exciting given that the enzymes are favorable targets for agents that might enhance or inhibit cell signaling and function. TAM receptors represent a potentially high-reward area of investigation into the causes of autoimmunity.

Theresa T. Lu, MD, PhD
Hospital for Special Surgery, New York

Dr. Lu, a pediatric rheumatologist, proposes viewing Type 1 interferons in a novel way: as pro-inflammatory compounds that lead to the growth of lymph node blood vessels. Could this development set the stage for the inappropriate immune system responses characteristic of lupus? This represents a whole new way of thinking. And if it bears fruit, it could lead to new therapies designed to limit the growth of lymph node blood vessels and halting lupus progression.

Martin Weigert, PhD
University of Chicago

Dr. Weigert, an established lupus researcher, will examine the role of Light Chain (L-Chain) editors in producing the self-targeted antibodies that can cause damage to organs and tissues in lupus. The study will examine whether the expression of L chain editors correlates with disease activity. If successful, Dr. Weigert's research could lead to the development of a revealing novel lupus assay (test) and new treatment.

Organ-Specific Research

Lupus attacks major organ systems. The LRI funds studies to figure out how and what can be done about this. Some are done in people directly, and some are done using tissue

from humans—often just a step away from clinical research.

**Cardiovascular: Amy S. Major, PhD
Vanderbilt University School of
Medicine, Nashville**

Doctors still don't have good answers as to why blood vessels in people with lupus tend to prematurely narrow and harden, a condition called atherosclerosis that sometimes results in fatal heart attacks and devastating strokes. Dr. Major will feed a normal, non-high fat diet to lupus-prone, atherosclerosis-susceptible mice (a model she aims to develop) to observe whether the animals quickly develop hardened arteries, all the while examining the effect of slight changes in cholesterol (serum lipoproteins) and the immune system.

**Central Nervous System:
Roland G. Henry, PhD
University of California at
San Francisco**

An expert at viewing subtle brain changes with high-technology imaging tools such as MRI machines, Dr. Henry will track brain imaging markers in people with lupus to see if they correlate with cognitive dysfunction (problems with memory, attention, and concentration)—an issue for many with lupus. If specific lupus-related disease processes in the brain can be linked to cognitive impairment, treatment of this profoundly difficult complication becomes a possibility. Dr. Henry has used this approach in people with multiple sclerosis and other conditions, but is new to lupus research.

**Kidney: Marcus Clark, MD
University of Chicago**

Dr. Clark provides clinical evidence that B lymphocytes—immune cells that are believed to make antibodies to the body's own tissues in lupus—invade the kidney and directly contribute to damage there. To carry out an extended exploration of why this is important and describe just what role B cells play in lupus nephritis, he will

use human tissue from kidney biopsies. The research represents a new direction for Dr. Clark, an established lupus investigator in basic lymphocyte biology. If fruitful, the findings could profoundly shift thinking on how lupus kidney disease first starts, and treatment options.

**Studies Using Human Tissue
Janis Burkhardt, PhD
Children's Hospital of Philadelphia**

Dr. Burkhardt will examine human cells for information on how the body modifies the HS1 protein, a poorly understood molecule that normally helps regulate the activation of T lymphocytes. Do people with lupus inherit a variant of this protein that gives rise to the disease? If correct, Dr. Burkhardt, an established immunology investigator new to lupus research, will continue with a second study phase that examines a living mouse with altered HS1 function.

**Zhixin (Jason) Zhang, PhD
University of Alabama at
Birmingham**

Dr. Zhang will examine the origins of disease-generating anti-DNA antibodies in lupus. To do this he will use a micromanipulation technique to obtain single cells from human tissue, tracing the involvement of VH gene replacement products in germinal center reactions, as he suspects that they may be the origin of the high-affinity anti-DNA antibodies.

New Treatments

Many of the year 2005 research studies could lead to urgently needed therapy breakthroughs for lupus. The following three are particularly promising in this regard.

**Pascal Alard, PhD
University of Louisville**

Lupus-prone mice are deficient in regulatory T cells, which play an important role in the development of autoimmune disease. Components of infectious agents (such as bacteria) can prevent lupus and are thought to have

immune-regulating properties. Dr. Alard, an investigator new to lupus research and collaborating with other scientists in a group lab, proposes targeting the molecules involved in this process and using them to enhance the number and function of regulatory cells. The goal is to in this way prevent or modulate lupus in the mouse, and then go on to apply the same approach to people with the disease.

**Felipe Andrade MD, PhD
Johns Hopkins University School
of Medicine, Baltimore**

Currently the closest stage to a lupus cure is remission, a disease-free period that can develop spontaneously or with therapy, and which in some cases enables the patient to stop treatment indefinitely. Using peripheral blood cells from patients in remission, Dr. Andrade aims to find the molecular pathways involved when natural remission occurs. Preliminary data are sparse, but point to findings that could potentially be extremely important. The novel hypothesis comes from an investigator who has studied autoimmune diseases for some time and recently established his own independent research program.

**Inez Rogatsky, PhD
Hospital for Special Surgery, NY**

Dr. Rogatsky, an investigator new to the study of lupus, will use mice and mouse blood cells to explore the possibility that glucocorticoids work in an entirely different way than previously thought: by interfering with a protein that regulates the production of interferon. At some point most people with lupus take glucocorticoids such as prednisone. While quite effective in relieving disease symptoms, they can cause devastating side effects when taken in large amounts or for long stretches. Dr. Rogatsky's research could lead to the development of more selective and less toxic glucocorticoid-like drugs.



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



Michael and Carol Weisman, Margaret Dowd



Jason Perline, Florence Forman, Sheri and Steve Alexander



Gari and Ira Dansky, Andrea O'Neill



Adam, Arty, and Betsey Selkowitz

Investing in LRI's Future, and Yours

The most common type of planned gift is a bequest, which can be made through a living trust or by including the LRI in your will as a beneficiary of cash, securities, real estate, or personal property. Bequests should include the LRI's tax ID number (06-1565950) and a statement such as: I bequeath to the Lupus Research Institute, Inc., a not-for-profit corporation of the State of New York, having its principal office at 149 Madison Avenue, Suite 205, New York, NY 10016, the sum of \$_____ for its general corporate purposes.

Bequests can be designed in many ways, so always consult your attorney and tax advisor for guidance on writing your will and the tax implications of any planned gift. For further information, call Andrea O'Neill, Director of Development, at 212-685-4118, or email her at aoneill@lupusny.org.

Record Number of LRI-Funded Research Presentations at ACR Meeting

More than 10 novel lupus research posters and abstracts funded by the LRI were introduced at the American College of Rheumatology (ACR) /Association of Rheumatology Health Professionals (ARHP) Annual Scientific Meeting in mid-November. Thousands of scientists, rheumatologists, health professionals, media members, and others attended this major meeting at the San Diego Convention Center in southern California.

At least six LRI-funded research posters and abstracts from the grant recipients of 2002, and four from the group funded in 2004, were presented.



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