DRIVING DISCOVERY *through innovation*

A DECADE OF IMPACT IN LUPUS RESEARCH

Lupus Research Institute

Discovery

Just a decade ago, in an era of advances in medical technology and clinical discovery, private sector research in lupus was small and limited. More than 50 years has passed without the approval of a new treatment option and only modest progress had been made toward further understanding the disease.

In late 1999, as 1.5 million Americans faced the pain and devastation of lupus, patients, families and the nation's leading researchers came together to establish the Lupus Research Institute (LRI).

The Institute was founded on the principle that the private sector has the unique opportunity to pursue new and creative scientific approaches. These novel research concepts, while unlikely to be supported through conventional funding sources, are the very ideas that have the potential to drive discovery in a complex and understudied disease.

By creating a robust platform for scientific innovation, the LRI has raised the bar in lupus research – an accomplishment that would not be possible without its pioneering investment and commitment to redefining the scope and pace of progress in lupus.

Recently, the LRI commissioned an independent review of funded (and completed) projects over its first decade to evaluate the success and impact of this new and vigorous approach to lupus research. The review quantifies the **success** and impact of the LRI initiative by evaluating how funded studies contributed new insights into lupus, led to the **growth** of the lupus research community, and **leveraged** large-scale follow-on funding for future research advancements that give hope to people with lupus.

10 years of research

80 percent success rate

Substantive impact ▶

HIGH RISK LEADING TO GREAT REWARD: THE NUMBERS SPEAK FOR THEMSELVES

Funding Successful Research and Driving Discovery

- **80%** of investigators were successful and have published their discoveries in top peer-reviewed journals and/or obtained major follow-on funding to take the next step in their LRI-funded research
- Results have been published in **123** original peer-reviewed research papers, including 30 landmark papers, that serve as a foundation for future research by informing and guiding new investigation
- LRI research has been cited over **4,000** times by researchers in the field

Leveraging LRI-Funded Studies — $22 Million Generates $100 Million*

- **$100 million** in follow-on funding for lupus research was secured from the LRI's $22 million investment
- Includes **$84 million** awarded from the National Institutes of Health (NIH)

Changing the Field by Spurring the Growth of Lupus Research

- **40%** of researchers came from other disciplines to work on lupus for the first time
- **80%** of the researchers new to lupus have remained in the field, many building new labs
- **220** scientists are now working on research that would not have happened without the LRI's commitment to new ideas and novel research

Translating Discoveries into New Treatments, Picking Up the Pace

- **20%** of LRI grant holders already have quickly embarked on pathways translating novel research to the clinic
- Several patents for new biomarkers or therapeutic approaches are already filed or approved as a result of LRI-funded research.

**The LRI has funded 108 investigators and invested a total of $30 million to date; this report analyzes the work of the 75 who have completed their 3-year Novel Research Grants totaling $22 million*

Innovation

FUNDING SUCCESSFUL RESEARCH AND DRIVING DISCOVERY

Findings from LRI-funded studies are among the most pivotal discoveries in lupus and autoimmunity research over the past decade – delivering results that private sector research had not previously attained. Spanning multiple organ systems and molecular aspects of the disease, scientists now look to these discoveries to inform and guide their current projects, and consistently cite LRI discoveries as a foundation for their investigations.

Immune System. In 2004, **Ian Rifkin, MD, PhD** (Boston University School of Medicine) demonstrated that dendritic cells are activated by DNA-autoantibody complexes through an immune receptor (TLR9) for bacterial DNA. This work, published in the *Journal of Experimental Medicine*, is viewed as one of the most important discoveries in lupus of the past decade and has provided novel insight into how a lupus autoantibody can activate the cells that initiate adaptive immune responses involved in lupus pathogenesis. Dr. Rifkin was awarded a $9.9 million NIH grant following this discovery to continue his research.

Kidneys. In 2002, **Chaim Putterman, MD** (Albert Einstein College of Medicine, New York) identified a new target of autoantibodies in the kidney. This finding, published in the *Journal of Immunology*, provided new insight into the mechanism of kidney damage in lupus and novel ways to monitor lupus nephritis. He was then awarded two NIH grants valued at $5.5 million to pursue his discoveries.

Central Nervous System. In 2004, **Betty Diamond, MD** (then at Albert Einstein College of Medicine in New York) provided the first evidence that autoantibodies are responsible for neurological complications of lupus. This finding, published in the journal *Immunity*, provided the first mechanistic understanding of CNS lupus, and she subsequently was awarded a $6.5 million NIH program grant to develop novel strategies for dealing with this devastating lupus-related manifestation.

Lupus Biomarkers. In 2004, **Mary Crow, MD** (Hospital for Special Surgery, New York) showed that genes regulated by interferon are potential biomarkers for lupus flare. This work, published in *Arthritis & Rheumatism*, has stimulated numerous pharmaceutical companies to test blocking interferon pathways as a possible therapeutic approach in ongoing lupus clinical trials.

Genetics. In 2006, **Silvia Bolland, PhD** (then at Rockefeller University, New York) showed that a strain of lupus-susceptible mice carry an extra copy of the gene for an immune receptor (TLR7) for virus RNA, which helps explain why these mice develop autoantibodies to their own RNA. This work, published in *Science*, provided novel insights into molecular pathways of the innate immune response that can lead to lupus. It also identified new targets for lupus treatments that are being actively pursued by a number of biotech companies.

$100

million for new research

LEVERAGING LRI-FUNDED STUDIES— $22 MILLION GENERATES $100 MILLION

A total of $22 million was invested in the six grant groups reviewed as part of this report. To date, the original investment has expanded into $100 million in follow-on lupus research funding from the NIH, other non-profit funding organizations and industry.

- **45 of the investigators (60 percent) obtained large-scale funding to expand their LRI research**
- **50 grants, valued at over $84 million in total, were awarded to the LRI investigators by the NIH**

Over 220 research scientists are working to further develop research themes that originated from LRI-funded work. This critical mass of scientists includes principal investigators, as well as fellows and graduate students, who are being equipped with the knowledge and skills they need to be future research leaders in lupus.

CHANGING THE FIELD

Recognizing that most medical breakthroughs come from unexpected directions and new perspectives, the LRI has aimed to fund scientists with the most promising hypotheses, regardless of whether they have conducted lupus research in the past.

By planting the seeds of lupus research across a new group of scientists, the potential for future innovation and discovery in lupus research continues to grow rapidly.

Marcus Clark, MD

University of Chicago

In examining small bits of tissue taken from the inflamed kidneys of people with lupus, Dr. Clark found activated B cells. He now has an NIH grant for $1.7 million to further explore, explain and expand on this major discovery.

Additionally, the University of Chicago group was awarded one of the nation's nine "Autoimmunity Center of Excellence Grants" based in part on work supported by the LRI. The prestigious 5-year award for $4.2 million will enable Dr. Clark and others to further explore and expand upon new directions in lupus.

"The LRI strategy of funding novel scientific ideas in lupus has more than demonstrated its power. The LRI model strengthens the lupus research landscape by moving novel concepts forward to secure large-scale federal funding, and expanding targets for eventual treatment strategies that can benefit patients."

—William E. Paul, MD, chief of the Laboratory of Immunology at NIAID-NIH and chair of the LRI Scientific Advisory Board

Growth

Greg Lemke, PhD

Salk Institute for Biologic Studies, La Jolla

Neurobiologist Dr. Greg Lemke was one of 30 LRI investigators who had not previously worked on lupus. LRI funding allowed him to become an established researcher in autoimmunity with a new company and several patents aimed at developing therapeutics for lupus.

Before his LRI grant, Dr. Lemke researched the role of the TAM receptor tyrsosine kinases and noticed that mice genetically engineered to lack this family of receptors developed an autoimmune illness similar to human lupus.

Dr. Lemke believed he had discovered a fundamental new control switch for turning off dangerous inflammation. But his idea was premature for NIH funding.

The LRI's scientific advisors saw the potential and awarded him a three-year novel research grant in 2005. Just two years later, Dr. Lemke and his team published findings in the prestigious journal, *Cell*, which showed how TAM receptors prevent out-of-control inflammatory responses and autoimmunity. Dr. Lemke went on to be awarded $1.4 million in NIH funding to further develop this work.

"Without the LRI, this project would have stopped and a fundamental discovery in immunology would not have happened!"

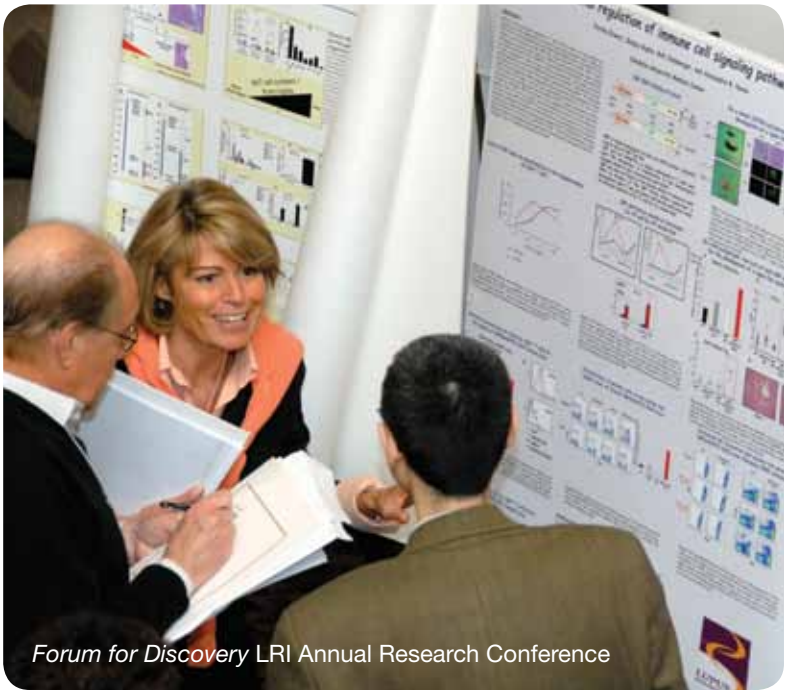
—Dr. Lemke

GROWING LUPUS RESEARCH

In fact, **40 percent** of LRI-funded investigators (30 out of 75) had not conducted lupus research. Many were leading molecular or cell biologists who had not previously examined autoimmune disease.

Sparked by their LRI research, **80 percent** (24 of 30) have continued to work on lupus after the completion of their LRI grant, with many shifting the focus of their labs entirely to lupus.

Barbara Vilen, PhD's (University of North Carolina at Chapel Hill) previous work had focused on understanding the basic molecular mechanisms of B-cells —the cells that make antibodies. After receiving her 2001 LRI grant, Dr. Vilen provided fundamental new insights into how B-cells malfunction in lupus and attack the body's own cells and molecules. Lupus is now the primary focus for Dr. Vilen and the six members of her research group. She has obtained $2.8 million in NIH funding to continue the work originating from her LRI study.



Forum for Discovery LRI Annual Research Conference

220

scientists at work on all new research

The LRI stands for hope and the possibility of a future of a life without lupus. Our scientists are now doing groundbreaking research—especially in the biology of human lupus—and leveraging millions at the NIH. Because of this extraordinary progress, I am very hopeful for lupus patients like me, my young niece, and the many others who struggle daily with this disease.

—Jennie DeScherer, person with lupus, mother, wife, long-time LRI supporter

TRANSLATING DISCOVERIES INTO NEW TREATMENTS, PICKING UP THE PACE

Translating fundamental discoveries to clinical applications is a complex and arduous path. However, patients and clinicians will be encouraged by the fact that **20 percent** of LRI-funded investigators already are moving their research discoveries from the bench to the clinic.

Seven patents for new biomarkers or therapeutic approaches have now been filed or approved as a result of LRI-funded research. In many cases, pharmaceutical or biotech companies have licensed these technologies and are now developing novel therapeutic agents.

Fast-Forwarding Human Studies

The LRI is also leading the charge in funding research on cutting-edge technologies that can fast-forward human studies in lupus and autoimmunity. These new technologies also propel LRI's recently launched initiative in **"Human Lupus Biology"** by permitting researchers to use human material (cells, blood, tissue), rather than animals, to generate discoveries applicable to the human disease and help researchers understand how their findings will impact human systems.

Accelerating Progress, New Treatments and the Cure

While past achievements have significantly impacted the field, the LRI is committed to taking its research and contributions to the next level.

DELIVERING HOPE TO PATIENTS

As its next decade begins, the LRI remains steadfast in its determination to take risks, think outside the box, and bring only the best new ideas and imaginative, creative new science to lupus.

Bevra Hahn, MD, and Maureen McMahon, MD

University of California at Los Angeles

At first, the LRI was the only institution willing to fund Dr. Bevra Hahn and Dr. Maureen McMahon's novel idea that a certain form of "good" cholesterol (high density lipoprotein, or "HDL") linked to heart health actually might play a counterproductive role in lupus.

With LRI funding, the two established that people with lupus with elevated levels of an HDL subtype known as "pro-inflammatory" HDL (piHDL) are 10 times more likely to develop atherosclerosis.

In fact, piHDL appears to provide a more reliable marker for cardiovascular risk in people with lupus than traditional risk factors alone, and Drs. Hahn and McMahon have gone on to obtain $1.6 million in NIH and other follow-on funding to support a lab of 15 scientists to find new ways to detect, prevent, and treat lupus-related atherosclerosis.

"We are so grateful to the LRI. Without them, this idea would not have seen the light of day."

—Dr. Hahn

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About Lupus

Lupus is a perilous and chronic autoimmune disease that primarily afflicts young women in their childbearing years. The immune system attacks the body's own tissues and vital organs, making the illness a leading cause of premature cardiovascular disease, heart attack, stroke, and kidney disease among young women. Finding the cause, the cure and new treatments for lupus is a complex and challenging process.