

Exploring the Drivers of Lupus Via Endogenous Retroviruses

The study of the human genome—in all its fascinating complexity—continues to have a profound impact on many dimensions of biomedical research. Yet so much is still to be deciphered about the ways:

- 1.** building blocks of life interact with the trillions of cells that make up the human body
- 2.** related chemical compounds work together ... and
- 3.** viruses and bacteria interface with healthy cells.

To discover ways the human genome can transform lupus research and alleviate suffering of patients worldwide, the **Lupus Research Alliance** (LRA) looks to the world's brightest scientists for bold insights.

Akiko Iwasaki, PhD, from Yale School of Medicine, is one of them. Looking at sequences of endogenous retroviruses, she and her team have discovered an important link to lupus.



Dr. Akiko Iwasaki

This finding is a breakthrough that suggests we are on the cusp of an exciting new era of lupus treatment and eradication—which is why the LRA was proud to award its prestigious **Lupus Insight Prize** to Dr. Iwasaki this year.

Her team at Yale analyzed 3,220 unique sequences of endogenous retroviruses—genetic segments of retroviral origin that make up approximately 8% of the human genome. This painstaking investigation has identified specific retroviral sequences that are elevated in immune cells of lupus patients—a contributing factor in disease pathogenesis.

Under Dr. Iwasaki's guidance, the team developed a human endogenous retrovirus map (ERVMap) and found that over 100 segments are strongly elevated in the peripheral blood mononuclear cells of patients with lupus. Specifically, these elevated levels are linked to an increase in type-1 interferon, a main driver of lupus.

Dr. Iwasaki also found that endogenous retroviruses force immune cells called neutrophils to release spiderweb-like structures known as NETs, which have been shown to promote inflammation in lupus.

"The 2022 Lupus Insight Prize awarded to Dr. Akiko Iwasaki recognizes her highly innovative work on endogenous retroviruses triggering autoantibody production in lupus patients and supporting an autoimmune inflammatory pathway in neutrophils. In addition to revealing mechanistic insights this research also highlights the heterogenous nature of the disease and suggests potential new therapeutic interventions. We are excited to have Dr. Iwasaki as part of the Lupus Research Alliance research community," said **Teodora Staeva, PhD**, Chief Scientific Officer at the LRA.

The Lupus Insight Prize—and its \$100,000 award—recognizes an outstanding accomplishment by an investigator who has published a novel and important research insight into lupus. Dr. Iwasaki's work offers the scientific community a more detailed view into the connections between human genes and the mechanisms by which lupus is triggered.

In her acceptance of the award, Dr. Iwasaki looked to the next challenge, *"I am eager to use this award to further understand the association between the endogenous retroviruses and lupus-like disease in long COVID patients to ultimately improve their disease treatment outcomes,"* she said.

The real promise of Dr. Iwasaki's work is that it will likely open new avenues for lupus diagnosis and treatment—and may even uncover new connections between lupus and other autoimmune diseases.

Dr. Iwasaki's breakthrough suggest we are on the cusp of a new era of disease treatment and eradication—which is why the LRA awarded her the prestigious Lupus Insight Prize.

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The Lupus Research Alliance Awards \$9 Million in Global Effort to Accelerate Breakthroughs

Three international research teams are recipients of the **LRA's Global Team Science Award** to advance groundbreaking efforts focusing on lupus remission, gut microbiome, and ancestry/genetics.

GLOBAL TEAM SCIENCE AWARD PROPELS DISCOVERY

On August 24, 2022, the LRA proudly announced the newest grantees of our **Global Team Science Award** (GTSA)—a major international effort that aims to speed the pace of lupus research. Three international research teams—from 14 institutions across four continents—are bringing their collective expertise in immunology, rheumatology, neurosciences, biomedical engineering, genomics and genetics, and public health to shed new light on lupus and ways to treat it.

The LRA has awarded each of these teams \$3 million over the next three years, enabling the GTSA to support interdisciplinary, collaborative projects that use groundbreaking technologies to accelerate effective, personalized lupus treatments.

The 2022 GTSA teams are headed by world-renowned lupus researchers: **Betty Diamond, MD**, Director of the Institute of Molecular Medicine and Maureen and Ralph Nappi Professor of Autoimmune Diseases, Feinstein Institutes for Medical Research, United States; **Martin Kriegel, MD, PhD**, Chief of Rheumatology and Head of the Department of Translational Rheumatology and Immunology, University of Münster, Germany; and **Eric Morand, MD, PhD**, Head of the School of Clinical Sciences, Monash University, Australia.

*The creation of the Global Team Science Award represents a defining research moment in the history of our organization," said **Albert T. Roy**, President and CEO of the LRA. "This Award has allowed us to mobilize some of the world's most renowned researchers and position them to work collaboratively on some of the most important research questions facing lupus. We are excited about the advances in lupus research that will be achieved through this initiative."*

MEET ALL THE GTSA INVESTIGATORS

The Global Team Science Award represents the LRA's strategy of defining lupus heterogeneity, enabling patient stratification, and promoting collaborative global cutting-edge research. The following is a list of all the amazing investigators who are working on each of the three teams.

TEAM 1

Betty Diamond, MD

The Feinstein Institute of Medical Research

David Eidelberg, MD

The Feinstein Institute of Medical Research

Hilda Fragoso-Loyo, MD

National Institute of Medical Science and Nutrition Salvador Zubrin

David Isenberg, MD

University College London

TEAM 2

Martin Kriegel, MD, PhD

University of Münster

Ilana Brito, PhD

Cornell University

Eran Elinav, MD, PhD

Weizmann Institute of Science

George Tsokos, MD

Harvard Medical School

Nissan Yissachar, PhD

Bar-Ilan University

TEAM 3

Eric Morand, MD, PhD

Monash University

Emma Davenport, PhD

Wellcome Trust Sanger Institute

Michael Inouye, MD

University of Cambridge

James Peters, MD

Imperial College London

Timothy Vyse, PhD

King's College London & King's Health Partners

TEAM 1

Probing Heterogeneity in Immune Cell Behavior

Led by corresponding investigator Dr. Diamond, this two-project initiative aims to bring better understanding about the



Dr. Betty Diamond

immune system of patients in remission by identifying causes of lupus in heterogeneity. Lupus is heterogenous—meaning symptoms are many ... vary widely from patient to patient ... and that one therapeutic is not going to work for everyone.

Dr. Diamond and her team will be studying patients in remission who are not on immunosuppressive medications. This approach will help them learn the different features of immune cells in patients in remission, whether any cells predict relapse, and how cells change when patients do relapse.

The LRA is confident that the GTSA will make significant advances in lupus research—advances that have the potential to radically change outcomes for lupus patients. *"With the rapid evolution of science and technology, we are learning more about lupus than ever before,"* said Albert T. Roy, President and CEO of the LRA. *"Today, we are poised to accelerate the speed of discovery to address vast unmet medical needs, a more personalized approach to treatment—and ultimately the eradication of lupus."*

The researchers will then determine if patients in remission experience lupus-related cognitive issues and if there is an association between brain function and immune cell features.

What this study means for people with lupus ... *"Our findings will help inform our understanding of immune cell heterogeneity and brain function in lupus patients,"* said Dr. Diamond *"We also hope to shed light on potential connections between immune cell abnormalities and cognitive complications, which may be an overlooked problem in lupus patients in remission."*

TEAM 2

Identifying Gut Microbes that Trigger Lupus via Leaky Gut

With GTSA funding, Dr. Kriegel is building on a prior investigation that was the first to link a gut organism to lupus. As



Dr. Martin Kriegel

corresponding investigator, he now seeks to identify the specific gut microbes that trigger the misdirected immune system responses that lead to lupus.

This team is employing a comprehensive approach to uncover the microbes that escape the intestines via "leaky gut" to trigger autoimmune inflammation in patients with active disease.

Dr. Kriegel and his team will use mouse models to investigate if intestinal microbes that are suspected of causing lupus in people cause lupus-like symptoms in mice.

What this study means for people with lupus ... *"Our past work in murine models showed that microbes living in the digestive tract can*

trigger damaging immune system activity if they escape the gut," said Dr. Kriegel. *"Now, we are translating our research to lupus in humans by identifying microbes that cause or worsen lupus. Our ultimate goal is to develop a new set of lupus diagnostics and treatments that target the 'bad' gut bacteria."*

TEAM 3

Identifying Ancestry-specific Lupus Profiles to Uncover New Genetic Causes of Lupus

Corresponding investigator Dr. Morand and his team aim to identify the distinct molecular pathways and underlying genetics driving ancestral-specific differences in lupus symptoms.



Dr. Eric Morand

In their studies of five different ancestral groups—Europeans, Afro-Caribbeans, South and East Asians, and Indigenous Australians—the team is using the latest scientific technology to identify the ancestry-specific genetic variations associated with molecular pathways that are linked to lupus. To identify potential genes that drive lupus, the researchers will use advanced computational technology to analyze their enormous trove of data.

What this study means for people with lupus ... *"Our project explores the high variation in lupus symptoms and disease severity observed among different ancestral groups,"* said Dr. Morand. *"This research will generate a massive amount of data that we can use to identify potential genes that drive or promote lupus. We hope these findings will identify new targets for treating and preventing the disease."*

Two Leaders One Mission

This is a time of transition for the LRA.

Kenneth M. Farber, who has been the guiding force behind the organization's many accomplishments for the past 6 years has stepped down as President and Chief Executive Officer. During his tenure, Ken greatly helped transform the LRA into the world's premier private lupus research organization. Ken will continue to offer invaluable contributions as President-Emeritus through the end of the year.

With Ken at the helm, the LRA remained unwavering in the support of the best new science to prevent and treat lupus. He saw the organization through a landmark merger that united leading lupus research organizations to unprecedented advances. And throughout the pandemic, Ken was the calm, reassuring voice of reason during a tremendously challenging time for everyone in the lupus community.

Today, we also look to **Albert T. Roy**, who has assumed Ken's role of President and Chief Executive officer for leadership. No stranger to the LRA, Al created and ultimately served as Executive Director of Lupus Therapeutics, the LRA's clinical research affiliate.

"As impressive as Al's credentials are, it's his kindness and compassion that are the most important assets for his new job," said Ken. *"He is dedicated to improving the lives of people with lupus. I know by passing the baton to Al that the lupus community will have a passionate, dynamic, caring, and highly effective champion."*

The entire organization is united in our gratitude to Ken for his tremendous leadership—and we are united in our support of Al and the unique skills he brings to propel the organization forward.

Long-time Supporter LADA Donates \$150,000 to LRA-Funded Research

Big thanks go to **Lupus and Allied Diseases Association, Inc.** (LADA) for their \$150,000 donation given at their Annual Lupus Charity Golf Classic.

LADA President & CEO

Kathleen A. Arntsen (center) presented the check to LRA's **Dorey Neilinger, Ian Kirkman,** and **Albert T. Roy**, bringing their support to nearly \$1 million.

"We are grateful to receive this very generous gift and thankful for the unwavering support LADA has contributed to the LRA over the years," said Mr. Roy.

"Led by President/CEO and fierce patient advocate Kathleen Arntsen, LADA works tirelessly to achieve our shared vision of life without lupus."

"As a patient-led organization, we have always believed wholeheartedly in investing in groundbreaking quality research here at the Lupus and Allied Diseases Association," stated President and CEO Kathleen Arntsen. "Because of this conviction, we recognized that from its inception, the Lupus Research Alliance was the research institute that LADA needed to support and are honored to have continued to do so for over two decades."

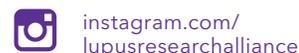


Visit lupusresearch.org to make a donation, learn more about lupus and our funded lupus research, or find out about our *Walk with Us to Cure Lupus* program.



100% of all donations goes to support lupus research programs because the Lupus Research Alliance Board of Directors funds all administrative and fundraising costs.

For the latest, up-to-date information about lupus you can join our online community on:



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