LUPUS RESEARCH ALLIANCE

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LUPUS research UPDATE

# Scientific Discovery: From Lab to You

Making new and efficacious lupus therapies available to patients has long been a major focus of the Lupus Research Alliance, and today we've taken an important step toward that aim.

Based on a breakthrough discovery made by **Betty Diamond, MD**, in her laboratory, **Meggan Mackay, MD, MS**, is about to start a clinical trial to test whether a drug can prevent brain cell damage in people with lupus that leads to problems with concentration and memory.

A significant piece of this story that we are excited to share is that the very drugs that will be tested in our Lupus Therapeutics' trial – known as ACE inhibitors – are already being used to treat high blood pressure. This means these drugs have the Food and Drug Administration (FDA) stamp of approval and have worked safely for people over several decades, so testing them as a treatment for lupus could result in enormous savings in time and financial resources.

Considering that it takes between 10 to 15 years – *and a staggering average price tag of $1.5 billion* – to test and bring a new drug to market, the clinical trial Dr. Mackay is about to undertake is truly significant.

## THE GENESIS OF THIS IMPORTANT TRIAL

In 2004, Lupus Research Alliance grantee Dr. Diamond made an important discovery – a subset of anti-DNA antibodies can cause cognitive and emotional alterations in lupus patients if they cross the blood-brain barrier, a protective barrier surrounding the brain.

Specifically, Dr. Diamond and her team used a murine model to show that some lupus autoantibodies attach to neurons in the brain, causing them to die. The dead neurons are then cleared by other cells in the brain, called microglial cells. This "clean up squad" of microglial cells becomes activated, leading them to attack and destroy healthy neurons and synapses (places where neurons communicate with each other) that are necessary for several functions, including generating and retaining memories.

The team then discovered that a common and safe class of medications for blood pressure, ACE inhibitors, also control the activation of the microglial cells. Several kinds of ACE inhibitors have been approved by the FDA for treatment of hypertension; some of these can cross the blood brain barrier and some cannot.

ACE inhibitors were then used in the murine model and the ACE inhibitor that was able to cross the blood brain barrier stopped the microglial cell over-activation and preserved neuron function in the mice. *(More details on the actual trial follows.)*

*Dr. Betty Diamond*

*Dr. Meggan Mackay*

One of the important reasons why clinical trials for cognitive function in lupus have not been possible so far is that there have been no objective methods established to measure cognitive function other than neuropsychological testing, which is often unreliable because cognition can be influenced by depression, medications, infections, other illnesses, and more. Using highly sophisticated brain imaging in people with lupus, Drs. Diamond and Mackay found that high levels of the damaging autoantibodies correlated with increased metabolism in specific brain regions and with poor performance on cognitive testing. These studies suggested that the increased brain metabolism was a marker for cognitive impairment related to the damaged neurons and activated microglial cells.

## THE TRIAL: Potential for Vast Numbers of Patients

*"Dr. Diamond discovered one of the autoantibodies that causes nerve cell dysfunction and results in over-activated microglial cells that cause further neuron damage – and our aim is to block the microglial cell activation and ultimately prevent this damage,"* said Dr. Mackay.

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She is taking what was initially learned in the lab from the murine model to assess and treat neuropsychiatric dysfunction in people with lupus.

Dr. Mackay believes this is just the start of piecing together the different mechanistic pathways that lead to cognitive problems in lupus, such as trouble with concentration and memory. This is important work – as much as 80% of all lupus patients experience neuropsychiatric problems, like memory and mood disorders, anxiety, and depression.

*"The challenge in human illness is to find a way to objectively measure brain damage from lupus autoantibodies or activated microglial cells that correlates with cognitive problems that are attributable to lupus,"* explained Dr. Mackay. *"We obviously cannot sample human brain tissue!"*

Because of the limitations of studying the human brain, Dr. Mackay uses sophisticated scanning technology to image the brains of lupus patients. In the process, she discovered a reproducible pattern of increased metabolism in certain areas of the brain, including the hippocampus – one of the big centers of memory formation. Increased metabolism in some brain regions correlated with high levels of the autoantibody and poor performance on neuropsychological testing, suggesting that the increased metabolism may be a marker for damaged neurons and activated microglial cells.

The clinical trial Dr. Mackay has designed aims to stop microglia cell activation using ACE inhibitors, a class of drugs used to treat hypertension.

For more evidence that she was on the right track, Dr. Mackay looked to their cohort of lupus patients who were imaged once a year for two years to see if metabolism changed over time. It just so happened that a small number of these patients were already taking ACE inhibitors.

*"When we looked at the patients who were on the protective ACE inhibitor that crossed the blood brain barrier, compared to the others in our group, we saw that the regional metabolism in the brain actually decreased,"* stated Dr. Mackay.

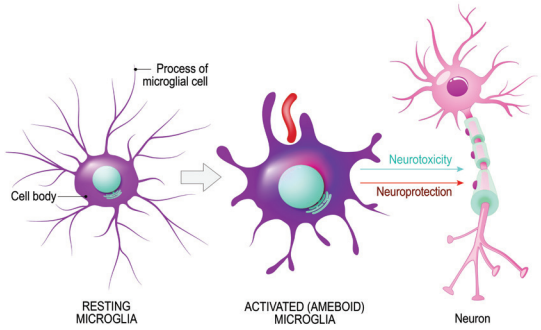
All this critical data contributes to the formation of Dr. Mackay's hypothesis: lupus patients treated with an ACE inhibitor that crosses that blood brain barrier will show significant decreases in brain metabolism after 12 months of treatment compared to lupus patients treated with an ACE inhibitor that does not cross the blood brain barrier. The team will also measure microglial cell activation directly with a different imaging technique and assess improvement in neuropsychological testing.

The Lupus Research Alliance is proud to help fund this pioneering work through its clinical trial affiliate, Lupus Therapeutics, and Dr. Mackay is grateful for the opportunity to bring her ideas to fruition.

*"Help from the Lupus Research Alliance, in all of its iterations, has been huge – for all of my colleagues and me. We wouldn't be at this stage – of actually conducting a clinical trial – without the support of this incredible organization,"* beamed Dr. Mackay.

Improving the day-to-day lives of people with lupus takes an organization like the Lupus Research Alliance … its many generous donors … and the most brilliant minds in lupus research working together.

*"Together"* – as we have witnessed with Drs. Diamond and Mackay – is the operative word!




*Microglia are key players in neurodegenerative and neuroinflammatory diseases like lupus. ACE inhibitors can block the damage caused by these cells.*

## A PROMISING NEW THERAPY

As our name implies, the Lupus Research Alliance aims to forge partnerships and bring other players to the table to better understand and treat lupus – and our latest venture holds the promise of a new therapy.

We – and our affiliate, Lupus Therapeutics – are about to collaborate with **Takeda Pharmaceutical Company Limited**, to evaluate the investigational biologic TAK-079 in a nationwide study to be conducted in 20 research centers across the United States. Many of these centers are members of Lupus Therapeutics' Lupus Clinical Investigators Network (LuCIN).

TAK-079 is an antibody that is produced in the laboratory using human DNA sequences. In preclinical studies, TAK-079 attached to and inhibited CD38, a protein found on many immune cells that are involved in producing autoantibodies. Data from a study with healthy volunteers suggested that TAK-079 is generally well tolerated and showed a decrease in the number of immune cells that expressed CD38.

This study aims to evaluate the safety of TAK-079 among patients with moderate to severe disease activity that has not responded well enough to standard lupus treatment.

# Seeing Our Research Endeavors Through a Fresh Lens

The Lupus Research Alliance is proud to welcome renowned expert in rheumatology and immunology, **Gary Koretzky, MD, PhD**, as co-chair of our Scientific Advisory Board (SAB). He will co-chair the SAB with the distinguished Dr. Mary "Peggy" Crow.

*"Dr. Koretzky's background is an ideal match to help guide scientific endeavors at the Lupus Research Alliance,"* said Dr. Crow.

As Vice Provost for Academic Integration at Cornell University, Dr. Gary Koretzky creates and implements initiatives that facilitate research collaborations and integrate academic units between Cornell campuses in Ithaca and New York City.

Dr. Koretzky's previous positions include Vice Dean at Weill Cornell Medicine, Vice Dean for Research at Weill Cornell Medical College, and Dean of the Weill Graduate School. He was also the founding director of the Signal Transduction Program of the Abramson Family Cancer Research Institute and Vice Chair for Research in the Department of Medicine at the University of Pennsylvania.

Before holding these key positions, Dr. Koretzky was the Francis C. Wood Professor of Medicine, Vice Chair and Chief Scientific Officer of the Department of Medicine, Investigator, and Director of the Signal Transduction Program of the Abramson Family Cancer Research Institute at the University of Pennsylvania.

Dr. Koretzky has deep ties to the biomedical research community as a member of the Council of the American Association of Immunologists, a Fellow of the American Association for the Advancement of Science, a member of the National Academy of Medicine, and a Fellow of the American Academy of Arts & Sciences. He previously served as Editor-in-Chief of *Immunological Reviews* (2002–2012), President of the American Society of Clinical Investigation (2000), and Councilor of the Association of American Physicians (2008–2012). Dr. Koretzky's research focused on T cell receptor signaling in health and immune system diseases.

Even in school, Dr. Koretzky seemed destined to leave his mark on medicine. He received his AB from Cornell University ('78) and earned his MD and PhD (Immunology) degrees at the University of Pennsylvania ('84). Dr. Koretzky then pursued clinical training in Internal Medicine and Rheumatology at the University of California at San Francisco. He re-entered the laboratory as a postdoctoral fellow, examining the molecular events associated with T cell activation.

Dr. Koretzky moved to the University of Iowa in 1991 where he

*Dr. Gary Koretzky*

continued his research examining the biochemistry and molecular biology of signal transduction in hematopoietic cells until he moved to the University of Pennsylvania in 1999.

His current research aims to better understand the signal transduction events that occur following engagement of the T cell antigen receptor.

Dr. Koretzky's commitment to the highest standards of quality in research – plus his decades of experience in rheumatology and immunology – will undoubtedly propel the Lupus Research Alliance to new heights.

## FORUM FOR DISCOVERY

In November, top-flight research scientists, pharmaceutical industry representatives, and advocates met in New York City to take part in **Forum for Discovery** on November 28th - 30th, 2018. This annual scientific conference is orchestrated by the Lupus Research Alliance.

More than 20 Lupus Research Alliance-funded investigators described their latest research in detail, illuminating ways to make cross-sector and cross-discipline partnerships possible.

Rich scientific discussions followed as the audience engaged in questions. Overall, the Forum served as an incubator that sparked ideas for new research directions.

Attendees were pleased to hear about the exciting advances in lupus research. Here is a sample of the topic areas that were discussed:

**Genetic and Susceptibility Factors in Lupus**

**Immune Clearance Defects**

**Taming Aberrant DC and B Cell Responses**

**Addressing Adaptive Immunity Defects in Lupus**

**Novel Therapeutic Approaches and Translational Challenges**

**Mechanisms and Implications of End Organ Damage**

# Lupus News Corner

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## LUPUS LUMINARY LUNCHEON FOR SCIENCE

Celebrating our 10th year of recognizing "women of achievement" across all industries, we have renamed our Lupus Handbag Luncheon to truly reflect the mission of the Lupus Research Alliance as the world's leading lupus research organization.

The **Lupus Luminary Luncheon for Science** will honor innovative and inspiring women while providing an opportunity to catch up with friends and go home with a fantastic handbag. The event will take place on May 7, 2019 at the Plaza Hotel in New York City.

## Research Supporters Dive In

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plunge

TO FREEZE OUT LUPUS

Friends of the Lupus Research Alliance rose to the challenge and dove into the frigid Atlantic on Feb 9, 2019 to raise both awareness about the disease and funds for research. We thank each and every participant of the **2019 Plunge to Freeze Out Lupus** for braving the icy water to take a stand for lupus research.

## Distinguished Innovator Awards

*Dr. Vijay Kuchroo*

*Dr. Nir Hacohen*

With deep pride, we announce the two latest recipients of our Dr. William E. Paul Distinguished Innovator Award in Lupus and Autoimmunity. **Vijay Kuchroo, PhD**, is studying ways to harness regulatory T and B cells as a new approach to lupus treatment. **Nir Hacohen, PhD**, is seeking better ways to treat lupus kidney disease.

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.

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walk WITH US TO CURE LUPUS

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

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