Research Portfolio Summary 2012

Alliance *for* Lupus Research

PREVENT. TREAT. CURE.

THE ALR'S RESEARCH PORTFOLIO SUMMARY—A Vigorous Response to Finding a Cure for Lupus

The Alliance for Lupus Research is turning what used to be considered "science fiction" into reality by funding dozens of the most daring, innovative research projects each year.

Together, these investigations or studies form the ALR Research Portfolio Summary (RPS). Each Research Portfolio Summary includes a synopsis of all scientific research investigations that are funded by the organization in a particular year. Target Identification in Lupus (TIL), Functional Genomics and Molecular Pathways (FGMP), and special funded projects like the International SLE Genetics Consortium (SLEGEN) and the ImmunoChip study.

As evidenced by our 2012 Research Portfolio Summary, the ALR is working on many fronts to stop lupus in its tracks. Our strategy is a coordinated effort—one that leverages resources and avoids duplication of effort and inefficiency.

The ALR's objective is to aggressively work to bring treatments from the laboratory to patients' bedsides in the shortest time possible. And the scientific investigations that are currently being funded are seeking to identify potential genetic causes of lupus, while developing novel approaches for treatment and prevention.

To share these ideas with other scientists, donors, and anyone interested in learning more about the specific types of studies that the ALR is funding, the current ALR Research Portfolio Summary and several summaries from prior years are available on the ALR website.

These ALR-funded studies run the gamut of scientific exploration—from looking to replace diseased immune cells with healthy ones… to understanding why the majority of people with lupus will develop kidney problems… to deleting certain cells in the body that trigger immune system reactions.

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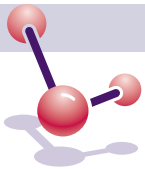


Target Identification in Lupus Grantees

Under our Target Identification in Lupus (TIL) grant program, investigators leverage a two-year, up-to-$400,000 award to remove the barriers to new treatments and a possible cure. All research funded under the TIL program is based on realizable goals for translation into therapeutic discovery programs – that is, research that can move quickly from the laboratory to the patient's bedside. Researchers also have the opportunity to apply through a non-competitive progress report for a third year of funding for up-to-$200,000.

Betsy Barnes, PhD
UMDNJ-New Jersey Medical School

Targeting IRF5 activation for the treatment of lupus

While we still don't understand all the underlying causes of lupus, we do know that it tends to run in families, suggesting a strong genetic component. Indeed, researchers have already identified several genes associated with the disease. One such gene encodes for the transcription factor interferon regulatory factor 5 (*IRF5*), which helps control the expression of several inflammatory molecules that contribute to the disease.

Dr. Barnes and her team found that people with lupus have significantly higher levels of IRF5 expressed in primary immune cells than healthy people, and that this higher expression is associated with known changes in the *IRF5* gene that are linked to lupus risk. In addition, recent data suggests that IRF5 is continually activated in the blood cells of people with lupus but not in those without the disease.

With their ALR grant, the researchers plan to modify the activation status of IRF5 in the immune cells of lupus patients, thus altering the ability of IRF5 to trigger inflammatory responses that likely contribute to the disease.

What this study means for people with lupus: Results from these studies will not only contribute to a greater understanding of the actions of IRF5, but could aid in the development of new treatments that target the protein to prevent lupus and its symptoms.

Joseph Craft, MD
Yale University

Follicular Helper T Cells in SLE: Characterization and Therapeutic Targets

Patients with lupus develop autoantibodies (also called antinuclear antibodies, or ANA) that cause tissue inflammation in organs such as the kidneys. These autoantibodies are made by B lymphocytes. In order to produce the autoantibodies, however, B cells require help from other lymphocytes called T cells. The ongoing T cell/B cell interaction in the spleen, lymph nodes, and tonsils are critical for autoantibody production in lupus.

With their ALR grant, Dr. Craft and his team will begin to dissect the signals that permit such interactions and identify characteristics of these abnormally activated T cells in people with lupus They also plan to see if potential treatments now in clinical trials affect T cells that help B cells make autoantibodies.

What this study means for people with lupus: The goal of this work is to identify existing and new therapeutic targets for people with lupus.

Rujuan Dai, PhD
Virginia Polytechnic Institute and State University
Targeting the miR-182-96-183 Cluster to Ameliorate Lupus

The hallmark of lupus is the breakdown of tight immune regulation, leading to the production of large amounts of autoantibodies against "self." This results in the chronic inflammation that eventually damages multiple organs, including skin, joints, blood vessels, and kidneys. Due to the complexity of Lupus, the precise cause remains an enigma, with no cure. Thus, there is a pressing need for a new approach to understand and treat the disease.

Dr. Dai's project will examine the role of newly discovered microRNAs (miRNAs) in the development and treatment of lupus. These molecules have emerged as key to governing immune regulation. Disruption of miRNA development or function in immune cells leads to immune tolerance breakdown and autoimmunity in mice.

Dr. Dai and her group recently reported increased production of one cluster of miRNA molecules (miR-182-96-183) in 3 mouse lupus models. Importantly, this cluster targets genes that play critical roles in controlling immune function and preventing autoimmune dysfunction.

With their grant, the group will test the central hypothesis that the miR-182-96-183 cluster contributes to the development of autoimmune diseases like lupus, possibly by regulating *FOXO* gene expression, and that preventing or reducing production of these miRNA molecules could, in turn, reduce or prevent lupus-related inflammation and symptoms. In addition, they will develop transgenic mice that overproduce this miRNA cluster in immune cells so they can continue to investigate its underlying role in autoimmune diseases.

What this study means for people with lupus: This study will not only provide important insights into the contribution of miRNA to the underlying development of lupus, but the information it generates may eventually lead to the development of innovative miRNA-based therapeutic strategy for lupus treatment and/or prevention.

Syamal Datta, MBBS
Northwestern University
Peptide Vaccine Suppressing Autoantigen-Specific Response in Human Lupus

The cells and molecules, also called antibodies, of the immune system fight foreign organisms. Sometimes, however, these defenses can react against the body itself. Normally, this self-reactivity is kept in check by special regulatory T cells called Treg. In autoimmune diseases like lupus, however, such regulatory cells are lacking, leading to abnormal reactivity against cell components such as DNA and histone proteins that bind to DNA (nuclear autoantigens).

Dr. Datta and his team found that replacing diseased immune system cells with stem cells that can grow healthy immune system cells creates a new source of Treg cells to repair the deficiency. It also helps maintain patients in true immunological remission. The Treg cells generated after stem cell transplantation are potent in reducing the risk of relapse and other complications from the disease and the ongoing medical treatments. They are not found in patients who achieve apparent remission via conventional drug treatments.

However, stem cell therapy is a drastic measure with significant risks that should only be tried in those in whom nothing else works. To avoid such a risky procedure, Dr. Datta and his team have developed a natural, nontoxic vaccine therapy using certain peptides or small bits of proteins that generate similar Treg cells and cause immunologic remission of the disease in lupus-prone mice.

With this grant, Dr. Datta's group will use the peptides to induce similar, autoantigen-specific regulatory T cells in peripheral blood of lupus patients in cell cultures. They also plan to identify genes and protein expression profiles of the potent Treg cells to identify unique surface markers and define the mechanisms and molecular pathways involved in their generation, maintenance and regulatory activity in humans.

What this study means for people with lupus: The ability to compare genes and proteins expressed by Treg cells before and after a stem cell transplant offers a unique opportunity to understand these remission-inducing suppressor cells and address new issues critical for developing immune-regulating therapies for people with lupus. Results from this study would ultimately be able to be used to screen the best therapeutic peptide for maintaining lupus patients in true remission by inducing autoantigen-specific Treg cells, or by infusing Treg cells created in culture.

Michael Denny, PhD
Temple University
Abnormal Neutrophil Development in SLE

We know that several parts of the immune system are involved in lupus. Dr. Denny and his team focus on the development and alteration of immune cells called neutrophils. These white blood cells are the most prevalent of all immune system cells and are crucial for responding to bacteria and fungi.

Dr. Denny and his team have identified an abnormal pool of neutrophils in people with lupus. They also developed a way to very quickly isolate these cells from blood samples for study. With this grant, they will try to understand whether these abnormal neutrophils arise from an alteration in cell development. In particular, they will look at the genetic level of the cell to identify alterations in genes that are critical for the proper development and maturation of neutrophils. Identifying the underlying mechanism responsible for the abnormalities is the first step in controlling the neutrophils involvement in disease or, possibly, eliminating them all together.

What this study means for people with lupus: Identifying the genetic causes of these neutrophil alterations could open the door to new therapies.

Betty Diamond, MD
The Feinstein Institute for Medical Research
Dendritic cell dysfunction as a path to SLE

Dendritic cells trigger reactions in the immune system. Dr. Diamond and her team previously showed that deleting a specific gene in dendritic cells leads to the development of lupus in animal models. With this grant, they will explore exactly *how* these abnormal dendritic cells change the response of immune system cells and cause lupus. This is particularly important research because the gene they're examining has already been identified as one that increases risk of lupus.

What this study means for people with lupus: These studies will provide important new insights into how lupus develops and progresses, providing valuable information that could be used to develop new treatments or even identify ways to prevent the disease in high-risk individuals.

Shu Man Fu, MD, PhD
University of Virginia
Progressions and Biomarkers of Proliferative Lupus Nephritis

The majority of people with lupus will eventually develop kidney problems as the disease attacks the kidneys and its blood supply. Called "proliferative lupus nephritis," the condition often leads to end-stage renal disease that requires either chronic dialysis or kidney transplantation, both of which have a significant impact on the quality of life.

Dr. Fu's laboratory has identified three stages of lupus nephritis, acute, transitional, and chronic glomerulonephritis (GN), in an animal model. They also found that the gene expression of affected kidney cells is different and distinct for each stage. With their ALR grant, they want to confirm their findings and use laser capture microdissection techniques and gene array analyses to biopsy kidney specimens from lupus patients with proliferative GN. Then they can determine if the genetic changes they saw in the animal model can be applied to humans. They also want to see if the resulting proteins from these genetic aberrations appear as potential biomarkers in the urine, where they could be used to more accurately and easily stage the disease.

What this study means for people with lupus: Lupus nephritis is not only difficult to treat, it is also difficult to diagnose and track, requiring a kidney biopsy to identify the stage of the disease. Finding biomarkers that could be used to track the progression of the disease would not only help with its management, but is important in designing clinical trials for new drug development.

Caroline Jefferies, PhD
Royal College of Surgeons in Ireland
Ro52 and Siglec-E as therapeutic targets in SLE

Among the various immune system abnormalities that underlie lupus are proteins called interferons that immune system cells normally release during viral infection. However, in people with lupus, these interferons are released at other times, leading to abnormally high levels. They not only trigger inflammation, but are also involved in activating the immune system to produce autoantibodies that drive the pathology of this disease.

Thus, strategies that reduce interferon levels could also reduce lupus symptoms and slow or even halt the progression of the disease, possibly restoring the immune system to normal. Dr. Jefferies' lab focuses on identifying just such strategies. So far, they have found two molecules called Ro52 and Siglec-E, that stem the production of interferon.

With their ALR grant, they will see if activating these proteins can reduce lupus symptoms.

What this study means for people with lupus: This work could ultimately lead to the development of SLE treatments that target the Ro52 and Siglec-E molecules.

Mariana Kaplan, MD
University of Michigan
Lupus and the Inflammasome

People with lupus develop blood vessel damage that increases their risk of early heart attacks. This blood vessel damage is also thought to contribute to the severity of the kidney disease that occurs later in the disease. Dr. Kaplan's team has suggested that one mechanism leading to this accelerated blood vessel disease is related to an imbalance between cells that damage and those that repair the lining, or vasculature, of blood vessels. The researchers have previously reported that a molecule called interferon (IFN) alpha plays a crucial role in this process, promoting premature atherosclerosis and kidney damage progression.

They recently found that IFN-alpha suppresses a molecule called interleukin-1 (IL-1) beta and increases levels of another called IL-18. Both play a role in inflammatory processes. IFN-alpha also activates the machinery that processes these two cytokines, called the inflammasome.

With their grant, Dr. Kaplan and her team will use human and animal systems to better understand how IFN-alpha interacts with the inflammasome machinery, triggering blood vessel damage. They will focus on a specific inflammasome component, caspase-1, exploring how IFN-alpha alters its role to impair blood vessel function and repair.

They will also investigate how IFN-alpha reduces production of IL-1 beta and the impact this has on blood vessel function in lupus cells.

What this study means for people with lupus: Identifying the inflammasome as an important mechanism of organ damage and blood vessel abnormalities in SLE could lead to the development of new therapies to prevent the devastating complications of the disease.

Vicki Kelley, PhD
Brigham and Women's Hospital
Distinguishing CSF-1 and IL-34 As Therapeutic Targets for Lupus Nephritis

Kidney failure is a primary cause of disease and mortality in people with lupus. Macrophages, immune system cells that release inflammatory molecules, are major contributors to kidney disease. Dr. Kelley and her team discovered that a molecule critical in the development of macrophages and expressed by macrophages, called CSF-1, could be a good target for treatment. Using a mouse model of lupus nephritis, they found if they deleted CSF-1, they prevented lupus nephritis, while increasing its presence hastened nephritis.

CSF-1 also exists in humans, with higher levels in the kidney, blood, and urine correlating with greater kidney damage and disease activity. In addition, their preliminary data suggests that high levels of CSF-1 in the urine and blood may be a harbinger of lupus nephritis even before clinical signs of damage occur. Detection of CSF-1 could lead to earlier treatment, avoiding kidney damage altogether.

Recently, IL-34, a second molecule that binds to the CSF-1 receptor was discovered. Although IL-34 resembles CSF-1, they are not identical. However, Dr. Kelley's work indicates that both are more prevalent in the kidney, blood and urine in a mouse model of lupus nephritis.

With this grant, Dr. Kelley and her group hope to better understand the role of CSF-1 and IL-34, particularly their different and shared roles in the development of lupus nephritis. Their goal is to determine if these molecules are distinct therapeutic targets and biomarkers for predicting and tracking lupus nephritis in patients.

What this study means for people with lupus: Pharmaceutical companies have already developed compounds to block CSF-1 and its related molecules, with clinical trials expected to begin soon. Dr. Kelley's studies could provide important information for the development and use of such drugs as they offer the promise of producing new treatments for lupus nephritis. This could lead to earlier treatment, avoiding kidney damage altogether.

Terri M. Laufer, MD,
University of Pennsylvania
Follicular Helper T Cells: Altered Differentiation in Lupus

Systemic lupus erythematosus (SLE) is characterized by the presence of antibodies directed against the patient's own cells and DNA. Although the disease is caused by damaged white blood cells, autoantibodies enable diagnosis and contribute to the organ damage that occurs.

Thus, identifying the pathways that lead to autoantibody formation could provide therapeutic targets for the treatment of lupus.

With this grant, Dr. Laufer and her team will focus on a type of helper T cell called T follicular helper cells (TFH), which direct the development of antibodies. TFH cells normally function to direct B cells to make antibodies against pathogens and vaccines. However, an increase in their number or function is associated with lupus, and their accelerated development or persistence is believed to drive the production of those dangerous autoantibodies. Indeed, people with lupus and significant organ damage have higher levels of TFH cells in their blood.

The ALR grant will enable the researchers to use unique strains of mice to determine how genetic susceptibility to lupus alters the differentiation and function of TFH cells. They will also investigate options to reverse this differentiation.

What this study means for people with lupus: These experiments hope to directly identify biochemical and cellular pathways that can provide important new targets for drug development to treat and possibly prevent lupus.

Tanya Mayadas, PhD
Brigham and Women's Hospital
Analysis And Treatment Of Organ Damage In A Humanized Mouse Model Of Lupus

Systemic lupus erythematosus (SLE) is a chronic, inflammatory autoimmune disorder that affects multiple organs and is associated with abnormalities at all levels of the immune system. Neutrophils, which are white blood cells that are important for defense against infections, can inflict tissue injury in lupus.

Recently, researchers discovered variations of genes important in the activation of white blood cells that may increase susceptibility to developing lupus. Some, including those that code for receptors that bind antibodies, FcγRIIA, FcγRIIIB, and the integrin Mac-1 (ITGAM), are present on neutrophils. The overall objective of this grant is to decipher how these receptors may contribute to organ damage in lupus.

Dr. Mayadas and her team established a model of lupus nephritis (kidney disease) that develops after blood from lupus patients is transferred into genetically engineered mice that express the uniquely human FcγRIIA and FcγRIIIB proteins on neutrophils.

With this grant, they plan to:

- Determine how neutrophils induce organ damage after antibodies in blood serum from lupus patients are transferred into mice
- Identify compounds that inhibit FcγRIIA and determine if they can prevent organ damage in the mice that receive lupus blood serum

What this study means for people with lupus: These experiments may lead to a better understanding of the causes of lupus-related organ damage. In the future, this could lead to therapies designed to interrupt the molecular cascade responsible for this damage.

Alessandra Pernis, MD
Hospital for Special Surgery
Effector Tregs in Lupus

Defects in the proper regulation of the immune system are fundamental to the development of lupus. Regulatory T cells (Tregs) are a type of T cell that normally prevents the immune system from attacking "self".

Recent studies find that a protein called IRF4 controls Treg function. Dr. Pernis and her group have identified 2 related molecules, Def6 and SWAP-70, that, in turn, regulate IRF4. They found that mice lacking these two molecules (DKO mice) spontaneously develop a lupus-like syndrome that, similar to human lupus, primarily occurs in females. Interestingly, the mice develop a mild form of the disease, which is associated with a marked increase in activated Tregs.

They also found that Tregs express both Def6 and SWAP-70. These findings led the researchers to hypothesize that Def6 and SWAP-70 regulate the function of Tregs via their ability to control IRF4. They also hypothesize that the expansion of these activated Tregs in the DKO mice helps dampen the autoimmune inflammation. The goal of their current proposal is to employ cutting-edge genetic approaches to assess the regulation and role of activated Tregs in lupus.

What this study means for people with lupus: Dr. Pernis and her team hope that a better understanding of the molecular mechanisms that endow Tregs with a potent ability to moderate lupus disease activity will provide crucial insights into the best ways to generate functional Tregs to correct the dysfunctional immune responses that result in lupus.

Shiv Pillai, MBBS, PhD
Massachusetts General Hospital
Targeting the SIAE pathway in lupus

We know that the risk of developing lupus is likely related to several rare genetic variants, or abnormalities. Of particular interest are rare genetic changes that affect the function of the protein the gene encodes for, rather than more "common" variants identified in the large, genome-wide association studies that have already been conducted.

Dr. Pillai and his team are employing a way to identify all such "rare" genetic variants by sequencing the gene's coding segments, or exons. The exons are like letters that form words; while the words together form the story, or, in the case of genetics, the protein the gene is responsible for making. This approach is called "complete exome sequencing," and Dr. Pillai and his team have already used it to sequence genes in people with lupus. In addition, they performed a battery of tests on each participant to examine immune cell function.

Now they will use their ALR grant to put the two together—the clinical features of the disease, including immune function, with the genetic variants. The goal is to obtain a comprehensive understanding of the genetic basis of lupus.

What this study means for people with lupus: Identifying specific defective genetic pathways can help identify new targets for novel therapies.

David Pisetsky, PhD, MD
Duke University Medical Center
Nucleic Acid Binding Polymers in the Treatment for SLE

A key underlying abnormality in the immune system in lupus is the production of antinuclear antibodies (ANA) that bind to the proteins or nucleic acids (DNA and RNA) from the cell nucleus. In fact, high ANA levels are used as a marker for diagnosis and prognosis. In lupus, these autoantibodies can form immune complexes with molecules such as DNA that are released from the cell nucleus, usually as the cell dies. These complexes may then stimulate inflammation as well as deposit in the kidney, causing damage.

The immune complexes that form in lupus have unusual properties since the bound molecules (DNA and RNA) can themselves have immunological activity. When in the form of complexes, these nucleic acids can trigger immune system abnormalities that promote autoimmunity. This activity results from the ability of DNA and RNA to stimulate nucleic acid receptors or sensors that are on the inside of the cell. Normally, DNA and RNA in the blood may not be able to bind to these receptors; but when they are available as immune complexes, DNA and RNA can get into the inside of the cell and access these receptors to promote immune disturbances.

Current therapies for lupus are based on non-specific immunosuppressive agents that, while effective, have limited benefits for many patients and significant side effects. To develop more targeted therapies, researchers are looking at blocking the stimulation of the internal nucleic acid receptors, including toll-like receptors (TLR) and non-TLR systems. Compounds that block TLR 7 and 9, which respond to RNA and DNA respectively, have demonstrated benefits in mice models; since the compounds don't block non-TLR sensors, however, they may have limited efficacy. Also, compounds that inhibit the TLRs may affect the immune response to viruses and other infections.

Dr. Pisetsky and his team are exploring an alternative strategy to block responses to nucleic acids by investigating the use of nucleic acid binding polymers (NABPs). These polymers can bind tightly to DNA and RNA and prevent the formation of immune complexes and the resulting stimulation of internal receptors. The hope is that the polymers will be able to block the ability of extracellular nucleic acids to stimulate immune system activity that can underlie autoimmunity.

Their plan is to:

- Define the activity of a series of NABPs, assessing their ability to block stimulation of various immune cells
- Assess the activity of the NAPBs in mice stimulated with DNA to determine the appropriate dosing for clinical studies
- Determine the ability of NABPs to block autoimmune disease in mouse models of lupus

What this study means for people with lupus: These experiments provide the first step in moving NABPs into clinical trials in patients to develop a new strategy to treat lupus by blocking immune responses induced by complexes.

Shruti Sharma, PhD
University of Massachusetts Medical School
Innate Sensing of AT-rich DNA During Autoimmunity

Numerous immune system components contribute to disease development and progression in lupus. These include toll-like receptors (TLR), particularly TLR7 and TLR9. These proteins recognize RNA or DNA from dying cells and trigger inflammation in lupus patients by activating immune cells such as dendritic and B cells. Dendritic cells produce inflammatory molecules called type I interferons while B cells generate autoantibodies that eventually cause organ damage in the later stages of the disease.

With their ALR grant, Dr. Sharma and her colleague, Dr. Fitzgerald hope to discover what triggers autoimmune diseases like lupus and rheumatoid arthritis (RA). They suspect that the DNA released from dying cells contains clues to this event. Specifically, it appears that the location of the DNA may affect the disease differently than we initially thought. For instance, in autoimmune diseases like RA, abnormal DNA accumulates *within* cells and triggers pathways independently of TLR activation. Similarly, in lupus it appears that a different pathway operating separately from TLR9 activation may be responsible for the initial production of interferons, exacerbating subsequent symptoms and organ damage. This pathway may be related to the "nature" of the accumulated DNA. In other words, the location of the DNA within the cell and the enrichment of certain parts of the DNA could provide a clue as to its role in the disease.

The researchers also plan to use complex genetic models to investigate specific proteins involved in detecting this buildup of DNA.

What this study means for people with lupus: This research can help identify important and novel targets and pathways in the development and progression of lupus that could lead to new therapeutic targets.

Hideki Ueno, MD, PhD
Baylor Research Institute
Altered T Follicular Helper Cell Subsets In Active Pediatric Lupus

Uncontrolled generation of autoantibodies is a hallmark of lupus. Animal studies show that a type of helper T cells, called T follicular helper (Tfh) cells, contribute to the development of the disease and the dysfunctional autoantibodies. Yet, very little is known about whether Tfh cells play a role in the development of *human* lupus.

Preliminary data from Dr. Ueno and his team suggest that Tfh cells do play a role in lupus development. With their ALR grant, they plan to determine how these cells differ in quality and quantity in pediatric lupus patients from those in healthy children. They will also investigate whether such alterations correlate with disease severity and/or specific organ damage.

What this study means for people with lupus: This project will establish a cornerstone for the team's long-term goal, which is to develop novel therapeutic approaches for lupus that reprogram altered Tfh responses.

Paul J. Utz, MD
Stanford University
Target Identification in SLE Using CyTOF and Multiplexed Assays

A hallmark of lupus is the production of autoantibodies that recognize "self" molecules when they should only respond to foreign molecules. Studies by Dr. Utz' lab and other investigators have identified important roles for 2 classes of molecules in lupus: inflammatory interferons and cytokines, which are proteins that immune cells release to fight off infections and which damage organs like the kidney; and toll-like receptors (TLRs), which appear to control the development and severity of SLE.

With their grant, Dr. Utz and his team will identify ways to tell which autoantibodies are most active in which patients. They will do this thanks to two cutting-edge technology platforms developed in Stanford labs. The first involves printing thousands of biomolecules onto glass slides, which provides a huge amount of data in just a few hours, and then correlating the presence of autoantigen complexes with a "biosignature" related to the individual patient's disease.

The second technology uses a new methodology called CyTOF, which analyzes patient blood cells to study their defects and responses to potential therapies such as rituximab (Rituxan) and belimumab (Benlysta).

They will also explore whether defects in the way these proteins communicate and interact with each other could also be useful biomarkers and/or novel targets for drugs.

What this study means for people with lupus: Ultimately, these techniques could become the mainstay of all clinical trials in SLE, improving our ability to demonstrate effectiveness and ushering in an entirely new era of patient-specific, customized therapies, or personalized medicine.

Joan Wither, MD, PhD
Toronto Western Research Institute, Canada
Identification of Biomarkers for Patient Stratification in Lupus Nephritis

Despite significant improvement in the prognosis of SLE over the past 30 years, people with lupus still tend to have higher mortality rates than those without, often because of kidney disease. Kidney disease, called lupus nephritis, typically develops within the first 5 years of a lupus diagnosis. Yet the condition appears different in every patient. Some suffer more kidney damage earlier in the disease, others very little; some respond well to treatment, others do not.

Unfortunately, there are currently no reliable clinical or laboratory parameters that enable doctors to determine how the disease is progressing or how patients respond to therapy. The only way to tell how much damage has occurred and assess response to treatment is with a kidney biopsy, which is an invasive procedure.

Dr. Wither is part of the LuNNET (Lupus Nephritis New Emerging Team) group, which consists of rheumatologists, nephrologists, pathologists, and biostatisticians. It was formed to develop biomarkers to identify patients who share certain biological characteristics of their nephritis, providing valuable information about the disease progression and response to therapy.

With their ALR grant, the LuNNET group plans to use the large database of renal biopsies, blood, plasma, blood RNA and DNA, and urine it has collected from lupus patients to identify novel biomarkers. They will use technologies that enable them to simultaneously test multiple genes and proteins to identify novel biomarkers. They will also examine gene expression in the kidney biopsies, as well as protein levels in urine samples. They will then correlate these gene/protein expression patterns with disease-causing and clinical variables to identify potential biomarkers.

During the second phase of the study, Dr. Whither and her group will try to validate these biomarkers with additional kidney biopsies and determine any potential variation over time.

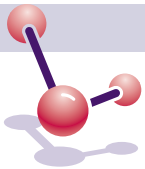
What this study means for people with lupus: The data obtained through this study could help identify biomarkers to improve the diagnosis, monitoring, and treatment of people with lupus-related kidney disease.

Nan Yan, PhD
UT Southwestern Medical Center
Identification of Endogenous Nucleic Acids as Targets in Lupus

Approximately 2 percent of people with lupus have mutations of the *TREX1* gene, making it one of the most common causes of single-gene regulated lupus. Such rare but highly frequent causes of lupus are important to study because they provide immediate insight into its underlying causes.

Interestingly, mutations in *TREX1*, as well as in other genes involved in regulating and metabolizing nucleic acids (the building blocks of genes), are linked to many autoimmune diseases related to inflammatory markers such as elevated type-I interferon expression. One of these is Aicardi-Goutières syndrome (AGS). Most people with AGS have mutations in one of five genes: *TREX1*, *RNASEH2A*, *2B*, *2C* and *SAMHD1*. These all produce enzymes that regulate or metabolize nucleic acids. People carrying mutations in these genes, or expressing defective enzymes, display lupus or lupus-like phenotypes, making it critical to identity their nucleic acid substrates.

What this study means for people with lupus: With their ALR grant, Dr. Yan and his team plan to identify endogenous nucleic acids in human cells that could be used as biomarkers to track lupus disease progression. Dr. Yan and his team will also evaluate methods for preventing these nucleic acid substances from stimulating unintended immune responses that may lead to lupus, and/or interrupting their activities. This could result in new treatments for the disease.



Functional Genomics and Molecular Pathways in SLE

This grant mechanism was designed to help researchers move forward from the knowledge gained from the findings of the ALR-funded SLE Genetics Consortium (SLEGEN). Selected investigators receive Research Grants of up to $350,000 for two years or Pilot Grants of up to $75,000 for one year. Grantees will focus on determining how the genes identified by SLEGEN may have a role in the disease, and provide further information about the molecular pathways modulated by these genes. Ultimately, the hope is that data from these investigations will lay the groundwork for a way to "turn off" the disease at the genetic level.

John Atkinson, MD
Washington University School of Medicine
Complement Mutations in End Stage Renal Disease Lupus Patients

With this grant, Dr. Atkinson and two colleagues (Drs. Jane Salmon and Robert Kimberly) are combining forces to determine how genetic variations in complement system genes contribute to kidney disease in people with lupus.

The complement cascade is an important part of the immune system. It helps the host to clear away pathogens like viruses and bacteria as well as damaged tissues and cells. Deficiencies in the complement system lead to lupus and contribute especially to kidney disease.

The researchers will identify variants or mutations in genes of the complement system to see how they contribute to the disease process in lupus.

They will focus on genetic variants that may be involved in lupus-related end-stage renal disease (ESRD) in which the kidneys fail and individuals require dialysis or a kidney transplant. To do this, they will sequence genes in people with lupus-related ESRD; in those with lupus but who do not have kidney disease; and in a group of normal controls. They have two primary goals:

- Establish that mutations in the complement system increase the risk of ESRD in people with lupus
- Determine the frequency of the genetic variants in people with lupus compared to controls

What this study means for people with lupus: Identifying genetic variants that contribute to kidney damage in people with lupus will increase our knowledge of how lupus comes about and suggest alternative means to treat the disease.

Richard Bucala, MD, PhD
Yale University
Function of the Polymorphic MIF Locus in SLE

Dr. Bucala and his team have identified common variants, or genetic differences between people with and without lupus, of the gene for the immune regulator, macrophage migration inhibitory factor (*MIF*). This protein directly contributes to the severe, organ-damaging manifestations of lupus. Dr. Bucala and his team have developed new therapies directed at *MIF* that recently entered clinical testing for lupus nephritis, a development made possible with a previous ALR grant. Nonetheless, learning more about how the *MIF* gene functions will enable researchers to improve the effectiveness of these and other treatments.

With their new grant, Dr. Bucala and his team will investigate how the *MIF* influences the function of the autoantibody-producing B lymphocytes that cause lupus. Their goal is to identify the unique DNA-binding proteins that regulate how variant forms of the *MIF* gene function.

What this study means for people with lupus: Providing molecular insight into how *MIF* gene variants contribute to lupus will accelerate the application of *MIF*-based drugs and provide the first "personalized medicine" approach to treating lupus patients based on their genetic susceptibility.

Jane H. Buckner, MD
Benaroya Research Institute at Virginia Mason
The Impact of Genetic Variants on B cell Development and Function in SLE

Systemic lupus erythematosus is an autoimmune disorder with a strong genetic component. It is characterized by B cell production of antibodies that inappropriately recognize self-tissues. These autoantibodies contribute to lupus pathogenesis.

To understand how autoantibodies develop in lupus, Dr. Buckner and her team are studying sequence variants in B cell genes that have been associated with susceptibility to lupus. They include those that code for the B cell enzyme *BLK* and the B cell scaffolding protein *BANK1*.

Dr. Buckner's team found that the sequence variants in the *BLK* and *BANK1* genes are associated with reduced expression of these genes in B cells in healthy individuals and those with lupus. These expression changes are accompanied by alterations in the cells' normal development.

With this grant, Dr. Buckner and her team will investigate how these genetic variants impact normal B cell function and development and contribute to autoantibody production. They will first determine if the *BANK1* genetic variants alter the expression of these genes in specific types of B cells, particularly the B cell subpopulations where auto reactive B cells are normally deleted or deactivated.

Second, they will evaluate the impact of each *BANK1* variant on signaling through the B cell receptor, or *BCR*. The *BCR* signal is important in removing or deactivating auto reactive B cells during the cell's development so they don't develop into abnormal, autoantibody-producing cells.

Finally, Dr. Buckner's team will determine whether the genetic variants in *BANK1* specifically lead to the accumulation of B cell subpopulations that harbor auto reactive cells and the development of B cells that produce autoantibodies.

What this study means for people with lupus: These studies will provide an expanded understanding of one of the mechanisms of disease in lupus, the development of autoantibodies, and will help define new targets for diagnosis and treatment.

Jose C. Crispin, MD
Beth Israel Deaconess Medical Center
Mechanisms Through Which Protein Phosphatase 2A (PP2A) Promotes SLE

T lymphocytes are essential immune regulators. That means they work to fine tune immune responses and determine how those responses occur. However, T cells do not function properly in people with systemic lupus erythematosus (SLE). In fact, there is good evidence that T cell defects contribute to the immune system dysfunction that underlies lupus.

One T cell abnormality in people with lupus is increased levels of an enzyme called PP2A. This enzyme plays an important role in regulating certain cellular proteins and, thus, cell functions. These include cellular division, death, and movement, as well as specialized functions such as the secretion of certain proteins. Therefore, faulty regulation of PP2A levels could, theoretically, contribute to lupus.

In order to determine if abnormally high expression of PP2A can independently contribute to lupus, Dr. Crispin and his group studied animal models that enabled them to show that high levels of PP2A increase susceptibility to kidney inflammation, a common problem in lupus. Further investigation revealed that high PP2A levels enable cells to produce abnormal amounts of a pro-inflammatory molecule called IL-17. Importantly, T cells from people with lupus also produce high levels of IL-17. Thus, the study confirmed that high levels of PP2A can independently contribute to the development of lupus.

With their grant, Dr. Crispin and his team will determine just how high PP2A levels contribute to autoimmunity. They will do this by studying the regulation of the IL-17 gene to better understand how PP2A regulates it. They will then learn how PP2A affects the generation of regulatory cells, which normally curb the inflammatory, IL-17-producing cells.

What this study means for people with lupus: This work will determine the molecular pathways that link a known defect in the T cells of people with lupus with the development of organ damage. A better understanding of this process will help identify better targets for future therapies.

Lindsey Criswell, MD, PhD
University of California, San Francisco
Functional Genomics and Pathway Analysis of the MCH Region in SLE

Dr. Criswell and her collaborators will use a large database of DNA, blood and other biospecimens, as well as genetic and clinical data, from more than 15,000 individuals to link genetic variants with key clinical aspects and biomarkers in those with lupus. One goal of the work is to transform current understanding of the major histocompatibility complex (MHC) region on genes and its relationship with non-MHC lupus genes to better understand how the MHC contributes to the disease. Major histocompatibility complex molecules are involved in immune responses as well as autoimmunity.

Specifically, the researchers will:

- Identify MHC region variants most likely to be related to lupus by sequencing DNA data from 3,800 individuals with lupus and comparing it with DNA from 12,000 individuals without the disease
- Identify complex molecular networks and cellular pathways for MHC and non-MHC variants involved in disease susceptibility and expression
- Perform DNA methylation and gene expression studies of MHC variants in lupus. To do this, they will recruit 200 additional patients who were diagnosed with the disease less than 5 years ago, and 200 individuals without lupus.

What this study means for people with lupus: A greater understanding of the genetic contributions to lupus will help identify new pathways for prevention and treatment approaches.

Yanick Crow, PhD
University of Manchester
Pathways Linking Tartrate-Resistant Acid Phosphatase, Interferon, and Lupus

Dr. Crow and his team recently demonstrated that people with changes in the *ACP5* gene have a very high risk of developing lupus. These patients also show elevated blood levels of interferon, an inflammatory molecule thought to contribute to the damaging effects of lupus on various parts of the body. High levels of interferon are a sign of lupus in many patients. *ACP5* codes for a protein called tartrate resistant acid phosphatase (TRAP). These findings suggest a role for TRAP in the development of lupus by altering control of interferon.

There is some evidence that people with mutations in *ACP5* also have higher blood levels of a protein called osteopontin, which is expressed in bone and regulated, in part, by TRAP. Osteopontin appears to play a role in the production of interferon. This finding raises the possibility that TRAP deactivates osteopontin, and that a failure of this deactivation results in an inappropriate up-regulation of interferon.

With their grant, Dr. Crow and his collaborator Keith Elkon, MD, from the University of Washington, will investigate how TRAP expression is regulated in human immune cells, concentrating particularly on the relationship between TRAP, osteopontin and type I IFN stimulation.

What this study means for people with lupus: A better understanding of the role of TRAP in interferon metabolism could help to identify new treatment targets for lupus.

Yun Deng, MD
University of California, Los Angeles
Does Differential miRNA Binding Explain Allelic Risk of TLR7 for SLE

Recent evidence suggests the importance of innate immunity in the development of systemic lupus erythematosus. The toll-like receptor 7 (TLR7), which helps guide responses against self antigens and activates the inflammatory type I interferon (IFN) pathway, plays a pivotal role in the disease's development.

An earlier study from Dr. Deng's laboratory confirmed a variant form of the *TLR7* gene that is associated with lupus. This mutation results in higher *TLR7* expression and a more robust type IFN-1 signature, both of which are implicated in the development of lupus.

MicroRNAs (miRNAs) have emerged as important regulators of gene expression. Mutations in miRNA target sites can affect their regulatory roles, thus affecting cellular function. One question Dr. Deng and her team will explore is the role of miRNAs in regulating *TLR7* expression. They will focus on whether the miRNAs thought to target the *TLR7* gene at and around the location of the identified mutation could lead to changes in the expression of *TLR7* and other IFN-related genes.

What this study means for people with lupus: This project will help identify the molecular mechanism underlying the variant form of the *TLR7* gene, implicate an important role of specific miRNA in regulating *TLR7* signaling, and may lead to the potential application of miRNA-based targeted therapy in lupus.

Di Feng, PhD
UMDNJ-New Jersey Medical School
Identifying IRF5-Mediated Pathways In Normal And SLE B Cells

Numerous genes, proteins and enzymes are involved in the underlying dysfunction of lupus. One such protein is interferon regulatory factor 5 (IRF5). This protein regulates key pro-inflammatory molecules, or cytokines, such as interferon alpha (IFNα), interleukin (IL) IL-6, IL-12, and tumor necrosis factor alpha (TNFα), which are elevated in people with lupus.

However, little is known about the contribution of IRF5 to the development of human lupus. Based on murine studies, it is thought that IRF5 may play a role in the B cell dysfunction of lupus by affecting B cell activation, proliferation, differentiation, autoantibody production, and cytokine expression, among other processes.

With their grant, Dr. Feng and his team will explore two key questions: What is the essential function of IRF5 in human B cells, and how does IRF5 influence the ability of B cells to produce the destructive autoantibodies that are the hallmark of lupus?

What this study means for people with lupus: Results from this study will determine how IRF5 contributes to lupus-related B cell dysfunction. A greater understanding of the role of this protein can provide new targets for treatment.

Peter K. Gregersen, MD
Feinstein Institute for Medical Research
Functional Analysis of Csk: A Newly Defined Risk Gene for Lupus

In recent years, researchers, many of them funded by the Alliance for Lupus Research, have identified a plethora of genes and genetic variants likely responsible for the dysfunctional immune responses that underlies lupus.

Dr. Gregersen and his team identified one such gene, *Csk*, which is directly involved in setting the threshold for immune cell activation, or their "call to action." It is also associated with several other autoimmune disorders, including scleroderma and celiac disease.

The team has found a particular genetic variation in this gene that influences how much of the *Csk* protein is produced, particularly in B cells, which produce the autoantibodies that are the hallmark of lupus. The team also showed that the amount of *Csk* in B cells, particularly B cells early in their development, have a profound effect on the number of these cells and their ability to be activated. They have also found that *Csk* interacts with other known risk genes for lupus, including *Lyn* and *PTPN22*.

With their grant, Dr. Gregersen and his team will explore further the role *Csk* plays in B cell aberrations and the development of lupus.

What this study means for people with lupus: A better understanding of the role of *Csk* in B cell regulation and the development of lupus could help identify new approaches to therapy or even opportunities to manipulate B cells early in their development so they can't contribute to the development of autoimmune diseases like lupus.

Terry K. Means, PhD
Massachusetts General Hospital
In Vivo Validation And Characterization Of Allelic Variants In Lupus

Genome-wide association studies such as the SLE Genetics consortium have identified numerous genetic variants associated with an increased risk of lupus. However, a major barrier in lupus research is the lack of a rapid high-throughput system, a special kind of technology that can validate these candidate variants and determine if they truly do contribute to lupus.

Dr. Means and his team have developed and optimized a novel approach to express human, lupus-related genes in animal models. This approach can rapidly generate animal models that harbor an immune system developed with cells that express human genetic mutations.

With this grant, the team will use their animal models to study the effects of human lupus-related risk genes on the development and progression of lupus.

What this study means for people with lupus: These studies will provide a rich pipeline of molecular targets that could be fast-tracked for the development of lupus-related treatments.

Derry Roopenian, PhD
The Jackson Laboratory
Novel Approach to Modeling the Functional Genomics of Human SLE in Mice

Like most autoimmune syndromes, the genetic predisposition to lupus is complex. We see this complexity in genetic association studies that have identified anomalies in more than 30 genes that provide small, but significant, contributions to the disease. However, only when several of these genetic variations occur simultaneously does the disease itself result. Thus, it is difficult to translate these complex genetic patterns into a biological explanation of the specific anomalies that cause lupus, and even more challenging to apply this information to benefit people with lupus.

With their grant, Dr. Roopenian and his team will use a mouse model to explore these issues. They will mimic the genetic changes seen in humans with lupus in the mouse and observe the results of such abnormalities. They will combine this information with gene expression studies to discover the molecular pathways that determine susceptibility and resistance to lupus in mice.

What this study means for people with lupus: Conducting studies in mice to specifically address genes we already know affect the risk of lupus in humans should provide important information for predicting, understanding, and treating lupus and related disorders in humans.

Anne Satterthwaite, PhD
University of Texas Southwestern Medical Center

Functional Relationships Between the Lupus Susceptibility Loci Lyn and Ets1

A key contributor to lupus is the production of antibodies that recognize the body's own components (autoantibodies). These antibodies, which are produced from B cell-derived plasma cells, collect in various tissues and organs, including the kidney, causing inflammation and tissue damage.

Two genes involved in the development of lupus, *Lyn* and *Ets1*, limit production of these plasma cells in mice. Without either of those genes, mice develop a lupus-like autoimmune disease. Dr. Satterthwaite, her colleague Lee Ann Garrett-Sinha, PhD, and their teams have shown that B cells that lack *Lyn* also have reduced *Ets1* levels, suggesting that the two genes operate in a common pathway to control the development of plasma cells and the production of autoantibodies.

With their grant, they will test the hypothesis that *Lyn* normally prevents autoantibody production by promoting the expression of the Ets1 protein. Among the questions they will explore:

- Does *Lyn* act in B cells or some other cell type to control *Ets1* expression?
- Which pathways regulated by Lyn are involved in altering *Ets1* expression?
- Does *Lyn* control the expression of the *Ets1* gene or regulate the stability of the Ets1 protein?

They will also explore the consequences of reduced *Ets1* levels in *Lyn*-deficient B cells, and determine whether low levels of *Lyn* and *Ets1* together contribute to the development of autoimmunity. They will also restore normal *Ets1* levels in *Lyn*-deficient B cells to see if this prevents autoantibody production.

What this study means for people with lupus: Defining and characterizing this novel pathway may reveal new therapeutic targets that could prevent the antibody-related tissue damage.

Katherine Siminovitch, MD
University Health Network

Defining Functional Implications of a Human SLE Risk Allele in Mice

Among the many genes now shown to contribute to the development of lupus is *PTPN22*, a gene that codes for a tyrosine phosphatase called Lyp. Lyp is found only in blood cells and is important for suppressing T lymphocyte activity. Many people with lupus express a variant form of Lyp called Lyp620W. However, we don't know how this variant contributes to the disease process.

With this grant, Dr. Siminovitch and her team hope to identify the pathways that link the Lyp620W variant to risk for lupus. To do so, they will study mice that express this variant. Initial work with these animals found numerous immune cell defects, particularly, "hyper" activation of T and B lymphocytes. Analysis of these mice also revealed that the variant protein is unstable and is broken down too quickly ,resulting in very low levels in the mouse lymphocytes. The team then showed that these abnormalities also occur in cells from humans expressing the Lyp620 variant. These findings suggest that the *PTPN22* gene variant causes reduction in Lyp levels and in the ability of Lyp to suppress immune cell activation. The result is immune cell hyperactivity.

Dr. Siminovitch and her team will now further define the Lyp variant's effects on T and B cell functions, particularly activation, movement, and development. For instance, they will compare how cells from mutant and normal mice divide or migrate in response to select stimuli, and examine the cells' secretion of inflammatory cytokines involved in autoimmune responses.

They will also study T and B lymphocyte development in the mouse model to assess whether the variant alters early elimination of autoreactive cells, which occurs in people with normal immune systems, but may be reduced in those with lupus.

Another set of studies will define the variant protein's effects on autoimmunity and how this genetic variant interacts with other genetic variants to cause lupus.

What this study means for people with lupus: Defining the pathways related to a specific genetic variant could identify new targets for treatment.

William Tansey, PhD
Vanderbilt University Medical Center
Characterization Of PHRF1; A Ubiquitin Ligase Implicated In SLE

Effective strategies to prevent, diagnose, treat, and cure lupus will ultimately be based on a detailed understanding of the genetic pathways involved in the disease. Over the past 15 years, researchers have made great strides in identifying genes that increase the risk of lupus, but there is still a great deal of work required to understand the function of these genes and their role in the disease.

Dr. Tansey's work centers on a gene called *PHRF1*, thought to be involved in lupus. However, there is little understanding of how the gene functions or of its contribution to the disease.

Dr. Tansey and his team have identified versions of *PHRF1* and learned that these genes display characteristics that suggest some relevance to lupus. Because related genes from other species often show identical behavior, they hypothesize that the human version of *PHRF1* shares these same molecular functions.

With their grant, the team will study the other versions of *PHRF1*, particularly with respect to how they control gene expression relevant to immunity and other lupus-related events.

What this study means for people with lupus: These studies will provide much-needed information that will allow researchers to assess the molecular contribution of *PHRF1* to lupus. The results of these and other studies will eventually enable researchers to design diagnostic or therapeutic strategies based on PHRF1 that could help diagnose lupus early and/or treat and prevent it.

Betty Tsao, PhD
University of California, Los Angeles
Functional Genomics of SLE-associated SMG7/NMNAT2 Locus

Genome-wide association studies (GWAS) have greatly expanded our understanding about genetic variants linked to the risk of lupus. However, simply knowing the link between a genetic variant and lupus is just the first part of a story. Far more important, however, is understanding how that genetic variant affects the immune system and results in lupus.

With this grant, Dr. Tsao and her team will explore the underlying mechanism of the newly identified *NMNAT2*/*SMG7* risk locus, an "address" of two neighboring genes, to better understand its role in lupus.

The *NMNAT2* gene regulates energy metabolism, primarily in the brain, but its role in lupus is unclear. In contrast, *SMG7* serves as a "cleaner" in cells, controlling mRNA quality, gene expression and alternative splicing, which are important for the production of autoantibodies in lupus.

Earlier studies showed a link between lupus-associated *SMG7* variants and reduced expression of *SMG7*, while decreased *SMG7* levels appear to lead to elevated production of antinuclear autoantibodies, the most prevalent autoantibodies in lupus.

These studies will focus on whether dysfunction in messenger RNA surveillance systems resulting from the lupus-associated *SMG7* variants may be a unique mechanism contributing to the development of lupus.

What this study means for people with lupus: Greater understanding of the underlying pathology of lupus—what goes wrong at the cellular and molecular level—will enable the development of treatments that target those abnormalities.

SLEGEN Consortium—ImmunoChip Study

The SLEGEN project has realized tremendous success since the ALR's initial founding of the group in 2005 and is now taking the research to a whole new level. Utilizing the most advanced technology available, called the ImmunoChip, SLEGEN scientists are more closely examining the genes that were identified in the most recent round of studies. This highly specialized and powerful tool is allowing researchers to engage in an even greater level of detail because the information contained on the ImmunoChip is based completely on findings from previous genetic studies, which means the information is extremely focused and specific. The new technology offers scientists the amazing ability to study hundreds of thousands of genetic variants – 250,000 to be exact – in more than 10,000 participants.

This landmark study will allow SLEGEN scientists to study - in unprecedented detail -ethnicity and lupus, autoimmune disease commonalities, and gene variants & biologic pathways. Understanding the genetic basis may help clinicians more closely predict when an individual might develop lupus and the complications he or she may experience and to what degree, leading to effective disease management and more precise treatments.

The realistic hope is that the ImmunoChip study will reveal, in enormously expanded detail, the critical roles that genetic variance and ethnicities play in predisposing an individual to developing lupus, age of disease onset and lupus-related complications common with the disease.

ABOUT ALR

The Alliance for Lupus Research (ALR) is working tirelessly to create a world where lupus no longer exists. We believe the solution to lupus is research focused on better treatments, prevention and a cure. We support the most promising research projects from scientists at the most prestigious hospitals, universities and medical schools throughout the world. Because our Board of Directors funds all administrative and fundraising costs, one hundred percent of your donation goes directly to support research programs. Together, we will find a cure for lupus.

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Because ALR's Board of Directors funds all fundraising and administrative costs, 100% of all donations received goes to support lupus research programs.

To make a donation to ALR, please visit our website, www.lupusresearch.org, mail a check to ALR at 28 West 44th Street, Suite 501, New York, NY 10036, or call us toll-free at 800-867-1743.