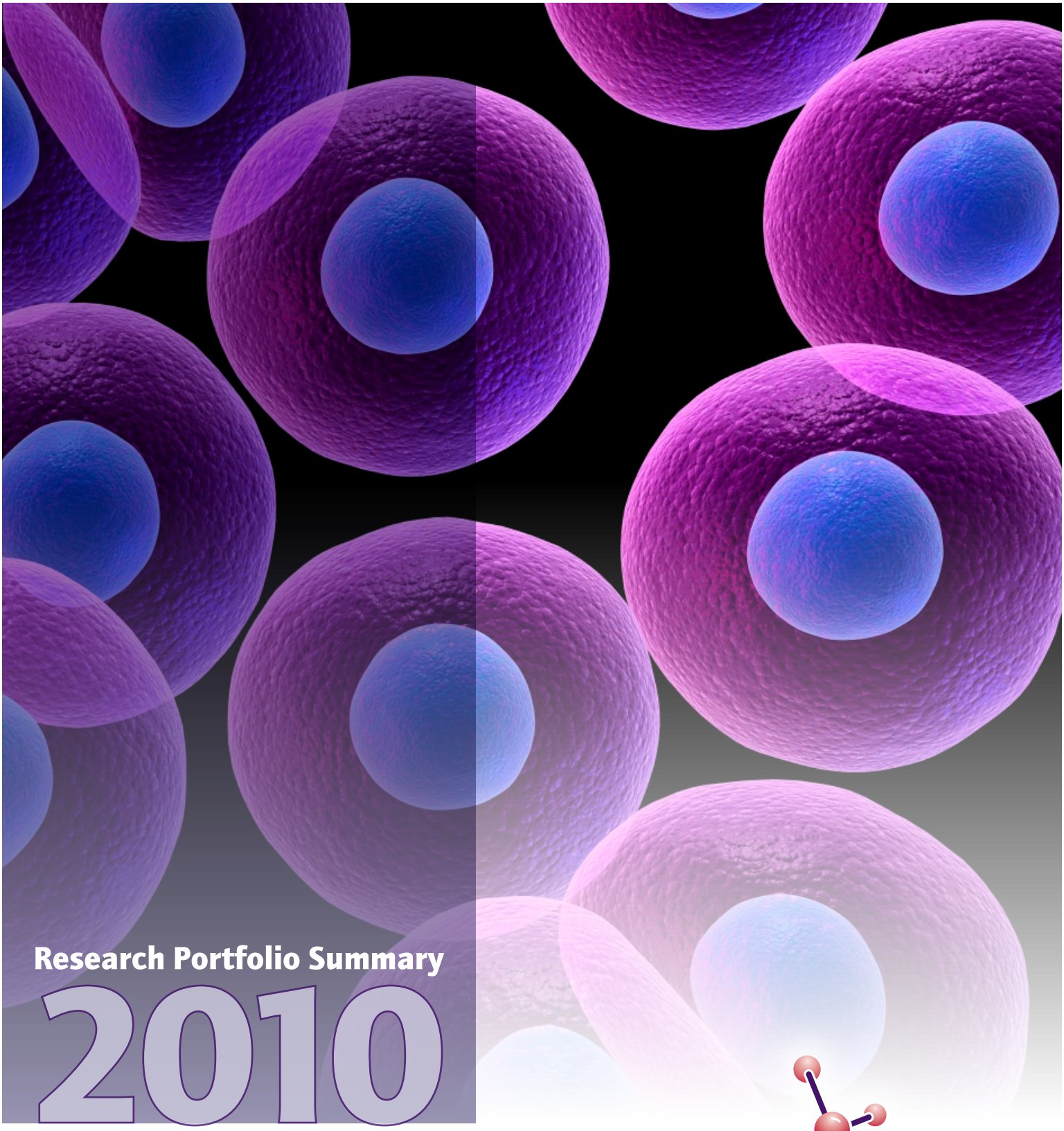
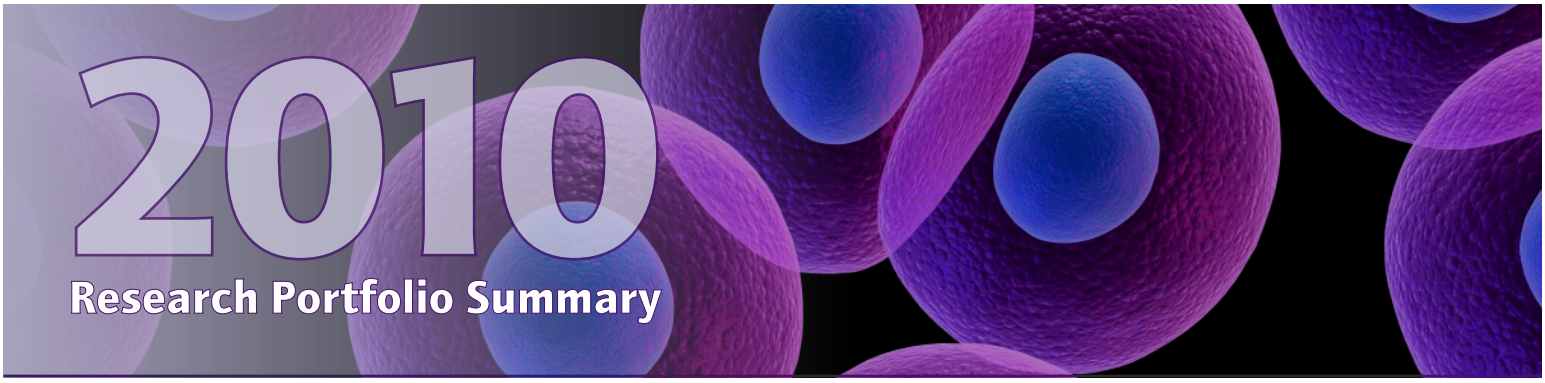


Research Portfolio Summary

2010

Alliance *for* Lupus Research

PREVENT. TREAT. CURE.

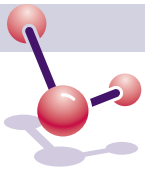


Target Identification in Lupus Grantees

Beginning on page 4

Functional Genomics and Molecular Pathways in SLE

Beginning on page 10



Target Identification in Lupus Grantees

Under our Target Identification in Lupus (TIL) grant program, investigators leverage a two-year, up-to-$500,000 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.

Harini Bagavant, PhD
University of Virginia
Modulating Renal Responses: A Novel Therapeutic Approach in Lupus Nephritis

Lupus glomerulonephritis (GN) is most common effect of lupus on the kidneys. It develops as a result of the abnormal immune response to self that is the hallmark of lupus, as well as from the infiltration of immune cells into the kidney. However, we still don't know the exact mechanisms that result in the loss of kidney function.

Recent evidence suggests that kidney cells, especially glomerular mesangial cells, respond to the immune insult and contribute to the ultimate progression of the disease. Dr. Bagavant and her team have developed specialized cellular "vehicles" called immunoliposomes that can deliver drugs to the glomerulus in mice. They load the immunoliposomes with a fluorescent dye or a protein, inject them into the tail vein of normal and diseased mice, and watch as the carriers quickly move through the circulatory system to the glomerulus, primarily escaping detection from the immune system. Most importantly, these vehicles are able to deliver their contents directly to the mesangial cells.

Dr. Bagavant and her team will use their grant to further study this sytem. They plan to load the immunoliposomes with different therapeutic agents that can block various molecules in mesangial cells, the same cells that make kidney disease worse. They will initially test these agents in a mouse model of GN, with the long-term goal of advancing to human studies. e neuronal damage in mice during specific periods of fetal development.

What this study means for people with lupus: The concept of targeting therapies specifically to the organ affected by the autoimmune processes of lupus is a unique idea. If successful, it may open up a vast repertoire of therapeutic agents that can be used to treat lupus in humans.

Nina Bhardwaj, MD, PhD
New York University School of Medicine
Inducing Tolerance in SLE through Modulation of Apoptotic Cell Receptors

In systemic lupus erythematosus (SLE, or lupus), the immune system generates abnormal, autoreactive responses that target self antigens released by dying cells. There is an urgent need to develop approaches to prevent these processes or, at the very least, induce immune system tolerance for them. Tolerance is the process by which immune system cells are "taught" to recognize self from nonself proteins. Part of the problem with lupus is that immune system cells, particularly T and B cells, mistakenly view "self" proteins as foreign and develop antibodies against them or otherwise try to destroy them, leading to significant tissue damage.

Dr. Bhardwaj's team focuses on the role of dendritic cells, white blood cells that are often the first to identify pathogens and "present" them to T cells, which then develop an appropriate response. In their work, Dr. Bhardwaj's team has found that dendritic cells can be manipulated to induce tolerance.

With this grant, they plan to generate tolerogenic dendritic cells (TDC) that silence autoimmune T cells and block B cell antibody production. They found they can develop TDCs by aggregating certain receptors on the surfaces of dendritic cells. In healthy individuals, these receptors normally engage and then remove dying cells from the body (including those containing autoantigens) to prevent autoimmunity. Current studies are looking at which receptors exist on dendritic cells in people with lupus, and how similar are they to those from healthy people. The team will also explore novel ways to manipulate these receptors, including using pieces of dying cells to "turn off" dendritic cells.

What this study means for people with lupus: This study identifies a novel approach to halting the autoimmune process, one that could lead to the development of new therapies.

Robert Eisenberg, MD
University of Pennsylvania, Philadelphia, PA
Distal Ig Receptor Revision in the Production of SLE Autoantibodies

A central feature in the underlying process of systemic lupus erythematosus is the production of autoantibodies against DNA and other self molecules. This occurs because B lymphocytes, which normally only produce antibodies to foreign substances like flu viruses, are somehow induced to produce autoantibodies, which then attack self tissue. The production of these autoantibodies signifies the failure of the process of tolerance, in which B cells learn not to view self molecules as foreign.

Several studies have suggested that abnormal changes in genes that code for the autoantibodies themselves may underlie the disease process. With this grant, Dr. Eisenberg and his team will explore the hypothesis that the loss of self tolerance in lupus is due to a rearrangement of antibody genes (receptor revision) that changes the specificity of the resultant antibody. If this genetic process occurs very late in the development of the B lymphocyte, then there is no opportunity for normal tolerance mechanisms to silence newly created autoreactive antibodies.

What this means for people with lupus: If this receptor revision mechanism is a key player in the autoimmune response of lupus, then the pathways, receptors, and regulators essential to this mechanism would provide a number of potential therapeutic targets.

Keith Elkon, MD
University of Washington
Lysis of Immunostimulatory Nucleoproteins in SLE

A characteristic feature of lupus is the presence of autoantibodies directed against self antigens, which causes overactive immune response and inflammation. Over the last several decades, investigators have characterized the antigens in lupus, finding that most are nucleoproteins (nuclear or cytoplasmic proteins attached to the nucleic acids DNA or RNA) released from one's own dead and dying cells.

There is increasing evidence that nucleoproteins accumulate in patients with lupus because the cells responsible for clearing them away don't work properly. Then autoantibodies bind to the nucleoprotein antigens to form antigen/antibody or "immune" complexes, which cause tissue inflammation. When the nucleoprotein complexes enter cells, the nucleic acid activates special receptors called toll-like receptors (TLR), triggering the release of inflammatory proteins called cytokines.

One of these cytokines, interferon-alpha, has been strongly implicated in systemic lupus.

With this grant, Dr. Elkon and his team will use a mouse model to degrade the nucleic acid component of the immune complexes so they cannot be deposited in tissue or activate

TLRs. They will also investigate whether nuclease therapy is effective once the disease has already begun by administering nucleases to mice with active disease and monitoring their disease activity.

What this grant means for people with lupus: This study provides information on a new avenue of exploration for compounds to treat lupus and its complications without suppressing the overall immune system.

Chaim O. Jacob, MD, PhD
University of Southern California
Targeted DNA Capture and Parallel Sequencing to Identify Causal Mutation

Numerous genetic mutations related to lupus have been identified. However, much work remains to better understand that specific genetic mutations that underlie the disease processes. Dr. Jacob and his team have been at the forefront of this genetic research. With this grant, they plan to identify variants in 9 genes related to lupus to better understand the specific pathways related to the disease.

What this means for people with lupus: Discovering and characterizing genetic factors responsible for lupus is crucial in understanding the pathology of the disease and providing new novel targets for future therapies.

Vicki Kelley, PhD
Brigham and Women's Hospital, Inc.
Colony Stimulating Factor 1: A Therapeutic: Target for Lupus Nephritis

Kidney failure is a major cause of disease and death in people with lupus. Tracking molecules that play a role in lupus-related kidney disease, or lupus nephritis, could help identify identifying therapeutic targets and biomarkers for this illness. This latter goal is particularly important because it is very difficult to detect lupus nephritis in the early stages of the disease, before kidney damage occurs. The "gold standard" for diagnosis and determining disease severity is an invasive kidney biopsy. However, such biopsies can't be repeated very often. So identifying non-invasive strategies for early detection, to determine disease severity, and to monitor therapeutic responsiveness, such as levels of certain molecules in the blood or urine, is critical for improving treatment.

Dr. Kelley and her team are targeting colony stimulating factor 1 (CSF-1) as a potential biomarker. These molecules stimulate the growth of white blood cells called macrophages, which are central to kidney disease. Studies in lupus-susceptible mice show that CSF-1 can promote lupus nephritis. In addition, the researchers have seen a dramatic rise in CSF-1 levels in the kidney, blood, and urine of patients with lupus nephritis compared to levels in healthy individuals. Thus, they hypothesize that CSF-1 is a potential therapeutic target and biomarker for human lupus nephritis.

They will use their grant to test this hypothesis in unique mutant lupus-susceptible mice. In one experiment, they will see if blocking the CSF-1 receptor can improve signs and symptoms of lupus nephritis in these mice; in another, they will see if levels of CSF-1 in the circulation and kidney contribute to the disease process of lupus nephritis. Finally, they will test the hypothesis that CSF-1 in the blood or urine could be used to identify and predict disease activity in people with lupus nephritis.

What this means for people with lupus: Understanding the distinct roles of CSF-1 in the circulation and kidney is central to tailoring therapeutic approaches that target CSF-1 and treat lupus nephritis.

Sergei V. Kotenko, PhD
UMDNJ-New Jersey Medical School
Inhibition of Type I and Type III IFNs by Poxvirus-Encoded Soluble Proteins

Interferons (IFNs) are multifunctional proteins that not only help induce resistance to viral infections, but also help regulate a variety of immune responses to other pathogens and pathological conditions. Because IFNs are robustly produced in response to many immunological threats, it is important that their production be tightly controlled, with most of their genes maintained in the "off" position.

However, it appears that in people with lupus, this regulation of IFN expression does not work properly. Instead, certain types of IFNs contribute to the underlying mechanism of the disease itself. Thus, one promising avenue of research into lupus therapies is the development of anti-IFN agents, or IFN antagonists.

A new type of IFN discovered in recent years that may be related to lupus is IFN lambda, or type III IFN, which is similar to well-characterized type I IFN. Dr. Kotenko and his team discovered a viral protein (Y136) that can inhibit both types of IFN. This virus-encoded IFN antagonist, along with another viral protein, B18, which inhibits all type I IFNs (but not type III IFNs), present a unique opportunity for developing strong and specific inhibitors of type I and type III IFNs and, potentially, treating lupus.

With this grant, the researchers plan to investigate the possibility that type III IFNs are involved in pathogenesis of SLE. They will also try to create IFN antagonists that can be used to treat the disease.

What this study means for people with lupus: This study could lead to the development of important new therapies for the disease.

Kun Ping Lu, MD, PhD
Beth Israel Deaconess Medical Center
The Prolyl Isomerase PIN1: A Novel Therapeutic Target in SLE

Recent studies into the underlying mechanisms of lupus have shown that dysregulation of the immune response pathway TLR/IRAK1/IRF/IFN plays a major role in the disease. Errors in this pathway can lead to overproduction of certain hormones, particularly interferon alpha, a major culprit in lupus development. Thus, studies on how this pathway becomes dysregulated are important in identifying potential targets for new therapies.

Dr. Lu and his team previously discovered a new enzyme called PIN1 that controls protein function and plays a major role the development of numerous diseases, including cancer. Earlier work by Dr. Lu and his team suggest that PIN1 might play a major role in the development of lupus. In these studies, they found higher activity of PIN1 in peripheral blood cells of lupus patients. Importantly, Pin1 controlled the activation of the TLR/IRAK1/IRF/IFN pathway. When the researchers removed the PIN1 gene in mice and immune cells, they prevented overproduction of interferon alpha. These results led them to hypothesize that PIN1 may represent an attractive, more specific and safer novel drug target for lupus than those currently available.

With this grant, the researchers plan to test their hypothesis in three ways:

- Comparing changes related to PIN1 activity and expression in immune cells from healthy individuals and those with lupus to determine the potential role of the enzyme in human lupus
- Using animal and cell models to determine the role of PIN1 during the pathogenesis of lupus
- Delivering a highly potent and specific PIN1 peptide inhibitor specifically to certain immune cells to evaluate whether it prevents the development of lupus or suppresses lupus disease activity in cells and mouse models

What this means for people with lupus: These studies and the further development of targeted PIN1 inhibitors may represent an exciting new treatment strategy for lupus.

Mark J. Mamula, PhD
Yale University
Antigen Trafficking Between APCs as a Therapeutic Target for SLE

Specialized immune cells called antigen-presenting cells (APCs) play a role in directing immunity against self-antigens, the process that leads to lupus and other autoimmune conditions. One type of APC are B cells, which not only have a unique ability to capture specific proteins but also play an important role in the underlying pathogenesis of lupus. Although we don't yet know exactly how B cells trigger lupus, one theory suggests that it may be related to the way in which B cells bind specific self antigens then transfer them to other APCs. This would result in a strong autoimmune response against the known lupus antigens.

Dr. Mamula and his team have conducted research showing that human B cells do, indeed, transfer antigens to other APCs called dendritic cells. These cells "turn up the volume," or

amplify, the autoimmune response. The researchers have also identified a receptor on the surface of APC cells called Scavenger Receptor A (SR-A) that enables this process to occur.

With their ALR grant, Dr. Mamula and his team will try and identify small molecules that block the SR-A surface protein. These antagonists would prevent autoimmune antigens from connecting with and entering the cell, thus inhibiting the autoimmune response. The researchers also plan to evaluate the role of this antigen transfer in the development of lupus by studying lupus-prone mice who do not express the SR-A protein. In these studies, they also hope to learn more about the timing of antigen transfer from human B cells to APCs in the presence of SR-A inhibitors, and evaluate the ability of SR-A inhibitors to block autoimmunity.

What this study means for people with lupus: This study will help determine if SR-A is a potential therapeutic target to prevent lupus autoimmunity. The small molecule inhibitors identified by these studies should be potential therapeutic candidates for the treatment of lupus.

Laurence Morel, PhD
University of Florida
Retinoic Acid Regulation of T Cell Homeostasis in Lupus

Retinoic acid is form of vitamin A that has strong anti-inflammatory effects. In mice, studies find that it prevents and reverses a type of lupus nephritis (kidney disease). Recent studies have shown that retinoic acid appears to increase the number of regulatory or noninflammatory T cells, which, in turn, reduces the number of inflammatory T cells, which contribute to the development and symptoms of lupus and other autoimmune diseases. Reducing the numbers of these cells can help stem the autoimmune response that is the hallmark of lupus.

Dr. Morel and her team will use their grant to study retinoic acid in mouse models of lupus to see if this is, indeed, the mechanism responsible for the compound's beneficial effect in lupus nephritis. They will also investigate whether this mechanism is responsible for the increased numbers of inflammatory T cells in people with lupus.

What this study means for people with lupus: The results of these experiments will help determine how to target the retinoic pathway in lupus treatment to restore a balance between regulatory and inflammatory T cells.

Timothy Niewold, MD
University of Chicago
Role of ILT Receptors in Human Lupus

Type I interferons are important immune system signaling molecules that normally function to defend the body against viruses. Increasing evidence suggests that overactivation of the type I interferon pathway increases the risk of developing lupus and is linked to increased disease activity in those who already have the disease.

The interferon 1 signaling pathway could be a prime target for lupus therapies. However, we don't know enough about how the molecules are regulated in humans. Thus, Dr. Niewold and his team will use their grant to study immune system molecules called immunoglobulin-like transcripts 3 and 7 (ILT3 and ILT7). These molecules exist on the surface of immune cells, acting to turn off inflammatory immune responses. They can also reduce the production of type I interferon, something Dr. Niewold's lab demonstrated in preliminary studies in human cells. This suggests that the ILT molecules could be useful as a target for lupus-related therapies.

The researchers plan to identify the molecule or molecules that normally activate type 1 interferon signaling via ILT3. They will also measure ILT molecules in the blood cells of people with lupus, and determine whether ILTs are related to disease activity, clinical disease features, and/or serum type I interferon levels. Finally, they will test the function of ILT molecules in human blood cells to determine their impact upon type I interferon signaling.

What this means for people with lupus: Completing these studies will lead to improved understanding of the role of ILT receptors in lupus, essential knowledge for the development of therapies that target the interferon pathway.

James Oates, MD
Medical University of South Carolina
The Role of Sphingosine Kinase in SLE

Current treatments for lupus nephritis — lupus-related kidney disease — are often ineffective. They also have significant side effects, including infection and sterility. Thus, it is important to find new approaches for treating this often fatal disease.

Researchers have discovered a new class of compounds that can prevent inflammation in mouse models of rheumatoid arthritis and inflammation of the colon. One such compound, ABC294640, inhibits the activity of a protein called sphingosine kinase, which converts the lipid sphingosine into the inflammation-causing sphingosine-1-phosphate

With their ALR grant, Dr. Oates and his team plan to determine the ability of ABC294640 to prevent lupus nephritis in lupus-prone mice. Early studies using ABC294640 in these mice suggest that mice treated with this compound live longer and are less likely to develop signs of kidney disease.

In a second study, the researchers will treat the mice with either ABC294640, traditional therapy (cyclophosphamide), or a combination of both to determine if the new compound works as well as traditional therapy in treating disease once it occurs, and if combining it with cyclophosphamide works better than the traditional therapy on its own. They will also conduct studies to investigate just how ABC294640 works to prevent disease.

Finally, the researchers will study people with lupus for signs that sphingosine kinase also contributes to lupus nephritis in humans.

What this study means for people with lupus: The ultimate goal of these studies is to provide preclinical studies required before human trials can be started to evaluate ABC294640 as a treatment for lupus nephritis.

Andras Perl, MD, PhD
SUNY Upstate Medical University
Mitochondrial Hyperpolarization in Lupus T Cells

Dr. Perl and his group have discovered a series of molecular defects in the mitochondria of T lymphocytes that may account for the dysfunctional actions these cells exhibit in people with lupus. Mitochondria are small cellular factories that produce fuel in the form of ATP. In lupus patients, mitochondrial defects lead to diminished production of ATP, compromising survival and appropriate functioning of cells. These cellular abnormalities also prevent the programmed destruction of self-aggressive T lymphocytes. Instead, the researchers found that this mitochondrial dysfunction causes abnormal cell death, called necrosis.

This type of cell death stimulates other cell types, initiating a relentless inflammatory response. They also discovered that nitric oxide plays a key role in the mitochondrial dysfunction of these lupus T cells. In fact, after exposure to nitric oxide, T cells of healthy donors temporarily behave like those from lupus patients.

Dr. Perl plans to use the ALR grant to precisely identify how nitric oxide works in the T cells of lupus patients and to identify other contributing factors to the mitochondrial dysfunction.

What this study means for people with lupus: Better understanding the mechanism of nitric oxide in the cells of lupus patients may provide new targets for treatments to correct malfunctioning mitochondria.

Alessandra Pernis, MD
Hospital for Special Surgery
Role of Rho GTPases and Their Activators in Lupus Pathogenesis

An underlying cause of systemic lupus erythematous is abnormalities in T cell regulation. There are several subtypes of T cells, and recent research suggests that a specific type called Th effector cells may be involved in lupus. Dr. Pernis and her team have identified a unique molecule called IBP (IRF-4 binding protein) that is activated when Th effector cells are called into action, and which helps control their cell function. The researchers found that mice deficient in IBP develop a lupus-like syndrome that, like human lupus, primarily affects females and is marked by the presence of abnormally activated T cells.

With previous ALR funding Dr. Pernis and her team gained critical insights into the molecular mechanisms responsible for the T cell abnormalities in IBP-deficient mice. Their findings revealed that these abnormalities are associated with increased activity of a unique class of kinases (enzymes that can change the function of proteins). They also found that preventing the activity of these kinases could prevent the kind of T and B cell abnormalities seen in IBP-deficient mice. They found similar abnormalities in these kinase activities in other lupus-prone mice strains, suggesting this molecular pathway may provide a target for possible treatments.

With their current grant, Dr. Pernis and her team plan additional studies to better understand these molecular mechanisms in the lab, in mice and in humans. They will also investigate whether targeting this pathway might not only prevent but also treat lupus in the mouse model.

What this study means for people with lupus: Since drugs that inhibit these kinases are already used to treat other medical conditions and have only minimal side effects, this research could be rapidly translated into a new treatment for lupus.

Ian R. Rifkin, MD, PhD
Boston Medical Center
Adiponectin and Adiponectin Receptors in Lupus and Lupus Atherosclerosis

Two major complications related to lupus are lupus nephritis (kidney disease) and atherosclerosis (a thickening of the blood vessel wall that leads to heart attacks and strokes). Both are caused, at least in part, by excessive inflammation.

In earlier research in animal models, Dr. Rifkin and his team found that two diabetes drugs, rosiglitazone and pioglitazone, reduced inflammation and the incidence of lupus nephritis and atherosclerosis. They also found that the drugs appear to work by triggering production of a protein called adiponectin. Adiponectin itself is an anti-inflammatory molecule that is involved in regulating metabolism.

With this grant, the researchers will explore the underlying mechanism for adiponectin's anti-inflammatory effects. Specifically, they will see whether cellular receptors that adiponectin binds to, called AdipoR1 and AdipoR2, and which trigger many of the metabolic effects of adiponectin, also play a role in preventing inflammation.

What this means for people with lupus: These studies may help identify adiponectin receptors as novel targets for new anti-inflammatory therapies that could prevent or treat lupus nephritis and atherosclerosis, either together with rosiglitazone and pioglitazone or separately.

Lars Rönnblom, MD, PhD
Uppsala University
Functional Consequences of Type I IFN System Gene Variants in SLE

Immune system cells typically produce interferons in response to viral infections. In people with lupus, however, they produce interferons even without a viral infection. These interferons contribute to several hallmark symptoms of lupus, including fever, fatigue, muscle tenderness and low white blood cell count.

For more than 10 years, Dr. Rönnblom and his team have been investigating the molecular basis and genetic background for this increased interferon production. So far, they have identified small changes in three genes within the interferon system that are strongly associated with lupus. They have also identified possible associations between additional interferon-related genes and lupus. These genes code for important proteins that can affect both the production of and the response to interferon. Their work also suggests that common variants of these genes influenced not only susceptibility to lupus but also disease manifestations.

For instance, the gene STAT4 is connected to the production of anti-dsDNA antibodies, a classic marker of severe disease in people with lupus. Dr. Rönnblom and his team have also seen that these gene variants have an additive effect, meaning that the more variants an individual has, the higher their risk of the disease.

This grant is a renewal of an earlier ALR grant that will enable the researchers to continue their work. With this renewal, the team plans to clarify the consequences of these gene variants, investigate how they are expressed in different immune system cells, and explore how they affect cellular function. They will also work to further identify the relationship between the gene variants and clinical manifestations of lupus.

What this study means for people with lupus: These studies will contribute to our understanding of the genetic and molecular events in lupus. Better understanding the signaling pathways and molecules required for the abnormal autoimmune response is important in the development of new therapies for the disease. In addition, the work identifying other genes related to the interferon system may eventually help doctors predict an individual's risk for lupus.

Derry C. Roopenian, PhD
The Jackson Laboratory
Function Dissection of Interleukin-21 in Lupus

Dr. Roopenian and his team have been investigating the role of a new and promising molecular target, interleukin 21 (IL21), in the development of lupus. This protein is typically produced in low levels by CD4 T cells, a type of immune system cell that is important in lupus. In people with lupus, CD4 cells provide too much IL21, overstimulating other immune system cells and leading to the classic manifestations of the disease.

Dr. Roopenian and his team found that interrupting the IL21 signal in lupus-prone mice keeps them from developing the disease. Thus, they plan to use their grant to determine exactly how this works: What role does IL21 play in lupus? What other roles does the protein play in the immune system? Does IL21 operate the same in humans? Overall, their work should provide fundamental information about this pathway that will be critical to the development of any treatments targeting IL21.

What does this study mean for people with lupus? This genetic-based work may help identify a novel treatment pathway for the development of new drugs to prevent and treat lupus.

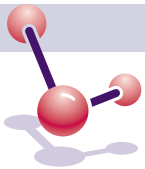
Marie-Laure Santiago-Raber, PhD
Centre Médical Universitaire
Selective Blocking of the Plasma-Cell Survival Factor APRIL in SLE

Current treatments for lupus involve a variety of non-specific anti-inflammatory and immunosuppressant agents that are relatively ineffective and have significant side effects. Targeting specific cellular and/or molecular pathways in the disease could lead to more effective therapies with fewer negative effects.

We know that in people with lupus, cells from the immune system called B cells produce antibodies against "self" components. They produce these antibodies after changing into plasma cells. Normally, plasma cells that produced autoantibodies should die through a mechanism called apoptosis. But proteins called APRIL enable the survival of these plasma cells by protecting them from apoptosis.

With their ALR grant, Dr. Santiago-Raber and her team plan to destroy these autoantibody-secreting plasma cells in animal models of lupus by blockading their access to APRIL. Their goal is to see if this affects the development and consequences of the disease.

What this study means for people with lupus: The results from this work will provide valuable information into the role of APRIL in the development of lupus, and will show whether blockading APRIL will reduce lupus severity in animal models. Eventually, this work could lead to the development of new treatments.



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.

Marta Alarcon-Riquelme, MD, PhD
Oklahoma Medical Research Foundation
Dissecting a Novel Molecular Genetic B-Cell Pathway in Lupus

Dr. Alarcon-Riquelme and her team have identified several lupus susceptibility genes, genes that make people more likely to develop lupus. However, they do not know how these genes lead to the development of the disease.

With this grant, the researchers will focus on two genes, BANK1 and BLK. Their own data suggests these genes may play a role in the toll-like receptor (TLR) pathway, a critical signaling pathway with which cells communicate with each other. Previous research found that this pathway is very important in the development of lupus, triggering the production of autoantibodies and highly inflammatory substances such as alpha-interferon that underlie the disease process. Up to 70 percent of all people with lupus produce too much alpha-interferon.

The researchers want to better understand the role of these two genes in the TLR9 pathway. As part of their investigation, they will work with human cell lines that do not express these genes. This will enable them to see if the lack of genetic expression changes the ability of cells in the TLR9 pathway to respond and produce inflammatory chemicals.

They will also use an animal model that does not express the genes so they can test the effects of certain stimuli on the animals' immune systems. The researchers will also see if deleting one or both genes leads to the development of autoantibodies or kidney inflammation, and how that development occurs.

What this means for people with lupus: The results of this research will increase our knowledge of the rule of susceptibility genes in the development of lupus, enabling the construction of models and systems for testing potential therapeutic substances that could affect the underlying cause of the disease, not just its symptoms.

Jane H. Buckner, MD
Benaroya Research Institute at Virginia Mason
The Impact of Genetic Variants on BCR Signal Transduction in SLE

We now know that several genes increase the risk of systemic lupus. Understanding how these genes contribute to the mechanisms that cause the disease is an important next step in learning why an individual develops lupus.

Some of these genes are found only in B cells, immune system cells that play an important role in the development of lupus. Three such genes, BANK1, BLK and PTPN22, are involved in the signaling receptor pathway in B cells, vital for B cell development, maturation and function. This signaling pathway ensures that B cells that produce antibodies to protect us from pathogens respond appropriately when needed, while "rogue" B cells that produce autoantibodies, or antibodies against "self," are destroyed. If the B cell receptor signaling does not work properly, it can lead to the development of autoantibodies and autoimmunity, the hallmarks of lupus.

Given that these three genes are involved in B cell signaling and are linked to a higher risk of lupus suggests that this signaling receptor pathway is important in the development of the disease.

With this grant, Dr. Buckner and her team will examine how alterations in these three genes may contribute to SLE by altering the B cell receptor signaling pathway. The initial studies will be conducted with samples from healthy individuals who carry the genes, enabling the team to identify how each gene impacts the pathway.

Next, they will study how B cell receptor signaling is altered in people with lupus, focusing on the underlying causes of these alterations, including additional genes that may play a role. Finally, they will examine how these alterations result in autoreactive B cells escaping regulation and contributing to disease development.

What this study means for people with lupus Understanding the role of these genes and the B cell receptor pathways in lupus will enhance our ability to predict and treat the disease.

Sumit Chanda, PhD
Burnham Institute for Medical Research
Systems-based Analysis of IRF-5 Activation

Innate immunity is the first line of defense against infection. This immediate immune response begins when the immune system detects structures in bacteria or viruses called pathogen-associated molecular patterns (PAMPs), which are usually not present in the individual. Immune cells recognize PAMPs via host-encoded pattern recognition receptors (PRRs), which, when activated, trigger several events in the cell that lead to the destruction of the pathogen. However, if the pathways that govern this innate immune protection go awry, autoimmune diseases like lupus can result.

Dr. Chanda and his team have been focusing on a major PPR called toll-like receptor. Studies indicate that abnormalities in toll-like receptor 7 (TLR7) signaling can contribute to the onset of lupus. Using a new technology known as RNA interference, they have scanned the human genome for factors that contribute to the activity of the TLR7 pathway. These studies provide, for the first time, a comprehensive understanding of the global molecular architecture that governs this important component of the human immune system.

With this grant, Dr. Chanda and his team will use their earlier findings to identify the specific molecules that regulate the TLR7-mediated innate immune responses. Their studies should confirm the activity of these factors in cells affected by lupus and provide important insights into the molecular components that underlie lupus.

What this study means for people with lupus: It will help identify new biomarkers that can be used to identify the disease and its progression, as well as new targets for drug development.

Robert Clancy, PhD
New York University School of Medicine
ITGAM R77H: Genotype/Phenotype Relationships in Dendritic Cells

Genetic discoveries have great potential to help us understand the factors that contribute to tissue injury in systemic lupus erythematous. In this study, Dr. Clancy and his team plan to build on new understandings of a variation in a gene that codes for a protein called ITGAM. This protein is found on white blood cells. Its job is to remove tagged substances, typically pathogens or dead cells or cell fragments, from circulation. It also provides a signal that prevents immune cells from activating against self tissue, a process called tolerance. Lack of tolerance is a major cause of autoimmune diseases like lupus.

What we don't know is whether variations in the gene that encodes for ITGAM results in changes in the protein and its function. That's what this study is designed to investigate.

Researchers will test the hypothesis that a genetic variation causes the protein to function poorly, contributing to the development of autoimmunity. To test this prediction, researchers will obtain DNA from people with and without lupus and test for the gene variation. They will then evaluate the ability of the protein produced by the genetic variation to increase or reduce tolerance. If successful, this study could be an important demonstration of a structural difference between common and variant forms of ITGAM with a consequence to specific functional properties of the immune system.

What this means for people with lupus: If the variant of the ITGAM protein prevents immune tolerance, people with the genetic variant can be followed more closely to see if they develop lupus. For those who already have the disease, it could highlight a new candidate for drug therapy to "fix" the protein or make up for its weaknesses in controlling the immune system.

Betty Diamond, MD
Feinstein Institute for Medical Research and Albert Einstein College of Medicine
Functional Basis of Lupus Susceptibility: Tyrosine Kinases Blk and Csk

Although more than 20 genes have now been convincingly associated with lupus, we still don't understand how these genes contribute to the development of the disease.

With this grant, Dr. Diamond and her team will conduct a detailed analysis of two of the genes associated with lupus to better understand their role in the disease. They suspect that genetic variations in two molecules, the tyrosine kinases Blk and Csk, reduce the activation of B cells, enabling autoreactive immune cells to escape detection and multiply. The presence of such autoreactive B cells among other mature B cells likely presents a key risk factor for the development of lupus.

What this study means for people with lupus: Defining one or more key regulatory pathways in human B cells that lead to lupus opens the way for more precise definitions of disease subsets, as well earlier and more effective diagnosis. In addition, these studies will provide options for various treatments based on well-defined immune regulatory mechanisms.

Averil Ma, MD, PhD
University of California-San Francisco
Function of TNFAIP3/A20 Genetic Variants in SLE

Although we still don't know what causes lupus, recent genetic studies have provided important clues. For instance, Averil Ma, MD, PhD, of the University of California-San Francisco, and his team have found that mutations in and around the A20 gene are associated with the risk of developing SLE. They also discovered that A20 is a powerful anti-inflammatory protein that prevents spontaneous inflammation.

The team has recently created a new mouse model in which A20 is removed from B lymphocytes, the immune cells that help make the autoantibodies that cause disease in lupus. They found that these mice spontaneously develop several characteristics of human lupus.

Based on these findings, Dr. Ma and his team plan to use their grant to better understand how A20 predisposes people to develop lupus. First, they will examine A20 expression levels and A20 dependent functions in lymphocytes from people with lupus. They will then test blood cells from these individuals and correlate these findings with genetic analyses. The team will also study the development of lupus in their genetically modified mice.

What this study means for people with lupus: This proposal represents a unique opportunity to dramatically enhance our understanding of how A20 causes SLE. This understanding will help researchers identify specific compounds that could prevent SLE, possibly moving the field closer to developing effective treatments.

Fred Perrino, PhD
Wake Forest University Health Sciences
TREX1 Mutations in SLE

One of the hallmarks of lupus is the presence of antibodies that react to DNA molecules found circulating in the blood of affected individuals. Although we don't know the source of the DNA molecules, we do know that in adults about 100 billion cells a day undergo normal cell death processes. Part of these processes involve disassembling the cells and the 2.9 billion base pairs of DNA that comprise the human genome in each cell.

Dr. Perrino and his team have identified a gene called TREX1 that encodes for a powerful DNA disassembly enzyme that appears to be responsible, in part, for the circulating DNA fragments. Mutations in this enzyme enable the persistence of DNA from dying cells, triggering an immune response. The effects of this immune response vary, but the failure of TREX1 to eliminate DNA from dying cells might be at the root cause of the aberrant immune reaction seen in some patients.

With this grant, Dr. Perrino and his tem plan to create a lupus TREX1 mutant mouse model to determine how TREX1 enzyme dysfunction leads to the development of lupus and related autoimmune disorders.

What this means for people with lupus: These experiments will provide new insights into the origins of lupus and promising new avenues for the development of novel therapeutic strategies to treat the disease.

Erik J. Peterson, MD
University of Minnesota
Modeling the PTPn22 Systemic Lupus Susceptibility Allele

Researchers have recently identified several genes that most likely contribute to the development of lupus. These findings, in turn, have triggered a flood of research into the underlying function of those genes and their potential contributions to the disease.

With their grant, Erik Peterson, MD, of the University of Minnesota, and his team plan to focus on one specific "risk gene:" PTPn22. They will use genetically altered mice and cell lines from people with lupus to explore more fully the role this gene plays in the abnormal immune system pathways of lupus. Dr. Peterson and his team suspect that the protein produced by this gene, LypW, reduces the signaling ability of T cell receptors, enabling "self-reactive" T cells to survive and contribute to the tissue damage that is a hallmark of lupus.

What this study means for people with lupus: This study should improve our understanding of how this gene increases the risk of lupus, providing important information for future drug development.

Earl Silverman, MD
The Hospital for Sick Children
How Genes Determine SLE Phenotype and Outcome

Systemic lupus erythematous is a multi-organ system disease that likely results from a complex interaction of genes and the environment. The disease can begin at almost any age, from infants as young as 1 year to individuals in their eighties and even nineties. However, the younger the patient, the more severe the disease tends to be, although its course differs in every patient. Thus, different genes may be involved based on when someone develops lupus.

So far, however, genetic studies have found one common set of genes in both children and adults with SLE. No one has looked to see whether the amount of genetic changes in children with lupus differ from those in adults with the disease.

In addition, the varying manifestations of lupus from patient to patient suggest that interactions between lupus-related genes and non-lupus-related genes my influence the course of the disease.

This grant will be used to try and answer both questions: are there differences in the number of genetic mutations between children and adults with lupus? And are there interactions between organ-specific genes and lupus-related genes that help explain the different manifestations of the disease? If so, are these interactions similar in adults and children?

To investigate these questions, Dr. Silverman and his team will assess 1,000 to 2,000 adults and a similar number of children with lupus in this international study.

What it means for people with lupus: Identifying children who have a high genetic risk for lupus will add to our understanding of the pathogenesis of the disease and help explain why it occurs throughout the lifespan. In addition, examining the role of non-lupus genes in patients with lupus will provide important information about how other genes influence the outcome of lupus. Better understanding both of these processes will enable researchers to identify new targets for therapy and to better target existing therapies for children and adults with lupus.

Jun Yan, MD, PhD
University of Louisville
Regulation of Autoreactive B Cells by Integrin ITGAM/CD11b

The autoimmune responses that underlie lupus are characterized by the presence of autoantibodies (autoAbs) and T cells that turn their protective defenses against self tissue rather than invader pathogens. Genetic studies suggest that a mutation within a gene called integrin CD11b increases the risk of developing lupus, and, in those who do develop the disease, results in a more severe course.

Preliminary data from Dr. Yan's group suggests that CD11b is expressed on all stages and subsets of B-lymphocytes. These lymphocytes are responsible for producing the autoantibodies that attack self tissues and organs. Strikingly, B cells with CD11b mutations divide more rapidly and survive better than those without the mutation. Thus, it appears that the CD11b mutation may make it easier for this lymphocyte subset to become activated and drive disease processes.

This grant will be used to better understand the role of the mutation in those pathways.

What it means for people with lupus: Better understanding the genetic mutation and its role in lupus can help identify novel targets for new drug development.

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.

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