Research Portfolio Summary

2009

Alliance *for* Lupus Research

PREVENT. TREAT. CURE.

2009 Research Portfolio Summary

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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-$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, Charlottesville, VA

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.

Lindsey A. Criswell, MD, MPH, University of California, San Francisco

Genetic Predictors of Thrombosis in SLE

Some people with lupus are much more likely to have a stroke or experience other complications related to blood clotting (thrombosis) than those without the disease. Dr. Criswell and her team hypothesize that specific genetic changes predispose these individuals to thrombosis.

With their ALR grant, the researchers hope to determine the thrombotic status of 1,750 people with lupus based on their history of venous or arterial clots, pregnancy-related complications due to thrombosis, and/or production of

antiphospholipid antibodies, which have been linked to an increased risk of blood clots. They will also research reports of genetic changes associated with thrombosis in the general and/or lupus population and estimate the magnitude of these associations, and will screen their lupus patients for genetic changes that the biotechnology company Celera has already found are associated with thrombosis.

Finally, they will also identify potentially important interactions between those genetic markers and risk factors such as smoking, oral contraceptive use or antiphospholipid antibody production.

What this study means for people with lupus: Identifying genetic changes that influence the risk of stroke and other thrombotic episodes in those with lupus could help researchers develop new approaches to prevention and treatment.

Keith Elkon, MD, University of Washington, Seattle

Lysis of Immunostimulatory Nucleoproteins in SLE

A characteristic feature of lupus is the presence of autoantibodies directed against self antigens, which causes overactive autoimmune 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.

Shu Man Fu, MD, PhD, University of Virginia, Charlottesville

Identification of Genes Conferring End-Organ Resistance in Lupus Nephritis

During the past several years, Dr. Fu's laboratory has developed a novel animal mouse model to investigate susceptibility genes for systemic lupus. His group identified two regions in the mouse genome, one located on chromosome 1 and the other on chromosome 12 that contribute to the risk of acute and chronic lupus-related kidney disease. His group also generated new strains of mice that are resistant to the development of lupus kidney disease.

In addition, Dr. Fu and his team have identified unique genes that are either over- or under-expressed in the resistant mouse strain when compared with the parental strain from which the resistant strain was developed. With this grant, Dr. Fu and his team will use these mouse strains to identify candidate genes that confer resistance to the development of lupus kidney disease.

What does this study mean for people with lupus: Identifying the genes responsible for resistance to lupus kidney disease may provide future opportunities for new therapeutic interventions.

Sarah Gaffen, PhD, University of Pittsburgh, Pittsburgh, PA

IL-17RC: A Novel Target for Anti-Cytokine Therapy

Chemical messengers called cytokines play an important role in driving the inflammation that ultimately causes tissue damage in lupus. They act by binding to specific molecular receptors, so understanding precisely how cytokines and their receptors interact may provide a basis for designing more effective treatments.

One such cytokine is interleukin (IL)-17, which is over-expressed in patients with lupus and rheumatoid arthritis. The receptor for IL-17 is very poorly defined. However, recent biochemical studies by Dr. Gaffen's team and other groups have shown that there are at least two molecules within the IL-17 receptor that could serve as targets for cytokine-blocking agents: IL-17RA and IL-17RC. In animal models, blocking IL-17RA has been shown to alleviate symptoms of rheumatoid arthritis, and many efforts are underway in the pharmaceutical industry to target IL-17RA. In contrast, very few studies of IL-17RC have been reported.

With this grant, Dr. Gaffen and her team will use a mouse model of lupus to gain a fundamental understanding of the molecular nature of the IL-17 receptor. They will focus on how IL-17RC interacts with IL-17RA and whether soluble forms of IL-17RC can be used to block IL-17-mediated inflammation.

What this study means for people with lupus: A better understanding of the IL-17 receptor and its interaction with IL-17RC and RA could lead to the development of new treatments for lupus and other autoimmune conditions.

Bevra Hahn, MD, University of California, Los Angeles
Novel Targets for Identification and Treatment of Atherosclerosis in SLE

Atherosclerosis is a major cause of illness and death in people with lupus. However, traditional risk factors such as smoking, family history, obesity and diabetes do not necessarily identify those individuals with lupus who will develop atherosclerosis. Thus, clinicians need other markers to determine who is at risk of the disease so they can initiate treatment to prevent long-term damage.

One such marker may be pro-inflammatory HDL (piHDL). With two years of previous ALR funding, Dr. Hahn and her team have shown that people with lupus and piHDL are 9.5 times more likely to have plaque in the carotid artery (an artery in the neck that is a marker for atherosclerosis) than those who do not have piHDL.

With this current grant, the researchers will investigate whether piHDL causes acceleration of atherosclerosis and whether it might provide a way to predict the future development of atherosclerosis over time; try to identify a molecular mechanism for piHDL-induced atherosclerosis by identifying changes in gene expression that distinguish lupus patients with piHDL and plaque from those without; test the hypothesis that current treatments for people with lupus can reduce piHDL scores, improve the protective capacity of HDL and reduce the risk of atherosclerosis; and explore whether novel or current therapies can alter piHDL levels, plaque burden and lupus disease activity in a mouse model of lupus and atherosclerosis.

What this study means for patients with lupus: Information learned from these studies can be used to not only identify people with lupus who are at risk for atherosclerosis, but to develop therapeutic strategies to reduce that risk.

John Harley, MD, PhD,
Oklahoma Medical Research Foundation, Oklahoma City
Genes from SLEGEN, the Lupus Genetics Consortium

The ALR-supported International Lupus Genetics Consortium (SLEGEN) has published its work demonstrating 13 genes associated with lupus. In addition, it is clear that many additional genetic effects are important in lupus, with some evidence suggesting more than 100 genes are involved. Dr. Harley and his team have focused their efforts on genes that appear to be involved in lupus, but for which convincing evidence is still lacking.

With this grant, they will work to replicate the evidence for genetic involvement in more than 12,000 people of European, African, Hispanic and Asian descent. Their goal is to explain how genetic differences work at the level of DNA differences between individuals. The genetic basis of the disease could then be used to develop new diagnostic tests and new therapies that, hopefully, will work better at preventing and treating lupus than current options.

What this study means for people with lupus: It will enhance our understanding of lupus to allow the development of new diagnostic, therapeutic and preventive strategies, as well as help usher in the era of personalized medicine for people with the disease.

Marianthi Kiriakidou, MD,
University of Pennsylvania, Philadelphia, PA
Profile and Function of B-Cell Specific MicroRNAs in a Murine SLE Model

Although the mechanisms that lead to the unexpected activation of the immune system in systemic lupus are not well understood, it is accepted that aberrant B cell responses play a key role in the disease.

Dr. Kiriakidou and her team are currently exploring the expression of microRNAs (miRNAs), a novel class of regulatory RNAs (ribonucleic acids) thought to play an important role in the regulation of gene expression, in B cells from mouse models of lupus. Their goal is to investigate the role of B cell miRNAs in the pathogenesis of lupus and determine whether miRNAs can be used as markers of lupus activity and/or as potential novel therapeutic tools.

What this study means for people with lupus: This study could provide new markers for diagnosing lupus and tracking its progression. It could also help identify new therapeutic targets.

Sergei V. Kotenko, PhD,
UMDNJ-New Jersey Medical School, Newark
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.

Mark J. Mamula, PhD, Yale University, New Haven, CT

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.

Ann Marshak-Rothstein, PhD, Boston University

Activation and Inhibition of TLR Activity in Autoreactive B Cells

Systemic lupus is characterized by the excessive production of a wide range of autoantibodies such as chromatin and ribonucleoproteins specific for self antigens that contain DNA or RNA. These antibodies and/or immune complexes deposit in blood vessel walls, kidney cells and joints, contributing to complications endemic to lupus. Studies from Dr. Marshak-Rothstein's laboratory and others' find that these complexes are particularly effective at switching on the immune system, often working through a family of receptors called toll-like receptors or TLRs.

One receptor, TLR7, recognizes mammalian RNAs. Exactly which mammalian RNAs this receptor recognizes, and how this recognition triggers autoimmune disease, remains a key question. Thus, one goal of this project is to better define the properties of mammalian RNA that lead to TLR reactivity and identify the pathological and environmental conditions that might favor the release of these forms of RNA.

Another goal is to determine how TLR activation of scavenger cells (cells that clean up dead cells) regulates the response to and removal of cell debris.

The final goal is to extend the analysis of potential TLR7 inhibitors to other types of small molecules.

What does this study mean for people with lupus? Identifying ways to inhibit TLR7 and TLR9 may provide important therapeutic strategies for people with lupus and other systemic autoimmune diseases.

Chandra Mohan, MD, PhD, University of Texas Southwestern Medical Center, Dallas

Kallikreins in Lupus Nephritis

The pathogenic mechanisms leading to kidney disease, or nephritis, in lupus remain unclear. Likewise, the molecules that determine the degree of kidney damage in lupus also remain unknown. Recently, Dr. Mohan and his team highlighted kallikreins as potential candidate genes and disease-modifying agents in lupus nephritis. Kallikreins are enzymes that can modulate several disease pathways in the kidneys as well as other tissues.

With this grant, they plan to determine the importance of kallikreins in lupus nephritis and to sequence the kallikrein genes in mouse and human lupus. These studies will shed light on the genetics of lupus nephritis, increase our understanding of the pathogenic origins of lupus nephritis, and provide new targets for therapeutic treatments.

What does this study mean for people with lupus? This study may identify an entirely new mechanism for lupus nephritis, providing numerous new targets for future treatments and preventive strategies.

Laurence Morel, PhD, University of Florida, Gainesville, FL

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.

John D. Mountz, MD, PhD, University of Alabama at Birmingham

Disruption of Autoreactive Germinal Centers as a Novel Therapy for Lupus

Germinal centers are specialized collections of immune cells, including B cells, T cells, and dendritic cells, that promote the production of antibodies in response to infection or immunization. In lupus, however, these germinal centers form spontaneously. It has been speculated that this spontaneous formation may be a key factor in the production of the autoreactive antibodies that cause tissue damage.

Using a new mouse model of lupus, Dr. Mountz and his team are analyzing the cascade of molecular signals that act on B cells to initiate or stabilize the formation of germinal centers. For instance, they have found that one such process is related to the production of interleukin 17 (IL-17) by T cells and IL-23 by dendritic cells. IL-17 drives contacts between B and T cells that lead to the spontaneous formation of germinal centers. New results from Dr. Mountz's laboratory suggest that IL-23 drives B cell antibody production. With their ALR grants, the researchers will try to determine if blocking this and other processes could reduce the production of autoantibodies and the development of autoimmune disease.

What does this study mean for people with lupus? These studies may not only form the basis of new therapies but may also provide insights into the effects of existing therapies that are based on IL-17.

James Oates, MD, Medical University of South Carolina, Charleston

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.

Alessandra Pernis, MD, Columbia University Medical Center, New York City

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.

Fred Perrino, PhD, Wake Forest University, Winston-Salem, NC

Targeting Dysfunctional Nucleases in Lupus

A hallmark of systemic lupus is the presence of antibodies that react to DNA molecules found circulating in lupus patients. Those affected produce autoantibodies to their own DNA. Although the source of this DNA has not been firmly established, it is known that billions of cells undergo normal cell death processes each day. Normally, part of this process requires that the DNA in these cells be disassembled and disposed of to prevent the inappropriate activation of the immune system.

Dr. Perrino and his team previously identified the TREX1 gene, which encodes a powerful enzyme that appears to be partly responsible for this DNA disassembly process. When the TREX1 enzyme does not function properly, the DNA from dying cells persists, triggering an immune response. While the effects of this immune response vary in people with lupus, the failure of TREX1 to eliminate DNA from dying cells may lie at the root cause of the aberrant immune reaction in some patients with lupus.

With their ALR grant, Dr. Perrino and his team will use molecular studies of TREX1 to develop a lupus TREX1 mutant mouse model and determine how TREX1 enzyme dysfunction leads to the development of systemic lupus and related autoimmune disorders.

What does this study mean for people with lupus? These experiments will provide new insights into the origins of lupus and offer promising new avenues for the development of novel therapeutic strategies to treat the disease.

Shiv Pillai, MBBS, PhD, Massachusetts General Hospital, Boston, MA

SIAE and Susceptibility to Lupus and Rheumatoid Arthritis

With his ALR grant, Dr. Pillai and his team plan to examine a single gene in patients with rheumatoid arthritis and lupus as well as in healthy individuals. This gene encodes an enzyme called sialic acid acetyl esterase (SIAE). The researchers' preliminary studies in mice genetically engineered to lack SIAE showed they also had unusually active B lymphocytes, immune cells that play a major role in disease activity in lupus and rheumatoid arthritis. The researchers also found that without SIAE, B lymphocytes secreted antibodies against the mouse's own DNA and proteins, "self" antibodies or autoantibodies, resulting in the mouse developing a lupus-like disease.

In human studies, the researchers found numerous mutations in the SIAE gene in people with lupus and rheumatoid arthritis, but not in those without the diseases. Their goal now is to extend these studies to firmly establish the link between SIAE and lupus and rheumatoid arthritis.

What this study means for people with lupus: If the connection between the genetic mutations and the autoimmune diseases is confirmed, it could lead to the development of therapies that alter events in the pathways that SIAE regulates, short-circuiting the disease process.

Ian Rifkin, MD, PhD, Boston Medical Center Corporation

PPAR Gamma and Adiponectin in Lupus Nephritis and Atherosclerosis

Two major complications related to lupus are lupus nephritis, or kidney disease, and premature atherosclerosis, or heart disease. One mechanism thought to be involved in both is the inability of the immune system to clear away dead cells, or "impaired apoptotic cell clearance." This cellular debris builds up, contributing to the underlying inflammation responsible for both conditions.

With their ALR grant, Dr. Rifkin and his team plan to study potential novel treatments for this. In their preliminary work, they found that the diabetes drug rosiglitazone (Avandia) significantly reduced nephritis and atherosclerosis in two types of mice bred to exhibit a lupus-like disease. This drug also has significant anti-inflammatory effects, due to its ability to activate a cellular receptor called peroxisome proliferator-activated receptor gamma, or PPARg.

Once activated, PPARg leads to increased levels of a chemical called adiponectin, which has anti-inflammatory properties and is also able to control the clearance of apoptotic cells. Dr. Rifkin and his team will also use the ALR grant to determine how much of rosiglitazone's beneficial effect might be due to its effect on adiponectin levels. To do this, they

will breed mice with lupus-like disease that are deficient in adiponectin and see how well rosiglitazone works in reducing lupus-related complications.

What this study means for people with lupus: The possibility of new compounds to prevent and treat lupus nephritis and lupus-related atherosclerosis.

Lars Rönnblom, MD, PhD, Uppsala University, Uppsala, Sweden
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, Bar Harbor, ME
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, Switzerland
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.

ALR Pilot Grantees

Under our Pilot Grant program, investigators use a one-year award of up to $75,000 to pursue high-risk but promising approaches to possible near-term results.

Vikki M. Abrahams, PhD, Yale University, New Haven, CT

Effect of Antiphospholipid Antibodies on Trophoblast Function in Pregnancy

Antiphospholipid syndrome is a condition in which the immune system produces antibodies against proteins that bind to phospholipids, a fatty substance in cell membranes. This makes blood stickier than normal, increasing the risk of blood clots. Antiphospholipid syndrome can be primary, existing on its own, or secondary to another autoimmune condition, particularly lupus. Women with either primary or secondary antiphospholipid syndrome not only have a high risk of blood clots and stroke, but also of miscarriage and pregnancy-related complications such as preeclampsia and preterm labor.

Part of the problem during pregnancy is that antiphospholipid antibodies appear to target the cells of the developing placenta, called the trophoblast. This disrupts the cells' normal function, causing inflammation and cell death where the placenta attaches to the woman's uterus. These changes, in turn, affect the development of the placenta, preventing its attachment to the uterus, and change maternal blood vessels that connect with the placenta. This, of course, results in significant problems with the pregnancy.

With this grant, Dr. Abrahams and her team plan to study the impact of antiphospholipid antibodies on trophoblast function and survival, as well as how the trophoblast interacts with the mother's blood vessels. Their findings will advance our understanding of the underlying mechanisms behind recurrent pregnancy loss and pregnancy complications such as preeclampsia and preterm deliveries in women with antiphospholipid syndrome.

What this study means for women with lupus: While women with APS are at high risk for pregnancy loss and pregnancy complications, it is currently impossible to predict which APS patients will have an adverse pregnancy event. The overall goal of this research is to develop better ways of diagnosing potential problems and to find new treatments to improve the long-term health of the mother and fetus.

Dominique Gatto, PhD, Garvan Institute of Medical Research, Darlinghurst, Australia

Role of EBI2 in the Development of Murine Lupus

The ability of the immune system to fight infection relies on the ability of immune cells to move within organs, so that they can encounter invading pathogens. Immune system cells are guided in this migration by so-called homing receptors, which recognize localization signals. While this receptor family plays an essential role in directing the movement of white blood cells for efficient responses against pathogens, dysregulation of homing receptors can result in the initiation or progression of autoimmune disorders like lupus. Thus, identifying and characterizing molecules that regulate immune cell localization is crucial to our understanding of the causes of lupus and its complications.

Dr. Gatto and her team have found that Epstein-Barr virus-induced gene 2 (EBI2) receptors, found on white blood cells, are required for the correct migration of lymphocytes (immune system cells) during the immune response. However, people with lupus have lower levels of these receptors. Could the low levels of these receptors somehow play a role in the development of the disease? To find out, Dr. Gatto and her team will use their ALR grant to better understand how EBI2 receptors are involved in the migration of immune cells and the relevance of these receptors and the gene that encodes for them in lupus. They have created a mouse model that lacks the EBI2 gene in immune cells, mimicking low levels of EBI2 on the white blood cells of people with lupus. Their analysis will help determine if these mice are more susceptible to lupus-like disease and/or display increased production of autoantibodies, similar to what is observed in autoimmune diseases in humans.

What this study means for people with lupus: These studies will help validate the role of EBI2 in lupus and in antibody-mediated autoimmune diseases in general. This understanding might shed light on novel immunological processes that contribute to the disease, providing new approaches to treat and/or reverse the symptoms.

Jessica A. Hamerman, PhD, Benaroya Research Institute at Virginia Mason, Seattle, WA

Regulation of TLR Responses as a Mechanism for ITGAM Association with SLE

We know that several genes are associated with the risk of developing lupus. One of those genes is called the ITGAM gene, and three variants, or mutations, in this gene have been specifically linked with an increased risk of lupus. This gene encodes for a protein found on the surface of white blood cells called macrophages. The protein helps control the amount of inflammatory proteins that macrophages release when fighting an infection.

With their grant, Dr. Hamerman and her team plan to investigate whether the ITGAM protein produced from lupus-related ITGAM genes have a defect in their ability to regulate inflammation and, if so, if this defect is a potential mechanism for the increased risk of disease. To address this question, they plan to examine mouse macrophages that do not express ITGAM and compare their inflammatory response to normal mouse macrophages. They will also express the variants of ITGAM associated with human SLE in mouse macrophages and measure how these variants affect the magnitude of the inflammatory response.

What this study means for people with lupus: These studies may help define one mechanism by which ITGAM variants increase susceptibility to SLE, paving the way for new targeted therapies.

David S. Pisetsky, MD, PhD,
Duke University Medical Center, Durham, NC

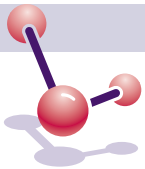
The Role of Microparticles in the Pathogenesis of SLE

Immune complexes play an important role in inducing inflammation and tissue injury in people with SLE. These complexes, which circulate in the blood, consist of antibodies to components of the cell nucleus (antinuclear antibodies or ANA) bound to DNA or RNA molecules that come from the cell nucleus.

When these complexes collect in tissue, they cause inflammation and injury, especially in the kidney. The complexes can also stimulate the production of inflammatory mediators such as interferon, which can result in the immune system changes that drive the autoimmunity of lupus. While there has been extensive investigation of ANA production, little is known about the source of the antigens themselves (which stimulate the antibody production) and how these antigens are expressed in the blood.

Recent studies from Dr. Pisetsky's laboratory suggest that the target antigens (DNA and RNA) exist within substances called microparticles that are released from dead and dying cells. With this grant, Dr. Pisetsky and his team plan to explore the theory that microparticles provide the source of molecules that eventually form lupus-stimulating immune complexes. The investigators will study how ANA binds to microparticles; analyze the number of microparticles in the blood of people with lupus; evaluate the relationship between microparticle numbers and disease activity; and define the immunological properties of microparticles that contribute to lupus.

What this study means for people with lupus: These experiments will increase our understanding of the basis of immune complex formation in lupus and, hopefully, lead to new treatments and markers of disease activity.



Functional Genomics and Molecular Genetic Pathways in SLE

This new 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.

Jane H. Buckner, MD, Benaroya Research Institute at Virginia Mason, Seattle, WA

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 women 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, La Jolla, CA

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.

Betty Diamond, MD, Feinstein Institute for Medical Research and Albert Einstein College of Medicine, New York City, NY

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, San Francisco, CA

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.

Erik J. Peterson, MD, University of Minnesota, Minneapolis, MN

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.

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.

Alliance for Lupus Research, 28 West 44th Street, Suite 501, New York, New York 10036, 800-867-1743

Alliance *for* Lupus Research

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.