

2017-18

research

PORTFOLIO SUMMARY



lupusresearch.org

The largest private funder, the Lupus Research Alliance, is driven by one central goal – to improve the lives of people living with the disease, today and in the long term. As of 2017, the organization has funded \$182 million in lupus research programs, leading to key discoveries that are improving diagnosis and treatment while pushing closer to prevention and a cure. We believe that scientific research is the most powerful way we can achieve this goal. Further, we believe that by both pushing the limits of scientific exploration and shepherding new discoveries as they evolve into potential treatments, we can best seize every opportunity to impact the lives of those with lupus. Our strategy is a coordinated effort – one that leverages resources and fosters collaboration to avoid duplication of effort and inefficiency. The Lupus Research Alliance advances under one roof the full spectrum of innovation across fundamental and translational research to clinical trials. The end goals – to speed new treatments, to prevent lupus and to ultimately cure it.



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GRANT FUNDING PROGRAMS

The **Dr. William E. Paul Distinguished Innovator Award in Lupus and Autoimmunity** provides outstanding scientists with substantial support (\$1 million) for up to four years to conduct novel research into the fundamental causes of systemic lupus erythematosus and so provide new directions towards a cure. We welcome novel, hypothesis- or discovery-driven proposals in human and/or animal-model based lupus research. The research proposal must aim to uncover the fundamental causes of lupus and present a compelling vision of how the discovery would lay the groundwork for a cure, prevention, or a highly effective therapy. Applications are judged primarily on the novelty and potential of the research proposal, and the strengths and track record of the investigator. Emphasis will be on the rationale for the hypothesis rather than the amount of preliminary data. Continuations of long-term research projects will not be considered. Successful applicants will be outstanding investigators who have demonstrated creativity and productivity in their field of research. We encourage applications from investigators in diverse disciplines including, but not limited to, immunology, genetics, molecular-, cell- and systems biology.

The **Novel Research Grant (NRG)** program provides early stage support with three-year \$300,000 grants for high-risk, high-reward, idea-driven, novel research projects relevant to basic, translational or clinical investigation in lupus. Exceptionally creative and innovative, projects advance novel scientific hypotheses in lupus, aim to stimulate investigation of underexplored pathways, and initiate transformative discoveries that can drive the development of safer and more effective treatments. Open to the global research community, the Novel Research Grants foster

investigations into the fundamental mechanisms of lupus and its complications, explorations of novel targets and pathways, and novel technologies. Applications from investigators in diverse disciplines, including those who may not have worked in lupus previously are encouraged. The Novel Research Grants mechanism also encourages projects based on novel explorations of lupus biology – including innovative studies that use human material.

The **Target Identification in Lupus (TIL)** grant program provides \$600,000 grants for up to three years to: (1) characterize key steps in the pathogenesis of the disease that will allow for the development of new therapeutic agents; (2) promote basic and clinical research studies to identify and/or better characterize promising lead compounds for lupus treatment; and (3) support research that facilitates the clinical evaluation of innovative approaches to the prevention or treatment of lupus and its complications. This research is intended to be highly focused on lupus and, as such, should lead directly to knowledge that will facilitate drug discovery and/or testing of new treatments. These therapies may be used to treat systemic or organ-specific manifestations of lupus, although they may find applicability in the setting of other autoimmune or inflammatory illnesses. As the goal of this program is to advance the treatment of lupus, any research funded must be based on realizable goals for translation into therapeutic discovery programs. Targets can include small molecules, biologic agents, vaccines, gene therapy, as well as novel approaches in public health and risk reduction. We welcome applications proposing research that will apply knowledge gained in other disease areas (e.g. cancer, metabolic diseases) to mechanisms relevant to lupus.

If you have questions about any of the Lupus Research Alliance grant mechanisms, please contact Diomaris Gonzalez, Director of Grant Programs at dgonzalez@lupusresearch.org or 212-218-2840.



2017 DIA GRANTEES

Michael Carroll, PhD

Children's Hospital Boston,
Boston, MA

Dysregulation of Interferon Signaling in Neurons Triggers CNS
lupus

John Mountz, MD, PhD

The University of Alabama at Birmingham,
Birmingham, AL

B-cell Control Point Dysregulation in African Americans in SLE

2016 DIA GRANTEES

Shu Man Fu, MD, PhD

University of Virginia, Charlottesville, VA

Local Factors Contributing to Pathogenesis of Proliferative
Lupus Nephritis

Boris Reizis, PhD

New York University School of Medicine,
New York, NY

Origin, Regulation and Therapeutic Targeting of Extracellular
DNA

2015 DIA GRANTEES

Tanya N. Mayadas, PhD

Brigham and Women's Hospital and Harvard
Medical School, Boston, MA

IgG glycans, FcγRs and Renal Elements Dictate Antibody
Pathogenicity in SLE

Eric Morand, MD, PhD

Lupus Clinic at Monash Health, Australia

GILZ: Glucocorticoid mediator, B cell regulator, and Lupus
Target

2014 DIA GRANTEES

Zhijian 'James' Chen, PhD

University of Texas Southwestern Medical Center,
Dallas, TX

Roles of the cGAS Pathway in Lupus

Douglas Green, PhD

St. Jude Children's Research Hospital, Memphis, TN

Non-canonical Autophagy, Phagocytosis, and SLE

Randolph Noelle, PhD

Dartmouth College, Hanover, NH

Targeting the VISTA pathway Prevents Fatal Systemic Lupus

2017 TIL GRANTEES

Roberto Caricchio, MD

Temple University, Philadelphia, PA
The Role of Bacterial Infections in the Pathogenesis of Lupus

Laura Carrel, PhD

The Pennsylvania State University College of Medicine, Hershey, PA
Targeting the Inactive X chromosome in Lupus

Katherine A. Fitzgerald, PhD

University of Massachusetts Medical School, Worcester, MA
Characterization of STING SAVI Gain of Function Mutations in Mice

Chandra Mohan, MD, PhD

University of Houston, Houston, TX
ALCAM in Lupus

Peter A. Nigrovic, MD

Brigham and Women's Hospital, Boston, MA
Defining New Targets in Lupus Through Identification Of Non-Coding SNPs

Janos Peti-Peterdi, MD, PhD

USC/University of Southern California Los Angeles, CA
Targeting Endogenous Glomerular Repair in Lupus Nephritis

Betty Tsao, PhD

Medical University of South Carolina Charleston, SC
Finding Druggable Pathways Affected by the R90H-NCF1 SLE Risk Variants

2016 TIL GRANTEES

Anne Davidson, MBBS

The Feinstein Institute for Medical Research, Manhasset, NY
The Role of TLR8 in Lupus Nephritis

Rong Fan, PhD

Yale University, New Haven, CT
Dissecting the Effector Function of Pathogenic Tfh Cells in Human Lupus

Roger Greenberg, MD, PhD

University of Pennsylvania, Philadelphia, PA
BRISQ DUB Activity as a Novel Target for Lupus

Ming-Lin Liu, PhD

University of Pennsylvania Health System, Philadelphia, PA
A Novel Target for Neutrophil NETosis in Lupus Skin Inflammation

Mark J. Mamula, PhD

Yale University, New Haven, CT
Therapeutic Inhibitors of Antigen Presentation Pathways in SLE

Laurence Morel, PhD

University of Florida, Gainesville, Gainesville, FL
Targeting Follicular Helper CD4 T Cells in SLE

Kerstin Nündel, PhD

University of Massachusetts Medical School, Worcester, MA
TLR9 Regulates Axl Dependent Migration of Autoreactive B Cells



2015 TIL GRANTEES

Michael Carroll, PhD

Children's Hospital, Boston, MA

Investigating the Mechanisms of Lupus-associated CNS Dysfunction

Joseph Craft, MD

Yale University, New Haven, CT

Characterization and Function of CD4 T Cell Subsets in Lupus

Lindsey Ann Criswell, MD, MPH

University of California, San Francisco, CA

The Contribution of Epigenetics to SLE Phenotype and Outcome

Keith Elkou, MD

University of Washington, Seattle, WA

The Cyclic GAMP Pathway in SLE

Charles 'Garry' Fathman, MD

Stanford University, Palo Alto, CA

Understanding the MoA of Low Dose IL-2 as a Potential Therapy for SLE

Shu Man Fu, MD, PhD

University of Virginia, Charlottesville, VA

IL-2 and IL-33 as Therapeutic Agents for Lupus Nephritis

Wael Jarjour, MD

The Ohio State University, Columbus, OH

Jian Zhang, MD

University of Iowa, Iowa City, IA

Regulation of T Follicular Helper Cells in SLE by E3 Ubiquitin Ligase Cbl-b

Caroline Jefferies, PhD

Cedars-Sinai Medical Center, Los Angeles, CA

Estrogen-dependent MicroRNAs as Potential Targets for the Treatment of SLE

Maria Kontaridis, PhD

Beth Israel Deaconess Medical Center, Boston, MA

Role for SHP2 as a Therapeutic Target for Systemic Lupus Erythematosus

Michele Kosiewicz, PhD

University of Louisville Research Foundation, Inc., Louisville, KY

Sex and Microbiota Influence on Immunoregulation and Disease in BWF1 Mice

Carla Rothlin, PhD

Yale University, New Haven, CT

Protein S: At the Crossroads of Thrombosis and Inflammation in SLE

William Stohl, MD, PhD

USC/University of Southern California, Los Angeles, CA

Therapeutic Targeting of FcγRIIb on B cells in SLE

Betty Tsao, PhD

Medical University of South Carolina, Charleston, SC

Targeting IL-10 Producing B cells in SLE

Sheng Xiao, PhD

Brigham and Women's Hospital Boston, MA

Role of Tim-1 in Kidneys During Lupus

Nan Yan, PhD

UT Southwestern Medical Center, Dallas, TX

Glycans and Glycosylation Defects as Novel Targets in Lupus

2018 NRG GRANTEES**Andre Ballesteros-Tato, PhD**

University of Alabama at Birmingham,
Birmingham, AL

Immunotargeting of T Follicular Helper (Tfh) Cells for SLE Treatment

Betsy Jo Barnes, PhD

The Feinstein Institute for Medical Research,
Manhasset, NY

Unexpected Role(s) for IRF5 Risk Variants in SLE Pathogenesis

Jason S. Knight, MD, PhD

University of Michigan, Ann Arbor, MI

Neutrophil Elastase as a Therapeutic Target in Lupus

Frances E. Lund, PhD

University of Alabama at Birmingham,
Birmingham, AL

Characterization of Chemokine Producing Effector B Cells in SLE

Keisa Williams Mathis, PhD

University of North Texas Health Science Center at
Fort Worth, Fort Worth, TX

Targeting Nicotinic Receptors to Reduce Inflammation Associated With SLE

Laurence Morel, PhD

University of Florida, Gainesville, FL

Targeting Immunometabolism and Co-stimulation in Combination Therapies in Lupus

Alessandra B. Pernis, MD

The Hospital for Special Surgery, New York, NY

Regulation of CD11c+Tbet+ B Cells in Lupus

Ziaur Rahman, MD, PhD

Pennsylvania State University College of Medicine,
Hershey, PA

Mechanisms of the Autoimmune Germinal Center Response in SLE

Amr Sawalha, MD

University of Michigan, Ann Arbor, MI

Targeting EZH2 in Lupus

2017 NRG GRANTEES**Mridu Acharya, PhD**

Benaroya Research Institute at Virginia Mason,
Seattle, WA

Autophagy Components and B cell Activation during SLE

Natalia Giltiy, PhD

University of Washington, Seattle, WA

Anti-BDCA 2-Targeted Therapy for SLE

Shaun Jackson, MD, PhD

Seattle Children's Hospital, Seattle, WA

B Cell-Intrinsic Cytokine Reg of Spontaneous Germinal Ctr Formation in SLE

Andrea Knight, MD

The Children's Hospital of Philadelphia, PA

Multi-level Biomarkers for Psychiatric Disorders in Pediatric Lupus

Vipin Kumar, PhD

University of California, San Diego, CA

Targeting Type II NKT cells for a Novel Therapeutic in Lupus

Christian Lood, PhD

University of Washington, Seattle, WA

Impaired Mitochondrial Clearance in Systemic Lupus Erythematosus

Anthony Rongvaux, PhD

Fred Hutchinson Cancer Research Center,
Seattle, WA

Mitochondria, Caspases and Type I Interferons in Autoimmunity

Guo-Ping Shi, DSc

Brigham and Women's Hospital, Boston, MA

Cathepsin S Inhibitor-modified Treg cells Mitigate Murine SLE

John Zhang, DVM, PhD

Medical University of South Carolina, Charleston, SC

A Novel Approach for Treating Lupus by Inhibiting Fli1 Transcription Factor

Zhiqiang Zhang, PhD

The Methodist Hospital Research Institute,
Houston, TX

Oxidized Mitochondrial DNA Employs APEX1 in Neutrophils to Control Lupus

2016 NOVEL GRANTEES

Vikki M. Abrahams, PhD

Yale University, New Haven, CT
Role of Infection in Obstetric Antiphospholipid Syndrome

Julio A. Camarero, PhD

USC/University of Southern California,
Los Angeles, CA
Therapeutic Selective Targeting of BAFF Receptors

Lindsey Ann Criswell, MD, MPH

University of California, San Francisco, CA
Pesticides and Chemical Exposures, DNA Methylation, and SLE Phenotypes

Stefania Gallucci, MD

Temple University, Philadelphia, PA
Bacterial Amyloids from Biofilms Break Tolerance in Lupus

Lee Ann Garrett-Sinha, PhD

The Research Foundation for The SUNY on behalf
of University at Buffalo, NY
Understanding the Pathway Regulated by the Lupus
Susceptibility Gene Ets1

Hui-Chen Hsu, PhD

The University of Alabama at Birmingham, AL
Repopulation of Tolerogenic B Cells Post B Cell Depletion
Therapy in Lupus

Laura Mandik-Nayak, PhD

Lankenau Institute for Medical Research,
Wynnewood, PA
IDO2, a Novel Therapeutic Target for the Treatment of Lupus

Timothy B. Niewold, MD

New York University School of Medicine
New York, NY
Tolerogenic Dendritic Cells in Human Lupus

Robert Hal Scofield, MD

The University of Oklahoma Health Sciences
Center, Oklahoma City, OK
Sex Disparity in Lupus is Driven by Putative X-Linked Genes

Barbara J. Vilen, PhD

The University of North Carolina at Chapel Hill, NC
Cross Sectional and Longitudinal Studies of Immune
Complexes in SLE

Matthew T. Weirauch, PhD

Cincinnati Children's Hospital Medical Center –
Research Foundation, Cincinnati, OH
A Free Website for Discovering Non-Coding Lupus-Associated
Variant Function

Tianfu Wu, PhD

University of Houston, TX
PLK1, a Potential Novel Therapeutic Target for Lupus

SUMMARIES OF CURRENT RESEARCH

2017 DIA RESEARCH SUMMARIES**Michael Carroll, PhD**

Children's Hospital Boston

Dysregulation of Interferon Signaling in Neurons Triggers CNS lupus

Dr. Carroll is studying why and how lupus attacks the brain and central nervous system (CNS). CNS lupus refers to neuropsychiatric issues experienced by many people with lupus, including headaches, confusion, depression, and memory and vision problems as well as seizures, strokes or changes in behavior. Dr. Carroll discovered a link between CNS lupus and a loss of "synapses"—or the connections between nerves that allow the flow of information in the brain, much like bridges allow cars to pass from one stretch of roadway to the next. Importantly, the synapse bridges that are destroyed in lupus are in a specific area of the brain that controls behavior.

A major breakthrough for understanding CNS lupus, Dr. Carroll found that an antibody that blocks interferon, a key molecule of the immune system, could prevent CNS lupus by defending these synapses from attack. With his Distinguished Innovator Award, Dr. Carroll will investigate why these particular synapses are destroyed in lupus and how shutting off interferon could protect against damage to the central nervous system.

What this study means for people with lupus

The study is transformative as it not only suggests a new approach to treatment, but also provides a mechanism for tracking the disease in people with lupus.

John Mountz, MD, PhD

The University of Alabama at Birmingham

B-cell Control Point Dysregulation in African Americans in SLE

Dr. Mountz is investigating a new explanation for how lupus develops and the reason some people are at greater risk for flares and kidney disease. He found that patients with high levels of the molecule interferon beta (IFN- β) within their early developing ("baby") B cells (the immune cells that grow to become autoantibody-producing cells) are more likely to have higher levels of autoantibodies and kidney disease. Among those individuals, African American patients, who are disproportionately affected by lupus, had higher levels IFN- β in these cells compared to Caucasian patients. Dr. Mountz will use his Distinguished Innovator Award to determine if the high level of IFN- β production within these baby B cells causes them to grow into adult autoantibody-producing B cells that trigger lupus.

What this study means for people with lupus

The results of Dr. Mountz' study will form a solid foundation to develop treatments that block IFN- β for use in people with lupus and the identification of biological markers to identify lupus patients, especially among the African American population, at high risk of flares and kidney disease, who may respond to interferon therapies.

2016 DIA RESEARCH SUMMARIES**Shu Man Fu, MD, PhD**

University of Virginia

Local Factors Contributing to Pathogenesis of Proliferative Lupus Nephritis

Dr. Fu's work hopes to turn traditional views on lupus nephritis upside down and could change how it is treated dramatically. He hypothesizes that the kidney itself can drive kidney disease, not as a complication of systemic lupus, but as an independent process. His team has shown that kidney cells help promote development of kidney failure because they release molecules such as C1q, a protein that helps activate a part of the immune system.

What this study means for people with lupus

Dr. Fu's study aims to reveal how these C1q molecules released by kidney cells determine which patients develop kidney failure. They hope to identify whether targeting C1q offers a potential therapy and if measuring the levels of this molecule in the urine can help diagnose severity of kidney damage and monitor response to treatment.

Boris Reizis, PhD

New York University School of Medicine

Origin, Regulation and Therapeutic Targeting of Extracellular DNA

Dr. Reizis and his team are pursuing a novel idea that could explain what causes lupus, why flares develop, and how a treatment might be developed to prevent the attack. It has been shown that billions of cells die every day in our blood and release their DNA packaged into small containers called microparticles. They believe that the abnormal buildup of DNA in these microparticles can cause the immune attack to begin and that the microparticles may provide vehicles for the DNA to travel throughout the body, causing the immune system to attack specific organs in their wake.

What this study means for people with lupus

Dr. Reizis will study how the DNA-carrying microparticles form and how the body normally gets rid of this DNA. They also plan to develop techniques that eliminate this DNA to provide a basis for future lupus treatments.

2015 DIA RESEARCH SUMMARIES

Tanya N. Mayadas, PhD

Brigham & Women's Hospital and Harvard Medical School

IgG Glycans, Fcgrs and Renal Elements Dictate Antibody Pathogenicity in SLE

Lupus occurs when antibodies called autoantibodies deposit in tissues and serve as a stimulus for the white blood cells of your body to mistakenly attack the body's own healthy cells or tissues. In 30 to 60 percent of lupus patients, autoantibodies will accumulate in the kidneys causing lupus nephritis, one of the most severe manifestations of lupus that causes inflammation in the organ and can lead to kidney failure. However, autoantibody deposits do not necessarily induce kidney inflammation. Dr. Mayadas proposes to identify those characteristics that make certain autoantibodies more likely to cause lupus nephritis. She and her team will specifically research why and how autoantibodies accumulate in some lupus patients but not others, and determine the autoantibody characteristics that promote white blood cell accumulation, thus providing a basis for therapies designed to prevent kidney disease.

What this study means for people with lupus

Dr. Mayadas and her team aim to identify specific characteristics of circulating autoantibodies that make them more likely to trigger inflammation in the kidney and cause renal damage. They will also investigate why and how autoantibodies accumulate in some lupus patients but not others, providing a basis for therapies designed to prevent kidney disease.

Eric Morand, MD, PhD

Lupus Clinic at Monash Health

GILZ: Glucocorticoid Mediator, B Cell Regulator, and Lupus Target

Glucocorticoids are a type of steroid used to treat over 70 percent of lupus patients to reduce the immune response and the resulting inflammation. Unfortunately, glucocorticoids have very severe side effects including possible permanent organ damage and an increased risk of death, so safer treatments are urgently needed. Dr. Morand recently discovered a protein called GILZ that is produced by glucocorticoids and reduces inflammation when activated. With GILZ there appears to be none of the side effects usually associated with steroids, and the protein appears to play a very specific role in lupus, acting only on B cells (a type of white blood cell). In this research, Dr. Morand will improve our understanding of the role of GILZ in the immune system with the goal of using it as a new therapeutic target.

What this study means for people with lupus

Dr. Morand and his team have discovered a protein GILZ that may be a factor in causing lupus. If so, they will investigate if

GILZ is a target for a safer therapy to replace the widely used steroids which can cause severe side effects that contribute to permanent organ damage and increased mortality.

2014 DIA RESEARCH SUMMARIES

Zhijian 'James' Chen, PhD

UT Southwestern Medical Center

Roles of the cGAS pathway in Lupus

Lupus patients commonly have elevated levels of interferon, proteins that signal the presence of pathogens such as viruses, parasites or bacteria, and autoantibodies, antibodies which mistakenly attack good cells, that are targeted at DNA. This suggests that abnormal stimulation of the interferon pathway – which helps regulate the immune system's response to foreign invaders – plays a significant role in lupus. Recently, their lab discovered a new enzyme called cGAS. When activated by attaching to DNA, the enzyme starts a chain of events that eventually induces the production of interferons and other molecules that stimulate the immune system. Dr. Chen proposes that activation of the cGAS pathway may be a major cause of lupus and that compounds that block cGAS activity may be developed into effective drugs for the treatment of lupus. His study aims to determine if cGAS could be used as a potential target for a new lupus medicine.

What this study means for people with lupus

Dr. Chen's team has discovered an essential new process that alerts the immune system to viruses by sensing the presence of 'foreign DNA within cells'. With the Distinguished Innovator Award, they will explore their hypothesis that this pathway malfunctions in lupus, causing the immune system to attack its own DNA.

Douglas Green, PhD

St. Jude Children's Research Hospital

Non-canonical Autophagy, Phagocytosis, and SLE

SLE may be caused, in part, by a failure to properly dispose of cells that die in our bodies every day. Dr. Green and team have found a process they call LAP that functions in the disposal of dying cells that are eaten by macrophages. Mice that have macrophage defects in LAP develop lupus-like disease with age. Dr. Green's team will study how LAP serves to prevent disease and develop ways to restore the control of autoimmunity to cells and animals with these defects. This will pave the way to novel treatment strategies for SLE.

What this study means for people with lupus

Dr. Green will investigate whether a new pathway he and his team discovered that safely disposes of dead cells goes awry in lupus, causing the immune system to attack the body's cells and tissues. His team will apply their innovative approach to the treatment of lupus in animal models, which will lead the way to new strategies for treating lupus in patients.

Randolph Noelle, PhD

Dartmouth College

Targeting the VISTA Pathway Prevents Fatal Systemic Lupus

In lupus, the immune system mistakenly attacks patients' own cells. Dr. Noelle's team discovered a molecule called VISTA that serves as an "off" switch for the immune system and thus might provide a way to quell these attacks. They have found that certain mouse proteins termed antibodies flip the VISTA switch and turn down the immune system in mice. They now want to take the next step toward using VISTA to treat lupus.

What this study means for people with lupus

Dr. Noelle's group will test whether human antibodies work in mice that carry the human version of VISTA, which will give us a better indication of whether the antibodies will work in lupus patients. They also want to determine how these antibodies affect the immune system.

2017 TIL RESEARCH SUMMARIES**Roberto Caricchio, MD**

Temple University

The Role of Bacterial Infections in the Pathogenesis of Lupus

With his TIL grant, Dr. Roberto Caricchio is studying whether usually harmless, common bacterial infections, such as urinary tract infections, might be an environmental trigger of lupus onset and flares in genetically at-risk individuals. Normally, a bacterial infection sets off the immune system to make antibodies and take other actions to fight off the invading bacteria. Dr. Caricchio's theory is that in people who are susceptible to lupus, those infections also cause the immune system to make antibodies that recognize and attack a person's own body. Dr. Caricchio will look specifically at urinary tract infections (UTIs) in people with and without lupus. Some bacteria that cause UTIs produce a protein called "curli" that can bind to DNA and form a compound that triggers lupus in mouse models.

What this study means to people with lupus

Preliminary evidence shows that individuals with lupus have antibodies against this curli/DNA compound. Dr. Caricchio will investigate whether curli/DNA antibodies can predict lupus in at-risk people and if UTIs in people who have lupus create curli/DNA compounds in their blood that cause flares. This exciting research could open a new avenue of approaches to treat and even prevent lupus.

Laura Carrel, PhD

The Pennsylvania State University College of Medicine

Targeting the Inactive X Chromosome in Lupus

Lupus affects nine times more women than men. One explanation for this phenomenon lies in the difference between women's and men's chromosomes, the long pieces of DNA within each cell that contain our genes lined up one after the other, like recipes in a cookbook. Biologically women have two X chromosomes, while men have one X and one Y chromosome. Dr. Laura Carrel is investigating how this difference in the number of X chromosomes might cause women to be more susceptible to lupus than men. Normally, in a woman's cells, the genes on one of her X chromosomes are active and those on the other are turned off or inactive. But Dr. Carrel has shown that in all women, about 10% of genes on the "inactive" X chromosome escape from the inactivation process and are actually active. She hypothesizes that the level of gene activity on the inactive chromosome might be even higher in women with lupus. To test this theory, Dr. Carrel will study the immune cells of women with and without lupus to find X chromosome genes that are more active in women with lupus.

What this study means to people with lupus

This research project will help us understanding the biology of lupus and point to new targets for drug discovery.

Katherine A. Fitzgerald, PhD

University of Massachusetts Medical School

Characterization of STING SAVI Gain of Function Mutations in Mice

SAVI (STING-associated vasculopathy with onset in early infancy) is a disease caused by a mutation in the gene that makes a protein called STING. In patients with SAVI, the STING protein is locked in its "on" position, causing immune cells to be constantly active. These active immune cells create inflammation that damages tissues throughout the body in a manner that is similar in many respects to lupus. While lupus is caused by more complex genetic and environmental factors than SAVI, the STING pathway may also play a role in lupus. Dr. Katherine Fitzgerald is exploring how the mutant STING protein goes rogue to trigger the lupus-like symptoms in mice.

What this study means to people with lupus

By focusing on the simpler model system of a single-gene disease like SAVI, Dr. Fitzgerald will gain new information about the STING pathway that can be applied to develop new treatment approaches for SAVI and lupus patients.

Chandra Mohan, MD, PhD

University of Houston

ALCAM in LUPUS

Lupus nephritis (kidney disease) is one of the most serious complications of lupus. With the TIL grant support, Dr. Chandra Mohan will build on his existing discoveries to evaluate a potential new therapeutic target for lupus nephritis. In comparing the levels of 1,100 proteins in the urine of lupus patients and healthy controls, Dr. Mohan already found several differences, and one in particular stood out. The protein ALCAM (activated leukocyte cell adhesion molecule) was consistently higher in those with lupus compared to the controls. ALCAM is a small molecule on the outside of T cells of the immune system that helps the T cells move through the tissues of the body, including the kidney.

What this study means to people with lupus

Dr. Mohan will now find out how ALCAM is involved in lupus nephritis and evaluate whether it is a good target for new drug development to prevent or treat the complication.

Peter A. Nigrovic, MD

Brigham and Women's Hospital

Defining New Targets in Lupus Through Identification of Non-Coding SNPs

Scientists have found more than 50 regions of DNA that contribute to lupus risk. At least 35 of these DNA regions regulate gene activity—they serve as magnets that attract proteins, which in turn, act as control switches that determine whether a gene is more or less active. Variations in gene activity influence a person's biology—for example, whether they are more or less likely to develop a disease like lupus. The TIL grant will enable Dr. Peter Nigrovic to study each of these 35 DNA control centers to determine how they contribute to lupus risk. Dr. Nigrovic will identify the proteins that interact with the DNA regions using state-of-the-art technologies.

What this study means to people with lupus

Once the control proteins are known, he will be able to build up a more complete picture of the genes and biological pathways that cause lupus. This line of research is expected to discover new targets for treatments to prevent or cure lupus.

Janos Peti-Peterdi, MD, PhD

USC/University of Southern California, Los Angeles

Targeting Endogenous Glomerular Repair in Lupus Nephritis

Dr. Janos Peti-Peterdi studies what goes wrong with the kidneys in people with lupus and how kidneys damaged by lupus can be repaired. He has developed a pioneering research technique, known as "intravital imaging," to use a highly sensitive microscope to directly examine in fine detail the kidneys in an animal model of lupus. He will also test two potential treatments for lupus nephritis and observe whether they are effective at repairing the kidneys by regenerating damaged cells.

What this study means to people with lupus

Using the insights and data gained as a springboard, Dr. Peti-Peterdi will then focus his research on patients with lupus nephritis to find ways to help their kidneys heal. This research project promises to improve treatment of lupus nephritis for the benefit of all patients with this serious complication.

Betty Tsao, PhD

Medical University of South Carolina

Finding Druggable Pathways Affected by the R90H-NCF1 SLE Risk Variants

Dr. Betty Tsao found a mutation in a specific gene, NCF1, that predicts increased risk for several autoimmune diseases, including lupus. The mutation causes a reduction in the amount of reactive oxygen species (ROS), small chemicals that contain oxygen and other elements that are formed as a normal byproduct of the body's metabolism. Hydrogen peroxide is one example of an ROS. Interestingly, ROS are normally thought of as troublemakers in the body, causing stress and tissue damage that contribute to many diseases, as well as signs of aging. To understand why a reduction in ROS might lead to lupus, Dr. Tsao will create an animal model with the mutated NCF1 gene.

What this study means to people with lupus

This model will allow her to understand how reduced ROS affects immune system cell function. Ultimately, Dr. Tsao expects to find new targets in the NCF1/ROS pathway for drug development to prevent or treat lupus.

2016 TIL RESEARCH SUMMARIES

Anne Davidson, MBBS

The Feinstein Institute for Medical Research

The Role of TLR8 in Lupus Nephritis

Dr. Davidson has discovered that one immune system protein, TLR8, may help foster lupus nephritis, the kidney inflammation that is a leading cause of illness and death in lupus patients. By using lupus-prone animals in which they have introduced the human TLR8 protein, they will investigate whether higher amounts of TLR8 induce inflammation and worsen kidney deterioration. They will also determine how the extra amounts of TLR8 regulate the function of kidney-resident immune cells that accelerate lupus nephritis. Drugs to block proteins that are related to TLR8 are already under development, and the study could indicate whether creating drugs to block TLR8 is worthwhile.

What this study means to people with lupus

Dr. Davidson's new Lupus Research Alliance-funded project promises to help illuminate how lupus leads to kidney damage and why the disease is more common in women than in men. The results may help the pharmaceutical and biotech industries decide which proteins to target with potential treatments.

Rong Fan, PhD

Yale University

Dissecting the Effector Function of Pathogenic Tfh Cells in Human Lupus

Immune system cells communicate with each other by releasing chemicals known as cytokines. Dr. Fan and his team have created a microchip that allows us to eavesdrop on immune cells by measuring what cytokines they are producing. They will use this microchip to analyze blood cells from lupus patients. They plan to profile a type of T cell that promotes the tissue destruction of lupus, determining which cytokines these cells release and how they respond to treatment.

What this study means for people with lupus

Dr. Fan and his team developed a microchip that can monitor the biomolecules released by immune cells. They anticipate that the chip will reveal how one type of T cell triggers tissue damage in lupus and provide clues about how to prevent it.

Roger Greenberg, MD, PhD

University of Pennsylvania

BRISC DUB Activity as a Novel Target for Lupus

Dr. Greenberg and his colleagues have discovered that mice that lack a certain cluster of interacting proteins, known as BRISC, don't develop lupus. Their previous research identified several molecules that block BRISC and might be able to quell lupus symptoms. They now plan to test whether these molecules are beneficial in mice that develop the disease. They will also fine-tune the molecules to make them more effective, with the hope that they will lead to new therapies for the disease.

What this study means for people with lupus

Dr. Greenberg has identified a new culprit in lupus, a group of interacting proteins. He and his team are developing molecules that will block these proteins, which could lead to new treatments for lupus.

Ming-Lin Liu, PhD

University of Pennsylvania Health System

A Novel Target for Neutrophil NETosis in Lupus Skin Inflammation

Lupus patients develop skin rashes in response to sunlight and other triggers. Immune cells called neutrophils promote these lesions by spewing out their DNA. Dr. Liu has discovered that a protein known as ROCK is crucial to this process. She and her team will now test whether blocking ROCK stops neutrophils from releasing their DNA, thereby reducing skin inflammation in mice that are prone to lupus. The results of their study could suggest new ways to reduce skin rashes in lupus patients.

What this study means for people with lupus

Skin rashes are common in lupus patients. Dr. Fan's research will ask whether preventing certain immune cells from releasing their DNA curbs skin inflammation.

Mark J. Mamula, PhD

Yale University

Therapeutic Inhibitors of Antigen Presentation Pathways in SLE

B cells are doubly destructive in lupus. They can directly stimulate T cells to attack patients' own tissues. Dr. Mamula has found that they also indirectly trigger T cell attacks by interacting with other immune cells. Although current lupus drugs can prevent B cells from directly stimulating T cells, they do not stop B cells from interacting with other immune cells. The goal of his research is to discover molecules that thwart B cells' indirect effects on the immune system and identify approaches to potential new treatments for the disease.

What this study means for people with lupus

Dr. Mamula is working to identify molecules that block one harmful impact of B cells and reduce the tissue damage triggered by these cells.

Laurence Morel, PhD

University of Florida

Targeting Follicular Helper CD4 T cells in SLE

A specific type of T cell drives the tissue damage that occurs in lupus. These cells need more energy than normal cells, and that might be their Achilles heel. Dr. Morel has found that the numbers of these T cells in mice can be reduced with common diabetes treatments such as metformin that deprive the cells of the sugar they need to survive. Now, her team plans to test whether these drugs can be used as a lupus therapy that will eliminate the problematic T cells.

What this study means for people with lupus

Dr. Morel and her group want to determine whether lupus can be treated by shutting off the food supply to immune cells that promote the disease.

Kerstin Nündel, PhD

University of Massachusetts Medical School

TLR9 Regulates Axl Dependent Migration of Autoreactive B Cells

In lupus, proteins in the immune system known as toll-like receptors help trigger the damaging effects of the disease. But one of the proteins, known as TLR9, is the black sheep of the toll-like receptor family—it reduces the severity of lupus symptoms. Dr. Nündel's research suggests that TLR9 is helpful because it prevents immune cells known as B cells from moving into tissues where they can cause injury. She now wants to uncover how TLR controls B cells' movements and identify an approach for treatment that can stop their migration.

What this study means for people with lupus

The immune system is the villain in lupus, but one immune system protein appears to protect patients' cells. Dr. Nündel seeks to find out how and whether this insight can lead to a potential treatment.

2015 TIL RESEARCH SUMMARIES

Michael Carroll, PhD

Children's Hospital Boston

Investigating the Mechanisms of Lupus-associated CNS Dysfunction

Various neuro-psychiatric symptoms appear in lupus patients, and the underlying causes of these symptoms have not been well studied. It is clear that some neuro-psychiatric symptoms appear early during the course of the illness. The timing of their appearance may offer clues as to the biochemical alterations associated with the development of these early symptoms. Notably, studies in a mouse model of lupus suggest that certain neuro-psychiatric symptoms appear prior to detectable changes in brain chemistry. Recently, Dr. Carroll found that in this lupus mouse model early onset neuropsychiatric symptoms are accompanied by the presence of key immune signaling molecules (cytokines) that are known to regulate certain neuron functions in adults. It is possible that the behavior of these cytokines is, in turn, influenced by lupus-specific components of the immune system. These components (autoantibodies) mistakenly work against patients' own tissues or cells. Such autoantibodies are produced by immune system cells (B cells). Dr. Carroll's preliminary studies have already identified a cytokine (IFN- α) that contributes to the development of neuro-psychiatric symptoms in a mouse model of lupus. In the current study, Dr. Carroll will investigate the hypothesis that cytokines induced by lupus-specific autoantibodies trigger nerve dysfunction. He will also explore how one of the earliest events in the development of lupus, the breakdown of B cell tolerance, impacts the nervous system.

What this study means for people with lupus

The neuropsychiatric symptoms associated with lupus are complex, and as the disease progresses both these symptoms and the biological changes underpinning these symptoms change. Dr. Carroll's research holds the long-term goal of identifying novel therapeutic targets for some neuropsychiatric manifestations of the disease. Using a mouse model of the illness, Dr. Carroll is seeking to generate scientific knowledge that in the future could be used to develop lupus treatments.

Joseph Craft, MD

Yale University

Characterization and Function of CD4 T Cell Subsets in Lupus

CD4 T helper (Th) cells are white blood cells that help to combat invading germs. In people with lupus, however, these cells are regulated improperly and play a central role in causing the harm associated with the illness. How these cells influence the lupus disease process has not yet been adequately characterized, although CD4 Th cells are

implicated in the inflammation associated with lupus. Dr. Craft suspects that understanding the biochemical signals that lead to damaging CD4 Th cell activities in people with lupus will, in turn, bring scientists closer to elucidating relevant disease pathways. Working with both a lupus mouse model and cells derived from lupus patients, he will seek to uncover key cellular and molecular signals affecting types of inflammation relevant to lupus. He will do this by probing the role of CD4 Th cells called Th1 and follicular helper (Tfh) cells in causing harm in lupus. So, Dr. Craft is seeking to gain greater understanding of specific cells that, for poorly understood reasons, may be directed against patients' own cells and tissues, leading to disease symptoms.

What this study means for people with lupus

Dr. Craft is attempting to characterize the activities of certain cells that play a key role in promoting inflammation in lupus. Once disease pathways have been better characterized, new, effective therapies might be developed while existing therapies might be better directed to appropriate targets. Thus, his longer-term goal is to identify new therapeutic targets and to optimize the use of current therapies.

Lindsey Ann Criswell, MD, MPH

University of California, San Francisco

The Contribution of Epigenetics to SLE Phenotype and Outcome

The essential genetic structure – in other words, the DNA sequence of a cell – may remain unchanged while, at the same time, multiple factors, including environmental factors, may lead to long-term changes in the expression of a cell's genes. Epigenetics is the area of biology that studies such processes and activities. Accumulating evidence points to the role of epigenetic changes in autoimmune diseases, including lupus. The link between a person's susceptibility to developing lupus and environmental factors may reside (in part at least) in epigenetic activity. In addition, the study of epigenetics may provide clues as to why specific treatments are most effective in subsets of lupus patients. Previously, Dr. Criswell had completed preliminary studies demonstrating that people with severe lupus symptoms and people with mild lupus symptoms exhibit different patterns of epigenetic changes. Dr. Criswell's current research project aims (1) to use data from an ongoing longitudinal study and to apply a novel methodology to determine which specific cell subpopulation(s) are responsible for epigenetic differences between lupus patients with severe versus mild disease. She will simultaneously explore whether epigenetic changes influence response to treatment. In addition, she will (2) further characterize epigenetic changes associated with lupus by exploring correlations with levels of gene expression. She will study quantitative gene expression patterns.

What this study means for people with lupus

Dr. Criswell's overall goal for this project is to define the mechanisms through which differences in epigenetic alterations influence the pattern and severity of symptoms in individual lupus patients and certain types of lupus patients. Further, it is known that several medications currently approved to treat other illnesses successfully target epigenetic mechanisms; and Dr. Criswell would like to determine if some of these medications might provide benefit to lupus patients. (And, if so, the fact that these medicines are known to be safe and have been approved by the Food and Drug Administration (FDA) as therapies for other illnesses should hasten their availability as therapies for lupus.)

Keith Elkon, MD

University of Washington

The Cyclic GAMP Pathway in SLE

Researchers have recently identified a previously unknown pathway involved in the production of type 1 interferons – powerful stimulators of the immune system – which plays a role in the development of lupus. This new finding demonstrated the importance of an enzyme called cGAMP synthase (cGAS). It is now known that cGAS, in turn, encourages the production of cGAMP (cyclic-GMP-AMP) and cGAMP, in turn, binds to and activates a protein named STING leading to the production of type 1 interferons. Previously, Dr. Elkon has detected activation of the cGAS pathway in some (not all) patients with lupus. Using mass spectrometry and additional approaches, he will now explore what an activated cGAS pathway means for a lupus patient. For example, are these people with early onset or late onset disease? Do they have more or less severe disease? Do they have a specific subtype of the disease? He will also investigate the specific cell types in which cGAS is activated and will explore what stimulates such activation. His research holds the potential to elucidate pathogenic mechanisms relevant to the illness. Dr. Elkon's current research has a second aim as well: laboratory experiments suggest that three drugs currently used to treat malaria might be reengineered so they can be used to inhibit the cGAS pathway. He will, initially, study the modified drugs in mouse models of lupus. These drugs are already known to have an excellent safety profile in the setting of lupus.

What this study means for people with lupus

Dr. Elkon's research seeks to, first, identify a novel biomarker for lupus, and explore what that biomarker might tell us about the disease and whether it can be implicated in some (but not all) people with the illness. And, second, his research will investigate, through mouse studies of modified drugs, whether these drugs might be safely tested in people with lupus.

Charles 'Garry' Fathman, MD**Stanford University****Understanding the MoA of Low Dose IL-2 as a Potential Therapy for SLE**

Interleukin 2 (IL-2) is one of the immune system's signaling molecules. Therapy with low dose IL-2 has proven efficacious and safe in two diseases similar to lupus: chronic graft-versus host disease (GVHD) and hepatitis C virus (HCV) vasculitis. The therapy achieves both expansion of regulatory T cells (Tregs) and diminished levels of pro-inflammatory chemicals (cytokines) in the blood of treated persons, and has been found to be safe. Tregs are able to suppress aberrant pathological immune responses and so guide the immune system not to attack healthy tissue. The mechanism of action of low dose IL-2 has not yet been fully elucidated, while it is known that this mechanism of action is related to the presence on Tregs of a specific receptor (the high affinity IL-2 receptor). The presence of this receptor permits the preferential activation of this subset of regulatory T cells (Tregs) without activation of T helper cells. Will therapy with low dose IL-2, or a related approach, prove to be effective in lupus patients?

What this study means for people with lupus

Dr. Fathman's current project seeks to elucidate the mechanism of action underlying the use of low dose IL-2 as a therapy, and to determine whether signaling cascades similar to those described can be activated in Tregs derived from lupus patients. In addition, he will search for complementary therapies that could, along with low dose IL-2, lead to the restoration of Treg function in lupus patients.

Shu Man Fu, MD, PhD**University of Virginia****IL-2 and IL-33 as Therapeutic Agents for Lupus Nephritis**

Regulatory T cells (Tregs) inhibit pro-inflammatory responses and, thus, function to suppress aberrant pathological immune responses. Tregs help guide the immune system so that it does not attack healthy tissue; therefore, Tregs have an important role in autoimmune diseases like lupus. In particular, Tregs help to modulate lupus nephritis. Dr. Fu has developed a novel hybrid molecule that targets Tregs. This molecule links the activities of two important components of the immune system, IL-2 and IL-33. In this form, the two interleukins work together to target Tregs. Preliminary data indicates this novel molecule (called IL233) is an effective treatment in a mouse model of lupus nephritis. In the current project, Dr. Fu will (1) perform further studies confirming that the IL-2 and IL-33 combination both protects against autoimmune kidney disease and reverses the effects of established lupus nephritis, (2) explore IL233's mechanism of action (in other words, what it does and how it does what it does) and (3) using a mouse model of lupus investigate whether and how IL-233 might be used as the foundation of a new lupus therapy.

What this study means for people with lupus

Dr. Fu's research has the potential to both lead to the development of a new therapeutic agent and, because IL233 enables new ways of manipulating Tregs, to expand the capabilities of researchers to perform laboratory studies of Tregs.

Wael Jarjour, MD**The Ohio State University****Jian Zhang, MD****University of Iowa****Regulation of T Follicular Helper Cells in SLE by E3 Ubiquitin Ligase Cbl-b**

Among the multiple arms of the immune system involved in lupus, the activation of certain specific cells (polyclonal CD4+ T cells and B cells) may be described as being a hallmark of the disease. These B cells are, in turn, regulated by cells called T follicular helper (Tfh) cells. While a growing body of evidence points to the crucial roles of Tfh cells in lupus, the mechanism of activation of Tfh cells is currently not well understood. Preliminary data from Drs. Jarjour and Zhang's experiments suggest that an enzyme (a ligase) called Cbl-b controls relevant Tfh development in a mouse model of lupus. In the present study, Drs. Jarjour and Zhang will (1) use a mouse model of the illness to investigate further whether and how Cbl-b regulates Tfh cell development. In addition, (2) they will explore the role of Cbl-b in regulating Tfh cells derived from the blood of lupus patients (with more and less severe illness) and healthy people (to serve as experimental controls). Among the steps Drs. Jarjour and Zhang will take will be to knock down Cbl-b and assess how this step affects the abilities of human Tfh subsets from lupus patients. Further, (3) they will study whether Cbl-b regulates Tfh differentiation in cells derived from humans.

What this study means for people with lupus

Drs. Jarjour and Zhang's studies are highly focused. Therefore, the possibility exists that this research will lead to the clear identification of therapeutic targets and will facilitate the discovery of lupus therapies.

Caroline Jefferies, PhD**Cedars-Sinai Medical Center****Estrogen-dependent microRNAs as Potential Targets for the Treatment of SLE**

It is well known that lupus affects more women than men, and so perhaps it is not surprising that estrogen has been found to play a role in the pathogenesis of lupus, although the nature of this role may not be identical for all people with lupus. Over-activation of the estrogen system leads to a series of interactions, some of which affect microRNAs, small pieces of genetic material that function to regulate the levels of proteins in our bodies. Among the functions of microRNAs is

to regulate the immune system. In the pathogenesis of lupus, these micro RNAs and associated proteins do not always function as they should and, thus, contribute to the over-activation of the immune system present in people with lupus. Dr. Jefferies and her team have identified a panel of estrogen-dependent, differentially expressed microRNAs in white blood cells (monocytes), some of which are upregulated and some of which are downregulated in lupus as compared with controls. Many of the microRNAs identified have putative targets that are important in regulating immune pathways that are effected in lupus, such as anti-viral detection pathways which are over-activated, thus leading to enhanced levels of a cytokine interferon that is known to drive the disease. For example mir-381 appears to target TRIM21, a known autoantigen in SLE, which also has a key role in regulating interferon (IFN) production. Furthermore, she has shown that estrogen receptor antagonists are able to reverse the enhanced production of an array of immune system components, for example, type I interferons (IFNs and IL-23), both of which are important in the pathology of SLE. Taken together, these findings have led Dr. Jefferies to hypothesize that estrogen-regulated microRNAs may play a key role in the development of lupus by causing changes in the functioning of key inflammatory pathways. These findings indicate the potential of targeting the estrogen system in SLE treatment.

What this study means for people with lupus

It is possible, although not proven, that estrogen modifying drugs may potentially serve as effective therapies for certain lupus patients. The current project will focus on understanding the role estrogen-regulated microRNAs play in lupus – with the aim of identifying novel targets, and perhaps microRNA-based therapies, to treat the disease. In addition, the project will seek to identify the subsets of patients who might most benefit from estrogen-antagonist therapies.

Maria Kontaridis, PhD

Beth Israel Deaconess Medical Center

Role for SHP2 as a Therapeutic Target for Systemic Lupus Erythematosus

SHP2 is an enzyme, a protein that helps regulate certain activities in the human body. Among other functions, SHP2 helps modulate the body's response to stress by inducing inflammation. Previously, Dr. Kontaridis demonstrated that there is elevated SHP2 activity in the cells of people with lupus, a finding that suggests SHP2 is involved in the disease mechanism underlying lupus. Using a newly created, potent, and specific inhibitor for SHP2, Dr. Kontaridis then conducted experiments in a mouse model of lupus. Just six weeks of treatment with this inhibitor improved disease symptoms and prevented kidney and spleen damage. Importantly, the inhibitor caused no harmful side effects. She then isolated specific cells of the immune system directly affected by SHP2 activity and showed that SHP2 caused increased growth in a specific subset of these cells, causing the increased

inflammatory response that ultimately leads to the organ and tissue damage associated with lupus.

What this study means for people with lupus

Taken together, Dr. Kontaridis' experiments suggest that inhibiting SHP2 activity might prove beneficial for people with lupus – although this has not yet been proven clinically. If in the future the approach does prove beneficial for patients, then this research will have identified a new, potent, and targeted lupus therapy.

Michele Kosiewicz, PhD

University of Louisville Research Foundation, Inc.

Sex and Microbiota Influence on Immunoregulation and Disease in BWF1 Mice

Male sex steroids (androgens) appear to protect men from developing lupus, and even men with a genetic susceptibility to the disease appear to be protected through this mechanism. Recent studies have shown that androgens affect the bacteria that naturally live in the digestive tract and that, in turn, these bacteria (the gut microbiota) influence the activities of androgens. For example, recent research suggests that the microbiota and androgens may collaborate to protect male mice from autoimmune diseases, such as type 1 diabetes. Using a mouse lupus model, Dr. Kosiewicz's preliminary studies have found that the microbiota and related factors differ between females and males, and transfer of male microbiota to female mice protects the females from disease and increases mouse length of life. It may be (but this has not been proven) that substances (metabolites) produced by the microbiota of males protects males through activation of certain immune system components. Perhaps such substances (or the entities that produce these substances) would be useful in treating lupus in females. In the current study, Dr. Kosiewicz will (1) use a mouse model of lupus to identify certain products of gut microbiota influenced by androgens; (2) explore the role of various products of male-imprinted gut microbiota in preventing lupus; and (3) determine the role of specific immune cells (intestinal dendritic cells) in these protective processes.

What this study means for people with lupus

Dr. Kosiewicz will test the hypothesis that androgen-modified male microbiota produce substances that protect against lupus by acting through specific immune cells. She hopes the current research will lead to the development of novel lupus therapies that make use of the products of microbiota. (She would also like to discover similar therapies that target other autoimmune diseases).

Carla Rothlin, PhD

Yale University

Protein S: at the Crossroads of Thrombosis and Inflammation in SLE

Many lupus patients experience abnormal blood clotting and consequent serious consequences for health. Dr. Rothlin has been investigating a protein that functions in healthy people to inhibit clot formation, a protein named Protein S (PROS1). The rare variants of PROS1 that appear in some lupus patients impair the anticoagulation function of PROS1, and it may be that PROS1 mutations affecting blood clotting constitute a risk factor in lupus (although this has not been proven). Previously, some of these same variants had been found in people with blood clotting diseases. Recently, Dr. Rothlin has shown that PROS1 not only affects blood clotting but is, as well, a potent anti-inflammatory molecule: it inhibits the immune response. However, whether mutations in PROS1 alter its antiinflammatory function and thereby contribute to autoimmunity in lupus patients is unknown. She hypothesizes that both the loss of PROS1's anticoagulant function and the loss of its antiinflammatory signaling role each contribute independently to the etiology of lupus – and, furthermore, that when both of these inadequacies appear together the risk of lupus and of the development of a more serious form of the disease is exacerbated. Her current project will (1) characterize both the anticoagulant and anti-inflammatory functions of rare PROS1 variants derived from the blood of lupus patients and (2) in a mouse model of lupus determine the direct contribution of the loss of both of these functions of PROS1 to the development of lupus.

What this study means for people with lupus

Dr. Rothlin's research will explore the relative contribution to the disease mechanism (or mechanisms) of lupus of the two biological properties of Protein S – the effect on clotting and the effect on the immune response. The findings may help characterize subgroups of lupus patients. (Identifying subgroups of patients is important because, for example, some therapies may be more effective for some patients than for others.) In addition, her research may guide the design of future lupus therapies related to PROS1 activities.

William Stohl, MD, PhD

USC/University of Southern California

Therapeutic Targeting of FcγRIIb on B cells in SLE

B cells function in ways vital to the immune system, allowing humans to ward off and better cope with often-hostile bacteria, viruses, and other foreign matter. However, B cells also play a central role in the development of lupus, as they possess the capacity to attack not only foreign invaders but also to mistakenly work against patients' own cells and tissues. It might be therapeutic to inhibit those B cells that promote disease; but this would be beneficial only if this is accomplished in a way that does not undermine the protective

capacity of B cells. What does the human body itself do to regulate B cells? Without depleting the supply of B cells, the human body regulates B cells by inhibiting them. In the normal, healthy functioning of the immune system, immune complexes (IC) down-regulate ongoing immune responses by co-engaging cognate BCR with FcγRIIb. (The B cell receptor [BCR] is a specialized receptor protein present on the surface of B cells. The Fc region receptor II-b [FcγRIIb] is a surface receptor protein that modulates B cell activity.) Certain specific monoclonal antibodies (mAbs) – proteins that scientists have produced in a laboratory – function in ways similar to the way a healthy immune system regulates B cells, and, so, might be developed as a lupus therapy. Dr. Stohl has bred lupus-prone mice possessing the human FcγRIIb gene. In the current project, he will use mAbs in a mouse lupus model to assess the effects of BCR/FcγRIIb co-engagement on B cell activation. In addition, he will investigate how such BCR/FcγRIIb co-engagement affects the clinical, immunological, and pathological features of a mouse lupus model.

What this study means for people with lupus

Having a single agent that effects high-affinity co-engagement of the BCR complex and FcγRIIb can potentially inhibit the activation and functioning of the B cells associated with lupus. Will an mAb prevent the development of lupus in a mouse model of the disease? Will it effectively and safely treat established disease in mice? Dr. Stohl hopes his research will lay a foundation for a novel lupus therapy

Betty Tsao, PhD

Medical University of South Carolina

Targeting IL-10 Producing B cells in SLE

Interleukin-10 (IL-10) is a cytokine that, in multiple ways, helps to regulate the immune system. IL-10 appears to play a role in the pathogenesis of lupus: (1) elevated levels of IL-10 in the blood of lupus patients correlates with elevated disease activity and promotes B-cell hyperactivity and autoantibody production (2) early results of a novel anti-IL-10 monoclonal antibody treatment in lupus patients appear promising, and (3) specific genetic variants of the IL-10 gene are associated with increased risk for developing lupus and other autoimmune diseases. Assessing IL-10 gene cluster variants, Tsao and colleagues recently identified the crucial lupus-risk allele. In addition, they demonstrated that this allele (1) has genomewide significance, (2) exhibits a dose-dependent relationship to elevated levels of IL-10 in the blood circulation of lupus patients and healthy controls, and (3) preferentially binds to a transcription factor (Elk-1). In people possessing the implicated genetic variant, activation of Elk-1 augments IL-10 production. An unexpected finding of this research was that Elk-1 activation constitutes a general feature of lupus and active lupus disease is associated with increased proportions of B cells expressing both IL-10 and activated Elk-1, which promotes production of IL-10 and autoantibodies. In healthy people, IL-10 producing B cells (B10 cells) function to regulate the immune system; in lupus, they function abnormally.

Tsao and colleagues propose to study the major defective mechanism(s) responsible for the overproduction of IL-10 and of the defective regulatory function of B10 cells; they will then be able to target specific mechanisms – leading to a reduction of disease activity.

What this study means for people with lupus

The long-term goal is to develop a new therapeutic approach to lupus that might in the near future be tested in a mouse model of the disease.

Sheng Xiao, PhD

Brigham and Women's Hospital

Role of Tim-1 in Kidneys during Lupus

Lupus nephritis, the most common manifestation of the disease, is associated with increased risk of end-stage renal disease and death. Dr. Xiao's research focuses on a molecule that might play an important role in generating kidney damage in lupus patients. Various teams of scientists have given this single molecule several different names: one is kidney injury molecule (KIM-1) and another is T-cell immunoglobulin and mucin domain 1 (TIM-1). Elevated levels of KIM-1/TIM-1 are not found in the kidneys of healthy people. However, high levels of KIM-1/TIM-1 are present in the kidneys of people with lupus nephritis (as well as in the kidneys of people with kidney injury and of people with kidney diseases unrelated to in human biology lupus). The role of KIM-1/TIM-1 in lupus nephritis and other kidney disorders has not been well studied. During successive stages of research, Dr. Xiao has generated several varieties of mutant mice relevant to the investigation of the role of Tim-1 in lupus nephritis: some of these mice lack certain functions associated with Tim-1, other sets of mice he has generated overexpress Tim-1 in kidney cells, and still other sets of mice exhibit a lack of Tim-1 in certain contexts. Other teams of scientists have published additional studies relevant to Dr. Xiao's investigations.

What this study means for people with lupus

Knowledge about the possible role of KIM-1/TIM-1 in lupus nephritis has accumulated. Plus, a number of mutant mouse models and other tools relevant to the study of the possible role of KIM-1/TIM-1 are now available. Dr. Xiao hopes to determine conclusively if Tim-1 affects lupus nephritis in animal models of the disease – and, if it does, to arrive at a scientific understanding of how this occurs. Such understanding would likely provide insights into the disease mechanism of lupus in people. The long-term hope is that this research will lead to the development of novel therapeutic strategies for treating lupus nephritis in lupus patients.

Nan Yan, PhD

UT Southwestern Medical Center

Glycans and Glycosylation Defects as Novel Targets in Lupus

In the human body, the adequate functioning of numerous proteins is dependent upon interactions with sugar molecules, and the modification of proteins by sugar molecules (called glycosylation) plays several important roles in the immune system. In a subset of lupus patients (and in some people with other autoimmune diseases) glycosylation is defective. Dr. Yan recently discovered that the protein that is encoded by the lupus-associated gene known as TREX1 regulates processes that link aberrant glycosylation and autoimmune disease. The previous known function of TREX1 is its DNase activity that clears immunogenic DNA in the cell which would otherwise trigger DNA sensing pathway leading to autoimmune diseases such as Aicardi-Goutières syndrome (AGS). In the current project, Dr. Yan discovered a new function of TREX1 that is independent of its DNase activity, and this new function provides a better explanation for a subset of lupus patients carrying TREX1 frame-shift mutations. Dr. Yan's group seeks to understand how these mutations mold the disease process and how, in a different set of patients, mutations in TREX1 lead to the development of an illness called retinal vasculopathy with cerebral leukodystrophy (RVCL). He will use TREX1 patient samples and related mouse models for these studies.

What this study means for people with lupus

Dr. Yan hopes to identify glycosylation defects and to isolate relevant autoimmune substances. If such discoveries are achieved they might possibly both elucidate a novel disease mechanism underlying lupus and serve as biomarkers for broader identification of more patients with similar defects. In addition, Dr. Yan will test both in mice and in cells derived from lupus patients a medication that potentially can correct problems with glycosylation. Several aspects of the research might potentially lead to the development of new lupus therapies. Notably, such therapies might prove particularly effective in subsets of lupus patients either carrying defective TREX1 gene or having glycosylation defects in general, and this is a reason Dr. Yan will also seek to identify biomarkers permitting the identification more of those patients in the latter subset.

2018 NOVEL RESEARCH GRANT RESEARCH SUMMARIES

Andre Ballesteros-Tato, PhD

University of Alabama at Birmingham

Immunotargeting of T Follicular Helper (Tfh) Cells for SLE Treatment

Dr. Ballesteros-Tato is exploring an important interaction between two different cell types of the immune system as a new avenue for targeted drug development in lupus. Specialized immune cells—T follicular helper (Tfh) cells—act as a support system to aid and nurture the B cells, a cell type that produce self-damaging antibodies. It is these antibodies that attack the bodies of people with lupus, damaging their kidneys, brain, skin, and other organs. Dr. Ballesteros-Tato will use his Novel Research Grant to look for ways to selectively eliminate Tfh cells without knocking out other types of T cells that are part of a healthy immune system. He expects that such a treatment would, in turn, power down lupus-related B cells and block disease progression.

What this study means for people with lupus

Currently, no treatments can break the bond between Tfh cells and B cells in people with lupus. Dr. Ballesteros-Tato's research focuses on this interesting pathway and may lead to innovative directions for the development of new drugs that can add to the therapy arsenal for people with lupus.

Betsy Jo Barnes, PhD

The Feinstein Institute for Medical Research

Unexpected Role(s) for IRF5 Risk Variants in SLE Pathogenesis

Scientists know that for many people some of the risk for lupus is genetic—that is, inherited through their family line. The gene for interferon regulatory factor 5 (IRF5), a key player in the immune system, has been strongly linked to a higher risk for lupus. This means that some versions of the IRF5 gene are more likely to be found in people with lupus, although carrying the high-risk gene does not guarantee that a person will develop lupus. Dr. Barnes wants to understand how these different, high-risk versions of IRF5 help turn a healthy immune system into one that drives an autoimmune attack that leads to lupus. With her Novel Research Grant, she will compare IRF5 in people who carry high-risk versions of the IRF5 gene but do not have lupus with IRF5 in healthy people with low-risk versions of the gene. This study explores a very early stage in lupus development and may reveal why the immune system is triggered to begin an autoimmune attack.

What this study means for people with lupus

Dr. Barnes' research focuses on people who are at high risk of developing lupus because of their genes, yet who have healthy immune systems and no signs of autoimmunity. If she

finds differences in IRF5 that help steer the immune system down a path toward lupus, her study may reveal new targets for the treatment of or, even, the prevention of lupus.

Jason S. Knight, MD, PhD

University of Michigan

Neutrophil Elastase as a Therapeutic Target in Lupus

Dr. Knight studies how a type of immune cell called a neutrophil contributes to lupus and its complications. In a model of lupus, he found that turning off neutrophil elastase, a protein made in the neutrophils, reduces autoimmunity, kidney disease, and blood clotting that can lead to strokes. Building on this intriguing discovery, Dr. Knight is now mapping out the molecular pathways that elastase uses to damage the kidneys, heart, and blood vessels in lupus. This innovative research project will create a solid foundation for the development of drugs that target elastase as a potential lupus treatment.

What this study means for people with lupus

Dr. Knight has identified a new player in the development of lupus and its complications—neutrophil elastase. His Novel Research Grant will reveal whether elastase is a good target for the development of a new type of treatment for people with lupus.

Frances E. Lund, PhD

University of Alabama at Birmingham

Characterization of Chemokine Producing Effector B Cells in SLE

B cells of the immune system make antibodies that are essential for the body's defense against infectious diseases; yet, in autoimmune diseases like lupus, some B cells mistakenly go on the offense and attack the body itself instead of focusing on destroying bacteria or viruses. Dr. Lund's ultimate goal is to improve on existing therapies that remove all B cells from a person's immune system—such therapies treat autoimmunity but also leave patients vulnerable to new infections. With her Novel Research Grant, Dr. Lund is learning as much as she can about a unique population of B cells found in some people with lupus, but not in people without lupus. These cells ("T-bethi B cells") have high levels of a gene-controller protein called T-bet. Understanding how these particular B cells are different could reveal new targets for safer drug therapy in lupus.

What this study means for people with lupus

By fully characterizing a specific type of B cell found in some people with lupus, Dr. Lund's research paves the way for developing better, targeted therapies that specifically block the B cells that make lupus-related antibodies without affecting B cells that produce antibodies to fight infections.

Keisa Williams Mathis, PhD

University of North Texas Health Science Center at Fort Worth

Targeting Nicotinic Receptors to Reduce Inflammation Associated With SLE

Chronic, long-term inflammation can damage organs throughout the body, including the brain, in people with lupus. Dr. Mathis has discovered that nicotine, a chemical found in tobacco products, can reduce inflammation; however, nicotine is too toxic overall to be used as a treatment in people with lupus. In this exciting translational project, Dr. Mathis is exploring other, nontoxic molecules that might work like nicotine to heal inflammation, but without causing serious side effects. In addition, she will examine whether this type of therapy can reduce inflammation in the brain and, in turn, eliminate negative behavior changes caused by lupus.

What this study means for people with lupus

Dr. Mathis hopes to identify a new treatment for chronic inflammation in lupus that is safe, highly effective, and free of toxic side effects. Importantly, her Novel Research Grant will show whether reducing inflammation in the brain with such treatments can reverse behavioral symptoms of lupus.

Laurence Morel, PhD

University of Florida

Targeting Immunometabolism and Co-stimulation in Combination Therapies in Lupus

In a previous study, Dr. Laurence Morel showed that drugs which make less sugar available to immune cells could stop the development of lupus in a model of the disease. Sugar is important for many cell processes, so reducing the amount available has a similar effect as when a person eats less food—the cell's activities slow down and it has less energy to fuel an attack. The same treatment also helped immune cells taken from the blood of people with lupus act more like healthy, non-lupus immune cells. Dr. Morel hopes that this treatment might help three existing drugs - belimumab, abatacept, and ruplizumab - that have small effects in people with lupus - to work better. With support from her Novel Research Grant, she will test combinations of sugar-reducing drugs like metformin, a drug widely used in diabetes, with the three lupus treatments to see whether she can slow the disease or reverse kidney damage in lupus models.

What this study means for people with lupus

Dr. Morel is pursuing a highly promising translational research project aimed at treating lupus and its complications. Because she is working with drugs like metformin that are already approved for use in people, any positive results could be easily translated into clinical trials to test the efficacy of her drug combinations in people with lupus.

Alessandra B. Pernis, MD

The Hospital for Special Surgery

Regulation of CD11c+Tbet+ B Cells in Lupus

Dr. Pernis studies a unique type of B cell that has been linked to several autoimmune diseases, including lupus. These "CD11c+Tbet+" B cells have unusually high amounts of two proteins: CD11c, which hangs like a hook on the outer surface of the cell, and T-bet, a protein in the center of the cell that controls the on/off switch for some genes. CD11c+Tbet+ B cells make autoantibodies—or antibodies that mistakenly attack a person's own tissues and, thus, trigger diseases like lupus. Dr. Pernis will use her Novel Research Grant to learn how CD11c+Tbet+ B cells are made, what molecular pathways help control the function of T-bet in the center, and how and why the cells are triggered to make autoantibodies in lupus.

What this study means for people with lupus

Dr. Pernis expects her research on CD11c+Tbet+ B cells to fill in vital pieces of the puzzle of how lupus develops. By understanding why these cells develop and how they work, she hopes to find vulnerable points that can be targeted with novel drugs that are specially designed to stop or reverse the disease process in lupus.

Ziaur Rahman, MD, PhD

Pennsylvania State University College of Medicine

Mechanisms of the Autoimmune Germinal Center Response in SLE

Dr. Rahman will use his Novel Research Grant to map out how the molecular pathways that govern antibody production areas called germinal centers differ in people with lupus from those in healthy individuals. Germinal centers are locations inside a person's spleen and lymph nodes where immune B cells that make antibodies develop their ability to fight infections or, in the case of lupus, to attack a person's tissues. Correcting the defects in lupus-related germinal centers could reduce or block the development of disease-causing B cells and the tissue-targeting antibodies they make that cause so much damage in people with lupus.

What this study means for people with lupus

Dr. Rahman's research on germinal centers represents a novel target for understanding and, ultimately, treating lupus. Understanding the role of germinal centers in lupus should uncover new targets for drug development to complement existing therapies.

Amr Sawalha, MD

University of Michigan

Targeting EZH2 in Lupus

Dr. Sawalha discovered that the DNA of particular immune cells (CD4+ T cells) changes in people with lupus as the disease progresses. In a process called “methylation,” new molecules are added to the DNA, like ornaments hung on a Christmas tree. Methylation of the DNA changes the proteins that are produced and the functions that are turned up or down in the cell. These changes cause the cells to be more active and, so, more able to damage organs. He also found that a protein called EZH2 is a key participant in DNA methylation in CD4+ T cells. With his Novel Research Grant, Dr. Sawalha will delve into the effects of EZH2-led methylation in CD4+ T cells in lupus and look for ways to disrupt the methylation process in CD4+ T cells using new or existing drugs.

What this study means for people with lupus

Dr. Sawalha is studying how the EZH2 protein changes the DNA in immune cells to make them more likely to launch an autoimmune attack on a person’s body. Importantly, several drugs that turn off this protein are already in clinical trials as potential cancer treatments. The results of Dr. Sawalha’s research could provide support for testing these new drugs to treat people with lupus as well.

2017 NOVEL RESEARCH GRANT RESEARCH SUMMARIES**Mridu Acharya, PhD**

Benaroya Research Institute at Virginia Mason

Autophagy components and B cell activation during SLE

The B cells of lupus patients are hyperactive, causing inflammation and damage to tissues. By studying mice, she has discovered a new molecular control switch for these cells. In their new study, they want to find out more about how this control switch works in human B cells and why it doesn’t function properly when people develop lupus. Some patients carry varying versions of the switch proteins, and they also want to investigate how these differences affect whether someone gets lupus. Better understanding of the control switch will help efforts to develop new treatments that flip it on in patients with lupus.

What this study means to people with lupus

Dr. Acharya’s group has found a new pathway in lupus, having identified proteins that normally work together to prevent B cells, a type of immune cell that releases disease-fighting molecules, from targeting patients’ cells. Working with human B Cells, she will investigate why these proteins fail to put on the brakes in lupus and potential new treatments to get them working properly again.

Natalia Giltiy, PhD

University of Washington

Anti-BDCA 2-targeted Therapy for SLE

Our cells store their DNA by wrapping it around proteins called histones. People with lupus show abnormal immune system responses against their own DNA and against histones. She thinks that histones are a little like the substances that cause allergies – they stimulate the immune system inappropriately, but controlled exposure to them may reduce this reaction. Their strategy to prevent these “allergic” reactions involves delivering small bits of self-proteins to key immune cells known as dendritic cells, which control the responses of other immune cells. They have developed molecules known as antibodies that hone in on dendritic cells and bring the histone fragments along with them. They hypothesize that exposing dendritic cells to the fragments will curb the immune system reaction against histones, and the new study will test this approach in mice that are prone to lupus. The goal is to apply their work to the development of a new therapy for lupus patients.

What this study means to people with lupus

Dr. Giltiy’s team plans to teach the immune system to tolerate the body’s own cells in much the same way that allergy shots

curb abnormal reactions to allergens. This novel approach to inducing immune system “tolerance” has never been applied to lupus before and may lead to a new effective treatment.

Shaun Jackson, MD, PhD

Seattle Children’s Hospital

B cell-intrinsic Cytokine Reg of Spontaneous Germinal Ctr Formation in SLE

B cells usually protect us from bacteria and viruses, but in lupus they release proteins, known as antibodies, that target patients’ own cells. Researchers don’t know which immune system molecules spur B cells to start making these destructive antibodies. In their study, they will use mice to test whether specific immune system molecules, called cytokines, activate B cells to promote production of these antibodies. By identifying the specific signals that trigger B cells to attack patients’ own cells, they hope to provide clues that will allow researchers to develop new, targeted lupus treatments.

What this study means to people with lupus

In lupus, B cells release proteins that damage patients’ own tissues. Dr. Jackson and her colleagues are taking a fresh look at B cells, zeroing in on two recently identified molecules that may act as signals to promote immune attacks. Identifying the specific signals responsible for activating B cells and producing dangerous autoantibodies will inform development of potential targeted lupus treatments.

Andrea Knight, MD

The Children’s Hospital of Philadelphia

Multi-level Biomarkers for Psychiatric Disorders in Pediatric Lupus

Up to 50% of young people with lupus have neuropsychiatric disorders, but many of these patients don’t receive the treatment they need. Her study will ask whether a variety of tests, including brain scans with magnetic resonance imaging (MRI) and analysis of proteins in blood samples, can help identify which patients have these disorders due to lupus. They anticipate that the results of the study will lead to early detection and targeted treatment of neuropsychiatric disorders in young people with lupus.

What this study means to people with lupus

Young people with lupus often have neuropsychiatric disorders like depression or anxiety, which may be caused by brain inflammation. Dr. Knight is developing a new biomarker to better detect and diagnose neuropsychiatric disorders like depression and anxiety that are common in pediatric patients so they can receive treatment and get relief sooner.

Vipin Kumar, PhD

University of California, San Diego

Targeting Type II NKT cells for a Novel Therapeutic in Lupus

Dr. Kumar found that certain immune cells accumulate in the kidneys of mice with a lupus-like disease. His research has shown that molecules structurally related to sulfatide that stimulate these cells can prevent kidney disease in animal models of lupus. One such analog has been used for the treatment for the tropical disease leishmaniasis. In his new study, he wants to determine whether this lipid analog can reduce kidney damage in lupus-prone mice. If successful, the results could lead to clinical trials to examine whether the selflipid analogs can also serve as a treatment for kidney disease in lupus patients.

What this study means to people with lupus

Some immune cells drive renal damage in lupus, but others serve a protective role. Dr. Kumar’s lab is testing a novel hypothesis backed by his preliminary data; he will explore a drug used to fight tropical parasites as a potential oral medication to prevent and treat kidney damage in lupus.

Christian Lood, PhD

University of Washington

Impaired Mitochondrial Clearance in Systemic Lupus Erythematosus

The energy our cells need comes from structures known as mitochondria that serve as power plants. He recently found that some immune cells throw out their mitochondria, which trigger inflammation and promote development of disease. In the current study he proposes to investigate how the body normally disposes of the released mitochondria so that they don’t cause inflammation and find out if those cleanup mechanisms don’t work well in lupus patients. Those results may provide new opportunities for developing lupus therapies, as well as identify novel biomarkers to monitor, and potentially predict, development of disease.

What this study means to people with lupus

Dr. Lood’s group discovered a new cause for the out-of-control inflammation of lupus. Certain immune cells normally eject the mitochondria power plants that provide them with energy. The team is exploring a new treatment approach by examining whether people with lupus do not properly remove mitochondria, thus sparking inflammation. This highly novel project is likely to lead to new targets for therapy and new biomarkers for evaluating disease progression and response to treatment.

Anthony Rongvaux, PhD**Fred Hutchinson Cancer Research Center****Mitochondria, Caspases and Type I interferons in Autoimmunity**

The immune system molecules known as interferons protect us from infections, but they also spur tissue damage in lupus. Dr. Rongvaux has discovered a previously unknown mechanism by which interferons may cause or worsen lupus. Using state-of-the-art technologies, he is investigating how some proteins, known as caspases, block this novel interferon mechanism. He also will test molecules that stimulate caspases, some of which are under development as potential treatments for diseases such as cancer, to determine if they reverse lupus symptoms in mice.

What this study means to people with lupus

Dr. Rongvaux is using state-of-the-art technology to study a newly discovered process that may cause or worsen lupus and whether molecules involved in this process are potential targets to validate and advance new treatments that may reverse symptoms.

Guo-Ping Shi, DSc**Brigham and Women's Hospital****Cathepsin S inhibitor-modified Treg cells Mitigate Murine SLE**

Regulatory T cells serve as the immune system's dimmer switch, turning down attacks by immune cells. One factor causing regulatory T cells to fail in lupus patients might be the protein cathepsin S. This protein switches on another protein, known as toll-like receptor 7, that curbs the body's production of regulatory T cells and prevents them from inhibiting the immune system. Dr. Shi will test whether blocking cathepsin S reduces lupus symptoms in mice by increasing the lifespan of regulatory T cells and boosting their ability to rein in the immune system. If the study is successful, it might be possible to block cathepsin S in regulatory T cells and then use the cells to treat lupus patients.

What this study means to people with lupus

Particular T cells normally keep the immune system under tight control, but they malfunction in lupus, permitting other immune cells to attack patients' tissues. Dr. Shi and his colleagues are investigating the enzyme Cathepsin S in controlling these regulatory T cells, to restore their ability to control other defensive cells. Testing in human cells, Dr. Shi's novel and important study has the potential to lead to the development of a novel therapy to prevent and treat lupus.

John Zhang, DVM, PhD**Medical University of South Carolina****A Novel Approach for Treating Lupus by Inhibiting Fli1 Transcription Factor**

Lupus patients with active disease produce higher-than-normal amounts of the protein Fli-1 in their immune cells. The more of the protein they make, the worse their symptoms are. He has found that the drug topotecan, a therapy for ovarian cancer and other types of cancers, curbs production of Fli-1 and reduces the signs of inflammation in cells. He will test whether the drug has beneficial effects in lupus-prone mice. His results will help demonstrate whether the drug has potential as a lupus treatment in patients

What this study means to people with lupus

Dr. Zhang's team is confirming their initial findings and now testing in human cells whether the chemotherapy topotecan could offer an effective treatment to reduce inflammation in lupus. Topotecan blocks Fli-1, a protein Dr. Zhang and his team have determined worsens lupus symptoms.

Zhiqiang Zhang, PhD**The Methodist Hospital Research Institute****Oxidized Mitochondrial DNA Employs APEX1 in Neutrophils to Control Lupus**

The immune system keeps watch for viral DNA that signals we have an infection. In lupus, immune cells identify DNA from patients' cells as dangerous. Some of the DNA released by their cells comes from mitochondria, the structures that provide energy for our cells. Dr. Zhang has identified several proteins that may recognize this DNA, including one known as APEX1. In his new study, he will test whether APEX1 detects mitochondrial DNA and spurs the immune system attacks. His results could provide important information for the development of safer and more effective approaches for the prevention and control of lupus without unwanted side effects.

What this study means to people with lupus

The immune system mistakenly attacks lupus patients' own DNA. Dr. Zhang's study is testing whether the protein he just discovered, APEX1, is responsible for sounding a distress call that stimulates our defensive cells – an impressive discovery that would allow researchers to develop new ways to prevent this false alarm.

2016 NOVEL RESEARCH GRANT RESEARCH SUMMARIES

Vikki M. Abrahams, PhD

Yale University

Role of Infection in Obstetric Antiphospholipid Syndrome

Women with antiphospholipid syndrome, a clotting disorder that can occur in lupus patients, are at high risk for pregnancy complications like miscarriage and preeclampsia, which causes hypertension and swelling. It's known that in women with lupus, antiphospholipid antibodies can attack the placenta and change its normal function of maintaining a healthy pregnancy. Dr. Abrahams' study will test whether bacterial infections make pregnant women more susceptible to the effects of antiphospholipid syndrome, and if this susceptibility worsens the pregnancy complications brought on by the syndrome. Her research will help find better ways to predict and prevent pregnancy complications in women with antiphospholipid syndrome, dramatically improving the long-term well-being of both mother and child.

What this study means for people with lupus

Dr. Abrahams' novel study aims to predict and prevent traumatic complications such as miscarriages and preeclampsia – hypertension and swelling – that can occur in pregnant women who have the blood clotting disorder antiphospholipid syndrome.

Julio A. Camarero, PhD

USC/University of Southern California

Therapeutic Selective Targeting of BAFF Receptors

Despite compelling evidence that the molecule BAFF, which stands for B-cell activating factor, plays a significant role in the development of lupus, current treatment that targets this molecule offers only a modest, if any, clinical benefit to patients. Dr. Camarero's research will study the therapeutic effect of targeting a specific set of BAFF receptors that seems to be the main culprit in causing damage. Selective inhibition of two of the BAFF receptors could offer a novel and superior treatment for lupus.

What this study means for people with lupus

Dr. Camarero's innovative research aims to improve on the current treatment which uses antibodies to eliminate the molecule known as BAFF that stimulates the production of B-cells. He and his team will target specific receptors, molecules that respond to and activate the BAFF molecule, rather than BAFF itself, to increase effectiveness and provide a new and exciting treatment for lupus.

Lindsey Ann Criswell, MD, MPH

University of California, San Francisco

Pesticides and Chemical Exposures, DNA Methylation, and SLE Phenotypes

It is believed that both genetic and environmental risk factors play a role in causing lupus. Unfortunately, very little is known about the role of environmental exposures in the disease, including the effects of pesticides and other chemicals that may turn genes on and off by a process called DNA methylation.

Previous research has shown that patients with severe cases of lupus have had changes to their DNA through methylation, but how and why this occurs is still poorly understood. In this groundbreaking study, she will determine whether particular chemical exposures influence DNA methylation and disease outcomes in lupus. Dr. Criswell will do this by using a new, pioneering technology to analyze blood samples from patients with severe cases of the disease. This innovative technology enables her team to analyze the samples for hundreds of chemicals at a time – the first time this type of research has been conducted in lupus. They will then be able to determine what role, if any, exposure to these different chemicals has had on patients with severe manifestations of lupus.

What this study means for people with lupus

The more researchers can learn about what causes lupus, the more they can do to treat and possibly prevent this debilitating disease. In Dr. Criswell's novel research, her team will be using cutting-edge technology to analyze the influence of hundreds of chemicals on blood samples from lupus patients in the hopes of discovering how pesticide and chemical exposures may result in severe forms of the disease.

Stefania Gallucci, MD

Temple University

Bacterial Amyloids from Biofilms Break Tolerance in Lupus

Bacterial biofilms are bacterial communities that are abundant in the human microbiome but also found in chronic infections such as ear or urinary tract infections. Dr. Gallucci proposes that protein fragments known as curli, which are produced by bacterial biofilm infections, may trigger the onset of lupus (as well as subsequent flares in the disease), and the production of anti-curli antibodies by immune system may participate and be a measure of disease activity.

Using mice with lupus and samples from lupus patients, her study will research whether: 1) exposure to curli-expressing bacteria stimulate the development of lupus symptoms, 2) these bacterial infections can be used as therapeutic targets to decrease inflammation and prevent flares, 3) curli antibodies can be used as biomarkers for the disease.

What this study means for people with lupus

Dr. Gallucci's study will explore whether infections affecting the entire body caused by bacteria that typically live harmoniously on the skin, gut, respiratory tract, etc., can trigger lupus initially and if they cause flares as the disease progresses. If so, the next step will be to explore implications for treating and possibly preventing this devastating disease.

Lee Ann Garrett-Sinha, PhD

The Research Foundation for The SUNY University at Buffalo

Understanding the Pathway Regulated by the Lupus Susceptibility Gene Ets1

The Ets1 gene creates a protein also called Ets1 that regulates how B cells block the production of antibodies. As a result, some lupus patients who have low levels of this protein have high levels of autoantibodies. Dr. Garrett-Sinha's research will improve our understanding of why some patients who have low levels of the Ets1 protein have increased levels of autoantibodies, how B cells from human lupus patients with low levels of the Ets1 protein are different from normal B cells and what happens when we increase the Ets1 protein to try and affect B cells. They will then be able to suggest ways that might restore the Ets1's levels and develop new treatments for lupus.

What this study means for people with lupus

Dr. Garrett-Sinha will explore why in some lupus patients a specific gene, Ets1, produces lower levels of a protein that helps restrict production of autoantibodies. With this insight, she aims to identify ways potential treatments could restore proper levels of this important protein and reduce autoantibody production in lupus patients.

Hui-Chen Hsu, PhD

The University of Alabama at Birmingham

Repopulation of Tolerogenic B Cells Post B Cell Depletion Therapy in Lupus

One way lupus is triggered is when B cells go haywire and start producing autoantibodies. Although current therapies that deplete B-cells can eliminate them for six months or longer, a significant number of SLE patients show only temporary and limited improvement.

To improve the effectiveness of this treatment, which does not provide long-term beneficial therapeutic outcomes to many patients, Dr. Hsu's research aims to: 1) Better understand why many patients do not show greater improvements after B cell depletion, 2) Explain why the disease-causing B cells return after treatment and then use this explanation to, 3) Develop strategies to overcome the current treatment defects to create a novel, more effective treatment for lupus.

What this study means for people with lupus

While B cells are considered a major disease-causing cell population in lupus, current therapies to destroy them have – surprisingly – not been any more effective in reducing symptoms than standard drugs used to treat lupus. Dr. Hsu aims to identify why eliminating these cells is not effective and use that information to develop a new, improved therapy with lasting benefits for lupus patients.

Laura Mandik-Nayak, PhD

Lankenau Institute for Medical Research

IDO2, A Novel Therapeutic Target for the Treatment of Lupus

A common characteristic of lupus is the presence of antibodies directed against the body's own tissues, known as autoantibodies. Understanding the factors that activate and perpetuate the production of these autoantibodies is important in the design of therapeutic strategies for the prevention and treatment of this debilitating autoimmune disease.

Dr. Mandik-Nayak's novel research will investigate a potential treatment, a new monoclonal antibody that targets the immune-regulating enzyme IDO2, and that, she believes, will interfere with the production of autoantibodies involved in lupus. In the future, this promising drug could lead to new treatments for lupus and its related symptoms.

What this study means for people with lupus

Dr. Mandik-Nayak and her team are excited to test the effectiveness of a potential new treatment – a newly developed monoclonal antibody – to inactivate an enzyme they found is responsible for driving the production of autoantibodies that attack the body's own tissues.

Timothy B. Niewold, MD

New York University School of Medicine

Tolerogenic Dendritic Cells in Human Lupus

Specialized cells known as plasmacytoid dendritic cells (PDCs), that typically help regulate the immune system, also trigger autoimmune disease when they are activated in lupus. Though many studies have identified factors that increase the inflammation caused by these cells, very little is known about proteins called negative regulators that suppress the activation of PDCs in lupus.

Dr. Niewold's team plans to study two important negative regulators that decrease PDC activation in lupus patients. Crucially, their research will reveal information about how naturally existing molecules suppress PDC activity; this unique and groundbreaking insight could facilitate novel therapies that leverage this natural suppressive capacity.

What this study means for people with lupus

Dr. Niewold's research aims to identify ways to reduce the numbers of specialized cells called PDCs known to cause inflammation in lupus. Understanding how PDC production is reduced naturally will inform development of new treatments that can suppress these disease-causing cells.

Robert Hal Scofield, MD

The University of Oklahoma Health Sciences Center

Sex disparity in Lupus is Driven by Putative X-Linked Genes

Why women are significantly (90%) more likely than men to be diagnosed with lupus is not well understood. Until recently, scientists believed the disparity was due to the influence of sex hormones. However, researchers are now considering the possibility that women, with two X chromosomes, receive a double dose of X-linked genes that somehow predispose them to the disease. (Since men have XY chromosomes, they would only have one dose of X-linked genes.) Dr. Scofield's study will research whether the double dose of genes located on the X chromosome does indeed explain the sex-bias found in lupus.

What this study means for people with lupus

Dr. Scofield's research will examine if having two X chromosomes, rather than the X and Y in men, brings along a double dose of genes that may predispose women to lupus. This insight will get us one step closer to understanding what causes this complex disease.

Barbara J. Vilen, PhD

The University of North Carolina at Chapel Hill

Cross Sectional and Longitudinal Studies of Immune Complexes in SLE

The clearance of dying cells is critical for the immune system to function properly, and the body's inability to properly dispose of these cells has been implicated in lupus. Dr. Vilen and her group recently discovered that defects in the disposal of dead cells lead to the accumulation of antigens and the subsequent production of autoantibodies to these antigens, and that this promotes many of the disease symptoms associated with lupus in mice.

In their new research, they will evaluate whether lupus patients exhibit this defect in the disposal of dead cells. They will enroll patients with both mild to severe disease and assess whether they are able to properly dispose of dying cells. In addition, they will determine whether there is a correlation between the increased disposal of dying cells and a decrease in disease activity.

What this study means for people with lupus

Dr. Vilen is exploring if lupus flares can be caused by the production of autoantibodies that occurs when the body is unable to properly dispose of dead and dying cells. If so, finding a way to correct this defect will provide a potential target for new treatments.

Matthew T. Weirauch, PhD

Cincinnati Children's Hospital Medical Center – Research Foundation

A Free Website for Discovering Non-Coding Lupus-Associated Variant Function

By consolidating all of the available data-sets on genes and lupus onto one free website, Dr. Weirauch's team will provide a vital tool that will enable investigators to advance our understanding of how genetics influence lupus onset and progression.

Their unique initiative will create an interactive website that enables researchers to develop and test their hypothesis regarding the connections between genes and lupus using the website's sophisticated analysis capabilities.

What this study means for people with lupus

By bringing together all of the available data on genes and lupus, the novel website developed by Dr. Weirauch and his colleagues will provide scientists worldwide with a powerful, new tool to research the links between genetics and lupus. This resource will contribute significantly to the collective understanding of how genetics play a role in the disease and lay the foundation for the development of new therapies.

Tianfu Wu, PhD

University of Houston

PLK1, a Potential Novel Therapeutic Target for Lupus

Dr. Wu and his team's previous research demonstrated that an enzyme known as PLK1 plays a role in lupus. With their Novel Research Grant, they will test if blocking the enzyme PLK1 in mice with lupus reduces inflammation and other symptoms. They will also examine blood samples of lupus patients to see how inhibiting this enzyme affects human immune cells. If successful, their research will provide a new, exciting target for lupus treatments.

What this study means for people with lupus

Dr. Wu will study how the enzyme PLK1 affects the immune system and if blocking its activity can reduce inflammation and other symptoms of lupus. He and his team believe that blocking this enzyme can provide a viable therapeutic target for treating lupus.