Alliance *for* Lupus Research

Volume 4, 2007

Lupus Research Update

IN THIS ISSUE:

Meet the Investigator

Laura Julian: Searching for Answers in the Brains of People with Lupus

Laura J. Julian was 21 and just out of college with twin degrees in psychology and Spanish, when she first learned about lupus. She'd begun volunteering — and was then hired — to work in the lab of a prominent lupus neuropsychologist at National Jewish Medical and Research Center in Denver. "My very first job was working with people with lupus on issues like cognitive functioning and depression," recalled Dr. Julian, now an Assistant Professor and clinical neuropsychologist at the University of California in San Francisco (UCSF). "I was completely perplexed by this condition." She found it fascinating to observe how the challenges of such a complex condition impacted an individual's mental and cognitive health functioning.

"I am so appreciative that the ALR has given me an opportunity to contribute to lupus research, and hopefully make a difference."

When she left Denver to pursue her master's and doctorate training in clinical neuropsychology at Pennsylvania State University, those early experiences stayed with her. She decided to focus on the neuropsychological and affective consequences of chronic medical conditions, including multiple sclerosis and lupus. She completed her fellowship training at UCSF where she now works on evaluating the neuropsychiatric consequences of lupus.

This year, Dr. Julian became part of the first class of the Alliance for Lupus Research's (ALR) Pilot grantees. The $75,000 award enables her and her co-investigators to conduct a study on the potential biochemical causes underlying the high rates of depression and cognitive impairment in people with lupus. Their study is part of a larger ongoing investigation at UCSF on depression, cognitive functioning, advanced neuroimaging markers and disease status in lupus.

An estimated one out of three patients enrolled in her lupus studies report clinically significant depressive symptoms, Dr. Julian said. In addition, she noted, approximately half of all people with lupus experience cognitive impairment, or problems with thinking skills, learning, memory, attention and concentration. Both conditions can impair a person's ability to function normally, contributing to overall disability.

"Do the underlying lupus autoimmune disease processes contribute to these symptoms, or is there also some contribution from the stress of living with a difficult to manage disease?" she asks. Or, she adds, do both interact to make patients more vulnerable to depression and cognitive impairment?

CONTINUED ON PAGE 2

JUST THE FACTS

Who:
Laura Julian, Ph.D., Assistant Professor, Department of Medicine, the University of California, San Francisco

ALR funding:
$75,000

Research focus:
Memory impairment and depression in SLE: Role of NMDA receptors

Most likely, Dr. Julian said, the underlying causes for depression and cognitive impairment are multifactorial: a combination of lifestyle issues and the strain of living with a chronic illness, considered "psychosocial" causes, plus some impact from the underlying autoimmune disease and treatments that affect the brain.

With her ALR Pilot grant, Dr. Julian has focused on one hypothesis: the role of glutamate in depression and cognitive impairment in people with lupus. Glutamate is a neurotransmitter that acts as a kind of messenger in the brain, helping transmit signals from one neuron to another. It plays a large role in the ability to learn and remember things, as well as in depression, and every brain cell contains receptors for glutamate. These receptors are called N-methyl-D-Aspartate (NMDA) receptors.

However, glutamate can overactivate these receptors, resulting in a process called excitotoxicity, which damages and kills nerve cells. This process is believed to underlie numerous neurological conditions, including multiple sclerosis, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease and Huntington's disease.

People with lupus may be specifically vulnerable to NMDA-receptor dysfunction because some have anti-NMDA receptor antibodies in their blood. In fact, animal studies conducted by well-known lupus researcher Betty Diamond, MD and her team at Columbia Medical School found that high levels of this antibody can lead to memory impairment, emotional dysfunction and microscopic dysfunction in brain neurons in mice.

Among the questions Dr. Julian and her co-investigators want to understand is if there is any correlation between blood levels of anti-NMDA antibodies and alterations in glutamate receptor functioning in the brain. Their work may also provide some preliminary clues as to whether NMDA antibodies pass through the normally impenetrable blood/brain barrier and, once through, how (or if) their presence affects glutamate and its interaction with NMDA receptors.

To visualize glutamate receptors, the researchers will inject a radioactive tracer into patients that, during brain scans, depicts NMDA receptors. They will then observe how the receptors function in patients with lupus compared to healthy controls. "If we find that the receptor functioning is altered in patients with anti-NMDA antibody in their blood, it would be a very important clue as to what might be causing their problems," she said. "But we may also find that while there's no association with the antibody, there are still changes in receptor function. This would also advance our knowledge in important ways."

If they do find that glutamate is a possible link to understanding neuropsychiatric lupus, it could provide a neurological target for therapies to address depression and cognitive impairment in people with lupus.

Dr. Julian and her team are currently finalizing institutional approvals for the study, and have already identified people with lupus for participation. "I am just so appreciative that an organization like the ALR has given a junior researcher like myself an opportunity to contribute to lupus research and, hopefully, make a difference," she said.

Most motivating in her work, she said, are the patients and their families. "They live with this very difficult condition every day and still find the time to contribute to research and promote awareness for lupus in their communities — this is what is most inspirational."

Alliance for Lupus Research
WalkwithUs
TO CURE LUPUS

Alliance for Lupus Research Walks Across the USA

Join the ALR and take steps toward a cure for lupus! Our spring 2008 ALR Walk season is heating up. Check out the list of dates and locations for an ALR Walk near you.

Don't see your city on the list? Contact us via email or toll-free, to learn how to bring an ALR Walk to your hometown.

Boca Raton, FL	March 16
Sarasota, FL	April 13
Austin, TX	April 19
Tampa, FL	May 3
San Antonio, TX	May 3
Long Island, NY	May 18 (tentative)
Kansas City, MO	May 17
Seattle, WA	TBA
Las Vegas, NV	May 17
Central New Jersey	June 7 (tentative)
Boston, MA	June 14
Northern New Jersey	TBA
No. Michigan	TBA
Detroit, MI	May 3
Baltimore, MD	TBA

Beverly Hayden (L), and Charlene Grimes (R)

Lavern Hayden

The Faces of Lupus

Lavern Hayden, Chickamauga, GA

Q: What is your connection to lupus?

A: My wife Beverly has lupus. She was diagnosed at age 13 and has suffered many complications from the disease, including attacks on her heart that required a pacemaker, and on her kidneys, which required aggressive chemotherapy.

Q: How did you become involved with the ALR?

A: Four years ago, we were invited to attend an informational meeting hosted by the ALR in Chattanooga where we heard about efforts to raise money for a cure through the ALR walks.

Q: How do you support the ALR?

A: We formed an ALR Walk team, "Overcomers," and have since raised over $7000. We are always looking for opportunities to get our community involved as well as to share what the ALR is doing. Our fundraising involves a mailing campaign, approaching customers, holding yard sales and organizing benefit concerts. I developed a theme for our team to describe how we can help those with lupus use the name of the disease itself: Love, Understand, Pray, Uplift, Serve.

Q: Why do you support the ALR?

A: I support the ALR because lupus almost took my wife away from me and my children. I support the ALR in hope that one day a cure may be found to help my wife as well as the many others who are affected by this devastating disease.

Advocacy Update

Defense Department Includes Lupus in Medical Research

Thanks to the efforts of ALR's hundreds of volunteer advocates, ALR chair Robert Wood Johnson IV, and our Congressional champions, Senators Charles Schumer and Hillary Rodham Clinton, lupus has again been listed as a disease eligible for funding under the Department of Defense's (DoD) Peer Reviewed Medical Research Program.

Inclusion in the $50-million program is highly competitive. The ALR is proud to have initiated this effort and worked for its continued success since our initial inclusion in 2004. We also gratefully acknowledge Senator Arlen Specter, who was instrumental in our initial listing.

While our ultimate goal is the creation of a dedicated federal DoD program for lupus research, this continued listing is an important milestone in our effort to uncover new funding sources as we work towards a cure.

The $50-million allocated for the DoD medical research program does not include a guarantee or set amount of funding for lupus research. Rather, it is a competitive, open, peer-reviewed research proposal process that allows lupus researchers to compete for funding. A request for proposals will be announced soon.

ALR-Funded Investigators Receive Large Grants From DoD

Since 2004, the Department of Defense's medical research program has awarded approximately $5-million to lupus investigators throughout the country, many of whom have also received ALR funding. These include Prasad Devarajan, MD, of Children's Hospital of Cincinnati, Betty Diamond, MD, of the Feinstein Institute, Emily Gillespie, PhD, of the University of Minnesota, and Stephen Tomlinson, PhD, of the Medical University of South Carolina.

JUST THE FACTS

What the study showed:
Lupus activates distinct molecular programs in damaged kidneys.

What it means:
Defining specific disease processes in subgroups of people with lupus could help explain differences in outcome and treatment responses seen in people with lupus and enable clinicians to better target specific treatments to specific patients.

What's next:
Evaluate these pathways in a second independent group of patients and relate them to patients' disease status, and develop a panel of markers to predict disease course and response to therapy.

ALR funding:
$423,366

Rao PS, Bertheir CC, Eichinger F, Henger A, Cohen CD, Kretzler M and ERCB consortium. Differential renal transcriptional profiles characterize distinct subgroups of patients with Lupus Nephritis. Presented at ASN Renal Week 2007, October 31-Nov 5, 2007.

Identifying the Genetic Underpinnings of Lupus Nephritis

Lupus impairs the lives of patients by damaging multiple organs via an aggressive autoimmune process. Inflammation of the kidney, called lupus nephritis (LN), is one of the most severe complications in people with lupus. Yet lupus nephritis is highly variable and unpredictable, making tailored treatments difficult. In addition, current methods of classifying the kidney damage are descriptive, with very limited predictive power, and don't provide any insight into the underlying disease mechanisms.

In work presented at the American Society of Nephrology's Renal Week in early November, ALR grantee Matthias Kretzler, MD and his team, including Panduranga Rao, MD, presented information gleaned from genetic analyses of kidney biopsies on patients with lupus nephritis and normal controls. Using gene expression techniques, they were able to identify several kidney-specific molecular mechanisms that drive progressive renal failure in lupus nephritis. These included pathways that are involved in programmed cell death; pathways of immune activation (like interleukins, which activate immune cells); and tissue remodeling and regeneration.

They found two distinct subgroups within the biopsies. Each group's biopsy exhibited a different genetic expression even though patients had similar clinical characteristics. This is an important finding, said Dr. Kretzler, as it could possibly explain why the current method of grouping patients based on a cellular evaluation may, in fact, be erroneous, and could explain why individual patients within each group respond differently to treatment.

The next step is to further dissect out the pathways of these molecular mechanisms and correlate the findings at the genetic level to actual disease status, said Dr. Kretzler. "This would help us explain why there is a variable response to treatment and may enable us to devise treatments based on our knowledge of which biochemical pathway is active in that particular patient."

New Gene Variant Contributes to Lupus and Rheumatoid Arthritis

Decades of painstakingly difficult work into the genetic underpinnings of lupus and other autoimmune diseases have shifted into overdrive in the past couple of years as researchers take advantage of new scientific techniques. Instead of identifying genetic abnormalities by tracing the disease through families, today's researchers use gene scanning and gene chip technologies to quickly evaluate DNA from thousands of unrelated individuals, enabling them to identify "misspellings," also known as "variants" or "polymorphisms," in the millions of base pairs (adenine-thymine and guanine-cystosine) that spell out the genetic code. A variant means a gene may not code properly, perhaps not making the right protein, not making enough or behaving in other abnormal ways.

Numerous aberrant genes are believed to underlie lupus and the disease processes related to them, and ferreting them out has become a major focus of the Alliance for Lupus Research (ALR). One major finding comes from Elaine F. Remmers, Ph.D., a staff scientist in the Genetics and Genomics Branch at the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

She and her team, which includes ALR International SLE Genetics Consortium (SLEGEN) members Timothy Behrens, MD, Lindsay Criswell, MD, and Peter Gregersen, MD, have worked for 10 years to find genetic factors in diseases like rheumatoid arthritis (RA) and lupus. For much of that time, the investigators focused on time-consuming family-linkage studies. Recently, however, they have been able to use the newer techniques described earlier to study a region identified on chro-

mosome 2 by the previous linkage studies, analyzing DNA from 3,000 patients with rheumatoid arthritis (RA) and 1,000 patients with lupus. By comparing the frequency of the variants in patients with controls, they were able to identify the STAT4 gene variant as a culprit in susceptibility to both diseases. Their findings were published in September 2007 in an online edition of *The New England Journal of Medicine*.

"This is one of the few studies of a genetically complex disease where the linkage studies led us to a region in which we found a gene variant that seems to be associated with disease susceptibility," said Dr. Remmers. "It's a hard way to go; we know that now. And with newer markers and methodologies for genotyping and looking at associations we would go about it differently today. But we started this work 10 years ago by collecting data on RA patient families for our first linkage study. It has been very satisfying to follow up those linkage studies and come up with a genetic variant of a gene that is consistently associated with disease."

The STAT4 gene makes a protein that helps moderate the effects of inflammatory immune chemicals implicated in lupus and RA, such as interleukin-12 and some types of interferon. It also controls the differentiation of T cells into TH-1 cells, and may contribute to the development of TH-17 cells, both of which seem to play a role in maintaining chronic inflammation in the body.

In the United States, this form of STAT4 is present on about 10 chromosomes of the general population, but 31 chromosomes of people with lupus. Through their work, the researchers suspect that one copy of the gene increases the risk of developing RA by about a third, and of developing lupus by about 55 percent. Two copies of the gene likely increases the risk of RA by 60 percent, and more than doubles the risk of lupus.

And the correlation between lupus and RA? "There have been several associations for regions and genes found in more than one autoimmune disease," said Dr. Remmers. Indeed, one theory suggests that certain variants in the genome may contribute to autoimmunity in a general sense, just as others contribute to autoimmunity in a specific sense (i.e., in lupus only; or RA only; or Crohn's disease only).

After identifying the linkage with RA, Dr. Remmers said her team looked at a possible association with lupus because of earlier linkage studies that weakly implicated the same region of the genome. One reason the variant seems to confer a greater risk for lupus than RA may be that genetic factors that contribute to lupus seem to contribute more in terms of susceptibility than genetic factors in RA.

Identifying Aberrant Signaling Pathways in B Cells of People with lupus

Although B cells play a key role in the development and disease progression of lupus, we still don't know exactly what goes wrong with these cells and why. However, several research teams around the world are investigating this question. Several studies have found that genetically manipulating certain signaling axes, or pathways, creates a lupus-like disease in animal studies. These signaling pathways work like communication networks in which certain substances are released or inhibited, determining how cells communicate with one another. When these systems fall out of balance, disease and tissue damage often result.

While manipulating the pathways can cause a lupus-like disease, it doesn't show whether those aberrant pathways already exist in spontaneously occurring lupus. To investigate that question, ALR grantees Tianfu Wu, PhD, and Chandra Mohan, MD, PhD, both from the University of Texas Southwestern Medical Center in Dallas, and their team examined multiple signaling pathways in B cells from mouse lupus models. They found an elaborate network of hyperactivated signaling cascades, suggesting that "B cell activation in lupus may not be restricted to isolated signaling cascades — indeed, almost all of the signaling pathways

JUST THE FACTS

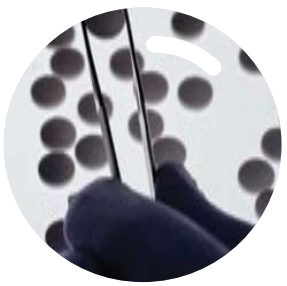
What the study showed:
A common variant form of the STAT4 gene may be linked to the development of lupus.

What it means:
If the findings are confirmed, it could provide new targets for treatments.

What's next:
To better understand how this series of noncoding variants works in terms of the gene expression and confirm any link with the disease.

Related ALR funding:
International SLE Genetics Consortium: $2.2 millon

Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, de Bakker PI,W Le JM, Lee HS, Batliwalla F, Li W, Masters SL, Booty MG, Carulli JP, Padyukov L, Alfredsson L, Klareskog L, Chen WV, Amos CI, Criswell LA, Seldin MF, Kastner DL, Gregersen PK. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N Engl J Med*. 2007; 357:977-86.



JUST THE FACTS

What the study showed:
Several hyperactivated signaling pathways in B cells in mouse models of lupus.

What it means:
The identification of several new targets for therapy in lupus.

What's next:
Conduct studies in people with lupus to see if the same pathways are activated. If so, use the information to develop interventions to stem the disease.

ALR Funding:
Tianfu Wu: $75,000
Chandra Mohan: $1.5 million

Wu T, Qin K, Kurepa Z, Kumar KR, Liu K, Kanta H, Zhou XJ, Satterthwaite AB, Davis LS, Mohan C. Shared signaling networks active in B cells isolated from genetically distinct mouse models of lupus. *The Journal of Clinical Investigation*, 2007, 117(8): 2186–2196.

examined seemed to be dysregulated in lupus B cells." Translation: The communication network within B cells is all turned on, which seems to correlate with disease progression even in different mouse models of lupus. The results of their work were published in the August 2007 issue of *The Journal of Clinical Investigation.*

Understanding the complexity of the dysregulation or upregulation among signaling pathways, as well as their interactions, are critical early steps in developing drugs to target those pathways and, ideally, arrest the disease process. In their study, the team focused on one particular pathway: the P13K/AKT/mTOR axis, and the proteins released in response to signals sent through this pathway. This is a common pathway in cancer, and several compounds are already under investigation to interrupt it. When Dr. Wu's team tested one of these compounds (rapamycin, an anti-rejection drug) in the mouse lupus model, they found it improved the disease in the mice, in particular arresting kidney damage and limiting autoantibody production.

Premature Atherosclerosis in Lupus

As patients with lupus live longer, they face much greater risks of chronic conditions like atherosclerosis than people without lupus. They also develop it much earlier and without many of the traditional risk factors such as smoking, dyslipidemia and hypertension. Numerous researchers, including several ALR-funded scientists, are exploring the reasons behind this, as well as looking for biomarkers to identify high-risk patients early to allow for preventive measures.

Here, we report on two such efforts: One focused on premature atherosclerosis in adults; the other in children.

Implicating Endothelial Progenitor Cells in Lupus-Related Atherosclerosis

Alliance for Lupus Research (ALR) researcher Mark S. Segal, MD, Associate Professor of Medicine at the University of Florida in Gainesville, has been focusing on the possible role of endothelial progenitor cells (EPC) in premature atherosclerosis. In a paper published in the November 2007 issue of the journal *Arthritis and Rheumatology*, he and his colleagues reported on work linking low levels of these cells with high levels of interferon-1 (IFN-1) and endothelial dysfunction, a marker for atherosclerosis.

Endothelial progenitor cells originate in the bone marrow, can differentiate into endothelial cells (which line blood vessels), and are involved in processes such as endothelial vessel repair, which can prevent or limit the development of atherosclerosis. Previous studies find that low levels of these cells are linked to an increased risk of atherosclerosis. "The question was what we would see when we measured them in people with lupus," said Dr. Segal.

Indeed, his study found that blood from people with lupus contained lower levels of EPC cells than blood from people without the disease. Levels were even lower in patients whose blood also exhibited high levels of IFN-1. High levels of IFN-1 are correlated with more severe disease in lupus. Another link: high IFN-I levels were associated with blood vessel dysfunction in people with lupus.

So what's behind the link between low EPC levels and high IFN-1 levels? One theory points to interferon receptors on EPC cells, said Dr. Segal. High interferon levels might overwhelm the EPCs, he said, leading to apoptosis, or cellular "suicide." But that's just a theory. The next step is to examine the association in animal models to get a better sense of the cause and effect. And, of course, to show that the increased interferon levels that lead to decreased EPC levels are the reason behind the apparent increased cardiovascular risk.

JUST THE FACTS

What the study showed:
People with lupus with high levels of interferon-1 also have low levels of endothelial progenitor cells (EPC), which repair blood vessels, and early signs of atherosclerosis.

What it means:
Researchers are closing in on a potential marker and the underlying mechanism of premature atherosclerosis in people with lupus.

What's next:
To examine the association between EPC and IFN-1 in animal models to get a better sense of the cause and effect. And, of course, to show that the increased interferon levels that lead to decreased EPC levels are the reason behind the apparent increased cardiovascular risk.

ALR funding: $237,000

Pui Y. Lee , Yi Li, Hanno B. Richards, Fay S. Chan, Haoyang Zhuang, Sonali Narain, Edward J. Butfiloski, Eric S. Sobel, Westley H. Reeves, Mark S. Segal. Type I interferon: a novel risk factor for EPC depletion and endothelial dysfunction in SLE. *Arthritis and Rheumatology*, 56(11) Nov 2007: 3759-3769.

Blood Lipid Abnormalities in Children with Lupus

About one in five people with lupus are children. Given the significantly increased risk of premature atherosclerosis in people with the disease, it's likely that the longer one has lupus, the greater the risk of blood vessel damage associated with atherosclerosis. Since children are even less likely than adults to exhibit the traditional risk factors for atherosclerosis like smoking and uncontrolled hypertension, it appears that an important risk may stem from cholesterol abnormalities. And, indeed, studies find that people with active lupus have higher rates of very low-density lipoprotein (VLDL) and triglycerides — which can increase plaque buildup in vessels leading to atherosclerosis — and low levels of so-called "good" cholesterol, or high-density lipoproteins (HDL), which acts like garbage trucks to escort the "bad" cholesterol out of the bloodstream. In addition, a common treatment for lupus — systemic corticosteroids — can increase blood lipid levels.

In a study published in the online edition of the September 1 issue of the *Journal of Rheumatology*, Canadian researchers from The Hospital for Sick Children and the Department of Pediatrics at the University of Toronto in Canada obtained blood cholesterol readings of 54 children with lupus before they started corticosteroid treatment. The researchers found that most children (63 percent) had at least one lipid abnormality, primarily elevated triglyceride levels. They also found abnormally low levels of HDL (24 percent) and abnormally high total cholesterol levels (20 percent).

In addition, half the children with lupus-related kidney abnormalities had abnormally low HDL levels and most had abnormally high triglyceride levels, at least twice as high as in patients with no kidney involvement. Further analysis suggested that triglyceride levels were highest in patients with active kidney disease. Since we already know that reduced albumin levels related to lupus kidney disease is associated with elevated triglycerides, this suggests that another process may be contributing to high triglyceride levels in those with the disease.

The researchers suggest treating people with lupus for elevated triglyceride levels rather than overall cholesterol levels.

JUST THE FACTS

What the study showed:
The majority of children with lupus tested had at least one cholesterol abnormality, primarily high triglycerides.

What it means:
High triglyceride levels are an important risk factor for atherosclerosis, which occurs earlier and more often in people with lupus than in those without. However, it is still not clear how lipid abnormalities contribute to the accelerated atherosclerosis in people with lupus.

What's next:
More research regarding the possible role of lipid abnormalities in premature atherosclerosis in people with lupus.

Tyrrell PN, Beyene J, Benseler SM, Sarkissian T, Silverman ED. Predictors of Lipid Abnormalities in Children with New-Onset Systemic Lupus Erythematosus. J Rheumatol. 2007 Sep 1; [Epub ahead of print]

Drug Research & Development News

In each issue of LRU, we are pleased to share with you the latest news in the development of lupus treatments.

Of the eight new biological agents now being utilized in clinical trials in systemic lupus, — an achievement in and of itself, compared to the scarcity of clinical trial activity in lupus in the late 1990's — the Alliance for Lupus Research (ALR) has been directly supportive of research that has helped validate the therapeutic target for four of the eight. These four are asterisked in the list below.

Drug Name	Company, City, State
Rituxan*	Genentech, San Francisco, CA
Anti CD 22*	Immunomedics, Morris Plains, NJ
Lymphostat B*	Human Genome Sciences, Rockville, MD
MEDI 545* (interferon pathway)	Medimmune, Gaithersburg, Maryland
Riquent	La Jolla Pharmaceuticals, San Diego, CA
Edratide	Teva Pharmaceuticals, Petach Tikva Israel
Abatacept	Bristol-Myers Squibb, Princeton, NJ
Anti IL10	Schering Plough Corp, Kenilworth, NJ

Below is the latest news on several of these trials in progress – for more news, please see previous issues of LRU, or visit our website at **www.lupusresearch.org**.

Edratide: Israel's Teva Pharmaceuticals Industries Ltd announced in early September that edratide, a synthetic peptide being evaluated for use in lupus, did not meet its primary endpoint of reducing disease activity during a 26-week Phase II clinical trial. However, the drug, which is administered as a weekly injection, proved to be safe and well tolerated. Further analyses of the drug's performance in the trial are ongoing.

Epratuzumab: In late August, UCB and Immunomedics reported positive results from a follow-up phase I/II trail of epratuzumab for the treatment of lupus. Phase I of the trial analyzed the effect of the drug on certain types of B cells, showing that the drug targets naïve and transitional B cells. Phase II, designed to analyze epratuzumab's ability to inhibit B-cell activation found the drug stopped the overactivation of B cells in patients with lupus, but did not affect normal B cells in participants without the disease. Based on these results, Immunomedics is moving forward with the drug's development.

Atacicept: ZymoGenetics, Inc., and Merck Serono announced in early October that they had reached an agreement with the Food and Drug Administration (FDA) to conduct a pivotal clinical trial with atacicept in patients with lupus nephritis. This is one of two clinical studies that would form part of the companies' application for marketing authorization. The randomized, double-blind placebo-controlled multi-center clinical trial will be conducted at sites in North America, Europe, Latin America, and Asia, with approximately 200 patients with active lupus nephritis enrolled. The goal is to demonstrate that atacicept is safe and effective compared to placebo.

The companies plan to conduct a second study in patients with general systemic lupus erythematosus, for which a similar review process of the trial design and protocol is ongoing.

Atacicept works by interrupting the cytokine process that promotes B-cell survival and autoantibody production.

And the latest on CellCept, which has been used "off-label" for treatment of lupus nephritis:

CellCept® (mycophenolate): Roche and Aspreva Pharmaceuticals Corp., which was pursing development of this transplant drug for use in patients with lupus nephritis, announced in September that they would not proceed with its development after initial results from a Phase III clinical trial showed the drug did not meet its primary objective of demonstrating superiority to mycophenolate mofetil, currently used to treat lupus nephritis.

Alliance *for* Lupus Research

PREVENT. TREAT. CURE.

Because our Board of Directors pays all operating expenses, 100% of all donations to the ALR go directly to supporting medical research. To make a donation to the ALR, please visit our website **www.lupusresearch.org**, mail a check to ALR at 28 West 44th Street, Suite 501, New York, NY 10036, or call us toll-free at **800-867-1743**.

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