New Discoveries and Clinical Advances from HSS Rheumatology

Hospital-wide OA Collaborations

New Research in Stopping RA Inflammation

Biomarker for RA Drug Effectiveness

The Power of Patient Registries

The Nation-wide PROMISSE Study

New Cardio Prevention for Lupus Patients

Interview with the New Physician-in-Chief
HSS scientists and rheumatologists have pinpointed a cellular pathway that can halt the painful and destructive inflammatory response of the immune system gone awry in rheumatoid arthritis. It’s the immunoreceptor tyrosine-based activation motif coupled receptor – or ITAM pathway.

“'It completely turns things off,'” reports Lionel Ivashkiv, MD, Associate Chief Scientific Officer, who led the multi-center study. “'What we saw was the ITAM pathway triggering a complete inhibition of the inflammatory response.'”

Until now, the ITAM pathway had never been established – or even studied – as specifically involved in rheumatoid arthritis. But it had been shown to suppress so-called Toll-like receptors on pathways that promote inflammation. The team thought perhaps a secondary pathway might be involved.

That second pathway (DAP12-Syk-Pyk2-p38-MSK) was found and with it, a first-time role for calcium signalling downstream of the ITAM activated receptors. The team speculates the ITAM pathway helps integrate the extensive cross-talk that must necessarily happen among the cytokines of the many pathways involved in inflammation.

Discovering exactly how the ITAM pathway can so fully stop the inflammatory process will be the team’s next focus. Aiming, as Dr. Ivashkiv notes, “'To develop new treatments that can harness or control the ITAM pathway’s natural ability to stop inflammation completely. Ultimately bringing freedom from pain due to inflammation to arthritis sufferers everywhere.'”

In the 20 years or so I have been studying regulation of inflammation, this seems to be the most potent inhibitory mechanism we have ever seen.”

Lionel Ivashkiv, MD, Associate Chief Scientific Officer, David H. Koch Chair in Arthritis and Tissue Degeneration
Rheumatologists may one day be able to test in advance which patients with rheumatoid arthritis will benefit from expensive biological response modifier TNF-antagonist drugs – or biologics – and which will not. This is because a new study has indicated that RA patients with the most elevated type 1 interferon levels tend to be those who responded most favorably to TNF-antagonist biologics.

Lower Type 1 Interferon, Lower Response

Physician-in-Chief Mary K. Crow, MD, led this initial study for HSS, in conjunction with University of Southern California. A 35-patient sample was divided into three groups: RA patients who received a TNF-antagonist drug, RA patients who got no drug, and healthy volunteers. Using the Disease Activity Score in 28 joints, the patients were treated, then evaluated to determine whether they had a moderate, good, or no response to the drug. Comparing the three groups, higher levels of type 1 interferon prior to treatment were found in the blood of patients who benefited most. Lower levels were associated with lower response.

More Good Response Indicators

Patients who had an increased IFN-beta/alpha ratio – meaning they had more IFN-beta – were also more likely to respond to TNF-antagonist therapy. Another indication of good response was significantly higher baseline levels of IL-1 receptor antagonist in plasma samples when compared with nonresponsive or moderate responders. If wider studies prove consistent with these promising early findings, the results could represent a new tool for improved management of patients with rheumatoid arthritis.

Knowing whether a TNF-antagonist biologic will help a patient’s rheumatoid arthritis can save time, money, and patients investing emotionally in the possibility of relief. As Dr. Crow adds, “For those who demonstrate low levels of blood interferon activity, that information might be useful to guide patients to alternative treatments that might be more likely to work for them.”

“Treatment with these drugs is very expensive; the drugs can cost $16,000 or so per year. If you are going to use them, you would like to know that they are likely to work in your patient.”

- Mary K. Crow, MD
  Physician-in-Chief,
  Joseph P. Routh Chair in Rheumatic Diseases in Medicine
Doctors and scientists from every specialty at Hospital for Special Surgery have united to launch the HSS Osteoarthritis Initiative. Their goal: tame the nation’s number one disability challenge – osteoarthritis.

HSS Rheumatology has led groundbreaking insights into the molecular mechanisms of the inflammatory process in autoimmune conditions, how joints deteriorate, and how to manage quality-of-life issues in chronic inflammatory conditions. This same expertise can help expand the understanding of arthritis from simply being a “wear and tear” disease, to determining how inflammation plays a pivotal role, and how to bring relief to patients at every stage of the disease.

Interdisciplinary investigation teams in the HSS Osteoarthritis Initiative meet regularly

As the nation’s largest specialty hospital devoted to orthopedics, rheumatology and the science of human mobility, HSS is uniquely positioned to both promote immediate, life-enhancing solutions and uncover key cellular answers that can both prevent and treat the disease.

Inflammation Experts Bring Their Knowledge

Physician-in-Chief Mary K. Crow, MD, is a world authority on the molecular mechanisms of inflammation in autoimmune conditions. She brings that expertise to bear on her current testing of ways inflammatory cells may play a role in disease progression and joint deterioration in OA.

Using samples of synovial tissue and joint fluid gathered in HSS surgeries, Dr. Crow and Carla Scanzello, MD, PhD, have already documented that certain inflammatory molecules were increased in the joints of patients who were found to have early OA. Currently, the team is investigating how molecular changes in the synovium might result in cartilage damage. They’re hoping to find clues to why some people develop severe OA while others only have milder symptoms.

Rich Data, Right Questions

HSS Rheumatology’s long experience with translating key discoveries into life-enhancing treatments can help investigatory teams hone in on promising areas of study.

Because HSS performs more joint replacements than any other hospital – over 8000 a year– biosamples from the operating room are backed with rich data, pre-and-post surgical imaging, wide-ranging patient experiences and long-term follow-up through extensive patient registries. Plus, biosamples can easily be obtained from every level of disease progression, including initial repairs of damaged tendons or bones. Early injury is known to lead to early OA. HSS Rheumatologists can combine their unique knowledge of early detection of inflammatory conditions with the extensive HSS patient data to help speed studies seeking ways to prevent injury from being an inevitable precursor to OA.

“OA affects every part of the joint: the bone, ligament, tendon, cartilage and even the muscles surrounding the joint. You can’t think of it as just a cartilage disease. OA is really the failure of an organ.”

- Steven A. Goldring, MD
Chief Scientific Officer,
St. Giles Research Chair
From One HSS Landmark Discovery to the Nation’s Largest Ever Investigation of Pregnancy Loss in Lupus:

The PROMISSE Study

Jane Salmon, MD, and her team rewrote the knowledge banks about pregnancy loss in women with lupus when they established that the complement system – not widely believed thrombosis – was the cause. And now, Dr. Salmon is leading a nationwide study that could change the field even more: The PROMISSE Study. (Predictors of Pregnancy Outcome: BioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus)

The PROMISSE Study is a ten-year, multi-center project funded by the National Institute of Arthritis, Musculoskeletal and Skin Diseases of the National Institutes of Health. 700 pregnant volunteer patients with lupus and/or antiphospholipid antibodies, as well as disease-free subjects, will be closely monitored every month of their pregnancy.

Early Findings Already Helping

Over 590 patients have already been enrolled. First studies show that timing of conception with regard to lupus activity affects outcomes. Conception when the disease is inactive is associated with rare flares during pregnancy and improved likelihood of delivering healthy babies. Also, the presence of lupus anticoagulant – a specific subset of antiphospholipid autoantibodies – is highly associated with poor pregnancy outcome, while anticardiolipin antibodies, alone, are not strong predictors of pregnancy complications.

The Discovery That Changed It All

Before 2001, thrombosis was widely assumed to be the cause of miscarriages in women with antiphospholipid antibodies and lupus. Preventing thrombosis was standard procedure. Yet, that treatment – anticoagulation throughout pregnancy – was risky, unreliable, and did not consistently result in more successful pregnancies.

Then Dr. Salmon and her team discovered why: thrombosis, in and of itself, wasn’t responsible for pregnancy loss. The real culprit was the complement system. Since that landmark finding, Dr. Salmon and her lab have shown in experiments in animal models that inhibiting complement system activity in vivo can prevent fetal loss and growth restriction associated with antiphospholipid antibodies.

"Women with lupus can have normal pregnancies when they work together with their doctors. First, they can time conception when disease activity is not present. Then they can maintain continual close follow-up to anticipate potential problems.

In the PROMISSE Study, we are collecting data, prospectively, from 700 women and assessing activity of inflammatory and immune pathways throughout their pregnancies. Our goal is to find new ways to predict outcomes and new targets for treatment."

– Jane Salmon, MD,
Attending Rheumatologist;
Senior Scientist;
Collette Kean Research Chair;
Co-Director, Mary Kirkland Center for Lupus Research

The PROMISSE Study
Click here to learn more at HSS.edu
Key findings in the history of pioneering research on lupus and cardiovascular disease at HSS:

First establishing the connection: 28% of lupus patients tracked over 3 years developed progressive atherosclerosis - significantly over the American norm. Inflammation, a hallmark of autoimmune disease, may be a trigger.

Increased plaque progression found to be associated with increased levels of the proinflammatory cytokine IL-8, whose levels are commonly raised in lupus.

Patients receiving aggressive immunosuppressive therapy for lupus less likely to develop heart conditions.

Analyses of HSS patient data revealed the left ventricle of lupus patients was significantly increased in mass.

The endothelial cells of lupus patients show evidence of activation by interferon-alpha.

New CVD Prevention Program

A comprehensive new program at HSS will help patients who have lupus – or have been diagnosed as aPL positive – to prevent cardiovascular disease. HSS led the discoveries establishing that patients with Systemic lupus erythematosus (SLE) have an increased chance of developing atherosclerosis. (Details, below left.) Elevated levels of antiphospholipid antibodies (aPL) are also known to increase the chances of a person developing artery blocking clots.

Potential Model for Lupus Cardio Care

The new CVD Prevention Program at the Mary Kirkland Center for Lupus Care launches an integrated model for helping reduce heart attacks in patient with lupus. Patients will be evaluated for traditional cardiac risk factors such as blood pressure, blood glucose, cholesterol levels, body mass index, diet and exercise habits, smoking status, aPL profile, and medication usage. Non-traditional and lupus-specific risk factors will also be measured.

A staff nutritionist, physical therapist, and program coordinator will help develop specifically-tailored lifestyle and education programs. A summary report of CVD risk assessment will be provided to referring physicians. The CVD Voice newsletter, will keep patients advised of news and information about their condition and heart disease. As well as provide interesting tips and ideas for staying healthy.
The HSS Patient Registries are a rich resource for innovative insights, testing ideas from clinical observations, refining theories, and speeding the translation of discoveries into clinical trials that can bring new treatments helping people’s lives.

— Michael P. Lockshin, MD
Attending Physician; Director, Barbara Volcker Center for Women & Rheumatic Disease; Co-Director, Mary Kirkland Center for Lupus Research & Care

With over 265,000 patient visits annually, HSS is the largest specialty hospital in the nation devoted to orthopedics and rheumatology. And every HSS patient is invited to become a research partner by joining a Patient Registry.

That’s why, Hospital for Special Surgery’s extensive patient registries can provide some of the largest and deepest informational tools for current and future research in the entire field of musculoskeletal medicine. The hospital now has 30 registries covering different conditions and patient groups.

Over 1000 Patients in the Lupus Registry

The Mary Kirkland Center at HSS has been advancing Lupus research – and enhancing patients’ lives – since 2001. And the long-term relationships developed with patients at the Center have helped enroll more than 1000 volunteers into the HSS Lupus Patient Registry.

Preetima Persad, MPH, is the Kirkland Care Center manager and knows each patient personally. As she explains, “People with lupus are sometimes wary of participating in an ongoing study. When you develop and maintain a professional friendship with the patients, they are more than happy to continue.”

From Observation to Breakthrough

Ground-breaking advances have come from initial observations seen in the large patient volume at HSS that could then be quickly examined using the rich HSS databases. Examples include: establishing the connection between heart disease and lupus, as well as the current nationwide PROMISSE study for preventing pregnancy loss in autoimmune conditions. Patient registries are going to play an important role in the interdisciplinary collaborations of HSS Osteoarthritis Initiative.

(Click here for more on the OA Initiative)
A. There are many challenges. Rheumatologists have improved the treatment of rheumatoid arthritis and other inflammatory arthritis syndromes substantially. But still, patients rarely achieve remission. Lupus, scleroderma, and myositis remain diseases that do not have highly active therapies other than those that result in important long term toxicities.

Perhaps the biggest challenge in rheumatology, from the public health standpoint, is the pain and disability associated with osteoarthritis. OA is an increasingly prevalent problem in the aging population.

Every specialty at HSS is involved in the evaluation and management of patients with OA, and we have united our clinical expertise with the HSS Osteoarthritis Initiative. With our large patient volume, clinical databases and access to patient tissue, rheumatologists and researchers are working with surgeons, radiologists and others to identify the most promising new research directions. Our goal is to optimize the current approach to treatment of patients with OA, while pursuing research studies that will lead to prevention of disease progression.

Rheumatologists can bring a deep understanding of the underlying mechanics of an inflammatory disease to the interdisciplinary collaborations. Rheumatologists are also on the frontlines of treating patients at their earliest encounters with the disease, which provides an opportunity to perform translational research aimed at preventing advanced OA.

Q. What are the strongest challenges you see in the field of Rheumatology right now? How are you hoping HSS can provide leadership in meeting them?

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Q. Translational research is a hallmark of both your work and HSS. What strengths of the Rheumatology Division do you hope to emphasize in its contributing to both translational research and advances in clinical care?

A. One is the strong collaboration among researchers and clinicians at HSS. Another is participation of our patients in the considerable translational research that we do here. I also hope to continue to recruit talented physician-scientists – people who will sustain our tradition of strong translational research. HSS offers unique opportunities to doctors to be able to conduct significant research while also having a thriving clinical practice. Being able to personally see and treat patients enriches both research and patient care.

Q. Where does the basic science suggest the next area of clinical progress in lupus management will be?

A. I am looking forward to hearing how the clinical trials of therapies that inhibit the interferon-alpha pathway are progressing, as that is the area of focus of my own lab.

Q. What are the opportunities that excite you most about your new role as Physician-in-Chief?

A. It is interesting to learn about the management side of the hospital and particularly how we can best incorporate an academic focus in our clinical care activities. It is also exciting and challenging to motivate and incentivize the Department of Medicine faculty to develop their individual careers to be both rewarding to each of them, individually, while making important contributions to the mission of HSS.

Q. For you, what makes Hospital for Special Surgery unique?

A. The dedicated people and collaborative style.

Q. What opportunities in research or patient care particularly interest you about the potential for interdisciplinary collaborations at HSS – especially in the age of technology?

A. Many, including continued opportunities to identify biomarkers of disease activity and targets for therapy in lupus and scleroderma. Also the new opportunities for working with the orthopedic surgeons, radiologists, and other HSS specialists, to organize translational research targeting osteoarthritis and inflammatory arthritis.

Q. What aspects of doing research at HSS would you find most difficult to recreate at other academic centers?

A. The close interactions among research staff and clinicians. Even the physical proximity of our hospital and clinics with the research building facilitate that. So does the close involvement of rheumatologists and internists in the HSS Department of Medicine with the surgeons in the perioperative medical care of surgical patients. That side-by-side involvement stimulates a culture of collaboration among internists and surgeons. Other institutions do not have the same physical proximity of faculty and specialized focus on musculoskeletal and immune-mediated diseases that we have at HSS.

Q. Are there unique areas of research at HSS that you encourage Rheumatology Fellows to be sure to follow?

A. Our fellows regularly hear from us regarding the translational research initiatives. I also encourage exposure to advances by our more “basic” researchers who study cell signaling and gene regulation mechanisms.