



HSS Rheumatology Research News

Click/Tap Any Area to See Recent Studies



Lupus



Rheumatoid Arthritis



Inflammation & Autoimmunity



Osteoarthritis



Scleroderma



Health-Related Quality of Life, Ethics, & Education



HOSPITAL
FOR
**SPECIAL
SURGERY**



HSS Lupus Research

[Click/Tap Any Topic for Details & Authors](#)



Mary K. Crow, MD,
Physician-in-Chief

New Method of Predicting Severe Lupus Flares: Change of Levels of Anti-dsDNA Titers

Bigger changes more likely to indicate a severe flare



Jane E. Salmon MD,
Collette Kean
Research Chair

Favorable Prognosis in a Large, Prospective Multicenter Study of Lupus Pregnancies

PROMISSE study shows 80% favorable outcomes



Michael Lockshin, MD
Attending Physician

Effects of Treatment with Fasudil on Lupus Pathogenesis in Lupus-Prone Mice

How ROCK inhibitor drug impacts lupus disease activity



Alexandra Pernis, PhD
Senior Scientist

Mucocutaneous Lupus Flares Have the Strongest Association with High Type I Interferon Levels

IFN-I levels rise higher with mucocutaneous lupus flares



Doruk Erkan, MD
Assistant Attending
Rheumatologist

SLE Monocytes are Less Responsive to the Anti-Inflammatory Signals of interleukin-10 When Immune Complexes are Present

Illuminating the paradox of elevated levels of
anti-inflammatory IL-10 in an autoimmune disease



Kyrious Kirou, MD
Assistant Attending
Physician

Heart Disease and Lupus: Novel Samples of the Endothelium Reveal Molecular Changes Potentially Implicating Atherosclerosis

Unique sampling method reveals potential cellular
indicators with implications for developing heart disease

[HSS Research Menu](#)

[Lupus Studies](#)

New Method of Predicting Severe Lupus Flares: Degree of Change of anti-DNA Titers

Next Lupus Study

Back to Lupus Menu

Authors

HSS:

Nancy Pan, MD

Rolando Duculan, MD

Stephen L. Lyman, PhD

Mary K. Crow, MD

Kyriakos A. Kirou, MD

Hospital Saint Joseph

Saint Luc, Paris:

Isabelle Amigues, MD

Interfaith Medical Center, Brooklyn:

Faiza Aziz, MD

While 76% of US rheumatologists test blood levels of anti-DNA titers to monitor disease activity in patients with lupus, there are conflicting reports about this measurement's utility. Studies show patients can have increased anti-DNA titers, yet display no clinical lupus symptoms. Conversely, increased disease activity has occurred in patients with low, or even absent, anti-DNA titers.

Now, HSS Rheumatologists have found that measuring the extent of change – not just the levels – of anti-DNA titers can more accurately predict a patient's oncoming clinical flare. A dramatic increase in *double-stranded anti-DNA* (anti-dsDNA) titers may herald a severe SLE flare within the next 6 months.

The study matched 23 patients who had experienced a severe flare in the past year with 45 control patients who had not. A significant number of the patients who experienced severe flares showed a rapid surge in anti-dsDNA titers within 6 months before the flare. The more dramatic the surge, the more severe the flare. However, the rapid surge was not predictive of a renal flare.

Larger studies can help fully establish how rapidly rising anti-DNA titers may be used as a possible early-warning signal of oncoming severe lupus flares.

HSS Research Menu

Favorable Prognosis in a Large, Prospective Multicenter Study of Lupus Pregnancies

Next Lupus Study

Back to Lupus Menu

Authors:

HSS

Jane E. Salmon, MD
 Michael D. Lockshin, MD
 Lisa R. Sammaritano, MD
 Lamya Garabet
 Emily R. Reeves
 Marta M. Guerra, MS

New York University School of Medicine

Jill P. Buyon, MD

Albert Einstein College of Medicine

Mimi Kim, ScD

University of Toronto and LifeQuest Centre for Reproductive Medicine,

Carl A. Laskin, MD

Univ of Utah:

Ware Branch, MD
 Allen D. Sawitzke MD

Johns Hopkins University School of Medicine

Michelle Petri, MD, MPH

Oklahoma Medical Research Foundation

Joan T. Merrill, MD

HSS Research Menu

The PROMISSE* Study is the nation's largest ever prospective investigation of pregnancy complications in women with lupus. Its 10-year, multi-center research grew from the ground-breaking discoveries by Jane Salmon, MD, and her team, that the complement system – not widely believed thrombosis – was the trigger of pregnancy loss, preeclampsia and growth restriction.

Now, a recent PROMISSE study shows that a favorable pregnancy outcome is highly likely if a woman's lupus is stable at conception and remains so throughout pregnancy.

80% of the 333 women studied had a favorable outcome. Further, women whose lupus was clinically stable at the baseline measurement taken at the beginning of pregnancy rarely developed flares of any degree.

Of the 63 adverse outcomes in the study, the majority were associated with severe flares during pregnancy, high titer aPL antibodies, and higher levels of uric acid at baseline.

This large, prospective study can help reassure patients with stable lupus contemplating pregnancy, as well as suggest parameters that merit caution. It suggests that waiting for clinical stability to consider conception will minimize the risk of adverse outcome.

* *PROMISSE stands for Predictors of pRegnancy Outcome: BioMarkers In antiphospholipid antibody Syndrome and Systemic Lupus Erythematosus) Over 700 women have been enrolled. PROMISSE is funded by the National Institute of Arthritis, Musculoskeletal and Skin Disease (NIAMS) of the National Institutes of Health.*

Effects of Treatment with Fasudil on Lupus Pathogenesis in NZB/W F1 Female Mice

Next Lupus Study

Back to Lupus Menu

Authors

HSS:

Roslynn A. Storzaker

Partha S. Biswas

Sanjay Gupta, MD

Weijia Yuan, MB

Li Song

Uma Chandrasekaran

Alessandra B. Pernis

Columbia University

Medical Center:

Govind Bhagat, MBBS

Two molecular messengers – the cytokines IL-17 and IL-21 – are well-established participants in inflammation in lupus. To produce IL-17 and IL-21, the body requires a transcription factor called IRF4. The ability of IRF4 to drive the production of IL-17 and IL-21 can be controlled by specific proteins, which phosphorylate IRF4. These specific proteins are called Rho Kinases – or ROCKs. There are drugs that can block this reaction, which are called ROCK inhibitors. Fasudil is a ROCK inhibitor.

In an earlier mouse study, the research team found that Fasudil reduced IL-17 and IL-21 production and ameliorated autoimmune symptoms. Now, the team sought whether Fasudil could also treat lupus in a different mouse model of lupus – NZB/W F1 Females. The mice were given 100mg of Fasudil in their drinking water starting at either 18 or 24 weeks of age. A control group received no drug.

The Fasudil-treated mice exhibited improvements in many parameters of inflammation. Importantly, kidney health benefitted and mortality was reduced.

Blood levels of anti-dsDNA antibodies were down, as were all six serum immunoglobulin isotypes investigated (IgG1, IgG2a, IgG2b, IgG3, IgM and IgA). The development of severe proteinuria and mortality was significantly reduced in Fasudil treated mice, when treatment was started at 18 weeks of age. Further studies are required to determine the specific mechanisms by which ROCK inhibitors altered the inflammatory responses in NZB/W F1 lupus-prone mice to determine Fasudil's potential as a treatment for lupus.

HSS Research Menu

Mucocutaneous Flares Have the Strongest Association with High Type I Interferon Levels in Patients with Systemic Lupus Erythematosus

[Next Lupus Study](#)[Back to Lupus Menu](#)

Interferon (IFN) is a protein that plays an important role in the first line of defense against viral infections. However, for patients with autoimmune conditions like lupus, the production of this molecule can lead to over activation of the immune system and have harmful effects on the body. Patients with lupus have elevated levels of type I IFN (IFN-I) and during a lupus flare, those levels can rise even further.

This study sought to determine whether lupus flares of specific organs of the body correlated with high levels of IFN-I. The answer is yes. IFN-I level was most elevated during mucocutaneous flares when compared with musculoskeletal and renal flares.

Authors

HSS:

Elzbieta E. Jacek
Mikhail Olfieriev, MD
Rolando Duculan, MD
Nancy Pan, MD
Mary K. Crow, MD
Kyriakos A. Kirou, MD

Estacio de Sá University,
Rio de Janeiro, Brazil
Vinicius Domingues

Lupus flares can involve various parts of the body. Mucocutaneous flares refer to symptoms involving skin and mucous membranes, such as the mouth, and are manifested by skin rashes, hair loss and mouth sores. Other lupus flares affect internal organs such as kidneys and the brain, or are musculoskeletal, involving joints.

IFN-I levels of 36 patients with lupus were measured during regular visits. Information about the kinds of flares patients were experiencing, if any, was recorded. IFN-I levels varied in individual patients during the course of their disease and roughly correlated with disease activity. The median IFN-I levels were highest with mucocutaneous flares but less so with musculoskeletal and especially renal flares.

These results indicate a special role of IFN-I in the pathogenesis of mucocutaneous flares in patients with lupus and suggest that blocking IFN-I with special therapies currently in development might benefit such patients.

[HSS Research Menu](#)

SLE Monocytes are Less Responsive to the Anti-Inflammatory Signals of Interleukin-10 When Immune Complexes are Present

In a healthy immune system response, the cytokine *interleukin-10* (*IL-10*), is a key molecular messenger signaling “stop inflammation”. Yet, IL-10 is often elevated in patients with lupus. Why do patients with a condition hallmarked by excess inflammation have raised levels of a cytokine that is supposed to stop inflammation?

Next Lupus Study

Back to Lupus Menu

A recent HSS study found that the receptors of certain immune system cells called *CD14+ monocytes* are complicit. Persistent exposure to circulating immune complexes, as occurs in autoimmune conditions like lupus, appears to alter the *CD14+ monocytes* receptors’ ability to receive IL-10’s “stop inflammation” signal.

Authors:

HSS:

Weijia Yuan, MD

Stephen J. DiMartino,
MD, PhD

Patricia B. Redecha, BS

Lionel B. Ivashkiv, MD

Jane E. Salmon, MD

Cultured *CD14+* monocytes from healthy donors and patients with lupus were treated with human *immunoglobulin G* (IgG), an immune system molecule that responds to harmful invaders. During an immune response, IgG suppresses IL-10 and stimulates *CD14+* monocytes to produce their own cytokines triggering inflammation to help fight the invasion. Response over, IgG restriction lifts, IL-10 signals “stop inflammation” and *CD14+* monocytes cease producing inflammatory cytokines. In this study, the healthy monocytes did just that. The lupus monocytes did not. They produced more inflammatory cytokines TNF- α and IL-6 than did the healthy cells.

In the study, there were no actual invaders for IgG to fight. Except in lupus there is: the body itself. Immune complexes from the body’s misguided autoimmune response are always circulating. IL-10 may be signaling the actual condition – no invasion, stop inflammation – but for the lupus monocytes, persistent immune complexes indicate a different reality: an invasion that never ends. IL-10 raises the “stop signal”, but as this study shows, that signal is limited in lupus.

HSS Research Menu

Heart Disease and Lupus: New Findings of Molecular Changes in the Endothelium Potentially Implicating Atherosclerosis

Since their pioneering studies establishing lupus as an increased risk for premature heart disease, doctors and scientists at HSS have continued to reveal unique cellular indicators of the early onset of atherosclerosis in lupus patients.

Back to Lupus Menu

Molecular changes in the cells lining the blood vessels – or the *endothelium* – can signal early dysfunction leading to heart disease. Pin-pointing ways lupus endothelial cells behave differently than healthy endothelial cells could give clues why lupus patients develop atherosclerosis at a younger age, as well as serve as biomarkers of early developing heart disease.

Authors

HSS:

Diana Goldenberg, MD, MPH

Danieli C. Andrade, MD, PHD

Mary K. Crow, MD

Mikhail Olfieriev, MD

Jane E. Salmon, MD

Columbia University Medical Center:

Paolo C. Colombo, MD

Duygu Onat, PhD

Using a novel method of vein tissue sampling, a new study found unique cellular reactions with potential implications for heart disease in lupus: a marked interferon inducible signature and an associated decrease in transforming growth factor beta (TGF- β) signaling genes.

The interferon (IFN) pathway is one of the main immune system contributors to inflammation. TGF- β is a protein that helps control differentiation and proliferation of cells. Using a new sampling method, endothelial cells were collected from 14 patients with lupus and 10 without. The samples were taken from arm veins using endovascular wires, then separated using magnetic beads coated with endothelial specific antibodies.

Micro array analysis showed that in the lupus cells, interferon is being upregulated while genes that signal for TGF- β are being downregulated – the opposite of healthy cells. The new sampling technique may offer a way to use endothelial cells from arm veins to reveal unique cellular changes leading to early atherosclerosis in lupus.

HSS Research Menu



*Carl Blobel MD, PhD
Virginia F. and William R.
Salomon Chair in
Musculoskeletal Research*

HSS Rheumatoid Arthritis Research

Click/Tap Any Topic for Details & Authors

A Rapid and Reversible Mechanism Regulates ADAM17 and Controls Access to its Catalytic Site

New discoveries of the cellular mechanisms of the ADAM that cleaves TNF-alpha



*Lisa Mandl, MD, PhD
Assistant Attending
Physician*

Tweaking the Timing of Stopping Anti-TNF Medications Before Knee Replacement Surgery

Considering correlating timing to drug biological half life

In Mice: Deficiency of ADAM17 – or TACE – Prevents Arthritis

No ADAM17 – or TACE – meant no arthritis



*Theodore R. Fields, MD
Attending Physician*

Incorporating the Patient Perspective in Research

Developing a Patient-Focused Evaluation for an Early RA Support and Education Program



*Susan Goodman, MD
Assistant Attending
Rheumatologist*

Do Patients with Rheumatoid Arthritis Expect Less From Total Knee Arthroplasty?

Compared to patients with OA, patients with RA found to expect less from their knee replacement surgery

HSS Research Menu

RA Studies

A Rapid and Reversible Mechanism Regulates ADAM17 and Controls Access to its Catalytic Site

Authors

HSS:

Sylvain M. Le Gall, PhD
Thorsten Maretzky, PhD
Priya D. A. Issuree
Carl P. Blobel, MD, PhD

Department of
Respiratory Care and
Immunology, Merck
Research Laboratories

Xiaoda Niu
Daniel Lundell

Christian-Albrechts-
University, Kiel, Germany
Karina Reiss, PhD
Paul Saftig, PhD

Ontario Cancer Institute,
University of Toronto
Rama Khokha, PhD

Anchored on the membranes that encapsulate cells in the body are glycoproteins that can act as molecular signaling switches releasing and transforming other proteins – also bound on cell membranes – into action. These glycoproteins are called ADAMs, short for *a disintegrin and metalloprotease*. ADAMs have cell-to-cell communication abilities and pathway triggering effects that are many and far-reaching.

The process by which one protein, like an ADAM, releases and transforms another protein from a cell membrane is called *cleavage*. In cleavage, the amino acid chain that tethers the protein to the cell membrane is, essentially, broken apart – or *cleaved* – in a specific place to trigger a specific result.

One particular ADAM, known as ADAM17, is responsible for cleaving several significant molecular participants in an immune system response, including *tumor necrosis factor alpha* (TNF- α), the key cytokine messenger that signals for increased inflammation. (ADAM17 is also known as TACE for *TNF- α convertase*.) Drugs that block TNF- α are important treatments of rheumatoid arthritis.

Before ADAMs can go cleave other membrane-bound proteins, they must first be summoned into action. Much remains to be known about how ADAMs are activated.

But now, an HSS study has identified specific cellular mechanisms that control ADAM17's activation. What's more, the team found that ADAM17's activation is both rapid and reversible.

(continued, [click/tap here](#))

[Back to RA Menu](#)

[HSS Research Menu](#)

(continued)
Rapid and Reversible
Regulation of ADAM17

Previous Page

Back to RA Menu

Next RA Study

HSS Research Menu

Discovering that ADAM17 can be swiftly activated – and swiftly called off – helps explain how the immune system can use ADAM17 to quickly release more TNF- α , or other immune response participants, that increase inflammation.

Proteins have parts that can change or transform called domains. An ectodomain is a domain that extends outside the cell membrane when the protein is anchored. When activated ADAMs cleave other proteins from cell membranes the process is called “*protein ectodomain shedding*”, because the ectodomain is “shed” away from the rest of the protein. The ADAM that cleaves the ectodomain into “shedding” is called a *sheddase*.

ADAM17 is the *sheddase* that causes the TNF- α ectodomain to shed. This is vitally important in an immune system response. Because the TNF- α ectodomain has the soluble, usable part of TNF- α . Once shed, the now soluble TNF- α ectodomain can start signaling for inflammation.

ADAMs are like scissors. Before they can go cleave something, they have to be opened. This active part that opens and closes is called an ADAM’s “catalytic” site.

The team pinpointed ADAM17’s catalytic site and found that when ADAM17 participates in an immune system response, its catalytic site is open and exposed. Using a very tight binding inhibitor of ADAM17, called DPC333, the team saw how the inhibitor quickly bound to ADAM17 on active cells, but not quiescent ones.

These new findings present a range of targets for therapies that could prevent ADAM17 from releasing TNF- α and other inflammation builders, or even possibly prevent misguided autoimmune reactions from triggering in the first place.

**Tweaking the Timing of Stopping Anti-TNF Medications
Before Knee Replacement Surgery**

When patients with rheumatoid arthritis (RA) are scheduled for surgery, their anti-TNF medications are routinely stopped. Anti-TNF drugs prevent inflammation by blocking cellular signaling for an immune system response. Stopping the drugs lets the signals proceed, increasing the risk of inflammation-triggered RA flares. Yet, a certain amount of inflammatory response from the immune system is necessary for aspects of surgical healing – like repairing cut tissue and fighting off post-surgical infection. Stopping the drugs allows that response.

Authors

HSS:

Beverly Johnson, MD
Susan M. Goodman, MD
Michael Alexiades, MD
Lisa A. Mandl, MD, MPH

Few studies have examined withholding anti-TNF medications and post-operative disease flares. Now, an HSS study, investigating the issue in total knee replacement, has found that timing the anti-TNF drug withdrawal does not appear to reflect the biological half life of the medication.

Larger studies will be needed to fully validate the findings, but this new study raises the possibility that more thoughtful stopping times, which correlate with how long the drugs stay active in the body, could result in shorter withdrawal periods, thus reducing the risk of RA flares.

Back to RA Menu

HSS Research Menu

The research team utilized data from the large HSS Total Joint Replacement Registry, which holds information on over 20,000 surgical patients at the hospital. Through a retrospective chart review, they identified 194 patients with RA who had total knee replacement surgery at the hospital between June 2007 and May 2010. Of those patients, 41.4% were taking anti-TNF medications for their RA. 86% of that group were instructed to stop taking the anti-TNF medications, usually from 2 to 4

(continued, [click/tap here](#))

(continued)

Timing Withholding of Anti-TNF Medications

weeks before the procedure, but at various times, with no seeming regard for how long the drugs stay active in the body. Data was collected on self-reported flares within 1 month of surgery as well as adverse events at 6 months. Medication charts were correlated to document any treatment.

Self-reported RA flares were higher in the group who stopped their anti-TNF medication (22.4% vs. 16.9%), but the difference was not significant. Post-operative adverse events were rare, only 7 occurred in any of the patients with RA, 4 of those among the anti-TNF medication group, not a significant association.

[Previous Page](#)

[Back to RA Menu](#)

[Next RA Study](#)

The 3 most commonly used anti-TNF medications all have a different biological half life, yet the withdrawal times prescribed for the patients were usually longer than the medication actually stays effective in the body.

For the drug *etanercept*, which has a half-life of 3 to 5.5 days, the average stop time was 2.4 weeks prior to surgery. For *adalimumab*, which has a half-life of 1.4 to 2.9 weeks, the average stop time was 4.6 weeks. For *infliximab*, which has a half-life of 1 to 1.7 weeks, the average stop time was 4.9 weeks.

The longer the RA medication is withheld, the more risk a patient has for RA flare. Yet, the low risk of adverse events suggest that perhaps there is room for tweaking the timing the drug is held to be more reflective of how long the medications stay active in the body.

Larger studies should examine if more pharmacologically based timing of anti-TNF medication withdrawal prior to surgery might minimize the risk of post-operative RA flares, while still maintaining the excellent surgical outcomes.

[HSS Research Menu](#)

Deficiency of TACE – or ADAM 17 – in Myeloid Cells Prevents Arthritis in Mice

In an immune system response, one of the key cellular messengers that signals for inflammation to occur is the cytokine *tumor necrosis factor-alpha* (TNF- α). Drugs that block TNF- α have shown success in treating rheumatoid arthritis by reducing inflammation.

Authors:

HSS:

Priya Issuree
Thorsten Maretzky, PhD
Jane E. Salmon, MD
Carl Blobel, MD, PhD

Keio University

School of Medicine:

Tokyo, Japan:

Kei Horiuchi

Now, a recent HSS study shows that removing the enzyme that triggers TNF- α into inflammation signaling action – called TACE or ADAM 17 – from myeloid cells in mice can prevent arthritis.

TNF- α is first synthesized in the body as a protein bound to the membrane of a variety of cells, including myeloid cells of the immune system like neutrophils and monocytes, cells that are prominently involved in rheumatoid arthritis.

In order for TNF- α to do its inflammation-signaling job, it has to be released from the cell membrane and converted into a usable soluble form. This happens by a process known as *cleavage*. The bonds of the amino acid chain forming the proteins of the cell membrane are broken apart – or *cleaved*. Cleavage is specific. It happens in a certain spot in the amino acid chain to create a specific result – in this case release and conversion of TNF- α – and is triggered by a specific enzyme just for that purpose, in this case TACE, which appropriately stands for *TNF- α -converting enzyme*.

So, what would happen if TACE is blocked? Theoretically, no TACE, no cleavage. No cleavage, no TNF- α released and converted to signal inflammation. And what this study discovered is in mice, no TACE, can mean no development of early arthritis.

(continued, [click/tap here](#))

[Back to RA Menu](#)

[HSS Research Menu](#)

(continued)

Deficiency of TACE – or ADAM 17 – Prevents Arthritis

[Next RA Study](#)

[Back to RA Menu](#)

[Previous Page](#)

Mice were generated with myeloid cells that were missing TACE. One of the ways to trigger arthritis in mice is by a molecular process known as *K/BxN passive serum transfer*. So *K/BxN* serum was injected in the mice missing TACE in their myeloid cells. The mice should have developed arthritis. However, the HSS scientists found that this didn't happen. Neither inflammation levels, nor ankle thickness measurement, showed development of arthritis.

The mice had no TACE to cleave TNF- α into inflammation signaling action, so arthritis did not develop. Thus showing the importance of TACE, myeloid cells, and TNF- α in arthritis development, especially in the early onset of the disease.

And how targeting the small molecules that inhibit TACE, and thus prevent the release of soluble TNF- α , could provide an alternate approach to existing therapies.

THE IMPORTANCE OF UNDERSTANDING ADAMS

TACE has another name, and that is ADAM 17. The formal name for the entire family of molecules that cleave protein bonds of cellular membranes so that cellular components are released and/or converted into action is a *disintegrin and metalloprotease* or ADAM. In the known number of ADAMs, TACE is number 17.

The HSS Arthritis and Tissue Degeneration Program, led by Carl Blobel, MD, PhD, has one of the nation's leading research programs investigating the working complexities of ADAMs.

Discovering ways to control ADAM activity could lead to the development of new therapies in arthritis, autoimmune conditions, wound healing, and even cancer.

[HSS Research Menu](#)

**Incorporating the Patient Perspective:
Developing a Patient-Focused Evaluation of
an Early RA Support and Education Program**

Treatments and programs aiming to help patients improve their quality of life, ought, logically, to know what patients believe “improved quality” really is. Yet, investigator-developed questions used in effectiveness research, even in quality of life studies, may not reflect what patients consider most important.

Recognizing this disconnect, discussions in the field now seek to include patient-identified criteria in outcomes studies. With one of the largest Divisions of Rheumatology in the world, HSS is in a unique position to help speed this change.

The HSS Early Arthritis Initiative developed and runs a support and education group especially for people recently diagnosed with RA within the past year. Members meet monthly to learn more about managing the illness, share the support of peers, and then complete evaluations about program impact.

The group’s aim to increase patient quality of life makes them an excellent resource for bringing patient opinion to practices. Responses from initial assessments of 40 group members were reviewed to gather data about which program outcomes mattered most to recently diagnosed patients. A focus group of 8 participants probed deeper, with an ear to patient language and meaning of outcomes.

(continued, click/tap here)

Authors:

HSS:

- Meredith K. Wolrich, LCSW
- Adena Batterman, LCSW
- Roberta Horton, LCSW, ACSW
- Linda Leff, RNC
- Theodore R. Fields, MD
- Vanima Lalsa, LMSW

Back to RA Menu

HSS Research Menu

(continued)
Incorporating the
Patient Perspective

Results found important patient-identified needs include: easily obtained, good information about RA; enhanced communication with MDs; sharing experiences with others; feeling less anxious; feeling more hopeful and confident about managing RA; and not feeling alone with RA.

Next steps: The results will be used to create questions for a new program evaluation which reflects the outcomes identified in the focus group. Individual group members will be interviewed one-to-one to ensure that the new evaluation questions, grounded in patient language, truly capture the intentions and concerns of the patients of the program it serves.

[Previous Page](#)

[Back to RA Menu](#)

[Next RA Study](#)

[HSS Research Menu](#)

Do Patients with Rheumatoid Arthritis Expect Less From Total Knee Arthroplasty?

Patients with rheumatoid arthritis (RA) who have total knee replacement often do not achieve the same functional results as patients with osteoarthritis (OA). Yet, patients with RA are surprisingly satisfied. Satisfaction can be the results of not just improved pain and function, but also by fulfillment of pre-operative expectations.

Authors

HSS:

Hassan Ghomraw,
PhD, MPH

Lisa A. Mandl, MD, MPH

Beverly Johnson, MD

Michael Alexiades, MD

Susan M. Goodman, MD

A recent HSS study sought to compare expectations between patients with RA and OA about *total knee arthroplasty* (TKA).

From the HSS Total Joint Registry, 62 RA patients having TKA were identified and matched to 124 OA controls. None had previous joint replacements. 87.1% were women, average age was 64.7 ± 9.7 years. Their activity score corresponded with “being able to walk around the house and for several blocks without assistance”. Their expectations about post surgical improvements were reported using the validated Hospital for Special Surgery Expectations Survey of 19 specific daily functions and activities.

Compared to matched patients with OA, patients with RA had clinically meaningful differences in overall expectations prior to TKA.

(continued, [click/tap here](#))

[Back to RA Menu](#)

[HSS Research Menu](#)

(continued)
Expecting Less
From TKA

The patients with RA had lower expectations for multiple individual activities on the HSS Expectations survey, including “Improve ability to perform daily activities” (work, chores) and “Improve ability to interaction with others” (take care of others, play with children).

On none of the 19 individual improvement possibilities did the patients with RA outrank the expectations of patients with OA.

These lowered expectations may explain why patients with RA have a higher degree of satisfaction with lower functional outcomes.

It is possible that patients with RA may be inappropriately accepting poorer outcomes than are possible in the anti-TNF era of improved daily function, and not optimizing their post surgical possibilities.

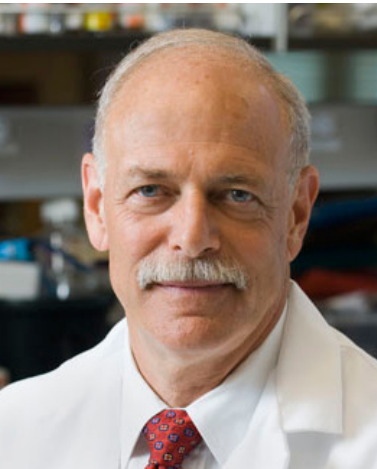
[Previous Page](#)

[Back to RA Menu](#)

[HSS Research Menu](#)

HSS Osteoarthritis Research

[Click/Tap Any Topic for Details & Authors](#)



*Steven R. Golding, MD, PhD
Chief Scientific Officer
St. Giles Chair*

Synovitis and Arthroscopic Partial Meniscectomy: Two-Year Post-Surgical Outcomes

Following outcomes of patients whose osteoarthritis was discovered during surgery, not on x-rays before the procedure

Multiple Pathways in Cartilage Metabolism Converge Upon the Regulation of One Enzyme: MMP-13

Three different cellular pathways all converge upon regulation of one enzyme: MMP-13



*Mary B. Golding, PhD
Senior Scientist
Director, HSS Laboratory
for Cartilage Biology*

[HSS Research Menu](#)

[OA Studies](#)

Synovitis and Arthroscopic Partial Meniscectomy: Two-Year Post-Surgical Outcomes

Biopsies taken during surgical repair of damaged joint tissues can reveal evidence of osteoarthritis (OA) not detectable in pre-surgical x-ray imaging. Established OA has been associated with longer surgical healing and poorer outcomes. But what about previously undetected OA? Does OA first discovered during surgery also mean poorer outcomes for that procedure? In this study, the answer is no.

Authors

HSS:

Edward F. DiCarlo, MD
Steven R. Goldring, MD

Rush University Medical Center,

Chicago:

Carla R. Scanzello, MD, PhD
Veero Kanda, MD

New England Baptist Hospital:

Anthony S. Albert, MD
John C. Richmond, MD
Brian McKeon, MD

In a recent two-year follow-up of patients whose OA was not evident on x-rays, but discovered during arthroscopic partial meniscectomy, poorer outcomes did not occur. Further, those patients' self-perception of improvement in pain, and function, was comparable to patients who did not have OA.

Two years ago, in an earlier study, 33 patients with no evidence of OA on their radiographic imaging underwent arthroscopic partial meniscectomy to repair a torn meniscus of the knee. The meniscus is one of two crescent-shaped cartilage “cushions” in each knee that help protect bone ends and distribute weight during movement.

Despite no evidence of OA on their pre-surgical imaging, 43% of the patients showed evidence of *synovitis* in tests on samples taken during the procedure. Of the group with synovitis, a majority (80%) had evidence of OA on direct cartilage examination. Synovitis is arthritic inflammation of the *synovial membrane* of the knee. The synovial membrane surrounds the knee joint and both produces and encapsulates *synovial fluid* – an almost clear, viscous fluid that lubricates

(continued, [click/tap here](#))

[Back to OA Menu](#)

[HSS Research Menu](#)

(continued)
Synovitis and
Arthroscopic Partial
Meniscectomy

the joint, reduces friction during movement, and nourishes the cartilage in the knee.

Synovitis hurts. The inflamed membrane hurts; it also starts producing more synovial fluid which causes swelling, and more pain, because the extra fluid is held inside the inflamed membrane.

The patients whose synovitis was first discovered during surgery actually reported greater pain before the meniscectomy than did the patients with no synovitis. The presence of pain, and other symptoms, was associated with expression of the CCL19 gene and the CCR7 receptor in the synovial tissue.

The most recent study showed that, over time, at multiple follow-up points, including the latest review at 2 years, the patients whose synovitis and OA were first discovered during the meniscus repair, did not have poorer outcomes. Importantly, they experienced pain relief and improved function comparable to patients without synovitis or OA, indicating that these patients are responsive to surgical intervention.

Pain and other symptoms were measured by the Lysholm score –a patient questionnaire measuring knee-specific symptoms and dysfunction. Lysholm scores at 16 weeks, 1 year and 2 years after the arthroscopy showed increased satisfaction with the results.

The results of this 2-year follow-up do not match the poorer outcomes usually associated with patients whose OA is evident on x-rays before surgery. It is possible that longer follow-up is needed to identify patients who develop progressive knee symptoms, or increased arthritis, after surgical intervention for meniscal tears.

[Next OA Study](#)

[Back to OA Menu](#)

[Previous Page](#)

[HSS Research Menu](#)

Multiple Pathways in Cartilage Metabolism Converge Upon the Regulation of One Enzyme: MMP-13

For patients with osteoarthritis (OA), one aspect of the condition is not hard to understand: *Less cartilage equals more pain*. For doctors and scientists searching for OA treatments, full understanding of the pathways of cartilage destruction, cartilage growth, and the problems created by cartilage's inability to repair itself remain some of the most complex molecular mysteries in medicine.

Authors

HSS:

Mary B Goldring, PhD
Miguel Otero, PhD
Darren A Plumb, PhD
Cecilia Dragomir, MD
Marta Favero, MD
Karim El Hachem
Ko Hashimoto, MD, PhD
Helmtrud I Roach, MsC
Eleonora Olivotto, PhD
Rosa Maria Borzi, MD
Kenneth B Marcu, PhD

Now, an HSS study has determined particular signaling points and mechanisms in 3 essential cartilage processes – loss by wear-and-tear, inflammation damage, and the growth of new cartilage cells – that show how all the differing cellular pathways converge upon regulation of one enzyme: MMP-13.

MMP-13 – ENZYME OF CARTILAGE BREAK DOWN

MMP-13 is one of a class of zinc-dependent *endopeptidases* called *matrix metalloproteinases* – abbreviated MMPs. *Endopeptidases* are enzymes that break apart the peptide bonds in molecules somewhere in the middle, not the end, of the chain of amino acids holding the protein bonds of the cell together. Even more specifically, MMP-13 is the major type II, collagen-degrading *collagenase*, that breaks down collagen in cartilage.

While stress, wear-and-tear and inflammation all use different ways to initiate similar cellular pathways to impact cartilage, at some point, their damage results in cartilage loss. That's when, the HSS team found, MMP-13, the enzyme of collagen cartilage break down, is signaled to join the process.

(continued, click/tap here)

[Back to OA Menu](#)

[HSS Research Menu](#)

(continued)

MMP-13

[Back to OA Menu](#)

[Previous Page](#)

MMP-13 – ENZYME OF NEW CARTILAGE GROWTH

The unique way that cartilage forms new cells also involves MMP-13, but as part of how the process can go awry. Chondrocytes start as *mesenchymal stem cells*. These stem cells differentiate to start the process of becoming either new cartilage or new bone. Chondrocytes make a scaffold of a collagen-rich matrix across which new chondrocytes grow.

A major challenge in cartilage repair is that no consistently reliable way has been found to encourage new chondrocytes to survive and grow across any matrix or scaffolding, natural or tissue-engineered – though several promising possibilities have been developed by HSS collaborations of doctors, scientists, and bioengineers. Knowing how and where MMP-13 is involved in the break-down of cartilage can help find new ways to stabilize it.

MMP-13 – POTENTIAL TARGET OF NEW CARTILAGE SAVING THERAPIES

Being involved in so many essential cartilage processes, MMP-13 is an important target for developing new, far-reaching arthritis therapies. The HSS Laboratory for Cartilage Biology headed by Mary Goldring, PhD, continually aims to uncover new therapeutic possibilities as they seek to unravel the intricate cellular steps of cartilage creation and destruction, from beginning to end.

Using their innovative investigatory approach including unique models of primary human and mouse chondrocytes, cell lines, and mouse genetic models to manipulate gene expression, the team can pinpoint new molecular targets for therapies, as well as develop new strategies for new cartilage growth and tissue engineering.

[HSS Research Menu](#)



*Mary K. Crow, MD, PhD
Physician-in-Chief*



*Robert F. Spiera, MD
Director, Vasculitis and
Scleroderma Program*



*Jessica K. Gordon, MD
Assistant Attending
Physician*

HSS Scleroderma Research

Click/Tap Any Topic for Details & Authors

Imatinib in the Treatment of Scleroderma: Results of a 1-Year, Phase IIa, Single-Arm, Open-Label Clinical Trial

Assessing the safety and effectiveness of tyrosine kinase inhibitor drug in treating patients with systemic sclerosis

Pulmonary Hypertension in Scleroderma: Comparing Pulmonary Arterial and Pulmonary Venous Hypertension

Comparing two forms of an important cause of death in patients with systemic sclerosis

Prevalence of Celiac Antibodies in Patients with Scleroderma

Using newer methodology to test 72 patients with systemic sclerosis for celiac disease, a condition that causes intestinal reaction to eating gluten

HSS Research Menu

Scleroderma Studies

Imatinib in the Treatment of Scleroderma: Results of a 1-Year, Phase IIa, Single-Arm, Open-Label Clinical Trial

Systemic sclerosis (SSc) – or scleroderma – has many debilitating manifestations and few reliably effective treatments. A 1-year clinical trial at HSS of the drug *imatinib* for the treatment of scleroderma, showed tolerability in a majority of patients treated. Additionally, most of the patients in the trial improved during the course of the study.

Next SSc Study

Scleroderma Menu

Authors

HSS:

Robert F Spiera, MD
Jessica K Gordon, MD
Jamie N Mersten
Cynthia M Magro, MD
Mansi Mehta, MD
Horatio F Wildman, MD
Stacey Kloiber, RN
Kyriakos A Kirou, MD
Stephen Lyman, PhD
Mary K Crow, MD

Vascular conditions and fibrosis often develop in patients with SSc, leading to different clinical issues including lung and skin disease. Two cellular messengers that trigger fibrosis – the cytokines *transforming growth factor beta* and *platelet derived growth factor* - use pathways involving the proteins called *tyrosine kinases*. Imatinib, and other drugs like it, inhibit relevant tyrosine kinase; this has been shown in experimental models to decrease fibrosis. The drugs are currently used to treat leukemia and gastrointestinal stromal tumors.

In this 1-year, phase IIa, open-label clinical trial, 30 patients with diffuse cutaneous systemic sclerosis were treated with a goal of 400mg daily of *Gleevec*, a commercial form of imatinib. 24 patients completed the trial. Improvements were found.

A significant decrease in skin thickness and improvement in skin morphology was confirmed by blinded dermatopathological analysis. Skin scores decreased by 6.6 points – or 22.4% – at 12 months. This change was evident starting at 6 months of treatment and seen in patients with both early and late-stage disease. Forced vital capacity (FVC) of the lungs improved by 6.4%, and the diffusion capacity remained stable. Improvement was significantly greater in patients without interstitial lung disease. Health-related quality of life measures improved or remained stable.

Gleevec treatment was tolerated by most patients. Although adverse events were common, most were mild to moderate. The improvements in skin thickening and FVC warrant the next steps of double-blind, randomised, placebo-controlled treatment testing.

HSS Research Menu

Pulmonary Hypertension in Scleroderma: Comparing Pulmonary Arterial and Pulmonary Venous Hypertension

Authors

HSS:

Jessica K. Gordon, MD
Kamini Doobay
Kara Fields

Weill-Cornell

Medical College, NYC
Evelyn Horn, MD

Medical University of South Carolina:

Marcy B. Bolster, MD

The Center for Rheumatology, LLP Albany, NY:

Lee S. Shapiro, MD

University of Michigan, Ann Arbor:

Dinesh Khanna, MD, MSc

University of Utah School of Medicine:

Tracy M. Frech, MD

Jefferson Medical College, Philadelphia:

Chris T. Derk, MD

(AUTHORS CONTINUED
ON NEXT PAGE)

An important cause of death in patients with Systemic Sclerosis (SSc) – or scleroderma – is pulmonary hypertension (PH), a condition where the blood pressure between the heart and lungs is elevated. HSS is part of a multicenter study following patients who have SSc and PH to assess factors affecting their prognosis. The study is called *Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma* – or PHAROS.

In a recent PHAROS project, two different types of PH in scleroderma were compared. 127 patients with SSc and *Pulmonary Arterial Hypertension* – or PAH – which is the most common form of PH in patients with scleroderma were compared to a group of 32 patients with SSc and *Pulmonary Venous Hypertension* – or PVH.

By comparing the PAH group and the PVH group, the study was able to identify trends in clinical features and describe functional examinations that can help doctors correctly diagnose which of the two forms of PH a patient might have.

Clinically, patients with PVH are more likely to be African-American, younger, male, and have *diffuse cutaneous (dc)SSc*. 20% of patients with PVH had positive *anti-Sci70* test results versus 6.7% of patients with PAH.

Right heart catheterization testing showed differences between the two groups. Right heart catheterization is essential in making the diagnosis of PH. The test is required to differentiate between the two groups because only a right heart catheterization can provide information regarding the pulmonary capillary wedge pressure. Pulmonary vascular resistance (PVR) is useful in distinguishing the groups. PVR was significantly lower in PVH.

(continued, [click/tap here](#))

(continued)
 Pulmonary
 Hypertension
 in SSc

Differences were also observed between the groups with respect to pulmonary function testing and echocardiographic testing. The chart below, shows the comparisons.

How these categorizations and test differences affect the prognosis of patients with scleroderma and PH will be examined in long-term follow-up studies by the PHAROS collaborators.

Next SSc Study

Scleroderma Menu

Previous Page

Authors
 (CONTINUED)

Johns Hopkins
 University:
 Laura K. Hummers, MD

University of Texas
 Health Science Center
 at Houston:
 Maureen D. Mayes, MD

Georgetown University
 Medical Center:
 Virginia D. Steen, MD

PHAROS Investigators,
 Washington, DC

HSS Research Menu

SSc Pulmonary Hypertension Comparison

	PAH (n= 127)	PVH (n=32)	P-Value
Age (median, range)	61.00 (34, 84)	55.50 (35, 78)	0.015
Disease Duration (median, range)	7.32 (0.02, 43.2)	6.9 (0.2, 19.2)	0.47
Gender (% female)	84%	70%	0.045
Ethnicity (%)	83% Caucasian 9% Black 8% Other	60% Caucasian 27% Black 13% Other	0.019
SSc Subtype (%)	72% Limited 24% Diffuse	41% Limited 50% Diffuse	0.003
ECHO DATA			
Systolic PAP - mmHg	60 (31, 46)	49 (17, 38)	0.005
Ejection Fraction - %	60 (45, 82)	60 (25, 77)	0.49
Left Atrial Diameter - cm	3.7 (2.4, 6.3)	4.1 (2.1, 5.2)	0.50
PFT DATA			
Forced Vital Capacity - % pred, median (range)	81.7 (43, 123)	65.4 (27, 99)	<0.001
Diffusion Capacity - % pred, median (range)	38.9 (14, 98)	36.5 (13, 97)	0.40
FVC/DLCO Ratio	2.02 (0.95, 6.08)	1.69 (0.46, 2.96)	0.03
RHC DATA			
Pulmonary Artery Systolic Pressure - mmHg	55 (30, 119)	46 (36, 87)	0.004
Mean PAP- mmHg	35 (25, 75)	32.5 (26, 60)	0.11
PCWP -mmHg	10 (2, 17)	21 (16, 35)	<0.0001
PVR - dyn·s·cm ⁻⁵	368 (106, 999)	189.3 (56, 828)	<0.0001

Prevalence of Celiac Antibodies in Patients with Systemic Sclerosis

Celiac disease is an autoimmune condition that affects the small intestine, and develops due to gluten sensitivity. Gluten is a protein found in many grains including wheat, rye, malt, spelt and barley. Eating foods with gluten – i.e. cereal, bread and pasta - can cause severe gastrointestinal symptoms including abdominal pain and diarrhea. Celiac disease affects about 1% of the population and is becoming more widely recognized.

Systemic sclerosis (SSc) is a form of scleroderma, another debilitating autoimmune condition, which causes thickening of the skin and scarring of internal organs. SSc patients have digestive problems similar to those with celiac, and therefore it is difficult to tell these two diseases apart. Prior research has suggested that patients with SSc are at higher risk of developing celiac disease. Routine blood tests for celiac antibodies are a simple way to screen patients with SSc for this disease. In the past decade, two small studies found celiac antibodies in 7% and 10% of SSc patients.

Results from a newer study from the Hospital for Special Surgery (HSS) suggest that this may be an overestimation. 72 patients with SSc from the HSS Scleroderma Registry were tested for celiac antibodies using new and more sensitive antibody tests. Results showed that only 3 out of the 72 patients – or 4% - tested positive for celiac antibodies.

Patients with scleroderma in the study suffered from gastrointestinal symptoms in no correlation to the existence of celiac positive antibodies. However, even 4% positive results, still greater than the larger population, suggests considering the non-invasive blood tests for celiac antibodies when symptoms are present. Because for patients who do have celiac disease, no relief from the digestive distress is possible until gluten is removed from the diet.

Scleroderma Menu

Authors

HSS:

Lindsay J. Forbess, MD
Jessica K. Gordon, MD
Kamini Doobay
Morgana L. Davids
Robert F. Spiera, MD

New York

Presbyterian Hospital:

Brian P. Bosworth, MD

HSS Research Menu



Thomas A.J. Lehman, MD
Chief, Pediatric
Rheumatology

HSS Health-Related Quality of Life, Ethics, and Education Research

[Click/Tap Any Topic for Details & Authors](#)



C. Ronald MacKenzie, MD
Associate Attending
Physician

Quality of Life Across Continents: Comparing Disease Damage, Disability, Age, and Duration in Pediatric Lupus

Four continent survey of 436 young patients with lupus and 406 parents using the 5-face SMILEY© scale



Jessica R. Berman, MD
Assistant Attending
Physician

Ethical Issues in Rheumatology: A Survey of the American College of Rheumatology Membership

Common ethical issues and concerns found among American rheumatologists



Stephen A. Paget, MD
Physician-in-Chief
Emeritus

Expanding and Enhancing Teaching: Report from the New HSS Rheumatology Academy of Medical Educators:

Innovative educational and teaching career development program

Factors That Influence Appointment Compliance Rates In a Specialized Lupus Clinic

Socioeconomic factors – not forgetting or health condition – biggest reasons for missed appointments



Steven K. Magid, MD
Attending Physician

Successful Influenza Vaccine Intervention in a Rheumatology Clinic Population

New, nurse-specific intervention program increased flu vaccine compliance rate from 6% to 21.4%% in just one season

[HSS Research Menu](#)

[HRQOL, Ethics & Education Studies](#)

Quality of Life Across Continents: Comparing Disease Damage, Disability, Age, and Duration in Pediatric Lupus

HSS Pediatric Rheumatologists helped develop an innovative measuring scale using 5 standardized “smiley faces” allowing children to answer health questions by pointing to the face that best expresses how they feel.

Next Study

The 5-face system evolved into the *Simple Measure of Impact of Lupus Erythematosus in Youngsters*© – or *SMILEY*© – Collaborative. The SMILEY Collaborative recently began an ongoing comparison of how pediatric lupus affects patients around the world.

Back to HRQOL, Ethics, & Education Menu

Authors:

International SMILEY
Collaborative Group,
Including at HSS:

Margaret G.E. Peterson, MD
Alexa B. Adams, MD
Emma J. MacDermott, MD
Thomas J. A. Lehman, MD

Robert Wood Johnson
Medical School-UMDNJ:
Lakshmi N. Moorthy, MD

436 children with pediatric lupus and 406 of their parents used the SMILEY picture scale to responded to the same 24 brief questions about *Health Related Quality Of Life (HRQOL)*. The main factors of comparison were: Disease Damage, Disability, Age, and Duration. Respondents spanned four continents: North America ((US= 170 Mexico= 10, Puerto Rico=7), Europe (South America Brazil= 89, Argentina= 11) and Asia. Of the 436 patients, 356 were girls.

Children in Asia had the best child-reported HRQOL in the global survey. Children in North America had the worst. Significant differences across the globe were also found in Disease Damage and Duration. South America had the longest duration - median 34 months – North America the shortest – median 22 months.

There were also some differences in the how the children felt lupus effected themselves and their social lives, but no differences in “Limitation and Burden of SLE”. The parent-report of HRQOL did not always follow the trend of the child-report HRQOL.

HSS Research Menu

The important global effort of the SMILEY Collaborative will expand and continue.

Ethical Issues in Rheumatology: A Survey of the American College of Rheumatology Membership

Rheumatologists treat chronic and complex diseases that deeply affect people's lives. Yet, almost no studies have addressed the ethical considerations in the field. In order to more fully understand the scope of potential ethical problems, the *Committee on Ethics and Conflict of Interest* of the *American College of Rheumatology (ACR)* polled their membership.

Authors

HSS:

C. Ronald MacKenzie, MD

Jefferson University,
Philadelphia

Michele Meltzer, MD

Albert Einstein College
of Medicine, NY

Elizabeth A. Kitsis, MD

Four main categories were surveyed:

- 1) Perceived frequency of ethical issues in rheumatology
- 2) Identification of activities that pose ethical problems in member's rheumatological practice
- 3) Extent of education members have received in bioethics
- 4) Interest in additional learning activities related to bioethics

A survey using 14 closed-end and 4 open-ended questions was developed, pilot tested, and sent electronically to 5,500 US members of the ACR. A second offer for participation was sent to increase the response rate. 771 members (14%) responded.

Respondents generally agreed there were ethical issues in rheumatology, more frequently in clinical research (61%) and clinical practice (44%) than basic research (26%).

The top ethical issues reported were: the high costs of treatment to society (51%) or to patients (48%) and the practice of defensive medicine (45%).

(continued, [click/tap here](#))

(continued)
**Ethical Issues in
Rheumatology**

Next Study

**Back to HRQOL, Ethics,
& Education Menu**

Previous Page

Ethical issues in clinical practice were reported at a lower rate and included: conflict of interest in profiting from the over-utilization of infusions (10%); physician-pharmaceutical relationships (9%); and providing care for those with limited or no insurance (8%)

A much higher level of industry-related activities were identified as posing ethical problems: serving on boards of directors (76%) and serving on an industry-sponsored speakers bureaus (66%).

58% percent of respondents had received formal training in bioethics; 89% indicated an interest in additional education.

The ACR membership survey suggests that ethical problems in rheumatology are of concern to rheumatologists. Further, there is a perceived need for educational resources directed at helping members deal with such professional challenges. These results suggest that an active discourse and more formal education in bioethics should be a professional priority.

HSS Research Menu

Expanding and Enhancing Teaching: Report from the New HSS Academy of Rheumatology Medical Educators

Next Study

Back to HRQOL, Ethics, & Education Menu

Few academic rheumatologists have been educated how to educate. Further, not every gifted teacher finds that investing extra time in academia produces equal enhancement of a clinical career. Now, HSS has created a new educational and teaching career development program that will help HSS Rheumatologists become the best trained teachers in the field.

The new HSS Academy of Rheumatology Medical Educators will provide HSS Rheumatologists with formal education on best teaching practices, seek funding for innovative instruction methodology, establish rigorous academic guidelines, and provide career development support for any clinicians who desire to focus more deeply on teaching.

Authors

HSS:

Jessica Berman, MD

Juliet Aizer, MD

Anne R. Bass, MD

Mary K. Crow, MD

Edward J. Parrish, MD

Laura Robbins, DSW,
CSW, MSW

Jane E. Salmon, MD

Stephen A. Paget, MD

University of Vermont, Burlington:

William L. Cats-Baril, PhD

A recent, day-long Planning Retreat launched the Academy. The HSS Division of Rheumatology Faculty was surveyed both pre and post their participation in the retreat. 83% completed the survey before the retreat, and 46% after.

Before the retreat, over 94% of those surveyed agreed “*I have the commitment to be a great teacher*”, but only 36% felt they had the “*understanding of the latest pedagogical techniques*”. Barriers to teaching included having “*the time to be a great teacher*” (pre-retreat 39%; post 24%) and “*the resources and tools to teach well*” (pre-retreat 32%; post 16%)

A larger number than expected agreed or strongly agreed that “*I would like to be part of an Education Academy and move along a Clinician-Educator track*” (pre-retreat 42%, post 68%). With the new HSS Rheumatology Academy all interested clinicians will be able to realize their teaching goals.

HSS Research Menu

Factors That Influence Appointment Compliance Rates In a Multi-Disciplinary Specialized Lupus Clinic

Next Study

Back to HRQOL, Ethics, & Education Menu

Authors

HSS:

Pretima G. Persad, MPH

Su Jin Kim, LCSW

Kyriakos A. Kirou, MD

Doruk Erkan, MD

The Mary Kirkland Center for Lupus Care at HSS is one of the country's largest and most important centers for advancing the treatment and quality of life of patients with lupus. The Center for Lupus Care Clinic serves patients of all incomes and socioeconomic statuses.

A recent study has shown that problems related to income and socioeconomic factors – including transportation and child care – are the main determinants of whether patients can keep their needed clinic appointments.

143 clinic patients treated on Medicaid and Medicare were identified and their pre-study appointment compliant rates measured. During the study, patients received reminder phone calls the day before their appointment. If they missed the appointment, a follow-up call asked why. Only 5% of patients didn't show because they forgot. And the group's compliance rate was 67% pre-study, 69% after it.

The main reasons for missed appointments were socioeconomic. 44% had transportation difficulties - including ambulettes not showing up, no car in the household, and not enough money for public transportation or taxi. 19% had lack of child care. 12% had job related conflicts. No correlations of lupus condition, age, ethnicity, or other demographics were found between the study group from the overall clinic population to affect compliance rate.

HSS Research Menu

The study indicates that improving transportation services and providing access to temporary childcare for medical appointments could aid in increasing patients ability to receive care at necessary follow-up appointments.

Successful Influenza Vaccine Intervention in a Rheumatology Clinic Population

Between their abnormal immune systems and the frequent use of immunosuppressive medications, people with autoimmune conditions are at higher risk for “getting the flu”. In addition, a bout of influenza may require patients to stop taking their immune system inhibiting medications, which can result in complications. Yet, of the 1514 patient visits to the HSS Division of Rheumatology Clinic only 100 - or 6% - were vaccinated against influenza during the 2009-2010 season.

Using a new, nurse-specific intervention program, HSS was able to increase the clinic’s 6% influenza vaccine compliance rate to 21.4% in just one season.

Posters and flyers promoting the health benefits of the influenza vaccine were posted in the clinic reception areas and exam rooms. Using a paper survey – in English or Spanish – a registered nurse asked all patients a) if they had been vaccinated b) if they wanted to be vaccinated c) or if they refused, the reason for refusal of the vaccine. Stickers were placed on patient charts with their vaccination status. Patients that refused were personally educated on the importance of receiving the influenza vaccine by a registered nurse.

The intervention worked. Vaccination compliance increased from 6 to 21.4%. For the 2011-2012 season, nurse-specific intervention will continue, building on this successful program, refining strategies and increasing patient education about the importance of patients with autoimmune conditions receiving the influenza vaccine.

Back to HRQOL, Ethics,
& Education Menu

Authors

HSS:

Sherece Black, RN

Sarabjit Brar, RN

Lee Chang

Sylvia Chico

Donald Makowski, RN

Virginia Haiduc, MD

Steven K. Magid, MD

Julie A. Pollino-Tanner, RN, MA

Julita C. Reyes-Canu, RN

Ann M. Rakowicz, BSN, RN

Monica C. Richey,

MSN, ANP-BC/GNP

HSS Research Menu

HSS Inflammation & Autoimmunity Research

[Click/Tap Any Topic for Details & Authors](#)



*Lionel B. Ivashkiv, MD,
Associate Chief
Scientific Officer
David H. Koch Chair
in Arthritis and Tissue
Degeneration*

New Discovery: How Tumor Necrosis Factor Can Also Turn Inflammation Down

Revealing the first cellular mechanisms showing how TNF can turn down inflammation



*Alexandra Pernis, PhD
Senior Scientist*

Two Proteins Regulating IRF4 May Coordinate T and B Cell Interactions and Prevent Systemic Autoimmunity

DEF6 and SWAP-70 are shown to be structurally related components of molecular network ensuring coordination of T and B cells and preventing systemic autoimmunity



*Robert F. Spiera, MD
Director, Vasculitis and
Scleroderma Program*

Mental Health Found to Predict Disease Flare in Wegener's Granulomatosis

Patients reporting lower mental health found more likely to flare than patients reporting lower physical health

Immune-Complex Induced Inflammation Augmented in the Absence of Nicotinic Acetylcholine Receptors in Mice

The $\alpha 7$ Nicotinic Acetylcholine Receptor ($\alpha 7nAChR$), which responds to the neurotransmitter acetylcholine, can affect immune complex deposit caused inflammation.



*Jane E. Salmon MD
Collette Kean
Research Chair*

[HSS Research Menu](#)

[Inflammation & Autoimmunity Studies](#)

New Discovery: How Tumor Necrosis Factor Can Also Turn Inflammation Down

Many proteins have a homeostatic function – they can regulate conditions both up and down attempting to achieve balance. Even though tumor necrosis factor (TNF) is one of the most potent cytokines known to signal for increased inflammation in an immune system response, the HSS Arthritis and Tissue Degeneration Lab, directed by Lionel B. Ivashkiv, MD, felt that TNF could act to reduce inflammation as well. There were hints throughout the literature, but no clear cellular mechanisms were established about this potential suppressive function. Until now.

Authors HSS

Sung Ho Park
Kyung-Hyun Park-Min, MD
Janice Chen
Xiaoyu Hu, MD, PhD
Lionel B Ivashkiv, MD

An HSS study has revealed, for the first time, a cellular mechanism showing how the powerful pro-inflammatory protein TNF also suppresses aspects of inflammation. The mechanism involves a protein known as *glycogen synthase kinase 3-beta* – or GSK3 – and a gene induced by TNF called tumor necrosis factor alpha-induced protein 3 – or *TNFAIP3* – that encodes the A20 protein

In the study, the lab isolated human inflammatory cells of the immune system called macrophages and monocytes, treated the cells with TNF, then challenged the TNF-treated cells with lipopolysaccharide (LPS), a large molecule that stimulates receptors important in inflammation.

Results showed that TNF suppressed the inflammatory response of the macrophages and monocytes. Then, mice were given low doses of TNF followed by high doses of LPS. The TNF protected the mice from the effects of high dose LPS, which is usually lethal. *(continued, [click/tap here](#))*

(continued)

How TNF Can Turn Down Inflammation

[Previous Page](#)

[Next Inflammation &
Autoimmunity Study](#)

[Inflammation &
Autoimmunity Menu](#)

[HSS Research Menu](#)

Macrophages are the same cells that migrate into joints in RA and make inflammatory cytokines like TNF. Thus, TNF being able to control inflammatory response in the same cells that make TNF to help trigger that response, shows TNF can regulate itself and has a homeostatic function.

The lab's earlier experiments with a drug that can inhibit GSK3 as well as experiments with RNA interference of A20, which can block A20 gene function, helped identify how the protein and gene are part of the cellular mechanism by which TNF acts to suppress inflammation.

TNFAIP3 is one of the best linked genes to rheumatoid arthritis, and there are polymorphisms in TNFAIP3 that have been linked to RA pathogenesis. The lab hypothesizes that patients who make less A20 are more susceptible to inflammation and, thus, rheumatoid arthritis.

These findings could be used to develop potential new therapies for RA. One approach to treating RA could be to increase A20 levels in patients who naturally make less A20 by manipulating GSK-3, since this study showed that GSK-3 influences A20.

The findings could also be applied to other diseases besides arthritis. In RA, boosting A20 might reduce inflammation. But in other cases, such as cancer, where the macrophages are suppressed, then A20 expression would be inhibited. Less A20 would allow more immune system cells needed to fight harmful invaders to proliferate.

Two Proteins Regulating IRF4 May Coordinate T and B Cell Interactions and Prevent Systemic Autoimmunity

Next Inflammation &
Autoimmunity Study

Inflammation &
Autoimmunity Menu

Author

HSS:

Alessandra Pernis, PhD

When healthy immune systems respond to invasion by harmful organisms, T and B cells lead the way, carefully orchestrating their response. In autoimmune conditions, the orchestration between T and B cells goes awry and T and B cells mistakenly start attacking one's own body. Now, an HSS study has revealed new details about the mechanisms that normally control the coordination between T and B cells.

The study found that two gene-encoded proteins – known as DEF6 and SWAP-70 – control *interferon regulatory factor 4* (IRF4) a transcription factor that regulates the activation of T and B cells. DEF6 and SWAP-70 were shown to be two structurally related components of a complex molecular network that ensures the proper coordination of T and B cell interactions and prevent the development of systemic autoimmunity.

In the study mice deficient in DEF6 were crossed with mice deficient in SWAP-70 to produce offspring deficient in both - called DKO mice. The DKO mice spontaneously developed a lupus-like autoimmune condition.

T and B cells in the DKO mice started sending conflicting, not carefully orchestrated, instructions mediated by the cytokine IL-21, a molecular messenger that normally signals for increased antibody production in an immune response. T helper cells started disregulating production of IL-21, while B cells simultaneously increased IL-21 responsiveness.

HSS Research Menu

Naive T Cell helpers only express DEF6, but B cells express both DEF6 and SWAP-70. Without either protein, B cells acted aberrantly leading to exaggerated B cell activation, germinal center formation, and plasma cell differentiation. Findings also showed that DEF6 and SWAP-70 are differentially employed at distinct stages of B cell differentiation to selectively control the ability of IRF4 to drive the expression of specific target genes.

Mental Health Found to Predict Disease Flare in Wegener's Granulomatosis

Next Study

Inflammation & Autoimmunity Menu

Authors

HSS:

Morgana L. Davids
Huong Do, MS
Robert F. Spiera, MD

Boston University School of Medicine:

Gunnar Tomasson, MD
Peter A. Merkel, MD, MPH

Genentech Inc:

John C. Davis, MD, MPH

Cleveland Clinic:

Gary S. Hoffman, MD

University of Michigan,

Ann Arbor:

W. Joseph McCune, MD

Mayo Clinic

Ulrich Specks, MD

Duke University Medical Center:

E. William St Clair, MD

Massachusetts General Hospital:

John H. Stone, MD, MPH

While emotional stress has been anecdotally suspected to contribute to flares of autoimmune disease, no studies have looked at mental health as a risk factor for the onset of flares in patients with vasculitis.

Now, a study of 143 patients with a form of vasculitis, *granulomatosis with polyangiitis* (GPA, also known as Wegener's granulomatosis) has found that patients' mental health condition had more impact on their likelihood for immediate disease flares than did their physical health.

All the patients in this retrospective analysis had experienced at least 6-month's sustained remission while participating in the Wegener's Granulomatosis Etanercept Trial. In that trial, patients had maintained a self-scored health survey at each follow-up visit. The survey – the Short Form 36 Health Survey – had both a physical and mental component. Scores are measured on a scale of 0 to 100, with 100 being the healthiest.

Examining the relationship between scores and likelihood of disease flares within three months, the investigators found that a 5-point lower mental condition score at the preceding visit was associated with a 19% increased likelihood of having a flare at the current visit – a significant association; while a 5-point lower physical score at one visit was not associated with an increased risk of flare at the next visit.

This documentation of the significant impact of mental condition on flares calls for further, larger studies into how mental health affects physical health in autoimmune conditions like GPA or Wegener's granulomatosis.

Immune Complex Induced Inflammation Augmented in the Absence of Nicotinic Acetylcholine Receptors in Mice

In a healthy immune system response, cells fighting an invasion attach to the harmful organisms and form an *immune complex*. Fight won, no more harmful organisms to attach, no more circulating immune complexes.

In autoimmune conditions, when the body's own cells are mistaken for harmful invaders, immune complexes keep forming and circulating. Eventually, the complexes deposit in tissue – from joints to kidneys – causing inflammation, damage, and disease flares.

Authors

HSS:

Milena Vukelic, MD
Gloria Koo, PhD
Patricia M. Redecha
Jane E. Salmon, MD

An HSS study has found that the $\alpha 7$ Nicotinic Acetylcholine Receptor ($\alpha 7$ nAChR), which responds to the neurotransmitter *acetylcholine*, can affect cellular responses to immune complex deposit and attenuate inflammation.

The study expands upon the team's earlier work showing specific ways a neural network called the "*cholinergic antiinflammatory pathway*", involving receptors of the neurotransmitter acetylcholine located on neutrophils and monocytes, can act to decrease inflammation.

In this study, the team stimulated an immune system response in neutrophils of mice missing $\alpha 7$ nAChR and their wild type littermates. The absence of $\alpha 7$ nAChR led to more potent reactions, especially exaggerated early influx of leukocytes and increased release of mediators of tissue damage at sites of immune complex deposition.

(continued, click/tap here)

(continued)

Absence of $\alpha 7nAChR$

The findings suggest that tonic stimulation of $\alpha 7nAChR$ attenuates Fc α R- and C5aR-mediated activation, and that $\alpha 7nAChR$ decrease signaling through the NF κ B-proinflammatory cytokine axis, a pathway that activates resident and newly recruited leukocytes.

Examination of common sites of immune complex deposit showed that mice without any $\alpha 7nAChR$ had, in some places, 245% larger neutrophil accumulation than their wild littermates.

[Previous Page](#)

[Inflammation & Autoimmunity Menu](#)

That $\alpha 7nAChRs$ play a critical role in suppressing inflammation at sites of immune complex deposition suggests new strategies for preventing or limiting immune complex-triggered damage such as that seen in lupus and rheumatoid arthritis.

[HSS Research Menu](#)

HSS Rheumatology Research News

Tap Any Area to See Recent Studies

Lupus

Rheumatoid
Arthritis

Inflammation &
Autoimmunity

Osteoarthritis

Scleroderma

Health-Related
Quality of Life,
Ethics, & Education

HOSPITAL
FOR
**SPECIAL
SURGERY**

