

Winter 2022

Division of Rheumatology & Immunology Annual Newsletter



The Division of Rheumatology and Immunology at the Medical University of South Carolina (MUSC) has a long and illustrious track record in the study and treatment of rheumatic diseases and in the mentoring and training of leaders in the field of rheumatology. Under the leadership of **Jim Oates, M.D.**, the division enjoyed another productive year marked with accomplishments in education, research, and patient care.

The division maintains outstanding disease-focused clinical programs that drive its reputation for excellence in the treatment of rheumatic diseases. In 2021, MUSC Health's rheumatology program was ranked 17th best in the country by *U.S. News & World Report* and has consistently placed in the top 20 annual rankings for the past 13 years.

The division is internationally recognized for its care and research relating to systemic lupus erythematosus (SLE) and systemic sclerosis (scleroderma). Division faculty lead the MUSC SmartState Center for Inflammation and Fibrosis Research which focuses on developing new

therapies and education programs for inflammatory and fibrosing rheumatic diseases such as lupus and scleroderma.

The division maintains a robust research program and had another successful year, securing support from a variety of external sources, including the NIH (NIAMS, NIMHD, NHLBI) Lupus Foundation of America, Lupus Research Alliance, Scleroderma Research Foundation, and Rheumatology Research Foundation. In FY21, division faculty were successfully awarded \$8.4M in research funding. Within the MUSC Rheumatology Fellowship Program, the division continues to recruit top candidates to the program, with over 182 applicants from across the country this year.

The publications, honors, and grant funding received by division faculty this year highlight the quality and ingenuity of work being done in the division to advance our knowledge and treatment of rheumatic diseases through scientific discoveries, cutting-edge treatments, and the training of clinicians and scientists.



#17
IN THE NATION
MUSC
RHEUMATOLOGY

12,427
FY21
OUTPATIENT
OFFICE VISITS

\$8.4M
FY21
RESEARCH
FUNDING

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*On the Cover, The MUSC Lupus
Erythematosus research group
(also known as M.U.S.C.L.E.) is
comprised of faculty and staff with
interests in clinical, translational,
and basic research related to lupus
and community outreach to improve
knowledge and awareness of lupus.*

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MESSAGE FROM THE DIRECTOR



For the Division of Rheumatology & Immunology, 2020-21 was a challenging and exceptional year. Despite the COVID-19 pandemic and its effect on all aspects of life, we have remained resolute in our commitment to find innovative solutions to care for our patients, mitigate disparities in health care, conduct research, and educate our students, residents and fellows.

The division continues to have a robust clinical presence, and in 2021, MUSC Health's rheumatology program was ranked 17th best in the country by *U.S. News & World Report*. In response to the COVID-19 pandemic, our division was able to quickly pivot to telemedicine and maintain the ability to provide care to our large number of patients with systemic autoimmune diseases at high risk for infection.

The division continues to be a highly productive research enterprise with \$8.4M in extramural funding and several high-impact publications in *Genes, Arthritis and Rheumatology, Annals of Rheumatic Diseases, Lupus Science and Medicine, American Journal of Physiology Lung Cellular and Molecular Physiology, and the Journal of Clinical Investigation (JCI) Insight*. New grants in FY21 included an NIH R01 awarded to **Drs. Paula Ramos** and **Diane Kamen** for a novel study investigating how social factors might influence lupus in African American women through epigenetic changes. Also of note, **Dr. Gary Gilkeson** received a renewal of his NIH T32 Training Grant in Inflammatory and Fibrosing Diseases and **Dr. Carol Feghali-Bostwick** received a renewal of her K24 NIH grant to mentor physician scientists in patient-oriented, clinical, and translational scleroderma research and an R21 to study extracellular matrix signatures of lung fibrosis. **Drs. Richard Silver** and **Galina Bogatkevich** received an R41 for preclinical development of M10 as a therapy for scleroderma. **Dr. Melissa Cunningham** received an R01 to study the role of estrogen in lupus, **Dr. Jim Oates** received a VA Merit Award and a Lupus Research Alliance Award to study targeted treatment for endothelial dysfunction in lupus nephritis. **Dr. Betty Tsao** received a Lupus Research Alliance Award to study polyamine catabolism in lupus and **Dr. Deanna Baker Frost** received a Scleroderma Foundation award to study the role of estradiol in scleroderma.

Seamless integration of education has been the hallmark of the division's activities, as we mentor and train the next generation of academic leaders in rheumatology. Our competitive fellowship program offered three first-year positions and attracted over 182 applicants.

The current times try us, but the achievements presented in this report underscore our strength and commitment to meet the challenges of the pandemic in our mission to provide exceptional care for all.

Jim Oates, M.D.

Professor and Director, Division of Rheumatology & Immunology
Vice Chair for Research, Department of Medicine

Four Convenient Locations:

Rutledge Tower Clinic
135 Rutledge Avenue, 5th Floor
Charleston, SC 29425

East Cooper Medical Pavilion
1600 Midtown Avenue - 2nd Floor
Mount Pleasant, SC 29464

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MUSC Rheumatology Clinics:
843-876-0615

West Ashley Medical Pavilion
2060 Sam Rittenberg Boulevard
Charleston, SC 29407

MUSC Health - Nexton
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Summerville, SC 29486

Schedule a Virtual Visit:
muschealth.org/virtual-visits

CAROL FEGHALI-BOSTWICK, PH.D.

Commitment, Curiosity, and a Generous Spirit Drive Fibrotic Disease Research

Article by Kat Hendrix, Ph.D.

Two things motivate **Carol Feghali-Bostwick, Ph.D.**, Distinguished University Professor and SmartState® and Kitty Trask Holt Endowed Chair for Scleroderma Research, to come to work every day. “I feel a commitment to the patients to keep pushing for an answer and a cure. But I also just love the excitement of research. There’s nothing else I’d rather be doing than getting up and seeing what’s new today,” says Feghali-Bostwick.

She was drawn to fibrotic diseases, in part, because of the wide-ranging applicability of any advances in the field. “Fibrosis can affect any organ in the body,” says Feghali-Bostwick. “It’s the end result of many common diseases—for example, diabetic nephropathy often ends with fibrotic kidney disease. So, anti-fibrotic therapies are likely to have a broad impact and our work has a wide reach.”

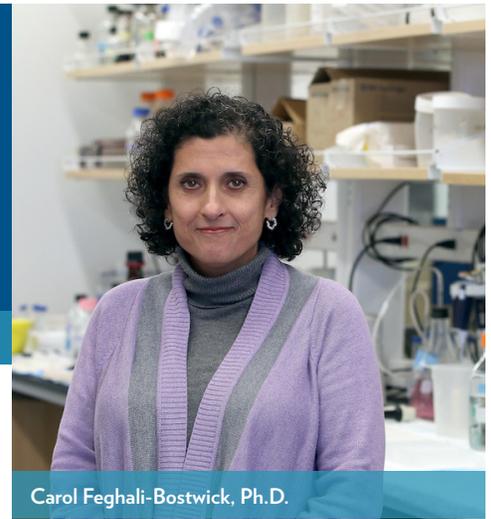
Research teams in her lab focus on investigating fibrotic mediators and the mechanisms by which they can cause disease. Specifically, she and her teams develop models of fibrosis to test pro- and anti-fibrotic factors using human skin and lung tissue cultures. “We go beyond in vitro testing in dishes and in vivo studies in mice by testing the efficacy of anti-fibrotic therapies to stop fibrosis and the ability of profibrotic agents to cause fibrosis in human tissues. Because, as we so often discover, things that work in mice are often ineffective in humans,” says Feghali-Bostwick.

The team also investigates epigenetic changes in DNA methylation to better understand why some people develop fibrotic disease while others do not. A recent study of scleroderma in discordant twins—identical sibling pairs

in which one developed scleroderma while the other did not—led to significant new findings. “When we compared their epigenetic and gene expression profiles, we could identify novel genes that had never before been reported to be associated with scleroderma,” says Feghali-Bostwick. “It was an exciting finding because these genes presented new targets for therapy.”

A separate study of anti-fibrotic agents identified a novel enzyme in the glycolic pathway that can cause fibrosis. “We had never before thought that an enzyme involved in glycolysis could cause fibrosis. So, that was also a new finding,” she says.

While these breakthroughs initially led to publications in high-impact journals including the *Annals of Rheumatic Diseases* and *JCI Insight*, their impacts reach much further. “The epigenetic and gene expression changes have provided leads for other investigators to follow in their own research,” she says. “The antifibrotic peptide has already been licensed to a company that will take it into human trials and hopefully lead to a new antifibrotic therapy.” This is in addition to a previous, novel small molecule therapy that her research team characterized.



Carol Feghali-Bostwick, Ph.D.

In their latest study published in *JCI Insight*, Feghali-Bostwick’s team found that the E4 peptide reverses fibrosis in human and mouse tissues by activating an antifibrotic pathway that is common to all organ systems. The findings are significant because they suggest that the peptide could be effective at reversing fibrosis in multiple organ systems.

Feghali-Bostwick also has a deep commitment to mentorship and serves as director of the MUSC ARROW program (Advancement, Recruitment, and Retention of Women) which aims to support and recruit women in research. “I don’t want everyone else to struggle like I did early in my career. If we can accelerate their advancement and make it easier for the next generation, that would be a good legacy to leave,” she says.

This year, Feghali-Bostwick received a renewal of her NIH K24 award to provide continued support of her passion for mentorship. “I want to help foster the next generation of investigators in scleroderma to ensure a pipeline of junior investigators who are well-trained and have the support they need to be successful,” she says.

Her commitment to research, scientific curiosity, and generosity of spirit, reflect the best qualities we can hope to find in science and medicine and a shining example for those who follow in her footsteps.

Researchers take a multifaceted approach to Understanding Autoimmune Disease Disparities



L-R: Diane Kamen, M.D., Quinette King, and Paula Ramos, Ph.D.

The disproportionate rates at which some autoimmune diseases strike African American women are among the most glaring disparities in medicine. About 90% of people with lupus and 60% of those with scleroderma are women, and the majority identify as African American or Hispanic.

Paula S. Ramos, Ph.D., and **Diane Kamen, M.D.**, have spent years trying to identify the causes for these striking inequities and recently received funding from the National Institutes of Health for a novel study investigating how social factors might influence lupus in African American women through epigenetic changes. “Many studies analyze biospecimens but not social factors, or they collect social data but not biological samples,” says Ramos. “For each participant, we’re collecting genetic data from blood samples as well as social exposure data, including sociodemographic, behavioral, racial discrimination, and social support data.” The study will also consider disease severity, comorbidities, and outcomes.

It is well established that genetic risk factors can increase vulnerability to developing certain diseases. It is also known that social factors such as housing instability, racial discrimination, poverty, trauma, and violence impact disease development. “What we don’t know,” says Kamen, “is how these things interact to affect our biology and influence disease development or severity. Why do some people develop autoimmune disease while others with similar environmental exposures and genetics do not? Can we identify environmental or genetic protective factors to help prevent people at risk from developing lupus or reduce their disease severity?”

They chose to study lupus, not only because African American women have more severe disease and worse outcomes, but also because it is a prototypical autoimmune disease. “It’s the mother of all autoimmune

diseases,” explains Kamen. “The basis of autoimmune disease is that the immune system attacks healthy cells and tissues, and many are focused on one area of the body. For example, MS (multiple sclerosis) attacks the nervous system and RA (rheumatoid arthritis) attacks the joints. But antibodies from lupus attack many different types of cells in many different parts of the body. Patients can have multiple different organ systems affected at the same time.”

Lupus is also highly unpredictable, frustrating patients who often live on a roller-coaster of flares and remissions as well as health care providers who must frequently adjust treatment to keep it at bay. Even getting a correct diagnosis can be challenging. “Lupus onset can be insidious. It can come on very slowly,” says Kamen. “Some people go years with non-specific symptoms before someone finally puts it together as lupus and gets them the right treatment. Unfortunately, some people already have scarring from chronic inflammation before they get a correct diagnosis.”

Both Ramos and Kamen agree that if their study can help explain how multiple social factors influence lupus, it will be a great step forward. “We’re measuring DNA variation, DNA methylation, and gene expression at the genome-wide level in the major immune cell types such as T-cells, B-cells, and monocytes. We want to understand how social factors like racial discrimination affect lupus outcomes through epigenetic changes, taking into account genetics and other sociodemographic factors. We’ll specifically look at the effects of social factors on DNA methylation and gene expression,” explains Ramos. “We can then compare to see if differences in gene expression are associated with social factors. For example, do participants who report more racial discrimination have different gene expression patterns than those who report less?”

Unravelling associations among so many overlapping risk

factors is a daunting analytical challenge, but the crux of their work is its human face. Without the participation of African American women with lupus, their project would go nowhere. “We want to make sure study participants and the broader African American community are included and feel this project is of value to them,” says Ramos. “Often, in historically marginalized populations, researchers collect samples for study but don’t give participants feedback on what they found or request feedback on research directions. The people who made the research possible are not included as partners in the research.”

Fortunately, other MUSC researchers, including the late Ida Spruill, Ph.D., have laid a strong foundation for community-based, participatory research in South Carolina’s coastal communities. In the 1990s, they began holding regular meetings with community members to talk about proposed and ongoing studies, community priorities, and how study results are relevant to their daily lives.

“Over twenty years ago, Ida Spruill helped form a community-based Citizens Advisory Council to help endocrinology researchers from MUSC study why diabetes disproportionately affected African Americans in the Sea Islands around Charleston,” says Kamen. “Dr. Gilkeson and I went to a community advisory board meeting back in 2002 and talked about how lupus, like diabetes, was also a chronic disease with higher morbidity and mortality in their community. They were very open to helping us. One woman on the board actually had lupus and another had a relative who died of it. So, they were very aware of its impact and welcomed us with open arms. It was the beginning of a wonderful, trusting, collaborative relationship that we’re still involved in today—thanks to Dr. Spruill’s really visionary work.”

While they acknowledge that it is an ambitious project, Ramos and Kamen think that understanding how social factors affect gene regulation and how the resulting gene expression patterns affect lupus, could turn up insights that may open new avenues for helping patients. “We hope to see some positive effects of things like social support that may offset detriments like racial discrimination or low socioeconomic status,” says Ramos.

“Doing something to reduce the disparities we see in clinic is what makes me eager to go to work every day,” says Kamen. “To help figure out how potentially modifiable factors influence the development of autoimmune diseases like lupus that have terrible impacts on patients, their families, and the broader community.”

Article by Kat Hendrix, Ph.D.

ACTIVE CLINICAL TRIALS

COVID / Autoimmune disease:

- Booster Effects with Autoimmune Treatments in Patients with Poor Response to Initial Covid-19 Vaccine

Systemic Lupus Erythematosus:

- A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)
- Pilot Trial of Belimumab in Early Lupus
- Study of Anti-Malarials in Incomplete Lupus Erythematosus (SMILE)
- Efficacy, Safety, and Tolerability of JBT-101 in Systemic Lupus Erythematosus
- A Multi-Center Study to Characterize the Long-Term Safety and Efficacy of BMS-986165 in Subjects with Systemic Lupus Erythematosus
- A Phase 2 Dose Ranging Study to Evaluate the Efficacy and Safety of AMG 570 in Subjects with Active Systemic Lupus Erythematosus (SLE) With Inadequate Response to Standard of Care Therapy
- Utilizing patient navigators to address barriers to care related to access to preventive and specialty healthcare, medication adherence, and health literacy in SLE for minority patients.
- Social factors, epigenomics, and lupus in African American women (SELA)
- Impact of Pathogenic and Protective Environmental Exposures on Autoimmune Disease

Lupus Nephritis:

- Clinical Outcomes, Resource Utilization, Cost and Quality of Life of Lupus Nephritis Patients in a Prospective International Inception Cohort

Refractory Lupus:

- A Phase II Controlled Trial of Allogeneic Mesenchymal Stem Cells for the Treatment of Refractory Lupus

Systemic Sclerosis (Scleroderma):

- Genome Research in African American Scleroderma Patients (GRASP)
- Combining of anti-fibrotic effects of Pirfenidone with Mycophenolate to treat scleroderma-related interstitial lung disease
- Collaborative, National Quality and Efficacy Registry for Tracking Disease Progression in Systemic Sclerosis (Scleroderma) Patients
- Evaluation of Brentuximab Vedotin for Diffuse Cutaneous Systemic Sclerosis
- A Phase 2, Randomized, Placebo-controlled, Double-blind, Open-label Extension Multicenter Study to Evaluate the Efficacy and Safety of KD025 in Subjects with Diffuse Cutaneous Systemic Sclerosis

Where are they now?

This map depicts locations of our graduating fellows from the past 47 years (majority in academic medical centers).



Under the leadership of **Faye Hant, D.O.**, the Rheumatology Fellowship Training Program is fully accredited and comprised of six clinical and research fellows selected from a competitive pool of candidates. Fellows are supported in part by an NIH T32 Training Grant (Gary Gilkeson, M.D., PI). The program offers fellows the opportunity to see a wide array of rheumatic disease patients in a variety of clinical settings, to participate in clinical and basic research, and to obtain advanced training leading to a master's degree in clinical research.

2021-22 Fellows:

Sean Carter, M.D.

Jessica English, M.D.

Bradley Collins, D.O.

Jennifer Schmidt, M.D.

Whitney Elg-Salsman, D.O.

Ana Tucker, M.D.

Multidisciplinary Research Aims to Identify Cancer Patients at Risk for Immune Related Adverse Events



The growing use of multidisciplinary teams for clinical decision-making recognizes the fact that bringing multiple medical perspectives together often produces better patient outcomes. Previously done only in rare or complex cases, having a variety of providers discuss diagnosis and treatment options for individual patients is now a routine process of care in many MUSC divisions.

Multidisciplinary efforts also reach beyond the bedside to the lab bench where researchers now more often collaborate to answer questions that cross medical fields. **Whitney Elg-Salsman, D.O.**, a third-year fellow in the Division of Rheumatology and Immunology, is one of the next-generation of scientists who are asking multifaceted questions. "There's a unique overlap between oncology and rheumatology. The intersection I'm looking at is between immune checkpoint inhibitors (ICIs)—which activate the immune system so your own body will attack a tumor—and immune-related adverse events (irAEs) that occur when the immune system becomes overactivated," says Elg-Salsman. These irAEs can affect almost any organ system and range from life-threatening conditions such as colitis and pneumonitis to inflammatory syndromes such as arthritis that severely deteriorate patients' quality of life.

The first ICI (ipilimumab, an anti-CTLA4 drug) was approved to treat metastatic melanoma in 2011 and the class has steadily expanded since then to include anti-programmed death receptor-1 (PD-1) and anti-PD ligand-1 (PDL-1) agents. They are now approved to treat multiple cancer types as either primary or adjuvant therapy. While ICIs have improved overall survival and the length of time without cancer progression, the rate of irAEs with ICI therapy is very high. "For me, that begs the questions, 'What's driving this? What's the pathogenesis? And, can we find biomarkers for it?'" says Elg-Salsman.

Along with her research mentors, **Gary Gilkeson, M.D.**, and **John Wrangle, M.D.**, Elg-Salsman is conducting novel research that aims to reduce irAEs in cancer patients undergoing ICI treatment. "We're using phage immunoprecipitation sequencing—or PhIP-Seq—in a new way to see if we can find biomarkers to help us identify who is at high risk for irAEs," she says.

The possibilities are exciting and could herald a change in how ICI therapy is prescribed and monitored to help patients reach their treatment targets. Eventually, this research could contribute to changing how ICI therapies are designed and made. Findings from this research might also apply to treatment decisions in other areas, particularly rheumatic diseases.

RHEUMATOLOGY FACULTY

General Rheumatology



DeAnna Baker Frost, M.D., Ph.D.
Assistant Professor
Special Interests: Estrogen in scleroderma; autoimmune diseases



Melissa Cunningham, M.D., Ph.D.
Associate Professor
Special Interests: Systemic lupus erythematosus; lupus nephritis; neuropsychiatric lupus



Gary Gilkeson, M.D.
Distinguished University Professor
Associate Dean for Faculty Affairs & Faculty Development
Special Interests: Lupus; retroperitoneal fibrosis; ethnic and sex disparities in lupus; mesenchymal stem cells as therapy in autoimmune diseases



Faye Hant, D.O., MSCR
Professor and Director,
Rheumatology Fellowship Program
Special Interests: Scleroderma; CTD related interstitial lung disease; rheumatoid arthritis



Diane Kamen, M.D., MSCR
Professor
Special Interests: Autoimmune diseases; systemic lupus erythematosus; clinical research studies



Jim Oates, M.D.
Professor and Division Director;
Richard M. Silver Endowed Chair in Rheumatology & Immunology;
Vice Chair for Research, DOM
Special Interests: Lupus nephritis; endothelial dysfunction; biomarkers of atherosclerosis and glomerulonephritis in lupus



Katherine Silver, M.D.
Assistant Professor of Medicine and Pediatrics
Special Interests: Scleroderma and connective tissue diseases; juvenile scleroderma; juvenile arthritis



Richard Silver, M.D.
Distinguished University Professor
Vice Chair, Development
Special Interests: Scleroderma; CTD associated ILD and PAH; childhood rheumatic diseases

General Rheumatology



Edwin Smith, M.D.
Professor
Special Interests: Scleroderma; raynaud's phenomenon; rheumatology



Grace Berlin Suppa, D.O.
Assistant Professor
Special Interests: General rheumatology and telehealth



Celine Ward, M.D.
Assistant Professor
Special Interests: Systemic connective tissue diseases: lupus, myositis, scleroderma, vasculitis; inflammatory arthritis: rheumatoid arthritis, psoriatic arthritis

Research Faculty



Alexander Awgulewitsch, Ph.D.
Professor
Special Interests: Roles of Hox transcriptional regulators in development and disease; genetics



Galina Bogatkevich, M.D., Ph.D.
Associate Professor
Special Interests: The cellular and molecular mechanisms of pulmonary fibrosis in scleroderma



Carol Feghali-Bostwick, Ph.D.
Distinguished University Professor and Kitty Trask-Holt Endowed Chair for Scleroderma Research
Special Interests: pathogenic mechanisms in fibrosis; development of anti-fibrotic therapies; mentoring



Stanley Hoffman, Ph.D.
Professor
Special Interests: Cell-cell and cell-extracellular matrix (ECM) adhesion; translational research on fibrotic diseases



Margaret Markiewicz, M.D.
Assistant Professor
Special Interests: Endothelial cell dysfunction in systemic lupus erythematosus; angiogenesis

Research Faculty



Tamara Nowling, Ph.D.
Associate Professor
Special Interests: Lupus nephritis; the role of glycosphingolipid metabolism in renal cell function in lupus nephritis; mechanisms of renal cell and T cell dysfunction in lupus



Paula Ramos, Ph.D.
Assistant Professor
Special Interests: Genetic etiology of autoimmune diseases & their ethnic disparities; systemic lupus erythematosus; systemic sclerosis



Betty Tsao, Ph.D.
Professor and Richard M. Silver SmartState Endowed Chair
Special Interests: Investigations in genetics, epigenetics, biomarkers and targeted treatment of systemic lupus erythematosus



Xian-Kui (John) Zhang, Ph.D.
Associate Professor
Special Interests: Autoimmune disease; B cell development; monoclonal antibody development and its application

Pediatric Rheumatology



Mileka Gilbert, M.D., Ph.D.
Assistant Professor, Pediatric Rheumatology
Special Interests: Pediatric rheumatology; steroid joint injections; lupus research



Natasha Ruth, M.D., MSCR
Professor and Director, Pediatric Rheumatology
Special Interests: Rheumatic diseases in children; systemic lupus erythematosus

MUSC RHEUMATOLOGY FACULTY NEWS & AWARDS



D. Baker Frost



D. Kamen



M. Cunningham



J. Oates



C. Feghali-Bostwick



R. Silver



M. Gilbert



B. Tsao

Deanna Baker Frost, M.D., Ph.D., Assistant Professor, received the Excellence in Patient Satisfaction Award from the MUSC Department of Medicine, 2021 Awards Day.

Melissa Cunningham, M.D., Ph.D., Associate Professor, was named the 2021 Mary Betty Stevens Young Investigator Prize award winner by the Lupus Foundation of America.

Carol Feghali-Bostwick, Ph.D., Distinguished University Professor and Kitty Trask-Holt S.C. SmartState® Endowed Chair for Scleroderma Research, received the Top Ten Publishers Club Award from the Department of Medicine, 2021 Awards Day.

Mileka Gilbert, M.D., Ph.D., Assistant Professor, Pediatric Rheumatology, was awarded the MUSC 2021 MLK Humanitarian Award.

Diane Kamen, M.D., MSCR, Professor, received the Top Ten Publishers Club Award from the Department of Medicine, 2021 Awards Day.

Jim Oates, M.D., Professor and Division Director, was one of 11 recipients of the 2021 Lupus Innovation Awards from the Lupus Research Alliance.

Richard Silver, M.D., Distinguished University Professor and Vice Chair for Development, received The MilliPub Club award from the MUSC Department of Medicine, 2021 Awards Day.

Betty Tsao, Ph.D., Professor and SmartState® Endowed Chair in Inflammation Research, was one of 11 recipients of the 2021 Lupus Innovation Awards from the Lupus Research Alliance.