With an invaluable assist from all of our dedicated faculty, 2018 was another banner year for NYU Langone Health’s Division of Rheumatology.

This year the American College of Rheumatology (ACR) acknowledged the division’s accomplishments, awarding high honors across three levels: master, young investigator, and fellowship. Furthermore, NYU Langone is represented in the ultimate leadership position, the ACR 2019 presidency.

The Judith and Stewart Colton Center for Autoimmunity continues to push our scientific boundaries with its new pilot awards and unique pilot projects, our Psoriatic Arthritis Center is thriving as a research launchpad, and other collaborations have led to groundbreaking discoveries in lupus.

With the reallocation of several faculty to the new Science Building, we anticipate novel approaches inspired by their close proximity to accomplished scientists in other disciplines—and of course the breathtaking views. Our T32 trainee program has raised the bar for our fellowship as we see unprecedented interest in academic and leadership careers.

Our research spans so many diseases. To name a few advances, new data extend the efficacy of hydroxychloroquine to prevent cutaneous neonatal lupus, serum albumin predicts renal health in lupus, and murine models suggest that activation of mucosal immunity precedes the development of arthritis.

As we ring in 2019, please join us in the continued pursuit of unrelenting excellence at the bench, at the bedside and in the lecture halls.

JILL P. BUYON, MD
Sir Deryck and Lady Va Maughan Professor of Rheumatology
Director, Division of Rheumatology
and Co-director, Colton Center
Department of Medicine
A New Push through the Clinical Pipeline

In collaboration with NYU Langone’s Office of Therapeutics Alliances, researchers on two of the center’s previous pilot projects have taken major steps toward translating their scientific findings to clinical use.

One effort, led by Boris Reizis, PhD, professor of pathology and medicine, co-director Colton Center, is targeting the enzyme DNASE1L3 as a potential therapeutic agent for lupus. Dr. Reizis’s group has developed a mouse model with DNASE1L3 deficiency which exhibits features of systemic lupus erythematosus, particularly renal disease. The researchers are working to develop methods to treat disease by targeting this pathway.

In a second project, led by Gregg J. Silverman, MD, professor of medicine and pathology, researchers are working to develop a blood test based on a biomarker that could predict lupus nephritis. Dr. Silverman found that the gram-positive bacterial genus *Ruminococcus*, identified in the gut microbiome of some lupus patients, may contribute to kidney disease and that these patients carry blood-borne antibodies against the microbe.

The project, led by Theresa L. Wampler Muskardin, MD, assistant professor of medicine and pediatrics, has uncovered preliminary data indicating that type 1 interferon levels in the blood may predict a patient’s response to tumor necrosis factor (TNF) inhibitor drugs. Dr. Wampler Muskardin is now working to validate her hypothesis in a large clinical cohort. At the same time, she is staining synovial tissue in the joints of patients with rheumatoid arthritis to clarify the underlying biology of the type 1 interferon pathway and the pathway’s ability to predict a TNF inhibitor nonresponse.
ISOLATING GENES TO MAP THE ORIGINS OF DISEASE

In collaboration with Jef D. Boeke, PhD, professor of biochemistry and molecular pharmacology and director of the Institute for Systems Genetics, Dr. Niewold is leading a team of researchers seeking to identify the most critical regions of interferon regulatory factor 5 (IRF5), a gene linked to risk for lupus. “When we look at the areas potentially causing the risk, there are at least four suspects and they are always in the room,” Dr. Niewold says. “You can never question them separately.”

Using Dr. Boeke’s high-throughput method to create synthetic chromosomes, the team is isolating and analyzing each implicated gene region on separate chromosomes—and in various combinations—to determine which region or synergy of regions may be driving the elevated risk. “This same approach could then be extended to other genes, and you could really start to map the origins of autoimmune disease,” says Dr. Boeke.

A promising line of inquiry at NYU Langone Health’s Psoriatic Arthritis Center is aimed at uncovering whether and how gut microbiota can warn of autoimmune-linked alterations—and potentially improve patient response to therapeutic interventions.

Jose U. Scher, MD (Photo credit: Karsten Moran)
THE ROLE OF PREBIOTICS IN IMPROVING THERAPEUTIC INTERVENTIONS

In follow-up research, investigators are asking whether modifying patients’ microbiota before treating them with methotrexate might improve their outcomes. With funding from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), Fardina Malik, MD, instructor of medicine, is leading a pilot study with 20 PsA patients to explore whether a prebiotic rich in medium-chain fatty acids might modify patients’ gut microbes in a way that improves methotrexate’s efficacy. “We believe that expansion of certain gut bacteria can alter methotrexate activation and hence improve absorption and efficacy,” Dr. Malik says. “Increase in blood T regulatory cells as a result of medium-chain fatty acid administration might act synergistically with anti-inflammatory action of methotrexate.”

In a related study of 40 patients, the researchers concluded that the baseline microbiota of rheumatoid arthritis patients prior to methotrexate therapy could help predict their response to the therapy four months later. The findings revealed that if certain signatures were present in a patient’s microbes, response to methotrexate was significantly better than in patients without those signatures.

PREBIOTICS APPEAR TO ENABLE INFLAMMATION REDUCTION

Dr. Scher, in collaboration with Sergei Koralov, PhD, associate professor of pathology, found that a gain-of-function mutation introduced in the STAT3 gene of mouse T cells led to an overproduction of inflammation-promoting interleukin 17 (IL-17)—and the mice showed clear signs of psoriasis and psoriatic arthritis (PsA). However, when the researchers fed the mice prebiotics, they saw a noticeable shift toward production of more protective microbes. The same prebiotic intervention in wild-type mice led to an increase in the number of inflammation-fighting regulatory T cells.

“The results from this promising animal model prompted a series of human studies. In one, administering medium-chain fatty acids as a prebiotic in healthy individuals appeared to diversify their gut microbiota and to expand the population of regulatory T cells in their blood. “We saw more bacteria overall and, in particular, more reportedly beneficial bacteria,” Dr. Scher says. “So, now we have a proof of principle that a single modification correlates with an increase in the body’s inflammation regulators,” he says.

Dr. Scher’s group is carrying out the same procedure with PsA patients. The next step, he says, will be to correlate that increase in beneficial microbes and regulatory T cells with an improvement in symptoms in PsA patients.

“Biologic therapies are incredibly costly, so if we can conclude that prebiotics assist in the effectiveness of methotrexate and other oral anti-rheumatic drugs, that’s an invaluable amount of benefit for patients and cost savings for the entire healthcare system.”

—Jose U. Scher, MD

A POTENTIAL EXPLANATION FOR IL-17I-MEDIATED GUT INFLAMMATION

The same concept can be applied to other medications, such as the interleukin-17 inhibitor (IL-17i). This drug class, commonly prescribed to patients with PsA and spondyloarthritis (SpA), has the well-known and seemingly paradoxical side effect of exacerbating Crohn’s disease in some patients. Research at the gut level, led by Julia Manasson, MD, postdoctoral T32 research fellow, and colleagues, suggests significant changes in the microbiota of SpA patients receiving IL-17i therapy, with some patients showing a notable increase in Candida albicans yeast in the intestinal lumen. The same change was not observed in patients receiving tumor necrosis factor blockade therapy. This increase in yeast production upon IL-17i treatment, Dr. Scher says, may explain why certain patients who already have subclinical gut inflammation go on to develop clinically overt inflammation and Crohn’s disease.
Expanding the Landscape of Clinical Trials for Lupus

With its large portfolio of NIH-sponsored, industry-backed, and investigator-initiated interventional and observational trials targeting systemic lupus erythematosus (SLE), NYU Langone Health has vigorously pursued the disease from its biological beginnings to the final course of treatment. In combination with its rich basic science program, the forward-looking clinical trials unit is committed to bringing highly promising therapeutic interventions to the full spectrum of SLE patients.

Clinical investigators are now broadening their reach with innovative studies that could open the door to noninvasive diagnostics and new drugs initially developed for other conditions. Amit Saxena, MD, assistant professor of medicine, says NYU Langone’s ambitious efforts include taking part in new investigations of MRI-based methods for diagnosing lupus nephritis and steroid-induced osteoporosis and other trials to determine whether anti-psoriasis medications might benefit lupus patients as well.

**NOVEL DIAGNOSTIC COULD TRANSFORM BONE-LOSS TRACKING IN LUPUS**

The collaborative Bone Quality in Glucocorticoid-Induced Osteoporosis study is testing whether a new, MRI-based protocol developed by Gregory Chang, MD, MBA, associate professor of radiology, might help identify glucocorticoid-induced osteoporosis in lupus patients. “We are evaluating the idea that osteoporosis due to glucocorticoid exposure might be different from other types of osteoporosis,” says Dr. Saxena. That finding could suggest that the dual-energy X-ray absorptiometry (DXA) bone density scan, the current standard of care, may not capture differences in the reduced bone mass and microarchitectural deterioration of bone tissue of lupus patients.

The research compares the new MRI protocol with DXA scans to examine potential bone loss in lupus patients with or without glucocorticoid exposure. An early evaluation of the DXA data did not show an association of low bone density with glucocorticoid use, a risk factor. This result suggests that a DXA scan alone may be insufficient to determine whether bone loss has occurred, especially based on traditional definitions of osteoporosis or osteopenia in younger patients.

If the new MRI method proves effective, “this could really change the standard of care,” says Dr. Saxena. “We have a lot of younger patients with lupus who have been exposed to steroids and we don’t really know how to monitor or treat them for their bone loss. This might give us a new direction in how aggressively we should be following them.”

—Amit M. Saxena, MD
NYU Langone’s industry partnerships are further enriching the clinical trial program by allowing medical researchers to study SLE’s origins and associated complications, examine the utility of prediction and response biomarkers, and give patients the opportunity to participate in studies of cutting-edge therapeutic approaches.

With support from AMPEL BioSolutions, a multicenter trial now in the enrollment stage will compare kidney biopsies with four separate MRI-based imaging techniques for diagnosing presumed lupus nephritis. The Dynamic Imaging of Variation in Lupus Nephritis (DIVINE) trial will evaluate how well the imaging techniques compare to biopsies in measuring blood flow, perfusion, cellularity, fibrosis, and atrophy in the patients’ kidneys.

Beyond their invasive nature, biopsies can carry significant side effects and yield confounding pathology results, says Dr. Saxena. “The study will compare the results of those techniques to give us a sense of whether we could noninvasively diagnose patients with lupus nephritis,” he explains. “That could be another potential game changer.”

**TESTING PSORIASIS DRUGS FOR POTENTIAL ANTI-LUPUS ACTIVITY**

Several trials have taken an innovative tack in investigating the uses of new drugs. One multicenter phase II drug trial, sponsored by Bristol-Myers Squibb, is exploring the anti-lupus potential of a highly selective oral tyrosine kinase 2 (TYK2) inhibitor.

TYK2 has multiple effects on the body’s immunomodulatory and inflammatory responses, Dr. Saxena says. Although TYK2’s mediation of immune signaling may be critical to normal immune responses in healthy individuals, accumulating evidence suggests that aberrant expression of the protein may lead to signaling that promotes autoimmunity. A separate study recently published in the New England Journal of Medicine suggests that the TYK2 inhibitor can effectively treat plaque psoriasis as well.

“There is always the question of overlap, particularly in regard to skin disease in lupus and psoriasis, and the possibility that some medicines might be useful for both,” he says.

Accordingly, another multicenter clinical trial, just beginning enrollment for phase III after successful phase II results, is testing the anti-lupus effects of ustekinumab (Stelara), which is already approved for psoriasis and psoriatic arthritis. The randomized, double-blind, placebo-controlled study aims to recruit about 500 participants.

**SHARED PATHOLOGY COULD CREATE POSSIBILITY**

The trials, Dr. Saxena says, could contribute to opening an exciting new avenue of investigation. “It’s a question of examining other medicines approved for psoriasis, in light of anecdotal evidence suggesting that some of them might also be helpful in lupus,” he says. Such examinations might reveal whether a shared mechanism of action against similarities in the pathogenesis of lupus and psoriasis rashes could indeed benefit both groups of patients. If so, the medical center promises to be at the forefront in further expanding the anti-SLE arsenal.

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**Disclosure:** Jill P. Buyon, MD, has previously served as a paid consultant to Bristol Myers Squibb.

“Genetic variations at APOL1 are conserved in people of predominantly West and Central African ancestry because they provide an evolutionary advantage in resisting African trypanosomiasis,” says Dr. Blazer. However, her latest research suggests that among Ghanaian systemic lupus erythematosus (SLE) patients, the APOL1 polymorphisms carry the considerable downside of heightened risk of progressive renal disease, organ damage accrual, and mortality.

“APOL1 polymorphisms, G1 and G2, linked to lupus-associated renal disease and mortality in a Ghanaian cohort”

Lupus is far more common and more severe in its manifestations among people of African ancestry than among Caucasians. Ashira Blazer, MD, assistant professor of medicine, is investigating this disparity from the vantage point of two specific polymorphisms, G1 and G2, of medicine, is investigating this disparity from the vantage point of two specific polymorphisms, G1 and G2, in the gene for apolipoprotein L1, or APOL1.

We now have more evidence to suggest that there are additional benefits of hydroxychloroquine, especially among mothers who have the candidate autoantibodies that put their child at risk for neonatal lupus.”

—Peter M. Izmirly, MD, MSC1

Hydroxychloroquine helps prevent neonatal lupus rash

Peter M. Izmirly, MD, MSC1, assistant professor of medicine and leader of the Manhattan Lupus Surveillance Program, a population-based lupus registry, has recently focused on benefits and limitations of hydroxychloroquine (Plaquenil), a medication widely used by lupus patients and shown to hold ongoing disease in check. Dr. Izmirly reasoned that it might also benefit pre–lupus women at risk for a pregnancy complication of neonatal lupus.

The finding’s of Dr. Izmirly’s group first suggested that mothers with SLE and antibodies to SSA/Ro (a risk factor for the development of neonatal lupus in an offspring) who take hydroxychloroquine may be at reduced risk for having a child with cardiac manifestations of neonatal lupus. In a subsequent study, Dr. Izmirly and colleagues showed that hydroxychloroquine could likewise decrease the recurrence rate of neonatal heart block in subsequent children born to at-risk mothers with SLE or Sjogren’s Syndrome or even those with no rheumatic disease. Those results led to an ongoing prospective study to test the drug’s benefits in a larger cohort.

“But there are other manifestations of neonatal lupus,” Dr. Izmirly says. “Skin manifestations are not as serious as the cardiac manifestation but do come with their own potential complications, such as scarring. We now have more evidence to suggest that there are additional benefits of hydroxychloroquine, especially among mothers who have the candidate autoantibodies that put their child at risk for neonatal lupus.2 Pooling resources and data with collaborators in Toronto and Paris, Dr. Izmirly’s group led a retrospective study examining the ability of hydroxychloroquine to prevent neonatal lupus rash. The study, recently published in the *Annals of the Rheumatic Diseases*, included 262 children who developed the rash after birth and 434 children who remained healthy despite exposure to the same auto-antibodies. In the analysis, limited to mothers with an autoimmune disease who stayed on hydroxychloroquine throughout their pregnancy, children were significantly less likely to develop a rash than were children born to mothers who did not take the drug.


The roughly 60 percent risk reduction held up in analyses limited to mothers diagnosed with lupus and was even stronger among infants examined within a month of their birth, when they would be more likely to retain some of the drug in their system. “No matter how we looked at it, the data suggested that hydroxychloroquine reduced the risk,” Dr. Izmirly says.

Doctors commonly prescribe the drug to prevent lupus flares during pregnancy. “So this is more evidence to suggest that there are additional benefits of hydroxychloroquine,” says Dr. Izmirly, “especially if mothers have the candidate autoantibodies that put their child at risk for neonatal lupus.”

**SINGLE-CELL TRANSCRIPTOME PROFILES MAP THE CELLULAR LANDSCAPE IN LUPUS NEPHRITIS**

Treatment decisions in lupus nephritis are still based primarily on renal histology. A multicenter collaboration with researchers Thomas Tuschl, PhD, Rockefeller University, and Chaim Putterman, MD, Albert Einstein College of Medicine, in the NIH-supported Accelerating Medicines Partnerships suggests that single-cell RNA-seq (scRNA-seq) analysis may offer more detailed insights into the disease’s genesis, better categorization of pathological subtypes, and clearer information on which to base prognosis and treatment decisions.

Jill P. Buyon, MD, the Sir Deryck and Lady Va Maughan Professor of Rheumatology and director of the Division of Rheumatology, and co-director Colton Center, and Robert M. Clancy, PhD, professor of medicine, led the NYU Langone portion of the collaboration. The researchers conducted scRNA-seq analysis on kidney biopsy tissue collected from nine lupus nephritis patients and two healthy transplant donors.

By capturing single renal cells from the tissue samples, sequencing the cDNA, and aligning the sequences to the human reference genome, the team generated a gene-expression matrix and transcriptome profile for each cell. For example, differential gene expression analysis and cell lineage markers revealed elevated levels of interferon response genes in the collecting duct cells, distal convoluted tubule cells, and endothelial cells of lupus nephritis patients. In the lupus nephritis samples, the impact of disease was widespread, including the expression of fibrotic factors by non-immune cells, such as the collecting duct cells and distal convoluted tubule cells. Within reach, there will be an association between expression by a panel of genes and the outcome of aggressive lupus nephritis with utility to guide the choice of therapeutic intervention.

“This single-cell sequence analysis of renal biopsy tissue from lupus nephritis patients has helped us create a cellular atlas that could be invaluable to studying the disease’s heterogeneity,” Dr. Clancy says.

**NYU Langone Researchers Awarded at ACR Annual Meeting**

At the 2018 American College of Rheumatology (ACR) annual meeting in Chicago, researchers at NYU Langone Health received multiple awards, reflecting their many contributions to the field. Jill P. Buyon, MD, was recognized as a Master of the ACR, one of the organization’s highest honors, for her contributions to the specialty’s understanding of lupus in pregnancy.
RECOGNIZING RESEARCH INTO LUPUS’S GENETIC ROOTS

Timothy B. Niewold, MD, the Judith and Stewart Colton Professor of Medicine, professor of pathology, and director of the Judith and Stewart Colton Center for Autoimmunity, has contributed to both basic and clinical research with multiple studies aimed at understanding how genes influence the pathogenic cytokine patterns that give rise to lupus in humans. Those contributions were recognized with the ACR’s Henry Kunkel Young Investigator Award, given annually to a researcher 45 years of age or younger.

The recognition brings Dr. Niewold full circle: Henry Kunkel, the award’s namesake, was a lupus researcher at New York’s Rockefeller University, where he described some of the early autoantibodies used to diagnose the disease. Dr. Niewold’s first research mentor had been a postdoctoral fellow in Dr. Kunkel’s lab. Dr. Kunkel’s group studied lupus in humans at a time when addressing the disease beyond cell cultures or mouse models was thought to be impossible. The lab validated its approach with a series of important findings, and Dr. Niewold says Dr. Kunkel’s focus on patients helped shape his approach to human immunology.

FELLOWSHIP AWARDS EMPHASIZE SPECIALTY EDUCATION

Michael H. Pillinger, MD, professor of medicine and biochemistry and molecular pharmacology, and director of the Rheumatology Fellowship Program, received a prestigious Amgen Fellowship Training Award from the Rheumatology Research Foundation. The one-year award will partially fund a promising rheumatology fellow in the division’s two-year program.

Separately, Shudan Wang, MD, was recognized with a Distinguished Fellow Award for her analysis of membrane attack complex deposition in lupus nephritis. Dr. Wang’s research suggested that the membrane attack complex of complement activation, specifically C9, is associated with hypertension and poor response to treatment. Dr. Wang’s special staining technique may have important implications for management of lupus nephritis. Dr. Wang also examined the cardiovascular safety of arthritis medications.

I’m particularly proud of our faculty this year, as they were recognized at every level—across the master, researcher, educator, and fellow categories.”

—Jill P. Buyon, MD

Paula Marchetta Appointed ACR President

Paula Marchetta, MD, MBA, professor of medicine and CEO and managing partner of Concorde Medical Group PLLC, was named ACR president for the 2018-19 term, becoming the seventh NYU Langone faculty member to lead the organization since its inception. As president, Dr. Marchetta says she will continue to involve fellows and other young investigators in outreach efforts, expanding the ACR’s global reach to help meet the growing demand for rheumatology education.

David Daikh, MD, PhD, and Paula Marchetta, MD, MBA

Yamen Homsi, MD, MPH

Yamen Homsi, MD, MPH, recently joined NYU Langone Health as section chief of the Division of Rheumatology at NYU Langone Hospital—Brooklyn. Dr. Homsi received a Master of Public Health from Northeastern University in Boston, completed residency training at the University of Massachusetts, and was a rheumatology fellow at Albany Medical Center. He is board certified in internal medicine and rheumatology and joint executive director at SUNY Downstate Medical Center. He has participated in pivotal clinical trials in both systemic lupus erythematosus and rheumatoid arthritis.

His clinical research interests include:
- Idiopathic inflammatory myopathies among African American and Afro-Caribbean populations
- Prevalence of pulmonary arterial hypertension in minority patients with rheumatoid arthritis
- Comparison of patients with rheumatoid arthritis with and without interstitial lung disease

As section chief, Dr. Homsi will work closely with our division to build a strong rheumatology presence in Brooklyn to fulfill our missions of patient care, education, and research.

Expanding our Rheumatology Footprint

NYU Langone Researchers Awarded at ACR Annual Meeting

Paula Marchetta Appointed ACR President

FELLOWSHIP AWARDS EMPHASIZE SPECIALTY EDUCATION

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Tuition-Free Initiative Addresses High Student Debt

NYU School of Medicine announced in August 2018 that it will begin offering full-tuition scholarships to all current and future students in its MD degree program regardless of need or merit—a bold effort to simultaneously address the rising costs of medical education and still attract the best and brightest students to careers in medicine. “This decision recognizes a moral imperative that must be addressed, as institutions place an increasing debt burden on young people who aspire to become physicians,” says Robert I. Grossman, MD, the Saul J. Farber Dean of NYU School of Medicine and CEO of NYU Langone Health.

For more information go to med.nyu.edu/school
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