



2016 / YEAR IN REVIEW

Rheumatology

TRANSLATING

RESEARCH TO
IMPROVED CARE

12%

PATIENT VOLUME
INCREASE

TOP 10

IN *U.S. NEWS & WORLD
REPORT*

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Dear Colleagues and Friends:



A handwritten signature in black ink that reads "Jill P. Buyon".

JILL P. BUYON, MD

Lady Va and Sir Deryck Maughan
Professor of Rheumatology

Director, Division of Rheumatology,
Department of Medicine

This was an exciting year of growth and collaboration for our division: We accelerated applications of truly personalized medicine while extending our reach well beyond the walls of NYU Langone.

Among our 16 open clinical trials for lupus, for example, we are investigating the promising drug anifrolumab, exploring new uses for the older injectable drug corticotropin, and testing the safest way to wean patients from the immunosuppressant mycophenolate mofetil.

With the expansion of FDA-approved drugs for psoriatic arthritis, researchers in our Psoriatic Arthritis Center are likewise helping patients understand which options are best for them while clarifying their underlying molecular mechanisms. And through the division's Judith and Stewart Colton Center for Autoimmunity, we are elucidating how the largely unexplored frontiers of the human microbiome may provide biomarkers for autoimmune diseases, modify the effects of therapies, and even suppress inflammation and reverse autoimmunity.

We have partnered with other research institutions to identify skin-based biomarkers that might mirror the activity within patients' kidneys and thereby signal, mitigate, or even prevent lupus nephritis. Our renowned Research Registry for Neonatal Lupus enables close tracking of both the mothers and their affected and unaffected children and has revealed that the emergence of autoimmune conditions is more common in the children with heart block. Utilizing the more recently established division-wide biorepository, SAMPLE (Specimen and Matched Phenotype Linked Evaluation), another new effort enables close tracking of patients' long-term progress, while revealing longitudinal data about later-onset problems—such as psoriasis and other autoimmune conditions recently discovered among a significant fraction of patients with neonatal lupus. Another new effort is studying whether an MRI-based method may be better than dual-energy X-ray absorptiometry to reliably diagnose glucocorticoid-induced osteoporosis. We are also exploring the molecular mechanisms that may help bariatric surgery reduce the knee pain of osteoarthritis patients, and identifying biomarkers that may point to the most effective pain relief pathways.

With our unprecedented access to data and growing expertise, we are learning more than ever about rheumatic conditions and why some treatments are effective for some patients, but not others. We know that we still face immensely challenging diseases, but we also know that we are making undeniable and exciting progress toward reducing the toll of autoimmunity and inflammation on patients and their families.

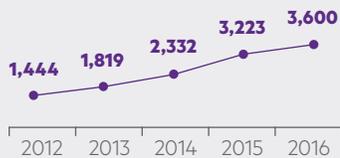
Division of Rheumatology

Clinical Care

3,600

PATIENTS SEEN MONTHLY,

marking a substantial increase over the past five years



TOP 10

**IN THE COUNTRY
FOR RHEUMATOLOGY**



in *U.S. News & World Report's* "Best Hospitals"

12

**OUTPATIENT PRACTICES
IN THE NYC AREA**

Research

646

CHILDREN

in NYU Langone's Research Registry for Neonatal Lupus (RRNL)

54

ACCEPTED ACR ABSTRACTS

including 12 oral presentations

NEW NIH AWARDS

ADAM MOR, MD, PhD

R01 Grant: "Novel mechanisms regulating PD-1 signaling and function"

STEVEN ABRAMSON, MD

R21 Grant: "Control of Bone Homeostasis by MT1-MMP Signaling"

**JILL P. BUYON, MD; ROBERT CLANCY, PhD;
H. MICHAEL BELMONT, MD;
PETER IZMIRLY, MD**

UH2 Nested Supplement: "Multi-Ethnic Translational Research Optimization (METRO) Lupus Consortium"

ASHIRA BLAZER, MD

NIH Loan Repayment Program: "Heritable Endotheliopathy and Apolipoprotein L1 Risk Traits in SLE (HEARTS)"



NYU Langone Medical Center

Education & Training

8

FELLOWSHIP POSITIONS

200

FELLOW APPLICANTS

101

FACULTY MEMBERS

250+

ATTENDEES

at NYU Langone's Advanced
Seminar on Rheumatology

Numbers represent FY16 (Sept 2015–Aug 2016)
unless otherwise noted



#10

**IN THE NATION
BEST HOSPITALS**

and nationally ranked in 12 specialties, including top 10 rankings in Orthopaedics, Geriatrics, Neurology & Neurosurgery, Rheumatology, Rehabilitation, Cardiology & Heart Surgery, and Urology. Nationally ranked in Cancer, Diabetes & Endocrinology, Ear, Nose & Throat, Gastroenterology & GI Surgery, and Pulmonology



#11

**IN THE NATION
BEST MEDICAL SCHOOLS
FOR RESEARCH**

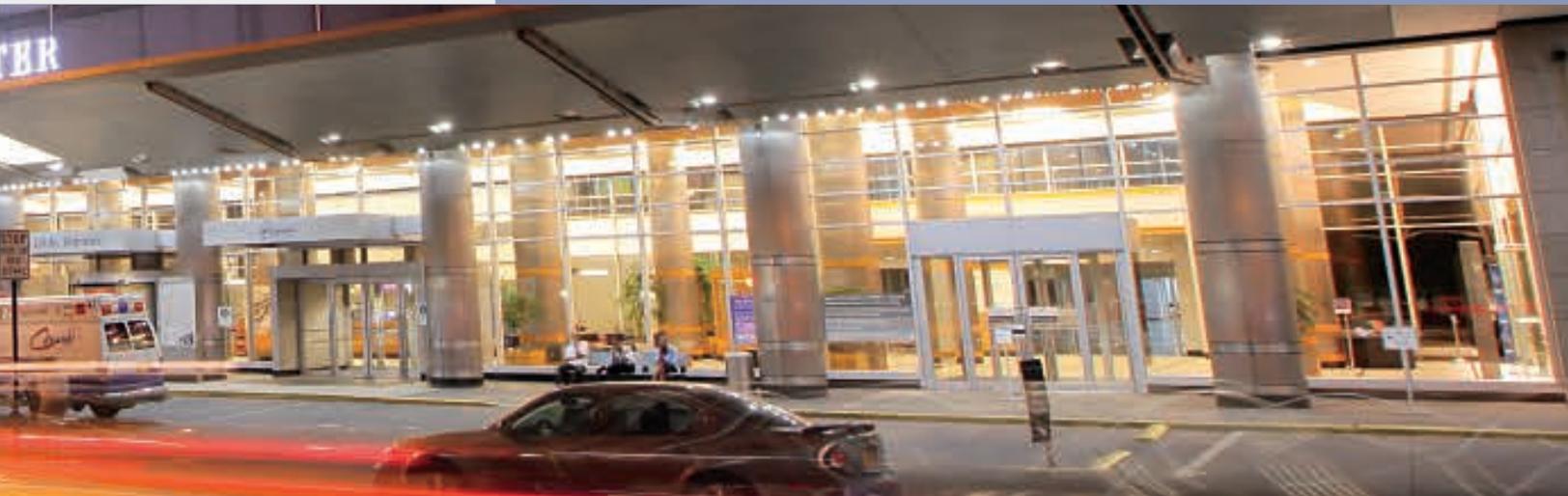
and a leader in innovation in medical education, including accelerated pathways to the MD degree



LEADER

**IN QUALITY CARE
AND PATIENT SAFETY**

and recognized for superior performance as measured by Vizient's nationwide 2016 Quality and Accountability Study



Transformation Through Innovation and Growth

New Evidence Links Lupus with Gut Microbiome Imbalance

Recent NYU Langone research suggests that intestinal bacteria may aid the development of systemic immune responses and autoreactivity, and help resolve tissue inflammation and injury.

Gregg J. Silverman, MD, professor of medicine and pathology, is leading an interdisciplinary effort to clarify the links between the intestinal microbiome and lupus. The collaboration, supported in part by the Colton Center for Autoimmunity, has led to the first association between clinical SLE and a gut microbiome imbalance, namely a decrease in overall bacterial diversity and specific bacterial blooms. The results, Dr. Silverman says, suggest that candidate species may act as triggers for the initial disease and subsequent flares.

To uncover the links, he and colleagues used next-generation sequencing to profile 16S bacterial rRNA genes from the gut

microbiomes of 83 ethnically diverse SLE patients and 16 healthy volunteers. For the controls and a subset of patients, the researchers also fractionated fecal samples for endogenous IgA-coated bacteria and non-coated bacteria.

From the genomic bacterial extracts, the researchers discovered that the microbial composition of SLE patients was not only markedly different from that of their healthy counterparts, but also highly variable within the population. Specifically, the SLE microbiomes hosted less bacterial diversity and was significantly increased in Proteobacteria and decreased in Firmicutes, compared with the healthy controls. The group also found an expanded population of the anaerobic microbe *Prevotella copri*, recently linked to new-onset rheumatoid arthritis, in a subset of SLE patients, but not in the healthy controls.

One hypothesis for the variances is that the inflammatory mechanisms of lupus may increase oxidative metabolism in the body. This shift, Dr. Silverman says, may yield a decrease in protective and pro-homeostatic anaerobic bacteria like Firmicutes. Their diminishing numbers, in turn, could allow microbes such as Proteobacteria to fill the vacuum. Other bacteria might also gain a foothold, causing a breach in the immunologic tolerance and a decline in T cell-mediated regulation. Eventually, the chain of events could yield an increase in organ-damaging autoantibodies.

As research continues to fill in the blanks, “The emerging picture could point toward more targeted ways to block inflammation and pathogenesis by altering a patient’s microbiome,” notes Dr. Silverman.

↓ Gregg J. Silverman, MD



Harnessing a Natural Nuclease for the Rational Immunotherapy of SLE

Within the past five years, scientists have linked null and partial mutations in the gene encoding the serum protein DNASE1L3, a secreted nuclease, to familial and sporadic systemic lupus erythematosus, respectively. The nuclease is now a promising target for a lupus therapy being pursued by Boris Reizis, PhD, professor of medicine and pathology, and Timothy Cardozo, MD, PhD, associate professor of biochemistry and molecular pharmacology.

The research, drawing upon both Dr. Reizis's expertise in experimental immunology and Dr. Cardozo's experience in protein engineering, suggests that the nuclease normally helps digest DNA and chromatin released during apoptosis, thereby preventing them from becoming self-antigens. Accordingly, a DNASE1L3 deficiency or hypofunctioning of the enzyme leads to elevated DNA levels in patients' plasma.

So far the collaborators have made significant progress in understanding how the DNASE1L3 nuclease relates to the development of lupus. Relying in part on a

3D structure modeled by the Cardozo lab, the scientists have characterized the enzyme's unique properties and DNA substrate. In a June 2016 study in *Cell*, they further reported that mice lacking the DNASE1L3 gene rapidly developed autoantibodies to DNA and chromatin, followed by the onset of an SLE-like disease.

Their research has led to insights into how to use the nuclease in lupus treatments. For instance, they learned that treating the afflicted animals with circulating DNASE1L3 delayed the autoreactivity, perhaps by preventing autoantibodies from binding to the chromatin or DNA-containing microparticles released by apoptotic cells. "Our study reveals a new mechanism that could be harnessed for biological therapies for lupus and other autoimmune diseases," Dr. Reizis says. Natural production of DNASE1L3 by the body's dendritic cells and macrophages also suggests that the nuclease, if its efficacy is confirmed, could be safely given to patients as an anti-SLE biologic.



↑ Boris Reizis, PhD

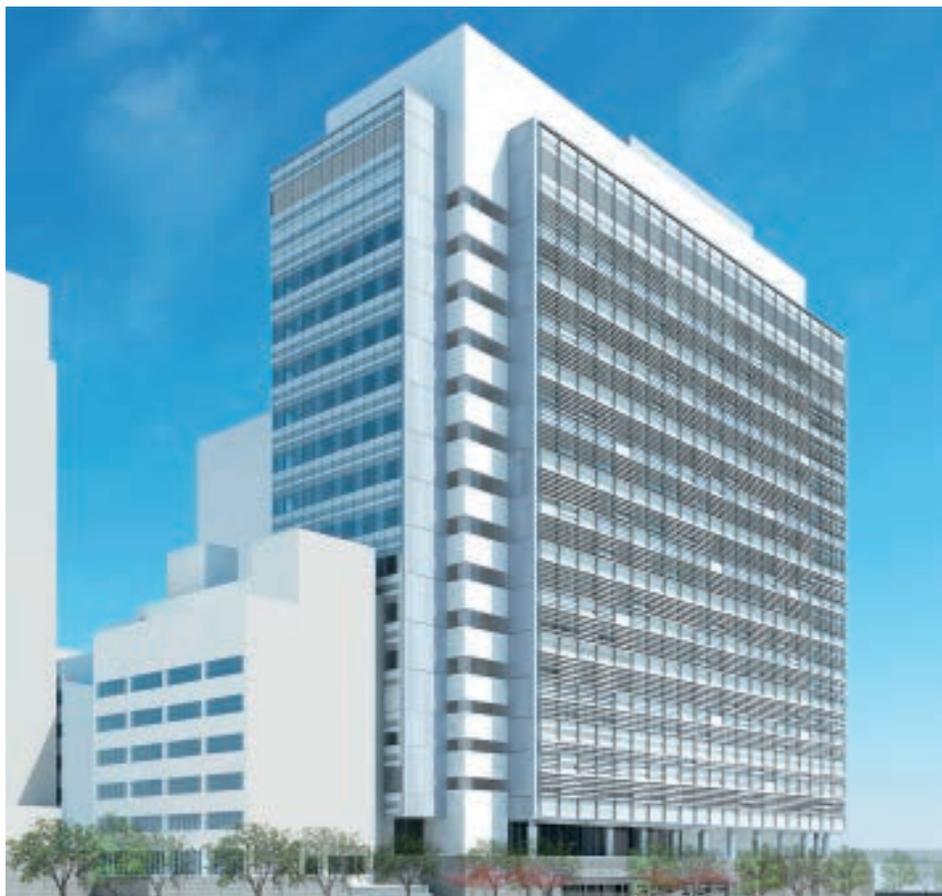
NYU LANGONE MEDICAL CENTER AFFILIATION WITH WINTHROP-UNIVERSITY HOSPITAL BRINGS EXPANDED AND ENHANCED HEALTHCARE NETWORKS TO LONG ISLAND

NYU Langone Medical Center and Winthrop-University Hospital on Long Island have reached an agreement to affiliate the institutions' extensive healthcare networks. NYU Langone, with more than 150 ambulatory sites throughout the region, will complement Winthrop-University Hospital's main campus, multiple ambulatory sites, and network of 66 faculty and community-based practices in more

than 140 locations extending from eastern Long Island to Upper Manhattan.

The affiliation will further expand NYU Langone's presence on Long Island, while enhancing Winthrop's inpatient and outpatient services with improved access to NYU Langone's wide range of medical and surgical specialties.

"This agreement publicly confirms our confidence that an affiliation will allow both of our institutions to collaborate and share best practices to better meet the healthcare needs of the communities we serve," says Robert I. Grossman, MD, the Saul J. Farber Dean and CEO of NYU Langone. Pending regulatory approval, the institutions are aiming to complete their affiliation in spring 2017.



New Checkpoint Inhibitor Targets Could Abate Autoimmune Response

As researchers pursue new targets to depress autoimmunity, new signs point to checkpoint inhibitors, which are currently the focal points of several anti-cancer strategies. Backed by an NIH R01 grant, Adam Mor, MD, PhD, assistant professor of medicine and pathology, is working toward a future rheumatic therapy by investigating checkpoint inhibitors that target the programmed death-1 (PD-1) protein linked to inflammatory diseases.

Rather than blocking PD-1 to increase T cell activity—the strategy used in cancer research—the same molecular pathway could be manipulated to increase PD-1 activity and turn down the immune system when necessary, says Dr. Mor. Such a PD-1-based treatment could offer the advantage of controlling T cell behavior without killing the cells.

First, researchers need to understand how the PD-1 signaling pathway works, including the mechanism behind its inhibitory effect. With support from the Rheumatoid Research Foundation, Dr. Mor is leading an unbiased study aimed at clarifying how PD-1 regulates T cells.

Recently, his group discovered that PD-1 can slow T cells by regulating the Rap1 protein, perhaps by altering its role in cell adhesion. With the help of genetically modified T cell clones, the team is also mapping out the PD-1 “interactome.” Using high-resolution microscopy, the lab is confirming interactions among a sizeable roster of proteins, including both suppressors and promoters, then comparing them with mouse models of autoimmunity to help narrow down what Dr. Mor says are some “very attractive targets.”

New Science Building to Enable Stronger Collaborations

Soon, Division of Rheumatology researchers will be working out of NYU Langone’s Science Building—a new facility encompassing more than 385,000 square feet and 10 floors of laboratory space dedicated to research, including wet laboratory space, core facilities, a new vivarium, conference spaces, and public amenities in an expansive, integrated environment. The building’s design will help strategically integrate research facilities and services so that investigators, students,

faculty, and clinicians can work more efficiently and collaboratively. Its laboratory floors are designed to be open, efficient, flexible and easily adaptable with cutting-edge, shared equipment to accommodate advances in research over time.

“We’re looking forward to getting our researchers under one roof and to see the fruitful collaborations that will enable,” says Jill P. Buyon, MD, the Lady Va and Sir Deryck Maughan Professor of Rheumatology and director of the Division of Rheumatology.

Awards and Honors

→ **Bruce Cronstein, MD**, the Dr. Paul R. Esserman Professor of Medicine, was designated a Master of the American College of Rheumatology.

→ **Paula Marchetta, MD**, clinical associate professor of medicine, was elected treasurer of the American College of Rheumatology.

→ **Mark Philips, MD**, professor of medicine, was elected as fellow of the American Association for the Advancement of Science.

→ **Jose U. Scher, MD**, assistant professor of medicine, was selected as an FDA Arthritis Advisory Committee Member and an ACR Psoriatic Arthritis Guideline Development Group Member.

Fellows

FIRST YEAR FELLOWS

Benjamin Friedman, MD

Residency: Mount Sinai

Julie Nusbaum, MD

Residency: Cornell

Michael Toprover, MD

Residency: NYU Langone Medical Center

Shudan Wang, MD

Residency: Cornell

SECOND YEAR FELLOWS

Nicola Berman, MD

Residency: Hospital of the University of Pennsylvania

Research projects: Effects of Caffeine on Bone Density; Building a Cohort of Males with Osteoporosis to Identify Risk Factors and a Need for Screening

Mentor: Stephen Honig, MD

Julia Manasson, MD

Residency: NYU Langone Medical Center

Research projects: Cutaneous Microbiota in Psoriasis and Psoriatic Arthritis; Gut Microbiota in Reactive Arthritis

Mentor: Jose U. Scher, MD

Vinicius Domingues, MD

Residency: Cornell

Research projects: Mining Biomarkers Related to Outcome of SLE Patients with Secondary APS; Serum Albumin as a Predictor of Activity in SLE Nephritis

Mentors: Robert Clancy PhD, and H. Michael Belmont, MD

Anna Zeron, MD

Residency: Montefiore Medical Center, NYU Langone Medical Center

Research Project: Exploring Systemic Lupus Erythematosus in the Geriatric Age

Mentor: Jill P. Buyon, MD

THIRD YEAR FELLOW

Sabina Sandigursky, MD

Residency: Albert Einstein College of Medicine, Montefiore Medical Center

Research Project: How PD-1 Expression is Altered in Patients with Rheumatoid Arthritis

Mentor: Adam Mor, MD, PhD

FINDING THEIR MENTOR MATCH

To pair up fellows with an appropriate mentor and research project, the division held a research day "speed dating" session in which researchers were on the clock to give a quick overview of their projects and what they were looking for in a match. Fellows then gave overviews of their own backgrounds and research interests, and they paired up on research projects.



Translational Research: Foundations for Cutting-Edge Care

NYU LANGONE IS LEADING RESEARCH EFFORTS THAT ARE CHANGING
TREATMENT OPTIONS FOR PATIENTS WITH RHEUMATOLOGIC DISEASES

↑ H. Michael Belmont, MD

Reducing Glucocorticoid-Induced Fractures in Patients with Rheumatic Diseases

Steroid-treated rheumatic disease patients—including those with lupus and RA—are at higher risk for bone density loss and developing osteoporosis, often at an unexpectedly young age. Glucocorticoid-induced osteoporosis (GIO), in fact, is the most common secondary form of the disease, though it is under-diagnosed and under-treated.

H. Michael Belmont, MD, professor of medicine, says managing these lupus patients can be complicated by compression fractures of the vertebrae, fractures of the distal radius, and intertrochanteric fractures of the femur, among others. And yet rheumatologists and radiologists often have insufficient advanced warning that fractures might occur. “We know that the standard diagnostic tool to identify patients at greatest risk of these fractures and of developing various degrees of osteopenia and osteoporosis—namely the dual-energy X-ray absorptiometry, or DXA, scan—may underestimate the risk,” Dr. Belmont says. Researchers have linked that shortcoming to a poor relationship between the fracture risk in GIO and estimations of real bone mineral density by DXA and the Fracture Risk Assessment Tool (FRAX).

COLLABORATION WITH RADIOLOGY

In September 2016, the NIH awarded NYU Langone researchers led by Gregory Chang, MD, associate professor of radiology, a five-year, \$2.6 million R01 grant to study whether MRI-based imaging may provide a more reliable diagnostic alternative. The collaboration with Dr. Belmont, Amit Saxena, MD, assistant professor of medicine, and other researchers in the Division of Rheumatology assesses whether a new 3T MRI test of proximal femur microarchitecture and strength can detect skeletal fragility in glucocorticoid-treated patients and identify those in need of osteoporosis therapy.

So far, the collaborators have shown that their MRI method is reproducible and offers bone quality information that DXA does not. If the new test reliably predicts fractures, physicians could use it to figure out whether they should taper the dosage of corticosteroids

for at-risk patients or deliver concurrent anti-resorptive or anabolic agents to treat osteoporosis. “We may be able to characterize patients as having high, moderate, or lower risk,” Dr. Belmont says. “The MRI method could guide the intensity and duration of steroid treatments and identify which patients need co-management of glucocorticoid-induced osteopenia or osteoporosis.”

EARLY RESULTS PROMISING

The joint study has begun enrolling the first of 40 lupus patients who have been newly prescribed glucocorticoids, and 40 control patients without the steroids. Having adjusted for bone mineral density and disease severity, the collaborators hypothesize that the patients on glucocorticoids will display more detrimental changes in their femoral neck cortical thickness, trabecular thickness, separation, number, connectivity, and whole femur stiffness than the controls. To directly compare the diagnostic methods, each group will receive DXA and MRI tests at 0, 12, and 24 months.

In addition, the study will assess 138 patients with inflammatory arthritis who have used glucocorticoids for more than 12 months; of those, the researchers expect that 41 will have fragility fractures. The team hypothesizes that adding the MRI-enabled microarchitecture measures to the DXA and FRAX tests will improve the accuracy of models in predicting fracture status.

Better risk markers could significantly increase the value of ACR guidelines for managing GIO patients and improve outcomes, Dr. Belmont says. An imaging test that more reliably identifies patients at risk provides a window of opportunity for interventions that will reduce the toll of glucocorticoid-induced fractures.

Leading the Charge in Clinical Trials for Lupus

NYU Langone's sizeable lupus research portfolio includes 16 currently enrolling clinical trials launched by individual researchers, the NIH, and pharmaceutical industry partners.

One of the most promising efforts is a collaboration with other academic institutions and London-based AstraZeneca to investigate the drug anifrolumab. At the 2015 American College of Rheumatology meeting, study leaders presented encouraging results from a Phase II clinical trial of more than 300 patients. The monoclonal antibody elicited a therapeutic response in 29 percent of patients given a higher dose and in 34 percent given a lower dose. By contrast, a placebo yielded a response in only 18 percent.

"We're just at the forefront of the investigation, but we have seen some very promising results in the Phase II trials," says Amit Saxena, MD, assistant professor of medicine. The Phase III clinical trial, now underway, aims to enroll 360 patients in all. The therapeutic strategy is based on past observations of elevated interferon signatures in the cells of patients with lupus. Several pharmaceutical companies have since created products that inhibit interferon activation, and anifrolumab is the first to progress to a Phase III trial.

REVIVING AN OLD DRUG TO COUNTER CYTOPENIAS

In one of the division's investigator-initiated trials, Dr. Saxena and colleagues are exploring a new use for the old drug Acthar, a subcutaneous injection of corticotropin. The endogenous hormone normally helps the body create corticosteroids to fight inflammation, similar to the mechanism of prednisone. Corticotropin, however, also seems to stimulate other receptors that induce separate anti-inflammatory mechanisms.

The drug, on the market for years, has been used for multiple sclerosis and dermatomyositis, and less frequently as a last-line therapy for lupus. Dr. Saxena is investigating whether Acthar also might help treat the relatively rare lupus manifestation of autoimmune cytopenias, particularly low platelets and low red blood cells.



↑ Amit Saxena, MD

The therapeutic strategy, he says, is based on Acthar's ability to halt the production of autoantibodies; autoimmune cytopenias occur when autoantibodies bind and destroy the patient's own blood cells. Many lupus medications also produce a lowered blood count as a side effect, meaning that some patients require a lifelong regimen of steroids—with their own harmful side effects—to raise their blood counts.

Acthar, Dr. Saxena says, might provide a better alternative for treating a patient population that has often challenged physicians. The trial has begun enrolling the first of 25 patients and is testing whether a medium or high dose of the hormone enables physicians to safely taper off the use of steroids.

TESTING WHEN TO WITHDRAW AN IMMUNOSUPPRESSANT

In a separate NIH-sponsored observational trial, the division's clinical researchers are joining other sites in studying the effects of withdrawing mycophenolate mofetil, MMF, a drug that is frequently prescribed for nephritis and other lupus manifestations.

"It's an immunosuppressing medicine so there is potential for side effects like infections, but we have never had a clear protocol for when we should feel it safe to discontinue the medication," Dr. Saxena says. In the absence of consistent guidelines, physicians have had to devise their own strategies.

The study's main objective, then, is to describe the impact of withdrawing the medication in patients with "quiet" symptoms. In the Phase II clinical trial of 120 patients, half of the randomized group is remaining on MMF while the other half is being tapered off of the drug. "It's a simple trial, but it's one that really will have a significant clinical impact because if we have guidelines then it's really going to change the way that all rheumatologists across the country are going to practice," Dr. Saxena says.

SUBSEQUENT AUTOIMMUNITY IN CHILDREN WITH NEONATAL LUPUS

In some mothers with lupus, Ro autoantibodies can cross the placenta and cause neonatal lupus, manifested by a transient rash or heart block in some of the children. As part of his research, Dr. Saxena has leveraged the NIAMS and NYU School of Medicine Research Registry for Neonatal Lupus to evaluate the health of these children as they age. A new study based on questionnaires and medical records suggests that more children with heart disease at birth have developed autoimmune disease compared to those with a rash or no manifestations.

The finding, Dr. Saxena says, fits with previous studies that revealed psoriasis-associated genetic markers in some of the children. "The other interesting finding was that these autoimmune diseases were more prevalent in patients who had heart block especially those who had the most severe disease," Dr. Saxena says. The consequence, he says, is that such children may be more prone to inflammation or autoimmunity later in life.

The results, he adds, should prompt a new vigilance among physicians and encourage them to rethink their assumptions that children with neonatal lupus are susceptible only to passively acquired autoimmunity. "This is the first result that gives us the idea that there might be something about these kids that makes them prone to autoimmunity beyond the mother's antibodies," he says.

Assessing the Impact of Obesity on Knee Osteoarthritis After Bariatric Surgery

Although obesity is a well-known risk factor for knee osteoarthritis (OA), much less is understood about how well bariatric surgery can alleviate patients' knee pain and to what extent changes in mechanical load, metabolism, or other factors are involved in pain reduction.

Recent research led by Jonathan Samuels, MD, associate professor of medicine, is suggesting that post-surgical pain reduction may be influenced in part by molecular mechanisms that go well beyond weight loss. Addressing obesity and knee pain in OA patients will require a comprehensive approach rather than focusing solely on the affected joint," Dr. Samuels says.

In the study, Dr. Samuels and colleagues prospectively identified knee pain in 176 patients considering sleeve gastrectomy, gastric bypass, or laparoscopic gastric band surgery. For the 150 patients who eventually underwent bariatric surgery, the researchers tracked whether their subsequent weight loss affected OA-related pain and mobility, based on the Knee Injury and Osteoarthritis Outcome Score questionnaire given at baseline and one, three, six, and 12 months. The researchers also collected blood samples at all time points to assess serum and plasma levels of potential OA biomarkers.

The study found that bariatric surgery did indeed improve patients' knee OA symptoms, with proportionately more relief for those who lost more weight. The results, however, came with an important caveat. Although participants' weight loss continued quickly through 12 months, most relief occurred within the first month after surgery—before patients had lost the bulk of their weight—and then plateaued. "They still had pain relief sustained over time, but we're finding that for the improvement in pain, the majority of the change happens during the first month," Dr. Samuels says.

PAIN RELIEF MIGHT DEPEND ON METABOLIC CHANGES, NOT JUST WEIGHT LOSS

The finding is significant because it points to pain relief factors beyond those reducing the mechanical burden on the knees. "If it was just weight loss, their pain would continue to improve over the course of a year," Dr. Samuels says. "But we think there's some metabolic change that happens, like metabolic cascades that affect the knee osteoarthritis, and that those changes continue over the course of a year." The surgery, for instance, might trigger metabolic changes that alter the entire gastrointestinal system.

Dr. Samuels and colleagues are now investigating several biomarkers isolated from patients' blood samples, including leptin and IL-1Ra. So far, they've found that levels of many markers were significantly higher in obese knee OA patients than in non-obese counterparts—and declined over the first year after bariatric surgery, potentially contributing to the relief in knee pain experienced by those patients.

The researchers are hoping to replicate the findings in a larger patient cohort and identify the relevant post-surgery metabolic changes beyond lower food intake. Complementing these studies, the division is one of four sites in a multicenter trial comparing pain improvement in extremely obese patients who undergo a total knee replacement to those who first opt for bariatric surgery instead.

↓ Jonathan Samuels, MD



Dr. Samuels and colleagues are also poring through the last decade of bariatric surgeries at NYU Langone Medical Center and identifying all surgery patients who had knee pain as a comorbidity. “We’re going back retrospectively and surveying them on how their pain has improved over the course of their post-operative time,” he says. By addressing obesity-osteoarthritis from multiple angles with these various projects, he adds, a more robust picture may emerge that could help shape further research questions and potential treatments for osteoarthritis.

NEW INSIGHTS ON THE EFFICACY OF VISCOSUPPLEMENTATION FOR KNEE OA

Although physicians commonly use hyaluronic acid viscosupplementation to treat knee osteoarthritis, reported patient outcomes have varied widely—leading some professional societies to discourage its use. Dr. Samuels and colleagues evaluated many factors involved in those injections in search of potential predictors of why they may be successful, such as the anatomic location of the needle, and the efficacy of a single-injection formulation to a more traditional injection given once a week for three weeks. The researchers also assessed whether differences in weight, age, and osteoarthritis severity influence a patient’s response to the therapy.

Based on a two-month assessment of 226 patients with knee OA, his team and collaborators in the Orthopaedic Surgery Department found that the single-shot versions of hyaluronic acid were no less helpful than the multi-week viscosupplementation injections. Likewise, obesity didn’t significantly impact patients’ response. Younger patients responded better than older patients, however, with those older than the age of 70 improving the least, and those with less severe radiographic disease showing a slight trend toward more improvement.

The results, presented at the 2016 American College of Rheumatology Meeting, could help tailor hyaluronic acid regimens to maximize their appropriate and cost-effective use in knee OA patients.

Research and New Drugs Yield Better Choices for Psoriatic Arthritis Patients

A flurry of new FDA-approved drugs that significantly improve skin inflammation and joint pain in psoriatic arthritis has given NYU Langone's Psoriatic Arthritis Center an expanded suite of options for the more than 1,300 patients it sees every year.

"It's a very exciting time, with many more available treatments that can lead to better outcomes," says Jose U. Scher, MD, professor of medicine, who co-directs the center along with Soumya M. Reddy, MD, assistant professor of medicine.

The growing menu of options presents clinicians with a new challenge: deciding which therapy is best for each patient. By tapping into the center's singular blend of clinical and translational research expertise, physicians and patients are able to make informed choices. "It's critical to understand not only the clinical aspects of new treatments, but also the molecular processes," says Dr. Scher. "That helps us explain to our patients why one option might be better than another for them."

A BIG PUSH IN TRANSLATIONAL AND MICROBIOME-RELATED RESEARCH

Among the center's many research efforts, Dr. Scher and Sergei Koralov, PhD, assistant professor of pathology, are studying the pathology of IL-17 cytokine overproduction in animal models, examining how blocking the molecules released by pro-inflammatory Th17 cells can provide relief to human patients. By clarifying the anti-cytokine mechanism of new monoclonal antibodies targeting the IL-17 pathway, researchers hope to create a basis for physicians to recommend the promising medications to specific patients and their potential side effects in the intestine.

Another line of research, led by Dr. Scher has found that patients with psoriatic arthritis have a lower diversity of commensal organisms in their intestinal tract than either healthy individuals or those with psoriasis alone. Following that observation,

107

ATTENDEES
AT THE 2016 CME COURSE:

Advanced Seminar on Psoriasis and Psoriatic Arthritis hosted by NYU Langone

NYU Langone researchers, including Andrea L. Neimann, MD, clinical assistant professor of dermatology, are assessing whether similar differences might be detectable via skin microbiome samples. "Skin swabs are taken from patients looking to characterize the cutaneous microbial composition of psoriasis patients who don't develop psoriatic arthritis and those who do," says Dr. Neimann. In a complementary approach, the group is feeding commensal bacteria or their metabolites to lab animals and assessing the impact on their skin and joints.

A separate project is exploring how gut microbes may modulate clinical treatments—a potential reason why medications such as oral methotrexate have variable efficacy in patients. Preliminary evidence suggests that the makeup of a patient's gut microbiome prior to methotrexate therapy may help predict their response. The accumulating knowledge of how such drugs are metabolized by intestinal flora could provide similar insights into new-onset rheumatoid arthritis, which shares many of the same treatments.

↓ Eileen Lydon, MA, ANP-BC, Jose U. Scher, MD,
and Soumya M. Reddy, MD



UNCOVERING THE BENEFITS OF CROSS-DISCIPLINARY CARE

In one of the center's external partnerships, PPACMAN (Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network) is investigating whether a collaborative approach to patient care—like the one available to psoriatic arthritis patients at NYU Langone's multidisciplinary Center for Musculoskeletal Care—yields more benefits than the prevailing standard of care. The joint effort with 10 other institutions and foundations in the United States and Canada, which is also establishing a combined longitudinal database to enhance scientific potential, has generated significant interest within the research community.

NYU Langone investigators are also designing clinical trials with industry partners and as national leaders in policy and training initiatives. In one example, Dr. Scher and colleagues are helping the American College of Rheumatology develop guidelines for psoriatic arthritis, and are advising the FDA on medications winding their way through the clinical pipeline.

HUNTING FOR AUTOIMMUNITY-LINKED GUT MICROBES

Multiple research projects supported by the division's Judith and Stewart Colton Center for Autoimmunity are revealing new associations between the human microbiome and autoimmune conditions. One effort led by Ken Cadwell, PhD, and P'ng Loke, PhD, both associate professors of microbiology, suggests that changes in the microbial environment may be linked to an increasing incidence of Crohn's disease and other autoimmune diseases in the developed world.

In particular, their work has found that such autoimmunity may be associated with an altered gut microbiota and decreased exposure to helminths. In mice, they discovered that helminth exposure triggers the growth of *Clostridiales* bacteria, which may reverse intestinal disease by inhibiting a pro-inflammatory species, *Bacteroides vulgatus*, from colonizing.

Among a group of indigenous Malaysians, Dr. Cadwell and Dr. Loke found that helminth infections led to similar gut microbiota changes. The collaborators are hoping to isolate new *Clostridiales* strains from that population and test the microbes' ability to suppress inflammation—possibly revealing a new treatment strategy in the process.

Collaborative Effort Taking Aim at Pediatric Lupus Nephritis

In the 1990s, H. Michael Belmont, MD, professor of medicine, discovered one of the first known skin-based biomarkers to reflect lupus activity when he found that up-regulation of adhesion molecules in endothelial cells from non-lesional, non-sun-exposed skin on a patient's buttocks could predict disease severity. Nearly two decades later, Robert Clancy, PhD, associate professor of medicine, and Peter Izmirly, MD, assistant professor of medicine, extended this discovery by demonstrating that in patients with lupus nephritis, the unaffected skin mirrored endothelial cell activation.

As part of an ambitious effort in both adult and pediatric patients, NYU Langone researchers and collaborators at Albert Einstein College of Medicine and Rockefeller University are now taking a similar tack to identify cells and mechanisms associated with lupus nephritis. With a growing database of pediatric patients, the effort could reveal vital clues about why lupus triggers kidney damage in some children and adolescents and how it might be prevented or managed during those critical years.

"It's mostly agnostic science: an opportunity to identify transcripts reflective of genes and ultimately proteins that may be biomarkers for lupus renal disease and lupus renal disease prognosis, as well as an opportunity to identify potential new pathological pathways in lupus renal disease," Dr. Belmont says. To do so, the team is using a single-cell RNAseq method to measure the transcriptome activity of each cell type within skin and kidney biopsies and then zero in on transcriptional signals that show significant up-regulation or down-regulation.

The eventual goal, he says, is to find a less invasive biomarker of lupus-associated kidney damage. "If the eyes are the mirror to the soul, we're trying to determine if the skin is a mirror to the pathological processes in the kidney," Dr. Belmont says. "It is obviously far simpler to obtain a skin biopsy than a kidney biopsy." For pediatric patients, it would also be far gentler.

CLARIFYING SUBTLE PATTERNS AND PATHWAYS OF DISEASE

The research, funded through a 2014 NIH Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus (AMP RA/Lupus) grant, is led by Jill P. Buyon, MD, the Lady Va and Sir Deryck Maughan Professor of Rheumatology and director of the Division of Rheumatology (overall principal investigator of the grant) along with Dr. Clancy, and Dr. Izmirly.

Directly comparing each skin biopsy to its kidney counterpart will help the researchers identify the most relevant commonalities and differences. "We're doing this on people who have undergone kidney biopsies for a likely diagnosis of lupus nephritis, and we're using this new technology on both of these samples to get a better understanding of what's going on in individual cell types," says Dr. Izmirly.

Collaborators Howard Trachtman, MD, the Martin Shkrel Professor of Pediatric Nephrology in the Department of Pediatrics, Laura Malaga-Dieguez, MD, PhD, assistant professor of pediatrics, and Philip Kahn, MD, assistant professor of pediatrics, are helping to identify and recruit pediatric cases with probable lupus nephritis that require a renal biopsy.

Among their other questions, the researchers are hoping to answer whether pediatric lupus nephritis displays different molecular signals than in adults. "By expanding our outreach to this population, we might actually detect signals or some understanding of the nuanced differences between adult and pediatric patients," Dr. Izmirly says.



↑ Francis Appeadu-Mensah and Peter Izmirly, MD

Accumulating data from the New York region's diverse pediatric population may likewise help point out other distinctions. "There may be subtle differences that can be understood by these different racial and ethnic backgrounds," Dr. Izmirly says. "Perhaps they are different signaling pathways that all converge on the end result of kidney disease, but they're subtly different among disparate ethnicities and races."

MAKING STRIDES TOWARD SEAMLESS TRANSITIONS OF CARE

The collaborative work is also addressing what is all too often a critical gap in transitions between pediatric and adult lupus care and the absence of solid research on how best to remedy it. Due to their close working relationship, NYU Langone's Lupus Group and Pediatric Lupus Group are sharing best practices and establishing protocols to ensure seamless handoffs. "This is an area where a good transition can make a big difference in the patient's care," Dr. Izmirly says.

Some lupus manifestations and treatment regimens, for example, can disproportionately impact adolescent patients' emotional and psychological wellbeing. Steroid medications, in particular, can lead to side effects such as weight gain, acne, and other cosmetic issues that significantly increase a teenage patient's insecurities.

Strategies that have already been adopted, such as appointments that include both pediatric and adult lupus providers, can ease the anxiety during handoffs and encourage transitioning patients to begin assuming more responsibility for their own care.

Close Monitoring of Lupus Patient with High-Risk Pregnancy Yields a Healthy Infant

A 31-year-old Asian female previously diagnosed with lupus at NYU Langone was considering pregnancy and referred in April 2016 to Jill P. Buyon, MD, the Lady Va and Sir Deryck Maughan Professor of Rheumatology, director of the Division of Rheumatology, and director of the Lupus Center.

The extensive initial counseling took into account what Dr. Buyon calls “the triple threats of pregnancy: maternal health, placental health and fetal health.” While the three are clearly intertwined, Dr. Buyon reviewed each separately with the patient. The patient had a history of thrombocytopenia, a manifestation of lupus that can raise red flags for maternal health during a pregnancy. Fortunately, her disease had never included any renal involvement.

The biggest concern for placental health, Dr. Buyon determined, was the patient’s positive test for the lupus anticoagulant. From recent studies published in *Arthritis and Rheumatism* and the *Annals of Internal Medicine*, Dr. Buyon and colleagues linked the presence of the lupus anticoagulant to an adverse pregnancy outcome rate of 58% among women with lupus, due to placental insufficiency. The adverse outcomes include “fetal or neonatal death, delivery before 36 weeks, a small-for-gestational-age neonate, and preeclampsia,” Dr. Buyon says.

On the bright side, the absence of antibodies to SSA/Ro or SSB/La suggested that the patient’s potential offspring would not be at risk for congenital heart block, meaning that she wouldn’t need weekly echocardiographic surveillance.

COLLABORATION WITH HEMATOLOGY AND MFM SPECIALISTS

For what would be a high-risk pregnancy, Dr. Buyon consulted with hematology specialist Bruce Raphael, MD, clinical professor of medicine, and maternal-fetal-medicine specialist, Shilpi Mehta-Lee, MD, assistant professor of obstetrics and gynecology, to develop a comprehensive care and monitoring plan.

After successfully conceiving, the patient visited NYU Langone in March 2016 during her fifth week of pregnancy. She was experiencing joint pain on rare occasions and swelling in her thumbs, but no rashes, ulcers, or other major symptoms. The patient was also entered into a new study of Dr. Buyon’s in which complement activity, measured by cell based complement activation products (CBCAPS), is being evaluated as a prognostic marker of obstetric outcome and lupus flares during pregnancy. Her care team recommended that she remain on hydroxychloroquine therapy to reduce any subsequent lupus flares. While acknowledging the potential risk posed by the patient’s platelet count of 79,000, the team considered preeclampsia a greater threat and advised a daily regimen of low-dose aspirin.

The patient’s platelet count subsequently dropped to 55,000, then to 49,000 and finally to 36,000 by May, when it was accompanied by vaginal spotting and gum bleeding. Her pregnancy was otherwise progressing normally, and the doctors prescribed 20 milligrams of prednisone, which successfully boosted her platelet counts and allowed the team to eventually taper the dose down to 10 milligrams.

At 22 weeks of pregnancy, fetal growth continued to progress normally and the patient felt well despite some nose bleeds and very minor bruising. Her platelet count remained at 50,000, and she tested negative for antibodies to DNA. Although her low platelets remained a significant concern, the high-risk pregnancy team decided to keep the mother-to-be on the low-dose aspirin regimen and on 10 milligrams of prednisone to retain the necessary balance between a lower clotting risk and a higher quantity and quality of platelets.



↑ Shilpi Mehta-Lee, MD, and Jill P. Buyon, MD

PLANNING FOR DELIVERY

At 31 weeks of pregnancy in September 2016, the patient complained of a rash on her fingertips. The condition appeared consistent with leukocytoclastic vasculitis but the team also considered hyperemia of pregnancy. “My major concern was the steady drop in the patient’s platelets,” Dr. Buyon says. “This coupled with the lupus anticoagulant and risk of preeclampsia made the balance of maintaining the low-dose aspirin therapy very challenging.” The team discussed whether to consider IVIG to raise the patient’s platelet count above 75,000, which would increase the safety of an epidural during labor. To minimize the risks, the team also made plans to induce labor at about 36 weeks if the fetus continued growing well and biophysical profiles remained reassuring.

Despite those plans, a lab test at 35 weeks revealed rising liver transaminase levels, to 104 and 171, though the patient’s platelet count remained steady at 47,000. The differential diagnosis included HELLP syndrome (hemolytic anemia, elevated liver enzymes and low platelets) and intrahepatic cholestasis of pregnancy. While a lupus flare was also considered given the recent fingertip rash, Dr. Buyon and colleagues deemed it less likely given the absence of any other clinical symptoms, the lack of DNA antibodies, and normal blood pressure, complement and urinary protein levels.

The team gave the patient ursodiol for possible cholestasis and betamethasone to accelerate fetal lung maturity in the anticipation of an early delivery. In the ensuing hours, however, she developed high blood pressure, a drop in platelet counts to 36,000, increasing transaminase levels, rising LDH and schistocytes on smear— all supporting the HELLP diagnosis. Given her low platelets, the care team deemed an epidural unsafe. They instead opted for a C-section under general anesthesia and prepared the patient by transfusing platelets and giving her stress doses of solumedrol, plus magnesium sulfate to prevent seizures.

A HEALTHY BABY BOY

The patient’s doctors delivered a baby boy, while the therapeutic course helped the new mother’s platelets continue to rise as her transaminase levels decreased. Although the case confirmed Dr. Buyon’s pre-pregnancy prediction of an early delivery, the careful monitoring and balancing of benefits and risks paid off. After only a few days, the healthy mother and baby were both discharged from the hospital and able to return home.

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AMERICAN COLLEGE OF RHEUMATOLOGY 2016 ANNUAL MEETING ABSTRACTS ACCEPTED FOR ORAL PRESENTATION

Tubulointerstitial Damage Is an Independent Predictor of End Stage Renal Disease in Lupus Nephritis Patients with Mild to Moderate Renal Impairment
Session: Systemic Lupus Erythematosus – Clinical Aspects and Treatment I: Nephritis
Bojana Jovanovic, Hina N. Khan, Wenzhu Mowrey, Peter M. Izmirlly, Daniel Schwartz, Jill P. Buyon, Chaim Putterman, Beatrice Goilav and Anna R. Broder

Longitudinal Patterns in SLE Response to Standard of Care Therapy: Implications for SLE Clinical Trial Design
Session: Systemic Lupus Erythematosus – Clinical Aspects and Treatment II: Clinical Trial Design
Mimi Kim, Joan T Merrill, Kenneth Kalunian, Bevra H. Hahn, Anita Roach, Peter M. Izmirlly, and the Lupus Foundation of America Collective Data Analysis Initiative Group

Predictive Factors of Adherence to Treatment in an International Prospective Study of Blood Hydroxychloroquine Levels in SLE Patients with Flares
Session: Systemic Lupus Erythematosus – Clinical Aspects and Treatment III: Novel and Current Therapies
Nathalie Costedoat-Chalumeau, Frédéric A. Houssiau, Peter M. Izmirlly, Véronique Le Guern, Sandra V. Navarra, Meenakshi Jolly, Guillermo RUIZ-IRASTORZA7, Eric Hachulla, Nancy Agmon-Levin, Yehuda Shoefeld1, Francesca Dal'Ara, Jill P. Buyon, Christophe Deligny, Ricard Cervera, Estibaliz Lazaro, Holy Bezanahary, Gabriel Baron, Gaëlle Leroux, Nathalie Morel, Jean-Francois Viillard, Christian Pineau, Lionel Galicier, Ronald van Vollenhoven, Angela Tincani, Hanh Nguyen, Guillaume Gondran, Noel Zahr, Jacques Pouchot, Jean Charles Piette, Michelle Petri and David A. Isenberg

Impact of in Utero Hydroxychloroquine Exposure on the Risk of Cutaneous Neonatal Lupus Erythematosus
Session: Reproductive Issues in Rheumatic Disorders
Julie Barsalou, Nathalie Costedoat-Chalumeau, Adey Berhanu, Cesar Fors-Nieves, Ummara Shah5, Patrick Brown, Carl Laskin, Nathalie Morel, Kateri Levesque, Jill P. Buyon, Earl Silverman and Peter M. Izmirlly

Platelet FCYRIIa Polymorphism H131R Associates with Subclinical Atherosclerosis and Increased Platelet Activity in SLE
Session: Systemic Lupus Erythematosus – Human Etiology and Pathogenesis I
Sara Rasmussen, Harmony Reynolds, Jill P. Buyon, Sokha Nhek, Jonathan Newman, Jeffrey Berger, Robert M. Clancy

Dermal Fibroblasts from Patients with Lupus Nephritis Express an Anti-Fibrotic Transcriptome

Session: Systemic Lupus Erythematosus – Human Etiology and Pathogenesis I
Robert Clancy, Evan Der, Kemal Akat, Anna Broder, H. Michael Belmont, Peter M. Izmirlly, Beatrice Goilav, Thomas Tuschl, Chaim Putterman, Jill P. Buyon

Membrane-Type 1 Matrix Metalloproteinase Controls Osteo- and Chondrogenesis by a Proteolysis-Independent Mechanism Mediated by its Cytoplasmic Tail
Session: Biology and Pathology of Bone and Joint
Qing Yang, Mukundan Attur, Thorsten Kirsch, You Jin Lee, Shoshana Yakar, Zhongbo Liu, Steven B. Abramson and Paolo Mignatti

Binding of Periostin to Discoidin Domain Receptor-1 (DDR1) Promotes Cartilage Degeneration By Inducing MMP-13 Expression.
Session: Biology and Pathology of Bone and Joint
Yang Qing, Paolo Mignatti, Austin Rammie, Thorsten Kirsch, and Mukundan Attur

The Impact of Obesity on Knee Osteoarthritis Symptoms and Related Biomarker Profiles in a Bariatric Surgery Cohort
Session: ACR/ARHP Combined Abstract Session: Orthopedics and Rehabilitation
Thayer Mukherjee, Fernando Bomfim, Evan Wilder, Lauren Browne, Kayleigh Toth, Shira Aharon, Janice Lin, Renata La Rocca Viera, Christine Ren-Fielding, Manish Parikh, Steven B. Abramson, Mukundan Attur, Jonathan Samuels

Apolipoprotein L1 Risk Variants Associate with Prevalent Cardiovascular Disease in African American Systemic Lupus Erythematosus Patients
Session: Systemic Lupus Erythematosus – Clinical Aspects and Treatment IV: Biomarkers
Ashira Blazer, Robert M Clancy, H. Michael Belmont, Peter M. Izmirlly, Androo Markham and Jill P. Buyon

Development of Autoimmune Diseases and Genetic Predisposition in Children with Neonatal Lupus and Their Unaffected Siblings
Session: ACR/ARHP Combined Abstract Session: Pediatric Rheumatology
Aaron Garza Romero, Peter M. Izmirlly, Hannah C. Ainsworth, Miranda C. Marion, Carl Langefeld, Robert M. Clancy, Jill P. Buyon, Amit Saxena

Economic Evaluation of Damage Accrual in an International SLE Inception Cohort
Session: Systemic Lupus Erythematosus – Clinical Aspects and Treatment V: Damage and Morbidity
Megan Barber, Ian N. Bruce, Murray Urowitz, John G. Hanly, Li Su, Juanita Romero-Diaz, Caroline Gordon, Sang-Cheol Bae, Sasha Bernatsky, Daniel J Wallace, Joan T. Merrill, David A. Isenberg, Anisur Rahman, Ellen M. Ginzler, Michelle Petri, Mary Anne Dooley, Dooley Rheumatology, Paul R. Fortin, Dafna D Gladman, Jorge Sanchez-Guerrero, Kristján Steinsson, Rosalind Ramsey-Goldman, M Khamashta, Cynthia Aranow, Graciela S. Alarcón, Barri J. Fessler, Susan Manzi, Ola Nived, Andreas Jönsen, Asad Zoma, Ronald F van Vollenhoven, Manuel Ramos-Casals, Guillermo Ruiz-Irastorza, S. Sam Lim, Kenneth C. Kalunian, Murat Inanc, Diane L. Kamen, Christine A. Peschken, Søren Jacobsen, Anca Askanase, Jill P. Buyon, Chris Theriault, Vernon Farewell, and Ann E. Clarke

Intestinal Microbial Dysbiosis in SLE Is Linked to Elevated IgA and Induction of Autoimmunity
Session: Systemic Lupus Erythematosus – Human Etiology and Pathogenesis II
Doua F. Azzouz, Lelise Getu, Celine Anquetil1, Jill P. Buyon and Gregg J. Silverman

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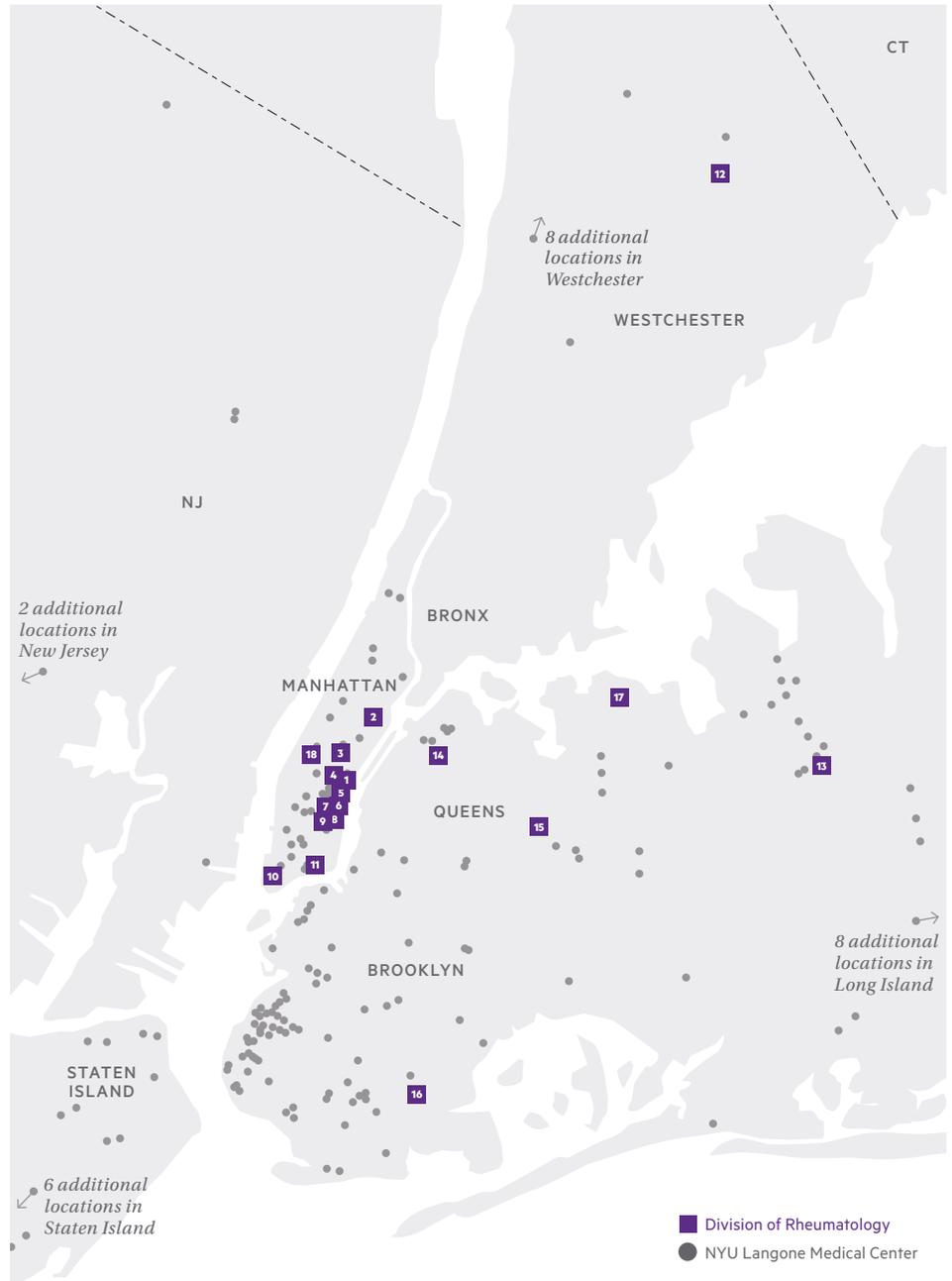
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NYU Langone By the Numbers*

1,519 Beds	100 Operating Rooms	145,907 Emergency Room Visits	68,602 Patient Discharges	3,850,000 Outpatient Faculty Practice Visits	9,649 Births	
3,584 Physicians	4,899 Nurses	574 MD Candidates	80 MD/PhD Candidates	233 PhD Candidates	397 Postdoctoral Fellows	1,472 Residents and Fellows
4,381 Original Research Papers**	550,500 Square Feet of Research Space	\$334M NIH Funding	\$328M Total Grant Revenue			

*Numbers represent FY16 (Sept 2015–Aug 2016) and include NYU Lutheran
**Calendar year 2015

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On the cover: Light micrograph of discoid lupus erythematosus on a scalp



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