

**OUR COVID-19
EFFORTS**

Read about NYU Langone Health's response to the challenges of the COVID-19 pandemic.
See insert.



Rheumatology

2020 HIGHLIGHTS

COVID-19 Risk for Immunosuppressed Patients

Research Determines Whether Patients Prescribed Immunosuppressants Face Increased Risk

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Reducing Risks for Lupus Patients Across the Age Spectrum

Studies Seek to Identify and Reduce Adverse Outcomes During Pregnancy and for Seniors

See page 4.

Lupus Patient Facing Thrombocytopenia and Anemia

Treatment Regimen Prevents Relapse and Provides Effective Solution

See page 7.



Cover image: Lymphocytes / T-cells
RENDERING: SKETCHFAB

JILL P. BUYON, MD

Lady Va and Sir Deryck Maughan Professor of Rheumatology
Director, Division of Rheumatology
Director, Lupus Center

MESSAGE FROM THE CHAIR



2020 was a year like no other, and NYU Langone Health's Division of Rheumatology rose to the challenge. As the COVID-19 pandemic swept through New York, we joined colleagues across divisions and institutions bringing out the internist in all of us to join the front lines and care for gravely ill patients while continuing to carry out critical clinical and laboratory research.

In the midst of the first wave, our division quickly mobilized expertise to launch two essential studies, the results of which offered much-needed reassurance to patients with systemic lupus erythematosus and inflammatory arthritis and their physicians. The data suggested that immunosuppressants (except in some cases glucocorticoids) do not significantly alter the risk for worse COVID-19 outcomes, meaning that patients could safely maintain their medications such as anticytokine therapy.

Despite the pandemic and attesting to the wide spectrum of diseases that we study, several multicenter clinical trials have helped us identify and lessen the risk of adverse autoimmune or rheumatologic outcomes, from preventing congenital heart block in newborns to safely withdrawing hydroxychloroquine in seniors with lupus. New National Institutes of Health (NIH) grants are facilitating research to untangle the complex molecular pathways underlying inflammation in osteoarthritis and Behçet's uveitis. In addition, remarkable new support from Judith and Stewart Colton will extend the reach of the Colton Center for Autoimmunity in nurturing a wide array of promising research collaborations in our mission to translate bench discoveries to patient care.

Many challenges remain, but the year has only strengthened our resolve to lead the way in conducting innovative research and improving patients' quality of life.

Jill P. Buyon, MD

Lady Va and Sir Deryck Maughan Professor of Rheumatology
Director, Division of Rheumatology
Director, Lupus Center



#8

IN U.S. NEWS &
WORLD REPORT

58,000+

OUTPATIENT
VISITS

\$11M+

IN GRANT
FUNDING

105+

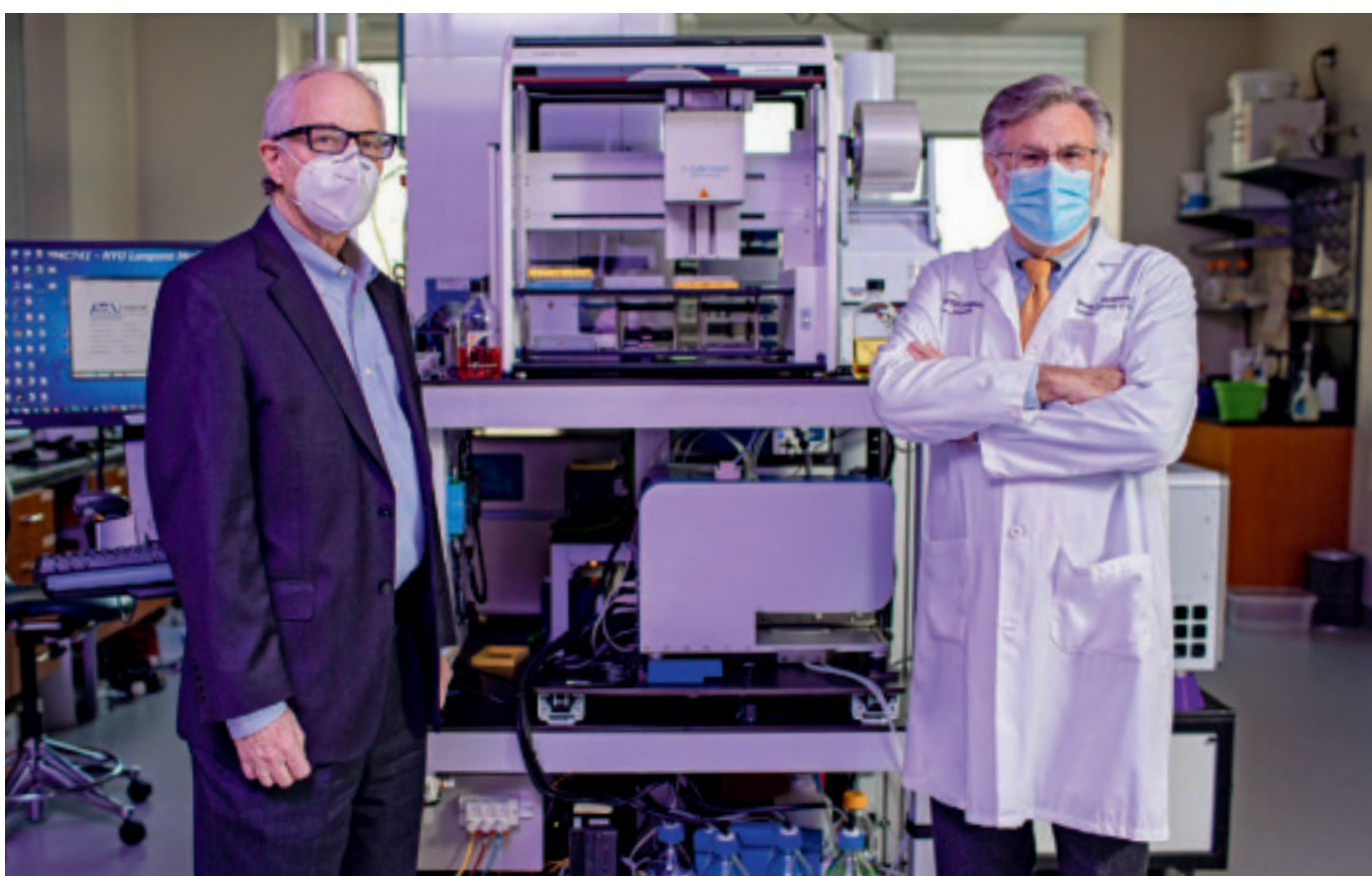
FACULTY
MEMBERS

New Research Collaboration Probes IL1RN Haplotypes to Identify Inflammation Modulators and Targets for Osteoarthritis Therapy

Researchers have implicated the pro-inflammatory cytokine interleukin-1 (IL-1) in a wide variety of diseases, such as osteoarthritis, rheumatoid arthritis (RA), diabetes, and obesity.

Steven B. Abramson, MD, the Frederick H. King Professor of Internal Medicine, professor of pathology, and chair of the Department of Medicine at NYU Langone Health, has long studied how IL-1 can propagate and exacerbate the disease process.

That research effort has more recently expanded to include investigations into how the anti-inflammatory IL-1 receptor antagonist, IL-1Ra, can counter IL-1 and modulate the inflammatory response. Based on intriguing findings about how certain gene variants may influence osteoarthritis risk and severity, a new National Institutes of Health (NIH) research grant will help Dr. Abramson and collaborators seek out IL-1-related targets for inflammatory disease prevention and treatment.



▲
Jef D. Boeke, MD and Steven B. Abramson, MD

**SPECIFIC IL1RN HAPLOTYPES
CAN PREDICT OSTEOARTHRITIS
RISK AND SEVERITY**

To help clarify the inflammatory process, Dr. Abramson and collaborators, including Mukundan G. Attur, PhD, associate professor of medicine, and Jonathan Samuels, MD, associate professor of medicine, examined several variants of the IL-1Ra-encoding IL1RN gene in the knee joints and cells of osteoarthritis and rheumatoid arthritis patients. In particular, a haplotype designated TTG predicted which at-risk patients would go on to develop knee osteoarthritis and was associated with more severe radiographic osteoarthritis as well as new onset RA. “It’s a marker of both severity and increased risk for incident osteoarthritis,” Dr. Abramson says.

Their 2019 study in osteoarthritis patients, published in *Annals of the Rheumatic Diseases*, suggested that the IL1RN TTG haplotype produced less IL-1Ra protein. “So one explanation for the finding is that these people with the gene are deficient in the endogenous inhibitor of IL-1, which is driving the disease,” Dr. Abramson says. Conversely, a separate haplotype called CTA yields more IL-1Ra protein production and may be protective.

In collaboration with Jef D. Boeke, PhD, professor of biochemistry and molecular pharmacology and the Sol and Judith Bergstein Director of the Institute for Systems Genetics, a new NIH grant may help clarify how each gene haplotype modulates inflammation, influences

the associated gene regulatory networks, and contributes to the mechanics of disease pathogenesis. In particular, the research will focus on a haplotype block, or a section of DNA including multiple genes adjacent to the IL1RN gene. The researchers hope to learn whether any of the neighboring genes have inflammatory properties of their own, a synergistic effect on IL1RN, or even a more dominant effect on the underlying inflammatory pathway. “One reason to do that is if you’re developing a drug, you might find that one of these other genes is a better target than IL1RN,” Dr. Abramson says.

**ASSEMBLON-AIDED RESEARCH
MAY OPEN NEW WINDOW INTO
IL-1-DRIVEN DISEASES**

One key to the unique research effort is Dr. Boeke’s expertise in using CRISPR-Cas9 genome-editing system technology to construct a series of what his lab calls assemblons, or precisely altered haplotype blocks. Led by Dr. Attur, the collaborators will then transfect embryonic stem cells with the manipulated DNA and use in vitro assays to gauge the effects of the putative risk and protective IL1RN haplotypes. “The genetic manipulation is very technical. But if we can succeed, it allows us to really define the role of these haplotypes, not just in osteoarthritis but in other IL-1–driven diseases,” Dr. Abramson says.

After differentiating the engineered embryonic stem cells into macrophage cells, the researchers will measure production of the IL-1Ra protein.

“We’ll also be stimulating the macrophages in an inflammatory way and looking at the profile of inflammatory mediators that they produce,” Dr. Abramson says. Experiments may reveal whether stimulated macrophages that carry the protective IL1RN CTA haplotype, for example, produce more IL1-Ra protein and fewer pro-inflammatory mediators such as IL-1, cyclooxygenase-2 (COX-2), and tumor necrosis factor (TNF). In the same way, sequential knockouts of other genes in the assemblon may clarify their own contributions to each haplotype’s effects.

If the researchers can zero in on the principal drivers of disease through their in vitro experiments, they plan to inject the engineered embryonic stem cells into mice models of osteoarthritis and RA. The in vivo studies of the gene regulatory network may help determine how specific gene variants influence disease outcomes.

The research could have broad implications for understanding IL-1–associated inflammatory diseases and for personalizing anti-IL-1 therapies. “It might be that in personalized medicine, anti-IL-1 treatments will be more effective in patients who have a deficiency of IL-1 receptor antagonist,” Dr. Abramson says. A patient who produces abundant IL-1Ra, on the other hand, may not benefit from receiving more of it as a therapy. Alternatively, the research may suggest that the IL1RN haplotypes are exerting their influence mainly by modulating other genes with key roles in the disease pathogenesis. “It may be that they will emerge as targets that people hadn’t even thought about in those diseases,” he says. ■



**Researchers Assess
COVID-19 Risk in
Immunosuppressed
Patients**

Among patients with systemic lupus erythematosus (SLE) and inflammatory arthritis (IA), two new studies by NYU Langone clinicians have provided some valuable answers to two big questions. Immunosuppressants prescribed for the autoimmune conditions, they found, do not significantly alter the risk for worse COVID-19 outcomes. Nor do the patients themselves appear to have risk factors materially different from those of the general population, though expanding study cohorts will offer greater clarity.

**PATIENTS WITH LUPUS AND
GENERAL POPULATION
SHARE SIMILAR COVID-19
HOSPITALIZATION RISK FACTORS**

When the COVID-19 pandemic hit New York, rheumatologists were flooded with phone calls and messages from worried patients with SLE or IA. No one knew for sure whether continuing with their medications would put the patients at higher risk for poor COVID-19 outcomes.

In one of the largest analyses of its kind, published in July in *Arthritis & Rheumatology*, research performed at NYU Langone concluded that for patients with SLE with PCR-confirmed COVID-19, variables predicting hospitalization matched those of the general population. “Our study shows findings similar to other studies: It doesn’t look like immunosuppressants, including biologic agents, significantly increase the risk of patients being hospitalized with COVID-19,” says first author Ruth Fernandez Ruiz, MD, a postdoctoral fellow in the Division of Rheumatology. “I think that’s very reassuring.”

For the study, which was generously funded by Bloomberg Philanthropies and the Beatrice Snyder Foundation, the researchers recruited and followed 226 adult patients with mild to severe lupus between mid April and early June. Dr. Fernandez Ruiz and colleagues recruited most of the patients from the well-established NYU Langone Lupus Cohort and supplemented



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—Ruth Fernandez Ruiz, MD



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—Rebecca Haberman, MD

that group with other patients identified via referrals or medical record queries. Of the 41 patients additionally diagnosed with COVID-19, 24 were hospitalized and four died. Although the small sample size limited strong conclusions about hospitalization and mortality predictors, Dr. Fernandez Ruiz says the study did not identify any risk factors specific to SLE, such as taking mycophenolate mofetil, azathioprine, or other immunosuppressants, which were assessed in aggregate. In addition, patients with lupus taking hydroxychloroquine were not at any higher or lower risk of hospitalization.

The analysis did, however, identify being non-white, having a higher body mass index, and having at least one comorbidity as independent predictors of hospitalization. Although less conclusive, the study also suggested a trend toward higher risk among patients taking systemic steroids. “That’s something that will be very important to figure out,” Dr. Fernandez Ruiz says, “but I would be more cautious with steroid use than with other medications and carefully balance the risk of active disease and flares against the risk of COVID-19.”

She and colleagues, including senior author Peter M. Izmirly, MD, associate professor in the Department of Medicine, are now expanding the size of their lupus study cohort to better understand the risks and potential mechanisms underlying susceptibility or protection. In addition, they’re assessing the SARS-CoV-2 antibody status of all patients with SLE to identify asymptomatic COVID-19 infections among the subset who never received PCR testing and to clarify any medication-associated risks.

NO HIGHER RISK FOR MOST INFLAMMATORY ARTHRITIS THERAPIES, BUT CAUTION WARRANTED FOR GLUCOCORTICOIDS

For a separate study, also among the largest of its kind at the time of its July 2020 publication in *Arthritis & Rheumatology*, researchers found that patients with rheumatoid arthritis, psoriatic arthritis, or spondyloarthritis were no more likely to be hospitalized for COVID-19 than the general population in the New York City metropolitan region. In addition, the study concluded that those patients with IA on maintenance anti-cytokine biologic therapies were not at higher risk of being hospitalized or having worse outcomes for COVID-19. “Our study’s biggest impact is the idea that patients can safely stay on their medications to prevent a large portion of them from developing flares that could then lead to worse outcomes,” says first author Rebecca Haberman, MD, a clinical instructor of rheumatology.

Over a two-month period, the researchers recruited 103 patients with symptomatic COVID-19 infections who were being treated for IA. Of that total, 80 had a PCR-confirmed COVID-19 diagnosis; the other 23 had highly suspicious cases but were not tested. Of the 103 patients, 27 required hospitalization and four died. Those who did require hospitalization for COVID-19, the analysis found, were significantly more likely to be older or to have comorbid hypertension or chronic obstructive pulmonary disease—risk factors likewise observed in the general population.

The researchers, including senior author Jose U. Scher, MD, associate professor of medicine, did find an increased hospitalization risk associated with chronic steroid use, though Dr. Haberman cautions that the uncertainty due to the small sample size means more research will be required to determine the true risk. As a follow-up, she and colleagues are recruiting more patients with IA and COVID-19 to validate and refine their conclusions. As part of the expanding research, the investigators are taking nasal swabs and blood samples to measure the patients’ SARS-CoV-2 antibody levels and determine the overall infection prevalence.

Both Dr. Fernandez Ruiz and Dr. Haberman cite the extensive research infrastructure at NYU Langone as a fundamental advantage in allowing them to launch their respective research projects so quickly, with additional financial support from the National Institutes of Health (NIH) and multiple philanthropies. The team effort during a difficult time, Dr. Haberman says, made all the difference in getting the research out rapidly. “Most of us leading the study were serving hospital wards, taking care of COVID-19 patients as we did this research,” she says. “Yet in the midst of this crisis, we were still able to gather a lot of data that could aid other clinicians.” ■

New Trials Assess Lupus Risks During Pregnancy and Throughout the Life Span

Clinical Trials Led by NYU Langone
Rheumatologists Are Helping to
Identify and Reduce the Risk of Adverse
Outcomes in Patients with Systemic
Lupus Erythematosus (SLE)
Across the Age Spectrum

The studies demonstrate how expectant mothers can monitor for signs of congenital heart block (CHB) at home, how hydroxychloroquine (HCQ) can help lower the risk of this life-threatening condition in newborns, and how the same drug may be safely withdrawn in older patients who discontinue it because of ocular toxicity concerns. “We’re talking about rheumatology studies that are covering the human life span, from a pregnant woman and her fetus to seniors with lupus,” says Jill P. Buyon, MD, the Lady Va and Sir Deryck Maughan Professor of Rheumatology and director of the Division of Rheumatology and Lupus Center at NYU Langone. “It speaks to NYU Langone’s strong capability to lead multicenter trials in rheumatology.”

HYDROXYCHLOROQUINE SIGNIFICANTLY REDUCES RISK OF CONGENITAL HEART BLOCK

In roughly 1 out of every 15,000 live births, CHB can lower a newborn’s heart rate to a dangerous 50 beats per minute or less. Of the 80 percent of newborns with CHB who survive, nearly 3 in 4 will eventually require a pacemaker, and some will need a heart transplant.

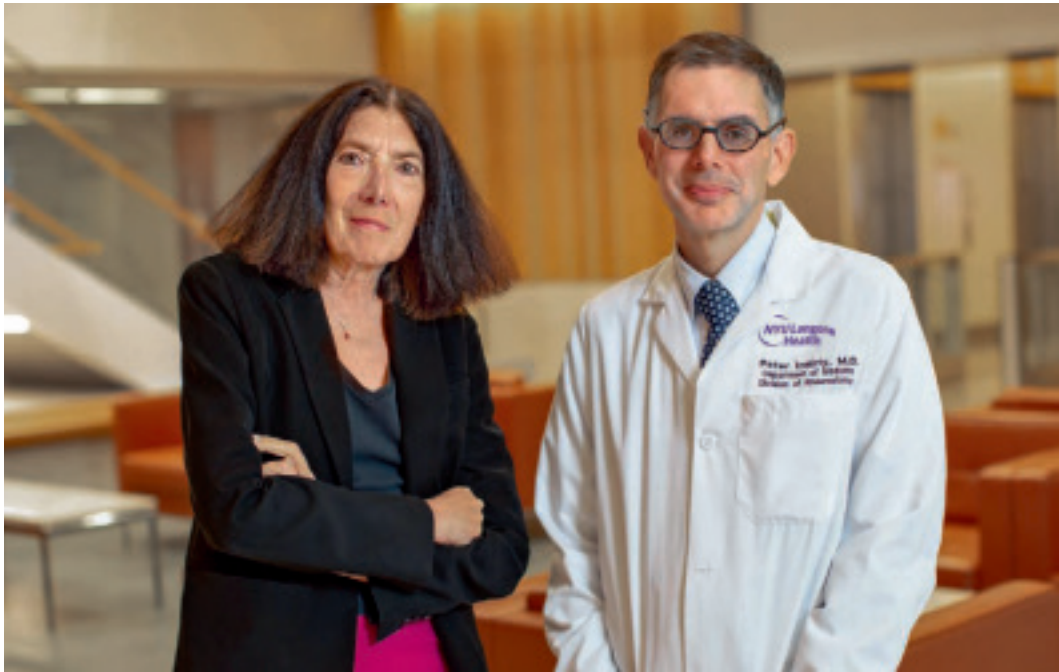
Women with anti-Sjogren’s syndrome A/Ro (anti-SSA/Ro) antibodies are at particularly high risk (they can have SLE or Sjogren’s syndrome or be entirely asymptomatic), and studies have suggested that those who give birth to a child with CHB have a recurrence rate of 18 percent or more in subsequent births. A new open-label study led by NYU Langone researchers, however, has found that giving women HCQ (prescribed as Plaquenil®) early in pregnancy can more than halve the recurrence rate, to about 7.5 percent.

The extensive analysis, recently published in the *Journal of the American College of Cardiology*, suggests that HCQ can be a powerful preventive during high-risk pregnancies. “Our study shows hydroxychloroquine as the first safe and highly effective drug for preventing at-risk pregnant women from having another child with congenital heart block,” says lead author and rheumatologist Peter M. Izmirly, MD, associate professor of medicine at NYU Langone.

In the Prospective Open Label Preventive Approach to Congenital Heart Block with Hydroxychloroquine (PATCH) study, researchers enrolled 63 pregnant women from across the country who had anti-SSA/Ro antibodies and who had previously given birth to a child with CHB. The women were given 400 mg of HCQ daily before completion of 10 weeks of gestation, and then followed through their pregnancies and evaluated for any signs of CHB.

Of the 63 patients, the study identified five cases of CHB, including four in a subset of 54 patients who received no potentially confounding medications. The evaluations met the efficacy endpoint, with recurrence rates of 7.9 and 7.4 percent, respectively, or less than half of the historical 18 percent rate. Although subsequent analyses will be important for validating the results, Dr. Izmirly says data collected to date for all anti-SSA/Ro antibody-positive pregnant women seen at NYU Langone clinics support the significant decrease in CHB recurrence among those given HCQ.

“The implication now is that a woman who previously had a child with heart block might be prescribed hydroxychloroquine as a safe prophylaxis,” says Dr. Buyon, the study’s senior author. Given that many women are unaware of their anti-SSA/Ro antibody status until their child is diagnosed with CHB, the results also could bolster the case for expanding screening and for providing first-time pregnant women who test positive for the antibodies with HCQ as a preventive, she says.



Jill P. Buyon, MD and Peter M. Izmirly, MD

HYDROXYCHLOROQUINE NOT ASSOCIATED WITH FETAL QT INTERVAL ABNORMALITIES

As an extension of the PATCH study, the researchers investigated the potential for cardiac toxicity in the neonates of anti-SSA/Ro antibody-positive mothers taking HCQ. Past research had reassuringly suggested that such toxicity manifest as a dangerously lengthened QTc interval on electrocardiograms (ECGs) did not occur. But Dr. Buyon notes that most such studies relied on women’s self-reported adherence to HCQ despite well-documented adherence shortfalls.

The PATCH study overcame such bias by measuring HCQ levels during each trimester in maternal blood and cord blood and then comparing these levels with the newborn’s QTc intervals. Study collaborator Deborah Friedman, MD, a pediatric cardiologist at New York Medical College in Valhalla, evaluated the neonate ECGs and measured their QT intervals to detect any abnormalities.

Excluding those neonates diagnosed with heart block, the resulting analysis, published in the journal *Circulation: Arrhythmia and Electrophysiology*, showed no relationship between HCQ levels and the QTc interval. Of the 45 neonates included in the analysis, ECG measurements suggested that five did have a prolonged QT interval, with three deemed only marginally abnormal and two clearly abnormal. “We saw no negative clinical consequences in any of these cases, however,” Dr. Buyon says. “Based on our results, this study has helped to assure the safety of hydroxychloroquine during pregnancy.”

Despite the many challenges associated with the complicated and time-consuming trials, she and Dr. Izmirly say, NYU Langone has been able

to draw upon its sizable patient cohorts and highly supportive collaborators to marshal its resources and collect vital information with immediate clinical applications.

SENIORS WITH SLE NOT AT HIGHER FLARE RISK AFTER HALTING HYDROXYCHLOROQUINE

Despite a broad consensus that HCQ is safe and efficacious for preventing SLE flares, as well as considerable evidence of its utility in preventing blood clotting and organ damage, more sensitive ophthalmology measurements have raised concerns about ocular toxicity associated with long-term use in seniors. A groundbreaking study by NYU Langone rheumatologists found that patients 55 years or older who withdrew from HCQ after long-term use were at low risk for disease flares, suggesting that the drug can be safely discontinued due to toxicity concerns or other reasons. The encouraging results of the retrospective study, published in *Arthritis Research and Therapy*, have garnered a planning grant from the National Institutes of Health for an expanded confirmatory trial of 330 patients who are at least 60 years old.

Dr. Izmirly, the study’s lead author, says a prospective randomized trial by Canadian researchers concluded that withdrawing HCQ after only a few years of administration in younger patients with SLE increased the risk of flares. But few researchers had explicitly examined the risks associated with stopping the drug in older patients after long-term use.

When patients were matched by age, gender, and race, Dr. Izmirly and colleagues showed that SLE flare rates were similarly low over a one-year follow-up period among older patients who either continued or discontinued HCQ after taking it for at least five years. The study included 26 patients who withdrew from the drug and 32 who continued taking it, and Dr. Izmirly cautions that the small study requires validation with a larger cohort. “We can’t say anything definitively, but it gives us some reassurance that patients whose lupus was inactive at the time and who stopped the drug due to eye toxicity have a pretty good chance of remaining inactive,” he says.

The planned follow-up study—a prospective, randomized trial—should provide firmer conclusions. “But there were no data previously,” Dr. Izmirly says. “At least now we can give our older patients some guidance on their risk of flaring if they withdraw from hydroxychloroquine.” ■

“

It speaks to NYU Langone’s strong capability to lead multicenter trials in rheumatology.”

—Jill P. Buyon, MD

STOP BLOQ Trial Aims to Detect and Reverse Congenital Heart Block

NYU Langone researchers are leading a multisite study assessing the potential for an at-home fetal heart rate monitor to quickly detect CHB during pregnancy. The trial, Surveillance and Treatment to Prevent Fetal Atrioventricular Block Likely to Occur Quickly (STOP BLOQ), is being funded by the National Institute of Child Health and Development.

Among the study’s aims is to investigate whether the titer of maternal anti-SSA/Ro antibodies can be used for risk stratification. In addition, the team is assessing whether pregnant women can use home fetal heart rate monitoring to identify any abnormalities, and whether second-degree heart blocks discovered through the study can be reversed via rapid treatment with intravenous immunoglobulin (IVIG) and dexamethasone.

Dr. Buyon is co-leading the trial with Bettina Cuneo, MD, professor of pediatrics and obstetrics at the University of Colorado, in collaboration with Dr. Izmirly and a site team led by Colin K. Phoon, MD, associate professor of pediatrics and director of the Pediatric and Fetal Echocardiography Lab at NYU Langone. An initial pilot study of 300 patients led by Dr. Cuneo showed that pregnant women can be taught to listen for and identify abnormal fetal heart rates, paving the way for a planned follow-up with a larger cohort.

Researchers at NYU Langone will first measure the titer levels of 1,300 pregnant women with confirmed anti-SSA/Ro antibodies. “If the patient has a titer that meets or exceeds the threshold, we will consider her to be at greater risk for having a child with CHB, and she will then begin home monitoring to track the fetal heartbeat,” Dr. Buyon says. The researchers expect about 850 women will meet that titer cutoff, and about 30 fetuses will develop second-degree heart block.

During the monitoring phase, from 17 weeks through 25 weeks gestation, women with high-titer anti-SSA/Ro antibodies will self-monitor three times a day with an at-home Doppler device. These recordings will be sent to cloud storage via a phone app. If the mother perceives an abnormal rate or rhythm, an immediate alert is sent to the cardiology team for review. If the cardiologist agrees with the abnormality, an urgent echocardiogram will be done. If it confirms second-degree block, the mother will immediately receive IVIG and dexamethasone. The researchers hope that very rapid treatment of an incomplete block will reverse the condition injury and prevent permanent and complete third-degree block.

“This study has definite potential, particularly in times of COVID-19, to empower women to help identify a fetal heart problem early enough to make a difference,” Dr. Buyon says.



Johannes Nowatzky, MD

Deciphering the Molecular Mechanisms of Behçet’s Uveitis

The Division of Rheumatology at NYU Langone Health has long been known as a regional, national, and international referral center for Behçet’s syndrome. A National Institutes of Health (NIH) research grant awarded to Johannes Nowatzky, MD, assistant professor of medicine and leader of the division’s Behçet’s syndrome and inflammatory eye disease program, has now helped the Behcet’s Syndrome Center claim another distinction as one of the only federally funded sites working to unlock Behçet’s syndrome intricate disease mechanisms.

CLARIFYING THE CONTRIBUTIONS OF TWO GENE VARIANTS

Behçet’s uveitis, which strikes about 50 to 70 percent of people with Behçet’s disease, is a severe form of eye inflammation that can lead to blindness in both eyes if not treated. “Behçet’s disease has a lot of potential to cause morbidity, and even mortality through other disease manifestations, like involvement of the central nervous system or large blood vessels,” Dr. Nowatzky says. More common in Turkey, Iran, Israel, and other parts of the world, the disease has received relatively little attention by researchers in the United States.

To help clarify Behçet’s syndrome risk factors and molecular drivers, Dr. Nowatzky’s NIH-funded immunology research focuses on two polymorph genes that have been epidemiologically linked to an increased risk. One, known as HLA-B*51, encodes a variant of the human leukocyte antigen

(HLA) molecule that regulates immune function. Although the HLA-B*51 variant has long been associated with Behçet’s syndrome—it increases the risk three- to four-fold and is found in about 70 to 80 percent of all patients—researchers haven’t understood why.

In 2013, a group of NIH researchers working with collaborators in Turkey discovered that a variant of a second gene called ERAP1, which encodes an enzyme known as endoplasmic reticulum aminopeptidase 1, may further elevate the disease risk through epistasis with HLA-B*51. In individuals who carry HLA-B*51, a group of polymorphisms within ERAP1, called Hap10, yields an 11-fold increase in the risk for Behçet’s syndrome. “It confers the strongest risk that we currently know of,” Dr. Nowatzky says.

As part of the major histocompatibility (MHC) class I antigen presentation pathway, the ERAP1 enzyme trims peptides for a proper fit in the binding groove of HLA molecules such as HLA-B51.

The bound peptides can then be presented on the cell surface—a key step in T cell recognition and activation. Although ERAP1 normally cuts to a 9-mer target, the Hap10 variant’s low enzymatic activity results in insufficient trimming and overly long peptides.

Dr. Nowatzky hypothesizes that packaging of longer peptides in HLA molecules, including HLA-B51, alters the immune response in a way that can lead to Behçet’s syndrome and its characteristic uveitis. To study the potential contribution of ERAP1 and HLA-B*51, his lab is using CRISPR-Cas9 genome editing to knock out or modify the ERAP1 gene and study the resulting activity of HLA-bearing cells in immunofunctional assays. “When we change this gene, we’re looking at how the peptidome changes, meaning all of the proteins that are bound to HLA-B51,” Dr. Nowatzky says. “Then we look at how these genetically modified cells behave with other cells they are supposed to stimulate or to inhibit, especially CD8 T cells.”

The researchers are also comparing the immune phenotypes of patients with severe Behçet’s syndrome from Turkey and the United States who carry the ERAP1 Hap10 risk variant with those who don’t and with healthy individuals. With cells collected from the anterior chamber of the eye, additional research is characterizing T cell antigen specificities to understand which molecules they bind and how ERAP1 mutations alter that activity.

BEHÇET’S SYNDROME RISK VARIANTS MAY SHIFT PATIENTS’ IMMUNE RESPONSE

So far, the research has suggested that even patients who are heterozygous for ERAP1 Hap10 have an altered immune phenotype characterized by shifts in their CD8 T cell, CD8 natural killer T (NKT) cell, and natural killer (NK) cell compartments. “This risk variant may have a larger clinical significance than we thought in the beginning, because patients who are homozygous for this genetic alteration are quite rare—they make up only 5 to 10 percent of the patients who are HLA-B*51 carriers,” Dr. Nowatzky says. “Ones who are heterozygous for ERAP1 Hap10 are much more common, about 30 to 40 percent.”

In cells with an ERAP1 knockout, he adds, “We see that this really shifts the HLA class I peptidome towards the presentation of longer peptides compared to what the case is when you have a fully functional ERAP1.” Consistent with his hypothesis, co-culture experiments suggest that the alteration changes the immune response as measured by CD8 T cell function, activation, and proliferation.

“With this project, we may be able to find a mechanistic explanation that allows us to understand how HLA-B*51 mediates this disease in a certain subset of patients,” Dr. Nowatzky says. Connecting the dots will be important for designing therapies tailored for that patient subgroup. “The bigger picture is that if you understand one mechanism well—one that drives this disease for a subgroup of people—it will very likely propel your understanding for other subgroups of patients, too,” he says.

The new research grant, Dr. Nowatzky says, is a welcome validation of his decision to pursue a difficult line of inquiry into a complex, multisystem disease that has been widely misunderstood by many rheumatologists and ophthalmologists. By deciphering the molecular mechanisms of Behçet’s uveitis, he says, the effort may lead to a better grasp of its origins, methods for risk-stratifying patients, and the means to reduce its damaging effects via targeted therapies. ■

Successful Resolution of Thrombocytopenia and Anemia in a Patient with Lupus

When Confronted with a Complicated Case of Thrombocytopenia, Clinicians Relied on Expert Knowledge and a Meticulous Strategy to Investigate the Condition and Identify an Effective Treatment

TIMELY TESTS REVEAL SEVERE LUPUS EXACERBATION THROUGH THROMBOCYTOPENIA

A 34-year-old woman from Brooklyn who had been previously diagnosed with systemic lupus erythematosus (SLE), lupus nephritis, and end-stage kidney disease requiring hemodialysis encountered a new complication in April 2019. After providers at a dialysis center in lower Manhattan had difficulty accessing an arteriovenous fistula that had been grafted in her left arm to provide access for the dialysis, they transferred her to the emergency department at NYU Langone's Tisch Hospital.

Once in the emergency department, doctors recognized that she was facing a more immediate threat of asymptomatic but severe thrombocytopenia: Her platelet count of 168,000 in February 2019 had dropped to 2,000. Serial lab tests upon her admission also revealed progressive anemia, with a significant drop in hemoglobin levels that continued to fall over the next 48 hours.

DIFFERENTIAL DIAGNOSES KEY TO DETERMINING THROMBOCYTOPENIA ETIOLOGY IN LUPUS

H. Michael Belmont, MD, professor in the Department of Medicine and medical director at NYU Langone Orthopedic Hospital, says clinicians should be aware of the broad differential diagnoses of thrombocytopenia in SLE. Most commonly, these include autoimmune thrombocytopenia (AITP) with antibodies to platelet membrane antigens (such as glycoproteins IIb/IIIa, Ib/IX, or Ia/IIa); AITP plus autoimmune hemolytic anemia (AIHA), also known as Evans syndrome; and a non-criteria manifestation of antiphospholipid syndrome.

Clinicians, though, also need to consider less common etiologies, including those in which the thrombocytopenia is accompanied by evidence of a thrombotic microangiopathic hemolytic anemia (TMHA) process such as thrombotic thrombocytopenic purpura (TTP) with an immunoglobulin inhibitor of the ADAMTS13 protein.

Other possibilities include complement-mediated hemolytic uremic syndrome (HUS) either as the consequence of an acquired immunoglobulin inhibitor of factor H or another complement regulatory protein, or coincidence in SLE of an inherited disorder of complement regulation. A deficiency of complement factor H-related plasma proteins and autoantibody-positive form of hemolytic uremic syndrome (DEAP-HUS) also may be seen in lupus. Rarely, HUS can occur due to the coincidence of a Shiga toxin-producing *Escherichia coli* (STEC) infection in a patient with lupus.

Other etiologies of thrombocytopenia in patients with lupus include disseminated intravascular coagulation (DIC); heparin-induced thrombocytopenia thrombosis (HIT/T); amegakaryocytic thrombocytopenia; acquired aplastic anemia due to humoral or cell-mediated inhibition of the myelopoietic progenitor cells, or both; hypersplenism with platelet sequestration secondary to cirrhosis or due to the splenomegaly that can be observed with nodular regenerative hyperplasia and non-cirrhotic portal hypertension; and coincidental drug-induced immune thrombocytopenia (DITP).

RECOGNIZING MICROANGIOPATHIC HEMOLYTIC ANEMIA AS A MECHANISM OF THROMBOCYTOPENIA ASSISTS WITH FOCUSING DIFFERENTIAL

The patient's lab tests showed an absence of elevated double-stranded DNA or antiphospholipid antibodies, but modest hypocomplementemia. Dr. Belmont says the patient's initial presentation raised concerns that she might have Evan's syndrome with simultaneous AITP and AIHA. The case's unusual presentation ran contrary to the general clinical rule that SLE disease activity is less intense with progression to end-stage kidney disease. The clinical team nevertheless started the patient's initial treatment with parenteral steroids and intravenous gamma globulin, but her bicytopenia persisted. However, further testing revealed elevated lactate dehydrogenase (LDH), low haptoglobin, and a negative direct antiglobulin test result. Diagnostic testing also revealed the absence of spherocytes in the peripheral blood smear typical of AIHA, but the presence of significant schistocytes as seen with TMHA.

Based on the presence of TMHA in the setting of lupus, Dr. Belmont recommended an ADAMTS13 activity test, which showed an enzymatic activity of less than 5 percent. Based on a diagnosis of secondary TTP in SLE, NYU Langone doctors administered a treatment regimen of steroids, plasma exchange with fresh frozen plasma, and rituximab. The patient responded well, with her ADAMTS13 activity increasing to 90 percent. Additionally, her LDH and haptoglobin levels normalized, accompanied by improvement in her hemoglobin and hematocrit levels as well as an increase in her platelet count to 101,000.

A test for heparin-induced thrombocytopenia was positive for antibodies to platelet factor 4, although a negative result in the confirmatory serotonin release assay cast doubt on the diagnosis. Regardless, the medical team minimized the use of heparin with her hemodialysis out of an abundance of caution.

H. Michael Belmont, MD



APPROPRIATE TREATMENT
REGIMEN RESOLVES
THROMBOCYTOPENIA AND
PREVENTS RELAPSE

By mid-July 2019, the patient reported feeling well at a follow-up appointment, with no rash, alopecia, or arthritis, previous hallmarks of her SLE. Further, she had no fever, oral ulcers, shortness of breath, pleuritic chest pain, nausea, vomiting, abdominal

pain, edema, or headaches. Her platelet count had rebounded to 170,000, and her ADAMTS13 activity remained high, at 81 percent.

Since her hospitalization, the patient has remained on a 5-mg dose of prednisone, 200 mg of hydroxychloroquine three times a week, and 1,000 mg of mycophenolate mofetil twice a day. She has not had a relapse of her thrombocytopenia since the initial event.

Dr. Belmont is providing maintenance courses of rituximab at six-month intervals to prevent a

recurrence of TTP and reappearance of the anti-ADAMTS13 antibody. This case, he says, illustrates the potential for severe lupus exacerbation despite progression to end-stage kidney disease and initiation of hemodialysis. In addition, he says, it underscores the importance of considering TMHA as the mechanism of thrombocytopenia in patients with lupus with a differential diagnosis that includes secondary TTP on the basis of an acquired immunoglobulin inhibitor of ADAMTS13. ■

Colton Center Nurtures a Growing Pipeline
of Clinical Applications

A significant gift from Judith and Stewart Colton compounds their 2014 generosity to name the Judith and Stewart Colton Center for Autoimmunity. This new gift will extend the Center’s reach and further its aim of helping a wide array of promising research collaborations reach the clinic. The center, which launched in 2013, has funded more than two dozen pilot projects involving multiple disciplines as well as the Institute for Systems Genetics and the Center for Human Genetics & Genomics. “I’m definitely excited about the reach we’ve had across the institution,” says Colton Center director Timothy Niewold, MD, Judith and Stewart Colton Professor of Medicine and professor of pathology.

Those pilot projects, in turn, have attracted more than \$30 million in external grants—a three-fold return on the initial investment. “As the

center matures, our aspirational goal for its second phase is to have it function like a pipeline and keep the promising projects in our portfolio moving toward clinical application,” Dr. Niewold says.

One such project has been led by Boris Reizis, PhD, the Samuel A. Brown Professor of Medicine and Pathology, and Jill P. Buyon, MD, the Lady Va and Sir Deryck Maughan Professor of Rheumatology. The collaborators linked a deficiency of the DNASE1L3 enzyme activity to lupus in both mice and human patients and showed that the enzyme helps degrade extracellular DNA which is known to serve as a major immune stimulant for this autoimmune condition. With backing from NYU Langone’s Office of Therapeutics Alliances, the project is focusing on the enzyme as a potential therapy.

For another line of research, the Colton Center for Autoimmunity has partnered with NYU Langone’s Center for Data Science and the NYU Courant Institute of Mathematical Sciences to hire a new faculty fellow. This new investigator will apply artificial intelligence methods to biological and clinical datasets toward the goal of predicting which patients with autoimmune conditions such as rheumatoid arthritis might respond to specific therapies. In addition, a newly funded pilot study will apply AI to muscle tissue biopsy slides from patients with dermatomyositis, to see whether this method can map out immune interactions such as potential B cell-T cell communications.

“We’re going to continue to have really exciting, out-of-the-box basic discoveries, and pull in outstanding scientists from across multiple disciplines and campuses,” Dr. Niewold says. “Now we’re going to cultivate some of these great ideas so that investors can run with them and help make the clinical applications a reality.”

“
We’re going to continue to have really exciting, out-of-the-box basic discoveries, and pull in outstanding scientists from across multiple disciplines and campuses.”
—Timothy Niewold, MD

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COVID-19–related Publications from the Division of Rheumatology

NYU Langone researchers have led many efforts to better understand the impact of COVID-19 across nearly every medical specialty, with 617 publications in 2020. The Division of Rheumatology contributed to this research with publications that included:

Fernandez Ruiz R, Masson M, Kim MY, Myers B, Haberman RH, Castillo R, Scher JU, Guttmann A, Carlucci PM, Deonaraine KK, Golpanian M, Robins K, Chang M, Belmont HM, Buyon JP, Blazer AD, Saxena A, Izmirly PM. Leveraging the United States epicenter to provide insights on COVID-19 in patients with systemic lupus erythematosus. *Arthritis & Rheumatology*. December 2020; 72(12): 1971-80.

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ABOUT NYU LANGONE HEALTH

Leader in Quality

NYU Langone’s emphasis on continuous improvement inspires teams to continually raise the bar on quality and safety across our growing network in Manhattan, Brooklyn, Queens, Long Island, Staten Island, and Florida. NYU Langone’s Tisch Hospital, Kimmel Pavilion, NYU Langone Hospital—Brooklyn, and NYU Langone Hospital—Long Island were awarded an “A” as well as a Top Hospital award as part of the fall 2020 Leapfrog Hospital Safety Grades. NYU Langone Hospitals achieved Five Star ratings on CMS Hospital Compare effective October 2019 and is the only major academic medical center in the New York metropolitan region to attain a Five-Star Quality rating.



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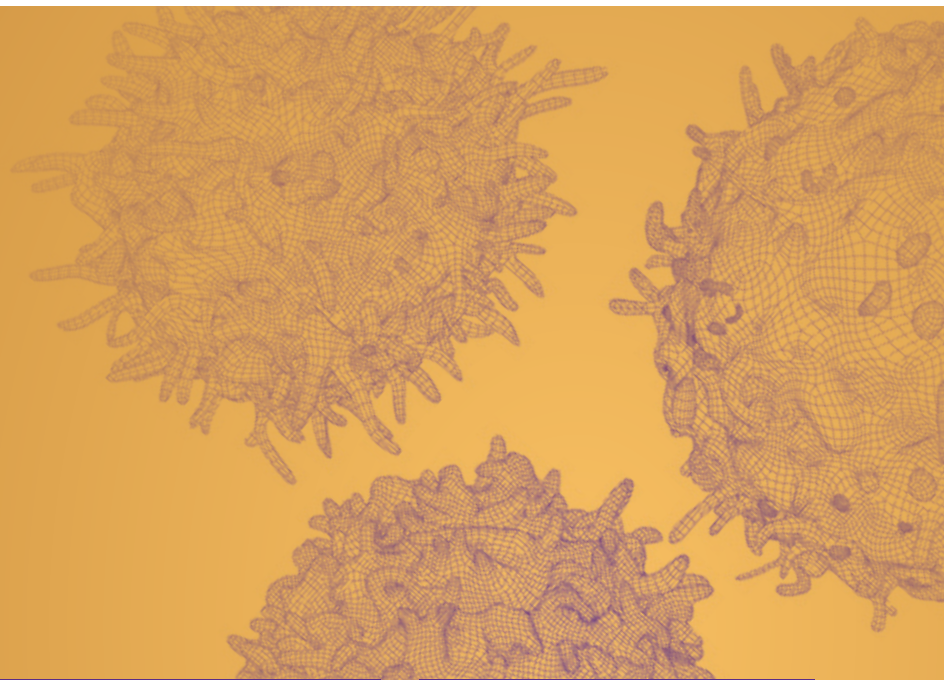
As COVID-19 has added new urgency to nationwide physician shortages, debt burden, and lack of diversity, we remain committed to our accelerated pathways to the MD degree and full-tuition scholarships regardless of need or merit at the recently renamed NYU Grossman School of Medicine and the new primary-care focused NYU Long Island School of Medicine.



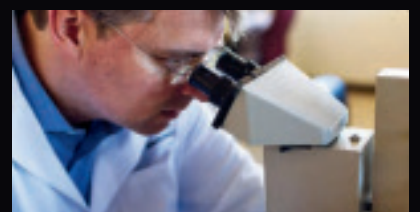
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Rheumatology

2020 HIGHLIGHTS



Research Investigates
Inflammation Modulators
and Genetic Targets for
Osteoarthritis Treatment
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Behçet's Uveitis Intricacies
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That Clarifies Risk Factors
and Molecular Drivers
See page 6.