

ADVANCES IN RHEUMATOLOGY

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The rheumatology program at NewYork-Presbyterian Hospital is comprised of faculty affiliated with Weill Cornell Medicine and Hospital for Special Surgery, and Columbia University Vagelos College of Physicians and Surgeons. The program provides state-of-the-art care to patients with the broad range of inflammatory and autoimmune diseases, pursues groundbreaking research at both the laboratory level and through clinical studies, and offers comprehensive training to medical residents and fellows.



NewYork-Presbyterian Rheumatology ranks #3 in the nation.

Elevating Research with Broad-Based Collaborations in Pediatric Rheumatology

A little more than 20 years ago, **Karen Brandt Onel, MD**, began her medical career as an assistant attending pediatrician and assistant scientist in the Division of Rheumatology at Hospital for Special Surgery. After nine years, Dr. Onel accepted a position at the University of Chicago as Program Director of the Pediatric Rheumatology Training Program and then Section Chief of Pediatric Rheumatology. In December 2016, Dr. Onel returned to HSS as Chief of Pediatric Rheumatology, having learned some important truths along the way.

“Hospital for Special Surgery is a remarkable institution for pediatric rheumatology,” she says. “When I left I wanted an opportunity to spend some time in a children’s hospital, and I had a wonderful 12 years and some great and unusual experiences that were distinctive to working on the South Side of Chicago. The most important thing that I learned by leaving HSS is that in a field like pediatric rheumatology where the diseases are



Dr. Karen B. Onel

relatively unusual, you can forget what patients bring to the equation. When you stay in one place you have a feeling you know the right way to do

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Perspectives and Progress in Systemic Lupus Erythematosus

For nearly two decades, **Anca D. Askanase, MD, MPH**, has sought answers to the many questions surrounding systemic lupus erythematosus (SLE), a rare and complex disease involving multiple organs and diverse clinical manifestations. Dr. Askanase, an internationally renowned SLE clinician, diagnostician, and researcher, is the first to admit that

lupus poses unique challenges to both doctors and patients. “I have been fortunate enough to have learned a great deal about lupus, both in the lab and through years of hands-on patient care, but I find myself humbled by the fact that I am always learning something new in addressing the toll lupus can take on a patient and their family, both physically and emotionally,” says Dr. Askanase, Director of both the Lupus Center and Rheumatology Clinical Trials at NewYork-Presbyterian/Columbia University Irving Medical Center. “To continue to be schooled in SLE means that there is still more learning to be done to address all of the needs of the disease and the patients affected by it.”

While the challenges of lupus are many, Dr. Askanase and her Columbia colleagues remain undaunted. “Lupus has evolved, and I do think we have made

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“Over the past 15 years I’ve been part of both the big success story of Benlysta® [belimumab], which was the first new drug approved to treat SLE in half a century, but also the many promising drugs that failed to succeed in Phase 3 clinical trials. We’ve learned from both the successes and the failures.”

— Dr. Anca D. Askanase

In proud collaboration with



Elevating Research with Broad-Based Collaborations in Pediatric Rheumatology (continued from page 1)

things, but you forget that this is affected by your location, the kinds of patients that you treat, the staff you work with, and the resources that are available to you.”

“The patients I treated in Chicago were very different from those I’d treated in New York,” continues Dr. Onel. “My time in Chicago made me much more focused on collaborative research because that is the only way that you can address the variabilities that patients bring – from different sites and different races, ethnicities, and socioeconomic classes. For example, some of our diseases vary in severity to some extent by ethnicity. It was a very rewarding experience.”

“Chronic recurrent multifocal osteomyelitis is a rare inflammatory bone disease that affects 1 in 1,000,000. It’s poorly understood, very distinctive in pediatrics, and is too rare for any one institution to get to the bottom of it. So, we are participating in a working group across the country to study this disease.”

— Dr. Karen B. Onel

Collaboration is Key for Rare Diseases

Dr. Onel says that she has returned to New York “much more invested in collaboration. When you realize there is so much to do, working as a group is the only way we are going to take care of children with rare diseases. There is no question about that.”

In returning to HSS, Dr. Onel is also coming back to the roots of her medical education at NewYork-Presbyterian. After earning her medical degree at Weill Cornell Medicine, Dr. Onel pursued residency training in pediatrics at NewYork-Presbyterian/Columbia University Irving Medical Center. She then went on to complete a clinical fellowship in pediatric rheumatology at HSS.

Dr. Onel’s clinical expertise focuses on children and young adults with lupus, juvenile inflammatory arthritis, vasculitis, uveitis, chronic non-infectious osteomyelitis, dermatomyositis, and the periodic fever syndromes. Through her research, she is gaining a greater understanding of the causes of rheumatic illnesses, as well as evaluating the safety and tolerability of new treatments. To that end, she partners with other institutions to define evidence-based best treatment practices, particularly for children with juvenile idiopathic arthritis, systemic lupus erythematosus, and recurrent non-infectious osteomyelitis. She has authored numerous papers, reviews, and book chapters on pediatric rheumatology. In addition, she serves as a reviewer for several scientific journals, including *Arthritis and Rheumatism*, *Lupus*, *Seminars in Arthritis and Rheumatism*, and *Pediatric Rheumatology*.

“I’ve always been very interested in clinical and basic translational research,” says Dr. Onel, who serves on the Finance and Ethics Committees and Chairs the Systemic Juvenile Arthritis Study Group of the Childhood Arthritis and Rheumatology Research Alliance (CARRA). “The truth is we rise together, or we stand alone. We need to do more research, more studies, more clinical trials, and publish more papers. We also need to be open to trying new paths. In addition, we need to foster more studies nationwide.”

Key CARRA trials underway across the country include STOP-JIA (Start Time Optimization of Biologic Therapy in Polyarticular JIA), FROST (FiRst-line Options for Systemic JIA Treatment) and the CARRA Registry. The common denominator in all of these trials

is collaboration, says Dr. Onel. “We have been able to enroll more than 400 children into STOP-JIA from around the country. In the past, these numbers would never have been possible and the opportunity to ask and answer these very important questions would have been lost.”

Dr. Onel is also a member of the Advisory Council of the Pediatric Rheumatology Collaborative Study Group (PRCSG). “The PRCSG Advisory Council reviews all of the clinical trials proposals,” says Dr. Onel. “The Advisory Council decides what trials are appropriate scientifically and feasible for our network.” This past July, the PRCSG Advisory Council had an overview review published in the *Pediatric Rheumatology Online Journal* of the strategies employed by the study group to achieve drug and biologic approvals for children with pediatric rheumatic diseases, particularly juvenile idiopathic arthritis. The novel trial designs utilized for more efficient testing of innovative drug candidates have all been developed or co-developed by the PRCSG research network.

“One of my goals is to collaborate more with colleagues at Weill Cornell and at Columbia,” adds Dr. Onel. “Dr. Alexis Boneparth, a pediatric rheumatologist at Columbia, and I have already reached out to each other.”

The proximity of HSS to Memorial Sloan Kettering Cancer Center also offers opportunities to share discoveries. “The overlap with cancer and inflammatory disease is interesting,” says Dr. Onel. “We are looking at some of the children who are receiving transplants and are immunodeficient. This is a group with a lot of rheumatic disease overlap. Some of the new drugs that they are using for adults, the checkpoint inhibitors, may have implications for children. It has not necessarily been the case yet in children, but we suspect that the use of immunomodulators is going to increase.”

Dr. Onel is also studying chronic recurrent multifocal osteomyelitis, a rare inflammatory bone disease that affects 1 in 1,000,000. “The numbers are too small. If we are going to do this by ourselves, we are never going to get to the answer of what people actually need,” she says. “At HSS we’ve started doing whole body MRI, which is standard of care now, and we are participating in a working group across the country to understand this disease. It’s poorly understood, very distinctive in pediatrics, and is too rare for any one institution to get to the bottom of it.”

Another area of interest for Dr. Onel is juvenile arthritis. “We are going to work with the Sports Medicine physicians at HSS to formally look at children with juvenile arthritis who are treated and feeling well to see if participation in athletics can produce an effect that is good, bad, or otherwise,” she says. “For instance, if a child has wrist arthritis, is it appropriate for him or her to play volleyball after treatment? What we want to do is leverage the strengths that we have here at HSS to answer questions that really matter for kids and their families.”

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For More Information

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Perspectives and Progress in Systemic Lupus Erythematosus *(continued from page 1)*



Dr. Anca D. Askanase

extraordinary progress,” she says. “We are certainly doing more than we did 15, 20, and 30 years ago. Today, we have a better understanding of the disease, how to treat it, and more treatment options,” continues Dr. Askanase. “In 1950, mortality from lupus was about 50 percent. We’re at a place now where the 10-year mortality is less than 10 percent but that is too much because lupus is a disease of young women.”

“Most importantly,” continues Dr. Askanase, “we have come to understand the unique insights that patients offer into managing their own disease and have developed tools that make patients active team members in most effectively treating their SLE.”

On the Road to Newer Therapeutics

The standard tools for combating lupus include an arsenal of drugs – antimalarials, nonsteroidal anti-inflammatory drugs, corticosteroids, cytotoxics, and immunosuppressants – all of which improve disease activity but put patients at risk for long-term consequences from both low-level, active SLE and from the medications themselves. “Part of the revolution in lupus care going back to the 1990s was the insight that we could use mycophenolate mofetil, an organ transplant medication with relatively tolerable side effects, instead of the old chemotherapy agent, cyclophosphamide, which could truly incapacitate patients,” says Dr. Askanase.

“Over the past 15 years I’ve been part of both the big success story of Benlysta® [belimumab], which was the first new drug approved to treat SLE in half a century, but also the many promising drugs that failed to succeed in Phase 3 clinical trials,” says Dr. Askanase. “We’ve learned from both the successes and the failures.”

One important lesson that Dr. Askanase and the lupus community have learned is the need to create the same culture of excitement and appreciation for the research and development in SLE as exists in cancer research in order to raise SLE’s profile both among the medical and patient communities. “The potential for change is huge, and we have so many promising studies on the horizon and in the pipeline. However, there are simply not enough patients who know about these fantastic opportunities to fill all of the studies,” says Dr. Askanase. “Physicians need to discuss with their patients the advantages of participating in clinical trials – even in the placebo arm.”

Trials of new lupus drugs are often decades long and require thousands of patient participants to reach their goal: approval of a new therapy that can save the lives of patients with SLE. For example, in 2011, after a more than 60-year lag with no new medicines specially targeting lupus, the FDA approved the use of Benlysta, a monoclonal antibody, which represented a breakthrough in lupus drug development. Benlysta spent more than a decade in development and testing before it reached patients. Dr. Askanase served as a Principal Investigator in the Phase 3 clinical trial of Benlysta and several Phase 4 clinical trials designed to further understand the role and the use of the medication in special populations.

“What’s different about Benlysta is that it targets a specific lymphocyte stimulator (BLyS), or B-cell activating factor, that is both elevated in lupus patients and correlates with SLE activity,” says Dr. Askanase. “Using novel techniques, researchers first identified an anti-BLyS antibody that blocks the activity of the BLyS. This discovery allowed scientists to take this important breakthrough from the laboratory bench to the bedside by creating a drug that would block BLyS and then offering it to patients in a clinical trial. Benlysta shined a light on lupus and now there are other promising drugs targeting different mechanisms that are currently in late phases of development and are desperately seeking lupus patients for clinical trials.”

Patient participation in clinical trials is the primary factor in fine-tuning a new drug so that it might potentially deliver on its initial promise. For example, Dr. Askanase cites anifrolumab, a monoclonal antibody that targets interferon α receptor 1 (IFNAR1), currently in Phase 3 clinical trials. “We were part of the anifrolumab study and were enormously disappointed to learn that one of the Phase 3 trials did not meet its endpoint,” says Dr. Askanase. “Hopefully we will learn from this trial how to improve trial design and outcomes and succeed in the quest for better therapies for lupus.”

Improving Outcomes Measures in Lupus

The failure of so many promising lupus drugs after long-term trials has often confounded clinicians who depend on patient and physician reporting to gauge the efficacy of these new therapies. It underscores the need for a simple, scalable index that accurately measures disease progress and can provide reliable endpoints for international trials and quality measures for busy clinical practices. “Both physician assessments and patient experiences are important to know about, since they are complementary but not superimposable aspects of disease activity,” says Dr. Askanase. However, clinician-reported outcome (ClinRO) and patient-reported outcome (PRO) measures for SLE frequently differ, and it is unclear whether discrepancies reflect different assessments of specific symptoms or different perspectives about which symptoms are important.

“Physicians are taught to evaluate disease activity, length, severity, and medication side effects separately,” says Dr. Askanase. “Without clear instructions, patients may report mixed perceptions of what they view as key side effects – such as irreversible scarring, steroid-induced weight gain, situational anxiety or depression, fatigue, and pain – that unfortunately do not always help accurately assess the improvement or worsening of disease activity that doctors utilize in assessing outcomes.”

To address these issues, Dr. Askanase, in partnership with the Lupus Foundation of America (LFA), helped design the LFA-REAL™ (Rapid

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Perspectives and Progress in Systemic Lupus Erythematosus *(continued from page 3)*

Evaluation of Activity in Lupus) tool. This simple but versatile instrument based on additive, organ-specific scales with separate and overlapping physician and patient components, accounts for this divergence of perspectives while also directing attention on symptoms responsive to immunotherapies.

The PRO part of the LFA-REAL™ was developed based on FDA guidance using in-depth patient input and cognitive debriefing to ensure it was understandable and included patients' priorities. A similar approach invited community-wide input into the LFA-REAL™ ClinRO structure and content. In early validation studies the instrument showed great potential with low inter- and intra-rater variability, consistency among investigators, and reliability in tracking disease activity progress over time.

Patient Input: Critical to Effective Drug Development

As the LFA-REAL™ confirmed, people living with systemic lupus erythematosus are uniquely positioned to help clinicians refine their understanding of the therapeutic context for drug development and evaluation. To that end, in 2017, top decision makers at the Food and Drug Administration heard from over 550 people impacted by lupus as part of the FDA's Patient-Focused Drug Development (PFDD) Initiative. In collaboration with the Lupus and Allied Diseases Association, Lupus Foundation of America, and Lupus Research Alliance, the two-day workshop allowed regulators to better understand the perspectives of people with lupus in order to better assess the risks and benefits of drugs under review.

Dr. Askanase was the only physician invited to address the attendees, which included patients, family members, and representatives from regulatory agencies and industry. She described the unpredictability and individuality of lupus, detailing the inadequate treatments for lupus, their varying effectiveness, and challenging side effects.

"I was honored to have a featured role in trying to present the complexity of this disease and explain why the world needs to listen to patients' voices," says Dr. Askanase. "We want to make sure that they are heard and are a part of the drug development process in order to provide the best improvements in their symptoms and quality of life."

The major themes that emerged from the meeting included the substantial burden of disease in women, particularly among women of color; the considerable variability and heterogeneity of symptoms among people with lupus across their lifespan; the broad impact of the disease and treatment side effects on an individual's work, social, and family life, self-esteem, and quality of life; and the inadequacy of currently available treatments.

Likening lupus to the "Cinderella" of diseases, unique to each patient and hidden from everyday view, Dr. Askanase says she is nevertheless encouraged that many people who once shied away from acknowledging that they had the disease are now coming forward. "Over the past decade we've seen a change in that regard," she says. "I'm very grateful to all of the celebrities and public individuals who have revealed either that they have lupus or know someone with lupus. I think it sends a good, positive message to the world of patients and also to the doctors who take care of lupus patients that we are all in this together."

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For More Information

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