DIVISION OF RHEUMATOLOGY
NEW FRONTIERS
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Leading in education, therapeutic approaches, and innovative research
A message from the Chief

Leading in education, therapeutic approaches, and innovative research

The UNMC Division of Rheumatology is recognized both nationally and internationally as a leader in innovative treatments for rheumatoid arthritis, for outcomes and database research and for treatments of gout. Further, the division has an unparalleled record of educating fellows, residents and students on the rheumatic diseases. Our mission is to continue pursuing ground breaking approaches in research, clinical care and education in rheumatic diseases.

UNMC researchers have made major contributions to rheumatology through the conduct of investigator-initiated clinical trials in The Rheumatology and Arthritis Investigational Network (RAIN) over the past two decades. RAIN is recognized internationally as the largest network of its kind in the United States that specializes in RA investigator-initiated clinical research. The RAIN network was responsible for multiple innovative studies including the initial trial and subsequent worldwide prominence of “Triple Therapy” in the management of rheumatoid arthritis (NEJM 1996).

The Nebraska Arthritis Outcomes Research Center (NAORC) was established in 2007 by the generous donation by Ruth and Bill Scott and represents a collaborative effort of our division with the UNMC Department of Orthopaedics.

Researchers from the Division of Rheumatology, in efforts both at UNMC and the Omaha VA Medical Center, actively collaborate on a national and international level to address important clinical questions:

1. NAORC researchers recently conducted the largest study ever demonstrating an association between gum disease and the risk of developing rheumatoid arthritis. The results suggest that treatments aimed at gum disease could play an important role in arthritis treatment and prevention. This study involved investigators at UNMC and VA medical centers in Omaha, Dallas, Washington and Salt Lake City. This work has led to collaborations with investigators from across the U.S. and in Europe.

2. The multicenter, multi-national Rheumatoid Arthritis Comparison of Active Therapies (RACAT) study was led by our division at the Omaha VA and UNMC and included NAORC investigators. The study, published as the lead article in the July 25, 2013 issue of the New England Journal of Medicine, demonstrated clearly that a combination of conventional generic medications (Triple Therapy) works as well as newer, more expensive biologic medicines in the treatment of rheumatoid arthritis. Thus, providing the potential of huge cost savings without sacrificing quality.

3. Another national program directed by our division is the Veteran Affairs Rheumatoid Arthritis (VARA) registry created more than 10 years ago. This registry is the largest and best characterized, predominantly male RA cohort in the world. VARA, in addition to Omaha, now includes enrollment sites at 11 VA medical centers across the country including those located in Birmingham, Brooklyn, Dallas, Denver, Iowa City, Jackson, Little Rock, Portland, Philadelphia, Salt Lake City and Washington, D.C.

We strive to provide exceptional comprehensive clinical care. For example, UNMC is a leader in musculoskeletal ultrasound. This valuable tool provides physicians with better information about the conditions they treat. Future rheumatologists are educated through the fellowship program in the Division of Rheumatology. Our fellows have a perfect 100 percent pass rate on rheumatology boards for the entire history of our program. Our residents and fellows frequently have the opportunity to participate in research and present at the annual American College of Rheumatology conference.

Current advances in rheumatology and exciting and promising avenues make rheumatology a vibrant and growing one. UNMC’s Division of Rheumatology is proud to have the people, programs and cutting-edge research projects to participate in these advances, helping position the division to support our patients and those around the world.
Nebraska Arthritis Outcomes Research Center puts UNMC on cutting edge

Center’s Opening a great milestone for research, education at UNMC.

Medical education:
A fresh perspective

Amy Cannella, MD, MPH, sees exciting new educational opportunities for students and fellows.

The reader

Alan Erickson, MD, serves as an “expert reader” of films for the Rheumatology division.

Lupus study becomes international affair

Dr. Michlene Hearth-Holmes’ collaboration expands the demographics of the RAIN database.

The puzzle of ‘the loss of self-tolerance’

Lynell Klassen, MD, has spent a career grappling with one question: Why do people react to their own tissue?

An icon in rheumatology

A superlative internist, Dr. Gerald Moore’s biggest impact may be his legacy of committed and talented students.

Registry, research offer insights into RA risk factors

Ted Mikuls, MD, MSPH, is spearheading two efforts aimed at helping rheumatoid arthritis sufferers.

On the RISE

Kaleb Michaud, PhD, is helping use technology and databases to better serve RA patients.

RAIN man

Dr. James O’Dell and the Rheumatology and Arthritis Investigational Network have led UNMC to an international profile in RA research.

A top-tier team player

Dr. Geoffrey Thiele’s cross-departmental collaborations link RA research with other disciplines.

Faculty Publications & Research Awards

The Division of Rheumatology is a national and international leader in the diagnosis and treatment of diseases that affect the joints, connective tissue diseases, and autoimmune diseases. We are pursuing state-of-the-art approaches in research, clinical care, and education programs in rheumatic diseases, with areas of expertise to include rheumatoid arthritis, osteoarthritis, granulomatosis with polyangiitis, gout and systemic lupus erythematosus. Private donations have led to the founding of the Nebraska Arthritis Outcomes Research Center (NAORC), have directly supported the world renowned Rheumatology and Arthritis Investigational Network (RAIN), and have allowed us to lead research efforts devoted to improving the quality of life for our patients.
Nebraska Arthritis Outcomes Research Center puts UNMC on cutting edge

Dr. Mikuls. “Our collaborations have led to important work in several areas and now includes active and highly productive work with investigators from the Colleges of Public Health, Pharmacy, and Dentistry among others.”

Since its inception in 2007, NAORC has made substantial progress in research focused on gaining a better understanding of arthritis risk, its impact on patients and the best treatment strategies. In addition to leading cutting edge research programs and supported in large part by initial NAORC funding, center faculty members have:

- expanded the center’s reach both nationally and internationally;
- grown the research infrastructure at UNMC and the Omaha VA for arthritis-focused investigations;
- trained the next generation of arthritis researchers; and
- developed a strong publication portfolio.

NAORC’s goals over the next five years are to continue to expand these efforts with targeted, strategic faculty recruitments and expansion of currently available infrastructure supporting clinical and translational arthritis research.

NAORC ACCOMPLISHMENTS SINCE 2007 INCLUDE:

Cutting Edge Research

- **The Treatment of Rheumatoid Arthritis**
  The multicenter, multinational RACAT study was led by Omaha VA and UNMC NAORC investigators. Recently published in the *New England Journal of Medicine* (July 2013) and receiving national media attention, the study showed that a combination of conventional generic medications works as well as newer, more expensive biologic medicines in the treatment of rheumatoid arthritis.

- **Novel Methods of Drug Delivery in Arthritis**
  NAORC research efforts have led to highly innovative strategies of selectively delivering arthritis treatments to the inflamed joint. By targeting (and limiting) drug delivery to the diseased joint, these new treatment approaches hold substantial promise in limiting common drug-related toxicities that complicate arthritis management. Pilot studies...
examining the use of these novel drug delivery systems in treating joint replacement failure (loosening of implants) has been funded directly with NAORC-provided funding.

• The Benefits and Safety of Total Joint Replacement NAORC research efforts have demonstrated for the first time using meta-analysis that shoulder replacement surgery leads to substantial improvement in overall quality of life for patients suffering from end-stage shoulder arthritis. More recent efforts have focused on finding new ways of detecting infections impacting joint replacements and examining the impact and risk of procedures among those with rheumatoid arthritis.

• Links Between Oral Health and Arthritis NAORC researchers recently conducted the largest study ever completed demonstrating an association between gum disease with the risk of developing rheumatoid arthritis. The results suggest that treatments aimed at gum disease could play an important role in arthritis treatment and prevention.

• Novel Methods of Treating Gout As part of a NIH-funded program project grant, NAORC researchers are examining new ways of delivering gout care with the goal of improving outcomes in an often poorly managed condition.

• New Animal Models of Arthritis NAORC research efforts have for the first time led to the development of a new animal model for rheumatoid arthritis, one that more closely mimics human disease and that will be vital in examining new treatment paradigms in disease.

Building Support for State-of-the-Art Arthritis Research

• Registries and Biobanks NAORC leads the nation in the development of biorepositories and linked patient registries. These resources are vital in translating scientific discoveries into the arthritis clinic and serve as a research resource not only for UNMC investigators, but also for investigators both nationally and internationally. Efforts include the National Data Bank for Rheumatic Diseases (NDB), the VA Rheumatoid Arthritis Registry (VARA), the Rheumatology and Arthritis Investigational Network (RAIN) Database and, most recently, the Arthritis Internet Registry (AIR). NDB, RAIN, and AIR efforts have been led by Dr. Michaud with funding support from NAORC. NAORC support has allowed Dr. Michaud to develop and maintain links between registries and electronic health record data.

• FOCIS Center of Excellence Based on efforts to date, UNMC’s NAORC was designated a Federation of Clinical Immunology Societies (FOCIS) Center of Excellence. UNMC is one of only 62 centers nationally with this recognition.

• State-of-the-Art Imaging in Arthritis NAORC researchers have developed and refined novel methods for precisely characterizing joint damage resulting as a consequence of arthritis. These efforts include the acquisition of state-of-the-art micro-CT scans (using predominantly NAORC funds) to characterize disease models in addition to the dynamic ultrasound in arthritis patients, a noninvasive approach that can be used in diagnosis and to guide therapeutic joint injections.

• Lupus Clinic Led by Dr. Michelenes Hearth-Holmes, NAORC faculty have established the new state-of-the-art Lupus Clinic in the Division of Rheumatology, a clinic that will serve as a vital resource for lupus researchers at UNMC. With this clinic as the foundation, UNMC now has a NIH-funded research portfolio in lupus and is participating in studies examining lupus treatments.

• Examining the Impact of Arthritis and its Treatment in U.S. Veterans NAORC has led efforts to expand clinical research programs to the Omaha VA, spearheading two large national cooperative studies examining arthritis treatment. Additional ongoing VA research includes the national VA Rheumatoid Arthritis Registry (VARA) and more recent efforts focused on improving the quality of gout care.

Attracting the Best and Brightest Researchers at UNMC and Elsewhere

• Collaborations of center researchers have expanded across the University of Nebraska system and now include: Dong Wang, PhD (UNMC College of Pharmacy); Kaihong Su, PhD (UNMC Department of Pathology); Jason (Zhixin) Zhang, PhD (UNMC Department of Pathology); Fang Yu, PhD (UNMC College of Public Health); and Jeffrey Payne, DDS (UNMC College of Dentistry), among others.

• National and international collaborations now include researchers at top-tier institutions in the U.S. (Stanford University, Johns Hopkins, Mayo Clinic, University of California San Francisco, and Harvard to name a few) in addition to arthritis research centers in Europe (Kennedy Institute in the U.K., the Karolinska Institute in Stockholm and others).
Amy Cannella, MD, MS, sees exciting new educational opportunities for students and fellows. Dr. Cannella, fellowship director for the UNMC Division of Rheumatology, and her colleagues, are sharing that excitement, as well as dedication to their chosen field, with each group of internal medicine students, residents and fellows.

Dr. Cannella described three major educational efforts in the division:
• The fellowship program with a 100 percent board pass rate;
• Education of the internal medicine residents;
• Medical student education (M2 and M3).

The division has two incoming fellows per year to complete a two-year fellowship at UNMC (with an option for a third year of research).

“These are very educationally oriented fellowships,” she said. “We have a lot of didactic teaching and a pretty intense curriculum that includes clinical rheumatology, musculoskeletal ultrasound and bone health.”

Fellows attend the American College of Rheumatology’s annual meeting, senior fellows go to the “state-of-the-art” meeting, and senior fellows also participate in a national ultrasound curriculum—a new initiative that is part of the changing world of rheumatological education.

“Ultrasound has been increasingly picked up by many specialties,” Dr. Cannella said. “It shows us what the tissues look like under the skin. We can see if there’s pathology, and it can direct treatment. We can diagnose, treat, and educate patients in real time at the clinic visit.”
Musculoskeletal ultrasound also provides physicians with better information about the conditions they are seeking to treat.

“It’s good for patients to understand the pathophysiology of the disease,” Cannella said.

“Rheumatologists are making decisions in real time about what’s going on in terms of the joint or the tissue. Patients love it.”

The rheumatology internal medicine resident training curriculum includes regular inpatient and outpatient teaching rounds, a distinct pre- and post-test evaluation, a computer-based x-ray and photographic case series and a didactic lecture series. Third year medical students may choose a rheumatology elective during their internal medicine clerkship, an opportunity not always available in other subspecialties.

“Residents and students also attend our didactic teaching sessions for the fellows,” Dr. Cannella said.

For the M2 musculoskeletal core, the division currently is redesigning the curriculum.

“We’re trying to flip the classroom,” she said. Efforts include a video game to teach about gout, live patients for medical students to interact with, more interactive, case-based activities and videotaped lectures students can watch on their own time.

“Students have changed, and have different learning needs and styles then when I was in the classroom,” Dr. Cannella said. “They don’t like to sit in lecture for hours—they want to do some things on their own and then come in and have the discussion.”

“Rethinking medical education can be hard for some of us because medicine honors tradition. Ultimately, we want to be sensitive to our learners’ needs, while instilling the same work ethic, humility and passion for medicine that was passed down to us.”
The reader

Alan Erickson, MD, serves as an “expert reader” of films for the Division of Rheumatology.

Dr. Erickson joined the UNMC Division of Rheumatology in 2007 as a clinical rheumatologist, which remains the focus of his work today.

Thanks to James O’Dell, MD, who recognized Dr. Erickson’s deep interest in radiography, and the late John Sharp, MD, who mentored Dr. Erickson in the techniques of reading and scoring x-rays. Today he has rapidly become recognized as an “expert reader,” an essential part of such research efforts as the Rheumatoid Arthritis Comparison of Active Therapies (RACAT) trial and other studies like it, examining the effects of rheumatoid arthritis (RA) treatments. Along with Dr. Tim Moore from the UNMC Department of Radiology, Dr. Erickson read and scored films from the RACAT study, results that were published in the New England Journal of Medicine in July of 2013.

In addition to reading films from the RACAT study and other national RA investigations, Dr. Erickson is reading films for the Veterans Affairs Rheumatoid Arthritis (VARA) registry, a large national cohort of U.S. veterans with RA.

“In a registry like the VARA registry, a lot of time we’re just looking at x-rays for one point in time,” Dr. Erickson said. “When we are trying to assess the severity of individual patients’ inflammatory arthritis, like RA, we want to know—Do they have evidence of joint damage? Do they have joint erosions and joint narrowing?”

As an expert reader of the radiographs, Dr. Erickson looks specifically for bony erosions and narrowing using a protocol that’s called the Modified Sharp Scoring Method—named after the physician mentor who taught the technique to Dr. Erickson.

“It’s a well-established radiographic assessment tool used in rheumatology to assess x-rays,” Dr. Erickson said. “I was fortunate enough to be taught the method by Dr. Sharp after he visited us at UNMC in 2007.”

Dr. Erickson spent several days working with Dr. Sharp to learn the basics. Dr. Sharp subsequently sent Dr. Erickson batches of x-rays to examine and score himself, so the two men could compare their notes and conclusions.

“Most importantly, it’s about consistency. When readers look at x-rays, not everybody sees an erosion, not everybody sees narrowing—there’s a degree of subjectivity to this.”

But consistency is paramount.

“Do you always call erosion erosion? Do you always call narrowing narrowing?” Dr. Erickson asked. “When I’m looking at an x-ray, and then I’m looking at an x-ray taken 24 weeks later, we want to see if there are changes in the radiographs. It’s important that a change in the radiographs over time reflects a true change over time, not a variability based on whether or not I had a good night’s sleep.”

More recently, Dr. Erickson has assisted in research efforts including a study examining the relationship between severe gingivitis and RA led by Ted Mikuls, MD, MSPH, at UNMC. As part of this study, the team found that the presence of periodontitis (a severe form of gum disease) was associated with more x-ray damage among RA patients, findings that were recently published in Arthritis & Rheumatology.

“I act as a resource for Dr. Mikuls, Dr. Michaud, and Dr. O’Dell in their research trials,” Dr. Erickson said. “I fulfill a function that is necessary so that these registries can function the way they need to function, and the research trials can do what they need to do.”

Dr. Erickson is proud to be assisting in the Division of Rheumatology’s cutting edge research.

“These are important trials that are definitely affecting how we look at and treat rheumatoid arthritis,” he said. “It’s exciting to be a part of that.”
Michelene Hearth-Holmes, MD, MEd from the Division of Rheumatology has made substantial strides in developing UNMC’s growing presence in research focused on systemic lupus erythematosus (SLE). She currently shares a close collaboration with Kaihong Su, PhD, Department of Pathology and Microbiology, on Dr. Su’s NIH-funded grant work examining novel biomarkers in SLE.

Dr. Hearth-Holmes’ role has been to act as the clinical conduit for this groundbreaking research, obtaining regulatory approvals, identifying a cohort of lupus patients from the UNMC Lupus Clinic that she directs, and tracking patients’ clinical data over the five-year study duration. Study participants are seen annually and when they have disease flares. Autoantibody tests are then administered by Dr. Su and her laboratory personnel to measure a novel biomarker she discovered called anti-NOD27 antibody. Circulating levels of this novel biomarker were found to be significantly elevated in patients with SLE compared to healthy control volunteers based on preliminary results from the study.

Dr. Hearth-Holmes said a very interesting aspect of the study, which occurred fortuitously, was a connection made with a clinician in the Dominican Republic, Dr. Esthela Loyo, at the Hospital Regional Universitario José Maria Cabral y Baez.

Dr. Loyo’s son, who was doing a sub-internship at Creighton University, heard Dr. Su give a talk there. After the lecture, he told Dr. Su that his mother had many patients with lupus in the Dominican Republic where she practiced, and that he would speak to her about Dr. Su’s research. Collaborations took off from there. It turned out that Dr. Loyo follows about 300 patients with lupus, all Hispanic.

Although there are lupus patients all over the world, Dr. Hearth-Holmes said she did not realize there were so many from a single clinic alone in the Dominican Republic. Because they are all Hispanic, unique from most U.S. disease cohorts, this opens the doors for exploring even more questions focused on ethnic differences in disease expression.

Consent forms and questionnaires have been translated into Spanish specifically for use in the Dominican Republic with patients enrolled in the UNMC-sponsored Rheumatology and Arthritis Investigational Network (RAIN) database. This database serves as a research resource to examine determinants of arthritis outcomes among patients with a variety of diagnoses. This will substantially expand the demographics of the RAIN database, which was developed almost 10 years ago and is now widely used among rheumatology researchers nationally and internationally. With extensions into the area of SLE and into the Dominican Republic and beyond, RAIN researchers continue to make progress in gaining important insights into arthritis and other autoimmune conditions.

Dr. Hearth-Holmes’ cross-continental work in support of SLE research is an important part of that progress. The collaboration with Dr. Loyo is just one example of how UNMC’s Division of Rheumatology is reaching across borders to research and battle lupus and other autoimmune diseases.
Lynell Klassen, MD, has spent a career grappling with one question: Why do people react to their own tissue?

“That’s a funny word—an immunological word—but what it really means is, why do people start reacting to their own tissues?” he says.

Sitting at a table in his office on the UNMC campus, he talks about his career: The early work at the National Institutes of Health, in what he calls “the dark ages” of the 1970s; the development of the Experimental Immunology Laboratory (EIL), currently being directed by his colleague, Geoffrey Thiele, PhD; and later, the studies of alcoholic liver disease he hoped would shed insight into environmental factors—specifically alcohol—and how they affect autoimmune responses.

“People ask me, ’What were you doing studying alcoholic liver disease as a rheumatologist who did bone marrow transplants?’” he says with a laugh. “There were opportunities at each institution I’ve been at, to use different model systems to look at this question—how do you lose self-tolerance or develop autoimmune disease?”

A rheumatologist, Dr. Klassen joined UNMC in 1982 and served as Vice Chair of Medicine and Chief of Rheumatology at UNMC, where he initiated the EIL, co-directed UNMC’s Bone Marrow Transplant Program and founded the HIV clinic. He served on the National Institutes of Health National Institute on Alcohol Abuse and Alcohol National Advisory Council. He also held key posts with the American College of Rheumatology and American College of Physicians (ACP).

Among his many awards, Dr. Klassen was inducted as a master of the ACP in 2011. In the 98-year history of the ACP, only a handful of other Nebraska physicians have received the master designation, which is given to physicians exhibiting preeminence in practice or medical research, holding positions of high honor or making significant contributions to medical science or the art of medicine.

Currently, Dr. Klassen serves as Internal Medicine Chairman at UNMC and sees rheumatology patients in clinic one to two days a week.

But he still has time to wrestle with the research subject that has fascinated him since the beginning of his career. The classic disease example of loss of self-tolerance, he says, is systemic lupus erythematosus—the body reacts against itself destroying its own organ tissues. The question is, why does this happen to some people and not others?

Over the years, Dr. Klassen and his colleagues have studied a variety of different models to answer that question—a lupus animal model; examination of graft vs. host disease (GVHD), a consequence of bone marrow transplant; and studying the environmental effect of alcohol in causing the loss of self-tolerance.

From 2000-2010, his work earned him an NIH MERIT (Method to Extend Research in Time) Award for innovative studies in the role of immune responses in alcohol-associated tissue damage. He is one of only three UNMC researchers to ever receive the prestigious MERIT Award.

He continues to grapple with the puzzle of self-tolerance.

“There are several exciting things happening now,” he says. “First, it appears that there are certain patterns of antibody responses to the cell proteins that clearly differentiate people at risk for heart attacks, and heart disease. It appears that there are other antibody profiles that predispose people, or predict people who are going to get rheumatoid arthritis.

“So why do you have this same reaction to a certain protein or piece of process; why does it look different in this disease process vs. that disease process?”

“There’s certainly a genetic base for that, and there’s certainly an environmental base for that,” he said. “So we’re trying to figure out where all of those things fit together.”

It’s a puzzle that’s lasted a professional lifetime—but Dr. Klassen is nowhere near ready to give up.
A superlative internist, Dr. Gerald Moore’s biggest impact may be his legacy of committed and talented students.

He’s an icon in rheumatology,” Dr. Cannella said. “He’s an icon in medical education. He’s given his entire life to education. He brings a lot of enthusiasm, he is very practical in his approach to patient care, and he’s a wonderful teacher.”

A native of Lincoln, Dr. Moore graduated from Nebraska Wesleyan University in 1967 before advancing to UNMC, where he earned his MD in 1971. He has received more than $1 million in grant and contract funding for studies on medical education, but his interest in education is not simply academic. A long string of awards for his exemplary teaching skills include the LeeRoy Meyer Dedicated Teacher Award, presented in 2012 by the American College of Physicians (Nebraska Chapter); several UNMC Internal Medicine Top Teacher Awards, the most recent in 2010; the 2008 Hirshmann Golden Apple Prize (pre-clinical), awarded by the UNMC College of Medicine Class of 2008, and a slew of others.

A current fourth-year medical student, Marshall Davis, says Dr. Moore is a superlative instructor. “He spends a lot of extra time individually with the students, especially in clinic,” Davis said. “We’d sit down and go through the case, and he’ll usually go through a few teaching points for each patient. Sometimes, when you work in groups, you don’t get that individualized attention – with Dr. Moore, that’s definitely there.”

Ted Mikuls, MD, MSPH, cites Dr. Moore—“a great rheumatologist with a foundation as a great internist”—as a major influence, not only on Dr. Mikuls, but on other senior faculty in the department, as well.

“As a student, there was never any ambiguity about expectations or feedback. As a student, if you don’t know where you stand with Dr. Moore, you probably need a hearing check,” Dr. Mikuls said. “What has set him apart from other instructors is his simultaneous respect for what many think of as ‘old school’ values in medicine—like the central role of the history and the art of the physical exam—and how he has been able to successfully blend this with new technologies and other innovative ways to communicate with students across the spectrum of medical school training.”

Small joint symmetrical synovitus means rheumatoid arthritis.”

“I can remember my lectures with him as a medical student,” said Amy Cannella, MD, MPH, now a colleague of Dr. Moore’s at UNMC. “Every time I see a patient with rheumatoid arthritis, I hear him in my head.”

From 1974, when he was the chief resident and an instructor at UNMC’s Department of Internal Medicine, to today, Dr. Moore has had an impact on medical education at UNMC. Today, Dr. Moore serves as the Senior Associate Dean for Academic Affairs for the College of Medicine and Professor in the Division of Rheumatology in the Department of Internal Medicine.

As Senior Associate Dean, he oversees the College of Medicine admissions process, educational program for students and residents as well as faculty development issues. He has been an administrator in the College of Medicine for over 20 years, but continues to see patients in both Rheumatology Clinic as well as patients on the general internal medicine inpatient service.
Ted Mikuls, MD, MSPH, is spearheading two efforts aimed at helping rheumatoid arthritis sufferers

Dr. Mikuls, Professor of Internal Medicine, is spearheading two efforts that could make a big difference for the millions of people suffering with rheumatoid arthritis (RA): an examination of a possible cause of RA and a patient registry that continues to offer valuable insights into RA risk factors and outcomes.

The question of whether periodontal disease could be a cause of RA is the focus of research being done by investigators in the Division of Rheumatology at UNMC.

Led by Dr. Mikuls in collaboration with VA hospitals in Omaha, Dallas, Salt Lake City, and Washington D.C., the research initiative has enrolled 617 arthritis patients to take part in the study.

Several studies have shown statistical correlations between severe gum disease and RA. While correlation does not equate to causation, UNMC researchers are looking more closely at the issue.

“We’re assessing the possible role of different bacteria that live under the gums,” Dr. Mikuls said. “Early research from our group and others suggests that at least one of these bacterial species causing gum disease may trigger the early immunity that characterizes rheumatoid arthritis.”

But research for its own sake is not the point, Dr. Mikuls emphasizes. It is only a step toward the real goal.

“Who cares if we can say there’s this relationship?” Dr. Mikuls said. “That does not get us anywhere. The ultimate goal is to develop an intervention to treat or even prevent rheumatoid arthritis in the first place.”

This may involve better management of the bacteria that is present in a person’s gums or more effective cleaning methods. While those in the periodontal community are already working to develop advances in this area, any evidence linking RA to periodontal disease (PD) might help direct these advances.

In addition to studying those who contract RA, the study also looks at family members of patients who develop antibodies for the disease but don’t yet have the disease. This is part of how the study seeks to understand the early role of PD in the development of autoimmunity that leads to RA.

One result the UNMC researchers hope to achieve is a set of recommendations that would allow people to take proactive steps many years before they become susceptible to RA, as well as insight that can be helpful to those who are involved in periodontal care.

To address the aims of the study, an international multidisciplinary research team was gathered with extensive expertise in the epidemiology and immunology of RA and periodontitis and includes Dr. Jeffrey Payne from the UNMC College of Dentistry. The team’s access to important and highly unique patient populations will allow for the first
The ultimate goal is to develop an intervention to treat or even prevent rheumatoid arthritis in the first place.

Ted Mikuls, MD, MSPH

comprehensive examination of the association of PD and related bacterial infections with RA.

Dr. Mikuls also heads Veteran Affairs Rheumatoid Arthritis registry (VARA), a large national VA cohort of patients with RA, among the largest such in North America.

The registry, created by Omaha VA and UNMC researchers, contains information about military veterans with RA. It may offer important insight into RA risk factors and outcomes in this highly unique patient population. More than 2 million Americans suffer from RA, and since females compose more than two-thirds of those with the disease, most research of the disease concerns females.

The veterans registry, VARA, stands to be an important source of information in the study of males with the disease, said Dr. Mikuls, who oversees the registry at the Omaha division of the VA Nebraska-Western Iowa Health Care System.

“While fewer men suffer from RA, that doesn’t discount the fact that men compose a significant portion of RA sufferers,” Dr. Mikuls said. “Because the veteran population is so overwhelmingly male, we are in a special position to gather information about men suffering from this disease.”

“Males account for almost 90 percent of the roughly 2,128 veterans with information in VARA—making it perhaps the nation’s top source of information about male RA sufferers,” Dr. Mikuls said.

Dr. Mikuls initiated VARA at the Omaha VA in 2003. The database contains clinical and biological information about the patients. VARA includes a large biorepository of DNA, serum, and patient plasma collected at the time of enrollment.

At first, information came just from local veterans with RA, but today VA medical centers in Birmingham, Brooklyn, Dallas, Denver, Iowa City, Jackson, Little Rock, Portland, Philadelphia, Salt Lake City and Washington, D.C., contribute information to the database.

In RA, the immune system promotes inflammation of the joints, leading to joint deformity and functional disability.

Scientists know little about what causes RA, but most believe both genetics and the environment play a role in the disease.

The VARA registry allows researchers to examine specific medical and biological information about several thousand male RA sufferers to see what genetic and environmental factors may have played a role in the patients’ disease.

Leading RA scientists from around the nation, including Dr. James O’Dell from UNMC, have collaborated in research endeavors capitalizing on data collected in VARA.

“The vast amount of detailed information available to the database really makes this a critically important research resource,” said Dr. O’Dell.
Kaleb Michaud, PhD, is helping use technology and databases to better serve RA patients.

Dr. Michaud isn’t afraid to think outside the box when it comes to using technology to better serve physicians and their patients.

He is working in collaboration with the American College of Rheumatology (ACR) on the Rheumatology Informatics System for Effectiveness (RISE) Registry, launched this year. The project’s long-term goal is to have all of the rheumatology clinics in the country enrolled and connected, providing a pool of electronic medical records available through the registry. UNMC Division of Rheumatology is one of the early adopters.

For academic centers, this can be tricky, Dr. Michaud said, because of the steps involved with institutional review boards, contracts and other considerations. “But in the end, the goal would be that any rheumatologist can quickly see how their patients or how their practice is doing compared to everybody else in the country,” he said. “So there’s that immediate feedback and quality improvement aspect.”

Dr. Michaud is an expert when it comes to databases. Since coming to the medical center in 2007, he has become involved with the Veteran Affairs Rheumatoid Arthritis registry (VARA), the RAIN Database as its Principal Investigator, and as co-founder of the Arthritis Internet Registry (AIR). He also spends much of his time working and collaborating with others as Co-director of the National Data Bank for Rheumatic Diseases (NDB), the world’s largest patient-reported research databank for rheumatic disorders, with more than 40,000 patients.

He is involved with many other projects and research at UNMC: he has a lead role in the Nebraska Arthritis Outcomes Research Center (NAORC), is a recipient of a new investigator award from the Arthritis Foundation to study the cost-effectiveness in total joint replacement in RA patients, received a NIH Challenge grant to investigate the cost-effectiveness of biological medications in RA treatment, and received an investigator award from the Rheumatology Research Foundation for assessing mortality in RA—but the RISE Registry has been an ongoing concern for Dr. Michaud. In fact, he was a member of the original subcommittees and task forces that helped create the first phase of the project, the Rheumatology Clinical Registry. The resource still exists, in fact, and is used to collect data on many patients, but it doesn’t have any direct tie-in with their electronic medical records.

The RISE Registry could be utilized to address research questions, quantify which treatments and drugs are working and how well, and determined what rheumatologists
are prescribing for certain conditions or sub-conditions—any number of uses.

“There’s a multitude of questions that can be asked,” Dr. Michaud said. “It has to start with actually having clinics connect.”

Dr. Michaud estimates that about 20 clinics will be connected in 2014, with adoption picking up quickly.

“You can easily see this ramping up to 100 clinics in two years, and up to 500 in three to five years,” he said.

With a multitude of measures for “quality” facing rheumatologists, from payers, national insurance, and the Centers for Medicare and Medicaid Services, the registry can help define what these measures should be.

“Payers and other organizations are constantly looking for new measures, especially measures that might be helping to cut their costs,” he said. “We need data to back up whether these measures are useful. No one wins when you have a rheumatologist who’s punished by an insurance company or a payer—because they see him as being too expensive or prescribing too many expensive treatments—but he actually has high-severity and more complicated patients compared to somebody else. The registry will provide data to back that up.”

With the registry, “we’re hoping to not have to measure things twice,” Dr. Michaud said. “Once it’s in the electronic medical record, you can just take it directly from there. That’s what RISE is all about.”

Yes, he admits, there is still work to do. But in the end, RISE will improve patient health, facilitate reporting requirements, and impact research that will advance rheumatology.

It’s a project on the RISE—and Dr. Michaud is one of the people who is helping lift it.
Dr. James O’Dell and the Rheumatology and Arthritis Investigational Network have led UNMC to an international profile in RA research.

As the leader of the Internal Medicine Residency Training Program for more than 30 years, Rheumatology Division Chief James O’Dell, MD, has directed the training of more than 600 UNMC residents – researchers and physicians who will shape treatment in internal medicine and care of arthritis patients for years to come.

But Dr. O’Dell’s impact doesn’t stop there. He also is considered a pioneer in rheumatoid arthritis (RA) research.

Under Dr. O’Dell’s leadership, clinician-scientists at UNMC have garnered an international reputation in the treatment and research of RA. Since 1989, faculty members have repeatedly been responsible for breakthroughs in RA treatment – most notably pioneering the use of “Triple Therapy,” or combinations of disease-modifying medications to treat RA. Triple Therapy became popular in 1996 when UNMC and researchers from the Rheumatology and Arthritis Investigational Network (RAIN), led by Dr. O’Dell, published a landmark study in the New England Journal of Medicine.

RAIN has been critical to better understanding RA treatment at the patient level. Directed by Dr. O’Dell since its inception more than 20 years ago, RAIN has become an internationally respected and productive investigator-initiated research network. The national consortium includes 40 rheumatologists in six states who participate in the design and enrollment of patients in clinical protocols. In addition, the first international site, in the Dominican Republic, began participating in RAIN in 2013.

RAIN was among the first to report correlations of treatment responses in RA with genes regulating the immune system. RAIN studies have also shown that a commonly used acne drug and antibiotic, minocycline, provided significant improvement for a subset of people with early RA.

Dr. O’Dell, who also served as President of the American College of Rheumatology in 2012, was the principal investigator for the Rheumatoid Arthritis Comparison of Active Therapies (RACAT) trial. Funded by the Veterans Administration (VA), this $18 million study involved 16 VA sites, eight sites in Canada and 12 sites in the RAIN group, which included the Omaha VA Medical Center and UNMC. For the first time, the RA 353-patient study combined a biorepository, and strong prospective economic data with a double-blind randomized clinical trial.

The cooperative blinded study found that the use of less-expensive combination disease-modifying anti-rheumatic drugs (DMARDs) produced the same clinical benefits as a much more-expensive biological treatment.

Results were published in the July 25, 2013 edition of the New England Journal of Medicine.

“Before the study, there was a general belief that biologics have significantly more potency, but this study has proven that not to be the case in this patient population,” said Dr. O’Dell. “This study shows when conventional therapy is used before biologics, there should be a significant cost-savings not only to patients, but to the health care system.”

Dr. O’Dell said that one of the main reasons for the study is that the cost of treating RA has increased significantly and is now more expensive per patient than diabetes, primarily because of the use of biologic therapies.

“We are looking for the safest and most effective medications,” Dr. O’Dell said. “The study shows that patients who start on the conventional combination therapy do just as well as people who start on a much more expensive therapy.”
Dr. O’Dell also co-authored one of the largest clinical studies ever done to prove RA patients can start on low cost monotherapy.

The study was part of the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial, which received great international interest. Of 755 patients in the 26-state study, 377 started on methotrexate alone and 28 percent did not need to be stepped up to another treatment. Other step-up treatments were a “combination” or “triple therapy” of methotrexate, sulfasalazine and hydroxychloroquine, or a biologic treatment of methotrexate plus etanercept. This was very significant because the cost of triple therapy is less than $1,000 compared to the etanercept therapy cost of over $20,000 per year. Further, the potential for rare but serious toxicity has been a concern with the biological products.

“...the use of of less-expensive combination disease-modifying anti-rheumatic drugs (DMARDs) produced the same clinical benefits as much more expensive biological treatment.”

James O’Dell, MD
A top-tier team player

Dr. Geoffrey Thiele’s cross-departmental collaborations link RA research with other disciplines.

Dr. Thiele knows the importance of sharing his lab for a greater good. A career research scientist in the VA system, he directs the Experimental Immunology Laboratories (EIL) at the Omaha VA and UNMC, which have been existence since 1982. There, he leads efforts to link rheumatoid arthritis (RA) research with other disciplines.

He currently helps to direct the efforts of two national VA bio-repositories, including the Veteran Affairs Rheumatoid Arthritis (VARA) registry and the more recently developed Crystal Registry (a large, multicenter gout cohort from the VA). When specific studies are initiated, the EIL also runs many of the assays to evaluate the immune parameters associated with RA, such as Western blot, ELISA, immunohistochemistry and nephelometry.

Over the years, Dr. Thiele has collaborated with numerous UNMC faculty, notably in four specific areas of research:

- To study alcoholic liver disease, with Lynell Klassen, MD, Chair of the UNMC Department of Internal Medicine and a division faculty member
- To evaluate the relationship between periodontal disease and RA with Ted Mikuls, MD, MSPH
- To investigate the latest outcomes in RA studies with James O’Dell, MD
- To study the effects of the immune system in atherosclerosis in relation to RA with UNMC cardiologist Dan Anderson, MD, PhD

Geoffrey Thiele, PhD

Recently, Dr. Thiele worked with a team of researchers – including cardiologist Dan Anderson, MD, PhD, on the discovery of a test that determines whether a patient has a lethal form of coronary artery disease by focusing on malondialdehyde-acetaldehyde (MAA), a molecule that appears to indicate the presence of coronary artery disease.

Dr. Thiele's work includes a growing number of cross-departmental collaborations. Currently, Drs. Thiele and Mikuls have been working with Dong Wang, PhD, in the UNMC College of Pharmacy, studying nanoparticles as a new way of delivering anti-inflammatory RA drugs at the site, rather than systemically.

Recently funded work with Kaihong Su, PhD, in the Department of Pathology and Microbiology, investigates the role of anti-neutrophil antibodies to initiated kidney damage in systemic lupus erythematosus (SLE) using a precision—cut kidney slice model as target tissue.

Additionally, studies with Laura Bilek, PhD, in the School of Allied Health Professions, have focused on the effects of exercise on the inflammatory markers in RA and resultant disease activity.

As a “seasoned scientist”, Dr. Thiele has played a key role in helping newer faculty and students in the division develop their interests in the rapidly expanding area of translational RA research.

“With the increased emphasis by the NIH and VA to perform research with higher clinical significance and translational potential, the studies performed by our group have generated the baseline data from which other investigators will be able to start,” said Dr. Thiele. “Because these samples have been well-characterized, an investigator can immediately perform studies asking more specific questions, allowing them to rapidly ask questions and get their answers.”

Dr. Thiele’s many collaborative efforts have paved the way for a number of new investigations and studies at UNMC. His impact, and his work at EIL, transcends a single discipline—and the Division of Rheumatology is pleased to have him as a partner.


Research Awards

Mike Duryee, M5, Research Coordinator, Division of Rheumatology, received the first Daughton Award for a non-faculty employee whose professional activities such as teaching, publications or scholarly research exceed what is normally expected of individuals in the position. The award was named for David Daughton, who had an exemplary career in the area of smoking cessation research and education in the Department.

Marshall Davis, M4 received a Student Research Award for his initiative and exemplary work on his research project. Davis’ work resulted in two national presentations.

Bryant England, a current second year internal medicine resident at UNMC, was recently awarded a prestigious Resident Research Preceptorship Award from the Rheumatology Research Foundation. The project, mentored by Dr. Ted Mikuls in the Division of Rheumatology, will examine the role of both traditional and novel risk factors in predicting cardiovascular mortality in patients with rheumatoid arthritis.

check out the Amazon bookstore to purchase a copy!
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