

The Arthritis Progress Report

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Russell/Engleman
Rheumatology Research Center

UCSF

Division of Rheumatology

Novel Technology Moves into Clinical Trials

One effective treatment for many autoimmune diseases?

A potentially revolutionary and universal approach to treating a broad spectrum of autoimmune diseases—including lupus, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, and many more—will be tested in a clinical trial by the UCSF Division of Rheumatology. The Russell/Engleman Rheumatology Research Center is helping to underwrite the cost, supplementing NIH funding for UCSF's Autoimmunity Center of Excellence.

The new technology—called autologous regulatory T-cell therapy—uses patients' own cells. It is based on a theory advanced by UCSF investigators that all autoimmune diseases might respond to a treatment that corrects their common underlying immunologic disorder. A strong and growing body of evidence supporting this theory has been developed by Division of Rheumatology scientists and others associated with UCSF's Autoimmunity Center of Excellence, directed by Dr. David Wofsy,

Professor of Rheumatology.

"Rigorous laboratory research over the past 10 years has tested this approach in a mouse model for lupus," says Dr. Wofsy, referring to investigations led by UCSF's Dr. David Daikh. "We have determined that regulatory T-cells can be removed from the body, stimulated to have stronger and better function, and safely re-infused to produce a positive effect."

An FDA-approved clinical trial with about 20 UCSF lupus patients is expected to start in early 2015. The goals are to test for safety and optimal dosage. The technology is now in a clinical trial for diabetes patients at UCSF.



Some of Dr. Maria Dall'Era's lupus patients will volunteer for the study starting next year.

If the phase 1 trials at UCSF and elsewhere go well, phase 2 trials—to test for efficacy among larger numbers of patients—should begin in 2016. The process of establishing effectiveness and safety typically takes 7-10 years before a new treatment is approved by the FDA and becomes widely available, says Dr. Wofsy. "If it works, it will be revolutionary."

Excellence & Breadth

In an era when NIH grant renewals are highly uncertain because of extreme budget reductions, the UCSF Division of Rheumatology stands out for having two major research initiatives renewed by the federal agency. These are the:

Autoimmunity Center of Excellence. This group's work is featured in the article above. The NIH recently renewed this grant for an unprecedented third five-year cycle with \$5 million. Of the nine original NIH-designated Autoimmunity Centers of Excellence, UCSF's is the only one to have been renewed for all three cycles.

Multidisciplinary Clinical Research Center. The purpose of the five-year, \$7 million renewal grant—one of eight in the

country—is to reduce health disparities in rheumatic diseases by race/ethnicity and socioeconomic status.

"Because these two grants fund a broad spectrum of research within the field of rheumatology—basic and clinical research, clinical trials, health outcomes studies and epidemiological investigations—their renewals are important evidence of our division's uniquely broad excellence," says Dr. David Wofsy, Associate Director of the Russell/Engleman Rheumatology Research Center.

UCSF Clinic Stands Out as National Model

“Treat-to-target” approach introduced for rheumatoid arthritis

What seems like a routine patient-doctor conversation is, in fact, a big step forward in rheumatology care. Fifteen minutes into his quarterly visit with UCSF’s Dr. Andrew Gross, Richard Rossi—a 60-year-old rheumatoid arthritis patient—asks, “What do you think we should do?”

Dr. Gross turns his computer screen toward Mr. Rossi, points to two numbers, and says, “Three months ago your disease activity score was 4.8, and today it’s 4.9. You’re still at a moderate level, which means you’re at higher risk of significant joint damage over time. Let’s talk about adjusting your medications to bring down your score to 3.2, which gets you into the low level.”

What makes this conversation unusual is Dr. Gross’s reference to his patient’s disease activity score. That’s a number on a scale of 0 to 9.3 that indicates the overall status of his rheumatoid arthritis (RA). Very few rheumatology clinics use such a score, although there is strong evidence of its value in improving patient outcomes.

The disease activity score enables rheumatologists, for the first time, to “treat to target.” That means the doctor and patient set a measurable goal, evaluate progress periodically, and adjust therapy accordingly. It’s common in almost all fields of medicine where laboratory results—such as cholesterol levels—are easily available. But until recently, this approach was not possible in treating RA because there was no meaningful, single number to target.

Treat-to-target is strongly advocated nationally by UCSF’s Dr. Jinoos Yazdany, who has a major platform through the American College of Rheumatology. A rheumatologist, Dr. Yazdany is an investigator in the UCSF Division of Rheumatology’s Health Outcomes Group. She says the treat-to-target approach will significantly improve the overall quality of care for rheumatology patients.

“The use of outcome measures in rheumatoid arthritis is very powerful,” says Dr. Yazdany. “Now patients can use data to track their progress, and doctors can share their data to see how their patients are doing compared to colleagues. This helps us create a learning health system where we continuously strive to improve.”

Dr. Yazdany and Dr. Gross, director of the UCSF Rheumatology Clinic on the Parnassus campus, collaborated to develop the disease activity score integrated last year into the clinic’s electronic medical records.

The score comes from a calculation based on data from various sources. Some comes from patients, who complete two forms when they arrive. They indicate how they think they are doing with their RA on a scale of 0 to 100, and they rate their



Dr. Andrew Gross says rheumatoid arthritis patient care and research is improving because all patients now get scores indicating the overall status of their disease.

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recent pain levels. They also answer a series of questions—such as, “Does your health now limit you in lifting or carrying groceries?”—on a scale of 1 to 5.

Data from the rheumatologist also go into the calculation. This includes the number of tender and/or swollen joints found during the patient exam, and an assessment of the patient’s disease status on a scale of 0 to 100. The results of blood tests for markers of inflammation, if available, are also considered.

By the time the conversation turns to next steps, the patient’s disease activity score shows up on the doctor’s computer. For Dr. Gross, “It’s a valuable clinical assessment tool because the score brings together a great deal of complex information into a single number. It’s objective, and it’s much more reliable than going back through my notes. Immediately I can see whether the patient is getting better or worse.

“And it’s a game changer as a research tool because it gives us objective, clinical data that’s easy to search for in our database. For example, this information is being analyzed for a UCSF study to determine if prescribing a biologic drug to RA patients whose joint disease is well controlled reduces their risk of heart disease. The results could save lives.”

Alumni Spotlight: Linda Bockenstedt

“The program allowed me to custom design my training to acquire the skills I wanted.”

Many of today’s leaders in the field of rheumatology—working in academic medicine, clinical practice and industry—spent two to four memorable years in the UCSF Rheumatology Fellowship Program. That’s where they trained in the subspecialty of rheumatology after receiving their medical degrees. That’s also where they acquired the skills to stay on the leading edge of their profession throughout their careers. The program is highly competitive, and only one applicant in 25 is accepted.

When she arrived at UCSF, 1989 alumna Dr. Linda Bockenstedt knew she wanted a career in academic medicine, blending research, patient care and teaching. That’s what she enjoys today as the Harold W. Jockers Professor of Medicine at Yale University.

Q: Is there one experience that stands out from your rheumatology fellowship?

Bockenstedt: I cared for a woman who was dying from complications of a lupus-scleroderma overlap syndrome. Helping her—knowing I didn’t have medicines that were going to make her better—was challenging. That experience reinforced the need to understand rheumatic diseases at the molecular level. The patient’s family and I bonded—I still see her husband (now in his 90s) and daughter when I visit San Francisco.

Q: What’s your research focus at Yale?

Bockenstedt: My laboratory studies focus on a tick-borne infection called Lyme disease that, in its late stages, causes an arthritis with features of rheumatoid

arthritis. We refer to it as “infectious in origin, rheumatic in expression” and hope that investigating it will give clues to factors that trigger autoimmune rheumatic diseases.

Q: What’s the most important skill you learned at UCSF?

Bockenstedt: Perhaps it was gaining the confidence to be autonomous and independent. By the time I returned to Yale, I felt comfortable treating a wide variety of rheumatic diseases and teaching fellows came naturally.

Q: What people stand out in your memory?

Bockenstedt: David Hellman and Michelle Petri—both outstanding clinicians—were my primary mentors in the clinical arena. Ken Sack and Ken Fye were taking on more active roles in the clinic toward the end of my time there. In research, I worked under the guidance of Art Weiss to learn cellular aspects of human immunology, and the scientific training was very rigorous.



Dr. Linda Bockenstedt

Q: What else about your fellowship stands out?

Bockenstedt: The learning experience was quite broad. The spectrum of diseases encountered was impressive. We were taught by both community and academic rheumatologists, orthopedists and allied health professionals, learning different perspectives. I was fortunate to obtain training in pediatric rheumatology, which even today is not offered by many programs. Overall, there was a good group of people to discuss the different aspects of patient care.

In research, I also learned the importance of having strong mentors during one’s career, which probably influenced my becoming the director of faculty development here at the Yale School of Medicine.

Focus on Rare Diseases *Continued from back page*

finding alternative therapies.

The long-term outcomes, so far, are very promising. “We see many patients 14 years out who don’t look like they have AS,” says Dr. Lianne Gensler, who heads up the investigations. “We also know that patients who exercise regularly have much

better functional outcomes than people who don’t.”

Dr. Gensler is conducting a clinical trial of apremilast as an alternative to TNF inhibitors. “This is a potentially important advance because it could broaden our options for treating AS, providing alternatives to NSAIDs and TNF inhibitors.”

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Focus on Rare Diseases

Studies on spondylitis and vasculitis

The Russell/Engleman Rheumatology Research Center supports investigations on an extremely broad range of diseases that destroy joints, bones, muscles, cartilage and other connective tissues, hampering physical movement. This occasional column will feature studies by UCSF Division of Rheumatology scientists on diseases that are relatively unknown to the general public or afflict small numbers of patients.

Vasculitis: Rare and life-threatening

Vasculitis refers to a family of autoimmune diseases that involves inflammatory destruction of arteries, veins and capillaries. Dr. Sharon Chung, director of the UCSF Vasculitis Clinic, is one of only a handful of physicians in the West with expertise in diagnosing and treating the disease. Diagnosis is often delayed until a life-threatening medical problem, such as kidney failure, occurs.

“Vasculitis used to be universally fatal,” says Dr. Chung. “Research over the past 30 years has found medications to treat patients and keep them alive. Now we’re trying to understand the causes, identify less toxic treatments, and find better diagnostic tools.”

Dr. Chung is utilizing genomics—the scientific study of large sections of genetic material—in an investigation of the type of vasculitis that primarily affects the lungs and kidneys. She has conducted state-of-the-art studies using next-generation sequencing on about 75 patients. She expects the results will enable her to identify rare genetic mutations associated with vasculitis and help determine the biologic pathways that are important in the disease.

“With this knowledge, we can develop drugs targeting these pathways that don’t have the serious side effects of current therapies,” she says.



Courtney Streig's chronic AS pain required her to give up her career as a geologist and move home with her parents. She has not responded to two TNF inhibitors, and Dr. Lianne Gensler may prescribe a third one.

In the future, Dr. Chung hopes her studies will also lead to genetic tests for widespread use in diagnosing vasculitis. “With genetic tests, patients may be diagnosed and treated more quickly, which would lead to better disease outcomes.”

Ankylosing spondylitis: encouraging news

Ankylosing spondylitis (AS) is an arthritis of the spine that usually starts when the patient is 20-40 years old. It is a potentially debilitating disease that can result in the patient being severely hunched over. Unlike most autoimmune rheumatologic diseases, AS is 2 to 3 times more common in men.

Fourteen years ago, UCSF made a major breakthrough in discovering that TNF inhibitors—a relatively new class of biologic drugs at the time—often had a dramatic impact on the pain and inflammation of AS. This was the first biologic treatment for the disease and is still the only effective therapy beyond non-steroidal anti-inflammatory drugs (NSAIDs).

Research on AS at UCSF today focuses on assessing the long-term health status of patients taking TNF inhibitors and