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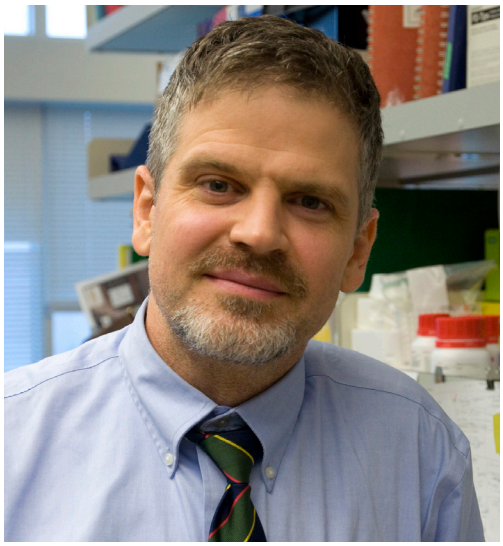
Breakthroughs could apply to other autoimmune diseases

Stopping Rheumatoid Arthritis Before the Pain Starts

By Todd Neff

In an era of cholesterol testing, 3-D cardiac imaging and drug-eluting stents, it's easy to forget that the first sign of heart disease used to be a heart attack.



Kevin Deane, MD, is working not only to diagnose rheumatoid arthritis before it develops, but also to prevent it entirely.

Today, the first sign of rheumatoid arthritis is still often an attack of joint pain.

Rheumatologist Kevin Deane, MD, and colleagues in the University of Colorado School of Medicine's Division of Rheumatology are working to change that. Deane and collaborators are at the vanguard of an international effort to identify the biomarkers and other signatures of rheumatoid arthritis (RA) and quell the disease years before it destroys joints and shortens lives.

They hope the insights they are gaining – among them, that RA's initial trigger may happen in the lungs – can ultimately help curtail or prevent not only RA, but other autoimmune diseases, such as type 1 diabetes and lupus.

The benefits could be significant from both a clinical and financial perspective. Rheumatoid arthritis affects roughly 1 percent of the U.S. adult population, with direct and indirect costs amounting to nearly $40 billion a year in this country alone.

Deane is focusing on detecting and understanding the roots of what's known as "preclinical" RA. That's the term for individuals with abnormalities of biomarkers and other signatures of RA-like autoimmunity in the bloodstream but still none of the joint pain, stiffness and swelling associated with full-blown RA.

Roots. Deane's work in RA builds on efforts in other conditions, including type 1 diabetes, to understand the earliest steps in the development of autoimmune disease. At the University of Colorado, such work in diabetes has been led by Marian Rewers, MD, PhD, now the Barbara Davis Center for Diabetes's interim director; and Jill Norris, MPH, PhD, who now chairs the Colorado School of Public Health's Department of Epidemiology.

A decade into that effort, Norris and Michael Holers, MD, chief of the CU School of Medicine's Rheumatology Division, recognized that the model for type 1 diabetes, where abnormalities of biomarkers precede the first elevations of blood sugar, might work for RA, too. They created a research umbrella to study the natural history of RA, called "Studies of the Etiology of Rheumatoid Arthritis," or SERA. Deane, who was a rheumatology fellow at the time the work began, is now helping to move the SERA project in the direction of disease prevention.

His motivation is straightforward.

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"Most doctors now, and most people in general, want to prevent disease before it happens," he said. "Or, at the very least, find those with disease at such an early stage that significant injury to the body has not yet occurred."

In the case of preventing RA, there have been serious hurdles. First, researchers have to find people harboring the seeds of RA but who are without symptoms. Given the disease's relative rarity, Deane likened a blind search for preclinical RA patients to one that seeks drivers who will be in a car accident.

But there are ways to increase the odds of finding those who are at high-risk for future RA. Members of certain Native American groups have a roughly 8 percent prevalence of RA, for example. Those with close relatives who had or have RA have a 5 percent to 7 percent risk of having the disease.

Still, given the small percentage of at-risk individuals, finding them is a task that demands mass screening. The SERA project has addressed this by testing about 2,000 people who have a relative with RA; also, some 9,000 people have been tested through a unique collaboration between CU, the 9HealthFair and the Arthritis Foundation.

Testing, testing. Deane and colleagues also test those who may be at risk for future RA because of dozens of environmental factors, genes and proteins linked with RA development. Importantly, the science has moved forward to the point that blood tests can predict with about 80 percent certainty whether a patient with a certain set of biomarkers will develop RA, Deane said.

But even in samples full of red flags, it's still hard to draw firm conclusions. For example, researchers know that RA is caused by some combination of genetic and environmental factors. Smoking boosts risk, but most smokers escape RA. Most people with genes linked to RA – 20 percent to 30 percent of the population have them – never end up with the disease. Also, even if someone who is at high-risk for future RA can be identified, determining the timing at which they develop disease remains elusive. The disease could come next year, in five years, in a decade or further yet into the future, Deane said.

"Because of these issues, we're trying to refine the model," Deane said, "although, based on what we know now, it is very reasonable to start trying to prevent RA and at the same time learn more about how the disease develops."

A bit of work. To help do that, Deane has applied for a National Institutes of Health grant for a multi-center clinical trial to prevent RA. It would involve screening 15,000 people with the aim of finding 200 with a high risk of RA, then treating them in a randomized, placebo-controlled fashion with a drug proven to slow the disease's advance in the hopes of halting the progression to symptomatic RA altogether.

In addition, closely following these subjects' biomarker profiles while tracking their disease progression (or lack thereof) could provide insights into who gets RA, who doesn't, and what biomarkers in what genetic contexts are most telling, Deane explained. The trial, under review this month, could start as soon as early 2014.

These are largely unexplored areas. But prevention trials in RA are already underway elsewhere. Specifically, a Dutch study launched in 2009 has been infusing 90 preclinical RA patients with a powerful drug or a placebo, the hypothesis being that a single infusion of the drug can slow or stop the development of the disease. Its results will probably change people's fundamental perceptions of RA as being something "we only treat once you get a swollen joint," Deane said.

Deep breath. While Deane and other SERA colleague believe that we know enough about RA to start a prevention trial now, Deane's ultimate goal is to work backwards to the root causes of the disease, which could yield a better understanding of even more effective approaches to prevention.

That will, as Dean put it, just take "a bit of work." In particular, Deane, Holers, Kristen Demoruelle, MD, and others at CU have done pioneering work in identifying the lungs as the potential spark for the immune response that flares into rheumatoid arthritis. That research involved the creation of a $30 test using saltwater to harvest secretions from the depths of a patient's lungs. Developing this technique alone took 18 months.

"SERA investigators are inventing the tools as well as the ideas," Holers said.

It's another sign that research in RA has reached a crucial point, he said. There are new biomarkers, there's an increased interest in prevention, and there's a consensus that earlier treatment – even, perhaps, before the arthritis flares up – is better treatment. What's more, he added, the lessons of RA can probably be applied broadly

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to the 100 or more autoimmune diseases that in total affect some 8 percent of the population.

"They all appear to follow this process of biomarkers showing up years prior to any clinical disease," Holers said. "This finding provides a conceptual framework for screening all of these diseases in aggregate using array techniques, and then tailoring follow-up and prevention to the biomarkers you see."