

RHEUMATOLOGY



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Getting to the heart of the problem

Our body's blood vessels are a million tiny rivers, flowing fast with the oxygen-giving, energy-bringing and disease-fighting components that make it possible for us to live.

But for people with certain diseases that affect the joints and connective tissues, those rivers often get jammed up, stiffened, or even completely blocked. The result: a far higher level of cardiovascular disease among people with lupus, rheumatoid arthritis, and other rheumatic diseases.

What's even worse, this increased risk of heart attacks, high blood pressure, strokes, and other cardiovascular crises occurs far earlier in life among people with rheumatic diseases than among the general population.

For instance, young women with lupus might have a risk of atherosclerosis (hardened arteries) that's 50 times greater than healthy women their age—and as a result, might suffer heart attacks in their 40s. And one in seven people with scleroderma may develop pulmonary hypertension—a potentially fatal form of high blood pressure in the vessels that connect the heart and the lungs.

In both cases, the link between cardiovascular and rheumatic disease can be deadly.

Why do these two seemingly unrelated conditions go hand in hand? Scientists are hard at work to find out, and some of the leaders in the field internationally are part of the U-M Rheumatology division. At the same time, today's rheumatic disease patients need help right away, to reduce their risk of cardiovascular disease or to manage the two conditions simultaneously.

In 2007, Michigan rheumatologists and their research teams made several major advances in the quest to understand the links between blood vessels and connective tissue disorders. New clinical trials, laboratory findings, and other achievements built up the advancements of previous years.

Inflammation and lupus

For several years, a team led by **Mariana Kaplan, MD**, and **W. Joseph McCune, MD** (*below*), has been probing the blood vessels of patients with Systemic Lupus Erythematosus (SLE)—the disease commonly known as lupus. For two million Americans, lupus arises when the body's own immune defenses begin attacking the skin, joints, organs, and other body parts. Most of these patients are women, and most are under age 45 when they're diagnosed. And most of them will die prematurely because of the disease.



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In previous research, Kaplan, McCune, and their colleagues had found another pattern of premature death: The death of the cells, that line blood vessels, called endothelial cells or ECs. Having found that these cells appear to “commit suicide” through a process called apoptosis far more often in lupus patients than in healthy people, the team set out to find the reason why.

In a paper published in the journal *Blood* in 2007, they reported their answer. The bottom line: People with lupus were much more likely to have lower levels and abnormal versions of two types of cells that are crucial to repairing damage to blood vessel walls. Even more telling, the researchers were able to draw a link between these abnormalities and an inflammatory molecule called interferon-alpha.

The team made the discovery through a detailed molecular analysis of blood samples taken from 135 U-M lupus patients who did not yet have signs of atherosclerosis, and a group of 66 comparable people without lupus. The study was funded by grants from the Alliance for Lupus Research, the Lupus Research Institute, the Anthony S. Gramer Fund in Inflammation Research, the National Institutes of Health, the Carol and Herb Amster Lupus Research Fund, and the Klein Lupus Research Fund.

The team looked at both endothelial progenitor cells (EPCs), the type of cells that give rise to the ECs that line blood vessels, and another kind of cell, called circulating angiogenic cells or CACs. Both types of cells are crucial to the body’s ability to repair damaged blood vessels, or just to replace aging cells as they wear out.

The lupus patients had less than half the number of EPCs per unit of blood than the non-lupus patients—and the deficit was present no matter how severe a patient’s lupus was. And, when the EPCs and CACs were exposed to conditions that should have prompted them to settle down and form a layer of interconnected cells—just like they would do in a blood vessel—the cells taken from lupus patients were far less likely to do so.

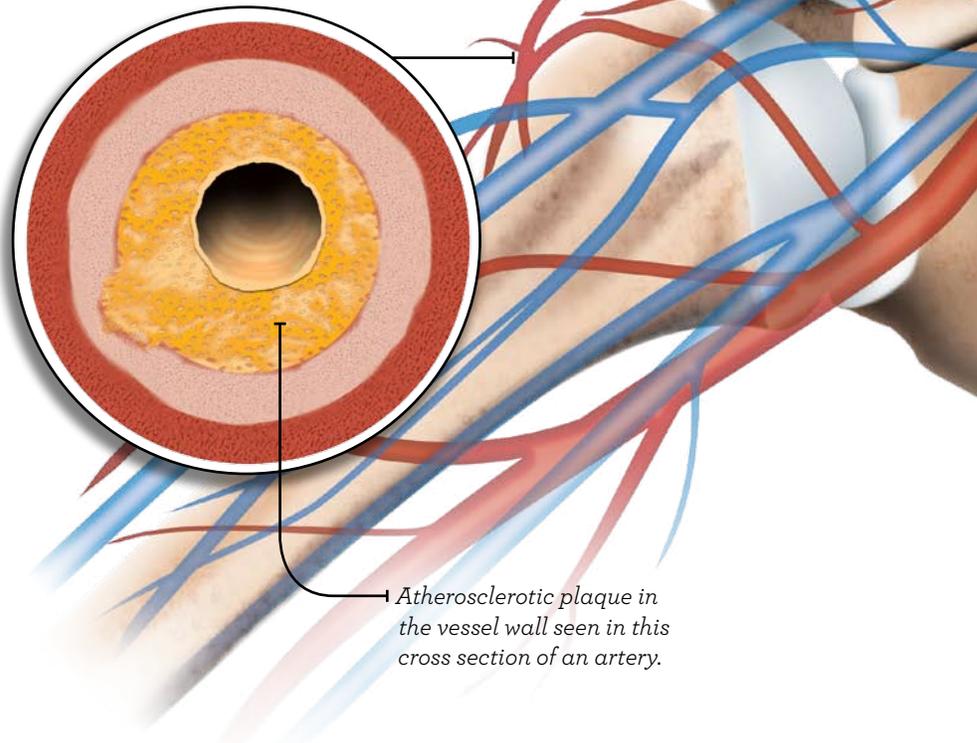
To probe this issue further, the researchers performed molecular analyses that zeroed-in on interferon-alpha, a molecule involved in both the inflammation and blocking of the formation of new blood vessels. Interferon-alpha is a target of cancer-fighting drugs because of its potential to keep tumors from sprouting new capillaries, which can feed the growth of the cancerous tissue. It’s also suspected of being involved in the self-attacking process launched by the immune system of a person with lupus.

And indeed, the U-M team was able to show—for the very first time—that interferon-alpha triggered the apoptotic death of endothelial progenitor cells, leading to abnormal vascular-lining repair. They confirmed this finding by demonstrating that lupus patients’ vascular cells functioned normally when given a molecule that blocks interferon-alpha.

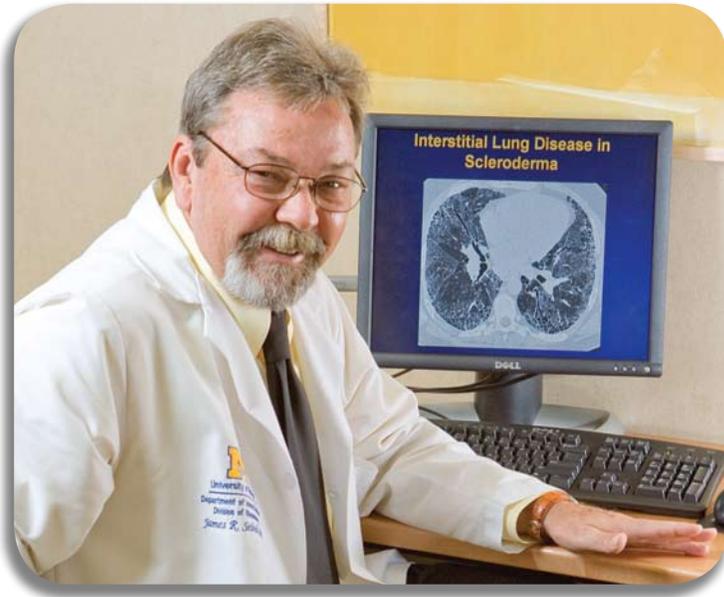
In the months since making these discoveries, the team has been exploring whether interferon-alpha might play a similar role in other rheumatic diseases where premature cardiovascular disease is known to occur. They are also trying to further understand the molecular mechanisms by which interferon-alpha causes abnormal vascular repair and atherosclerosis, both in human and animal models of lupus.

Dr. Kaplan has also launched a randomized, placebo-controlled, double-blind trial in people with rheumatoid arthritis to test the effect of a diabetes drug called pioglitazone. This drug, one of a class of compounds called PPAR-agonists, helps down-regulate the production of inflammatory molecules.

Among other things, the new study is looking to see if it improves the function of blood vessel lining cells and the flexibility of blood vessel walls. This might represent the first step to assess if pioglitazone could be effective in the prevention of premature vascular damage in autoimmunity. This drug may also represent an important therapeutic intervention in lupus, and Dr. Kaplan is performing pre-clinical lupus studies with it.



Atherosclerotic plaque in the vessel wall seen in this cross section of an artery.



Scleroderma and pulmonary hypertension

Even as their U-M colleagues explore the cardiovascular connection in lupus and rheumatoid arthritis, a team led by **James R. Seibold, MD** (*left*), is examining the role of blood vessel injury in scleroderma—a chronic scarring disease of young women and the most fatal of the rheumatologic disorders.

Progressive scarring of blood vessels occurs throughout the body of patients with scleroderma. All patients have Raynaud's phenomenon, which affects blood flow in the fingers and toes, and around 50 percent of patients each year develop an ulcer of the fingertips. Blood vessel involvement in the kidneys, heart, and lungs are the dominant influences on a scleroderma patient's survival.

The University of Michigan Scleroderma Program works closely with faculty of the Cardiovascular Medicine Division to manage scleroderma patients who have high blood pressure in their lungs, and to develop and test new clinical strategies to diagnose and treat such patients. In fact, U-M is a destination for patients with all forms of pulmonary hypertension, whether related to scleroderma, other connective-tissue disorders, or with no known cause.

In 2007, the team launched a pilot clinical trial to test an inhaled drug called iloprost in adults with pulmonary hypertension and scleroderma-related lung disease. They also worked with collaborators at U-M and Georgetown University to establish a database of scleroderma patients who have pulmonary hypertension, or who are at risk of developing it, and who will allow the researchers to study their skin and blood. Also this year, Drs. Seibold and **Vallerie McLaughlin, MD**, of Cardiology were co-authors on another study that showed that a drug called Sitaxsentan could be effective in patients who had PH and a connective tissue disorder. Other research includes detailed studies of the biology of defective blood vessel growth and repair in the skin of scleroderma patients in collaboration with **Alisa Koch, MD** (*left*), of Rheumatology. Newer research initiatives include leadership of a large study focused on improved techniques of early diagnosis and novel therapies for vascular injury.

In the end, a combination of treatment trials and basic research will help elucidate the best course of action to prevent and treat cardiovascular disease in people with rheumatic disorders.