

# The Right Frame

*Sometimes you have to tear down an old idea to find a new solution.*



*Harry Dietz went back to the drawing board to rethink the cause of Marfan syndrome—and now he has a treatment in clinical trials.*

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HARRY DIETZ

Elena Dorfman

FIFTEEN YEARS AGO, HARRY C. DIETZ AND HIS RESEARCH GROUP MADE A BIG

*discovery: mutations in the fibrillin-1 gene cause Marfan syndrome, a genetic disease that weakens connective tissues in the body, including the structural meshwork of blood vessels, and can lead to sudden death if undiagnosed. ¶ The celebration, however, was short-lived. “Things began to look problematic almost immediately,” recalls Dietz, an HHMI investigator at the Johns Hopkins University School of Medicine. “Because fibrillin-1 is a structural*

protein—and very important during development—there was a suggestion that people with Marfan syndrome are born without a proper quotient or quality of elastic fibers.” Yet he knew that figuring out a way to compensate for the missing elastic fibers—particularly during early development—was a challenge that molecular medicine was not ready to handle.

“The possibility of finding a productive treatment strategy was analogous to repairing a house with a rotten frame,” he says. “There is no way you could imagine addressing the situation without tearing the house down and starting over.”

As researchers considered their options during what Dietz calls “those dark days,” one question in particular gnawed at Dietz: How could a disease with such complex characteristics—overgrowth of bones, thickened mitral valves, aortic aneurysm, craniofacial deformities, lung problems—be explained by structural deficiency alone? “It just didn’t add up,” he recalls.

To build a new intellectual framework, scientists in Dietz’s lab turned to a mouse model of Marfan syndrome they had developed by genetically engineering a mutation in the *fibrillin-1* gene. They knew that people with Marfan syndrome often develop problems that resemble emphysema—with widening of the air spaces that can lead to rupture of the lungs—so they first focused on any lung abnormalities they saw in the mutant mice.

They did not expect to find lung problems in the young mice because they believed this kind of destructive emphysema occurs later in life—the cumulative result of stresses over time. “We thought that only over the course of months to years would we begin to see structural damage to the lung,” Dietz recalls.

“Instead, we saw a diffuse widening of the air spaces in the absence of any evidence of tissue damage or inflammation in the lung right from the day of birth.”

That observation led to a radical change in Dietz’s thinking. He began to suspect that many features of Marfan syndrome—for example, the fragile aorta that eventually ruptures—might not be caused by a simple weakness of the tissues imposed by deficiency of a structural protein. Instead, he started looking for abnormal patterns in a developmental program. In research spanning several years, Dietz and his colleagues proved time and again—in studies of the lungs, aorta, and mitral valve—that the culprit was excessive levels of a critical developmental signaling molecule called transforming growth factor beta (TGF-beta) that is normally regulated by fibrillin-1.

The next step was to see if they could prevent features of Marfan syndrome by blocking such signaling abnormalities, which led them to losartan, a blood pressure medication that other researchers had found to be active against TGF-beta in studies of chronic renal disease.

Dietz and his colleagues at Hopkins set up a study in mice to compare losartan, propranolol (a blood pressure agent that is used prophylactically in Marfan patients to prevent tears in the aorta), and a placebo. The study, published in the April 7, 2006, issue of *Science*, revealed that the mice that received losartan showed no progression of aneurysm formation and even an apparent reversal of aortic pathology.

“Those mice had normal aortic root growth, normal aortic root size, and normal aortic wall thickness and architecture,” says Dietz. “Essentially, losartan-treated Marfan mice could not be distinguished from normal mice.” Losartan improved other manifestations of Marfan syndrome in the mice, as well, including abnormal lung development.

Dietz is optimistic that additional research will show that losartan might actually remodel the abnormal architecture of the aortic wall. It is also possible, he adds, that lessons learned from these studies could be applied to other causes of aortic aneurysm. Dietz and his collaborators have recently shown that two other aortic aneurysm syndromes, Loeys-Dietz syndrome and arterial tortuosity syndrome, are also caused by altered TGF-beta signaling. “Aortic aneurysm is a major public health burden,” says Dietz. “About one to two percent of the population in industrialized countries dies from it. We are now targeting the more common forms of aneurysm for study.” ■

—JIM KEELEY

### Children’s Study Begins

Encouraged by Dietz’s work, the National Institutes of Health (NIH) is launching a multicenter clinical trial to assess whether losartan might be used to prevent aortic aneurysm in children with Marfan syndrome. The trial will be coordinated by the Pediatric Heart Network, established in 2001 to improve outcomes and quality of life in children with heart disease. Recruitment of patients may begin by the end of summer 2006.

“This is the first therapy for Marfan syndrome that was born of a systematic effort to elucidate the pathogenesis of the disease,” says Dietz. “It is a rare example of things living up to the promise expressed at the launch of the Human Genome Project: If we can identify the genes responsible for a disease, then we will uncover unanticipated mechanisms behind the disease and be in a better position to design rational therapeutic strategies.”

Information about the clinical trial is available from the National Marfan Foundation at [www.marfan.org](http://www.marfan.org) or (800) 8-MARFAN.