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Blood Pressure Medication May Revolutionize Treatment of Marfan Syndrome

A commonly prescribed blood pressure medication may provide the first ray of hope in preventing potentially deadly complications of Marfan syndrome, a genetic disease that weakens the structural meshwork of blood vessels. People who have Marfan syndrome have a high risk of developing aortic aneurysm, which can lead to rupture of the heart's largest artery, causing sudden death.

In studies published in the April 7, 2006, issue of the journal *Science*, Howard Hughes Medical Institute researchers at Johns Hopkins University School of Medicine have shown in mice that the drug losartan, which is manufactured by Merck and sold under the brand name Cozaar, can prevent progression of Marfan syndrome and may also restore normal architecture to the wall of the aorta.

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— **Harry C. Dietz**

Marfan syndrome is a connective tissue disorder that affects about one in 5,000 individuals. Manifestations include long bone overgrowth, lens dislocation, emphysema, thickening and dysfunction of the heart's mitral valve, and aortic aneurysm with a predisposition for early vascular rupture and sudden death.

Losartan attenuates development of aortic aneurysm by lowering the activity of a pervasive developmental molecule called transforming growth factor beta. In a sea change in thinking about the origins of the disease, researchers have recently discovered that transforming growth factor beta — not simply a defect in a structural protein — is most likely responsible for the syndrome's catastrophic developmental defects.

This is the first therapy for Marfan syndrome that was borne of a systematic effort to elucidate the pathogenesis of the disease, said the senior author of the study, Harry C. Dietz, a Howard Hughes Medical Institute investigator at Johns Hopkins. I think that this is a rare example where things lived up to the promise that was expressed upon launching 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.

On the basis of data presented in the study published in *Science* and presentations that Dietz has made to scientists at the National Institutes of Health (NIH), the NIH is planning to launch a multicenter clinical trial to assess whether losartan might be used to prevent aortic aneurysm in children with Marfan syndrome. The clinical trial will be coordinated by the Pediatric Heart Network, which was established by the National Heart, Lung, and Blood Institute in 2001 to improve outcomes and quality of life in children who acquire or are born with heart disease. Recruitment of patients may begin by the end of summer 2006, Dietz said.

Although the clinical trials will ultimately decide the safety and efficacy of losartan treatment for patients with Marfan syndrome, Dietz said the drug's long track record as an anti-hypertensive gives him reason for optimism. This drug has an exceptional tolerance profile. It's one of the 'go-to' drugs when people do not tolerate other anti-hypertensive medications. And it has received Food and Drug Administration approval for use in children, he said.

In 1991, Dietz and his colleagues made a significant breakthrough when they showed that mutations in the *fibrillin-1* gene cause Marfan syndrome. Fibrillin-1 is a protein that is required during development to make elastic fibers in a range of tissues throughout the body. But the cause for celebration was relatively short lived, as researchers soon realized that therapy for a systemic connective tissue disorder, such as Marfan syndrome, would be a difficult challenge indeed.

After that discovery, Dietz recalled, things began to look very pessimistic almost immediately. Since fibrillin-1 was 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. So this really suggested that at birth, someone with Marfan syndrome already has an obligate predisposition for tissue failure later in life. To put it another way, people with Marfan never made enough of the elastic fibers that they could only make during embryogenesis.

In the early 1990s, researchers such as Dietz knew that figuring out a way to compensate for the lack of elastic fibers - particularly during early development - was a challenge that molecular medicine was not yet ready to handle. It suggested to us that the possibility of finding a productive treatment strategy was very remote, said Dietz. It's analogous to having a house with a rotten frame. There is no way you could imagine addressing the situation without tearing the house down and starting over.

As researchers in the Marfan's field considered their options during what Dietz calls those dark days, some, including Dietz himself, began to call into question the structural integrity of their understanding of the syndrome. One question in particular gnawed at Dietz: How could a disease with such a complicated phenotype - overgrowth of bones, thickened mitral valves, craniofacial deformities, lung abnormalities - only be explained by structural deficiency? It just didn't add up, he said.

In the course of their work, Dietz's lab developed a mouse model of Marfan syndrome by genetically engineering a mouse with a mutation in the fibrillin-1 gene. Genetically engineered mice are a standard way of probing the developmental function of the genes that have been altered. To help in puzzling through some of the questions that had arisen in Dietz's mind, the scientists first focused on the abnormal lung tissue in the mutant mice.

They knew that people with Marfan syndrome could develop problems that resemble destructive emphysema - which involves widening of the air spaces and can lead to rupture of the lungs. When they examined the lungs of their mice, they expected to see evidence of destruction and inflammation in the lung tissue, said Dietz. They did not think they would see emphysema-like problems in their mice early in development because the prevailing notion was that the structural changes in the tissues of Marfan syndrome patients were the cumulative result of stresses over time. In the aorta, for example, those stresses would gradually wear down the weakened vessel until a catastrophic rupture occurred. We thought that over the course of months to years we would begin to see structural damage to the lung. Instead, we saw a diffuse widening of the air spaces in the lung right from the first day of birth without any evidence of tissue destruction or inflammation.

That observation led Dietz's group to a radical change in their thinking about the nature of Marfan syndrome. Instead of the disease being caused by loss of a structural protein that then places a burden on tissues that can be further weakened by stresses, such as blood pressure, over time, they reasoned that perhaps a more ubiquitous developmental signal is missing from birth. In their fibrillin-1-deficient mice, for example, they found that loss of that critical signal is what caused the lungs to develop improperly. Without that signal, the alveoli — small air sacs in the lungs — do not form normally, leading to widening of the air spaces in the lungs.

In several years' worth of work, the researchers proved that time and again the critical developmental culprit was transforming growth factor beta. All of the defects that were observed in the mouse model of Marfan syndrome could be attributed to an increase in transforming growth factor beta signaling in a variety of tissues, including the lungs, aorta and mitral valve.

The next logical step was to see if they could prevent the excessive signaling of transforming growth factor beta. Since aortic aneurysm is the only Marfan syndrome phenotype associated with significant mortality, the researchers chose to focus on that problem first. They were looking for a safe drug that could attenuate the formation of aortic aneurysm in the mice by dialing down

the amount of transforming growth factor beta activity in the blood vessels.

Their search turned up losartan, a blood pressure medication that other researchers found to have activity against transforming growth factor beta in studies of chronic renal disease. Since losartan both lowered blood pressure and antagonized the activity of transforming growth factor beta, the researchers thought it might have a double benefit in Marfan patients.

Dietz and his colleagues at Hopkins proceeded to set up a clinical trial on mice to compare losartan, propranolol — a blood pressure agent that is the existing standard of care for Marfan patients — and a placebo. The three groups of mice were followed prospectively and all analyses were done blinded to genotype and treatment.

The studies showed 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, said Dietz. Coming out of the study, pathologists who were blinded to the genotype and treatment arm of the mice could not distinguish losartan-treated Marfan mice from normal mice.

Dietz is optimistic - although more work remains to be done - that losartan might actually remodel the abnormal architecture of the aortic wall. It is also possible that lessons learned from these molecular studies of Marfan syndrome could be applied to other syndromic and non-syndromic cases of aortic aneurysm. For example, Dietz said, might an increase in transforming growth factor beta be involved there as well? The answer, at least in part, appears to be yes. Over the past two years, Dietz's group and collaborators at Ghent University in Belgium have tied excessive transforming growth factor beta signaling to two other aortic aneurysm syndromes (Loeys-Dietz syndrome and arterial tortuosity syndrome).

Aortic aneurysm is a major public health burden, said Dietz. About one to two percent of the population in industrialized countries dies from aortic aneurysm and rupture. So we are now targeting the more common forms of aneurysm for study.