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A Small Molecule for a Large Disease

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Almost three decades ago, Victor McKusick and I reviewed Marfan's syndrome in the *Journal* and advised traditional medical and surgical approaches to management.[1] The holy grail at that time was the cause of this autosomal dominant condition, based on the common presumption that understanding the cause would lead directly to effective therapy. In fact, life expectancy improved dramatically in subsequent years for all but the most severely affected patients, despite a lack of understanding of the underlying connective-tissue defect.[2] Dissection of the aorta was and remains the most common cause of death. However, the evolution of ever more effective surgical techniques, applied prophylactically, substantially prolonged life.[3] Treatment with beta-adrenergic blockade retarded the rates of aortic dilatation and dissection.[4,5] Serious complications, including mitral regurgitation, cardiomyopathy, pneumothorax, deformity of the thoracic cage, myopathy, and diminished visual acuity, still afflict some patients, especially infants and children at the most severe end of the phenotypic continuum.[6] Ironically, as people live longer with Marfan's syndrome, features that previously were unlikely to cause problems, such as lumbosacral dural ectasia, become major issues.[7] In addition, new age-dependent features have been recognized, such as renal and hepatic cysts and biliary stones.[8]

In 1991, the basic defect in Marfan's syndrome was discovered to be mutation of *FBN1*, the gene that encodes the large extracellular glycoprotein fibrillin-1.[9] This discovery raised expectations of more effective therapies, or even cure. However, the initial interpretations arising from this discovery proved to be inaccurate. Given that the fibrillins are integral components of vascular elastic fibers, ocular zonules, and other extracellular supporting structures, the notion arose that the various features of Marfan's syndrome developed because of "weak" connective tissue. Neat as this concept was, it did not explain many aspects of the disease, including overgrowth of tubular bones, underdevelopment of muscle and adipose tissue, and decreased bone mineral density.

The creation of mouse models of Marfan's syndrome, by introducing mutations known to cause the human disease into the mouse fibrillin gene, permitted focused investigations of pathogenesis. The fibrillins contain several motifs, including multiple copies homologous to latent transforming growth factor β (TGF-β) binding protein (LTBP). The cytokine TGF-β is bound and kept inactive by the LTBP complex. Hence, a defect in fibrillin structure might be expected to reduce binding and increase the activity of TGF-β. A number of groups began exploring whether TGF-β had a role in Marfan's syndrome. Dietz and colleagues studied the mouse model and showed that affected tissues had clear evidence of overexpression of TGF-β. The development of cystic lungs (which in humans predipose to pneumothorax), myxomatous mitral-valve leaflets, and aortic dilatation are all associated with increased signaling by TGF-β. Moreover, these common features of Marfan's syndrome can be prevented in mice by administering an antibody that binds TGF-β.[10-12]

These results dramatically altered the understanding of the pathogenesis of this archetypal heritable disorder of connective tissue. Notions of therapy quickly switched from "strengthening" the extracellular matrix or replacing the defective fibrillin to modulating signaling through a reasonably well understood pathway. The idea of developing a small molecule that can be taken orally for treatment of the disease gained currency.

On the basis of studies in diabetic nephropathy, it was already known that angiotensin increases TGF-β levels, whereas angiotensin-receptor blockers (ARBs) lower these levels.[13] This led Dietz and colleagues to study ARBs in the mouse model of Marfan's syndrome. Remarkably, three prominent features of Marfan's syndrome in humans — dilatation of the aortic root, air-space widening, and skeletal myopathy — can be prevented and even reversed in the mouse model by treatment with losartan, which blocks angiotensin II type 1 receptors.[12,14]

The preliminary report by Brooke et al. in this issue of the *Journal* suggests that blocking angiotensin II type 1 receptors will benefit young patients with severe Marfan's syndrome.[15] However, this initial study requires confirmation and is currently being evaluated in a randomized trial in which losartan is being compared with atenolol.[16,17] Unless losartan proves to have a remarkably beneficial effect, and the randomized trial is stopped early, the results will not be available for 4 to 5 years, depending on recruitment. The primary end points of this trial involve the cardiovascular system, but ancillary studies that will explore the development of the skeletal, adipose, and muscle systems are being added.

The initial studies demonstrating the use of ARB therapy for the protection of the aorta in the mouse model of Marfan's syndrome have drawn widespread and often inappropriately enthusiastic notice in the scientific and lay communities for several years. Unfortunately, as a result, some families and patients have opted not to join the clinical trial and have even obtained prescriptions for ARBs from their own physicians. We all have a stake in supporting this trial, since it affords perhaps the best chance to validate a crucial hypothesis. We must remain cognizant of the fact that other mouse models of human genetic diseases have suggested beneficial therapies that either have not worked in humans or have been associated with undesirable effects.

Therefore, at this stage, the most appropriate course of action for patients with Marfan's syndrome and their physicians is to give serious consideration to enrolling in the trial.[17] For patients who are not eligible for the trial, such as those with previous cardiovascular surgery or chronic aortic dissection, an ARB is a reasonable choice if beta-blockade alone is not controlling either blood pressure or dilatation in any region of the aorta. For patients in these categories who do not have hypertension, if off-label use of an ARB is considered, it should be in addition to, but not substituted for, beta-blockade.

The discovery of the cause of Marfan's syndrome required a variety of approaches that all came together within a short time nearly two decades ago. If the preliminary findings by Brooke et al. are confirmed, the treatment of Marfan's syndrome will go down in history as an early triumph of translational medicine. Already it serves as a marvelous example of the importance of understanding pathogenesis as the key step in designing potentially effective therapies, and by extension, the continued relevance of classic basic sciences such as biochemistry, cell biology, pharmacology, and physiology in the era of genomic medicine.

Dr. Pyeritz reports receiving lecture fees and grant support from Genzyme and being a site principal investigator for the National Heart, Lung, and Blood Institute Pediatric Heart Network randomized trial of atenolol versus losartan in Marfan's syndrome, as well as a member of the Professional Advisory Board of the National Marfan Foundation and the Medical Advisory Board of the Canadian Marfan Association. No other potential conflict of interest relevant to this article was reported.

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