Old Drugs and New Tricks

As a former gene therapy researcher, I must confess that to me nearly all attempts at gene therapy for genetic disorders have been disappointing. The sad fact is that our immune system is its own worst enemy as far as gene therapy goes, clearing attempts to use vectors to introduce new genetic material into cells and organs without breaking a sweat. When I was a grad student I was fond of saying (probably not originally) that with gene therapy we were attempting to treat disorders we didn't understand, in systems we didn't understand, using gene vectors we didn't understand. At that time, many had the expectation that, like a medical 'Hail Mary', something good would come out the considerable efforts directed at gene-replacement based therapies.

Moving forward about a dozen years, the prospects for successful primary gene therapy for most disorders remain distant. However, remarkable gains – fueled by discoveries in genomics - have been made in understanding the pathophysiology of many genetic disorders, and are yielding therapeutic breakthroughs.

A particularly compelling story is the evolution of our understanding of Marfan syndrome (MFS). Readers may recall that MFS is one of the classic autosomal dominantly inherited disorders characterized by tall stature, disproportionately long limbs, dislocated lenses, and other connective tissue abnormalities. The most devastating consequence of the disorder is a predisposition to aortic root dilatation and aneurysm formation that all too frequently leads to death in early adulthood. Unfortunately, the disorder isn't all that rare, affecting about 1/5000 individuals - as a benchmark cystic fibrosis affects about 1/2500 Caucasians. MFS is caused by mutations in the Fbn 1 gene which encodes the protein fibrillin 1, a constituent of the extracellular matrix in connective tissues, including blood vessel walls.

Until the last few years, most investigators thought that MFS was a nearly hopeless case for targeted therapeutic interventions, largely because the defect was in a structural protein, rather than in an enzyme. In general, it is comparatively easy to come up with rational ways for treating disorders with enzyme replacement; however, it is much harder to conceptualize rescuing a disorder if the cause is a structural element defect. MFS patients were therefore relegated to risky surgical correction of developing vascular abnormalities, or marginally beneficial use of beta-blockers to slow blood vessel dilatation.

Not satisfied that a classical structural protein defect could explain all of the features of MFS, investigators made a key discovery a few years ago: defects in fibrillin-1 cause disregulation of transforming growth factor beta (TGF-beta) signaling in affected tissues. Using mouse models for MFS and TGF-beta neutralizing antibodies, groups were able to show rescue of the blood vessel abnormalities. This alone would be a remarkable scientific finding, but delivering antibodies over a long period to patients isn't a much more appealing clinical solution than the prospects of gene therapy. Then something bordering on magical happened. A group of very clever investigators recognized that an

already commonly used antihypertensive in the class of drugs known as angiotensin II type 1 receptor blockers (ARB) also interfered with TGF-beta signaling – and they tried the drug in the mouse Marfan model. The results published in *Science* in 2006 were nothing short of spectacular – the vascular consequences of the MFS could be prevented in the mouse model system.

This spectacular success, coupled with the grave prognosis for MFS and the known safety profile of the ARB drugs, has led to a large prospective human clinical trial funded by the National Heart, Lung and Blood Institute. The trial, comparing the effectiveness of losartan and atenolol in a pediatric to young adult (6 month to 25 years of age) population, will have as its primary outcome measurement of body surface adjusted aortic root dilatation with measurement at 2, 12, 24 and 36 months. Preliminary results are due out soon, and many in the field are expecting the trial will show clear, major, benefit from the use of ARBs.

It is interesting, and probably prophetic, that MFS treatment may soon be revolutionized through a careful tweaking of a formerly unrecognized important pathway, rather than through brute-force correction of the underlying genetic defect.   Expect that this will be the model for other formerly truculent genetic disorders; not the least of which appears to be cystic fibrosis, where in the last few months a drug targeting patients with a particular genetic variant (unfortunately not the most common) has shown promising results in phase 2 trials.   Although a dozen years have passed since I was a grad student, gene therapy remains the genomic medicine equivalent of a 'Hail Mary' – a play not to be counted on or out. The difference today is that the ground game is fundamentally sound: those four-yard gains may carry the contest for a variety of disorders.