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Report of the National Heart, Lung, and Blood Institute and National Marfan Foundation Working Group on Research in Marfan Syndrome and Related Disorders

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Aortic aneurysm and dissection is a common phenotype, accounting for 1% to 2% of all deaths in industrialized countries and ≈50 000 deaths annually in the United States.[1] In contrast to abdominal aortic aneurysm, thoracic aortic aneurysm, particularly in the ascending segment, commonly occurs in young individuals in the absence of identifiable environmental risk factors. Marfan syndrome (MFS) is the most common syndromic presentation of ascending aortic aneurysm, but other syndromes such as vascular Ehlers-Danlos syndrome and Loeys-Dietz syndrome (LDS) also have ascending aortic aneurysms and the associated cardiovascular risk of aortic dissection and rupture. Familial segregation of the risk for ascending aortic aneurysm can also occur in the absence of associated systemic findings of a connective tissue abnormality in patients with familial thoracic aortic aneurysm and dissection (FTAAD) or bicuspid aortic valve with ascending aortic aneurysm (BAV/AscAA). The knowledge gained through basic and clinical research focused on MFS has improved and will continue to improve the care of patients with these related conditions.

Recent paradigm-shifting discoveries about the molecular pathogenesis of MFS have highlighted the need for a focused research agenda to solidify the gains of the past 30 years and set the stage for future advances in MFS and related conditions. In April 2007, the

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Disclosures

Drs Milewicz, Pyeritz, Ramirez, Sakai, and Dietz sit on the Professional Advisory Board of the National Marfan Foundation and act as pro bono consultants.

National Heart, Lung, and Blood Institute (NHLBI) and the National Marfan Foundation convened a working group on research in MFS and related disorders to foster a multidisciplinary discussion. The working group, which included experts in cardiovascular disease, developmental biology, genetics and genomics, and proteomics, was charged with identifying opportunities and barriers to advancing the research agenda and developing recommendations to the NHLBI in the context of the Institute's strategic plan (http://apps.nhlbi.nih.gov/strategicplan/).

Marfan Syndrome

MFS is a systemic disorder of connective tissue caused by heterozygous mutations in the gene (*FBN1*) that encodes the extracellular matrix protein fibrillin-1.[2] The estimated prevalence of MFS ranges between 1 in 5000 and 1 in 10 000, without any ethnic or gender bias. Manifestations occur in many body systems, including the eye, skeleton, skin and integument, lung, and most importantly, the heart and blood vessels.[3] The primary cause of death is cardiovascular collapse due to aortic dissection, rupture, and pericardial tamponade. The prognosis and clinical outcome for people with MFS have improved steadily over the last 3 decades, largely owing to medical and surgical advances. In 1972, the average age at death and the median cumulative probability of survival for an individual with MFS were 32 and 48 years, respectively, but these had increased to 41 and 72 years, respectively, when reassessed in 1995.[4,5] Many of the current medical and surgical practices for the care of individuals with aortic aneurysm have either been developed or refined in MFS, in part because validated animal models have been developed. In addition, a highly motivated patient population has facilitated clinical research.

Current therapy for the cardiovascular complications of MFS consists of medical management, with the goal of slowing the rate of aortic root dilation, and surgery to prevent dissection when the aortic root reaches a diameter of ≈5 cm or is growing at a rate of more than 1 cm a year.[3] Medical therapy is usually with β-blockers, but ACE inhibitors and calcium channel blockers have also been used (reviewed in Keane and Pyeritz[6]). Although multiple small, largely retrospective and nonrandomized studies in people with MFS have suggested a benefit of β-blocker and other medical therapy, these treatments neither arrest abnormal aortic growth nor prevent the ultimate need for aortic surgery.

Prophylactic aortic root surgery is a noncontroversial strategy to prevent aortic dissection in MFS. The introduction in the late 1960s of the Bentall procedure, which involved replacement of the aortic valve, root, and proximal ascending aorta with a composite Dacron graft that incorporates an artificial valve, heralded a new era for Marfan therapy, with a better than 98% operative survival rate.[7] Many large surgical series documented the effectiveness and safety of this procedure for MFS, among other conditions, and over time, the aortic root dimension threshold for proceeding with surgery fell from ≈6.5 cm to the present dimension of ≈5 cm, a size at which most agree that the risk of dissection becomes markedly increased.[8] Alternative thresholds for surgical intervention, especially for adult patients with a small body size, have been proposed.[9] The most significant downside to this operation is the lifelong need for anticoagulants and the risk of infection in individuals with a prosthetic aortic valve. In the early 1990s, David and colleagues[10] introduced a "valve-sparing" approach that addresses these issues and that has been refined over time to ensure optimal valve function. Both short- and intermediate-term results have been excellent, and this procedure has emerged as the operation of choice in suitable patients at many of the leading surgical centers for the care of individuals with MFS.[11–20] Effective repair or replacement procedures are also available for the treatment of mitral valve prolapse and regurgitation stemming from myxomatous changes in MFS.[21]

Molecular Pathogenesis

The strict mendelian inheritance and high clinical penetrance of MFS made it ideal for successful use of a positional candidate strategy to identify the responsible gene (*FBN1*) and protein product, fibrillin-1.[2,22–24] Fibrillin-1 monomers aggregate to form complex extracellular structures called microfibrils that cluster at the margins of maturing elastic fibers during embryogenesis.[25] Fibrillin-1 is not needed for elastogenesis, as originally thought, but rather is critical for elastic fiber maintenance in postnatal life.[26,27] Early models of disease pathogenesis invoked an acquired weakness of affected tissues based on loss of structural integrity; however, manifestations of MFS such as myxomatous valve changes or long-bone overgrowth are not readily explained by this model. These findings more plausibly relate to abnormalities of cellular performance (proliferation, migration, and/or programmed death).

A breakthrough in understanding the pathogenesis of MFS came while researchers were studying lung disease in mouse models.[28] Because affected mice were born with abnormal lungs, rather than developing tissue destruction and inflammation over time, the “acquired weakness” model did not hold. Homology between fibrillin-1 and a second family of proteins called the latent transforming growth factor-*β* (TGF-*β*) binding proteins led to the hypothesis that microfibrils might contribute to the regulation of TGF-*β*, a growth factor molecule that instructs cellular performance. In keeping with this hypothesis, it was shown that fibrillin-1 can bind to latent TGF-*β* binding proteins and that free (activated) TGF-*β* was increased in the fibrillin-1–deficient lung.[28,29] Systemic administration of TGF-*β*–neutralizing antibody rescued lung septation in mouse models of MFS, which provided evidence for a cause-and-effect relationship.[28] Further animal work showed that myxomatous changes of the atrioventricular valves correlate with increased TGF-*β* signaling, increased output of TGF-*β*–responsive genes (including collagens), and excessive cellular proliferation and reduced apoptosis in valve leaflets.[30] Short-term administration of TGF-*β*–neutralizing antibody reduced valve length and thickness.

The success of TGF-*β*–neutralizing antibody in reversing pulmonary and mitral valve pathology led to a randomized and blinded trial of TGF-*β*–neutralizing antibody to modify aortic root changes in engineered mouse models of MFS.[31] This study showed a reduced rate of aortic root growth and improved aortic wall architecture. The next step was a study of losartan, an angiotensin II type 1 receptor blocker that had shown the ability to block TGF-*β* signaling in models of chronic renal disease. In Marfan mice, losartan provided dramatic protection, with normalized aortic root growth and aortic dimension and an aortic wall architecture that was indistinguishable from that seen in wild-type mice, even when given after aortic dilation had already begun.[31] Evidence suggests that angiotensin II type 1 receptor blockade reduces expression of TGF-*β* ligands and receptors and limits the production of potent activators of TGF-*β* such as thrombospondin-1. Losartan also rescued other manifestations of MFS in mouse models, including muscle regeneration and strength and pulmonary alveolar septation.[31,32]

Taken together, these data indicate that (1) many of the multisystem manifestations of MFS relate to excess TGF-*β* signaling, (2) TGF-*β* antagonism is a potential treatment strategy for human MFS, and (3) Marfan mouse models could provide a valuable resource to investigate the roles of TGF-*β* in tissue development and homeostasis and could be used to assess the therapeutic value of other strategies aimed at TGF-*β* antagonism or other mechanisms that relate to the initiation or maintenance of pathogenetic programs. Indeed, MFS mouse models were recently used to demonstrate that the matrix metalloproteinase inhibitor doxycycline improved aortic wall architecture and delayed aortic dissection.[33] Given that matrix metalloproteinases can contribute to the activation of TGF-*β*, it is possible that doxycycline and losartan will show synergistic effects.

Other TGF-β–Related Aneurysm Disorders

LDS is a recently described autosomal dominant condition that includes selected features that overlap with MFS, including arachnodactyly, anterior chest deformity, scoliosis, dural ectasia, and aortic root aneurysm.[34,35] Cardiovascular involvement can include congenital heart malformations, but most importantly, patients show widespread and aggressive vascular disease with arterial tortuosity and a strong predisposition for aneurysms and dissections throughout the arterial tree.[34,35]

Mutations that cause LDS occur in either of the 2 genes that encode the TGF-β receptor (*TGFBR1* and *TGFBR2*).[34,35] The skin, joint, and vascular manifestations of LDS can show substantial overlap with the vascular form of Ehlers-Danlos syndrome, a disorder caused by mutations in the type III collagen gene (*COL3A1*).[35,36] A phenotype now designated LDS-II, which is intermediate between LDS and vascular Ehlers-Danlos syndrome, is also associated with mutations in the *TGFBR* genes.[35]

Mutations in *TGFBR2* have also been reported in patients described as having MFS or FTAAD, a designation historically used to describe patients with thoracic aortic aneurysms (prominently involving the ascending aorta) in the absence of more widespread vascular disease or systemic features of a connective tissue disorder.[37–41] There are no apparent differences between the mutations that cause LDS and those described as causing MFS or FTAAD. Indeed, many of the identical mutations described as causing MFS or FTAAD have been found in families with typical LDS-I or LDS-II.[34,35,42] Further work is needed to determine whether all patients with TGF-β receptor mutations have or will develop distinguishing clinical features of LDS. The available data demonstrate increased TGF-β signaling in LDS patients in a context that is directly relevant to tissue development and homeostasis in vivo.[34,35] The mechanism by which mutant TGF-β receptors induce paradoxically enhanced TGF-β signaling in LDS remains incompletely understood.

Arterial tortuosity syndrome is a rare autosomal recessive disorder characterized by generalized arterial tortuosity, joint laxity, and skin hyperextensibility.[43] Sudden cardiovascular death is common early in life, but the precise cause of death is not known in the majority of cases. Ischemic events, critical arterial stenosis, and aortic aneurysms have been observed. Patients who survive to adolescence have a much better prognosis. Arterial tortuosity syndrome is caused by homozygous or compound heterozygous loss-of-function mutations in the *SLC2A10* gene encoding Glut10, a facilitative glucose transporter.[44] The arterial wall in arterial tortuosity syndrome shows excessive TGF-β signaling, as evidenced by nuclear accumulation of pSmad2 and increased output of TGF-β–responsive genes.[44]

Other Inherited Aneurysm Phenotypes

Familial Thoracic Aortic Aneurysm and Dissection

Historically, the diagnosis of FTAAD has been used to designate a heritable predisposition for ascending aortic aneurysm and dissection in the absence of systemic features of a connective tissue disorder. There is considerable intrafamilial and interfamilial clinical heterogeneity, including the degree of penetrance, age of onset, severity of manifestations, and the risk for other cardiac pathology beyond the ascending aorta.[45]

To date, 5 loci have been associated with a predisposition for autosomal dominant FTAAD on chromosomes 5q13-14, 11q23, 3p24-25, 16p12.2-13.13, and 10q23.3.[46–50] The locus on chromosome 16p correlates with mutations in the *MYH11* gene.[51] Affected individuals commonly have patent ductus arteriosus. The 3p locus correlates with mutations in *TGFBR2*.[41] At least a subset of these patients show widespread and aggressive vascular disease

and skeletal involvement reminiscent of LDS.[48] Mutations in *ACTA2*, estimated to account for 14% of FTAAD, are found in families, linked to the chromosome 10q locus.[50] Associated findings in a subset of patients include iris flocculi, livedo reticularis, and patent ductus arteriosus. In general, surgical management of FTAAD relies on many of the same principles and procedures used for MFS. Although dedicated studies in this patient population have not been performed, some centers advocate the use of medications to reduce hemodynamic stress. As in MFS, earlier intervention (ie, at 5.0 cm) may improve the outcome for valve-sparing procedures. These phenotypes emphasize the crucial importance of a detailed family history in any young or middle-aged person found to have an ascending aortic aneurysm or dissection, followed by clinical screening of relatives at risk.

Bicuspid Aortic Valve With Ascending Aortic Aneurysm

The partial or complete fusion of aortic valve commissures represents the most common form of congenital heart disease, occurring in approximately up to 1% to 2% of individuals, with a higher prevalence in males. BAV is part of a wider spectrum of associated left-sided heart obstructive lesions that include coarctation of the aorta and hypoplastic left heart syndrome. BAV shows high heritability, and the preponderance of family studies suggest autosomal dominant inheritance with incomplete penetrance and wide variability in clinical expression. A subset of individuals and families with BAV show ascending aortic enlargement. In a study of children with BAV, 12% showed marked aortic dilatation (z score >4.0) and 25% showed moderate dilatation (z score between 2.0 and 4.0) at the time of the initial echocardio-gram.[52] Among children with BAV and normal ascending aorta measurements at initial evaluation, 36% showed aortic dilatation at follow-up.[52] The genetic cause of BAV/AscAA remains largely unknown. Mutations in *NOTCH1* have been described in affected families,[53,54] but these account for a small fraction of BAV/AscAA, perhaps enriched for cases with early valve calcification or dysfunction.

The pathogenesis of ascending aortic aneurysm formation in this setting is also unknown. The hypothesis that aneurysm formation occurs as a consequence of perturbed blood flow through a stenotic valve is supported by data showing that aortic stenosis is a predictor of the rate of aneurysm growth and clinical outcome in both adults and children.[52,55] Other studies, however, have demonstrated aneurysms without hemodynamically significant valve disease.[56,57] Furthermore, family members of an individual with BAV/AscAA can show aortic aneurysm and dissection without the accompanying valve abnormality.[57] The emerging view is that BAV/AscAA and other associated left-sided heart obstructive lesions are variably penetrant primary manifestations of the underlying gene abnormality. This information is critical to the counseling and management of individuals and families with BAV/AscAA.

Human Therapeutic Trials

Several small therapeutic trials have been reported for individuals with MFS, but none has been conducted for patients with related conditions. Although most studies suggest that β-adrenergic blockers can slow the rate of aortic growth in MFS, others have failed to support this hypothesis.[58–64] ACE inhibitors (ACEIs) were postulated to have therapeutic value in MFS because of the potential ability to block apoptotic pathways.[65] An open-label, nonrandomized trial of ACEIs versus β-blockers in MFS showed apparent therapeutic value for ACEIs in terms of reduced aortic stiffness and smaller increases in aortic root diameter.[62] A more recent randomized trial of perindopril versus placebo in MFS revealed improved biomechanical properties of the aorta, slower aortic root growth, and lower levels of circulating TGF-β in a small number of patients treated for 24 weeks.[66] ACEIs inhibit the renin-angiotensin system by blocking the conversion of angiotensin I to angiotensin II and thus decrease signaling through both the angiotensin II type 1 and type 2 receptor (AT2)

pathways. Blocking the AT2 pathway can decrease apoptosis, but apoptosis was not observed in the ascending aorta of mouse models of MFS. Normal signaling through the AT2 pathway can antagonize TGF-β signaling, in theory a protective event in MFS,[31] and thus, there are theoretical concerns about reducing signaling through the AT2 pathway with ACEIs, although the perindopril study did not support this concern. In a rodent model of angiotensin II–induced abdominal aortic aneurysm, selective angiotensin II type 1 receptor blockade prevented aneurysm, whereas selective AT2 blockade increased both the frequency and severity of aneurysm.[67] However, ACEIs do not induce selective AT2 blockade, and these data are not from a Marfan animal model. Larger randomized trials of ACEIs and losartan will be needed to resolve these issues.

On the basis of the ability of losartan to rescue the cardiovascular phenotype in the mouse model of MFS, a small number of children with severe aortic dilatation have been treated with losartan, either alone or in addition to β-blockers, with up to 4 years of follow-up.[68] These data demonstrate a significant reduction in aortic root growth. Despite the promising nature of these results, they cannot substitute for a large, long-term randomized trial with sufficient power to assess the clinical value of losartan compared with β-blockade. The NHLBI-sponsored Pediatric Heart Network is currently conducting such a study in children and young adults with MFS.[69]

Recommendations

Bearing in mind the current state of the science, the Working Group discussed scientific opportunities and barriers to progress. The scientific opportunities to advance this field are conferred by technological advances in gene discovery, the ability to dissect cellular processes at the molecular level, imaging, and the establishment of multidisciplinary research teams. The barriers to progress are addressed through the following 5 key recommendations. All of these recommendations are based on and consistent with the goals and challenges in the NHLBI's Strategic Plan (http://apps.nhlbi.nih.gov/strategicplan/).

- Existing registries should be expanded or new registries developed to define the presentation and course of aneurysm syndromes. (NHLBI Strategic Plan Goal 2, Challenge 2.2.)

The prognosis and clinical outcome for people with MFS has improved steadily over the last 3 decades, both because of the ability to anticipate medical problems and the ability to apply medical and surgical protocols that have been developed and refined to meet the needs of this discrete patient population. Likewise, the basic science discoveries that have the potential to further revolutionize care for MFS would not have been possible before disease gene discovery, an event that also required the ability to discriminate MFS from overlapping phenotypes. Even if losartan or other therapies fulfill their promise, the new reality will undoubtedly be the need to define the new emerging clinical history of MFS that will only become evident once genetically imposed predispositions integrate with those imposed by aging and prolonged environmental influence.

The need for accurate prospective data that permit correlation of multiple complex determinants of outcomes is magnified for conditions that have been recognized only recently (eg, LDS), that have few discriminating manifestations (eg, FTAAD), or that are extremely rare (eg, arterial tortuosity syndrome). Examples of highly relevant questions include the following: How well do follow-up and treatment guidelines developed for MFS generalize to other genetically induced forms of thoracic aortic aneurysm? Are there clinical or imaging parameters that can inform patient counseling and management? Should guidelines developed for the broader cardiovascular community (eg, recent modification of American Heart Association guidelines to exclude mitral and/or aortic valve regurgitation as

an indication for bacterial endocarditis prophylaxis[70]) apply to individuals with systemic connective tissue disorders?

National or international registries that capture clinical information relevant to this broad patient population include the International Registry of Acute Aortic Dissection, the NHLBI-funded Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions registry (https://gentac.rti.org/), and the Aortic Valve Operative Outcomes in Marfan Patients registry. These efforts, although valuable, could have considerable value added by the collection of detailed longitudinal phenotypic and imaging data. Rather than being strictly observational, dedicated examinations and specialized imaging could be used to address specific clinical questions or hypotheses focused on a specific phenotype. The inclusion of a sufficient number of children will ensure adequate pediatric data to support management guidelines. In addition, a common nomenclature for data elements across registries will permit the robust aggregation of data from multiple sources.

- Biological sample collection should be incorporated into every clinical research program on MFS and related disorders, and funds should be provided to ensure that this occurs. Such resources, once established, should be widely shared among investigators. (NHLBI Strategic Plan Goal 2, Challenges 2.1 to 2.3.)

A central repository for standardized clinical sample collection, processing, and distribution should be formed. Whenever feasible, every sponsored initiative dedicated to the collection of phenotypic information relevant to aortic aneurysm conditions should collect and submit clinical specimens. This resource would greatly facilitate gene discovery efforts and other fundamental studies. There is a particular need to obtain specimens that are temporally associated with clinical events, such as the initiation of medical therapies, surgery, aneurysm progression, and vascular dissection or rupture, to identify diagnostic, prognostic, and therapeutic markers.

- An Aortic Aneurysm Clinical Trials Network (ACTnet) should be developed. Partnership in this effort should be sought with industry, academic organizations, foundations, and other governmental entities. (NHLBI Strategic Plan Goal 2, Challenge 2.4.)

The number of emerging therapeutic strategies for aortic aneurysm conditions parallels a refined understanding of their causes and pathogenesis. The Pediatric Heart Network trial of losartan versus atenolol has the true potential to inform the care of people with MFS in a comprehensive and rigorous manner; however, additional studies are needed to address other clinical questions in MFS, as well as other patient populations. The NHLBI network model provides an ideal structure to test new medical or surgical therapies in rare conditions, such as genetically induced aortic aneurysm. Additional TGF-β antagonists, such as neutralizing antibodies or Smad kinase inhibitors, may prove useful in isolation or in combination with angiotensin II type 1 receptor blockers. Agents with other or overlapping mechanisms of action with demonstrated or theoretical promise include matrix metalloproteinase and ACE inhibitors and angiotensin II type 2 receptor agonists, alone or in combination. An immediate hypothesis to be tested is that TGF-β antagonists will prove relevant to conditions other than MFS.

Given the relative rarity of genetically induced aortic aneurysm conditions, a network of centers will be needed to adequately test new medical or surgical therapies. As with the Pediatric Heart Network, such an effort would be greatly facilitated by centralized infrastructure and the availability of flexible funding strategies to permit rapid response to novel opportunities. Such collaboration may also be able to take advantage of new infrastructure resources becoming available through the National Center for Research

Resources' Clinical and Translational Science Awards Program or the National Institute of Health's Office of Rare Diseases.

- The identification of novel therapeutic targets should be facilitated by the development of genetically defined animal models and the expanded use of genomic, proteomic, and functional analyses. (NHLBI Strategic Plan Goal 1, Challenge 1.2.)

It is likely that elucidation of events that occur upstream (eg, mediators of TGF-β activation) and downstream (eg, transcriptional responses) of increased TGF-β signaling in MFS will result in the identification of novel therapeutic targets for this disorder. Parallel approaches should be directed at the identification of genetic modifiers of MFS. The paradigm established for MFS that a deficiency of a structural matrix element can initiate pathogenic perturbations of cell signaling should be explored for other connective tissue disorders, such as vascular Ehlers-Danlos syndrome. Such efforts will be facilitated by the development of genetically defined animal models and the expanded use of genomic, proteomic, and functional analyses. There is a specific need to develop robust in vivo reporter assays for the monitoring of the TGF-β (and other cellular) signaling cascades.

- The developmental underpinnings of apparently acquired phenotypes should be explored. This effort will be facilitated by the dedicated analysis of both prenatal and early postnatal tissues in genetically defined animal models and through the expanded availability to researchers of surgical specimens from affected children. (NHLBI Strategic Plan Goal 1, Challenge 1.1.)

The recent finding that TGF-β–induced developmental perturbations may lead to abnormal lung development and establish the structural predisposition for later-onset emphysema may prove relevant to other aspects of the Marfan phenotype and to genetically induced forms of myxomatous valve disease and/or aortic aneurysm in general. Elucidation of the developmental sequelae of relative fibrillin-1 deficiency and excess TGF-β signaling may explain known predispositions (eg, for dilation of vascular segments enriched for neural crest-derived vascular smooth muscle cells), reveal unanticipated predispositions or limitations of postnatal interventions, or indicate novel therapeutic strategies. This will require a more refined understanding of late (including postnatal) developmental events that contribute to tissue morphogenesis and homeostasis.

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