Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Therapeutic Opportunities of Marfan Syndrome: Current Perspectives

Xiaoying Feng[1,*], Chao Qu[2,*], Ping Jia[3,*], Ding Ding Zhang[4]

[1]College of Medical Technology, Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China; [2]Department of Ophthalmology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, People's Republic of China; [3]Department of Neurosurgery Nursing, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, People's Republic of China; [4]Key Laboratory for Genetic Disease in Sichuan Province, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ding Ding Zhang, Email zhangdd25@126.com

Abstract: Marfan syndrome (MFS) is a hereditary connective tissue disorder that is primarily caused by mutations in the fibrillin-1 (*FBN1*) gene. This disease predominantly affects the eyes, bones, and cardiovascular system, with cardiovascular complications posing the most significant threat to life. Currently, conventional treatments, which are based on pharmacological management and surgical interventions, aim to slow disease progression and manage life-threatening cardiovascular complications. Emerging technologies such as CRISPR-Cas9 gene editing and induced pluripotent stem cell (iPSC) have advanced the understanding of *FBN1* mutation heterogeneity and disease mechanisms beyond TGF-β signaling, providing novel platforms for drug discovery and personalized therapeutic exploration. This review explores recent progress in MFS therapies, focusing on surgical innovations, emerging medicine and therapeutic targets, while discussing the potential future applications of gene therapy.

Keywords: marfan syndrome, gene therapy, pharmacotherapy, surgery, iPSC

Introduction

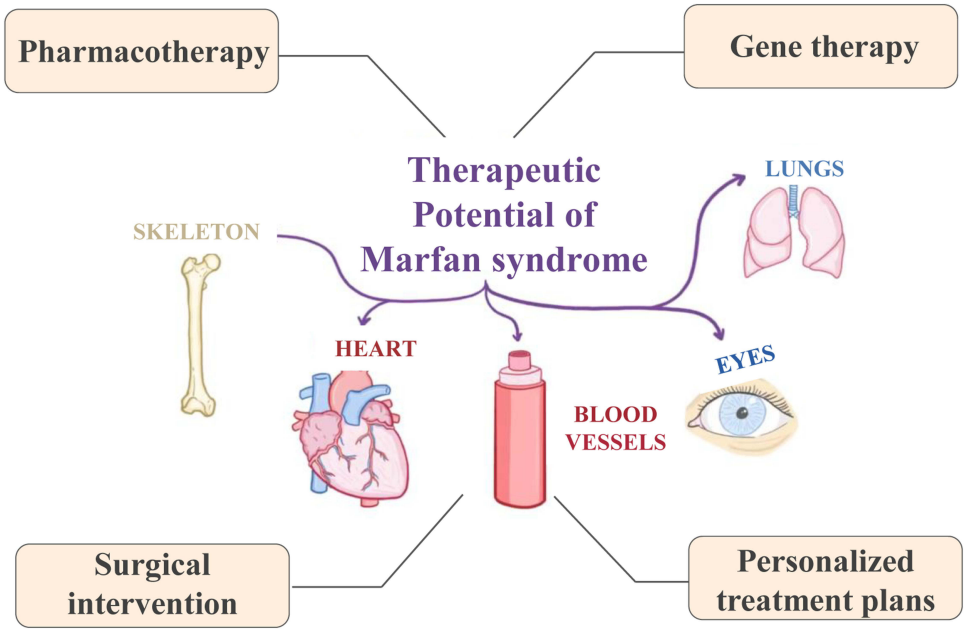
Marfan syndrome (MFS) is an autosomal dominant disorder with a prevalence of approximately 1/5000-1/3000.[1,2] Studies have shown that mutations in *FBN1* are responsible for about 90% of MFS cases.[3,4] The clinical manifestations of MFS are highly variable, even within the same family. Common symptoms include abnormalities of ocular, cardiovascular, skeletal, pulmonary, skin, and dural ectasia.[3,5] The most serious complication of MFS is the weakening of the connective tissue in the aorta, leading to progressive enlargement and risk of aortic dissection or rupture, which can be life-threatening.[6] It is critical for affected individuals to undergo multidisciplinary management to enhance their quality of life.

The management of MFS requires a knowledge approach, encompassing various pharmacological and surgical interventions along with lifestyle adjustments. Beta-blockers are typically the first choice for pharmacological therapy of MFS.[7,8] Angiotensin receptor antagonists (ARBs) like losartan have been studied for their ability to attenuate the activity of transforming growth factor-beta (TGF-β), a factor believed to be involved in the pathogenesis of MFS. In an 8-year follow-up study, Van Andel et al showed that ARB therapy decreased aortic events in MFS patients without causing side effects.[9] Surgical options are considered when medication cannot adequately control the dilation of the aorta or when other serious complications arise.[10] Lifestyle modifications are also crucial for managing MFS. Patients are often advised to avoid strenuous physical activities and contact sports that could put excessive strain on the heart and aorta. Additionally, genetic counseling can provide support for families regarding reproductive planning.

Gene therapy emerges as a promising frontier in the treatment of MFS, offering the potential to address the root cause of the disorder by targeting the genetic mutations that lead to gene deficiency or dysfunction. In 1998, Kilpatrick et al, demonstrated that antisense hammerhead ribozymes, small catalytic RNAs that can target and cleave specific RNA molecules, seem promising for Marfan syndrome therapy.[11] Kodolitschet al used snRNA for pre-translational repression

Received: 18 February 2025
Accepted: 19 August 2025
Published: 26 August 2025

Graphical Abstract



of *FBN1* expression in a cell line to block mutant gene expression.[12] These techniques have shown certain prospects in correcting *FBN1* gene mutations. In this review, the pathomechanisms of MFS to identify alternative therapeutic targets and targeted agents, as well as recent advances in gene therapy for MFS and the challenges that need to be faced before its application to the clinic will be discussed.

Pathogenesis

The pathogenesis of MFS is primarily associated with abnormalities in connective tissue that result from genetic mutations.[13] The *FBN1* gene encodes fibrillin-1, an extracellular matrix glycoprotein that is instrumental in elastic fiber formation.[14] Elastic fibers are key substances that maintain the structural integrity and elasticity of the body's tissues, especially in the heart, great vessels, lungs, eyes, and skeletal system.[15] Normal fibrillin-1 not only provides structural support but is also responsible for storing and regulating TGFβ activity. Fibrillin-1 anchors TGFβ in the extracellular matrix by interacting with TGFβ-binding protein (LTBPs).[3] Mutations in the *FBN1* gene disrupt this regulatory mechanism, resulting in a free and active state of TGFβ.[16] Free TGF-β binds to cell surface TGF-β receptors, initiating downstream signaling cascades (Figure 1A). MFS is strongly associated with the TGFβ pathway. Mutations in the *FBN1* gene trigger a series of pathologic changes, primarily in the form of life-threatening aortic aneurysm rupture. The main causes of aortic aneurysm formation are degradation of elastic fibers, smooth muscle cells (SMCs) apoptosis, immune cell infiltration, and overproduction of matrix metalloproteinases (MMPs).[17] Dysregulation of TGFβ signaling has been shown to cause MFS and MFS-associated thoracic aortic aneurysm (TAA). For example, mutations in *TGFBR1, TGFBR2*, or *SMAD2/3* lead to Loeys-Dietz syndrome, while mutations in the *SKI* gene are linked to Shprintzen-Goldberg syndrome.[18]

Nitric oxide (NO) signaling is associated with MFS aortic pathophysiology. Elevated NO production by inducible nitric oxide synthase (iNOS) under inflammation causes cell and tissue damage, and increased NO levels are found in MFS patient and animal model aortic sections.[19] NO dysregulation leading to aortic aneurysms involves iNOS, sGC, and PRKG1 may be clinical trials as targets for intervention in TAA.[20] Redox stress, driven by an imbalance between reactive oxygen species (ROS) production and elimination in the aortic wall, is a major focus in MFS research. NADPH oxidase 4 (NOX 4), xanthine oxidoreductase (XOR), and mammalian target of rapamycin (mTOR) signaling are key sources of

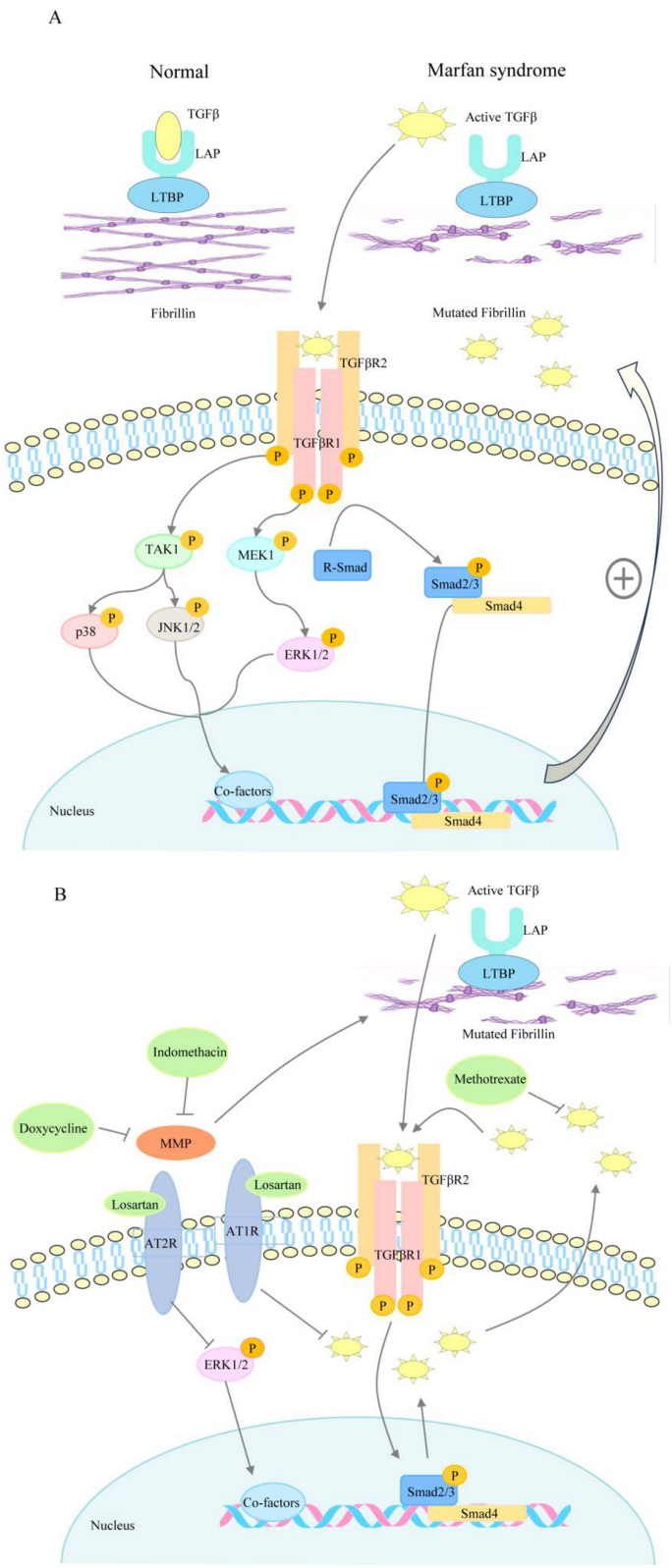


Figure 1 The transduction of TGF-β pathway signaling and mechanisms of drug action. (**A**) Extracellular microfibrils usually bind to large latent complexes composed, including TGFβ, latency-associated peptide (LAP), and latent transforming growth factor-b binding proteins (LTBPs). This interaction is proposed to suppress the release of free and active TGFβ. MFS leads to abnormal microfiber and failure of large latent complex sequestration and subsequent activation of TGF-β signaling cascades (right side). Free and active TGFβ interacts with its cell surface receptor and phosphorylation (P) of the R-Smad proteins (R-Smads 2 and 3), which form heteromeric complexes with Smad4 and translocate from cytoplasm to nucleus and mediate TGFβ-induced transcriptional responses. (**B**) Losartan acts on angiotensin receptors(ATR) to reduce TGFβ signaling activation. Methotrexate inhibits TGFβ activity. Doxycycline and indomethacin indirectly modulate the TGFβ signaling pathway through MMPs, thereby regulating extracellular matrix stability and TGFβ release.

https://doi.org/10.2147/DDDT.S523571

vascular ROS.[21] ROS may contribute to smooth muscle phenotypic transfer, apoptosis, and MMP activation leading to ECM remodeling.[22] Defective ECM affects neighboring mitochondrial function. Oller et al identify mitochondrial dysfunction and mtDNA depletion in *Fbn1* mice and MFS patients.[23] Chronic mitochondrial dysfunction causes cell exhaustion and impaired aortic repair, and is a key pathological mechanism in aneurysm formation in MFS.[24] Mitochondria-targeted therapies and mitochondrial enhancers may provide new treatment options for hereditary TAA.[25]

A comprehensive understanding of these mechanisms not only helps to elucidate the nature of diseases but also provides a theoretical foundation for devising novel therapeutic approaches. Notably, mutations affecting the TGF-β pathway underlie Loeys-Dietz syndrome, which shares overlapping pathogenic mechanisms with MFS. Future studies could explore whether these strategies apply to other aneurysmal syndromic diseases.

Pharmacotherapy

Pharmacologic treatment of MFS is aimed at limiting the rate of aortic growth, thereby preventing or delaying the need for surgical intervention and fatal complications.

Conventional Drug Therapy

Beta-blockers are first-line agents for MFS, slowing aortic root growth and reducing cardiovascular complications.[26,27] ARBs, such as losartan, offer a viable alternative by inhibiting angiotensin II to reduce blood pressure and TGF-β activity, thereby delaying aortic dilation in mice models.[28] Meta-analyses confirm that combined β-blocker/ARB therapy is superior to monotherapy in mitigating aortic pathology.[29–31] Wang et al showed no statistical differences in the number of aortic procedures, adverse effects, or mortality from cardiovascular events in patients treated with only a single agent.[32] Lacro et al found that compared with patients with MFS treated with a beta-blocker alone, the addition of ARBs further prevented or slowed aortic root dilatation and was able to reduce aortic arch dilatation in patients who had undergone aortic root replacement.[33] In September 2022, the Marfan Treatment Trialists' (MTT) Collaboration published a Meta-analysis of patient data on ARBs and beta-blockers.[34] The results showed that the combination of ARBs and β-blockers cuts the aortic root enlargement rate by at least half, which is anticipated to significantly delay the need for surgical intervention.[34] However, studies have limitations in sample size, design, dosage, and follow-up time.[30] Large-scale randomized controlled trials are needed to better assess long-term drug efficacy.

Current MFS drug treatments mainly target cardiovascular issues. Beta-blockers and ARBs are commonly prescribed medications to prevent heart damage and manage hypertension and heart failure.[35,36] In addition, drugs like angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), and renin inhibitors (RIs), etc. have been explored as potential therapeutic agents for MFS[37] (Figure 1B). However, while CCBs have demonstrated efficacy in slowing aortic growth among MFS patients, they may increase aortic dilatation and rupture risk in Marfan mice and patients.[38,39]

Existing drug therapies do not cure MFS but are mainly used to slow the progression of cardiovascular manifestations. Therefore, the development of more effective therapeutic strategies remains a research priority. A summary of drugs for MFS treatment is provided in (Table 1). Van Andel et al found resveratrol, in nuts, plants, and grape skins, aids aortic repair in rodent aneurysm models.[40] Huang et al showed that a novel vitamin B complex reduced aortic aneurysm volume and increased collagen deposition in $Fbn1^{C1039G/+}$ mice, stabilizing aneurysms.[41] Additionally, some studies note that men with MFS have a higher aortic disease risk than women, possibly due to estrogen levels.[42] Saddic et al showed that 17β-estradiol reduced aortic root dilatation and rupture in male Marfan mice by inhibiting the TNFα-NF-κB pathway, lowering MMP-2 and MMP-9 levels.[43] Mild inflammation promotes tissue repair, aortic remodeling, and angiogenesis, benefiting the aortic wall. Conversely, excessive inflammation can worsen aortic wall abnormalities and drive TAA progression. Thus, anti-inflammatory treatment is crucial for balancing inflammation and preventing TAA deterioration. Zhang et al found that inhibiting the complement C3a receptor reduced macrophage infiltration and broken elastic fibers in MFS mice.[44] Because redox stress and NO may contribute to aortic pathology in MFS, cobalamin (vitamin B12), a potent antioxidant, has emerged as a potential therapeutic agent. Kalyanaraman et al administered histidyl-cobinamide to $Fbn1^{C1041G/+}$ mice, which significantly reduced DNA, lipid, and protein oxidation in the proximal aorta.[45] This intervention effectively prevented pathological changes and attenuated aortic dilation.

Table 1 Summary of Therapeutic Drug in Marfan Syndrome

Categorization	Instance	Mechanism	Ref.
Beta-blockers	Atenolol, metoprolol, propranolol	Decreasing myocardial contractility, slowing heart rate, and reducing aortic wall pressure	[46,47]
ARBs	Losartan, valsartan	Dilating blood vessels, lowering blood pressure, reducing cardiac afterload	[28,48–50]
ACEIs	Enalapril	Inhibits the conversion of angiotensin I to angiotensin II to lower blood pressure, thereby reducing cardiac load and aortic pressure	[31,51]
CCBs	Amlodipin, verapamil	Blocking calcium ions from entering vascular smooth muscle cells to relax blood vessels, thereby lowering blood pressure	[38,52]
RIs	Aliskiren	Inhibition of renin activity to reduce angiotensin II production, thereby lowering blood pressure	[53]
Anti-inflammatory	Indomethacin, Celecoxib, IL-1IRA antibodies (X209), Methotrexate	Reduces inflammatory cell infiltration and inflammatory factor expression in aortic samples from *Fbn1* mice	[54–56]
MMP inhibitors	Doxycycline	Nonselective MMP inhibitor that reduces elastic fiber and collagen degradation and maintains structural integrity of the aortic wall	[57–61]
Antioxidant	Allopurinol	Inhibition of XOR activity and scavenging of ROS to achieve antioxidant effects	[62]
	apocynin	Non-specific NOX inhibitor reduces thoracic aortic aneurysm growth by inhibiting ROS	[63]
Hormone antagonist	Flutamide	Androgen receptor antagonist that reduces ERK signaling and MMP 2 activity	[64]
	Oxytocin receptor antagonist	Reducing the risk of aortic coarctation during pregnancy in Marfan mice by inhibiting ERK phosphorylation	[65]
Other drugs	Statins	Statins inhibit the Ras-dependent ERK (extracellular signal-regulated kinase) pathway, reduce MMP activity, and prevent progressive aortic root dilatation	[7,66–68]
	Resveratrol	Powerful antioxidant function, reducing oxidative stress, lowering MMP activity and protecting the extracellular matrix	[40,69–71]
	Rapamycin	mTOR inhibitor that reduces MMP9 and NOX1 mRNA expression levels	[72,73]
	Nicotinamide riboside	NAD^+ precursor that increases intracellular NAD^+ levels and restores mitochondrial metabolism	[23]

New Research Opportunities and Molecular Findings

Increasing studies focus on identifying novel therapeutic targets to stop MFS aortic growth. mTOR is an emerging molecular target, with its activation affecting TAA development.[74] Zaradzki et al injected rapamycin intraperitoneally into *Fbn1*$^{mgR/mgR}$ mice for two weeks and analyzed aortic changes by echocardiography, pathological staining, and immunofluorescence.[72] Rapamycin significantly inhibited mTOR downstream targets, including p-RPS6, tumor necrosis factor α, MMP-2, and MMP-9. Mathies et al showed that rapamycin also inhibits key oxidoreductase enzymes in SMCs of MFS mice, reducing SMC proliferation and migration to prevent TAA development.[73] Protein phosphatase 2A (PP2A) regulates the mTOR pathway through phosphorylation and dephosphorylation. Zhou et al orally administered the small molecule activator DT-061 to mice, which restored PP2A activity to inhibit the mTOR pathway, maintained the smooth muscle cell phenotype, and reduced extracellular matrix degradation, effectively mitigating aortic aneurysm progression.[75] The results show that reduced PP2A activity and hyperactivated mTOR signaling promote aortic dilatation and lesions. Targeting the PP2A-mTOR axis may be a potential therapeutic strategy for Marfan syndrome-associated aortic lesions.

PIEZO1 is a mechanosensitive ion channel, located in the cell membrane.[76] Yang et al established an MFS model in mice and explored PIEZO1's effects on MFS using specific knockout and PIEZO1 agonist injection.[77] Results showed increased inflammation, ECM remodeling, and TGF-β pathway activation in *Piezo1* knockout MFS mice. Injection of the PIEZO1 agonist Yoda 1 inhibited TGF-β pathway activation, enhanced ECM integrity, and protected VSMCs from apoptosis, thereby inhibiting and reversing TAA progression. Long-term Yoda 1 use exhibited no significant side effects, indicating good safety and therapeutic potential.[78] These findings suggest that PIEZO1 acts as a protective molecule, while PIEZO1 deficiency exacerbates MFS aneurysms. Targeting PIEZO1 signaling holds promise as a therapeutic strategy, with the agonist Yoda 1 being a strong candidate for clinical safety trials and potential development into a therapeutic drug.

Research in this field has been expanding, leading to the identification of several novel potential targets for mitigating the progression of TAA. However, it is essential to clarify the specific pathogenesis to identify novel targets for the treatment of MFS.

Surgical Treatment of MFS

Surgical treatment is essential in managing the multiple complications of the disease, especially in cardiovascular, ocular, and skeletal lesions.

Cardiovascular System

Survival in MFS patients primarily depends on cardiovascular disease severity. Cardiovascular manifestations include aortic root dilatation, aortic coarctation, and cardiac valvulopathy, with aortic root dilatation and coarctation being the most common and dangerous in MFS. Statistically, over 80% of individuals with MFS developed aortic root dilatation or mitral valve prolapse by age 18.[29] Surgery, particularly aortic root replacement (Bentall procedure) and valve-sparing root replacement (VSRR), is the main treatment for aortic root aneurysms and has improved patient survival.

Bentall Surgery is indicated in cases of significant dilatation of the aortic root and ascending aorta or the presence of severe aortic regurgitation, especially in patients with combined MFS. It uses an artificial vascular composite graft to perform replacement of the diseased site in the aortic root and reimplantation into the coronary artery. However, anticoagulation-related complications, such as bleeding or thrombosis, are major limitations after Bentall Surgery. And VSRR effectively solves this problem. Aortic root reimplantation (David surgery) is more complex and technically demanding than the Bentall surgery, but offers more opportunities for the patient. This method is for women of childbearing age who wish to preserve their fertility and avoid the side effects of anticoagulant medication, or for patients who are not suitable for lifelong anticoagulant therapy. Regardless of the underlying pathology, VSRR has a favorable survival rate and fewer complications compared to the Bentall procedure.

Regular monitoring of postoperative changes in aortic diameter, cardiac function, and neurologic function is essential for the management of the cardiovascular system in MFS patients. Timely surgical intervention, together with long-term comprehensive management, can effectively reduce the risk of cardiovascular events and significantly enhance patients' quality of life.

Eye System

High myopia, blurred vision, and ectopia lentis (EL) are the most common manifestations of the eye in patients with MFS, often appearing early in the course of MFS and progressing rapidly.[79] 45–87% of MFS patients have EL.[80] Therefore, ocular symptoms would also be emphasized in patients with MFS who do not present with typical cardiovascular symptoms. Eye exams such as slit lamp microscopy can help in the early detection of EL. Typically, individuals with obvious EL experience fluctuating or blurred vision or monocular diplopia. The optimal approach is surgical removal of the natural lens and insertion of an intraocular lens(IOL).[81] Lens removal and IOL fixation are challenging in MFS patients due to fragile banding fibers.[82]

The main surgical techniques currently used to treat EL in MFS patients include the following. The Simple capsular tension ring(CTR) procedure is relatively simple. It enhances the stability of the capsular bag by implanting a ring structure inside the bag to support the implanted IOL. CTR is suitable for adult patients with mild to moderate lens ectasia.[83,84] The modified capsular tension ring (m-CTR) is secured to the sclera on the outside of the eye by sutures to ensure greater stability.[85] It is indicated for children and adults with severe ectasia. Besides, Two-point scleral fixation provides high stability by fixing the IOL to the sclera with special sutures.[81] it is usually employed in cases where the lens capsule cannot be retained or is extremely unstable, despite it being more complicated. Some surgeries combine several of these methods, and the choice of surgery is tailored according to the individual's specific circumstances.[86]

Studies indicate that the majority of patients have improved postoperative vision regardless of the surgical technique used.[87] Best corrected visual acuity (BCVA) is one of the most important metrics for assessing the outcome of EL surgery. Chen et al carried out a study involving 109 patients with MFS who underwent IOL fixation by m-CTR. The findings indicated that patients' postoperative BCVA was significantly improved compared to preoperative levels, demonstrating a notable enhancement in vision.[88] Besides, age is one of the important factors affecting prognosis. By following 66 MFS patients after m-CTR implantation, Chen et al found that the older the patient, the more significant the decline in BCVA was after surgery.[82] Therefore, early diagnosis and treatment are more favorable for vision recovery in patients with MFS combined with EL.

The above studies are retrospective trials with limitations such as a small sample size of patients and a brief duration of follow-up. Future research needs to involve a larger number of patients who meet the criteria to determine the appropriate surgical methods.[89]

Skeletal System

In the skeletal system, MFS may lead to problems such as scoliosis, joint laxity, and skeletal deformities. Surgical treatment is an important tool in managing skeletal problems in patients with MFS. When the Cobb angle of scoliosis exceeds 40–50°, surgical treatment is usually recommended to avoid further worsening of respiratory insufficiency, back pain, and deformity.

Spinal deformity in MFS patients often presents as early-onset scoliosis (EOS). In such cases, traditional conservative treatments like casting or bracing are typically ineffective in halting the progression of the curve. For younger patients, growth-friendly surgery (GFS) represents a crucial option, designed to correct scoliosis while permitting continued spinal growth. Taniguchi et al noted that GFS may also be necessary for older MFS patients with EOS to achieve improved respiratory function.[90] For patients with large scoliosis angles or unsatisfactory outcomes from GFS, spinal fusion surgery might be required. This procedure can involve anterior release and posterior osteotomy followed by orthopedic fusion, securing the spine with screws and rods for long-term correction. Chotigavanichaya et al assessed clinical and radiographic outcomes following surgical scoliosis correction and posterior internal fixation fusion in MFS patients, demonstrating that this approach is safe and effective for treating MFS-related scoliosis, with no observed neurological complications or spinal derangements.[91]

Surgical intervention not only corrects cosmetic deformities but also alleviates symptoms such as dyspnea and back pain caused by scoliosis, thereby reducing the impact on cardiorespiratory function. Physical therapy and rehabilitation are required after scoliosis surgery to build strength and flexibility in the back muscles and improve spinal stabilization. Regular postural corrections and strengthening exercises help maintain the results of the surgery and reduce the risk of recurrence in MFS.

Application of Pluripotent Stem Cells in the Treatment of MFS

In recent years, the development of induced pluripotent stem cells (iPSCs) has generated optimism regarding the understanding of the pathogenesis of MFS and finding new therapeutic strategies. The generation of iPSC cells is mainly achieved by genetic reprogramming of mature somatic cells.[92] This process restores cells to an undifferentiated pluripotent state by introducing transcription factors such as Oct4, Sox2, Klf4, and c-Myc, which regulate the relevant genes.[93] iPSCs possess pluripotency similar to embryonic stem cells, meaning that they have the ability to differentiate into the various cell types that make up the body. iPSC induction methods commonly use viral vectors to deliver reprogramming factors, which results in their integration into the genome thereby enabling stable expression that facilitates the induction of iPSCs.[94] iPSCs have been utilized to model human development and diseases in vitro, screen pharmaceutical candidates, and develop cellular therapies.[94,95]

The iPSC-based cell model retains the genetic properties of the original cells and can be used for the study of disease analysis mechanisms. Granata et alstudied the pathogenesis of aortic aneurysm in MFS by iPSC derived from MFS patients.[96] They concluded through this model that p38 and KLF4 are engaged in the regulation of apoptosis in the aortic SMCs of patients with MFS. Nakamura et alconfirmed the pathological effect of integrin α-v in the development of aneurysms through the iPSC-derived SMCs model. They used integrin blockade in vivo to reduce related molecular activities, SMCs modulation, and aneurysm formation in the *Fbn1*$^{C1039G/+}$ Marfan mouse model.[97] Aalders et al developed an in vitro 3D culture model using cardiomyocytes and cardiac fibroblasts differentiated from iPSCs of MFS patients.[98] These models enhance understanding of specific cell contributions and disease mechanisms. It has been suggested that endothelial cell (EC) senescence is implicated in TAA pathogenesis.[99] Chen et al generated patient-specific iPSCs from MFS patients and differentiated them into ECs to mimic disease mechanisms.[100] The results confirmed that significant dysfunction and accelerated aging in the disease group and was associated with TGF-β and NF-κB signaling pathways. iPSC disease models have been employed to evaluate patient-specific cells by proteomic approaches. Iosef et al identified new protein markers connected to the MFS aneurysm phenotype through the iPSC SMC

model, providing data to support MFS genotype-phenotype correlation studies.[101] Additionally, the iPSC-derived cells were also applied to the screening and validation of therapeutic targets. Davaapil et al screened 1022 small molecules from the iPSC VSMC model and identified GSK3 β as a recurring target in the compound screen.[102] They utilized GSK3β inhibitors and gene knockdown techniques to enhance cell function and treated 3 MFS patients.

Despite the clinical application of iPSC in MFS is still in the research stage, its successful application in the establishment of disease models and the study of pathomechanisms offers a crucial basis for the development of novel therapeutic strategies in the future.

Gene Therapy for MFS

In recent years, advancements in molecular biology and genetic engineering technologies have prompted researchers to explore gene therapy as a potential solution to this issue. Gene therapy might restore normal function or alleviate a condition by repairing or replacing defective genes.

Adeno-Associated Virus-Mediated Gene Therapy

In gene therapy, the selection of appropriate delivery vectors is crucial. Adeno-associated virus (AAV) has become the preferred vector of choice in the field of genes due to its high safety profile, long-lasting holding expression, and wide host range. Ma et al summarized gene therapy drugs approved by national or regional drug regulatory agencies from August 1998 to August 2019.[103] Notably, three of the 22 approved gene therapy drugs use AAV as a vector.

The AP-1 pathway regulates MMPs, which degrade the extracellular matrix and elastic fibers.[104] Inhibiting AP-1 reduces MMP expression and protects elastic fibers. Arif et al used decoy oligodeoxynucleotides (dODN) to neutralize AP-1 activators and reduce MMP expression in mgR/mgR mice successfully.[105] Remes et al developed AAV-based delivery of AP-1 neutralizing RNA hairpin decoy oligonucleotide (hp dON) to prevent aortic elastolysis in $Fbn1^{mgR/mgR}$ mice.[106] Dihydroethylamine staining and Western blotting showed decreased ROS production, MMP expression, and monocyte infiltration. This study highlights the potential of AAV-based gene therapy.

P144, an inhibitory peptide derived from TGF-β receptor III, prevents TGF-β binding and activity.[107] Arce et al used AAV-mediated P144 delivery in the $Fbn1^{C1041G/+}$ mouse model, evaluating its effects on preventing aortic aneurysm formation.[108] The experiment was divided into two phases: prophylactic treatment (injected before aneurysm development) and palliative treatment (injected after aneurysm formation). Changes in the structure of the aortic wall and expression of TGFβ downstream products were observed by echocardiography, quantitative RT-PCR, and immunohistomorphometry. The results indicated that prophylactic treatment prevented aortic dilatation, while palliative treatment did not fully prevent aneurysm development, emphasizing the importance of early TGF-β mitigation in MFS.

Regnase-1 specifically recognizes and cleaves mRNA molecules with stem-loop structures, which are commonly found in the mRNAs of many pro-inflammatory cytokines.[109] Noormalal et al designed an AAV-based system to overexpress Regnase-1, reducing inflammation and preventing aortic aneurysms.[110] Immunohistochemistry and qt-PCR showed that mice had improved elastic fiber structure, reduced aortic diameter, and lower circulating levels of pro-inflammatory markers and TGFβ. This suggests that Regnase-1 effectively inhibits the inflammatory response and protects the structural integrity of the aortic wall.

The main limitation of these experiments is the absence of long-term studies to assess whether the proposed treatments extend the lifespan of Marfan mice. Future studies need to focus on the long-term effects of this therapy, especially in slowing or stopping aortic aneurysm development in MFS patients. Besides, the effects of different treatment time points should be explored to determine the most effective timing of intervention.

Genome Editing Technology

Gene editing refers to modifying specific genomic targets to achieve precise genetic alterations that affect an organism's genetic information and phenotype.[111] This technique relies mainly on nucleases such as CRISPR-Cas9, TALEN, and ZFNs to induce DNA cuts at specific sites, followed by the introduction of desired genetic changes via cellular repair mechanisms.[112] CRISPR-Cas9 is widely used due to its high efficiency and accuracy, facilitating gene function studies, disease modeling, and therapeutic strategy exploration. It employs artificially designed single-guide RNA (sgRNA) to

guide Cas9 to a specific DNA sequence, inducing a double-strand break (DSB) that enables gene insertion, deletion, or replacement.[113] As a powerful, cost-effective, and rapidly designed genome editing tool, CRISPR-Cas9 has been successfully applied across multiple species.[114]

The CRISPR-Cas9 system can be used to construct MFS animal models. CRISPR-Cas9 has been used to construct mouse models carrying specific *FBN1* mutations, which can mimic the clinical features of human MFS and are commonly used to study its pathogenesis and therapeutic strategies. Small animals such as rodents are not suitable as research models to mimic human surgical techniques for treating diseases of the cardiovascular or skeletal systems. Phenotypically similar large animals may help the creation of innovative treatment approaches for MFS patients. Umeyama et al used genome editing and somatic cell cloning to generate cloned pigs with *FBN1* mutations and their offspring.[115,116] These pigs exhibit phenotypes similar to those of MFS humans, including skeletal curvature, decreased bone density, and aortic elastic fiber rupture. However, pigs have the disadvantages of a long breeding cycle, high feeding costs, and the relative difficulty of gene editing technology. Zebrafish is highly homologous to total human genes, making them an ideal model for studying human genetic diseases.[117] Yin et al utilized CRISPR-Cas9 gene editing to enable zebrafish to mimic human *FBN1* defects and generate an $FBN1^{\pm}$ zebrafish model.[118] Huang et al performed identification and functional validation of *FBN1* variant nonsense mutations in a zebrafish model which aligns with the clinical.[119] These models provide better conditions for further studies on the pathogenicity of mutants and the advancement of new therapeutic approaches in MFS.

The CRISPR-Cas9 system has successfully repaired the *FBN1* pathogenic locus in MFS patient cells. Borsio et al used CRISPR-Cas9 to modify the *FBN1* gene in healthy donor hiPSCs.[120] Li et al applied CRISPR-Cas9 technology to repair *FBN1* mutations in iPSCs from MFS patients.[121] Genetically corrected cell lines exhibited a normal karyotype and maintained trilineage differentiation capabilities. Aalders et al generated iPSC lines carrying heterozygous variants of *FBN1* (c.7754 T >C) from patients with MFS. They repaired pathogenic variants with CRISPR-Cas9 technology and confirmed successful homology-directed repair via Sanger sequencing.[122] CRISPR-Cas9 successfully repaired the mutations in human iPSCs while maintaining the stem cell properties, providing valuable insights for the clinical translation of MFS gene therapy.

Base editor (BE) enables precise base modifications without inducing DNA double-strand breaks.[123] Komor et al designed a cytidine deaminase–CRISPR-Cas9 fusion to achieve direct C-to-T (or G-to-A) conversions through guide RNA.[123] Zeng et al identified a T7498C mutation in *FBN1* in an MFS patient as a BE correction candidate.[124] They microinjected a BE system containing corrected sgRNA to guide C-to-T transitions in fertilized eggs. Given that off-target mutagenesis is a principal issue in genome editing, the repaired embryos were characterized for safety. The results indicated that no off-targets or insertion deletions were detected, demonstrating that the system used to repair this site is safe and reliable. Compared with CRISPR-Cas9, BE avoids DSBs and reducing off-target risks and offering enhanced safety.

Future Perspectives

Despite significant advancements in MFS treatment over the past few decades, substantial work remains to be done. Individuals with MFS exhibit a notably higher incidence of aortic surgery compared to other patients undergoing vascular procedures.[125] The variability in patient responses to medications underscores the necessity for identifying additional therapeutic agents for MFS. This requires a clearer understanding of the pathogenic mechanisms underlying MFS and the discovery of novel therapeutic targets. Wang integrated bioinformatics and machine learning strategies provided four potential markers for MFS pathogenesis. This may provide a basis for future investigations into potential key candidate genes.[126]

Mouse models have illuminated critical aspects of MFS aortic pathology, but translating these findings to clinical applications remains challenging. Since researchers almost perform prevention studies in mice, such as TGF-β pathway antagonism to delay aortic dilatation. However, clinical MFS patients already have degenerated tissues that require drugs that promote tissue regeneration rather than merely aneurysm suppression. This stage-specific difference poses a challenge for translational medicine. Future studies should integrate stage-specific targets to bridge the gap between animal models and clinical needs. Looking forward, personalized medicine may allow for the selection of the most suitable drug combinations and dosages tailored to individual patients, thereby improving therapeutic outcomes and minimizing adverse effects.

Gene therapy represents theoretical promise for treating MFS, but clinical application faces three major obstacles: ① The complexity of gene mutations involved in MFS requires precise targeting strategies. ② A stable delivery system is essential for in vivo editing to effectively deliver the editing components into target cells. ③ Ethical considerations would be addressed regarding the manipulation of genetic material.

Gene editing may cause off-target effects by cleaving or modifying non-target DNA sequences. The *FBN1* gene encompasses over 3000 mutations, including point mutations, deletions, insertions, and others, complicating universal MFS gene therapy design. Notably, mutations vary both inter- and intra-familially, compounding this complexity. Current research primarily enhances target specificity through the development of nucleic acid endonuclease variants and optimizing guide RNA design. Computational algorithms and bioinformatics tools might predict potential off-target sites.[127] Secondly, achieving accurate gene delivery while avoiding off-target effects and ensuring long-term safety are critical considerations in gene therapy development. Viral vectors are preferred delivery vectors but carry the risk of inducing an immune response in the host. Non-viral delivery systems like nanoparticles and electroporation reduce immunogenicity and increase precision. Lipid and polymer nanoparticles enhance precision, specificity, and efficiency of Cas9.[128] A reliable delivery system also minimizes off-target effects. When applying gene editing as a clinical method, it is imperative to not only address off-target effects and delivery systems, but also establish an international ethical standards consensus, technology's applicable scope and regulatory pathway.

In summary, facilitating the translation of basic research findings into clinical applications is key to improving the treatment of MFS. Considering the complexity and variability of MFS, an effective treatment approach will necessitate a multidisciplinary and integrated management strategy. Specialists including cardiologists, ophthalmologists, orthopedic surgeons, geneticists, and psychologists will collaborate to develop personalized treatment plans. Such plans aim not only to prolong the patient's lives but also to improve their overall quality of life in a holistic manner.

Abbreviations

AAV, adeno-associated virus; ABE, adenine base editor; AP-1, activator protein-1; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor antagonists; BCVA, best corrected visual acuity; BE, base editor; CCBs, calcium channel blockers; CTR, capsular tension ring; dODN, decoy oligodeoxynucleotides; DSB, double-strand break; EL, ectopia lentis; EOS, early-onset scoliosis; GFS, growth-friendly surgery; CGBE, glycosylase base editor; HDR, homology-directed repair; hp dON, hairpin deceptive oligonucleotide; iPSC, induced pluripotent stem cells; IOL, intraocular lens; LBTP, latent Transforming Growth Factor Beta Binding Protein; MMPs, matrix metalloproteinases; MFS, marfan syndrome; mTOR, mechanistic target of rapamycin; m-CTR, modified capsular tension ring; NHEJ, non-homologous end Joining; PE, prime editor; p-RPS6, phosphorylated ribosomal protein S6; RIs, renin inhibitors; ROS, reactive oxygen species; SgRNA, single-guide RNA; SMCs, smooth muscle cells; TAA, thoracic aortic aneurysm; TGF-β, transforming growth factor-beta; TALEN, transcription activator-like effector nuclease; twin PE, twin prime editing; VITB, vitamin B complex; VSRR, valve-sparing root replacement; ZFN, zinc finger nuclease.

Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

Funding

This work was supported by grants from Chengdu Municipal Health Commission (2024025), Key Research and Development Project of Sichuan Provincial Science and Technology Department (2023YFS0311).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Marelli S, Micaglio E, Taurino J, et al. Marfan syndrome: enhanced diagnostic tools and follow-up management strategies. *Diagnostics*. 2023;13(13):2284. doi:10.3390/diagnostics13132284
2. Pollock L, Ridout A, Teh J, et al. The musculoskeletal manifestations of marfan syndrome: diagnosis, impact, and management. *Curr Rheumatol Rep*. 2021;23(11):81. doi:10.1007/s11926-021-01045-3
3. Coelho SG, Almeida AG. Síndrome de Marfan revisitada – da genética à clínica. [Marfan syndrome revisited: from genetics to the clinic]. *Revista portuguesa de cardiologia*. 2020;39(4):215–226. doi:10.1016/j.repc.2019.09.008
4. Wang JJ, Yu B, Sun Y, Song X, Wang DW, Li Z. FBN1 splice-altering mutations in marfan syndrome: a case report and literature review. *Genes*. 2022;13(10). doi:10.3390/genes13101842
5. Connolly HM, Niaz T, Bowen JM. What is Marfan syndrome? *JAMA*. 2023;329(18):1618. doi:10.1001/jama.2023.3826
6. Yang Y, Xie E, Liu Y, et al. Calcium promotes vascular smooth muscle cell phenotypic switching in Marfan syndrome. *Biochem Biophys Res Commun*. 2023;665:124–132. doi:10.1016/j.bbrc.2023.05.017
7. Chiu HH. An update of medical care in Marfan syndrome. *Tzu chi Med J*. 2022;34(1):44–48. doi:10.4103/tcmj.tcmj_95_20
8. Salik I, Rawla P. Marfan Syndrome. In: *StatPearls*. StatPearls Publishing LLC; 2024.
9. van Andel MM, Indrakusuma R, Jalalzadeh H, et al. Long-term clinical outcomes of losartan in patients with Marfan syndrome: follow-up of the multicentre randomized controlled COMPARE trial. *Eur Heart J*. 2020;41(43):4181–4187. doi:10.1093/eurheartj/ehaa377
10. Aranson NJ, Patel PB, Mohebali J, et al. Presentation, surgical intervention, and long-term survival in patients with Marfan syndrome. *J Vascular Surg*. 2020;72(2):480–489. doi:10.1016/j.jvs.2019.10.060
11. Kilpatrick MW, Phylactou LA. Towards an RNA-based therapy for Marfan syndrome. *Mol Med Today*. 1998;4(9):376–381. doi:10.1016/s1357-4310(98)01326-4
12. Montgomery RA. Inhibition of fibrillin 1 expression using U1 snRNA as a vehicle for the presentation of antisense targeting sequence. *Human Mol Genetics*. 1997;6(4):519–525. doi:10.1093/hmg/6.4.519
13. Zeigler SM, Sloan B, Jones JA. Pathophysiology and pathogenesis of Marfan syndrome. *Adv Exp Med Biol*. 2021;1348:185–206. doi:10.1007/978-3-030-80614-9_8
14. Ramachandra CJ, Mehta A, Guo KW, Wong P, Tan JL, Shim W. Molecular pathogenesis of Marfan syndrome. *Int J Cardiol*. 2015;187:585–591. doi:10.1016/j.ijcard.2015.03.423
15. Spencer M. Marfan syndrome. *Nursing*. 2024;54(4):19–25. doi:10.1097/01.NURSE.0001007604.09204.9a
16. Du Q, Zhang D, Zhuang Y, Xia Q, Wen T, Jia H. The molecular genetics of Marfan syndrome. *Int J Med Sci*. 2021;18(13):2752–2766. doi:10.7150/ijms.60685
17. Van Den Heuvel LJF, Peeters S, Meester JAN, Coucke PJ, Loeys BL. An exploration of alternative therapeutic targets for aortic disease in Marfan syndrome. *Drug Discovery Today*. 2024;29(7):104023. doi:10.1016/j.drudis.2024.104023
18. Rodrigues Bento J, Meester J, Luyckx I, Peeters S, Verstraeten A, Loeys B. The genetics and typical traits of thoracic aortic aneurysm and dissection. *Ann Rev Genomics Hum Genet*. 2022;23:223–253. doi:10.1146/annurev-genom-111521-104455
19. Oller J, Méndez-Barbero N, Ruiz EJ, et al. Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome. *Nature Med*. 2017;23(2):200–212. doi:10.1038/nm.4266
20. Toral M, de la Fuente-Alonso A, Campanero MR, Redondo JM. The NO signalling pathway in aortic aneurysm and dissection. *Br J Pharmacol*. 2022;179(7):1287–1303. doi:10.1111/bph.15694
21. Jiménez-Altayó F, Meirelles T, Crosas-Molist E, et al. Redox stress in Marfan syndrome: dissecting the role of the NADPH oxidase NOX4 in aortic aneurysm. *Free Radic Biol Med*. 2018;118:44–58. doi:10.1016/j.freeradbiomed.2018.02.023
22. You W, Hong Y, He H, et al. TGF-β mediates aortic smooth muscle cell senescence in Marfan syndrome. *Aging*. 2019;11(11):3574–3584. doi:10.18632/aging.101998
23. Oller J, Gabandé-Rodríguez E, Ruiz-Rodríguez MJ, et al. Extracellular tuning of mitochondrial respiration leads to aortic aneurysm. *Circulation*. 2021;143(21):2091–2109. doi:10.1161/circulationaha.120.051171
24. Zhang H, Tsui CK, Garcia G, et al. The extracellular matrix integrates mitochondrial homeostasis. *Cell*. 2024;187(16):4289–4304.e26. doi:10.1016/j.cell.2024.05.057
25. Marcos-Ríos D, Rochano-Ortiz A, San Sebastián-Jaraba I, Fernández-Gómez MJ, Méndez-Barbero N, Oller J. Mitochondrial dysfunction: a new hallmark in hereditable thoracic aortic aneurysm development. *Cells*. 2025;14(8). doi:10.3390/cells14080618
26. Pepe G, Giusti B, Sticchi E, Abbate R, Gensini GF, Nistri S. Marfan syndrome: current perspectives. *Appl Clinical Genetics*. 2016;9:55–65. doi:10.2147/tacg.S96233
27. Koo HK, Lawrence KA, Musini VM. Beta-blockers for preventing aortic dissection in Marfan syndrome. *Cochrane Database Syst Rev*. 2017;11(11):Cd011103. doi:10.1002/14651858.CD011103.pub2
28. Habashi JP, Judge DP, Holm TM, et al. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006;312(5770):117–121. doi:10.1126/science.1124287
29. Huang S-H, Lin C-Y, Wu M-H, Kang Y-N, Hui-Chiu H. The Effects of Medication Strategies on Cardiovascular Outcomes in Patients with Marfan Syndrome: a Consistency Model Analysis. *medRxiv*. 2023;2023.03.27.23287828. doi:10.1101/2023.03.27.23287828
30. Kang YN, Chi SC, Wu MH, Chiu HH. The effects of losartan versus beta-blockers on cardiovascular protection in marfan syndrome: a systematic review and meta-analysis. *J Formosan Med Assoc*. 2020;119(1 Pt 1):182–190. doi:10.1016/j.jfma.2019.03.018
31. Robertson DM, Truong DT, Cox DA, et al. Pediatric heart network trial of Losartan vs atenolol in children and young adults With Marfan Syndrome: impact on prescription practices. *Pediatr Cardiol*. 2023;44(3):618–623. doi:10.1007/s00246-022-02976-z

32. Wang Z, Deng X, Kang X, Hu A. Angiotensin receptor blockers vs beta-blocker therapy for Marfan syndrome: a systematic review and meta-analysis. *Ann Vasc Surg*. 2022;82:347–361. doi:10.1016/j.avsg.2021.12.073
33. Lacro RV, Dietz HC, Sleeper LA, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. *New Engl J Med*. 2014;371(22):2061–2071. doi:10.1056/NEJMoa1404731
34. Pitcher A, Spata E, Emberson J, et al. Angiotensin receptor blockers and β blockers in Marfan syndrome: an individual patient data meta-analysis of randomised trials. *Lancet*. 2022;400(10355):822–831. doi:10.1016/s0140-6736(22)01534-3
35. Hofmann Bowman MA, Eagle KA, Milewicz DM. Update on clinical trials of losartan with and without β-blockers to block aneurysm growth in patients with Marfan syndrome: a review. *JAMA Cardiol*. 2019;4(7):702–707. doi:10.1001/jamacardio.2019.1176
36. Deleeuw V, De Clercq A, De Backer J, Sips P. An overview of investigational and experimental drug treatment strategies for Marfan syndrome. *J Exp Pharmacol*. 2021;13:755–779. doi:10.2147/jep.S265271
37. Cicco S, DA M, Proietti M, et al. Antihypertensive treatment changes and related clinical outcomes in older hospitalized patients. *Eur J Clin Invest*. 2023;53(4):e13931. doi:10.1111/eci.13931
38. Doyle JJ, Doyle AJ, Wilson NK, et al. A deleterious gene-by-environment interaction imposed by calcium channel blockers in Marfan syndrome. *eLife*. 2015;4. doi:10.7554/eLife.08648
39. Rossi-Foulkes R, Roman MJ, Rosen SE, et al. Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan syndrome. *Am J Cardiol*. 1999;83(9):1364–1368. doi:10.1016/s0002-9149(99)00101-0
40. van Andel MM, Groenink M, Zwinderman AH, Mulder BJM, de Waard V. The potential beneficial effects of resveratrol on cardiovascular complications in Marfan syndrome patients–insights from rodent-based animal studies. *Int J Mol Sci*. 2019;20(5). doi:10.3390/ijms20051122
41. Huang TH, Chang HH, Guo YR, Chang WC, Chen YF. Vitamin B mitigates thoracic aortic dilation in Marfan syndrome mice by restoring the canonical TGF-β pathway. *Int J Mol Sci*. 2021;22(21). doi:10.3390/ijms222111737
42. Arnaud P, Milleron O, Hanna N, et al. Clinical relevance of genotype-phenotype correlations beyond vascular events in a cohort study of 1500 Marfan syndrome patients with FBN1 pathogenic variants. *Genetics Med*. 2021;23(7):1296–1304. doi:10.1038/s41436-021-01132-x
43. Saddic L, Escopete S, Zilberberg L, et al. 17 β-estradiol impedes aortic root dilation and rupture in male Marfan mice. *Int J Mol Sci*. 2023;24 (17). doi:10.3390/ijms241713571
44. Zhang F, Yao K, Liu Y, et al. Complement C3a/C3aR inhibition alleviates the formation of aortic aneurysm in Marfan syndrome mice. *BMC Cardiovasc Disorders*. 2024;24(1):417. doi:10.1186/s12872-024-04077-6
45. Kalyanaraman H, Casteel DE, Cabriales JA, et al. The antioxidant/nitric oxide-quenching agent cobinamide prevents aortic disease in a mouse model of Marfan syndrome. *JACC*. 2024;9(1):46–62. doi:10.1016/j.jacbts.2023.07.014
46. Teixido-Tura G, Forteza A, Rodríguez-Palomares J, et al. Losartan versus atenolol for prevention of aortic dilation in patients with Marfan syndrome. *J Am Coll Cardiol*. 2018;72(14):1613–1618. doi:10.1016/j.jacc.2018.07.052
47. Liu LH, Lin SM, Lin DS, Chen MR. Losartan in combination with propranolol slows the aortic root dilatation in neonatal Marfan syndrome. *Pediatr Neonatol*. 2018;59(2):211–213. doi:10.1016/j.pedneo.2017.07.005
48. Tehrani AY, White Z, Milad N, Esfandiarei M, Seidman MA, Bernatchez P. Blood pressure-independent inhibition of Marfan aortic root widening by the angiotensin II receptor blocker valsartan. *Physiological Reports*. 2021;9(10):e14877. doi:10.14814/phy2.14877
49. Spoto S, Valeriani E, Locorriere L, et al. Use of sacubitril/valsartan in Marfan syndrome-related cardiomyopathy: the first case report. *Medicine*. 2019;98(47):e17978. doi:10.1097/md.0000000000017978
50. Isselbacher EM. Losartan for the treatment of Marfan syndrome: hope fades. *J Am Coll Cardiol*. 2018;72(14):1619–1621. doi:10.1016/j.jacc.2018.07.051
51. Phomakay V, Huett WG, Gossett JM, Tang X, Bornemeier RA, Collins RT. β-Blockers and angiotensin converting enzyme inhibitors: comparison of effects on aortic growth in pediatric patients with Marfan syndrome. *J Pediatr*. 2014;165(5):951–955. doi:10.1016/j.jpeds.2014.07.008
52. Williams A, Kenny D, Wilson D, et al. Effects of atenolol, perindopril and verapamil on haemodynamic and vascular function in Marfan syndrome - a randomised, double-blind, crossover trial. *Eur J Clin Invest*. 2012;42(8):891–899. doi:10.1111/j.1365-2362.2012.02668.x
53. Hwang JW, Kim EK, Jang SY, et al. Comparison of the effect of aliskiren versus negative controls on aortic stiffness in patients with Marfan syndrome under treatment with atenolol. *Revista espanola de cardiologia*. 2018;71(9):743–749. doi:10.1016/j.rec.2017.10.028
54. Guido MC, Lopes NM, Albuquerque CI, et al. Treatment with methotrexate associated with lipid core nanoparticles prevents aortic dilation in a murine model of Marfan syndrome. *Front Cardiovasc Med*. 2022;9:893774. doi:10.3389/fcvm.2022.893774
55. Guo G, Ott CE, Grünhagen J, et al. Indomethacin prevents the progression of thoracic aortic aneurysm in Marfan syndrome mice. *Aorta*. 2013;1 (1):5–12. doi:10.12945/j.aorta.2013.13.007
56. Lim WW, Dong J, Ng B, et al. Inhibition of IL11 signaling reduces aortic pathology in murine Marfan syndrome. *Circ Res*. 2022;130 (5):728–740. doi:10.1161/circresaha.121.320381
57. Tehrani AY, Cui JZ, Bucky jones T, et al. Characterization of doxycycline-mediated inhibition of Marfan syndrome-associated aortic dilation by multiphoton microscopy. *Sci Rep*. 2020;10(1):7154. doi:10.1038/s41598-020-64071-8
58. Cui JZ, Lee L, Sheng X, et al. In vivo characterization of doxycycline-mediated protection of aortic function and structure in a mouse model of Marfan syndrome-associated aortic aneurysm. *Sci Rep*. 2019;9(1):2071. doi:10.1038/s41598-018-38235-6
59. Chung AW, Yang HH, Radomski MW, van Breemen C. Long-term doxycycline is more effective than atenolol to prevent thoracic aortic aneurysm in marfan syndrome through the inhibition of matrix metalloproteinase-2 and −9. *Circ Res*. 2008;102(8):e73–85. doi:10.1161/circresaha.108.174367
60. Lindeman JH, Abdul-Hussien H, van Bockel JH, Wolterbeek R, Kleemann R. Clinical trial of doxycycline for matrix metalloproteinase-9 inhibition in patients with an abdominal aneurysm: doxycycline selectively depletes aortic wall neutrophils and cytotoxic T cells. *Circulation*. 2009;119(16):2209–2216. doi:10.1161/circulationaha.108.806505
61. Xiong W, Knispel RA, Dietz HC, Ramirez F, Baxter BT. Doxycycline delays aneurysm rupture in a mouse model of Marfan syndrome. *J Vascular Surg*. 2008;47(1):166–72;discussion172. doi:10.1016/j.jvs.2007.09.016
62. Rodríguez-Rovira I, Arce C, De Rycke K, et al. Allopurinol blocks aortic aneurysm in a mouse model of Marfan syndrome via reducing aortic oxidative stress. *Free Radic Biol Med*. 2022;193(Pt 2):538–550. doi:10.1016/j.freeradbiomed.2022.11.001
63. Emrich F, Penov K, Arakawa M, et al. Anatomically specific reactive oxygen species production participates in Marfan syndrome aneurysm formation. *J Cell Mol Med*. 2019;23(10):7000–7009. doi:10.1111/jcmm.14587

64. Tashima Y, He H, Cui JZ, et al. Androgens accentuate TGF-β dependent Erk/Smad activation during thoracic aortic aneurysm formation in Marfan syndrome male mice. *J Am Heart Assoc*. 2020;9(20):e015773. doi:10.1161/jaha.119.015773
65. Habashi JP, MacFarlane EG, Bagirzadeh R, et al. Oxytocin antagonism prevents pregnancy-associated aortic dissection in a mouse model of Marfan syndrome. *Sci Trans Med*. 2019;11(490). doi:10.1126/scitranslmed.aat4822
66. Sato T, Arakawa M, Tashima Y, et al. Statins reduce thoracic aortic aneurysm growth in Marfan syndrome mice via inhibition of the Ras-induced ERK (Extracellular Signal-Regulated Kinase) signaling pathway. *J Am Heart Assoc*. 2018;7(21):e008543. doi:10.1161/jaha.118.008543
67. Tsigkou V, Siasos G, Mpletsa E, et al. Statins in aortic disease. *Curr Pharm Des*. 2017. doi:10.2174/1381612823666171115100829
68. McLoughlin D, McGuinness J, Byrne J, et al. Pravastatin reduces Marfan aortic dilation. *Circulation*. 2011;124(11 Suppl):S168–73. doi:10.1161/circulationaha.110.012187
69. Hibender S, Franken R, van Roomen C, et al. Resveratrol inhibits aortic root dilatation in the Fbn1C1039G/+ Marfan mouse model. *Arteriosclerosis Thrombosis Vasc Biol*. 2016;36(8):1618–1626. doi:10.1161/atvbaha.116.307841
70. Mieremet A, van der Stoel M, Li S, et al. Endothelial dysfunction in Marfan syndrome mice is restored by resveratrol. *Sci Rep*. 2022;12 (1):22504. doi:10.1038/s41598-022-26662-5
71. van Andel MM, Bosshardt D, Schrauben EM, et al. Effects of resveratrol on aortic growth in patients with Marfan syndrome: a single-arm open-label multicentre trial. *Heart*. 2024;111(1):11–17. doi:10.1136/heartjnl-2024-324343
72. Zaradzki M, Mohr F, Lont S, et al. Short-term rapamycin treatment increases life span and attenuates aortic aneurysm in a murine model of Marfan-syndrome. *Biochem Pharmacol*. 2022;205:115280. doi:10.1016/j.bcp.2022.115280
73. Mathies M, Krieg EM, Mohr F, Zaradzki M, Wagner AH. Effects of rapamycin on the expression of redox enzymes in aortic vascular smooth muscle cells from Marfan syndrome mice. *Pharmacology*. 2022;107(11–12):615–622. doi:10.1159/000526624
74. Li G, Wang M, Caulk AW, et al. Chronic mTOR activation induces a degradative smooth muscle cell phenotype. *J Clin Invest*. 2020;130 (3):1233–1251. doi:10.1172/jci131048
75. Zhou X, Xu Q, Hu X, et al. PP2A attenuates thoracic aneurysm and dissection in mouse models of Marfan syndrome. *Hypertension*. 2025;82 (4):665–679. doi:10.1161/hypertensionaha.124.23494
76. Zhao Q, Zhou H, Chi S, et al. Structure and mechanogating mechanism of the Piezo1 channel. *Nature*. 2018;554(7693):487–492. doi:10.1038/ nature25743
77. Yang P, Liu H, Wang S, et al. PIEZO1 attenuates Marfan syndrome aneurysm development through TGF-β signaling pathway inhibition via TGFBR2. *Eur Heart J*. 2025;46(10):958–974. doi:10.1093/eurheartj/ehae786
78. Komuro J, Takeda N, Komuro I. PIEZO1 as a potential therapeutic target in Marfan syndrome. *Eur Heart J*. 2025;46(10):975–977. doi:10.1093/ eurheartj/ehae882
79. Milewicz DM, Braverman AC, De Backer J, et al. Marfan syndrome. *Nat Rev Dis Primers*. 2021;7(1):64. doi:10.1038/s41572-021-00298-7
80. Li D, Qiao J, Huang D, Guo R, Ji J, Liu W. Novel and recurrent FBN1 mutations causing Marfan syndrome in two Chinese families. *Front Med*. 2022;9:1086844. doi:10.3389/fmed.2022.1086844
81. Dogaroiu AC, Dudau M, Dogaroiu C, Tataru CP. Visual outcomes in ectopia lentis in Marfan syndrome: a study of four surgical techniques in children and adults. *Medicina*. 2024;60(7). doi:10.3390/medicina60071098
82. Chen T, Deng M, Zhang M, Chen J, Chen Z, Jiang Y. Visual outcomes of lens subluxation surgery with Cionni modified capsular tension rings in Marfan syndrome. *Sci Rep*. 2021;11(1):2994. doi:10.1038/s41598-021-82586-6
83. Dhiman R, Kaur L, Sharma N, Pandey ML. Diverse presentations of ectopia lentis and lens coloboma in Marfan's syndrome. *Oman J Ophthalmol*. 2023;16(2):310–313. doi:10.4103/ojo.ojo_108_22
84. Shiraki A, Sakaguchi H, Nishida K. New, simple, and safe surgical technique for the removal of a dislocated capsular tension ring-intraocular lens-capsular bag complex. *Retinal Cases Brief Rep*. 2023;17(2):134–136. doi:10.1097/icb.0000000000001119
85. Zhang M, Chen T, Deng M, Chen Z, Jiang Y. Accuracy of IOL power calculation formulas in Marfan lens subluxation patients with in-the-bag IOLs and implantation of scleral-sutured single-eyelet modified capsular tension rings. *J Cataract Refract Surg*. 2021;47(11):1423–1429. doi:10.1097/j.jcrs.0000000000000649
86. Bulut MN, Göktaş E, Karadağ E, Bulut K, Oral AY, Ş Ş. Sutureless Scleral-fixated intraocular lens implantation in the treatment of congenital lens subluxation related to Marfan syndrome. *J Pediatric Ophthalmol Strabismus*. 2021;58(6):401–406. doi:10.3928/01913913-20210428-02
87. Dogăroiu AC, Dogăroiu C, Tătaru CP. Ectopia lentis surgery in Marfan's syndrome: from "couching" to the use of intracapsular tension rings. *Romanian J Ophthalmol*. 2022;66(1):2–7. doi:10.22336/rjo.2022.2
88. Chen Z, Zhang M, Deng M, et al. Surgical outcomes of modified capsular tension ring and intraocular lens implantation in Marfan syndrome with ectopia lentis. *Eur J Ophthalmol*. 2021:11206721211012868. doi:10.1177/11206721211012868
89. Erdogan G, Kandemir Besek N, Onal Gunay B, Agca A. Outcomes of three surgical approaches for managing ectopia lentis in Marfan syndrome. *Eur J Ophthalmol*. 2022;32(1):242–248. doi:10.1177/11206721211992950
90. Taniguchi Y, Tauchi R, Suzuki T, et al. Mid- to long-term radiological and respiratory outcomes following surgery for older early-onset scoliosis patients with Marfan syndrome. *Sci Rep*. 2024;14(1):23302. doi:10.1038/s41598-024-75413-1
91. Chotigavanichaya C, Vatidvarodom P, Ariyawatkul T, et al. Surgical outcome of scoliosis in patients with Marfan syndrome. *Spine Deformity*. 2022;10(6):1453–1460. doi:10.1007/s43390-022-00547-z
92. Zhu K, Ma W, Li J, et al. Modeling aortic diseases using induced pluripotent stem cells. *Stem Cells Transl Med*. 2021;10(2):190–197. doi:10.1002/sctm.20-0322
93. Velychko S, Adachi K, Kim KP, et al. Excluding Oct4 from Yamanaka cocktail unleashes the developmental potential of iPSCs. *Cell Stem Cell*. 2019;25(6):737–753.e4. doi:10.1016/j.stem.2019.10.002
94. Cerneckis J, Cai H, Shi Y. Induced pluripotent stem cells (iPSCs): molecular mechanisms of induction and applications. *Signal Transduct Target Ther*. 2024;9(1):112. doi:10.1038/s41392-024-01809-0
95. Davaapil H, Shetty DK, Sinha S. Aortic "Disease-in-a-Dish": mechanistic insights and drug development using iPSC-based disease modeling. *Front Cell Develop Biol*. 2020;8:550504. doi:10.3389/fcell.2020.550504
96. Granata A, Serrano F, Bernard WG, et al. An iPSC-derived vascular model of Marfan syndrome identifies key mediators of smooth muscle cell death. *Nature Genet*. 2017;49(1):97–109. doi:10.1038/ng.3723

97. Nakamura K, Dalal AR, Yokoyama N, et al. Lineage-specific induced pluripotent stem cell-derived smooth muscle cell modeling predicts integrin Alpha-V antagonism reduces aortic root aneurysm formation in Marfan syndrome mice. *Arteriosclerosis Thrombosis Vasc Biol*. 2023;43(7):1134–1153. doi:10.1161/atvbaha.122.318448
98. Aalders J, Léger L, Van der Meeren L, et al. Three-dimensional co-culturing of stem cell-derived cardiomyocytes and cardiac fibroblasts reveals a role for both cell types in Marfan-related cardiomyopathy. *Matrix Biol*. 2024;126:14–24. doi:10.1016/j.matbio.2024.01.003
99. Jauhiainen S, Kiema M, Hedman M, Laakkonen JP. Large vessel cell heterogeneity and plasticity: focus in aortic aneurysms. *Arteriosclerosis Thrombosis Vasc Biol*. 2022;42(7):811–818. doi:10.1161/atvbaha.121.316237
100. Chen Y, Zhu Y, Ren X, et al. Endothelial cell senescence in Marfan syndrome: pathogenesis and therapeutic potential of TGF-β pathway inhibition. *J Am Heart Assoc*. 2025;14(9):e037826. doi:10.1161/jaha.124.037826
101. Iosef C, Pedroza AJ, Cui JZ, et al. Quantitative proteomics reveal lineage-specific protein profiles in iPSC-derived Marfan syndrome smooth muscle cells. *Sci Rep*. 2020;10(1):20392. doi:10.1038/s41598-020-77274-w
102. Davaapil H, McNamara M, Granata A, et al. A phenotypic screen of Marfan syndrome iPSC-derived vascular smooth muscle cells uncovers GSK3β as a new target. *Stem Cell Rep*. 2023;18(2):555–569. doi:10.1016/j.stemcr.2022.12.014
103. Ma C-C, Wang Z-L, Xu T, He Z-Y, Wei Y-Q. The approved gene therapy drugs worldwide: from 1998 to 2019. *Biotechnol Adv*. 2020;40:107502. doi:10.1016/j.biotechadv.2019.107502
104. Zhang H-W, Wang X, Zong Z-H, Huo X, Zhang Q. AP-1 inhibits expression of MMP-2/9 and its effects on rat smooth muscle cells. *J Surg Res*. 2009;157(1):e31–7. doi:10.1016/j.jss.2009.02.015
105. Arif R, Zaradzki M, Remes A, et al. AP-1 oligodeoxynucleotides reduce aortic elastolysis in a murine model of Marfan syndrome. *Molecular Therapy - Nucleic Acids*. 2017;9:69–79. doi:10.1016/j.omtn.2017.08.014
106. Remes A, Arif R, Franz M, et al. AAV-mediated AP-1 decoy oligonucleotide expression inhibits aortic elastolysis in a mouse model of Marfan syndrome. *Cardiovasc Res*. 2021;117(12):2459–2473. doi:10.1093/cvr/cvab012
107. Dotor J, López-Vázquez AB, Lasarte JJ, et al. Identification of peptide inhibitors of transforming growth factor beta 1 using a phage-displayed peptide library. *Cytokine*. 2007;39(2):106–115. doi:10.1016/j.cyto.2007.06.004
108. Arce C, Rodríguez-Rovira I, De Rycke K, et al. Anti-TGFβ (Transforming Growth Factor β) therapy with betaglycan-derived P144 peptide gene delivery prevents the formation of aortic aneurysm in a Mouse model of Marfan syndrome. *Arteriosclerosis Thrombosis Vasc Biol*. 2021;41(9):e440–e452. doi:10.1161/atvbaha.121.316496
109. Egea G. Navigating toward gene therapy in Marfan syndrome: a hope for halting aortic aneurysm. *Mol Ther Methods Clin Dev*. 2024;32(1):101196. doi:10.1016/j.omtm.2024.101196
110. Noormalal M, Schmiedel N, Bozoglu T, et al. Regnase-1 overexpression as a therapeutic approach of Marfan syndrome. *Mol Ther Methods Clin Dev*. 2024;32(1):101163. doi:10.1016/j.omtm.2023.101163
111. Khalil AM. The genome editing revolution: review. *J Genetic Engin Biotechnol*. 2020;18(1):68. doi:10.1186/s43141-020-00078-y
112. Gaj T, Gersbach CA, Barbas CF. ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering. *Trends Biotechnol*. 2013;31(7):397–405. doi:10.1016/j.tibtech.2013.04.004
113. Gupta D, Bhattacharjee O, Mandal D, et al. CRISPR-Cas9 system: a new-fangled Dawn in gene editing. *Life Sci*. 2019;232:116636. doi:10.1016/j.lfs.2019.116636
114. Janik E, Niemcewicz M, Ceremuga M, Krzowski L, Saluk-Bijak J, Bijak M. Various aspects of a gene editing system—CRISPR–Cas9. *Int J Mol Sci*. 2020;21(24):9604. doi:10.3390/ijms21249604
115. Summers KM, Jafar-Nejad H. Genetic models of fibrillinopathies. *Genetics*. 2024;226(1). doi:10.1093/genetics/iyad189
116. Umeyama K, Watanabe K, Watanabe M, et al. Generation of heterozygous fibrillin-1 mutant cloned pigs from genome-edited foetal fibroblasts. *Sci Rep*. 2016;6(1):24413. doi:10.1038/srep24413
117. Fontana BD, Mezzomo NJ, Kalueff AV, Rosemberg DB. The developing utility of zebrafish models of neurological and neuropsychiatric disorders: a critical review. *Exp Neurol*. 2018;299(Pt A):157–171. doi:10.1016/j.expneurol.2017.10.004
118. Yin X, Hao J, Yao Y. CRISPR/Cas9 in zebrafish: an attractive model for FBN1 genetic defects in humans. *Mol Genetics Genom Med*. 2021;9(10):e1775. doi:10.1002/mgg3.1775
119. Huang S, Chen J, Wang Q, et al. Identification and functional validation of a novel FBN1 variant in a Marfan syndrome family using a zebrafish model. *BMC Genomics*. 2025;26(1):288. doi:10.1186/s12864-025-11471-7
120. Borsoi J, Farinha-Arcieri LE, Morato-Marques M, Delgado Sarafian R, Pinheiro M, Veiga Pereira L. Generation of genetically modified human induced pluripotent stem cell lines harboring haploin sufficient or dominant negative variants in the FBN1 gene. *Stem Cell Res*. 2021;54:102434. doi:10.1016/j.scr.2021.102434
121. Li T, Ma B, Yang H, et al. Generation of a CRISPR/Cas9-corrected-hiPSC (NCCDFWi001-A-1) from a Marfan syndrome patient hiPSC with a heterozygous c.2613A>C variant in the fibrillin 1 (FBN1) gene. *Stem Cell Res*. 2021;56:102543. doi:10.1016/j.scr.2021.102543
122. Aalders J, Léger L, Demolder A, et al. Generation of human induced pluripotent stem cell line UGENTi001-A from a patient with Marfan syndrome carrying a heterozygous c.7754 T > C variant in FBN1 and the isogenic control UGENT001-A-1 using CRISPR/Cas9 editing. *Stem Cell Res*. 2023;67:103036. doi:10.1016/j.scr.2023.103036
123. Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature*. 2016;533(7603):420–424. doi:10.1038/nature17946
124. Zeng Y, Li J, Li G, et al. Correction of the Marfan syndrome pathogenic FBN1 mutation by base editing in human cells and heterozygous embryos. *Mol Ther*. 2018;26(11):2631–2637. doi:10.1016/j.ymthe.2018.08.007
125. Jayarajan SN, Downing BD, Sanchez LA, Jim J. Trends of vascular surgery procedures in Marfan syndrome and Ehlers-Danlos syndrome. *Vascular*. 2020;28(6):834–841. doi:10.1177/1708538120925597
126. Wang G, Liu C, Wu Q, et al. Systematical analysis of underlying markers associated with Marfan syndrome via integrated bioinformatics and machine learning strategies. *J Biomol Struct Dyn*. 2024;42(11):5713–5724. doi:10.1080/07391102.2023.2233021
127. Nasrallah A, Sulpice E, Kobaisi F, Gidrol X, Rachidi W. CRISPR-Cas9 technology for the creation of biological avatars capable of modeling and treating pathologies: from discovery to the latest improvements. *Cells*. 2022;11(22). doi:10.3390/cells11223615
128. Aljabali AAA, El-Tanani M, Tambuwala MM. Principles of CRISPR-Cas9 technology: advancements in genome editing and emerging trends in drug delivery. *J Drug Delivery Sci Technol*. 2024;92105338. doi:10.1016/j.jddst.2024.105338