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DiNAQOR—At the heart of gene therapy discovery

Swiss-based DiNAQOR has developed a revolutionary gene therapy platform which combines gene-vector-promoter constructs with loco-regional delivery to the heart for the treatment of cardiovascular diseases. With its first AAV gene therapy program, DiNA-001, in development for the treatment of *MYBPC3* hypertrophic cardiomyopathy (HCM), the company and its platform is attracting significant partnering interest.

Cardiomyopathy is a disease in which heart muscle is typically weakened or distorted, and functionally impaired. This can cause symptoms such as chest pain, breathlessness or palpitations, and frequently leads to heart failure. While cardiomyopathy symptoms can often be controlled by medication, devices such as pacemakers, or surgery, there is no cure for heart failure, which causes more deaths than all cancers combined; half of heart failure patients die within five years of diagnosis, and the only hope for treating advanced disease is a heart transplant.

Poised to radically alter the outlook for cardiomyopathy patients is DiNAQOR, a private life sciences company founded in 2019 and headquartered in Switzerland. It has developed a pioneering gene therapy platform for the failing heart. "Cardiology is still in the stone age compared to immuno-oncology," said Johannes Holzmeister, a clinical cardiologist, and DiNAQOR's co-founder, chair and CEO. "We aim to change all that with our innovative gene therapy solutions to transform the lives of patients affected by cardiomyopathies."

Around half of all cardiomyopathies are caused by a mutation in a single gene normally expressed in heart muscle. The idea of medical gene therapy for these monogenetic cardiomyopathies is to replace the defective gene with one that functions properly. Essentially, a virus that has been modified to contain a therapeutic transgene (thus called a vector) is delivered to target tissue, where it incorporates the genetic material into the machinery of the cells, which then start producing the corrective protein. Precision is paramount, and historical efforts in cardiology gene therapy have been hampered by failure to efficiently deliver genetic material to where it is needed because of issues concerning mode of delivery, vector specificity and dosing.

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Fig. 1 | DiNAQOR's gene therapy platform.

A precision approach

Successful gene therapy requires safe and targeted provision of genetic material to the heart muscle, efficient transfection/incorporation into cardiac cells, and sufficient expression to correct the genetic problem, explained Holzmeister. Meeting all these key requirements, DiNAQOR has built a novel and innovative gene therapy platform that includes proprietary gene-vector-promoter constructs and their direct delivery to the heart.

Firstly, the viral vector. The company uses a non-replicating adeno-associated vector (AAV) to transport the genetic material to the heart cells. Particular serotypes of AAV are well known for high specificity for cardiac muscle, and this 'tropism' is a key ingredient for successful transfection. In a large number of mouse, non-human primate, and human studies, this AAV tropism has been shown to be three to ten times higher for the heart than other organs.

Then there is the cardiac-specific human troponin T promoter, which ensures that the gene of interest is predominantly expressed in the cardiac tissue. Driving strong gene expression in a heart-specific manner enables efficacy and avoids off target toxicity. This becomes particularly important for future in vivo gene-editing approaches.

Furthermore, DiNAQOR is developing a loco-regional delivery system that targets the heart muscle. Avoiding systemic circulation maximises gene delivery to and transduction of cardiac cells, while minimizing potential adverse effects that would arise from flooding the body with vectors. Moreover, loco-regional delivery enables gene therapy of the heart in adults.

First product candidate & pipeline

DiNAQOR's first product candidate, DiNA-001, is an AAV gene therapy program for the treatment of hypertrophic cardiomyopathy (HCM) caused by *MYBPC3* mutations (*MYBPC3* HCP) in patients with both high and clinically unmet needs. HCM is one of the most common genetic heart diseases, with about 500,000 patients diagnosed with HCM worldwide. Up to 60% of HCM cases have a genetic origin, and it is estimated that 40% of those

have mutations in *MYBPC3*, the gene that encodes cardiac myosin-binding protein C (MyBP-C). The protein modulates the interaction between actin and myosin, and its lower levels seen in *MYBPC3* HCM alter actin sliding velocities and maximal force. In an effort to compensate for the resulting impaired beat/contraction, the heart muscle grows abnormally large—HCM—which increases the risk of developing heart failure and life-threatening arrhythmias. As with all cardiomyopathies, there are currently no approved pharmacological treatment options available that address the underlying disease biology of HCM, and invasive surgery or heart transplantation may be the only options available for patients with advanced disease.

DiNA-001 was designed to treat cardiomyopathies caused by *MYBPC3* mutations by introducing an optimized transgene into the heart muscle to increase the expression of the normal protein. The initial proof of concept studies in human heart cells and engineered heart tissue showed that the gene-vector-promoter construct corrects MyBP-C protein levels/expression in the sarcomere and dysfunctional contraction, while in vivo studies in animals show the gene therapy is successfully delivered to and expressed in the heart, improving its function with negligible side effects.

Moreover, long-lasting effects from the therapy are anticipated. "Although the heart can grow by hypertrophy, heart cells usually do not divide after birth, suggesting that only one treatment may be necessary," explained Holzmeister. "However, we do not yet have data on this and are actively working on a re-dosing regimen with our loco-regional system as well."

Significant support for DiNAQOR's approach came in May 2020, when the company struck a preclinical collaboration and license agreement with biopharmaceutical company, BioMarin Pharmaceutical covering DiNA-001 for HCM. "BioMarin's commitment to DiNA-001 is a powerful validation of DiNAQOR's gene therapy platform," according to Holzmeister. "BioMarin's deep domain knowledge and capabilities in gene therapy manufacturing and their heritage in providing safe and effective medicines for patients suffering from rare, monogenic diseases made them the perfect partner to move our first candidate forward in a collaborative approach," Holzmeister added.

In addition to MyBP-C, DiNAQOR is working on a plethora of cardiac proteins that can be affected by mutations and cause disease. "We are looking at all the important proteins in the heart muscle, and our pipeline of preclinical programs addresses a range of cardiomyopathies," according to Holzmeister. "There are 1.7 million people in the European Union and the United States currently affected by cardiomyopathy, and approximately 800,000 of these individuals are carrying a monogenic mutation in DiNAQOR genes of interest," he said.

From discovery to manufacture—a gene therapy one-stop shop

In addition to innovative gene-vector-promoter constructs and loco-regional delivery, DiNAQOR's full platform contains all the elements necessary for successful research and development, including state-of-the-art analytics for testing potential treatments, and product supply capability.

Having established a collaboration with the University Medical Centre Hamburg-Eppendorf in Germany, DiNAQOR is able to test its innovative gene therapies in human induced pluripotent stem cell-derived engineered heart tissue. "By using mini organoids that beat like a heart, we are able to measure the force and very reliably determine cardiac strength," explained Holzmeister. "We can see whether a mutation results in less strength and can pre-test a potential reversal. This is much quicker than testing in animals, enabling us to translate to humans more efficiently."

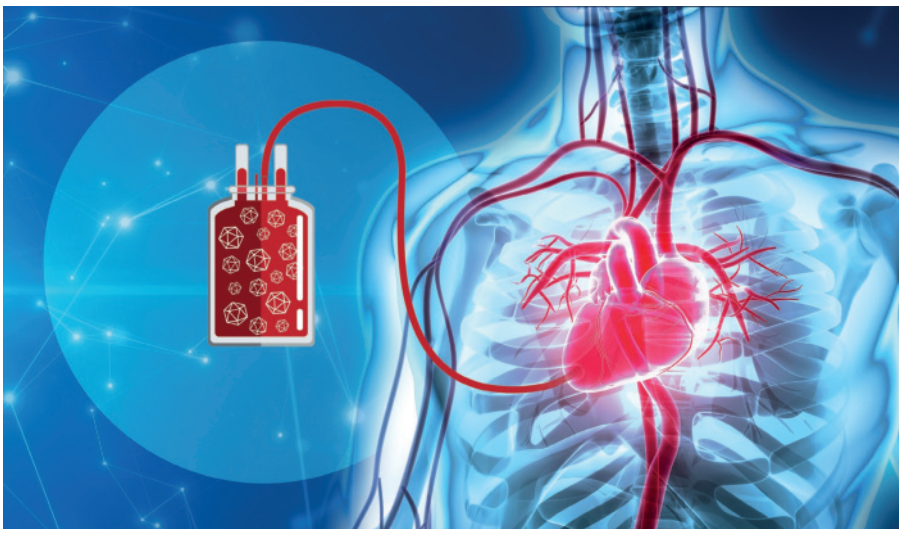

Fig. 2 | DiNAQOR's loco-regional delivery system for the heart.

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Additionally, through a partnership with Basel-based Lonza, one of the world's leading manufacturers of AAV gene therapy vectors, DiNAQOR also has the manufacturing capacity to rapidly produce clinical trial and commercial quantities of viral vectors. "This means we can guarantee an adequate product supply for all stages of clinical development and can scale up production as necessary," explained Holzmeister, who added that DiNAQOR has 9700 square feet of new laboratory facilities in Zurich, bringing its manufacturing and process development next door to the heart tissue platform, expanding its global R&D capabilities. "Vector development and manufacturing are instrumental for the success of gene therapy, thus the importance of having full control of these areas," he said. To this end, DiNAQOR recently appointed as its new chief technology officer, Eduard Ayuso, a leader in vectorology, and expert in vector design, manufacture, purification and optimization. Ayuso's mission will be to further evolve the company's technologies and support the rapid development of its pipeline.

Furthermore, DiNAQOR is planning to establish a best-in-class rapid genetic diagnostic service to accurately identify patients who would benefit from its cardiac gene therapies.

Partnering

DiNAQOR's platform is generating significant interest within the industry, and the company has already established several strategic partnerships with leading institutions and companies in cardiology and gene therapy R&D around the world to advance its cardiac gene therapy platform and pipeline.

In addition to its manufacturing deal with Lonza, the preclinical collaboration and license agreement with BioMarin, and its analytical alliance with University Medical Centre Hamburg-Eppendorf, in January 2020 DiNAQOR announced an exclusive research and licensing deal with London-based UCL to advance two of its discovery cardiac gene therapy pipeline programs into clinical development. Holzmeister stressed that early-stage partnerships are critical to expedite innovation in gene therapy R&D, and that the company is keen to explore more opportunities to collaborate and investigate new targets in 2021.

As momentum for gene therapies continues to build, with a team of leading pharmaceutical and biotechnology executives and academics with deep cardiology and gene therapy expertise, DiNAQOR is uniquely positioned to deliver successful treatments for the failing heart. The company has a deep understanding of and experience in cardiology and gene therapy and is committed to advancing novel and innovative solutions for patients affected by major monogenetic cardiomyopathies. "Our modular technology platform includes optimised gene-vector-promoter constructs, direct delivery to the heart, on-target expression, reliable vector supply, advanced analytics, and emerging diagnostics," said Holzmeister. "This holistic approach enables faster and more predictable development of gene therapies for patients with these devastating diseases."

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