might use the CRISPR/Cas9 system as part of their defense mechanism.

Obviously, the work of the American scientist Jennifer Doudna and the French scientist Emmanuelle Charpentier in 2012 was instrumental in advancing the use of CRISPR/Cas9 in medicine, and their discoveries rightfully earned them the Nobel Prize in Chemistry in 2020.[4]

We appreciate the constraints on manuscript length that may have limited the depth of information provided by Argirò et al.,[1] but some of their comments could give rise to confusion. It is incorrect to say that Doudna and Charpentier discovered the CRISPR/Cas9 system in 2012 and that 1 month later the European Medicines Agency approved the first gene therapy for lipoprotein lipase deficiency.

In relation to the paragraph on lamin-related cardiomyopathies, the only disease mentioned is Hutchinson-Gilford progeria syndrome (HGPS). HGPS is an extremely rare disease (1 case per 4 million births) caused by mutations in a highly specific region of the *LMNA* gene that produce an abnormal protein. LMNA-related cardiomyopathy is 400 times more common. Pathogenic variants in the *LMNA* gene are responsible for approximately 8.5% of DCMs in Spain, and none of these variants are associated with HGPS.

There are also other heart conditions not mentioned that may be amenable to gene therapy, including several with a potentially poor prognosis, such as Brugada syndrome, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. Unlike cardiomyopathies, channelopathies are not typically characterized by irreversible structural and functional changes at diagnosis.

PLN is one of the most widely studied genes in the field of cardiovascular research. It encodes phospholamban, a protein responsible for regulating calcium modulation in cardiomyocytes. Thousands of people with DCM have been found to carry the specific *PLN* mutation R14del. The creation of cell-based and animal models for investigating DCM will undoubtedly drive the development of treatments for other diseases.

A notable milestone in the development of gene therapy for cardiomyopathies was the correction of a pathogenic variant in *MYBPC3* in human embryonic cells derived from the gametes of a patient with hypertrophic cardiomyopathy. More recently, in 2023, a gene therapy clinical trial in the United States enrolled its first participant, who was successfully infused with a viral vector that delivered a working *MYBPC3* gene.

We agree with Argirò et al.[1] that gene therapy is a promising field, not only because of continuous advances to gene editing technology but also because of the opportunities offered by the discovery of a new set of prokaryotic defense systems, aptly named after protective deities from various cultures.[3]

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No artificial intelligence tools were used to write this article.

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M. Sabater Molina and J.R. Gimeno Blanes conceived, designed, wrote, and revised this article.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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In recognition of the Spanish origin of CRISPR/Cas9. Implications for the treatment of familial heart disease. Response

En reconocimiento del origen español del CRISPR/Cas9. Implicaciones para el tratamiento de las cardiopatías familiares. Respuesta

To the Editor,

We thank María Sabater Molina and Juan Ramón Gimeno Blanes for the interesting Letter and the opportunity to expand some important points regarding *LMNA*-cardiomyopathy, *MYBPC3* hypertrophic cardiomyopathy, and gene therapy approaches.[1]

The Letter underscored and clarified the importance of Dr Francis Mojica's contribution to the discovery of CRISPR. It was not our intention to misattribute the discovery of CRISPR but rather to emphasize the first use of the CRISPR/Cas9 complex as a genome editing tool.

Pathogenic variants in the *LMNA* gene may give rise to several phenotypes, including muscular dystrophy, lipodystrophy, and acrogeria. The cardiomyopathy spectrum encompasses approximately 7% of cases of genetic dilated cardiomyopathy, characterized by atrioventricular block, atrial arrhythmias, left ventricular dysfunction, and ventricular arrhythmias, with a mean age of onset of 40 years.[2] In *LMNA*-H222P iPSC-cardiomyocytes, *LMNA* shRNA silencing both endogenous alleles and *LMNA* cDNA and a lentiviral

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vector normalized the proportion of abnormal nuclei. In a mouse model (KI-LMNAdelK32), systemic administration of AAV2/9 vectors containing human mature lamin A alone or in combination with shRNA targeting p.K32del *LMNA* mRNA increased maximal survival and lamin A/C protein levels.[3]

An *MYBPC3* gene replacement approach has been developed (TN-201). Preliminary data in *Mybpc3*-/- mice show that TN-201 improved left ventricular hypertrophy, cardiac function, and lifespan relative to vehicle-treated *Mybpc3*-/- mice.[4] In October 2023, the first patient participating in the Phase 1b trial evaluating the safety of an intravenous infusion of TN-201 was dosed.

We would like to thank the authors and editors again for the opportunity to clarify these important aspects, and eagerly anticipate the emergence of new gene therapy approaches.

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All the authors contributed equally.

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E. Adler participates in the Scientific Advisory Board for Medtronic, Fuji, and SanaChief. E. Adler works as scientific officer for Lexeo Therapeutics, and as a consultant for Abiomed, AstraZeneca, Ionis, Medtronic, Abbott, and Novartis. E. Adler is part of the advisory board and shareholder for Rocket Pharmaceuticals. E. Adler is a founder of the scientific board and shareholder of ResQue Therapeutics. A. Argirò is a consultant for Lexeo therapeutics, and J. Ding has no conflicts of interest to declare.

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