Letters to the Editor

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

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

To the Editor,

We would like to thank Argirò et al.[1] for their excellent review of emerging gene therapy strategies for cardiomyopathies, recently published in *Revista Española de Cardiología*. We read with particular interest the sections on the various types of gene therapy and delivery systems, and found the review and summary table of ongoing clinical trials to be very useful.

Nonetheless, we would like to clarify some issues mentioned in the background section and the paragraph on cardiolaminopathies, and also share some thoughts on other inherited cardiomyopathies.

In relation to the history of CRISPR/Cas9, the work of the Spanish microbiologist Francis Mojica cannot be overlooked. Mojica coined the term *CRISPR* and discovered the immune system of bacteria through his work with archaea in the salt lakes of Santa Pola, Alicante, in 1993[2,3] (figure 1). While other researchers would later win international acclaim for converting CRISPR/Cas9 into a powerful gene editing tool in the fields of biology and medicine, the discovery of regularly interspaced short repeats dates back to the work of Mojica and others. Professor Mojica was the first to use the term *CRISPR* and the first to hypothesize that archaea and bacteria

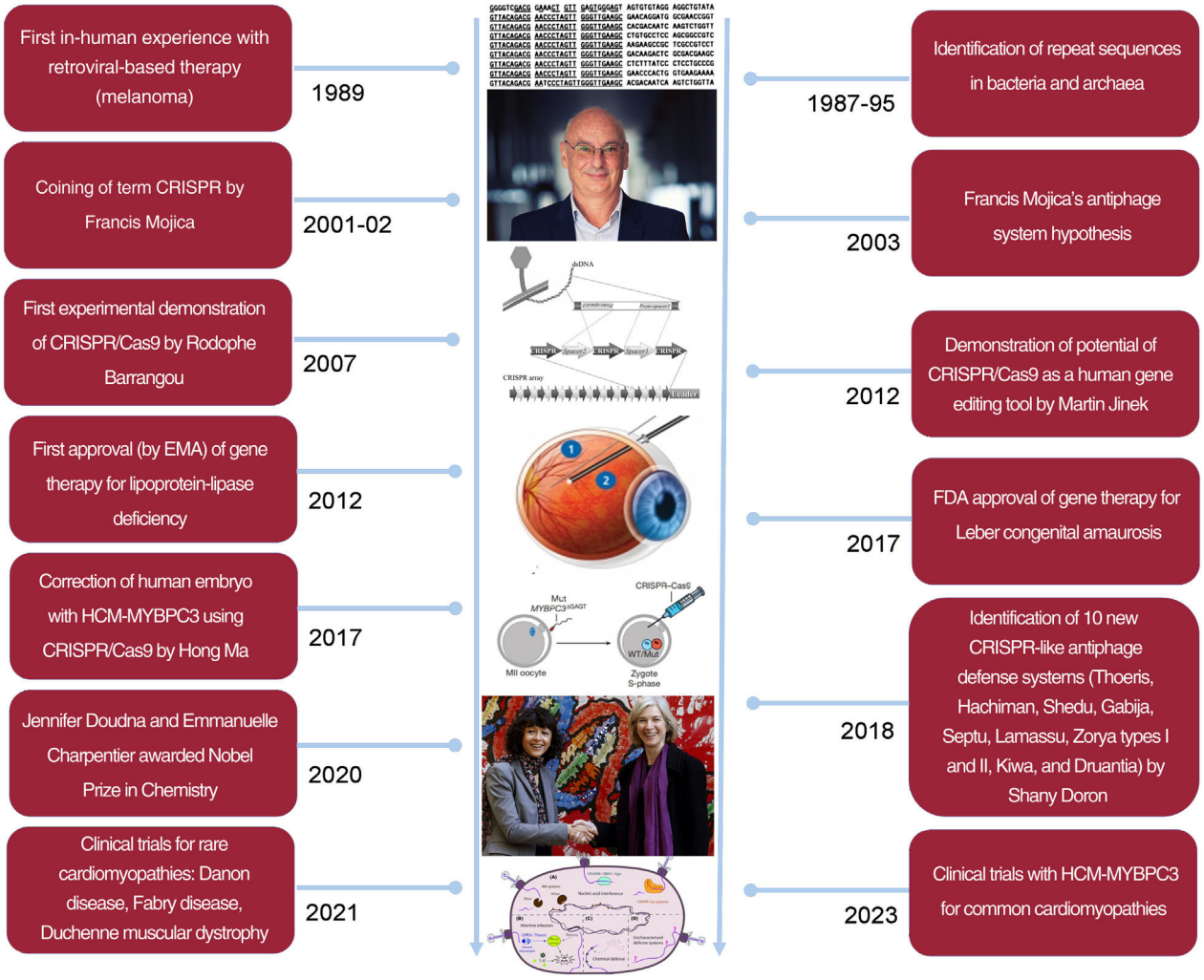

Figure 1. Milestones in the development of CRISPR/Cas9 and gene therapy for heart diseases. EMA, European Medicines Agency; FDA, Food and Drug Administration; HCM-MYBPC3, hypertrophic cardiomyopathy due to mutations in *MYBPC3*.

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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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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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