Press Release For Immediate Release

Genethon Announces Publication in *Nature Communications* of a Next-Generation Gene Therapy Vector for Muscle Diseases, Using AI Predictive Methodology to Improve Efficacy and Safety

- *Isabelle Richard, Ph.D., and her Progressive Muscular Dystrophies Team at Genethon have perfected an innovative methodology based on artificial intelligence (AI) to design a new generation of capsids for developing a more effective gene therapy vector for muscle diseases.*

- *The capsids use 20 times fewer gene therapy vectors, yet are more effective than natural AAVs, enabling more precise targeting of muscle and reducing the risk of liver damage.*

- *Genethon is currently working on the development of new capsids targeting other organs.*

PARIS, France (September 12, 2024) - Genethon, the pioneering French laboratory and leader in the research and development of gene therapies for rare diseases, announced today publication in *Nature Communications* of an article describing the use of artificial intelligence (AI) in designing a new generation of capsids, the structures that envelop genetic material of adeno-associated viruses (AAV), to improve gene therapies for muscle diseases.

The new capsids effectively target the muscle and avoid the liver, while reducing the doses of vectors required. These results pave the way for more effective gene therapies for neuromuscular diseases, while reducing the risk of side-effects and production costs.

The article, in the September 11 issue of *Nature Communications*, is titled **"An engineered AAV targeting integrin alpha V beta 6 presents improved myotropism across species."**

"The era of gene therapy for neuromuscular diseases has begun, and the complexity of these diseases requires us to constantly innovate to improve drug candidates targeting muscle. The new generation of gene therapy vectors we have designed is a game-changer in terms of efficacy and safety. It is currently being tested for various neuromuscular diseases," said Isabelle Richard, research director and head of the Progressive Muscular Dystrophies Team at Genethon.

"These results herald a new generation of more effective gene therapy products with fewer side effects, not only for muscle but also for other target organs in other diseases. They also underline the potential of our methodology for designing AAV vectors for gene therapy, and place Genethon's technological platform at the forefront of innovation," emphasized Frederic Revah, Chief Executive Officer of Genethon.

In neuromuscular diseases, the most widely used vector for transporting genetic material is the natural adeno-associated virus (AAV). However, a large proportion of injected vectors do not reach their target tissue, as they are eliminated by the liver. As a result, large doses are often required with potentially adverse effects.

To address this issue, Dr. Richard and her team used a molecule of interest present on the surface of human skeletal muscle cells, called Integrin Alpha V Beta 6, and then modified an AAV capsid to specifically target this receptor.

To achieve this, the team has developed a new methodology using artificial intelligence tools, based on protein structure prediction, to predict the efficiency and stability of the new capsid.

This methodology has made it possible to identify various variants, including a particularly promising one called LICA1. Tested on models of Duchenne muscular dystrophy and limb-girdle muscular dystrophy, neuromuscular diseases for which a high vector dose is required with natural AAVs, the team demonstrated the efficacy of the new capsid in muscle at a lower dose and without penetrating the liver.

About Genethon

A pioneer in the discovery and development of gene therapies for rare diseases, Genethon is a not-for-profit laboratory created by the AFM-Téléthon. The first gene therapy drug, to which Genethon contributed, was successfully marketed for spinal muscular atrophy. With more than 220 scientists and professionals, Genethon pursues its mission to bring life-changing therapies to patients suffering from rare genetic diseases. Thirteen products from Genethon's research are currently in clinical trials for diseases of the liver, blood, immune system, muscles and eyes. Seven other products are being prepared for clinical trials over the next five years. Find out more at www.genethon.fr

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