Development of microRNA-based TREATMENTS for MYOTONIC DYSTROPHY Type 1 by Translational Genomics Group

Dr. Artero's Lab, based in Spain (University of Valencia), is a pioneer in discovering therapeutic targets and innovative drug candidates for rare diseases

Dr. Artero working on rare diseases

Logo for TATAMI project aiming therapies against myotonic dystrophy

VALENCIA, VALENCIA, SPAIN, February 28, 2021 /EINPresswire.com/ -- Translational Genomics Group (Dr. Artero's Lab), a Spanish research laboratory affiliated to the University of Valencia (UVEG) and INCLIVA Biomedical Research Institute, is a pioneer in discovering therapeutic targets and innovative drug candidates for rare diseases, has announced the development of novel DM1 (Myotonic Dystrophy Type 1) therapies based on recent new knowledge on microRNA class molecules. Being the most common muscular dystrophy in adults, affecting around 90,000 people in Europe and 75,000 in the US, the researchers from the Translational Genomics Group announced that their DM therapy could help these people and improve their quality of life.

About Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 (DM1) is a life-threatening and chronically debilitating disease. The estimated incidence of the disorder worldwide is approximately one in 3,000-8,000 people, making it the most frequent adult muscular dystrophy. The disorder is inherited as an autosomal dominant trait, meaning that a child must inherit only one copy of the defective gene from one parent to develop the disease. Individuals born from individuals who are carriers of the mutated gene usually display age anticipation and higher severity for the clinical disease progression.

Currently, there is no cure available to arrest or retard disease progression. Therefore, possible treatments are urgently needed since clinical management is limited to symptomatic care.

DM1 displays a wide range for onset of the clinical signs, including neonatal and infantile, to later adult forms being diagnosed. In a common clinical path, DM1 patients always manifest an important degree of progressive locomotor muscle weakness, atrophy, and myotonia, with the addition of less known, but also frequent, respiratory and cardiac impairments connected to other muscles degeneration, eventually leading to premature death, neurological issues causing social disabilities, and features outside the neuromuscular spectrum, including diabetes, cataracts, and higher cancer incidence.

Caused by an expansion of CTG repeats in a non-coding region of the DMPK gene, DM1 was the first disease ever described for which the underlying cause of the pathology involves an RNA-gain-of-function (RNA toxicity) mechanism. Upon transcription, expanded CUG in DMPK mRNAs form stable hairpin structures retained in the cell nucleus where they contribute to the abnormal binding and functional depletion of important factors strongly involved in RNA metabolism. Specifically, the limited availability of Muscleblind-like family factors (MBNLs) is the most significant contribution to DM1 phenotypes, like cardiac conduction problems, myotonia, and insulin resistance. However, the causes of other former critical clinical features in DM1 patients, like the significant muscular atrophy, are still not understood.

About Translational Genomics Group (Dr. Artero's Lab):

Translational Genomics Group currently aims to identify therapeutic targets and develop innovative treatments for rare neuromuscular diseases (www.uv.es/gt). Very focused on DM1 from the very beginning, Dr. Artero and his team have provided the community with significant scientific advances that are now practical tools to push forward the development of novel drugs against DM1. Thus, their practical and rapid drug screening approaches have helped to identify and validate several chemical compounds, some licensed to the industry, for their further development in DM1. Dr. Artero´s long-term vision is highly relevant and transformative in filling in the gap between drug discovery and development in DM1 by leading the engagement of a multidisciplinary-driven effort to translate the results into actual treatments.

During the last years, Dr. Artero´s research has tracked to the DM1 field new actors to act together in a coordinated manner, intending to move novel candidate drugs to their next step. Research groups from top-notch European institutions such as Oxford University (UK) and CSIC (Spain), involved in medicinal chemistry of therapeutic oligonucleotides; Institute of Myology (France), developing novel animal model experimentation; IBEC (Spain), developing 3D tissue bioengineering; IIS Biodonostia (Spain), studying clinical evolution of the disease, are now directly involved in DM1 research through ongoing multidisciplinary projects like TATAMI (being funded by "la Caixa" Banking Foundation under the project code HR17-00268) or PROMETEO (being funded by regional Valencian Government) both coordinated by Dr. Artero. Significantly, non-scientific stakeholders are also involved in these projects to increase the chances of subsequent

efforts, including national (ASEM Federation) and international (Myotonic Dystrophy Foundation) patient associations, research transfer offices, and regulatory CROs. At this moment, Dr. Artero is pursuing the construction of an European network for DM1 translational research with the incorporation of additional partners at scientific and non-scientific levels.

About microRNAs and DM1

In the last years, Dr. Artero's group has pioneered the deciphering of small RNA regulatory molecules, called microRNAs (miRNAs), on distinct DM1 disease features.

By characterizing the miRNA-linked repression of the endogenous MBNL genes as an overlaid layer of regulation to the MBNL depletion pathway, they found two specific miRNAs (miR-23b and miR-218) that repress the expression of MBNL1 and MBNL2. Thus, the group has designed antisense oligonucleotides (AONs) that block the repressive miRNAs (antagomiRs), which have provided proof-of-concept to improve DM1-like alterations in a mouse model of the disease. Importantly, these results, under patent protection and recently published in the journal Nature Communications, led the creation, at the end of 2019, of a spin-off company of the University of Valencia, ARTHEx Biotech (www.arthexbiotech.com), that rapidly grown the interest of private investors at the bio & health field, completing an initial seed-round of 8M $ for the optimization of the drug candidate, subsequent preclinical regulatory studies, and design of the first clinical trial.

In a parallel research line, Dr. Artero´s group has recently published in Molecular Therapy Nucleic Acids how miR-7 contributes to the muscle atrophy phenotype in DM1 by studying its consequences replenishing or blocking miR-7 by using specific agomiR and antagomiR oligonucleotide molecules, respectively. Importantly, they highlighted that miR-7 dysfunction was linked to the alteration of catabolic muscle processes through autophagy- and atrophy-related pathways and support that restoration of miR-7 levels is a candidate therapeutic target counteracting muscle atrophy in DM1. A broader characterization of the molecular pathway for DM1 muscle atrophy is currently ongoing.

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