Myotonic dystrophy type 1
Advances in innovative therapy development

Muscleblind proteins

Myotonic dystrophy type 1 (DM1) is a rare, genetic, multisystem progressive disorder, with a recent estimated prevalence of 9.27 per 100,000 people, worldwide. Symptoms include muscle weakness and wasting, delayed muscle relaxation after contraction (myotonia), gastrointestinal symptoms and neurological impairment. These symptoms are highly variable between patients, and serious or even fatal manifestations include heart defects and respiratory failure. No effective treatment exists and there is a need to develop therapies that relieve symptoms and improve the quality of life of DM1 patients.

Translational research aims to translate scientific findings into real life benefits for patients. It is vital in order to expedite basic scientific discoveries into practical clinical treatments for, or prevention of, diseases. Using human cells and animal models, the Translational Genomics Group led by Dr Ruben Artero at the University of Valencia, Spain, works to gain a deep understanding of the complex molecular pathogenesis of DM1. In doing so, their valuable translational research enables therapeutic candidates to be identified and potential therapies to be evaluated.

DM1 main symptoms

Cognitive impairment
Cataracts
Arrhythmia
Respiratory difficulties
Gastrointestinal difficulties
Muscle weakness, amyotrophy

THERAPY STRATEGIES

Given that the loss of function of MBNL is a pivotal aspect of the pathophysiology of DM1, MBNL is a key target for therapy. One approach is to target the toxic RNA which inhibits MBNL protein function. Other approaches include trying to increase the amount of MBNL in the cell activity in cells while trying to regulate CELF1 levels. Three main categories of therapies are being explored to address this.

The first category are ‘small molecules’ which are often repurposed drugs already used in other diseases and with proven safety in humans. One sequence repeats from inhibiting MBNL1. One of the limitations of the ASO treatments is the insufficient delivery to certain tissues and conjugation to delivery systems is under investigation to address this.

Gene therapies are the third therapeutic category. Therapies to increase/decrease the expression of genes and proteins offer a viable option and warrant further research. Two approaches are commonly adopted: the use of viral vectors to deliver a gene that can be used to produce a protein, and CRSIPR/Cas9 systems to edit the mutated gene.

Although defined as a rare disease, globally, DM1 is debilitating for hundreds of thousands of people and there is a lack of effective treatment.

Different studies by the group published in Molecular Therapy: Nucleic Acids investigated antagomiR-218 therapy and uptake of antagomiR-218 in mice, demonstrating low toxicity and effective tissue delivery. Dose-dependent increases in MBNL protein levels and improvements in grip strength and myotonia were found. Effective treatments were observed four days after injection but reduced myotonia and improved grip strength benefits continued for several weeks. The study confirmed the true potential of this treatment for DM1 patients, and further research is ongoing.

We are now witnessing the advent of a new era of RNA-based drugs and vaccines. Compared to other chemical drugs, ASOs bind a very specific sequence, meaning they act in a highly targeted manner. Once a therapy target has been identified, antisense molecules can be used to inhibit the development of a disease. In the case of muscle tissue, they do not require complex delivery systems to get to the cells and block these mRNAs when molecules are tiny enough, a simple injection can be sufficient.

ARTHEX-BIOTECH
AND THE TATAMI PROJECT

The importance of translational research is undisputed, and without it, vital discoveries will not be implemented and affecting mRNA translation into proteins. They have been implicated in other diseases but are now being studied as potential therapeutic targets in DM1. In DM1, studies reveal there is an alteration to the miRNome, and numerous miRNAs are dysregulated. The Translational Genomics group has shown that the expression of DMPK toxic RNA increases the levels of miR-218, which repress the translation of MBNL proteins, and reduce its levels. By targeting miRNAs using ASOs engineered to be complementary to them (antagomiRs and blockmiRs), it is possible to restore MBNL function. They actively utilise miR-218 and miR-218, and in a study of human DM1 myotubes and a mouse model, the group demonstrated that treatment with these antagonimiRs increased MBNL levels and prevented irregular RNA splicing, improved myotonia and other pathological aspects of DM1.

There are numerous other drugs under investigation for their potential benefits in treating clinical manifestations of DM1 – particularly manifestations such as pain, myotonia, and daytime sleepiness – but they do not target the origin of the disease.

MICRO RNAs AS THERAPEUTIC TARGETS

Micro RNAs (miRNAs) are small non-coding RNAs which regulate mRNA levels and function by inducing their breakdown and affecting mRNA translation into proteins. They have been implicated in other diseases but are now being studied as potential therapeutic targets in DM1. In DM1, studies reveal there is an alteration to the miRNome, and numerous miRNAs are dysregulated. The Translational Genomics group has shown that the expression of DMPK toxic RNA increases the levels of miR-218, which repress the translation of MBNL proteins, and reduce its levels. By targeting miRNAs using ASOs engineered to be complementary to them (antagomiRs and blockmiRs), it is possible to restore MBNL function. They actively utilise miR-218 and miR-218, and in a study of human DM1 myotubes and a mouse model, the group demonstrated that treatment with these antagonimiRs increased MBNL levels and prevented irregular RNA splicing, improved myotonia and other pathological aspects of DM1.
The group’s translational strategy strives to overcome these challenges through multidisciplinary academic and industrial research which draws on a mixed model of public and private investment. Such collaborations are needed to facilitate funding and pool the required skills and knowledge to address the aforementioned challenges. A successful example of a collaboration between researchers and public and private funders is the group’s spin-off company, ARTHEX Biotech, and the TATAMI project consortium, where all the participant institutions are public, but the funding is private. Both initiatives aim to explore and develop candidate ASO therapies for DM1. ARTHEX Biotech investigates novel therapies for microRNAs manipulation in DM1, and is an excellent example of translating scientific findings into potential therapies. TATAMI (Therapeutic targeting of MBNL microRNAs as innovative treatments for myotonic dystrophy) is a project funded by La Caixa Foundation and carried out by an international consortium led by Artero’s Translational Genomics Group.

To progress this area of research, improved preclinical models and drug evaluation methods are urgently required. Moving beyond 2D culture methods to employ tissue engineering to create 3D muscle models which more closely represent in vivo conditions is an area of interest. The group has collaborated with TATAMI partner IBEIC to develop an in vitro 3D DM1 model of human skeletal muscle to be used in preclinical studies of DM1. Such models aim to further enhance our understanding of DM1 pathogenesis and facilitate evaluations of drug delivery and activity.

Although defined as a rare disease, DM1 is debilitating for hundreds of thousands of people and there is a lack of effective treatment. Overall, these innovative microRNA therapeutic targets are in the preclinical phase but offer great promise to be tested in the medium term in humans. With the rapid growth in our ability to obtain a wealth of genomic and proteomic data, it is hoped that further therapeutic targets will be discovered and effective clinical treatments developed. The Translational Genomics Group aims to be at the forefront of these RNA-based drug developments for the treatment of DM1, through ‘bench to bedside’ translational research.

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 Biography

Dr Artero is Full Professor in the Department of Genetics in the Faculty of Biology, University of Valencia. He leads the Translational Genomics Group, a joint group of the BIOTECMED (UV) and INCLIVA research institutes.

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Collaborators

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Personal Response

What are some of the challenges faced when researching a rare disease such as Myotonic dystrophy type 1?

As researchers, there are many challenges to face when investigating rare diseases, and the scarcity of patients to study is only the most obvious. However, the most worrying is that the transition of drug candidates from the lab bench to the bedside of patients is an extremely difficult process. Institutions lack appropriate support structures, and clinicians and researchers involved often lack proper training to engage the industry. It is necessary to improve the implication and cooperation of the different actors to achieve adequate treatments against diseases such as DM1.