The Translational Genomics Group, led by Dr Ruben Artero at the University of Valencia, Spain, conducts vital translational research. This significant preclinical research provides a platform for further studies to help address the unmet need for effective treatments. Through the team’s spin-off company, ARTHEx Biotech, they are also working to overcome resource limitations, contributing to a new era of RNA-based drugs.

**Myotonic dystrophy type 1 (DM1)**

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 treatments 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 treatments to be evaluated.

**DM1 main symptoms**

- **Cognitive impairment**
- **Cataracts**
- **Arrhythmia**
- **Respiratory difficulties**
- **Gastrointestinal problems**
- **Muscle weakness, atrophy, myotonia**

**OVERVIEW OF DM1 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 or its 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 example in phase II trials is Tidegusib, a regulator of CELF1 levels in DM1 leading to improvements in symptoms in childhood-onset DM1.

The next category are oligonucleotide-based therapies, consisting of short sequences of RNA or DNA with complementary or antisense sequences against a target RNA. The mechanisms of action of antisense oligonucleotides (ASO) include targeting abnormal DMPK transcripts and preventing pathogenic splicing patterns. Precursor mRNA forms mature mRNA that is translated into proteins, therefore if precursor mRNA is altered, this can affect the expression level and functionality of proteins.

Muscleblind proteins have fundamental roles in alternative RNA splicing, which is essential for normal cell physiology. Disruption of several signalling pathways contributes to the pathogenesis of DM1 also includes the altered splicing of hundreds of genes. In addition to the direct binding of toxic RNA to MBNL proteins, toxic RNA also activates antagonists of MBNL, namely CELF1 protein. Such activation results in a gain of function of CELF1, a protein involved in RNA processes including alternative splicing, which results in dysfunctional proteins and aberrant physiological processes manifesting in a broad variety of symptoms. The pathogenesis of DM1 also includes the disruption of several signalling pathways important for normal cell physiology.

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

**MicroRNAs (miRNA) and the DMPK toxic RNA**

MicroRNAs (miRNA) 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 are active against miR-23b and miR-218, and in a study of human DM1 myotubes and a mouse model, the group demonstrated that treatment with these antagoniRs increased MBNL levels and prevented irregular RNA splicing, improved myotonia and other pathophysiological 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.

**MicroRNAs as Therapeutic Targets**

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Different studies by the group published in Molecular Therapy: Nucleic Acids investigated antagomiR-23b therapy and uptake of antagoniR-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 delivery of antisense oligonucleotides (ASO) targeting antagoniRs 23b and 218 into DM1 myotubes and a mouse model supports the potential for ASO treatments to address the pathogenesis of DM1. These studies have led to the development of a new RNAi therapeutic for DM1, Tidegusib, which is currently in phase II clinical trials.

**Graphic showing how microRNAs block the synthesis of muscleblind proteins in those with Myotonic dystrophy type 1, and the difference between antimiroI and blockmiR ways of action.**
Behind the Research
Dr Ruben Artero

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 research institutes.

To progress this area of research, improved preclinical models and drug evaluation methods are much needed. Building on the team’s findings related to the beneficial effects of antagomiR-23b and antagomiR-218 in DM1 mice models, the group explore and test numerous ASO candidates which are further analysed in vivo in mouse models, before final characterisation in human cells. Following this project, resources and funding to take these findings into clinical trials is required so that a new RNA-based drug for the treatment of DM1 can hopefully be implemented. Such therapies could be further explored for use in other diseases.

References


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 translation 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 into the industry. It is necessary to improve the implication and cooperation of the different actors to achieve adequate treatments against diseases such as DM1.