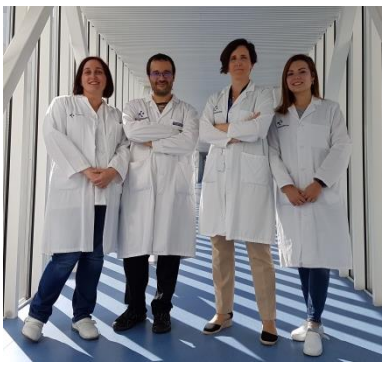
PERIODIC REPORT, PUBLISHABLE SUMMARY
CAREER INTEGRATION GRANT
Advanced Neuromuscular Treatment Screening (ANTeS)-618003

Neuromuscular disorders (NMDs) are highly incapacitating and lethal disorders for which there is no cure. Recently, the appearance of advanced personalised therapies targeting several of these disorders and the approval of a handful of orphan drugs has sifted this status quo. The development of these new drugs is slow due to the requirement of highly personalised approaches to these genetic disorders and to technical difficulties to evaluate the effects of these new therapies.

Duchenne Muscular Dystrophy (DMD), affecting approximately 23.000 boys in Europe, is caused by the deficit of dystrophin, a muscle protein. This deficit is due to mutations that alter the open reading frame of the DMD gene and a new class of drugs, antisense oligonucleotides (AOs), aim to restore dystrophin expression by a mechanism known as "exon skipping". However, as this disease is caused not by one but by many different mutations, each of these new drugs will only be applicable to a small percentage of DMD patients, as specific AOs will need to be designed and tested for each target exon. An important hurdle in the swift transfer of this new therapy into the clinic is the difficulty to evaluate dystrophin expression.



The Neuromuscular Disorders Group (www.arechavala-lab.com) at Biocruces Health Research Institute aims to develop new tools to accelerate the development of therapies for neuromuscular disorders. The objectives of our project were to develop new methods to quantify dystrophin in a microplate format (myoblot), test new treatments with this method, and establish a network of researchers and patients to advance in the development of new therapies.

<u>During these four years we have made big advances in the development of this new methodology and in the establishment of our group:</u>

- We have developed a new micro-plate format cell-based assay (an in-cell western known as 'myoblot') that enables the quantitative study of proteins directly on cultured cells. We have validated this new assay against standard methods and have successfully used it to differentiate between different sets of patients and to quantify response to treatment. We are already collaborating with other research groups outside our institution testing their compounds of interest in our myoblots and our method has been accepted for publication.

- Much of our efforts have also been directed at establishing a professional network, which we have successfully accomplished via previous and new collaborations. One of the new ones is COST action BM1207 (http://goo.gl/97UzUz) that facilitated the publication of several manuscripts with other network members. Dr. Arechavala-Gomeza has recently led a proposal for a new COST Action (under review), with +70 researchers of 21 European countries.

- We are also interested in the scientific career and in science communication. We are members of several scientific associations, like the Society of Spanish Researchers in the UK, the Marie Curie Alumni Association and the "Scientist Returned to Spain Association". Dr Arechavala-Gomeza has taken part in many career forums, like ERA Career days (https://goo.gl/edzyFM).

- A fundamental part of our efforts have been dedicated to disseminating our results and the state of the art to patient organisations and, with this in mind, we have translated texts into Spanish (http://goo.gl/3ITA70), routinely give talks to lay audiences, summer courses (https://goo.gl/f5FhmJ), revise grants for charities and keep an active webpage showcasing our work (www.arechavala-lab.com).

- The Neuromuscular Disorders Group was created in June 2013 with funding for the PI, a technician and a 3 year project grant. We are happy to have secured funding to continue with new projects for several more years and also to have been able to welcome new members to our team that will currently allow the extension of our research projects until at least May 2021.