Scientist SPOTLIGHT

Modeling Duchenne Muscular Dystrophy in a Dish

Q&A with Dr Amaia Paredes-Redondo, Research Scientist at Axol Bioscience

Axol Research Scientist, Dr Amaia Paredes-Redondo recently published findings from her post-graduate work in the lab of Dr Yung-Yao Lin, at Queen Mary University of London; and in collaboration with Dr Ivo Lieberam's group at King's College London. The paper titled: **'Optogenetic modeling of human neuromuscular circuits in Duchenne muscular dystrophy with CRISPR and pharmacological corrections'** is published in Science Advances, and focuses on using CRISPR-engineered human Pluripotent Stem Cells for modeling Duchenne muscular dystrophy (DMD). There is also a write up in CRISPR Medicine News.

We caught up with Amaia to find out more about her research on DMD and her current role here at Axol.

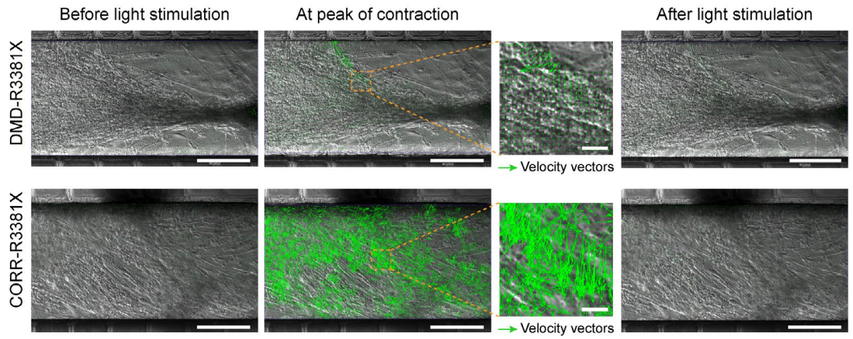
Why did you choose to work at Axol Bioscience?

I spent four years doing research on *in vitro* modelling of Duchenne muscular dystrophy (DMD), a rare genetic muscle disease. I wanted to apply my knowledge to other disorders and broaden my expertise in the field of disease modeling. A company the size of Axol and its portfolio seemed a very good fit.

As a scientist here at Axol, I am currently involved in iPSC reprogramming and gene editing projects. During my time here, I have already had the opportunity to work on several very interesting and challenging disease modeling projects.

Please describe the goals and main findings of your recent paper?

To date, there has been a lack of human-relevant pre-clinical models amenable to studying neuromuscular connectivity for a cure for neuromuscular disorders and for assessing the efficacy of drug candidates. To address this need, we developed an optogenetic model of DMD patient-derived neuromuscular circuits with CRISPR-corrected isogenic controls in compartmentalized microdevices. We found that DMD myogenic cultures have compromised myofiber contraction and dysregulated expression of genes affecting neuromuscular junction assembly compared to isogenic control cells. These phenotypic and genetic abnormalities responded to inhibition of TGFb signaling.



Functionally probing neuromuscular circuits *in vitro*. Figure shows particle image velocimetry (PIV) analysis in central compartments containing Duchenne's (DMD-R3381X) and CRISPR-corrected isogenic control (CORR-R3381X) neuromuscular circuits following light (optogenetic) stimulation of channel rhodopsin expressing motor neurons on day five. Representative images show before, during, and after optogenetic stimulation. Green arrows represent velocity vectors. Scale bars, 250 µm. Rescue of the dystrophin gene improves NMJ architecture and contraction. CREDIT: Paredes-Redondo et al. 2021

PHONE: +44 (0) 12237 751051 **U.S. TOLL FREE:** 1-800-678-2965 info@AxolBio.com https://www.axolbio.com

AXOL
Discovery Stems From Here

Amaia Paredes-Redondo, PhD
Research Scientist
Axol Bioscience

Amaia is a cellular and molecular biologist with expertise in disease modeling. She graduated from the University of Navarra, Spain. After her MSc at Imperial College London, she obtained her PhD in iPSC modeling for a muscle wasting disease from Queen Mary University of London.

Amaia is highly experienced in iPSC reprogramming and gene editing to model complex genetic disorders. She is now utilizing her knowledge as part of the Services and R&D team at Axol Bioscience ltd.

What do your findings mean for R&D scientists working on treatments for DMD?

Previous studies on DMD-patient derived iPSCs have either used: unrelated WT control cells, which do not account for the phenotypic variability inferred by the differences in genetic backgrounds between individuals; or gene-edited DMD cells with in-frame deletions in the dystrophin gene resulting in a shortened and only partially functional protein. To overcome these limitations, we generated isogenic controls by precise genome editing of a point mutation present in DMD-patient derived cells.

Also, after proving the functionality of our compartmentalized microdevices, we established a high-content imaging-compatible 96-well human neuromuscular circuit co-culture assay amenable for high-throughput drug screening and quantitative analysis of cellular phenotypes.

What does the future look like for DMD research and how do you think iPSCs are improving it?

DMD patients' muscles lose their ability to regenerate after physiological degeneration, so it is not an abundant primary material. Also, when primary muscle cells are cultured *in vitro* they stop proliferating at early passage. The use of patient-derived iPSCs together with newly developed transgene-free myogenic differentiation protocols overcome these limitations.

"During my time here at Axol, I have already had the opportunity to work on several very interesting and challenging disease modeling projects"

Amaia Paredes-Redondo, PhD
Research Scientist, Axol Bioscience

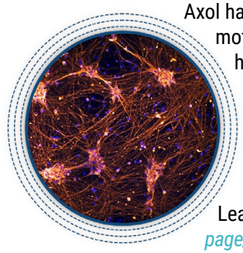
How important are co-culture iPSC models for R&D and assay development groups?

I think they are very important. Classic monotypic cell culture systems have limitations when recapitulating human physiology *in vitro*. To build biologically-relevant disease models, scientists have been working on co-culture of different cell types. These are useful in early-stage discovery, drug screening and assay development. And, will lead to a reduction in the number of compounds tested in animals.

Full Paper: *"Optogenetic modeling of human neuromuscular circuits in Duchenne muscular dystrophy with CRISPR and pharmacological corrections."*

https://www.science.org/doi/full/10.1126/sciadv.abi8787

Achieve rapid maturation of motor neurons in 14 days



Axol has developed human iPSC-derived motor neuron progenitors from both healthy and patient donors.

Our maturation accelerator media ensures rapid functional maturity of iPSC-derived motor neurons in two weeks.

Learn More at *https://www.axolbio.com/page/contact*

AXOL

Discovery Stems From Here

Axol is a leading provider of product and service solutions in the iPSC-based neuroscience, immune cell, and cardiac modeling for drug discovery and screening markets. Our custom research capabilities in gene editing, electrophysiology, reprogramming and differentiation means we can offer customers validated ready-to-use cell lines and a suite of services bolstered by deep scientific expertise and robust functional data - all with shorter lead times.

Get In Touch

Axol Bioscience Ltd.
Science Village, Chesterford Research Park
Little Chesterford, Cambridge
United Kingdom, CB10 1XL
PHONE: +44 (0) 1223 751051
US TOLL FREE: 1-800-678-AXOL (2965)
EMAIL: info@axolbio.com
https://www.axolbio.com/