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Dear Maxwell Biosystems HR members,

Isabel CHATO-ASTRAIN started her PhD in September 2021 in my laboratory under my supervision. Her PhD project aims to better characterize the pathophysiological impact of a recurrent 'missense' mutation in the *FMR1* gene, which leads to Fragile X syndrome. This neurodevelopmental disorder is the most common hereditary form of intellectual disability and a leading monogenic cause of autism. It results from the absence or dysfunction of an RNA-binding protein called FMRP, whose functional regulatory mechanisms are still poorly understood.

We initially demonstrated that the FMRP protein is modified by the small SUMO protein following the activation of type I metabotropic glutamate receptors. This modification allows for the local regulation of the release of FMRP-transported mRNAs, enabling the local translation of proteins essential for dendritic spine maturation (Khayachi et al., 2018, *Nat Commun*). Since the Fragile X missense mutation 'R138Q' in FMRP is very close to the SUMOylated lysine residue K130, we generated a new mouse model carrying this recurrent mutation, hypothesizing that it might impact the SUMOylation of FMRP and thus its function. We have since begun characterizing this new mouse line and have observed synaptic defects leading to behavioral abnormalities specific to Fragile X syndrome (Prieto et al., 2021, *Nat Commun*).

Isabel's PhD project directly builds on this initial work. It aims first to better understand the functional impacts of the Fragile X R138Q missense mutation and then, to analyze the effects of pharmacological treatments targeting SUMOylation to restore the function of FMRP-R138Q both *in vitro* and *in vivo*. Isabel is a motivated and scientifically curious young researcher. She quickly took responsibility for advancing both aspects of her PhD project in parallel and has developed extensive expertise and technical skills in synaptic biochemistry, cell biology, and confocal imaging. Her specific areas of expertise also include studies on local translation, membrane protein trafficking, and neuronal signaling. She regularly presents her research data through posters at national and international conferences and oral presentations at the laboratory's scientific events and retreats. I am confident that she possesses all the necessary qualities to successfully defend her PhD work on the 13th of March 2025.

Socially, Isabel is fully integrated into our research group. She provides advice and shares her expertise with other team and institute members. She has actively contributed to the laboratory's work on the regulation of synaptic SUMOylation by type I metabotropic glutamate receptors (Pronot

et al., 2022, *Cell & Mol Life Sci*). A review discussing recent advances in synaptic SUMOylation regulation, for which Isabel is the first author, has also been recently published in *Cells (Chato-Astrain et al., 2024)*. An additional research manuscript comprising part of Isabel's PhD work that she signs as the first author will also be soon submitted for publication in a high ranked journal.

Over and above her undoubted technical expertise, Isabel has a quick grasp of new concepts and the ability to formulate new and testable hypotheses. She was a constant source of stimulation, not only for me but also for the other team members. She is a hard worker, scientifically curious and always asking the right questions. I have no doubt she will perform well in her future job.

Isabel is highly motivated and over her PhD time in the lab she told me that her short-term ambition is to pursue a career combining communication and scientific research in the field of neuroscience. I thus believe the position she is applying for in your company could drive her well into this new career path. In my view, Ms CHATO-ASTRAIN is an ideal candidate for the kind of job you offer and I have absolutely no hesitation in recommending her in the highest terms as I think she will do really well in your company.

Yours sincerely,