## SUMMARY

The prion protein (PrP) is pathogenic when abnormally folded, causing the so-called Transmissible Spongiform Encephalopathies. Moreover, evidence shows that it mediates neuronal death in Alzheimer's Disease. Nevertheless, little is known about its roles, making it necessary to carry out further investigaions in order to elucidate the molecular mechanisms that underlie neurodegeneration.

Zebrafish (*Danio rerio*) display many advantages as animal model: it is easy to obtain a large offspring, and their embryos and larvae, which are transparent, develop fast and externally. Additionally, as vertebrates, they represent in a simple fashion molecular and behavioural processes in humans. Zebrafish express two paralogs of PrP: PrP-1 and PrP-2. PrP-1 is ubiquitously expressed in blastula and gastrula, mediating cell adhesion, whereas PrP-2 is expressed in the developing nervous system. Compared to PrP-1, there is no much information about PrP-2, even though it is more similar to the mammal PrP regarding sequence and expression pattern. Thus, we reasoned that it could be possible to know more about PrP by assessing PrP-2 functions.

In this study, we sought to take advantage of the aforementioned benefits of using zebrafish as animal model in this context, to validate two techniques and evaluate the cellular and behavioural effects of the PrP-2 knockdown induced by microinjection of morpholino oligonucleotides in early embryos. To this aim, we used immunohistochemistry and confocal microscopy to visualize abnormally-developed neuroanatomical structures in 24 and 48 hours post-fertilization embryos. This was complemented with behavioural analyses using 5 and 7 days post-fertilization larvae, proposing a possible physiological context to the found phenotypes and suggesting new approaches.

Our results show that both techniques offer relevant information about PrP function. We found alterations during gangliogenesis and axogenesis as a possible result of a defective cell communication during the nervous system development in treated embryos, likely mediated by the interaction of PrP and proteins like N-cadherin or NCAM. Besides, some changes in the swimming patterns were noted, which could be linked to the previously mentioned neuroanatomical alterations or to some pathways

mediated by neurotransmitters, such as the GABAergic one. Finally, we propose some novel ideas for future investigations in order to find the role of PrP-2.