**THESIS SUMMARY**

**WILD-TYPE HUNTINGTIN FUNCTION IN BDNF TRANSCRIPTION AND IN NEURAL DIFFERENTIATION**

Huntingtin is a large (348kDa) protein with a polymorphic stretch of glutamine near its N-terminus. Initial interest on huntingtin came from the fact that an expanded repetition of the CAG triplet (coding for glutamine) within the huntingtin encoding gene (HD) results in the inherited, autosomal dominant neurodegenerative disease known as Huntington’s disease.

Although the first studies were focused on the expanded (mutant) form of huntingtin accumulating data point out that the loss of normal (wild-type) huntingtin plays a role in the pathology (Cattaneo E. et al., 2001). Analysis of the HD gene sequence reveals its conservation throughout species evolution but the number of CAG triplets carried by the normal gene is different for each species (Kremer B. et al., 1994). This observation raised the idea that the CAG repeat is not crucial for normal htt function. Furthermore, deletion of CAG repeats in the HD gene results only in subtle behavioral and motor deficits in mice (Clabough EB. et al., 2006). An essential role of normal huntingtin has been established using HD gene knockout mice, where the absence of this protein leads to early embryonic lethality (Duyao MP. et al., 1995; Nasir J. et al., 1995; Zeitlin S., et al., 1995). Even though huntingtin function in embryonic development has been recognized, its function in brain development and throughout adult life is still an enduring research.

Unwrapping huntingtin physiological function in the adult brain will improve our knowledge on some of the Huntington’s disease features that remain elusive, such as the striatal selective loss. Despite huntingtin widespread distribution, only the striatum and the deeper layers of the cortex are selectively affected in the disease. Work from our lab has demonstrated that normal huntingtin is able to increase cell survival (Rigamonti D. et al., 2000; Rigamonti D. et al., 2001) and the production of brain derived neurotrophic factor, BDNF, a neurotrophin important for striatal cells survival (Zuccato C. et al., 2001; Zuccato C. et al., 2003).

In the present thesis, BDNF transcript level was assayed both in cortex and blood from a Huntington’s disease transgenic mouse model and results clearly show that levels decrease along disease progression. Together, this data opens the possibility of using BDNF mRNA level as a state biomarker for Huntington’s disease.

On the second half of this thesis, a Phylogenetic approach is proposed as an alternative way to identify, the still unclear, huntingtin functional domains. For this, we took advantage of an extremely useful cellular model- the huntingtin knockout embryonic mouse stem cells (ES Hdh-/-) (Duyao MP. et al., 1995; Nasir J. et al., 1995; Zeitlin S., et al., 1995). By following these cells, and their respective control (ES Hdh+/+) both in proliferation and under monolayer neural differentiation conditions, we have assayed their: i) survival vs apoptotic-dependent cell death, ii) tendency to maintain self-renewal properties, iii) ability to produce neural progenitors, iv) spatial organization of neural progenitors, v) neurogenic potential, vi) BDNF mRNA production and vii) propensity to escape neuronal differentiation.
Furthermore, the same assays were applied to an ES Hdh-/- cell line stably expressing the first 548 amino acids from normal human huntingtin, which have been previously reported to be a potential functional domain of this protein. Results from these studies sustain that normal huntingtin function is critical for cell survival, cellular spatial organization, commitment towards neuronal lineage, and regulation of BDNF transcription in the course of neural differentiation.