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Destructive potential of low-dose proton therapy (LDPT) on neurodegeneration disorders

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Radiotherapy (RT) is a safe and well-established medical treatment modality, defined by decades of clinical application, used alone or in combination with surgery and/or chemotherapy. It's used especially in cancer treatment, with the aim to destroy tumour growth while minimising damage to the surrounding healthy tissue[1-3]. One of the most important effects of RT, at a cellular level, is the ability to induce DNA damages leading directly or indirectly (through the induction of oxidative stress) to cell death[2,4]. Additionally, this therapy showed some successful results in the treatment of amyloidosis[5,6], a superfamily of chronic degenerative disorders caused by deposits of toxic protein aggregates in cells and tissues, especially regarding extra-cranial amyloidosis[1,2,7,8]. With that in mind researchers started to investigate the use of ionising RT against amyloid pathologies associated with AD[7,8]. Recently, low-dose RT (LDRT), with photons, has shown positive results on incurable neurodegenerative disorders such as Alzheimer's disease (AD) or Parkinson's disease (PD)[2,8].

Neurodegenerative disorders are the fourth most common cause of death in developed countries, and could surpass cancer by 2040, as predicted by the World Health Organization (WHO)[9]. They have no cure, and current treatments are merely symptomatic.

RT mechanism of action on systemic amyloid deposits is still not well understood[2], and a large amount of uncertainty remains regarding the impact of ionising radiation in the central nervous system[10]. Radiation-induced brain injury is a continuous and dynamic process and the mechanisms of its correspondence with the clinical manifestations are not fully understood[11]. The literature refers that is still necessary a more comprehensive understanding of the molecular and cellular processes underlying radiobiological responses of the brain[10]. The brain's tolerance to RT has been study for human brain tumours, giving privilege to the risk assessment of severe encephalopathy induced by radiation and trying to prove the relevance of parameters such as overall dose, overall treatment time, number and magnitude of dose-fractions[12] but it's also important to consider the volume that is irradiated and the radiation dose rate[11].

The cognitive effects are minimal when compared with the cognitive decline associated with AD and the probability of improving patients quality of life, especially if the total radiation dose is kept low, if we use a fractionated scheme and if critical brain structures are spared[7,12]. The literature suggest that the use of low-dose RT may not induce effects in cognition, cell functioning, DNA and gene expression, apoptosis, or pathological signs and that it can stimulate molecular and cellular protective mechanisms[10]. The use of low-dose RT can reduce amyloid load in the brain while the levels of oxidative stress and neuroinflammation are reduced, influencing cell function and neuronal survival, and helping to maintain cognitive abilities or even improve the cognitive performances of patients in AD advanced stages[2]. It is also important to keep in mind the ability of RT to overcome the blood-brain barrier, which is one of the most limiting factors of many pharmaceutics[2,8].

To improve the beneficial and therapeutic applicability of RT in human specific neurodegenerative conditions there is still a need of more studies to precisely define important factors such as: minimal necessary effective dose, best fractionated scheme, the genetic background-based response, the age-related effects and other possible factors not yet determined[13]. The overall aim of this PhD project is to analyse the destructive potential of low-dose proton therapy (LDPT) on the accumulation of toxic protein aggregates associated with these neurodegeneration disorders. Monte Carlo (MC) simulations will be confronted with experiments on purified amyloidogenic protein solutions and live-cell models of neurodegenerative disorders. Simulations will be validated by state-of-the-art spectroscopy and microscopy methods both in vitro and on cell models of some of these neurodegenerative disorders. The biochemical and biophysical mechanisms underlying the optimal proton therapy conditions for disruption of amyloid deposits will be characterized in close collaboration between LIP/BioISI (FCUL) researchers and the CMAM laboratory (Universidad Autónoma de Madrid -

UAM). The results of this multidisciplinary project will lay the groundwork for possible applications of proton therapy on a wide spectrum of neurodegenerative disorders.

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