CREATINE FOOD SUPPLEMENTATION IMPROVES THE PHENOTYPE AND DELAYS DISEASE ONSET OF THE CMVMJD135 MOUSE MODEL OF MACHADO-JOSEPH DISEASE

S. Duarte-Silva[1,2], A. Neves-Carvalho[1,2], J. Silva[1,2], A. Silva-Fernandes[1,2], **P. Maciel**[1,2]

[1]*School of Health Sciences, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal, Portugal*

[2]*ICVS-3B's, ICVS-3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal, Portugal*

sarasilva@ecsaude.uminho.pt

Machado-Joseph disease (MJD) is an autosomal dominant neurodegenerative disorder caused by the expansion of a polyglutamine tract (polyQ) in the C-terminus of the ATXN3 gene product, ataxin-3. Mitochondrial dysfunction has been implicated in several neurodegenerative diseases. Creatine administration increases brain concentrations of phosphocreatine and an inactivation of the mitochondrial permeability pore, exerting neuroprotective effects. Here we performed two pre-clinical trials – PCT1 and PCT2 - using the CMVMJD135 mouse model of MJD (groups of animals with a 133 and 139 CAG repeat mean respectively), to which creatine 2% supplemented food was provided either for 19 (PCT1) or 29 (PCT2) weeks. Oral administration of creatine led to an overall improvement in the motor phenotype of CMVMJD135 mice on both trials. Interestingly, in PCT1, with shorter creatine treatment duration but with less disease severity, the muscular strength deficits of the CMVMJD135 were improved, while in PCT2, corresponding to a longer treatment but a high severity disease condition those improvements were not so evident. Creatine-treated animals did, however, show improvement in both trials in motor coordination, limb strength and gait quality, as well as in other neurological parameters. Creatine chronic treatment delayed the onset of several symptoms and, in some cases, completely abolished the appearance of the phenotype. Furthermore, creatine treatment showed to be neuroprotective by increasing the calbindin staining in the Purkinje cell layer and reducing the astrogliosis in the brainstem of the CMVMJD135 mice. The present findings support creatine supplementation as a useful strategy to slow the progression of MJD.