Adenosine A<sub>2A</sub> receptors (A<sub>2A</sub>Rs) are G-protein coupled receptors that stimulate adenylyl cyclase activity. The most enriched A<sub>2A</sub>Rs brain region is the striatum, in which A<sub>2A</sub>Rs are largely restricted to GABAergic neurons of the indirect pathway, where they play out antagonistic interactions with dopamine D<sub>2</sub> receptors. Clinical trials have proven that antagonists of A<sub>2A</sub>Rs reduce the postsynaptic effects of dopamine depletion and lessen motor symptoms of Parkinson's disease (PD).

In this study, we have characterized that DNA methylation controls basal A<sub>2A</sub>R gene (ADORA2A) expression levels in human cell lines by quantitative chromatin immunoprecipitation and SEQUENON MassArray platform. Interestingly, we have shown increased DNA methylation percentage in the 5'UTR region of ADORA2A in the cerebellum with respect to the putamen of human post-mortem brains, showing an inverse relationship with A<sub>2A</sub>R levels in both cerebral regions. In parallel, we have shown that the upregulation of A<sub>2A</sub>Rs levels in the putamen of human post-mortem PD brains is not associated with any DNA methylation percentage lost in ADORA2A respect to age-matched control brains. However, we show that A<sub>2A</sub>R levels are reduced after a S-adenosylmethionine (SAM) treatment (a DNA methyl group donor) in SH-SY5Y and U87-MG cells. Therefore, considering that there is a low percentage of DNA methylation in the putamen of PD cases, this study shows the possibility of a SAM intervention (as a coadjuvant of A<sub>2A</sub>Rs antagonists) to reduce high A<sub>2A</sub>R levels detected in PD, which might allow reducing L-dopa dose.