**In vitro drug treatments reduce the deleterious effects of aggregates containing polyAla expanded PHOX2B proteins**

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Congenital central hypoventilation syndrome (CCHS) is a rare genetic disease characterized by a failure of autonomic control of breathing especially during sleep with decreased sensitivity to hypoxia and hypercapnia. In particular CCHS patients hypoventilate during sleep and, only in severely affected patients, also when they are awake. As no therapy has been discovered to ameliorate patients’ respiration, CCHS patients depend on mechanical ventilation such as tracheostomy, nasal mask or diaphragm pacing all their life. *PHOX2B* in frame duplications within a stretch of 20 alanine, leading to expansion form +5 to +13 alanine residues, and *PHOX2B* frameshift mutations, leading to aberrant C terminal regions, have been detected in CCHS patients.

Functional studies on the transcriptional activity of polyAla expansion on target genes, as *DBH*, has shown an inverse correlation between the length of polyAla expansion and the ability of transactivate *DBH* promoter compared to wild type protein, as a consequence of the mislocalization of polyAla expansions protein resulting in nuclear and cytoplasmic aggregates formation. Furthermore the length of alanine expanded stretches correlates with the severity of the phenotype in CCHS.

Recently therapeutic strategies has been tested for many polyalanine and polyglutamine repeat expansion disease, in particular the antibiotic Geldanamycin has shown to reduce aggregate formation in a *in vitro* model of CCHS disease. In this work we have been investigated the effects of molecules known to have proprieties in other polyGln or polyAla disease or already used in clinical trials for other pathologies. In particular, we report the effect of 17-AAG, ibuprofen, 4-PBA, curcumin, trehalose, congo red and chrysamine G on i) recovery of the nuclear localisation of polyA expanded PHOX2B, ii) rescue of transactivation of the PHOX2B promoter target *DBH*, iii) clearance of PHOX2B (+13 Ala) aggregates.

**In conclusion** our results show that 17-AAG and curcumin are the best performing molecules, tested in an *in vitro* model of CCHS, as they are able to restore the correct nuclear localization of the most severe polyAla expansion, to rescue the ability of transactivate *DBH* target promoter and to reduce aggregation of misfolded polyAla proteins. 17-AAG and curcumin toxicity effects is quite limited, as suggested clinical trial for other pathologies. We have also obtained evidences that the success of these treatments in our *in vitro* CCHS model is probably due by molecular mechanisms such as ubiquitin-proteasome (UPS), autophagy and heat shock protein (HSP) systems.