Poster Abstract – Session 2

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Strategies to promote the expression of the androgen receptor AR-A isoform lacking the polyglutamine tract in spinal and bulbar muscular atrophy

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Spinal and bulbar muscular atrophy is a neuromuscular disorder caused by a toxic polyglutamine (polyQ) expansion in the androgen receptor (AR). An isoform of the AR (AR-A) results from translation driven by an AUG(-II) downstream to the canonical AUG-I of AR. AR-A isoform lacks part of the N-terminal domain, including the polyQ tract. Redirecting the translation start site to the AUG-II might represent a strategy to avoid the expression of the toxic ARpolyQ, while preserving partial AR function of the shorter AR-A isoform. Strategies to switch the translation to AR-A isoform include the use of antisense oligonucleotides (ASO) to induce a steric blockage at the AUG-I encoding AR-B. To screen the ASO ability to switch AR-B to AR-A translation, we generated a reporter SH-SY5Y cell line (pScreen) expressing GFP or HiBit in frame with AUG-I or AUG-II, respectively. Ten ASOs were tested on pScreen cells, followed by HiBiT assay and GFP detection through western blot. The HiBiT assay showed that one ASO (#6) increased HiBiT-related luminescence normalised to cell viability, suggesting the induction of translation starting from the AUG-II. Instead, when we evaluated the reporter for AUG-I translation, ASO #6 also decreased GFP protein levels. In summary, there is evidence that the expression of AR isoforms can be modulated; however, the mechanisms underlying this regulation require further validation. Fundings: CN RNA & Gene Therapy, PNRR, CN3, Project CN00000041, Spoke 3