Mutant Androgen Receptor Alternative Translation Initiation as novel strategy to block toxicity in SBMA.

Chierichetti Marta[1], Cristofani Riccardo[1], Rusmini Paola[1], Ferrari Veronica[1], Tedesco Barbara[1 2], Cozzi Marta[1], Casarotto Elena[1], Pramaggiore Paola[1], Crippa Valeria[1], Galbiati Mariarita[1], Piccolella Margherita[1], Poletti Angelo[1]

[1]Dipartimento di Scienze Farmacologiche e Biomolecolari-Centre of Excellence on Neurodegenerative Diseases, Università degli Studi di Milano, Italia
[2] Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Spinal and Bulbar Muscular Atrophy is a neurodegenerative disease linked to a CAG repeat expansion in the Androgen Receptor (AR) gene, which is translated into a polyglutamine tract (polyQ) in the AR N-terminal region. ARpolyQ acquires neurotoxic properties and aggregates after testosterone binding.
Different start codons (AUGs) are involved in AR translation. I-AUG leads to translation of a full-length AR (AR-B) which includes the pathogenic polyQ tract in SBMA. II-AUG is located downstream to the CAG repeat leading to the translation of an alternative isoform named AR-A, this isoform does not contain the neurotoxic polyQ tract.
Here we started to characterize AR-A behaviour and to develop an effective strategy to selectively drive the AR translation from the II-AUG via antisense oligonucleotide (ASO) and a library of FDA approved drugs blocking ARpolyQ toxicity (GOF) without causing AR loss of function (LOF).
Through analysis of AR-A expression levels, transactivation activity, aggregates formation and co-expression of AR-A and AR-polyQ we demonstrate that depletion of the AR N-terminal region in AR-A: *i.* did not affect AR-A translation and stability *ii.* maintained its testosterone responsiveness, since AR-A had a lover transactivation capability compared to AR-B, but similar to ARpolyQ and *iii.* lead to the reduction of aggregate formation in ARpolyQ:AR-A ratio-dependent manner.
Using a double report screening vector designed to detect different AR isoforms expression in relation to the signal obtained we will perform ASO and drugs screening and, furthermore, we will understand the function of AR-A homodimer and AR-A:ARpolyQ heterodimer.