The neuromuscular disease Spinal bulbar muscular atrophy (SBMA) associates with loss of bulbar or spinal motoneurons and skeletal muscle atrophy. SBMA is caused by a mutation of the androgen receptor (AR) gene resulting in a protein with an elongated polyglutamine (polyQ) tract. AR polyQ acquires nuclear toxicity after binding testosterone, which induces AR nuclear translocation and AR polyQ misfolding. Misfolded AR polyQ is prone to aggregate, a process counteracted by the protein quality control (PQC) system. This system comprises chaperones and the degradative pathways (proteasome and autophagy). Several data suggest that misfolded AR polyQ is mainly processed via autophagy, and causes autophagy flux blockage. Restoration of a functional autophagy is beneficial to cells expressing misfolded AR polyQ. A peculiar form of autophagy is the “chaperone-assisted selective autophagy” (CASA), which relies on dynein-mediated retrograde transport of the CASA (HSPB8-BAG3-HSC70-CHIP) complex. This complex binds misfolded AR polyQ enhancing its clearance. In immortalized motoneurons (MNs) and MNs derived from SBMA iPSCs we found that inhibition of dynein-mediated retrograde transport reduces AR polyQ accumulation enhancing its clearance. This process is mediated by the HSC70 co-chaperone BAG1 which activate a compensatory mechanism alternative to HSPB8/BAG3. In the knock-in ARQ113 SBMA mouse model (KIARQ113), we found that in affected muscle both BAG1 and BAG3 are upregulated, with an increased BAG3:BAG1 ratio which preferentially routes misfolded AR polyQ to autophagy.

On these basis and on our previous in vitro studies, we tested bicalutamide (an antiandrogen which prevent AR nuclear translocation) and trehalose (an autophagy activator) in KIARQ113 mouse. We found found that mice survival was not significantly modified by the treatments, but an apparent positive trend was present. In Rotorod test KIARQ113 mice the impaired motor coordination was completely recovered by trehalose treatment. Bicalutamide administered at early stages worsened this phenotype (probably because of its anti-anabolic effects on muscle development), but recovered the motor coordination phenotype when administered at later stages (when muscle reached the adulthood stage). Grip strength test in KI mice showed decreased forelimb muscle force, which was further decreased by early, but not late bicalutamide treatment. Hystopathological analyses of mouse gastrocnemius reveal no variation associated to trehalose or bicalutamide treatment. Molecular analyses of gastrocnemius muscle of treated mice showed an increased PGC1alpha expression, paralleled by an increased mitochondrial DNA content and enhanced mitochondrial complex levels (particularly of complex V - ATP synthase subunits and complex III). Thus, the combined trehalose/bicalutamide treatment ameliorates muscle energy production and counteracts AR polyQ mediated toxicity in vivo.