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Inhibition of nonsense-mediated mRNA decay may improve stop codon read-through therapy for Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are genetic neuromuscular disorders that effect skeletal and cardiac muscle resulting from mutations in the dystrophin gene (DMD), coding for dystrophin protein. Read-through therapies hold great promise for the treatment of genetic diseases harboring nonsense mutations, such as DMD/BMD, as they enable complete translation of the affected gene. However, to date most read-through drugs have not achieved a cure for patients. One possible explanation for the limitation of these therapies for DMD/BMD is that they rely on the presence of mutant dystrophin mRNAs. However, the mutant mRNAs containing premature termination codons (PTCs) are identified by the cellular surveillance mechanism, nonsense-mediated mRNA decay (NMD) process, and are degraded. Here, we show that the combination of read-through drugs together with known NMD inhibitors have a synergistic effect on the levels of nonsense-containing mRNAs, among them the mutant dystrophin mRNA. This synergistic effect may enhance read-through therapies efficacy and improve the current treatment for patients. Furthermore, we have identified a chemical compound, MDB, which inhibits NMD. We show that MDB can enhance both dystrophin mRNA stability and the production of the dystrophin protein in the BMD patient-derived trans-differentiated cells.