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Tricyclo-DNA: highly promising antisense oligonucleotides for splice switching therapeutic approaches

Aurelie Goyenvalle
U1179 UVSQ-INSERM, University of Versailles saint Quentin,
Montigny le bretonneux, France

Antisense oligonucleotides (AON) hold promise for therapeutic splice-switching correction in many genetic diseases; however, despite advances in chemistry and design, systemic use of AONs is still limited due to poor tissue/cellular uptake. This talk will describe a novel class of AONs made of tricyclo-DNA (tcDNA), which displays unique pharmacological properties and unprecedented uptake in many tissues after systemic administration. These outstanding properties have been demonstrated in different mouse models of genetic diseases such as Duchenne muscular dystrophy (DMD) and Spinal muscular atrophy (SMA). DMD is a neurogenetic disease typically caused by frame-shifting deletions or nonsense mutations in the gene encoding dystrophin and characterized by progressive muscle weakness, cardiomyopathy, respiratory failure and neurocognitive impairment. While current naked AONs do not significantly enter the heart or cross the blood brain barrier, systemic delivery of tcDNA-AONs allow high levels of dystrophin rescue in skeletal muscles as well as in heart and to a lower extent in the brain. Our results demonstrate for the first time physiological improvement of the cardio-respiratory functions and correction of behavioural features linked to the emotional/cognitive deficiency associated with the lack of dystrophin.
These properties, together with the safe toxicology profile of tcDNA make this chemistry particularly attractive for future therapies in DMD patients as well as in other neuromuscular disorders or diseases eligible for splice-switching approaches requiring whole-body treatment.