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# Towards a New Era: New Therapeutic Advances for Genetic Disorders

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## Ray of hope for Metachromatic leukodystrophy (Sessa et al., 2016)

A safe and effective gene therapy may soon be available for Metachromatic leukodystrophy, a debilitating neurodegenerative disorder caused by Arylsulfatase A (ARSA) enzyme deficiency. Nine children with presymptomatic late-infantile or early-juvenile disease or early-symptomatic early-juvenile disease were enrolled in this open-label, non-randomised phase 1/2 clinical trial conducted by the Pediatric Clinical Research Unit in Milan. The study subjects received autologous hematopoietic stem cells transduced with a lentiviral vector encoding ARSA cDNA, after busulfan conditioning. All patients survived over a follow up period of 36 months. Eight patients, seven of whom received treatment when presymptomatic, had prevention of disease onset or halted disease progression. ARSA activity was reconstituted in the circulating haemopoietic cells and cerebrospinal fluid. There were no serious adverse events related to the medicinal product itself.

## Make way for MRT (Mitochondrial replacement therapy) (Kang et al., 2016)

Pathogenic mutations in mitochondrial DNA (mtDNA) are relatively common and lead to a wide range of clinical syndromes. Replacement of the mutant mitochondria with healthy donor ones has been attempted in four families with Leigh syndrome and one with Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes (MELAS) using the spindle transfer technique. The resulting embryos showed >99% donor mtDNA, which stably maintained in most, but reverted to the original haplotype in some. Specific D-loop polymorphisms responsible for selective replication of specific mtDNA haplotypes are believed to account for this reversal, amongst many other possible mechanisms. The study proposes choosing compatible donors with CSBII or other D-loop sequences resembling the maternal mtDNA to overcome this problem. This preferential replication of selective haplotypes was seen in most tested combinations, although the size of the study itself was small.

## Size alone does not matter! (Barbé et al., 2017)

Myotonic dystrophy is known to manifest in congenital forms, when the expanded CTG repeats are very large. However, large overlapping expansions have also been observed in those with classical and milder forms of the disease. This suggests the possible role of another genetic mechanism, which could potentially explain the phenotypic variability and the observed maternal transmission bias. CpG methylation of the *DMPK* gene, upstream and downstream of the CTG repeats, has been quantified in 79 samples across various age groups, phenotypes and inheritances and has been found to offer better genotype-phenotype correlation than the repeat size alone. Furthermore, the tendency of the repeats to either stabilize or undergo contractions during spermatogenesis due to the absence of methylation and the fact that methylation causes repression of proteins essential for spermatic survival seems to well explain the maternal bias. This study has found a near absolute correlation between the upstream methylation and maternal inheritance in congenital myotonic dystrophy and argues against CTG repeat size as

the only essential element associated with the severe phenotype.

## An old drug with a new indication! (Wassif et al., 2017)

Simvastatin, a routinely used hypocholesterolemic agent, could now potentially be a cheap and effective therapy in milder forms of Smith-Lemli-Opitz syndrome (SLOS), a genetic disorder caused due to the accumulation of the cholesterol precursor 7- dehydrocholesterol. This randomized, double blind, cross over trial in 23 patients in two 12-month treatment phases, with a 2-month washout period, showed significant reductions in dehydrocholesterol in the plasma and cerebrospinal fluid with simvastatin therapy, at a single daily dose of 0.5mg/kg for the first 6 weeks, followed by 1.0 mg/kg/day for the remaining 46 weeks of the trial. There was a notable clinical response in patients, in terms of reduced irritability, while on treatment.

This study is the first of its kind and explores the potential use of a relatively safe and well established drug in modulating the sterol composition & improving behaviour.

## References

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