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A glimmer of hope: newer treatment strategies for genetic disorders

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Smell and get well!

Drug delivery to the central nervous system, especially of large and charged molecules, has always proved challenging because of the inability of these molecules to efficiently cross the blood brain barrier. Invasive procedures like intrathecal or intraventricular injections are fraught with their own dangers. Intranasal therapy is an exciting alternative pathway to deliver drugs in to the CNS. The drug when administered in to upper parts of the nasal cavity travels via the olfactory nerves and trigeminal nerves to reach the CNS. Absorption through vasculature is also believed to occur. This approach effectively avoids certain problems of systemic administration like first pass metabolism, protein binding and systemic side effects. The onset of action is also fairly rapid.

A variety of neurotrophic factors and hormones have been successfully delivered in to the CNS using this method especially in neurodegenerative conditions like Alzheimer's disease, Huntington disease and Parkinson's disease. It has also been used in other conditions like seizures and stroke. Aly et al. have demonstrated that intra nasal therapy of plasmid DNA nano particles encoding glial cell line-derived neurotrophic factor had a neuroprotective effect in murine models of Parkinson's disease [Aly et al., 2015]. The cells transfected by the nanoparticle vector are likely to be pericytes. Intranasal therapy seems to be a very promising non invasive approach for CNS gene therapy.

NOEVel therapy for galactosialidosis

Galactosialidosis is a rare autosomal recessive lysosomal storage disorder caused by mutations in the *CTSA* gene. The gene encodes for protective protein/ Cathepsin A (PPCA). PPCA is found along with N-acetyl α Neuraminidase and β galactosidase in a lysosomal multi enzyme complex. Defect or deficiency of PPCA results in secondary deficiency of N-acetyl α Neuraminidase and β galactosidase thereby causing manifestations of galactosialidosis.

N-octyl 4 epi-β-valienamine (NOEV) is a chemical chaperone which *in vitro* has an inhibitory activity on the enzyme but *in vivo* interacts with mutant proteins and stabilizes them. NOEV showed promising results in mouse models of GM1 gangliosidosis. Hossain et al. have studied the effect of this molecule in cultured skin fibroblasts of patients with galactosialidosis [Hossain et al., 2015]. NOEV was found to result in significant increase in β galactosidase activity in these fibroblasts. Thus NOEV may be helpful in at least partly ameliorating the symptoms in galactosialidosis.

A new ray of hope for DMD

Duchenne muscular is the most common, severe childhood form of muscular dystrophy caused by mutations in the *DMD* gene. Heller et al. have demonstrated that over-expression of Alpha-7 integrin (ITGA7) using adeno-associated virus (AAV) delivery may be a useful therapeutic modality in this disease [Heller et al., 2015]. Alpha-7 integrin is a protein that in humans is encoded by the ITGA7 gene. Alpha-7 integrin is highly expressed in cardiac muscle, skeletal muscle and smooth muscle cells, and localizes to the Z-disc and costamere structures. It is a laminin receptor in skeletal muscle that, like the dystrophin-glycoprotein complex, links the extracellular matrix to the internal actin cytoskeleton. Mutations in ITGA7 have been associated with congenital myopathies and noncompaction cardiomyopathy, and altered expression levels of alpha-7 integrin have been identified in various forms of muscular dystrophy. The viral vector bearing this gene (rAAVrh.74.MCK.ITGA7) was delivered systemically at 5-7 days of age to the mdx/utrn(-/-) mouse deficient for dystrophin and utrophin. At 8 weeks post-gene transfer, widespread expression of ITGA7 was observed at the sarcolemma of multiple muscle groups. The in-

creased expression of ITGA7 significantly extended longevity and reduced common features of the mdx/utrn(-/-) mouse, including kyphosis. These results suggest that α7 integrin may be a potential therapy for DMD.

A small aperture to a larger view

Retinitis pigmentosa (RP) is a group of inherited disorders in which abnormalities of the photoreceptors or the retinal pigment epithelium (RPE) lead to progressive visual loss. No effective treatment is currently available for this condition. Pathogenic variants in more than 50 different genes or loci are known to cause nonsyndromic RP. Mutations primarily in genes expressed in rod photoreceptors lead to early rod death, followed by a slower phase of cone photoreceptor death. Reduction in HDAC4 expression during normal retinal development has been found to lead to apoptosis of rod photoreceptors and bipolar (BP) interneurons, whereas over-expression of HDAC4 reduces naturally occurring cell death of the BP cells. Guo et al. who had previously reported that HDAC4 over-expression in an Rd1 mouse model of retinal degeneration prolonged photoreceptor survival, have shown that expression of the short N-terminal domain of HDAC4 suppresses multiple cell death pathways in photoreceptor degeneration, and preserves even more rd1 rods than the full-length HDAC4 protein [Guo et al., 2015]. Expression of a short N-terminal domain of HDAC4 as a transgene in mice carrying the rd1 mutation also prolongs the survival of cone photoreceptors, and partially restores visual function. This modality thus appears to be a promising therapy for some forms of retinitis pigmentosa.

A whiff of fresh air!

Lloyd-Evans et al. have reported an ongoing double blind randomized control trial (RCT) for cystic fibrosis in two centers in the U.K. investigating non-viral CFTR gene therapy [Lloyd-Evans et al., 2015]. Nebulisation with plasmid DNA encoding the *CFTR* gene complexed with a cationic liposome has shown a significant but modest beneficial treatment effect with stabilisation of lung function with monthly dosing in a 12 months follow up period. No clinically important adverse events attributable to the treatment have been reported With the viral approaches showing restricted efficacy of repeated application, the results of this trial are encouraging.They provide the first proof of concept that repeated administration of non-viral *CFTR* gene therapy can safely change clinically relevant parameters, providing another step along the path of translational cystic fibrosis gene therapy.

Nipping the evil in the bud

A study conducted by Pievani et al. on the efficacy of allogenic bone marrrow transplant in newborn Mucopolysaccharidosis I (MPS I) mice observed that neonatal bone marrow transplantation (BMT) at a very early stage in life markedly reduces the signs and symptoms of MPS I before they appear and that it could offer a novel therapeutic opportunity for genetic disorders [Pievani et al., 2015]. Bones of transplanted MPS I mice showed significant improvements in radiographic, micro-computed tomography, and histological analyses. This study was based on the hypothesis that the first months of life represent the best window of opportunity for preventing bone deformities in Hurler children, given the observation that despite successful engraftment of normal donor hematopoietic stem cells, the musculoskeletal manifestations in MPS still deteriorate and that the long-term clinical outcome of Hurler patients is better when BMT is performed early in life.

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