GeNeXpreSS

Therapy for genetic disorders: How far have we come?

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How to make short a bit longer?

(Klag & Horton, 2016)

Achondroplasia is the most common chondrodysplasia in humans. Gain of function mutation in the *FGFR3* causes achondroplasia. *FGFR3* is a receptor tyrosine kinase, which negatively regulates growth plate activity, leading to short stature. C Natriuretic Peptide (CNP) was identified as an antagonist of fgfr3 in mouse models. CNP has a low plasma half life and hence a synthetic analogue, BMN111 was developed. BMN111 (Vosoritide) is the only candidate therapy to enter clinical trial. Recently the data of treatment of 26 children with a dosage of 15micro g/kg/ day for 6 months was released. Ten children showed 50% increase in annual growth velocity compared to their pretreatment rate. Only mild adverse effects like head ache, back pain and cough were noted. Future research is aimed at developing strategies to deliver the drug to the affected growth plate, so that adverse effects due to systemic administration can be minimized.

Modifying beta thalassemia by changing alpha genes (Mettananda et al., 2015)

Alpha globin genes have been identified as a target for modifying the disease phenotype in beta thalassemia. Alpha chain precipitation leads to most of the cellular pathogenic mechanisms of beta thalassemia. Alpha genes may be silenced by RNA interference. Voon et al. have shown a 50% reduction in alpha gene expression in murine primary erythrocytes, by using siRNA targeting alpha globin mRNA. This was associated with a significant improvement in phenotype. Xie et al. used lentiviral vectors with shRNA targeting alpha globin gene, producing transgenic mice with 25-30% less alpha globin. There is evidence that the upstream enhancer element MCS-R2 plays a critical role in alpha gene expression. Using genome editing tools like zinc finger nucleases and CRISPER cas 9, disruption of this single element has a potential to become an effective therapeutic strategy in beta thalassemia.

Gene therapy in Sanfilippo disease

(Ribera et al., 2014; OÇonnor & Boulis, 2015)

Sanfilippo disease (Type III MPS) is caused by mutations in the gene for alpha N acetyl glucosaminidase (NAGLU), causing accumulation of heparan sulfate in lysosomes, especially in the central nervous system. Ribera et al. injected AAV9 vectors encoding for NAGLU into the cerebrospinal fluid (CSF) of MPS Type III mice and demonstrated restoration of normal enzyme activity in the brain. Treated animals showed reversal of behavioral phenotype and extended the life span. Normal level of enzyme activity was noted in the CSF of canine models with pre-existing antibodies, after being treated with AAV9, demonstrating that CNS efficacy is not compromised in patients seropositive for AAV antibodies.

Ultrasound restores memory in Alzheimer disease (Leinenga & Gotz, 2015)

Amyloid beta peptide is responsible for the pathogenesis of Alzheimer disease. Gerhard Leinenga and Jürgen Götz, from Australia, used repeated ultrasound scanning on mice models with Alzheimer disease and showed that there was a significant decrease in the plaque burden compared to non treated mice. This was proposed as a novel non pharmacologic agent to improve the memory in Alzheimer disease.

References

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