GeNeXpreSS

# Innovative orphan drugs: a revolutionary evolution in the treatment of genetic diseases

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## Recombinant Ectodysplastin in X linked hypohydrotic ectodermal dysplasia[1-3]

X linked hypohydrotic ectodermal dysplasia is a relatively common genetic disorder characterised by the triad of hypotrichosis, hypohidrosis and hypodontia. *EDA*, the gene responsible for X-linked HED, produces ectodysplasin-A, a protein that is important for normal development of ectodermal appendages including hair, teeth, and sweat glands. Defects in the molecular structure of ectodysplasin-A may inhibit the action of enzymes necessary for normal development of the ectoderm and/or its interaction with the underlying mesoderm. Several isoforms of ectodysplasin are expressed in keratinocytes, hair follicles, and sweat glands. Gaide and Schneider compared the effect of antenatal versus postnatal EDA-A1 replacement, using EDI200, a recombinant EDAA1 replacement molecule, in the Tabby mouse model of XLHED. They found that the response to EDA-A1 replacement is significantly enhanced by antenatal maternal administration starting from embryonic Day 11. Another study by Mauldin et al. showed that neonatal treatment with recombinant EDA improved respiratory status in dogs with XLHED. It was shown that this treatment leads to partial to complete restoration of tracheal and bronchial glands. It was also found that prenatal EDA administration in treated dogs sustained the benefits on growth, infections, dentition, pulmonary function, and ocular inflammation. In mouse and dog XLHED models, administration of a single course of an EDA-A1 replacement protein (EDI200) resulted in permanent correction of the key phenotypic features, providing the first hope for an effective, targeted therapy.

## Correction of cholesterol accumulation in Niemann Pick disease type C patient–specific iPS cells[4]

Niemann-Pick type C (NPC) disease is a fatal inherited lipid storage disorder causing severe neurodegeneration and liver dysfunction. In 95% of the cases, it is due to mutations in the *NPC1* gene. NPC1 is a transmembrane protein and regulates cholesterol efflux. Loss of NPC1 function causes impaired cholesterol homeostasis that has a major impact on liver and brain. Maetzel et al. generated patient-specific NPC1 iPSCs (induced pluripotent stem cells) and isogenic mutant and control cell lines. They found that NPC1 iPSC-derived hepatic and neuronal cells showed reduced cell viability compared to their controls and displayed defects in cholesterol metabolism and impairment in autophagic flux. They used TALENs for the correction of the NPC1I1061T mutation. Transcription activator-like effector nucleases (TALENs) are artificial restriction enzymes generated by fusing a TAL effector DNA binding domain to a DNA cleavage domain. TALEN- rescued dysfunctional autophagic flux, thus implying that the defect in autophagy is directly linked to loss of NPC1 protein function. So, autophagy inducers can lead to increased cell viability in NPC1- deficient hepatic and neuronal cells. Mammalian target of rapamycin (mTOR) pathway inhibits autophagy, therefore mTOR inhibitors like Rapamycin can be used to induce autophagy. Some mTOR-independent autophagy enhancers can also be used like carbamazepine and verapamil. It was found that carbamazepine is the most potent drug in rescuing the defective autophagy phenotype in NPC1 iPSC-derived hepatic cells. So, the induction of autophagy is cytoprotective in the context of NPC

disease, and can improve cholesterol homeostasis in the liver and the brain.

## Targeting mTOR pathway in tuberous sclerosis[5,6]

Tuberous sclerosis is a neurocutaneous disorder causing various skin manifestations, brain abnormalities and involvement of other organs such as the kidney (angiomyolipomas, cysts, renal cell carcinomas), heart (rhabdomyomas, arrhythmias) and lungs (lymphangioleiomyomatosis). It is caused due to a mutation in the *TSC1* or *TSC2* gene, which encode hamartin and tuberin respectively, both of which inhibit AKT. AKT is responsible for activation of the mTOR pathway which has a role in cell growth, differentiation and vascular proliferation. Mutation in the *TSC1* or *TSC2* gene results in loss of inhibition of AKT and stimulation of the downstream mTOR (mammalian target of rapamycin) pathway. This forms the basis of treatment of TSC with mTOR inhibitors. Everolimus has been recently approved as a pharmacotherapy option for TSC patients with subependymal giant-cell astrocytomas (SEGAs) or renal angiomyolipomas (AMLs). Everolimus has been the first drug specifically licensed in the USA and Europe for the treatment of TSC patients aged ≥3 years with TSC-related SEGA who require therapeutic intervention, but are not candidates for curative surgical resection. Clinical evidence suggests that this treatment can also benefit other TSC-associated disease manifestations, such as skin manifestations, pulmonary lymphangioleiomyomatosis, cardiac rhabdomyomas, and epilepsy. Raffo et al. have demonstrated in animal models that mTOR inhibitors have an antiepileptic effect, decreasing seizures when started after epilepsy or preventing the development of epilepsy when initiated prior to the onset of seizures. Talos et al. have shown that mTOR inhibitors in animal models decrease both seizure susceptibility and later autistic-like behaviours. Therefore, the positive effects that mTOR inhibition has on a wide variety of TSC disease manifestations makes this a potential systemic treatment option for this multifaceted genetic disorder.

## Lovastatin in Neurofibromatosis 1[7]

Neurofibromatosis type 1 (NF1) is caused by mutations in the neurofibromin gene, an important inhibitor of the RAS pathway. NF1 patients show a high frequency of cognitive impairment and attention deficit disorder. In a mouse model of NF1, a loss of function mutation of the neurofibromin gene was found to result in increased gamma aminobutyric acid (GABA)-mediated inhibition which led to decreased synaptic plasticity and deficits in attention and performance. Lovastatin, a specific inhibitor of 3-hydroxy-3- methylglutaryl coenzyme A (HMG-CoA) which is commonly used for the treatment of hypercholesterolemia, is also a potent inhibitor of RAS/mitogen-activated protein kinase (MAPK) activity. Down regulation of the hyperactive RAS pathway by Lovastatin has been found to lead to an improvement of synaptic plasticity and restore learning and attention in mouse models of NF1. Mainberger et al. studied the effects of lovastatin on 11 NF1 patients and 11 healthy controls and found that lovastatin decreased intracortical inhibition and improved impaired synaptic plasticity and phasic alertness in patients with neurofibromatosis type 1.

## References


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