Preclinical development of a novel gene-based therapy for hereditary tyrosinemia type 1

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Hereditary tyrosinemia type 1 (HT1) is a lethal tyrosine-dependent inborn error of liver metabolism due to a deficient fumarylacetoacetate hydrolase (FAH) enzyme. It was historically treated by a tyrosine- and phenylalanine restricted diet, eventually followed by orthotopic liver transplantation (OLT). Nowadays, most patients can be effectively treated with the orphan drug nitisinone (NTBC), a potent inhibitor of the key enzyme 4-hydroxyphenylpyruvate dioxygenase (HPD) in combination with restricted protein intake without the need for OLT. However, inhibition of HPD by nitisinone leads to tyrosine accumulation in the blood resulting in impaired cognitive functioning of the patients and sight problems. Recent attempts have been made to develop gene therapeutic approaches that aim to restore the deficient FAH enzyme by its functional wild type version. Nitisinone withdrawal is then required to remove the metabolic block, hence putting the patients back at risk. As a possible solution, Jessie engineers an HPD enzyme variant with improved tolerance to nitisinone ($HPD^{\Delta ntbc}$) by directed protein evolution. As a proof-of-principle she will integrate $HPD^{\Delta ntbc}$ in adeno-associated viral vectors with liver tropism in combination with wild type FAH and evaluate the effectiveness of the therapy in a preclinical FAH-deficient mouse model of HT1 under nitisinone treatment.

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