SELECTED OPPORTUNITIES IN RARE DISEASES

Exon skipping therapy of Erythropoietic Protoporphyria (BIO 12380)

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EXON SKIPPING THERAPY OF ERYTHROPOIETIC PROTOPORPHYRIA (BIO 12380)

Product factsheet

Ex vitro POC
Human Primary cells

Indication

- Erythropoietic Protoporphyria (EPP, rare inherited disorder), mainly caused by a combination between an amorphic allele and a hypomorphic allele resulting from a common intronic SNP inducing aberrant splicing of mRNA encoding mitochondrial ferrochelatase (FECH). Resulting FECH reduced activity below a certain threshold induces accumulation of protoporphyrin IX in erythrocytes, plasma and skin.

Product

- antisense oligonucleotide preventing splicing of the cryptic exon inserted into the mutant IVS3 48C/T (rs2272783) FECH mRNA

Proof of concept

- improvement of wild type FECH mRNA production and protoporphyrin IX accumulation through correction of FECH exon 3-4 splicing demonstrated in cultured CD34+ derived erythroid progenitors from EPP patients.

Publication

- Antisense oligonucleotide-based therapy in human erythropoietic protoporphyria. *Oustric V et al; Am J Hum Genet. 2014 Apr 3;94(4):611-7*

Patent applications

- WO/2014/198890

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Proof of concept

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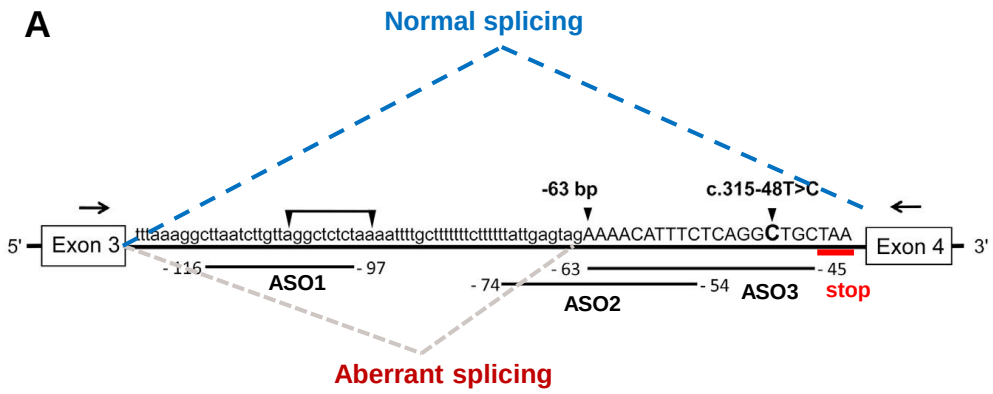
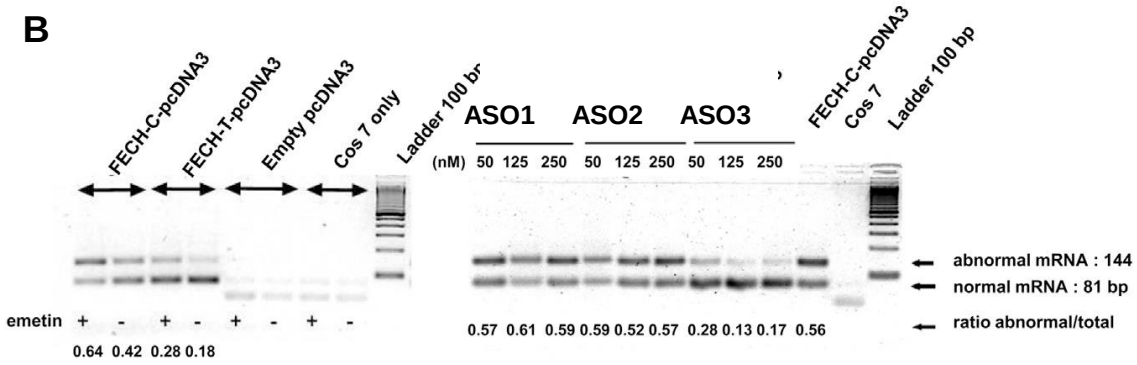
Repression of the aberrant splicing of Cryptic Exon 3–4 by a LNA-ASO Targeting Both the Cryptic Acceptor Splice Site and the 315-48C Region



(A) Schematic Representation of Exon 3–4 Splicing of *FECH* mRNA.
The c.315-48T>C transition modulates the splicing efficiency of a cryptic acceptor splice site.
LNA-ASOs targeting the putative cryptic branch point (ASO1), the cryptic acceptor splice site (ASO2), and the 315-48 region (ASO3) were designed.



(B) Inhibition of abnormal FECH splicing by three LNA-ASOs.
Cos7 cells were transfected with FECH-C ("normal allele") or FECH-T ("hypomorphic allele") together with ASO1, 2 or 3 at several concentrations. Aberrantly vs correctly spliced mRNAs were quantified by semi-quantitative PCR. ASO3 restores normal splicing.

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Proof of concept

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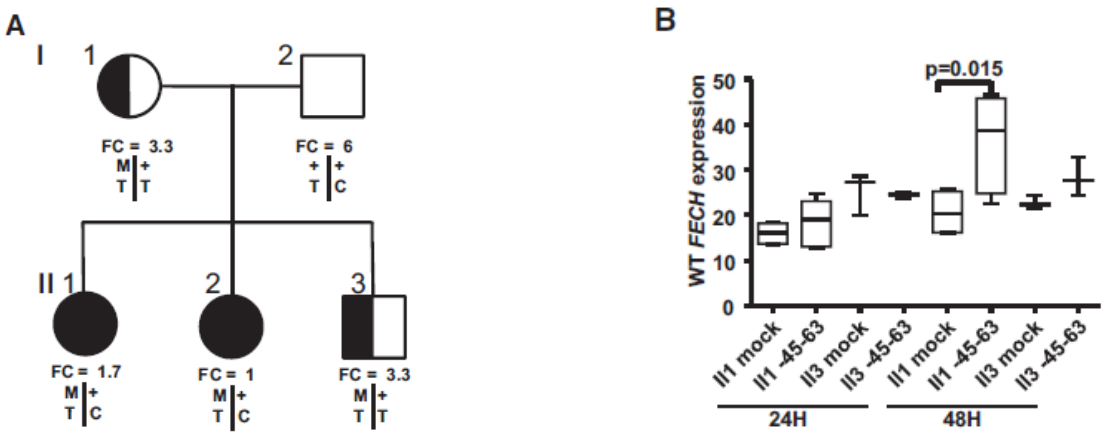
Restoration of WT FECH mRNA Production in the lymphoblastoid cell lines of EPP Subjects



Restoration of WT *FECH* mRNA Production in the LBCLs of EPP Subjects.
(A) Pedigree of the EPP-affected family. M indicates the c.709delT deleterious FECH mutation. T indicates the hypomorphic allele. C indicates the normal allele. Subjects I1 and II3 are asymptomatic carriers of the c.709delT mutation. Subjects II1 and II2 were EPP subjects.
(B) Quantification of *FECH* mRNA in subject LBCLs transfected with ASO3 or mock.

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