A-to-I editing

Adenosine-to-inosine editing is a reaction catalyzed by adenosine deaminases acting on RNA (ADARs) where adenosine residues are chemically converted to inosine residues by deamination reaction within dsRNA targets. Adenosine-to-inosine editing is a reaction catalyzed by adenosine deaminases acting on RNA (ADARs) where adenosine residues are chemically converted to inosine residues by deamination reaction within dsRNA targets.

Examples of different target RNAs for A-to-I editing and its wide applicability

Therapeutic need for A-to-I technology

Human disease-causing substitution mutations

Rationale of EON design

Computational tools for EON design

Functionalities of an EON is defined by sequence and chemical modification

Endogenous A-to-I machinery can be used therapeutically

Aximero® Technology

Aximero® Technology is targeted RNA A-to-I editing by endogenous ADAR proteins using ADARs targeting oligonucleotides (EONs) as a single-component therapeutic.

2'-OMe vs. RNA vs. DNA Digital droplet PCR (% edited mRNA)

Comparison of editing capability of 2'-OMe modified, fully Mod-X modified, partially Mod-X modified EONs

DNA nucleotides in the editing enabling region are compatible with editing activity

DNA nucleotides in the editing enabling region adapt to the local structural features of ADAR active site

DNA backbone and 2'-OMe modifications

Further enhance the combination of 2'-OMe and 2'-OMe modifications in the editing enabling region ensure stability against endo- and exonuclease degradation

DNA backbone and PS backbone modifications in the editing disabling region

FBS

Therapeutic A-to-I technology

Editing of GFP W57X reporter construct by overexpressed ADAR2 in HEK293 cell lysate with 200 nM EON.

Target RNA and EON

Optimization of EON sequence enables higher editing activity

2'-OMe EONs enable highly specific editing by endogenous ADAR proteins both in vitro and in vivo.

Summary

Aximero® Technology achieves targeted A-to-I editing of a therapeutically relevant model disease nonsense mutant IDUA mRNA in MEF cells with 100 nM EON.

EON with RNA

Comprehensive comparison of 2'-OMe backbone modification and PS backbone modification shows improved cellular uptake

Up to 24% of 2'-OMe modified EONs are modified by nucleases in the cellular environment

EON backbone modifications in terms of DNA backbone and PS backbone modifications in the enabling region

Optimized Mod-X EON by computational modeling ensures higher editing capability of target IDUA mRNA

Planar

EON backbone modifications in terms of DNA backbone and PS backbone modifications in the enabling region

Mod-X EON backbone modifications ensure higher editing capability of target IDUA mRNA

Optimized Mod-X EON by computational modeling ensures higher editing capability of target IDUA mRNA

ENAD

The Aximero® development timeline

Scan the code for a digital copy

http://www.proqr.com/axiomer018/