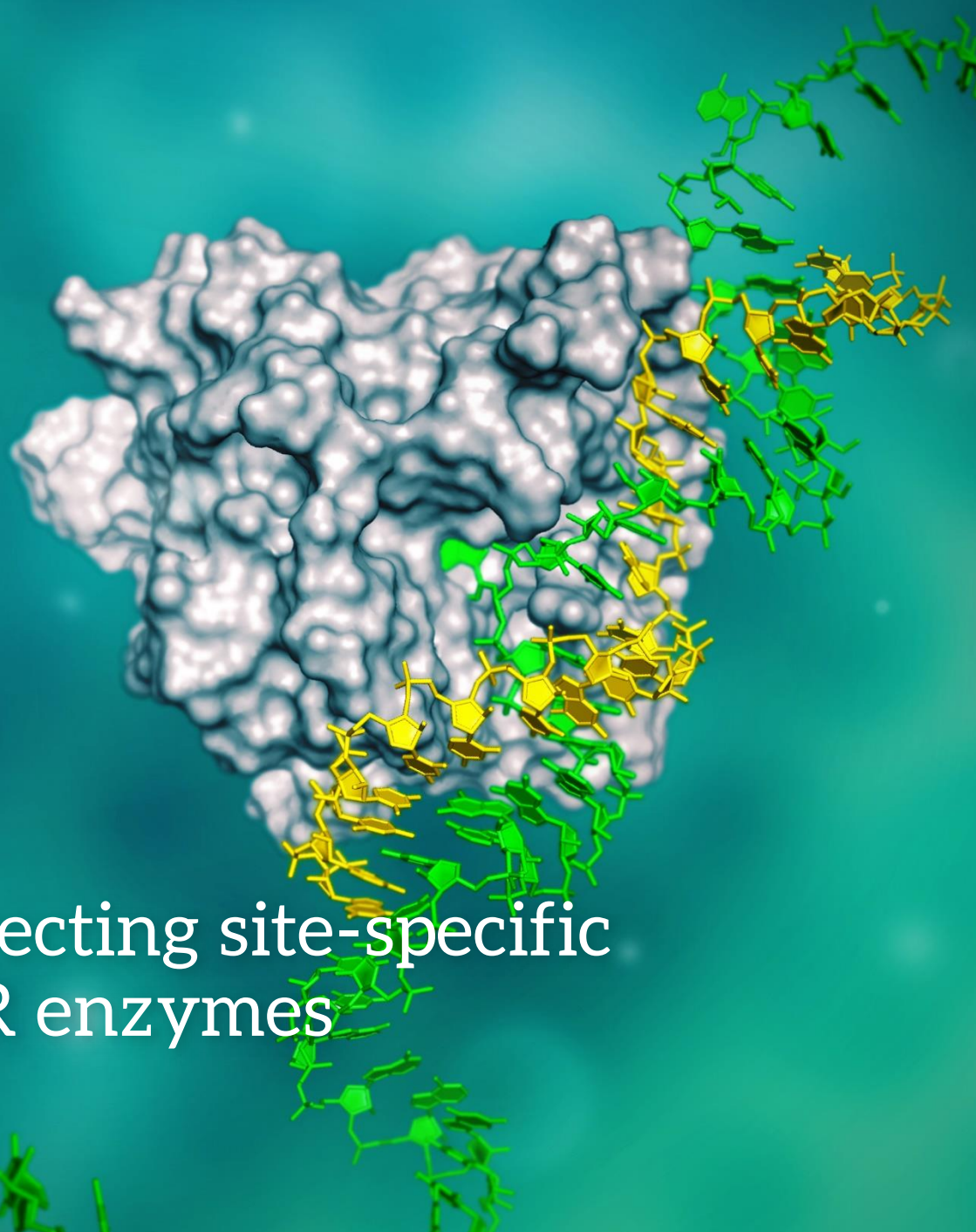
ProQR®

AXIOMER® TECHNOLOGY

Therapeutic oligonucleotides for directing site-specific A-to-I editing by endogenous ADAR enzymes



Forward looking statements

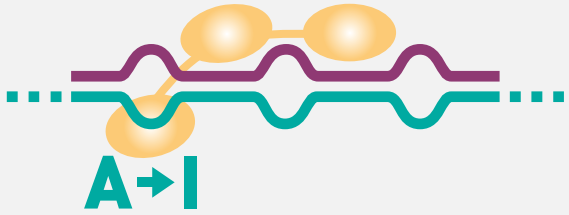
This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including but not limited to, statements regarding our strategy, future operations, future preclinical and clinical trial plans and related timing of trials and results, research and development, future financial position, future revenues, projected costs, prospects, therapeutic potential of our product candidates, plans and objectives of management, are forward-looking statements. The words "aim," "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Forward-looking statements represent our management's beliefs and assumptions only as of the date of this presentation. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those that may be described in greater detail in the annual report filed on Form 20-F for the year ended December 31, 2018 that we have filed with the U.S. Securities and Exchange Commission (the "SEC") and any subsequent filings we have made with the SEC. We have included important factors in the cautionary statements included in that annual report, particularly in the Risk Factors section, and subsequent filings with the SEC that we believe could cause actual results or events to differ materially from the forward-looking statements that we make.

Therapeutic potential

Axiomer RNA editing platform

Editing Oligonucleotide (EON) mediated A-to-I editing



Unique A-to-I RNA editing

- A-to-I editing in RNA
- Using endogenous ADAR
- ADAR is recruited by a single stranded Editing OligoNucleotide (EON)
- I is translated as a G, allowing to target G-to-A mutations
- Specific, potent and stable by *design*

Strong IP protection

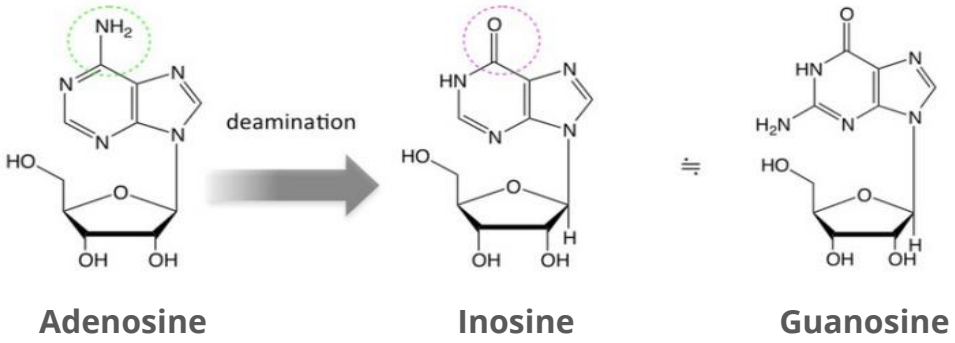
- Invented in house at ProQR laboratories
- Foundational patents owned by ProQR
- Unrivalled know how on EON design and high-throughput assays
- Key collaborations with ADAR experts in the world

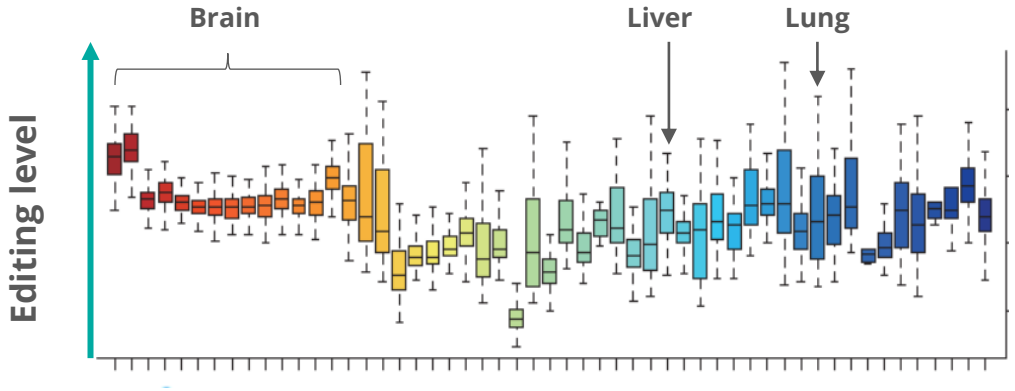
Broad applicability

- Axiomer technology can target G-to-A mutations
- 22,000 G-to-A mutations causing disease
- Broader applicability in RNA and protein engineering for medical purposes

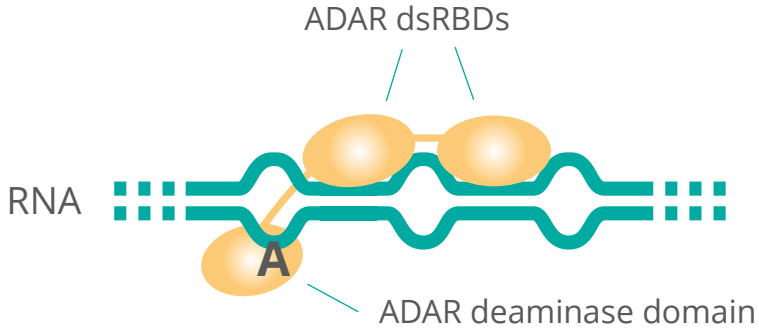
A-to-I editing: Therapeutic opportunity

The most prevalent editing event in human tissues





Adapted from Tan et al. 2017 Nature 550:249-254

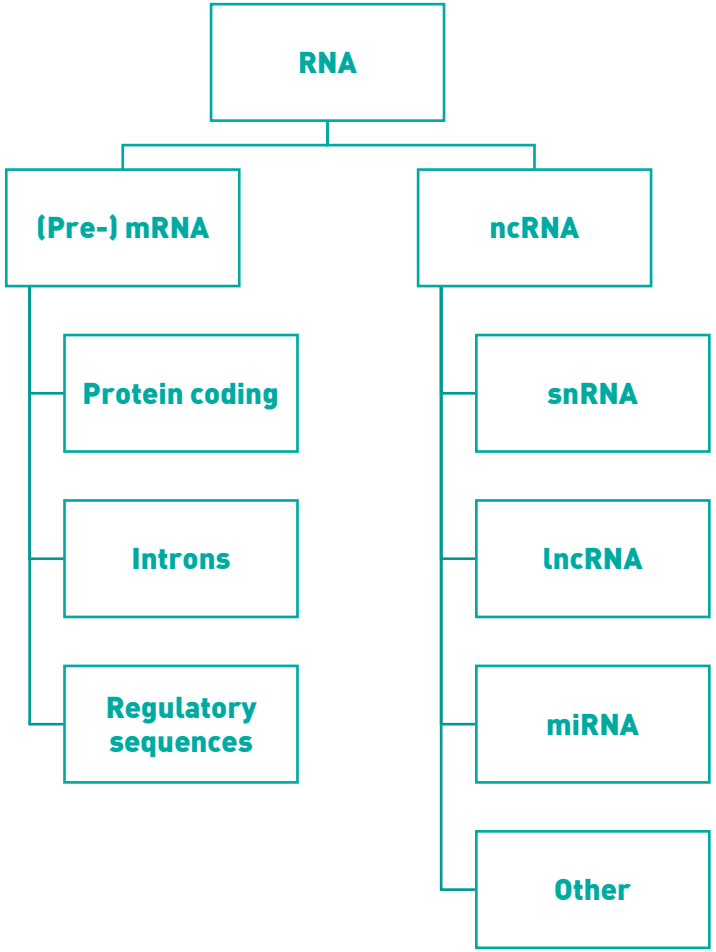


- Human catalytic ADARs: ADAR1 and ADAR2
- A-to-I editing occurs in both nucleus and cytoplasm

- No sequence dependence
- 4 million ADAR sites in the human transcriptome
- Extent of editing similar in most human tissues, making therapeutic editing feasible in all disease areas

Axiomer® is widely applicable

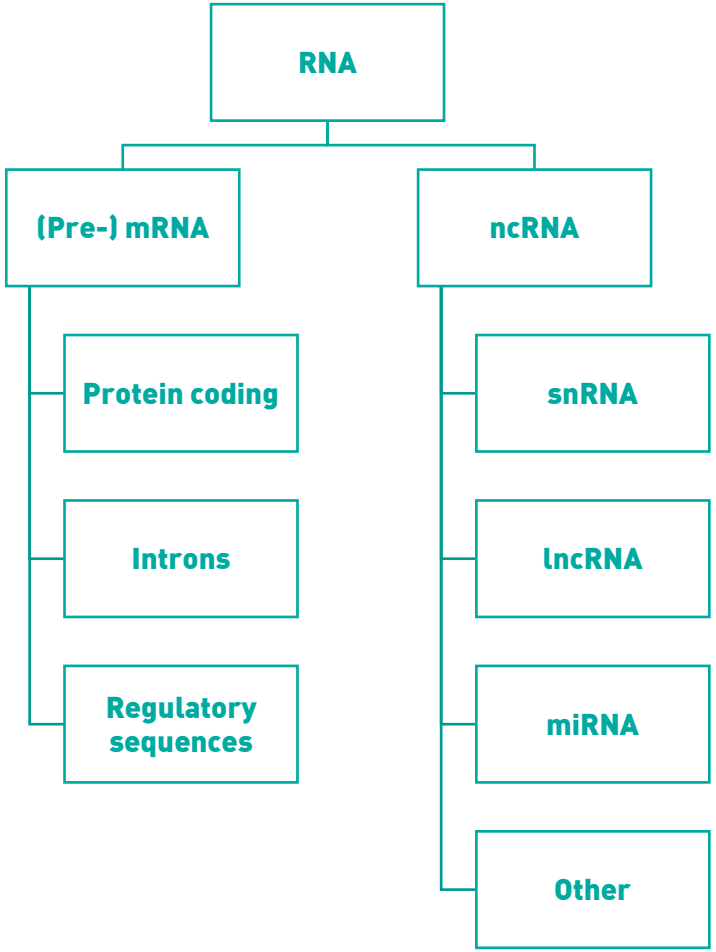
Examples of different target RNAs



Effect on RNA	Effect of therapy
Correct nonsense mutations	Restore translation
Correct missense mutations	Restore protein
Correct splice sites	Restore splicing of mRNA
Modify codon	Alter protein function
Modify protein binding	Alter expression
Modify 2° RNA structure	Alter expression
Alter regulatory sequence	Modify target RNA/DNA/ protein binding

Axiomer® is widely applicable

Stop codons as PoC for a wide class of disease indications



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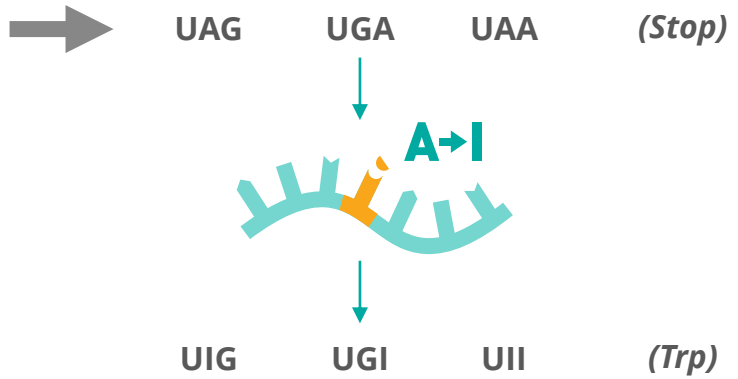


- Class of mutations resulting in complete loss of function
- First proof of concept for the Axiomer® approach

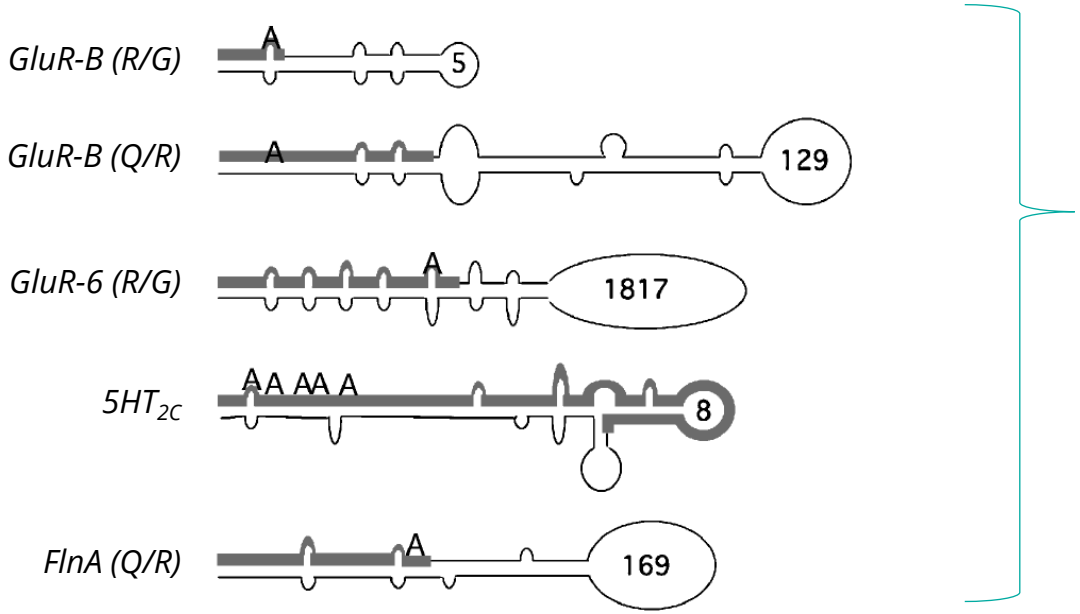
Axiomer® EONs

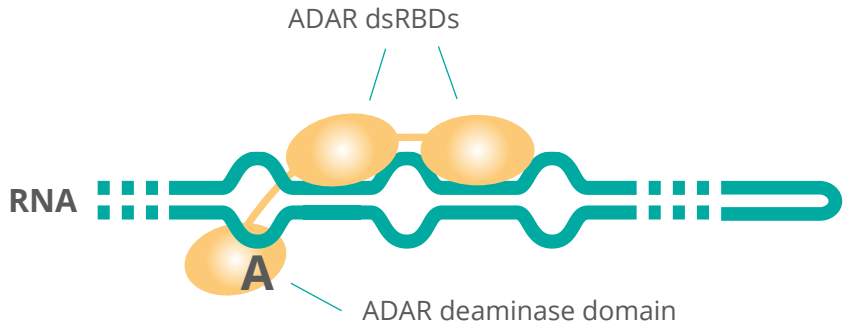
Molecular basis for targeted A-to-I editing

ADARs deaminate adenosine in dsRNA

Endogenous editing on natural substrates

ADAR targets:
Adenosines in dsRNAs with incomplete helices





Wahlstedt & Öhman 2011, WIREs RNA

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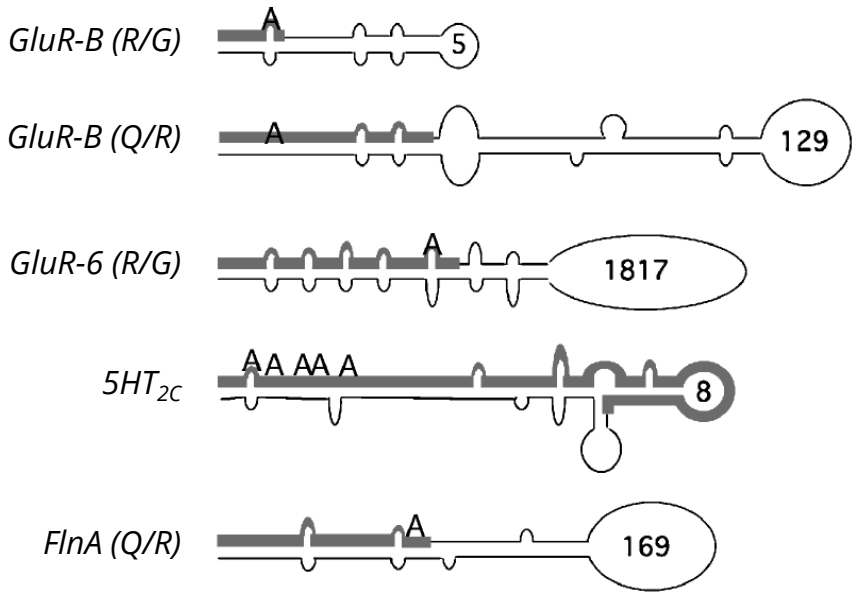
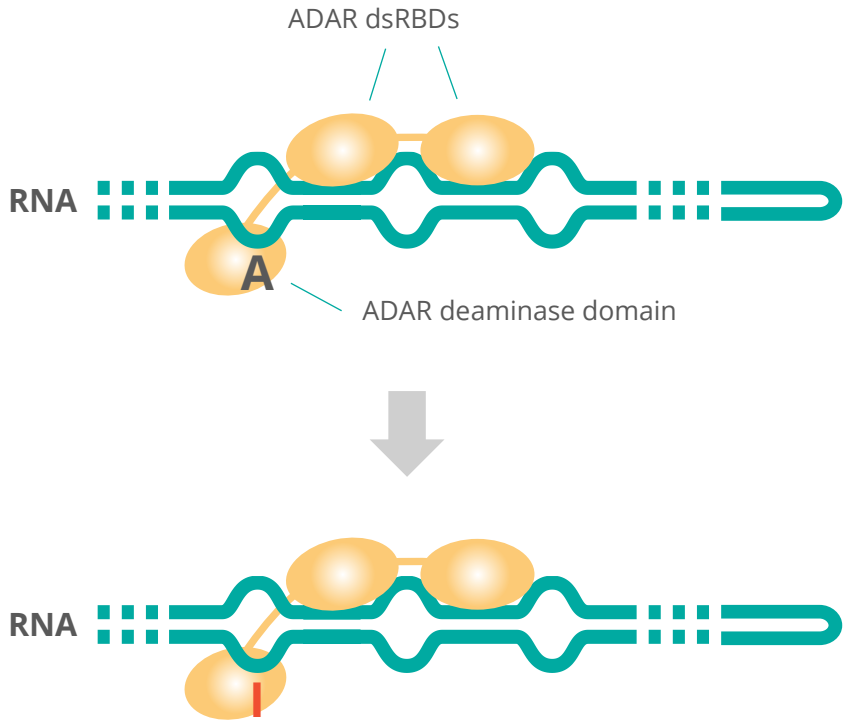
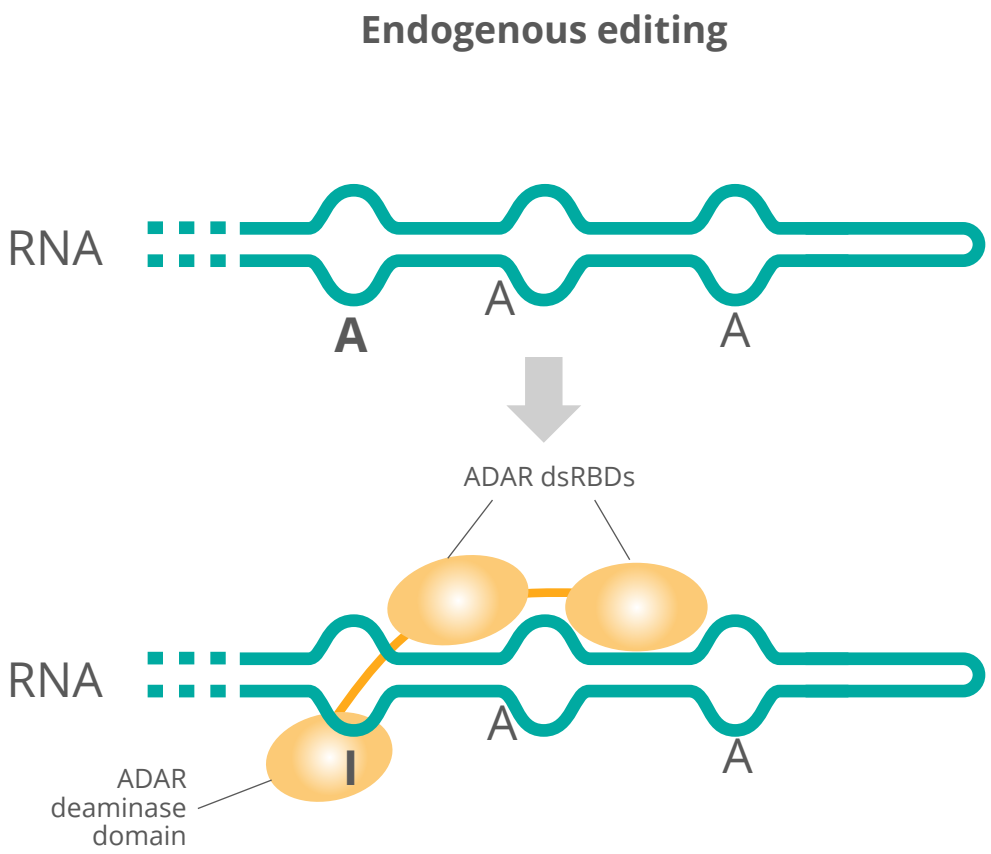




Wahlstedt & Öhman 2011, WIREs RNA

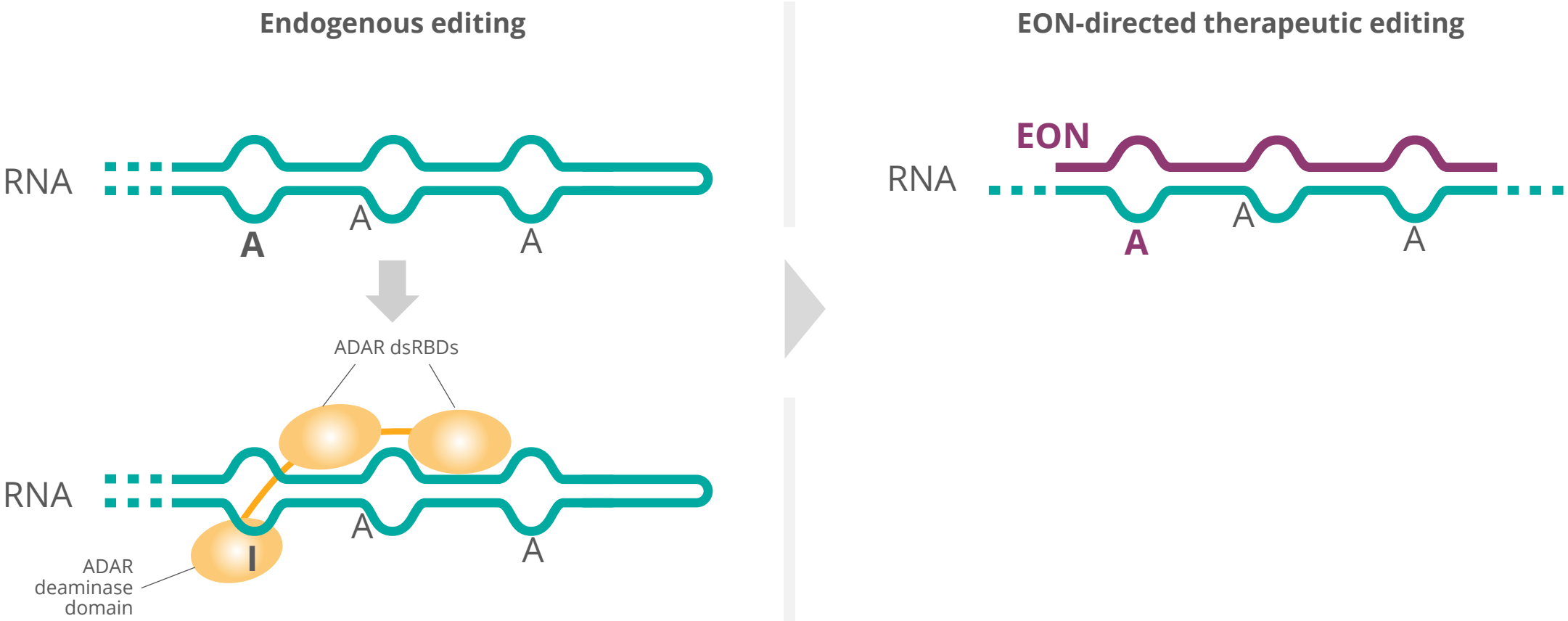
EONs designed for targeted editing (1)

Mimicking natural RNA editing



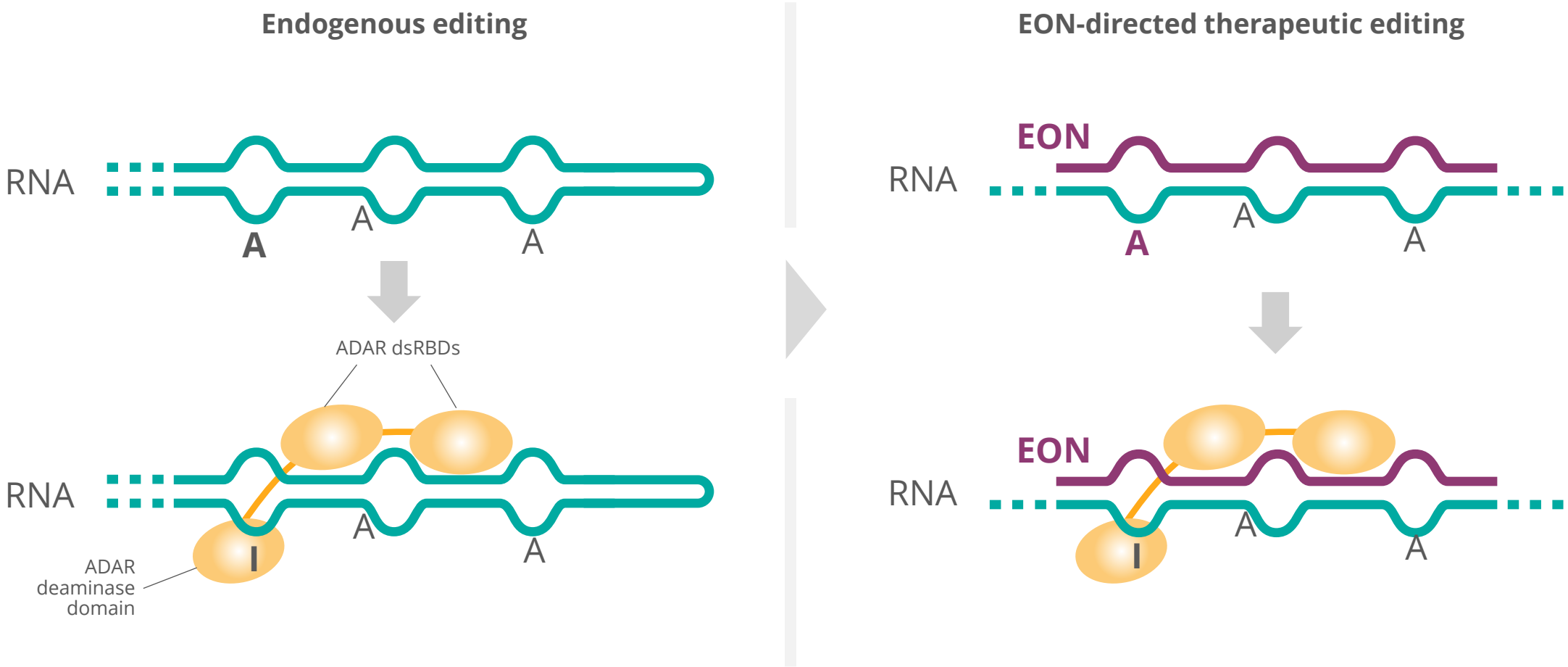
EONs designed for targeted editing (2)

EON and the target RNA form a double helix



EONs designed for targeted editing (3)

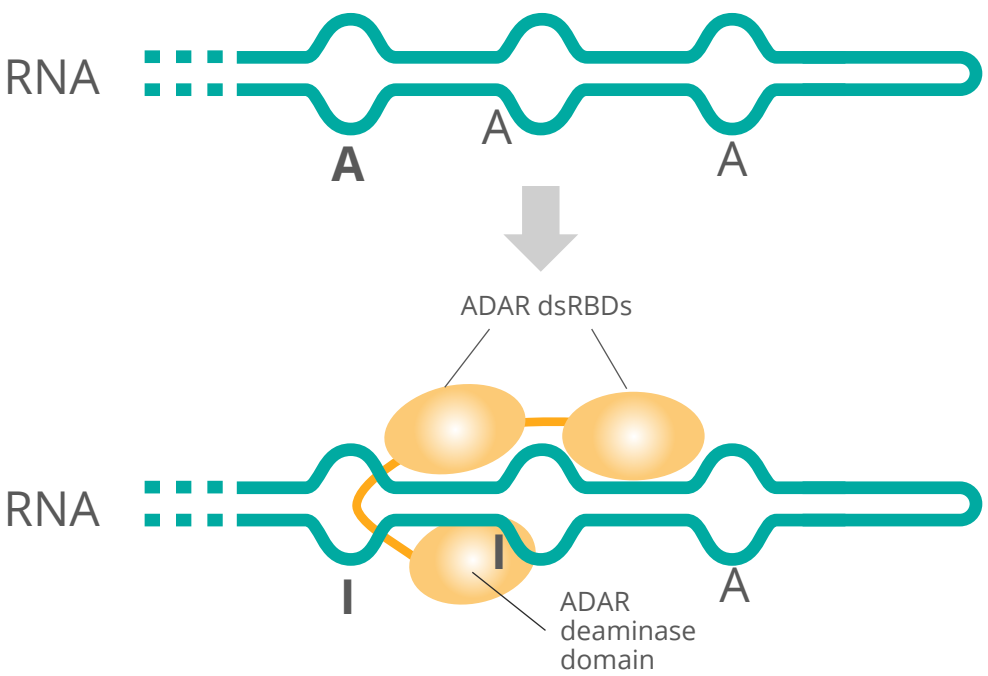
ADAR deaminates the target A in EON-target RNA helix



EONs designed for targeted editing (4)

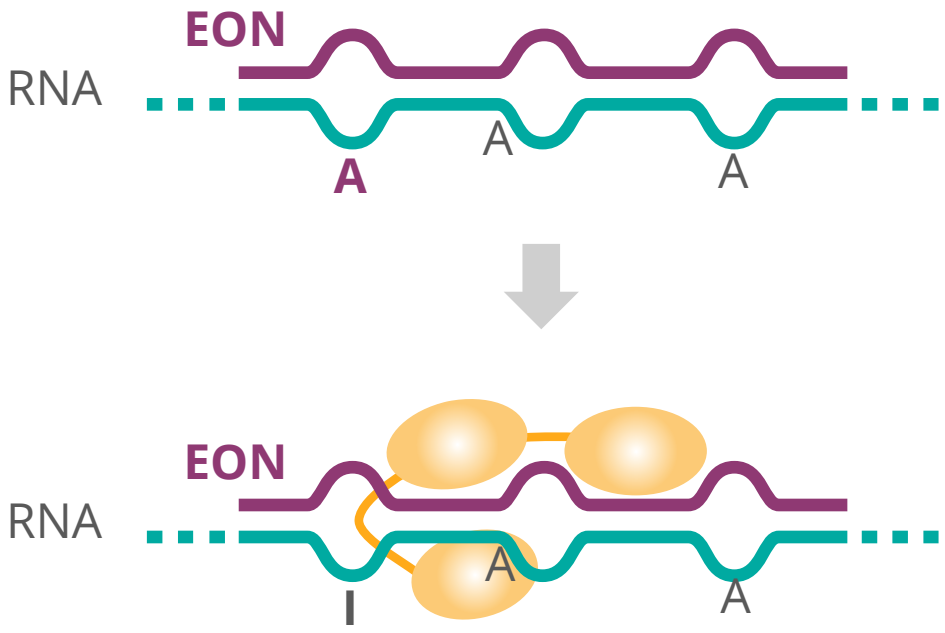
Advantage over RNA guides: Specificity

Endogenous editing



Editing site with RNA guides is flexible

EON-directed therapeutic editing



Editing site with EONs is precise:
No off-target editing even if deaminase domain shifts

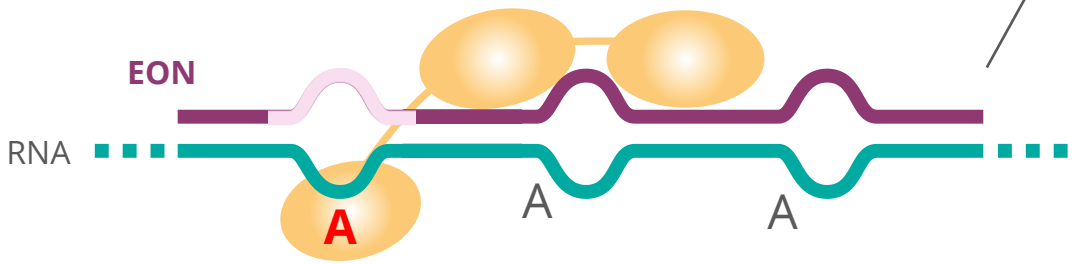
EONs designed for targeted RNA editing

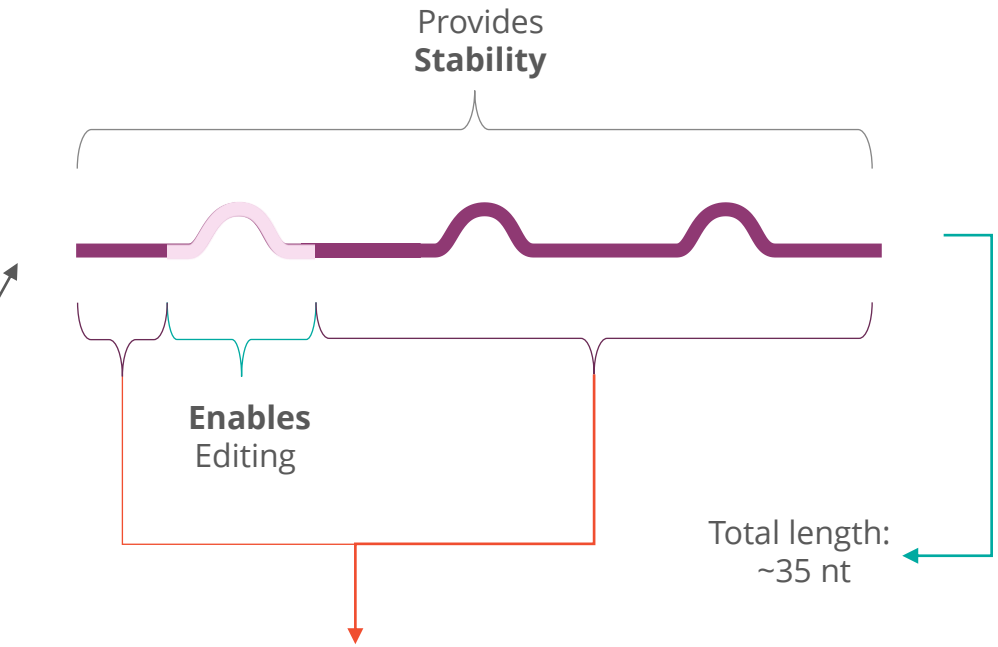
Functionality defined by sequence and chemistry

Sequence defines target RNA binding

EON chemical modifications define:

- Editing specificity
- Stability (nuclease resistance)
- Bioavailability
- Cell and tissue uptake





Structural basis for nt modifications

ADAR binding and catalysis require different modifications

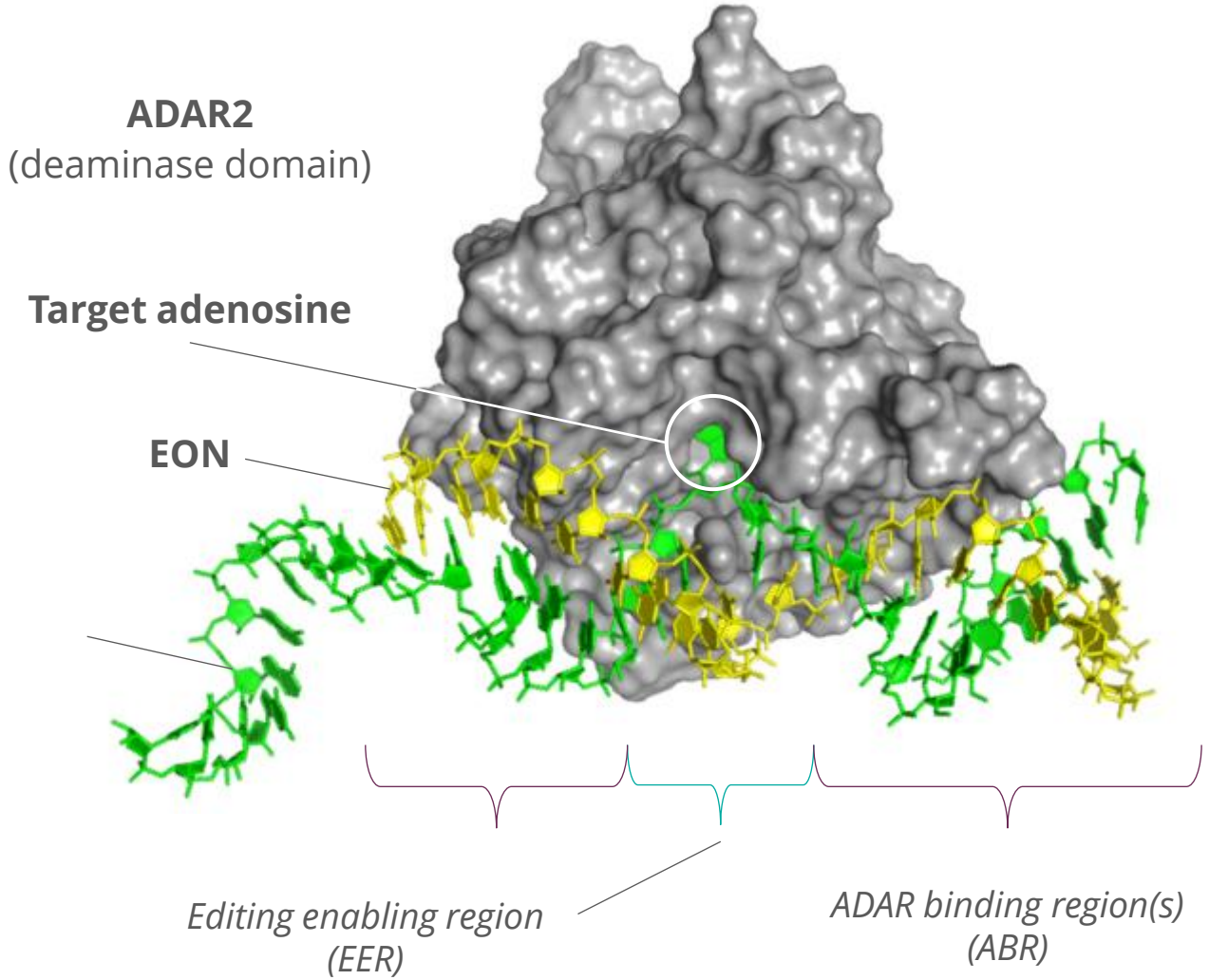
ADAR binding region

- Modifications that are compatible with ADAR binding, but do not fit in the catalytic center

Editing enabling region

- Modifications that fit into the catalytic center

Structural modelling provides a **basis for further optimization of EONs**



Axiomer® EONs

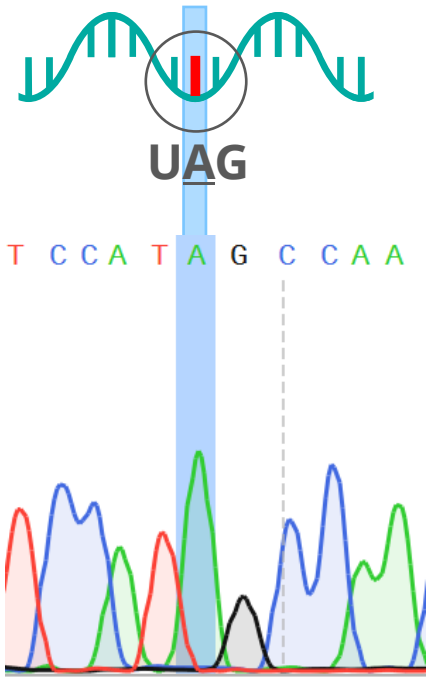
PoC studies for targeted editing

EONs can restore ORFs

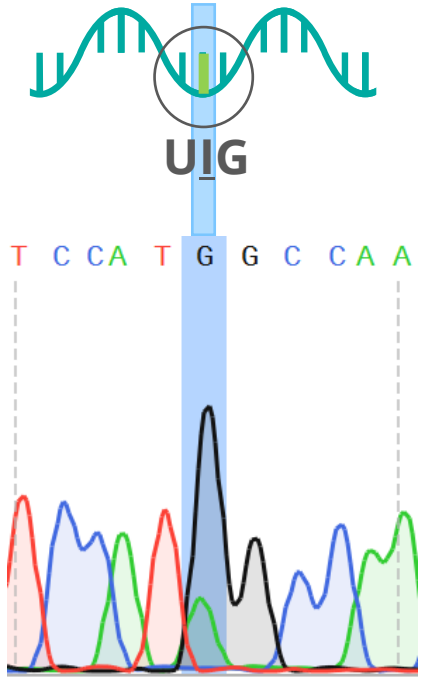
In vitro proof of concept in a GFP reporter

- GFP W57X reporter in Hepa1-6 cells
- ADAR2 overexpression
- Transfection with 100 nM EON
- Readout by Sanger sequencing of the RT-PCR product

W57X Mutation



Mutation treated with EON

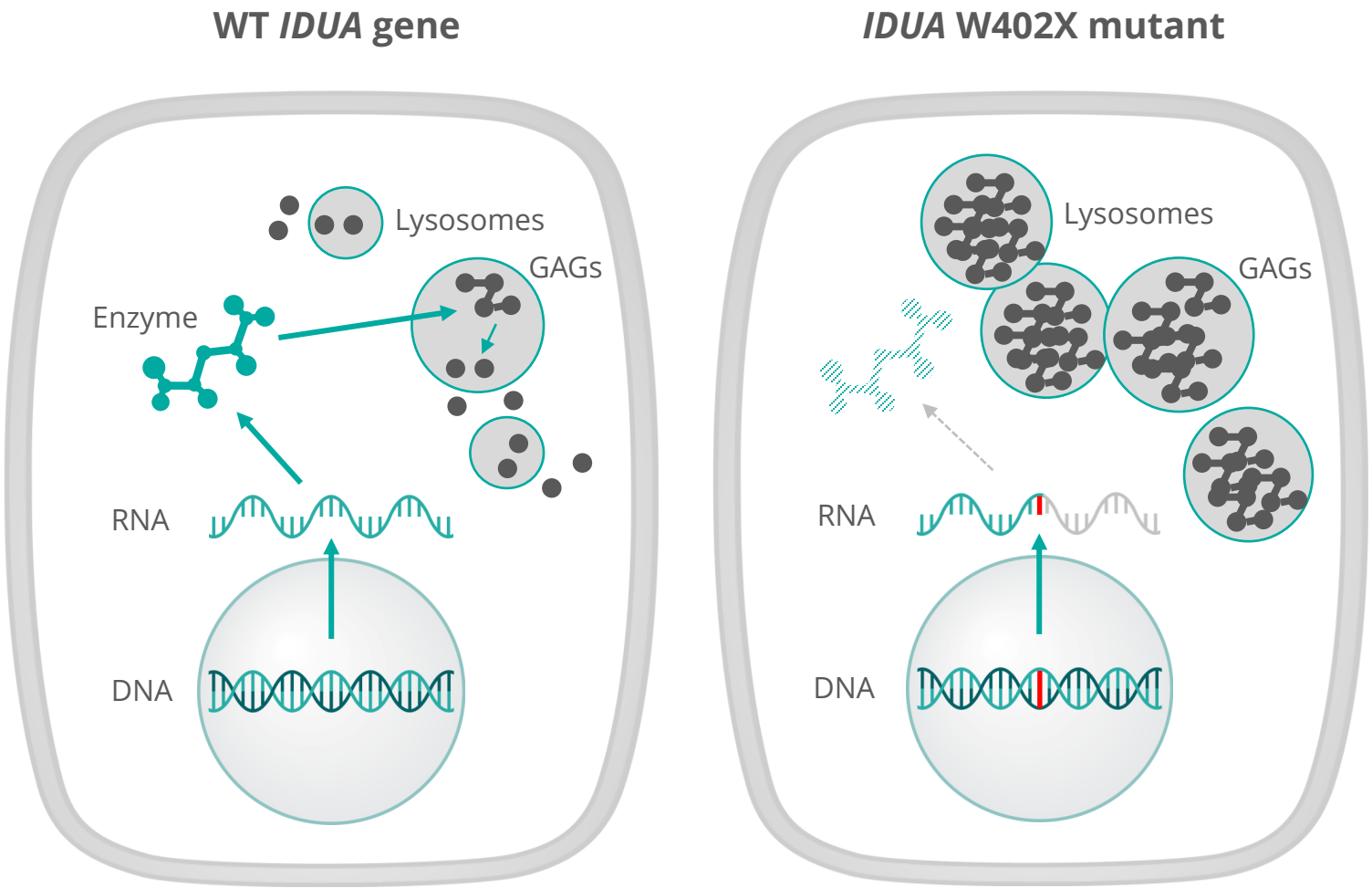


85% of transcript corrected by editing

Model system for *in vivo* PoC:
Hurler syndrome

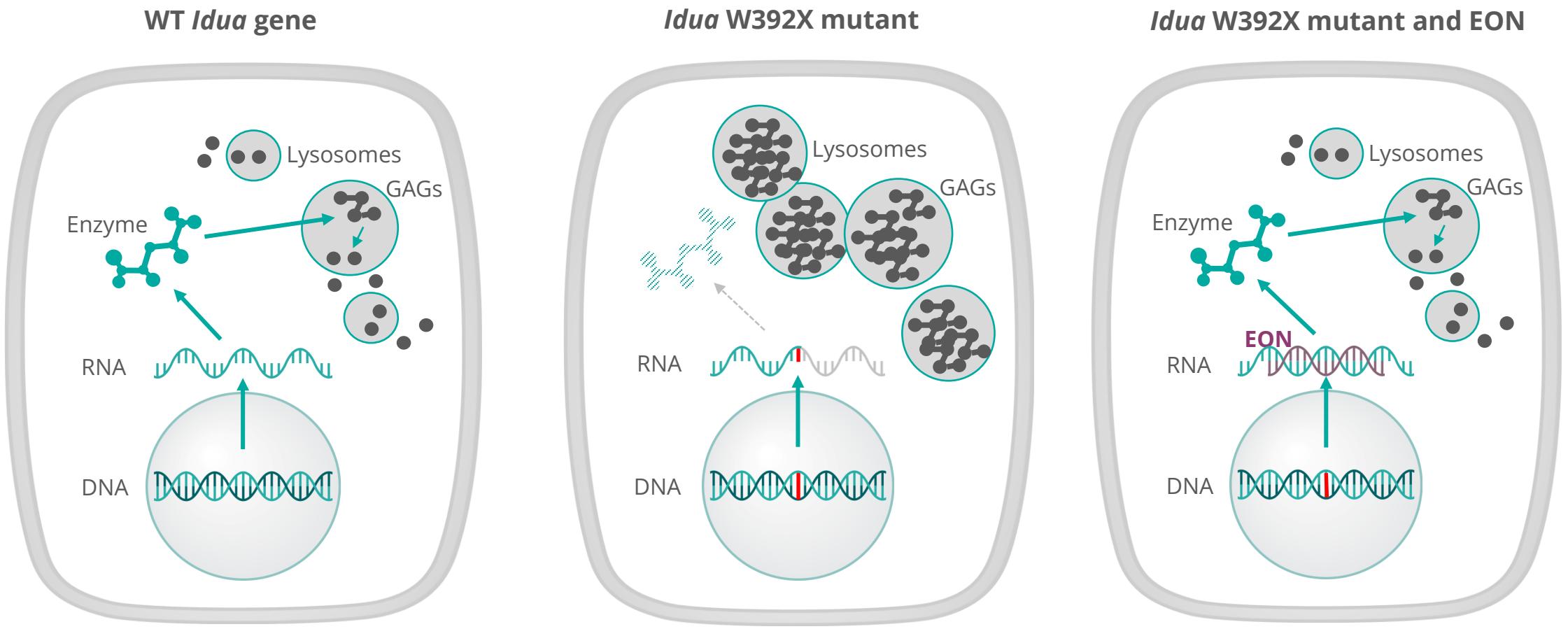
Hurler syndrome

- Mucopolysaccharidosis type I
- Mutations in the ***IDUA*** gene
- Deficiency of the lysosomal **iduronidase** enzyme
- Accumulation of glycosaminoglycans (**GAGs**)
- *IDUA* W402X mutation most common cause: **UGG -> UAG**



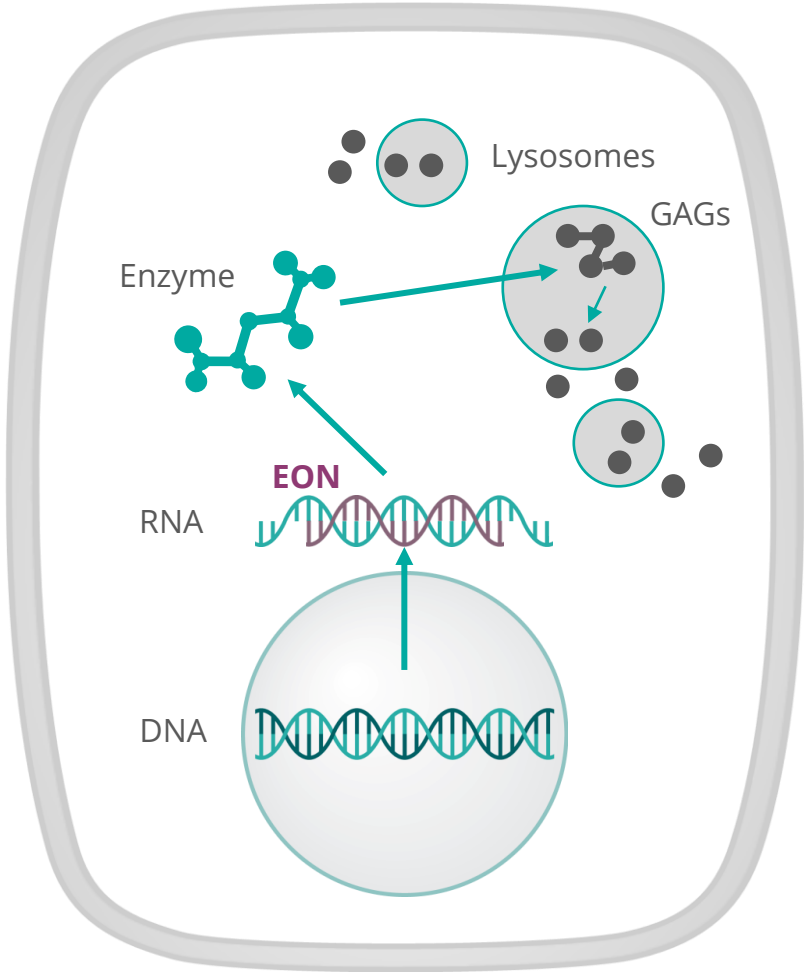
Hurler syndrome – mouse model

Therapeutic approach using Axiomer® EONs

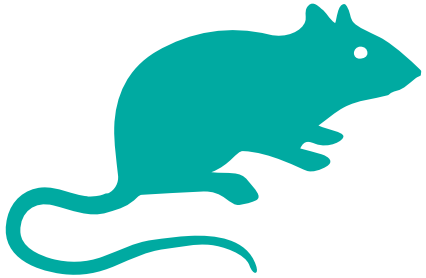


Hurler mouse model for targeted editing

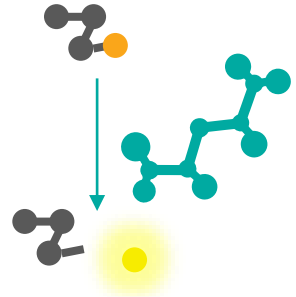
***Idua* W392X mutant and EON**



Readouts for restored function



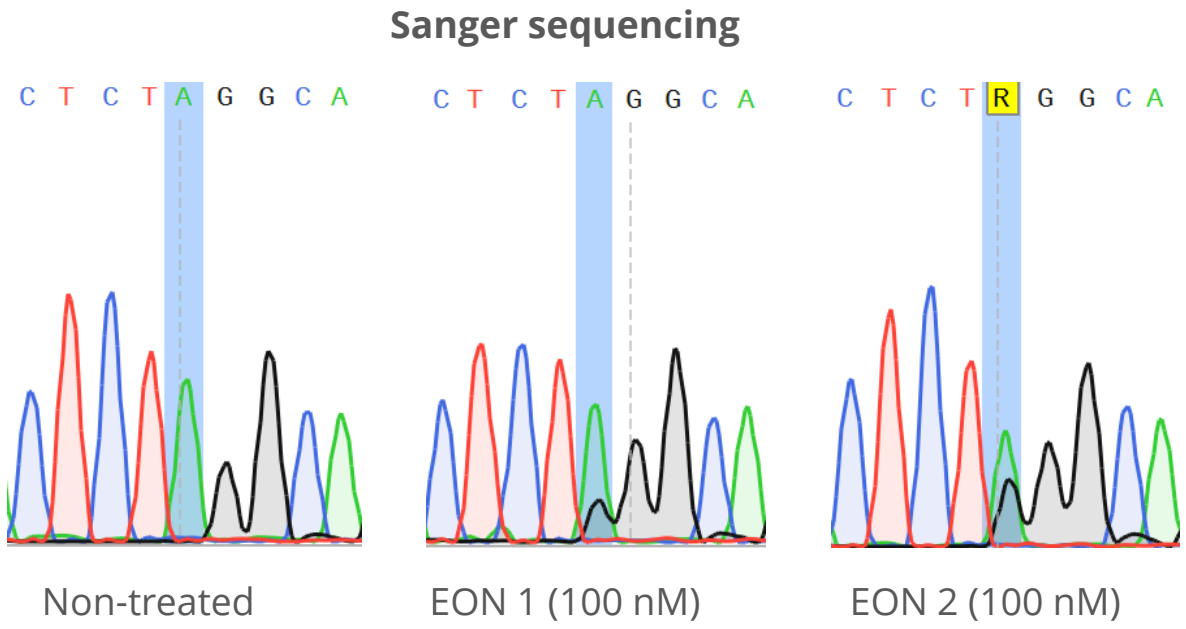
RNA sequence correction

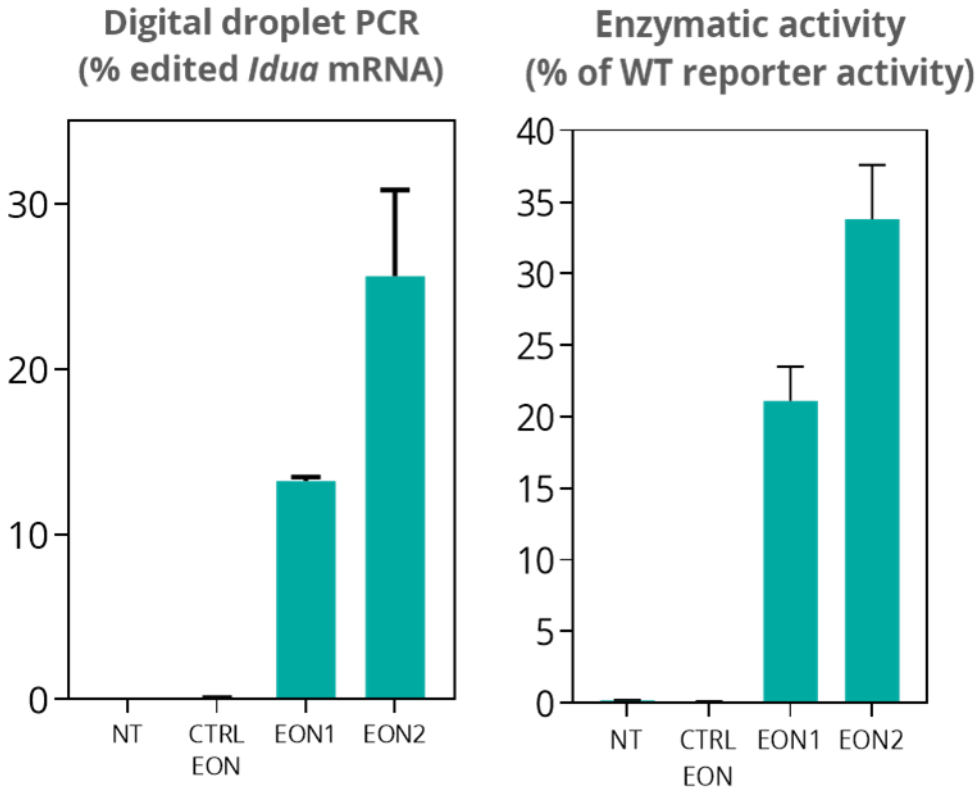


Enzymatic activity

EONs correct *Idua* mRNA *in vitro*

Correction mediated by endogenous ADAR

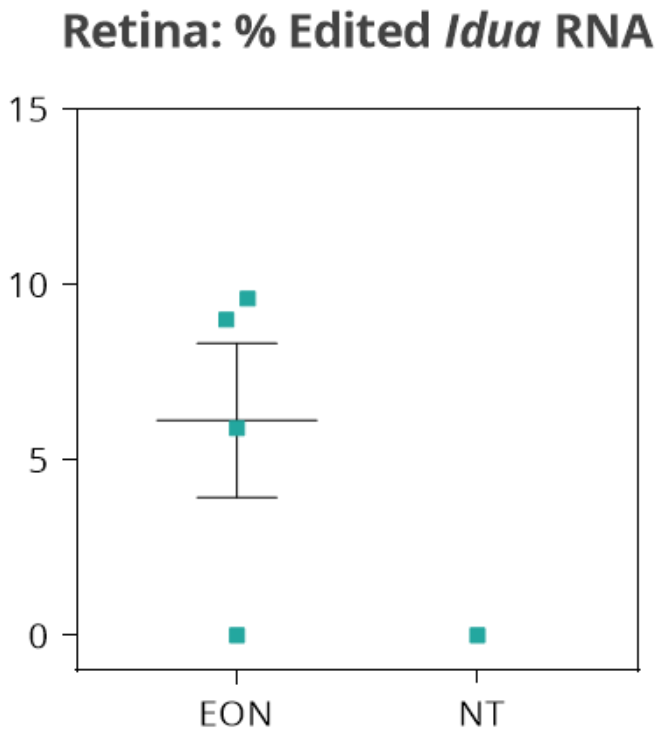




Idua W392X reporter construct in MEF cells with endogenous ADAR

EONs correct *Idua* mRNA *in vivo*

Correction mediated by endogenous ADAR



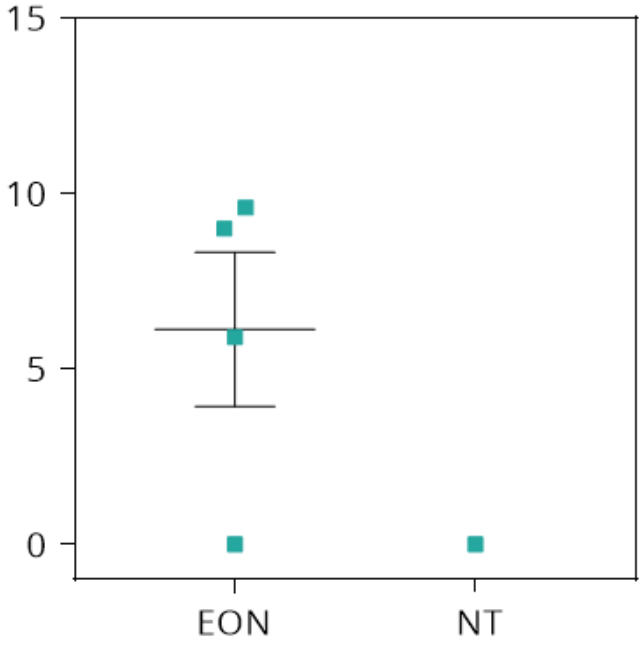
IVT injection of naked EON

Single dose 35 µg EON; 7 days

EONs correct *Idua* mRNA *in vivo*

Efficacy similar to early phase exon skipping oligos

Retina: % Edited *Idua* RNA



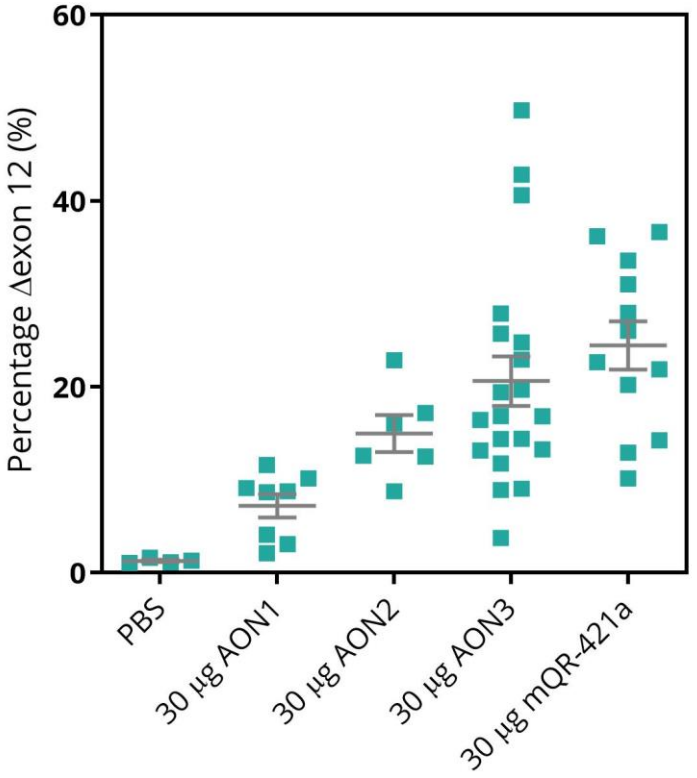
EONs are functional in vivo after single dose of 35 µg. EONs are equally efficacious as early splice-switching oligos at comparable dose.

Further EON optimization ongoing.

IVT injection of naked EON

Single dose 35 µg EON; 7 days

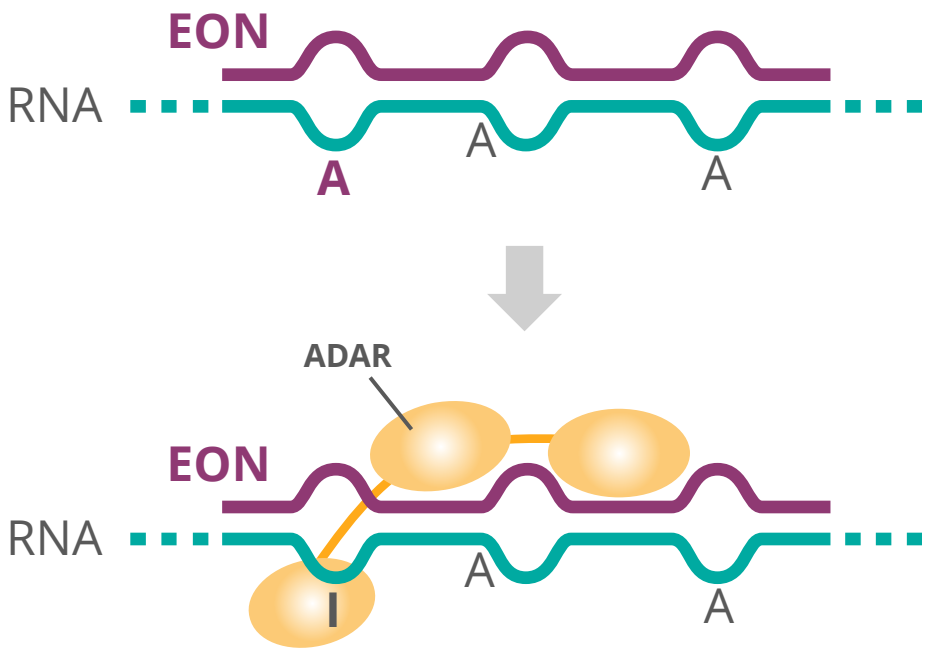
Retina: % Exon skip *Ush2a*



Splice-switching anti-sense oligos also needed optimization for improved skip levels.

QR-421a is now in clinical trials.

Summary: Axiomer® technology



- Editing Oligonucleotides (EONs) recruit **endogenous** ADARs to catalyze **A-to-I** editing
- Editing occurs at **specific** adenosines of **endogenous** RNA transcripts
- Axiomer® is a **single-component** technology to **reversibly** modulate cellular functions
- Rational EON design enables optimization of editing **efficiency** and **drug-like** properties

ProQR®