ProQR®

AXIOMER® RNA BASE EDITING TECHNOLOGY PLATFORM

For precision medicines

Ticker: PRQR

December 22, 2022

Agenda

Welcome
Sarah Kiely

Strategic Overview, Lilly Partnership Expansion
Daniel de Boer

Axiomer® RNA Editing Platform Technology
Gerard Platenburg

IP Overview
René Beukema

Q&A
Daniel de Boer
Gerard Platenburg
René Beukema

Speakers

Sarah Kiely
VP Investor Relations & Corporate Communications

Daniel de Boer
Founder & CEO

Gerard Platenburg
Chief Scientific Officer

René Beukema
Chief Corporate Development Officer

Forward looking statements

This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to", "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. Such forward-looking statements include, but are not limited to, statements regarding our strategy and future operations, statements regarding the potential of and our plans with respect to our technologies and platforms (including Axiomer®), our other programs and business operations, our current and planned partnerships and collaborators and the intended benefits thereof, including the collaboration with Lilly and the intended benefits thereof, including the upfront payment, equity investment, and milestone and royalty payments from commercial product sales, if any, from the products covered by the collaboration, as well as the potential of our technologies and product candidates; our updated strategic plans and the intended benefits thereof, our plans to seek strategic partnerships for our ophthalmology assets, and our financial position and cash runway. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this presentation. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, the risks, uncertainties and other factors in our filings made with the Securities and Exchange Commission, including certain sections of our annual report filed on Form 20-F. These risks and uncertainties include, among others, the cost, timing and results of preclinical studies and other development activities by us and our collaborative partners whose operations and activities may be slowed or halted due to shortage and pressure on supply and logistics on the global market; our reliance on contract manufacturers to supply materials for research and development and the risk of supply interruption from a contract manufacturer; the ability to secure, maintain and realize the intended benefits of collaborations with partners, including the collaboration with Lilly; the possible impairment of, inability to obtain, and costs to obtain intellectual property rights; possible safety or efficacy concerns that could emerge as new data are generated in research and development; general business, operational, financial and accounting risks; and risks related to litigation and disputes with third parties. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future, except as required by law.

Strategic Overview and Lilly Partnership Expansion

Daniel de Boer, Founder & CEO

About ProQR

Focus on Axiomer®

Exclusively focused on the development of proprietary Axiomer® RNA editing platform across multiple therapeutic areas; initial focus on liver and CNS diseases

Novel Mechanism of Action

Axiomer® discovered in ProQR labs in 2014 and uses well-proven modality of oligonucleotides to recruit a novel mechanism of action

Validated across multiple genes

Preclinical data demonstrate Axiomer® is broadly validated across multiple genes

ADAR

Axiomer® is ADAR-mediated RNA editing, recruiting endogenous adenosine deaminase acting on RNA (ADAR)

Two pillars underly strategy

- ProQR developing wholly owned pipeline: Initial targets to be disclosed in early 2023
- Selectively enter into partnerships: initial partnership with Lilly in Sept 2021, expansion announced Dec 2022

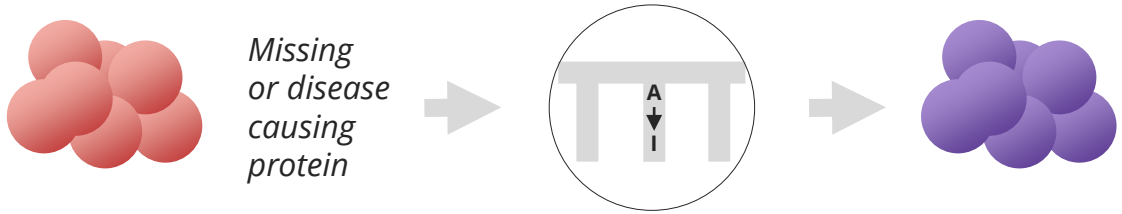
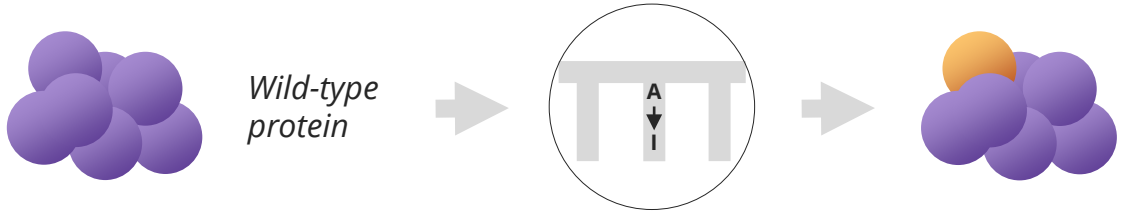
Ophthalmology partner

Seeking strategic partner for ophthalmology assets

Axiomer® platform and use cases

ProQR discovery of EONs guiding endogenous ADAR

- Highly specific and targeted platform
- Natural and endogenously expressed adenosine deaminases acting on RNA (ADARs)
- Modified synthetic editing oligonucleotides (EONs)
- Can correct or change an Adenosine (A) to an Inosine (I), which is translated as a Guanine (G)
- Broad therapeutic potential: common, rare diseases, wide variety of organs, and so-far undruggable targets

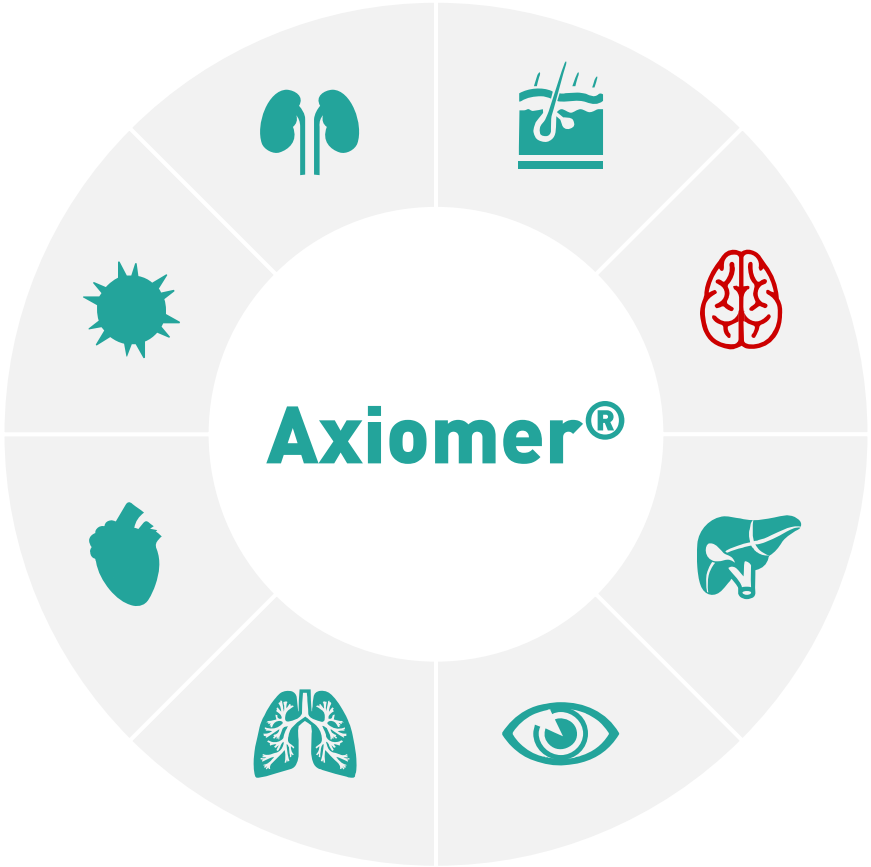
Sequence correction	Correction of genetic disease-causing mutation to a wild-type sequence (>20,000 disease causing G>A mutations described)	
Sequence modification	Modification of a wild-type protein to prevent or treat disease (modify characteristics, caspase sites, post translational modifications	

Axiomer® Strategy

ProQR will develop its own pipeline and selectively enter partnerships

Diversified value creation strategy

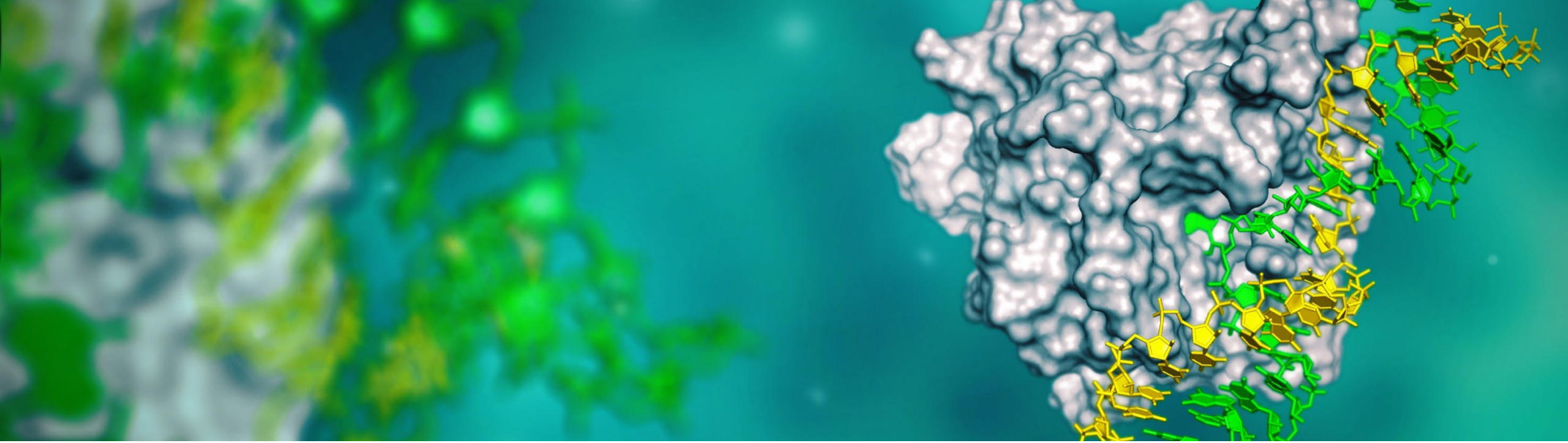
- ProQR to build **in-house pipeline** based on Axiomer® RNA editing technology platform.
  - Initial focus on **liver** and **CNS** applications
- Largely unencumbered platform, **great potential for additional Axiomer® partnerships**



- **Lilly partnership expansion** announced December 2022 – total partnership includes up to 15 targets and potential value of ~$3.9 B
- ProQR may **selectively enter additional partnerships**

Expansion of Axiomer® RNA licensing research collaboration to $3.9B

- Companies to develop editing oligonucleotides for five new targets and an option for an additional five targets using ProQR's proprietary Axiomer® RNA editing platform, for a total of 15 targets
- ProQR to receive $75 million consisting of an upfront payment and equity investment; additional $50 million to be paid to ProQR if Lilly exercises option for five additional targets
- ProQR eligible to receive up to $2.5 billion in milestones, plus royalties based on expanded collaboration
- Collaboration with Lilly now includes a total of up to 15 targets, with the potential for ProQR to receive up to $3.75 billion in research, development, and commercialization milestones, plus royalties
- ProQR to access Lilly delivery technology to use in its wholly-owned pipeline

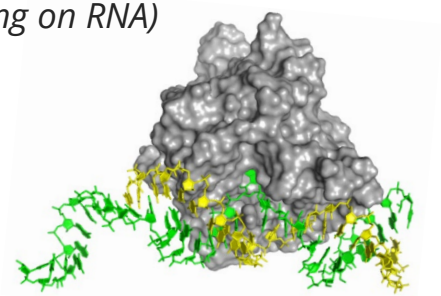


Axiomer® Overview

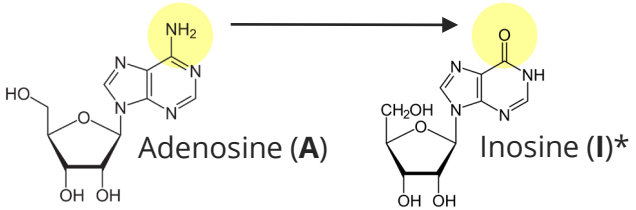
Gerard Platenburg, Chief Scientific Officer

What is ADAR editing?

ADAR *(Adenosine Deaminase Acting on RNA)*



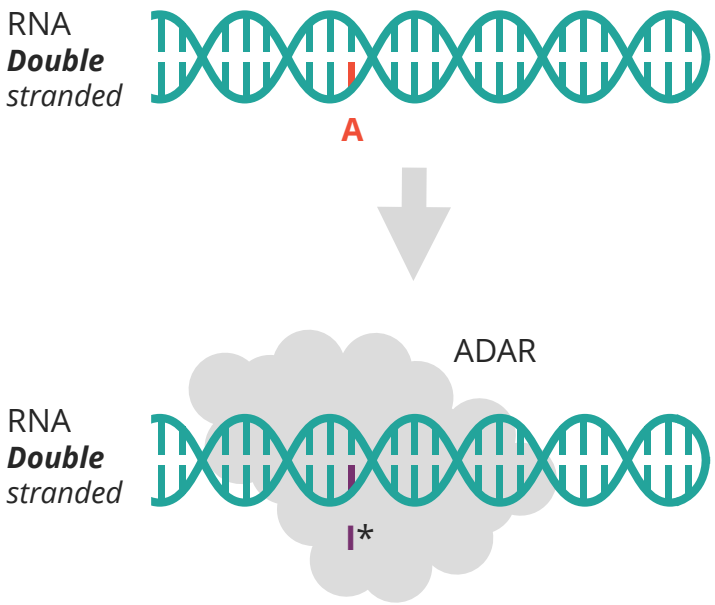
Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**



*Inosine will be read as Guanosine (**G**)

Natural ADAR editing

(A-to-I)



A = Adenosine **I** = Inosine *Will be read as **G** (Guanosine)

- ADAR normally binds to **double stranded structures** in RNA to perform A-to-I editing
- Later, during the translation process, the 'I' in the RNA is read as a 'G' (guanosine) by the cell

What is Axiomer®?

How Axiomer® works

- Uses short strands of synthetic RNA, called **EONs** (Editing Oligonucleotides)

  EON

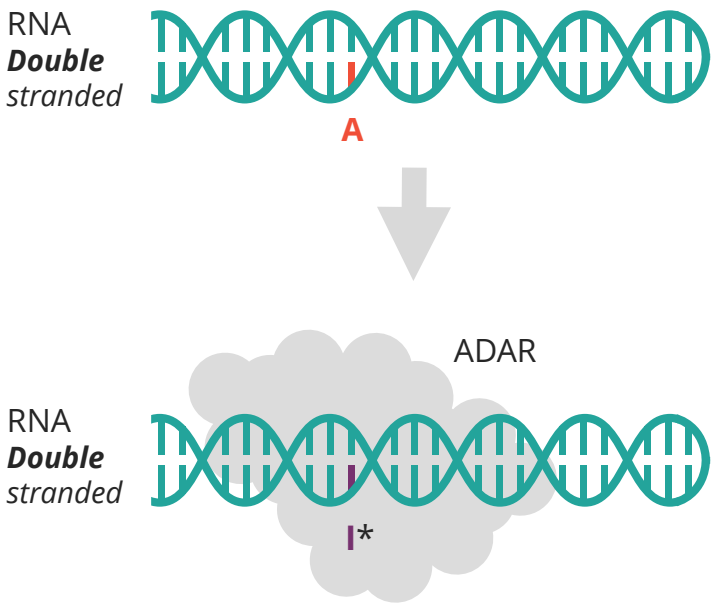
- EONs bind to the target (**single stranded**) RNA and mimics double stranded structure that attracts ADAR
- EONs attract ADAR to specific location in RNA to make A-to-I edit

Results

- RNA with disease-causing mutation is corrected back to normal RNA
- Function of protein is changed to help prevent or treat disease

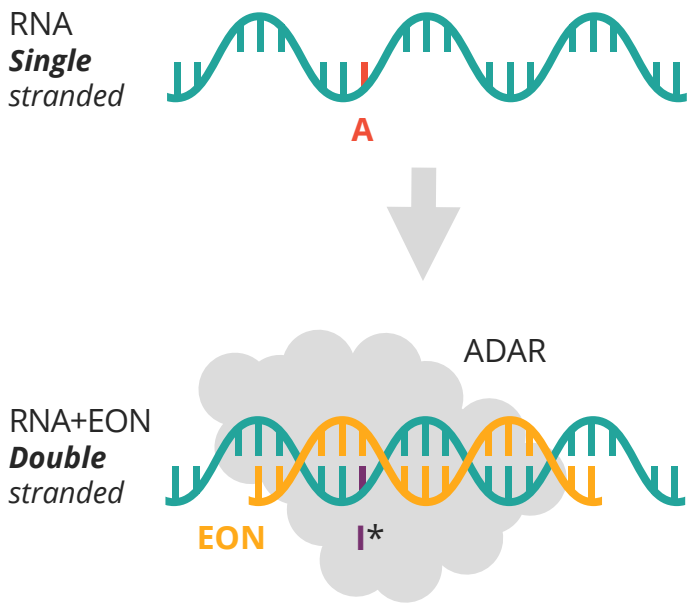
Natural ADAR editing

(A-to-I)



EON-directed therapeutic editing

(A-to-I)

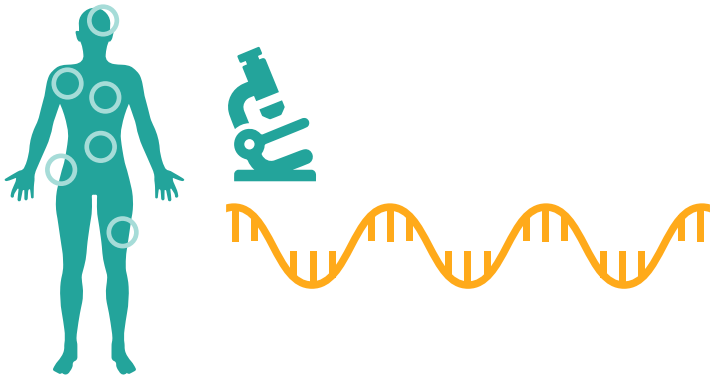


A = Adenosine **I** = Inosine *Will be read as **G** (Guanosine)

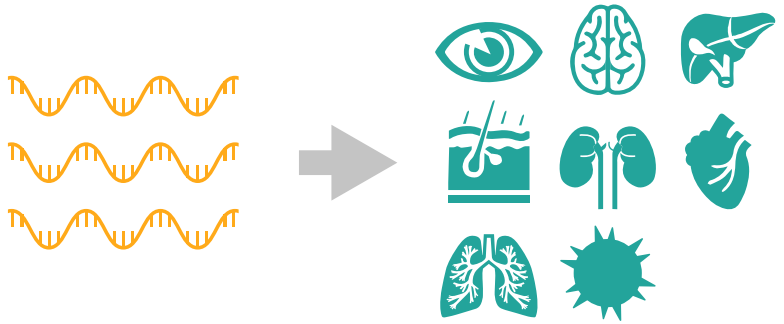
How does Axiomer® work?

Step by step

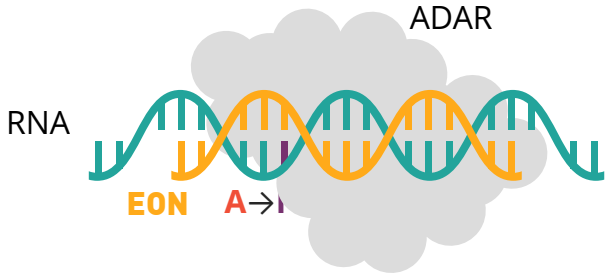
1 We identify where an A-to-I edit could treat disease, and design an EON



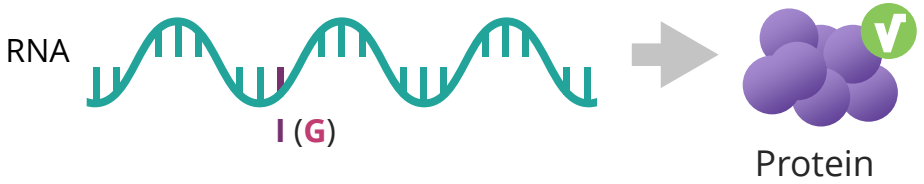
2 The EON is periodically delivered to the targeted organ or tissue



3 The EON binds to the target RNA and attracts ADAR to make an A-to-I edit



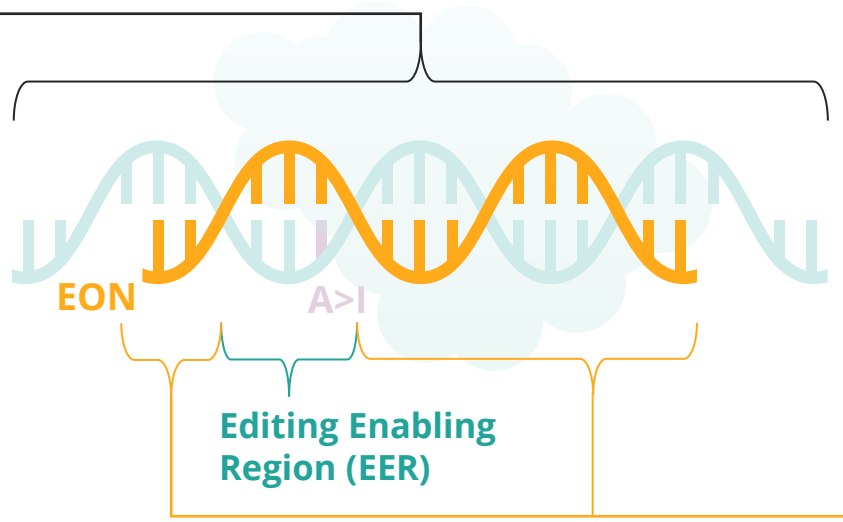
4 During translation, the 'I' is read as a 'G', resulting in a corrected or altered protein



ProQR expertise driving the development of optimized EONs for therapeutic use

Sequence defines target
RNA binding and provides stability

EON total length
Between ~25 - 30 nt



ADAR-binding region (ABR)
Backbone modifications enable ADAR binding, and disable off-target editing

Optimized sequence and chemistry define functionality

- Increase editing efficacy
- Bring metabolic stability
- Prevent off-target ('bystander') editing
- Ensure bioavailability (cell and tissue uptake)
- Offer safety and tolerability at therapeutic doses

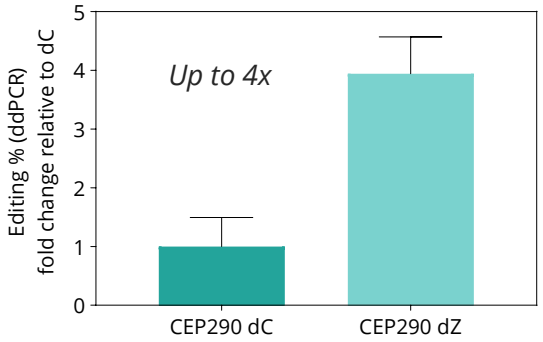
Improved editing obtained for several targets

dZ modification on EER improves editing in different cell types

ProQR – UC DAVIS Collaboration

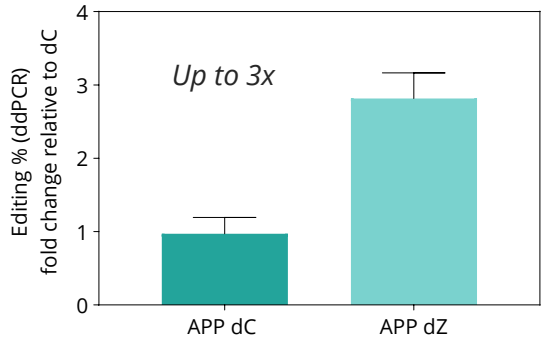
Editing of hCEP290 K1575X in human LCA retinal organoids

Gymnosis, 10μM single dose, N=8, 4 weeks



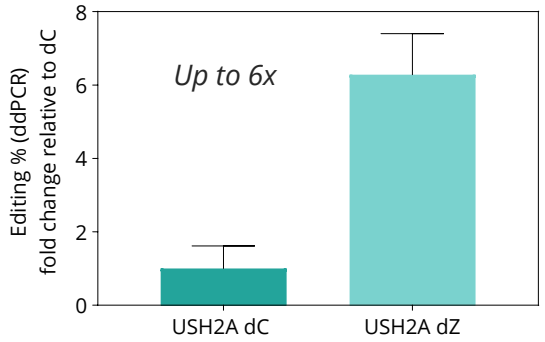
Editing of APP WT RNA in human retinal organoids

Gymnosis, 10μM single dose + 40μM CQ, N=6, 4 weeks



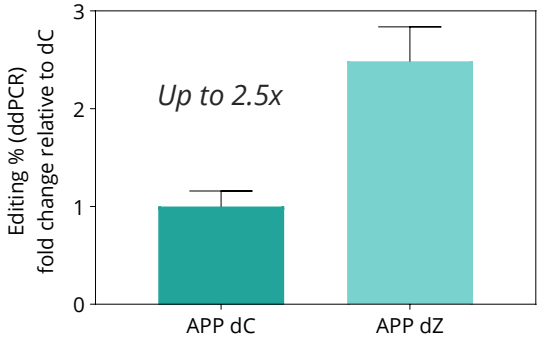
Editing of USH2A WT RNA in human retinal organoids

Gymnosis, 15μM single dose + 40μM CQ, N=4, 4 weeks



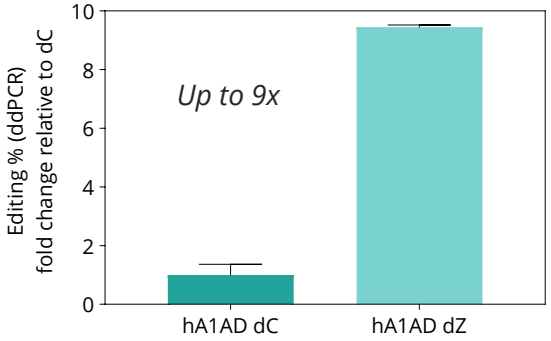
Editing of WT APP RNA in human ARPE-19

Transfection of 100nM EON, N=3, 48 hours

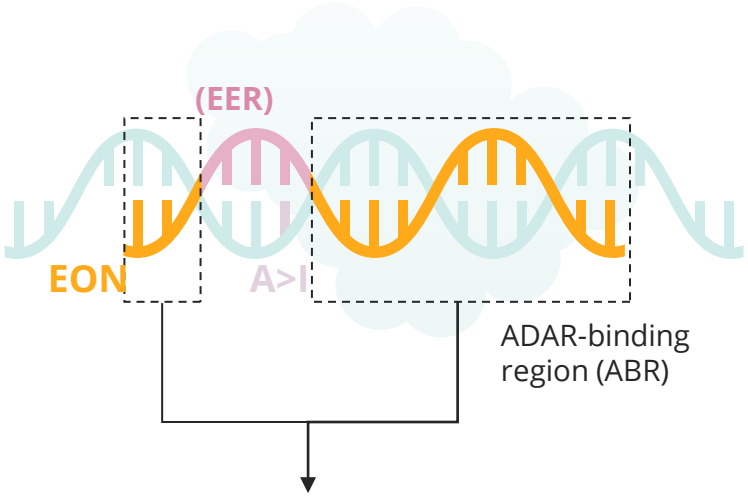


Editing of SERPINA1 E366K in A1AD patient hepatocytes

Transfection of 100nM EON, n=2, 48 hours



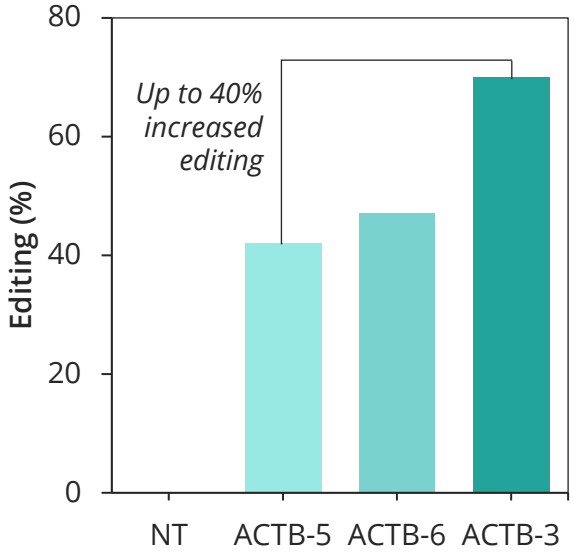
ADAR-binding region (ABR) modification greatly enhances editing



Backbone modifications enable ADAR binding, and **improve** stability

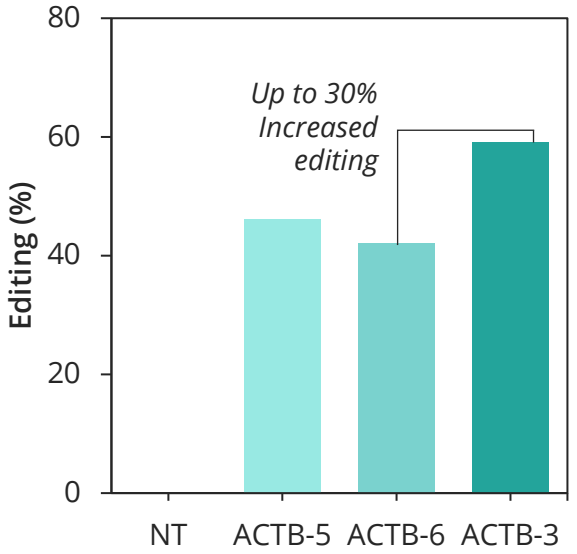
Editing of ACTB in human primary hepatocytes

(Gymnosis, 10uM, single dose, N=1, 48 hours, dPCR)



Editing of ACTB in human retinal pigment epithelium cells

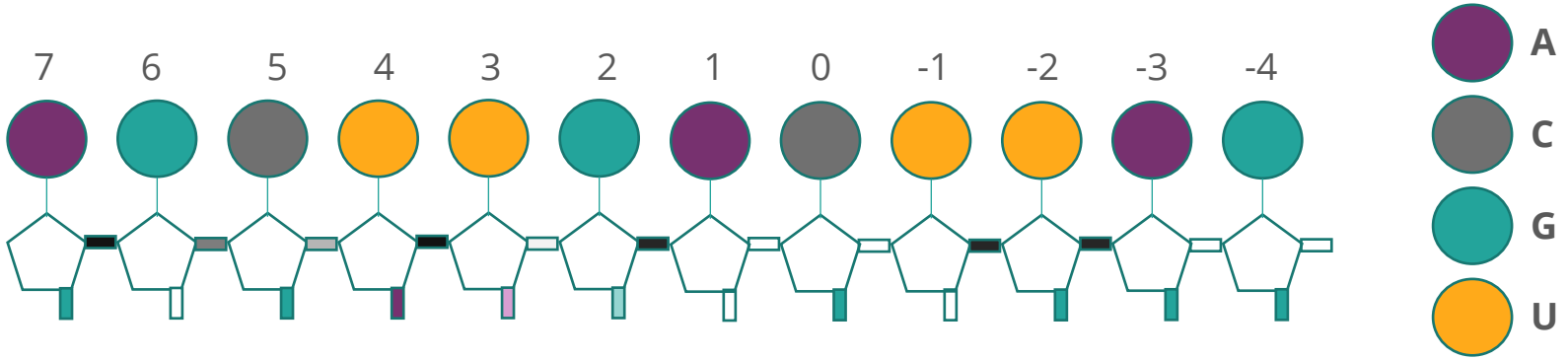
(Transfection, 100nM, single dose, N=1, 48 hours, dPCR)



- Chemical optimization greatly increases EON editing in positions within ABR region
- SAR screen of 2nd backbone modification for best position within ABR region ongoing

Focus on the EON design principles

EON



Aspect	Determined by	Modifications	Effects
Base	Target RNA	Mismatches and analogs	Improved PD
Ribose modification	ADAR structure	2’-H; 2’-OMe; 2’-MOE; 2’-F; 2’-NH2, LNA, TNA, diF, 2’-FANA	Improved PK and PD
Linkage	ADAR structure	PO; PS; PN; MeP; UNA; PAc	Improved PK and PD

This work led to a portfolio of 13 foundational platform patents

Axiomer® platform over time

Optimization is yielding stability improvements and efficacy increase in cells and in vivo

Optimization of Axiomer® in multiple models, targets and organs

Opening the pathway for new class of medicines targeting diverse types of diseases

The retina
as early proof of concept

The liver
as a promising area of development

The CNS
The CNS as the next frontier

Model targets

PoC therapeutic targets
Tool targets used for optimization

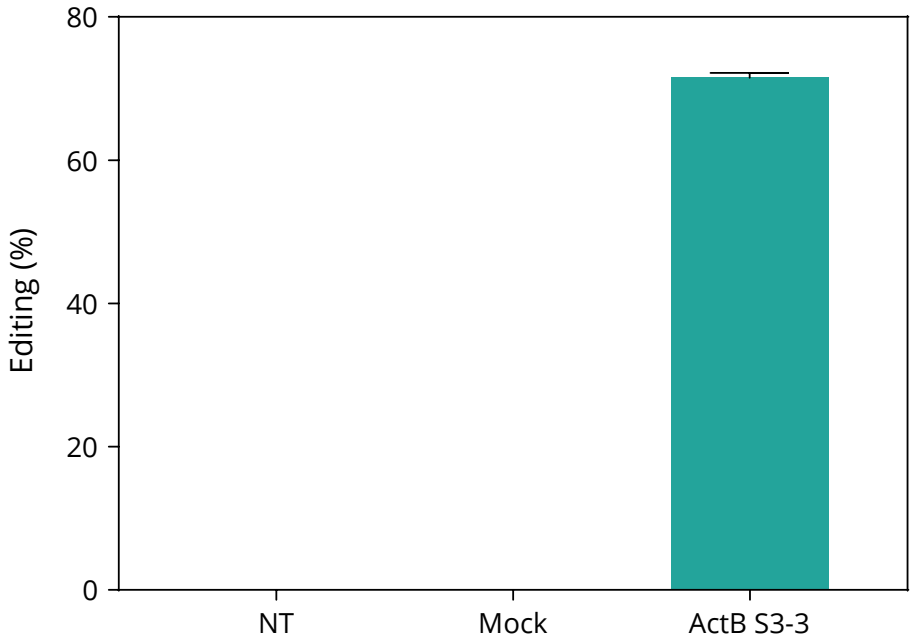
Pipeline targets

The retina as early proof-of-concept

Efficient editing of ACTB in mouse and human retinal cells

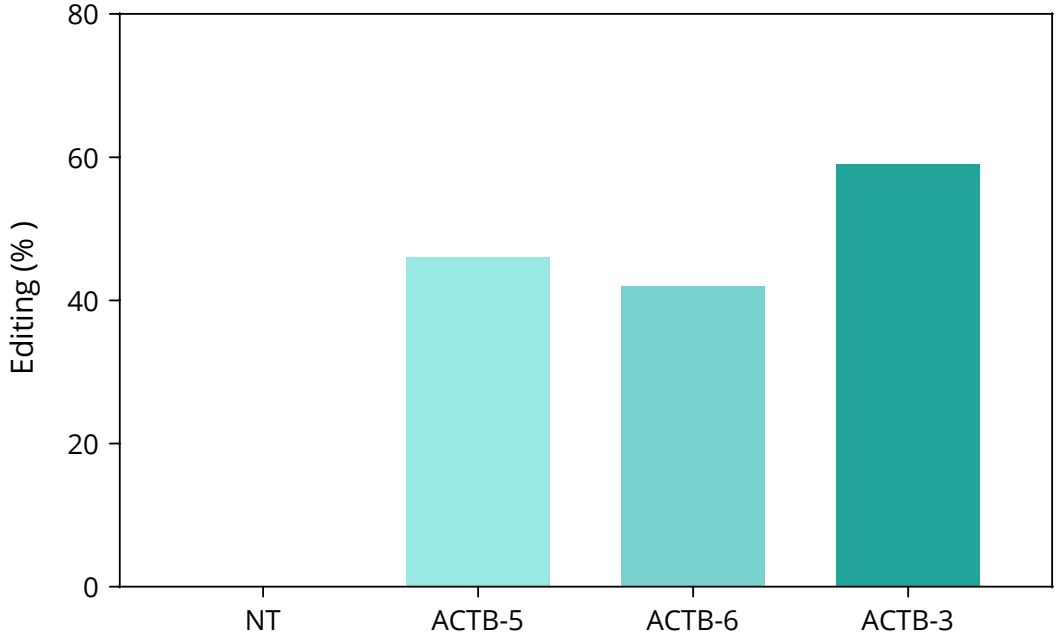
Editing of ACTB in mouse RPE cells

(Transfection, 100nM, single dose, N=2, 24 hours, Sanger sequencing)



Editing of ACTB in human RPE cells

(Transfection, 100nM, single dose, N=1, 48 hours, Sanger sequencing)



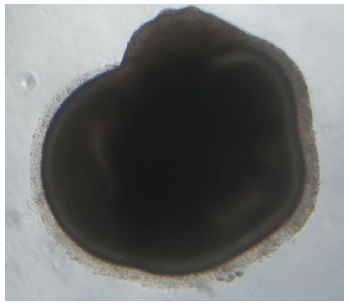
- Similar levels of editing of ACTB achieved in mouse and human models of retinal origin
- High confidence of translatability of the approach

The retina as early proof-of-concept

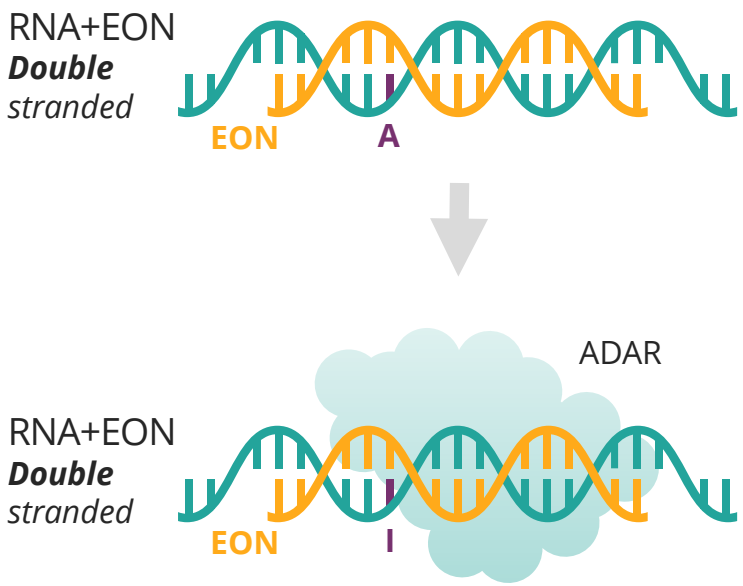
Efficiency confirmed in human retinal organoids with >40% editing achieved

Retinal organoid

225 days

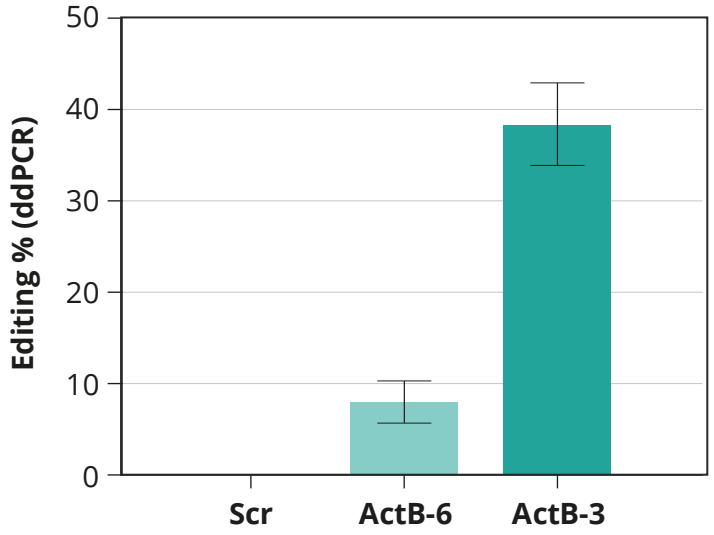


EON-directed therapeutic editing



Editing of ACTB in iPSC human retinal organoids

(Gymnosis, 20 uM, single dose, N=6, 7 days)



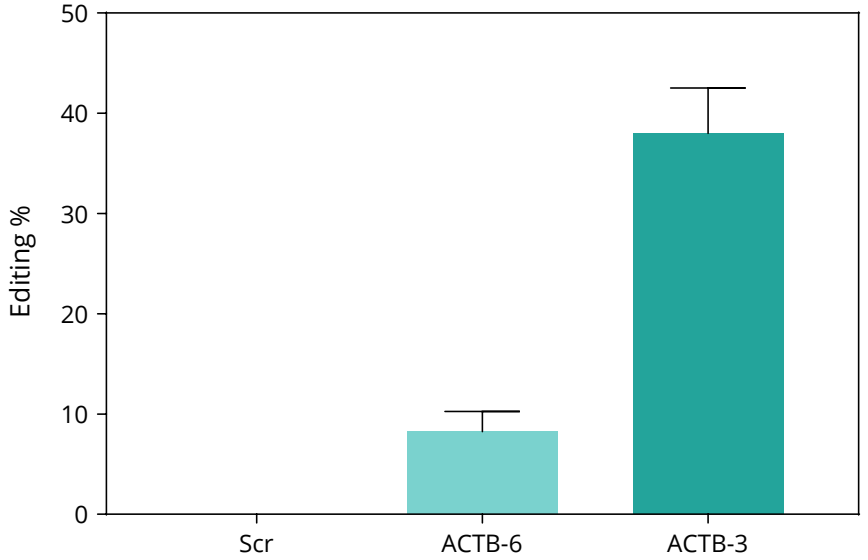
- Each chemical modification improves EON editing efficacy
- The highest editing efficacy increase is obtained for EONs with multiples modification combined
- Over 40% editing was observed after gymnosis

From model target to PoC therapeutic targets

Approx. 20% editing was observed after gymnosis for CEP290, a tool targets used for optimization

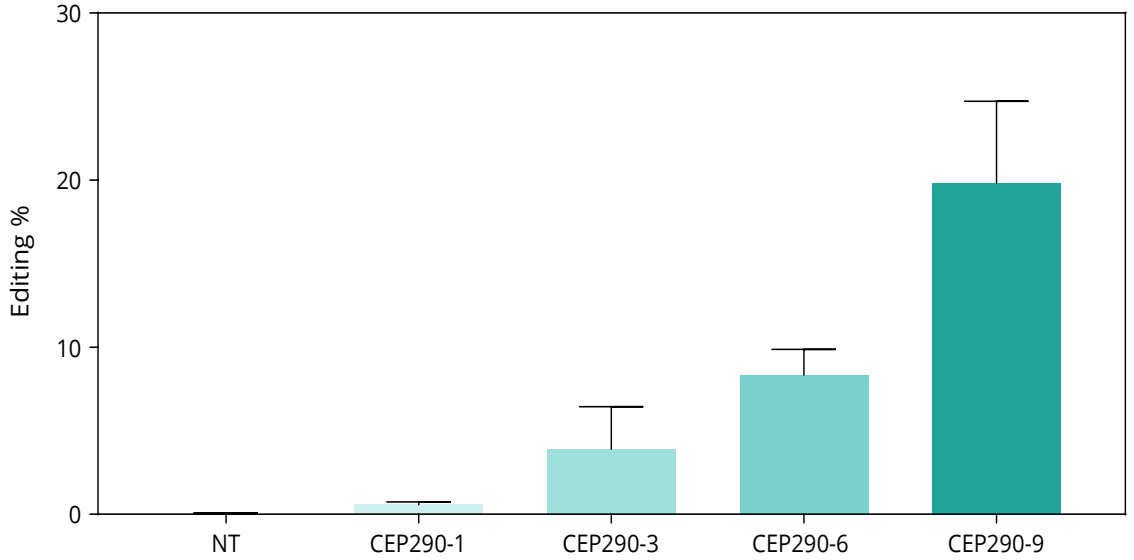
Editing of ACTB in human retinal organoids

(Gymnosis, 20 uM, single dose, N=6, 7 days, ddPCR)



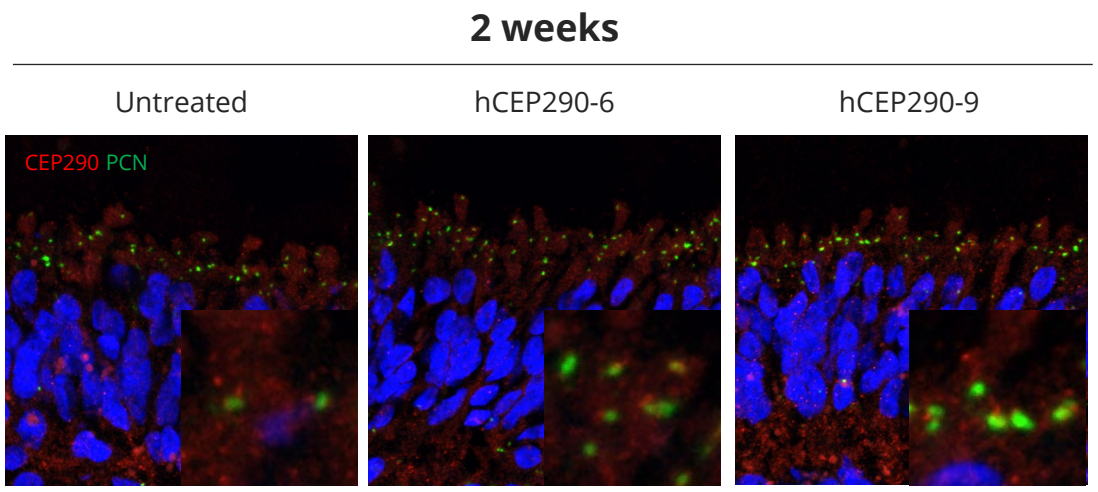
Editing of CEP290 in LCA human retinal organoids

(Gymnosis, 10uM, single dose, N=8, 2 weeks, ddPCR)

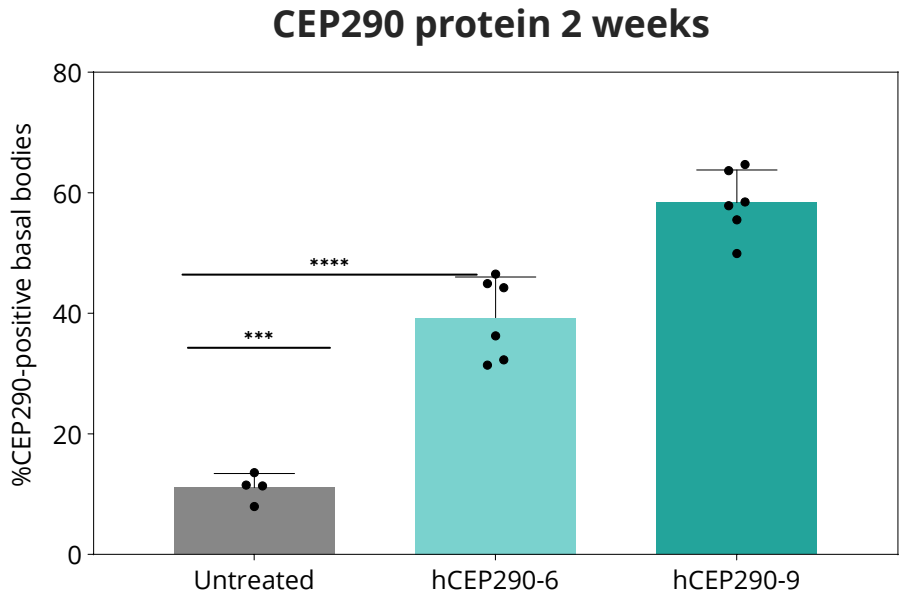


- Each chemical modification improves EON editing efficacy
- The highest editing efficacy increase is obtained for EONs with all modification combined
- Over 40% editing was observed after gymnosis for ACTB and over 20% editing observed after gymnosis for CEP290

Editing results in significant increase in CEP290 protein levels and intensity at the basal body



Mean ±SEM. Statistical significance was determined using Brown-Forsythe and Welch ANOVA test



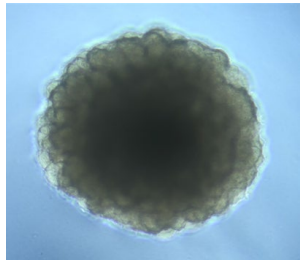
Significant increase in CEP290 protein levels and intensity was detected at the basal body of LCA07-3 organoids treated with hCEP290-6 and-9 after 2-weeks treatment

The CNS as the next frontier

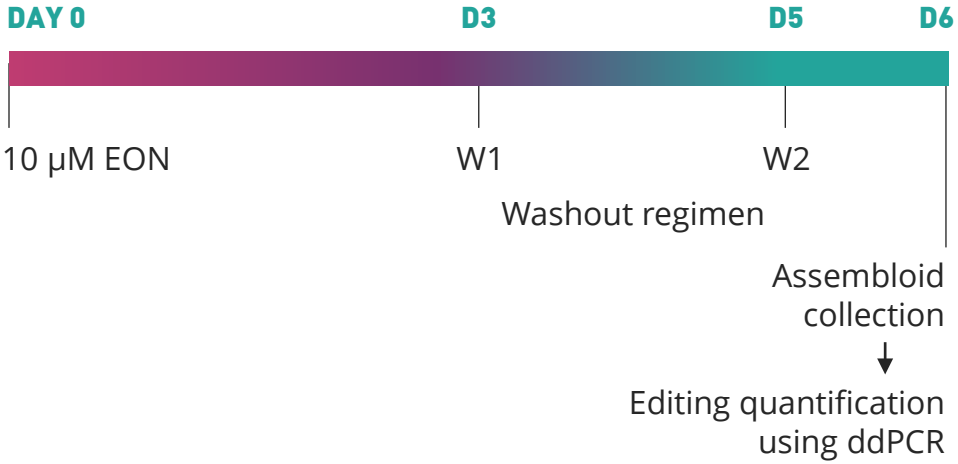
>30% editing was achieved in IPSC derived brain organoids

Human brain organoid

130 days

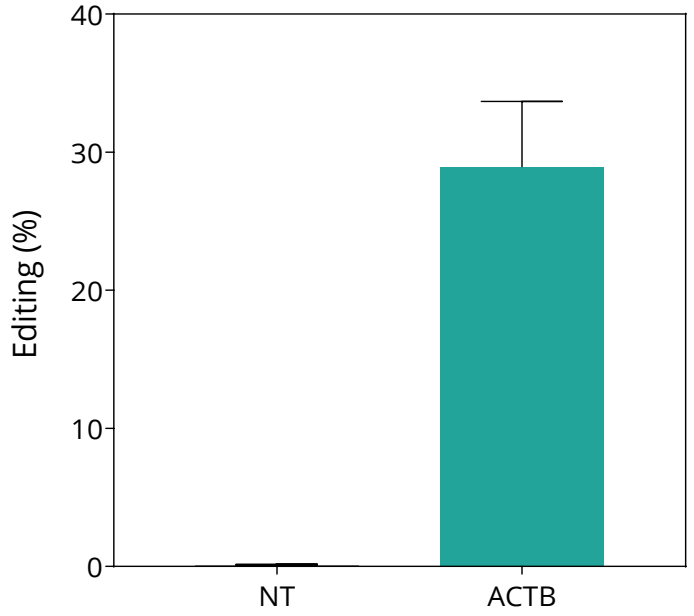


Gymnotic uptake



Editing of ACTB in IPSC derived brain organoids

(Gymnosis, 10uM, single dose, n=7, 6 days, ddPCR)

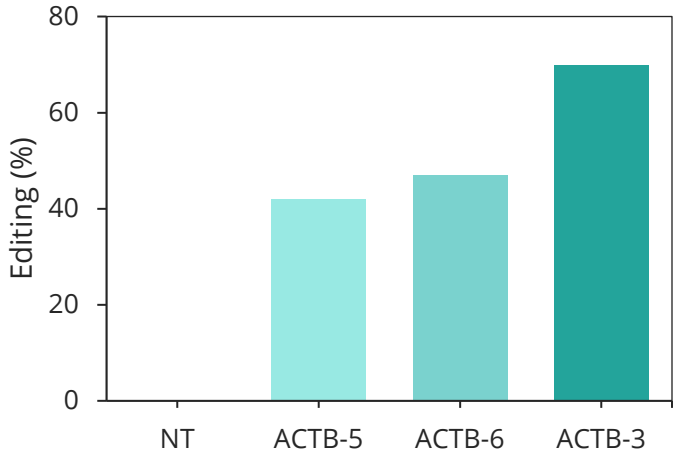


The liver as a promising area of development

High potential of EONs editing in the liver

Editing of ACTB in human primary hepatocytes

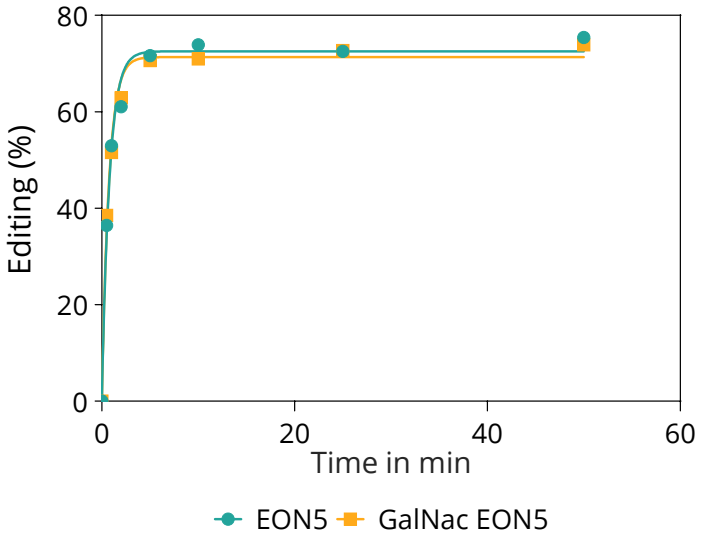
Gymnosis, 10uM, single dose, N=1, 48 hours, dPCR



- Similar levels of editing of ACTB achieved in several models of liver origin
- High confidence of translatability of the approach

GalNac does not interfere A-to-I editing *in vitro*

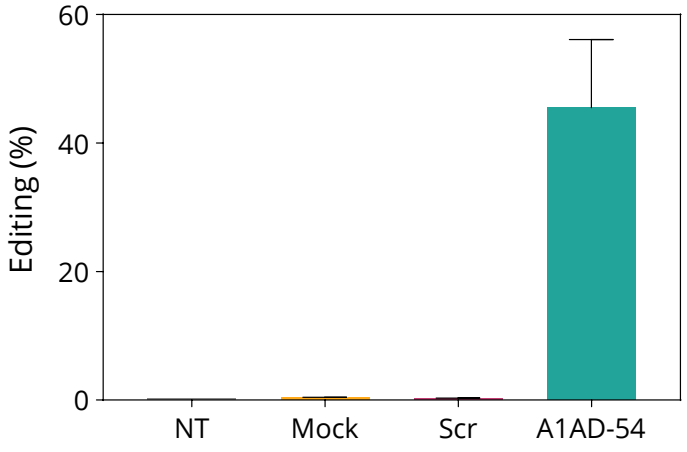
N=1, BEA assay



GalNAc appears not to interfere with ADAR binding or efficient RNA editing

Editing of SERPINA1 E366K in human A1AD patient hepatocytes

Transfection, 100 nM, single dose, N=2, 47 hours, dPCR



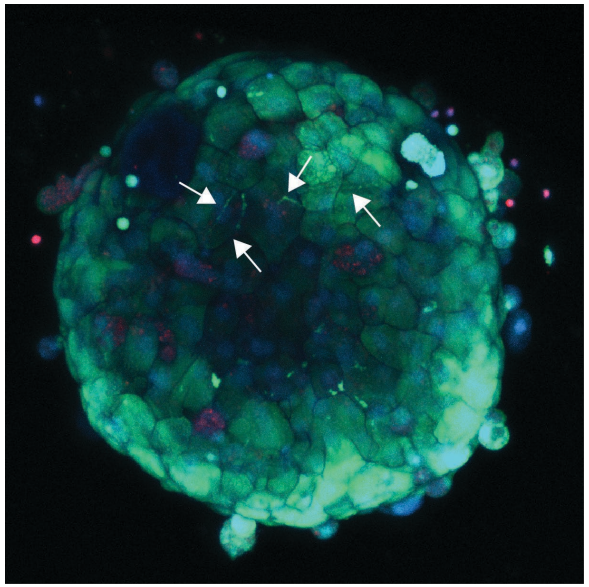
>50% Editing of SERPINA1 E366K in human A1AD patient hepatocytes

Editing in InSphero Human Liver microtissues (LMTs)

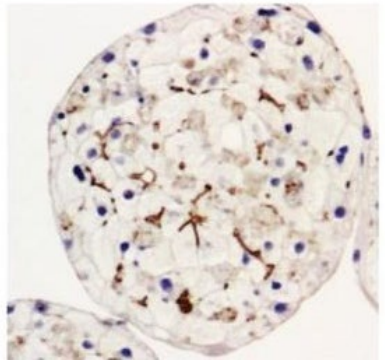
Primary hepatocytes, Kupffer cells and liver endothelial cells in 3D spheroid

Live image of Day 7 LMT

Stained with 5-CFDA (green), PI (red) and Hoescht (nuclei; blue)



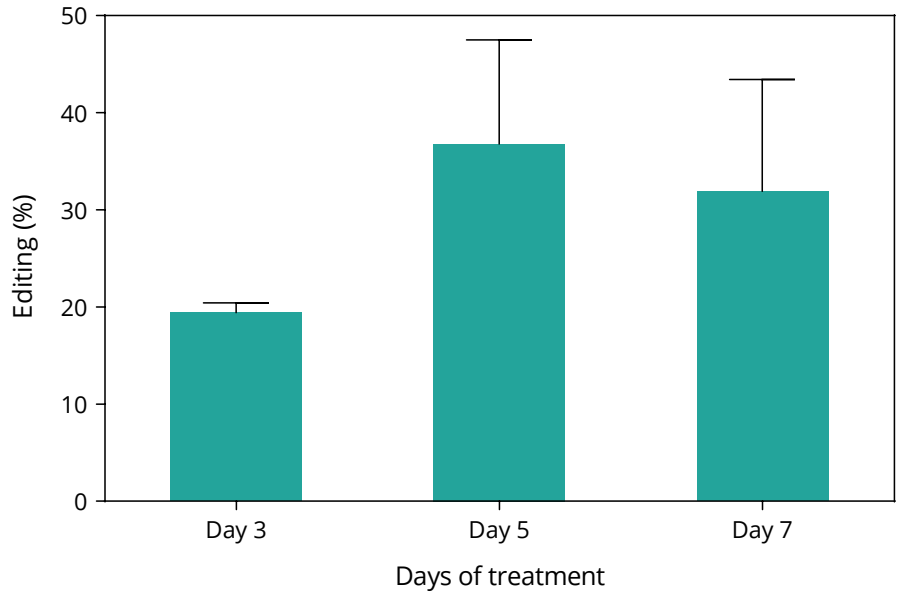
BSEP Bile Canaliculi
(InSphero data)



Presence of bile channels in LMTs by day 7
Fluorescent dye 5-CFDA secreted from healthy cells into bile channels (canaliculi)

Editing of ACTB in human LMTs

(Gymnosis, 5µM, single dose, 3 pools of 6 LMTs per condition, 7 days, dPCR)

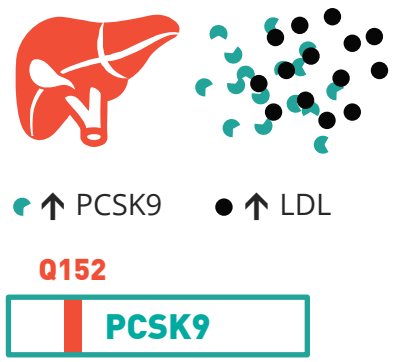


Treatment of LMTs with 5µM EON for 7 days results in up to 40% of edited ACTB.

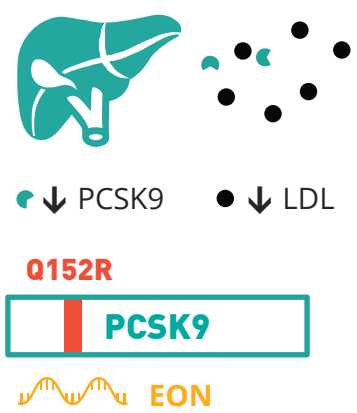
Liver targeted editing of PSCK9

De novo generation of a loss-of-function variant to lower PCSK9

FEH patients



Axiomer® edit

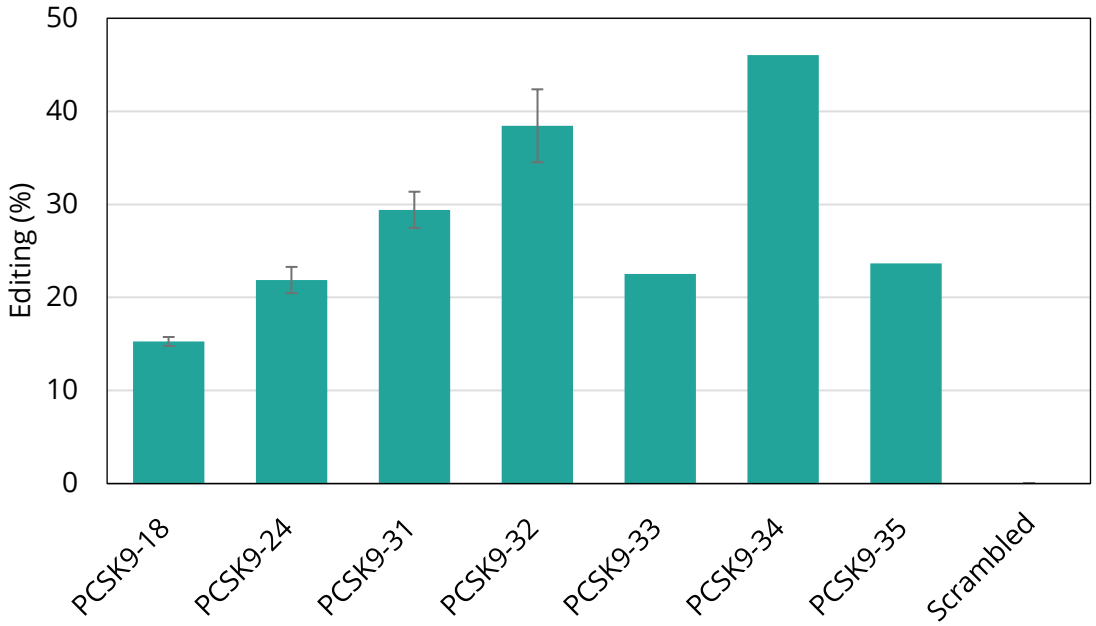


Disruption of PCSK9 autocleavage site reduces protein in bloodstream

- Less PCSK9 leads to increase of LDL-R on cells, decrease of 'bad' LDL in bloodstream
- Loss-of-function PCSK9 variant Q152H is associated with low plasma LDL cholesterol in a French-Canadian family and with impaired processing and secretion in cell culture

Percentage A→G editing of PCSK9 in transfected HeLa cells

Transfection, 100 nM, single dose, N=2, 48 hours, ddPCR



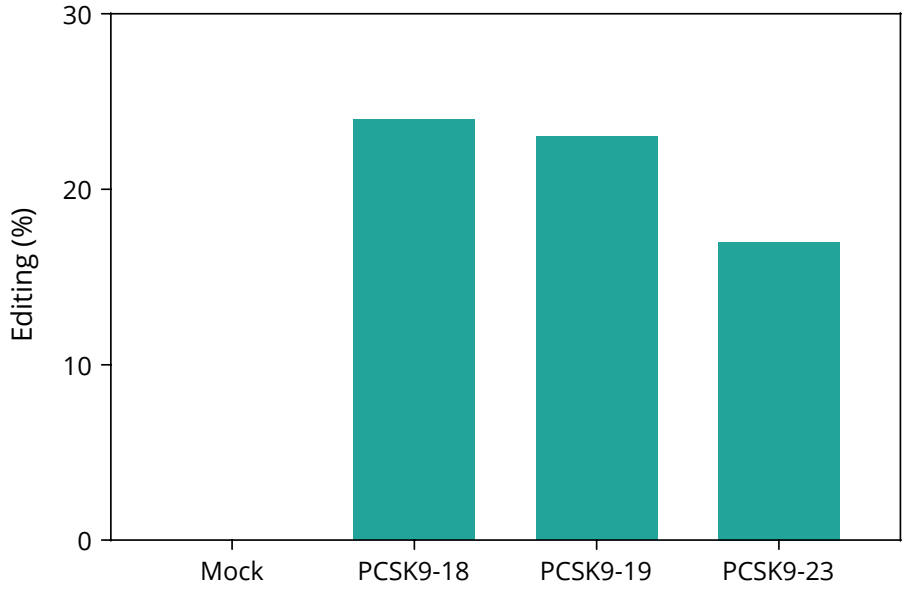
>40% Editing of PCSK9 mRNA in transfected HeLa cells

PCSK9 mRNA editing leads to reduced PCSK9 protein levels

Editing of PCSK9 mRNA results in a loss-of-function phenotype

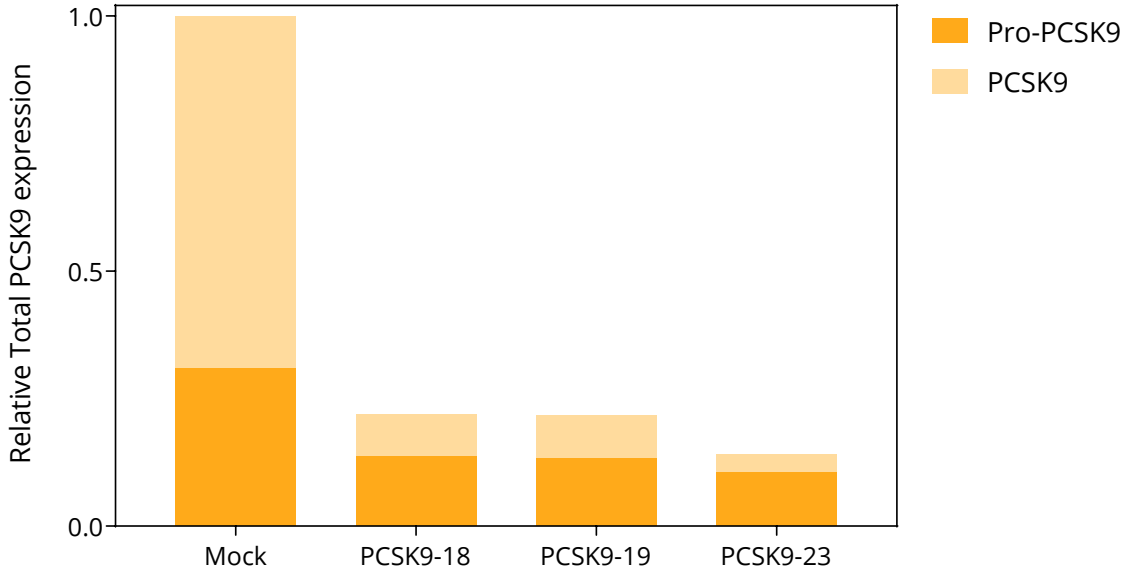
Editing of PCSK9 in HeLa cells

Transfection, 100nM, single dose, N=2, 48 hours, dPCR



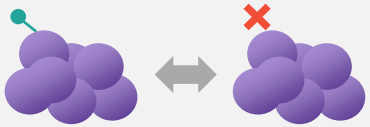
PCSK9 protein expression in HeLa cells

Transfection, 100nM, single dose, N=2, 48 hours, western blot



- Up to 25% precent A-to-I editing of PCSK9 mRNA detected using ddPCR assays
- EONs treated HeLa cells produce lower levels and more uncleaved PCSK9 protein
- Up to 80% reduction of total PCSK9 protein measured in treated samples
- Shift in the ratio cleaved to uncleaved PCSK9 observed; 70%:30% to 25%:75%

Axiomer® technology potential

Correction	Modulation / Regulation		Modification	
				
Repairing G-to-A mutations Thousands of G-to-A mutations described in literature	**Edit >400 different types of PTMs** *(Post-translational modifications)* To regulate protein activity, changes localization, folding, prevent immune escape and slows down degradation	**Change protein-protein interactions** Changes localization, folding and protein function and prevent immune escape of glycosylated tumor antigens	**Create new proteins** New proteins achieving loss or gain of functions that helps address disease	**Include protective variants** At the RNA level, to develop new functions that help prevent disease

Broad therapeutic potential

- ✓ Common diseases
- ✓ Rare diseases
- ✓ Target a wide variety of organs
- ✓ Treat so-far undruggable targets

RNA editing expert advisory board

Scientific Advisory Board

Art Levin
PhD

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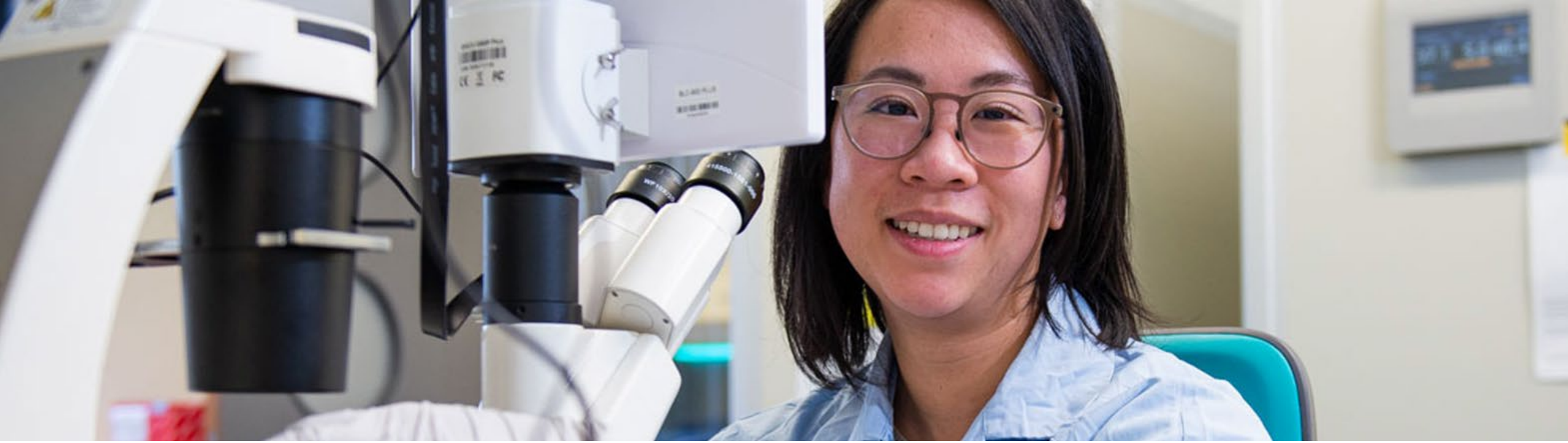
1850 MELIORA · UNIVERSITY of ROCHESTER MEDICAL CENTER



IP Overview

René Beukema, Chief Corporate Development Officer and General Counsel

Overview of Axiomer® related patents

Docket	Priority	Feature	Status
1 (0004)	17DEC2014	Targeted RNA Editing using endogenous ADARs	Granted CA CN EP IL JP NZ RU US ZA
2 (0013)	22JUN2016	Short EONs with wobble and/or mismatch base pairs	Granted IL JP KR US
3 (0014)	01SEP2016	Chemically modified short EONs	Granted EP KR NZ US ZA
4 (0016)	19JAN2017	EONs + protecting sense oligonucleotides	Granted US
5 (0023)	18MAY2018	EONs with phosphorothioate linkages, EONs with chiral linkages (*e.g.,* PS, PN)	Published
6 (0026)	11FEB2019	EONs with phosphonacetate linkages and UNA modifications	Published
7 (0029)	03APR2019	EONs with methylphosponate linkages	Published
8 (0031)	24APR2019	Targeted editing inhibition	Published
9 (0032)	13JUN2019	EONs with cytidine analogs for increased catalytic activity	Published
10 (0039)	23JUL2020	Split EONs	Published

In addition to the above, numerous patent applications are pending but have not yet been published.

ProQR expands its Axiomer® IP portfolio continuously.

ProQR Therapeutics

Investment Highlights

Quickly advancing toward the clinic

and a large number of potential therapeutic applications

Dominant and blocking IP position

Axiomer® platform protected by >10 granted patents families

Experienced Management Team

with deep RNA expertise

Strategic-partnership strategy for Axiomer®

as evidenced by Lilly collaboration, provides optionality and multiple value-creation opportunities

Strong balance sheet

as of September 30, 2022, cash runway into 2026, now upside with potential for additional BD-related upside

Q&A

ProQR®

IT'S IN OUR RNA