MCOPS12: From Research to Therapy

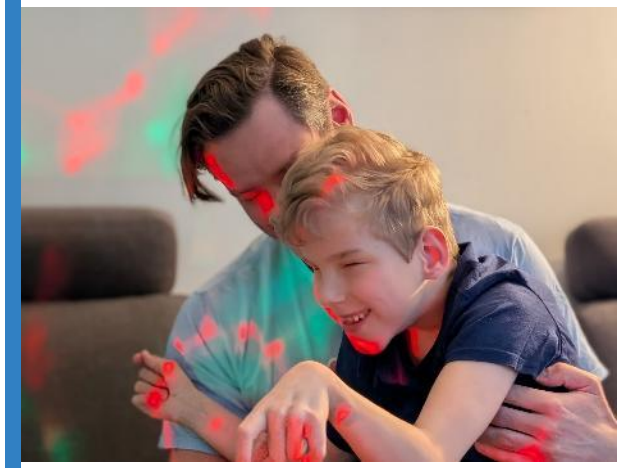
Cure MCOPS12

Dr. Reinhard Pell

Founder & Chairman, Cure MCOPS12
Director R&D, A Cure for Sophia and Friends

RARB Families Salzburg Conference, September 2026







A global academic & patient families initiative

2013

First publication describing MCOPS12 (RARB mutation)

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Université de Montréal

2019–2022

EU-funded research program

E-Rare CALLS

JTC 2018
Project RAinRARE

2020

Foundation of

Cure MCOPS12

2022

Foundation of

A CURE FOR SIENNA

2023

Foundation of

A Cure for Sophia and Friends

~600.000 €
fundraised for research & drug development

7 R&D programs
supported to date

https://www.rarbmutation.org/funded-rd-programs

Cure MCOPS12

Three research pillars for MCOPS12

RARB mouse models



Four different mouse models

- ***Rarb*** $^{-/-}$
- ***Rarb*** $^{R387C/+}$
- ***Rarb*** $^{L402P/+}$
- ***Rarb*** $^{+/-}$

Studies

- Behavioral analyses of movement & cognition
- Transcriptomics of brain samples
- Lipidomics of brain and blood samples
- Metabolomics & proteomics studies of blood samples

Clinical picture



Natural History study

- Neurological exam & video assessment
- Neurodevelopmental questionnaire & Vineland interview
- Neurological questionnaire
- Custom RARB questionnaire
- Brain MRI assessment

Biomarkers (?)

- EEGs
- Metabolomics & proteomics studies of blood (plasma) samples

Patient iPSC-derived neuronal cell models



- Generation of induced pluripotent stem cells (**iPSCs)** from a patient with a **p.Arg387Cys** (R387C) **mutation**
- Differentiation to **neural stem cells**
- Developing robust protocols for striatal (medium spiny neuron) cells

Functional assays

- Characterization of cell model
- Development of assays for cellular dysfunction

CHU Sainte-Justine Le centre hospitalier universitaire mère-enfant
Université de Montréal

igbmc institut de génétique et de biologie moléculaire et cellulaire

CHU Sainte-Justine Le centre hospitalier universitaire mère-enfant
Université de Montréal

RareLabs A DIVISION OF ALPHA ROSE THERAPEUTICS

UNI BASEL

Cure MCOPS12

On the quest for biomarkers

Clinical picture



Natural History study

- Neurological exam & video assessment
- Neurodevelopmental questionnaire & Vineland interview
- Neurological questionnaire
- Custom RARB questionnaire
- Brain MRI assessment

Biomarkers (?)

- EEGs
- Metabolomics & proteomics studies of blood (plasma) samples

What is a biomarker?

A biomarker is something in the body that can be measured, and that tells us something about health or disease. It is measured, not felt.

Why do they matter for neurological diseases such as MCOPS12?

Biomarkers serve as **additional** (secondary) **outcome measures in clinical trials** (and are often requested by health authorities for trial approval).

Examples (blood biomarkers/neurological diseases)

Metabolite: phenylalanine for phenylketonuria (PKU)
Protein: p-tau217 in Alzheimer´s disease

What´s next?

- **Metabolite screening** in blood plasma samples (20 patients + 20 controls)
- **Protein screening** in blood plasma samples (20 patients + 20 controls)

- For patients in the **US**: phlebotomy & logistics by **COMBINEDBrain**
- For patients in **Canada**: phlebotomy & logistics by **CHU Sainte-Justine**
- For patients outside US/CA: phlebotomy & logistics tbd / physician dependent

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Université de Montréal

A CURE FOR SIENNA

A Cure for Sophia and Friends

COMBINED
https://combinedbrain.org/

Cure MCOPS12

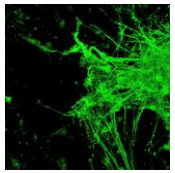
Patient derived cell models for drug development

Patient iPSC-derived neuronal cell models

- Generation of induced pluripotent stem cells (**iPSCs)** from a patient with a p.Arg387Cys mutation
- Differentiation to **neural stem cells**
- Developing robust protocols for striatal (medium spiny neuron) cells

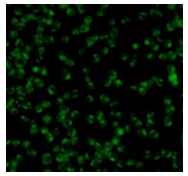
Functional assays

- Characterization of cell model
- Development of assays for **mitochondrial** (dys)function **&** low-density lipoprotein **(LDL)** (dys)function



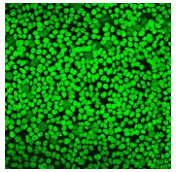
medium spiny neurons (MSN) (not reproducible)

Differentiation



Neural stem cells (NSCs)

Differentiation



Mutant & isogenic control iPSCs

Reprogramming





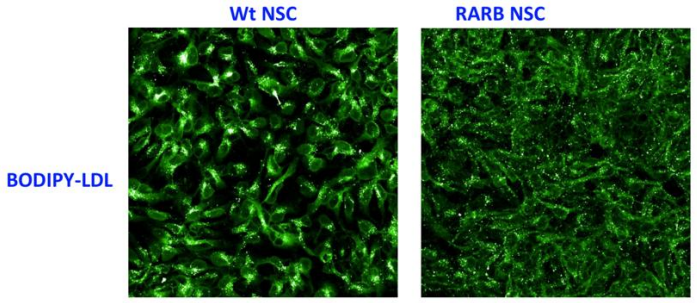
UNI BASEL

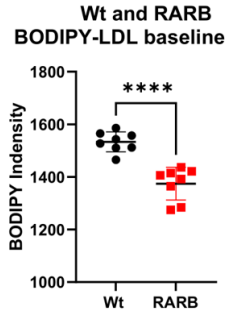
Tasks for 2027:

- Generate more iPSCs lines (male & female patients, diff. RARB variants)
- Establish & characterize MSN cell model
- Supervised by COMBINEDBrain

COMBINED

Functional assays:





A Cure for Sophia and Friends

RareLabs A DIVISION OF ALPHA ROSE THERAPEUTICS

Cure MCOPS12

Drug repurposing via high-throughput screening

GOAL: reduction of movement disorders, improvement of cognitive skills.

Why repurposing: much cheaper and faster than de-novo drug development.

Latest status: **BODIPY screening completed, data evaluation ongoing.**

RareLabs A DIVISION OF ALPHA ROSE THERAPEUTICS → NCATS COLLABORATE. INNOVATE. ACCELERATE.

Assay development

SMOL library, automated screening

STAGE 1

The SMOL library

~10,000 small molecules (SMOL)

- FDA-approved, clinical phase I–III, or of natural origin (vitamins & supplements)
- **possess an established safety profile**

STAGE 2

The "BODIPY & MMPI filter"

NCATS automated screening

- Compounds applied to **patient iPSC-derived** neural stem cells **(NSCs)**
- **BODIPY** readout identifies which molecules clear the lipid accumulation
- Shortlisted candidates are confirmed by a second screening (**MMPI**).

STAGE 3

Clinical translation

From hit to patient

- Hit compounds can be rapidly deployed for off-label use (in case it´s a market approved drug)
- Or enter a MCOPS12 clinical trial (fast-track: clinical phase II/III trial)

A Cure for Sophia and Friends

Cure MCOPS12

Cure MCOPS12

A personalized ASO medicine for Simon

Pioneering RNA therapies for MCOPS12



What is an Antisense Oligonucleotide (ASO) therapy?

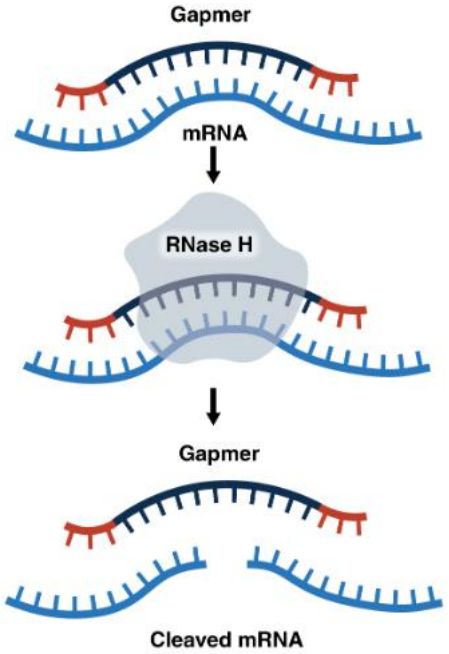
ASOs are short, **lab-made strands of genetic material** – built from the same building blocks as our own DNA or RNA

(i.e. **nucleotides**)

A "tiny, highly precise strip of tape that **sticks to one target inside a cell**: messenger RNA (**mRNA**) – the "recipe" a cell follows to make a protein

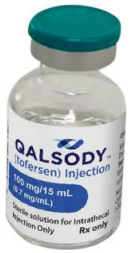
By binding to the target (mutant) mRNA, ASOs can either correct the recipe so a missing protein is produced again, or **destroy the recipe to stop a harmful protein from being made**

("**gapmer ASO"**)



- **Chemistry matters!** ASOs are chemically modified to increase stability, bioavailability & potency
- ASO medications for **(ultra) rare neurological disorders**: from many patients to N-of-1

SPINRAZA® (nusinersen) injection 12 mg/5 mL





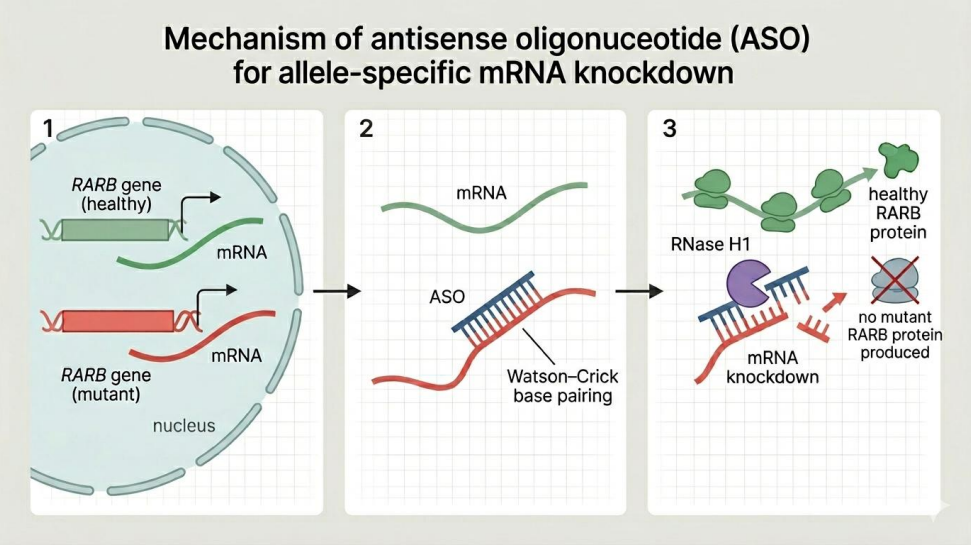
Milasen, Tim Yu, 2019

n-lorem FOUNDATION

Cure MCOPS12

Simon´s personalized ASO therapy: the concept

- **GOAL: reduction of dystonia, improvement of cognitive skills & quality of life**
- **Target:** *RARB* variant **c.1159C>T (p.Arg387Cys)**, a **dominant-negative** mutation
- **Mechanism:** Allele-specific antisense oligonucleotide (ASO) therapy for **mRNA knockdown of mutant *RARB* allele** (while preserving the wild-type allele)
- **Why allele-specific?** RARB protein is essential for postnatal brain development (e.g. neuroprotection of medium spiny neurons)[1]



Clinical & regulatory setting

Targeting the brain
Intrathecal administration
(3-4 times / year)

Named patient use
(Austria)
Approval by hospital ethics board

[1]*Ciancia et al., Progr. Neurobiol. (2022), 212, 102246*

https://www.rarbmutation.org/simons-aso-therapy

Cure MCOPS12

Allele-specific ASO therapy development workflow

Personalized for Simon, but a blueprint for many MCOPS12 patients.

Target identification & ASO design



Long-read sequencing
of *RARB* alleles

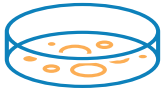
Target site identification
Additional variants on mutant *RARB* allele (SNPs, indels)

ASO design & in silico off-target evaluation

Completed

RareLabs ALPHA ROSE THERAPEUTICS

Efficacy & safety testing in Simon´s neuronal cell model



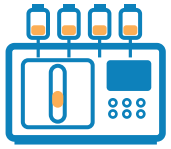
Efficacy testing
110 ASOs screened for allele-specific knockdown

Safety testing
- Immunotoxicity
- Cytotoxicity
- Off-target effects

Completed:
6 ASO candidates

RareLabs ALPHA ROSE THERAPEUTICS AstraZeneca

ASO manufacturing & QC testing



Non-GMP material
6 ASO candidates for 1st toxicology study

Completed

GMP material
Final ASO drug for 2nd toxicology study & clinical batch

Oct-Nov 2026

Hongene Biotech

Two toxicology studies in rats



1st study: 6 ASO candidates
Acute toxicity (4 weeks) & brain biodistribution

Jul – Sep 2026

2nd study: final ASO candidate
13 weeks GLP study

Jan – Mar 2027

Cure MCOPS12

Next step: clinical study protocol I

- **Definition of inclusion/exclusion criteria:** to be aligned with treating physician
- **Baseline exams:** Simon´s scores from ongoing **RARB Natural History Study** at CHU Sainte-Justine (movement disorders, neurodevelopmental), brain MRI, ECG, EEG, PET (^{11}C Raclopride) for D2/D3 receptor densitiy (optional)
- **Definition of adverse events (AEs) and serious adverse events (SAEs):** to be aligned with treating physician

- **Proposed dosing schedule:**

Day	Single dose (will be derived from GLP tox study)
Initial – day 0	5 mg
Dose escalation – day 28 (±3 days)	10 mg
Dose escalation – day 56 (±3 days)	20 mg
Dose escalation – day 84 (±3 days)	xx mg
Maintenance – every 90 (±7 days) days therafter	xx mg

- **ASO drug presentation:** Lyophilized powder in sterile vials (manufactured under GMP), for aseptic reconstitution at hospital pharmacy

Cure MCOPS12

Next step: clinical study protocol II

- **Proposed outcome measures:** primary, secondary, and exploratory - **to be aligned with treating physician**

Outcome measures	Measure description
Primary	
Safety and tolerability of multiple doses the ASO	Number, frequency, and severity of AEs and SAEs; changes in vital signs, ECG, physical examination; brain MRI (hydrocephalus)
Secondary	
Pharmacokinetics of the ASO in CSF and plasma after single and repeat dosing	ASO concentration in CSF prior to subsequent dosing; Time to steady state CSF concentration;
Exploratory	
Assess patient quality of life and functional ability by general questionnaires and patient reported outcomes	Protocols & **questionnaires from RARB Natural History Study**: Vineland-3, GMFCS, Global Dystonia Rating Scale, neurology exam, video assessment; patient reported outcomes tbd; **add. video assessments tbd**
Biomarkers - EEG	EEG (change in periodic power of beta bands)
Biomarkers - inflammatory (proteomic) biomarkers in CSF and/or blood plasma	**CSF:** change in interleukins, Nfl, more tbd; **blood plasma:** Nfl, more tbd
Biomarkers – metabolomic biomarkers in blood plasma	tbd

Cure MCOPS12






















Cure MCOPS12

Thank you!