A Cure for Sophia and Friends

FISCAL YEAR REPORT

2024-2025

Dear Friends, Supporters, and Families,

As we close out our second fiscal year, we reflect with deep gratitude on the progress we've made together. We set ambitious goals: to complete our drug repurposing program and identify new compounds to help our patients improve function in cognition and motor movement, complete our biomarker study, and host our first in-person MCOPS12 symposium. Thanks to your unwavering support, we are proud to report that most of these goals have been realized.

REFLECTING ON A CURE FOR SOPHIA AND FRIENDS SECOND YEAR

GLOBAL CONNECTIONS: OUR FIRST IN-PERSON CONFERENCE

This year marked a major milestone—our first in-person RARB family conference!

We were honored to welcome families from USA, Canada, Austria, Australia, New Zealand, and Ireland, with 20% of our global RARB community in attendance.

- We reimbursed hotel and transfer costs for all families traveling outside of Canada.
- We hosted a family and researcher dinner following the conference.
- Throughout the weekend, priceless networking occurred between families and researchers—building bridges of understanding and collaboration.

"Our experience at the conference was life changing to watch our daughter truly come out of her shell and feel comfortable to be herself was a blessing! We have a worldwide family who truly understands." – ***Collins Family***

"To finally meet and be able to hug these amazing people responsible for spearheading research towards a treatment for our little ones was truly life changing" – ***Flint Family***

GOAL 1:
COMPLETE
DRUG
REPURPOSING
STUDY

GOAL 2:
CONTINUE
DEVELOPING
ASO THERAPY

GOAL 3:
COMPLETE OUR
BIOMARKER STUDY
TO SUPPORT
CLINICAL TRIALS

RESEARCH HIGHLIGHTS

OUR TEAM'S MILESTONES

GOAL 1: COMPLETE DRUG REPURPOSING STUDY

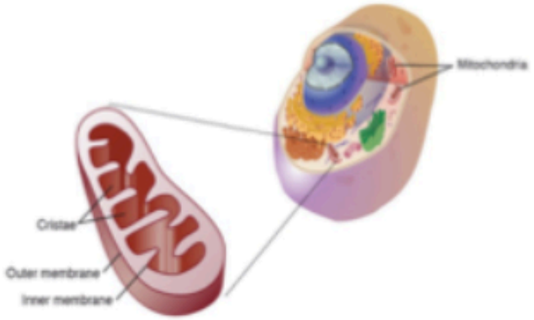
As a first step, our drug repurposing study identified a defect (mitochondrial dysfunction) in a MCOPS12 patient-derived cell model

This important finding will serve as a readout for the subsequent screening of 10,000 compounds at NCATS as of the end of our 24/25 fiscal year

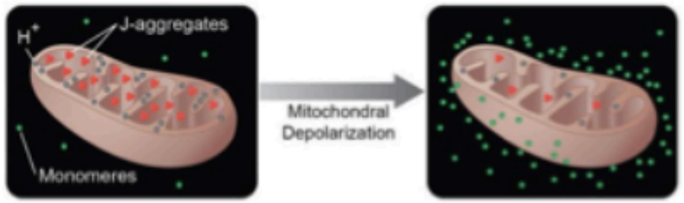
We are hopeful to have results in the first quarter of our 25/26 fiscal year to begin either off-label use or clinical trials depending on which compounds are identified.

DRUG DEVELOPMENT:
DRUG REPURPOSING PROGRAMS II

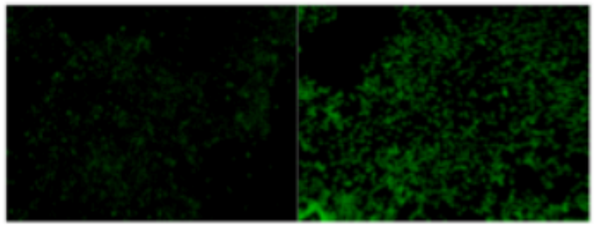
- **Program 2 (at Everlum Bio, USA; start Q2 2024, completed in Q4 2025):**
  - **~10000 drugs** (2400 FDA approved, 2600 completed Ph. I/II clinical trials, 5000 „natural compounds“ e.g. vitamins, minerals) are **tested in a patient-derived (R387C) neuronal stem cell (NSC) model**
  - **Readouts:** functional



Mitochondrial dysfunction in neuronal cells
(both in patients (R387C) and mouse models)



Detectable by a Mitochondrial Membrane Potential (MMP) Assay*



(healthy) control NSC **patient NSC**

- **Drug screening in Q4 2025:** for **successful candidates** there are **two options**:
  - off-label use (for market approved drugs & „natural compounds“)
  - MCOPS12 clinical trial (for drugs in clinical trials)

**MMP assay principle: in healthy cells, a dye accumulates in mitochondria showing red fluorescence.*
When mitochondrial membrane potential collapses after a chemical (FCCP) treatment, the dye remains in cytoplasm with green fluorescence.

GOAL 2: CONTINUE DEVELOPING A PERSONALIZED ASO THERAPY
to lay the groundwork for a possible ASO therapy for additional MCOPS12 patients

What is an ASO Therapy and Why Does It Matter?

Antisense Oligonucleotide (ASO) therapy is a cutting-edge approach that targets the RNA—the messenger that carries instructions from DNA to produce proteins. ASOs are short, synthetic strands of nucleic acids designed to bind to specific RNA sequences.

This can:

- Reduce harmful protein production
- Correct splicing errors
- Block translation of toxic proteins

Current ASO Achievements:

- Long read sequencing & bioinformatics identified several targets for ASO candidates
- A patient iPSCs-derived neuronal cell model was generated to test ASOs for efficacy
- Five ASO candidates showed significant knockdown of the mutant allele without affecting the wild type (healthy version).

For MCOPS12 patients

ASO therapy offers a precision tool to silence the mutant RARB gene while preserving the healthy version.

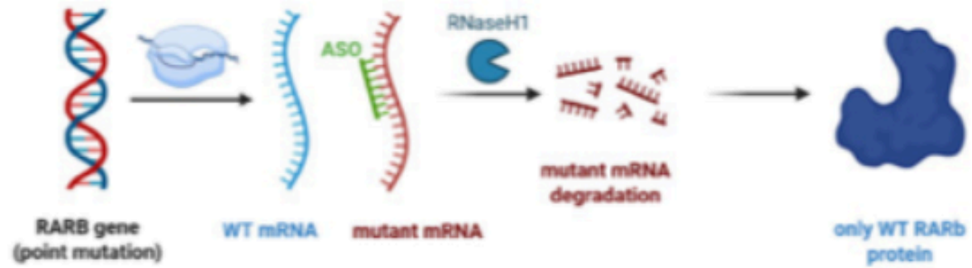
This targeted (allele-specific) approach minimizes side effects and holds promise for personalized genetic treatment.

DRUG DEVELOPMENT: PERSONALIZED ASO THERAPY

Antisense Oligonucleotide (ASO) for allele-selective mRNA knockdown

Why personalized?

ASO needs to target patient`s specific mutations

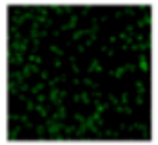


Long read sequencing of RARB alleles

Find additional targets for ASOs

design & synthesis of ASO candidates

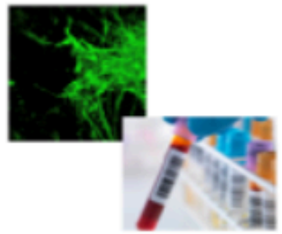
In-silico evaluation of off-target effects



ASO efficacy screening in patient iPSC-derived NSC model

readout: allele-selective mRNA knock-down (TaqMan assay)

5 ASO candidates with allele-specific knockdown (80-90%) !!



***In-vitro* toxicity & off-target assessment of ASO hit candidates**

Currently ongoing

ASO pharma-grade production

Brain biodistribution, pharmacokinetics & toxicity in rodents

Intrathecal ASO administration in the clinic

EU (EMA): Named patient use program

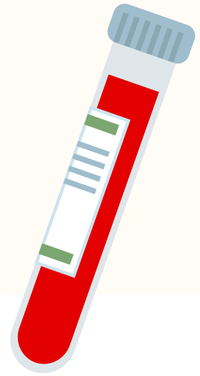
Regulatory approval

US (FDA): IND

GOAL 3: COMPLETE OUR BIOMARKER STUDY TO SUPPORT CLINICAL TRIALS

A biomarker study in a MCOPS12 mouse model is ongoing and we are hoping to begin biomarker discovery in MCOPS12 patients during our 2025-2026 fiscal year.

Cure MCOPS12



igbmc
institut de génétique et de biologie moléculaire et cellulaire

Why Biomarkers Matter

Biomarkers are measurable characteristics of the body that indicate abnormal processes or disease. They are essential in clinical trials, often serving as primary or secondary endpoints to evaluate the effectiveness of a treatment.

For MCOPS12, we are now working to identify neurological disease-specific biomarkers in patients—such as proteins and metabolites in blood or cerebrospinal fluid (CSF), and brain imaging markers. These biomarkers will be critical in helping us move forward with clinical trials once promising drug compounds are identified.

ACKNOWLEDGING OUR FOUNDATIONAL SUPPORT

rare village FOUNDATION

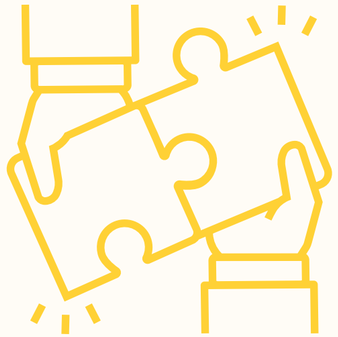
CAPITAL GROUP™

A Cure For Sienna

CHU Sainte-Justine

Michaud Research Lab-
CHU Sainte-Justine
Research Center
Université de Montréal

Prof. Jacques Michaud
Montréal, Canada



Thank you to our research partners at *CHU Sainte-Justine* who made our first in-person MCOPS12 family conference a success and continue their diligent work on our natural history study!

We remain deeply grateful to *Rare Village Foundation*, whose fiscal sponsorship enables us to continue fundraising and secure critical grants.

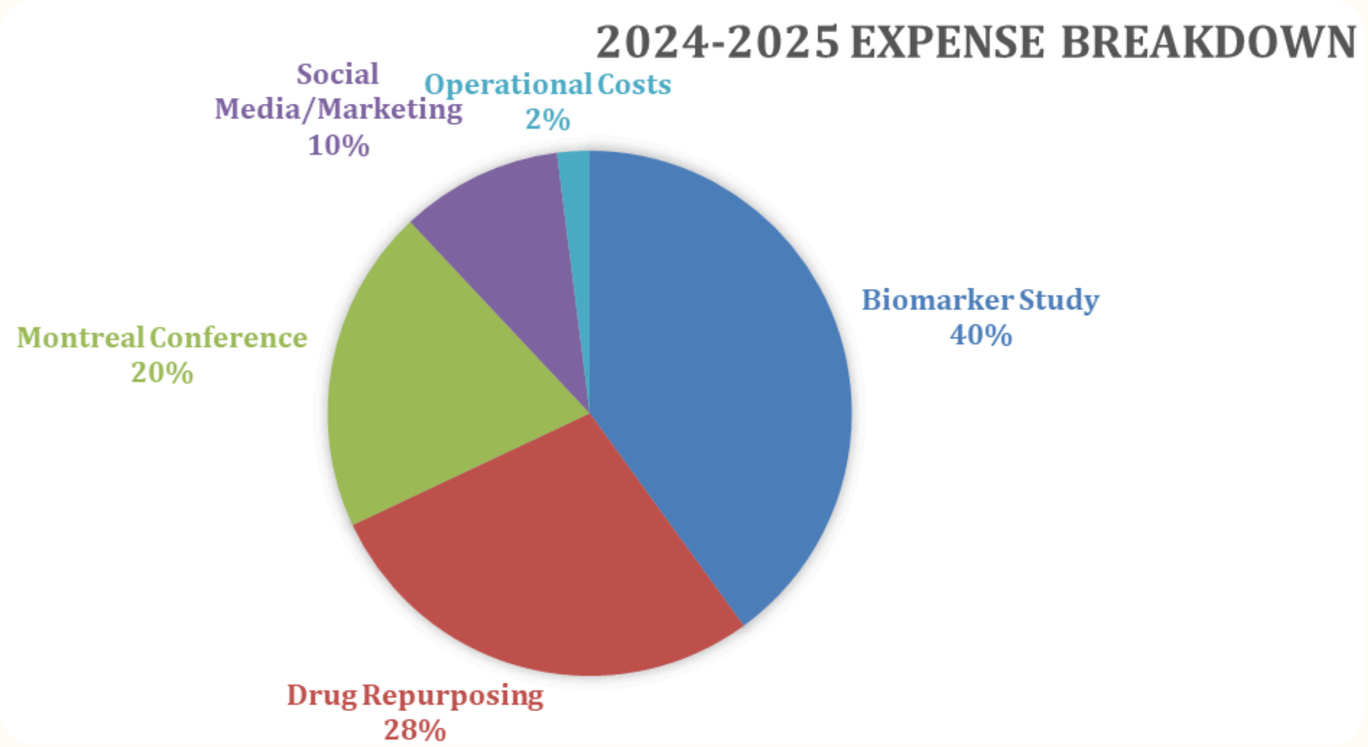
We also extend heartfelt thanks to *Capital Group*, whose continued advocacy and generosity have amplified our mission and expanded our reach.

FINANCIAL TRANSPARENCY & DONOR IMPACT

THANKS TO YOUR GENEROSITY, A CURE FOR SOPHIA AND FRIENDS RAISED JUST OVER

$84,000

These donations and many more directly funded our research projects, family conference, and operational costs—reflected in the pie chart below:



In addition to our corporate partner

Capital Group

We'd like to thank the following donors who have each contributed over $1500 for the last two years

- A Cure for Sienna
- Christine D'Amico
- Dawn Middleton
- Rischel Pike
- Amy Stein
- Barbara Vittuozo
- Scott Yacyshyn

A Cure for Sophia and Friends Advisory Board

Chelsey Oliver *Secretary*

Rischel Pike *Treasurer*

Reinhard Pell *Reseach and Drug Development*

S Gary Sutherland *Information Specialist/Website Designer*

and special thanks to **Heather Cawood** *incoming Social Media Director*

As we reflect on another year of progress, we remain humbled by the generosity and belief you've placed in our mission. Your support fuels our research, strengthens our community, and brings hope to families around the world.

With heartfelt gratitude,

Rachel Sutherland
Executive Director, A Cure for Sophia and Friends
www.acureforsophiaandfriends.com

HERE'S TO 2025–2026!

THANK YOU FOR BEING PART OF OUR JOURNEY. LET'S MAKE THIS YEAR EVEN MORE AMAZING TOGETHER!