A Cure for Sophia and Friends

2025 -2026

FISCAL YEAR REPORT

Dear ACFSAF Supporters,

On behalf of our MCOPS12 Patient Families, I'd like to extend a grandiose THANK YOU for your continued support over these past three years! I can't believe that we have been working towards solutions and building community for our families for three years now. Thanks to the growth of our board this past fiscal year and your financial giving, we have been able to launch multiple biomarker studies with Metabolon and Alamar that are being coordinated through our ongoing partnerships with CHU St Justine and IGBMC.
We are on the horizon of completing our drug repurposing study with AlphaRose Therapeutics. Thanks to the support of our sister organization, A Cure for Sienna, we are continuing our partnership with CHU St Justine to further data points with our natural history study and we have expanded our partnership, in conjunction with Cure MCOPS12, with IGBMC by supporting a 3 year research study with a PHD student to further research on translational science to obtain a holistic picture on the pathophysiology of MCOPS12.
We are eagerly looking forward to our second patient family conference in Salzburg, Austria in September. The researchers and doctors from CHU St Justine and IGBMC will be sharing updates on our continuing and new research goals, collecting additional patient data for our ongoing natural history study along with special focus groups allowing ample time for families to learn more about MCOPS12 Syndrome and share with other patient families.
To complete our research updates, we recently joined Combined Brain and are looking forward to partnering with them to begin the process of creating iPSC lines and cell models as our research focus for 2026/27.
Most importantly, we could not have advanced this far without your help and to that end we have listed all donors from the past three years to honor your gifts since we will be starting a brand new fundraising campaign this upcoming fiscal year. Your donations have allowed us to move forward with groundbreaking research for a hyper-rare mutation and as the mother of our beautiful Sophia, I could never thank you enough for the hope your assistance brings not only to Sophia, but to all MCOPS12 patients and their families. We look forward to the veritable plethora of possibilities for our families as we embark on this new fiscal year and the research that you have made possible.

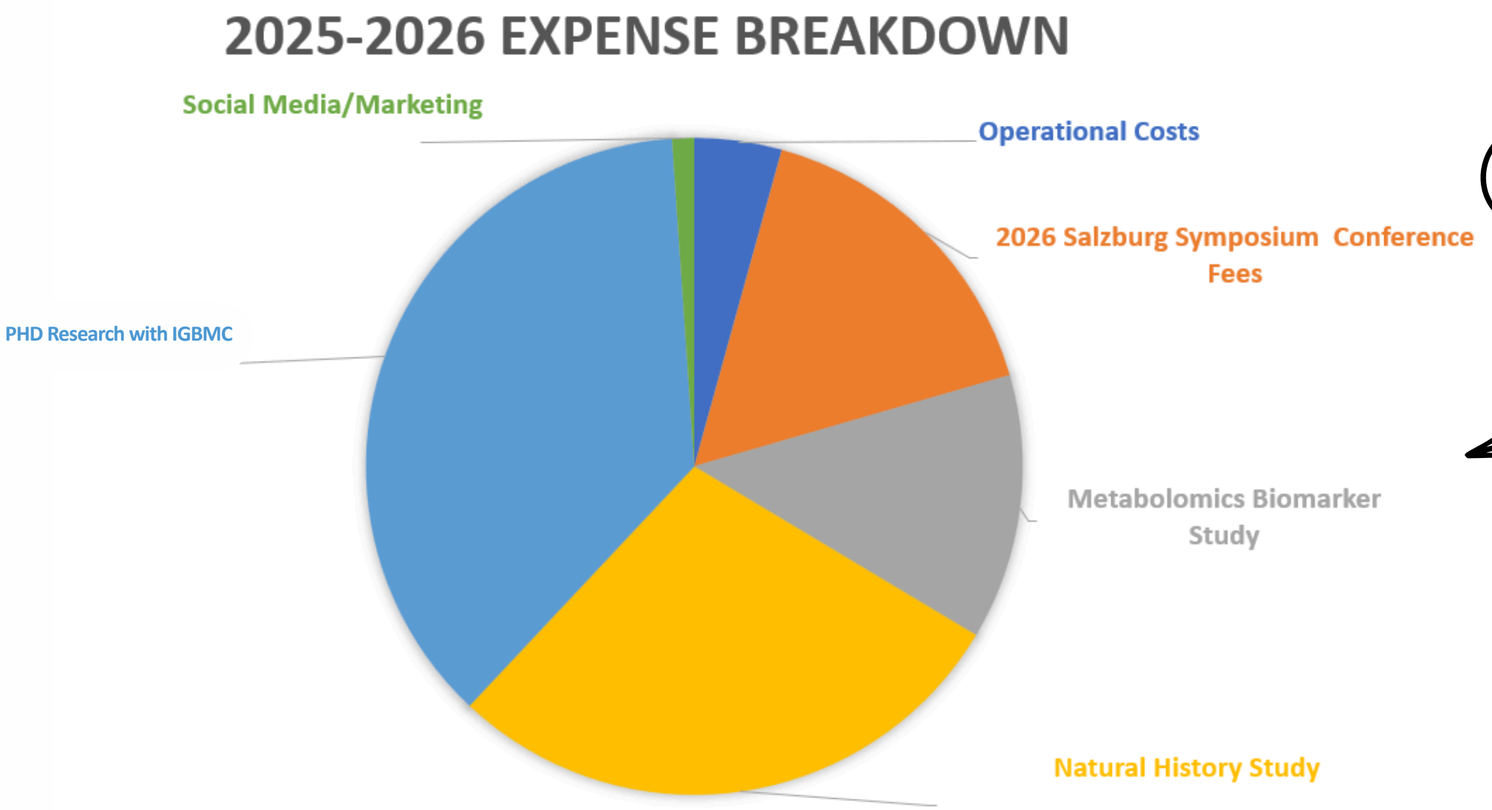
With Gratitude,
Rachel Sutherland
Executive Director, A Cure for Sophia and Friends

FINANCIAL TRANSPARENCY & DONOR IMPACT

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

$180,000

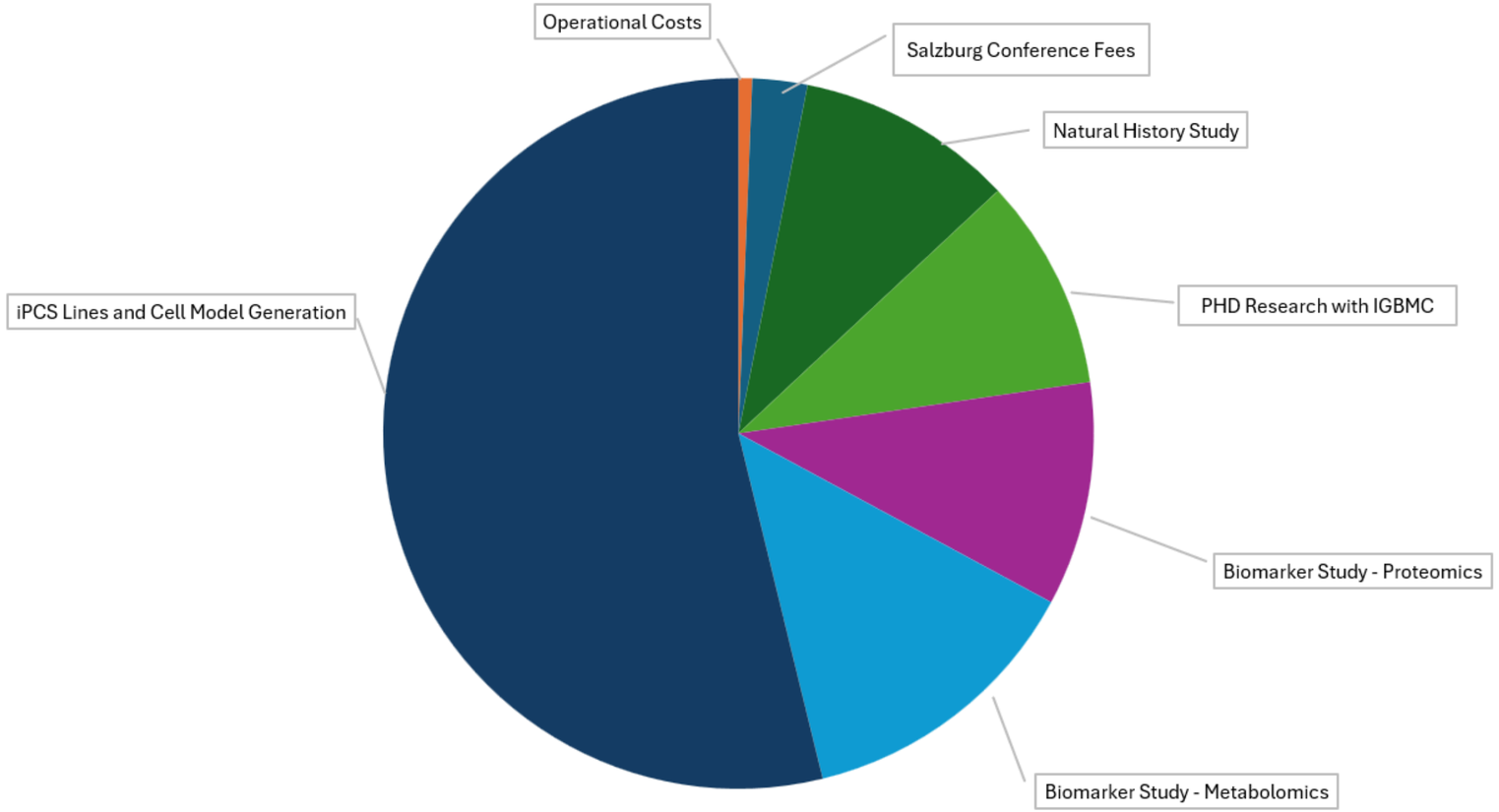
These donations and many more directly funded our research projects, family conference, and operational costs—reflected in the pie chart below:



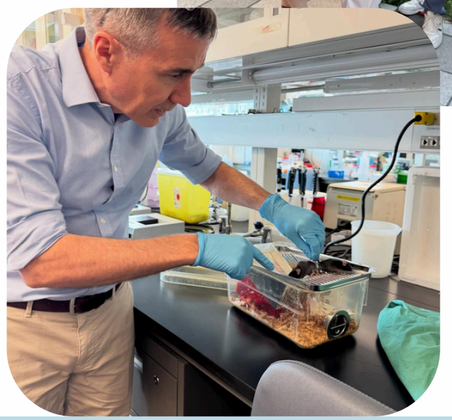
YOUR ONGOING SUPPORT AND FINANCIAL GIFTS HAVE LONG-TERM IMPACT

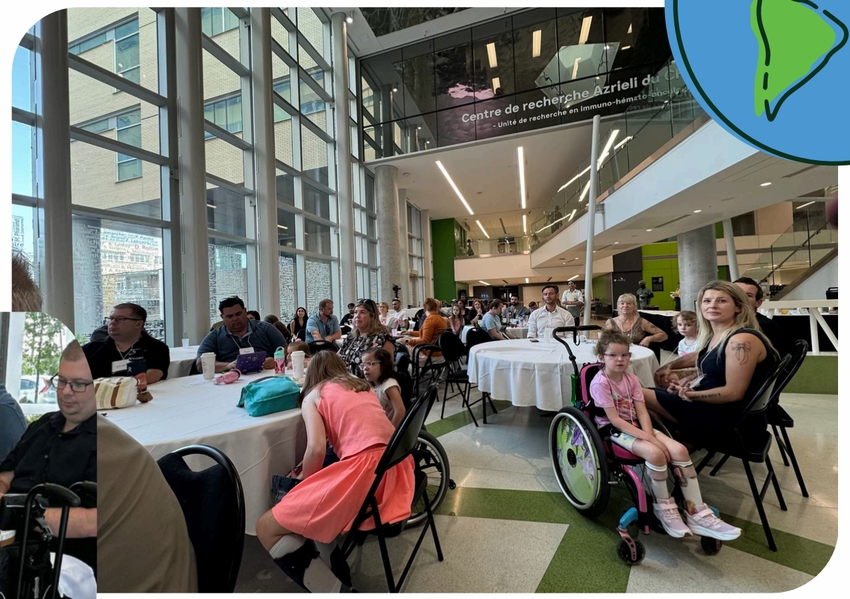
Your support in the upcoming year will continue to fund the following projects that are vital to our cause:
the Natural History Study, PhD Research with IGBMC and Biomarker studies, along with our upcoming initiative to begin generating iPSC lines and cell models.

PROJECTED 2026-2027 EXPENSES BREAKDOWN



PATIENT ENGAGEMENT





This year marked another major milestone—in coordinating our second in-person RARB family conference that will be held in Salzburg, Austria in September 2026!

We will be welcoming researchers and families from USA, Canada, Austria, Australia, New Zealand, Germany, France, Spain, Italy and Ireland with 20% of our global RARB community in attendance.

- Throughout the weekend, we are planning opportunities for networking between families and researchers—building bridges of understanding and collaboration, time for families to meet and discuss challenges and successes while parenting children with MCOPS12 and a time for 1:1 consult and data collection in support of our natural history study.

We're thrilled to share free copies of Nikki Mcintosh's book *Rare Mamas* with our families to support them on this unique journey through rare disease.

METABOLON & ALAMAR BIOSCIENCES- BIOMARKER STUDIES

CHU ST. JUSTINE & IGBMC STUDIES- NATURAL HISTORY STUDIES AND MOUSE MODELS

PHD RESEARCH WITH IGBMC

ALPHA ROSE- DRUG REPURPOSING STUDY

COMBINED BRAIN-CELL MODEL /IPSCS

RESEARCH HIGHLIGHTS

METABOLON & ALAMAR BIOSCIENCES- BIOMARKER STUDIES

Our biomarker studies with Metabolon and Alamar began in early 2026 with our mouse models and once MCOPS12 patients' blood samples (along with control samples) have been received we will begin to investigate proteins and metabolites which are distinctive for disease progression and/or amelioration after a medical treatment. As we shared last year, biomarkers are strongly recommended by health authorities as an additional/secondary endpoint to assess a drug´s efficacy in a clinical trial. In addition, the study will help us to better understand the pathology of MCOPS12.

Lets take a deeper look

Biomarkers were described as objectively measurable biological characteristics that indicate disease processes or responses to therapy. They are **essential** for:

-Supporting Natural History studies -Strengthening future clinical trial endpoints

-Complementing clinical outcome measures with objective data

METABOLOMIC STUDIES: METABOLON

WHAT RESEARCH ARE THEY PERFORMING?

- Analyze approximately up to 5,500 metabolites (untargeted analysis, 5,500 metabolites are included in their database)
- Scope includes both mouse and future patient samples

CURRENT STATUS

- Mouse blood plasma samples completed **June 2026**
- Analysis began early **July 2026**
- Results anticipated by the end of **Q3 2026**

PATIENT STUDIES

Pending ethical approval and logistics under the Natural History Study sponsor.

PROTEOMIC STUDIES: ALAMAR

WHAT RESEARCH ARE THEY PERFORMING?

Quantifies approximately 120 proteins (targeted analysis) related to neurological function

CURRENT STATUS

- Blood plasma samples completed **June 2026**
- Analysis in **July 2026**
- Results expected **Q3 2026**

PATIENT STUDIES

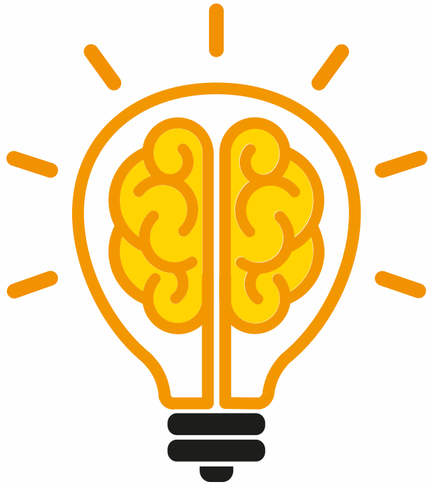
Dependent on ethical approval and sample logistics

CHU ST. JUSTINE & IGBMC STUDIES- NATURAL HISTORY STUDIES AND MOUSE MODELS

As we continue to discover new MCOPS12 patients, our researchers at **CHU St Justine** are working diligently to incorporate these families into our growing natural history study and continue to further data points by collecting EEGs, MRIs and other diagnostic studies with all patient families. Our natural history study coordinator, Valerie Chu, continues to be a wonderful asset in connecting our new families to our studies and assisting us with the coordination of our second patient family conference. Our CHU St Justine natural history researchers along with lead researcher, Wojciech Krezel, at **IGBMC** have agreed to work in conjunction with the companies processing our biomarkers so we can keep our data with our two primary research facilities to further expand on results from both studies.

EEG BIOMARKER (NATURAL HISTORY STUDY) CHU ST JUSTINE

- Initiated in conjunction with the MCOPS12 conference in Montreal in 2025
- Has been integrated into the Natural History Study
- EEG data show a **consistent abnormal frequency band** (beta-band) compared to healthy controls
- This abnormality supports EEG as a **promising and usable biomarker** for MCOPS12



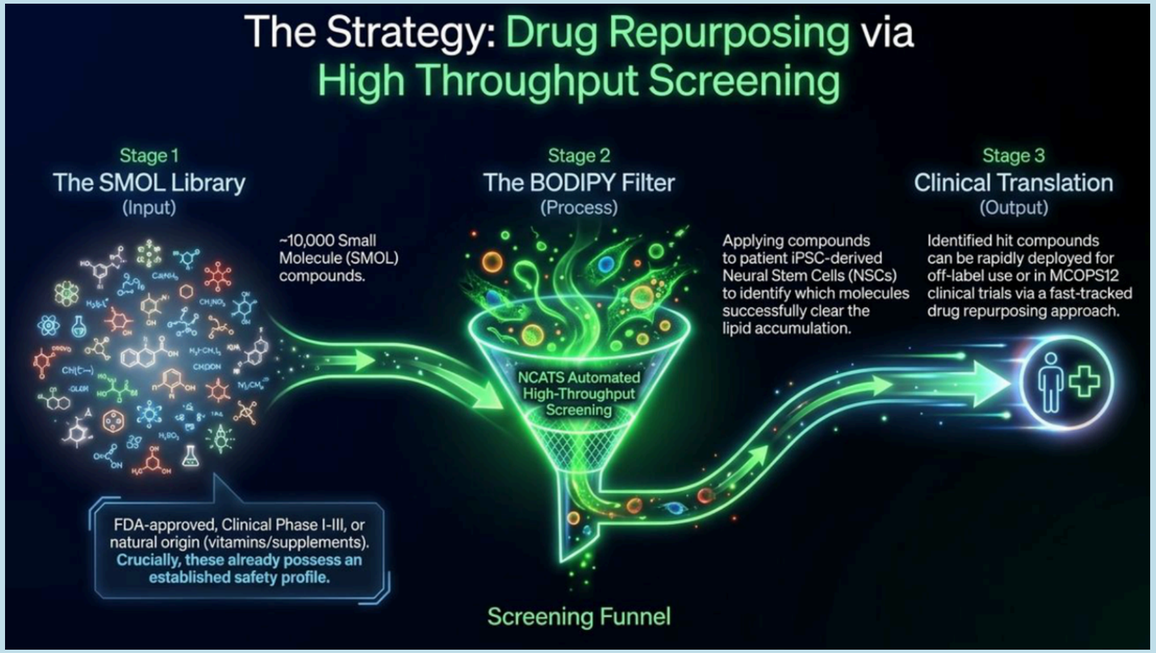
Lipidomic Studies (Mouse Models) IGBMC

- Conducted across **three MCOPS12 mouse models**, representing:
  - The most common mutation variant (**Rarb R387C**)
  - A rarer variant (**rarb L402P**)
  - A loss-of-function variant (**Rarb knockout/double mutant**)
- Post-mortem brain tissue analysis assessed cholesterol and ~30 lipid-related compounds
- Findings indicate an **imbalance in lipid metabolism**
- Similar metabolic disturbances are well documented in other neurological diseases
- Although preclinical, results provide important direction for patient studies

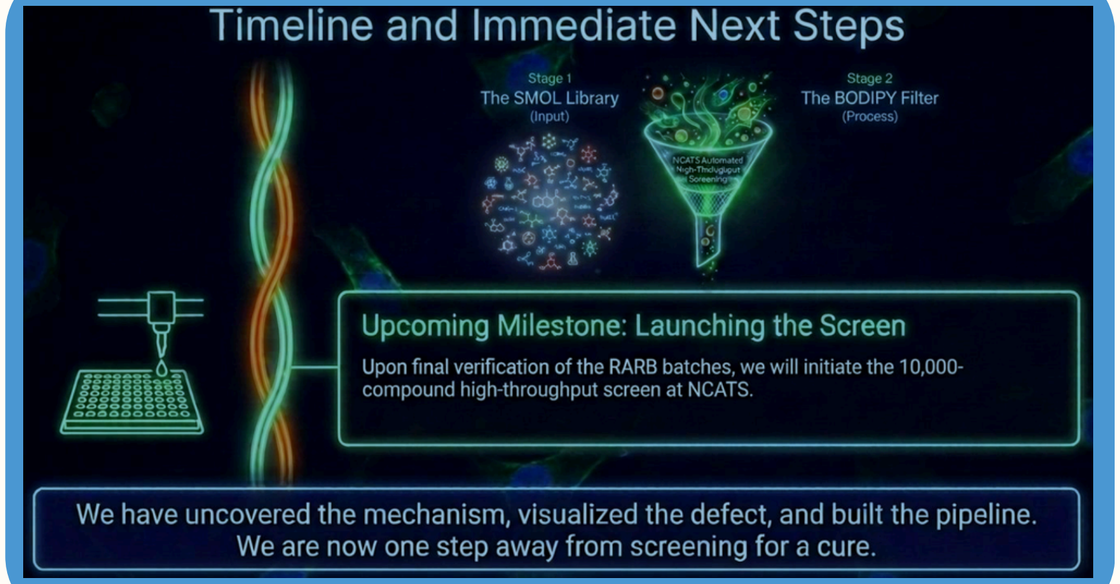
PHD RESEARCH WITH IGBMC

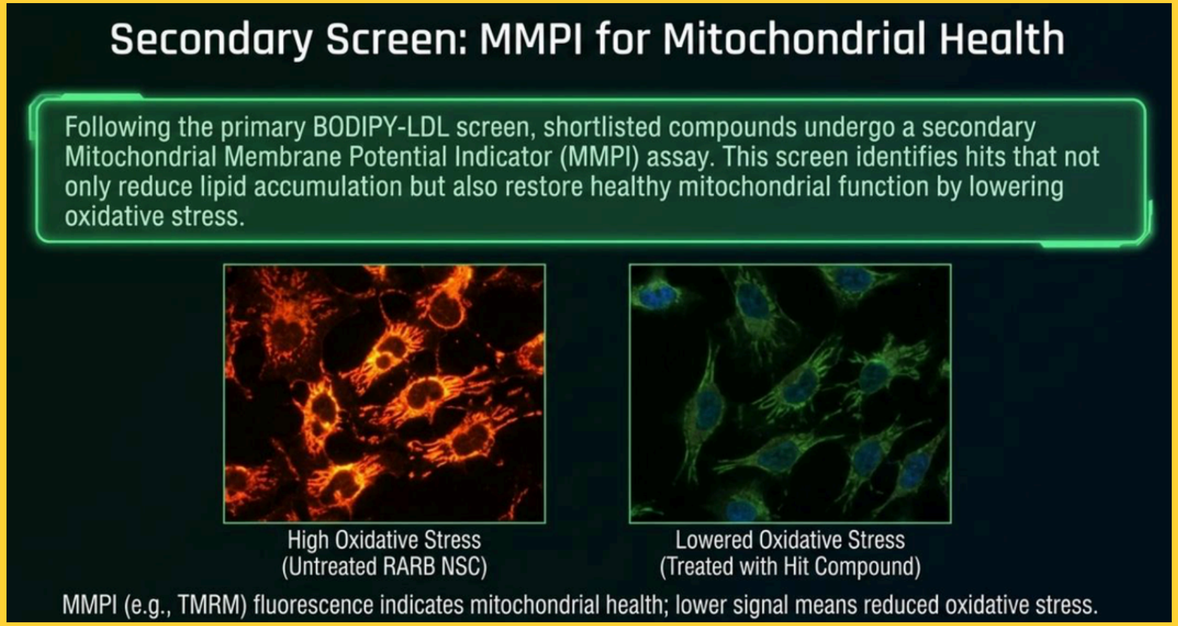
Although rare variants of retinoic acid receptor beta (RARb) have been identified as causal factors in MCOPS12, it is unclear how these variants lead to disease symptoms and whether they act through common or distinct mechanisms. The overarching goal of the research program carried out by the team of Dr Wojciech Krezel (IGBMC, France) is to elucidate these mechanisms to propose treatment strategies. To this end, the team has generated dedicated mouse models which carry various MCOPS12-causing RARb variants. These mice recapitulate, with high fidelity, a large array of MCOPS12 symptoms, including microphthalmia and various neurological symptoms, as well as their progressive character. Aseel MADI, a PhD student recently recruited with the help of ACFSAF funds, will use these animal models to conduct mechanistic analyses focusing on mitochondrial function, metabolism, and cell communication. Obtained data will be used to identify drug targets and design treatment strategies to be tested in mouse and patient-derived neural cells cultured in vitro followed by in vivo assays in mouse models. A parallel line of Aseel's research project focuses on biomarker discovery and involves collaboration with METABOLON and ALAMAR BIOSCIENCES, with further support from ACFSAF. Blood biomarkers identified in this study will be immediately useful as readouts of the efficiency of new therapeutic approaches. Obtained data will also synergize with a parallel biomarker discovery program in patients, carried out by the team of Dr Jacques Michaud (CHU Sainte-Justine, Canada), to facilitate patient stratification for future therapeutic approaches and determine the efficiency of such approaches.

igbmc
institut de génétique et de biologie moléculaire et cellulaire



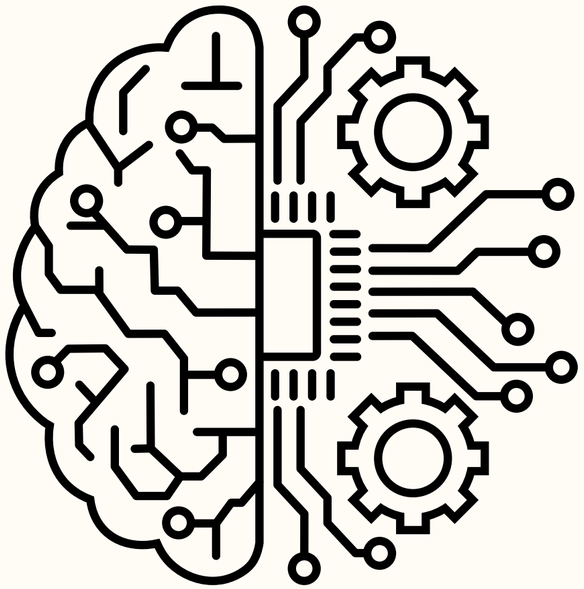
ALPHA ROSE THERAPEUTICS RARELAB





ALPHA ROSE-DRUG REPURPOSING STUDY

COMBINED BRAIN - CELL MODEL / IPSCS



As we look to completing our drug repurposing and biomarker study near the end of 2026, we are excited to focus towards an even bigger goal in beginning to create iPSC lines and cell models in collaboration with Combined Brain as we move into 2027. The absence of a robust patient-derived MSN model remains the **largest scientific gap**. A **phased, gated approach** beginning with iPSC generation is scientifically sound and financially prudent.

COMBINED

PATIENT-DERIVED NEURONAL CELL MODEL UPDATE

SCIENTIFIC RATIONALE

MCOPS12 pathology is strongly associated with dysfunction in specific brain regions:

Striatum – responsible for motor execution

Prefrontal cortex – involved in sensory processing and cognition

The striatum is primarily composed of medium spiny neurons (MSNs), which are central to motor symptoms. A robust MSN model is therefore considered critical for disease-relevant research and drug development.

COMBINED

PATH FORWARD

Re-initiating MSN development using a **new CRO or partner**, with a phased strategy:

1. Generate **new iPSC** lines from multiple MCOPS12 patients
   - Ideally 4–5 patients
   - Include different mutation variants
2. Differentiate iPSCs into **medium spiny neurons**
3. Perform disease characterization and develop assays suitable for drug screening

ACKNOWLEDGING OUR FOUNDATIONAL SUPPORT

Thank you to A Cure For Sienna for their co-sponsorship 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.

THANK YOU TO OUR AMAZING DONORS!

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