MENKES INTERNATIONAL ASSOCIATION

2023 Annual Report

Cover photo: Etna and Marco by Sofia Valero.

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Menkes International Association

2023 Annual Report

What sense would it make or would it benefit a physician

if he discovers the origin of a disease but could not cure nor alleviate them?

Paracelsus, 16th Century Pioneer in History of Medicine

Menkes International Association (MIa): Making Menkes Disease History

Menkes International Association
2023 Annual Report

Contents

Foreward

Dear Friends and Partners of Menkes International Association,

2023 was a year of growth and achievement for the Menkes International Association (MIa). Our mission is clearer than ever: we are committed to providing life-saving solutions to children suffering from Menkes disease. Our most notable achievement is expanding access to elesclomol-copper, the first new treatment in over 40 years since copper-histidine was introduced.

To manage this effort, we established **The Core**, a clinical team that supports physicians worldwide in treating Menkes children. They provide the best possible care, despite the disease's challenges. Additionally, our **Copper(less) Committee** offers scientific expertise and leads efforts to overcome dosing, formulation, and treatment challenges for children suffering from Menkes disease.

We work tirelessly with urgency, and none of this would be possible without your support.

We thank you for standing by us in this fight against Menkes disease.

Warm regards,

Aurora Mateos

FOUNDER AND DIRECTOR
MENKES INTERNATIONAL ASSOCIATION

Photo credit: Aurora Mateos

01

Mla 2023: Key Achievements

01 MIa 2023: Key Achievements

Menkes Patient Registry

MIa has launched the first and only global Menkes Patient Registry, providing a confidential platform that connects families, medical teams, and researchers to foster collaboration and accelerate the development of treatment. With 121 registered cases across 23 countries, this registry is vital in supporting clinical research and improving patient care.

Elesclomol-Copper Treatment

Since January 2021, MIa has successfully expanded access to elesclomol-copper treatment. After seeing remarkable improvements in the first treated child, Marco—who can now walk, run, and speak two languages—MIa has expanded access to elesclomol-copper treatment to other children worldwide. We work closely with local hospitals and authorities to ensure these treatments are safely administered.

Copper(less) Committee

MIa's Copper(less) Committee, an international group of experts, meets regularly to guide decisions regarding Menkes treatment. This multidisciplinary team evaluates patient progress, discusses treatment modifications, and ensures the highest standard of care. Their work is vital to advancing scientific understanding and improving the quality of life for Menkes patients.

Global Collaboration and Advocacy

MIa continues to build strong relationships with global health authorities, patient organizations, and scientific communities. We are now proud members of EURORDIS, an alliance of over 1,000 rare disease organizations, working together to improve the lives of patients worldwide. Our partnerships extend across national boundaries, ensuring that Menkes patients receive support no matter where they live.

Financial Accountability

MIa ensures full transparency and responsible use of its resources in financial management. In 2023, we raised €79,180, with €50,366 spent on key initiatives, including treatments, family travel support, and networking events. Our efforts are bolstered by volunteer contributions, ensuring that as much of our funding as possible directly supports Menkes children and their families.

Personal Impact

MIa is not just about medical research; it's about changing lives. Marco's story and those of other children receiving elesclomol-copper treatment are a testament to the power of hope and the life-saving impact of science. Families who once had no options are now seeing their children with Menkes disease grow and achieve milestones they thought were impossible.

Marco's Story: Once bound by the limitations of Menkes disease, Marco's treatment and recovery has provided hope to families across the world. His incredible progress—learning to walk, run, and communicate—serves as a beacon of possibility for other children. As the child of the founders of Menkes International Association (MIa), Marco's life and story are a public example of the hope and progress MIa is extending to other children with Menkes disease and their families. (add photo)

As MIa looks to the future, we are filled with optimism. With your continued engagement and support, we will continue to expand access to treatments, accelerate research, and, ultimately, make Menkes disease history.

02

Menkes Patient Registry

02

Menkes Patient Registry

In 2022, the Menkes International Association (MIa) launched the **first and only global Menkes Patient Registry**. This free online platform connects families of children with Menkes disease to a select group of medical and scientific research teams at accredited institutions. The registry allows families to access cutting-edge research and helps researchers collaborate on finding better treatments and work towards a cure for Menkes disease.

The importance of patient registries like this one cannot be overstated. According to Orphanet, they are essential tools in rare disease research, enabling data sharing that makes clinical research possible. By pooling patient data, we can better plan clinical trials, assess treatment effectiveness, and improve patient care. For rare conditions like Menkes, where treatments are limited, this type of data collection is critical for advancing medical understanding and developing new therapies.

As of September 23, 2024, **121 children from 23 countries** are part of this growing global registry, including:

Spain (12)
Argentina (15)
Belgium (1)
Brazil (31)
Canada (2)
Chile (1)
Colombia (8)
Costa Rica (1)
France (6)
Germany (1)

India (4)

Indonesia (1)

Israel (1)

Italy (5)

Lithuania (1)

Mexico (5)

Norway (1)

Poland (3)

Saudi Arabia (1)

Turkey (2)

United Kingdom (6)

United States (14)

This registry is not just a database—it's a lifeline for families seeking support and hope. It connects a community of patients, researchers, and clinicians, working together to fight Menkes disease.

Currently, the registry is managed by one dedicated volunteer, working part-time on weekends. Moving forward, we aim to secure funding to hire staff and expand this vital resource, ensuring it continues to serve families worldwide.

For more information, visit: Menkes Patient Registry

Funds raised: N/A

Funds spent: N/A

03

Elesclomol-Copper Treatments for Menkes Patients

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Elesclomol-Copper Treatments for Menkes Patients

Since January 2021, Menkes International Association (MIa) has been working to provide elesclomol-copper treatment to Menkes patients worldwide. This groundbreaking treatment, first tested successfully on a young boy named Marco, has brought hope to children suffering from this devastating disease. With the approval of national medical authorities, MIa is coordinating access to elesclomol-copper treatment in multiple countries, including Spain, where four cases are currently underway.

3.1 The Core

The Core is MIa's team dedicated to organizing the process of access to this exceptional treatment, led by Dr. Francesc Palau of Sant Joan de Déu Children's Hospital in Barcelona. Alongside a group of medical professionals, The Core ensures seamless communication between families, doctors, and researchers to provide the best care possible.

Following the decision of Dr Natalia Serrano to step down in June 2023, the Core members now include:

- Dr Francesc Palau (Coordinator, Hospital Sant Joan de Déu, and NeuroGene Senior Investigator, SJD Research Institute and CIBERER);

- Dr Elena Godoy, Pediatrician, Clinical advisor, Pediatric Complex Chronic patient and Palliative care unit, Regional University Hospital of Malaga; Ms. Rosa Marques, Neurological Pediatric Physiotherapist and Trainer Head of Clinical Pediatric Physiotherapist Teams

- Dr Stephanie Lotz, Clinical Investigator, Sant Joan de Déu Research Institute

- Dr Aurora Mateos, MIa Founder and Director

The Core meets weekly to monitor patient progress, assess treatment results, and discuss any challenges.

The Core's work goes beyond Spain, as they hold virtual meetings with doctors and families from other countries such as Germany, France, and the UK to offer guidance on starting treatments locally. They also collaborate regularly with Spain's **Medicines and Medical Devices Agency (AEMPS)** to review treatment reports.

Photo credit: Aurora Mateos

3.2 Patients

One of MIa's most impactful contributions is **expanding access to treatment**, something no other organization does for children with Menkes disease. The remarkable progress of Marco, who now speaks two languages, walks, and even runs, prompted MIa to extend treatment to other children worldwide.

To begin treatment with elesclomol-copper, MIa follows a strict process:

1. A request must come from the child's medical team.
2. The patient must be treated at their local hospital.
3. The family must provide consent to work with MIa.
4. All parties must agree to collaborate for the child's benefit.
5. National drug authorities must approve the treatment.

Photo credit: Aurora Mateos

Patient Stories

Patient 1: A Life Transformed

Patient 1, diagnosed with Menkes shortly after birth, began treatment with elesclomol-copper in early 2022. Now 3 years old, he has shown significant improvement in neurodevelopment. He can walk steadily, run, and even climb stairs—milestones previously unheard of for a child with Menkes disease. His language skills are also age-appropriate, and he has started reading and writing. Though he faces other health challenges, such as a pre-existing lung condition, his quality of life has vastly improved thanks to this treatment.

Patient 2: Making Strides

Patient 2, diagnosed prenatally due to family history, began treatment in 2023. After just eight months, this one-year-old has seen dramatic improvements, particularly in motor skills and development. While he still faces some challenges with gross motor function, he can now walk with assistance and stand up independently.

Patient 3: Overcoming Seizures

Diagnosed later than others, Patient 3 has been receiving treatment for four months. Despite facing severe developmental delays and a condition called West Syndrome, he has made modest but significant gains in muscle control, engagement with his surroundings, and even babbling. Though progress has been slower, the improvements in his quality of life are clear, the patient is progresively overcoming seizures.

Patient 4: A Brighter Future

Patient 4, who started treatment in October 2023, had severe developmental delays and was non-verbal. After starting elesclomol-copper, he has gradually improved in muscle tone, movement, and communication. Though his journey is just beginning, early signs point to a positive outcome.

Looking Forward

While MIa's work is not a clinical trial, it has proven to be a lifeline for these children. Each child has shown remarkable improvements in quality of life, giving families hope for the future. MIa remains committed to expanding this initiative, ensuring that no child is left waiting for treatment.

For more details on Marco's journey and media coverage, follow the links below:

Links to Media coverage of Marco:

- Marco, la esperanza de niños con Menkes (rtve.es)
- Un tratamiento experimental para Marco, el niño malagueño afectado por el síndrome de Menkes (canalsur.es)
- La evolución de Marco abre el camino a otros niños con la enfermedad de Menkes (EFE)
- La proeza de Marco, el niño sin cobre | Diario SurMarco, el niño con la enfermedad de Menkes que sobrevive gracias a un tratamiento pionero en España (ABC)
- The fight for Marco, the boy with no copper (Sur in English)
- El pequeño Marco consigue caminar gracias a un tratamiento pionero en España (Antena 3)
- Enfermedad rara de Menkes: Marco, el único niño del mundo con una terapia excepcional (EFE)
- La mejoría de Marco abre la puerta a otros niños con la enfermedad de Menkes (elDiario.es)

Funds raised: €50,000
Funds spent: €38,956.75

Including:

Hospital Sant Joan de Déu: € 13,182

SAS (Andalusian Public Health System): € 13,393

Other medical experts' bills: € 5,223

Core travelling: € 3,461

Families travel support: € 2,479 (2023), pending *bills from 2022: € 1,216*

04

Copper(less) Committee Activities

04 Copper(less) Committee Activities

The Copper(less) Committee is an international team of experts from various fields, dedicated to supporting patients with Menkes disease who are receiving elesclomol-copper (ES-Cu) treatments. This multidisciplinary group meets monthly to offer specialized advice and guide critical treatment decisions.

During these meetings, the committee reviews each patient's progress, adjusts treatment dosages as needed, and assesses whether to continue or modify the treatment plan. They also evaluate new patients for the therapy and continuously update scientific insights related to copper metabolism, which is crucial for improving patient outcomes.

The Committee's work ensures that every decision made for Menkes patients is grounded in the latest research and clinical evidence. By offering expert guidance, they help optimize treatment for children battling this rare disease.

Funds spent: N/A (All experts work pro bono)

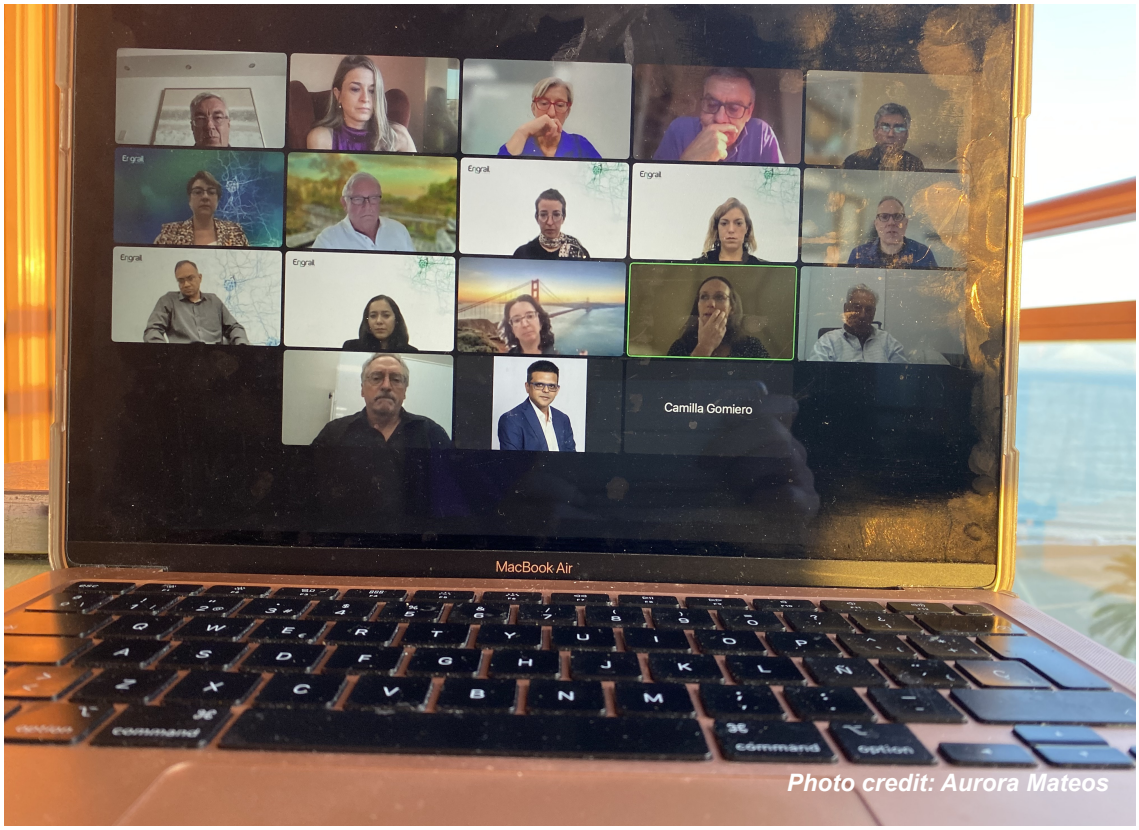

Photo credit: Aurora Mateos

05

Mla Networking

05

MIa Networking

5.1 EURORDIS Membership (September 2022 – present)

MIa is proud to be a full member of **EURORDIS-Rare Diseases Europe**, a non-profit alliance of over 1,000 organizations working to improve the lives of more than 300 million people worldwide living with rare diseases. As a member, MIa can now vote at the EURORDIS General Assembly and participate in shaping the future of rare disease advocacy.

In May 2023, MIa's Medical Director, **Denis Broun**, attended the EURORDIS Membership Meeting in Stockholm. This event brought together patient organizations, clinicians, and members of the pharmaceutical industry, creating valuable opportunities for MIa to network and share experiences with others dedicated to rare diseases. While some key issues, like diagnosis and treatment, were not fully addressed, MIa continues to engage and advocate for progress on these crucial topics.

https://www.eurordis.org

https://www.eurordis.org/es/eurordis-membership-meeting-emm-2023/

Funds raised: N/A
Funds spent: €200 per year for membership (if MIa's income is between €100,000 - €249,000 annually)

5.2 MIa and Menkes National Associations

In November 2023, MIa's Director attended the annual charity event hosted by **Angelli per la Vita**, the Menkes association in Italy. The event helped strengthen the bond between MIa and other national organizations dedicated to Menkes disease. The charity event raised €10,000, all of which was donated to support MIa's mission.

Funds raised: €10,000
Funds spent: €174

Photo credit: Angelli per la vita

Photo credit: Diego Facchinetti

5.3 MIa and AEMPS (Spanish Medicines Agency)

In collaboration with **CIPLA Therapeutics**, MIa is working on a project to distribute **copper-histidine (Cu-His)** free of charge to hospitals in developing countries. Cu-His is the only palliative treatment available for Menkes disease, a rare and life-threatening genetic disorder. Invented in the 1970s and used since then, it remains difficult to access for many children with Menkes, particularly in low and middle income countries.

Several Menkes national associations and doctors, especially from Brazil and Mexico, have asked MIa for help in securing Cu-His, as children are dying without access to this essential medication. In September 2023, MIa met with the **Spanish Medicines Agency (AEMPS)** to seek guidance on the humanitarian use of Cu-His. AEMPS provided valuable advice and a list of potential pharmaceutical partners, but challenges remain in making this initiative sustainable. MIa continues to work tirelessly to bring this life-saving treatment to those in need.

Funds spent: €283

06

Es-Cu Formulation Project: Development of Elesclomol-Copper Formulation with Cyclodextrins

06

Es-Cu Formulation Project: Development of Elesclomol-Copper Formulation with Cyclodextrins

This project focused on creating an innovative formulation that combines elesclomol-copper with cyclodextrins, which serve as carriers. Conducted in Santiago de Compostela, Spain by pharmacist Raul Varela, a member of the Copper(less) Committee, this initiative involved the collaboration of Professor Francisco Otero and his lab team.

A comprehensive series of preclinical studies were performed to assess various parameters, including solubility, quantitative analysis, stability, mechanical properties, and safety in both in vitro and organotypic models. Elesclomol, an experimental drug, holds promise in treating Menkes disease, a genetic disorder that impairs copper transport and leads to severe copper deficiency, resulting in significant neurological and developmental challenges. By enhancing copper availability in the body, the elesclomol-copper formulation aims to improve neurological outcomes for those affected. However, effective delivery has been hampered by the low solubility of this coordination complex in water. Cyclodextrins, known for their ability to enhance the solubility and stability of hydrophobic drugs, were incorporated into this formulation to address these challenges.

6.1 Methodology

The formulation process involved mixing elesclomol-copper with a carefully established mixture of cyclodextrins in an appropriate solvent. A sophisticated manufacturing method was employed, which combined alternating sonication and agitation with thermal adjustments to ensure optimal formulation.

6.2 Results and Conclusions

FTIR and XRD analyses confirmed the successful formation of the complex. The new formulation demonstrated a significant enhancement in solubility, achieving a five-fold increase compared to previous formulations and a 25-

fold increase compared to free elesclomol-copper in aqueous solutions.

Stability assessments indicated no significant degradation over six months, confirming good stability. The formulation also displayed favorable mechanical, thermal, physical, and chemical properties, maintaining a neutral pH and osmolality within acceptable ranges for subcutaneous administration. Importantly, organotypic models exhibited high cell viability, indicating low cytotoxicity.

The development of the elesclomol-copper formulation utilizing cyclodextrins has shown promising results in enhancing solubility and stability while preserving favorable physicochemical characteristics. These findings support the potential for further clinical development aimed at improving therapeutic efficacy for treating Menkes disease.

Total Amount Paid: €1,675

Note: Ruben Varela (PhD) contributed his expertise pro bono, while the Otero lab provided all assessments and necessary equipment.

06

Photo credit: Otero Espinar's lab

07

Mla website

07

MIa Website

[Launched: October 2021 – Ongoing]

In 2021, MIa launched its official website, which has since become a vital hub for sharing information and connecting families, researchers, and supporters worldwide. The website is regularly updated with the latest news, resources, and updates on MIa's progress in fighting Menkes disease.

The design and maintenance of the site have been generously provided by the team at **Texas A&M University** as an in-kind donation, led by **Jim Sacchettini**, Head of the Laboratory. **Sid Rath** and **Saswati Panda** manage the technical aspects, while **Aurora Mateos**, a MIa board member, ensures that the content is kept current and informative.

The website serves as a key resource for those seeking to understand Menkes disease and learn about the groundbreaking work MIa is doing to support children and families affected by the condition. It also facilitates donations, volunteer opportunities, and collaboration with researchers and medical professionals around the world.

Website: Menkes International

Amount paid: €311 (cost of web hosting via Bluehost)

Photo credit: Aurora Mateos

08

Communications and Continued Education

08

Communications and Continued Education

Members of MIa's **Copper(less) Committee** have actively shared their findings on the groundbreaking treatments for Menkes disease at several prestigious conferences. These include the **First European Workshop on Interdisciplinary Perspectives for Rare Genetic Neurodevelopmental Disorders** (Netherlands, April 2023) and the **European Night of Researchers** (Málaga, September 2023). Through talks, presentations, and posters, they have brought global attention to the progress being made with MIa's exceptional treatments.

In addition, MIa is preparing to publish a **scientific article** on the first two patients treated with elesclomol-copper (ES-Cu). These patients have had the longest follow-up, providing the most comprehensive data on the treatment's effectiveness. By sharing this knowledge with the scientific community, MIa hopes to contribute to further advances in Menkes disease treatment and move closer to the goal of initiating a clinical trial for the ES-Cu molecule.

Links: EU Reference Network ITHACA

Amount paid: Covered by external funding, not MIa.

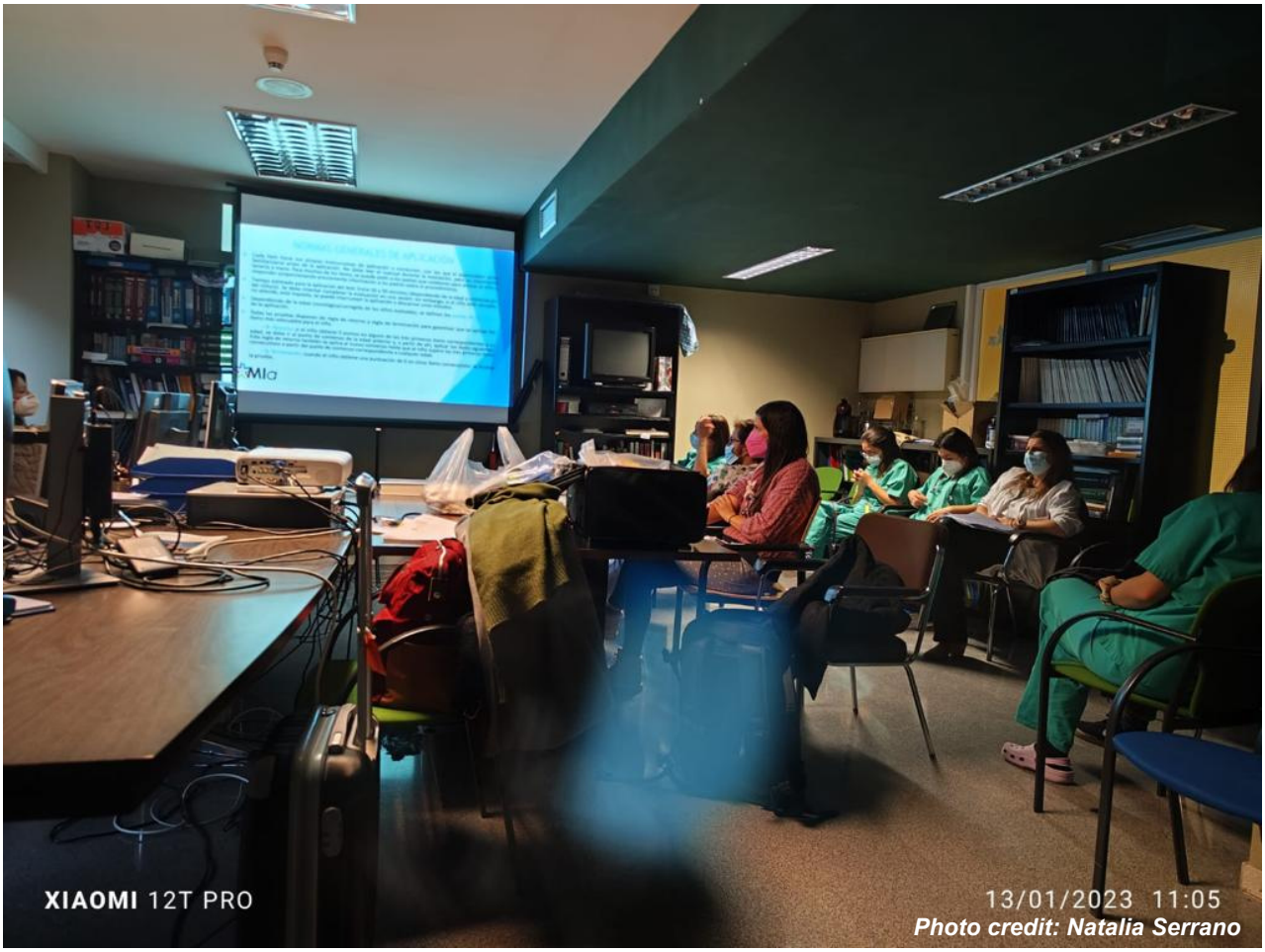

Photo credit: Natalia Serrano

09

Mla Charity Gala, February 2023

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On February 11, 2023, MIa held its first-ever **charity fundraiser** in partnership with the Friends of the Russian Museum of Malaga Foundation. The event took place at the Russian Museum in Malaga, gathering a group of 100 supporters who purchased charity tickets for €100 each. Additional donations were also made during the event, raising both awareness and crucial funds to support MIa's mission.

The event brought together **public figures** and advocates for MIa's cause. **Dr. Yusuf Hamied**, a philanthropist, explained the importance of copper in treating Menkes disease. **Aurora Mateos** and **Denis Broun** represented MIa's leadership, while **Dr. Francesc Palau** spoke about Marco's medical journey. **Vikram Sudarsan**, from Engrail, also shared insights into a promising new drug being developed for Menkes disease.

The event's success was enhanced by the contributions of renowned local chefs, including **Diego Gallegos**, **Juan Morcillo**, **Antonio Calderón**, and **Pablo Molina**. Their exceptional culinary skills were complemented by the support of local businesses such as **Calma Eladio Frutas y Verduras**, **Picking Málaga**, and **Bodega La Melonera**, among others.

The gala garnered significant public and media attention, with several prominent outlets covering MIa's efforts. Notably, Marco's inspiring story and MIa's work were featured on the front page of **Diario Sur**, Malaga's leading newspaper.

Links:

- Diario Sur: MIa Charity Lunch
- Russian Museum Charity Event
- 101TV Coverage
- YouTube Event Coverage

Total funds raised: €19,180
Expenses: €8,766 (including €6,416.29 for catering, €2,050 for planners, and €300 for additional ingredients)
Net income for MIa: €10,414

Mla Charity Gala, February 2023

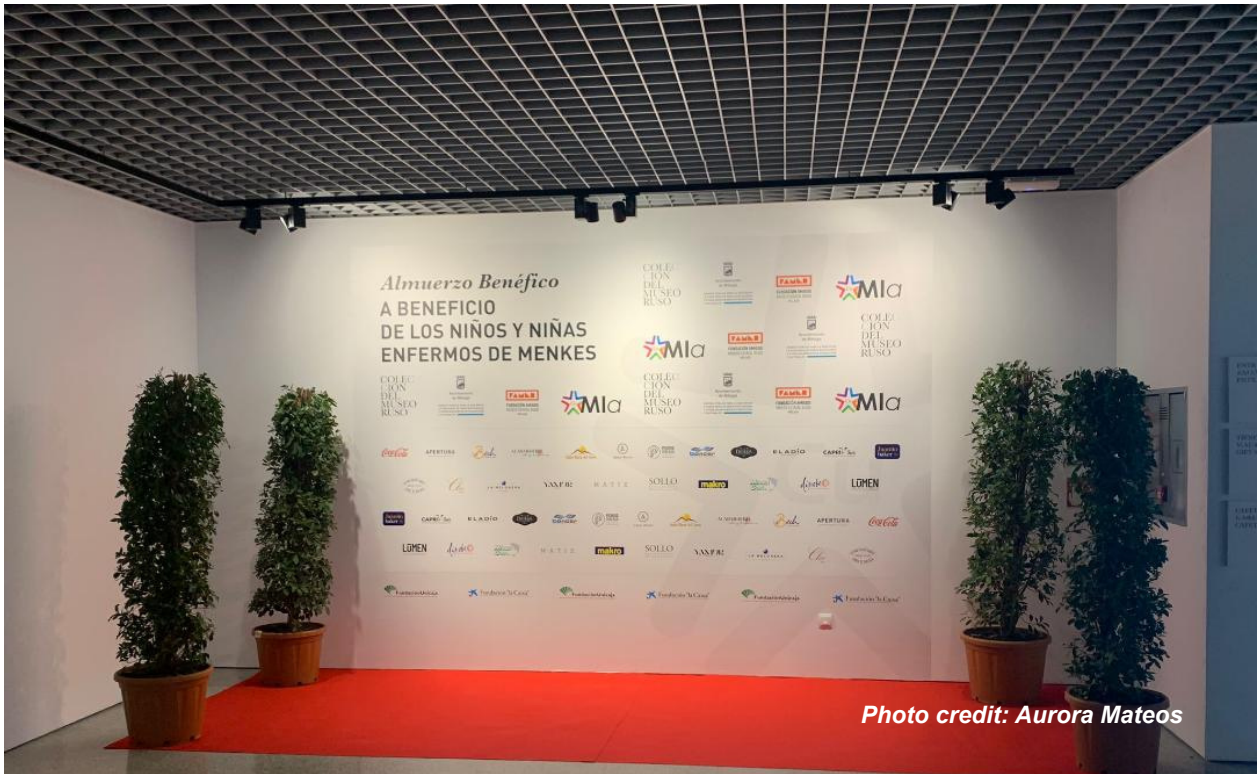

Photo credit: Aurora Mateos

10

Menkes International Association Boards

10 Menkes International Association Boards

Executive Board

The **Executive Board** of MIa is composed of dedicated individuals with personal connections to Menkes disease. They guide the organization's day to day operations and ensure that MIa continues to serve the families and children affected by this rare condition.

- Aurora Mateos (Executive Secretary) – Menkes relative
- Tote Portillo (Secretary) – Menkes relative
- Vicente Mateos (Treasurer) – Menkes relative
- Denis Broun (Medical Director)

The **Advisory Board** consists of experts from various fields who provide strategic advice and direction. While some members have personal connections to Menkes, others bring external expertise to strengthen MIa's work.

- Denis Broun (Pharmaceutical Adviser) – Non-Menkes relative
- Leonardo Cervera Navas (Data-Policy Adviser) – Non-Menkes relative
- Andrey Galaev (Adviser) – Menkes relative
- Jorge A. López (IT Manager) – Menkes relative
- Juan Mateos (Adviser) – Menkes relative
- Inma Mateos (Communications)-Menkes relative
- Irene Melo (Marketing) – Menkes relative
- Jean-Francois Pulvenis – Non-Menkes relative
- Vinay Saldanha (Policy Adviser) – Menkes relative

Copper(less) Committee

The **Copper(less) Committee** is an international panel of esteemed scientists and medical professionals who specialize in copper metabolism and Menkes disease. This multidisciplinary team advises MIa on the latest research and treatment developments, contributing significantly to the progress made in treating Menkes patients.

- Prof. Francesc Palau Martínez – Director, Copper(less) Committee; Director, Genetics and Molecular Medicine, Institut de Recerca Sant Joan de Déu, Barcelona, Spain

- Dr. Denis Broun – CEO, Givopax Pharmaceutical Company, Geneva, Switzerland

- Dr. Mercé Capdevila – Professor, Dept. of Chemistry, Universitat Autònoma de Barcelona, Spain

- Prof. Vishal Gohil – Associate Professor, Biochemistry & Biophysics, Texas A&M University, USA

- Dr. Elena Godoy – Specialist, Pediatric Complex Care and Palliative Care Unit, Regional University Hospital, Málaga, Spain

- Prof. Nina Horn – Retired Pharmacist and Menkes Researcher, Kennedy Center-Copenhagen University Hospital

- Prof. Svetlana Lutsenko – Professor of Physiology, Johns Hopkins University School of Medicine, Baltimore, USA

- Aurora Mateos – Leader of MIa, mother of Marco (first patient treated with Elesclomol-Copper)

• Prof. Victor Mangas – Assistant Professor, University of Valencia, Spain, Specialist in Pharmacokinetics and Bioequivalence

• Prof. Michael Petris – Professor of Biochemistry, University of Missouri-School of Medicine, Columbia, USA, Menkes Researcher

• Prof. James Sacchettini – Rodger J. Wolfe-Welch Foundation Chair of Science, Biochemistry & Biophysics, Texas A&M University, USA

• Prof. Joseph Standing – Professor of Pharmacometrics, UCL Institute of Child Health, London; Research Pharmacist, Great Ormond Street Hospital, London

• Dr. Prachi Trivedi – Associate Research Scientist, Gohil Lab, Texas A&M University, USA

Photo credit: Aurora Mateos