ISMRD ANNUAL REPORT FOR 2022

OUR MISSION
ISMRD is the leading advocate for families worldwide affected by a Glycoprotein Storage Disease. Through partnerships built with medicine, science and industry, we seek to detect and cure these diseases, and to provide a global network of support and information.

OUR VISION
We seek a future in which children with Glycoprotein Storage Diseases can be detected early, be treated effectively, and go on to live long, healthy and productive lives.

BOARD OF DIRECTORS (All non-salaried)
Carolyn Paisley-Dew President Australia
Mark Stark Treasurer USA
Shirley Jamil Secretary UK
Sarah Forsman Board Member USA
Darko Jamnik Board Member Slovenia
Patricia Gribel Board Member USA
Laurel Gregier Board Member USA
Lama Khalil Board Member Jordan
Tareq Qashou Board Member Jordan
Hussein Peeran Board Member USA

Our thanks go out to our hard-working Board Members, whose eclectic skills, experience and outlooks combine to keep ISMRD vibrant, fresh and forward-looking.

ISMRD Professional Advisory Board (All non-salaried)
Prof Richard Steet: Scientific Chair USA Sara Cathey USA
Steve Walkley USA Dag Malm Norway
Alessandra d’Azzo USA Charles Vite USA
Marc Patterson USA Amelia Morrone Italy
Thomas Braulke Germany Vish Koppaka USA
Enrico Moro Italy Jenny Klein USA

We would like to thank our Professional Advisory Board members for their invaluable input into scientific and medical matters.
OUR ACTIVITIES FOR 2022

Rare Disease Day 2022

ISMRD had its busiest Rare Disease Day ever in 2022. Thank you to all the family and ISMRD Board members who contributed and worked so hard to make this day such a success for ISMRD. Our activities included:

Family Stories on the ISMRD Website
We asked families to provide a story and photos about their family member for our website. We had a wonderful response with nine articles covering seven disorders and four countries.

Photos on Facebook
We also asked families to post photos on Facebook of daily life living with a rare disease. We were bombarded with photos:

- 67 photos
- 9 conditions (Galactosialidosis, Alpha-Mannosidosis, Beta-Mannosidosis, Fucosidosis, Sialidosis, Aspartylglucosaminuria (AGU), Mucolipidosis II, Mucolipidosis II/III and Mucolipidosis III)
- 13 countries (Australia, Brazil, Finland, Lithuania, Mexico, New Zealand, Norway, Saudi Arabia, Slovenia, Spain, Russia, the UK and the US).

Influencers
Various Board members contacted influencers they knew and ISMRD and our diseases were highlighted by them on Rare Disease Day.

360moms
Board Member Lama Khalil wrote a story about her son Rayan, who has Fucosidosis. It was published in 360moms, an influential Arabic magazine with a wide readership. We are working to put the story on our website.

Message of support to families from the Board
An email was sent out to families acknowledging how hard they work and expressing our admiration for them.

We entered NORD’s Show Your Stripes competition, with a design created by one of our members. Unfortunately, we didn’t win a prize.
EURORDIS Rare Disease Photo and Story Competition
ISMRD encouraged families to enter the EURORDIS Rare Disease Photo and Story Competition.

We also promoted the free NORD Rare Disease Day Celebration to our families.

Thank you again to all our families and Board members who contributed to making Rare Disease Day 2022 a great success for ISMRD.

Alpha-Mannosidosis and AllStripes
ISMRD assisted AllStripes to increase the number of patients in its Alpha-Mannosidosis Research Program. This program is aimed at helping researchers advance the treatment options for Alpha-Mannosidosis. For this research program, AllStripes was seeking a total of 25 participants. With the help of ISMRD, the AllStripes Research Program went from 14 participants to 19.

Chiesi Alpha-Mannosidosis FDA approval
ISMRD Board members, Mark Stark and Jenny Klein, provided in-person patient testimony to the FDA, to assist Chiesi in its bid to have Alpha-Mannosidosis enzyme replacement therapy, Lamzede, introduced into the USA.

Fucosidosis Survey for JCR Pharmaceuticals
ISMRD circulated a survey to Fucosidosis families on behalf of JCR Pharmaceuticals. The purpose of the survey was to get detailed information on the patient experience of Fucosidosis. The goal of this information was to provide JCR Pharmaceuticals with clear information about the physical and intellectual symptoms of Fucosidos in order to inform a possible human clinical trial of enzyme replacement therapy for Fucosidosis.

Survey responses went to Rare Disease Research Partners, who coordinated the final distribution logistics of the survey process for JCR Pharmaceuticals. The survey was available in English, Spanish, Russian and Greek.

The results of the survey resulted in a poster, “International online survey of fucosidosis: key symptoms and the family experience”, being made available at WorldSymposium 2023 in Florida. ISMRD President, Carolyn Paisley-Dew, was thrilled to be named a co-author on the poster. See the poster at Attachment A.
**PGT-M testing for Fucosidosis families in the UK**

ISMRD disseminated to Fucosidosis families a survey about the lived experience of Fucosidosis for the purpose of licensing the condition for use in preimplantation genetic testing for monogenic disorders (PGT-M) in the UK. All of the family responses helped Genetic Alliance UK compile a statement that accurately reflects the patient and family experience of those living with the condition. This statement informed the Committee’s positive decision. The Human Fertilisation and Embryology Authority (HFEA) has now authorised PGT-M to be used for this condition. Fucosidosis families in the UK now have the opportunity to have more children, without the fear of them having Fucosidosis.

We’d like to say thank you very much to all those Fucosidosis ISMRD members who took the time to complete the survey.

**ISMRD-Sponsored Feline Mucolipidosis Research**

**Gene Therapy Research in Mucolipidosis: To Evaluate AAV Gene Therapy in the Feline Model of ML II**

This research is ongoing. The cat colony has been moved from the University of Pennsylvania to the University of California, Davis. The feline GNPTAB gene has been cloned. The design of the AAV vector encoding the feline GNPTAB gene is complete. The vector has been tested in cell culture, and in wildtype mice. Three different doses of the vector have been evaluated in cats. Visual, cardiac, and skeletal systems were not corrected by the low or mid dose. The high dose appears to have resulted in partial correction of visual and skeletal systems. Function and structure of the heart were normal on echo. Histology is ongoing in the highest dose cohort.

**GNPTAB-related Disorders**

This research is ongoing. Cats display cardiovascular phenotypes that recapitulate human MLII with variable presence of congenital cardiac defects. A poster “Cardiovascular Manifestations of Mucolipidosis II: A Translational Feline Model” was received from Primary Investigator Allison Bradbury in December 2022. This is important work for helping to springboard future therapeutic discoveries.

See the poster at Attachment B.
**Fundraising and Donations**

**CouponBirds**

With the demise of AmazonSmile, a useful and regular fundraiser for ISMRD, CouponBirds is now being promoted to our members. Donations are currently small, but steady, and we hope that they will increase as more of our members begin to utilise CouponBirds. Join CouponBirds [here](#).

**Donations**

Donations totalling $10,536 were made to the ISMRD during 2022. These were from family members and friends, their workplaces, churches, fundraisers, Facebook and AmazonSmile. There were family members who asked their friends and family to donate to ISMRD in place of giving them a traditional birthday present, and those who raised funds in memory of a loved one. We also have Board members and ex-Board members who pay for various ongoing expenses for ISMRD.

We would like to thank each and every one of these individuals and organisations for their kind and generous donations.

**Online Presence**

ISMRD continues to increase and improve its online presence.

More languages were added to Google Translate on our website, in response to need. Additional donation sources e.g. CouponBirds and PayPal are now featured on the website, as are useful links like AngelFlights. We proudly display the NORD Platinum membership seal, and Candid’s Silver Seal of Transparency. We have introduced pop-ups for new or important items. These have included JCR Pharmaceutical’s development of an ERT for treating Fucosidosis; JCR’s securing of the resources required, through Medipal Holdings, to advance its Fucosidosis program; Rare Disease Day; and Mother’s Day. A website upgrade is anticipated for 2023.

ISMRD’s Facebook pages continue to flourish and provide important support and information for its members, and the wider community. They are also an important source of new memberships. The main page, the ISMRD Group page, is open to families only, to provide privacy as they discuss personal issues. All other pages are open to the public.
ISMRD receives an increasing number of requests from researchers, pharmaceutical companies and medical experts through its email address info@ismrd.org, as the go-to organization for information about the glycoproteinoses. Additionally, ISMRD is frequently contacted by new families through this channel.

**Conferences Attended**

Carolyn Paisley-Dew attended the Rare Voices Australia National Rare Disease Summit that was held in Sydney, Australia, 10-12 November 2022. The Summit had a focus on Rare Disease Advocacy and Shaping the Next Decade, all helpful in direction-finding for the future for ISMRD. Carolyn was also able to make some very useful connections.

**Financial Statement**

Income Statement for the 2022 calendar year
Balance sheet for the end of the year (Dec. 31, 2022)

**ISMRD CONTACT DETAILS**

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Turnersville, NJ 08012
USA

**E-mail:** info@ismrd.org
**Website:** www.ismrd.org
Attachment A

International online survey of fucosidosis: key symptoms and the family experience

Kohtarou Hamachi, Julie B Eisengart, Carolyn Pasley-Dew, Samantha Wiseman, Sarne Seo, Kazunori Tanizawa, Takayuki Egawa, Matthias Schmidt, Yuji Sato
UCRC Pharmaceutical Co., Ltd, Aichi, Japan; Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA; 169RE, Australia; 1RARE Disease Research Partners, Amersham, UK

INTRODUCTION

Fucosidosis is an allelic, enzyme deficiency disorder that affects approximately 150-200 people worldwide, and is the second most common lysosomal storage disease. Fucosidosis is a rare genetic disorder which affects the body's ability to break down a specific type of sugar called fucose. This leads to the accumulation of fucose in various tissues, particularly in the brain, liver, and kidneys. The symptoms of fucosidosis can vary widely, depending on the age of onset and the specific genetic variant responsible for the condition. Early diagnosis and treatment are crucial for managing the symptoms and improving quality of life for affected individuals.

OBJECTIVE

To understand the impact of fucosidosis on patients and their families and to evaluate the effectiveness of current treatment strategies in improving the quality of life for patients with fucosidosis.

METHODS

An international online survey was conducted in English, Chinese, Japanese, Korean, and Spanish. Participants were recruited through patient advocacy groups, healthcare providers, and social media platforms. The survey was anonymous and voluntary. The survey included questions about the patient's demographic information, the impact of the disease on daily life, and the effectiveness of various treatments. The results were analyzed using descriptive statistics.

RESULTS

Out of 353 respondents, 316 were adults and 37 were children. The mean age of the respondents was 39.5 years, with a range of 1 month to 86 years. The majority of respondents were from the United States (43%), followed by Europe (37%) and Asia (16%). The majority of respondents had a college degree or higher (67%). The most common symptom reported was fatigue, followed by joint pain and muscle weakness. The most common treatment reported was enzyme replacement therapy (58%), followed by supportive care (42%).

CONCLUSIONS

- The most common symptom reported was fatigue, followed by joint pain and muscle weakness.
- The majority of respondents had a college degree or higher.
- The most common treatment reported was enzyme replacement therapy, followed by supportive care.

Presented at the 18th Annual WORLDSymposium® February 23-26, 2023, Orlando, FL, USA, and virtual
Cardiovascular Manifestations of Mucolipidosis II: A Translational Feline Model

Alex Serna1, Victor Rivas1, Joanna Kaplan1, Carina Gonzales2, Amanda Crofton3, Jelena Wouters3, Alison Bradbury3, Heather Flanagan-Steele3, Joshua Stern1
1School of Veterinary Medicine, University of California, Davis; 2Abigail Wexner Research Institute Nationwide Children’s Hospital; 3Greenwood Genetic Center

Introduction
- MLI is an autosomal recessive lysosomal storage disorder caused by a GNPTAB mutation, affecting infant to juvenile cats.
- The mutation results in a Galβ1,4-GalNAcα-phosphatidylinositol biphosphatase (PomGnT) deficiency, preventing normal trafficking of and hydrolysis into lysosomes.
- Clinical presentation includes:
  - Stunted growth
  - Neurologic deficits
  - Heart valvular thickening
- High mortality rate (37±4 years), typically characterized cardiovascular disease leading to laminated congenital heart failure

A novel, naturally occurring feline MLI model has been generated.
- Autosomal recessive MLI
- Pathogenic GNPTAB nonsense mutation
- Enmun et al. 2019
- Cats display cardiovascular phenotypes that recapitulate human MLI with variable presence of congenital cardiac defects
- Studies implicating the genotype-phenotype relationship of feline MLI provide continued advancements in targeted novel drug therapies for humans.
- Study aims include expanding the MLI cat colony and further characterizing the disease in cats for human translational use.

Hypothesis
- Additional cardiovascular phenotypes observed in MLI-affected cats are explored to reveal pathogenic mechanisms with implications for the clinical and genetic variables, leading to new advancements in understanding heart failure. These findings will impact those observed in children with MLI and support use of the feline MLI colony in studies aiming to alter cardiovascular outcomes.

Methods
- Characteristics of 1D, 2D, Color & Spectral Doppler echocardiographic Parameters
- Gross and Histopathologic Characterization of MLI-Affected Kittens
- Methods and GenoMouse Model
- Whole Genome Sequencing

Results
- Figure 1: Pathogenetic Events of GNPTAB Mutations on Lysosomes
- Figure 2: ML mutation Expression & Phenotypic Characterization of ML-Affected Kittens
- (A) Bacterial or bacterial-like cells
- (B) Nuclei repressing pyrophosphatase of beta-sitosterol, triacylglycerol, and cholesterol
- (C) AEPA mutations result in bacterial-like cells
- (D) Nuclei repressing pyrophosphatase of bacterial-like cells
- (E) AEPA mutations result in bacterial-like cells
- (F) Nuclei repressing pyrophosphatase of bacterial-like cells

Conclusion
- The MLI cat colony has a hereditary gene's breed that will be established to produce additional affected kittens.
- A whole-genome association study to identify disease-modifying variants is in progress to further characterize the genetics of MLI cardiovascular pathogenesis.
- Expansion and maintenance of the MLI cat colony is essential for continued WGS efforts and for further characterization of cats as an important translational model to propose future therapeutic discoveries.

Acknowledgements

References
# Income Statement (Profit and Loss)

**International Society for Mannosidosis & Related Diseases**  
**For the year ended December 31, 2022**

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<th>Income</th>
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<tr>
<td>Donation - Amazon Smile</td>
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<td>Donation - Recurring payment</td>
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<td>Donation - Unrestricted</td>
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<td>Facebook Donations</td>
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<td>M. Research - Donation</td>
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| Gross Profit                | **10,534.34**|

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<td>Consulting &amp; Accounting</td>
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<td>Contractors &amp; Professional fees</td>
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<td><strong>Total Operating Expenses</strong></td>
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| Operating Income            | 1,019.91|
| Net Income                  | 1,019.91|
# Balance Sheet

**International Society for Mannosidosis & Related Diseases**  
**As of December 31, 2022**

<table>
<thead>
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<td><strong>Current Assets</strong></td>
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<td>Cash and Cash Equivalents</td>
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</tr>
<tr>
<td>Total Assets</td>
<td>96,702.95</td>
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</table>

| Liabilities and Equity | |
| **Equity** | |
| Current Year Earnings | 1,019.91 |
| Retained Earnings | 89,683.04 |
| Total Equity | 90,702.95 |
| Total Liabilities and Equity | 96,702.95 |