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 it's 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 ll, Mucolipidosis ll/lll and Mucolipidosis lll)
- 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 MLll with variable presence of congenital cardiac defects. A poster "Cardiovascular Manifestations of Mucolipidosis ll: 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	Attachment C
Balance sheet for the end of the year (Dec. 31, 2022)	Attachment D

ISMRD CONTACT DETAILS

Address:
3150 Almaden Expressway Ste 103
San Jose, CA 95118
USA

PO Box 683
Turnersville, NJ 08012
USA

E-mail: info@ismrd.org
Website: www.ismrd.org

Attachment A

P154

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

Kohtaro Hamauchi[1], Julie B Eisengart[2], Carolyn Paisley-Dew[3], Samantha Wiseman[4], Sairei So[1], Kazunori Tanizawa[1], Takayo Egawa[1], Mathias Schmidt[1], Yuji Sato[1]

[1]JCR Pharmaceuticals Co., Ltd, Ashiya, Hyogo, Japan; [2]Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA; [3]ISMRD, Australia; [4]Rare Disease Research Partners, Amersham, UK

INTRODUCTION

- Fucosidosis is an ultra-rare lysosomal storage disorder, with approximately 120 cases reported worldwide, caused by mutations in the *FUCA1* gene.[1–4]
- In patients with fucosidosis, fucose-containing compounds accumulate in somatic organs and the central nervous system, resulting in severe, progressive neurodegeneration.[1,3,4]
- There are no available treatments for fucosidosis except hematopoietic stem cell transplantation (HSCT).[1–4]

OBJECTIVE

- To understand the impact of fucosidosis on patients and their families' treatment expectations with the assessment of:
  - the most challenging symptoms
  - the impact of the disease on quality of life
  - preferred treatment outcomes.

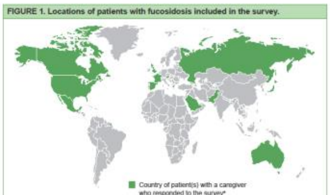
METHODS

- An international online survey was conducted in English, Greek, Japanese, Russian, and Spanish.
- Respondents were aged at least 18 years, able to provide informed consent, and were, or had been, the main caregiver of a patient with fucosidosis.
- The survey items comprised a mixture of formats including multiple choice, free text, and ranking. In the challenging symptoms section, respondents were asked to choose four symptoms from a list of 16 and rank the symptoms in order of how challenging they were to the patient, with rank 1 being the most challenging symptom.
- The survey was distributed internationally by the International Advocate for Glycoprotein Storage Diseases and the Society for Mucopolysaccharide Diseases, UK, and data were collected via Qualtrics XM, a secure web-based platform.
- Qualitative and quantitative analyses of the survey data were undertaken.
  - Frequencies were calculated for categorical variables; means, standard deviations, medians, and ranges were calculated for continuous variables.
  - Free-text responses were analyzed using an inductive thematic approach.
- Patients were stratified by sex and HSCT treatment status.

RESULTS

- In total, 28 respondents completed the survey from 13 different countries (**Figure 1**).
- Of the 28 patients included, 14 were female, and four had undergone HSCT (**Table 1**).
- The median age of the 22 patients who were alive at the time of the survey was 17.1 years (**Table 1**).
- The median age of death for the six deceased patients was 8.4 years (**Table 1**).

FIGURE 1. Locations of patients with fucosidosis included in the survey.



*UK (n=9), USA (n=6), Australia (n=1), Austria (n=1), Canada (n=1), France (n=1), Greece (n=1), Japan (n=1), Mexico (n=1), Pakistan (n=1), Russia (n=1), Saudi Arabia (n=1), Spain (n=1).

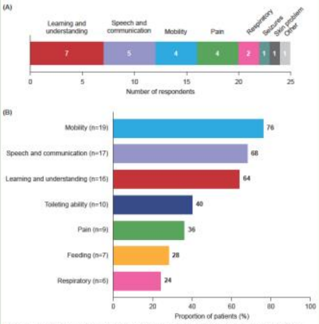
TABLE 1. Patient demographics and clinical characteristics.

	Sex		Treatment		Overall population (N=28)
	Female (n=14)	Male (n=14)	HSCT (n=4)	Non-HSCT (n=24)	
Patients, n (%)					
Alive	14 (100)	8 (57)	4 (100)	18 (75)	22 (79)
Deceased	0	6 (43)	0	6 (25)	6 (21)
Age at time of survey, years					
Mean (SD)	18.2 (12.6)	17.1 (10.1)	14.1 (12.4)	18.6 (11.5)	17.8 (11.5)
Median (range)	17.1 (3.1–55.5)	16.8 (5.2–31.9)	10.8 (3.1–31.9)	17.3 (3.9–55.5)	17.1 (3.1–55.5)
Age at death, years					
Mean (SD)	–	9.8 (5.6)	–	9.8 (5.6)	9.8 (5.6)
Median (range)	–	8.4 (5.0–20.3)	–	8.4 (5.0–20.3)	8.4 (5.0–20.3)
Age at transplant, years[a]					
Mean (SD)	4.9 (2.6)	0.5 (–)	3.8 (3.1)	–	3.8 (3.1)
Median (range)	4.4 (2.7–7.8)	0.5 (–)	3.5 (0.5–7.8)	–	3.5 (0.5–7.8)
Time since transplant, years[a]					
Mean (SD)	3.3 (2.8)	31.4 (–)	10.3 (14.3)	–	10.3 (14.3)
Median (range)	3.4 (0.4–5.9)	31.4 (–)	4.7 (0.4–31.4)	–	4.7 (0.4–31.4)

HSCT, hematopoietic stem cell transplantation; SD, standard deviation.
[a]Patients who received HSCT: female (n=3); male (n=1).

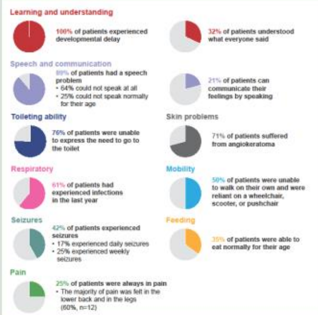
- The symptoms that were ranked as the most challenging by the highest proportion of respondents with fucosidosis were those that affect learning and understanding, followed by speech and communication (**Figure 2A**).
- Mobility was ranked as one of the four most challenging symptoms by the highest proportion of respondents (**Figure 2B**).
- Patients with fucosidosis had a wide range of clinical manifestations encompassing neurocognitive and somatic symptoms (**Figure 3**).
- Caregivers surveyed provided the following verbatim responses for their expectations of new treatments for fucosidosis.
  - "Improve the patient quality of life for as long as possible."
  - "Allow the child to have the same level of ability as healthy children the same age."
  - "Enable the child to communicate how they feel and their needs."
  - "Prevent the onset of dementia and organ failure."
  - "Improve mobility."
  - "No expectations that a new treatment will improve quality of life more than bone marrow transplant."

FIGURE 2. Symptoms rated as (A) the most challenging or (B) one of the four most challenging symptoms in patients with fucosidosis.*



*The list of symptoms that respondents were asked to rank comprised feeding, growth, hearing, heart disease, learning and understanding, mobility, other (please specify), pain, respiratory, seizures, skin problems, sleep, speech and communication, spleen and liver, toileting ability, and vision.

FIGURE 3. Proportion of patients with fucosidosis and challenging symptoms.



CONCLUSIONS

- This survey collected data on almost a quarter of known patients with fucosidosis worldwide.
- There is an unmet need for novel treatments in patients with fucosidosis, particularly treatments that improve learning and communication.
- Somatic symptoms are of significant concern for caregivers of patients with fucosidosis.
- Most families emphasized the need for the development of novel fucosidosis treatments.

REFERENCES

1. Kaur A et al. Cureus 2019;11:e6139.
2. NIH GARD Information: Fucosidosis. Available from: https://rarediseases.org/gard-rare-disease/fucosidosis/ (Accessed December 16, 2022).
3. Stepien KM et al. Genes (Basel) 2020;11:1383.
4. Willems PJ et al. *Am J Med Genet* 1991;38:111–31.

ACKNOWLEDGMENTS

The authors are immensely grateful to the participants of this survey, patient advocacy group, research organizations, and all those who assisted the studies, including International Advocate for Glycoprotein Storage Diseases (ISMRD), MPS Society UK, and Rare Disease Research Partners (RDRP). Editorial support was provided by PharmaGenesis Cardiff, Cardiff, and funded by JCR Pharmaceuticals Co., Ltd, Japan.

DISCLOSURES

KH, SS, KT, TE, and **YS** are employees/owners of JCR Pharmaceuticals Co., Ltd. **JBE** is a consultant/advisory board member for Denali, JCR Pharmaceuticals Co., Ltd, Orchard Therapeutics, Sanofi, and Takeda. CP-D has nothing to disclose. **SW** has received grant/research support from JCR Pharmaceuticals Co., Ltd. **MS** has stock ownership/stock options in and is an employee/owner of JCR Pharmaceuticals Co., Ltd and ArmaGen, Inc.

FUNDING

This study was sponsored by JCR Pharmaceuticals Co., Ltd, Japan.

This poster is intended for healthcare professionals only.

Presented at the 19th Annual WORLD*Symposium*™, February 22–26, 2023, Orlando, FL, USA, and virtual

Attachment B

UCDAVIS VETERINARY MEDICINE
Students Training in Advanced Research

Cardiovascular Manifestations of Mucolipidosis II: A Translational Feline Model

Alex Serna[1], Victor Rivas[1], Joanna Kaplan[1], Carina Gonzalez[1], Amanda Crofton[1], Jalena Wouters[1], Allison Bradbury[2], Heather Flanagan-Steet[3], Joshua Stern[1]
[1]School of Veterinary Medicine, University of California, Davis, [2]Abigail Wexner Research Institute Nationwide Children's Hospital, [3]Greenwood Genetic Center

Introduction

- MLII is an autosomal recessive lysosomal storage disorder caused by a *GNPTAB* mutation, affecting infant to juvenile children
- The mutation results in a GlcNAc-phosphotransferase defect, which prevents normal trafficking of acid hydrolases into lysosomes
- Clinical presentation includes:
  - Skeletal deformities
  - Neurologic lesions
  - Heart valve thickening
- High mortality rate (MST= ~5 years)
  - Poorly characterized cardiovascular disease leading to fulminant congestive heart failure
- A novel, naturally occurring feline MLII model has been identified
  - Autosomal recessive MOI
  - Pathogenic *GNPTAB* nonsense mutation
    - Exon 13 c.2644C>T; p.Gln882*
- Cats display cardiovascular phenotypes that recapitulate human MLII with variable presence of congenital cardiac defects
- Studies interrogating the genotype-phenotype relationship of feline MLII promise continued advancements in targeted novel drug therapies in humans
- Study aims include expanding the MLII cat colony and further characterizing the disease in cats for human translational use

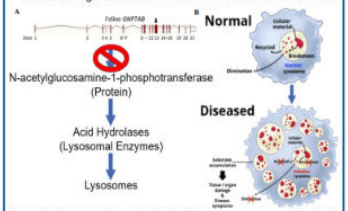
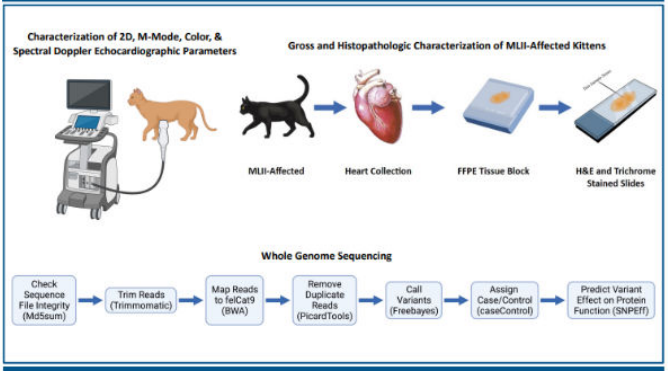


Figure 1. Pathogenic Effects of *GNPTAB* Mutation on Lysosomes. (**A**) ENSMBL illustration of *GNPTAB* gene body and downstream protein interactions. Black arrow represents positioning of previously identified *GNPTAB* MLII-associated mutation in cats. (**B**) Illustration of MLII molecular pathogenesis.

Hypothesis

Additional cardiovascular phenotypes observed in MLII-affected cats are explained by compound pathogenic mutations with implicated changes to the mitral and aortic valves, leading to volume overload and congestive heart failure. These findings will mimic those observed in children with MLII and support use of the feline MLII colony in studies aiming to alter cardiovascular outcomes.

Methods



Results

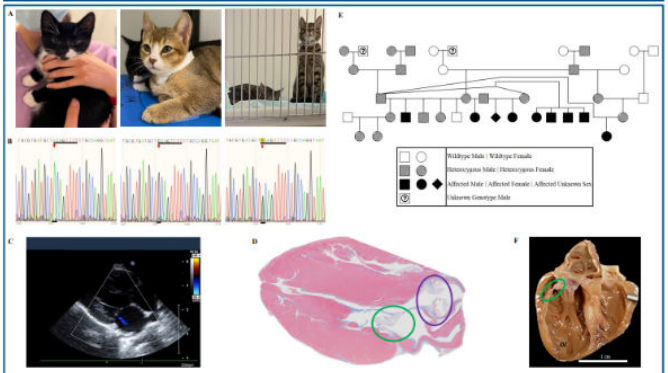


Figure 2. MLII Colony Expansion & Fine Clinical Characterization of MLII-Affected Kittens. (**A**) Addition of four new colony members; wildtype (left), heterozygous (middle & right-two). (**B**) Sanger sequencing genotyping of wildtype (left), heterozygous (middle), and homozygous (right) cats for *GNPTAB* mutation. (**C**) Right parasternal four-chamber long-axis view displaying mitral valve regurgitation (blue) in an unaffected MLII colony kitten. (**D**) Masson's Trichrome staining of a paraffin-embedded MLII-affected kitten heart depicting increased collagen deposition in the aortic (purple) and mitral valves (green). (**E**) Pedigree displaying expansion of the feline research colony. (**F**) 3-week-old formalin-fixed MLII-affected kitten heart displaying a dilated and thin-walled left ventricle (LV) with a thick mitral valve (green).

- Breeding efforts resulted in the addition of four kittens to the MLII colony
  - 3/4 kittens heterozygous for *GNPTAB* mutation
  - 1/4 kittens homozygous wildtype
- Echocardiograms for all but one unaffected cat were unremarkable
  - No volume overload
  - No valvular regurgitation
  - No chamber enlargement
- Trace mitral regurgitation was noted in one unaffected carrier
  - Disease progression is being monitored
- Increased collagen deposition in cardiac tissues was observed on Masson's Trichrome stains
  - Localization primarily to valvular structures
    - Aortic valve
    - Mitral valve
- 13 cat WGS files were successfully trimmed and mapped, and duplicate reads were removed
  - Average read depth of all covered positions: 25.3X
  - Average read depth of all positions, including zero-depth regions: 24.4X

Conclusion

- The MLII cat colony has 8 heterozygous cats; breeding pairs 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 MLII cardiovascular pathology
- Expansion and maintenance of the MLII cat colony is essential for continued WGS efforts and for further characterization of cats as an important translational model to propel future therapeutic discoveries

Acknowledgements

Stern Lab
National MPS Society
NIH National Institutes of Health
T35 OD010956
ISMRD
UCDAVIS VETERINARY MEDICINE

References

Attachment C

Income Statement (Profit and Loss)

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

	2022
Income	
Donation - Amazon Smile	148.90
Donation - Recurring payment	500.00
Donation- Unrestricted.	4,200.39
Facebook Donations	685.65
ML Research - Donation	5,000.00
Total Income	**10,534.94**
Gross Profit	**10,534.94**
Operating Expenses	
Conferences/Meetings	2,705.86
Consulting & Accounting	553.82
Contractors & Professional fees	229.35
Legal Expenses	25.00
ML Reserach Grant paid	6,001.00
Total Operating Expenses	**9,515.03**
Operating Income	**1,019.91**
Net Income	**1,019.91**

Attachment D

Balance Sheet

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

	DEC 31, 2022
Assets	
Current Assets	
Cash and Cash Equivalents	
California Account	90,702.95
Total Cash and Cash Equivalents	**90,702.95**
Total Current Assets	**90,702.95**
Total Assets	**90,702.95**
Liabilities and Equity	
Equity	
Current Year Earnings	1,019.91
Retained Earnings	89,683.04
Total Equity	**90,702.95**
Total Liabilities and Equity	**90,702.95**