

GALACTOSEMIA GAZETTE

ROUND SIX RESEARCH GRANT AWARD WINNERS

INSIDE THIS ISSUE:

<i>Gen. G and G Force Denver</i>	2
<i>Fundraising Updates</i>	3
<i>Galactosemia Graduate</i>	4
<i>Research Grant Process</i>	5
<i>Research Updates/Plans</i>	6-7
<i>GF Volunteer Form</i>	8
<i>Babble Boot Camp</i>	9
<i>Treasurer's Report</i>	10

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We welcome feedback on the Galactosemia Gazette. Please reach us anytime at newsletter@galactosemia.org.



By Dan Lambert & Seth Schwartz

The sixth round of research proposals resulted in 14 excellent submissions. This was a record as there had never been more than seven applications in previous rounds. The quality of proposals both in breadth and depth was very high and included several submissions on non-classic forms of Galactosemia. Five of the proposals came from researchers we did not know of previously, and four of the proposals were from researchers outside the U.S. The fourteen submissions totaled \$576,252, an average of \$41,161 per proposal.

The proposals were given composite scores based 50% on the grade of the GF research team and 50% on the grade of external peer reviewers. The research team is comprised of Kelley Foley, Christy Johnson, Dan Lam-



bert, Jonathan Mock, Owen Branson, Justin Burgett, and Beatrice Ortega all of whom bring strong technical background. There were some delays in the process, largely to address the challenge of finding enough peer reviewers. In the end two scientists reviewed and commented on each submission.

We are pleased to announce that four proposals were approved for funding by the

board. The total grant for this round is \$156,878, a record for the Galactosemia Foundation. Our sincerest thanks go out to everyone that was involved in this process including the researcher applicants, the research team, the peer reviewers, and the community members whose fundraising dollars empower this process. We truly wish we could fund all the projects and strongly encourage all applicants to participate

Round 6 Research Grant Award Projects (\$156,878):

	Bosch	Fridovich-Keil	Yue	VanCalcar
Title	"Towards individual prognostication in Classical Galactosemia"	"Defining the role of galactitol accumulation as a possible mediator of outcome in GALT-null fruit flies"	"Developing small molecule therapy for classic galactosemia by crystallography-based fragment screening"	"Untargeted analysis of the galactosemiacrobome"
Award	\$51,271	\$30,000	\$35,000	\$40,607

GENERATION G AND G-FORCE PREPARE FOR MILE HIGH CITY

By Nick Elliott

Hello, Galactosemia Family (and welcome to those who have recently joined our community). My name is Nick Elliott and Sabrina, my wife, and I recently began working with the Galactosemia Foundation. We are thrilled to be joining this amazing team. We will be specifically working with the G-Force and Generation G youth groups. Luckily for us, Jeannine and Linda (who have done it for several previous conferences) are holding our hands through all of this so we are not overwhelmed. We (Linda, Jeannine, Sabrina and I as well) have been busy communicating as we plan our "scouting" of Denver for next year's conference. We will be meeting in late July in Denver to make some final decisions about what we will have our amazing kids doing. While we didn't know much about Denver before, I have fallen in love with it



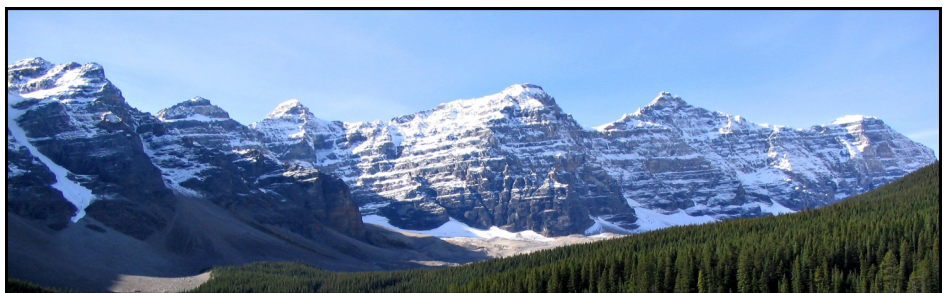
Nick and Sabrina Elliott



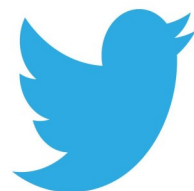
and think it is a fantastic place to have our conference. There are so many things to do and I don't want to ruin any surprises but we have a few new things in the works while also keeping some of the traditions that we all look forward to at each conference. We will have some things nailed down after we go to Denver for preparation this July, and look forward to updating you on what an incredible time we will have in Denver in 2018.

Just so that you will know us a little better please allow me to introduce us. We have three sons: Devin, 20; Jacob, 19; and Josh

who is 16. Josh has galactosemia. There is never a dull moment as many of you know when you have children but these three boys have definitely kept us on our toes and we wouldn't change a minute of it. Sabrina is a nurse in the Operating Room at Self Regional Hospital in Greenwood, SC. Thank God she had the medical background that she does to help us adapt to the life of having a child with Galactosemia. I am a Social Studies teacher at Woodmont High School in Piedmont, South Carolina. We look forward to meeting all of you at Denver next year!



Do you have a success story that you would like to share? If so please e-mail newsletter@galactosemia.org. We are always looking to celebrate achievements and accomplishments.



Follow us on Twitter for updates and information!
@GalactosemiaFDN

FUNDRAISING UPDATES

By Scott Saylor

It is critical for our organization to have families host fundraisers and make individual donations. We would not exist without these donations. We would not be able to fund research and keep our conference affordable without these donations. We thank all the families and individuals who help us meet our mission. For help starting your own fundraiser email scott.saylor@galactosemia.org

The 9th annual "Fore the Cause" benefiting Galactosemia Foundation teed off May 19th in Chesterfield, Va. Through the 8 years of this event over \$250,000 has been raised for the foundation. This year's event raised over \$39,000. Board Vice President Scott Saylor and his family started this event years ago when their son Jake was born. Multiple families with children with galactosemia are involved in this event. The Rodgers family, Stroop family and Berling family have been involved for multiple years.



Ellen Lester of Kodiak, Alaska, a grandmother of two children with galactosemia from Fairbanks, AK, started fundraising this year. She is asking her family and friends to donate to the Galactosemia Foundation in her grandchildren's names. Her sister did a "Blue Jeans for Rare Jeans" at her school in Wyoming and raised \$550. Teachers paid \$5 and students \$1 to wear jeans in March. Her daughter Jenny Davidson, mother of the two grandchildren, will be attending a rare disease fair in Seattle, Washington at Westlake Park on June 3rd that is held 11-4PM. She is looking for help to promote Galactosemia.

Keegan's Kause- Brian and Kelley Foley have been fundraising for several years. Brian ran a numbers squares game for the NCAA basket-



ball tournament where half the money went to GF and half went to the winners. Luckily some generous winners donated their winnings to GF and he expects the final benefit to GF to be about \$6000. He also runs an NFL survivor pool every fall. Since the last conference Keegan's Kause has raised almost \$13,000.

Tiffany Hoyne hosted her 2nd Annual Galactosemia Benefit Fundraiser in Manchester, TN. This year, Crystal Floyd, another fellow galactosemia mother in Manchester helped plan and carry out the fundraiser. Their goal was to raise \$5,000 from craft vendors, food vendors, a silent auction, raffles, and various kid-oriented activities. All galactosemia families were able to enjoy the activities FREE of charge.

Tiffany has also raised \$215 this year from having her local community participate in "Blue Jeans For Rare Genes." The community came together and bought blue jean ribbons to wear on Rare Disease Day for a donation of at least \$5.

Along with the above fundraisers, Tiffany has her own boutique that was inspired from her son, Connor Reese Hoyne. Reese's Genes Boutique's goal is to raise awareness and funds for the Galactosemia Foundation. Reese's Genes Boutique offers affordable and trendy items for women and children of all ages.

To date, Tiffany has raised \$1,000 for the Galactosemia Foundation. Tiffany raised a little over \$5,000 in 2016 and hopes to double those funds in 2017.

If you need help getting started with fundraising in your area, Tiffany would love to help you. She can be reached at connorsgalactosemiajourney@gmail.com.



Follow us on Pinterest for updates and information!

"Stewardship at its best engages donors with the impact and outcomes of their investments of time, wisdom, expertise, connections, and money."

— Karen Osborne



**Galactosemia
Foundation**
Linked for Life.

TYING THE KNOT AND RAISING FUNDS



Jojo Casale enjoying his Aunt's wedding day.

By Nicole Casale

Jessica and Joseph Lennon got married on May 20th 2017. As many know, there is a lot of planning and decisions that need to be made in order to make this day special. Luckily for them there was one decision that was an easy one: the favors. A favor is given to guests to thank them for their love and support on their special day. Rather than giving one to take home, they made a donation in their honor. Jessica's nephew Joseph, or Jojo (age 5), was diagnosed with Galactosemia at 5 days old.



Like many, Jojo had some major complications. Knowing the major need for funding for the disorder this was a way they could give back, knowing it would make a difference.

(Ed. Note: This was one incredible story about a creative way to fundraise for the Foundation. If you have thoughts or need help with fundraising, please do not hesitate to reach out to fundraising@galactosemia.org. Additionally, if you have any creative fundraising ideas that you have used, please share them with the galactosemia community.)

CONGRATULATIONS TO LOGAN DION



By Ann Hintz

Congratulations are in order for Logan Dion! This June, Logan graduated from Greeley West High School in Greeley, CO. He plans to start working with his dad at a commercial drywall company this August. Logan took construction classes in high school and did an internship last summer at Habitat for Humanity.

He is also enrolled at Aims Community College in Greeley, where he will begin courses this fall in construction design. In addition to Galactosemia, Logan has an Asperger's diagnosis, but he has never let these challenges be a barrier for him. He is an inspiration to his family and is excited for his future.



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Galactosemia Foundation

RESEARCH GRANT PROCESS: BEHIND THE SCENES

By Seth Schwartz

The research grant awards are an enormous project for the Galactosemia Foundation, second only to the Foundation Conference in terms of total effort. For this round of grants, the process spanned nearly 10 months, with applications opening on July 16, 2016 at the conference, closing on Jan 31, 2017, and awards being selected on May 21, 2017.

Applicants began by choosing a project of interest, evaluated its fit for their lab, worked with lab members (students, post-doctorates, or tenured staff) to write the applications, reviewed their documents with their University ethics boards, and then submitted their papers to the research team. Based on previous feedback, this research round had a longer application window, which permitted the researchers time to complete these steps proficiently.



For the Foundation, the largest efforts begin when the applications are received. Each proposal is reviewed and scored by members of the Research Team and by external "peer reviewers" - professionals with expertise in the subject matter. Many members of the research team go over each paper multiple times to ensure they give it a fair score. While each member of the Galactosemia Foundation Research Team has a technical background, they often have to do additional background research to understand the cutting edge approaches and technologies the researchers are proposing for their projects.

This round of applications gave the added challenge of finding enough peer reviewers to review the 14 proposals. The team preference is to have two peers grade each submission, however they were not anticipating having 14 proposals. One peer, Rich McEachin, is both a genetic research scientist and the father of a child with Galactosemia. He graciously volunteered to review all 14 proposals. The team was hugely thankful for this as it allowed them to have two peers to look over each paper, while also having one consistent voice throughout the feedback.

The board cannot thank the individuals involved behind the scenes in this process enough. Kelley Foley provided exceptional leadership as the head of the research team. Dan Lambert and Christy Johnson provided organizational history having been in-

involved in the GF research process almost from the very beginning. Dan and Christy also managed administration, liaising seamlessly between the researchers, the board, and NORD (when an outside opinion was needed). Jonathan Mock, Justin Burgett, Owen Branson, and Beatrice Ortega also made strong contributions to the team, especially in evaluating the applications.

Rich McEachin deserves a huge thanks for his contribution as do the other peer reviewers. This outstanding work would not be possible without you.

The Galactosemia Foundation is committed to encouraging and funding galactosemia research. The current plan is for grant cycles every two years that will open each conference and close the following January. This is only possible through donations to the Galactosemia Foundation Research Fund. There have been some outstanding fundraising successes in recent years, successes that directly fund these innovative projects. These will need to continue to achieve this objective. Similarly, the hard work of the research committee will need to continue. New members with technical background who can take on a concentrated project every other winter are always needed. Please contact fundraising@galactosemia.org for any questions on setting up a new fundraiser or research@galactosemia.org for any questions on assisting the research team.

Galactosemia Foundation

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DEVELOPING SMALL MOLECULE THERAPY FOR CLASSIC GALACTOSEMIA BY CRYSTALLOGRAPHY BASED FRAGMENT SCREENING

By Wyatt W. Yue, PhD



Currently, no effective therapies exist for Classic Galactosemia, a rare metabolic disorder caused by inherited mutations of the GALT gene, which encodes the enzyme galactose-1-phosphate

uridyltransferase (GALT) pivotal to galactose metabolism.

In this research proposal, we explore the potential of small molecule modulation on Classic Galactosemia, by adopting two drug

intervention strategies: (i) inhibitors targeting upstream of the defective GALT enzyme (i.e. GALK1) to reduce accumulation of galactose-1-phosphate (substrate reduction) and (ii) activators that specifically bind to the defective GALT enzyme to improve its folding, trafficking, and activity (pharmacological chaperoning).

To identify initial ligands for both strategies, we will adopt the structure-guided fragment screening method. This is a pioneering approach applying x-ray crystallography to screen a library of fragment molecules to identify those that bind to different regions of the protein. The fragment hits will be elaborated by chemical synthesis into a set of analogue compounds for further validation and optimization, using biochemical and biophysical methods aimed at studying their in vitro mode of action.

The proposal aims to deliver small mole-

cule leads that bind to GALK1/GALT, with potential for downstream optimization. Hits validated by biophysical methods will be made available to the open community for in vivo assessment in patient-derived cells and animal models of diseases. The long-term goal is for the community to develop the lead molecule(s) into clinically viable, drug-like candidate through downstream medicinal chemistry pipeline, and further validated in vivo via our established clinical collaborators

While fragment-based screening is emerging as a successful and widely-used approach for novel drug discovery in the pharmaceutical industry, to our knowledge this approach has not been performed for metabolic disorders such as galactosemia. We believe this approach could offer a robust long-term solution to small molecule therapy, first-in-class for galactosemia.

DEFINING THE ROLE OF GALACTITOL ACCUMULATION AS A POSSIBLE MEDIATOR OF OUTCOME IN GALT-NULL FRUIT FLIES

By Judy Fridovich-Kiel, PhD



Goal: The long-term goal of this project is to determine which of the metabolic perturbations that occur in classic galactosemia cause the complications experienced by pa-

tients. Our short-term goal is to test whether interventions that normalize galactitol level in a GALT-null fruit fly model of classic galactosemia improve acute and long-term outcomes.

Summary: One of the principal roadblocks to improving long-term outcomes of children and adults with classic galactosemia (CG) has been not knowing which of the metabolic perturbations that occur in patients with CG cause long-term complications. Specifically, the field has known for decades that patients with CG accumulate increased levels of galactose and its metabolites galactose-1P (Gal-1P), galactitol, and galactonate in blood and tissues, especially as infants after drinking milk. But which, if any, of these metabolites actually cause acute and long-term complications?

For many years Gal-1P was assumed

causal. The reasoning behind this assumption was as follows. First, Gal-1P accumulates to high levels in affected infants drinking milk, and declines, along with acute symptoms, when the baby is switched to low galactose formula. The correlation of acute symptoms with elevated Gal-1P is true, but not unique, since galactose, galactitol, and galactonate also accumulate in parallel. Further, decades of study have failed to show any association between Gal-1P accumulation and long-term outcome severity of treated patients. Second, patients with a variant form of galactosemia called galactokinase (GALK) deficiency, who accumulate galactose, galactitol, and galactonate, but not Gal-1P when drinking milk, were once thought spared many of the acute and long-term complications of CG, other than cataracts. In 2011, however, a report from Germany documented that close to 30% of a cohort of patients with GALK deficiency identified by newborn screening experienced cognitive disability as they grew, upending the conclusion that these patients do not suffer developmental problems. Finally, recent studies from our lab using a fruit fly model of CG demonstrated that blocking Gal-1P accumulation by deleting GALK in animals that were also missing GALT failed to rescue or even minimize the negative outcomes observed. In fact, loss of GALK, which effectively prevented Gal-1P accumulation, was itself harmful, and when

coupled with GALT deficiency, actually made some of the outcomes worse. Combined, these results contradict the assumption that Gal-1P is causal of long-term complications in GALT-deficiency, raising the obvious next question – then what is?

Here we propose to address this question by testing the next logical "suspect" after Gal-1P: galactitol. Specifically, we propose to ask whether preventing accumulation of galactitol prevents the complications seen in GALT-null fruit flies.

Galactitol is already known to cause the cataracts associated with untreated galactosemia, and has been suggested as a possible mediator of other outcomes. We propose to block accumulation of galactitol by using existing drugs that inhibit the enzyme aldose reductase, which makes galactitol. These drugs, called ARIs, are currently used to treat some of the complications of diabetes. Our Aims are to:

1. Define the dosage of ARIs needed to prevent or reverse the accumulation of galactitol in GALT-null fruit fly larvae and adults, and
2. Test whether inhibition of aldose reductase prevents acute galactose-sensitivity of GALTnull larvae and/or climbing and female reproductive defects of GALT-null flies. If yes, test whether inhibition of aldose reductase beginning later in larval development, or in adulthood, is able to reverse, rather than just prevent, these defects.

UNTARGETED ANALYSIS OF THE GALACTOSEMIA METABOLOME

By Sandy Van Calcar, PhD



Galactosemia is a genetic disorder caused by a deficiency of GALT, an enzyme that is required for galactose metabolism. Infants with galactosemia that consume

galactose derived from breast milk or lactose containing infant formulas are at high risk for life-threatening complications, including E.coli sepsis. Fortunately, affected infants can be identified by newborn screening, allowing for early removal of galactose from the diet and avoidance of acute complications. However, despite life-long galactose restriction, many patients develop cognitive, speech, and other disabilities. There are several theories about the underlying cause of these problems, including the possibility that over restriction of dietary galactose may actually exacerbate the symptoms. At this time, however, there are few biomarkers that either pro-

vide clues regarding the pathophysiology of these symptoms, or provide a means to assess the efficacy of potential new treatments.

The goal of this study is to use metabolomics to identify biomarkers that can be used for future research on the pathophysiology and treatment of galactosemia. Metabolomics is a relatively new approach to the study of human disease that utilizes technologies such as mass spectrometry and nuclear magnetic resonance spectroscopy to simultaneously quantify large numbers of metabolites, including lipids and polar molecules (i.e. sugars, organic and amino acids, nucleotides) from biological fluids.

To increase the likelihood of identifying novel biomarkers of galactosemia we intend to perform untargeted metabolomics analysis, in which the choice of metabolites that are measured is not limited to compounds that might be predicted to differ in patients with galactosemia based on the specific enzyme deficiency. We believe that using this unbiased approach will result in a much greater likelihood of identifying new information regarding pathophysiology that can inform new approaches to the monitoring and treatment of patients with

galactosemia.

For this pilot study, plasma and urine samples will be collected after an overnight fast from 10 patients with classic galactosemia who follow a galactose restricted diet. Samples will be collected from each study participant on two separate days in order to minimize the effect of random variations in metabolites associated with day to day changes in diet, activity, and other factors. Sample analysis will be completed at the Metabolomics Lab at the Pacific Northwest National Laboratory (PNNL) in Richland Washington. Results from patients with galactosemia will be compared to a normal control data set developed and utilized at PNNL.

Initial quality analysis of metabolomics data, as well as pathway mapping, will be completed by the metabolomics team at PNNL. Identification of disease associated metabolites, and/or patterns of metabolites, will be done via a combination of univariate, and multivariate (co-variance) analyses, respectively. These analyses will be performed in consultation with members of the PNNL Metabolomics group and the Biostatistics and Design Program at Oregon Health and Science University (OHSU).

TOWARDS INDIVIDUAL PROGNOSTICATION IN CLASSICAL GALACTOSEMIA

By Annet M. Bosch, PhD



Patients with galactosemia have difficulties metabolizing galactose (milk sugar) from breast-milk, infant formula and dairy products. Newborn screening prevents

death by early diagnosis and treatment but in spite of early treatment with the galactose restricted lactose free diet many patients suffer from cognitive and neurological impairment and impaired fertility which impact on their quality of life and independence and create a severe burden for patients and families.

The exact mechanism of these long term complications is poorly understood as is the large variability of severity of complications between patients. At this time, it is not possible to predict the severity of complications for the individual patient at the

time of diagnosis.

This may result in parents' anxiety, late treatment or unnecessary and potentially harmful treatment, and has major ethical and social implications. Furthermore, over-restriction of galactose may be harmful but at this time it is not possible to determine the optimal galactose intake for the individual patient.

Our hypothesis is that the long term complications result from abnormalities in the structure of protein (enzymes and hormones) and fat (myelin) in the brain and other tissues due to abnormalities in galactosylation, and that the individual ability to metabolize small amounts of galactose (residual oxidation capacity) determines the individual severity of galactosylation abnormalities and thus the individual outcome.

Ultimately, we aim to develop and validate new diagnostic methods enabling early prognostication and individualized treatment and support in Classical Galactosemia. The aim of the specific project of this grant application is to investigate the association of fibroblast (skin cells) galac-

tose oxidation capacity and of galactosylation abnormalities with outcome in patients with galactosemia. In this project, we will cooperate with prof E Treacy (Dublin, Ireland) and Prof G Berry (Boston USA). We will take the following steps:

1. measure the ability to metabolize galactose (residual galactose oxidation capacity) in cultured skin cells (fibroblasts) of patients with galactosemia
2. measure the severity of galactosylation abnormalities in these patients
3. relate the residual galactose oxidation capacity and the glycosylation abnormalities to the clinical outcomes of these patients to ultimately determine the prognostic value of these diagnostic methods.

This project is part of a larger study, in which all results of sub-projects will be combined aiming to develop and validate new diagnostic methods enabling early prognostication and individualized treatment and support in Classical Galactosemia.

*****Deadline for Board Applications is August 15, 2017*****

Specific Intentions for Service: (Please Rank)(fundraising, technology, special events, Policy, Awareness, Research, Finance, etc).

Why do you want to serve on the Galactosemia Foundation Board or Committee? (attach more pages if necessary)

Thank you for considering service on the Galactosemia Foundation Board

I will work in good faith with other board members as partners towards achievement of our goals

BABBLE BOOT CAMP

Looking for families with infants 6 months or younger with classic galactosemia to participate in the

Babble Boot Camp Research Study



What: *Babble Boot Camp is an online research study that runs from birth to 2 years. Families anywhere in the US can participate.*

Why: *We want to see if starting therapy at very early ages can minimize or prevent speech & language problems in children with classic galactosemia.*

Tell me more: *Parent/s or caregiver/s will meet weekly online with an expert on our team and collaborate on a plan to encourage speech & language development as part of their daily routines. For instance, they will learn how to help their babies reach typical milestones such as babbling and first words on time. There is no cost to participate. Families will be given a small stipend at the close of the study.*

Participation is voluntary.

Questions? Interested? Contact Dr. Beate Peter or Dr. Nancy Potter at Babblebootcamp@asu.edu or call (206) 713-5839.



Arizona State University



Washington State
University



The Speech Language Genetics Laboratory, directed by Dr. Beate Peter, focuses on identifying the genetic causes of communication disorders and turning this knowledge into new interventions for very young children at genetic risk.

TREASURER'S REPORT

Galactosemia Foundation

Statement of Activity

January 1 - June 30, 2017

	Total
Revenue	
Interest Earned	\$ 15.84
Gift In Kind Donations	873.32
Paul P Scholarship	525.00
Temporarily Restricted Donations	35,644.50
Unrestricted Donations	38,466.86
Total Revenue	\$ 75,525.52
Expenditures	
Golf Fundraiser Expenses	\$ 2,402.80
Dr. Annet Bosch Grant	51,269.00
Dr. Judith Fridovich-Keil Grant	30,000.00
Dr. Sandy Calcar Grant	40,607.00
Dr. Yue Grant	35,000.00
Bank Charges/Fee	465.39
Dues & Subscriptions	200.00
Freight & Delivery	30.00
Research Team Gifts	600.00
Legal & Professional Fees	1,700.00
Stationery & Printing	89.51
Telephone	179.70
Travel (2018 Conference Planning)	7,624.59
Website Hosting	207.84
Total Expenditures	\$ 170,375.83
Net Operating Revenue	\$ (94,850.31)

	Total
ASSETS	
Bank Accounts	
BUSINESS CHECKING (XXXXXX 3329)	\$ 228,305.46
PayPal Bank	97.50
Research Fund (XXXXXX 6770)	135,863.58
Scholarship Fund (XXXXXX 6788)	2,437.60
Total Bank Accounts	\$ 366,704.14
TOTAL ASSETS	\$ 366,704.14
LIABILITIES AND EQUITY	
Accounts Payable (A/P)	\$ 158,576.00
Equity	
Retained Earnings	302,978.45
Net Revenue	\$ (94,850.31)
TOTAL LIABILITIES AND EQUITY	\$ 366,704.14