

December 2010

## ML4 SCIENTIST AND ML4 DOCTOR RECEIVE PRESIDENTIAL AWARD



President Barack Obama poses for a group photo with the recipients of the Presidential Early Career Award for Scientists and Engineers in the South Court Auditorium of the White House Dec. 13, 2010. (Official White House Photo by Chuck Kennedy)

The Presidential Award is the highest honor bestowed by the U.S. government on outstanding scientists and engineers beginning their independent careers.

Two of the award winners, **Brian P. Brooks, M.D., Ph.D.** (National Institutes of Health) and **Haoxing Xu, Ph.D.** (University of Michigan) are ML4 doctors and scientists. **Dr. Brooks** is an eye doctor and researcher, who has examined many ML4 patients.

**Dr. Xu** won the Presidential award for “studies on the properties of the mucolipin family of transient receptor potential (TRP) proteins that regulate iron and calcium homeostasis in endosomes and lysosomes.” On the next page, Dr. Xu has written an article to explain how this research can improve the lives of children with ML4.

By **Haoxing Xu, Ph.D.** (University of Michigan)

TRPML1, the protein that is not functioning properly in the ML4 patients, is located in a tiny, interior pocket called the lysosome of the cell. To probe the function of TRPML1, researchers in my lab, the Xu laboratory at the University of Michigan, have recently developed a new and powerful electrophysiological method to directly study how TRPML1 functions in the tiny lysosome.

In this method, called lysosome patch clamp, an electrode is attached to a lysosome membrane to record the activity of individual or multiple proteins that serve as channels for charged particles (ions) moving in and out of lysosomes. With this method, our research team made two important discoveries. First, TRPML1 is indeed an ion channel that conducts both calcium and iron out of the lysosome. Second, a lipid molecule that is present only in the lysosome, serves as the signal to open the TRPML1 channel. Furthermore, TRPML1 from patients with mutations that caused more severe ML4 disease were the least capable of releasing calcium and iron. Patients with milder forms of ML4 were more proficient at releasing calcium and iron.

The lysosome is the cell's recycling center, an essential service for the cells in our body. Calcium is important to efficiently remove the recycled materials from the lysosome. The calcium problem in the lysosomes of ML4 patients slows down this process at a degree that still can be tolerated by most cells. However, when iron becomes trapped in the lysosome, rapid accumulation of the recycled materials occurs and is converted into a brownish waste material, called "lipofuscin", which is known as the "aging pigment."

Abnormal accumulation of lipofuscin is associated with a range of neurological disorders including Alzheimer's disease, Parkinson's disease, macular degeneration (a degenerative disease of the eye), and also contributes to the aging process. Because the speed of lipofuscin buildup is 10-100 times faster in ML4 patients than in normal individuals, we can think of ML4 as really early onset of aging. Two potential therapeutical approaches are designed based on these research findings. ML4 mutations cause more than 50% or 90% reduction of TRPML1's ability to release calcium and iron. One potential therapy for ML4 is to develop drugs that can boost the residual function of TRPML1 in some



patients, or their sister channels: TRPML2, and TRPML3. Such drugs will then be tested for their beneficial effects in the mouse models of ML4 (TRPML1 knockout mice are kindly provided by Drs. Susan Slaugenhaupt and James Pickel).

The second potential therapy is to decrease lipofuscin accumulation in ML4 cells by reducing the lysosome iron level, called lysosome iron chelation therapy. Several iron chelating drugs are available and iron chelation therapy is shown to be neuroprotective for patients and animal models of neurodegenerative diseases. Iron chelating drugs will be tested for their beneficial effects in the mouse models of ML4.

For more information about Dr. Xu's lab at the University of Michigan, and the ML4 research they are doing, please visit his lab website at <http://www.mcdb.lsa.umich.edu/labs/haoxing/>



**Dr. Xiaoli Zhang**, one of the researchers in Dr. Xu's lab, gave a talk at the "ML4 Family and Friends Fun Day" on August 22<sup>nd</sup>, 2010. Please see Pages 6 and 7 for the full article about this special day.

## MY BAR MITZVAH PROJECT TO RAISE MONEY FOR ML4

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Hi, my name is **Samuel Kalnitz** and I live in Atlanta, Georgia. For my bar mitzvah project this past October, I sold chocolate “Mitzvah Bars” to raise money for ML4 and autism. I chose autism because my 6 year old cousin, Alexa, is Autistic. I chose ML4 because Eden Gold’s family is very close to mine and I wanted to raise money in her honor.

I hope that the money raised will be helpful in supporting research that may provide Eden and other ML4 children like her with a better life. My father sells marketing and promotional items, so I decided to make my project more creative and fun by choosing a product to sell. We figured that everyone likes to eat chocolate, and people feel good when they buy something where the proceeds go to a good cause. Instead of using a regular candy bar, I decided to sell chocolate with popping candies in it. I also supported an Israeli company by buying the chocolate from a company in Israel.

I designed my own wrapper and my dad printed them for me. My siblings helped me wrap a total of 1000 bars and then we started selling them. I sold bars by phone, door to door, at Kroger, Blockbuster, organizational meetings, and at my synagogue’s mitzvah day. Friends and family helped me sell. Mitzvah Bars were sold to people in Atlanta, New York, Michigan, Virginia, Washington DC, California, and Maryland. I also had a website with links to the ML4 organization and Camp Yofi web pages, where some friends and relatives made direct donations.



*(Samuel Kalnitz, with cousin Alexa on the left, and Eden on the right)*

As of today, I raised over \$3,000. I feel very happy and proud that I raised this much money for such special causes. I hope that sometime in the future a cure will be found for all diseases. This was a great fund-raiser and one that I wish to continue to be involved in. If you know anyone who would like to sell Mitzvah Bars as a fund-raiser, I will be happy to assist in coordinating the project.

If anyone would like to use this idea for their Bar or Bat Mitzvah project, or would like to purchase Mitzvah Bars, feel free to contact me at (404) 388-8715.

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My name is **Heidi Tanenholz**. I am 9 years old. I have started an “ML4 Tween Siblings Group”. This is a group just for kids who have brothers or sisters with ML4.

I think the “ML4 Tween Siblings Group” is a good idea because it’s a chance for ML4 siblings to socialize by “skyping”, writing letters, emailing, and calling on the telephone. We live in different locations all around the world! When we have ML4 parties we come together and play. Even when some families can not come, it’s OK!

We can discuss the way we care for our ML4 siblings. For example, we can tell how we play with them and interact with them. Also we can give each other tips on how to help in a way we did not know before. This group will ROCK!



*Arielle, Heidi, Mariah, and Ellie, ML4 Tween Sibs*

My name is **Arielle**. I am 8 years old. I live in Pacifica CA. I have a sister named Carin who has ML4. It is hard because in some ways she's a baby and in other ways she's a six year old.

She walks really well on her walker, and she can understand what we say to her. She can tell us what she wants and doesn't want. But sometimes she's like a baby because she screams a lot, she can't talk, and she wants all the attention she can get. She's also really cute.

When she's mellow, she says this word over and over. It sounds like "gakoom". Everybody in my family loves to hear it.

I share a bed with Carin and though she sometimes kicks me off the bed and wakes me up in the morning, she is really fun to snuggle with and it's great to have her as a sister.



*Carin and Arielle*



*Nina and Heidi, ML4 Tween Sibs*

## AN ML4 GRANDMOTHER'S PERSPECTIVE

Hello!! My name is **Pat Owens** and I am the mother of seven, grandmother to nine, and great grandmother to two. I am so honored to have been asked to write this article, but at the same time, I am a little worried that I might not do justice to all of the other grandmothers out there. Being a grandmother is a privilege and if you are lucky enough to be one, your life is blessed in ways you could not have imagined before becoming a grandparent.

In 2005 our family was blessed with a new member of our family, and for me personally it meant another grandchild was added to the others when my middle son married his wife Lisa and she brought with her a gorgeous young lady named **Ashley Graffam**. Ashley is now a 16-year-old beautiful young lady with a smile that lights up a room. In spite of the fact that Ashley lost her sight as a result of her MLIV disease, she is totally aware of her surroundings and recognizes everyone's voice and never fails to respond with that amazing smile of hers.

Ashley holds a special place in my heart and the hearts of everyone in our family. Before retiring I worked for over 25 years at our local Board of Education in Frederick County, Maryland, and many of those years were spent as an administrator in our school bus transportation office. As part of my job, I had to be certified to drive all modes of transportation serving all groups of students and this included our special needs students attending Rock Creek special needs school.

From the start, it was my preference to drive the special needs students. No matter the level of physical or mental challenges these children were facing, they always greeted me with a smile. And, I will never forget, that although there were often significant periods of time between the times of my driving a particular bus of special needs students, they always remembered me and greeted me with excited recognition.

So even before Ashley came into our lives in 2005 when her mother married my middle son, special needs children held/hold a special place in my heart. Since Ashley came into my life, I have been privileged to be able to care for her on countless occasions and travel with her on family vacations.



*Ashley Graffam and Pat Owens*

I have also watched with love and pride as Ashley taught our family, especially her new brothers and many cousins, about physically and mentally challenged individuals. Most, if not all of them, had never interacted directly with a special needs person. Now, they take part in her activities and help with her care. They adore her and it has been very rewarding to watch those friendships grow and to see my other grandchildren become sensitive to the needs of special needs individuals. Ashley has taught them a lot.

Ashley loves music of all kinds, but Elvis Presley is her favorite singer. She claps her hands in tune to the music and jumps, laughs, and squeals, to demonstrate her enjoyment of the music. She has been known to demonstrate quite loudly her displeasure when the entertainment is winding down.

I am grateful to be a part of all of my grandchildren's lives, and for all of the love they have brought to my life. I wear many hats as a grandmother, and in fact am the President/CEO of GrandFamilies Of America [www.grandfamiliesofamerica.org](http://www.grandfamiliesofamerica.org) This national organization provides support and resources to grandparents/relatives raising children. We direct families to resources within their communities.

Every time I help a family connect with resources, I am reminded of how lucky I am to be blessed with so many wonderful grandchildren. All of them are different in their own way, but they appreciate each other for their differences. And Ashley has contributed to all of our lives in a very positive and loving way. We love her very very much.

## 2010 “ML4 FAMILY AND FRIENDS FUN DAY”

By Susan Tanenholz, ML4 Foundation Board Member

August 22<sup>nd</sup>, 2010 was “ML4 Family and Friends Fun Day”, in Baltimore, Maryland. It was held on the campus of the Maryland School for the Blind, which generously donated the use of their beautiful Arts Center for our party.

We were delighted and thankful to have twelve ML4 families travel from all over the world, from as far away as Brazil, to attend our party. Extended family and friends also joined us for this very special day. We were honored to have seven ML4 doctors, scientists, and researchers in attendance as well.

**Paul Tanenholz**, President of the ML4 Foundation, welcomed all of the guests. Then the microphone was

passed around to each family, so that they could introduce themselves. Next, the doctors and scientists spoke at the podium, presenting their latest ML4 research.

The next few hours were filled with an abundance of food, hugs, tears, stories, and most of all, love. The children were entertained by a DJ, crafts, and a visit from “Elmo”.

For some of the ML4 families, it was their first time meeting another ML4 child. We had 12 beautiful ML4 children present, whose ages ranged from 2 to 25.

It was a fun day, an educational day, and a day filled with caring families, creating and nurturing lifelong friendships.



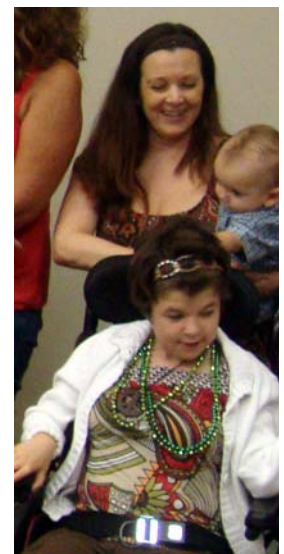
**Group Photo of 2010 “ML4 Family and Friends Fun Day”**

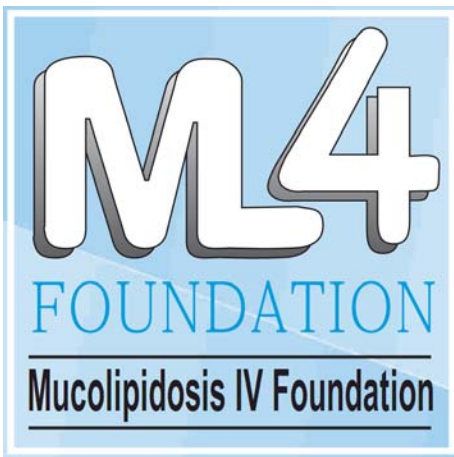


# MORE PICTURES FROM THE 2010 "ML4 FAMILY AND FRIENDS FUN DAY"



ML4 Doctors and Scientists pose with "Elmo"





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