Kennedy's Disease ASSOCIATION

KDA e-Xpress

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Chat with Dr. Maria Pennuto

A Portion of the Chat room conversation on November 7, 2009

Question/Comment: The KDA is honored to have Ms. Pennuto as our guest this morning. Maria got her Diploma in Biological Sciences In 1996, and then got her PhD in Molecular and Cellular Biology in 2000 in Italy. She made her first post-doc with Dr Larry Wrabetz in Italy working on a neurological disorder known as Charcot-Marie-Tooth disease type 1B, then joined Dr Fischbeck's lab at the NIH to work on SBMA, followed by a year in Dr Taylor's lab at the University of Pennsylvania. Understanding the pathological mechanisms in neurodegenerative disease pathogenesis is the main goal of her research. She later moved back to Italy, at the Italian Institute of Technology, where she is continuing the research started at the NIH and UPENN.
In the last five years, she decided to focus her research on SBMA. Her interest in protein modifications led her to investigate the functional role of modification of mutant androgen receptors by another protein, named AKT. This work led her to discover that modification of mutant androgen receptors by AKT reduces testosterone binding. Most importantly, she identified IGF-1 as the agent that promotes this modification in cell and mouse models of SBMA. This research has had a remarkable impact in the SBMA field, and may lead to the development of novel therapy for SBMA, as she will explain during the CHAT.
Thank you so much Maria Penutto for what you are doing for us with Kennedy's Disease!

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INSIDE THIS ISSUE

The KDA Board of Directors wish you and yours
A safe, healthy, and joyous holiday season!

Kennedy's Disease Association Awards Research Grants

November 19, 2009

I believe that one of the most important benefits the Kennedy's Disease Association (KDA) provides is funding for Kennedy's Disease research. Each year, the KDA sets aside at least 90¢ of every dollar donated to support research and education.

This year we received eight requests for funding. Unfortunately, donations are at the lowest level that they have been in several years. At a time when research is so important, it is difficult to only be able to support a few projects. For this reason, the board of directors has elected to dip into our operating reserves and savings to continue this important service.

The Scientific Review Board of the KDA reviewed all eight proposals. These proposals were then sent to outside reviewers for peer input, and funding decisions were based upon these reviews. The Board of Directors supports these recommendations.

The KDA is pleased to announce that three proposals will be funded.

#1. Parsa Kazemi-Esfarjani, B.Sc., Ph.D. is a researcher for the Department of Pediatrics, Division of Genetics, Institute for Genomic Medicine at the School of Medicine, University of California, San Diego

Grant Amount: **$25,000** (US)

Essentially this research will attempt to determine whether or not, and to what extent, the mutant androgen receptor (AR) in the muscle contributes to both muscle atrophy and motor neuron degeneration in Kennedy's Disease (KD). They have produced a mouse model of KD in which they can remove the mutant AR gene just in the muscle cells (this is due to a genetic manipulation), leaving the mutant AR intact in the rest of the cells. This type of research will hopefully show us which cells and tissues are the most important for the timing of the appearance of KD symptoms (i.e., the onset) and/or the pace of their progression. With this knowledge, we will be able to develop our therapies for KD more effectively and target them to the appropriate tissues.

#2. Maria Pennuto, Ph.D. Department of Neuroscience, Italian Institute of Technology, Genova, Italy

Grant Amount: **$20,000** (US)

This research is based on results that Maria found when she worked in Dr. Fischbeck's lab at NIH. She had found that a specific modification of the mutant androgen receptors (AR) results in decreased toxicity and that this modification was due to the activation of an enzyme known as PKA. She intends to investigate more thoroughly the relationship between PKA and toxicity and to search for drugs that may activate PKA and thus may lessen the effects of the mutant AR.

#3 Lenore Beitel, Ph.D. Lady Davis Institute for Medical Research, SMBD-Jewish General Hospital, Montreal, Quebec, Canada

Grant Amount: **$10,000** (US)

This research is to further study the role of the proteasome and its ability (or lack of ability) to degrade mutant androgen receptors (AR). She hopes to determine directly if the mutant AR really does 'clog' up the proteasome. Up to this point, most of the evidence for such an effect is circumstantial.

Chat with Dr. Maria Pennuto- cont'd from page 1

Question/Comment: Maria, what you have been researching is extremely important to us. I found this on the Internet: After growth hormone is secreted by the pituitary gland it is then taken into the liver where it is used to produce IGF-1. It is this substance "Insulin-like Growth Factor-1" which is responsible for many of the effects usually attributed to HGH (Human Growth Hormone). It increases lean body mass, reduces fat, builds bone, muscle and nerves. The last word is one of our favorites in that quote can you tell us more about your research with IGF-1?

Ms. Pennuto: This research started 5 years ago when I joined the NIH. I decided that an androgen receptor (AR) can be modified by Akt. Akt is regulated by IGF (insulin-like growth factor). Then I showed that IGF can also modify androgen receptors. So, to make a long story short, we can use IGF to make the androgen receptor less toxic.

Question/Comment: Maria, what is the difference between IGF-1 and IGF-1 for muscles. Are they both administered the same way, but just go to different places to do different things?

Ms. Pennuto: In our experiment done in MOUSE, we have used a MUSCLE SPECIFIC IGF. The main form of IGF in the body is the systemic IGF released by liver under the control of GH. Now, the muscle-specific form is not available as therapy, so now we are testing whether an FDA-approved drug works in mouse. So to use that in clinical trials for SBMA. It is administered as a systemic IGF; however, we have shown as proof of principle that we can give more IGF and attenuate the disease, so we hope to see an effect with this drug. IGF activates what we call a signaling pathway. This is the information coming from outside the cell and is transmitted inside. IGF activates Akt, which is a protein that can modify other proteins. We have shown that Akt modifies the androgen receptor (AR) through the addition of a small chemical group, a phosphate group. This modification reduces binding to testosterone which we know is the trigger of the disease.

Question/Comment: It is my understanding that this specific IGF-1 did not work for ALS patients, but did work with mouse models for ALS. Is that correct?

Ms. Pennuto: ALS: the same form of IGF that we used in mouse worked, but the drug that is FDA approved did not.

Ms. Pennuto: Now, the reasons why we believe this drug may work in SBMA are: 1) we have shown that IGF modifies AR (different from ALS, we have shown a specific effect of IGF on the mutant protein); 2) SBMA is different from ALS in terms of pathophysiology; 3) when the androgen receptor is modified by IGF, it gets disposed by the cell (another important difference with ALS).

Question/Comment: So, when you say it modifies the AR, do you mean that it somehow allows the AR to enter the nucleus for cleaning? Or, does it do something else?

Ms. Pennuto: Modified means that androgen receptor cannot bind ligand anymore and so does not enter the nucleus and remains in the cytosol where it gets degraded.

Question/Comment: I thought that is where we get strength - from the binding...

Ms. Pennuto: That is true, but only if the androgen receptor is mutated.

Question/Comment: And the aggregate is where we lose strength?

Ms. Pennuto: The binding to ligand makes it a bad protein, so if we can reduce ligand binding we can probably attenuate the disease even if side effects are associated with this than the androgen receptor loses it function.

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Going Mobile

By Susanne Waite, Founder, President Emerita

Mobility as defined by dictionary.com:
"Capable of moving or being moved readily."

Mobility as defined by the Waite's:
"Ability to get your life back by getting out and about!"

I remember, there were a couple years when Terry (who was diagnosed with Kennedy's Disease 13 years ago) didn't want to use any type of aid to help him walk or get around. Not even a cane. No way was he going to get in a scooter. A wheelchair was completely out of the question. That was the darkest time in our marriage. We couldn't go anywhere or do anything outside the house together. We had always been an active couple and here we were, seven years into our marriage, youthful, and we were sitting at home doing absolutely nothing for two years. Finally, Terry realized he needed help (and that he was bored!) It wasn't the end of the World. It was the start of a whole new Frontier!

Terry picked out a Jazzy power wheelchair (with fun doo-hickeys, like a hydraulic lift seat that would raise him up at work to appropriate heights and its top speed was 8 mph. I couldn't even keep up with it at a full run. He liked to 'race' it! Even I have to admit, it was fun to ride in!) At that time, we bought an exterior Silverstar wheelchair lift that hooked into the receiver hitch on the back of our Toyota 4-Runner that would raise it up from the ground and back down.

Recently, we decided it was time to retire our 18 year old loyal SUV. Terry researched what is available on the market, but this time, he wanted his 'legs' to ride inside (not out in the rain on the back of our vehicle.)

We found many auto manufacturers offer programs (when buying a new vehicle) to the disabled where they will reimburse a portion of the cost of modifications and installation of adaptive equipment to their brand of vehicle (the usual seems to be up to a $1,000.00 reimbursement). For more information, check out:
www.mcmobilitysystems.com/mobilityprograms.aspx

There may also be some local, state or federal assistance available in your area. I didn't research this, but you may want to.

If you have an older vehicle, you may be able to get your health insurance carrier to pay for all or part of these aids based on a doctor's prescription (depending on your health insurance plan and what it agrees to cover or not cover) – it is based on necessity, NOT convenience. So your doctor needs to do a thorough job describing why you need these aids.

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Chat with Dr. Maria Pennuto- cont'd from page 2

Question/Comment:	Is this similar as to how deutasteride works?
Ms. Pennuto:	In a way, yes, the deutasteride reduces the ligand; Akt/IGF reduces the binding to ligand.
Ms. Pennuto:	In both cases, the loss of androgen receptor capability to work is better that the conversion to a bad molecule which occur upon ligand binding. D. Merry just showed that retention of AR in the cytosol is protective, so any means we have to reduce ligand binding or the levels of ligand should be beneficial.
Question/Comment:	Because the binding of a mutant eventually causes the death of the AR? Is that correct?
Ms. Pennuto:	Binding of ligand causes the death of neurons, not AR. Binding of ligand causes the conversion of mutant AR into a death-causing molecule.
Ms. Pennuto:	The advantage of IGF is that it is not toxic and it has positive effects on muscle (makes muscle bigger and healthier). And positive effects of IGF are known for neurons and positive effects of IGF are known for neurons. If IGF reduces the ability of the AR to work. It is still better than having neurons dying for the activation of the mutant protein.
Question/Comment:	You commented earlier that there is no FDA-approved drug for the IGF-1 that you are using in the mouse models. Is that correct? You are attempting to use an approved drug that is similar?
Ms. Pennuto:	There is an FDA-approved drug, named IPLEX, which Dr Fischbeck now is testing in the SBMA mice.
Ms. Pennuto:	if this works, it will be used in clinical trials,
Ms. Pennuto:	in the meantime, we are generating viruses for production of the muscle-specific form of IGF
Question/Comment:	Aren't we more interested in nerves than muscles?
Ms. Pennuto:	Yes, but one thing that our work shows is just that it is possible to target muscle to rescue the motor neuron and this was quite unexpected. And opens to new therapeutic approaches. We can target muscle (more accessible than spinal cord). Muscle perhaps plays a primary role in disease rather than secondary to spinal cord
Question/Comment:	To find out more about IPLEX , go to http://www.insmed.com/iplex.php
Ms. Pennuto:	Do not forget that all this is based on a disease-specific mechanism that we have demonstrated. IGF may work because it modifies directly AR.
Question/Comment:	I remember reading that the earlier IGF-1 is used in a patient, the better chance to retain strength (later onset of symptoms). Is that correct?
Ms. Pennuto:	Yes, an intervention in muscle that results in a delay in the degeneration of muscle and neurons will be beneficial even after long time from exordium.
Question/Comment:	If we had a child (grandchild) with the defect, it might be beneficial to start the child on IGF-1 before onset...?
Ms. Pennuto:	Maybe, but this will be the doctor to decide. You cannot give IGF to children too early otherwise there might be side effects. But treatment started before symptoms may lead to a delay in the loss of motor neurons
Question/Comment:	How long do we have before the mouse trials are completed?
Ms. Pennuto:	I believe one year
Question/Comment:	Is part of the testing to determine an appropriate dosage for humans as well as whether it works?

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Going Mobile - cont'd from page 2

We decided to purchase a GMC Acadia and install an interior hoist to load a small scooter (Terry decided on purchasing the Pride GoGo Elite Traveler Plus for $1,300.00 – which is small enough to fit inside the back cargo area.) The cost of the hoist and installation was $2,400.00 (Call around to different suppliers/installers – we found the pricing to range up to $3,500! We drove to another area about 2 hours away from our home to save $1,100.00). GM's Mobility Program will be reimbursing us $1,000.00. Since the vehicle we purchased is equipped with the Onstar System (free for one year with the vehicle), GM's Mobility Program also gives us an additional 2 years of Onstar service for free.

I am thankful we found out about these programs. They are helping us continue to get out and live our lives!

Look for a chat in the upcoming months about "What to look for when buying a Scooter, Wheelchair or other aid."

KDA e-Xpress

A publication of the Kennedy's Disease Association.

Editor: Bruce Gaughran

Comments, suggestions, and questions should be sent to: **kennedysdiseaseinfo@gmail.com**

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Chat with Dr. Maria Pennuto- cont'd from page 3

Question/Comment:	If the mouse trial is successful, how long will the human trial be? 2 yrs? Double blind like the deutasteride?
Ms. Pennuto:	I think that because it is FDA approved it has been already used in humans. So a lot of info on dosage is already available for the clinical trial.
Question/Comment:	Well, this is certainly good news for us - a shining light on the horizon...
Ms. Pennuto:	I hope so ... when I started with this I did not imagine we would have led to all this. We keep working even on additional sides so that we can know better different aspects of and so develop therapy for the disease.
Question/Comment:	So, your lab is still working on this. Kurt's lab is testing it also. Is there anyone else involved?
Ms. Pennuto:	Yes, with Antonio Muar` in Rome. He is the guy that generated the IGF mice. He is generating now viruses that produce IGF. We will use his viruses in the SBMA mice. But I really hope that the experiment in mouse with IPLEX works so that a clinical trial can be initiated soon.
Question/Comment:	And, if IPLEX does not work, then you will continue to look for FDA-approved drugs that might?
Ms. Pennuto:	right, but also we will try to determine if we can use the viruses
Question/Comment:	But, they would have to go through the approval process before any human trials?
Ms. Pennuto:	Yes
Question/Comment:	Are you working on anything else right now?
Ms. Pennuto:	Yes, in addition to IGF I am also working on a different pathway … another molecule that like Akt modifies AR. It is still a long way out, however.
Question/Comment:	Were there any negative side effects in the mouse models that were administered IGF-1?
Ms. Pennuto:	Not that we know of
Question/Comment:	The deutasteride had some sexual side effects... anything known about IPLEX doing the same?
Ms. Pennuto:	I do not think there are sexual side effects with IPLEX
Question/Comment:	Well, Maria, I cannot thank you enough for all your support of the KDA and especially the associates of the KDA. Without people like you there would be no hope. You will never truly know how much your work means to us.

Dr. Diane Merry

Kennedy's Disease Research

On September 19, we had a wonderful chat with Diane E. Merry, Ph.D., who heads up the Department of Biochemistry and Molecular Pharmacology at Thomas Jefferson University in Philadelphia. She did an excellent job of explaining the status of her labs current Kennedy's Disease research projects as well as educating us on how the disease works (or does not work because of the mutation). If you did not participate in the chat, I would encourage you to take the time to read the transcript. If interested, follow this link: DianeMerryChat

What's a Blog?

By Lou Tudor – KDA Fundraising

When I first started selling educational computer software to school districts twenty years ago, some of the older administrators told me computers were just a fad…never meant to last…students only use them for games and adults don't have time to use them. It does my heart good to now see toddlers learning computer skills and folks with shaky hands able to write as they please. We've come a long way with technology! Today we have the capability of researching information we need in minutes, instead of hours…and sharing it with the world!

One of the best sites I've seen in a long time is http://kennedysdisease.blogspot.com
It's like reading a personal diary with all the author's thoughts, experiences and research layed out before us. "Bloggers" are people who like to write and who like sharing their work on the Internet. This particular website I recommend belongs to a very talented writer named Bruce Gaughran. We also know him as the President of the Kennedy's Disease Association. Bruce has done a tremendous job of putting together the answers to questions we sometimes think about, but haven't taken the time to find the answers.

"Living with Kennedy's Disease" contains lots of stories (some serious and some humorous) about his life on a daily basis. He also posts articles with useful information… like how to apply for Social Security-Disability, recent research findings on KD, profiles of young researchers, exercise programs, tips on using mobility devices, etc. It's a plethora of knowledge! Take a look and see if any of his writings spark your interest. He'd also love to hear your feedback or any questions you'd like him to explore.

Oh yeah, a blog (or weB log) is a relatively new type of website. It characteristically shows new entries of information in reverse order. The latest additions appear at the top.

Holiday Recipe

Low Fat Apple and Walnut Muffins

2 cups all-purpose flour
1 tsp baking soda
1/4 tsp ground cinnamon
1/4 tsp ground ginger
1/4 tsp ground allspice
1/4 tsp ground nutmeg
1/4 rounded tsp salt
2 large eggs
1 cup plus 2 tbls apple juice
2/3 cup buttermilk
2 tbls oat bran
2 small apples, chopped (Granny Smiths work well)
1/3 cup chopped walnuts

Preheat oven to 375°.

Mix together flour, baking soda, cinnamon, ginger, allspice, nutmeg and salt.

Mix together eggs, apple juice, and buttermilk. Stir flour mixture and oat bran into egg mixture until dry ingredients are just moistened. Do not over mix.

Gently stir in chopped apples and nuts.

Grease 12 standard size muffin cups or line with cupcake paper liners. Spoon batter into prepared muffin cups, filling 2/3 full. Bake for about 25 minutes, or until lightly golden and tops spring back when pressed.

Transfer muffin pan to wire rack to cool then turn muffins out on to rack to cool.

Enjoy these apple muffins as they are, or if you want to get a little decadent, add a bit of butter.

My Grandfather "Pops" Rannells

by Tiffany Beck

My grandfather "Pops," Charles Edward Rannells, passed away on July 29, 2009 after fighting Kennedy's Disease for 18 years, but really fought his whole life.

Everywhere my Pops went he would have a huge smile on his face and his big blue eyes would light up any room. He had a great sense of humor and was amazingly strong and inspiring to me and many others. Everyone he came in contact with was left with a lasting impression.

Pops was born on October 9, 1927, in Hampshire County, W.V. As a child, he was known as a mischievous little boy, and he always seemed to find trouble. He decided to learn to fly a plane before he was 16 and got his license as soon as possible.

During this time, my grandfather got the idea to fly his plane under the Shepherdstown Bridge, which crosses the Potomac River in Shepherdstown, W.V. This bridge is not that high over the water, and needless to say, many people still remember this event.

After high school graduation, he enlisted in the Air Force. After three years in the Air Force, he left the service and went to work with the U.S. Department of Agriculture as a federal-state inspector of fruits and vegetables. During the time of inspecting, he was physically fit and worked long hours all over the East coast.

In 1955, my Pops transferred within the federal government to work as a market news reporter. During this time, Pops traveled all over the United States and finally settled in Pittsburgh, Pa., covering the Pittsburgh Wholesale Market.

While doing this job, he walked 4 to 5 miles a day in all kinds of weather -- year around. After going to work at 5 a.m. and covering the market until about 10 a.m., he would walk 6 to 8 blocks to the Federal Building, where his office was located.

During this period he had no idea that he was not a hardy and healthy male. He enjoyed his job and loved talking with people from all over the country and enjoyed being physically active.

After retiring in 1982, he returned home to Martinsburg, W.V., and purchased a home that needed much work. My Pops enjoyed working with his hands and looked forward to doing the home improvements.

In 1988, he started getting weak in his arms and began losing weight. He let it go, thinking it was arthritis and would get better or go away. But it kept getting worse, and he was eventually referred to Johns Hopkins Hospital in Baltimore.

In October 1991, Pops was "correctly" diagnosed with Kennedy's Disease at Johns Hopkins. At that point, the problem was still localized in his left shoulder.

During the last couple of years, we saw the fastest and most serious deterioration in my Pops. He used a scooter as a means of transportation for getting around the neighborhood, or for going shopping or doing any activity that required much walking. He started using a cane, and during the last year he required the use of a walker.

I went to college close to my grandparents' house, so when I was stressed or needed to escape college life I would drive down Interstate 81 and would be at their house in less than 30 minutes. No matter what problems I was struggling with at school, Pops would greet me with a big smile and ensure me that everything would work out. He never told me that he was struggling; he always continued to smile and help me in any way he could. He would always put others first.

Article continued on right column

My Grandfather- cont'd from left column

After graduation, I moved with my husband, who was in the military, to Puerto Rico. After living there for a little over a year, I found out I was pregnant. As a carrier of KD, I was concerned about my child; especially since I later found out I was having a boy.

I shared this information with my Pops, and he told me that this child is a blessing and he has a purpose and God would not want it any other way. He also said that he had faith that my son, Charles "Raiden," would never experience the challenges he has faced. He told me that he firmly believes that a cure for KD will be found before too long. It amazed me that he would continue to be so positive even though his own health was fading quickly.

He participated in two protocols - one in Pittsburgh in 1995 and the recent one at National Institutes of Health, both of 2-year duration. He wanted to do anything in his power to help others, even though he felt it may be too late for him.

After Raiden was born, I moved home since my husband was deployed and I couldn't go with him. During this time, I spent a lot of time visiting with Pops; I knew his health was deteriorating and I wanted to spend as much time with him as I could. Looking back on it now, I thank God every day for the days I had spent with Pops.

Every visit, Pops would always be smiling and laughing. He would hold Raiden and talk to him about his childhood and about my son's future. As Raiden got older, Pops would take him on scooter rides.

My Pops is my hero and my role model. No matter what was given to him, he continued to live life to its fullest. At his memorial it was amazing to learn how many people he touched during his lifetime. My Pops was an amazing person and will be missed by many.

Do your holiday shopping online AND help KDA at the same time!

"If you're like me, you buy online, but forget to go to the KDA webpage first. Give the gifts that keep on giving…shop through our website. Ask your friends and family to do the same." -Lou Tudor, KDA Fundraising

When you bring up the KDA website http://www.kennedysdisease.org
Please use the green button on the right side of the homepage

In order for the Kennedy's Disease Association to receive a portion of the cost of the items you purchase from these companies (it doesn't cost you anything more) you must enter their website from the link buttons on the KDA webpage

amazon.com

The KDA gets 15% of purchase Price when you buy flowers here

Avon

Lillian Vernon

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Book a cruise though this travel company and the KDA gets 25% of the profits

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HICKORY FARMS

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