2014 KDA Conference most successful EVER!!

It's been said that in order to be successful, we must have the courage to think differently, courage to invent, travel the unexplored past, discover the impossible and conquer the problems along the way. The conference committee, doctors and researchers and attendees did all the above at the November conference held in Alexandria, Virginia!

The 2014 Committee members worked well together from the start, but really accelerated in Alexandria. We owe a debt of gratitude to all the volunteers who made it happen...

"Today's Dream...Tomorrow's Reality"

KDA President John Coakley
Committee Co-Chairs/Board Members Andrew Cassar and Lou Tudor

Committee members and Conference volunteers
Maria Montie          David Yelton          Bill Tudor          Pamela Watson
Linda Price           Dale Traxler         Kathy Thompson      Mike Goynes
Celine Cassar         Jack Durning         Mary Ann Tavares

The best part is that attendees had a good time together! We truly are a 2nd family and enjoy the camaraderie of new and established friendships. Everyone is made to feel welcome and encouraged to share stories of trials, tribulations and success. Where else can you mingle with the doctors and researchers who are working to find a cure for your disease? The KDA conference is a unique opportunity. We all know that research is costly. That's why we are so excited about the monies raised with fundraisers during the year and during the conference. That money is used exclusively for the Kennedy's Disease Association. Well over $32,000 was raised during the Thursday night auction alone! It's heartwarming to see our researchers participating with us and it is motivating for them to shake a hand and hug the people they are helping in their labs.

Let's all plan to attend the October 2015 conference which will be held in Chicago, Illinois. More information will be shared as soon as available. Throughout this newsletter are highlights from some of our presenters...
Last November, the KDA held its annual Kennedy’s Disease Conference in Alexandria, Virginia. As has been the case with all of our conferences, the last day was dedicated to research presentations and discussions by many of the researchers who strive to find a cure for KD. In my experience, the opportunity for the researchers to get to interact and to know the families of affected individuals is the best part of the conference. It allows the researchers not only to share their research findings with the affected families but allows the two groups to get to know each other. To the researchers, especially those in the early stages of their career, the interaction with KDers reinforces the concept that their research is important and affects the lives of real people. Similarly, the opposite is also true. It may sound trite, but the accessibility of the researchers to the attendees at the KDA conference is, in my experience, quite unique and is very valuable.

The researchers who came to the meeting were from most of the labs in the USA and Canada that make major contributions to KD research as well as some from across the pond. While there were no startling discoveries reported, their reports confirmed that we are making progress on understanding the mechanisms that underlie the muscle atrophy that those of us with KD experience. One major shift, or maybe I should say addition, that was discussed at the conference is the developing concept that KD is a muscle disease as well as a motor neuron disease. Strong evidence is accumulating that it may be possible to develop treatments that target the muscles instead of the neurons. This is significant as muscle tissues are much, much more accessible to drugs than is the brain and spinal cord.

The KDA Conference is also the site of the notification and presentation of the research grants funded by the KDA. This year, thanks to your donations and fund raisers, we doubled the funding level for our grants from $25,000 to $50,000! Two grants were awarded at the conference, one to Dr. Anna Pluciennik, a post-doctoral researcher in Diane Merry’s lab at Jefferson University in Philadelphia; and the other to Dr. Helen Miranda, a post-doctoral researcher in Al La Spada’s lab at UC-San Diego. While we were extremely pleased to award these grants, we were disappointed that we could not fund all of the excellent grant proposals that were submitted this year.

“Working together to find a cure”

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Recent evidence from a mouse model of Kennedy's Disease suggests that toxic androgen receptor may cause muscle weakness by impairing the function of calcium channels (known as "ryanodine receptors"), resulting in an abnormal concentration of calcium in the cell and the loss of muscle strength in Kennedy's Disease. The objective of the proposed research is to assess, in mouse models of Kennedy's Disease, the therapeutic effects of orally bioavailable, small molecule Rycals which are designed to repair these "leaky" calcium channels inside the cells of skeletal muscle, representing a potential clinical treatment for Kennedy's Disease and other muscle disorders, such as Duchenne muscular dystrophy. Recently, the experimental Rycal compound, ARM210, has shown promise in treating mice that show a disease resembling Duchenne muscular dystrophy (DMD) - showing significant positive differences in exercise capacity, muscle force, grip strength and the microscopic appearance of muscle tissue - and it will likely be tested in DMD patients in the near future. Two different Rycals were tested in a rapidly progressing, severe mouse model of testosterone-induced muscle dysfunction (HSA-AR mice) in Prof. Cindy Jordan's laboratory at Michigan State University. In the initial 2-week feasibility study design, mice were assessed for body weight, a variety of motor functions (forelimb grip strength, hang time, and voluntary movement in an "open field"), and concentrations of Rycal drugs in blood and skeletal muscles. Prof. Jordan will next test Rycals in a less severe mouse model of Kennedy's Disease (AR97Q mice), which will determine whether Rycals have the potential to protect motor function from disease in the face of polyglutamine-expanded androgen receptor.
The Study of The Androgen Receptor Gene

By: Lenore K. Beitel, Ph.D.
McGill University

Many different researchers and physicians around the world are studying Kennedy’s disease. The goal is to find out how the mutant androgen receptor, with its longer than usual stretch of glutamine amino acids (polyglutamine tract), causes this disease, and find ways to help men with KD. The usual functions of neurons and muscle cells can be affected in many different ways by the polyglutamine-expanded androgen receptor (polyGln AR).

One theory the Trifiro lab is studying is that the polyGln AR, or smaller pieces of this protein, can affect how proteasomes work and thus cause harm to specific cells. As I put it, “proteasomes are like the recycling bins or garburator of the cell”. They break up unneeded or misfolded proteins into amino acids that can be used to build new proteins. In other words, “Once a protein is laid on the doormat of a proteasome, it is taken inside the particle and ultimately disassembled like a Tinker Toy into amino acids that can be reassembled later into other proteins.” (Alfred L. Goldberg et al., Scientific American, January 2001). Carlos Alvarado, a student in our lab, has purified proteasomes from mammalian cells. He has shown that proteasome activity is lower when polyGln ARs are added to the test tube than when normal ARs are present. The proteasomes also appear to be slower at breaking down the polyGln AR than the normal AR. In my presentation I showed that the proteasome is a barrel-shaped complex of proteins. We are now doing experiments to find out which proteasome proteins the normal and polyGln AR can interact with. If we find any differences, this may help us understand why proteasome activity is reduced by the polyGln AR, and suggest ways to overcome this inhibition.
Analysis of Inconsistencies in Terminology of Kennedy's Disease and its Effect Upon Retrieval of Research

By Shelley Arvin, Associate Librarian, Cunningham Memorial Library, Indiana State University

It was noticed that Kennedy's disease is referred to by many different names on the Internet and in the literature. Because names are used to search for information about a disease, a librarian sought to find out how extensive was the problem and if she could offer a search solution. She collected all 788 records published between 1968 to 2010 which mentioned the disease and found 206 different name phrases for Kennedy's disease. Searching by the most common name, spinal and bulbar muscular atrophy, would retrieve only 40% of the 788 publications. Searching for all of the name versions of "Kennedy's disease" retrieved only 38.5% of the publications. Searching for all of the top 13 name variants retrieved 88.5% of the publications. The librarian analyzed the use of the different names over time and found some have become more common but none are yet rising to ascension. Based upon the name analysis and her knowledge of searching, the librarian suggested a standard search. This search could be cut and pasted into most search engines and professional databases to retrieve most of the literature. Adapting the suggested search as required, a professional librarian could help you find all of the existing literature that mentions Kennedy's disease. It is concluded that the terminology inconsistencies are extensive and still changing. Additional detail is available at the links below.

http://libguides.indstate.edu/sbma


The following is a link to the PowerPoint Presentation Shelly Arvin presented at the Conference, entitled “The Many Names of Kennedy Disease and how to Search Successfully”

https://docs.google.com/presentation/d/1GfOf7qi5nJ4R1J9Uv2xFqlnmb_25wbtAVCwPeyJpUCs/edit?usp=sharing

Presentation on Men and Depression

By Julie Binderman, Co-Director of Integrative Therapy of Greater Washington.

Licensed psychologist, Julie Bindeman presented a workshop on men and depression. Often times, depression in men is under diagnosed and is left untreated. Depression can have far-reaching implications beyond the individual, and can affect families, work, and in most severe cases, can result in death. The workshop explored symptoms to look for, treatment modalities, and encouraged a dialogue to begin about this important topic.

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KDA president John Coakley presided over the conference gala dinner and auction. He is a dynamo and helped raised a record breaking amount for KD research!!

Jack Durning and Mary Ann Tavares always have fun at the KDA conferences!
Therapeutics development for Kennedy’s disease

Kenneth Fischbeck, M.D., NINDS, NIH

Kennedy’s disease is caused by a repeat expansion in the androgen receptor gene. The repeat expansion causes some loss of the receptor’s function, but the main effect is to cause a toxic gain of function. That is, the expansion changes the receptor protein so that it becomes toxic to motor neurons and in mice. Androgen reduction with leuprorelin was found to block the disease onset and prevent the motor deficit in transgenic mice with the mutant protein. This raised the question of whether androgen reduction works in patients. Clinical trials of leuprorelin in Japan did not show a significant benefit when the drug was given for 48 weeks.

At the NIH we investigated another androgen reducing agent, dutasteride, in a two-year, randomized, placebo-controlled study in 50 subjects. There was no significant difference between dutasteride and placebo in muscle strength (the primary endpoint), although subjects on dutasteride reported better physical quality of life and fewer falls.

Clinical trials for Kennedy’s disease are challenging because of the slow disease progression (about 2% loss of muscle strength per year). To show a benefit in less than 2-3 years, it would help to have a treatment that improves muscle function rather than just slowing progression. Also, evidence indicates that to be effective the treatment should be started early in the disease course. We need good clinical outcome measures and markers to confirm the biological effects of the treatment, and we need better therapeutic targets. Treatments that block the disease mechanism or enhance protective responses have been found to be effective in mice. How do we translate these mouse treatments into drugs that work in patients?

In 2012 I did a six month sabbatical at Novartis Institutes for Biomedical Research in Cambridge, MA. Like other major pharmaceutical companies, Novartis does discovery research studying disease mechanisms, preclinical efficacy studies in animals, pharmacology and toxicology, and phase 1, 2, and 3 clinical trials to determine safety and efficacy in patients. Unlike other companies that focus on common disorders, Novartis is currently developing treatment for 40 different rare diseases. It chooses diseases to work on based on unmet clinical need, strong rationale for the therapeutic approach, favorable risk to benefit ratio, measures to confirm the drug’s biological effect, and clinical trial readiness. All of these factors apply to Kennedy’s disease.

We have now started a trial of Novartis compound BVS857 to determine whether it is safe and increases muscle size in Kennedy’s disease. The study is randomized, double blind, and placebo controlled. The placebo control is needed for comparison to clearly determine the effectiveness of the intervention. The primary outcome measures are adverse events and thigh muscle volume. Secondary measures include muscle function, lean body mass by DEXA scan, and drug levels. 38 subjects will be studied at four sites in Bethesda, MD; Orange, CA; Copenhagen, Denmark; Ulm, Germany; and Padua, Italy.

The study has two parts: Part A involves single dose escalation every two weeks in 8 subjects (6 BVS and 2 placebo), with drug levels, MRI, and muscle biopsies at start and finish; Part B will involve weekly dosing at the highest tolerated dose from Part A in 30 subjects randomized 2:1 BVS:placebo, with MRI, DEXA, and tests of muscle strength and function. Adult males with genetic confirmation of Kennedy’s disease, ability to walk for 2 minutes, and serum IGF-1 levels of 170 ng/ml or less will be included. Exclusion criteria are diabetes or hypoglycemia; history of Bell’s palsy; treatment with steroids, androgens, androgen reducing agents, beta agonists (e.g., clenbuterol, albuterol), or other anabolic muscle drugs in previous 3 months; history of cancer (other than skin cancer); and retinal disease.

Further information is available at www.clinicaltrials.gov, and from the following:
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We recognized the major fundraisers for 2014. Ed Meyertholen, John Coakley, Lou Tudor and Andrew Cassar hold checks to honor Jason Coopper for the Central NY golf tournament, Sara Kawa for the Queen Anne's 5k Maryland, Bob Tudor for his hand cycle marathon West Palm Beach, FL and Ed Noack for the Texas golf tournament.

Third Annual Queen Anne's Run

Sunday April 12, 2015

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