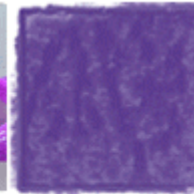


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Research Newsletter

December, 2011

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The Dravet Syndrome Foundation

is a volunteer-based, non-profit organization dedicated to raising research funds for Dravet syndrome and related epilepsies, while providing support to families.

There is currently no cure for Dravet syndrome. Please support our efforts to change that.

donate 

Special New Year's Edition Coming Soon with highlights from all of our 2011 Events!



AES Research Roundtable

The second annual DSF Research Roundtable was held on December 1, 2011 in Baltimore, MD. This meeting, held at the American Epilepsy Society Conference and sponsored by The Joseph and Catherine Johnson Family Foundation and Transgenomic Molecular Laboratory, brought together over forty international researchers, geneticists, neurologists, and other professionals with a strong interest in Dravet syndrome and related epilepsies. This year we were pleased to also include members of ICE Alliance, Dravet Syndrome UK, DSF Spain, and The Charlie Foundation To Help Cure Pediatric Epilepsy among our guests. The purpose of this annual roundtable is to establish a research roadmap to guide the DSF in funding research projects that address the critical challenges of this syndrome and to determine which projects will offer the most promising breakthroughs at the fastest pace. This strategy of prioritizing research needs by a consortium of experts allows the DSF to facilitate the development and implementation of better treatment options.

Lori O'Driscoll, DSF President, welcomed attendees to the meeting with a presentation of the video "[Braxton's Story for Piper's Song](#)." Dr. Jack Parent of the University of Michigan and Dr. Sooky Koh of Children's Memorial Hospital then moderated the scientific portion of the meeting. This began with three keynote presentations: Dr. Miriam Aza discussed the DSF Spain genetic testing program; Dr. Ingrid Scheffer provided a review of Dravet syndrome; and Dr. Linda Laux gave an overview of current and emerging therapies.

Investigators who received 2010 or 2011 DSF Research Grant Awards then reported on their recent progress. Allison Althaus, a senior graduate student in Dr. Parent's lab, presented her results on a project to investigate readthrough treatment of Dravet syndrome caused by nonsense *SCN1A* mutations. Dr. Sooky Koh gave an update on her project to address the role of brain inflammation after a seizure, introduce dietary intervention, and use enriched environments in a murine seizure model. Dr. Scott Baraban presented his work using a zebrafish *SCN1A* mutant model to screen for novel therapeutic agents to treat Dravet syndrome. Dr. Jane Hsiao, representing OPKO Health Inc., presented work on a novel technology aimed at increasing *SCN1A*-encoded protein production in brains of Dravet syndrome patients.

The final part of the program consisted of a data blitz by current researchers in Dravet syndrome and related fields. Dr. Francke Kalume presented work on the mechanism of sleep disturbances in a mouse model of Dravet syndrome. Dr. Lori Isom (in collaboration with Dr. Parent and Dr. Miriam Meisler) used human induced pluripotent stem cell neurons to reveal a novel mechanism of Dravet syndrome caused by *SCN1A* mutations. Dr. Heather Mefford reported progress in identifying genetic copy number variations in patients with inherited epilepsy. Dr. Alica Goldman showed her recent progress in extracting genetic information from multiple types of patient tissue samples. Finally, Dr. Tara Klassen gave an overview of her team's recent publication showing a number of novel human mutations linked to inherited epilepsy.

Overall, the program was a great success, providing not only new scientific information, but also invaluable opportunities for networking between academic and industry scientists, physicians, and parents of children with Dravet syndrome.



As I participate for the first time in the DSF Steps Toward A Cure walk in Schaumburg, Illinois, I am truly touched by the courage and awe-inspiring love of the Tischer family. Ryan and Jenny Tischer are the devoted parents of a precious Dravet angel named Madeline Anne "Maddie" Tischer. They have accomplished wonderful ways to honor their daughter while at the same time raising awareness and funds for the Dravet Syndrome Foundation.

Maddie's Mom described her as a beautiful, strong, fearless, happy, loving little girl. She loved Mickey Mouse Clubhouse and enjoyed playing with her Mom and Dad. But a story we are all too familiar with, Maddie had her first seizure at 4 ½ months old. Through testing, doctors diagnosed Dravet Syndrome at 12 months of age. At the tender age of 2, Maddie passed away after suffering pneumonia and a severe seizure on June 3, 2010. This terrible loss has given Jenny and her family the strength and passion to move forward and honor Maddie any way they can.

After attending the walk for the Dravet Syndrome Foundation last year, just three months of Maddie's passing, Jenny went back home and in three weeks with the help of family and friends put together the very first Maddie's Mall. Maddie's Mall consisted of about 7 different vendors coming together in one day and selling their products with 20 to 100% of the profits going towards the Dravet Syndrome Foundation. By the end of that day, Jenny said they raised several thousand dollars for the cause.

Jenny then took it to the next level and decided she wanted to do a walk in her town of Menomonee Falls, Wisconsin and so "Steps Toward a Cure, Movin' For Maddie" a 5k run/walk was born. With Jenny's dream big approach, they were able to garner a lot of support from many area businesses such as Harley Davidson, Home Depot, Radio Spots, and the local Fire Department just to name a few. With 150 participants in attendance on June 4, 2011, a year and day from Maddie's passing, her families tribute to her memory brought in more than \$25,000.

The Tischer Family has shown their dedication to raising money and awareness for research funded by the Dravet Syndrome Foundation by continuing these great events. The second annual Maddies Mall was held on October 20th in her hometown and included on-line shopping. The second annual "Steps Toward a Cure, Movin' For Maddie" will be held again in 2012. Jenny states, "I feel if I don't do something what would the purpose of her touching our lives have been. If anything else, if I can help just one family not go through what we went through then I have accomplished something."

I want to thank Jenny and Ryan for sharing Maddie's story with me I truly enjoyed meeting them and hearing "Maddie's funny stories." She is truly an angel. Their efforts are greatly appreciated by all Dravet families who continue to struggle and fight this syndrome. Our hope is that one day we can find a cure. Thanks to Maddie for touching so many lives. In her honor there is hope! You can read more about Maddie's story at www.maddietischer.net.



A Little "Luck" Goes A Long Way

When Clare and Michael Carey's daughter, Alexis, began having seizures at three-months-old, they felt helpless. At 17-months-old, Alexis (now 6) was diagnosed with Dravet Syndrome. Clare reports feeling isolated and overwhelmed for the first few years, but all of that changed in 2008 when she attended a Dravet family conference. "It was the first time I met other Dravet parents in person, and it lifted me out of my funk and made me think we needed to do something."

Clare wasted no time. In 2009 her family hosted a fundraising walk in their home town of Boise, Idaho. It was the first time she had done any fundraising, and, with help from Lori O'Driscoll, it was a big success. Although invigorated by the experience, and eager to do more to help, Clare and Michael decided that they did not want to host a walk every year. "We wanted to do something more fun. We hadn't had a babysitter or gone out on a regular basis, and we wanted to something that we could enjoy as well." At a friend's suggestion, they settled on a casino night.

When Clare began planning the First Annual Luck Be Alexis Tonight fundraiser in late 2010, she had never even heard of a casino night event. But she located a company that was willing to provide dealers, tables and accoutrements at a reasonable rate for nonprofits. Clare decided to hold the fundraiser at the Carey's home, sent out a "save-the-date" with her Christmas cards and then began the real work of planning in January 2011, only two months before the event. She settled on a Las Vegas theme, designed the invitations herself and hired

posting a request for vacation home donations at a local ski area where the Careys also have a home, she received 6 offers from complete strangers! Clare also succeeded in securing many other types of donations, including gift baskets, wine and restaurant gift certificates. And she did all of this while caring not only for Alexis, but for her two other children, Calvin (five) and Alanis (two).

On the day of the event, March 12, 2011, Clare received a big surprise. At 8:30 a.m. her doorbell rang, and she opened the door to find someone standing there dressed head-to-toe in Elvis garb. It took her quite a while to realize that it was her brother, Jason, who, along with her other brother Daren, had flown in from England as a surprise! Clare reports that she could not have made it through the event without the help of her brothers and her brother-in-law, who took charge of setting everything up and handling last minute logistics.

But the arrival of Clare's brothers was not the only surprise in store. A week before the event, the babysitter who was supposed to care for her kids at a neighbor's house that night was injured a car accident. As a result, Alexis stayed home and attended the event for the first hour. Given the amount of stimulation, Clare's sister took Alexis back to her room for the remainder of the evening, but Clare was thrilled that Alexis was able to attend for part of the evening, and that the guests could see for themselves the warm, loving little girl who had inspired the event.

The casino night was a huge success. Guests were asked to come in "wedding attire" (*i.e.*, a bridesmaid or wedding dress for the ladies and a suit or tuxedo for the men). Seventy people attended. Each guest paid an admission fee of \$50 and received \$500 of "funny money" to play with at the tables. Games included craps, roulette, black jack and Texas hold 'em. For those whose luck ran out, additional "funny money" was available for purchase. The Careys also held a raffle for a week long ski vacation and had huge success with the silent auction items. Throughout the evening, the caterers served drinks and hors d'oevres. Everyone had a fantastic time.

When all was said and done, the First Annual Luck Be Alexis Tonight event raised just shy of \$20,000. Because Clare kept the expenses down to approximately \$4,000, her family was able to donate over \$15,000 from the event to the DSF! Given this tremendous success, the Careys plan to host the Second Annual Luck Be Alexis Tonight fundraiser in June of 2012.

Dr. Jack Parent Research Update

["Readthrough Treatment of Dravet Syndrome Caused by Nonsense SCN1A Mutations"](#)

We are investigating the use of "readthrough" drugs as a novel therapy for Dravet Syndrome (DS) caused by premature termination codon ("nonsense") mutations. Two DS models are used to test the compounds: 1) a mouse DS model in which mice express a human DS-causing nonsense mutation of the *SCN1A* gene; and 2) a cell culture model consisting of neurons from patients with DS-causing nonsense mutations generated by reprogramming their skin cells obtained by skin biopsy. For the mouse studies, we are testing animals with one mutant and one intact copy of the gene, meaning they produce only half of the amount of full-length protein found in control animals. Readthrough drugs are so named because they can "read through" the premature termination signal (stop codon) and allow production of full-length protein. For the cell culture model, we thus far have generated neurons from two DS subjects with nonsense mutations in the *SCN1A* gene and are in the process of testing how readthrough compounds affect the abnormal brain cell excitability that we see in the culture dish. In the DS mouse model, we have seen promising preliminary results with a commercially available drug that has readthrough capabilities and we are in the process of testing the effectiveness of a novel readthrough compound that is more efficient than those that are commercially available. Our results are described in more detail below.

Gentamicin is a common antibiotic that has proven readthrough capabilities at higher doses. We treated 8 DS mice with gentamicin and 7 DS mice with placebo for two weeks beginning when the animals were three weeks old (roughly equivalent in age to a human infant or young child). The gentamicin or placebo was delivered by injection into the abdominal cavity once per day. After two full weeks of treatment, animals were subjected to hyperthermia-induced seizures (a febrile seizure model) and their behavioral responses were measured by at least two independent investigators. Hyperthermic seizures are induced by slowly raising the animals' body temperature from a normal resting internal temperature of 37.5⁰C to a final temperature of 42.5⁰C over 20 minutes, and monitoring their behavior for a total of 35 minutes. Most DS mutant and many control mice experience febrile seizures at some point during this challenge. We found that the temperature at which animals began to experience seizures and the overall severity of the seizures was not different between gentamicin-treated and placebo-treated mice, and results from both groups of animals did not differ from a second control group that had received no treatment prior to hyperthermia exposure.

In the previously described experiments we used a very high dose of gentamicin in order to try to account for the fact that gentamicin does not easily cross the blood brain barrier, meaning that it does not have good access to get from the blood into the brain. Our results suggested two possible conclusions: either gentamicin is ineffective at treating this DS model, or it simply was unable to cross into the brain at a high enough dose. In order to determine whether gentamicin may have therapeutic potential in this model, we bypassed the blood brain barrier and delivered gentamicin (or placebo) directly into one of the lateral ventricles deep inside the brain. Animals were implanted at 4 weeks of age with mini-osmotic pumps which delivered a continuous low-dose of gentamicin

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animals were tested for response to hyperthermia as indicated above. Gentamicin-treated animals tended to experience fewer, less severe seizures than placebo-treated animals, though temperature of seizure onset was similar. We are still in the process of controlling for potential acute anticonvulsant effects of gentamicin and replicating these findings, but we believe that they are very promising.

In addition to confirming animals' behavioral response to gentamicin treatment, we intend to determine the effectiveness of gentamicin for increasing protein production at the molecular level. An increase in protein product in animals with only one mutant copy of the gene will be difficult to detect with currently available methods, so we plan to do these experiments on animals with two mutant copies (and that thus normally make none of the sodium channel protein product of the *SCN1A* gene) and are currently in the process of generating these animals.

Through the generous gift of Dr. Richard Gatti, we have obtained a novel compound called BZ6, which was developed specifically for use as a readthrough drug. The Gatti laboratory and collaborators have shown, in cell culture, that it is more effective at increasing protein expression than traditional readthrough drugs such as gentamicin. Although this compound has not been tested for use in the brain, its size and chemical structure suggest that it may efficiently cross the blood brain barrier. For these reasons, we believe this compound is very promising for therapy in our model and potential translation to the clinic. We plan to test its effectiveness in the DS mice using the same treatment paradigm and febrile seizure tests that were done with gentamicin.

OPKO Research Update by Dr. Hsiao

The idea of up-regulating a gene where the mutation is the cause of an untreatable disease came to me about 18 months ago. As a scientist, I sensed that the platform designed by CURna could be an exceptional fit for treating Dravet syndrome. Within a few weeks, the first compound designed by CURna had shown a promising increase of the mRNA of *SCN1A* gene in a human cell line used as a screening tool in the lab. Since then, over 150 compounds have been designed to specifically target the *SCN1A* gene in a mouse and primate for further research.

OPKO acquired CURna in February of this year. We have established a 17,000 square foot Research & Development lab in Miramar, Florida. I have recruited scientists from Pfizer, as well as others with experience in drug development, for this project. Our team has a mission to continue work on other orphan diseases of gene mutation as well as gene targets which could benefit from enhanced production of functional endogenous proteins for the purpose of modifying metabolic, neuronal, dermatological and oncology disorders.

For Dravet syndrome, OPKO has selected three candidate compounds each for mouse and primate studies, and plans to test these compounds in the next few months as Proof of Concept. We will determine the level of sodium channel protein in the brain after dosing in a Transgenic mouse and primate. We will test the transgenic mice with EEG and 24 hour video monitoring to assess the seizure frequency and severity while testing these compounds. I am excited in the progress and committed to finding a treatment option.

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