

## The Anatomy of a Clinical Trial

*Jim Wolfe - Sunday, April 21, 2013*

On June 1, the Dana's Angels Research Trust will hold its annual benefit concert to fund research for a cure for Niemann-Pick Type C (NPC), a fatal, cholesterol storage disease that affects motor and neurological functions. Past concerts have featured Smokey Robinson, Frankie Valli and the Four Seasons and Natalie Cole. This year the Beach Boys will take the stage at the Palace Theatre in Stamford.

But that is not the biggest news from DART on the NPC front.

Greenwich resident Andrew Marella, 12, who was diagnosed with NPC when he was 5, has been accepted into a promising clinical trial testing a new treatment for NPC, which was developed in part with funds from DART. Andrew is the second Marella child to be diagnosed with the disease. DART was created in 2002 when Andrew's parents, Phil and Andrea Marella, found out that their daughter Dana, who is now 18, had Niemann-Pick Type C. Since then, DART has raised nearly \$3 million toward finding a cure for NPC -- and this clinical trial is an indication that those efforts may be paying off.



Dr. Steven Walkley

Dr. Steven Walkley, director of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center at Einstein Medical Center and Scientific Advisor for DART, has been instrumental in the discovery of using Cyclodextrin, the drug that will be tested in the clinical trial, as a treatment for NPC. Greenwich Time took a Time Out with Walkley to learn about NPC, Cyclodextrin, the clinical trial and what it may mean for the future -- and for Andrew.

Q: What is NPC?

A: Niemann-Pick Type C disease is a genetic brain disease in which cholesterol and lipids accumulate in brain cells. It is a lysosomal disease, meaning that the brain's "recycling center" (the lysosome) is not working normally and the brain cells accumulate non-recycled material as a result. NPC most often does not manifest at birth; rather, clinical symptoms generally become visible in affected children between the ages of 3- and 5 years old. The type of gene mutation may be responsible for this variable onset of symptoms, but at some point, the parents and patient will notice a compromise of function. Usually, once clinical signs begin, they progress

steadily and eventually become fatal.

Q: What is the significance of a treatment reaching the clinical trial stage?

A: It is through the combined effort of many scientists and the financial support of generous donors such as DART that we have been able to reach the clinical trial for a new treatment for NPC. DART and other charities have put their support behind an idea conceived of by Jonathan Jacoby, in creating a scientist-clinician-parent research group known as Support Of Accelerated Research for NPC disease (SOAR-NPC). Working with other NPC families and organizations, SOAR has created a multidimensional collaborative drug development program searching for an effective cocktail treatment for NPC. The collaborative efforts have focused on the initiation of a clinical trial at the National Institutes of Health (NIH) to systematically evaluate the safety and efficacy of Cyclodextrin therapy for the treatment of NPC. The exceptional work that has been done in NPC animal models has guided the design of a human clinical trial. Together with the Therapeutics for Rare and Neglected Diseases (TRND) group at the NIH, as well as several NPC researchers, Johnson & Johnson, and consultants from RRD International, LLC, the collaborative team has worked to submit an Investigational New Drug (IND) application to the FDA. The fact that the drug has been approved for a phase 1 trial in humans is a significant milestone in finding an effective treatment for this fatal brain disorder.

Q: What does this NIH trial involve?

A: New therapies must be tested rigorously in a controlled setting to make sure that they are both safe in humans and truly effective against the disease. While animal studies are suggestive, and help to provide the needed information to get to the trial stage, they are not definitive. The scientists have presented enough compelling data on this new treatment, Cyclodextrin, to have received approval from the FDA to begin with a Phase 1 clinical trial in humans. This is the necessary research to get to the next stage and hopefully find an effective treatment for NPC. The trial will have three stages and may take several years to complete before the drug can be approved for widespread use by the FDA. Andrew Marella and the other few children who are participating in the current NIH trial will help determine the safety of the drug in humans. The next phases will show the efficacy of the drug.

Q: What is Cyclodextrin?

A: Cyclodextrin is a man-made compound. It is used to make substances soluble, and so it is called a "solubilizer." The Cyclodextrin molecule is made from sugar molecules and is shaped a bit like a doughnut; that is, its molecules are arranged in a circle with a cavity in the middle (hence the naming with "cyclo" and "dextrin"). The cavity traps substances inside -- making them soluble in a water solution. There are several different types of Cyclodextrin molecules, and they are used for many different purposes. For example, Febreze uses Cyclodextrin to trap odorants inside the cavity and remove them. The clinical trial will use a beta-Cyclodextrin molecule, one that has already been approved by the FDA to solubilize FDA-approved drugs. This is the first time, however, that Cyclodextrin has been used as a drug itself.

Q: How does it work?

A: How it works to alleviate the storage of cholesterol and lipids in brain cells of NPC-affected animal models is still not fully understood. While studies in animals have shown that it is remarkably effective at doing this, it does not necessarily mean it will have the same results in humans. The leading theory is that the stored cholesterol and lipids will be trapped into the cavity of the Cyclodextrin and will be removed from the brain. A number of laboratories around the world are still trying to fully understand exactly how it is able to remove these stored products in brain cells.

Q: What role did you play in discovering the use of Cyclodextrin as a treatment for NPC?

A: The use of Cyclodextrin was discovered by a graduate student, Cristin Davidson, in my lab, and simultaneously by another lab in Texas. There was a study published in 2004 about another drug that had positive results in treating NPC. We were testing this drug in my lab in the Rose F. Kennedy Center at the Albert Einstein College of Medicine and found that it wasn't the drug that was reducing the cholesterol build-up but, rather, the vehicle (Cyclodextrin) that was being used to solubilize that drug. Through a series of controlled studies we then went on to establish that it was, in fact, the Cyclodextrin that was working, not the other reported drug. Thus the discovery of Cyclodextrin as therapy for NPC disease was serendipitous!

Q: What does one hope comes from a trial like this? Is the hope for a cure? Are there other benefits? Other uses for this drug?

A: Curing NPC would be the ultimate goal. We still have a way to go. In the meantime, while Cyclodextrin is not likely a complete cure, it is the most significant treatment identified to date. There is much more we hope to learn -- such as will this drug delay the onset of clinical disease if used early? Will it reverse some clinical disease symptoms if given later? How long will the drug be effective? At the moment, if we can help the children to gain 10 years or more of quality living, it is a start. This could provide the critical window of time to develop other therapies that are even more effective. While it is too early to know if Cyclodextrin would be effective in treating other diseases, there are theories that it might help patients suffering with Alzheimer's disease, and studies on this are in progress now.

Q: Specific to Andrew, what do you hope comes from his inclusion in this trial?

A: We are hoping that Andrew will benefit from this trial in addition to providing valuable information for others. We hope the Cyclodextrin might keep him from developing all the damaging side-effects from NPC. Andrew will be heading to the NIH soon to begin the trial. The doctors there will do surgery to implant a catheter into the fluid space in his brain. Then the Cyclodextrin will be administered directly into Andrew's cerebrospinal fluid every few weeks. This first clinical phase is expected to last throughout much of 2013.

For more about DART, NPC or DART's upcoming benefit concert, visit <http://danasangels.org>.