The 2010 Fifth International Scientific, Medical & Family Conference on Barth Syndrome: Report of Scientific/Medical Sessions

By

Matthew J. Toth, PhD
Science Director, Barth Syndrome Foundation

During the last week in July the Renaissance at SeaWorld hotel in Orlando, Florida was the venue one of the truly unique meetings that deals with a rare disease. Barth syndrome is a rare but serious genetic disorder characterized by cardiomyopathy (dilated or hypertrophic often with left ventricular noncompaction and/or endocardial fibroelastosis), growth delay, exercise intolerance or extreme fatigue, neutropenia, and cardiolipin abnormalities. On July 29-30, 2010 over 65 scientists, physicians, and healthcare professionals met to hear 26 speakers and to discuss the progress in Barth syndrome research and how it may lead to better treatments. In a separate but parallel set of meetings, over 40 Barth syndrome individuals with their families also met to discuss issues of specific importance to their situation. In total, over 300 people attended this conference. The informal mixing of scientists, physicians, healthcare professionals, patients, and patient families at common meals, at the poster session, and at the social function is an invigorating, valuable, and traditional part of this conference series.

This is the fifth conference that has been hosted by the Barth Syndrome Foundation (BSF), an international, non-profit, patient-advocacy organization which also sponsors a research grant program every year. 2010 marks the 10th anniversary of the founding of the BSF by family members. Many of the speakers over the two days of the scientific/medical (Sci/Med) sessions of the conference were previous grant recipients. The chairpersons for the Sci/Med sessions were: Richard Kelley (Johns Hopkins University, Baltimore, MD); Michael Schlame (New York University, New York, NY); Barry J. Byrne (University of Florida, Gainesville, FL); and Miriam Greenberg (Wayne State University, Detroit, MI). Also included this year was a keynote lecture, “The Pathophysiology of Mitochondrial Disease”, which was delivered by Professor Douglas C. Wallace, Director of the Center of Mitochondrial and Epigenomic Medicine, Children’s Hospital of Philadelphia and University of Pennsylvania.

The scientific and medical sessions of the 2010 conference were funded in part by grants from the Office of Rare Disease Research and the National Heart, Lung and Blood Institute of the NIH.

Animal models of Barth syndrome led off the Sci/Med sessions, and the initial reports of the tafazzin knockdown mouse (provided by the BSF to all interested researchers) were quite encouraging. Tafazzin is the gene which when defective is responsible for Barth syndrome. Previous efforts in several laboratories to make a knockout mouse model have been unsuccessful for unknown reasons. Zaza Khuchua (Cincinnati Children’s Hospital Medical Center, Cincinnati, OH) and colleagues, and Michael Kiebish (Washington University School of Medicine, St. Louis, MO) revealed that this knockdown mouse model possesses the cardiolipin abnormalities expected. Interestingly, Dr. Khuchua showed left ventricular dilation and muscle mass loss in 8 month old mice which were unremarkable for this at 2 months of age. Dr. Khuchua also showed abnormal mitochondrial morphology and other ultrastructural
abnormalities in various striated muscle tissue samples. Mindong Ren (New York University, New York, NY) revealed how the *Drosophila* model of tafazzin dysfunction is being used to screen for suppressors (such as calcium-independent phospholipase A2), which can reverse the cardiolipin and sterility phenotype found in these flies. Genevieve Sparagna (University of Colorado, Boulder, CO) showed that linoleic acid diet supplementation increased tetralinoleic cardiolipin levels in a rat model of heart failure (Spontaneously Hypertensive and Heart Failure rat model: SHHF) and an extended lifespan. Carol Moreno-Quinn (Medical College of Wisconsin, Milwaukee, WI) updated the group about making a tafazzin knockdown rat model. Using exercise as therapeutic treatment, Mark Tarnopolsky (McMaster University, Hamilton, Ontario) showed how mitochondrial DNA deletions in elderly people can be reversed by exercise and what this may mean for Barth syndrome, a unique mitochondrial disease. Todd Cade (Washington University School of Medicine, St. Louis, MO) is now testing this idea of supervised aerobic exercise training (cardiac rehabilitation) to determine its effects on Barth syndrome individuals.

Todd Cade along with Carolyn Spencer and Amy Roberts (both at Children’s Hospital of Boston, Boston, MA) presented the unique physiological characteristics of Barth syndrome individuals (such as the dramatically increased respiratory exchange ratio and stable blood oxygen saturation levels with an increasing exercise gradient). The Barth Syndrome Medical Database & BioRepository, which is supported by the BSF and now by Children’s Hospital of Boston, will collect and store these data and other relevant medical information for interested researchers to use.

Colin Steward (Royal Children’s Hospital, Bristol, England) has found many unrecognized cases of Barth syndrome in the Bristol area by pursuing the neutropenia aspect of the disease and following up on unexplained male fetal deaths in family histories. Dr. Steward related his experiences of setting up a National Specialized Service for Barth Syndrome in the UK and provided insights for establishing a similar group in the US. Bram van Raam (Sanford-Burnham Institute for Medical Research, La Jolla, CA) spoke about how calcium and the mitochondria impact the neutropenia symptom often found with Barth syndrome. Andrew Aprikyan (University of Washington School of Medicine, Seattle, WA) showed how tafazzin knockdown with siRNA increased the markers of apoptosis in myeloid but not lymphoid cells.

Because Barth syndrome is a mitochondrial disease, there were several presentations about how defects in this subcellular organelle could influence the symptoms of patients. Eyal Gottlieb (Beatson Institute for Cancer Research, Glasgow, Scotland) talked about how cardiolipin provides a signaling platform and how mitochondrial fission/fusion is defective in Barth syndrome fibroblasts. Charles Hoppel (Case Western Reserve University, Cleveland, OH) provided an overview of mitochondrial diseases by focusing on oxidative phosphorylation defects. John Lynn Jefferies (Texas Children’s Hospital, Houston, TX) spoke about the cardiomyopathy found in Barth syndrome, while Quan He (Henry Ford Hospital, Detroit, MI) showed how the knockdown of tafazzin by siRNA in rat neonatal cardiac myocytes caused hypertrophy. Peter Adhihetty (University of Florida, Gainesville, FL) revealed the progress made in understanding the problems with diaphragm weakness associated with mechanical ventilation and how mitochondrial-targeted antioxidants (Szeto-Schiller peptides) may be therapeutic. James Ntambi (University of Wisconsin, Madison, WI) showed how the skin is part of the metabolic network that involves energy intake, storage, and expenditure.
Jodi Nunnari (University of California, Davis, CA) brought out the importance of cardiolipin to mitochondrial fusion. Robert Jensen (Johns Hopkins University, Baltimore, MD) illuminated the important parallels between Barth syndrome and Dilated Cardiomyopathy with Ataxia (DCMA), and discussed how mitochondrial protein transport may link the common symptoms of these two genetically distinct but similar, rare conditions. Steven Claypool (Johns Hopkins University, Baltimore, MD) showed that mutated tafazzin proteins form unstable aggregates and fail to form the proper higher order protein complexes, while Ashim Malhotra (New York University, New York, NY) identified these higher order protein complexes using a Drosophila cell model of tafazzin expression. On a research angle, Christopher McMaster (Dalhousie University, Halifax, Nova Scotia) used a systematic genome wide analysis to identify genes that interact with the yeast tafazzin gene which included several involving mitochondrial protein import and protein stability. Interestingly, Dr. McMaster is adapting his system to analyze pharmaceutical compounds that interact with the same yeast tafazzin mutant which could lead to relevant drug discovery situations. Richard Epand (McMaster University, Hamilton, Ontario) spoke about the how cardiolipin may be involved in the interaction between the adenine nucleotide transporter protein and the mitochondrial creatine kinase enzyme. Grant Hatch (University of Manitoba, Winnipeg, Manitoba) showed how overexpression of monolysocardiolipin acyltransferase (MLCL AT-1) increases the tetralinoleoyl cardiolipin levels in and improves the viability of Barth syndrome lymphoblasts.

In addition to the above presentations, twelve posters were presented in a separate session that was well received by both the Sci/Med attendees and by the families of Barth syndrome individuals. The interactions between these two groups are extremely important as both groups get to know and appreciate the details and the problems each face—a perspective that often is lacking in other science/medicine-oriented meetings.

The Varner Award for Pioneers in Science and Medicine was presented to Daniela Toniolo and posthumously to Peter Vreken. Dr. Toniolo (Research Director, National Research Council of Italy, DIBIT-San Raffaele Research Institute, Milan, Italy) was recognized for her discovery of the tafazzin gene, and the late Dr. Vreken (Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands) was recognized as the first to publish on the cardiolipin dysfunction of Barth syndrome individuals.

Also unique to this conference is the “clinic” or information gathering session hosted by Barth syndrome physicians and researchers. This “clinic” serves at least two purposes: it allows the efficient collection of historical information and physiological data from patients with this rare disease, and it provides opportunities for patients and patient family members to hear from physicians who have a substantial experience in treating Barth syndrome individuals. In 2010 six distinct IRB-approved protocols were participated in by many of the Barth syndrome individuals who attended the conference. Most of the information collected is expected to lead to publications and/or to be available through the Barth Syndrome Medical Database & BioRepository which is open to all interested researchers.

The 2010 conference included the greatest number of speakers in its history of which only the Sci/Med speakers are mentioned here. The meeting was packed with new information and new developments. The individual presentations, for both the Sci/Med sessions and the family sessions, were recorded on
DVDs and will soon be available for a nominal cost by contacting the BSF (www.barthsyndrome.org). Given the breadth and quality of the work presented at this latest conference, the next meeting in 2012 is sure to reveal even further progress towards a specific treatment for this complex but compelling rare disease.