2010 was a particularly successful year in the Beggs laboratory! We completed our first pre-clinical treatment trial in a mouse model of congenital myopathy. In addition, we continued to improve our understanding of the role that selenoprotein N, cofilin 2, tropomyosin 3, myotubularin and other congenital myopathy genes play in muscle function. Our zebrafish models of potential congenital myopathies, and our mouse models of MmD, NM, and XLMTM, enhanced our knowledge of these diseases. In 2011, we look forward to maintaining this momentum towards developing better diagnosis and treatment for families affected with congenital myopathies. Our accomplishments are a reflection of the generous support and participation of families and colleagues like you.

Thank you for your support & Happy 2011!

MYOSTATIN INHIBITION IMPROVES LIFE SPAN AND STRENGTH IN MICE WITH XLMTM

Previously, Dr. Chris Pierson in our lab showed that smaller muscle fibers in boys with XLMTM correlated with increased severity of disease. This finding suggested that increasing the size of muscle fibers might lead to increased strength. Myostatin is a naturally occurring substance in our bodies that keeps our muscles from getting too big. By inhibiting or suppressing myostatin activity, we can increase muscle size. Myostatin deficiency occurs naturally and without any known harmful health effects in several different animals, including Belgian Blue cattle and Whippet dogs, and even rarely occurs in humans. Animals and humans with myostatin deficiency have larger muscles and increased strength. Using a myostatin inhibitor (MI) called ActRIIB-mFc (courtesy of Acceleron Pharma), Dr. Michael Lawlor and his team in the Beggs Laboratory treated our colony of XLMTM mice. Treatment of these mice lead to increased muscle size and weight, resulting in increased weight gain, temporary improvement in grip strength, and an extension of lifespan by 17 percent. A previous clinical trial of a different MI in adults with a mild form of muscular dystrophy showed the drug to be safe but did not identify any notable improvement in muscle size or strength. However, ActRIIB-mFc is a new design of MI that is thought to provide more complete myostatin inhibition. Unlike other neuromuscular diseases, congenital myopathies are often characterized by the smaller size and abnormal organization of the muscle fibers. Therefore, we are hopeful that myostatin inhibition will be a beneficial treatment for patients with XLMTM and other congenital myopathies. ACE-031 (the human version of ActRIIB-mFc) clinical trials have shown the drug to be safe in humans, and the drug is currently being tested for safety and optimal dosage in boys with Duchenne muscular dystrophy (DMD). If ACE-031 proves to be a successful treatment for DMD, we hope our study will make clear its great potential for MI therapy in patients with congenital myopathies (See Lawlor et al., *Am J Pathol*, 2011, in press).
RESOURCES FOR PATIENTS

General Resources:
Muscular Dystrophy Association (www.mdausa.org)
Genereviews (www.genereviews.org)
Genetics Home Reference (http://ghr.nlm.nih.gov/)

Connections to Families:
Facebook Groups at www.facebook.com
Yahoo Groups at groups.yahoo.com
HealthShare Groups at http://healthsharegroups.org
My MDA at mymda.mda.org
Search under: CFTD, Minicore, Myopathy, Myotubular, Nemaline, or Central Core Disease

Condition Specific Resources:
CFTD:
The Caytlon Wheeler Foundation (www.caytlonwheeler.org)
CNM/MTM:
The Frase Foundation (www.joshuafrase.org)
The Info Point for CNM/MTM (www.centronuclear.org.uk)
MTM Resource Group (www.mtmrg.org)
Myotubular Trust (http://www.myotubulartrust.com)
NM:
The NM Support Group (www.nemaline.org)
A Foundation Building Strength for NM (www.buildingstrength.org)

UPCOMING EVENTS

The MTM-CNMR Foundation is July 29-31, 2011 in Minneapolis, MN, USA (www.mtm-cnm.com).
For more info email mtmfamilyconference@gmail.com.

For more info, contact David McDougall: Davidmdc@hotmail.com.

WHOLE GENOME SEQUENCING – A MOVE FOR THE FUTURE

Ten years ago, we were only able to test one gene at a time – a very slow process when you consider that humans have over 20,000 genes, thousands of which are involved in muscle function. With completion of the Human Genome Project in 2003, we now have a map of all human genes, although we still do not know the functions of many of them. This map radically changed the future of genetic testing, as it laid the foundation for the development of whole genome sequencing (WGS). Today, we are able to examine all of a person’s genes at one time by using a sophisticated machine that probes each segment of the human genome (all of our genetic material) at once and then reads the genetic code. This testing will greatly change the capabilities of clinical and research genetic testing around the world, allowing for faster, more efficient, and soon-to-be less expensive testing. However, WGS is not without its pitfalls. It is currently expensive, often costing $10,000 or more per person. The amount of data produced is immense, complex and difficult to analyze. For example, every human is estimated to have between 250,000 and 1,000,000 novel DNA variations that have not previously been reported. We know many of these variants are probably benign, but distinguishing the harmful from the benign can be very difficult and time-consuming. With the cost so high and each individual having so many changes, it is currently not feasible to perform WGS on every single patient. Nevertheless, WGS is an exciting new tool that is allowing us to identify genetic changes much more easily and rapidly in certain families or groups of similar patients. As this technology matures over the next few years, we will expand the use of WGS to help us identify more genes associated with congenital myopathies.

RECENT EVENTS & KEY PUBLICATIONS

The Beggs Laboratory Has Moved! Our laboratory is now located on the 15th floor of the Center for Life Sciences Boston, across the street from the main Hospital.

Congratulations to Dr. Alan Beggs, our laboratory director, who was awarded full professorship at Harvard Medical School in July, 2010, and to Tanya Holmes, our previous research assistant, who is pursuing her Masters degree in Forensic Sciences. We welcome our new research assistant, Jennifer Little.


CLINICAL GENETIC TESTING

Commercial genetic testing is now available for many of the genes associated with the congenital myopathies. More information is available at www.genetests.org.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ASSOCIATED GENES (% of cases with mutations in given gene)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTD</td>
<td>TPM3 (20-30%) RYR1 (?) ACTA1 (6%) SEPN1 (rare)</td>
</tr>
<tr>
<td>CNM</td>
<td>DN1M2 (?) RYR1 (?) BIN1 (rare)</td>
</tr>
<tr>
<td>XLMCM</td>
<td>MTM1 (&gt;80%)</td>
</tr>
<tr>
<td>MmD</td>
<td>SEPN1 (30-50%) RYR1 (?) ACTA1 (rare)</td>
</tr>
<tr>
<td>NM</td>
<td>ACTA1 (15-25%) TPM2/ TPM3 (&lt;10%) NDB (~50%)* TNNT1/ CFL2 (rare)</td>
</tr>
<tr>
<td>RSMD**</td>
<td>SEPN1 (?)</td>
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</tbody>
</table>

* Full sequencing and specific testing for the exon 55 deletion, a mutation more common in the Ashkenazi Jewish population, are both available. ** Rigid spine muscular dystrophy

GENES & ZEBRAFISH

Zebrafish make an excellent model for muscle disease because they breed and develop quickly and their muscle structure is remarkably similar to humans. In the lab, Dr. Vandana Gupta and her team recently identified 13 new mutated fish families with neuromuscular disease, and they are now working to identify the genes associated with the disease in each fish (for more, see: http://vectorblog.org/muscle-weakness-sliding-into-place/). Thus far, two of the 13 genes were found to be associated with known forms of muscular dystrophy in humans, offering potential models for future studies of these diseases. Two of the other “mutants” have mutations in genes not previously associated with neuromuscular disease and may represent new genes associated with congenital myopathy or other muscle diseases. Once we learn more about these genes, we will test patients with congenital myopathies and use the fish to screen potential new drugs. Dr. Gupta and her team are working to identify the defective genes in the other nine fish families, with the hope of identifying several more genes associated with congenital myopathies. Identifying these new genes will lead to improved diagnosis for families in the future, as well as a better understanding of the specific defects in muscle function and potential areas for therapy.