BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Thornton, Charles A.

eRA COMMONS USER NAME (credential, e.g., agency login): CTHORNTON

POSITION TITLE: Professor of Neurology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Iowa, Iowa City, IA	B.S.	06/1981	General Science
University of Iowa, School of Medicine	M.D.	06/1981	Medicine

A. Personal Statement

I study the molecular pathogenesis and treatment of neuromuscular diseases, with a focus on myotonic dystrophy (DM). Our group was instrumental in establishing that DM involves a new mechanism for genetic dominance, in which there is a toxic gain-of-function by mutant RNA. We developed the first mouse model showing RNA toxicity. We developed the first therapies that mitigate RNA toxicity in mouse models. We developed antisense drugs that accelerate degradation of toxic RNA or block its interaction with RNA binding proteins. We have worked on small molecule and gene therapy approaches to reduce RNA toxicity. In partnership with biotechnology companies we developed the first RNA-targeted treatment that advanced to clinical trials in DM. We helped to elucidate several fundamental aspects of DM biology, including mechanisms for genetic instability of expanded repeats, effects of toxic RNA on activity of binding proteins, and effects of misregulated alternative splicing on muscle physiology. We take a vertically-integrated approach that extends from bench to clinical research to clinical practice. We frequently conduct parallel studies of DM patients and animal models, taking advantage of the respective strengths of each. Presently we are laying the groundwork for informative clinical trials of RNA-targeted treatments in DM. For example, we developed biomarkers to assess target engagement in mice and humans. Through a multicenter consortium that I direct, we are obtaining natural history and biochemical data to inform selection of endpoints and trial design. I have been involved in the training of more than 20 pre- or post-doctoral researchers who work on translational aspects of neuromuscular diseases. I direct the Wellstone Muscular Dystrophy Specialized Research Center in Rochester, an NIH-supported center of excellence that is now in its 16th year.

B. Positions and Honors

Positions and Employment

1981-1982	Intern, University of California at Los Angeles SFV Program
1982-1985	Neurology Resident, Oregon Health Sciences University, Portland, Oregon
1986	Honorary House Staff, National Hospital for Nervous Diseases, Queen Square, London
1986-1987	Instructor in Neurology, Oregon Health Sciences University
1987-1989	Fulbright Scholar and Lecturer in Neurology, University of Zimbabwe School of Medicine
1989-1991	Fellow and Instructor, Neuromuscular Disease Center, University of Rochester
1991-1992	Fellow in Experimental Therapeutics and Senior Instructor, University of Rochester
1992-1997	Assistant Professor of Neurology, University of Rochester
1997-2006	Associate Professor of Neurology, University of Rochester
2006-present	Professor of Neurology, University of Rochester
2012-present	Saunders Family Distinguished Professor in Neuromuscular Research

Other Experience and Professional Memberships

1980-present	Alpha Omega Alpha
1990-present	American Association of Neuromuscular and Electrodiagnostic Medicine
1991-present	American Academy of Neurology, Fellow
1991-present	Working Group on Experimental Therapeutics, University of Rochester
1997-2015	Muscle Study Group, Chair of Scientific Advisory Committee
2001-2015	Muscular Dystrophy Association, Medical Advisory Committee, member

2002-present American Neurological Association
2007-2013 NIH Peer Review: Member of Skeletal Muscle and Exercise Physiology Study Section
2012-present University of Rochester Center for RNA Biology, steering committee

Honors and Awards

1987 Fulbright Senior Lecturing Award (renewed in 1988)
1997 Paul B Beeson Physician Faculty Scholar, American Federation of Aging Research
2010 Jacob's Ladder Award in Neurogenetics
2011 Hans Steinert Award for Myotonic Dystrophy Research
2013 Carrell-Krusen Neuromuscular Award
2014 Myotonic Dystrophy Foundation Outstanding Research Achievement Award
2016 NIH Javits Neuroscience Investigator Award

C. Contributions to Science

1. Elucidation of RNA gain-of-function as a novel mechanism for genetic dominance. Recognition of this mechanism came largely through our work to derive the first mouse model that reproduces the physiological, biochemical, and histologic features of myotonic dystrophy type 1 (DM1). We showed that expression of expanded CUG repeats in the 3' untranslated region of mRNA leads to DM1-like changes in skeletal muscle, including nuclear foci of expanded CUG repeat (CUG^{exp}) RNA. We showed that expanded CUG repeats in RNA form stable secondary structures that bind and activate PKR, the double stranded RNA-activated protein kinase.

    a. Tian, B., White, R.J., Xia, T., Welle, S., Turner, D.H., Mathews, M.B. & **Thornton, C.A.** (2000). Expanded CUG repeat RNAs form hairpins that activate the double-stranded RNA-dependent protein kinase PKR. *RNA*, 6:79-87. PMCID: PMC1369895.
    b. Mankodi, A., Logigian, E., Callahan, L., McClain, C., White, R., Henderson, D., Krym, M. & **Thornton, C.A.** (2000). Myotonic dystrophy in transgenic mice expressing an expanded CUG repeat. *Science*, 289:1769-1773.

2. Elucidation of MBNL sequestration as a mechanism for RNA gain-of-function in myotonic dystrophy type 1 and type 2 (DM1 and DM2). Our collaborator, Dr Maurice Swanson, isolated Muscleblind-like (MBNL) proteins as the major CUG-repeat binding proteins in mammalian cells. In studies of muscle, cardiac, and brain tissue from DM1 patients, we showed that MBNL proteins are sequestered in nuclear foci of CUG^{exp} RNA, and that free MBNL is depleted from the nucleoplasm, and that loss of functional MBNL leads to misregulated alternative splicing and other changes of the transcriptome. These effects are recapitulated by deleting *Mbnl* genes in mice.

    a. Jiang, H., Mankodi, A., Swanson, M.S., Moxley, R.T. & **Thornton, C.A.** (2004). Myotonic dystrophy type 1 is associated with nuclear foci of mutant RNA, sequestration of muscleblind proteins and deregulated alternative splicing in neurons. *Hum Mol Genet*, 13:3079-3088.
    b. Mankodi, A., Lin, X., Blaxall, B.C., Swanson, M.S. & **Thornton, C.A.** (2005). Nuclear RNA foci in the heart in myotonic dystrophy. *Circ Res*, 97:1152-1155.
    c. Lin, X., Miller, J.W., Mankodi, A., Kanadia, R.N., Yuan, Y., Moxley, R.T., Swanson, M.S. & **Thornton, C.A.** (2006). Failure of MBNL1-dependent post-natal splicing transitions in myotonic dystrophy. *Hum Mol Genet*, 15:2087-2097.
    d. Osborne, R.J., Lin, X., Welle, S., Sobczak, K., O'Rourke, J.R., Swanson, M.S. & **Thornton, C.A.** (2009). Transcriptional and post-transcriptional impact of toxic RNA in myotonic dystrophy. *Hum Mol Genet*, 18:1471-1481. PMCID: PMC2664149.

3. Elucidation of chloride channelopathy as the molecular mechanism for myotonia in myotonic dystrophy. We showed that myotonia in DM results from loss of CLCN1 chloride channels, due to misregulated alternative splicing of the *CLCN1* transcript. Similarly, we showed that misregulated alternative splicing of *CACNA1S* can aggravate myopathy by causing abnormal gating of the $Ca_V1.1$ calcium channel.

a. Mankodi, A., Takahashi, M.P., Jiang, H., Beck, C.L., Bowers, W.J., Moxley, R.T., Cannon, S.C. & **Thornton, C.A.** (2002). Expanded CUG repeats trigger aberrant splicing of ClC-1 chloride channel pre-mRNA and hyperexcitability of skeletal muscle in myotonic dystrophy. *Mol Cell*, 10:35-44.
b. Wheeler, T.M., Lueck, J.D., Swanson, M.S., Dirksen, R.T. & **Thornton, C.A.** (2007). Correction of ClC-1 splicing eliminates chloride channelopathy and myotonia in mouse models of myotonic dystrophy. *J Clin Invest*, 117:3952-3957. PMCID: PMC2075481.
c. Tang, Z.Z., Yarotskyy, V., Wei, L., Sobczak, K., Nakamori, M., Eichinger, K., Moxley, R.T., Dirksen, R.T. & **Thornton, C.A.** (2012). Muscle weakness in myotonic dystrophy associated with misregulated splicing and altered gating of Ca(V)1.1 calcium channel. *Hum Mol Genet*, 21:1312-1324. PMCID: PMC3284119.

4. Development of targeted therapeutics for DM1. We developed RNA targeted therapeutics and demonstrated that muscle symptoms of myotonic dystrophy are largely reversible in mouse models. This led to Phase I/II clinical trials of antisense oligonucleotides that are currently being analyzed.

    a. Wheeler, T.M., Sobczak, K., Lueck, J.D., Osborne, R.J., Lin, X., Dirksen, R.T. & **Thornton, C.A**. (2009). Reversal of RNA dominance by displacement of protein sequestered on triplet repeat RNA. *Science*, 325:336-339. PMCID: PMC4109973.
    b. Nakamori, M., Gourdon, G. & **Thornton, C.A.** (2011). Stabilization of expanded (CTG)*(CAG) repeats by antisense oligonucleotides. *Mol Ther*, 19:2222-2227. PMCID: PMC3242663.
    c. Wheeler, T.M., Leger, A.J., Pandey, S.K., MacLeod, A.R., Nakamori, M., Cheng, S.H., Wentworth, B.M., Bennett, C.F. & **Thornton, C.A**. (2012). Targeting nuclear RNA for in vivo correction of myotonic dystrophy. *Nature*, 488:111-115. PMCID: PMC4221572.
    d. Carrell, S.T., Carrell, E.M., Auerbach, D., Pandey, S.K., Bennett, C.F., Dirksen, R.T., & **Thornton, C.A**. (2016). Dmpk gene deletion or antisense knockdown does not compromise cardiac or skeletal muscle function in mice. *Hum Mol Genet*, 25:4328-4338. PMCID: PMC5291200

5. Development of myotonia measurements and splicing biomarkers as quantitative indicators of therapeutic response in myotonic dystrophy. These measurements and biomarkers are currently being used to assess therapeutic effects in clinical trials.

    a. Moxley, R.T., Logigian, E.L., Martens, W.B., Annis, C.L., Pandya, S., Moxley, R.T., Barbieri, C.A., Dilek, N., Wiegner, A.W. & **Thornton, C.A**. (2007). Computerized hand grip myometry reliably measures myotonia and muscle strength in myotonic dystrophy (DM1). *Muscle Nerve*, 36:320-328.
    b. Logigian, E.L., Ciafaloni, E., Quinn, L.C., Dilek, N., Pandya, S., Moxley, R.T., & **Thornton, C.A.** (2007). Severity, type, and distribution of myotonic discharges are different in type 1 and type 2 myotonic dystrophy. *Muscle Nerve*, 35:479-485.
    c. Heatwole, C.R., Eichinger, K.J., Friedman, D.I., Hilbert, J.E., Jackson, C.E., Logigian, E.L., Martens, W.B., McDermott, M.P., Pandya, S.K., Quinn, C., Smirnow, A.M., **Thornton, C.A.** & Moxley, R.T., (2011). Open-label trial of recombinant human insulin-like growth factor 1/recombinant human insulin-like growth factor binding protein 3 in myotonic dystrophy type 1. *Arch Neurol*, 68:37-44. PMCID: PMC3374954
    d. Nakamori, M., Sobczak, K., Puwanant, A., Welle, S., Eichinger, K., Pandya, S., Dekdebrun, J., Heatwole, C.R., McDermott, M.P., Chen, T., Cline, M., Tawil, R., Osborne, R.J., Wheeler, T.M., Swanson, M.S., Moxley, R.T., & **Thornton, C.A.** (2013). Splicing biomarkers of disease severity in myotonic dystrophy. *Ann Neurol*, 74:862-872. PMCID: PMC4099006.

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1XExiY2glbp/bibliography/40176325/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R37 NS094393 (Thornton) 09/01/15–06/30/20
NIH
Therapeutic Modulation of Myotonic Muscular Dystrophy
The goal of this project is to define therapeutic properties of antisense drugs for myotonic dystrophy.
Role: PI

MDA Clinical Network (Thornton) 01/01/13-12/31/18
Myotonic Dystrophy Clinical Research Network
The goal of this project is to develop a multicenter Clinical Research Network for studies of myotonic dystrophy.
Role: PI

P50 NS048843 (Thornton) 09/30/03-08/31/23, recently extended to 2023
Wellstone Muscular Dystrophy Specialized Research Center
The goal of this Center is to delineate disease mechanisms, establish clinical endpoints and biomarkers for trials, and develop new therapies for myotonic dystrophy.
Role: PI and Director

R01 FD006071 (Johnson and Thornton) 09/15/2017-08/31/2022
Establishing Biomarkers and Clinical Endpoints in Myotonic Dystrophy Type-1
The goal of this project is to characterize natural history in a cohort of 500 patients, enrolled across centers in the Myotonic Dystrophy Clinical Research Network
Role: Co-PI

Completed Research Support

R21 NS093177 (Thornton) 07/01/15-06/30/18
Biomarkers of Therapeutic Response in Myotonic Dystrophy
The goal of this program is to develop splicing biomarkers of myotonic dystrophy for use in clinical research, trials, and clinical practice.
Role: PI

U01NS072323 (Thornton) 04/01/11-03/31/17
Antisense oligonucleotide treatment for myotonic dystrophy
The goal of this project was to develop an antisense drug treatment for myotonic dystrophy.
Role: PI

R01 AR 49077 (Thornton) 09/01/02-08/31/13
RNA-Mediated Disease Mechanisms in the Myotonic Dystrophies
The goal of this project was to define RNA dominant disease mechanisms in myotonic dystrophy.
Role: PI

R01 FD003716 (Moxley) 06/01/11-05/31/16
Phase II: Mexiletine Treatment of Myotonic Dystrophy
The goal of this project was to examine mexiletine as a treatment for myotonia in myotonic dystrophy. .
Role: Co-Investigator