BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Chamberlain, Joel Ranier	Research Assistant Professor (UW title for Assistant Professor in a clinical department)
eRA COMMONS USER NAME (credential, e.g., agency login) jrcham	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Tulane University, New Orleans, LA	BS	1987	Biology, with honors
University of Michigan, Ann Arbor, MI	PhD	1997	Cell & Molecular Bio
University of Michigan, Ann Arbor, MI	Postdoc	2000	Gene Therapy
University of Washington, Seattle, WA	Postdoc	2004	Gene Therapy
University of Washington, Seattle, WA	Postdoc	2005	Gene Therapy

A. Personal Statement

During my career I gave birth to daughter born 11/96 (graduate school) and twin boys 6/06 (early faculty).

The goal of the proposed research project is to further develop a therapeutic RNAi strategy to greatly reduce mRNA expression that leads to FSHD. I have published a **proof-of-principle** study of **systemic** delivery of short hairpin RNAs via AAV6 to reverse a muscle degenerative phenotype in the FRG1 mouse, while developing methods for silencing DUX4 expression in cultured FSHD myoblasts, postnatal mice expressing exogenous *DUX4* mRNA, and in the DUX4-2.5 (L42) mice all available in my laboratory, or other transgenic mice that may become available. I have recently targeted the *HSA* mRNA in the HSA^{LR} model of DM1 to mitigate the toxic RNA-gain-of-function effects of expression of the expanded CTG repeat (manuscript in preparation). **The studies proposed here are expected to move the RNAi approach forward quickly to provide key preclinical data**. My co-investigator, Dr. Stephen Tapscott, has identified human biomarkers that will be screened following DUX4 targeted knockdown in FSHD cells *in vitro* and has used synthetic siRNAs targeting DUX4 to reverse expression of the identified DUX4 biomarkers. I also have close collaborations with Dr. Dan Miller (UW, Seattle, WA) and Dr. Silvère van der Maarel (LUMC, Leiden, The Netherlands) that are both experts in the FSHD field. Development of RNAi-based therapies for FSHD and use of RNAi as a tool for understanding FSHD requires expertise in the fields of RNA biology, molecular biology, and gene therapy. My training is extensive in all of these areas. Prior to graduate school I trained in muscle and molecular biology in the lab of C. Thomas Caskey at Baylor College of Medicine, a Howard Hughes Laboratory Investigator and a leader in the field of human genetic disease of muscle. In graduate school I studied RNA biology with David Engelke, University of Michigan, who published early papers on expression of RNA ribozymes from strong RNA pol III promoters. He used these promoters to publish a seminal paper on expression of shRNAs to carry out RNAi. As a postdoctoral fellow in David Russell's laboratory at UW, I gained experience in gene therapy focusing on engineering AAV to carry out gene targeting to reverse a collagen disease phenotype in patient mesenchymal stem cells that resulted in a first-authored publication in *Science*. Subsequently, I initiated a program to develop RNAi for treating dominant genetic disease of muscle as a faculty member in the UW Department of Medicine, Division of Medical Genetics. This line of research combined my muscle and molecular biology experience prior to graduate school, my RNA biology experience in graduate school, and my gene therapy vector development skills as a postdoctoral fellow. I have initiated many productive collaborations, organizing a team of investigators that resulted in a gene therapy publication in *Science* as a postdoctoral fellow. I now have strong collaborations with experienced leaders in the FSHD field, mentioned above, and with Dr. Charles Thornton (URMC, Rochester, NY), PI of the Rochester Wellstone Center. My laboratory has made significant progress in initiating development of systemic RNAi vectors targeting *LacZ* (ROSA26 mice as test model), *DUX4, FRG1,* and *HSA*. I have deep insight into the challenges associated with adapting an RNAi treatment to the whole musculature and am well positioned in the muscle community in Seattle to continue developing this approach as a treatment for dominant muscular dystrophy.

B. Professional Positions and Honors:

Positions and Employment

1987-1989 Research Technician, Dr. C. Thomas Caskey,
Institute for Molecular Genetics, Baylor College of Medicine

1990-1991 Research Technician, Dr. David R. Engelke, Department of Biochemistry,
University of Michigan Medical School

1991-1997 Graduate Student, Dr. David R. Engelke, Molecular and Cellular Biology Program,
University of Michigan Medical School

1994 Teaching Assistant, Molecular and Cellular Biology, University of Michigan Medical School
1998-2000 Postdoctoral Fellow, Dr. Blake J. Roessler, University of Michigan Medical School
2001-2003 Senior Postdoctoral Fellow, Dr. David R. Russell, University of Washington School of Medicine
2004-2005 Acting Assistant Professor, Division of Medical Genetics, Department of Medicine,
University of Washington School of Medicine

2006- Research Assistant Professor, Division of Medical Genetics, Department of Medicine,
University of Washington School of Medicine

Honors

1987 Graduated with departmental honors in Biology (Tulane University)

1995 Outstanding Cellular and Molecular Biology graduate program research presentation –First place at CMB Annual Research Symposium
2000 National Research Service Award, National Institutes of Health
2002 Children's Brittle Bone Foundation, Post-doctoral Fellowship
2002 Travel Grant Award, American Society of Gene Therapy, Oral Abstract Presentation
2003 Keystone Symposia Scholarship "From Stem Cells to Therapy" Steamboat Springs, CO – Abstract selected for oral presentation

Professional Memberships

2000- Member, American Society for Gene and Cell Therapy

2005, 2009- Member, Oligonucleotide Therapeutic Society

2009- Member, American Society for Human Genetics

2010-11 Member, American Association of Neuromuscular & Electrodiagnostic Medicine

2011- Member, American Academy of Neurology

C. Selected Peer-reviewed Publications (selected from 18 peer-reviewed publications)**:**

Most relevant to the current application

Bortolanza, SB, Nonis, A, Sanvito, F, Maciotta, S, Sitia, G, Wei, J, Torrente, I, Di Serio, C, *Chamberlain, JR, and *Gabellini, D: AAV6-mediated systemic shRNA delivery reverses disease in a mouse model of facioscapulohumeral muscular dystrophy. *Mol Therapy* 2011; doi:10.1038/mt.2011.153. *Chamberlain and Gabellini co-corresponding authors.

Chamberlain JR, Deyle, DR, Schwarze U, Wang P, Hirata RK, Li Y, Byers PH, Russell DW: Gene targeting of mutant *COL1A2* allelles in mesenchymal stem cells from individuals with osteogenesis imperfecta. *Mol Ther* 2008; 16:187-193.

Chamberlain JR, Schwarze U, Wang PR, Hirata RK, Hankenson KD, Pace JM, Underwood RA, Song KM, Sussman M, Byers PH, Russell DW: Gene targeting in stem cells from individuals with osteogenesis imperfecta. *Science* 2004; 303:1198-1201.

Hirata R, Chamberlain J, Dong R, and Russell DW: Targeted transgene insertion into human chromosomes by adeno-associated virus vectors. *Nat Biotechnol* 2002; 20:735-738.

Chamberlain JR, Lee Y, Lane WS, and Engelke DR: Purification of the nuclear RNase P holoenzyme complex reveals extensive subunit overlap with RNase MRP. *Genes Dev* 1998; 12:1678-1690.

Additional publications of importance

Chamberlain, JR, and Chamberlain, JS: Muscling in: Gene therapies for muscular dystrophy target RNA. *Nat Medicine* 2009; 16:170-171.

Banks, GB, Combs, AC, Chamberlain, JR, and Chamberlain, JS: Molecular and cellular adaptations to chronic myotendinous strain injury in *mdx* mice expressing a truncated dystrophin. *Hum Mol Genet* 2008; 17:3975-3986. PMC2638580

Kesisoglou, F, Chamberlain, JR, Schmiedlin-Ren P, Katz A, Fleisher D, Roessler B, Zimmerman E: Chimeric Ad5 vectors expressing the short fiber of Ad41 show reduced affinity for human intestinal epithelium. *Mol Pharmaceutics* 2005; 2:500-508.

Thomas BC, Chamberlain J, Engelke DR, and Gegenheimer P: Evidence for an RNA-based catalytic mechanism in eukaryotic nuclear ribonuclease P. *RNA* 2000; 6:554-562.

Fan H, Goodier JL, Chamberlain JR, Engelke DR, and Maraia RJ: The human La antigen phosphoprotein can modulate processing of eukaryotic pre-tRNA. *Mol Cell Biol* 1998; 18:3201-3211.

Lee Y, Kindelberger DW, Lee J-Y, McClennen S, Chamberlain JR, and Engelke DR: Nuclear pre-tRNA terminal structure and RNase P recognition. *RNA* 1997; 3:175-185

Chamberlain JR, Pagán-Ramos E, Kindelberger DK and Engelke DR: An RNase P RNA subunit mutation affects ribosomal RNA processing. *Nucleic Acids Res* 1996; 24:3158-3166.

Chamberlain JR, Tranguch AJ, Pagan-Ramos E, Engelke DR. Eukaryotic nuclear RNase P: structures and functions. *Prog Nucleic Acid Res Mol Biol* 1996; 55:87-119.

Chamberlain JS, Chamberlain JR, Fenwick RG, et al.: Diagnosis of Duchenne and Becker muscular dystrophies by polymerase chain reaction: A multicenter study. *JAMA* 1992; 267:2609-2615.

Chamberlain JS, Farwell NJ, Ranier JE, Cox GA and Caskey CT: PCR analysis of dystrophin gene mutation and expression. *Journal of Cell Biochemistry* 1991; 46:255-259.

Chamberlain JS, Gibbs RA, Ranier JE, Nguyen PN and Caskey CT: Deletion screening of the Duchenne muscular dystrophy locus via multiplex DNA amplification. *Nucleic Acids Res* 1988; 16:11141-11156.

Chamberlain JS, Pearlman JA, Muzny DM, Gibbs RA, Ranier JE, Reeves AA and Caskey CT: Expression of the murine Duchenne muscular dystrophy gene in muscle and brain. *Science* 1988; 239:1416-1418.

D. Research Support

Ongoing Research Support

Muscular Dystrophy Association, Inc. Chamberlain JR (PI) 04/01/2012-3/31/2015
RNA interference-based treatment of FSHD modeled in mice
The goals of this project are to exogenously express *DUX4* in postnatal mice to establish bodywide muscle expression of DUX4 and reverse the toxic effects of its expression with systemic DUX4-targeted RNAi treatment.

Pacific Northwest Friends of FSH Muscular Dystrophy Chamberlain JR (PI) 07/01/2011-06/30/2012
Development of a postnatal mouse model of FSHD
The goal of this project is to establish an *in vivo*, postnatal mouse model of FSHD using AA6 delivery of DUX4 expression cassettes.

Completed Research Support

Muscular Dystrophy Association, Inc. Chamberlain JR (PI) 04/01/2010-3/31/2012

RNA interference as an investigative and therapeutic tool for FSHD (MDA172830)
The goals of this project are to develop and test RNA interference expression cassettes to reduce expression of a *DUX4* mRNA in cultured muscle cells *in vitro* and *FRG1* mRNA *in vivo* in the FRG1 mouse model of FSHD
Role: PI

R03 AR056107 Chamberlain JR (PI) 04/01/2008-3/31/2011
Development of RNA interference for treatment of myotonic dystrophy in the HSALR mouse
The goals of this project were to generate and test therapeutic RNA interference tools to reduce expression of a pathologic mRNA in a mouse model of myotonic dystrophy
Role: PI

Pacific Northwest Friends of FSH Muscular Dystrophy Chamberlain JR (PI) 07/01/2007-06/30/2009
Development of an RNAi-based therapy for FSHD
The goal of this project was to develop systemic delivery of therapeutic RNA interference for knockdown of *FRG1* and *DUX4* in the FRG1 mouse model of facioscapulohumeral muscular dystrophy and in a *DUX4* cell culture expression system
Role: PI

U54 HD47175 Chamberlain JS (PI) 08/01/2005 to 7/31/2007
The Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center: Seattle
The goal of this project was to develop vectors to delivery therapeutic RNA interference expression cassettes for targeting *lac*Z mRNA in the ROSA26 mouse as a test model for in vivo treatment of dominant genetic disease and to adapt this method to treatment of the HSA^{LR} mouse model of myotonic dystrophy.
Role: Faculty Fellowship Trainee