Research from a Global Perspective - The 2013 International Myotonic Dystrophy Consortium Report

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Baylor College of Medicine

- focused only on myotonic dystrophy, both type 1 and type 2
- first meeting was in 1997 and it has been held every other year since
- brings together basic researchers, clinical researchers and DM families

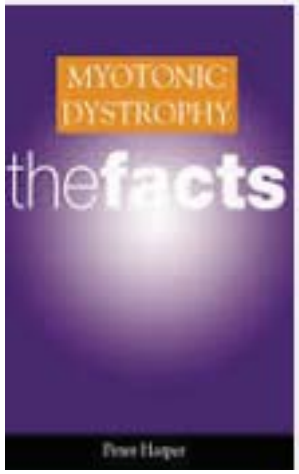
Clinical and basic researchers from around the world presented at IDMC-9

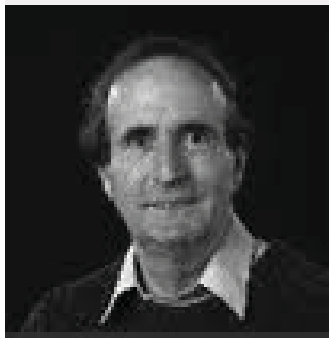
Overview

1. Multiple types of research presented and discussed
2. Basic Research Results
3. Clinical Research Results
4. Final thoughts

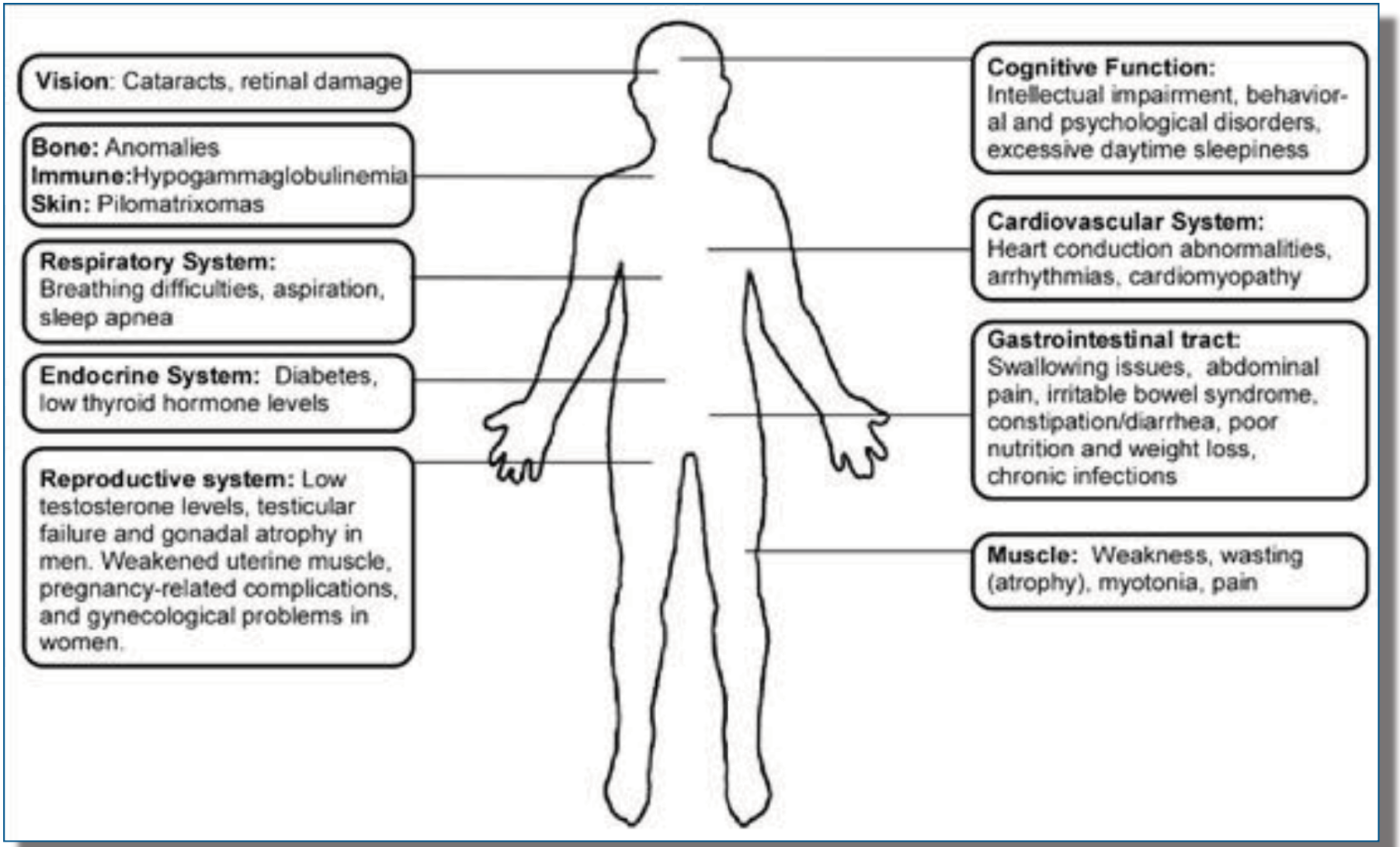
"[Myotonic dystrophy]... is probably the most variable disorder known in medicine, something that causes difficulties to doctors in recognizing it, as well as to patients and their families."

Prof. Peter Harper, "Myotonic Dystrophy: The Facts"





Myotonic dystrophy is the most common cause of muscular dystrophy in adults



From: Myotonic Dystrophy Foundation

Many kinds of research presented

Basic research – what goes wrong in the disease?

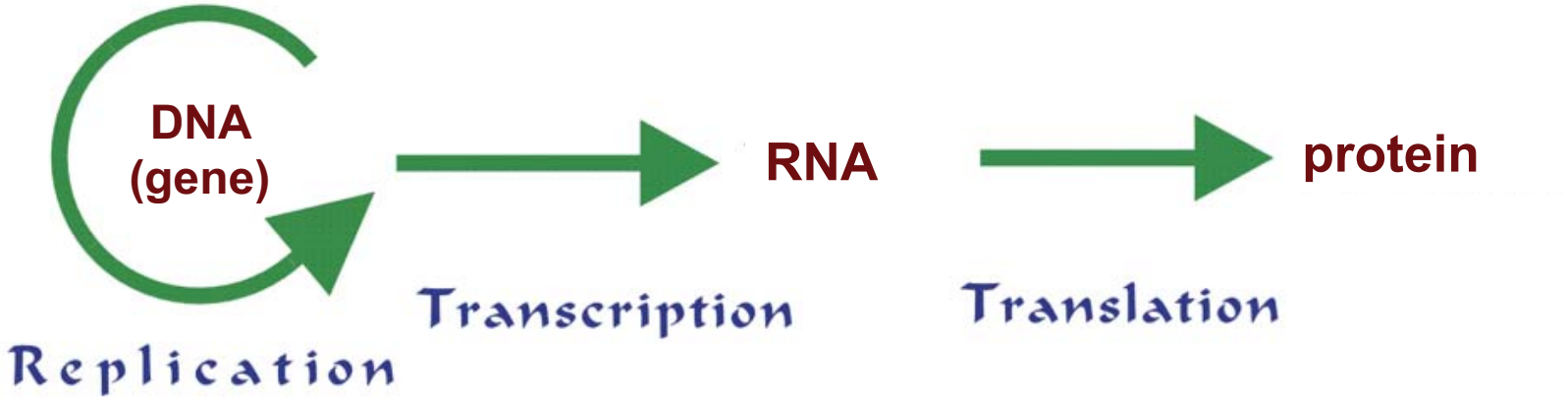
Basic research – basic testing for therapeutic approaches

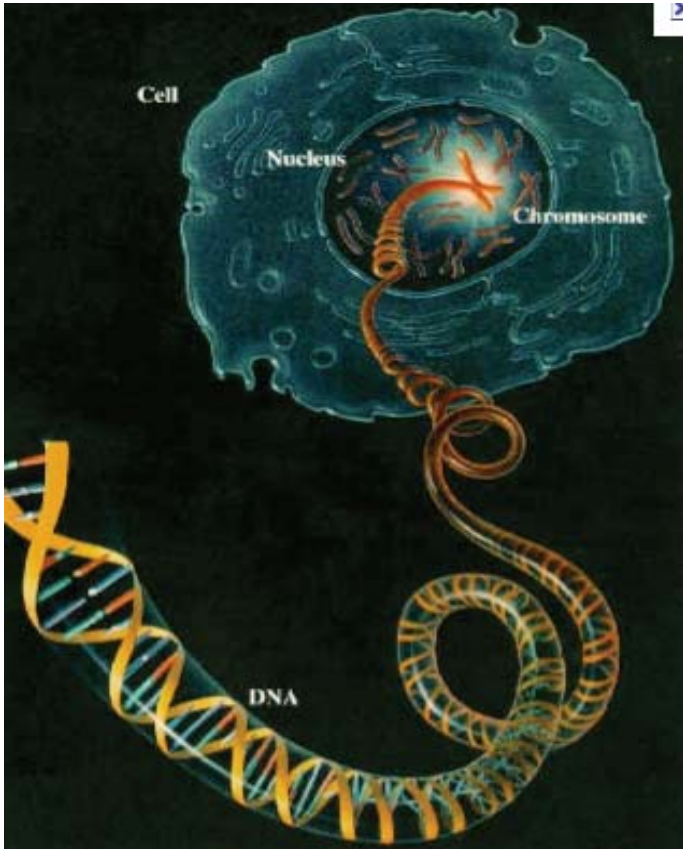
Clinical research – characterize features of the disease

Clinical research – how to provide support?

Clinical research – therapeutic trials


Basic Research


DNA
(gene)
RNA
protein
Transcription
Translation
Replication


Cell
Nucleus
Chromosome
DNA

G A T C A A T

The Myotonic Dystrophy 1 gene has extra DNA

from 80 to >4000 CTG repeats

Myotonic Dystrophy 1 gene (DMPK)

DNA
(*DMPK* gene)

CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG

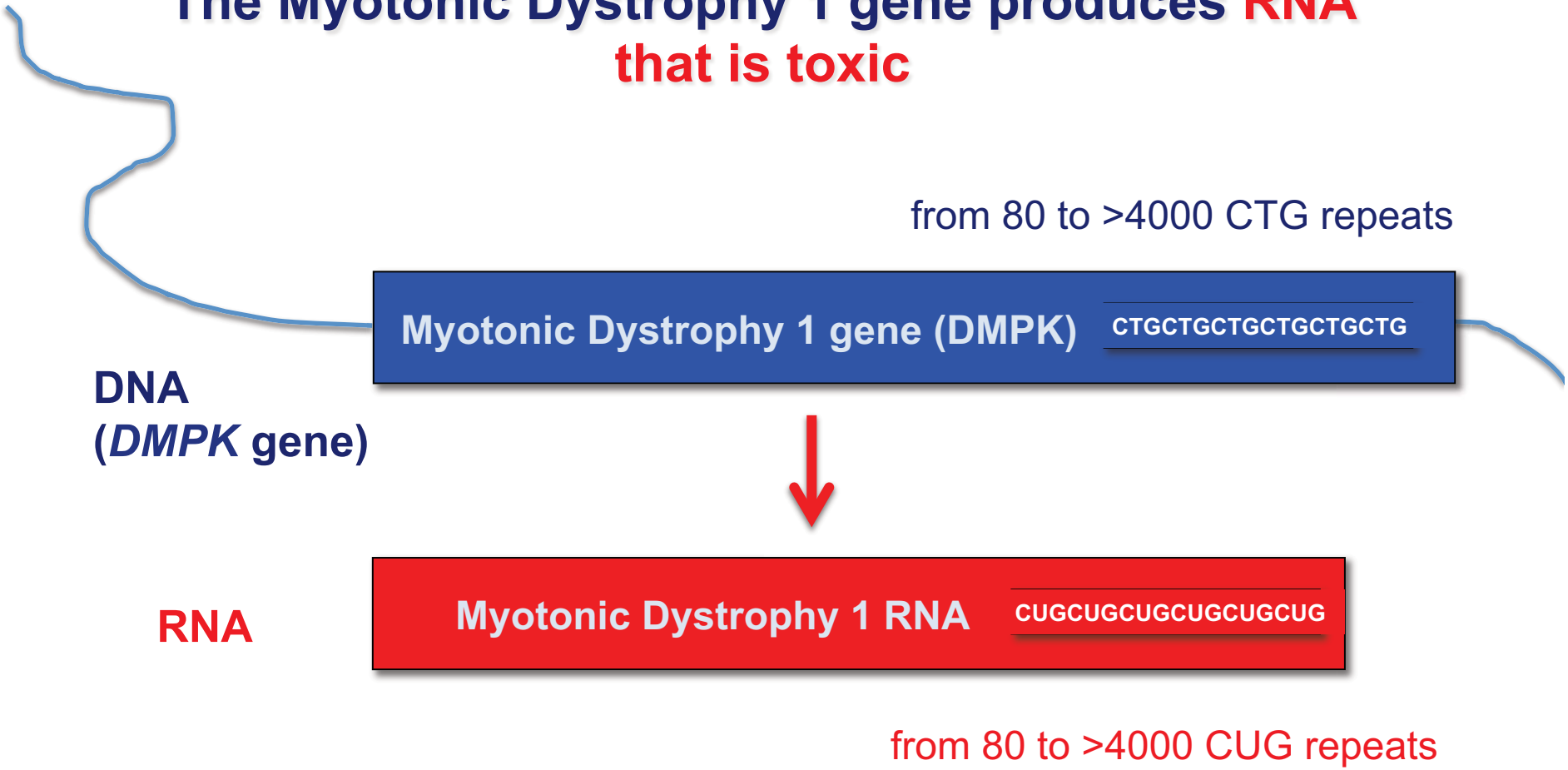
The Myotonic Dystrophy 1 gene has extra DNA

from 80 to >4000 CTG repeats

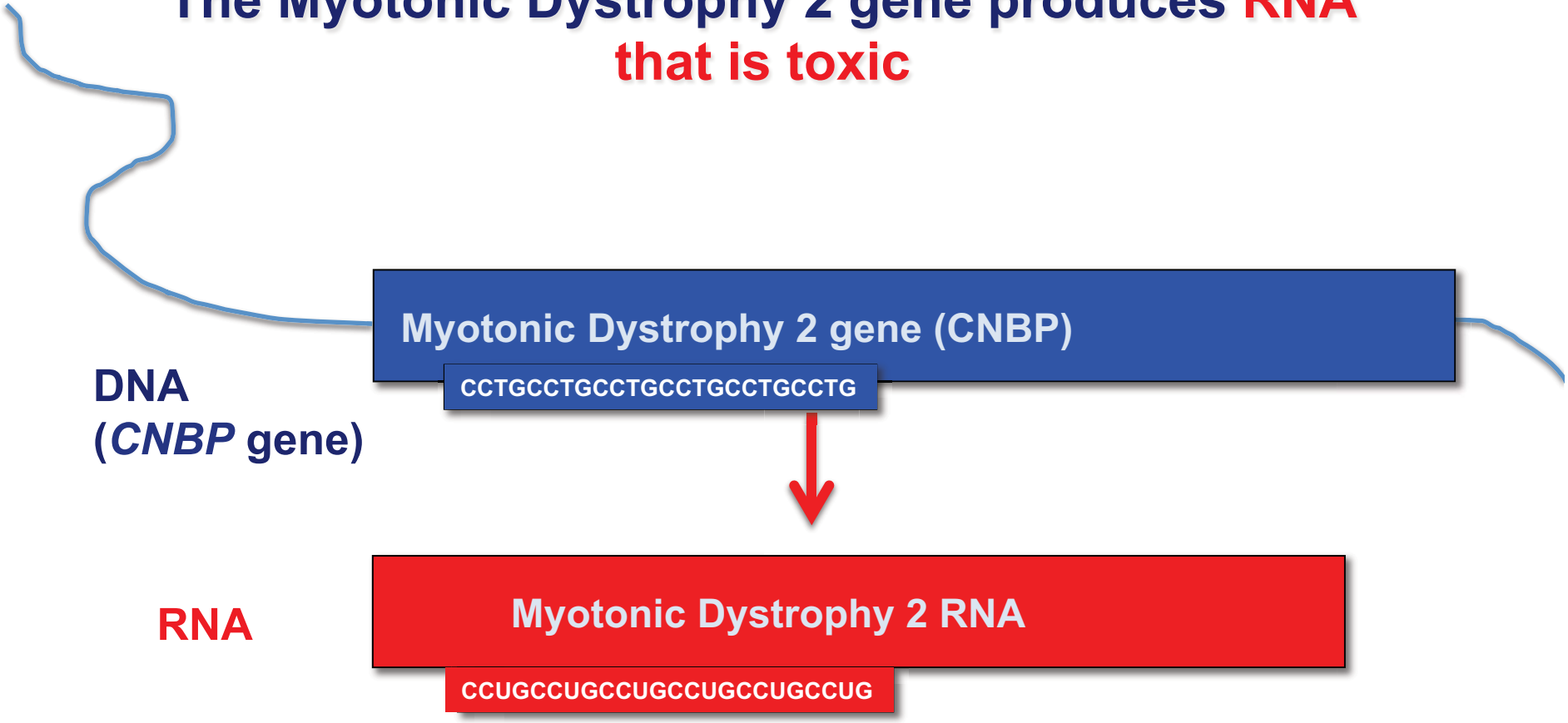
Myotonic Dystrophy 1 gene (DMPK) CTGCTGCTGCTGCTGCTG

DNA
(*DMPK* gene)

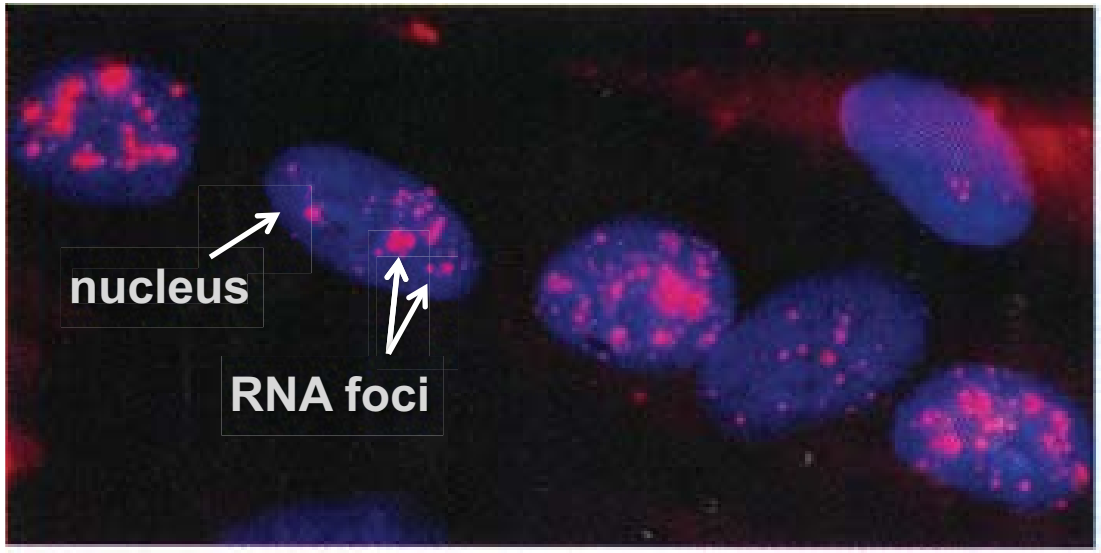
The Myotonic Dystrophy 1 gene produces RNA that is toxic



The Myotonic Dystrophy 2 gene produces RNA that is toxic



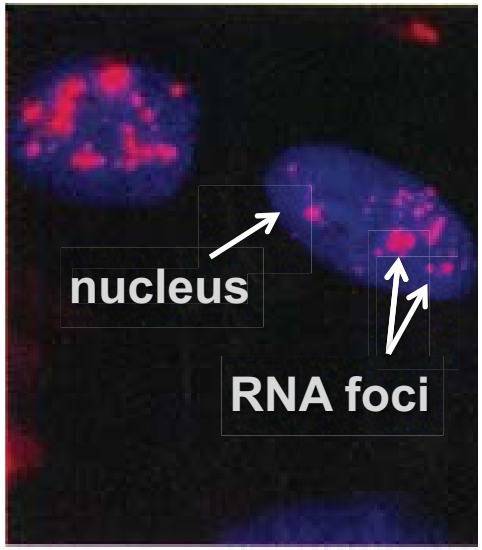
The toxic RNA gets stuck in the nucleus as “RNA foci”

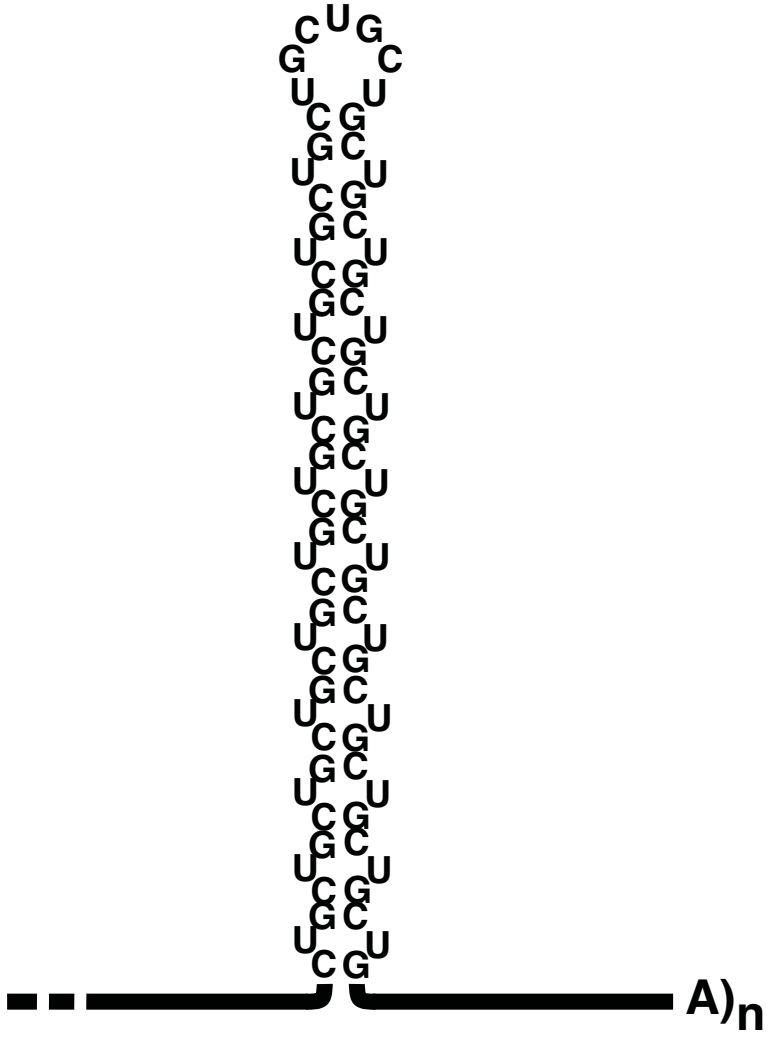


Davis et al.
PNAS 94, 7388-7393

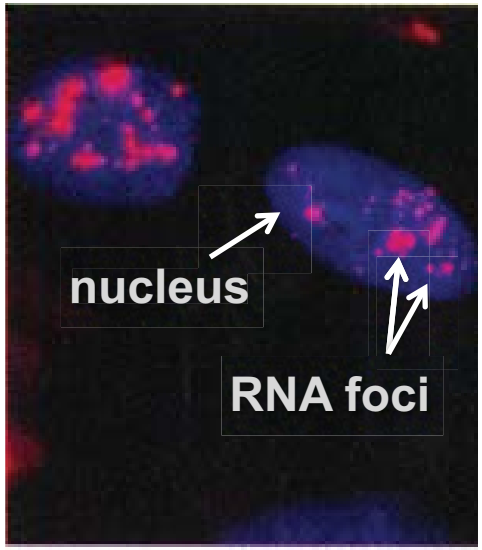
This repeat RNA disrupts normal functions in the cell

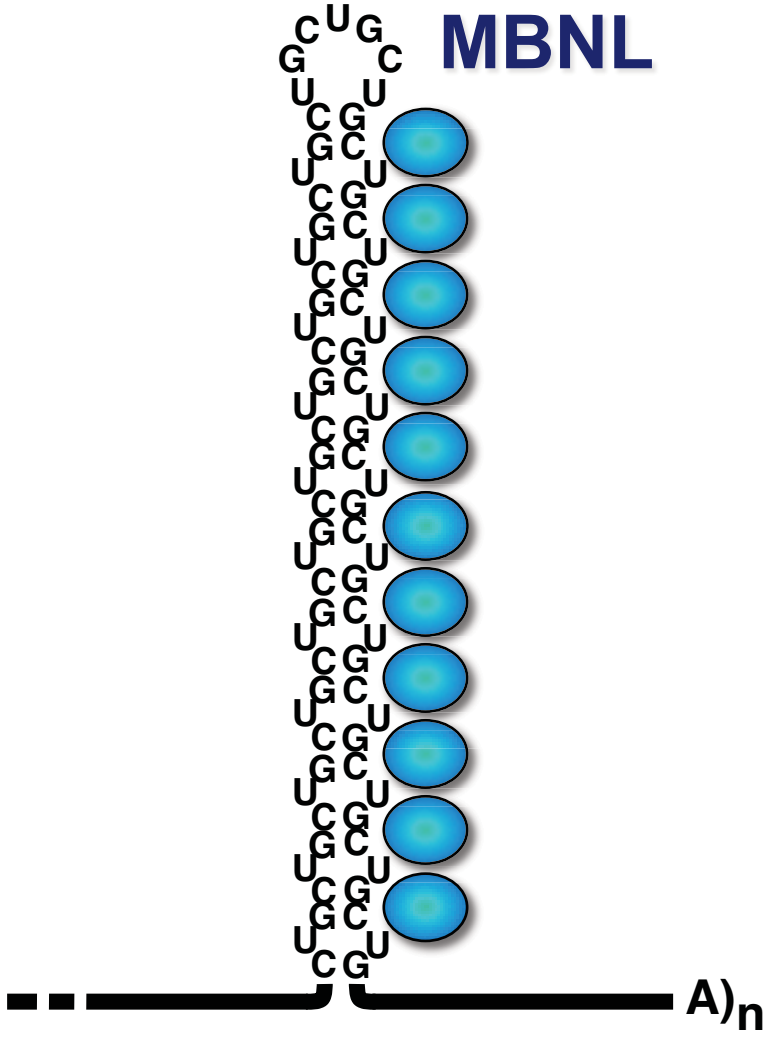
The toxic RNA gets stuck in the nucleus as “RNA foci”





The protein called MBNL binds to the repeat RNA and is inactivated





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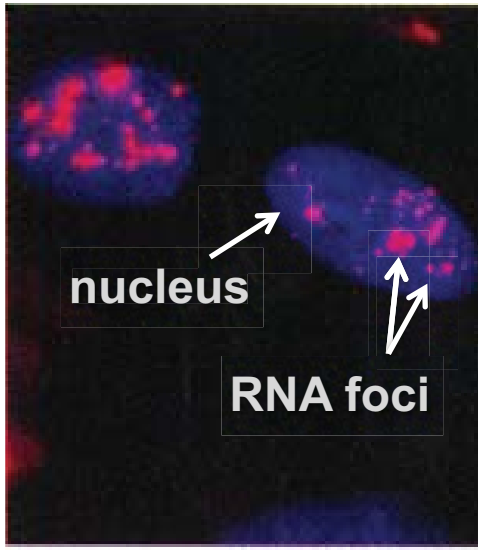

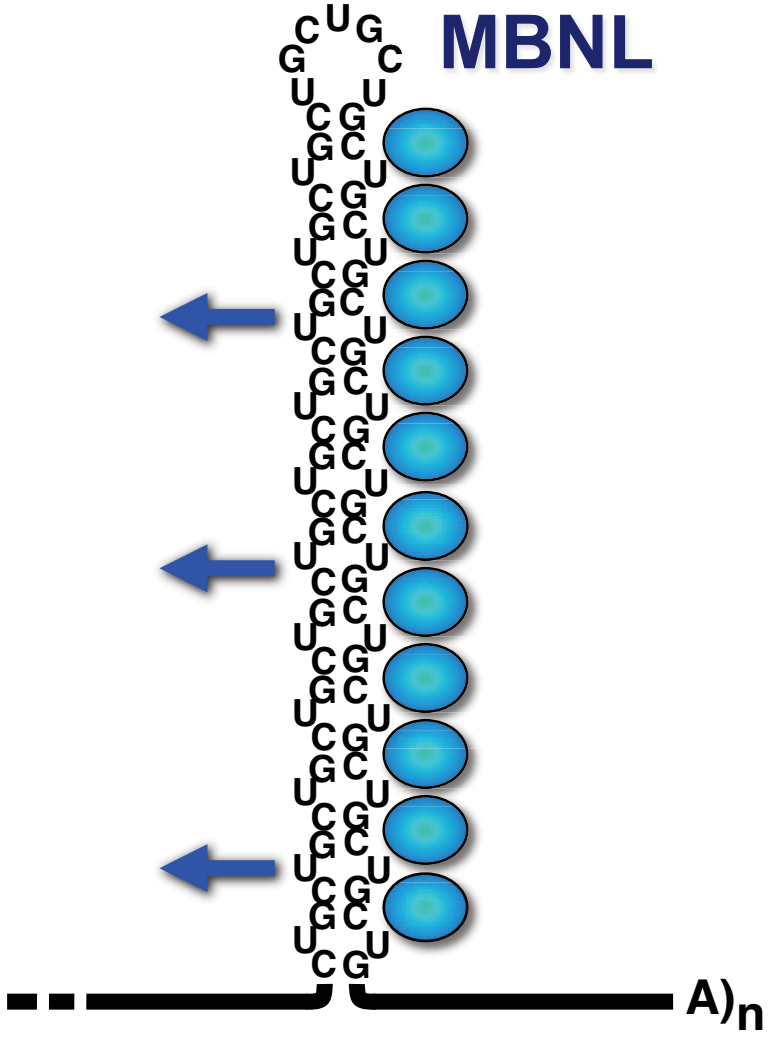

Experimental “models” for myotonic dystrophy

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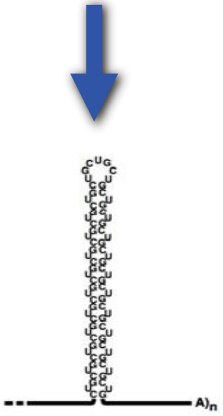
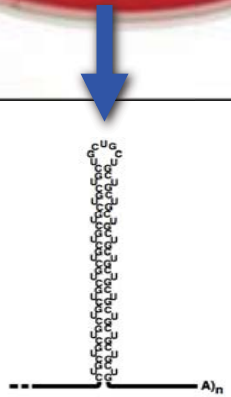
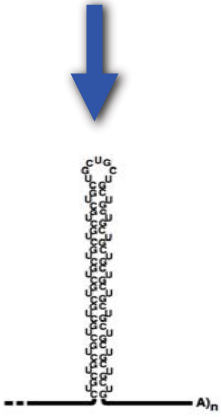
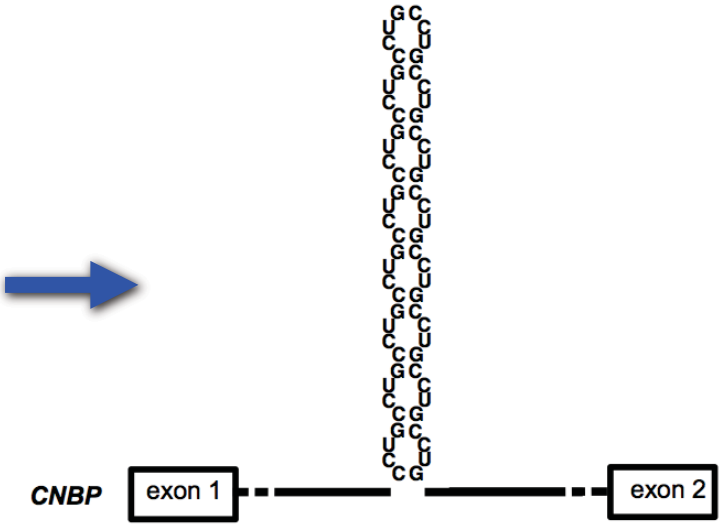






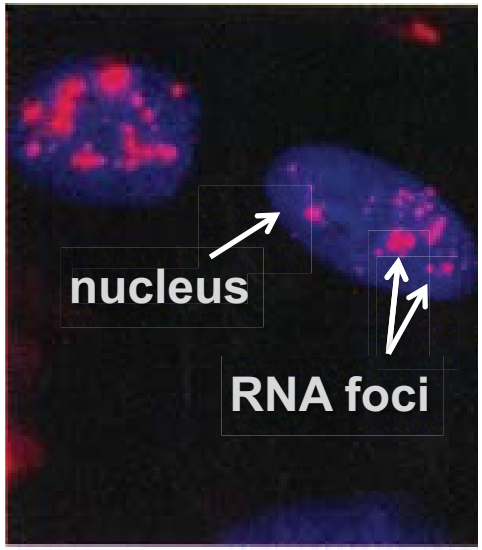
Muscle and Brain-specific Inducible Mouse Models of DM2

CLEARY John [1 2], MARGOLIS Jamie [3], ZU Tao [1 2], REID Tammy [1 2], LIU Yuanjing [1 2], CHAMBERLAIN Christopher M. [3 2 1], KANG Yuan-Lin [3], RANUM Laura P.W [1 2]



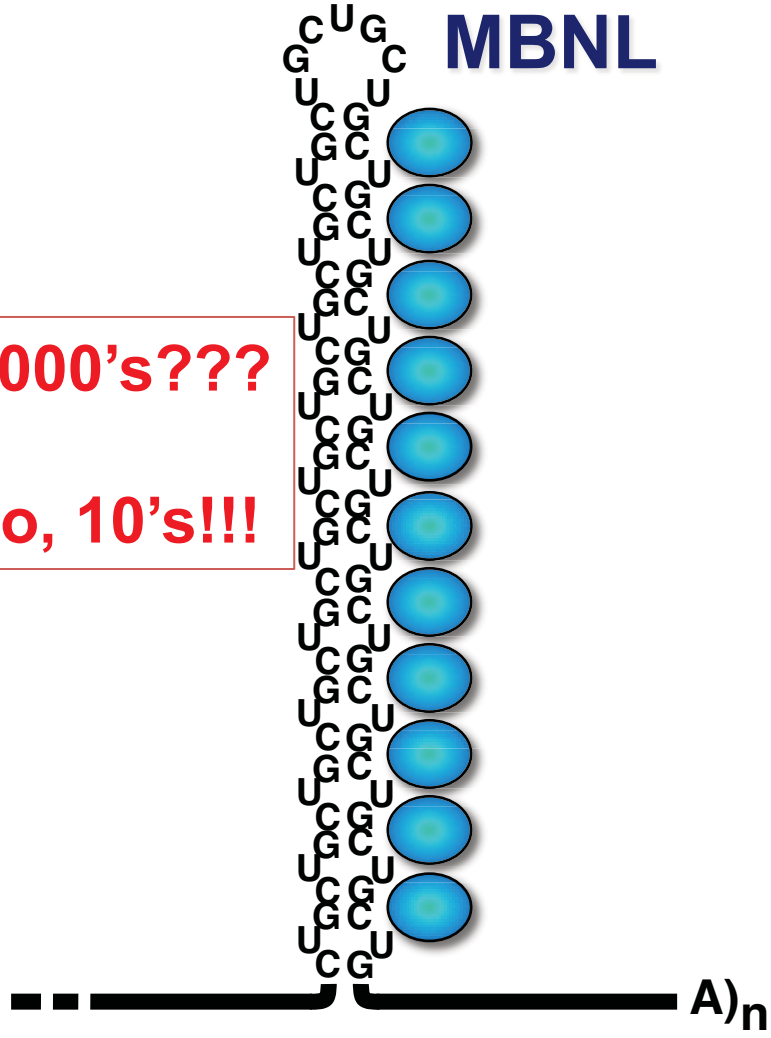
- CCUG)300 but not CCUG)5 cause DM skeletal muscle pathology in mice
- turning off the RNA reverses some features of the disease in muscle
- currently testing mice in which the RNA is produced in brain

A small number of RNA molecules cause the problem



1000's???

no, 10's!!!



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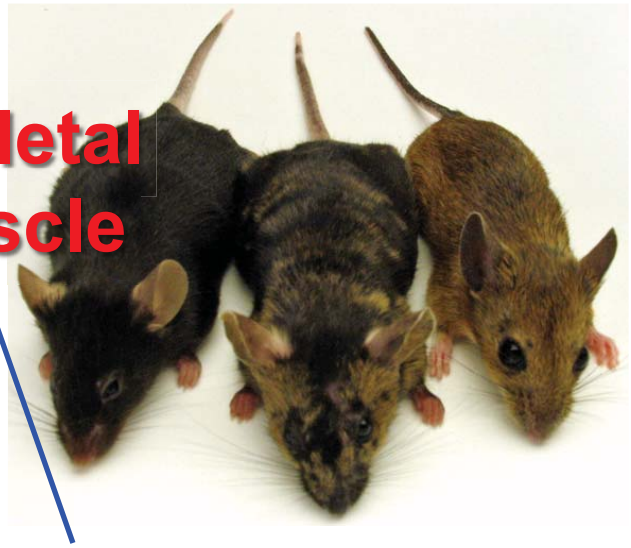
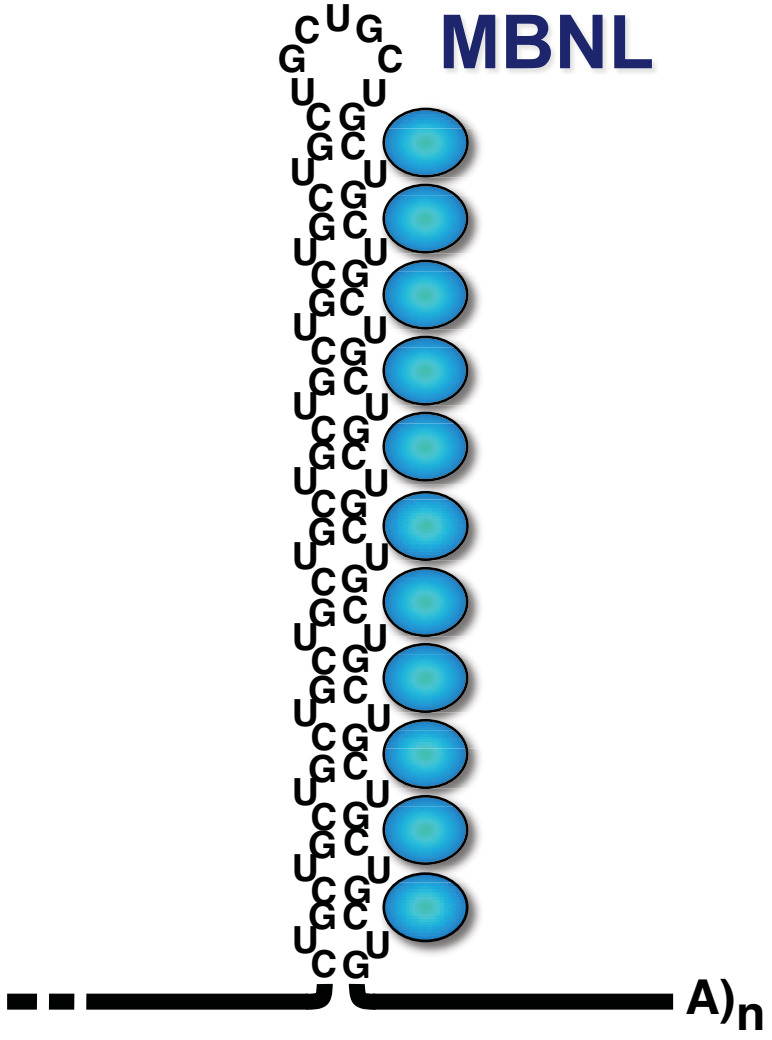


skeletal muscle

Mbnl1



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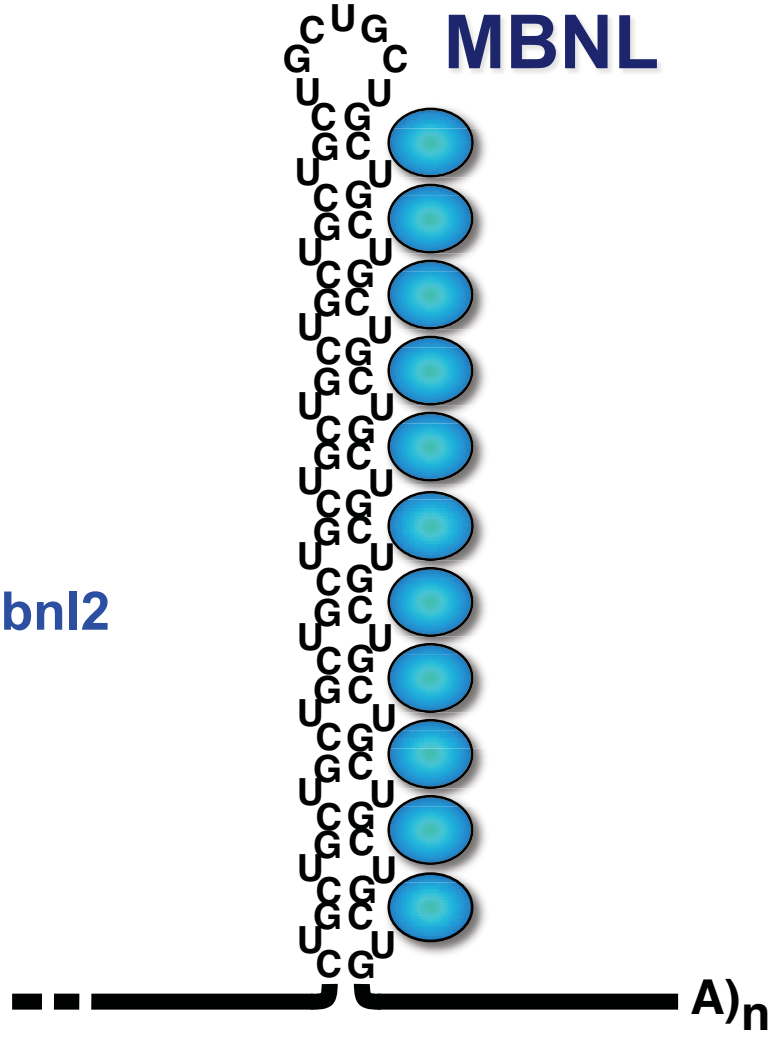

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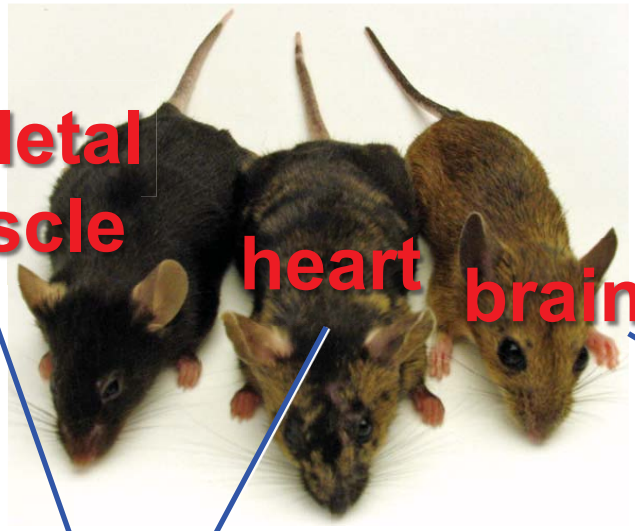
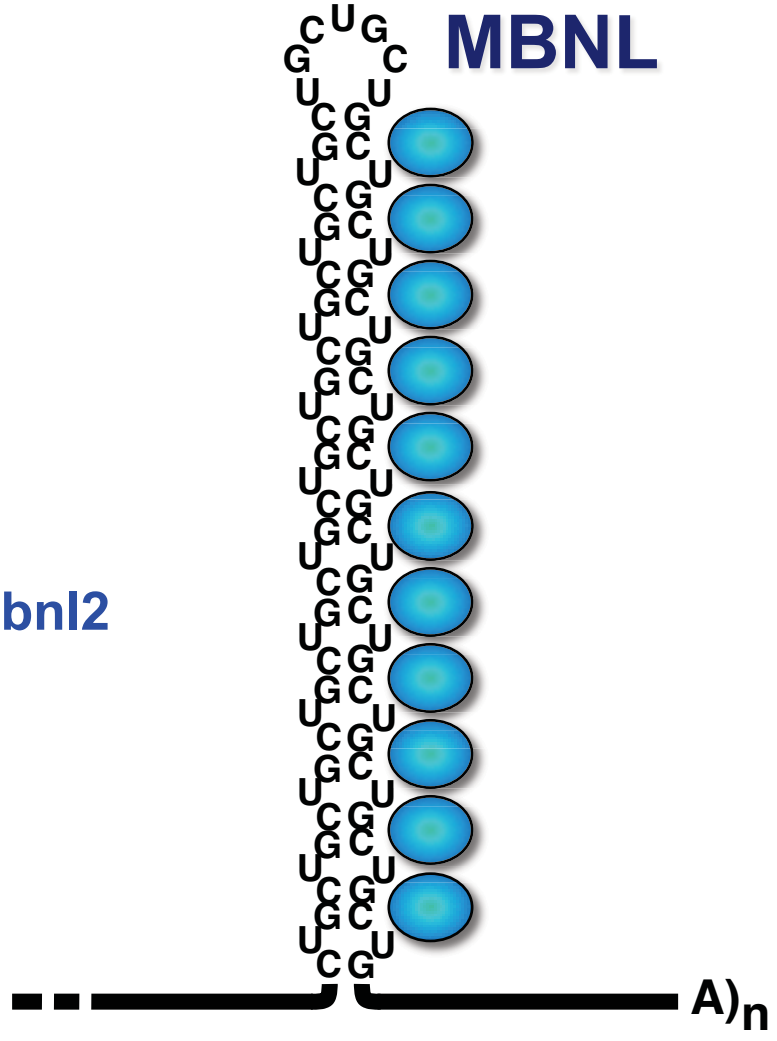
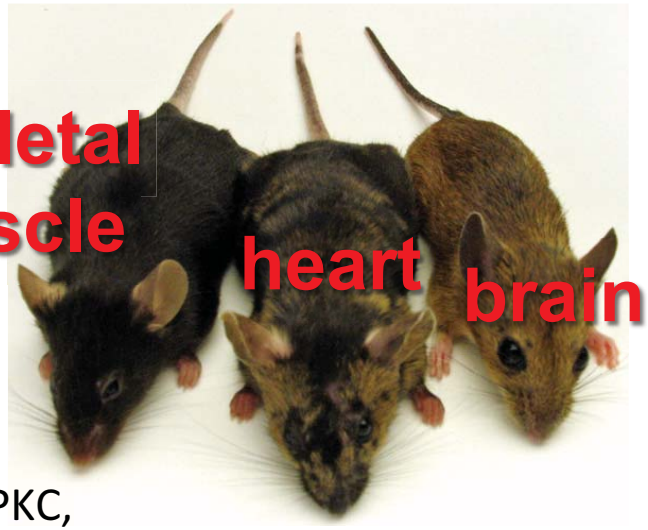




The toxic RNA can have effects on several genes



(BIN1, NKX2.5, GSK3ß, PKC, DMD

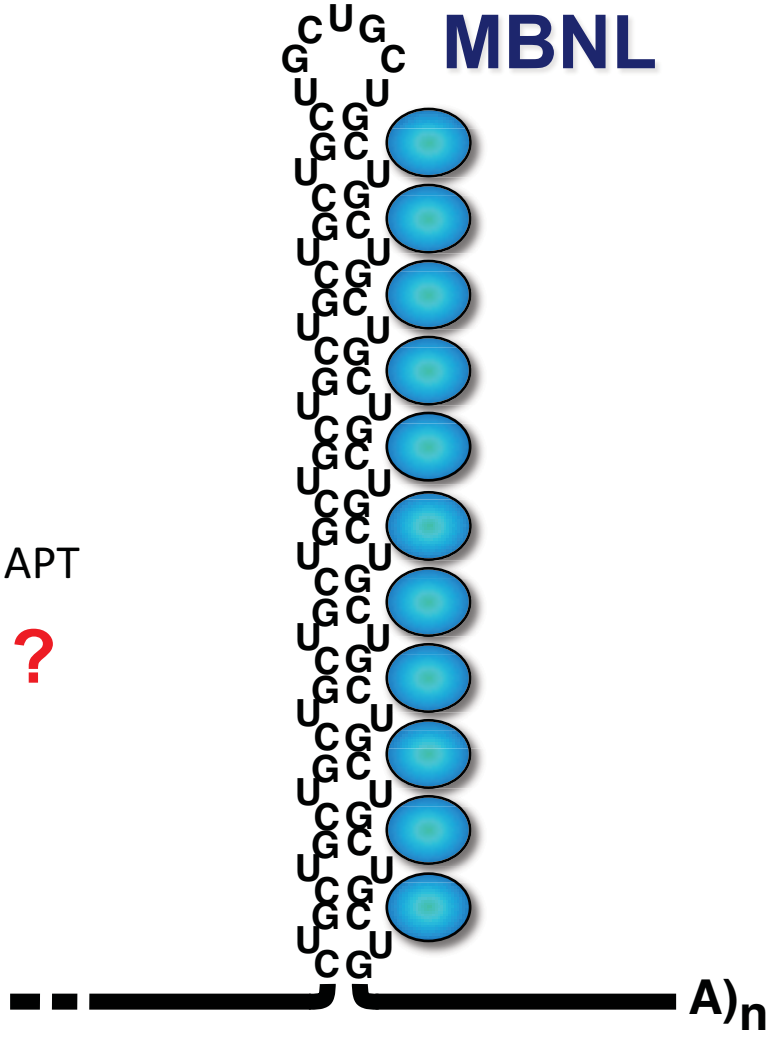
?

SCN5A

?

MAPT

?



Why does the disease get worse over time?

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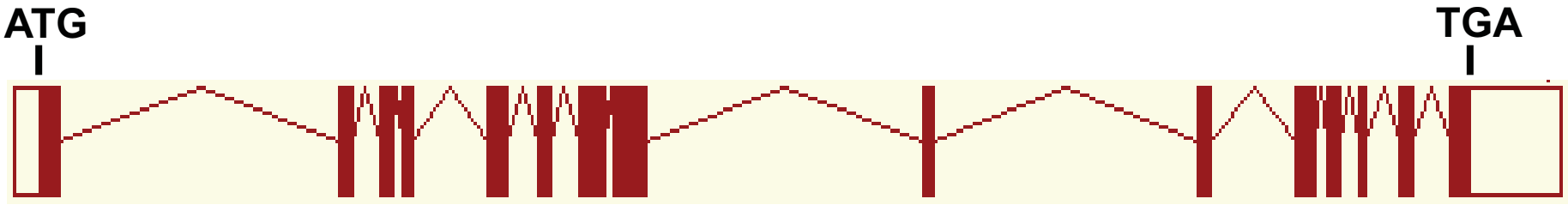
Many diseases are progressive

Why does the disease get worse over time?

Many diseases are progressive

1. The toxic RNA accumulates over time
2. Decreased capacity to maintain a healthy state as age
3. The repeat gets longer over time

Myotonic Dystrophy type 1 (DM1)

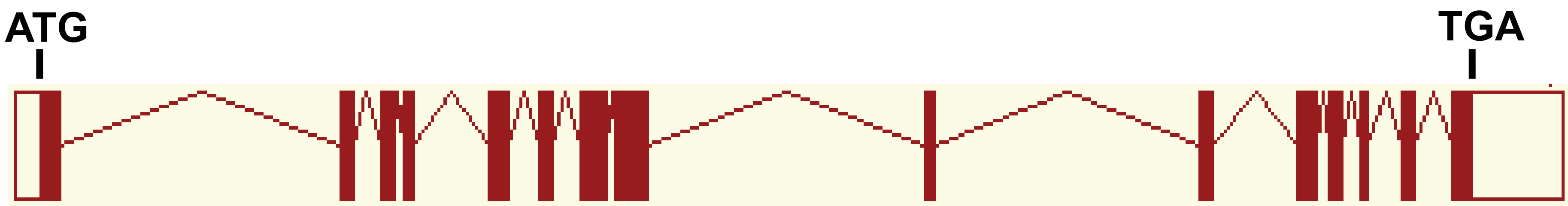


***DMPK* gene**

11 repeats

…CTTGTAGCCGGGAATGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGGGGGGATCACAGAC…

Myotonic Dystrophy type 1 (DM1)

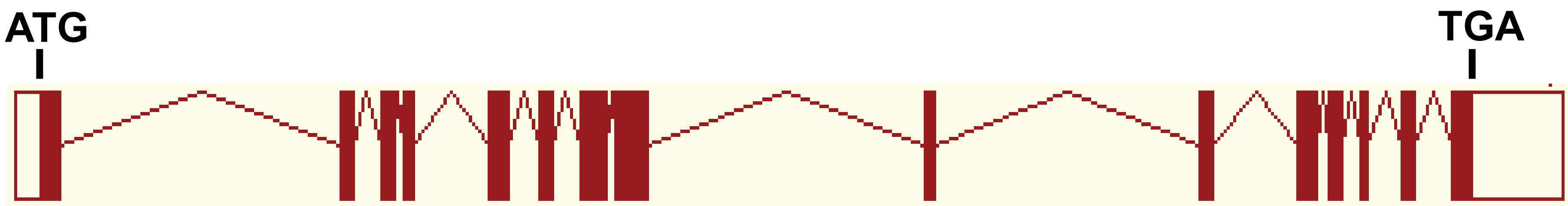


***DMPK* gene**

200 repeats

CTTGTAGCCGGGAATGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG
CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
GCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGC
TGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG
CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
GCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGC
TGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTG
CTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGGGGGGATCACAGAC…

Myotonic Dystrophy type 1 (DM1)



DMPK **gene**

1000 repeats

CTTGTAGCCGGGAATGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
GCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
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TGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGC
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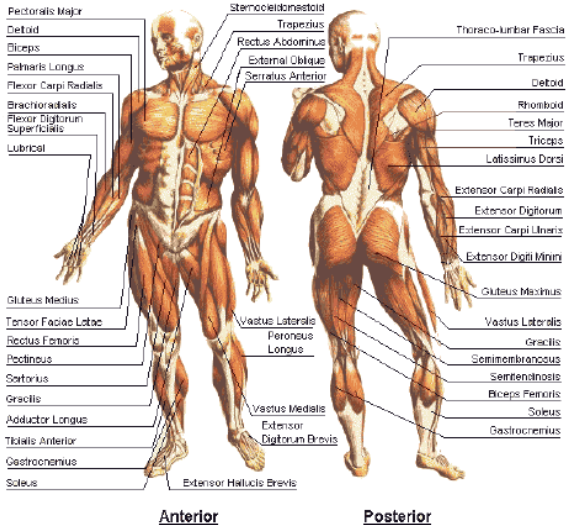
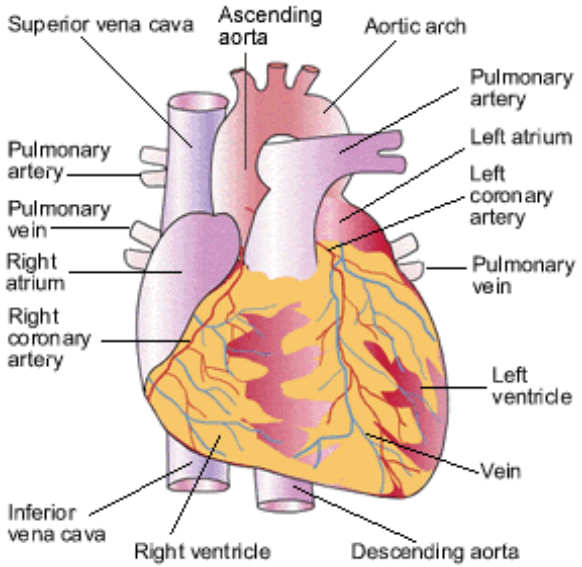
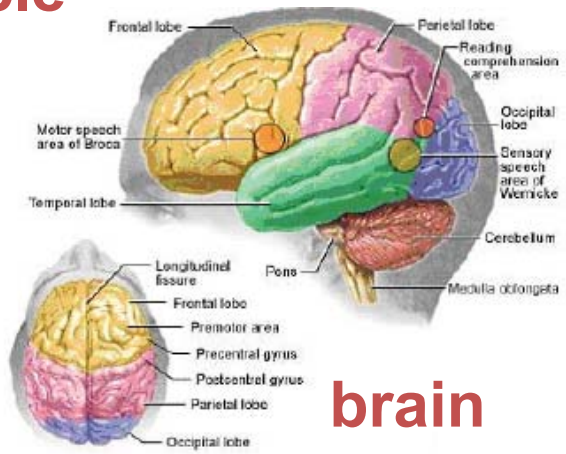


skeletal muscle

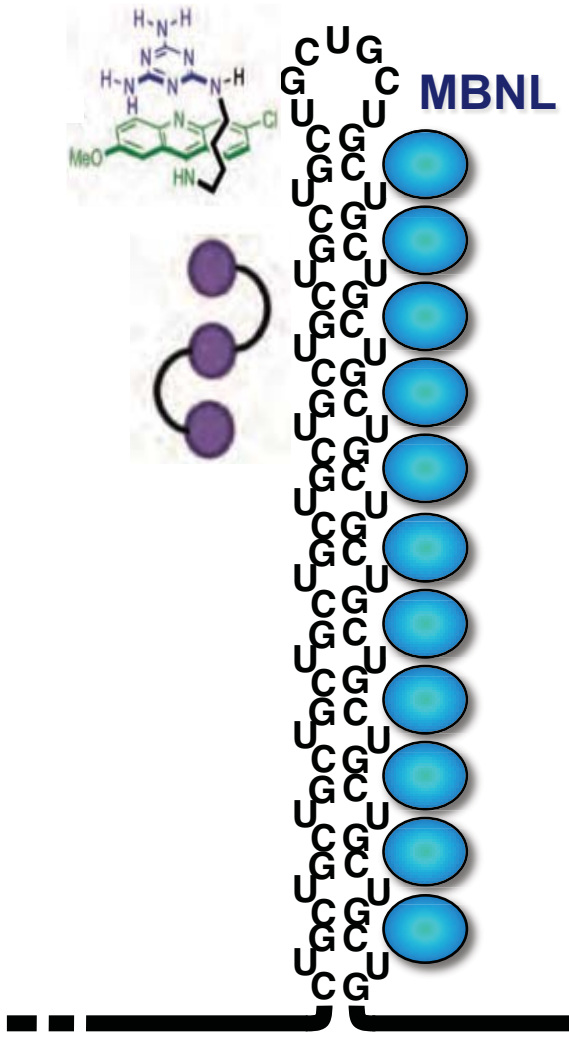


heart



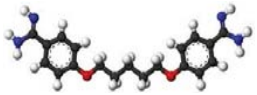
brain

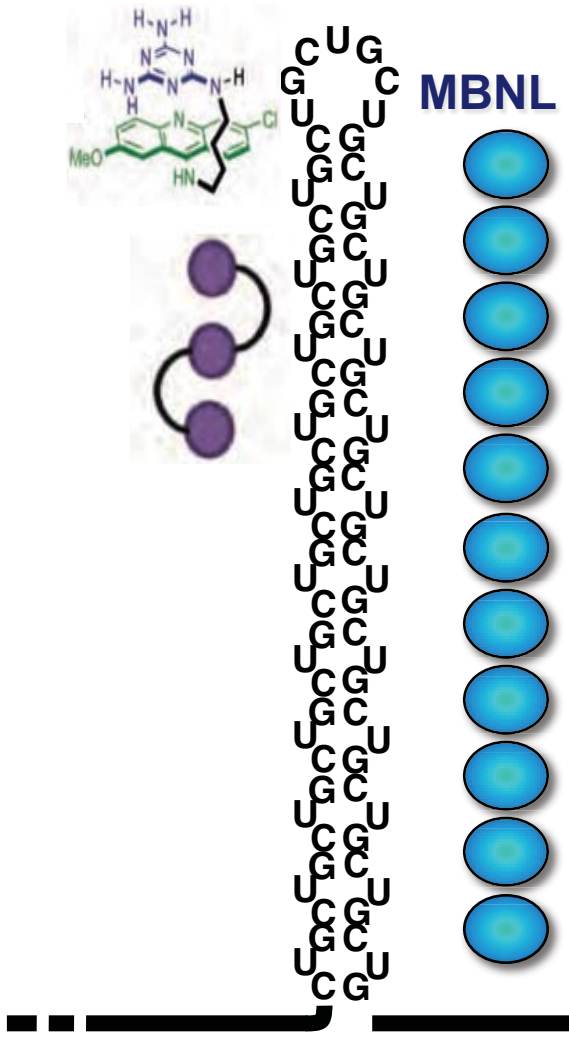
Experimental “models” for myotonic dystrophy



Small molecule screens

- strategic chemical design
- high throughput screens





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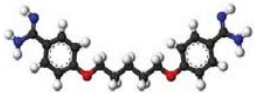

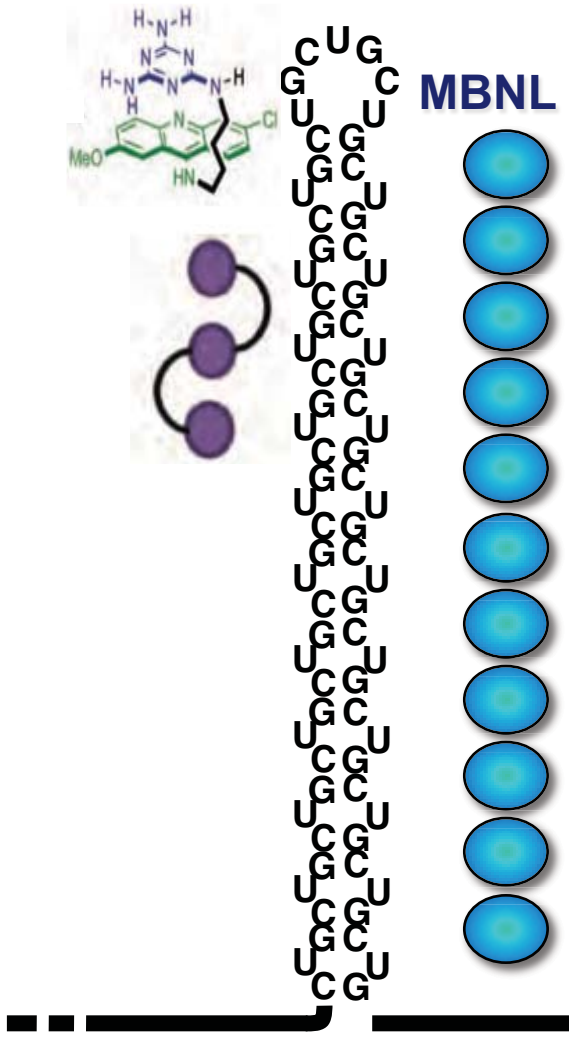

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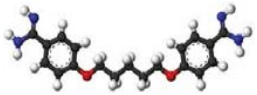
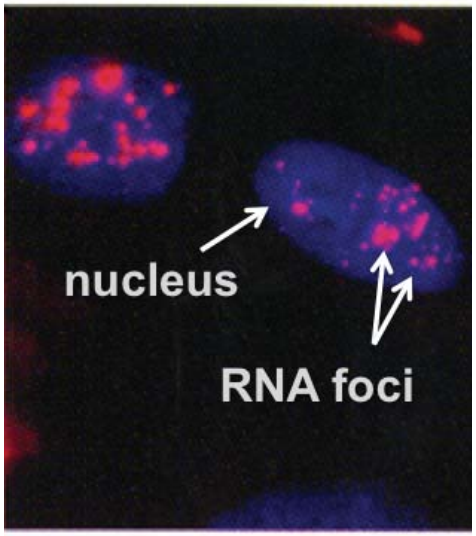
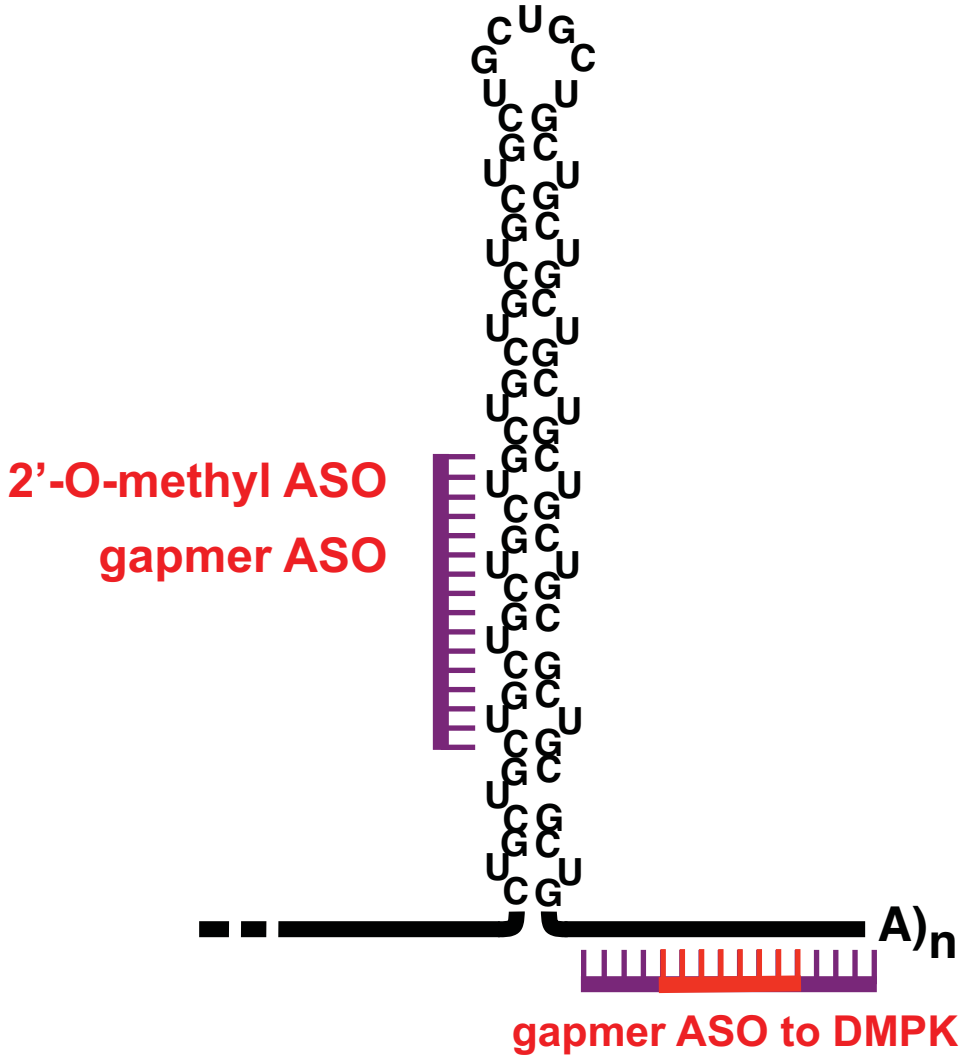
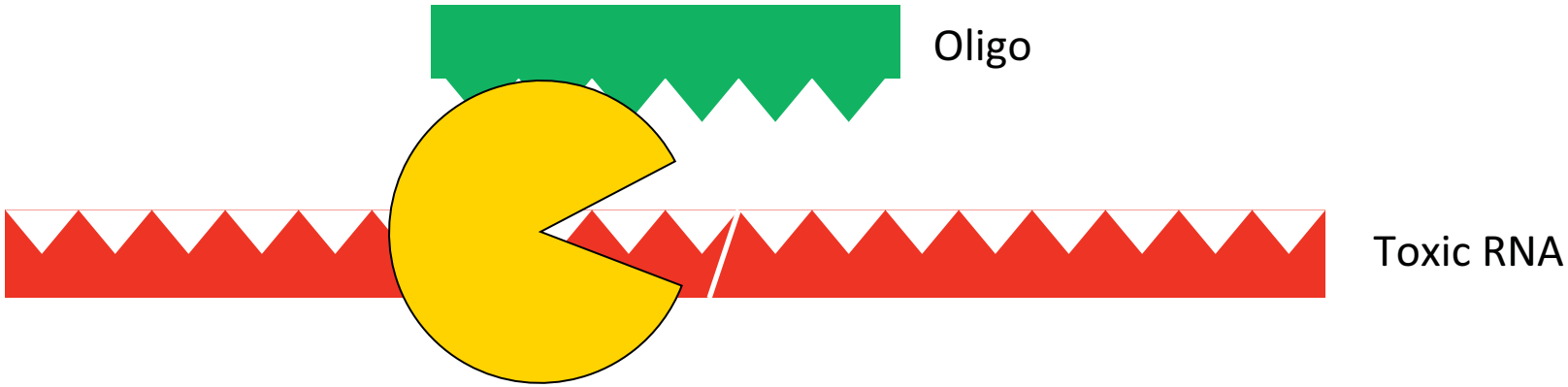




Antisense oligonucleotides



Targeted degradation of toxic RNA by gapmer ASOs



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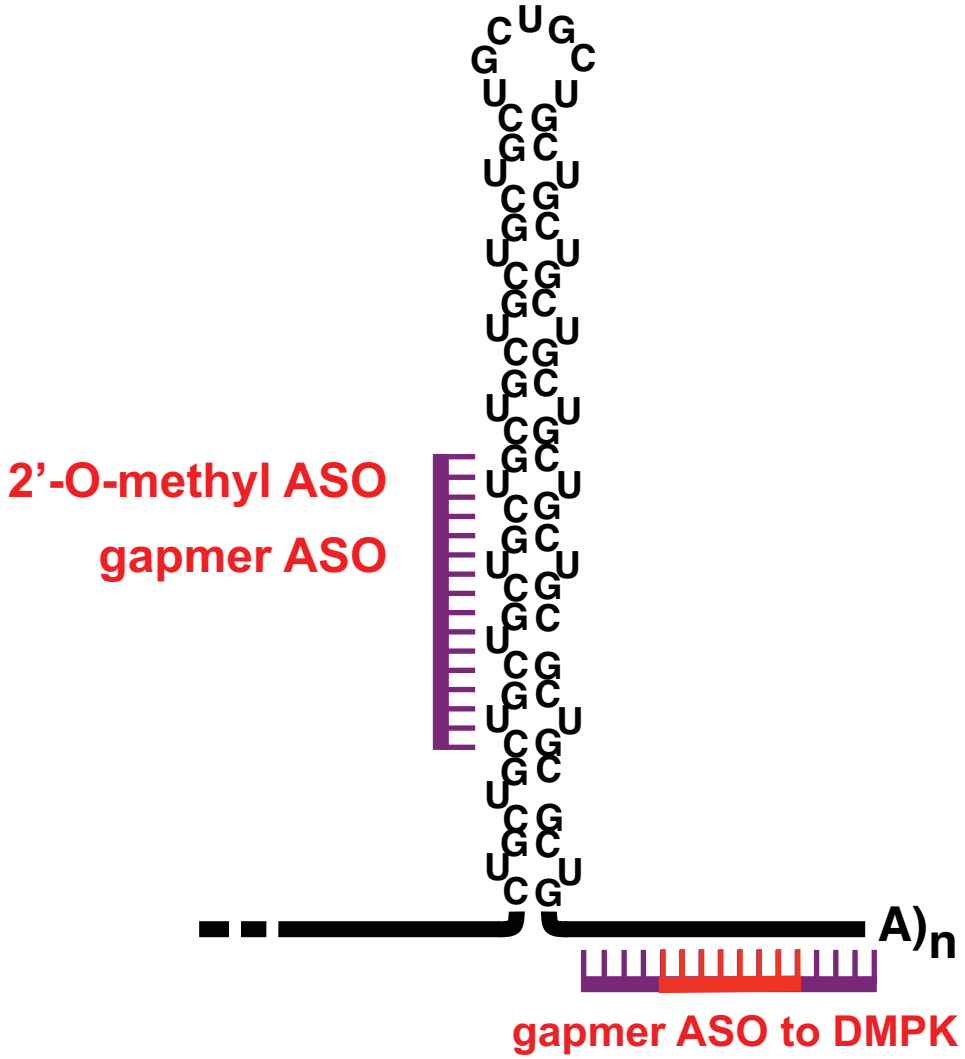
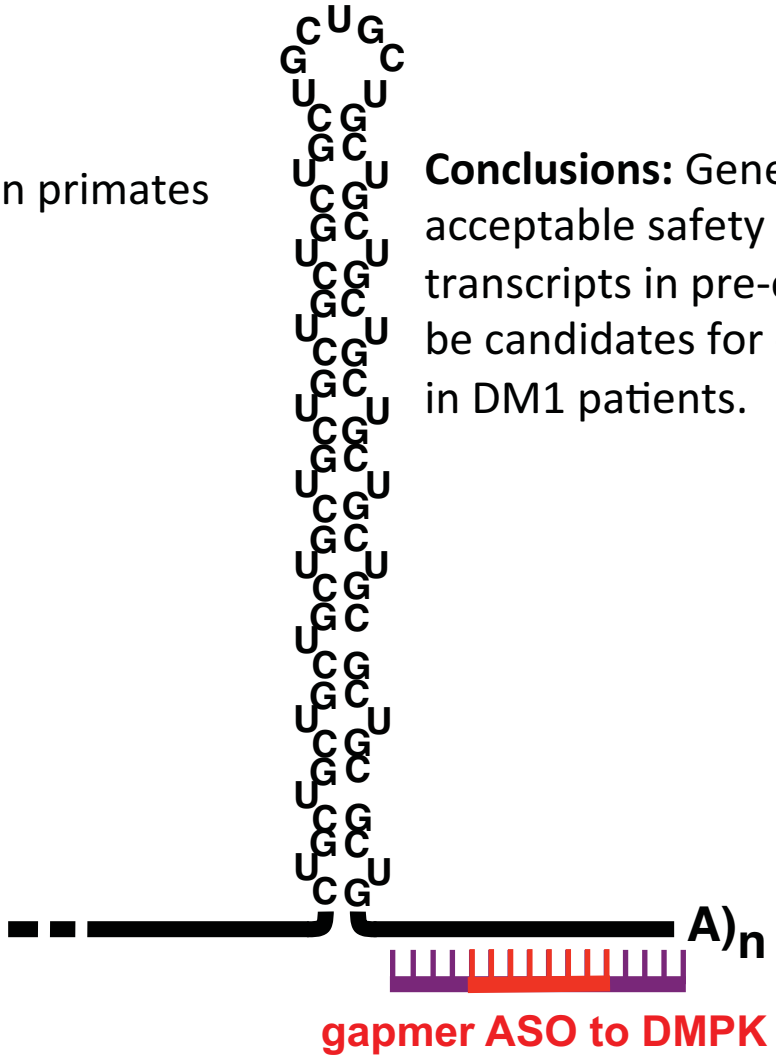


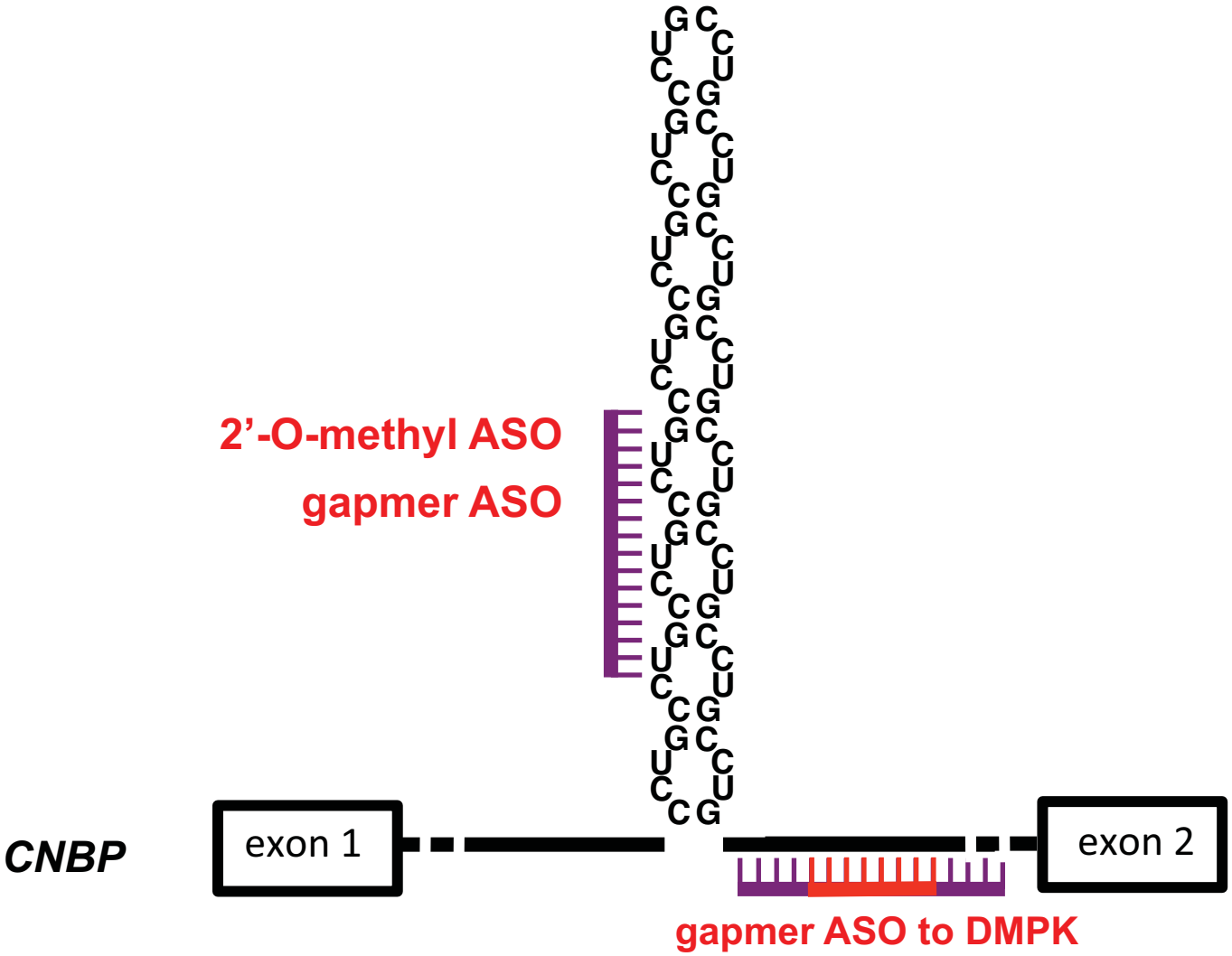
Antisense oligonucleotides

preclinical test in non-human primates (cynomolgus monkeys)

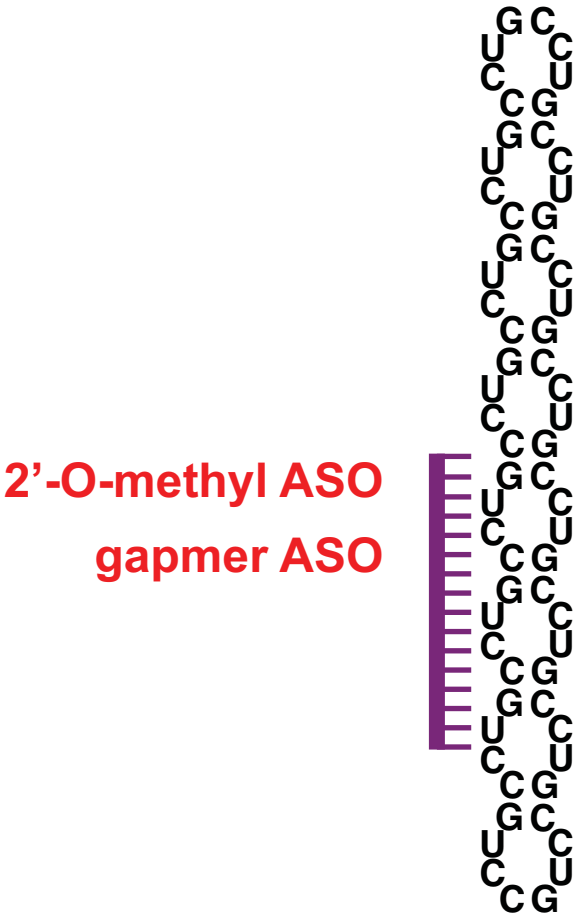


Conclusions: Generation 2.5 ASOs show acceptable safety and efficacy for h*DMPK* transcripts in pre-clinical studies and may be candidates for early phase clinical trials in DM1 patients.

Myotonic dystrophy, type 2 (DM2)



Myotonic dystrophy, type 2 (DM2)



Clinical Research

Saturday – concurrent breakout sessions

- **Daytime Sleepiness and DM:**
  This new session, which focuses on DM and sleep disorders, will be presented by Dr. John Day, Stanford University, and Dr. Belen Esparis, Mt. Sinai Sleep Disorders Clinic and mother of a child living with DM.
- **DM and the Central Nervous System:**
  Dr. Maurice Swanson, University of Florida, and Dr. John Day, Stanford University, will discuss the cognitive impacts of DM and the state of related research.
- **Daily Living Strategies for DM:**
  Dr. Cynthia Gagnon, University of Sherbourne, will present occupational therapy strategies that can help you manage DM and improve your day-to-day quality of life.
- **Exercise and Nutrition Updates:**
  Dr. Shree Pandya, University of Rochester, will share new DM exercise guidelines that community members need to know. She'll be joined by Lucille Mullins, Pediatric Dietician at Texas Children's Hospital who will discuss nutrition and eating strategies for people living with DM.

Cardiac referral in DM1

1. Age, ECG abnormalities and the severity of skeletal muscle weakness are associated with the risk of the first cardiac event
2. Cardiac events occurred in one-third of non-referred middle aged individuals followed for an average of 11 years.
3. Bottom line: talk to physician regarding getting referred to cardiologist
4. DM1 patients undergoing surgery should have cardiac and respiratory monitoring until full recovery.

William Groh, M.D.
Indiana University School of Medicine

Cancer in DM

1. Previous studies suggested a 2 fold increased risk of cancer in DM1

2. Swedish/US group followed >1000 DM patients for up to 21 years and found 2 fold increased risk consistent with other studies

3. Cancers are mainly colon, brain, ovary, endometrium.

4. DM2 has increased cancer risk that may involve the colon, brain, thyroid, pancreas, ovary, and endometrium.

Prevalence and Clinical Correlates of Sleep Disordered Breathing in Myotonic Dystrophy Type 1 and 2

Carácteres Abs_idMesa, BIANCHI Maria Laura Ester, LOSURDO Anna, DI BLASI Chiara, SANTORO Massimo, MASCIULLO Marcella, VALENZA Venanzio, DAMIANI Antonello, DELLA MARCA Giacomo, SILVESTRI Gabriella

- A high prevalence of Sleep Disordered Breathing (SDB) has been documented in DM1, while only few data are available regarding DM2.
- Evaluate the prevalence of SDB in 71 DM1 and 14 DM2; analyze correlations between SDB and various clinical features.
- 45% of DM patients reported poor sleep quality
- Sleep studies show 69% DM1 and 43% DM2 had Sleep Disordered Breathing.

Conclusion: In DM1, no clinical parameters appear predictive of SDB; in DM2 the degree of respiratory muscles involvement correlates with the severity of SDB.

Suggests importance of sleep breathing evaluation

Myotonic Dystrophies - Disorders of the Central Nervous System

RAKOCEVIC STOJANOVIC Vidosava [1], PERIC Stojan [2], PAVLOVIC Aleksandra [2], BRAJKOVIC Leposava [3], FILIPPI Massimo [4], KOSTIC Vladimir [1]

Aim: To investigate central nervous system involvement in patients with DM1 and DM2/PROMM

Fifty one DM1 patients, 20 DM2/PROMM patients and 34 matched healthy controls were included in the study.

PET scans showed reduced metabolism of glucose in the frontal and frontotemporal regions in DM1 and frontal and parietal regions in DM2

Magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) showed impairment in both white and grey brain matter in DM1 patients.

A Clinical Study of Myotonic Dystrophy Type-1 (DM1) Patients' Perception and Prioritization of Cognitive Symptoms

HEATWOLE Chad, JOHNSON Nicholas, LUEBBE Elizabeth, DILEK Nuran, MARTENS William, THORNTON Charles, MOXLEY, III Richard-Thomas

- 278 patients participated.
- identified 16 distinct areas of cognitive dysfunction.
- Patients reported cognitive symptoms that have the greatest effect on their lives: **decreased motivation, cognitive fatigue, decreased ability to think fast, and memory deficits.**
- Male participants reported more cognitive symptoms than female participants.

Clinical and basic researchers from around the world presented at IDMC-9

1999

How does the expansion cause disease?

Stages of Clinical Trials

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Maury Swanson, Ph.D.

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National Institute of General Medical Sciences (NIGMS)

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

MDA® Muscular Dystrophy Association

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