The Current Landscape of Muscular Dystrophy Research, an NIH Perspective

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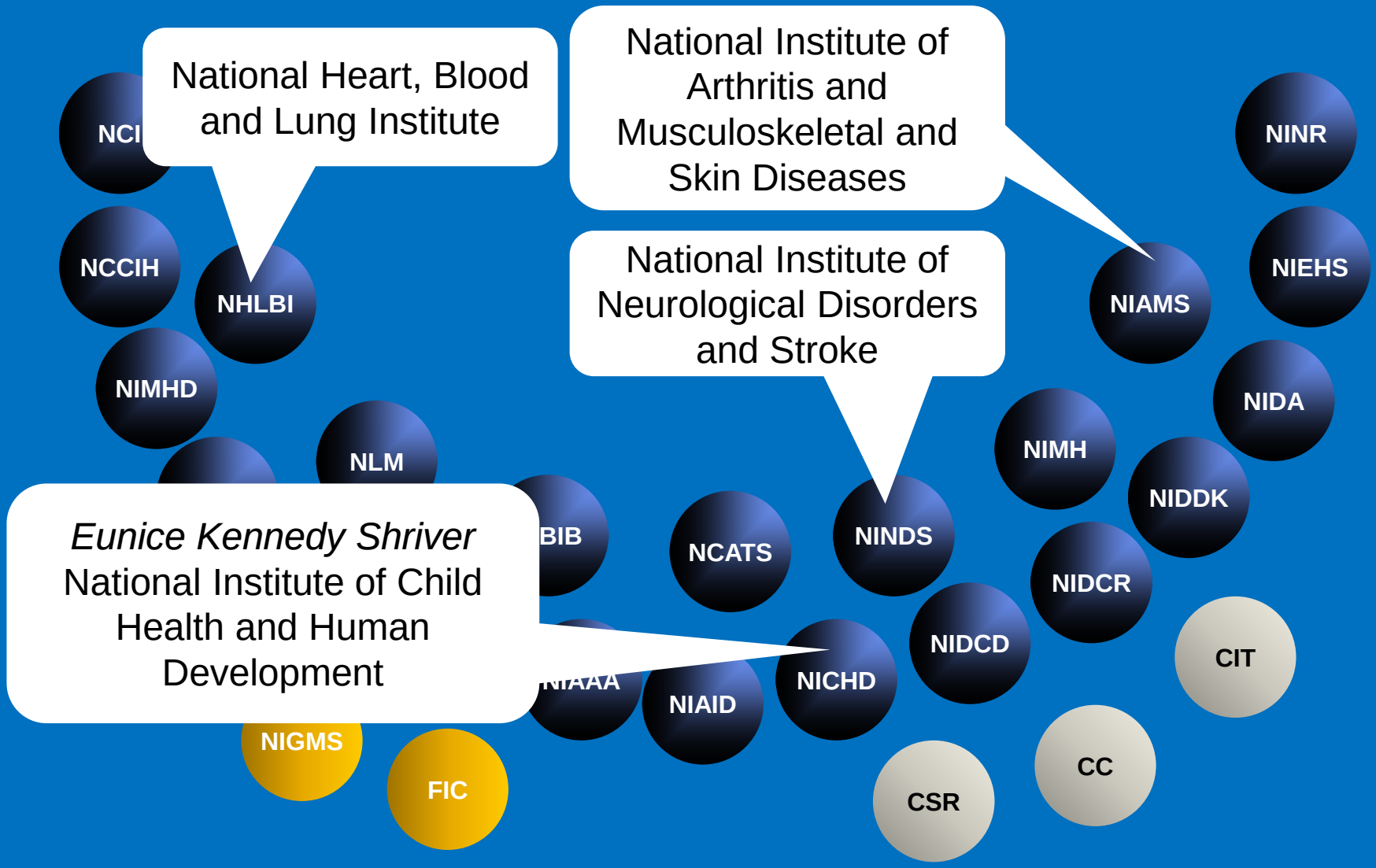
NIH Bethesda Campus

The National Institutes of Health



Examples of FY2015 NIH Disease Research Funding Levels

Condition	$ Millions
Muscular Dystrophy	$77
Duchenne Muscular Dystrophy	$30
Myotonic Dystrophy	$9
Facioscapulohumeral Dystrophy	$8
Charcot Marie Tooth Diseases	$14
Spinal Muscular Atrophy	$11
Parkinson’s Disease	$146
Amyotrophic Lateral Sclerosis (ALS)	$49

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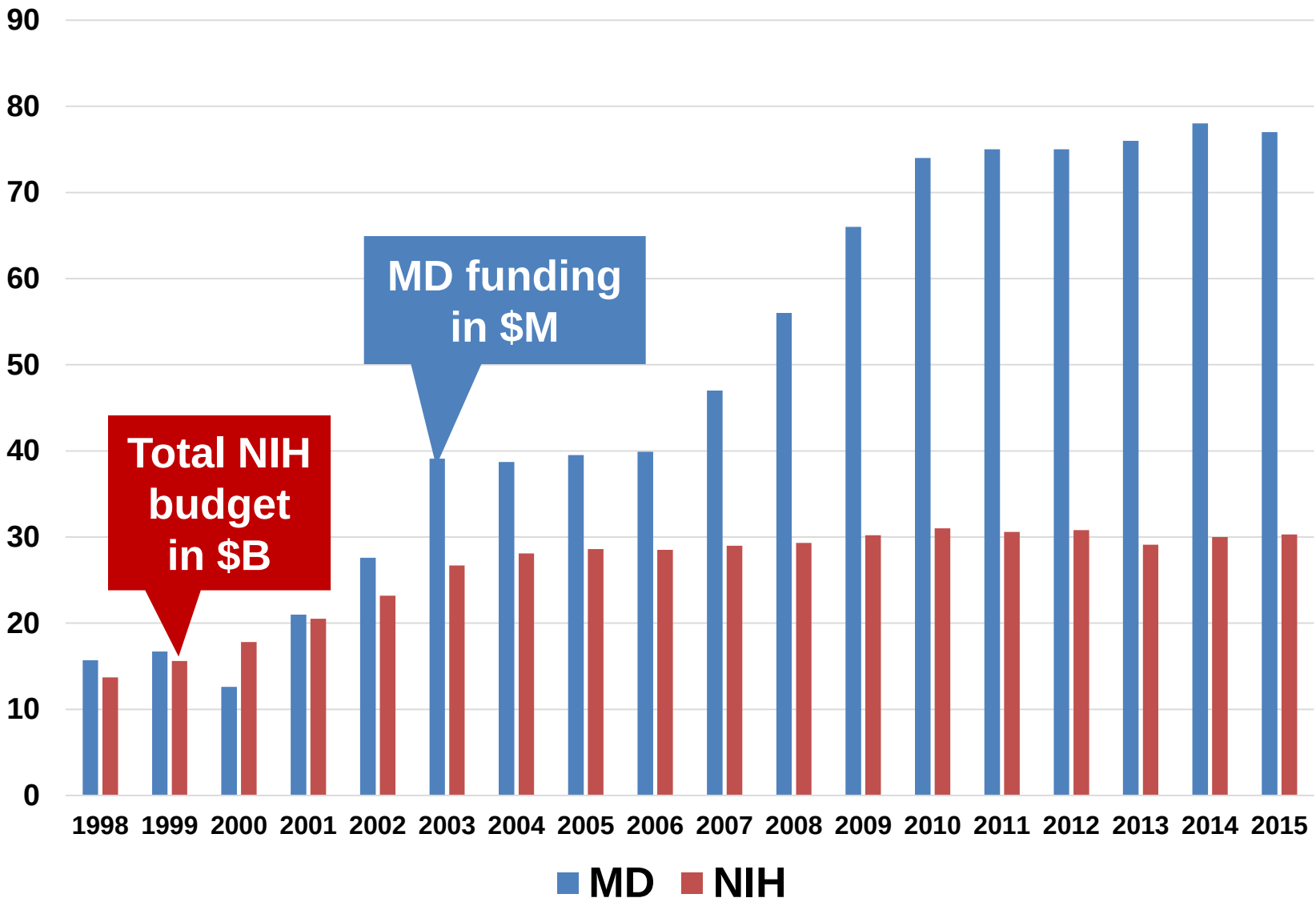
NIH Support for Muscular Dystrophy Research

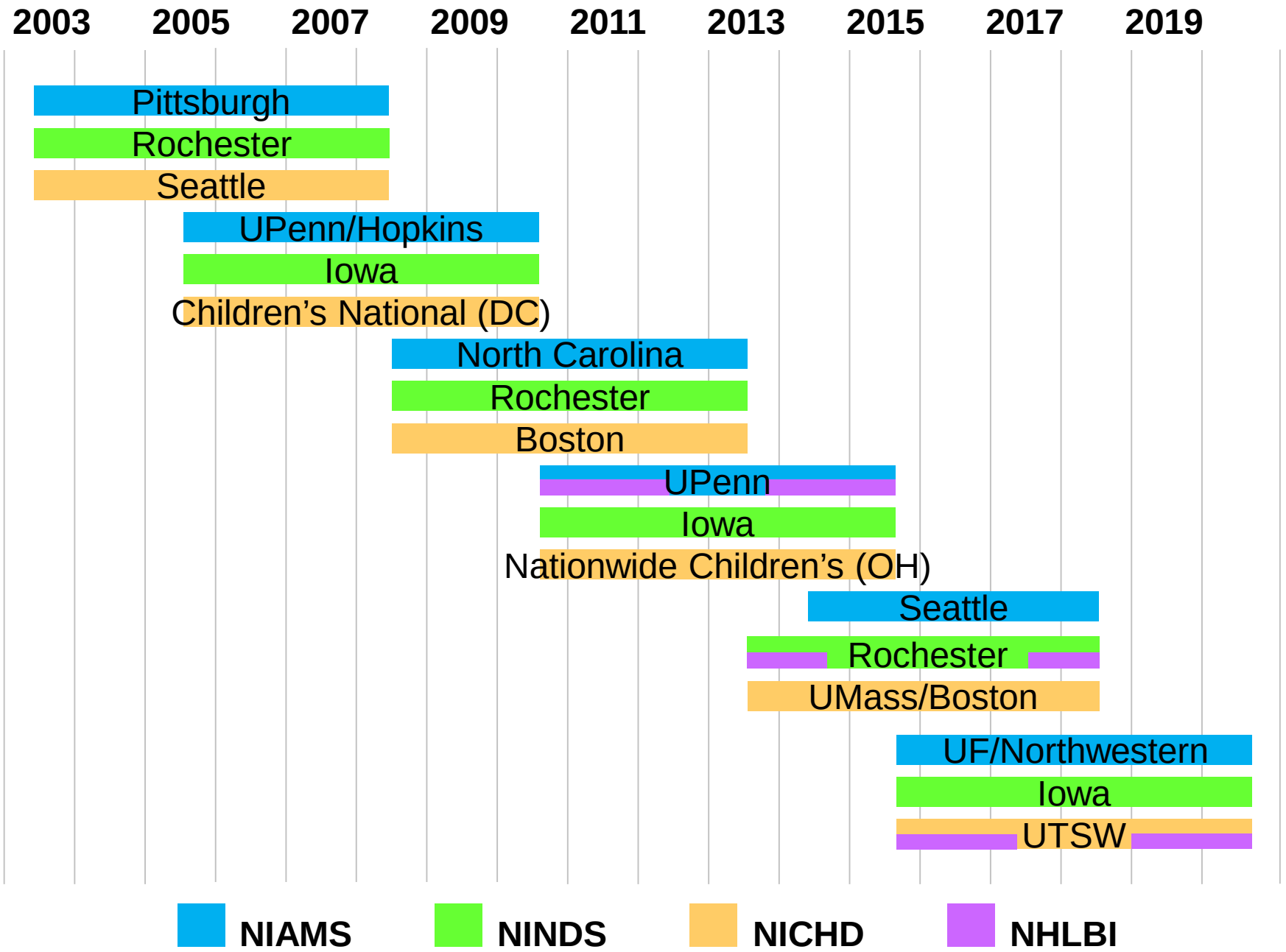


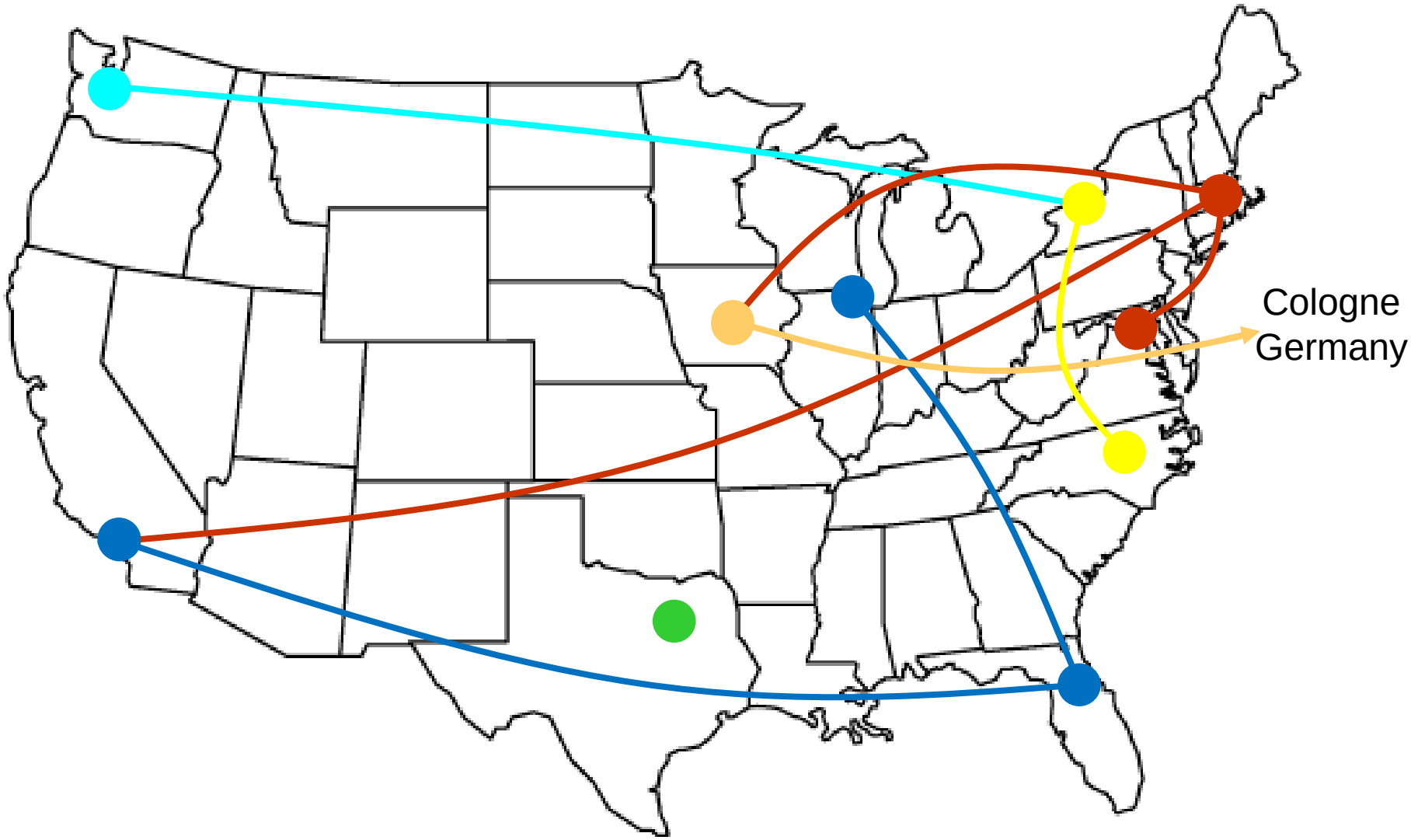
Paul D. Wellstone Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001, 2008, 2014 (MD CARE Act)

- Directed NIH to expand, intensify and coordinate research activities for the muscular dystrophies.
- Created the interagency Muscular Dystrophy Coordinating Committee
- Created a Centers of Excellence Program: The Wellstone Muscular Dystrophy Cooperative Research Centers

The NIH Wellstone Centers Program

- Established in 2003 in response to the MD CARE Act
- Supported by four- to five-year awards of $1M direct cost per year (~$1.5M total cost)
- Total of six Centers
- Each Center contains:
  - Two or more research projects with a common theme
  - A core facility shared with the greater MD research community
  - A core for training junior translational/clinical researchers


Wellstone Centers Program Timeline of Awards
2003
2005
2007
2009
2011
2013
2015
2017
2019
Pittsburgh
Rochester
Seattle
UPenn/Hopkins
Iowa
Children's National (DC)
North Carolina
Rochester
Boston
UPenn
Iowa
Nationwide Children's (OH)
Seattle
Rochester
UMass/Boston
UF/Northwestern
Iowa
UTSW
NIAMS
NINDS
NICHD
NHLBI

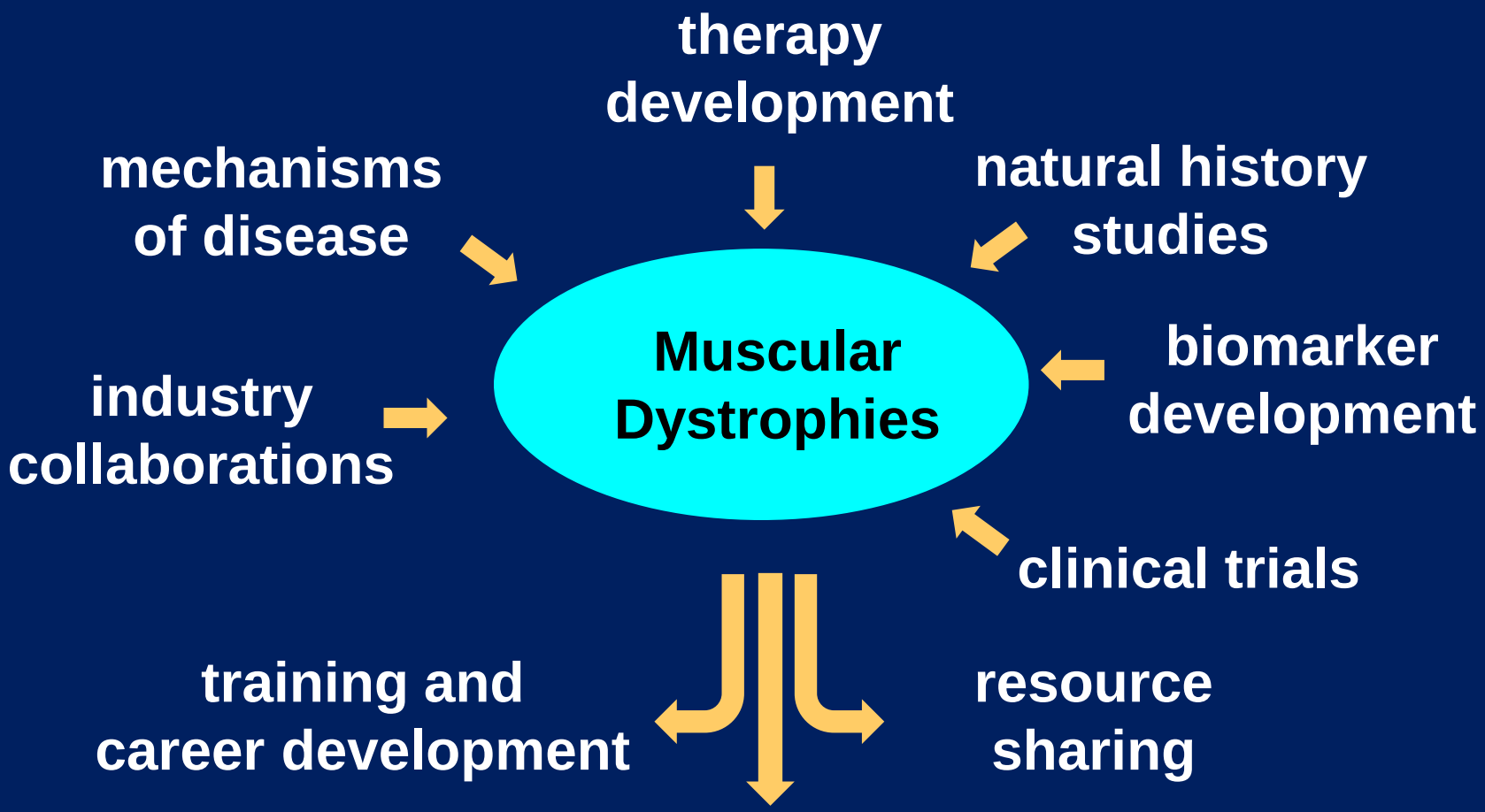


- UT Southwestern Medical Ctr
- UFlorida (Northwestern, UCLA)
- UMass (Boston Children's, Kennedy Krieger, UCLA, Iowa)
- University of Rochester (and Duke)
- U Washington (FHCRC, Seattle Ch Hos, Rochester)
- University of Iowa (Cologne)

Research Themes of the Current Wellstone Centers

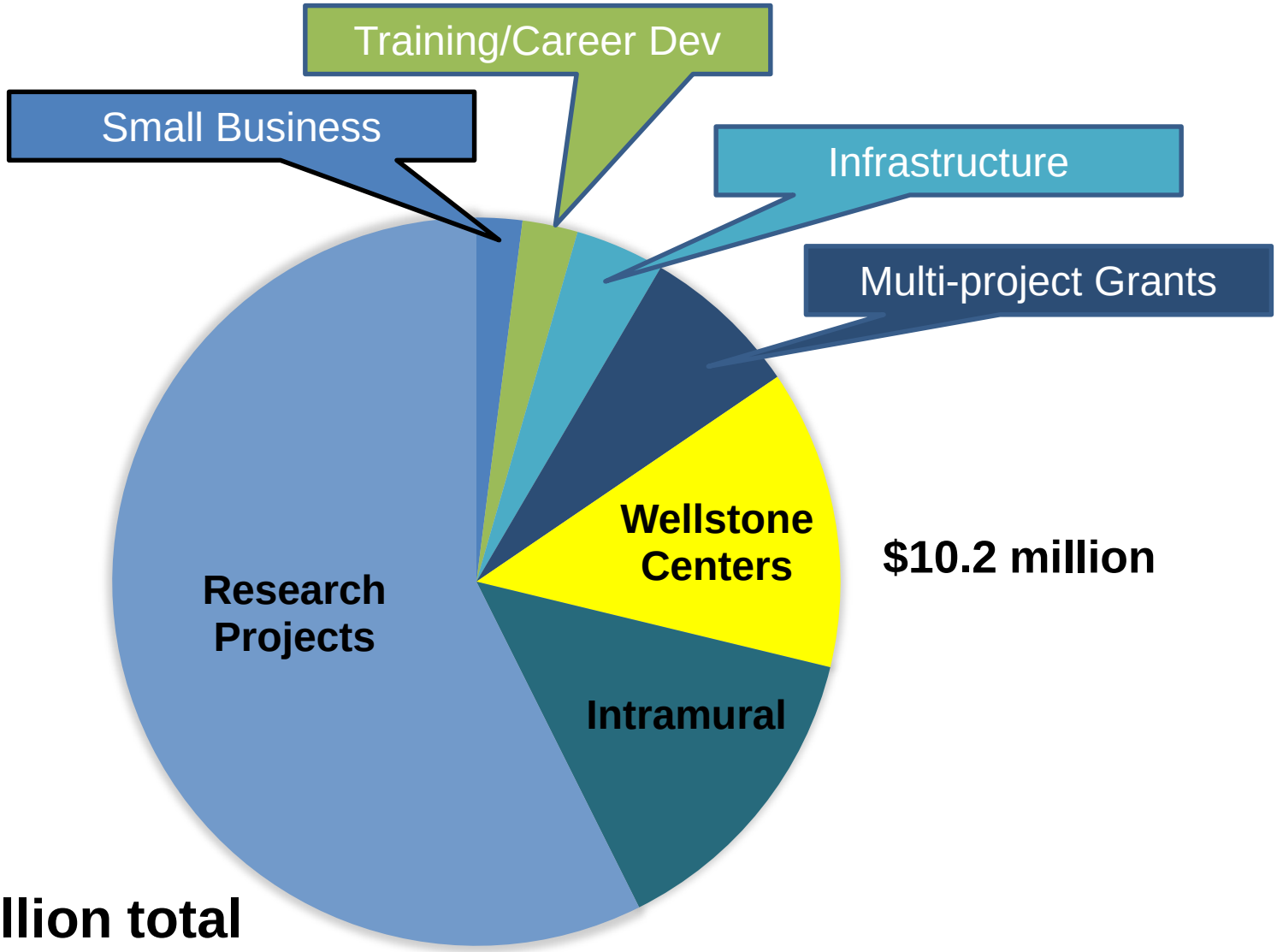
Iowa Campbell	Therapeutic strategies for dystroglycanopathies
Umass Emerson	FSHD: genetic modifiers, biomarkers and animal models
Rochester Moxley	Myotonic dystrophy pathophysiology, biomarkers and therapies
U Texas Southwestern Olson	Developing genomic editing treatment strategies for Duchenne muscular dystrophy
U Florida Sweeney	Failed regeneration in the muscular dystrophies: inflammation, fibrosis, fat
Seattle Chamberlain	Viral vector mediated gene transfer for DMD and FSHD; biomarkers and mechanisms of FSHD

Wellstone Centers of Excellence



Disease knowledge, targets, candidate therapeutics, treatments and strategies to reduce disease burden

FY2015 NIH Muscular Dystrophy Research Support



$10.2 million

$77 million total

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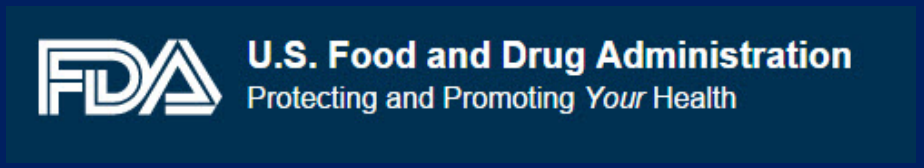
Muscular Dystrophy Coordinating Committee

Federal Agencies



Patient Advocacy Groups

Muscular Dystrophy Coordinating Committee

- Chaired by Steve Katz, Director of NIAMS
- Glen Nuckolls, Designated Federal Official
- Meetings held at the NIH, twice per year
- Open to the public, webcast and archived
- Recent meeting topics:
  - Certification of Care Centers
  - Clinical Biomarker Development and FDA Qualification
  - Public/Private Partnerships and Data Sharing
  - Patient Access to Care and Services

mdcc.nih.gov

- Meeting agendas and summaries
- Link to live meeting webcasts
- Membership roster and bios
- Spreadsheet of 2015 grant awards from MDCC member organizations
- 2015 Action Plan for the Muscular Dystrophies

Contents of the 2015 Action Plan

- Mechanisms of Muscular Dystrophy
  - Mechanisms common to several types of dystrophy (10)
  - Mechanisms related to specific types (5)
- Diagnosis, Screening and Biomarkers
  - Technology and other resources for diagnostic testing (5)
  - Data sharing/optimal use of information and materials (3)
  - Population screening (3)
  - Development of biomarkers (2)
- Preclinical Therapy Development
  - Modulation of muscle biology (2)
  - Cell and gene therapy/editing (5)
  - Improving the process of therapy development (6)
- Clinical Therapy Developm**ent**
  - Optimizing available therapies (4)
  - Cell and gene therapy/editing (2)
  - Improving the processes and resources for patient care (4)
  - Improving the process of therapy development (4)
- Living with Muscular Dystrophy
  - Quality of life and burden of disease (5)
  - Prioritizing and facilitating clinical trials (5)
  - Lifestyle, education and employment issues (5)
- Infrastructure
  - Facilitating mechanistic and target identification/validation studies (5)
  - Facilitating clinical trial readiness (6)

81 total objectives/goals

Contributors to the 2015 Action Plan

Mechanisms of Disease
- James Dowling
- Stanley Froehner
- Lou Kunkel
- Grace Pavlath
- Laura Ranum
- Melissa Spencer
- Silvere van der Maarel
- Howard Worman
- *Glen Nuckolls

Diagnosis, Screening and Biomarkers
- Kevin Flanigan
- R. Rodney Howell
- Priya Kishnani
- Katherine Mathews
- Steven Moore
- Rabi Tawil
- Krista Vandenborne
- *Tiina Urv

Preclinical Therapy Development
- Jeff Chamberlain
- Cristina Csimma
- Elizabeth McNally
- Lee Sweeney
- Stephen Tapscott
- Charles Thornton
- *Marielena McGuire
- *John Porter

Clinical Therapy Development
- Carsten Bönnemann
- Kate Bushby
- Paula Clemens
- John Day
- David Kass
- John Kissel
- Kathryn Wagner
- *Jonathan Kaltman

Living With Muscular Dystrophy
- Doug Biggar
- Chad Heatwole
- Susan Iannaccone
- Anne Kennedy
- Craig McDonald
- Chris Rosa
- Lisa Tuchman
- *Julie Bolen

Participating MDCC Members
- Valerie Cwik
- Brian Denger
- Alan E. Guttmacher
- Stephen Katz
- Story Landis
- Richard Olney
- Daniel Perez
- Anne Rutkowski
- Wanda Salzer
- Theresa San Agustin
- Bonnie Strickland
- Peter Wald

Other NIH Staff
- Tom Cheever
- Jonelle Drugan
- Lisa Kaeser
- Heather Rieff
- Ashlee Van't Veer

* Working Group Liaisons

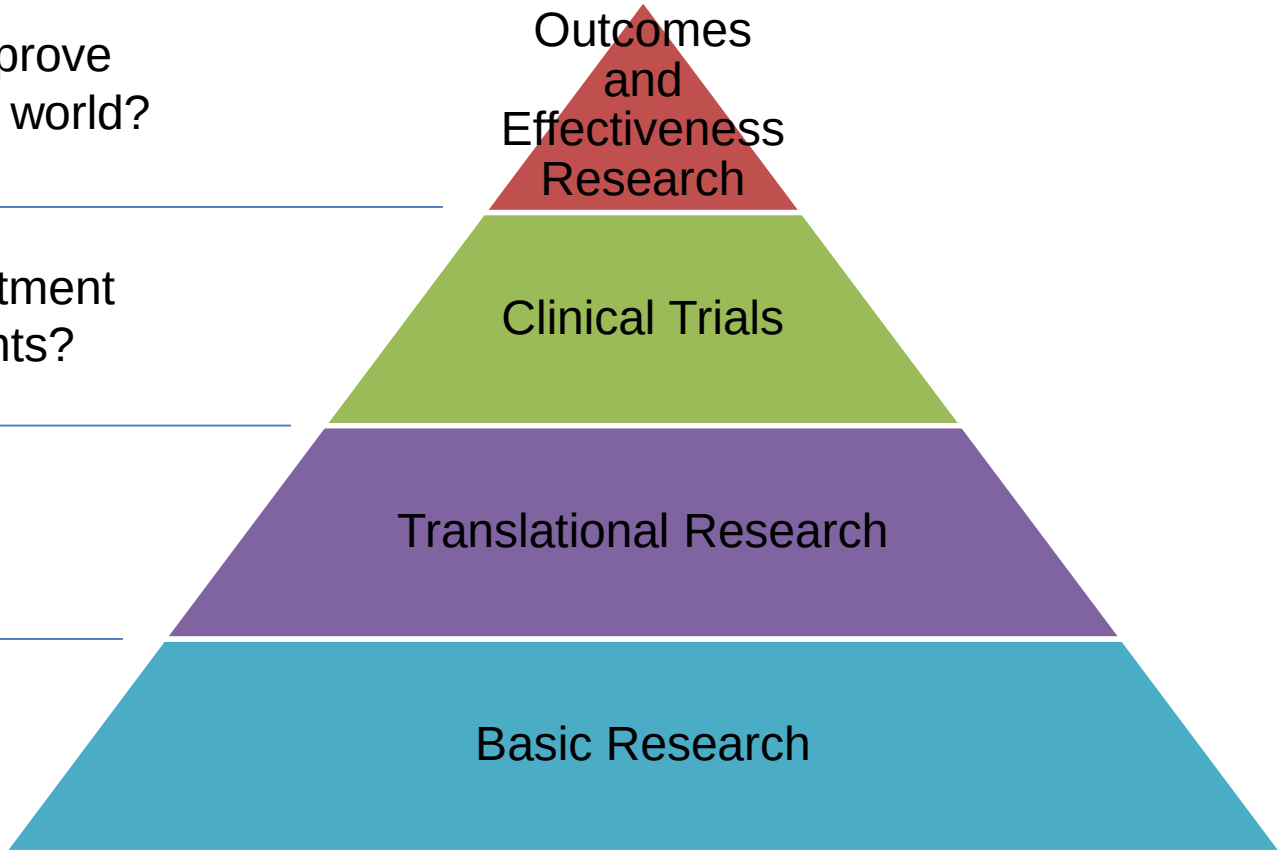
The Structure of the Biomedical Research

What can be done to improve patient's lives in the real world?

Does the candidate treatment work in a group of patients?

Can we develop a possible treatment?

Can we understand the biology?



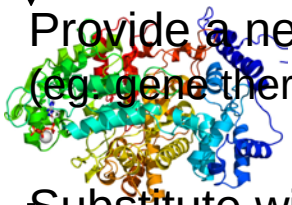
Treatment Strategies for the Muscular Dystrophies

Gene mutation

Modify mutated gene
(eg. CRISPR, exon-skipping, stop read through)

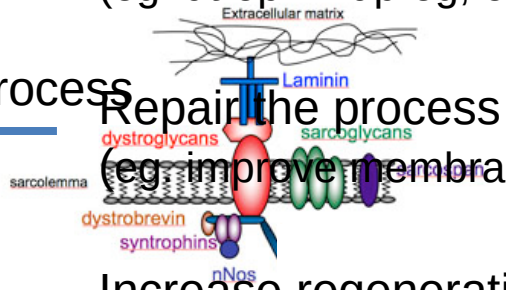
Provide a new copy of the gene
(eg. gene therapy)

Defective or no protein



Substitute with a different gene/protein
(eg. utrophin upreg, other glycosyltrans.)

Disrupted biological process



Repair the process
(eg. improve membrane repair)

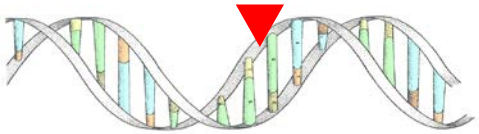
Increase regeneration
(eg. myostatin inhibitors)

Primary and secondary disease symptoms

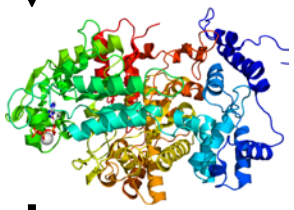
Block the processes the lead to the symptoms
(eg. block inflammation, fibrosis, cell death)

Disease Modifying Genes

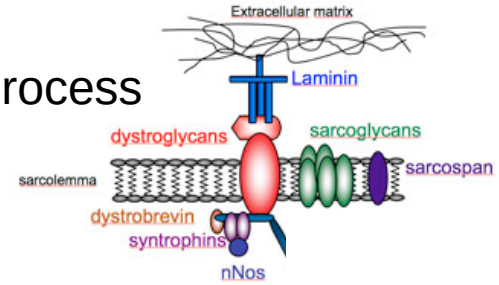
Gene mutation



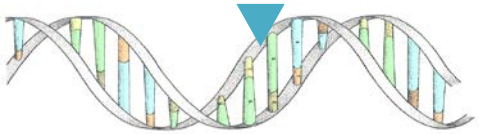
Defective or no protein



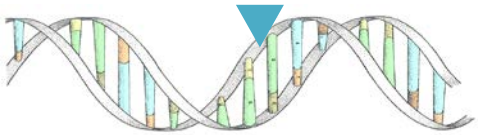
Disrupted biological process



Variations in other genes



Primary and secondary disease symptoms



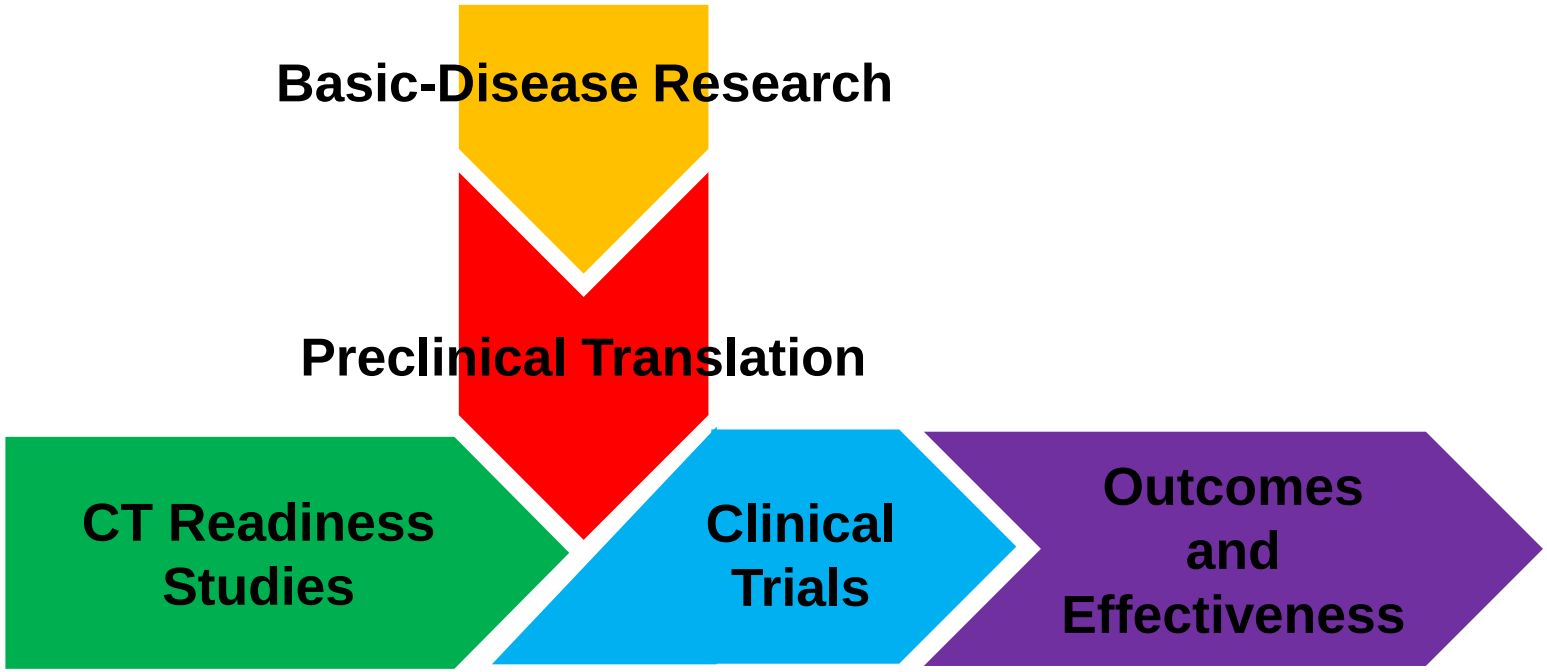
Duchenne Modifier Genes

Gene	Process affected
LTBP4	Fibrosis
Osteopontin/SPP1	Muscle regeneration
Annexin A6	Membrane repair
Jagged1	Muscle cell proliferation?
others	

Significance:

- Understanding of these genes may lead to novel treatment strategies
- Variations in these genes may modify other dystrophies and other diseases
- Genotyping may provide prognostic information for patients
- Genotyping may help explain results of clinical trials

An NINDS View of Biomedical Research

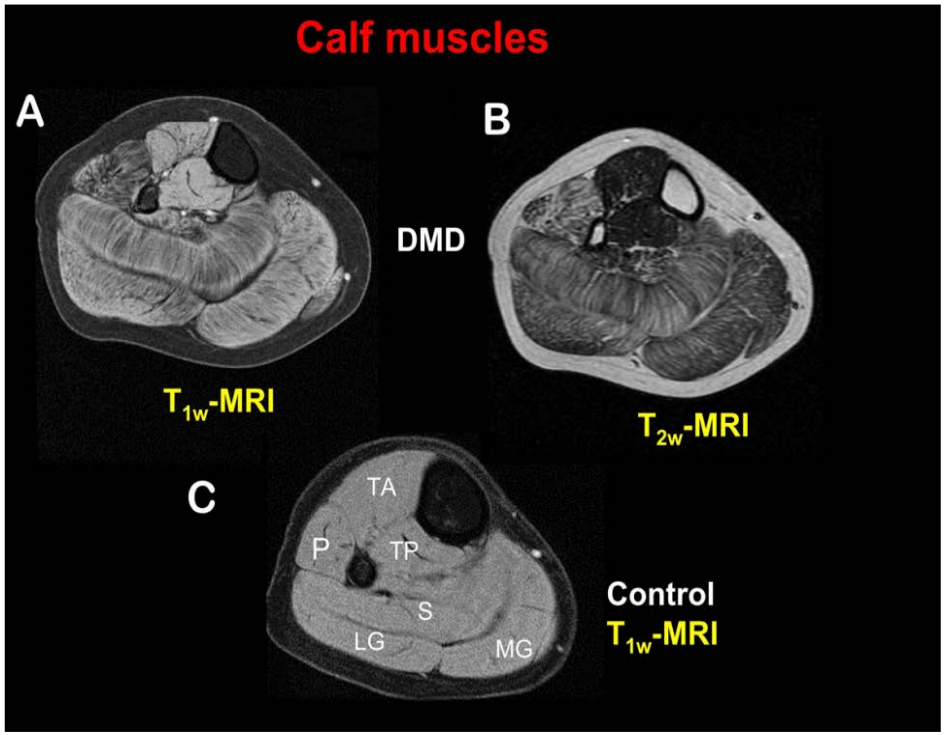


Clinical trial readiness studies answer questions such as:

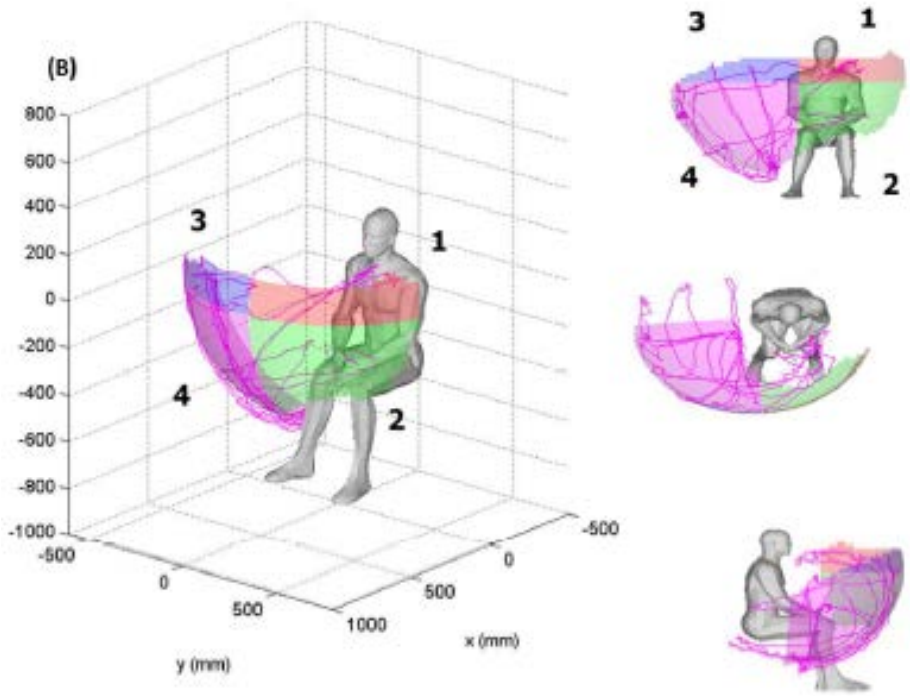
- **What are the characteristics and number of participants to enroll in the trial?**
- **What clinical tests should be used in the trial to determine whether the drug/biologic works?**

Advances in Biomarkers and Outcome Measures for the Muscular Dystrophies

Muscle Imaging



Quantitative Range of Motion



- Quantitative ultrasound
- Electrical impedance myography
- Serum proteomics biomarkers

Summary

- NINDS, NIAMS, NICHD, NHLBI and other NIH institutes have a long-term commitment to supporting research for the muscular dystrophies.
- The Wellstone Centers are focal points of research innovation, collaboration and sharing of resources.
- The MDCC promotes communication and collaboration among the Federal and private stakeholder organizations.
- The Action Plan for the Muscular Dystrophies is a consensus of guidance from thought leaders in the research community.
- Therapy development is advancing on many fronts, facilitated by ever increasing understanding of the mechanisms of disease.
- The discovery of modifier genes, and the development of improved disease-relevant biomarkers and outcome measures will increase the likelihood of success in future clinical trials.