



Therapy Development Process in Neurodegeneration

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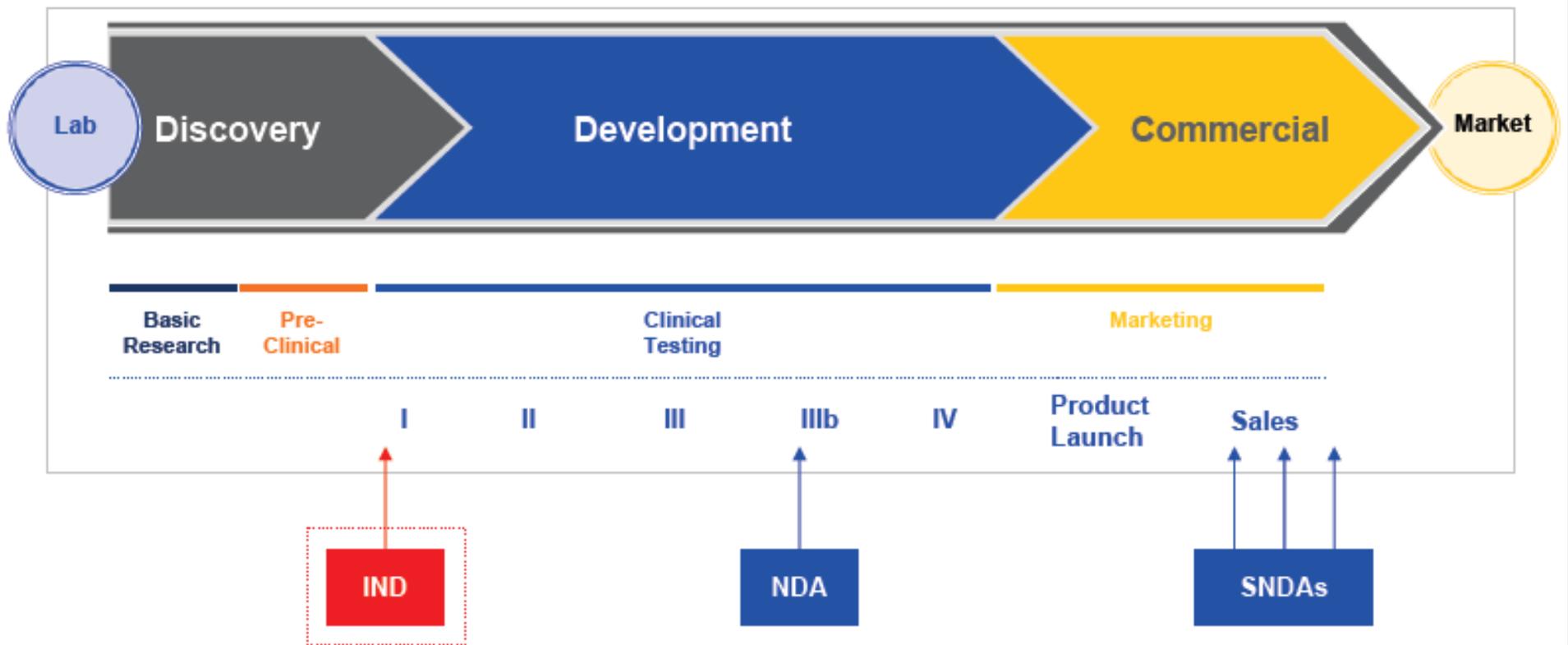
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Agenda

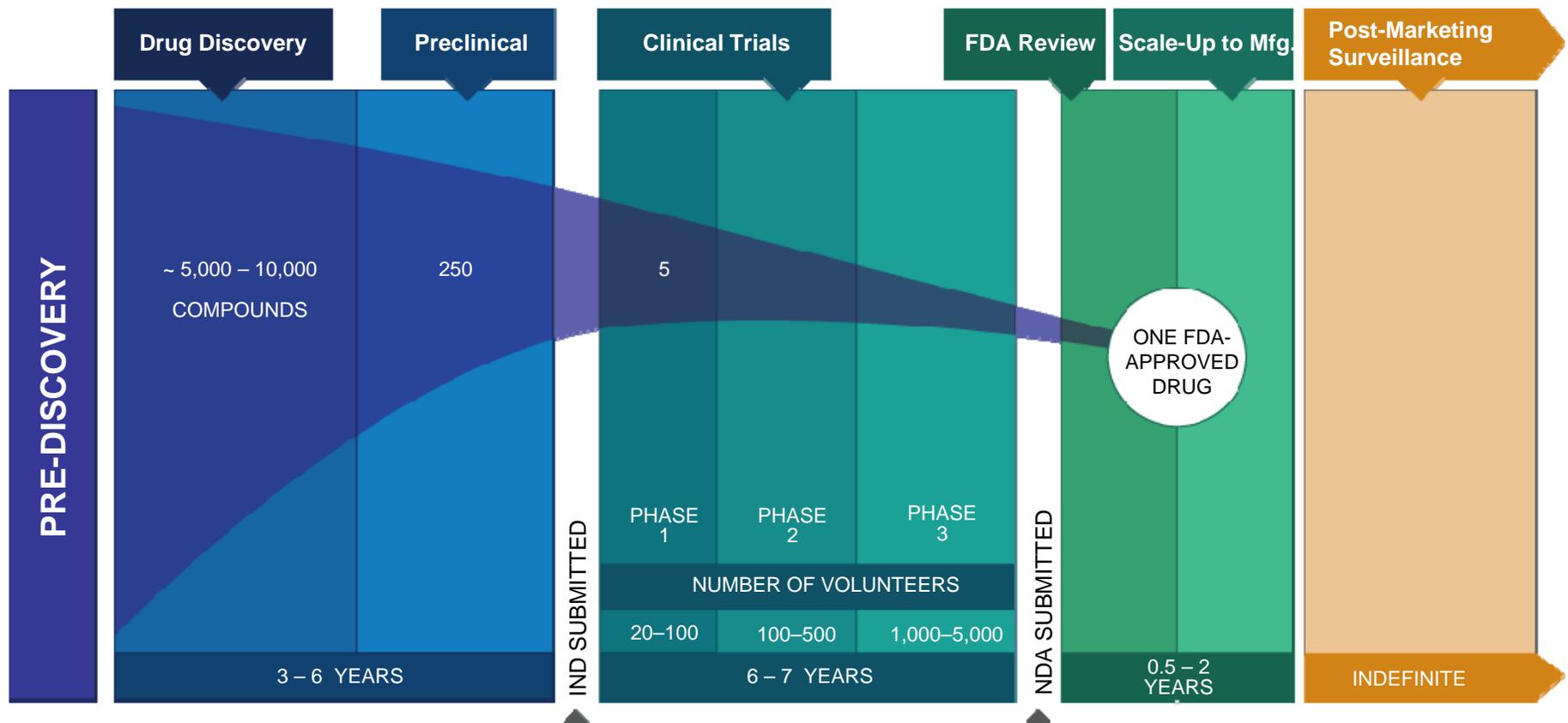
- Stages of therapy development
- Why therapy development is hard and usually fails and takes a lot of time and money
- Why the future is bright for new, effective and safe therapies
- What is Biogen Idec doing to develop therapies in neurodegenerative disorders including myotonic dystrophy?

The Investigational New Drug (IND) Application is the Platform for Drug Development



Drug Development Takes Longer Now

Developing a new medicine takes an average of 10–15 years and cost \$1.3B; the Congressional Budget Office reports that “relatively few drugs survive the clinical trial process”



Sources: Drug Discovery and Development: Understanding the R&D Process, www.innovation.org; CBO, *Research and Development in the Pharmaceutical Industry*, 2006.

Before Testing in Humans (preclinical phase)

- To Characterize potential adverse drug effects
 - Define potential organ or tissue damage induced by the drug
 - Define reversibility of toxicity
- To characterize pharmacokinetics (drug levels in blood)
- To characterize beneficial pharmacodynamic effects (does the drug do anything to the target in the body)
- To guide safe use in human clinical studies
 - To determine safe and reasonable starting doses
 - Provide monitoring guidelines for the clinical study
- Provide sufficient data to conclude that patients are not exposed to unreasonable risks

Federal and Company Roles in Research and Development

Government and biopharmaceutical industry research are complementary

Private Sector – \$65.3B¹



NIH – \$31.2B³

“There is an ecosystem of science and biotechnology. Public organizations, patient organizations, universities, Congress, FDA, all of this is an ecosystem that is envied in the rest of the world.”

– E. Zerhouni,
Director of NIH

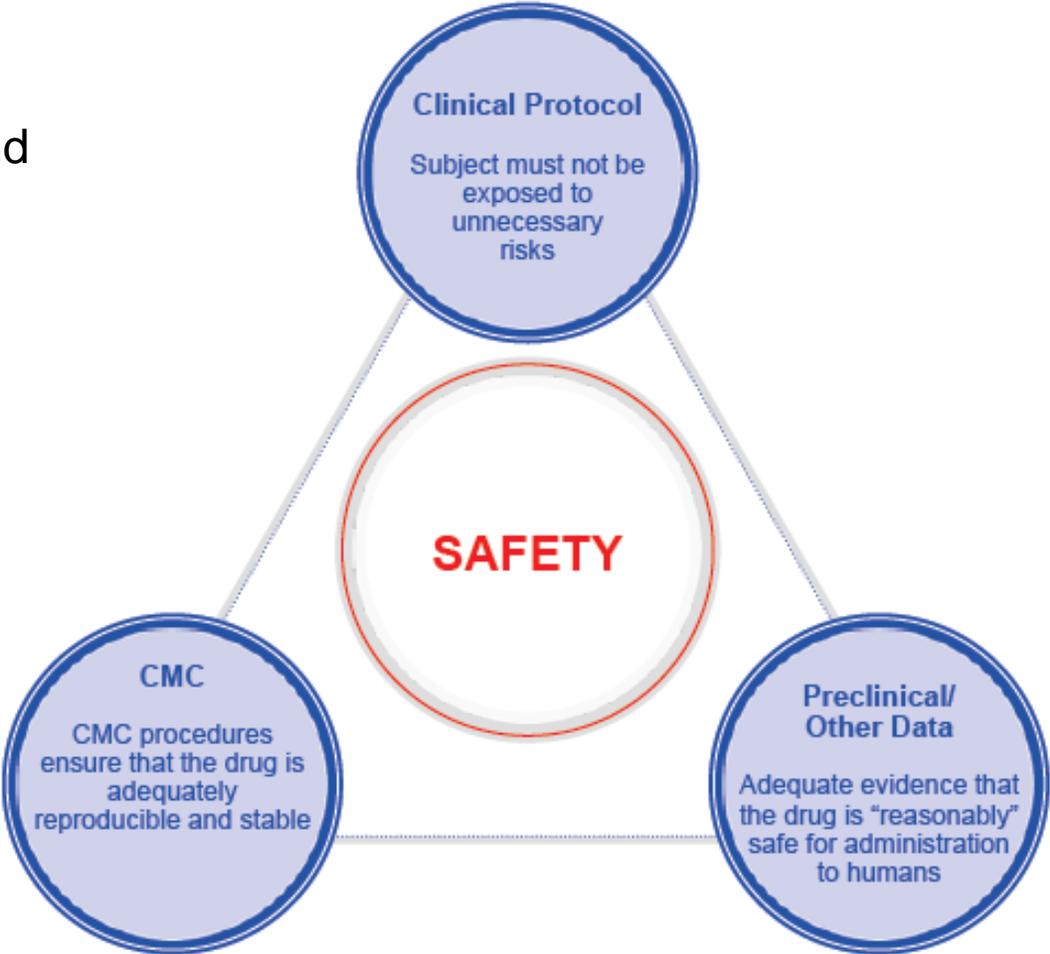
Sources: ¹Burrill & Company, analysis for PhRMA, 2010 (Includes PhRMA research associates and nonmembers) in PhRMA, “Profile 2010, Pharmaceutical Industry;” PhRMA, “PhRMA Annual Membership Survey,” 2010; ²Adapted from E. Zerhouni, Presentation at Transforming Health: Fulfilling the Promise of Research, 2007; ³NIH Office of the Budget, “National Institutes of Health: Enacted Appropriations for FY 2008-FY 2010,” <http://officeofbudget.od.nih.gov/pdfs/FY11/FY%202010%20Enacted%20Appropriations.pdf>.

What is an IND Why do we need it? (Investigational New Drug)

- An IND is permission by the FDA to conduct clinical trials in the United States
- Trials conducted outside the United States can also use an IND, in addition to the local CTA (Clinical trial application)

FDA Reviews the IND Primarily for Safety

CMC=chemistry,
manufacturing and
control



Phase 1 Clinical Goals

- Safety and tolerability
- Typically in healthy volunteers
- Drug levels in blood at various dosages
- Half life of the drug
- Adequate bioavailability after oral administration
- Alteration of metabolic pathways
- Evidence for pharmacologic activity

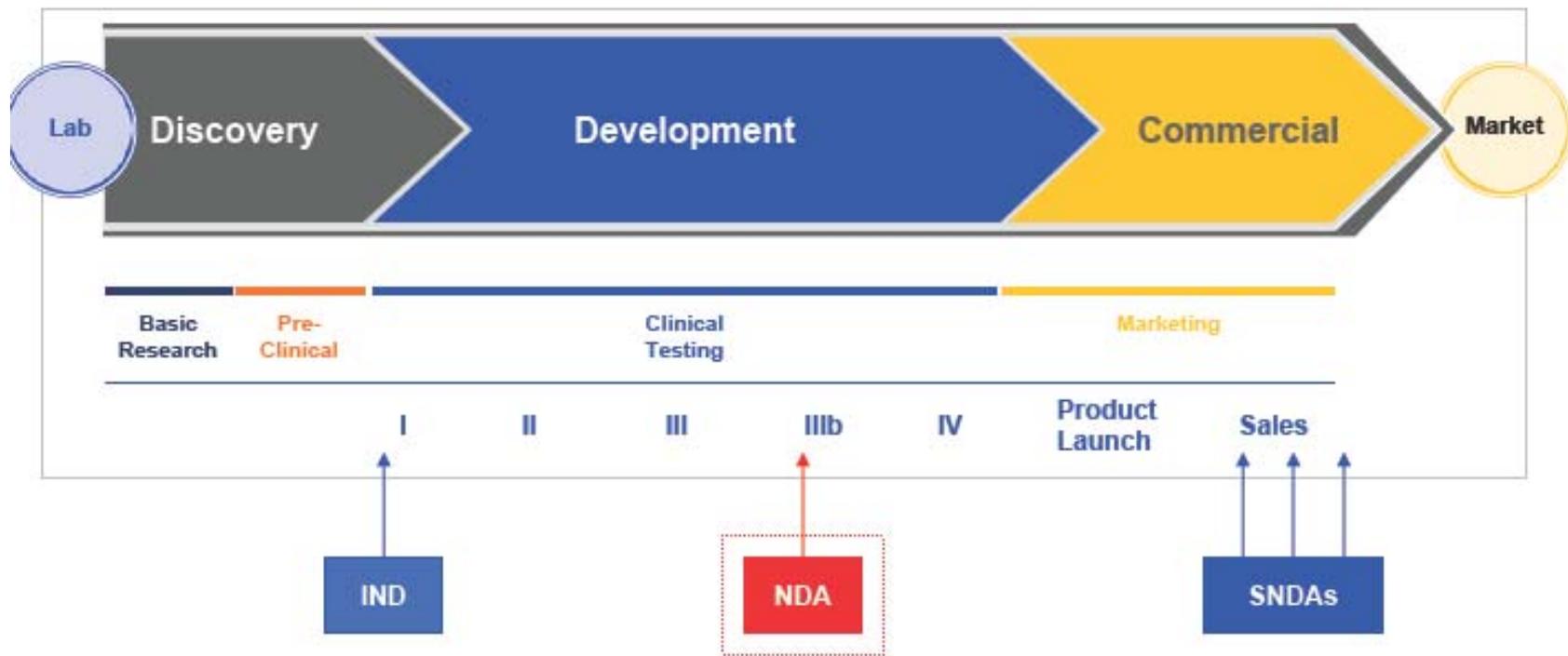
Phase 2 Goals

- Safety and tolerability in patients with the disease of interest
- Proof of Concept
 - “proof” that the concept is occurring in a human patient
 - Some clinical response or biochemical change that says “you’re on the right track”
- Dose response
 - Biomarker
 - Clinical endpoint
- Frequency of dose administration

Phase 3 Goals

- Pivotal trials necessary for approval
 - Confirm efficacy
 - Evaluate safety
- Need a validated, clinically meaningful endpoint (i.e. death or function)
- Need statistical significance (i.e. the observed benefit is not likely to be due to chance)
- Often compare with standard therapy
- Often need placebo to gain approval

The NDA is the Application for FDA Approval (Registration)



New Drug Application (NDA)

- If a NDA leads to approval, this means that FDA that permits the company to make its therapy available to patients outside clinical trials
- the FDA considers the following questions:
 - Safe and effective for proposed use?
 - Benefits outweigh its risks?
 - Drug's labeling appropriate?
 - Methods in manufacturing adequate to assure drug's identity, strength, quality and purity?
 - Procedures and controls in place to maintain drug's quality?

Fundamental Principle

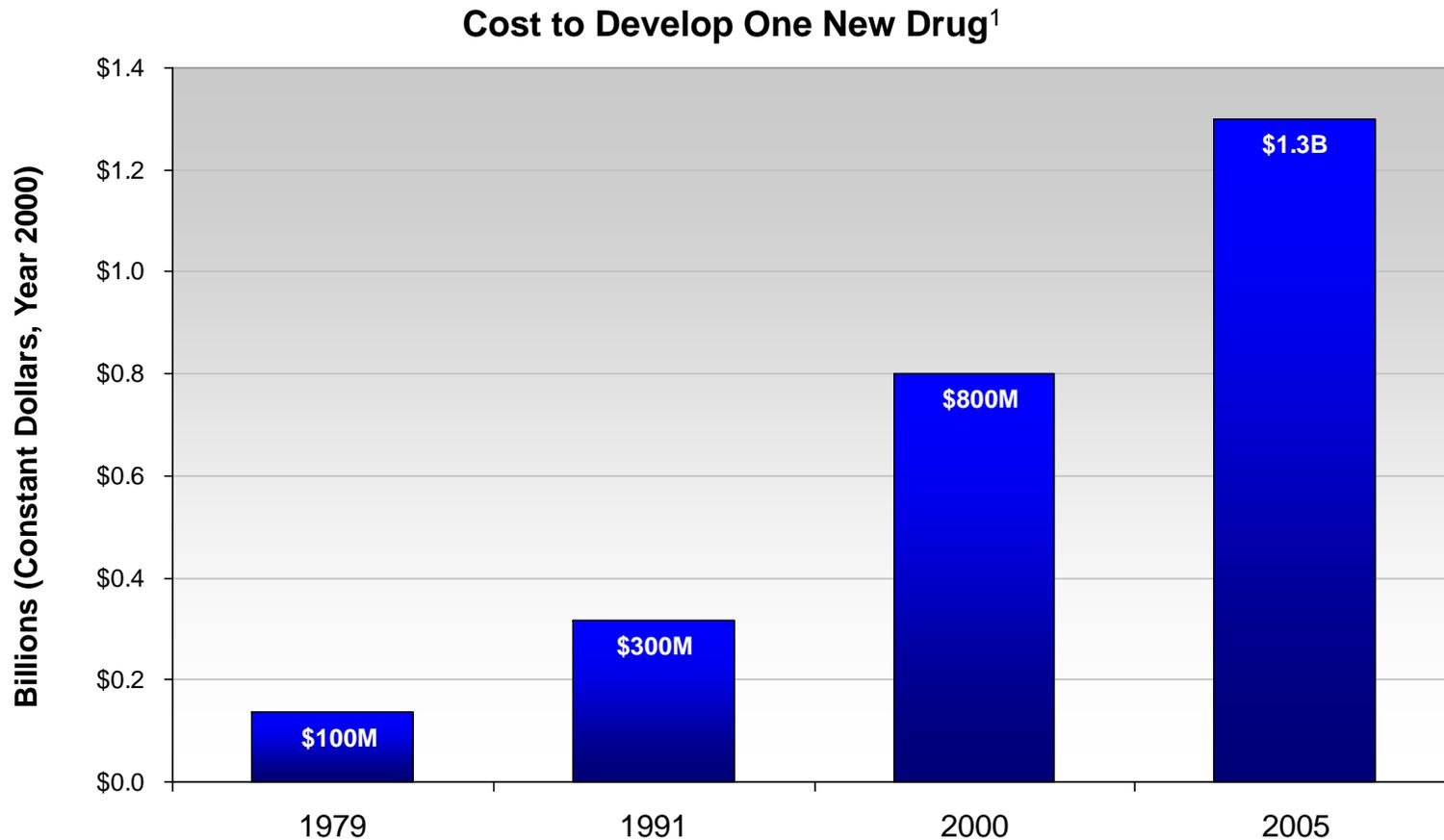
- No drug can be marketed in the United States until “substantial evidence” of its *quality, safety and effectiveness* has been provided to the FDA’s satisfaction

Phase 4 Goals

- New diseases or patient populations
 - Pediatrics
 - Pregnant women
- Compare to other approved drugs?
- New patient groups
- Pharmacovigilance (ongoing safety evaluation)

NOW SOME SOBERING FACTS ABOUT THERAPY DEVELOPMENT

The Cost of Developing a New Drug Has Greatly Increased

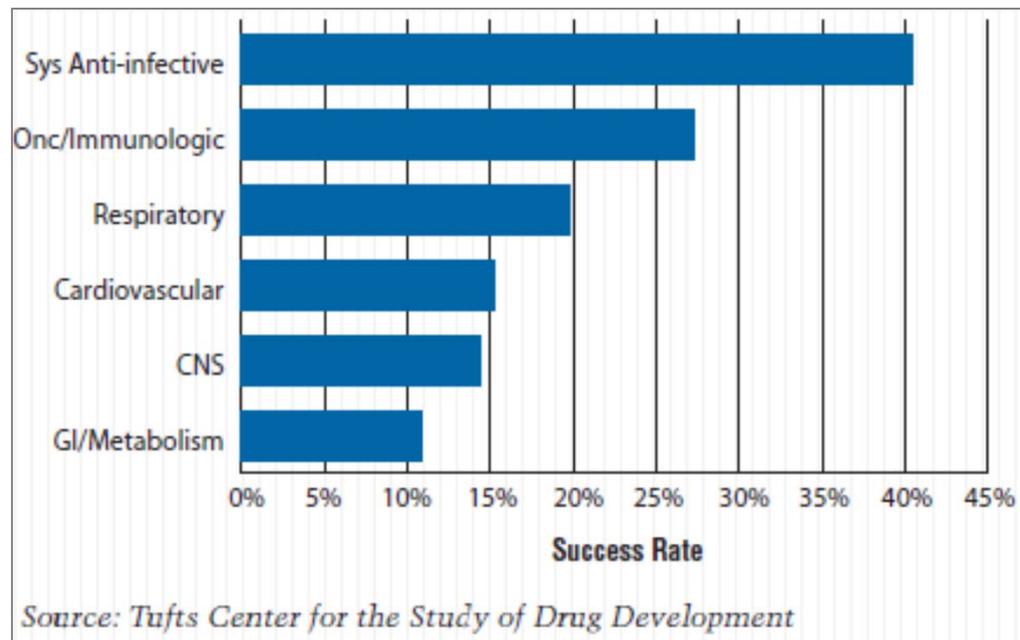


Sources: ¹J. DiMasi and H. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics*, 2007; J. DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 2003.

Probability of Success for Investigational Drugs Is Small

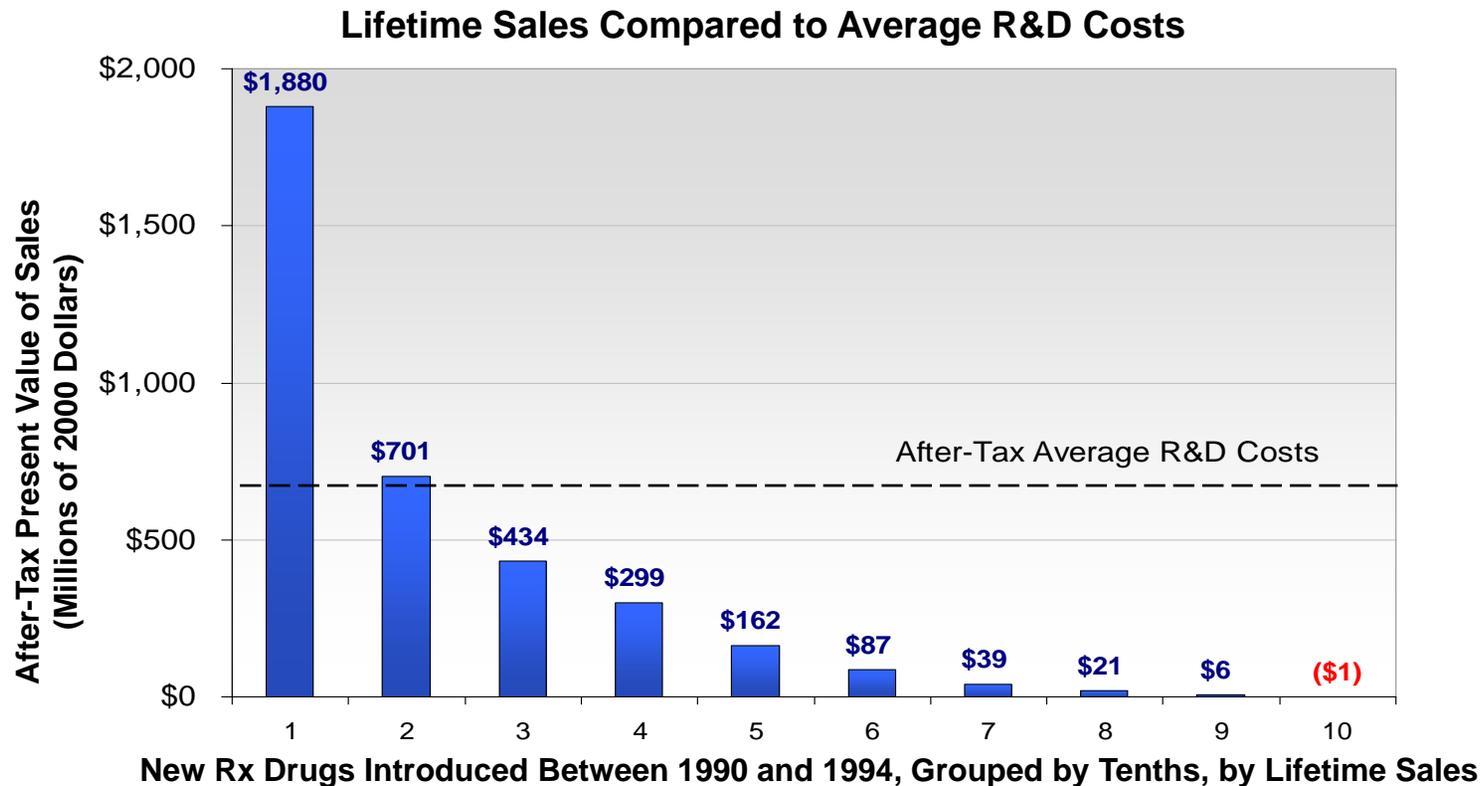
Approximately 20% of self-originated new drugs that enter clinical testing will receive U.S. marketing approval.¹

Clinical Approval Success Rates by Therapeutic Class¹



Source: ¹Tufts Center for the Study of Drug Development, "New drugs entering clinical testing in top 10 firms jumped 52% in 2003-05," Impact Report, 2006.

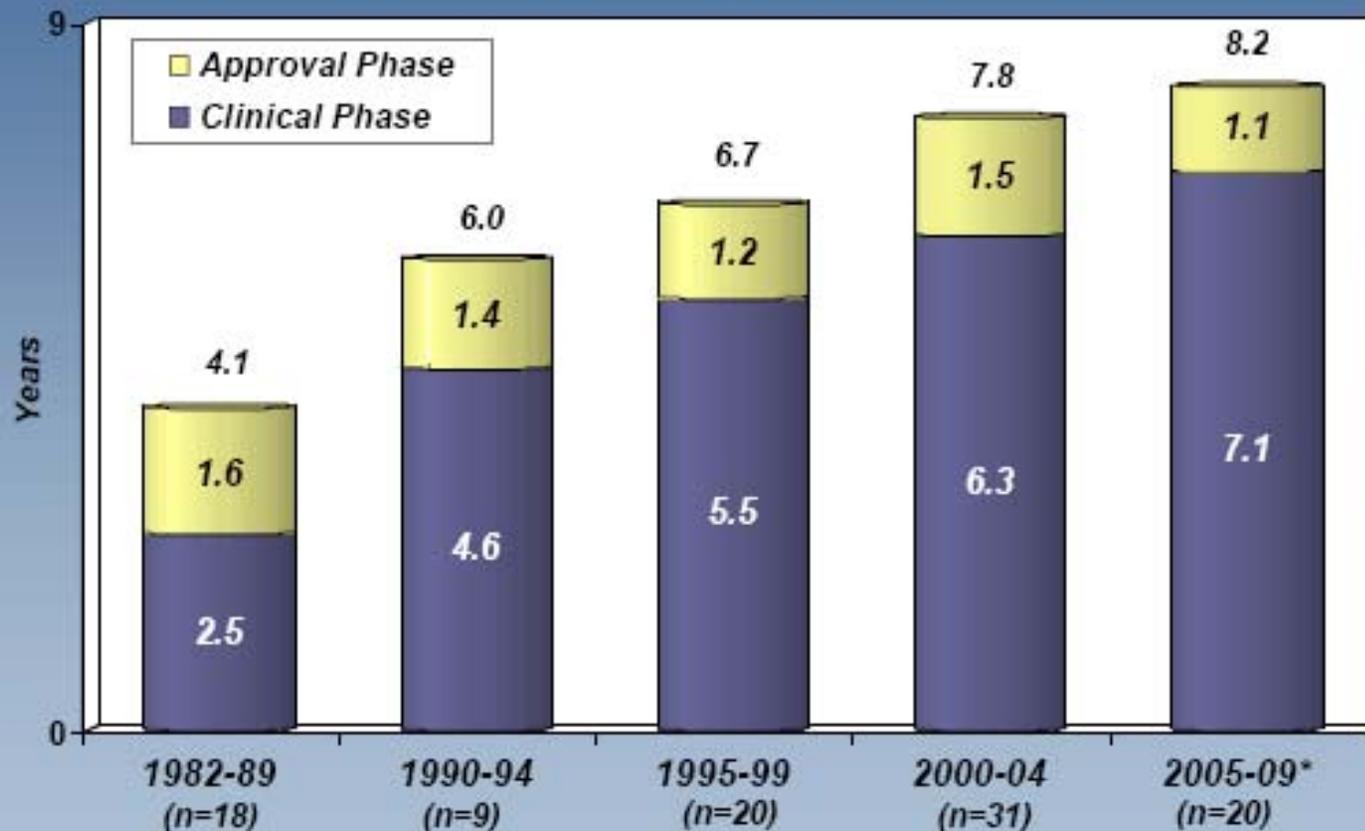
Even After Approval, Few Medicines Are a Commercial Success



Note: Drug development costs represent after-tax out-of-pocket costs in 2000 dollars for drugs introduced from 1990–94. The same analysis found that the total cost of developing a new drug was \$1.3 billion in 2006. Average R&D Costs include the cost of the approved medicines as well as those that fail to reach approval.

Sources: J. A. Vernon, J. H. Golec, and J.A. DiMasi, "Drug development costs when financial risk is measured using the Fama-French three-factor model." Health Economics, (2009). ; J. DiMasi and H. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," Managerial and Decision Economics, 2007.

Biopharmaceutical Development Times Are Increasing



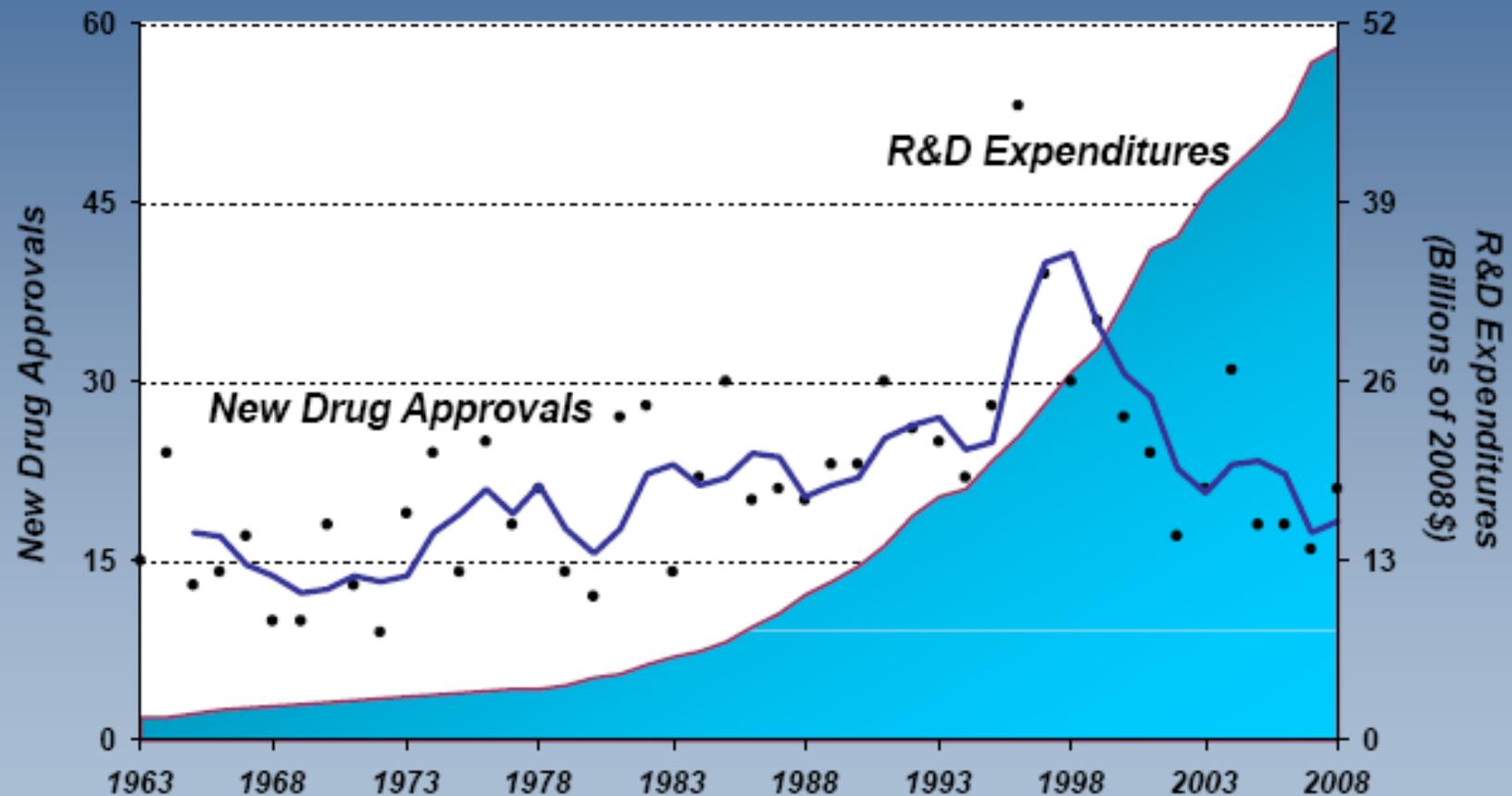
* Through 10/1/09

Source: Tufts CSDD, 2009



Tufts Center for the
Study of Drug Development
TUFTS UNIVERSITY

New Drug Approvals Are Not Keeping Pace with Rising R&D Spending



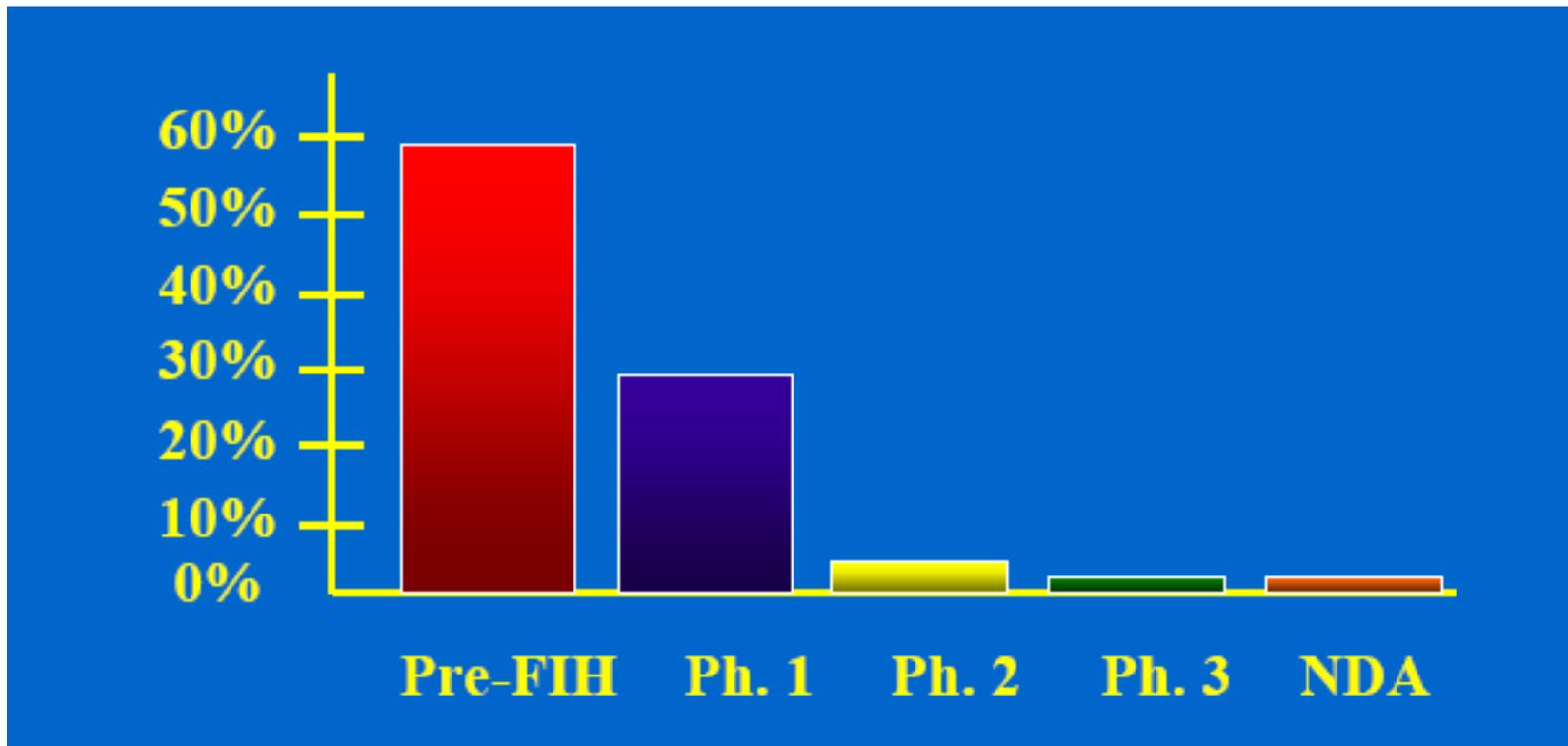
* Trend line is 3-year moving average; R&D expenditure adjusted for inflation

Source: Tufts CSDD Approved NCE Database, PhRMA, 2009



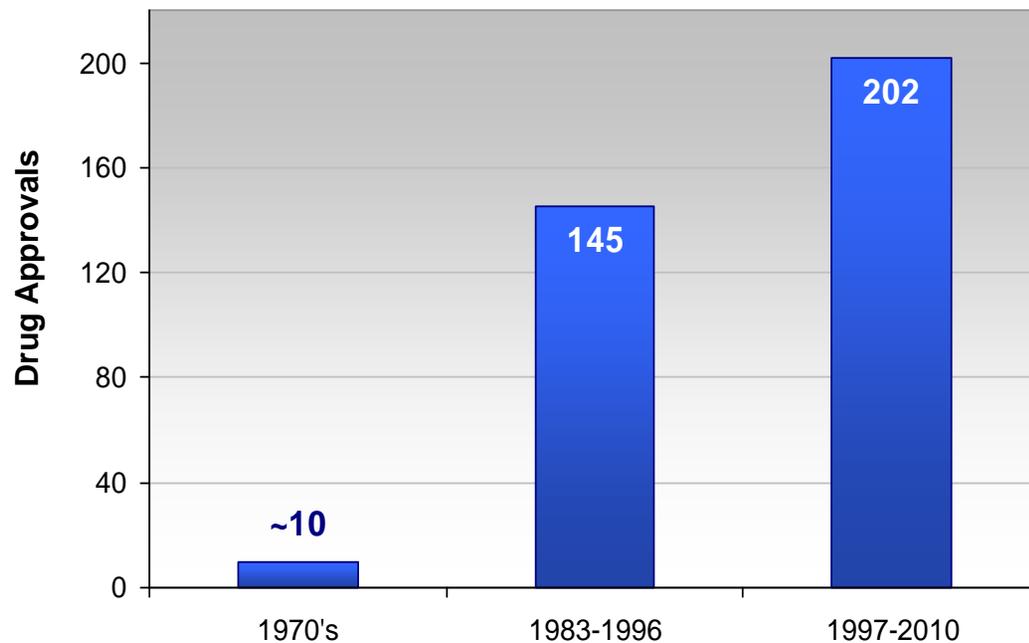
Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Ideal Distribution of Compound Attrition



Medicine Approvals for Rare Diseases

Drug Approvals for Rare Diseases Have Increased from Fewer than 10 to More than 202



Rare diseases are those that affect 200,000 or fewer people in the U.S. There are between 6,000 and 7,000 rare diseases affecting 25 million Americans.

The Orphan Drug Act (ODA) was passed in 1983 to encourage the research and development of medicines to treat rare diseases. Since then, the FDA has approved more than 200 medicines for rare diseases.

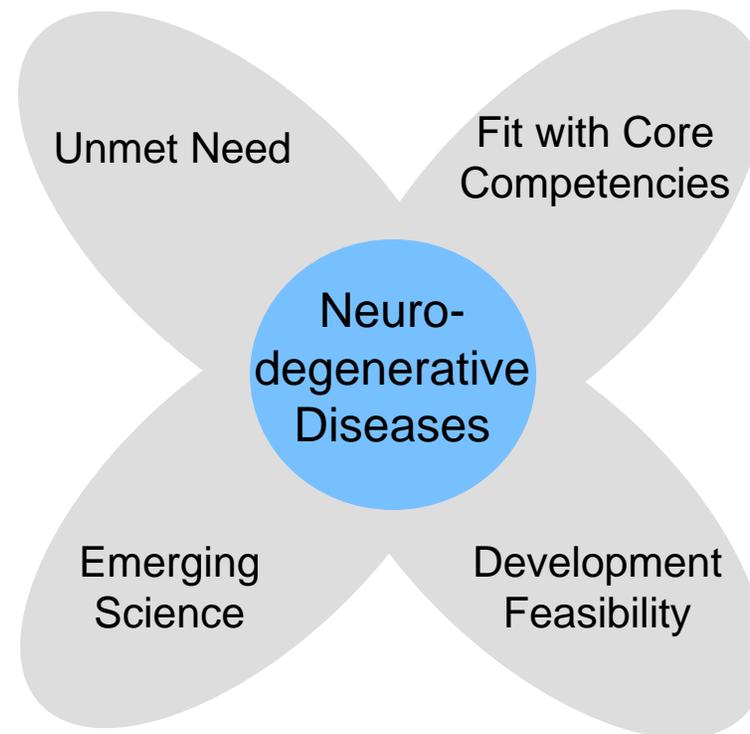
Note: All medicines approved for rare diseases include first-line approvals and subsequent approvals for new disease areas

Source: Food and Drug Administration, Office of Orphan Product Development, Orphan Drug Designations and Approvals Database, at <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm> Accessed August 2010] (for data from 1983–2010).

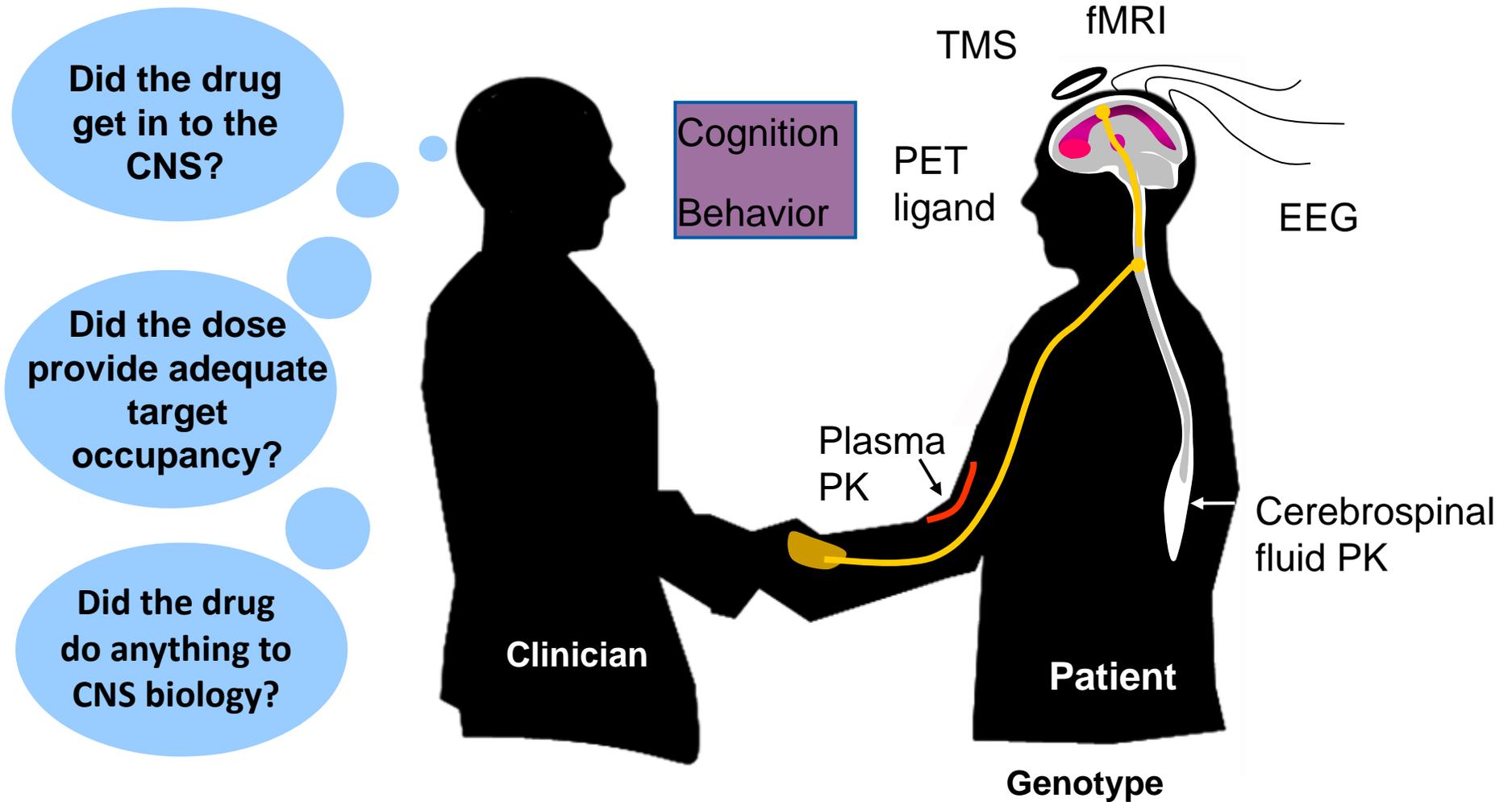
Ways to Improve the Efficiency of Drug Development

- Better understanding disease mechanisms
- Develop more specific and potent drugs
- Develop strategies to target the drug specifically to where it needs to go
- Better use of biomarkers to make informed decisions early in the process
- Personalized medicine
- Better consortia of clinical sites (i.e. NEALS)
- Bring the trial to the patient instead of the patient to the trial
 - Easier for the patient
 - Technology now allows for deep information capture
 - Can include more patients
 - “True patients”

Expansion of Biogen-Idec into Neurodegenerative Diseases (including myotonic dystrophy)



“Biomarker” = “Readout” needed for answering critical questions:

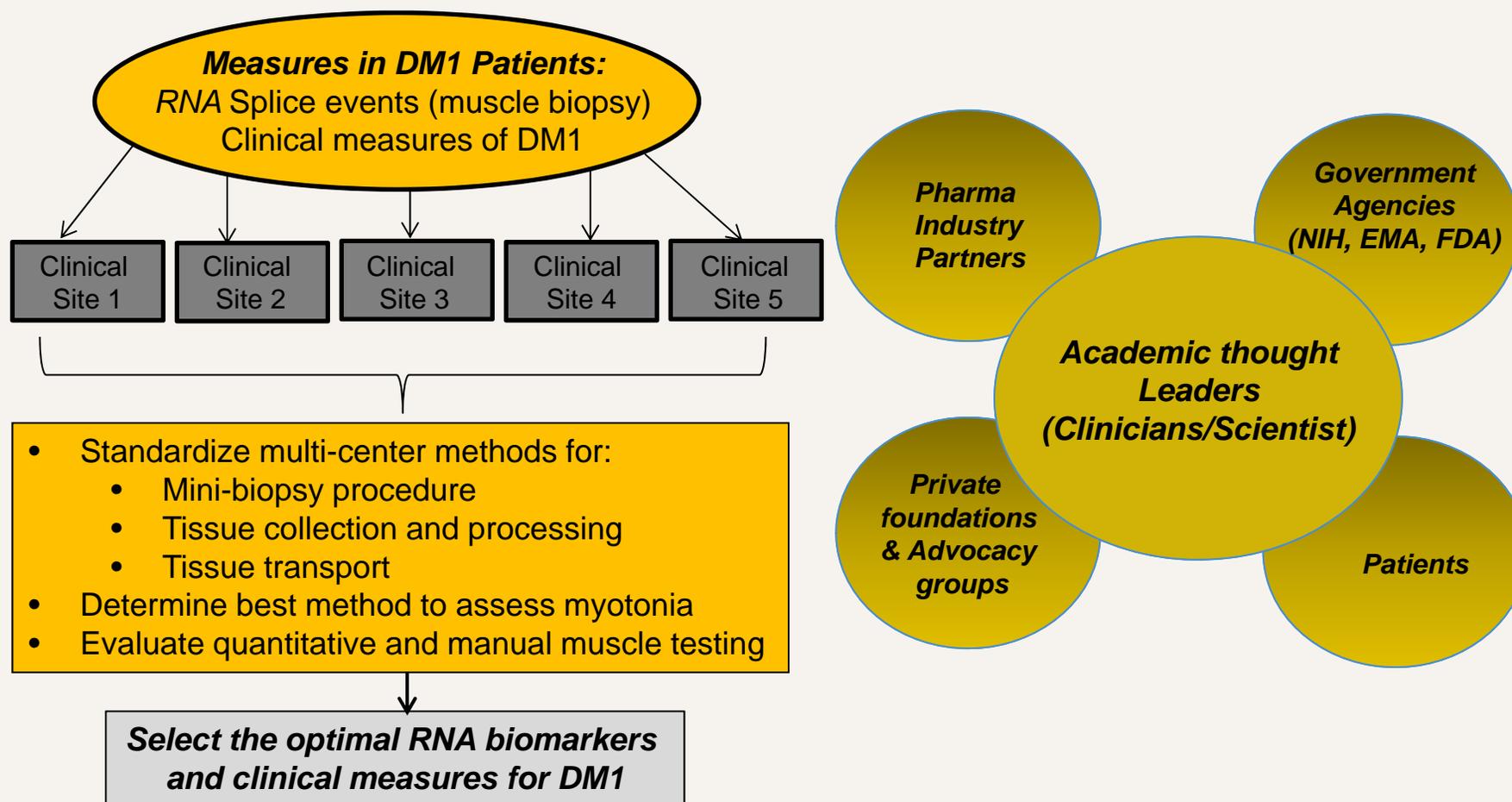


Summary

- Drug development is hard, long expensive and usually fails
- Drug development for neurologic disorders harder than for any other system
- New approaches make it likely that drugs will be developed and approved with increasing efficiency for neurologic disorders
- Our obligation to patients is to maximize the time and effort patients spend on trials of drugs that have a good chance of working

A Multicenter Natural History Study in Patients with Myotonic Dystrophy Type 1

It's all about Collaboration



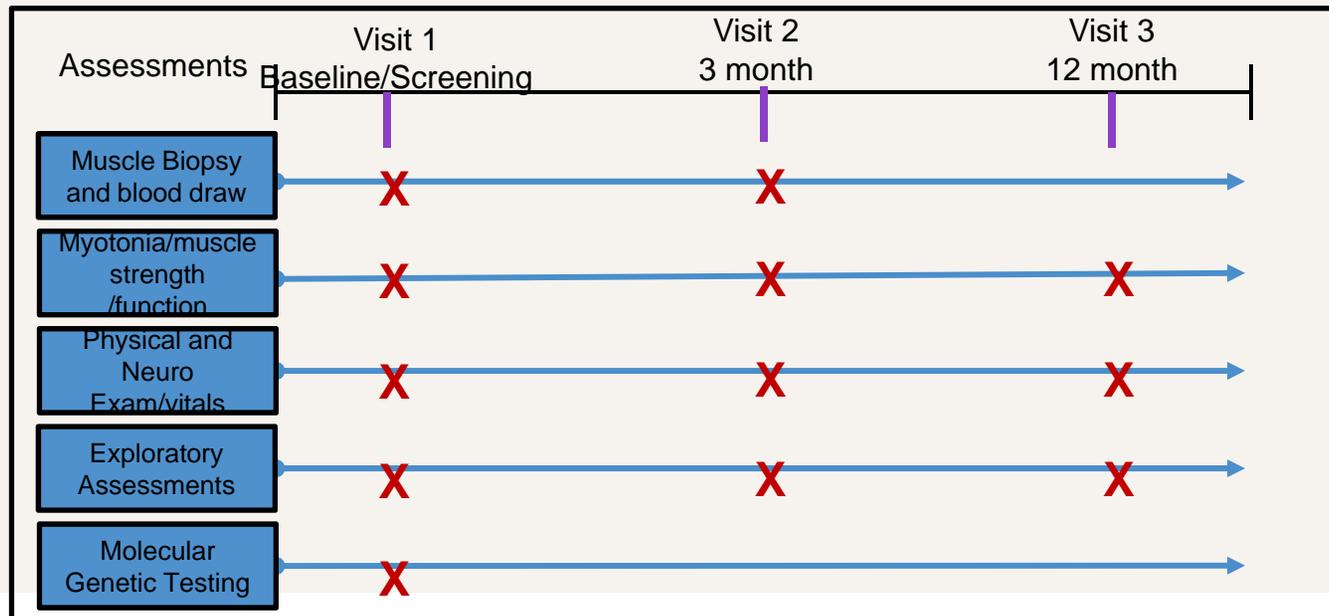
Primary Objective and Study Design

Primary Objective:

To evaluate the stability of muscle biopsy RNA splice events over a 3 month period as potential biomarkers for use in future DM1 therapeutic trials (Approximately 25 known splicing events will be analyzed)

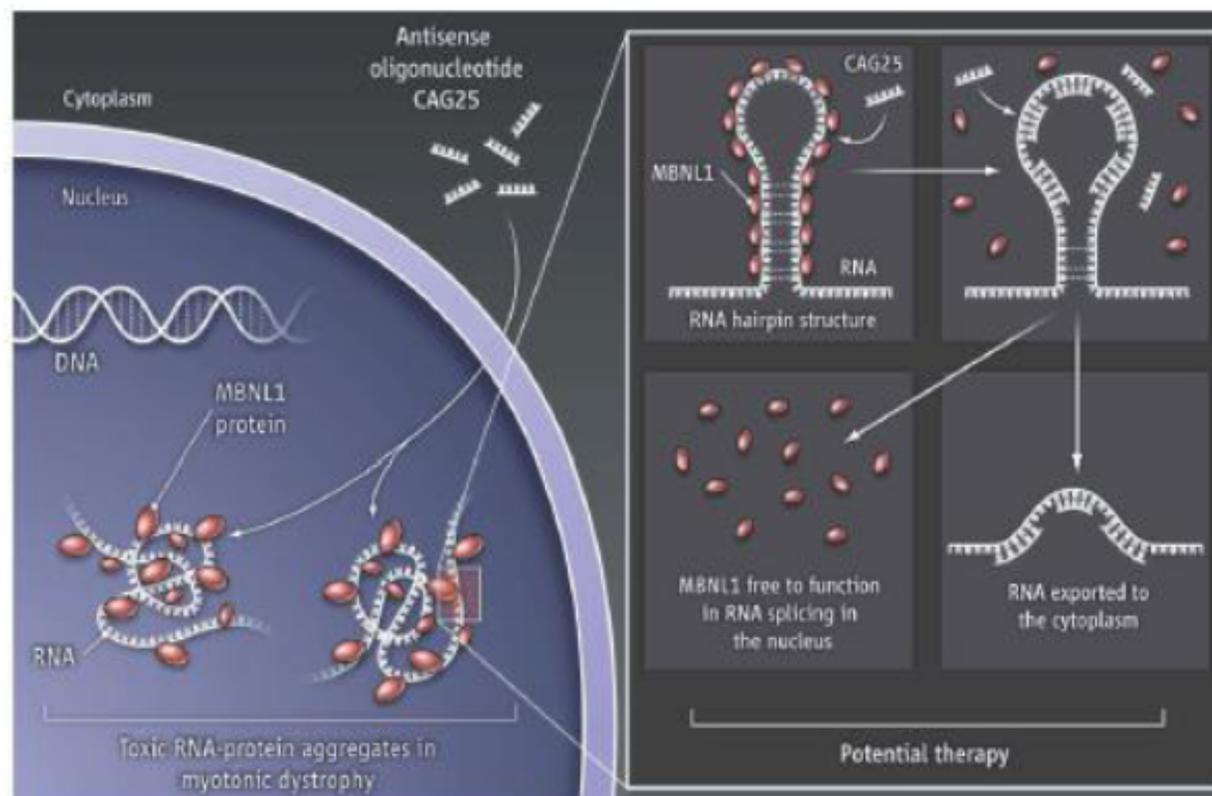
Study Population

- 100 male and female adult (18 – 70 yrs) DM1 patients enrolled at 5 centers
- DM1 onset after age 10
- CTG repeat > 70 (~ 3 patients/site with 70 – 100 repeat length)
- Ability to complete 6 minute walk
- No treatment will be administered



Antisense Strategies For Myotonic Dystrophy Type 1

Target the CUG Repeat with ASO, Displacing Muscleblind from the Nuclear Foci



From: Tom Cooper *Science* 325: 272-273, 2009



Reversal of RNA Dominance by Displacement of Protein Sequestered on Triplet Repeat RNA
Thurman M. Wheeler, et al.
Science 325, 336 (2009).
DOI: 10.1126/science.1173110

Triplet-repeat oligonucleotide-mediated reversal of RNA toxicity in myotonic dystrophy

Susan A. M. Mulders¹, Walther J. A. A. van den Broek², Thurman M. Wheeler³, Huib J. E. Croes⁴, Petra van Kulk-Romijn⁵, Sjoef J. de Klompe⁶, Denis Furling⁷, Gerard J. Platenburg⁸, Geneviève Gourdon⁹, Charles A. Thornton¹⁰, Be Wieringa¹¹, and Dorick G. Wansink^{1,2,11}

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DM1 Drug Development Strategy

- Multi-systemic disease
 - Skeletal muscle, cardiac, gastrointestinal tract, eye are affected
 - CNS also affected in childhood-onset type
- Initially focus on muscle aspects of the disease
 - Most affected system in patients
 - Multiple, well-studied outcome measures
 - Pre-clinical mouse models exist
 - Clear path to drug registration
- But also may see effects on cardiac and GI aspects of disease
 - ASOs distribution to these tissues is good
 - Cardiac and GI measures to be included in POC study (secondary outcomes)
- Determine timing and develop plan to explore IT delivery to address CNS aspects in childhood onset DM1
 - Could be added on later, as is being done with ERTS currently (i.e. MPS I, MPS IIIA)

DMPK/DM1 Clinical Overview

- DMPK ASO will be given systemically by SC injection
- Dose and frequency uncertain
- **In Phase 1 study**, will be able to obtain critical informative data
 - PD effect in muscle:
 - DMPK mRNA decrease (normal and nuclear-retained repeat)
 - DMPK downstream splicing changes (e.g. chloride channel, Titin, Serca1, etc.)
 - Myotonia clinical data
 - PK drug levels in muscle
- **Phase 2 study in Adult DM1 patients**
 - Symptomatic adult DM1 patients
 - 6 month treatment duration; 3 month follow-up
 - SC injections
 - 2 dose levels versus control
 - Study Outcomes:
 - » muscle strength (primary)
 - » myotonia decrease
 - » timed functional tests (possible registration endpoint)
 - Cardiac and GI outcome measurements
 - Safety and tolerability
 - Muscle biopsy for PD: DMPK mRNA change & splicing changes in downstream genes