Parent Project Muscular Dystrophy

LEADING THE FIGHT TO END DUCHENNE

ROLE OF ADVOCACY IN FACILITATING BASIC SCIENTIFIC RESEARCH

Purpose of Advocacy – Help Solve Important Problems

PPMD's Mission

END DUCHENNE

Duchenne

1:4600

X-linked, progressive

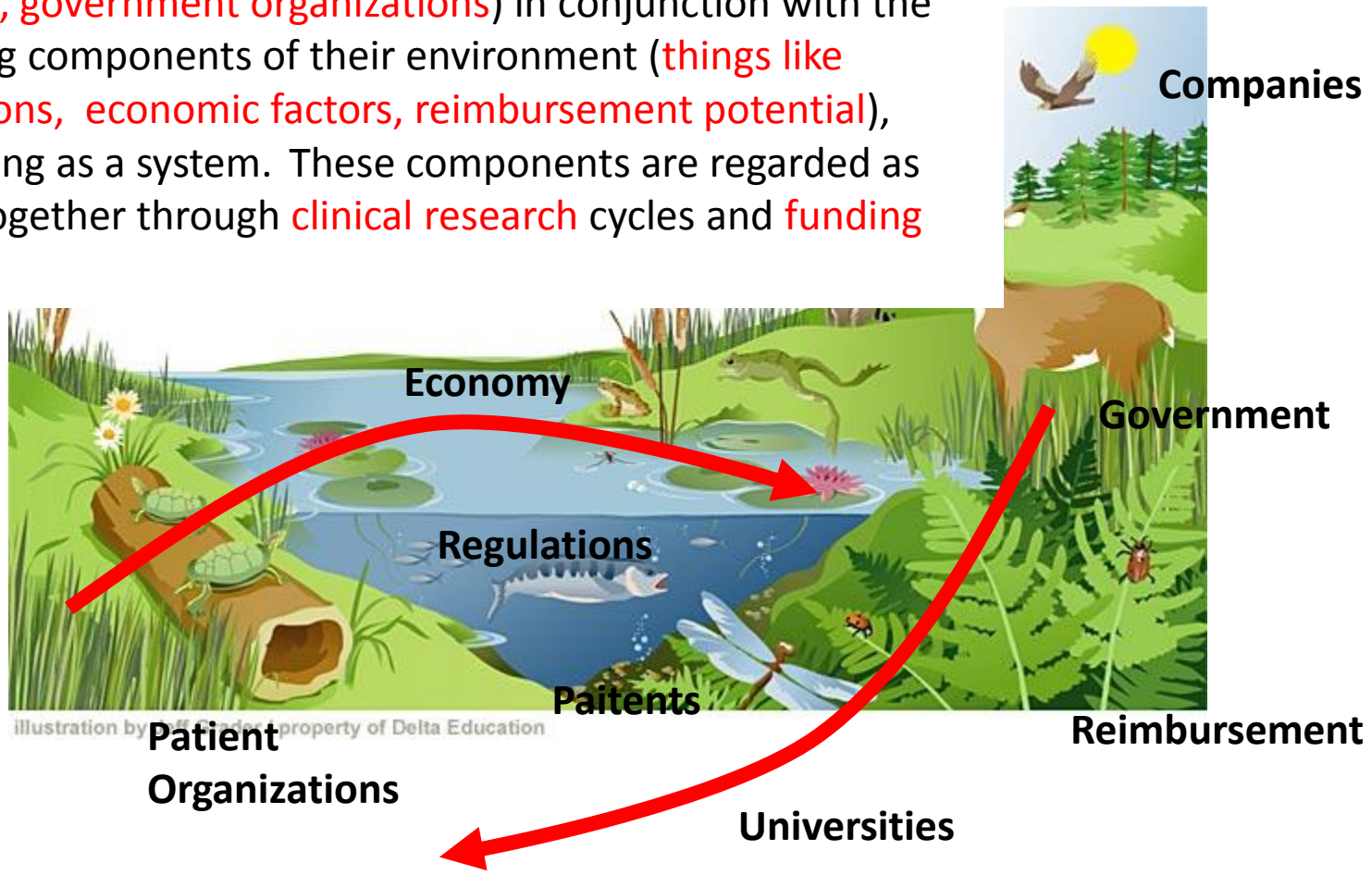
Largest gene in the human genome

40% spontaneous mutation

30% have learning/processing issues

Why are we here?

A drug development **ecosystem** is a community of stakeholders (universities, companies, patient organizations, patients, government organizations) in conjunction with the nonliving components of their environment (things like regulations, economic factors, reimbursement potential), interacting as a system. These components are regarded as linked together through clinical research cycles and funding flows



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PPMD Role in Drug Development: Filling in the Missing Pieces

PRECLINICAL

- Independent validation of results
- Funding "Valley of Death"

CLINICAL INFRASTRUCTURE

- Patient registries
- Endpoint development
- Clinical research networks

ADVOCACY

- Increased $$ for NIH, DOD, CDC
- Direct engagement of regulators

EDUCATION

- Drug development
- Clinical Trials
- Management of expectations

Challenges and Opportunities

SIZE OF GENE, CLINICAL VARIABILITY, VARIABLE CARE

Finances and fragmentation within rare disease

Academic research –overhead, tech transfer and time sharing/collaborating

N=1 experience:

Addressing challenges (harnessing complexity)

PRO – common data elements/curated/searchable

Genome studies – outliers

Task Force – barriers to dx, expand to all pediatric diseases where muscle wasting is primary symptom

Parallel protein signature (SomaLogic)

PLoS

Validation lab

RADD

TACT

Networks (Mirror Ped. Oncology and RDRCN) collective IRB and contract negotiation

IDENTIFYING PRE-COMPETITIVE PROJECTS

RADD

CONSOLIDATE NATURAL HISTORY DATA

FACILITATE /IMPROVE REVIEW – TACT

PPMD – RADD, TACT, SHIRE

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Parent Project Muscular Dystrophy is the largest nonprofit organization in the United States focused entirely on Duchenne.

PPMD's Three – Pronged Strategic Plan for Research

BETTER	FASTER	NOW
Those that will **improve the quality** of drug candidates entering clinical testing	Those that will **decrease the time** required to test drugs for Duchenne and Becker	Reviewing and testing approved drugs to **buy time for this generation** of boys

GLOBAL INVESTMENT FOR THERAPEUTICS TO END DUCEHENNE

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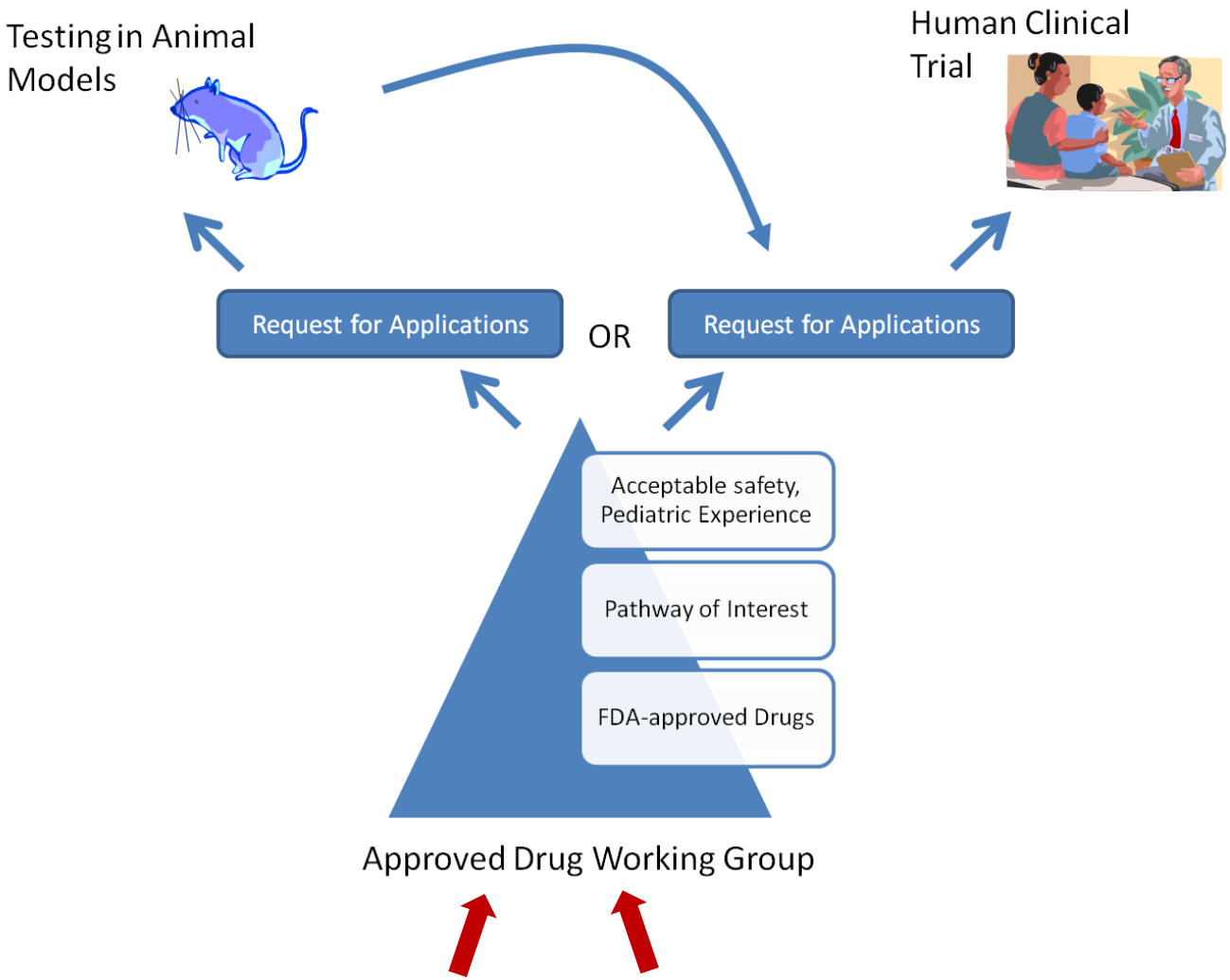
Now: Review of Approved Drugs for Duchenne (RADD) Working Group



Three-way collaboration between **Nationwide Children's Research Institute**, **Children's National Medical Center** and **TREAT-NMD** designed to prioritize FDA-approved drugs for further testing.

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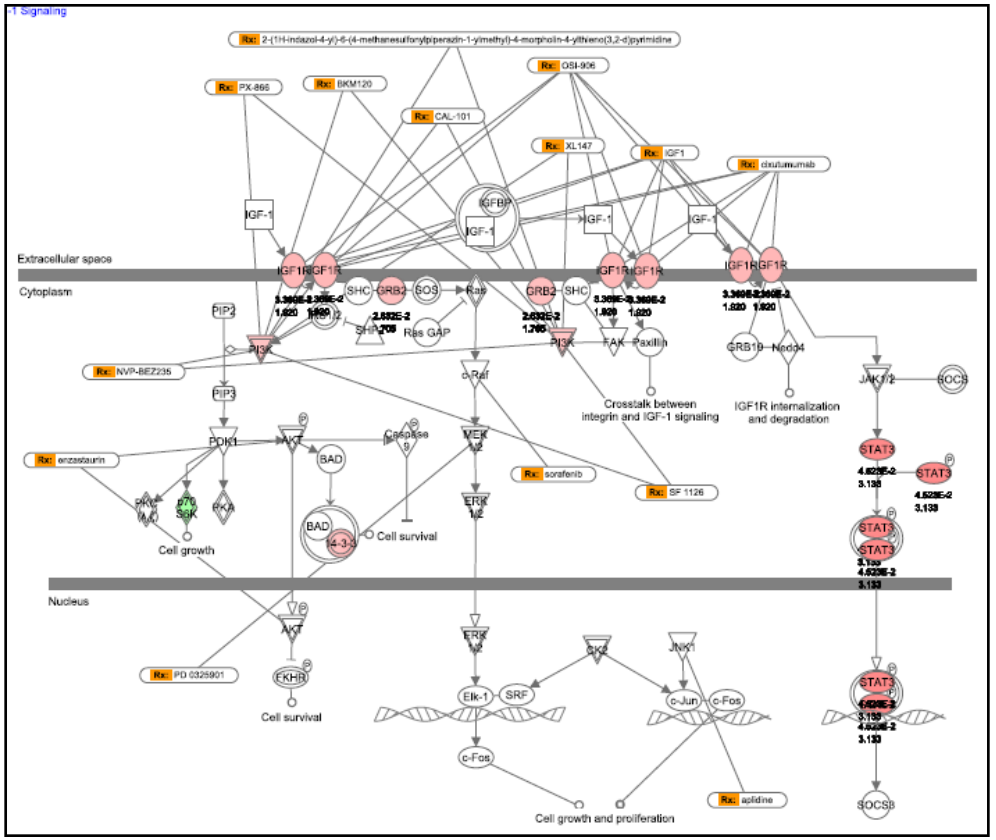
RADD: Target Identification and Validation

Review of Approved Drugs for Duchenne (RADD) Pathway Mapping Project

1. Published literature on preclinical models is annotated and entered into searchable database (180+ papers so far)

2. Gene Expression data from different models and stages is compiled



Partnering to Enable Drug Development for Orphan Disease

TACT

Treat NMD Advisory Committee for Therapeutics

Partners: Who we are

- TREAT-NMD: global network of excellence- EU-funded roots
  - Advancing diagnosis, care and treatment for neuromuscular disease (NMD)
  - Advisory committee for Therapeutics (TACT) established to evaluate potential therapies in an objective, comprehensive manner
- PPMD (Parent Project Muscular Dystrophy): US largest non profit organization focused on Duchenne Muscular Dystrophy (DMD)

Initiative

- TACT established in 2009 comprising volunteer experts from academia, industry, non-profit, patient advocacy to provide development advice to academia and industry
- Multidisciplinary, comprehensive input
- Addresses translational gap in NMD
- Independent of funding stream
- PPMD partnered with TACT and integrated TACT reviews in its diligence for funding

What TACT is addressing

- Fragmented and subjective approach to funding translation in NMD
- Lack of comprehensive review of both science and development potential of compounds
- Rigor of assessments variable across funders and researchers
- Compounds moving to clinic despite non compelling preclinical data leading to (predictable) failure in the clinic
- Often lacking realistic development perspective- limited industry participation
- Multiple compounds to go into clinic- limited number of patients

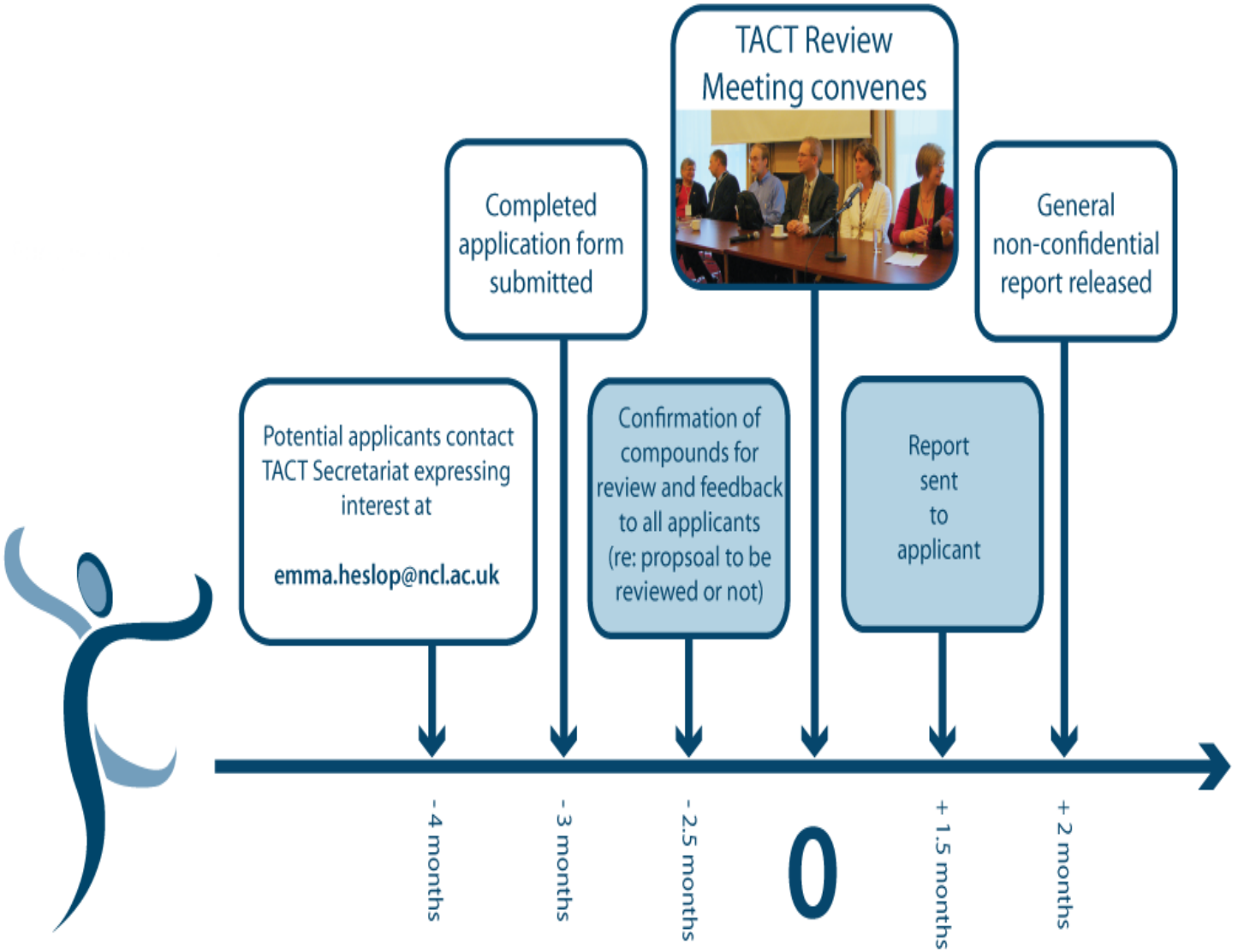
Sophisticated diligence process beyond the abilities of typical academic advisory committee resulting in

greatly increased credibility with non profit, industry and VC funders

Strategy

- Multidisciplinary, informed, objective
- Reviews and reports are confidential
- Credible with industry and funders
- Eliminate historical barriers between academia, industry, patient organizations
- Included NIH and FDA committee members
- No reinventing the wheel
- No duplication of already existing efforts
- TACT is directly addressing the IRDiRC principles and goals

TACT Review Process



Opportunities

Researchers

- A unique, multidisciplinary, review by disease and development experts
- A more informed and credible program
- More likely to get funded
- Enables cross talk with industry
- Training of young investigators
- Highly educational to academic researchers on realities of drug development

Patient organizations

- Comprehensive objective assessment- raise the bar
- Increase odds of clinical success

How We Work with TACT

- We use the same application forms
- We require grantees to undergo TACT review as a condition of funding; We fund and attend review meetings
- We may modify our grant requirements as a result of the TACT review

Benefits of Working With TACT

- More extensive access to experts than we could develop on our own
- Reduces burden on reviewers and applicants because centralized process can be shared among multiple groups

Accomplishments and Future

Accomplishments

- In less than 3 years, the “go to” committee for both industry and academia engaged in NMD translation- sponsor feedback
- 15 programs reviewed
  - 5 from academia
  - 10 from industry
  - Diseases: DMD, SMA, BMD, CMD
- Young investigator program established

Moving forward

- Continued funding critical
- Engage additional patient groups
- Willingness to export model to other rare diseases

Key points

- Successful integration of academia, industry and funder must haves for ability to translate in rare diseases
- Facilitated development timelines and progress to IND
- Shifts urgency from first to clinic to most informed to clinic
- Model can be exported to other rare diseases
- Minimizes duplication of effort and funding
- Future funding critical

Consolidating Natural HX Data

1. IRB approval for retrospective data analysis (
2. Ages of those in databases
3. Consistent steroid regimens
4. What endpoints used (10 m or 9 m walk time. As long as the time and distance walked is recorded, these can be normalized to a velocity), rise to stand and 4 stair climb are pretty standardminority. Height, and weight will also be useful to potentially adjust for growoth
5. What is needed to collaborate and combine data as far as privacy?
6. Validate and combine data in HIPAA compliant format I would focus on de-identified data, which by definition is already HIPAA compliant.
7. Need to talk about credit for study information

IN PARTNERSHIP WITH SHIRE

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Better: Increasing the Quality of Drug Candidates

- Identifying and directly supporting drug candidates with the greatest likelihood of success
- Partnering with TREAT-NMD's TACT program to provide deep and expert diligence
- Independently validating preclinical animal data through the testing core at U Penn
- Continuing to provide access to expert advice throughout the lifetime of a project

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Faster: Decreasing the time required to get a drug approved

- Recruiting for trials more quickly by funding Duchenne Connect to identify participants and then supporting their travel

- Improving measurements of success in clinical trials by developing biomarkers and validating new functional endpoints (ex. Non-ambulatory endpoints)

- Encouraging the use of centralized IRBs and supporting university contracting offices (Partnership planned with NeuroNEXT)

- Continuing efforts to identify boys with DMD at younger ages and in economically challenged areas

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Now: Prioritizing FDA approved drugs to test in DMD Now

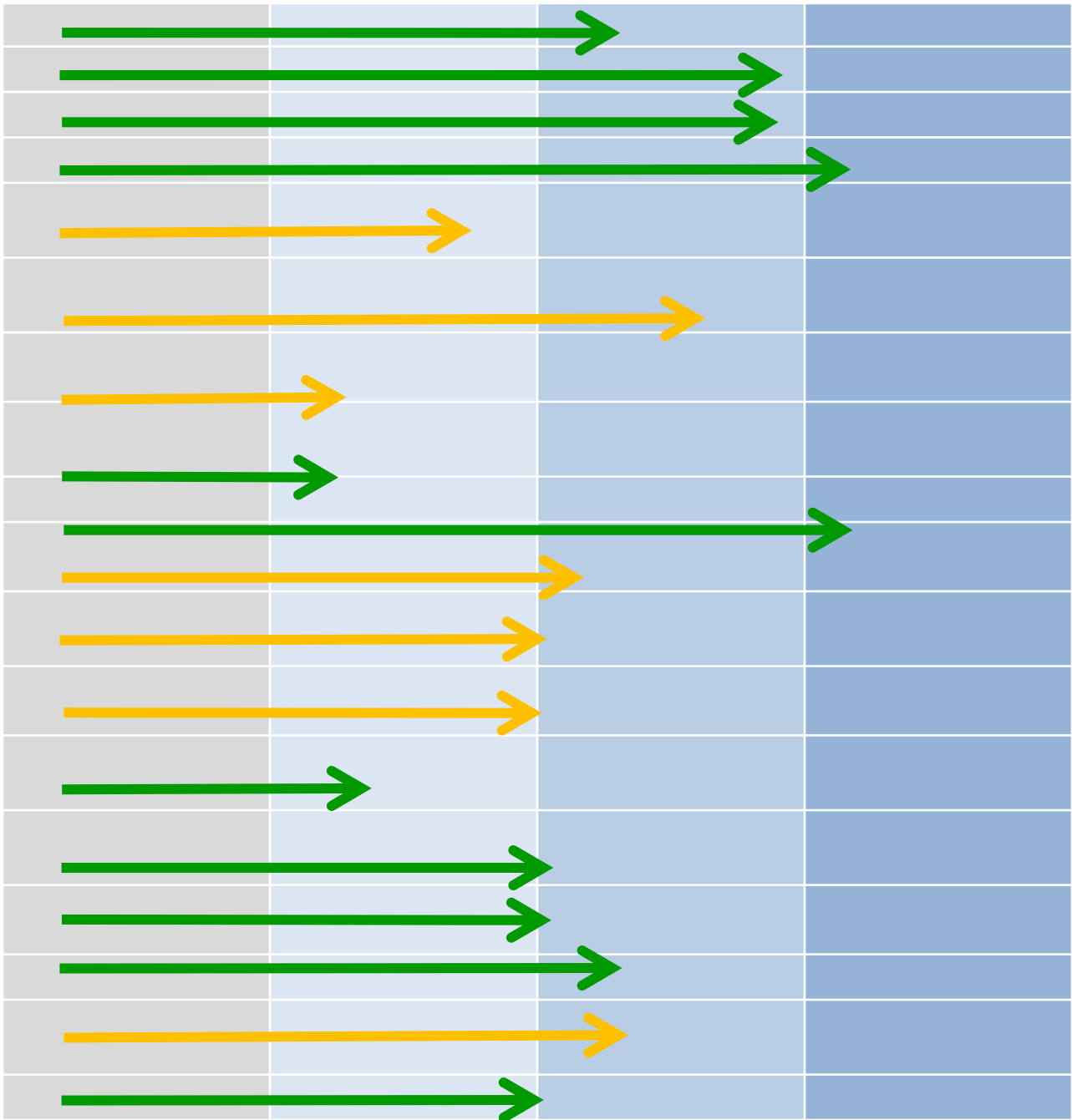
- Reviewing and evaluating all published studies that suggest that a given biochemical pathway is relevant

- Using software to create a weighted map of the pathways that are most likely to impact the disease and cross-referencing these with FDA approved drugs

- Creating a prioritized list of approved drugs that may either go directly into human testing or into additional animal testing

- Expanding the search to drugs that failed in clinical testing for other indications through partnerships with companies

Candidate or Target	Company or Institution
ACE-031	Acceleron
Ataluren	PTC Therapeutics
Eteplirsen	AVI Biopharma
Catena®	Santhera
Cialis® And Viagra®	Cedars-Sinai
Epigallocatechin-Gallate	Charity University, Berlin
Flavocoxid	University of Messina
Follistatin in AAV vector	Nationwide Children's
GSK 2402968	GSK
Increlex	Cincinnati Children's
Isosorbide dinitrate and ibuprofen	University of Milan
Losartan	Nationwide Children's
Mesangioblast transplant	Giulio Cossu
Minidystrophin gene transfer	Asklepios Biopharmaceuticals
Myoblast transplant	Jacque Tremblay
PRO-044	Prosensa
Revatio® (Sildenafil)	Kennedy Krieger Research Institute
SMT C1100	Summit PLC



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The Next Generation

Drug	Activity	Who
Biglycan	Utrophin-dependent mechanism	Tivorsan
Exon-skipping: exons 45, 53, 52, 55	Restores dystrophin reading frame	Prosensa
Exon-skipping: exon 50	Restores dystrophin reading frame	AVI Biopharma
Halofuginone	Blocks fibrosis	Halo Therapeutics
Laminin 111	Stabilizes cell membrane	Prothelia
L-arginine with HDAC inhibitors	Restores membrane signaling and gene expression	Sabine de la Porte
New stop-codon readthrough drugs	Read through point mutations in dystrophin gene	various
Muscle-building drugs	Block pathways that normally slow muscle growth	various
VBP15	Possible steroid replacement	Reveragen
Tamoxifen	Under investigation	Urs Ruegg
Utrophin upregulator	Experimental compound	PTC Therapeutics

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Projects Funded or Committed in 2012

Clinically Meaningful Outcomes for Duchenne Muscular Dystrophy Therapeutic Trials	Dr. Erik Henricson, University of California, Davis	Supplement Grant	$175,000
Early treatment with Aldosterone antagonism attenuates cardiomyopathy in Duchenne MD (Epleronone Trial)	Dr. Kan Hor, Cincinnati Children's Hospital Medical Center	Investigator Grant	$84,092.45
Preclinical investigation of tamoxifen in mdx mice prerequisite for a clinical trial in DMD patients	Dr. Urs Ruegg, University of Geneva	Investigator Grant	$164,100
TREAT-NMD Advisory Committee for Therapeutics (TACT). 5th Meeting, Arlington VA, USA. 28-29 April 2012	Dr. Volker Straub, University of Newcastle upon Tyne	Meeting Grant	$24,355
A Randomized, Double-blind, Placebo-controlled, Multiple-dose, Dose-escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Effects of HT-100 in Patients with Duchenne Muscular Dystrophy	Marc Blaustein, Halo Therapeutics, LLC	NEXT Grant	$100,000
Analysis of protein interactions mediated by micro-dystrophin in the mdx heart	Dr. Federica Montanaro, Ohio State University	Research Grant	$52,500
Recombinant Biglycan for Treatment of Duchenne and Becker Muscular Dystrophy	Joel Braunstein, Tivorsan Pharmaceuticals	Research Grant	$500,000

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Projects Funded or Committed in 2012 Cont.

Project	PI	Amount	Type
Long-term efficacy and side effect profile of compound A, a selective glucocorticoid receptor modulator in mdx mice	Kanneboyina Nagaraju	$50,000	Exploratory Award
Development of MEMRI as an outcome measure for pre-clinical studies in the mdx mouse	Volker Straub	$49,000	Exploratory Award
SERCA2a gene therapy for Duchenne cardiomyopathy	Dongsheng Duan	$280,424	PPMD Investigator Award
Magnetic Resonance Imaging as a Biomarker in Muscular Dystrophy - Supplement	Krista Vadenbourne	$59,598	Supplement
Exons 45-55 skipping with a cocktail antisense oligo	Toshifumi Yakota	$50,000	Exploratory Award
Genetic modifiers of DMD using exome sequencing	Stan Nelson	$100,000	Supplement
Predicting the benefit vs the side effects of corticosteroids in Duchenne muscular dystrophy -- Supplement	Berch Griggs	$50,000	Supplement

Life Cycle of Duchenne Muscular Dystrophy
With what we know now….