



Pilot Trials Now

Treating DMD Boys With Today's Science

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Pilot Trials Now

- An initiative focused on developing treatments for DMD by repurposing approved FDA drugs that have shown real potential in DMD animal models.
- Developed in collaboration between Charley's Fund Inc. (CFI) and the Nash Avery Foundation (NAF).

Why this method?

1. **Increase Speed:** Faster time to the DMD community since the drugs are FDA approved for other diseases.
2. **Reduce Cost:** Proof of concept Pilot Trial costs are substantially less and can identify trends to help determine if drugs help DMD boys
3. **Participation:** Allows other foundations to contribute to the initiative

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What is the value of repurposing FDA-Approved Drugs?

- Some drugs show real promise *in vitro* and in DMD animal model
- Safety and toxicity profiles well known to regulatory agencies
- DMD boys need treatments to keep them living and strong until new drugs hit the market (2-10 years)
- Partner with respected physicians to run pilot trials to ensure safety and do no harm

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Why is Pilot Trials Now needed?

- Several FDA-approved drugs show promise, but very few tested with DMD patients for translation
- Science is not limiting factor – cost, time and interest levels are:
 - Many approved drugs affect the same disease pathways
 - Clinicians lack time to raise funds to run trials
 - Burdensome administrative requirements
 - Low profit motive since drugs are approved and IP is owned

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How did we get to this point?

- Recognized need to identify promising FDA-approved drugs for DMD
- Invested and screened multiple FDA approved drug libraries *in vitro* and *in silico* against DMD relevant protein targets and pathways
- Screening efforts resulted in 40 FDA-approved drug hits
- Hired DMD pharmacologist to triage and prioritize list - 16 top FDA-approved drugs narrowed to 5.
- Collaborated with physicians to add more filters e.g. toxicity, pediatric use, etc...
- Collaborated with respected DMD researchers who tested promising drugs in mice
- Identified qualified Institutions and able clinicians to conduct trials
- CFI/ NAF has spent significant funds to get the program to this point

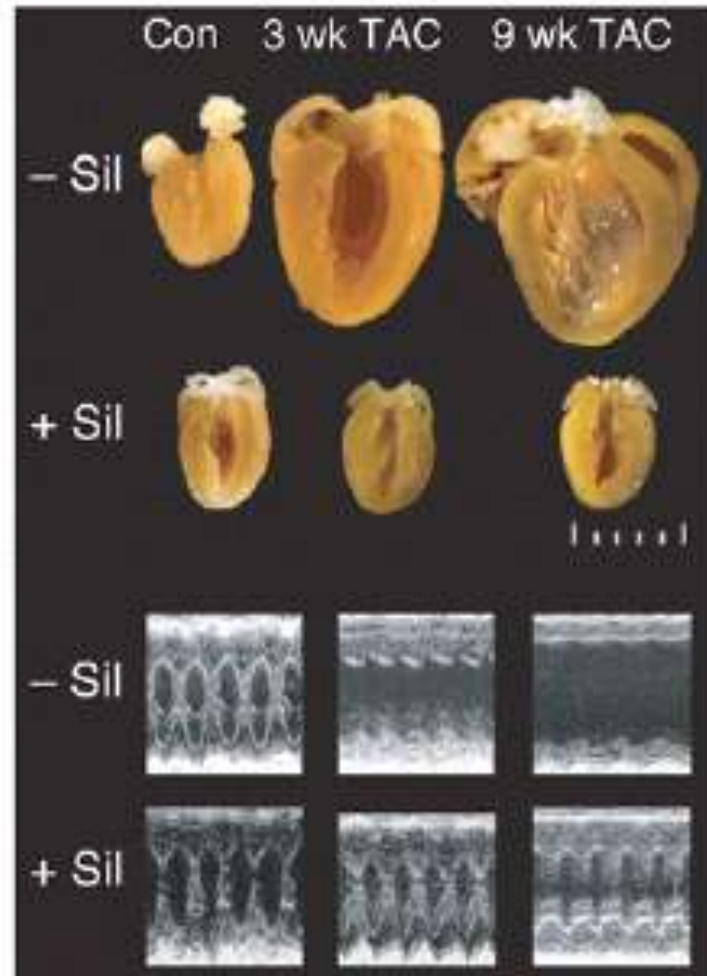
Sildenafil (Revatio or Viagra)

- PDE5 inhibitor: increases cGMP specifically
- Vasorelaxant properties first studied for hypertension and angina pectoralis
- Side effect of penile erections led to FDA approval for erectile dysfunction
- Safe in treatment of pediatric pulmonary hypertension
- Brand names: Revatio, Viagra

Transverse Aortic Constriction

Can Sildenafil reduce cardiac hypertrophy and fibrosis induced by DMD?

Mdx mouse model +/- sildenafil



Echocardiographic Analysis of Cardiac Function in mdx Mouse

Myocardial Performance Index (MPI)

Equals the time it takes blood to enter the LV through the mitral valve divided by the ejection time through the aorta. In the failing heart, the contraction and relaxation becomes slower, increasing MPI

Ea/Aa Ratio

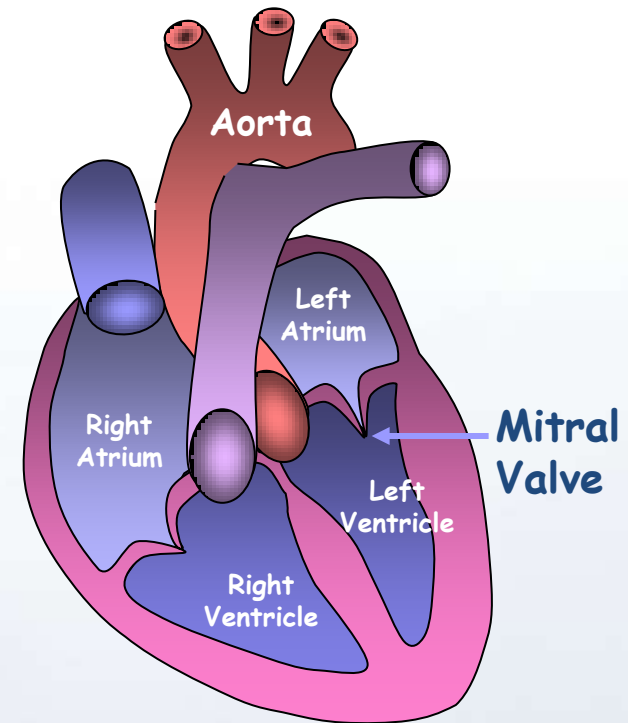
Ea wave: passive LV filling

Aa wave: atria push last bit of blood into LV

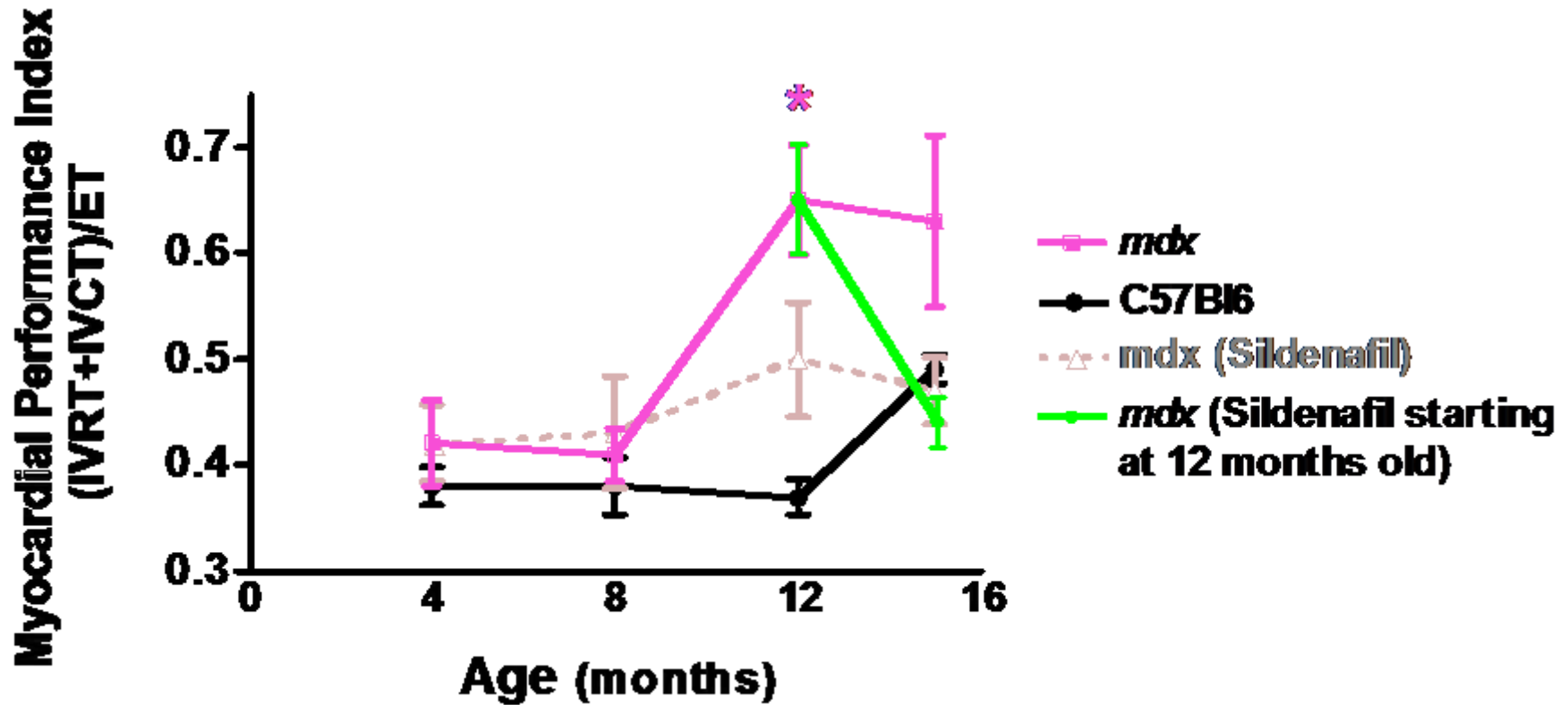
mdx mice show an Ea/Aa ratio <1 due to slow filling of LV (LV diastolic dysfunction)

% Fractional Shortening (% FS)

Measure of systolic function



Myocardial Performance Index



Sildenafil: Case Study 1

Trial Facts: Revatio (Sildenafil)

Site: Kennedy Krieger/Johns Hopkins School of Medicine – Baltimore, MD

PIs: Daniel Judge, MD, Kathryn Wagner, MD/PhD, David Kass MD

Pfizer collaboration to provide drug and placebo for the trial

Hypothesis: PDE5 inhibition with sildenafil will improve cardiac function in adolescents and adults with Duchenne muscular dystrophy

Sildenafil: Case Study 1

Intervention: Sildenafil (Revatio)

Regulatory: IND exemption

Sponsors: CFI/NAF/ Action Duchenne/Cure Duchenne/Janvir4Hope

Status: Recruiting; Two patients dosed

Age group: 16-30

Enrollment: 30 patients

Description: Evaluate cardiac function in adolescent DMD boys

Website: www.clinicaltrials.gov

Sildenafil: Case Study 1

Study Design: Phase II Randomized, Double-Blind, Placebo-Controlled

Duration: 12 months

Cohorts: 15 patients /arm - 6 months dose/placebo control
30 patients - 6 months crossover open label

Dosage: Oral single dose of 20 mg three times a day; placebo

Prior randomized dose-escalation studies have determined this dose is both safe and efficacious for the treatment of pulmonary hypertension and preeclampsia

Sildenafil: Case Study 1

Primary Objective:

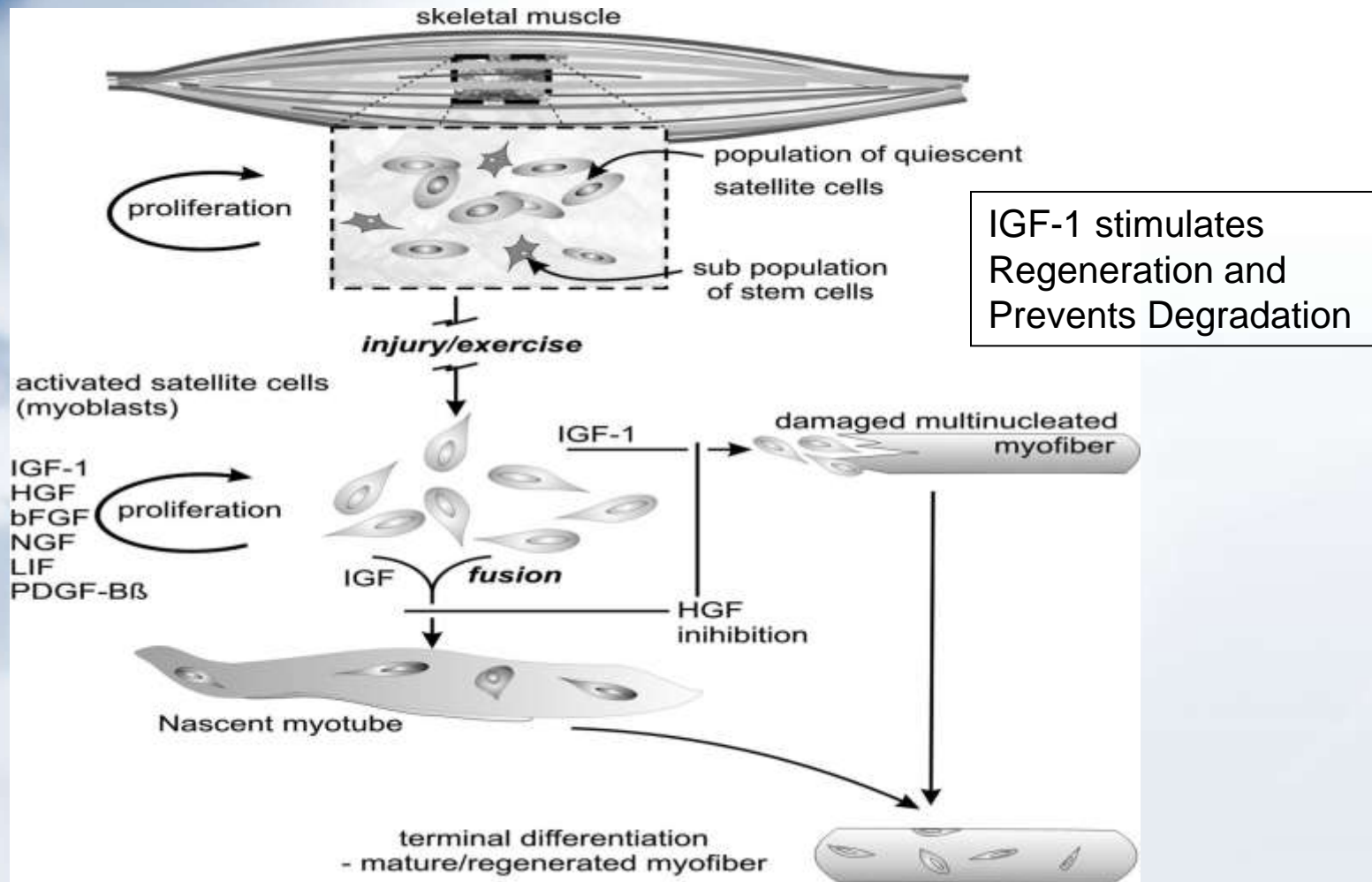
- To determine whether a 6 month trial of oral sildenafil compared to placebo improves cardiac contractile function in DMD as determined by $> 10\%$ decline in end-systolic volume as detected by cardiac magnetic resonance (CMR) imaging
- Left ventricular end-systolic volume (LVESV)
 - Change from baseline in LVESV after 6 months on sildenafil vs placebo
 - Change from baseline in LVESV after 6 months vs 12 months on sildenafil

Sildenafil: Case Study 1

Secondary End Points

- **Safety**
 - Frequency and grade of adverse events
- **Cardiac**
 - Systolic and diastolic LV function by MRI
 - Differences in LV mass and fibrosis by MRI
 - Brachial flow-mediated vasodilation
- **Skeletal muscle function**
 - Forced vital capacity
 - Pincher strength
 - Grip strength
- **Quality of Life**
 - InQol
 - SF36

Insulin-like Growth Factor-1



IGF-1: Case Study 2

Trial Facts: Increlex® (Insulin-like Growth Factor -1 (IGF-1); Ipsen)

Site: Cincinnati Children's Hospital Medical Center (CCHMC) Cincinnati, Ohio

PI: Drs. Meilan Rutter (PI), Brenda Wong, James Collins (co-PIs)

Ipsen (Tercica) collaboration to supply Increlex drug for trial

Primary Hypothesis: IGF-1 therapy improves/preserves muscle function in DMD vs controls

Secondary Hypothesis: Growth rate increase, improve/preserve cardio-pulmonary function and safety. May reduce the effects of GCs.

IGF-1: Case Study 2

Intervention: IGF-1 (Increlex)

Regulatory: IND exemption

Sponsor: CFI/NAF/Action Duchenne

Status: Active, not yet recruiting

Age Group: 5-16

Enrollment: 40 patients

Description: Evaluate whether IGF-1 therapy improves/preserves muscle function in DMD vs controls

Website: www.clinicaltrials.gov

IGF-1: Case Study 2

Study Design: Phase I/II, Prospective, Randomized, Open Label, Placebo Controlled Study

Duration: 6 month open label

Cohorts: 20 patients - control (standard GC therapy
0.75mg/kg/d Pred or 0.9mg/kg/d Defzt)
20 patients - IGF-1 plus standard GC therapy

Dose: single dose escalation; s.c.; 40ug/kg one week; 80ug/kg two weeks; 120ug/kg two weeks; 160ug/kg 19 weeks

Dose was established from IGFD and GH clinical trials.

IGF-1: Case Study 2

Primary Objective: To determine whether IGF-I therapy improves or preserves muscle function in DMD.

Outcome measures: Comparisons will be made between the IGF-I intervention group and controls.

Primary outcome measure: Difference in muscle function as measured by the 6-minute walk test distance

IGF-1: Case Study 2

Secondary outcome measures:

- Difference in muscle function by additional tests (muscle strength testing, timed Gower test, timed 10-meter run test, timed climbing of 4 steps, North Star ambulatory assessment scale)
- Difference in growth rate
- Difference in pulmonary function
- Difference in cardiac function
- Safety and tolerability of IGF-I in DMD

Pilot Trials Now - Summary

Current Status of the PTN Pipeline for DMD

- Identified and staged two promising drugs for pilot trials:
 - Sildenafil (recruiting)
 - IGF-1 (recruiting)
- Testing five additional drug candidates in mdx mouse model at CNMC in Washington DC, University of Bari, Italy and Psychogenics Inc., NY
- Identified four new drugs currently in clinical trials for other indications (known to the FDA but not approved yet)