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MidAtlantic FSHD Family Day
September 30, 2018

Clinical Research in FSHD

What is Clinical Research?

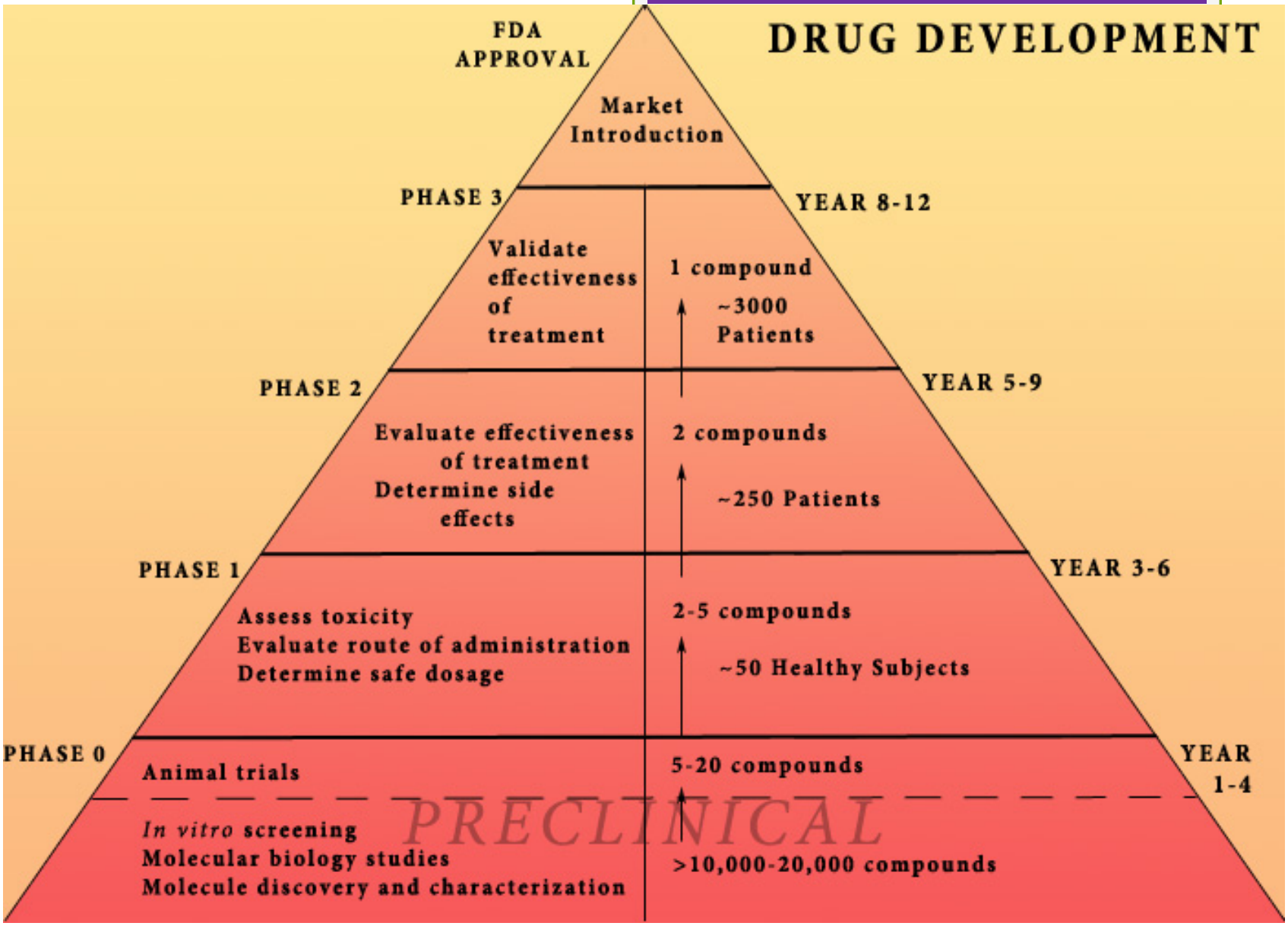
- Research with human volunteers (participants, subjects).
- Carefully conducted investigations to ultimately uncover better ways to treat, prevent, diagnose and understand human disease.

Human Subjects

- Safety and rights of human subjects must be protected
  - Study Design
  - Institutional Review Board (IRB):
    - an independent committee that consists of physicians, statisticians, and members of the community to ensure that clinical trials are ethical and that the rights of participants are protected.
  - Informed Consent
    - The process of learning the key facts about a clinical trial before deciding to participate, including the purpose, duration, required procedures, risks, potential benefits and who to contact
  - Data Safety Monitoring Board (DSMB)
    - An independent group of experts that advises the sponsor and the study investigators.
    - Responsible for periodically reviewing the study data
    - Makes recommendations concerning continuation, modification or termination of trial.

Types of Clinical Research

- Observational studies
  - Assess health outcomes in groups of participants
- Natural history studies
  - How does disease and health progress
- Prevention trials
  - Studies way to prevent disease in people who have never had the disease or prevent from returning (vaccine, medicine, lifestyle changes)
- Screening Trials
  - Test the best way to detect certain disease or health conditions
- Diagnostic Trials
  - Determine better tests or procedures for diagnosing a particular disease or condition
- Treatment Trials (or interventional study)
  - Tests new treatments, new combinations of drugs or new approaches to therapy to see whether safe and efficacious in a disease population
- Quality of life Trials
  - Measure ways to improve quality of life in people with chronic illness


DRUG DEVELOPMENT
FDA APPROVAL
Market Introduction
PHASE 3
YEAR 8-12
Validate effectiveness of treatment
1 compound
~3000 Patients
PHASE 2
YEAR 5-9
Evaluate effectiveness of treatment
Determine side effects
2 compounds
~250 Patients
PHASE 1
YEAR 3-6
Assess toxicity
Evaluate route of administration
Determine safe dosage
2-5 compounds
~50 Healthy Subjects
PHASE 0
YEAR 1-4
Animal trials
5-20 compounds
PRECLINICAL
In vitro screening
Molecular biology studies
Molecule discovery and characterization
>10,000-20,000 compounds

Clinical Trials

Phase I: Assess Drug Safety and Tolerability

- Healthy volunteers then target population
- Limited number of people
- Pharmacokinetics (i.e. Absorption, metabolism, excretion)
- Dose escalation
- 70% of new drugs pass this phase

Clinical Trials cont.

- Phase II: Assess Drug efficacy (and further evaluate safety)
  - Randomized
  - Controlled
  - Surrogate outcome measures
  - Short term
  - Small numbers
  - 22% drugs which enter Phase II go forward

Clinical Trials cont.

- Phase III: Large scale RCT to confirm efficacy and safety in a larger population
  - Hundreds of patients
  - Randomized, placebo-controlled
  - Long-term
  - Outcome measures similar to real world (function, quality of life)
  - Defines packaging insert content and allow marketing
  - 55% of drugs succeed phase III

Therefore ~8% of drugs that enter clinical trials are FDA approved

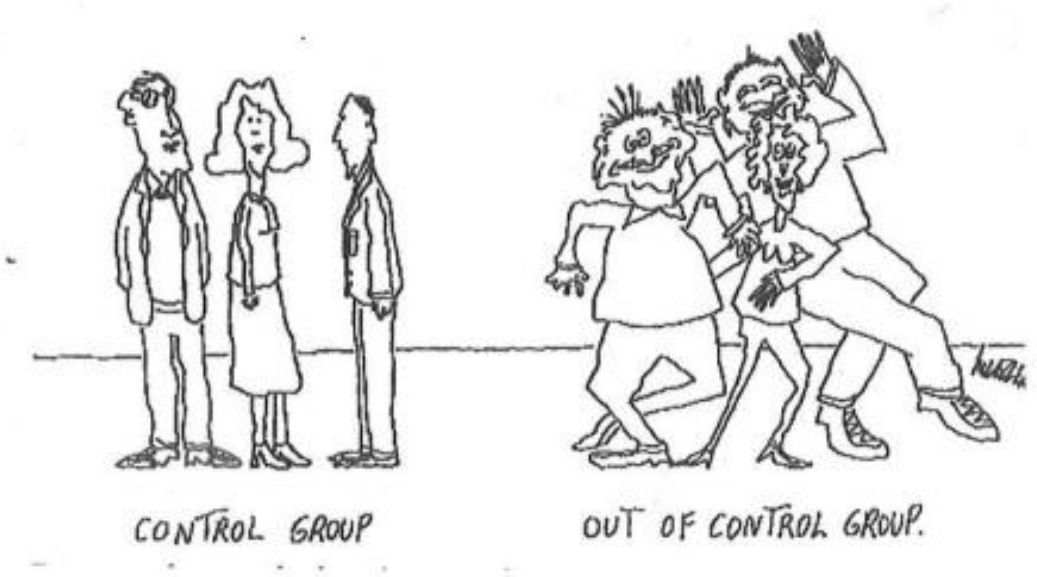
Randomization

- E.g. Assign 40 people randomly to 4 different treatment "arms"
  - Condition 1 = Wonderdrug 5%
  - Condition 2 = Wonderdrug 10%
  - Condition 3 = Wonderdrug 15%
  - Condition 4 = Placebo

- Assign each participant a unique participant number
- Use Randomizer algorithm to generate 1 set of 40 non-unique, unsorted numbers with a range from 1 to 4 (representing the condition numbers).
  - 3, 4, 4, 3, 2, 2, 4, 4, 1, 2, 2, 2, 1, 3, 3, 1, 4, 4, 2, 1, 3, 2, 1, 1, 3, 2, 3, 2, 4, 2, 2, 3, 3, 4, 2, 2, 1, 3, 4, 2

Control

- A comparison group that receives a placebo, another treatment, or no treatment at all.
- Does not have to be a 1:1 ratio to treatment (and frequently isn't)



Clinical Trials

- Phase IV
  - After a drug is approved by the FDA
  - Compare drugs with other drugs on the market
  - Define broader target population
  - Monitor long-term efficacy and safety

Members of a Study Team

- Principal Investigator (PI)
  - Usually a doctor
  - May have co- or sub-PIs
  - Ultimately responsible for wellbeing of patients and good data collection
- Clinical Trial Coordinator
  - may be a nurse, doctor or other professional
  - Makes the trial run smooth operationally
- Clinical Evaluator
  - Physical therapist
  - Measures function
- Nurse
  - Collect urine/blood
  - Administer treatment

Study Design

- Clinical research is conducted according to a protocol.
  - Who is eligible to participate
  - Detailed procedures
  - Length of study, number of visits, what information is to be gathered at each visit

Screening

- Informed Consent
- Eligibility
  - Inclusion and Exclusion criteria
  - Age, gender, type and stage of disease, previous treatment history, other medical conditions, other medicines
  - Reproducibility

Visits

Month Week: Day:	0	0 0 1	2	1	2	3	6 26 180	181	182	7	8	9	12 52
Informed Consent	X												
Inclusion/Exclusion	X												
Safety measures:													
Vital signs	X	Q 6hr	Q 6hr	X	X	X	Q 6hr	Q 6hr	Q 6hr	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology/chemistries	X		X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X
Efficacy measures:													
Cardiac MRI	X						X						X
Flow-mediated vasodilation (FMD)		X					X						
Electrocardiogram		X					X						X
Forced vital capacity		X				X	X					X	X
INQoL & SF-36		X				X	X					X	X
Pincher and grip test		X				X	X					X	X
Drug dosing:													
Inpatient administration		X	X				X	X	X				
Dispense 1 months' supply			X	X	X				X	X	X		
Dispense 3 months' supply						X						X	

Outcome measures

- Measures that are meaningful to patient's everyday lives
  - E.g. Longevity
  - E.g. Function
- Other Measures that known to correlate with meaningful measures (biomarkers)
  - E.g. 6 minute walk test

After the trial

- Information collected is studied
- Decision make whether to go forward with next phase
- Results often published in peer-reviewed journals
- Results specific to the individual participant are frequently not shared with the participant

Why participate?

- Play an active role in research and improving the treatment of disease
- Gain access to new treatments before they are widely available
- Receive regular and careful medical attention

Questions you want to ask

- Who is sponsoring the trial
- What is the participant burden
- What are the risks (of the treatment and of the studies)
- What is the degree of harm that could result
- What is the chance of harm occurring
- What will be billed to study versus patient
- What is the ratio of placebo to treatment
- Is there a commitment to an extension study

Why clinical research in FSHD now

- Medical Community learns about FSHD (natural history)
- Research Community learns how to study FSHD (biomarkers, imaging, endpoints etc.)
- Patient Community is engaged

"To my surprise and appreciation, I found myself immersed in a medical system that overflowed with passion for its work and for FSHD. I was surrounded by doctors, surgeons, nurses and aides who were attentive and engaged. I found myself looking forward to each visit and the exchange of information and knowledge. "

Natural history studies

- Clinical Trial Readiness to Solve Barriers to Drug Development in FSHD (RESOLVE)
  - Must be able to walk 30 feet without support
  - Visits at baseline, 3 mo, 12 mo and 18 mo
- Magnetic Resonance Imaging and Spectroscopy Biomarkers for Skeletal Muscle Disease
  - Visits at baseline, 3 mo, 9 mo, 15 mo and 21 mo

Testosterone and rHGH (STARFISH)

- University of Rochester
- Inclusion criteria
  - Able to complete a 6 minute walk test
  - PSA=<4.0
- Open label
- Primary outcome measure safety
- Secondary outcome measures serum levels of hormones, lean body mass

Acceleron ACE-083

- Inhibitor of TGF-beta family members (myostatin and activins).
- Myostatin normal acts to inhibit muscle growth
- Inhibiting the inhibitor causes increased muscle growth, muscle regeneration and decreased fibrosis

Acceleron

- Two part phase 2 trial
- Part 1
  - Open label, dose escalation study
  - Injection every 3 weeks for 12 weeks
  - Good safety and tolerability
  - 6.7% increase in total muscle volume (compared to -0.5 in control)
  - -4.8% change in fat fraction (compared to -0.8 in control)
- Part 2
  - Placebo controlled trial
  - Enrolling
  - Inclusion criteria include biceps or tibialis between grade 3 and 4+
  - 6 minute walk distance >=150 meters and =< 500 meters (without a brace)
  - Injection of bilateral muscles

Fulcrum

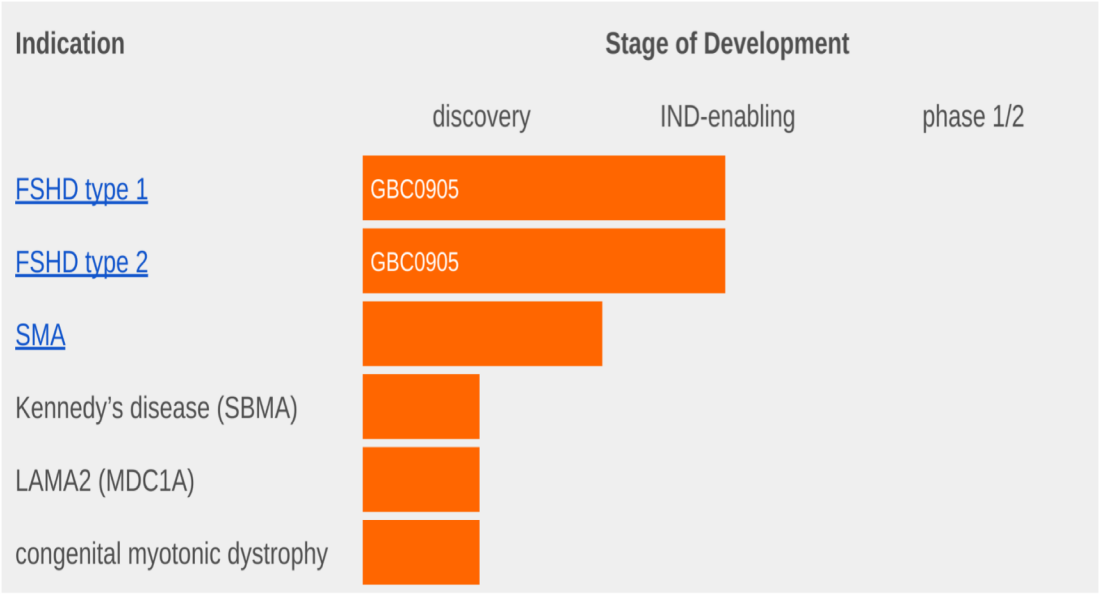
- Developing a small molecule that reduces DUX4 and DUX4 target genes
- Anticipates filing an IND in 2019
- Fulcrum has various preparatory biomarker studies ongoing
  - Reachable workspace
  - Needle biopsy and MRI study

GENEA BIOCELLS

PRECLINICAL CANDIDATE GBC0905

- San Diego-based company focused on developing therapeutics for orphan neuromuscular diseases

- lead candidate GBC0905 to treat FSHD type 1 and 2
- first DUX4-targeted drug to receive FDA orphan drug designation



GBC0905

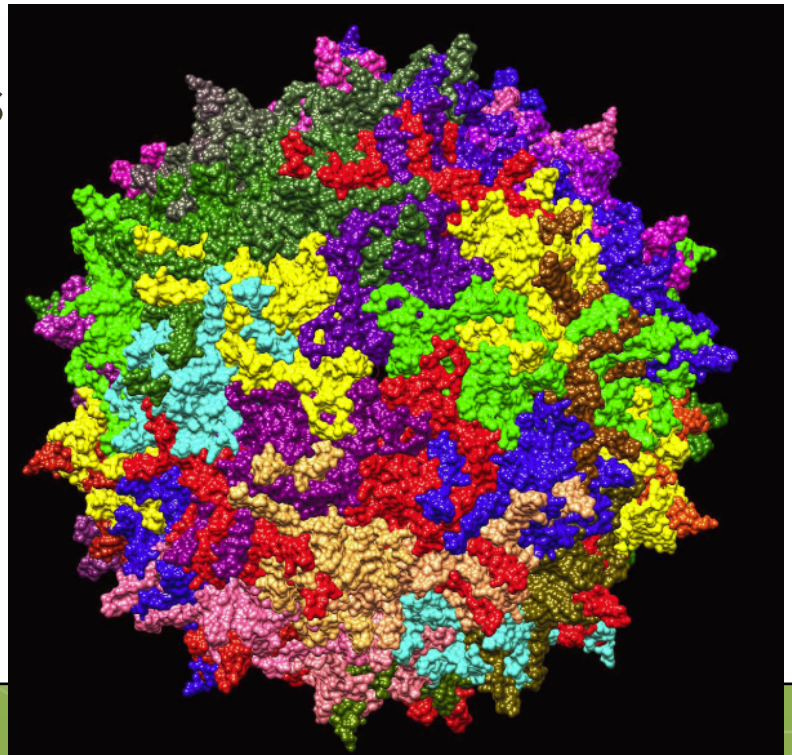
STATUS AND PLANS

- Genea Biocells:
  - demonstrated efficacy in a number of models and assays
  - mechanistically linked the drug's target to DUX4 expression
  - observed no cellular toxicity/no inhibition of myogenesis
- GBC0905 is a repurposed drug (but not on the market for other indications):
  - existing clinical data suggest the drug is safe, orally available and suitable for chronic administration

- IND-enabling studies in progress, clinical studies anticipated to start in 2019
- Genea Biocells have multiple backup series

Future studies

- Gene therapy: Adeno-associated virus (AAV) to knockdown DUX4
  - Nonpathogenic
  - Wide tropism to tissues
  - Delivers gene without Integrating into host genome



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