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Cell and Gene Therapy Products 2023 Symposium
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Objective

- Discuss the CMC/regulatory engagement regarding N=1 CRISPR development program as potential lessons for other ultra-rare efforts

CURE RARE DISEASE

My brother, Terry, suffered from an ultra-rare form of Duchenne Muscular Dystrophy (DMD)

RARE DISEASE PATIENTS ARE LEFT BEHIND

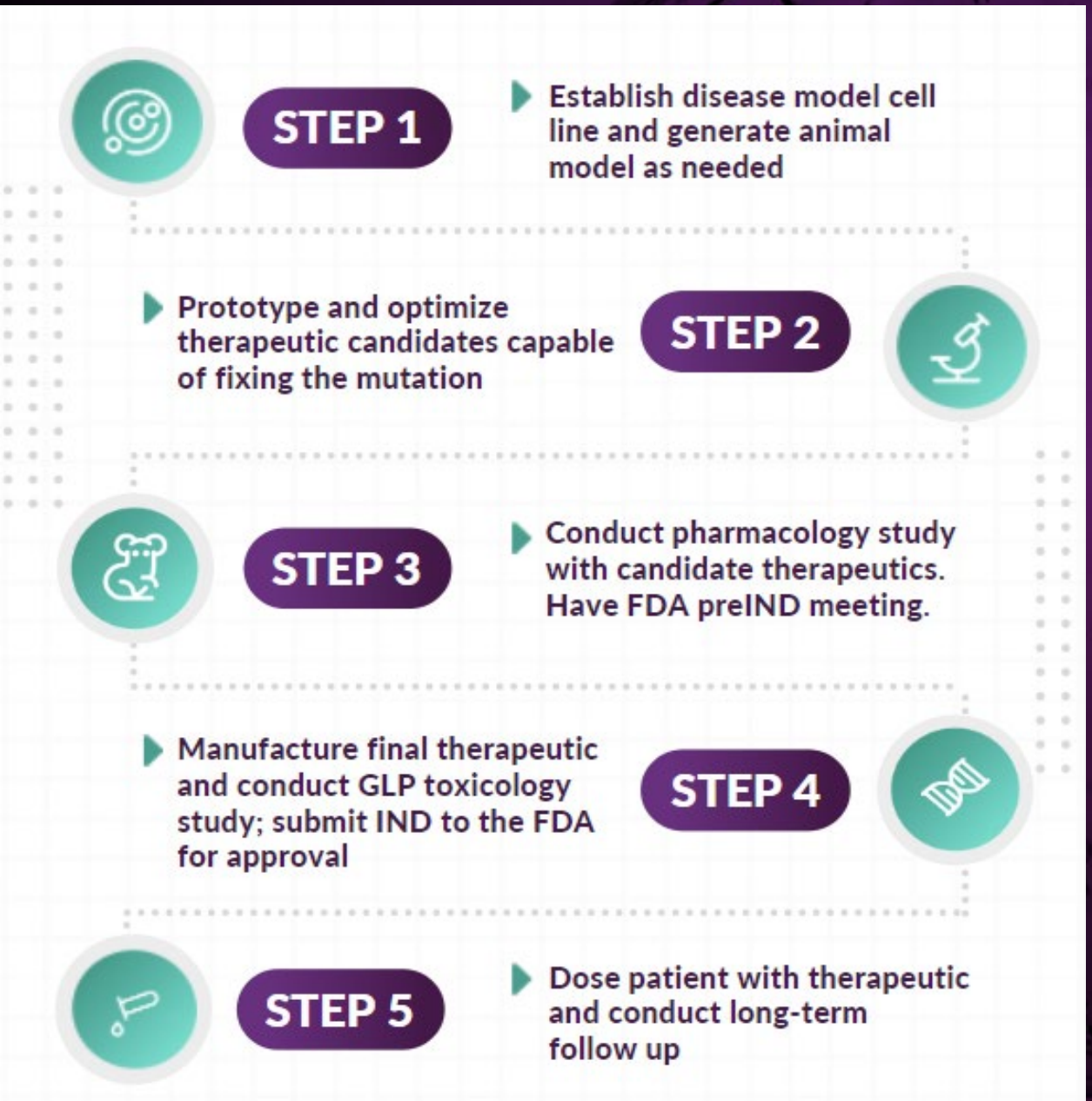
Economics incentivize developing drugs for common diseases, leaving many out - like my brother

The traditional one-size-fits-all model **does not work for the ultra-rare disease population**

Ultra-rare diseases are progressive, and patients can't wait – **they need interventions now**

Society needs a **new approach to treat rare disease patients**

Novel process to develop treatments for ultra-rare diseases



Cure Rare Disease has created a novel framework for ultra-rare disease drug development.

CURE
RARE DISEASE

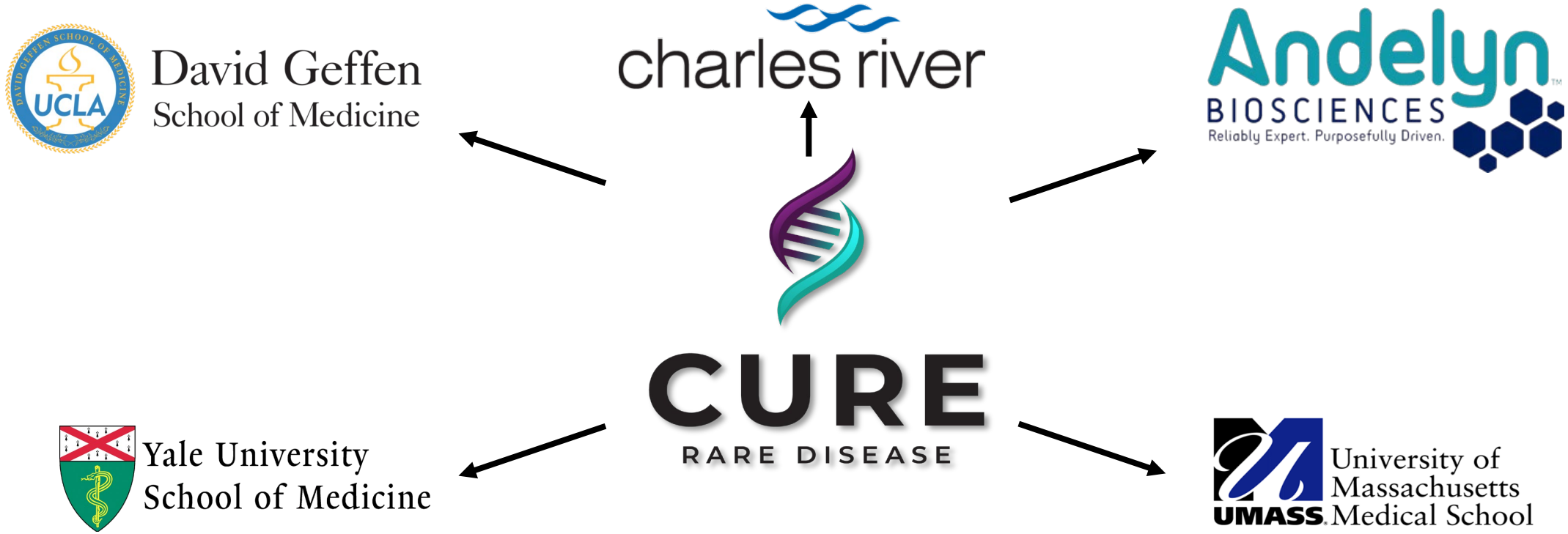
Overall Effort

AAV9 CRISPR Activation Therapeutic

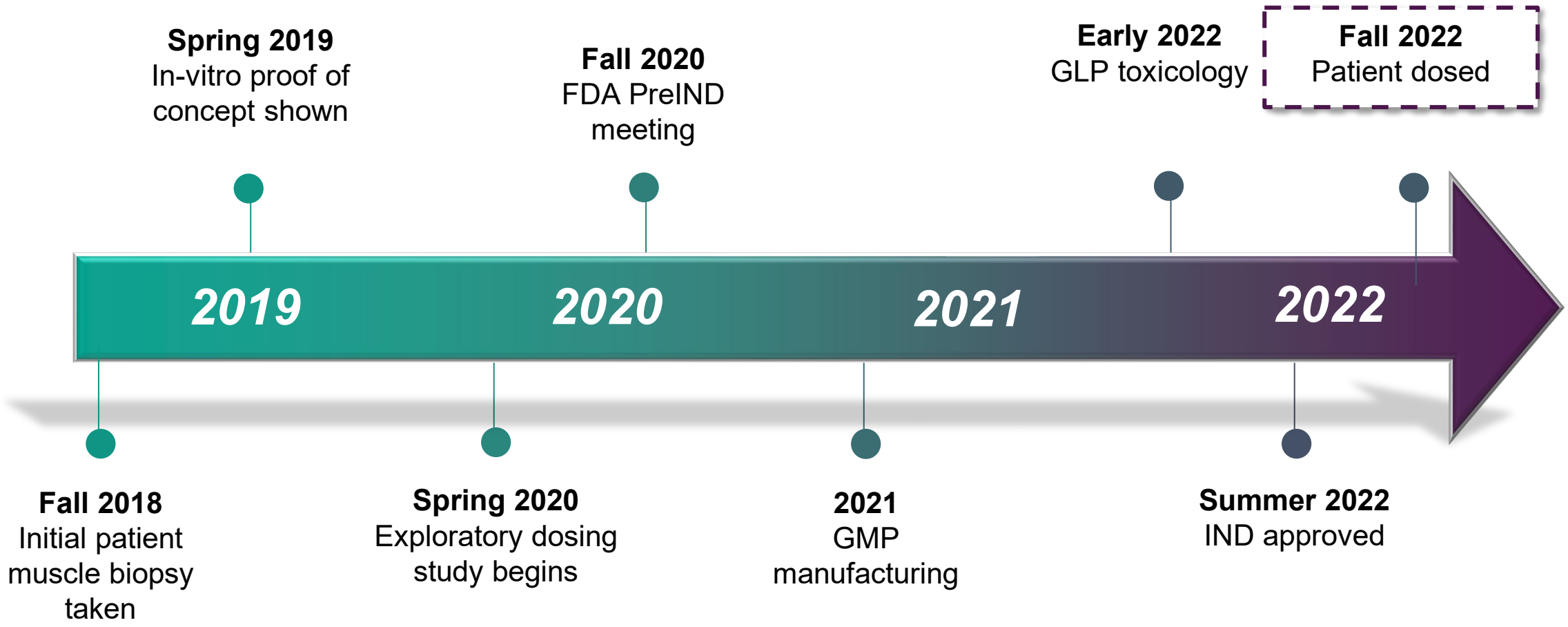
- Designed to upregulate alternative isoform of the dystrophin gene Dp427c
- Therapeutic's mode of action is via dSaCas9 which lacks endonuclease activity fused to VP64 transcription activation domains
- Targeted to promoter for DP427c transcript via guide RNA
- Designed for treatment of deletion of muscle promoter through exon 1 of the dystrophin gene
- N=1 clinical trial

CURE RARE DISEASE

The collaboration included industry and academic partners



Timeline of development program



Manufacturing Strategy for a single patient

Batch size

- (4) 200L adherent bioreactors used and produced a purified yield of 2.2E+16 vg (1E16 vg estimated)
- Concentration of 4.07E13 vg/ml

Titer & stability

- FDA allowed for the use of ddPCR ITR – qualified for clinical trial usage
- Stability study for 6 and 12 months measuring in-vivo potency, sterility, physical and infectious titer, pH, appearance, osmolality

Other QC/QA

For release

- Sterility (USP<71>)
- Endotoxin
- Titer
- Infectious titer (TCID50)
- Total protein
- Bacteriostasis
- Purity (SDS PAGE)
- Identity (DNA/protein)
- Osmolality
- pH
- Appearance (USP <631>)
- Aggregation

Purified Bulk DS release testing

- Vector plasmid titer
- Full:Empty (AUC)
- Host cell protein
- Residual DNA E1a & E1b (qPCR), BSA, endonuclease (ELISA)
- Replication competent AAV

CURE RARE DISEASE

Challenges with CMC for ultra-rare drug development

- COST! Millions of dollars to create GMP plasmid + AAV (though flexibility exists with GMP vs. GMP-like plasmid). No mechanism to pay for this.
- Uncertainty with yields creates an under/over production problem that has significant ramifications
- Regulatory flexibility exists for QC/QA needs and it's important to consult with FDA as challenges arise during/after production – can rebalance QC/QA assay needs
- We chose to use GMP AAV for GLP tox to avoid needing to produce another lot and avoid a cross over study – risky, but ended up saving time

GLP Toxicology Study

Therapeutic Administration

- hDMD D2/mdx mice were dosed once via intravenous (bolus) injection (vehicle control and test article-treated groups) or via subcutaneous injection (positive control group) of CRD-TMH-001
- Dose levels: 1 x 10^{14} and 2x 10^{14} vg/kg

Parameters and Endpoints

- Mortality, clinical observations, body weights, body weight gains, clinical pathology parameters, cytokine analysis, biodistribution and molecular pharmacodynamic analysis, anti-drug antibody parameters, splenocyte ELISpot analysis, immunochemistry evaluation, organ weights, and macroscopic and microscopic examinations

Results

- All animals survived to scheduled necroscopy
- No test article-related clinical observations or effects on body weight, hematology, cytokine analysis, splenocyte ELISpot analysis, or immunochemistry
- No test article-related macroscopic or microscopic findings
- CRD-TMH-001 (delivered by AAV9) targeted heart and skeletal muscle where expression of gene product (dSaCas9-VP64) was readily detected in dose responsive manner

CURE RARE DISEASE

PreIND Comments

- Provide device compatibility data (data showing the stability of vector in the intended clinical formulation and clinical delivery device) in IND submission
- Include description of how DP will be shipped to clinical site including: information on container, time and temperature limits, and transport conditions
- Provide copy of all key publications cited with comprehensive summary for each publication
- Ensure all CBER pre-IND comments are adequately addressed and include these responses in IND submission
- Provide an Investigator Brochure (IB) in the IND

IND Comments

- Justification of proposed immunosuppression regimen with data to support, including drug choices, dose, dosing frequency, and duration of use
- Propose a safety monitoring plan for long-term follow up
- Explicitly state primary, secondary, and exploratory endpoints
- Clarify dose that single subject will receive and total volume of product
- Clarify crossover between in-vitro dose and pharmacology dose

CURE RARE DISEASE

Early FDA involvement was important to rapid advancement of a FIH technology

- PreIND engagement to get guiding feedback
- Communication between preIND and IND submission
- FDA is learning how to navigate this new paradigm
- Critical to share learnings broadly with the community