The development of therapies for ultra-orphan disorders:

Challenges and successes in the development of enzyme replacement therapy for Mucopolysaccharidosis I

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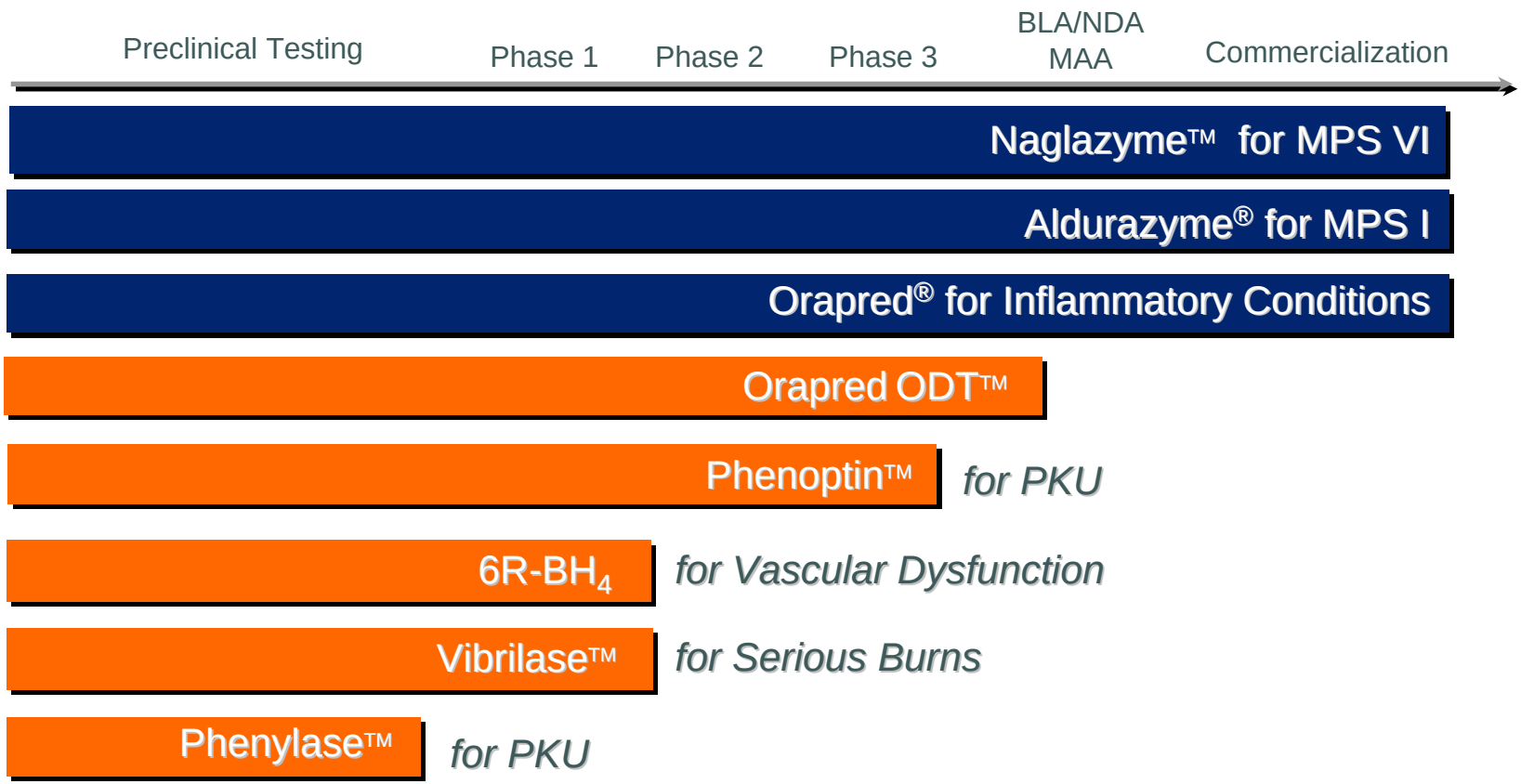
Company Overview

Fully-integrated Biopharmaceutical Company
Located in Novato, California

- Develop and commercialize products for serious diseases
- Approval of second metabolic product, Naglazyme™ in 2005
- Two approved metabolic products, third in Phase 3
- U.S. sales force seeing pediatricians
- Strong clinical, regulatory, development and manufacturing

Ultra-Orphan Products in BioMarin's Pipeline



Treating Ultra-Orphan or Rare Disorders: We know how but we will we?

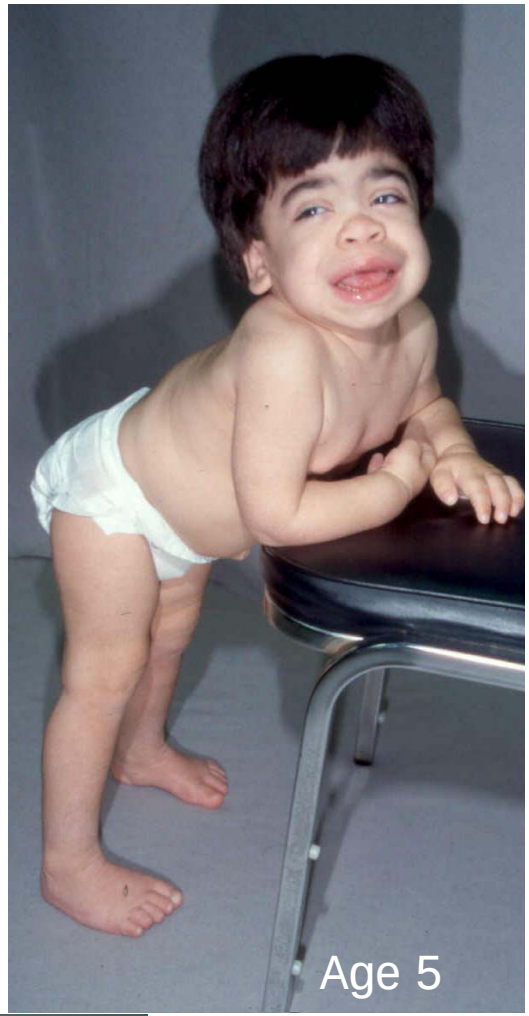
- Patients with rare disorders are underserved
  - Less knowledge and less interest
  - Limited clinical or treatment experience
  - Less political power
- Developing treatments for rare disorders
  - Lack of disease knowledge hampers clinical design
  - Lack of quantified clinical experience often hinders the definition and use of biochemical and clinical endpoints of disease
  - Lack of expertise and experience in development and regulation
  - Lack of funding

Development of Aldurazyme® (laronidase)
A recombinant human iduronidase for MPS I

- Ultra-rare disorder with incidence of 1:100,000 births
- Strong technical basis for treatment
- Challenge to get product manufactured and tested in humans
- Small biotech startup takes on the project and obtains funding
- Treatment successfully developed and approved in 2003
- Success factors
  - Patient support groups
  - The right size biotechnology company
  - Committed small group of project members

Mucopolysaccharidosis I (MPS I)
A lysosomal storage disorder

- Deficiency of lysosomal enzyme α-L-iduronidase
- Progressive accumulation of glycosaminoglycans (GAG)
- Multi-systemic, heterogeneous
- Severe morbidity and early mortality
- Rare (est. incidence 1:100,000)
- Significant unmet medical need



Treatment for MPS I Patients in 2003

- Symptomatic management
  - Palliates condition - does not prevent progression
  - Limited utility
  - High risk of anesthesia/surgical complications
- Bone marrow (stem cell) transplantation
  - Does treat some of medical problems
  - Mortality in 10-50%
  - Graft versus host disease in up to 50%

Mucopolysaccharidosis I: A challenge to treat

- Pervasive and profound disease in every body system
  - No patient treated with an approved drug today has as many medical problems as MPS I patients
  - Many affected tissues are less accessible to therapy (e.g. connective tissues)
- Chronic and progressive disease
  - Chronic scarring and injury accumulate over many years
  - Heterogeneous combination of irreversible and reversible components
- Rare disorder that will not allow for pharmaceutical development
  - Who will fund the development?

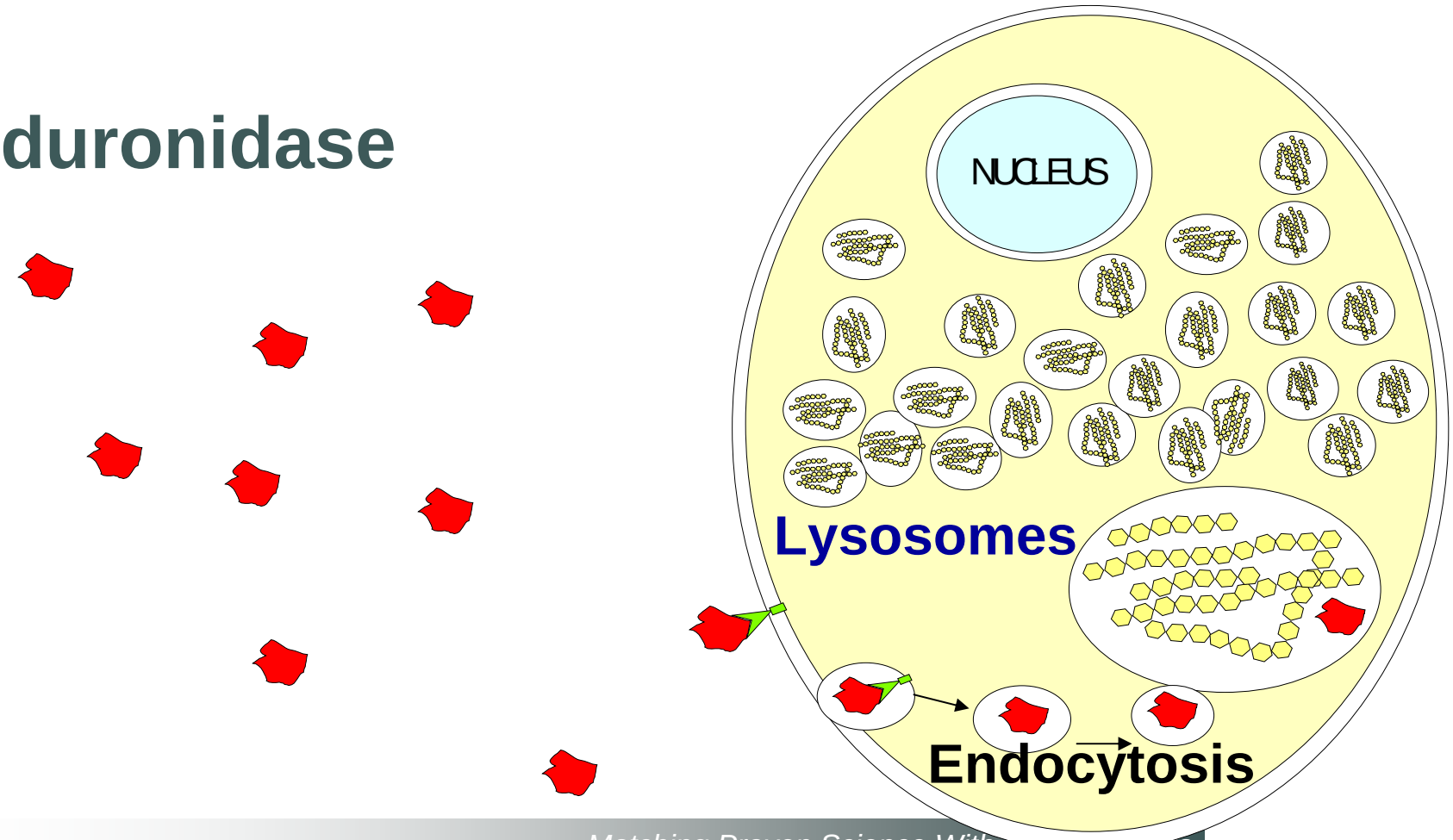
Why work on it? It will never happen.

Dr. Elizabeth Neufeld

Rationale for Enzyme Therapy of MPS I

Discovery of Correction in vitro 1968
Uptake of Iduronidase into MPS I Cells

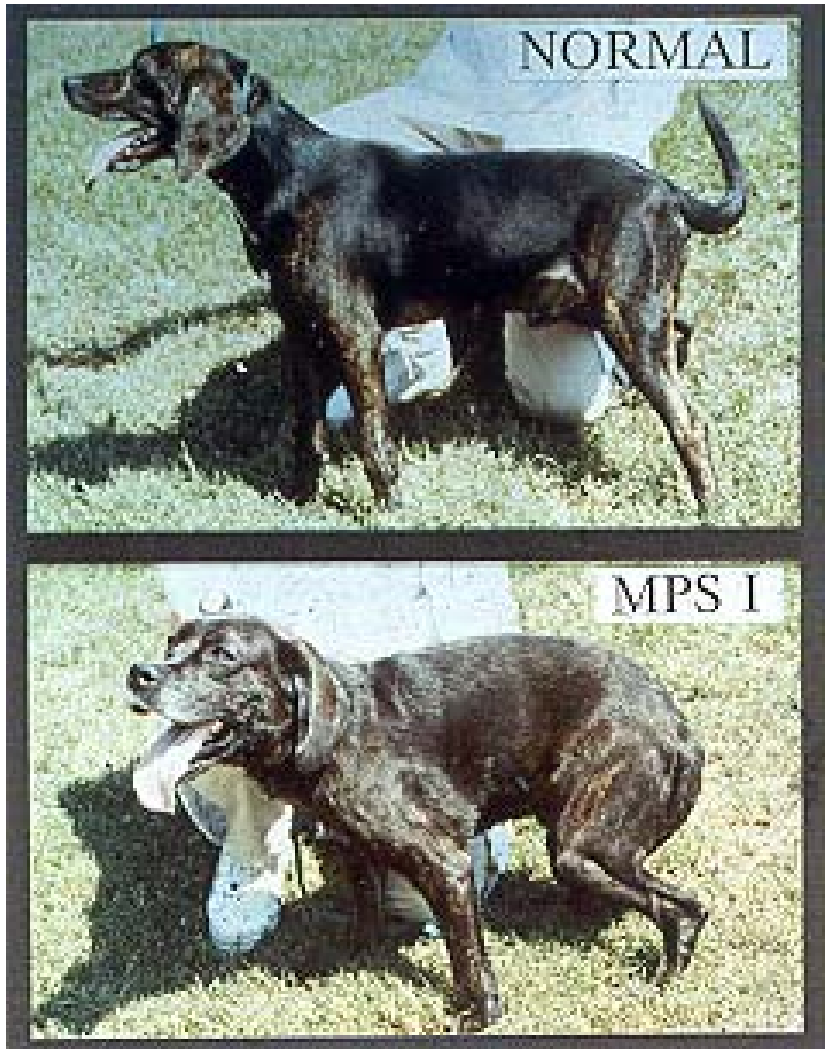
Iduronidase



Enzyme replacement therapy for MPS I

- Rationale and technical basis
  - Direct application of correction in vivo
- Good commercial model in Cerezyme®
  - Successful treatment on the market for Genzyme
- Requirements for reaching human studies
  - Recombinant sources of enzyme
  - Canine MPS I studies of efficacy and safety
  - Large scale production under GMP
  - Large scale money

Canine MPS I Model



Production Version 1

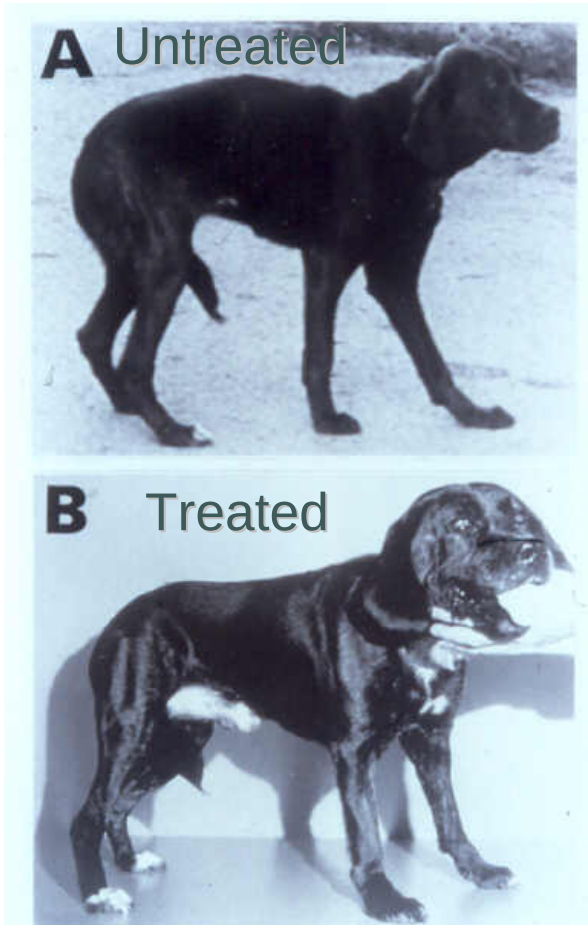
Microcarrier Culture of
Cell line 2.131

Circa 1993

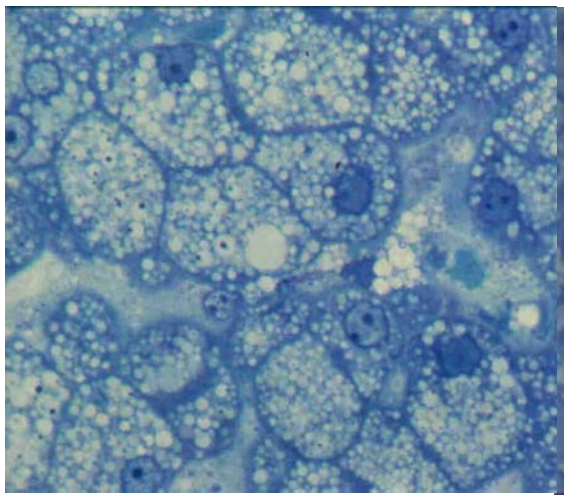
The challenge in treating the large canine model prepared the program for human trials

Canine MPS I Enzyme Replacement Studies

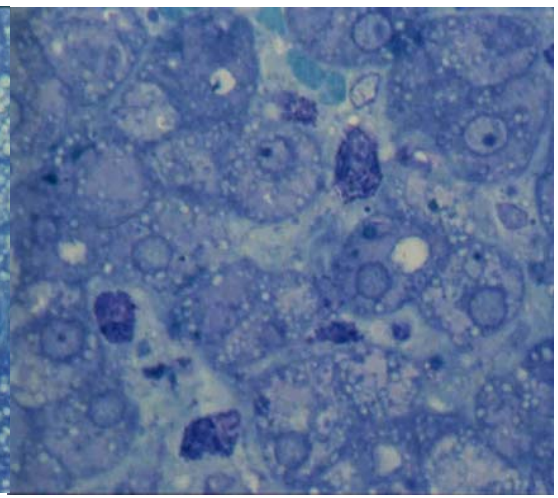
- Distribution to a wide variety of tissues
- Effective reduction in tissue GAG
- Effective minimum dose determined
- Limitations identified



Liver pretreatment



Liver post-treatment



Search for a company to fund the work for humans

- Xoma in 1993
  - Visited Santa Monica location, cordial but not interested
  - Had a really important sepsis product in development
- Amgen in 1993
  - “NBS I ? Sorry, I don’t know what time it is”
- Orphan Medical in 1993
  - Supportive and helpful but project too small and complicated
- Genzyme in 1993
  - “ This will cost $50 million to develop”
  - Correction: Actual cost now >> $100 million USD

How to fund development?

- **Write grants** — Never enough money for production
  No interest: not “sexy” science.’
- **Angel investor** — No star power
- **Start a foundation** — Could not find a rich widow

- **Develop a new thigh cream** — Tag Line:

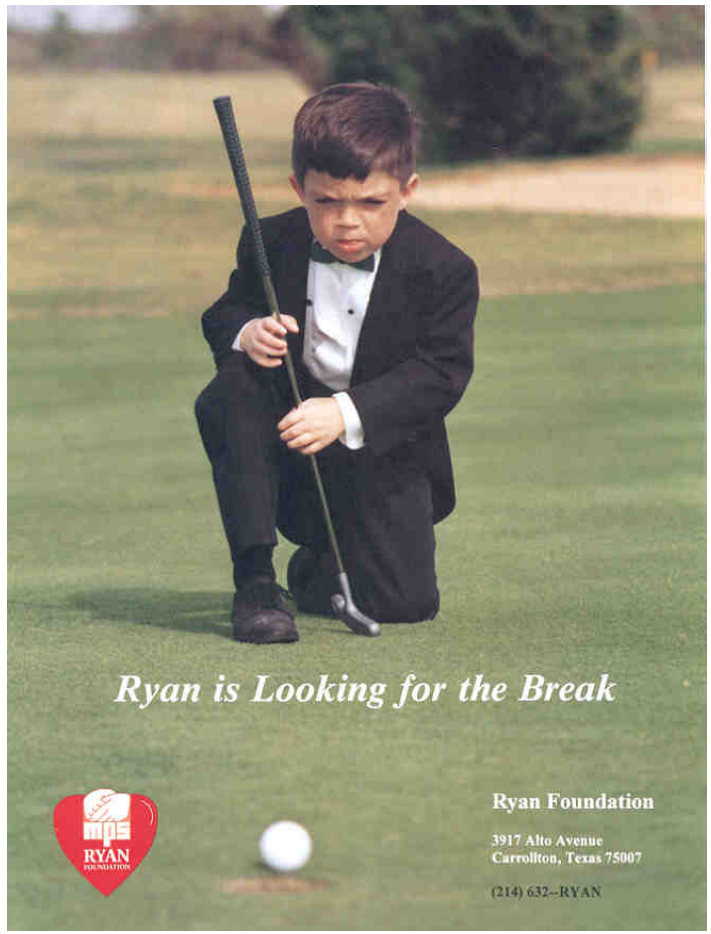
“Body sculpting”

enzyme cream now with real iduronidase

Sales of cream support therapeutic production and trials

The patients save the day: The Ryan Foundation

- Formed by Mark and Jeanne Dant for their affected son Ryan
- Raise money for research into a treatment
- First fundraiser: Bake sale in front of a bank: $242 total
- Directly funnel money to researchers
- Eventually raised $100-300,000 annually to support development



A small biotech company looking for products near to the clinic steps forward: BioMarin

- Fall 1996 John Klock and Grant Denison visit Dr. Neufeld and Kakkis at UCLA
- Fundraising in March 1997 and company formed
- April 1997 Research and Development Grant to Harbor-UCLA REI to manufacture and study enzyme therapy in MPS I
- September 1997 IND filed in the USA
- December 1997 First patient treated
- Genzyme joins the effort in September 1998 after data released on first clinical study

First Dose: December 19, 1997
Harbor-UCLA Medical Center

Entire production and clinical team

Aldurazyme is approved in the US and EU

- Phase 1/2 Study and Phase 3 Study completed from 1997-2002
- Approved in US in 2003
  - Positive FDA Advisory Committee Meeting:
  - 12-0 votes on FVC and 6MWT, Jan. 15, 2003
  - FDA approved on April 30, 2003 for US
- Approved in EU in 2003
  - Positive CPMP opinion in EU: Feb 20, 2003
  - EMEA approved on June 11, 2003 for EU
- Status in 2006
  - More then 400 MPS I patients on enzyme therapy in more than 30 countries worldwide

Lessons learned about developing a treatment for a rare disorder

- Strong biologic basis for the treatment
- Patient support groups help in the early phase
  - Important but not enough to finish
- Find corporate support from an appropriately sized company
  - For MPS I, it was a startup biotech
  - Genzyme was not interested until AFTER solid clinical data
- Need an early clinical success to drive funding
  - Clinical study grade material appropriate for Phase 1/2 studies
  - Small well-designed study that provides compelling data
- An appropriate commercial model for success will help get investors to support the work
  - BioMarin had Genzyme's success with Cerezyme

Finding the path forward today

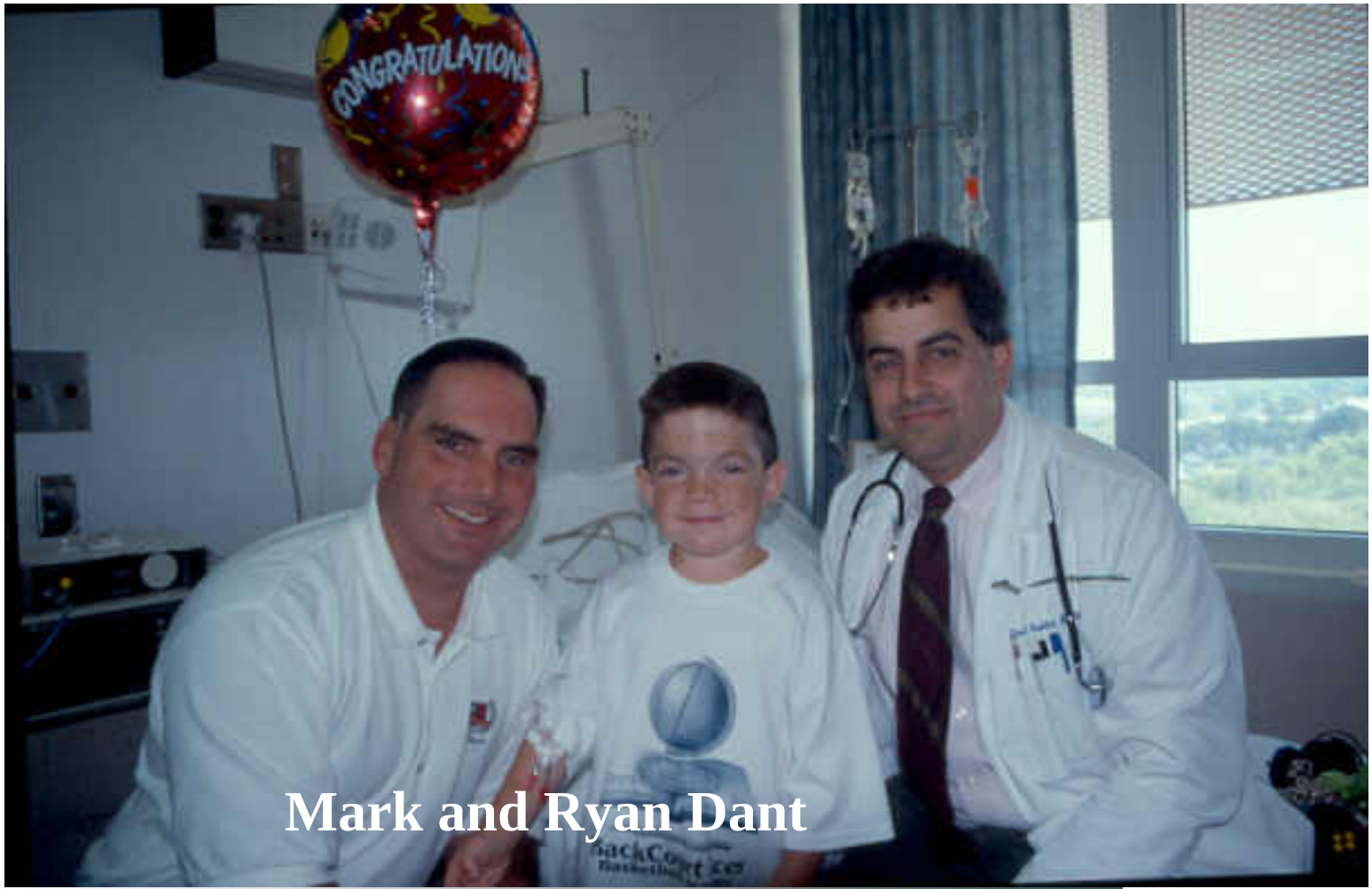
- Venture firms are not funding preclinical projects generally
  - Exception for proven drug models or powerful technology
  - Hard to sell preclinical stage programs in rare disorders but not impossible
- Large companies are looking for clinical stage products
  - Hard to get their interest with preclinical products
- Options for getting a project going:
  - 1) Search for startups or smaller company **with funds** in your therapeutic area that need additional products
    - Perhaps a company with one successful product that needs some early stage pipeline
    - Get a business development consultant to prepare an offering memorandum
  - 2) Form a virtual company, and obtain SBIR funding
    - More funds than typical RO1 grants and easier to get
    - Could be sufficient to reach a clinical study if production costs are reasonable
    - Hard to get the expertise needed to really drive development
  - 3) Angel investor or rich widow or connection to Bill Gates

Treating other ultra-orphan disorders
What are the challenges?

- Improve the knowledge base about the disorders
- Develop biochemical markers that can allow for more efficient clinical development
  - No validated surrogate endpoints in rare disorders
- Improve the regulatory process for ultra-rare products
  - Development path not optimal
  - Critical Path Initiative ongoing at FDA
- Solve the funding cost/product cost challenge
  - High development costs and rare disease means the drug will be very expensive to recover investment

Aldurazyme: 12 years in development

Project Start: July 1991 to FDA Approval: April 2003



Mark and Ryan Dant

Followup of Ryan 7 years later

16 yrs old in 2005

7 years on laronidase and just got his license and car