Annual Congress on Rare Diseases and Orphan Drugs

October 26, 2016

Dr. Tim Coté, MD, MPH

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Introducing the Speaker, Dr. Timothy Coté



- Over 23 years of Federal service at the FDA, NIH, and CDC
- Former Director of FDA Office of Orphan Products Development (OOPD)
- Signed decisions for 1400+ ODD applications
- Saw 150+ Orphan products go to market
- Founder and CEO at Coté Orphan

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Our Agenda

- Orphan History
- Why Orphans are Special
- Nitty Gritty of the Orphan Designation Process
- Review Issues for Orphans
- Pediatric Rare Disease Voucher
- HUD/HDE

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Abbey Myer: Grassroots Political Mover

- Rare Diseases: Individually infrequent but collectively common
- “They are like orphans in that they require special care.”
  ---Henry Waxman



NORD
National Organization

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Economic Realities: 1982

- Rare diseases = few pill buyers
- 1973-1982: 10 new drugs for rare diseases
- Roughly 7000 rare diseases;
  25 million people
- Congressmen/Senators besieged by parents/caregivers

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The New Deal of the ODA

- Get a drug designated with “orphan drug status”
  - Show (with data) that it’s “promising”
  - For treating <200,000 person in the US
- Do the clinical trials/get marketing approval
- Receive incentives:
  - MARKET EXCLUSIVITY
  - Tax credits
  - Fee exemptions

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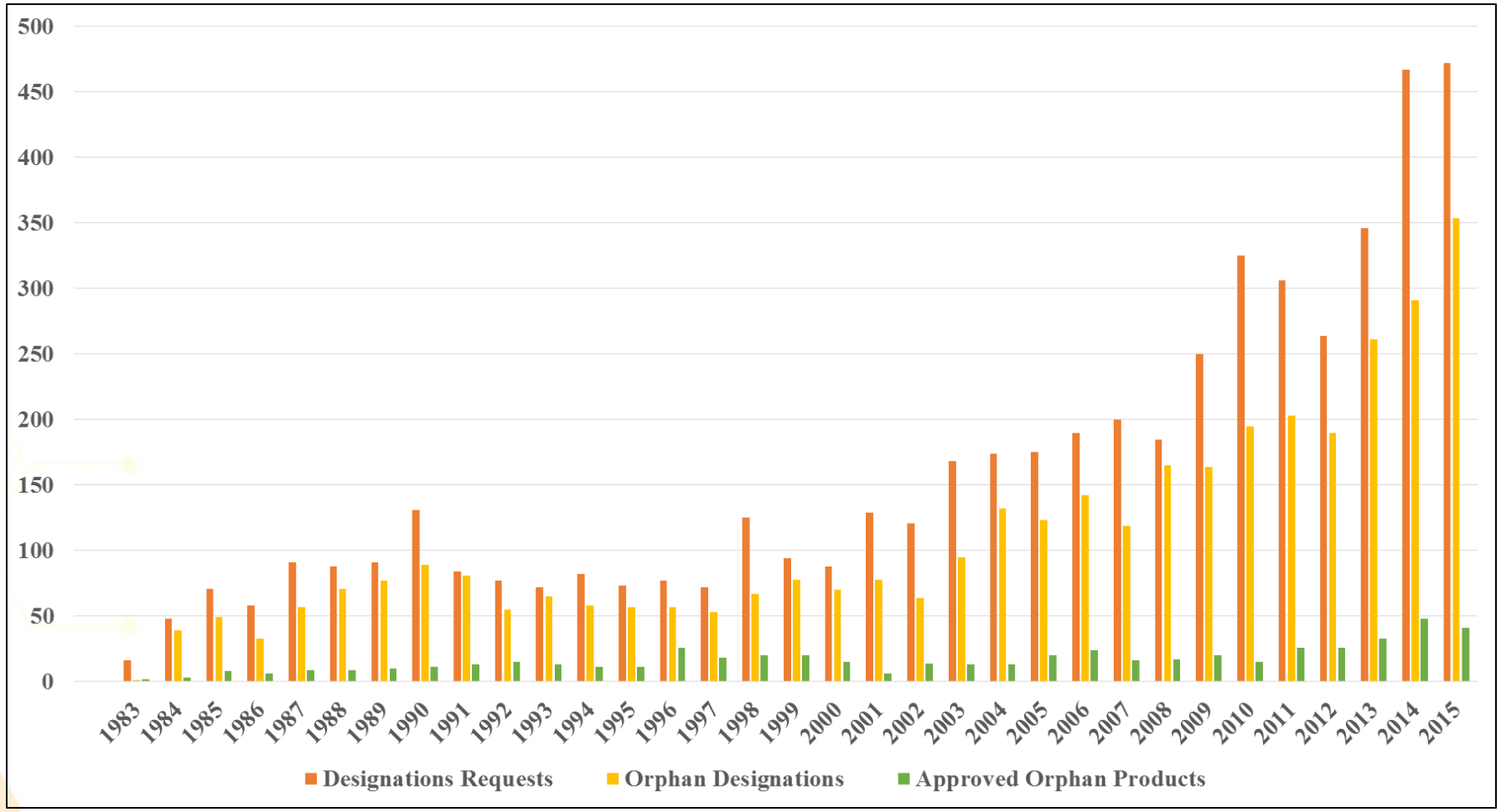
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Incentives of the 1983 ODA

- Statutory
  - Exclusivity
  - PDUFA fee exemption
  - 50% tax credits
  - PREA exemption
- Non-Statutory
  - OOPD support at review divisions
  - Orphans are Hot

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Orphan Drugs: A HUGE SUCCESS



Source: FDA/OOPD

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Orphan Drugs: A HUGE SUCCESS

- 12 orphans before 1983
- 531 approved orphan drugs today
- Treats about 200 rare diseases
  - Increasing overlap
  - Over 7,000 rare diseases

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Other Countries

- Europe: 1999
  - Steeped in Eurozone culture
  - Process-oriented
  - Bigger market (500M pop)
  - Weaker market
  - 1000 designations
- Japan
- Australia
- Taiwan, Korea, ROW



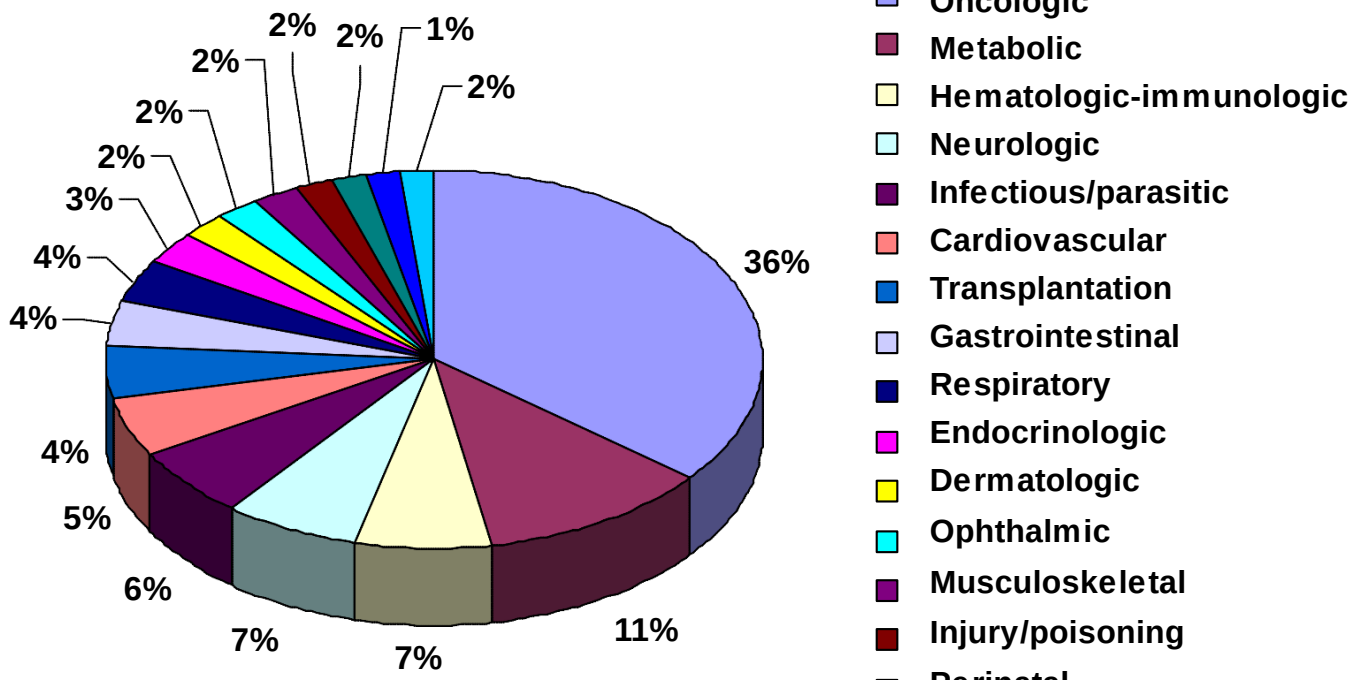
Source: orphan-drugs.org

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SO WHAT IS A TYPICAL ORPHAN DRUG?

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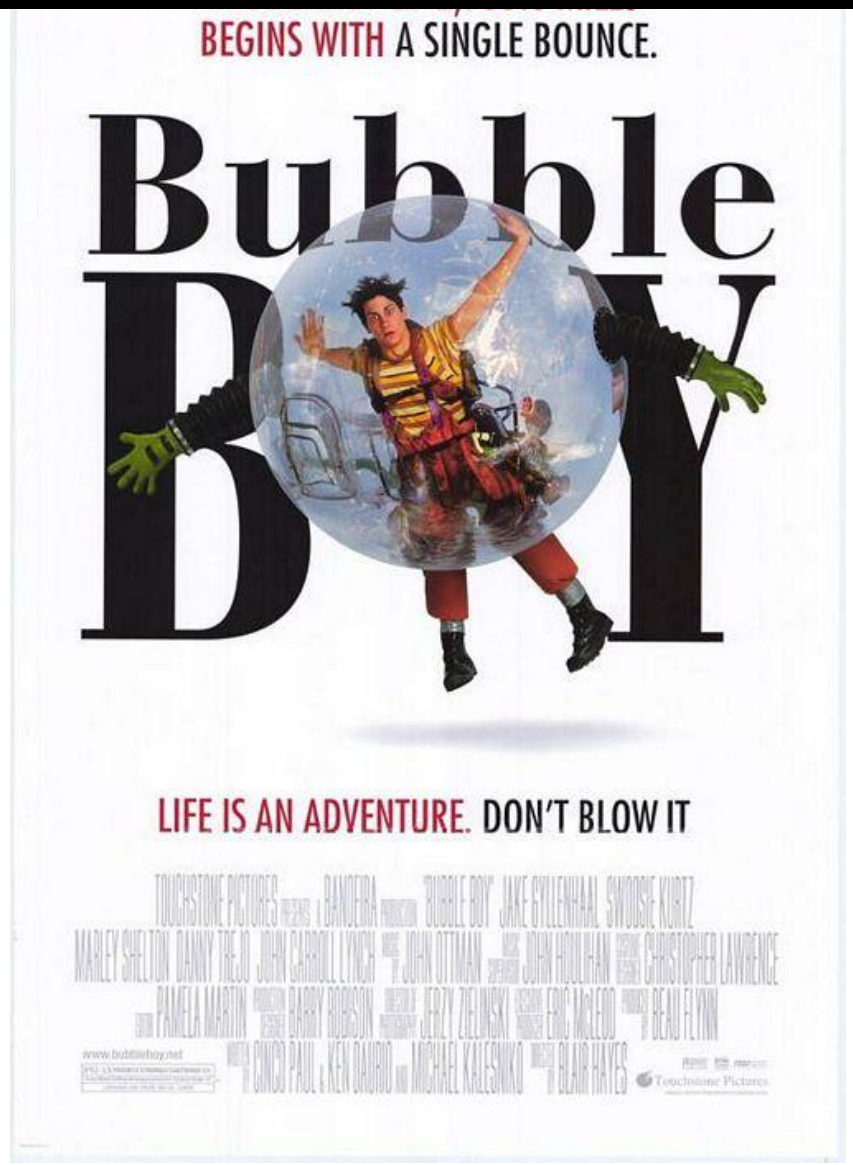
And all human pathology is targeted by designated orphan drugs*



*2000-2006

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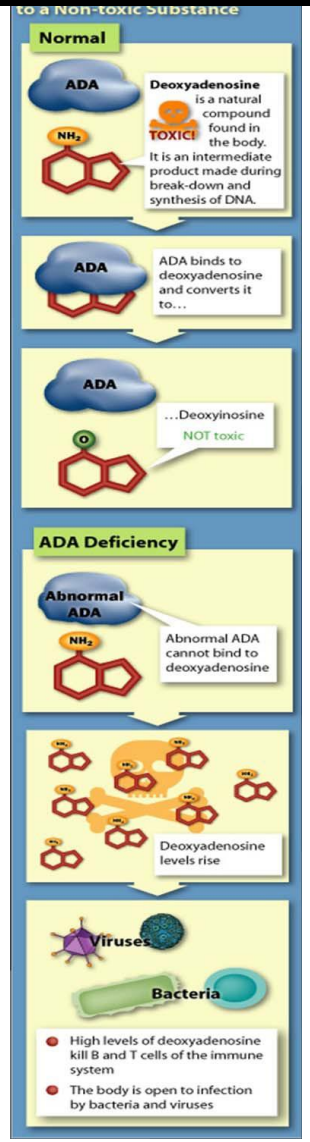
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Example: Adagen for ADA

- Population: 1:2x10^5 to 1:1x10^6 born with homozygous mutation
- Causes Severe Combined Immunodeficiency
- Adagen is one of the first orphan drugs (based on n=12!);

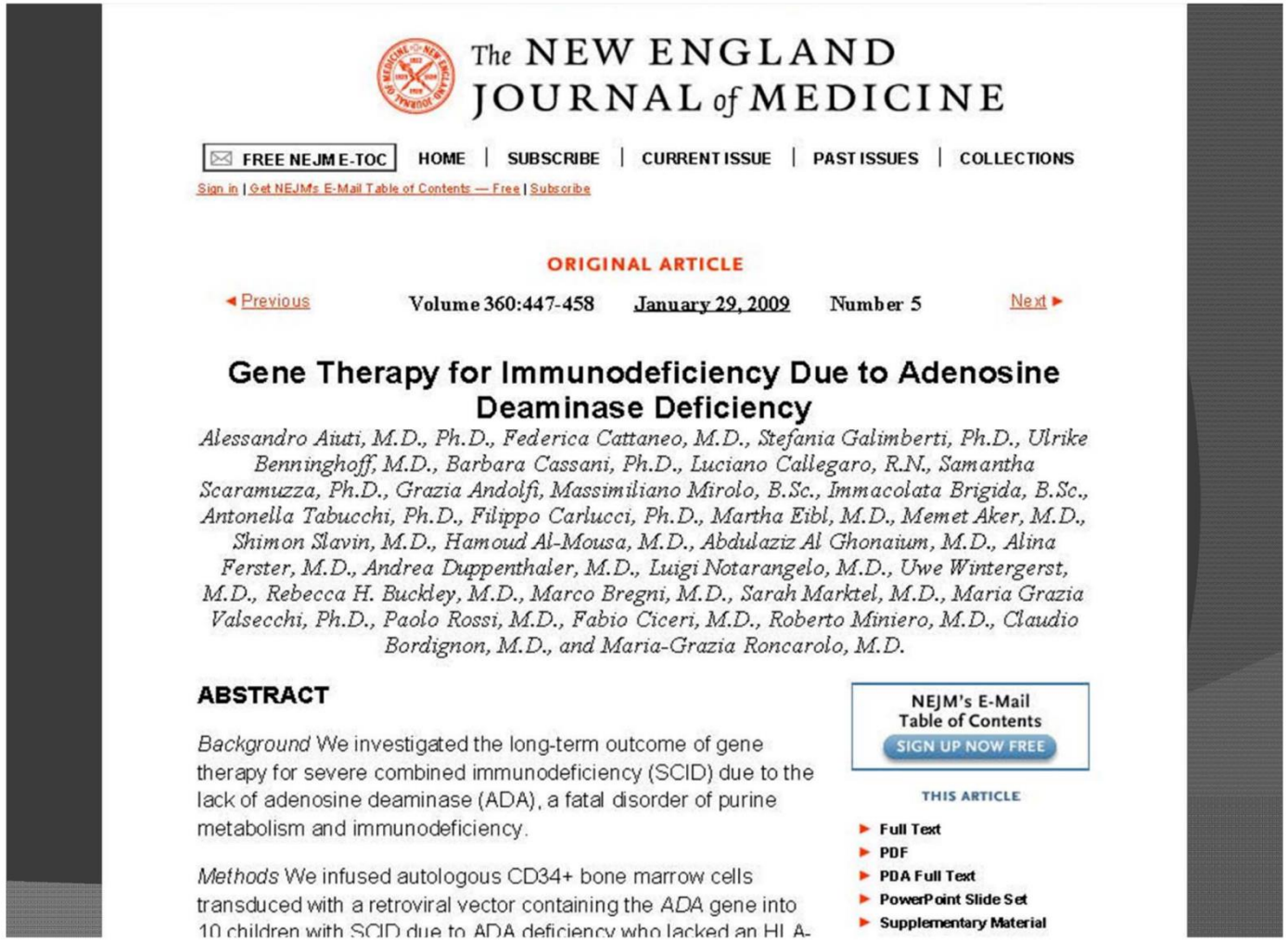
Enzyme replacement therapy

Designated in 1984



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

◂ Previous Volume 360:447-458 January 29, 2009 Number 5 Next ▸

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

Alessandro Aiuti, M.D., Ph.D., Federica Cattaneo, M.D., Stefania Galimberti, Ph.D., Ulrike Benninghoff, M.D., Barbara Cassani, Ph.D., Luciano Callegaro, R.N., Samantha Scaramuzza, Ph.D., Grazia Andolfi, Massimiliano Mirolo, B.Sc., Immacolata Brigida, B.Sc., Antonella Tabucchi, Ph.D., Filippo Carlucci, Ph.D., Martha Eibl, M.D., Memet Aker, M.D., Shimon Slavin, M.D., Hamoud Al-Mousa, M.D., Abdulaziz Al Ghonaium, M.D., Alina Ferster, M.D., Andrea Duppenthaler, M.D., Luigi Notarangelo, M.D., Uwe Wintergerst, M.D., Rebecca H. Buckley, M.D., Marco Bregni, M.D., Sarah Marktel, M.D., Maria Grazia Valsecchi, Ph.D., Paolo Rossi, M.D., Fabio Ciceri, M.D., Roberto Miniero, M.D., Claudio Bordignon, M.D., and Maria-Grazia Roncarolo, M.D.

ABSTRACT

Background We investigated the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) due to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

Methods We infused autologous CD34+ bone marrow cells transduced with a retroviral vector containing the *ADA* gene into 10 children with SCID due to ADA deficiency who lacked an HLA-

NEJM's E-Mail Table of Contents

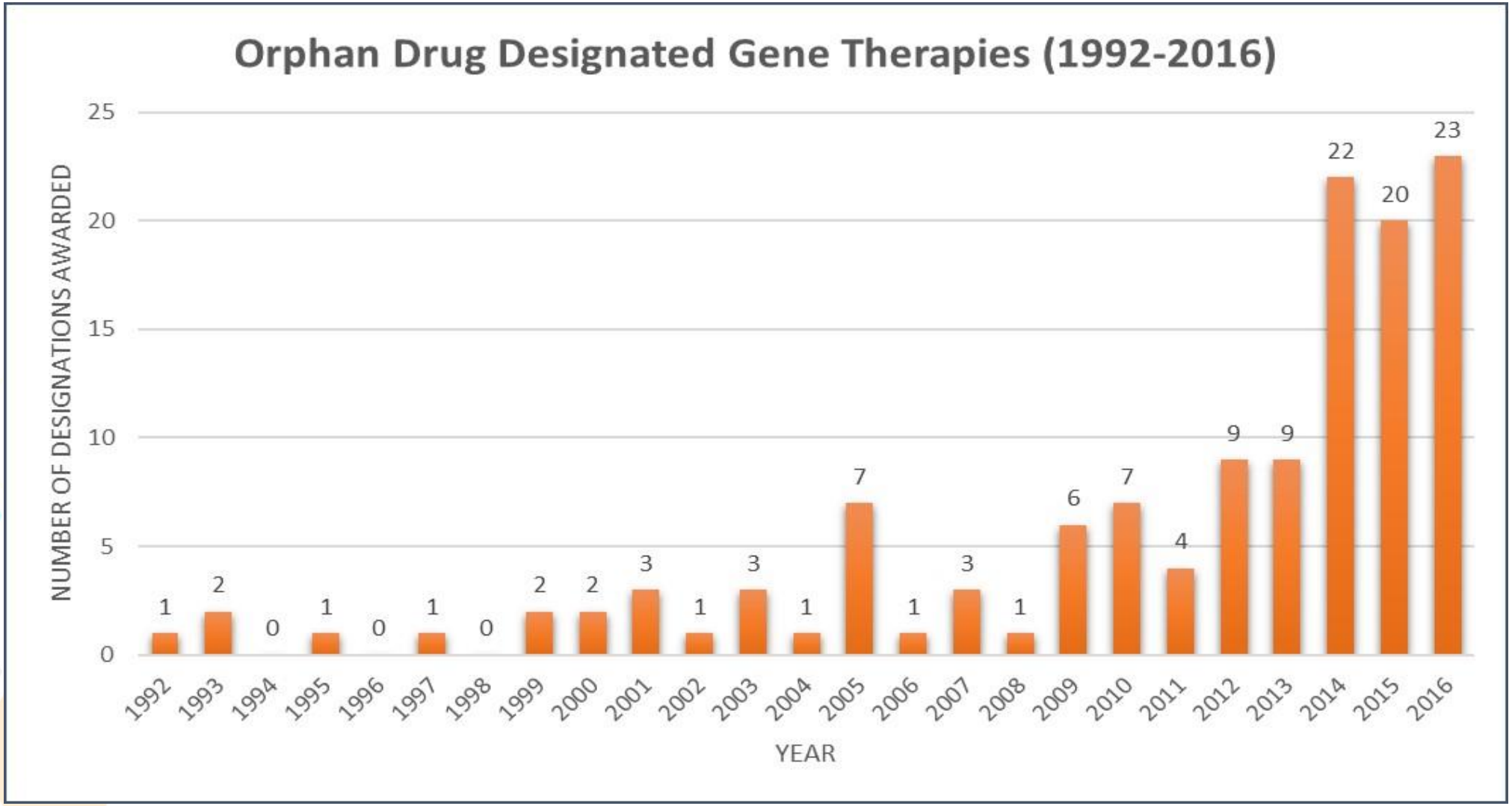
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Naglazyme for MPS Type VI (Maroteaux-Lamy syndrome)

- Mucopolysaccharidosis, liposomal storage disorder.
- Estimated only 1,100 persons world-wide
- Enzyme replacement can prevent these changes



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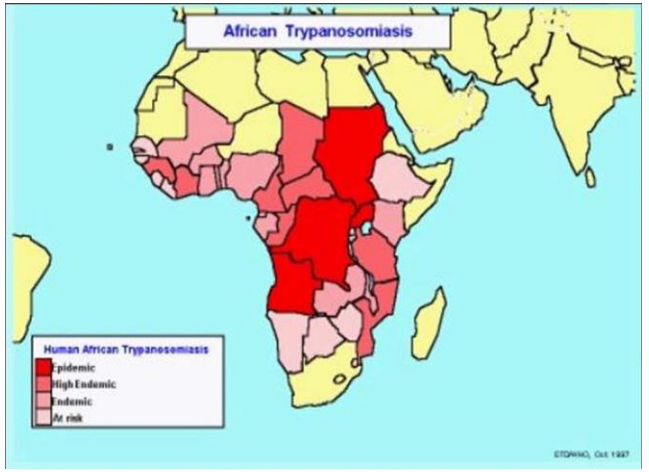
Enzyme Replacement Therapies

- Some of the most extraordinarily expensive treatments in the history of mankind (some $400,000/pt/yr)
- FDA does not regulate price
- Radically transformative benefits to patients lives
- Exclusivity lasts 7 years;
  knowledge is eternal

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Example: Eflornithine for African sleeping sickness

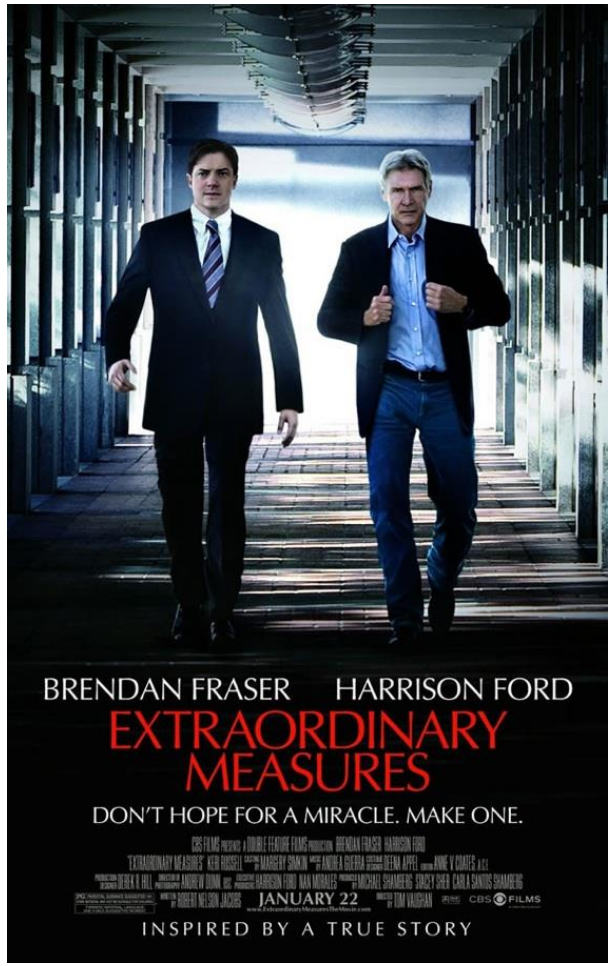
- Extremely rare disease in the US and Europe
- Treatment would be highly personalized, based on travel history



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Who has done this?

- Garage Science
- “BELLYFIRE”
- BIG PHARMA
  - Onco
  - Acquisitions
  - “Tardy to the Party”



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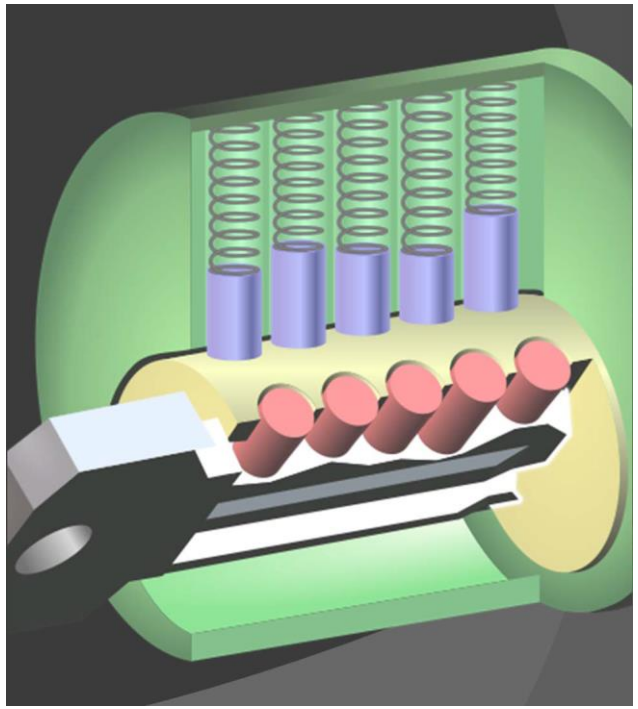
ORPHANS ARE SPECIAL!

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Orphans are special: Science

- Transformative, not incremental
- Often 1st therapies for dz
- Effect size and public health imperative speeds approval



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Orphans are special: Regulatory

- Resources: NORD article, KGI TMP
- FDA Attitude
  - Tx for common dz: PH threat
  - Tx for rare dz: PH opportunity
- FLEXIBILITY!
  - Number of clinical trials
  - Size of clinical trials
  - Design of clinical trials



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Orphans are special: High Touch!

- Patients are paramount
- Researchers: All thinkers are thought leaders
- Bandwidth per patient requirements are high



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Orphans are special: High Touch

- Patient relations at least as important as investor relations
- Enrollment, regulatory, marketing



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Orphans are special: Finances

- Can be comparatively small investments
- Can yield high returns for orphan indications
- Revenues relatively small, ROI relatively large
- Many models: ERT, Pt- sponsored, Academic Startup, Mid-sized
- PharmaKarma: Good things happen: Botox/Epo/Gleevec



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Big Pharma Cultural Impediments

- Unlearn
  - That it can't be done for such little money
  - That you can't secure approval with that kind of data.
- New Learning Needed
  - High touch



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About Orphan Drugs

Perceptions

- Faster Review Process
- Smaller Trials
- Fewer Trials
- Lower Evidentiary Bar

Realities

- Maybe, 6 mo to 28 years
- Yes, factor of 1
- Yes, factor of 1.5
- No, but more “flexibility”

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Summary

- Orphans drug development is passionate stuff
- Orphans are very different from non orphans
- Large companies can be disadvantaged by irrelevant experiences developing mass-market drugs
- Large companies are strongly advantaged with human and fiscal resources
- There is an enormous amount of need, new models beckon

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The Nitty Gritty of Orphan Designation Applications

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Strategy: When is it best to apply?

- Answer: As early as you can!
  (Medical rationale and prevalence criterion met)
- Optimizes tax credit benefit
- Optimizes assistance from OOPD
- Optimizes value with investors
- Immediately augments asset value

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FDA ODD: The Big Question

- **What is the disease?**
  - You propose, they decide.
- **Unwritten rules, a whole passel of 'em!**
- Ever changing (We are expected to improve…)
- At same time, eschew arbitrary and capricious decisions…
- (Non) utility of precedence
- Example: Rapidly progressive multiple sclerosis
- Example: Cystic fibrosis pneumonia
- Example: Evolving treatment of lymphomas
- Example: Pediatric diseases (UC/Crohns, Schitz, HIV/AIDS)

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FDA ODD: MEDICAL RATIONALE CRITERION

- Clinical data (60%)
- Animal model data (35%)—submit early!
- In Vitro data (5%)

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FDA ODD: PREVALENCE CRITERION

- Sources
  - US Government
  - CDC/NCHS
  - NCI/SEER
  - AHQR
- Europe/elsewhere: NOT (statute defines US stats)
- Medical Literature
- Olmstead County
- Other lit sources
- Claims data

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FDA ODD: PREVALENCE CRITERION (cont.)

- "But it's too rare, there IS no published epidemiology!"
  - 3 KOLs
  - Numbers, not "<200K"
- US Census Denominators
- Ranges

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FDA ODD: OOPD RESPONSES

- Timeline
  - Not statutory or in reg
  - My watch: 60 d
  - Since 2011: 90 d
  - Since 2016: 120 d

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FDA ODD: OOPD RESPONSES

- Outcome
  - 60% Orphan Designations Granted
  - Only half (30%) on first round
  - Information commonly requested under abeyance, detailed instructions
  - 40% held in perpetual abeyance (awaiting info)
  - <1% “denied”

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ODD SUMMARY

- Huge increases in asset value, $400K-$4M
- Comparatively small fee to get one ($40K, 10-100X ROI)
- Apply as early as possible to max benefits

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THANK YOU

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