

# Importance of Natural History Studies in Rare Diseases

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# Outline

- Why we need natural history data for rare diseases
- Natural history study definition
  - Historical controls
- Natural history and clinical development
- Key points

Begin with the end in mind...



# Natural History Studies

- Purpose: To inform drug development
  - Marketing approvals require design and conduct of adequate and well-controlled studies
  - Designing A & WC studies requires a scientific foundation upon which to build
    - Knowledge of disease NH is an essential element in the scientific foundation of any clinical development program
  - Rare diseases, in general, are poorly understood
    - Important and essential role for NH studies in rare disease drug development (IND phase) to facilitate efficient clinical development

# Rare Diseases and Orphan Drugs

- What is different about rare diseases and Orphan drugs?
  - Diseases are usually poorly or incompletely understood
    - Generally, the lower the prevalence, the less well we tend to understand them
  - Small populations
    - Limited opportunity for study and replication
  - Highly heterogeneous group of disorders
    - 7,000 different diseases
    - Often high phenotypic diversity within individual disorders
  - Usually little precedent for drug development within individual disorders
  - Often requires more (and more careful) planning than non-Orphan
    - Need a solid scientific base upon which to build an overall program

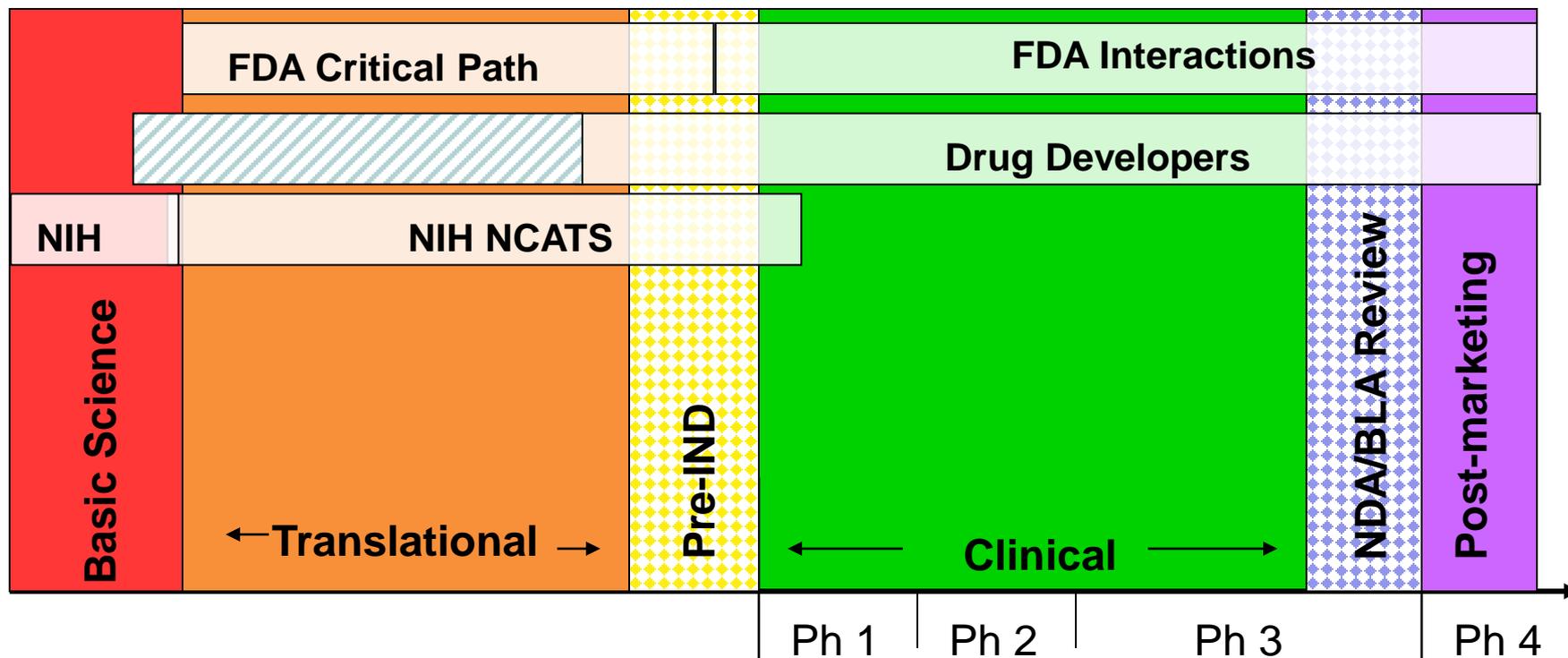
# CDER New Molecular Entities & New Biologic Approvals 2011-2012

## Disease Precedent ?

Yes	No
<p><b>2012</b> (as of May 13, 2012)</p> <p>Respiratory Distress Syndrome in premature infants</p> <p>Gaucher disease</p>	<p>Methotrexate toxicity</p> <p>Cystic Fibrosis <i>G551D</i> mutation</p>
<p><b>2011</b></p> <p>Organ rejection, kidney transplant</p> <p>Hodgkins lymphoma</p> <p>Hereditary Angioedema</p> <p>Acute lymphoblastic leukemia</p> <p>Transfusional iron overload</p> <p>Lennox-Gastaut</p>	<p>Advanced melanoma</p> <p>Melanoma <i>BRAF</i> mutation</p> <p>Medullary thyroid cancer</p> <p>Anaplastic systemic large cell lymphoma</p> <p>Alk+ non-small cell lung cancer</p> <p>Myelofibrosis</p>

• In same time period for non-rare disease indications: 24 NME/NBs, only 2 did not have disease precedent (8%)

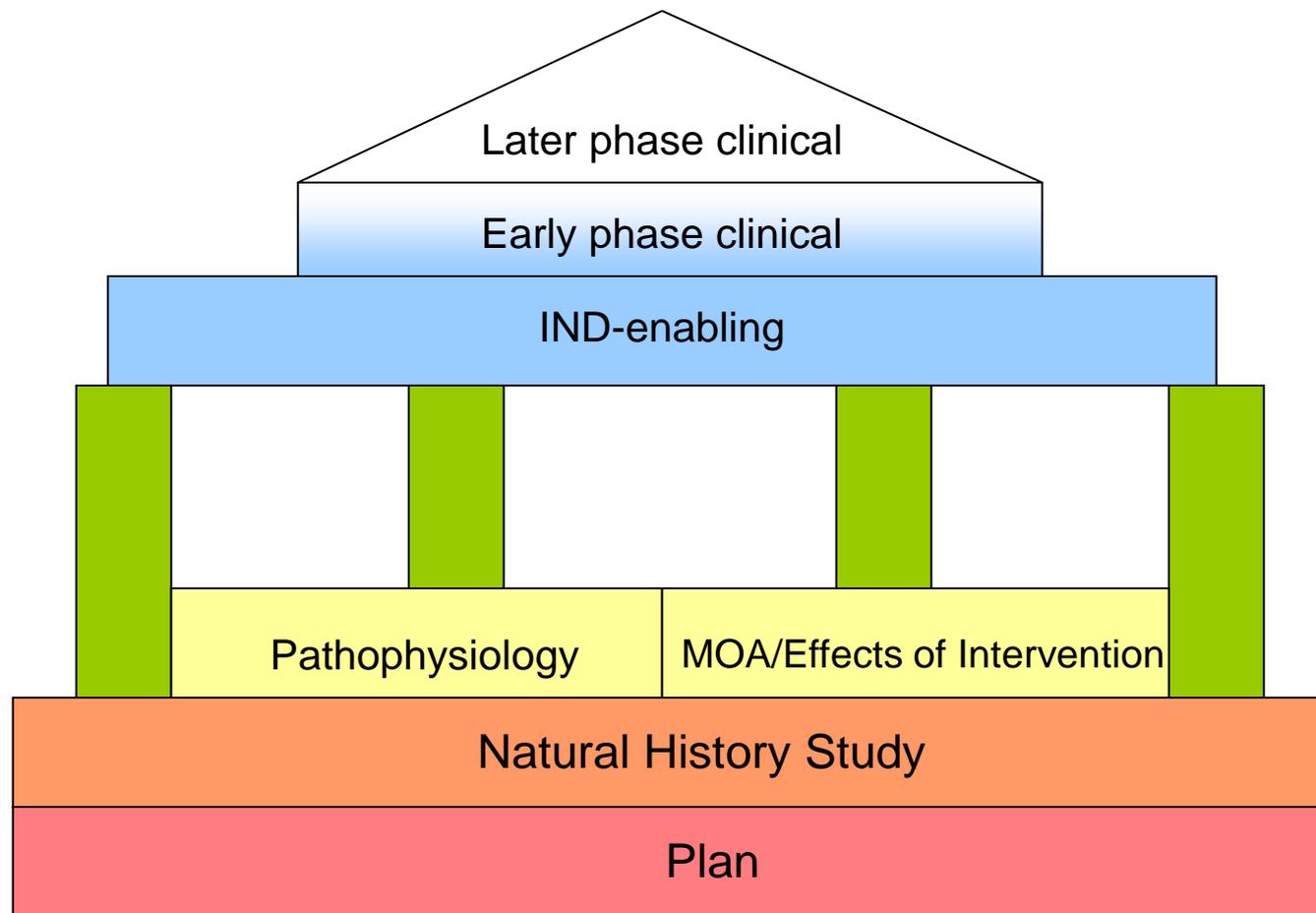
# Drug Development - Linear Concept



# Parallel Concept

- Efficacy trial design
  - Time course
  - Target population
  - COA
- 
- Pilot COAs
  - Safety
- 
- Non-clinical P/T
    - Population
    - Toxicities
  - Dose exploration
  - Bmkr/COA exploration
- 
- Biomarker and COAs ID and development
  - Assays/testing
  - Diagnostics
  - Animal models

# Foundation Building



# Adequate and Well-Controlled Studies

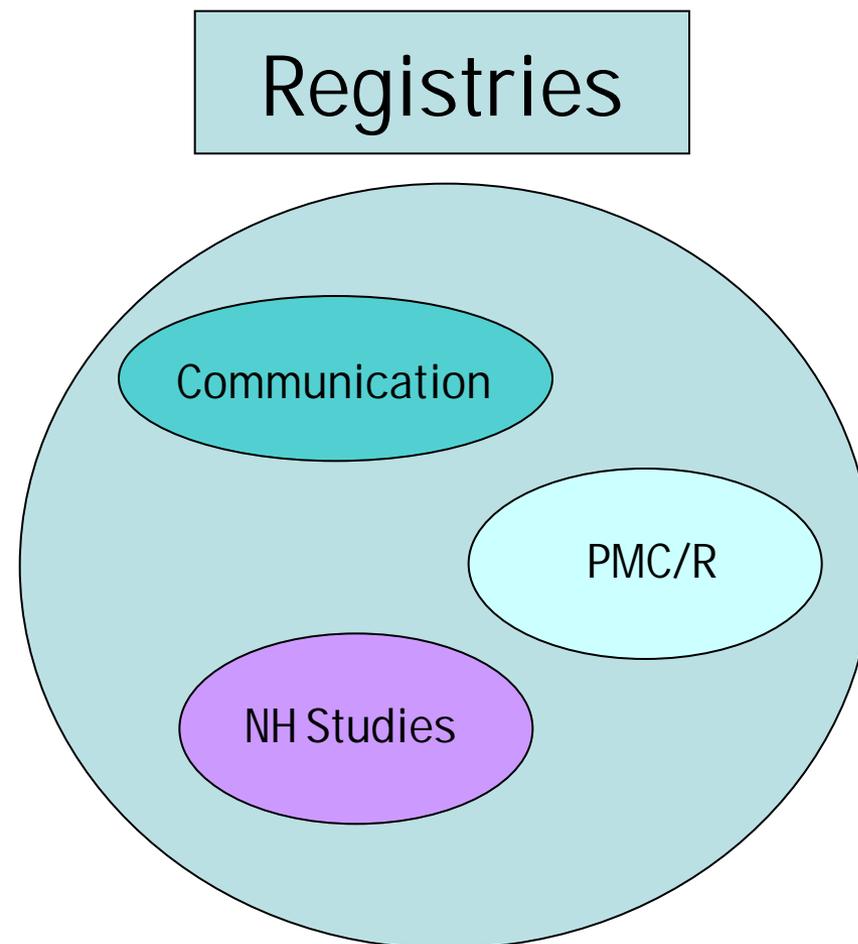
- A&WC studies require<sup>1</sup>
  - Research goal/objective
  - Valid comparison with a control
    - Concurrent (strongest) or historical
  - Appropriate selection of subjects
  - Method of assignment to treatment and control
  - Measures to minimize bias
  - Well-defined and reliable methods of assessing response
  - Adequate analysis of results

<sup>1</sup>21CFR314.126 Adequate and well-controlled studies

# Natural History Studies Definition

# NH Study Versus Registry

- Registry  $\neq$  NH Study
- Registries can include:
  - Communication
  - Post-marketing commitments/requirements  
e.g.,
    - Intervention assessment
    - Safety
  - NH Study
    - Specific purpose
    - Intended to be comprehensive, granular
    - Intended to describe the disease



# Natural History of a Disease

“The natural course of a disease from the time immediately prior to its inception, progressing through its presymptomatic phase and different clinical stages to the point where it has ended and the patient is either cured, chronically disabled or dead without external intervention”<sup>2</sup>

<sup>2</sup>Posada de la Paz M; Groft SC. 2010. *Rare diseases epidemiology*. Vol. 686

# Natural History Studies

- Track course of disease over time
- Identify demographic, genetic, environmental and other variables that correlate with disease and outcomes in the absence of treatment
- “Pillar of epidemiologic research on rare conditions”<sup>3</sup>
  - Many potential uses/functions of NH study data in addition to drug development, e.g.
    - Patient care, best practices
    - Research priorities identification
    - “centers of excellence” development, clinical trial readiness

<sup>3</sup>Institute of Medicine. 2010. *Rare Disease and Orphan Products. Accelerating Research and Development*

# Historical Controls

- Infrequent application of NH study or registry data
  - “usually reserved for special circumstances”<sup>4</sup>, e.g.:
    - diseases with high and predictable mortality
    - Effects of drug self-evident
- Purpose of any control is to measure what *might* have happened
- Historical control
  - Different patients using alternative treatment
  - During different times and in different places
  - Requires
    - Adequate documentation
    - Comparable patients or populations
    - Doesn't account as well for pertinent variables as concurrent controls can

# Historical Controls (2)

- Two general types
  - Informal/implicit
    - Based on general knowledge
    - E.g. change from baseline – implicit comparison to what would have happened without the intervention
    - Plainly reasonable when
      - Effect is dramatic, rapid following treatment, unlikely to have occurred spontaneously
  - Specific experience
    - Actively sought, often through a formally conducted NH study
    - Objective, verifiable measures
    - Must be a fair comparison to interventional study population

# Natural History and Clinical Development

# CDER NME & New Biologic Approvals in 2012<sup>6</sup>

## Rare

- Glucarpidase (MTX tox)
- Ivacaftor (CF *G551D*)
- Lucinactant (RDS newborns)
- Taliglucerase

## Common

- Ingenol (actinic keratosis)
- Axitinib (renal cell CA)
- Tafluprost (glaucoma)
- Peginesatide (anemia in CKD)
- Vismodegib (basal cell CA)
- Avanafil (erectile dysfxn)

<sup>6</sup>As of May 13<sup>th</sup> 2012, available at Drugs@FDA

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

# CDER APs 2012 - Disease Precedent

Rare		Common	
Yes	No	Yes	No
Lucinactant Taliglucerase	Glucarpidase Ivacaftor	Ingenol Axitinib Tafluprost Peginesatide Avanafil Vismodegib	

# Glucarpidase

- Indication: Treatment of toxic plasma methotrexate concentrations due to impaired renal function
- Full approval
  - Pharmacodynamic endpoint
    - Proportion of subjects with elevated MTX level who achieved rapid and sustained clinically important reduction (RSCIR) in MTX level  $\leq 1$   $\mu\text{mol/l}$

# Glucarpidase (2)

- Evidence of effectiveness
  - Analysis of subset of patients (n=22) in an NCI-sponsored study who had evaluable MTX levels post-glucarpidase administration
  - NCI trial: prospective, OL, historically-controlled, non-randomized single-arm compassionate use trial in 184 patients with high-dose MTX-induced nephrotoxicity and delayed MTX excretion.
  - “not feasible to prospectively study glucarpidase in a randomized placebo controlled trial for this indication...emergency situation that occurs unpredictably”<sup>7</sup>
  - 10/22 patients (45%) met criteria for RSCIR
  - All 22 patients >95% reduction in MTX for up to 8 days

<sup>7</sup>Patricia Dinndorf, M.D., Clinical Review BLA 125327, available at Drugs@FDA

# Glucarpidase (3)

- Historical Information
  - MTX available since 1948
  - Used for higher-dose (e.g., leukemias, sarcomas) as well as lower-dose (e.g., RA) indications
  - Large and long-term clinical experience
    - Effects, mechanism of action, toxicity, excretion and metabolism well understood
    - Adverse effects of toxic MTX levels well understood
      - E.g., MTX excretion curve and correlation with increased risks of toxicity and MTX  $C_{\max}$  and AUC, and repeated confirmation

# Glucarpidase (4)

- Historical Information cont.
  - “rapid and sustained plasma levels of MTX below this threshold in patients with renal compromise and toxic plasma levels of MTX due to delayed MTX clearance represents a pharmacodynamic endpoint that is judged to be a valid surrogate endpoint”<sup>7</sup>
  - “Given the extensive data... the (MTX) excretion curves are well-characterized and can be used as an historical control against which the results of this trial can be assessed for efficacy and is sufficient to provide a clear assessment of the treatment effect”<sup>8</sup>

<sup>7</sup>Patricia Dinndorf, M.D., Clinical Review BLA 125327, available at Drugs@FDA

<sup>8</sup>Patricia Keegan, M.D., Summary Review BLA 125327, available at Drugs@FDA

# Ivacaftor

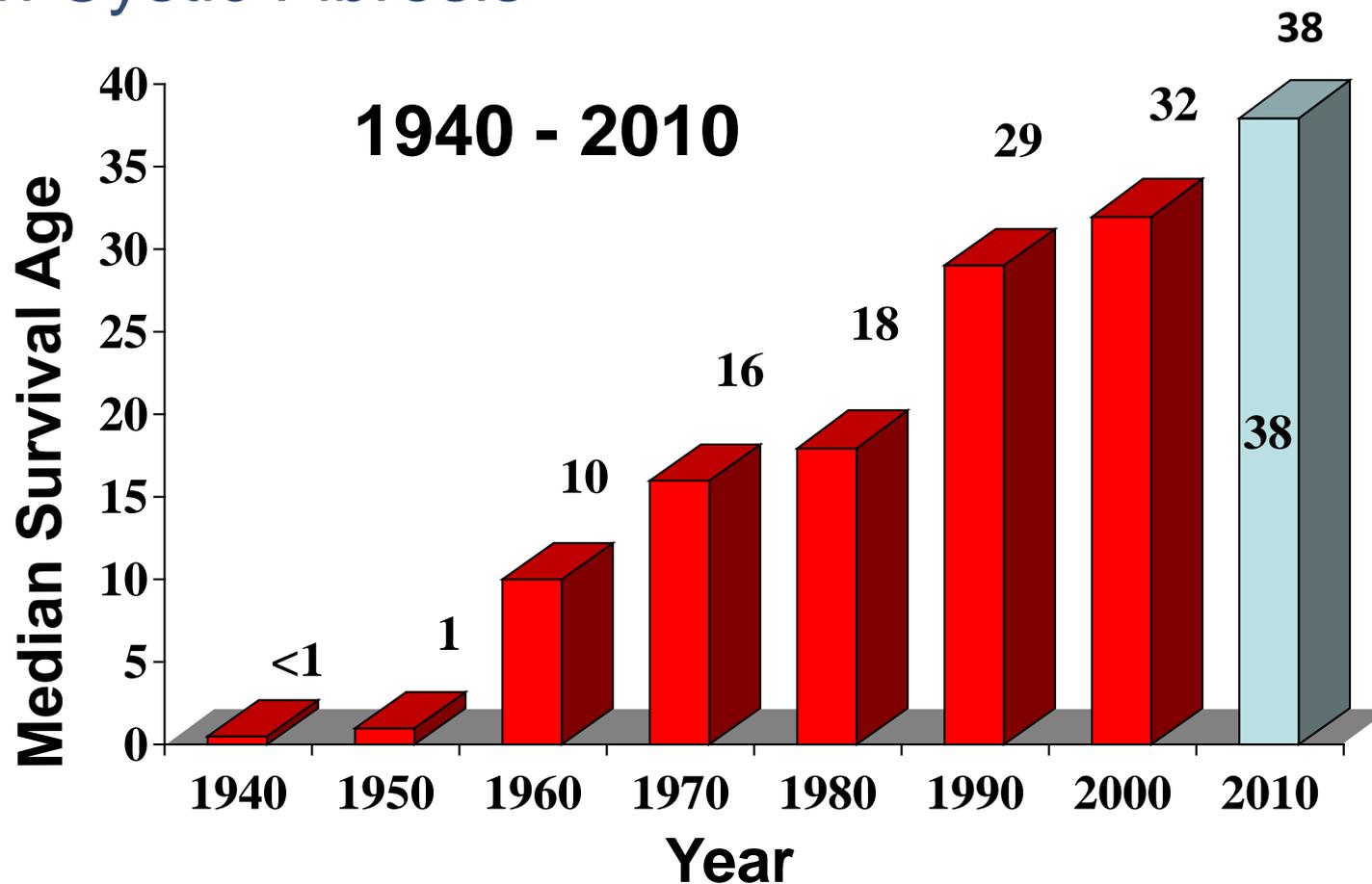
- Indication: Treatment of Cystic Fibrosis in patients age 6 years and older who have a *G551D* mutation in the CFTR gene
- Efficacy demonstrated in 2 R, DB, PC trials
- Robust demonstration of clinically meaningful benefit in several aspects of CF<sup>9</sup>
  - Lung function
  - Pulmonary exacerbations
  - GI function/substantial weight gain

<sup>9</sup>Badrul Chowdhury, MD, PhD, Summary Review NDA 203188, available at [Drugs@FDA](mailto:Drugs@FDA)

## Ivacaftor (2)

- Historical information
  - CF gene identified in 1989
  - Long-standing registry, disease well-described
    - CF registry and care network established in 1960
    - Extensive disease history prospectively collected which continues to inform research, development and patient care

# Median Survival Age of Patients with Cystic Fibrosis



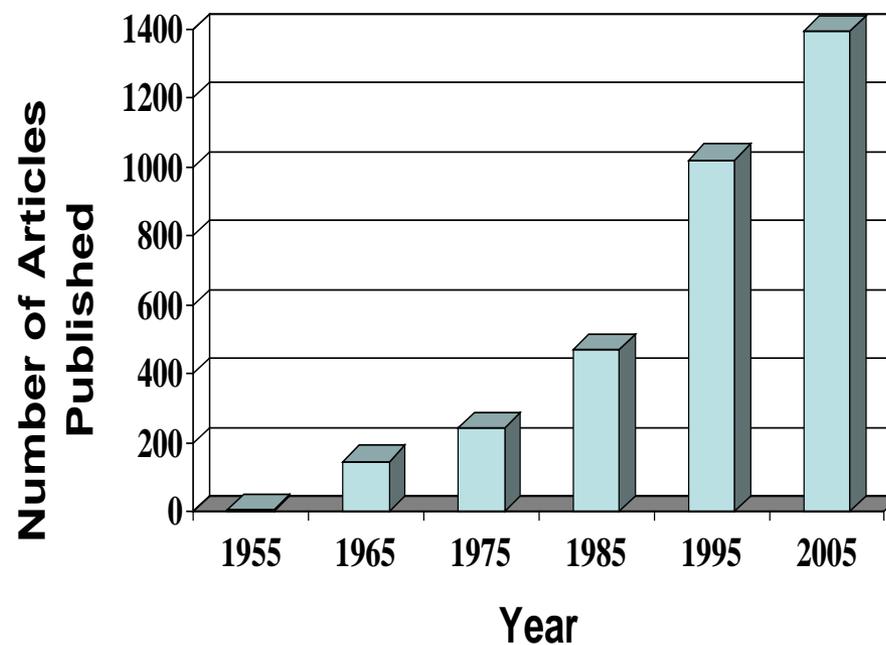
Source: Cystic Fibrosis Foundation, National Patient Registry

Slide courtesy of Preston W. Campbell, MD, CF Foundation. Used with permission

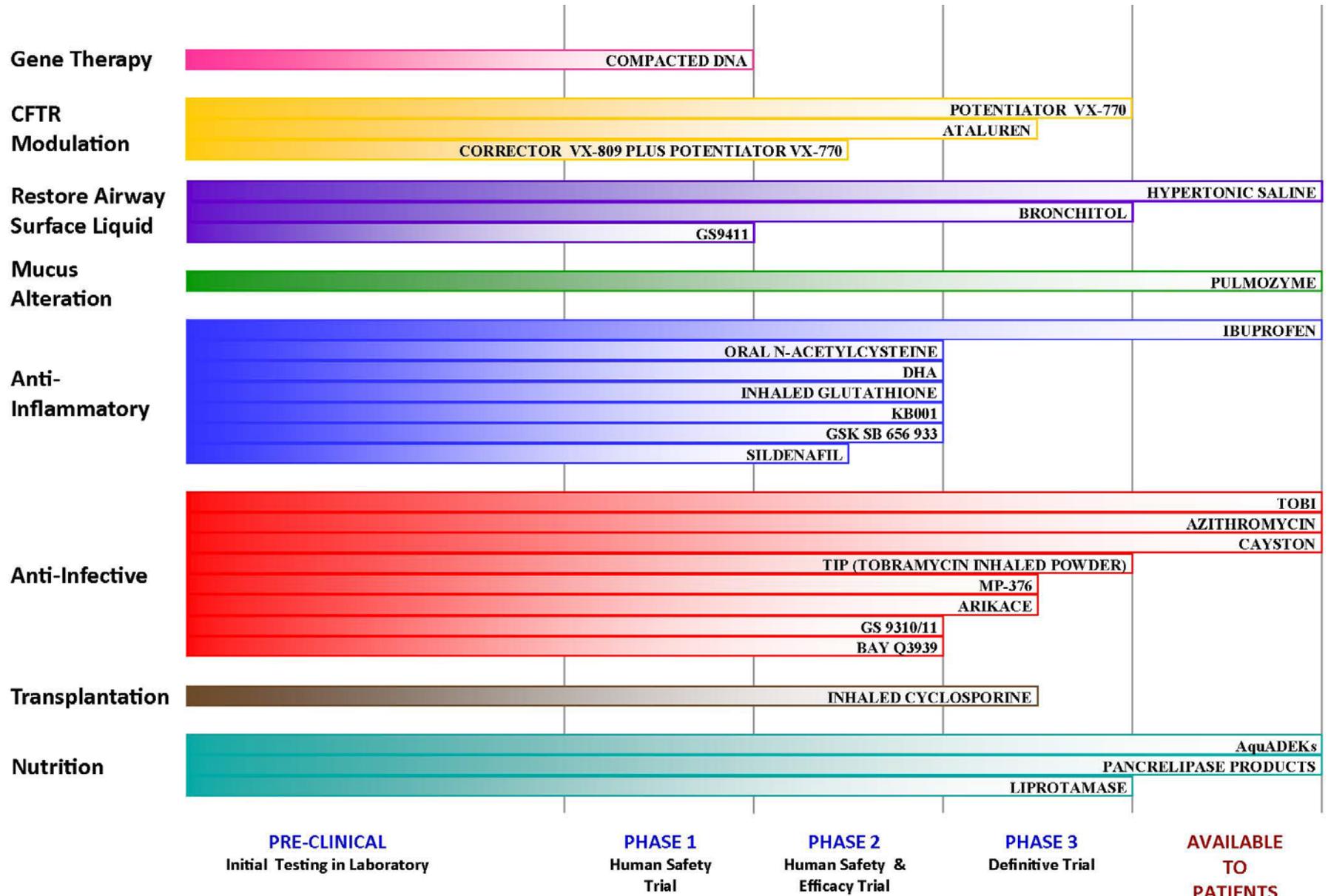
# CF Investments in Research Advance Science

- 1980 - research development program established
- 1985- CF basic defect described
- 1989- CF gene (CFTR) cloned
- 1990's- CFTR biology advances rapidly
- 2005- CFTR consortia funded as Manhattan-like projects to focus on CFTR trafficking, structure, and function

Cystic Fibrosis Publications in  
Medical/Scientific Journals



# CYSTIC FIBROSIS FOUNDATION THERAPEUTICS PIPELINE



Slide courtesy of Preston W. Campbell, MD, CF Foundation. Used with permission

# Key Points

## #1 NH data contribute to scientific foundation upon which drug development programs can be built

- Rational, scientifically-based drug development requires an understanding of the disease
- NH describes the disease - independent of individual investigational agents
- Most informative when NH study data are available early in development
  - Ideally before design of efficacy trials

## #2 Patient and caregiver involvement is important

- Engage all stakeholders early and on an ongoing basis

## Key Point #3



- Monolith<sup>10</sup> (**mon** •uh •lith)
  - an obelisk, column, large statue, etc., formed of a single block of stone
  - Something having a uniform, massive, redoubtable, or inflexible quality or character

<sup>10</sup>dictionary.com

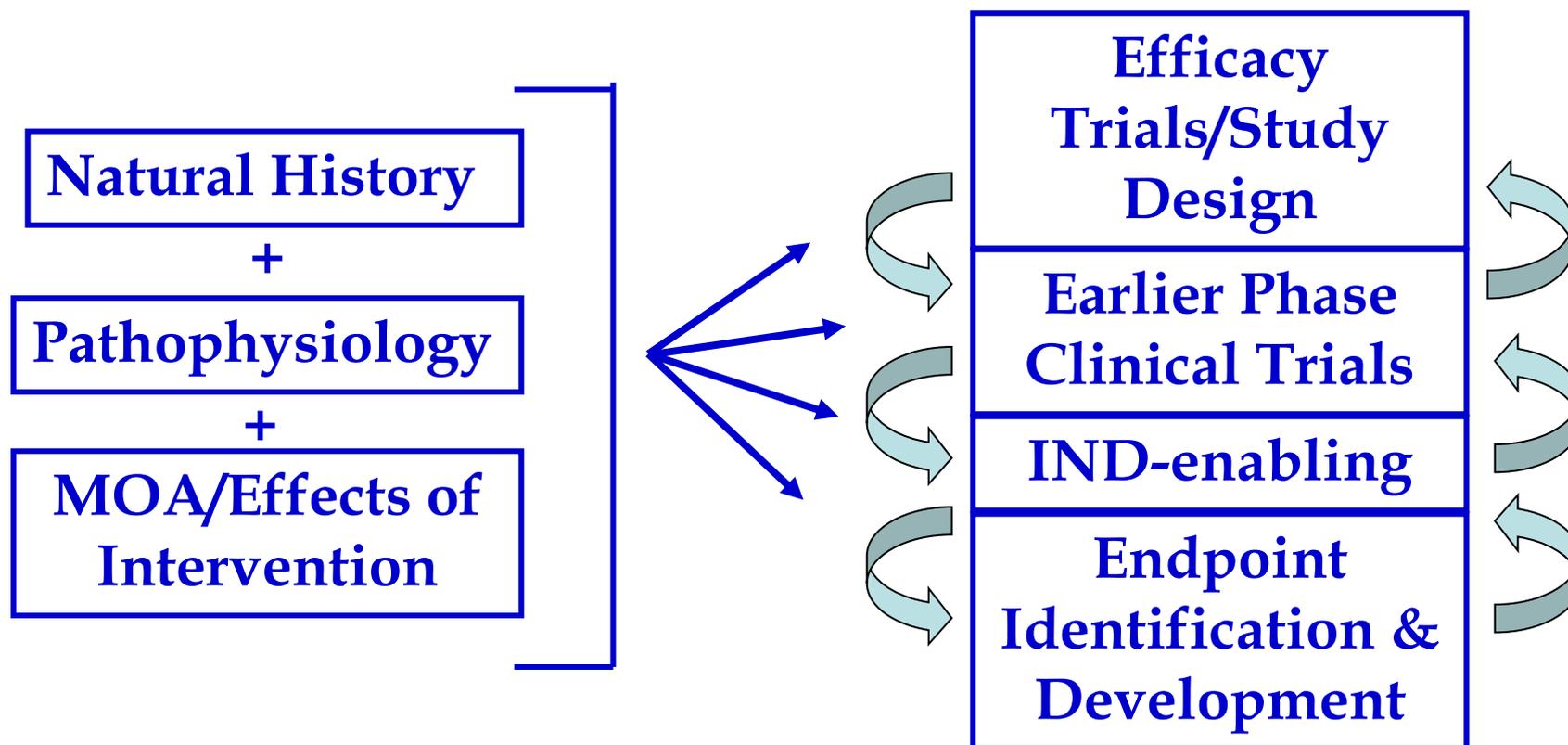
Rare diseases are a highly diverse collection of disorders

- Design and conduct of clinical development programs are highly individualized
- Dependant on disease and population under study, understanding of the intervention and its expected impact on the disease

# Key Points #4

Drug development as a continuum

Efficiency ≠ corner-cutting



# Questions?

