REGULATORY FITNESS IN RARE DISEASE CLINICAL TRIALS

A Workshop by the
FDA's Center for Drug Evaluation & Research and
NIH's National Center for Advancing Translational Sciences

May 16-17, 2022

WELCOME REMARKS

Kerry Jo Lee, MD

Associate Director for Rare Diseases

Division of Rare Diseases and Medical Genetics

CDER, FDA

WELCOME REMARKS

Philip John (PJ) Brooks, PhD

Acting Director

Division of Rare Diseases Research Innovation

National Center for Advancing Translational Sciences, NIH

SESSION 1: APPROACH TO DEMONSTRATING SUBSTANTIAL EVIDENCE OF EFFECTIVENESS FOR RARE DISEASE DRUG PRODUCTS

Moderator: Sheila Farrell, M.D.,
Medical Officer, DRDMG, ORPURM,
OND, CDER, FDA

Approach to Demonstrating Substantial Evidence of Effectiveness for Rare Disease Drug Development: Overview Considerations

FDA CDER & NIH NCATS Regulatory Fitness in Rare Disease Clinical Trials Workshop

May 16, 2022

Janet Maynard, MD, MHS

Director

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)

Office of New Drugs | Center for Drug Evaluation and Research | FDA

Disclosure

- This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred

- The materials presented are available in the public domain

Outline

- Regulatory framework
- Rare disease progress and challenges
- Rare disease trial design proposals
  - Common problems or limitations
  - Recommendations
- Innovation in drug development

FDA's Center for Drug Evaluation and Research (CDER)

- Making sure safe and effective drugs are available to improve the health of people in the United States

https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder

"To be approved for marketing, a drug* must be safe and effective for its intended use."**

"Effective" is codified in statute:

- Demonstrates "substantial evidence that the **drug will have the effect** it purports or is represented to have under proposed labeled conditions of use" (21 CFR 314.125, 21 CFR 314.126)
- A drug's effect must be clinically meaningful to patients

"Safe" can be interpreted as the determination that a drug's **benefits outweigh its risks for drug's intended use**

- Safety is considered in relation to the **condition treated, the efficacy purported, and ability to mitigate risk**

*For simplicity, the term "drug" is used in this presentation to mean both drugs and biologics

**http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf
Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products--Guidance for Industry

Regulatory Framework: Benefit-Risk

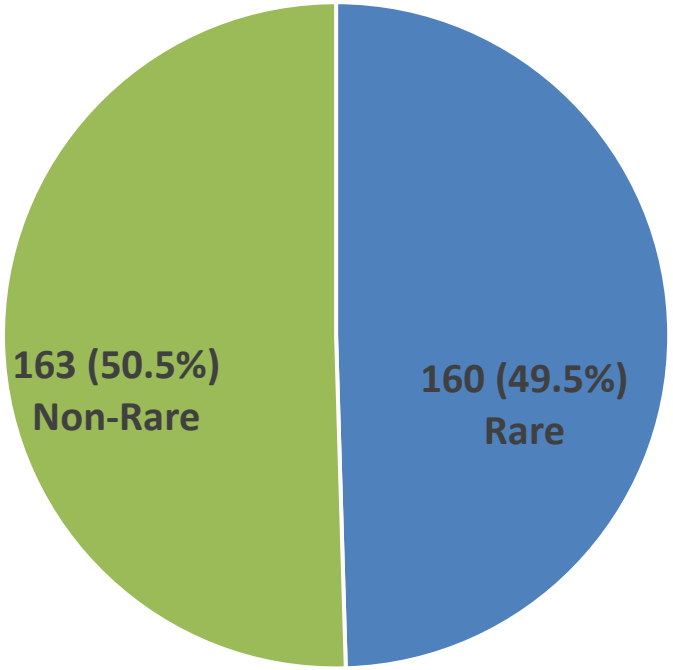
Evaluation of the demonstrated benefits and risks of a medical product, and

Making an informed **judgment** as to whether the expected benefits outweigh the potential risks associated with its expected use

Benefit-Risk Assessment for New Drug and Biological Products—Guidance for Industry

Rare Disease Progress

Total CDER Novel Drug Approvals 2015-2021



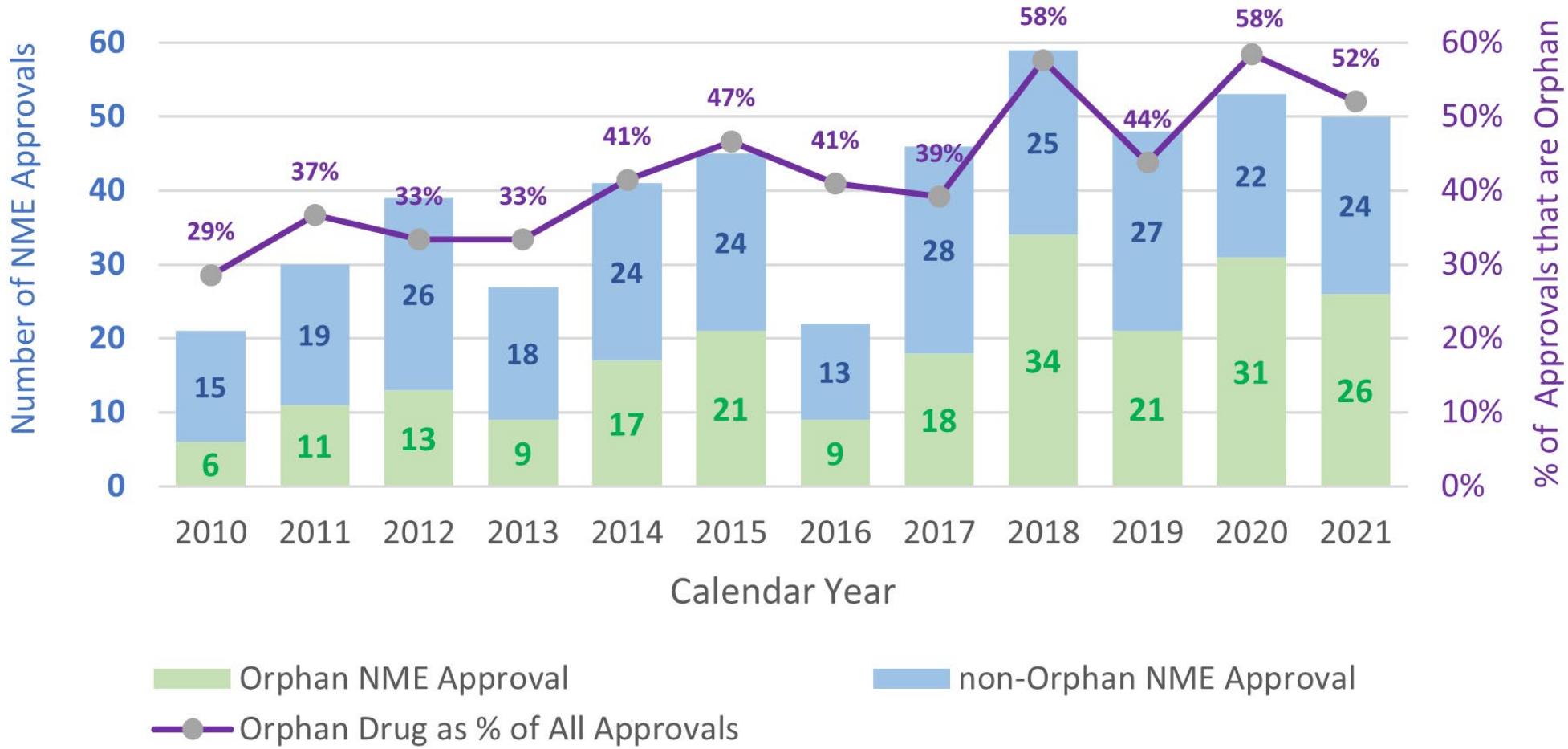
and… Over 600 treatments for rare diseases have been FDA-approved since the passage of the Orphan Drug Act (1983)

but… ~7,000 rare diseases

Vast majority do not have approved treatments

https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products
https://www.fda.gov/industry/developing-products-rare-diseases-conditions

Proportion of CDER Novel Drug Approvals that are Orphan



NME=New Molecular Entity

Rare Disease Product Development

- Rare disease product development is challenging
  - Requires multiple strategies and collaboration to facilitate optimal rare disease product development

Some Common Challenges in Rare Disease Drug Development

- Small and sometimes very small patient populations
- Genotypic/phenotypic heterogeneity within a disease
- Natural history often poorly understood
- Often serious/life-threatening, progressive, childhood onset
- Reluctance, at times, to randomize to placebo
- Lack of drug development tools (e.g., established efficacy endpoints)
- Limited, if any, regulatory precedent
- Incorporating regulatory flexibility while upholding regulatory standards

Substantial Evidence of Effectiveness

- Defined in the statute as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof"

The FD&C Act section 505(d) (21 U.S.C. § 355(d))

Key Features of "Adequate and Well-Controlled Investigations"

- Clear statement of study objectives
- Design that permits a valid comparison with a control
- Adequate assurance that subjects have the condition being studied
- Adequate measures to minimize bias of subjects, observers, and data analysts and assure comparability of treatment groups
- Well-defined methods for assessing treatment response
- Analysis of study results adequate to assess the effects of the drug

21 CFR 314.126

Common Problems or Limitations of Rare Disease Trial Design Proposals

- Nonrandomized design when a randomized trial is feasible and ethical
- Significant biases (e.g., external control, lack of blinding) that cannot be adequately overcome in the specific drug development program
- Limited understanding of the disease natural history to inform trial design, including study population, trial duration and endpoints
- Inadequate dose exploration
- Trial too short to detect a treatment effect for a slowly progressive disease
- Poorly chosen endpoint or heterogeneous disease with no single endpoint measuring benefit well
- Diet not optimized/standardized for diseases that require dietary management

Common Problems or Limitations of Rare Disease Trial Design Proposals

- Nonrandomized design when a randomized trial is feasible and ethical

These types of problems can lead to suboptimal, inefficient trial designs and/or biases

As a result, the trial may fail to detect a treatment effect that exists or may show a treatment effect when there isn't one

- Diet not optimized/standardized for diseases that require dietary management

Rare Disease Trial Design Recommendations: General Considerations

- Understand the disease natural history as early and comprehensively as possible
- Utilize trial designs that are designed to meet their stated objectives
- We encourage early and frequent interaction with the FDA review division
- Await FDA's review and comments before initiating a pivotal trial
- Minimize uncertainties that we can control (e.g., ensure excellent trial conduct)

Rare Disease Trial Design Recommendations: Rare Disease Stakeholders

- Patients, families, and stakeholders can provide key elements that can enable research and drug development for a disease
  - Helping bring together patients and families to engage academic scientists
  - Supporting the development of natural history studies and registries
    - Can provide both natural history data and facilitate future patient enrollment into clinical trials
  - Working with patient advocacy groups and organizations to help facilitate engagement of other stakeholders, such as industry and academia, that may be interested in working on the disease
  - Setting up Patient-Focused Drug Development meetings or Patient Listening Sessions to develop greater clarity on what matters to patients with the disease

Rare Disease Trial Design Recommendations: Randomization and Blinding

- Randomization and blinding are critical features for reducing bias
  - Should be the default approach if feasible and ethical
  - Essential for detecting small, but clinically meaningful effects
  - Important for subjective or effort-dependent endpoints
  - Can use trial design approaches to minimize placebo exposure
    - Dose-response, delayed start, randomized withdrawal, crossover designs
    - Adaptive design with pre-specified interim analyses
    - Master protocols
    - Unequal randomization
    - Rescue criteria

Rare Disease Trial Design Recommendations: Nonrandomized Controls

- Major limitation is bias due to lack of randomization and blinding
  - Are the treatment and control groups comparable?
  - Are the endpoints comparably assessed or impacted by lack of blinding?
  - Is the control group comparable in terms of the concomitant treatments, background standard of care, and endpoints available?
- Consider when
  - Randomization is infeasible or unethical
  - The expected treatment effect is large
  - The usual course of the disease is highly predictable
  - There is minimal bias on the endpoint from knowing treatment assignment

Rare Disease Trial Design Recommendations: Other Considerations

- FDA encourages innovative trial designs and creative thinking
  - Some examples:
    - Adaptive designs (e.g., for dose, trial duration)
    - Master protocols
    - Novel approaches to endpoints
  - Regardless of the approach, pre-specified analyses with type I error control are important; avoid data dredging and cherry picking

Innovation in Drug Development

- Select programs and initiatives to facilitate drug development
  - Patient-Focused Drug Development
    - Amplifying the patient voice
  - Guidance documents
  - Model-Informed Drug Development (MIDD) Pilot Program and Complex Innovative Trial Design (CID) Pilot Meeting Program
  - CDER's Rare Diseases Team
  - CDER's ARC Program
    - Accelerating Rare disease Cures

https://www.fda.gov/about-fda/innovation-fda

CDER Patient-Focused Drug Development (PFDD)

- Establishing the therapeutic context is an important aspect of benefit-risk assessment
  - Patients are uniquely positioned to inform understanding of this context

- PFDD is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation

- PFDD efforts include:
  - FDA-led PFDD Meetings
  - Externally-led PFDD Meetings
  - PFDD Methodological Guidance Series
  - Clinical Outcomes Assessment (COA) Grant Program

https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

Guidance Documents

- FDA's current thinking on a particular subject
  - Context of drug development
    - Intended to assist the pharmaceutical industry / academics in the development of drug products for the treatment of a specific disease or type of disease
    - Establishes expectations for drug approval / development
- Not a roadmap
  - Development programs have unique considerations
    - Thus, can use alternative approaches if the approach satisfies the requirements of the applicable statutes and regulations

http://www.fda.gov/RegulatoryInformation/Guidances/

Select Recent Cross-Cutting Guidances

- Real-World Data: Registries
  - Real-World Data: Assessing Registries to Support Regulatory Decision Making for Drug and Biological Products
- "N of 1" Therapies
  - IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations
  - IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Chemistry, Manufacturing, and Controls Recommendations
  - IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations
  - Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases

CID and MIDD Pilot Meeting Programs

- CID Pilot Meeting Program
  - Support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs
- MIDD Pilot Program
  - Facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, referred to as MIDD approaches

https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program
https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program

CDER's Rare Diseases Team

- **Mission**: To facilitate, support, and accelerate the development of drugs and therapeutic biologics for rare diseases
- A multi-disciplinary team located in the Division of Rare Diseases and Medical Genetics in ORPURM
- Select activities:
  - Providing advice to other review divisions on their rare disease programs
  - Promoting rare disease consistency across CDER's Office of New Drugs (OND)
  - Leading cross-cutting OND rare disease guidances, policies, strategic research, and workshops
  - Developing rare disease training and education
  - Engaging with internal and external stakeholders

Vision

Speeding and increasing the development of effective and safe treatment options addressing the unmet needs of patients with rare diseases.

Mission

CDER's Accelerating Rare disease Cures (ARC) Program drives scientific and regulatory innovation and engagement to accelerate the availability of treatments for patients with rare diseases.

https://www.fda.gov/drugs/CDERARC

Conclusions

- Development of safe and effective new drugs is central to FDA's mission
- Rare diseases are challenging, engage with FDA early and often
- Learn as much about the rare disease as possible to optimize trial design
- Ensure the pivotal trial(s) are "adequate and well-controlled"
- Collaboration is key to facilitating rare disease drug development


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Demonstrating Substantial Evidence of Effectiveness

CDER-NCATS Rare Disease Workshop
May 16, 2022

Jennifer Rodriguez Pippins, MD, MPH
Office of New Drug Policy
Office of New Drugs
Center for Drug Evaluation and Research

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

History

- Between 1938 and 1962, drug manufacturers were required to show only that their drugs were safe

- Concern in Congress grew about misleading and unsupported claims being made by pharmaceutical companies

- 1962 Drug Amendments (Kefauver-Harris) included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence" before approval

Effectiveness Requirement

- A new drug application (NDA) can be rejected if, among other reasons, there is:

  *"…a **lack of substantial evidence** that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; …" (21 U.S.C. § 355(d))*

Statutory Standard for SEE

- Substantial evidence is defined as:

*"evidence consisting of **adequate and well-controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" (21 U.S.C. § 355(d))*

Statutory Standard for SEE

- Before this standard, it was not unusual for manufacturers to cite clinical experience, case series, etc.

- Requiring adequate and well-controlled (A&WC) investigations as the only basis for concluding effectiveness was novel

- Plural of "investigations": Generally interpreted as requiring at least 2 A&WC trials, each convincing on its own, to establish effectiveness – "*independent substantiation*"

Statutory Standard for SEE

- The 1997 Food and Drug Modernization Act (FDAMA) amended statute to specifically allow a single trial and confirmatory evidence (CE) to establish SEE:

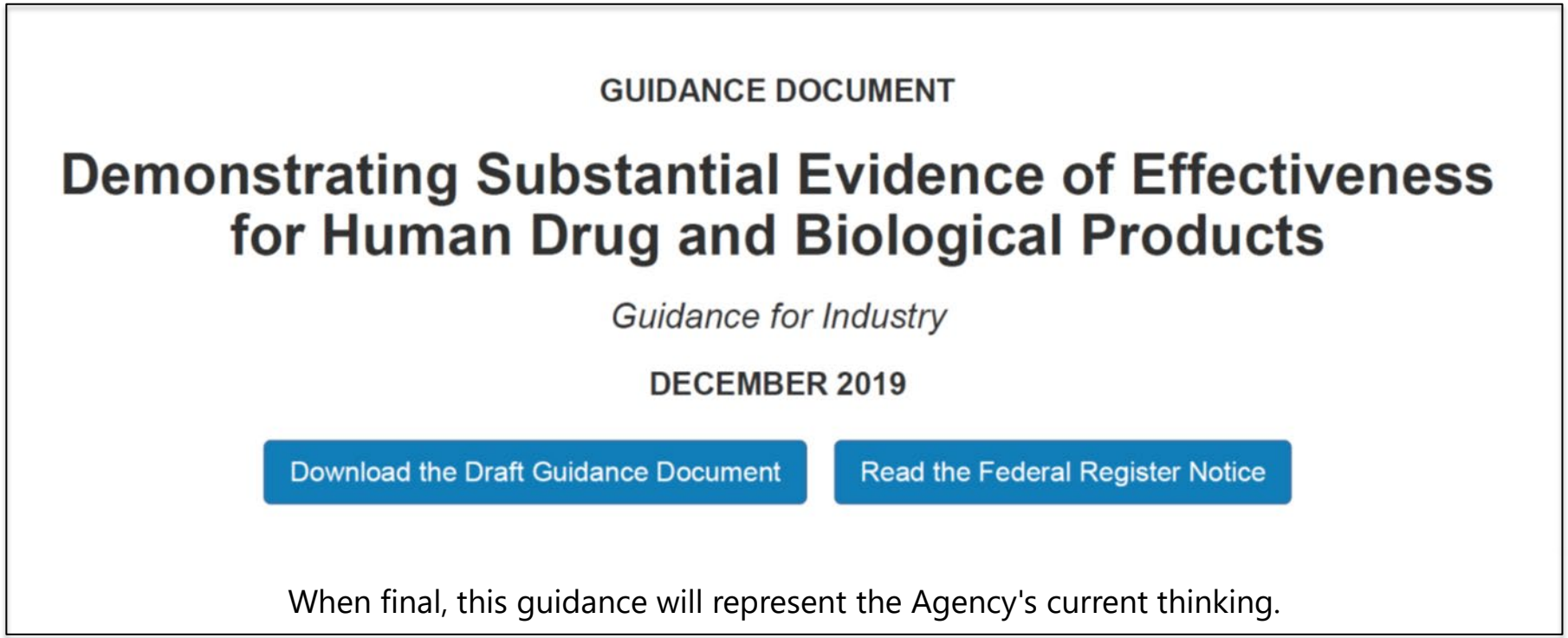
*"If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and **confirmatory evidence** (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." (21 U.S.C. § 355(d))*

Statutory Standard for SEE

- Confirmatory evidence provides substantiation of/support for the results of the single trial, thereby limiting the possibility of a false conclusion of effectiveness

- FDAMA does not define CE

2019 Effectiveness Guidance



GUIDANCE DOCUMENT

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Guidance for Industry

DECEMBER 2019

Download the Draft Guidance Document | Read the Federal Register Notice

When final, this guidance will represent the Agency's current thinking.

Demonstrating SEE

Substantial Evidence of Effectiveness

Adequate & Well-controlled Clinical Investigations

1 Adequate & Well-controlled Clinical Investigation PLUS Confirmatory Evidence

Demonstrating SEE

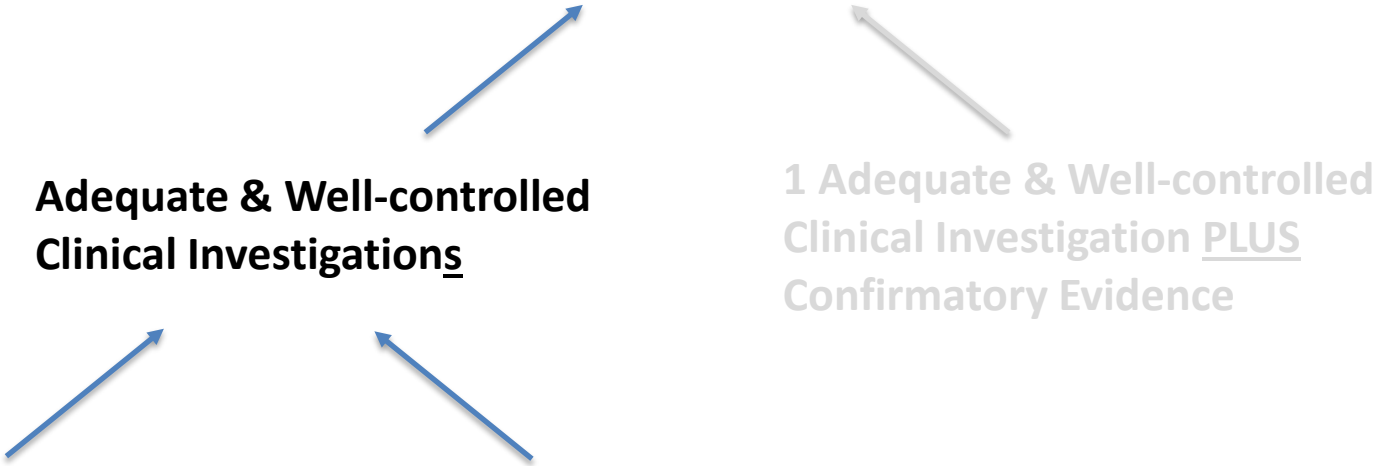
Substantial Evidence of Effectiveness

Adequate & Well-controlled Clinical Investigations

1 Adequate & Well-controlled Clinical Investigation PLUS Confirmatory Evidence

Demonstrating SEE

Substantial Evidence of Effectiveness



2 A&WC Trials

- A second trial provides substantiation of results
- Substantiation doesn't necessarily mean replication
  - Two positive trials with differences in design and conduct may be more persuasive (and more informative) than two identical trials
  - Examples:
    - Two trials that use the same endpoint but enroll somewhat different study populations within the same proposed indication
    - Two trials for the same disease using different (but related) endpoints could provide additional information about a drug's effect
- A trial in any "phase" of drug development may be A&WC

1 Large, Multicenter Trial

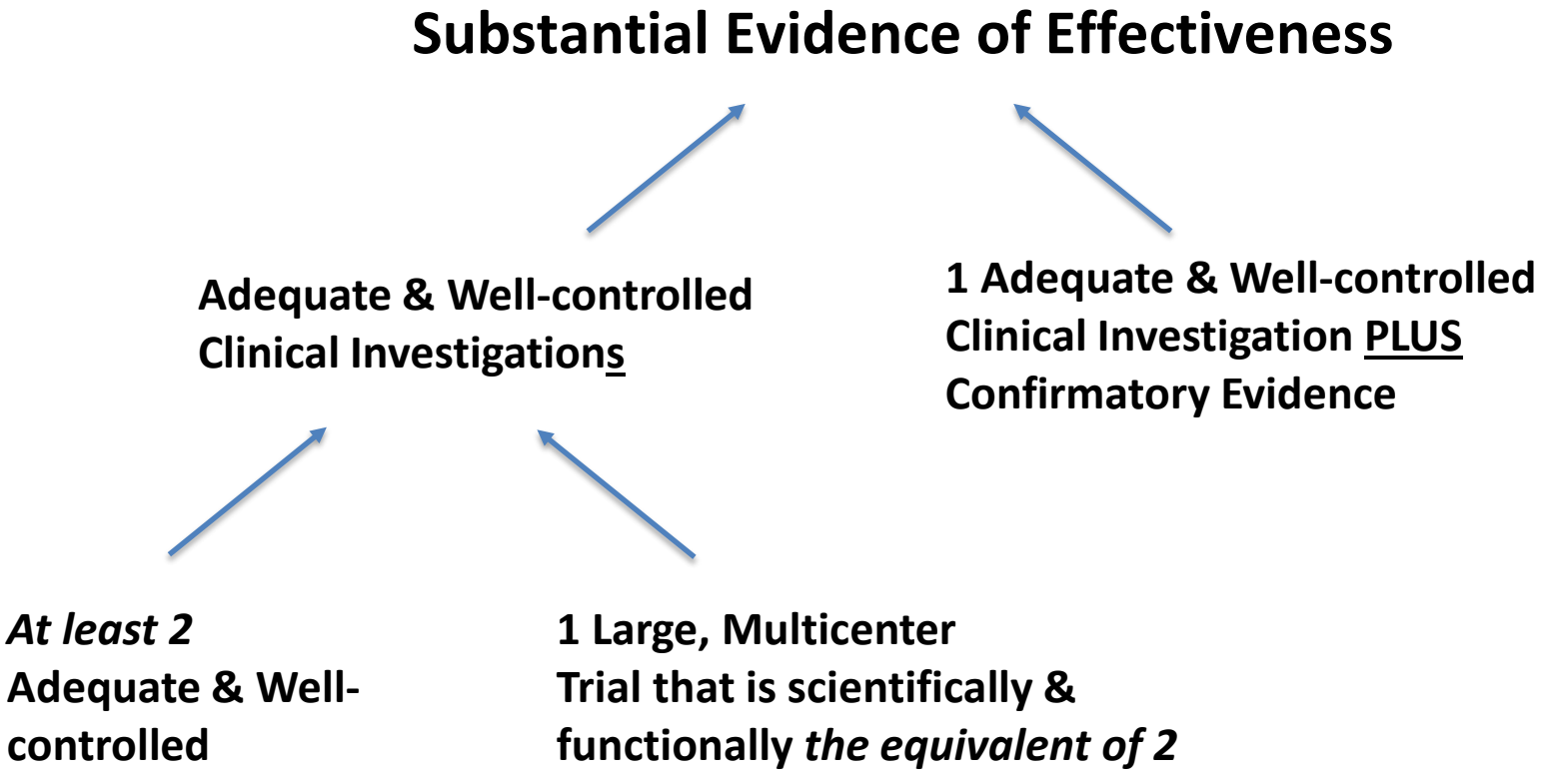
- The single trial (without CE) approach to demonstrating SEE is not specifically described in statute
- Guidance provides the rationale:

  "In general, substantiation of a drug's effectiveness obtained with two trials…will provide more convincing evidence of effectiveness than would a single trial. In some circumstances, however, there may not be a meaningful difference between the strength of evidence provided by a single large multicenter A&WC trial and that provided by two smaller A&WC trials. ***In such cases, the large multicenter trial can be considered, both scientifically and legally, to be, in effect, multiple trials and can be relied on to provide substantial evidence of effectiveness****."*
- This scenario is considered to be a subset of the 2 A&WC trials approach

1 Large, Multicenter Trial

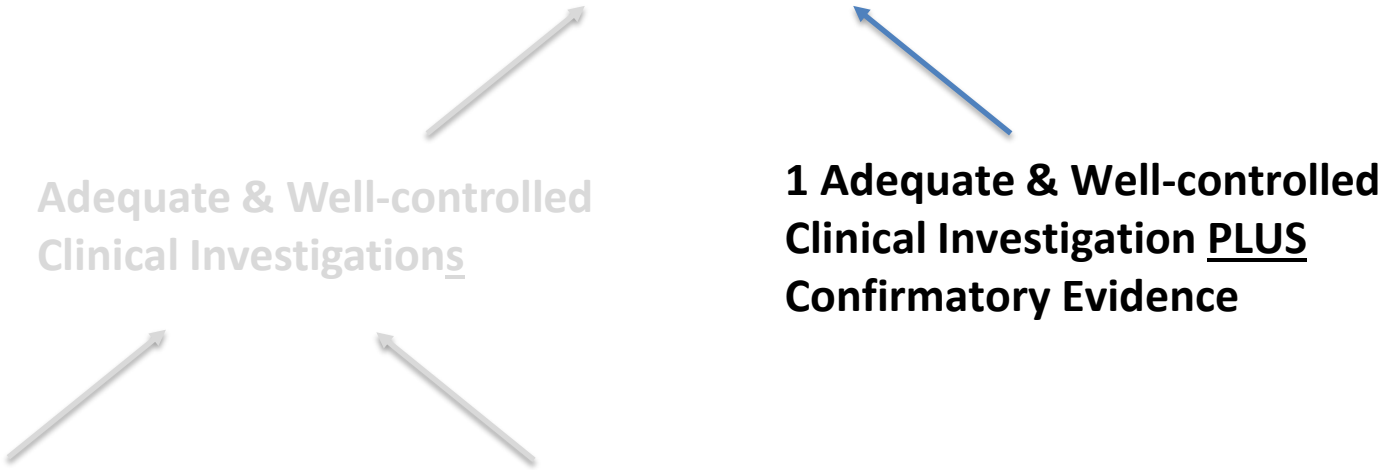
- Reliance on 1 large, multicenter trial should generally be reserved for when:
  - Trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe/irreversible morbidity, or prevention of a disease with a potentially serious outcome
  - Second trial would be impracticable/unethical
  - Results not driven by any single site
  - Consistent effects on distinct prospectively specified endpoints
  - Consistent across important patient subgroups
- Trial conduct should be thoroughly examined
- Findings from other trials that are not consistent could weaken the overall strength of evidence

Demonstrating SEE



Demonstrating SEE

Substantial Evidence of Effectiveness



1 Trial + Confirmatory Evidence

- FDA may determine that 1 A&WC trial + CE constitutes substantial evidence of effectiveness
- CE provides substantiation of results from the single A&WC trial
- Guidance identifies factors FDA will consider when making such a determination:
  - Persuasiveness of single trial, robustness of CE, disease considerations, whether it is ethical/practicable to conduct a second trial
- Sponsors considering a 1+CE approach to establishing effectiveness should discuss with the Agency

1 Trial + Confirmatory Evidence

- Examples of types of CE include:
  - Clinical trial data for the drug in a closely related indication
  - Mechanistic data
  - Additional data from the natural history of disease
  - Scientific knowledge about the effectiveness of other drugs in the same class

Flexibility

- Statutory standard of "substantial evidence" includes an element of expert judgment:
  - *"evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could **fairly and responsibly be concluded** by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" (21 U.S.C. § 355(d))*
  - *"**If [FDA] determines**, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." (21 U.S.C. § 355(d))*

Flexibility

- Regulation describes flexibility in applying the statutory standard:
  - *"… While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs* ***demand flexibility in applying the standards****. Thus FDA is required to* ***exercise its scientific judgment*** *to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards. FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy." 21 (CFR 314.105(c))*

Examples of When Additional Flexibility May Be Warranted

- For example, FDA may “fairly and responsibly” rely on study designs that produce less certainty in some circumstances

- Longstanding awareness that in certain settings a somewhat greater risk of a false positive conclusion, i.e., less certainty about effectiveness, may be acceptable when balanced against the risk of rejecting or delaying marketing of an effective therapy

- In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness

Examples of When Additional Flexibility May Be Warranted

- Life-threatening/severely debilitating conditions with unmet need

- Rare disease

- Flexibility may be warranted with respect to:
  - *Trial design*
  - *Trial endpoints*
  - *Number of trials*
  - *Statistical considerations*

Summary

- Statute requires that substantial evidence of effectiveness be demonstrated

- There are different approaches to demonstrating SEE
  - 2 A&WC trials
  - 1 large, multicenter trial that is the equivalent of 2
  - 1 A&WC trial + CE

- Statute and regulation describe the role of flexibility
  - Flexibility can be demonstrated by choice of trial design, endpoints, number of trials, and statistical considerations
  - Flexibility may be particularly relevant in the setting of life-threatening/severely debilitating disease with unmet need and rare disease

Role of Translational Science in Rare Disease Drug Development

Jeffrey Siegel, MD

Office Director

Office of Drug Evaluation Sciences (ODES)

OND / CDER / FDA

Regulatory Fitness in Rare Disease Clinical Trials

May 16, 2022

Introduction

- Translational science plays a key role in rare disease drug development
- Translational work, e.g., biomarkers, may not fulfill its potential in drug development unless the discovery phase is followed by adequate analytic and clinical validation
- Partnering with drug developers, consortia can allow translational science discoveries to fulfill their potential in drug development

BEST Resource: Biomarkers, EndpointS, and Other Tools

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:

- Biomedical scientists
- Translational and clinical researchers
- Medical product developers
- Patient/disease advocacy groups
- Government officials
- Clinicians

BEST (Biomarkers, EndpointS, and other Tools) Classification: Range of Biomarker Types

- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**

Measures of disease presence and status

- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measure aspects of response to treatment

BEST (Biomarkers, EndpointS, and other Tools) Classification: Range of Biomarker Types

- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**

Measures of disease presence and status

- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measure aspects of response to treatment

BEST (Biomarkers, EndpointS, and other Tools) Classification: Range of Biomarker Types

- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**

Measures of disease presence and status

- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measure aspects of response to treatment

BEST (Biomarkers, EndpointS, and other Tools) Classification: Range of Biomarker Types

- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**
- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measures of disease presence and status

Measure aspects of response to treatment

BEST (Biomarkers, EndpointS, and other Tools) Classification: Range of Biomarker Types

- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**

Measures of disease presence and status

- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measure aspects of response to treatment

CONSIDERATIONS FOR BIOMARKER UTILITY

Context of Use (COU): 1) BEST biomarker category and 2) how the biomarker impacts the clinical trial or drug development program

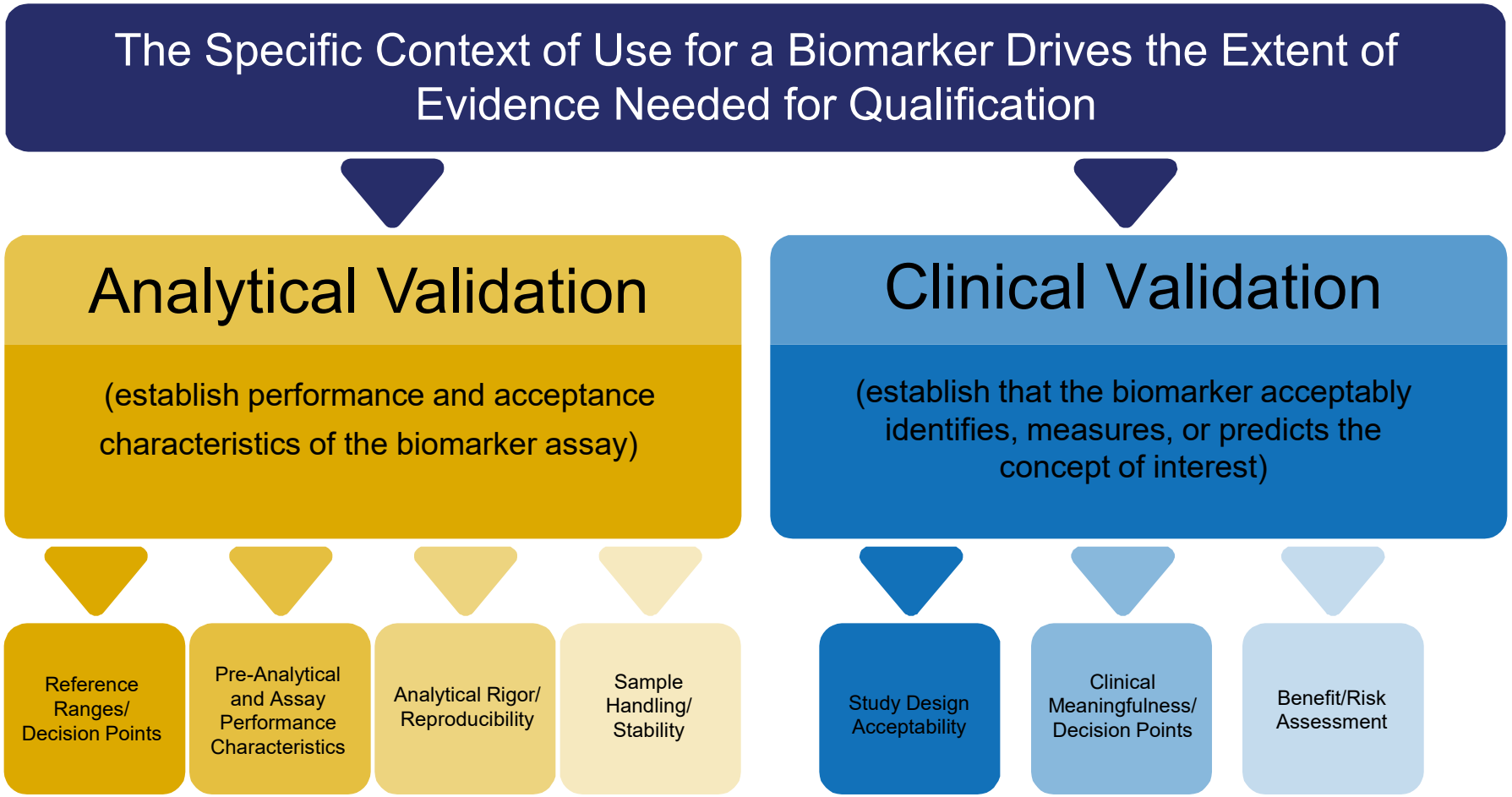
What question is the biomarker intended to address. Examples include:

- Inclusion/exclusion criteria for prognostic or predictive enrichment?
- Alter treatment allocation based on biomarker status?
- Result in cessation of a patient's participation in a clinical trial because of safety concern?
- Result in adaptation of the clinical trial design?
- Establish proof of concept for patient population of interest?
- Support clinical dose selection for first in human or Phase 3 studies?
- Evaluate treatment response (e.g. pharmacodynamic effect)?
- **Support regulatory acceptability of a surrogate endpoint for accelerated or traditional approval?**

"Total Kidney Volume, measured at baseline, is a prognostic enrichment biomarker to select patients with ADPKD at high risk for a *progressive decline* in renal function (defined as a confirmed 30% decline in the patient's estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and baseline eGFR as an enrichment factor in these trials."[1]

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf

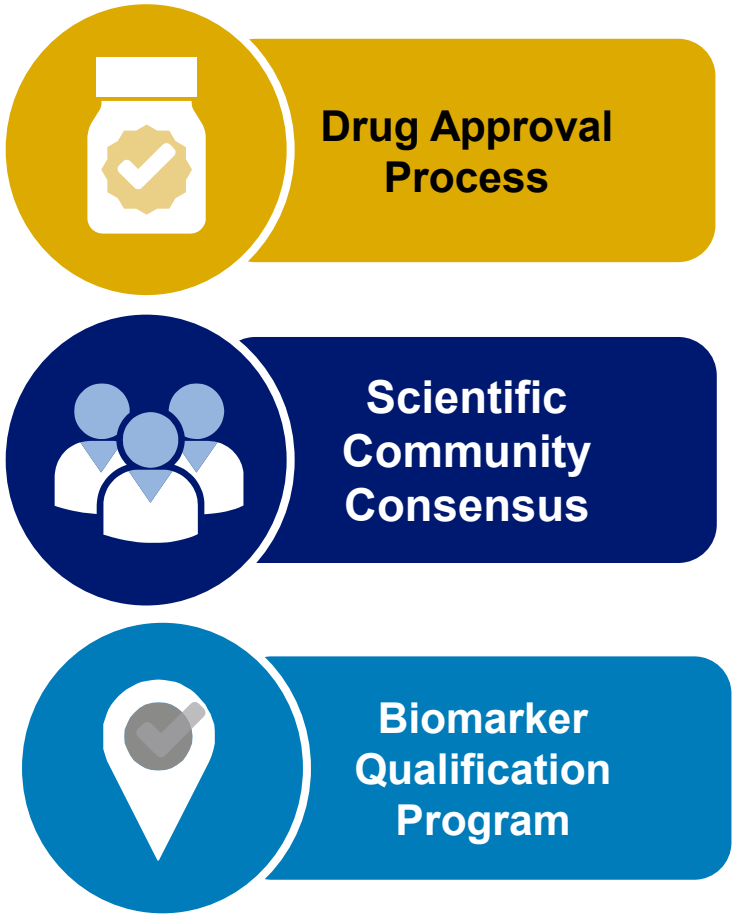
ANALYTICAL ASSAY AND CLINICAL VALIDATION CONSIDERATIONS IN BIOMARKER QUALIFICATION



Role of Translational science beyond biomarkers

- One of the approaches to demonstrating Substantial Evidence of Effectiveness described in the FD&C Act is with 1 adequate & well-controlled (A&WC)clinical investigation and confirmatory evidence (CE)
- When a drug is anticipated to be approved based on a single A&WC, there is a need for Confirmatory Evidence (CE)
- CE may take many forms, some of which involve translational evidence:
  - **Clinical Evidence from a Related Indication**
  - **Mechanistic Evidence**
  - **Pharmacodynamic Evidence in Humans**
  - **Evidence from a Relevant Animal Model**
  - **Natural History Evidence**
  - **Real-World Evidence**
  - **Evidence from Expanded Access Use of an Investigational Drug**

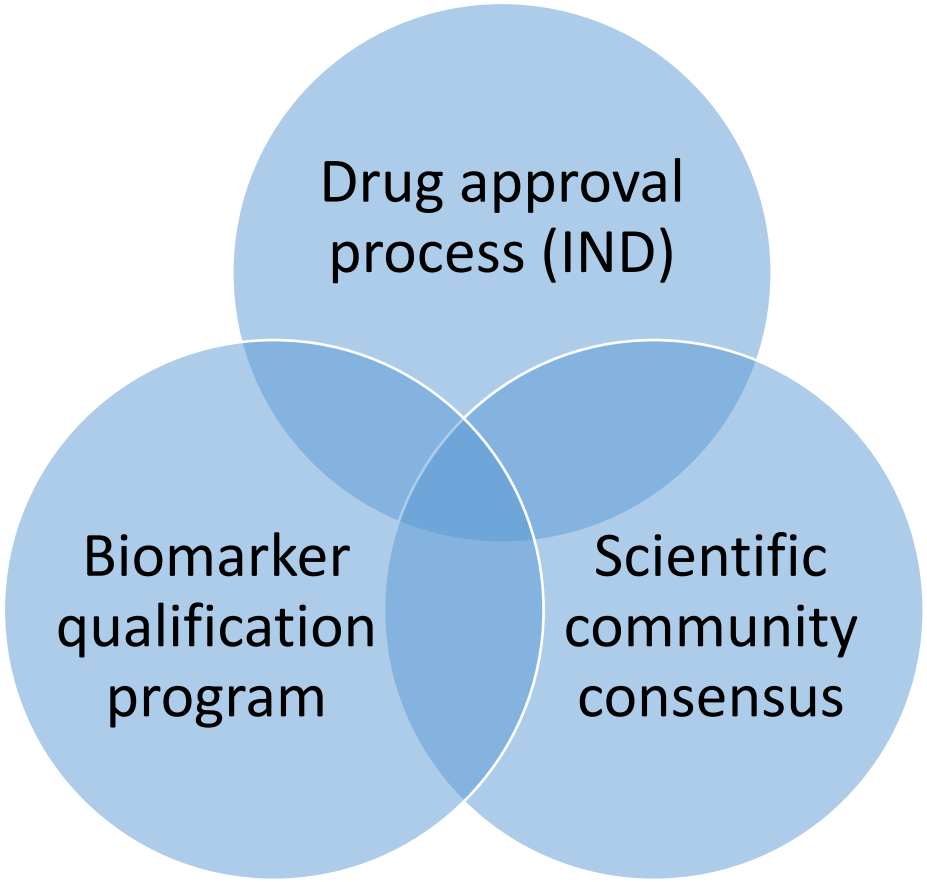
BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

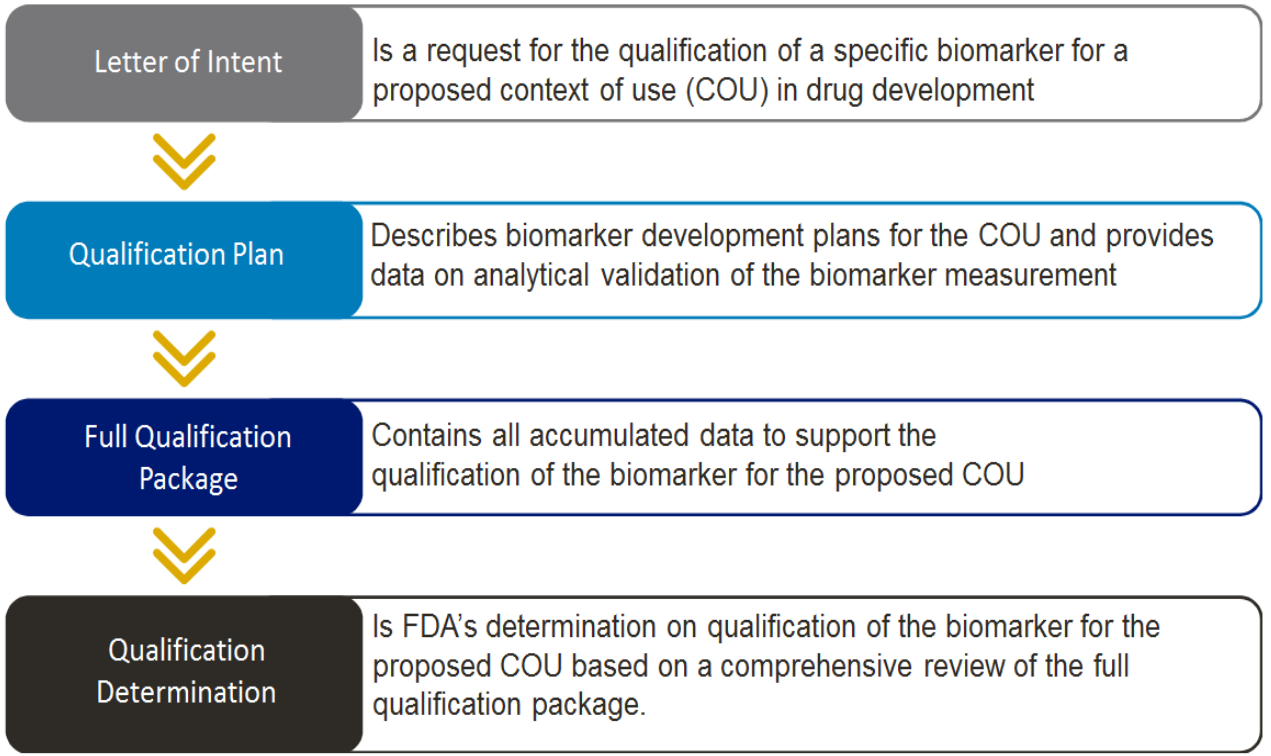
Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

INTERCONNECTED PATHS TO BIOMARKER VALIDATION



BIOMARKER QUALIFICATION AND 21ST CENTURY CURES DDT LEGISLATION

Biomarker Qualification Process

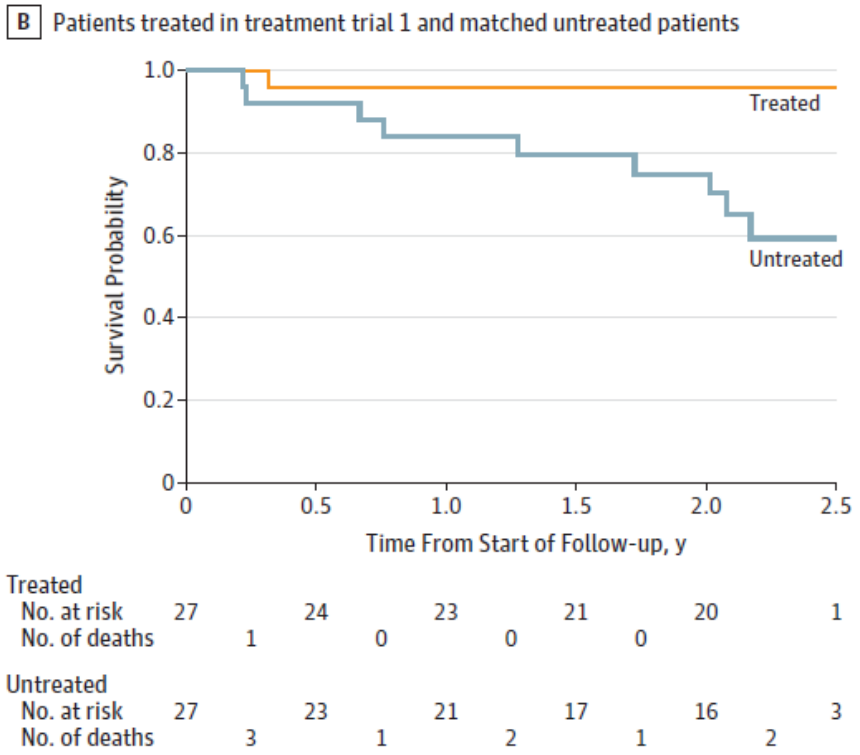


Example 1: Progeria

- Hutchinson-Gilford progeria syndrome (HGPS) – extremely rare, fatal, autosomal dominant segmental premature aging disease
- Death by heart failure at mean age 14.6 yrs
- Work from Francis Collins lab and colleagues at other institutions identified lamin A as the responsible gene demonstrated in animal models that mutations in lamin A gene phenocopied HGPS
  - Persistent farnesylation of lamin A causes damage as cells age
- Inhibitors of farnesylation ameliorate disease in animal models, including lonafarnib

Translational science contributions to developing effective therapy for HGPS

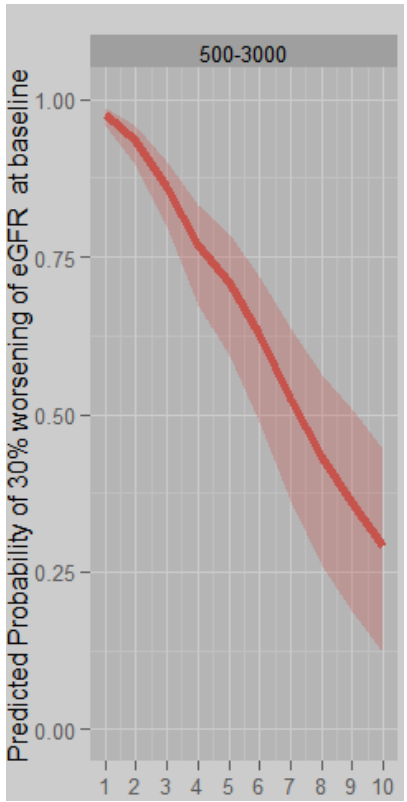
- Discovery of causal mutation
- Discovery of causal pathway
- Animal model recapitulated human disease
- Effective treatment identified in animal model → human clinical trials



Example 2: AD-PKD

- Consortium developed model relating TKV to progression of renal disease in autosomal dominant PKD (AD-PKD):
  - TKV progression model (continuous model endpoint over time)
  - Survival model (time-varying probability of reaching a 30% decline in eGFR)
  - Including covariates such as baseline eGFR and age

Age	TKV	Follow-Up Period	1-Probability of 30% Worsening of eGFR		
			Median	Lower	Upper
Baseline age=30yrs	Baseline TKV 1.7L	1	0.98	0.96	0.99
		2	0.93	0.90	0.96
		3	**0.86**	0.80	0.90
		4	0.77	0.67	0.83
		5	0.71	0.59	0.79
		6	0.63	0.49	0.72
		7	0.52	0.36	0.64
		8	0.43	0.26	0.56
		9	0.36	0.19	0.51
		10	0.29	0.12	0.45



Adapted with permission from Critical Path Institute

Progression of TKV biomarker for PKD

- Initially qualified as prognostic biomarker based on modeling results
- Subsequently applied in individual drug development programs
- Data supported acceptance by FDA review division as reasonable likely SE for accelerated approval

Importance of partnerships

- Qualification of biomarkers is highly resource-intense
- Academic groups may not have funds or necessary data to qualify biomarkers for regulatory decision-making
- Public-private partnerships like FNIH, Critical Path Institute can play important role
  - Intermediary between patient groups, industry, academia, regulators to develop novel DDT's
  - Key role is to collect trial data, share biosamples, integrate datasets, analyze and share data
  - Public workshops offer opportunity for all stakeholders to share views
- Biomarker developers may want to seek partnership with drug developers to assist in analytic validation/clinical validation and incorporating the candidate biomarker in prospective clinical trials


FDA
U.S. FOOD & DRUG
ADMINISTRATION

SESSION 1: APPROACH TO DEMONSTRATING SUBSTANTIAL EVIDENCE OF EFFECTIVENESS FOR RARE DISEASE DRUG PRODUCTS

Moderator: Sheila Farrell, M.D.,
Medical Officer, DRDMG, ORPURM,
OND, CDER, FDA

We'll be back after this short break...

SESSION 2: CASE STUDIES — AN ACADEMIC PERSPECTIVE

Moderator: Elizabeth A. Ottinger, Ph.D.,
Deputy Director of Programs &
Head of Project Management, DPI, NCATS, NIH

Hutchinson-Gilford Progeria Syndrome: an ultra-rare disease pathway to drug approval

Regulatory Fitness in Rare Disease Clinical Trials
May 16-17, 2022

Leslie B. Gordon, MD, PhD
The Progeria Research Foundation
Hasbro Children's Hospital & Alpert Medical School of Brown University
Boston Children's Hospital Boston and Harvard Medical School

Faculty Disclosures,
Leslie B. Gordon, MD, PhD

- Volunteer Medical Director, The Progeria Research Foundation

- In-kind donations: Receive medication for Progeria clinical trials from 3 drug companies (names not included at FDA's request) at no cost

- Sources of Funding for Research: The Progeria Research Foundation; FDA


CUTE
TO THE
RE

The Progeria Research Foundation - 1999

Mission

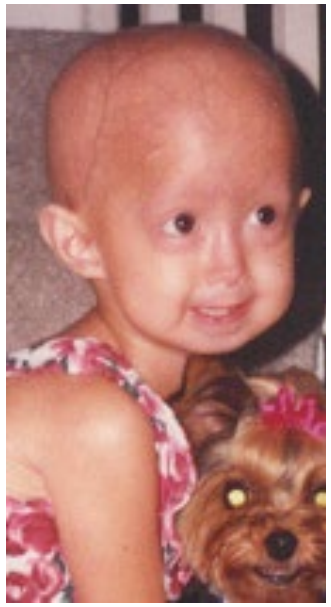
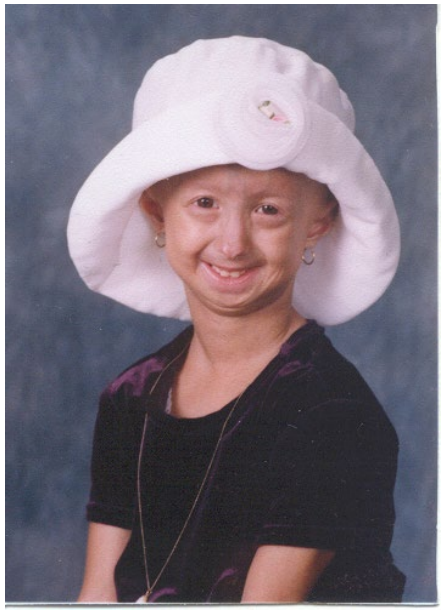
- ❑ Cause
- ❑ Treatment
- ❑ Cure

Together We *WILL* Find The Cure!

www.progeriaresearch.org

Progeria: An Ultrarare Fatal Premature Aging Disease

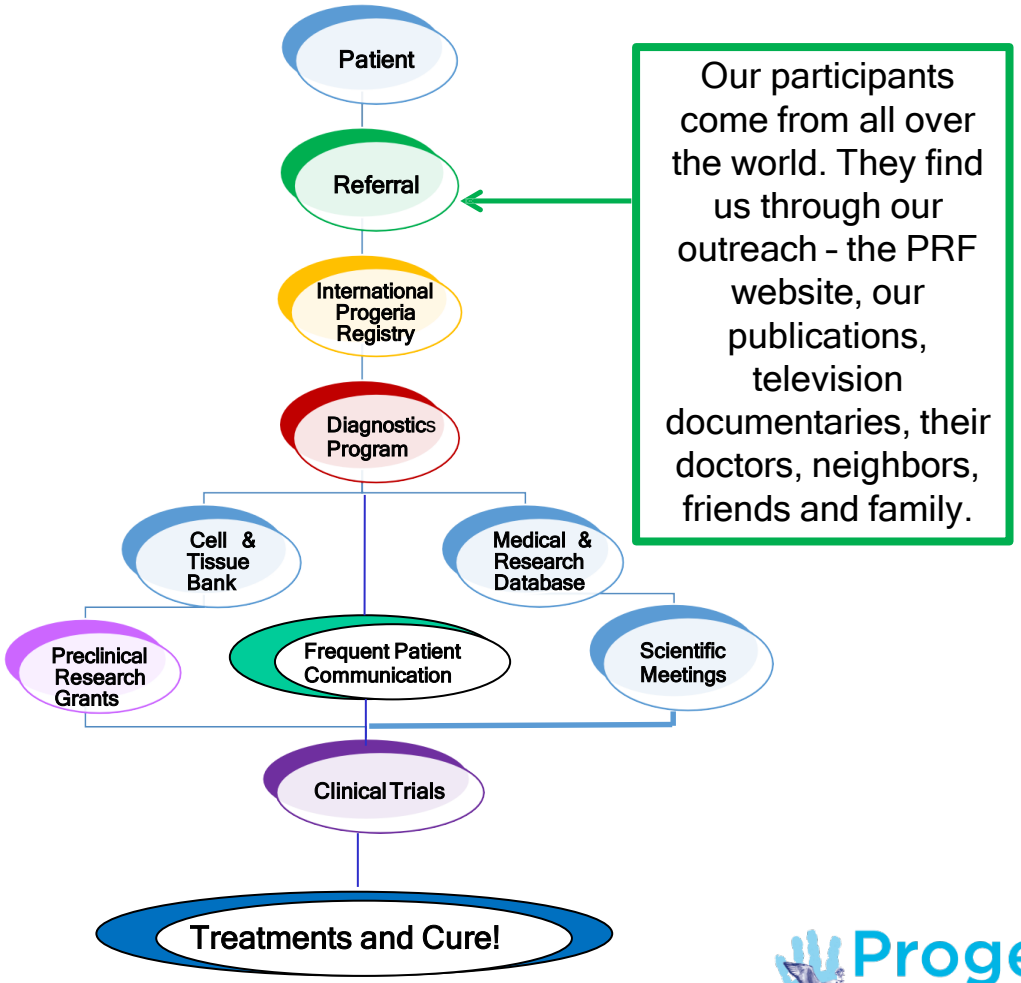


- Segmental “Premature Aging”
- Prevalence 1/20 million
- 19 children in US
- ~400 children worldwide

- Autosomal Dominant
- Lifespan Ave 14.5 yrs.
- Death due to premature atherosclerosis

PRF Programs: It All Starts With The Children



Our participants come from all over the world. They find us through our outreach – the PRF website, our publications, television documentaries, their doctors, neighbors, friends and family.

Progeria Research Foundation
FOR THE CHILDREN ♥ FOR THE CURE

2003 Gene Discovery

letters to nature

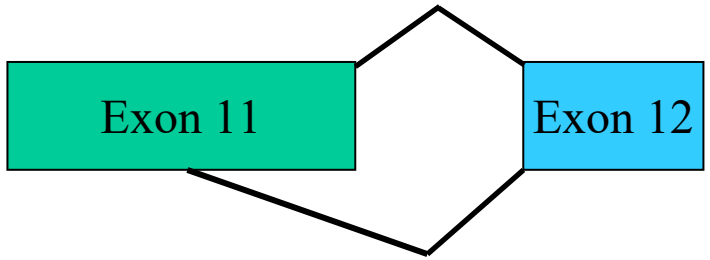
Recurrent *de novo* point mutations in lamin A cause Hutchinson–Gilford progeria syndrome

Maria Eriksson*, W. Ted Brown†, Leslie B. Gordon‡, Michael W. Glynn§, Joel Singer‖, Laura Scott‖, Michael R. Erdos*, Christiane M. Robbins*, Tracy Y. Moses*, Peter Berglund¶, Amalia Dutra*, Evgenia Pak*, Sandra Durkin§, Antonei B. Csoka#, Michael Boehnke‖, Thomas W. Glover§ & Francis S. Collins*

We were catapulted into a new phase…

HGPS is Caused by a Single Base Silent Mutation in the *LMNA* Gene (c.1824 C>T, G608G)

Mutation Optimizes *LMNA* Internal Splice Site



Mutant Splicing

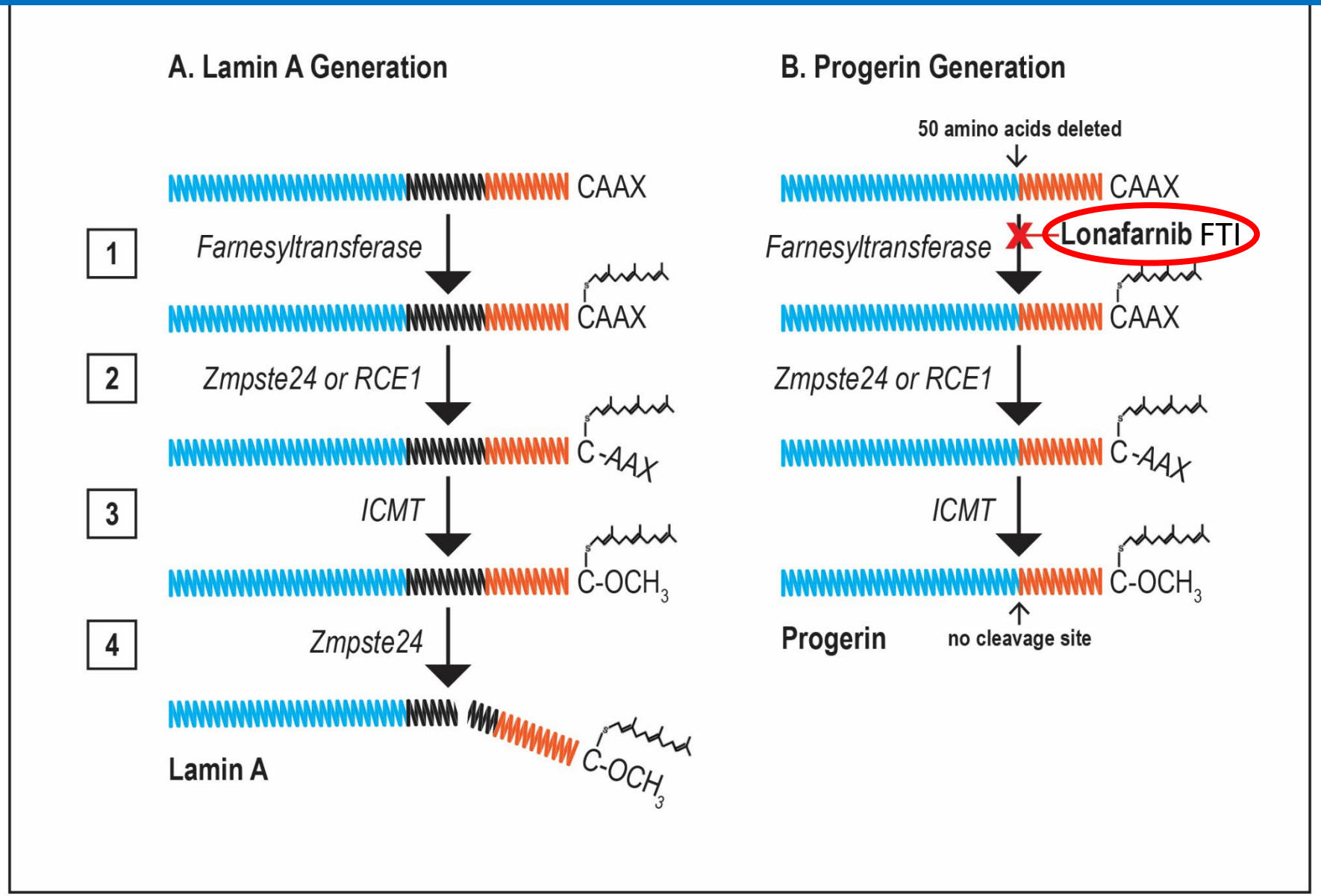
150 bp deletion (50 aa)

"progerin"

Lamin A: Inner Nuclear Membrane Protein

- Lines the inner nuclear membrane-Scaffolding
- Binds chromatin to effect transcription
- Structural and signaling effects
- Expressed by Differentiated Cell Types
- Undergoes post-translational processing that is defective in HGPS due to 50 aa deletion
- Thus, progerin is short, permanently farnesylated and toxic to cells

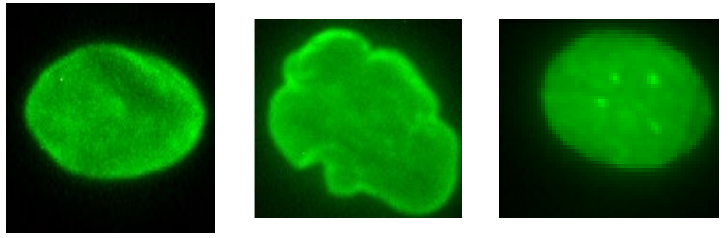
Biology Leads Us To Potential Treatment



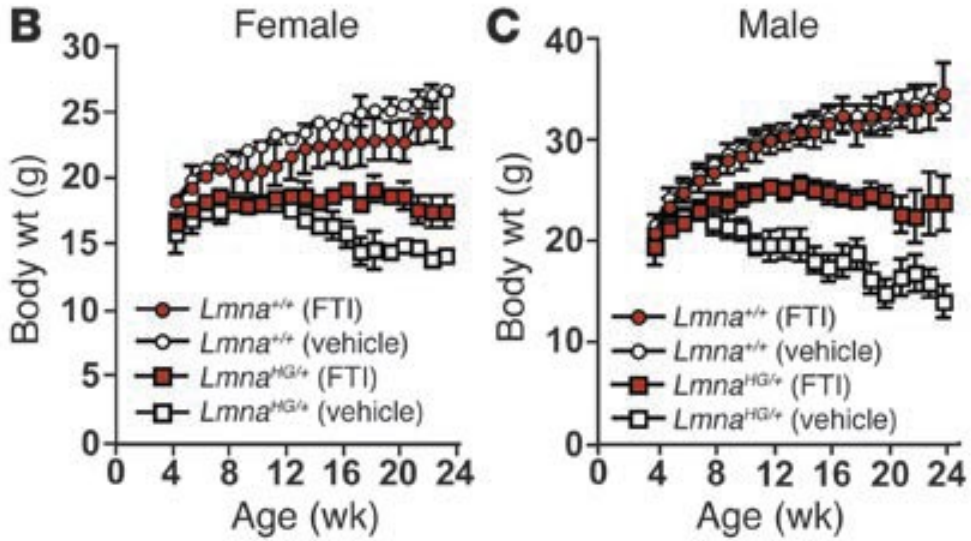
Pre-trial Preclinical Scientific Support for FTIs as Treatment in HGPS

Lonafarnib Normalized HGPS Fibroblasts (Capell et al, 2005)

ABT-100 (a different FTI) Improved Some Disease features in a Zmpste-24 deficient progeroid mouse model (Fong et al, 2006)
And a new HGPS mouse model (Yang et al, 2006)



Normal **HGPS** **HGPS with FTI**



Clinical Keys to First-ever HGPS Treatment Trial

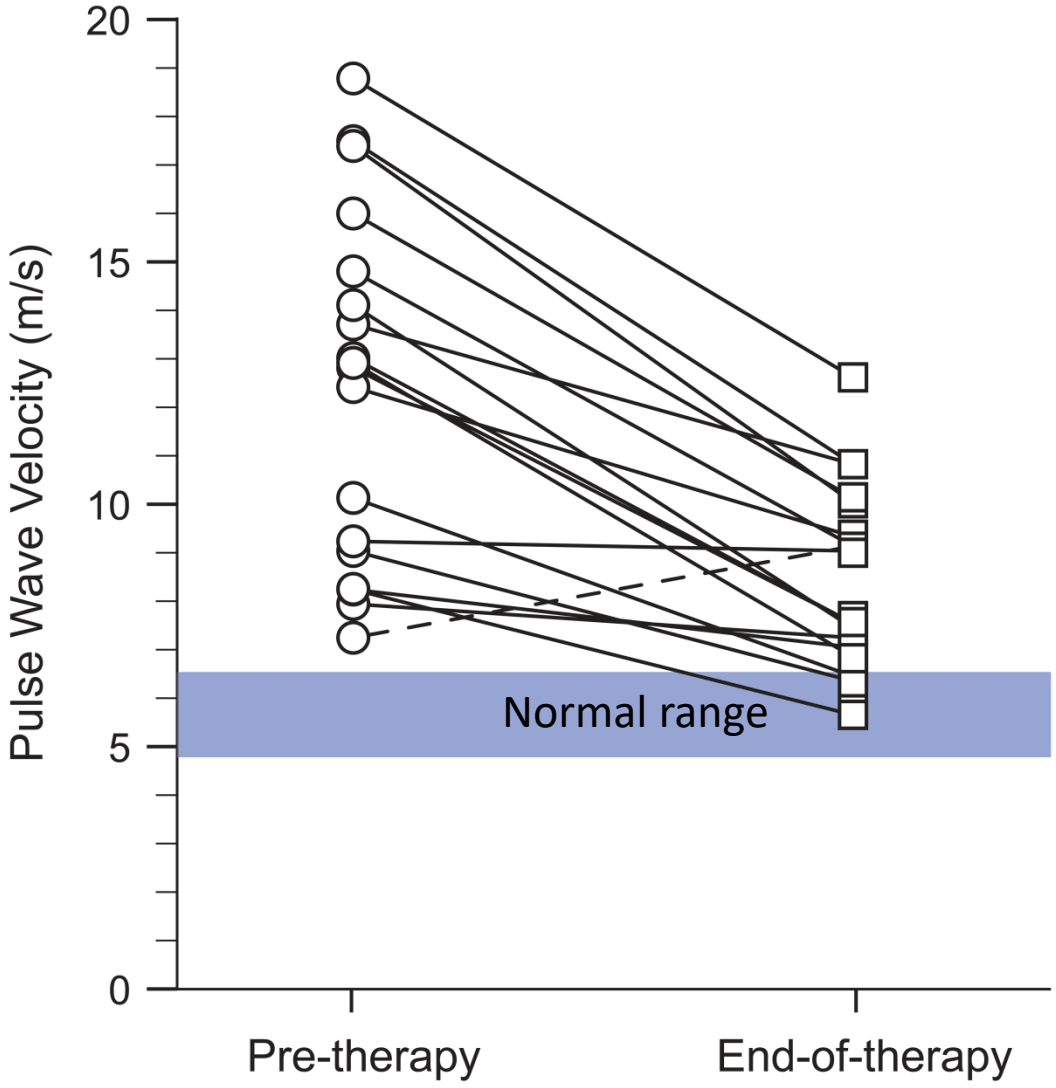
- Lonafarnib was repurposed for HGPS
- Already in clinical trials for children with cancer – MTD established in pediatrics
- PI was running lonafarnib clinical trials for children with brain tumors at DFCI/BCH
- Investigator-initiated trial at Boston Children's Hospital–> FDA did not need to agree to outcome for drug approval
- SPRI agreed to supply drug outside of its pipeline (followed by Merck and then Eiger)

We're Much Better When We're Together!

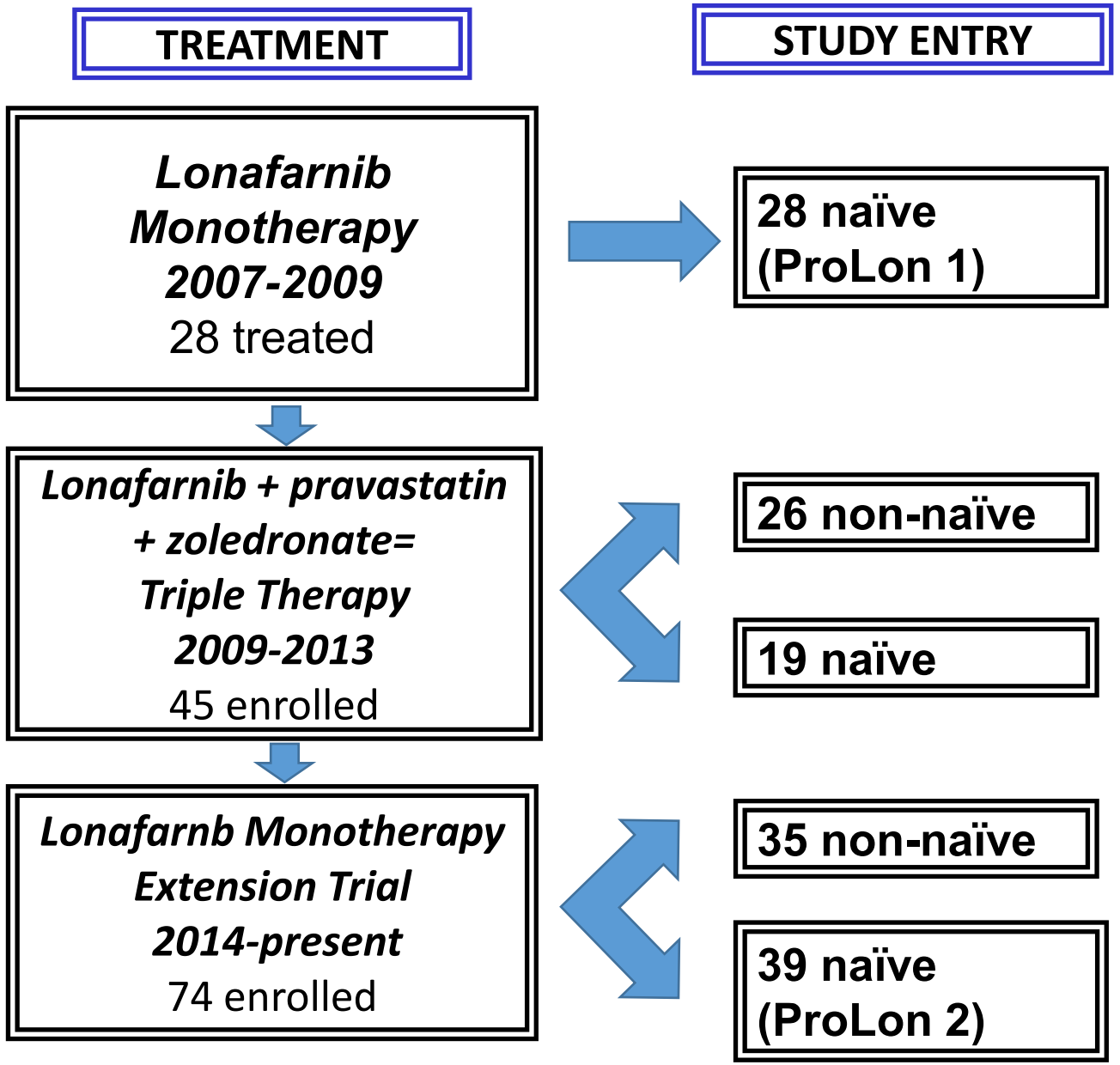
2007-2009: Investigator-inititated Open Label Single Center Trial of Lonafarnib in HGPS and Progeroid Laminopathies

- 28 Children Evaluated
- Improvement in 5 tests and 4 body systems
  1. Rate of weight gain – primary outcome measure
  2. Cardiovascular stiffness- cfPWV and echodensity
  3. Bone Structure
  4. Neurological Hearing
- Other systems remained the same:
  Bone Mineral Density, Fat, Joints, Hair, Dental

Pulse Wave Velocity Improved



- Inversely related to arterial wall distensibility (higher = stiffer vessels)
- Major predictor of adverse coronary events in aging adults
- Decreases of >1 m/s correlated with lower incidence of fatal heart attacks in general population


TREATMENT
STUDY ENTRY
Lonafarnib Monotherapy 2007-2009
28 treated
28 naïve (ProLon 1)
Lonafarnib + pravastatin + zoledronate= Triple Therapy 2009-2013
45 enrolled
26 non-naïve
19 naïve
Lonafarnb Monotherapy Extension Trial 2014-present
74 enrolled
35 non-naïve
39 naïve (ProLon 2)

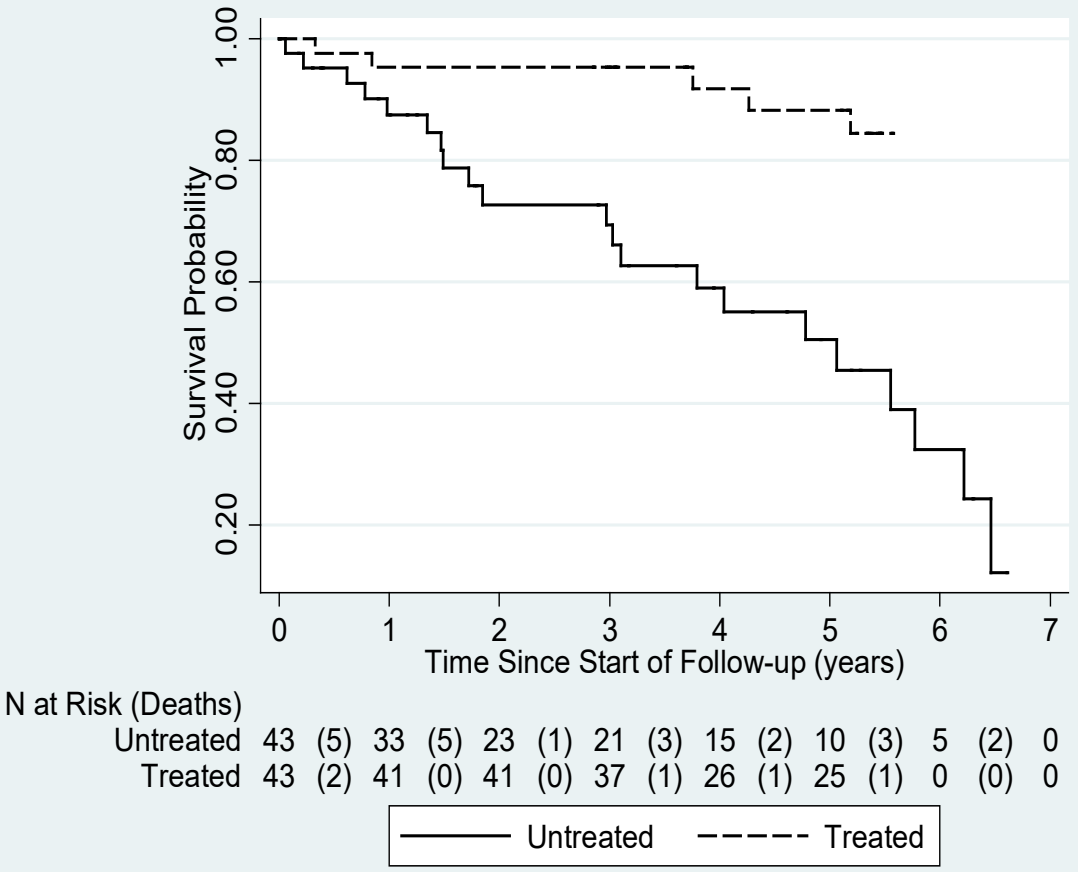
2014: Published survival advantage with lonafarnib therapy combining monotherapy cohorts

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Impact of Farnesylation Inhibitors on Survival in Hutchinson-Gilford Progeria Syndrome
Leslie B. Gordon, Joe Massaro, Ralph B. D'Agostino, Sr., Susan E. Campbell, Joan Brazier, W. Ted Brown, Monica E. Kleinman and Mark W. Kieran

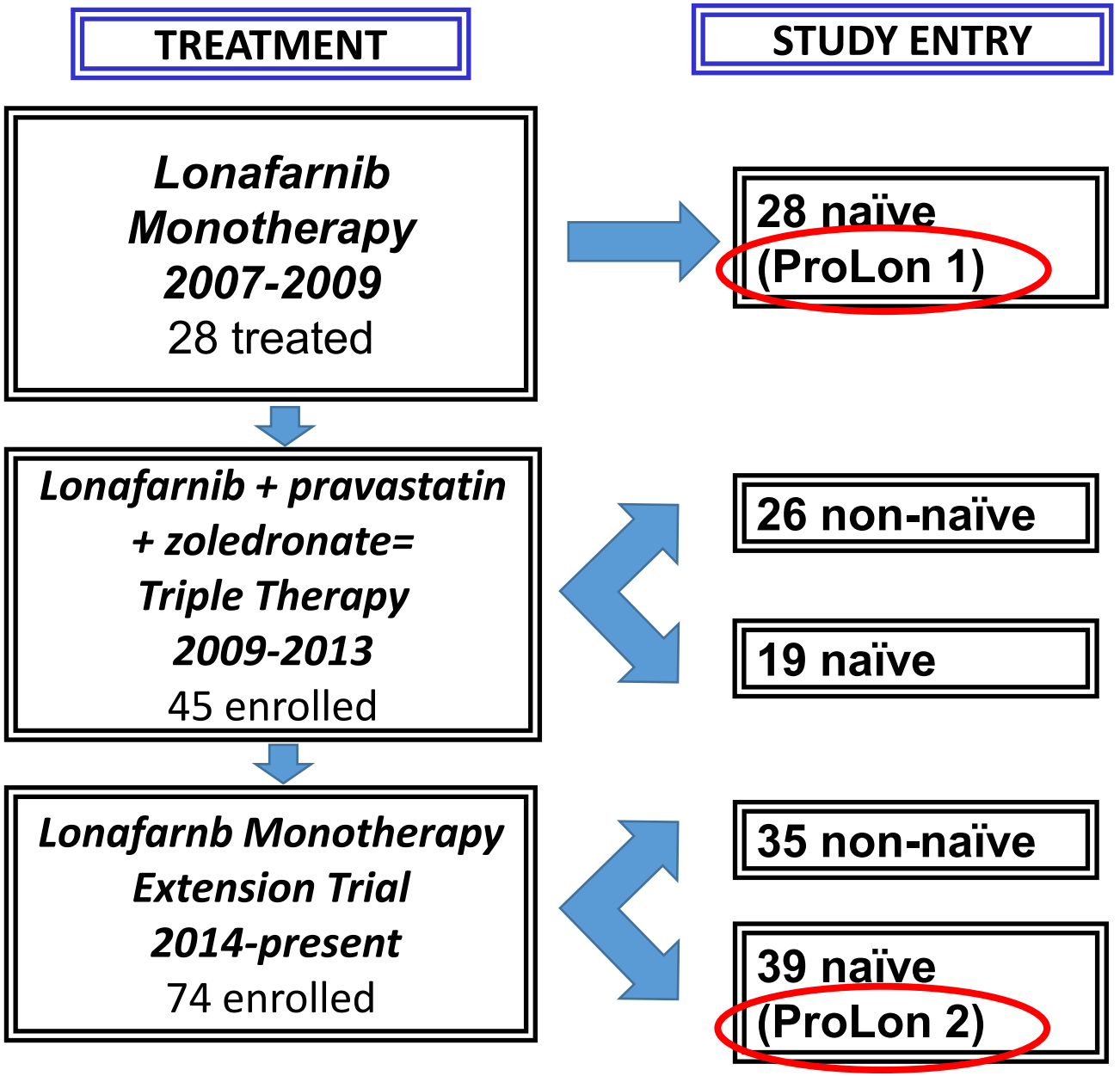
- Not included in trial protocols (open label)
- Used PRF Patient Registry for Controls



FDA Interactions Around Approval-worthy Outcomes

2015: FDA discussion at a meeting conducted in the context of an IND for a combination trial of everolimus + lonafarnib treatment

- discussed acceptable outcomes for drug approval
- cfPWV – not supportable due to 1) strength of data in adults and 2) no data on how cfPWV relates to cardiac outcomes in HGPS
- survival – possibly supportable if only monotherapy examined, not combination therapy

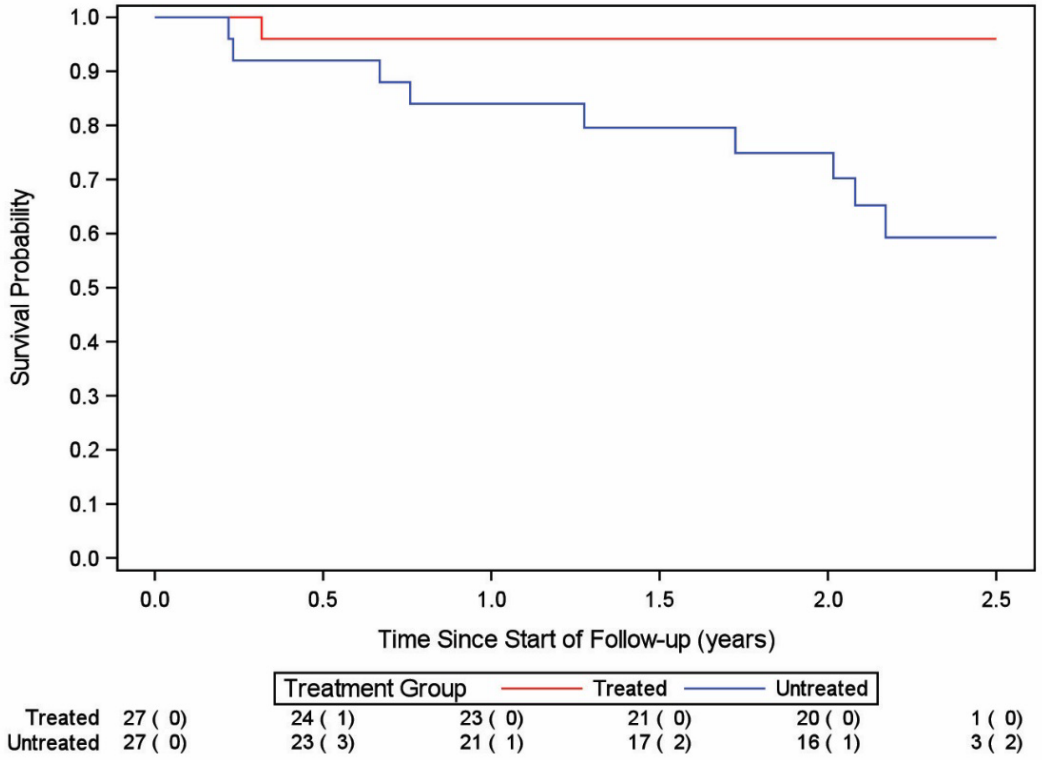

TREATMENT
STUDY ENTRY
Lonafarnib Monotherapy 2007-2009
28 treated
28 naïve (ProLon 1)
Lonafarnib + pravastatin + zoledronate= Triple Therapy 2009-2013
45 enrolled
26 non-naïve
19 naïve
Lonafarnb Monotherapy Extension Trial 2014-present
74 enrolled
35 non-naïve
39 naïve (ProLon 2)

JAMA | Preliminary Communication

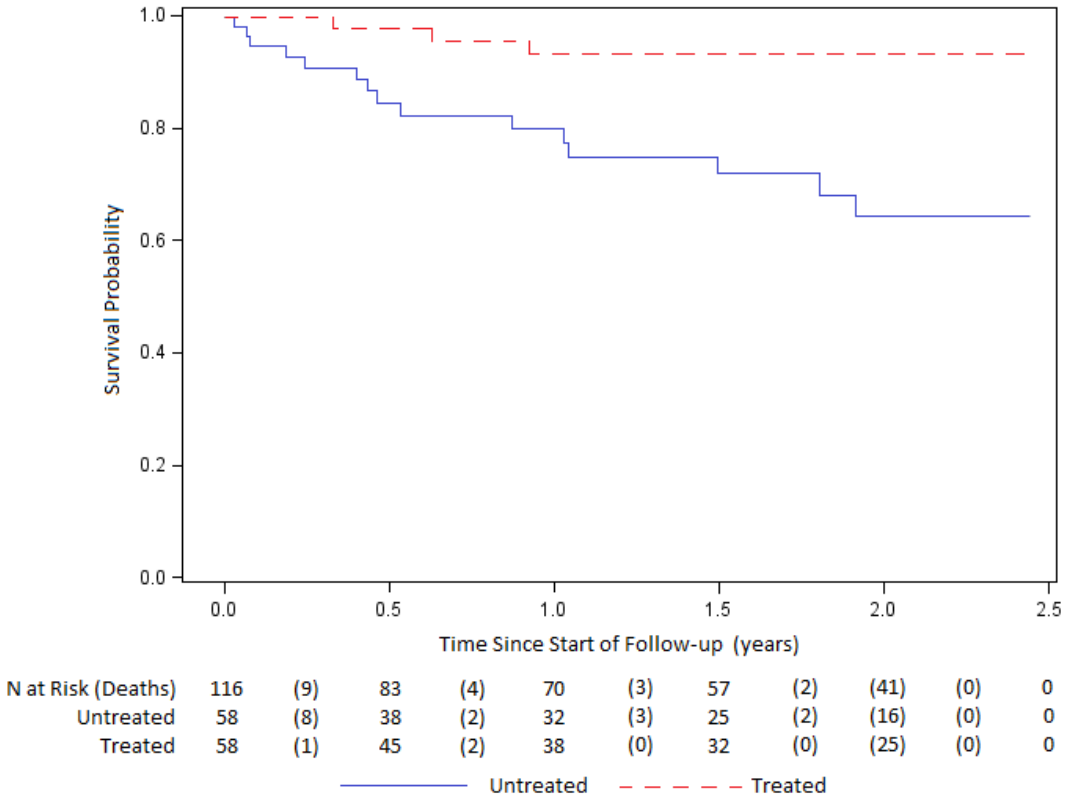
Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome

Leslie B. Gordon, MD, PhD; Heather Shappell, PhD; Joe Massaro, PhD; Ralph B. D'Agostino Sr, PhD; Joan Brazier, MS; Susan E. Campbell, MA; Monica E. Kleinman, MD; Mark W. Kieran, MD, PhD

ProLon1



ProLon1+ProLon2

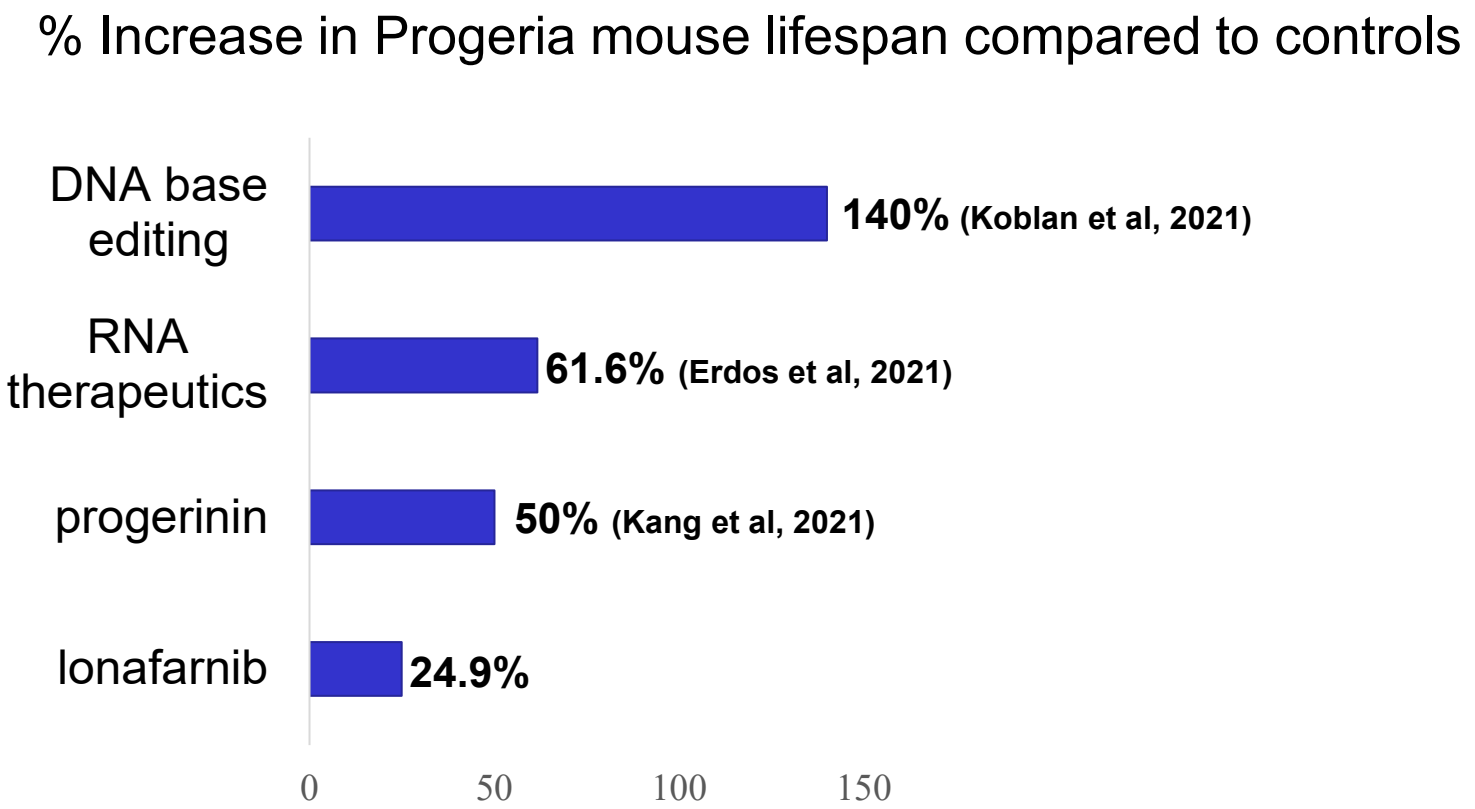


As of June 2019 cutoff date, extends average lifespan 2.5 years - FDA labeling

Nov 30, 2020: PRF Joins only 5% of Rare Diseases with Approved Drug

- Eiger Biopharmaceuticals – Interested in lonafarnib for Hepatitis Delta
- Eiger licensed lonafarnib from Merck; Progeria was a part of that arrangement, and entered into a collaboration and supply agreement with PRF (2018), with Eiger as sponsor of the NDA for Progeria
- Trial-to approval→13 years of continuous clinical trials

Future Trials are NOT Likely to be Repurposed Drugs

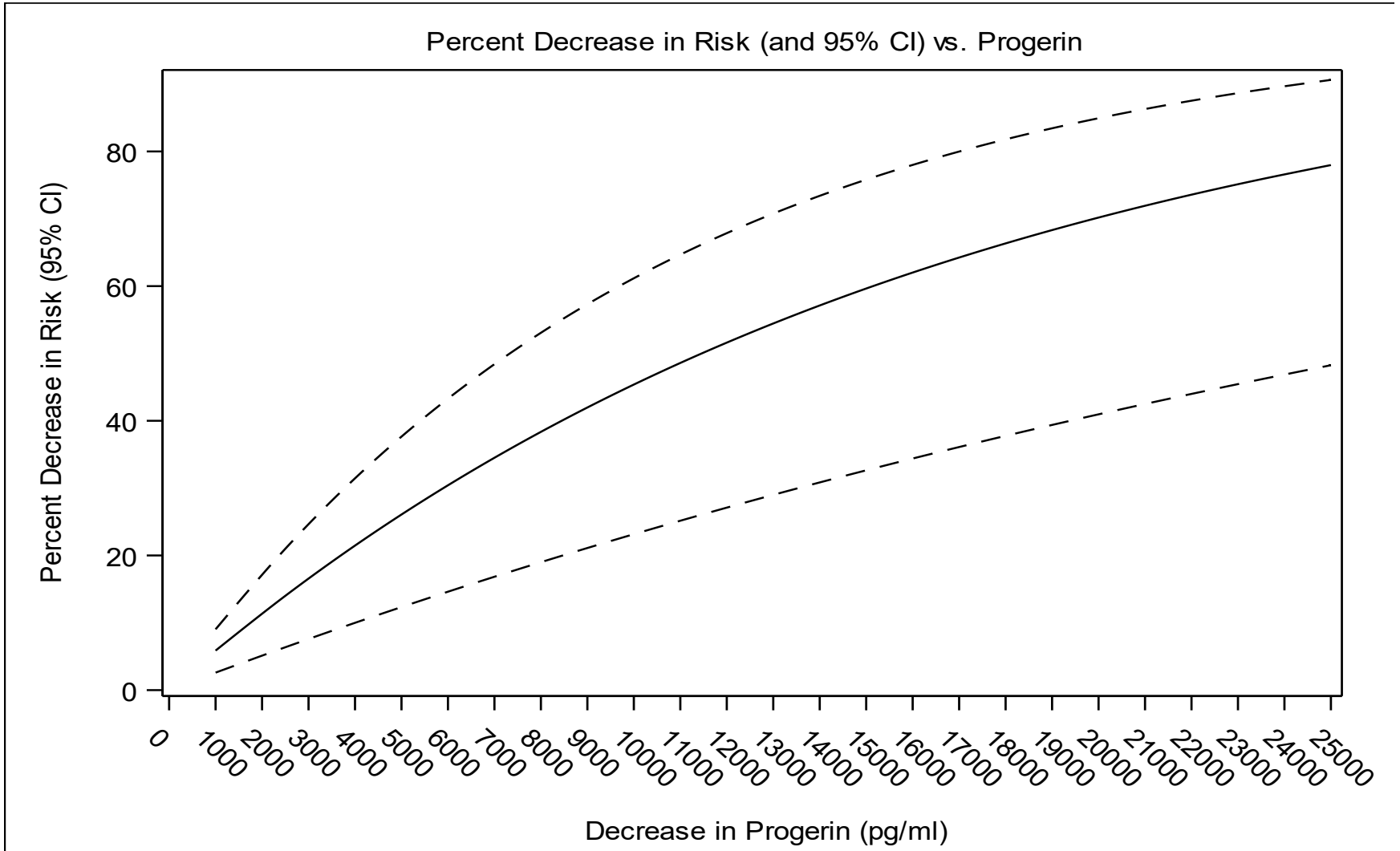


* Note that mouse models in use were not the same across all studies

What are the biggest challenges now?

- Most of the drugs being considered are first-in-human
- Survival Is Not a Viable Trial Outcome Measure in HGPS for Initial Drug Approval, especially with lonafarnib on board as standard of care
- We need outcome measures
  - Concentrating on developing a progerin biomarker in plasma
  - Clinical outcome – correlating cfPWV with survival in HGPS

Progerin Levels Predict Survival - Unpublished



Time-Dependent Progerin Survival Analysis, Adjusted for Age and Gender

Analysis includes Trial HGPS Patients (Classic Mutations)

Thank You!

Together We *WILL* Find The Cure!

www.progeriaresearch.org

Raphaela Goldbach-Mansky, MD, MHS

Senior Investigator & Chief

Translational Autoinflammatory Diseases Section

Laboratory of Clinical Immunology & Microbiology, NIAID, NIH

sBLA: Anakinra and Rilonacept in DIRA

NIH, pharma, CRO and the FDA

FDA workshop 2022
May 16th 2022

Raphaela Goldbach-Mansky, M.D., MHS
Translational Autoinflammatory Diseases Section
LCIM, NIAID, NIH, Bethesda, MD

National Institutes of Health

NIH National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases

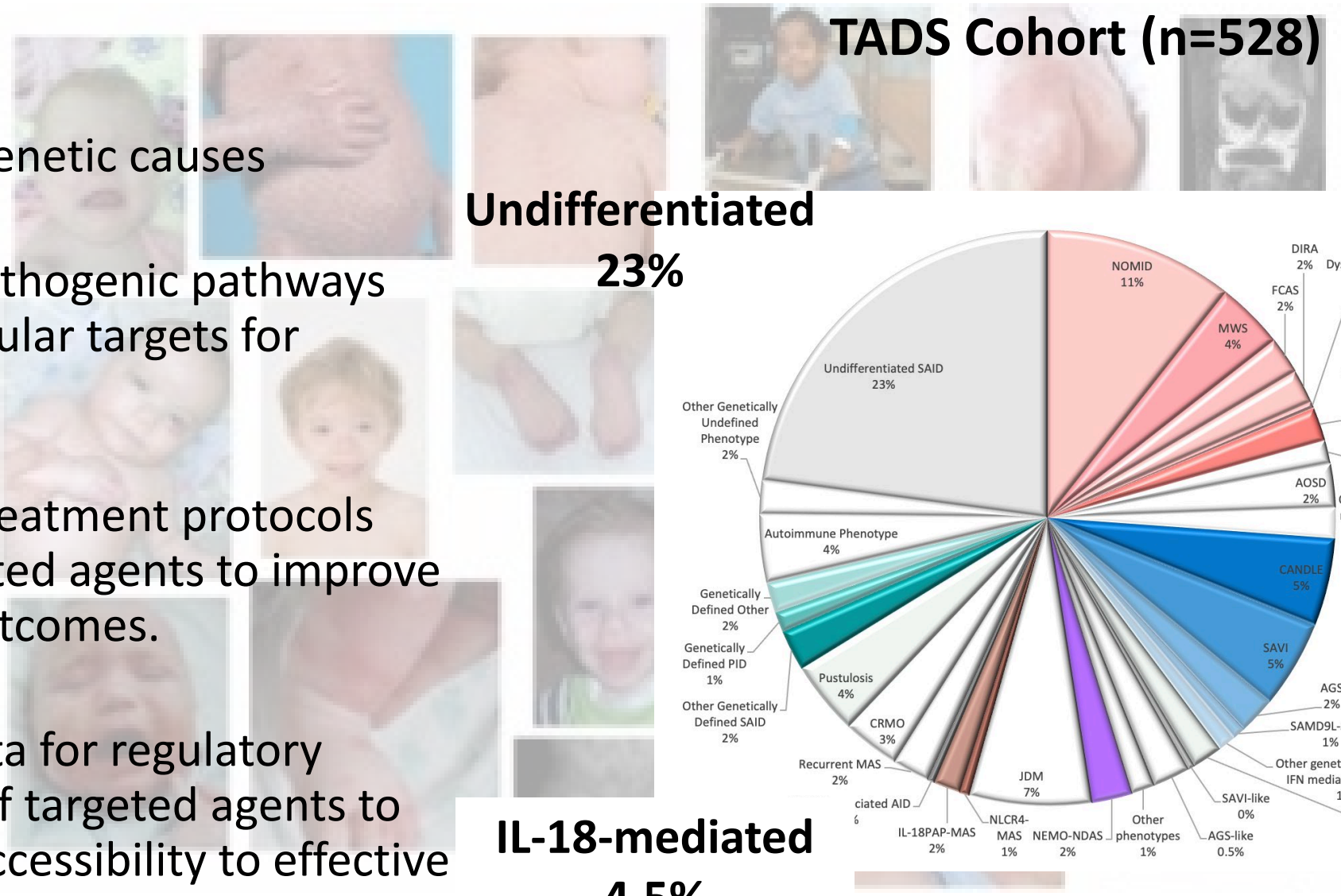
Disclosure Statement

Previous Study support under government CRADAs:

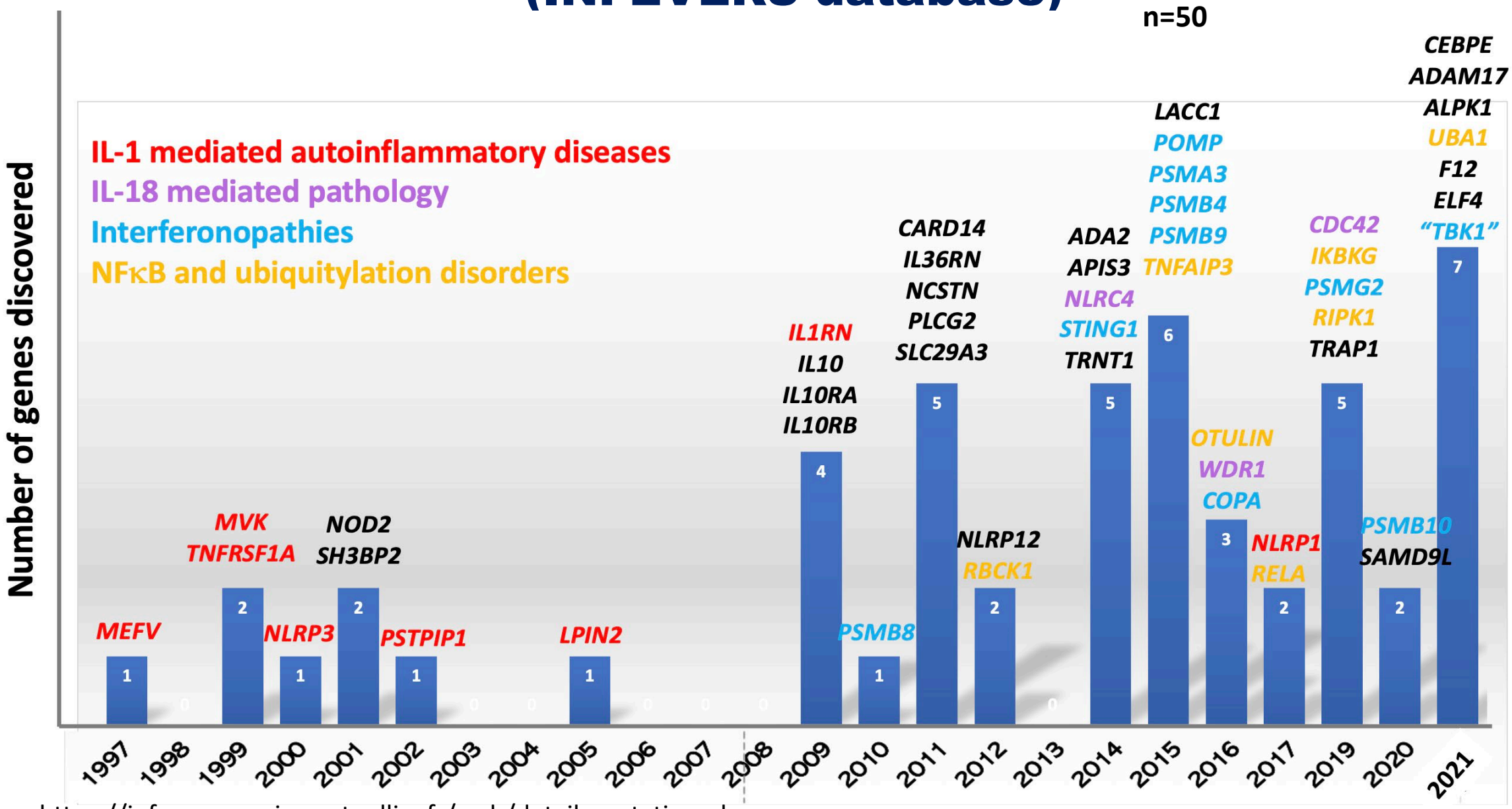
- SOBI
- Regeneron
- Eli Lilly
- IFM

Program Goals: Translational Autoinflammatory Diseases Section (TADS)

1. Discover genetic causes
2. Identify pathogenic pathways and molecular targets for treatment
3. Develop treatment protocols with targeted agents to improve disease outcomes.
4. Submit data for regulatory approval of targeted agents to improve accessibility to effective treatments



Discovery of genes that cause autoinflammatory diseases (INFEVERS database)

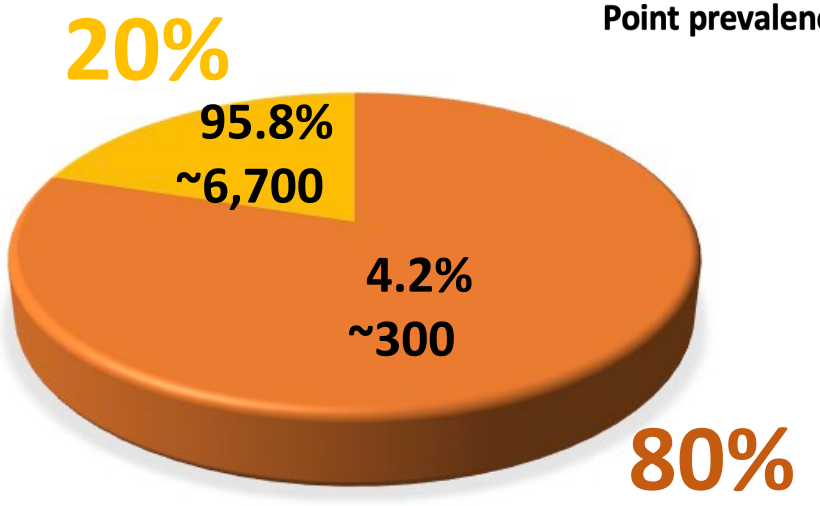


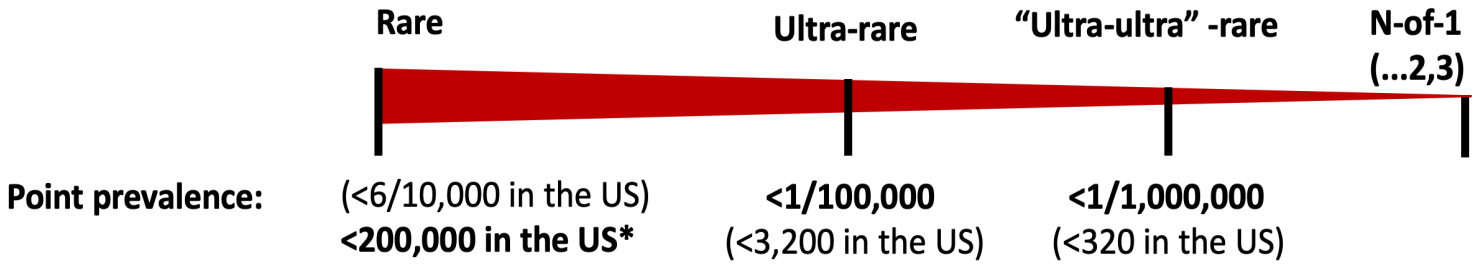
https://infevers.umai-montpellier.fr/web/detail_mutation.php

Treating patients with “ultra-ultra-rare” diseases

263–466 million patients worldwide
25-30 million in the US

DIRA patients worldwide:
~n=29





www.rarediseases.org

*Orphan Drug Act definition

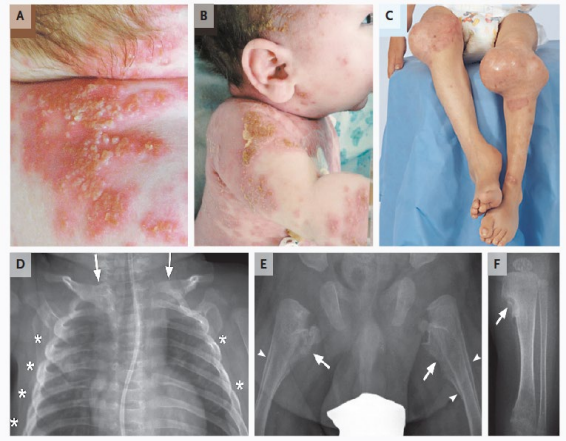
Challenges:

- **Design studies for “ultra-ultrarare” diseases**
- **Secure access to long-term treatment**
  - Insurances do not approve prescriptions of unapproved drugs
  - patients not eligible for patient assist program

Translational Research: DIRA (Deficiency of the IL-1 receptor antagonist)

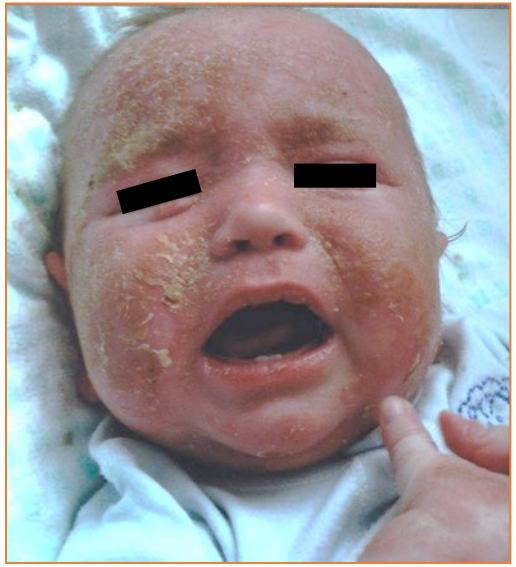
Late 2007 — **Empiric treatment with IL-1 inhibitor anakinra**

2008 — **Gene Discovery:** autosomal recessive loss of function mutations in *IL1RN*

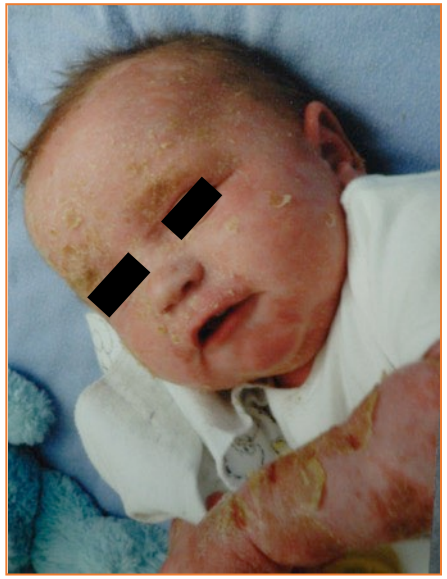


Aksentijevich I, Masters SL, Ferguson PJ et al.
NEJM 2009
(description of genetic mutation and clinical improvement)

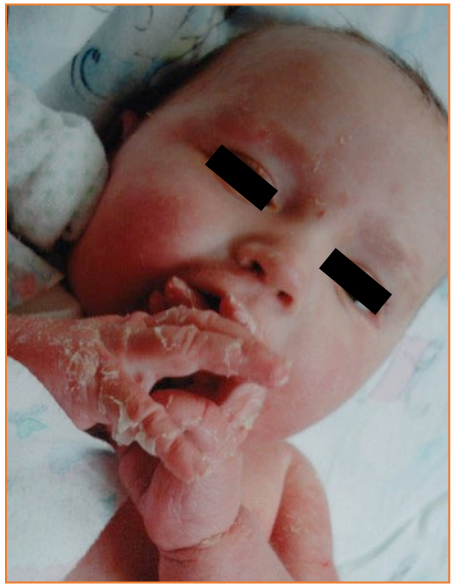
Before therapy



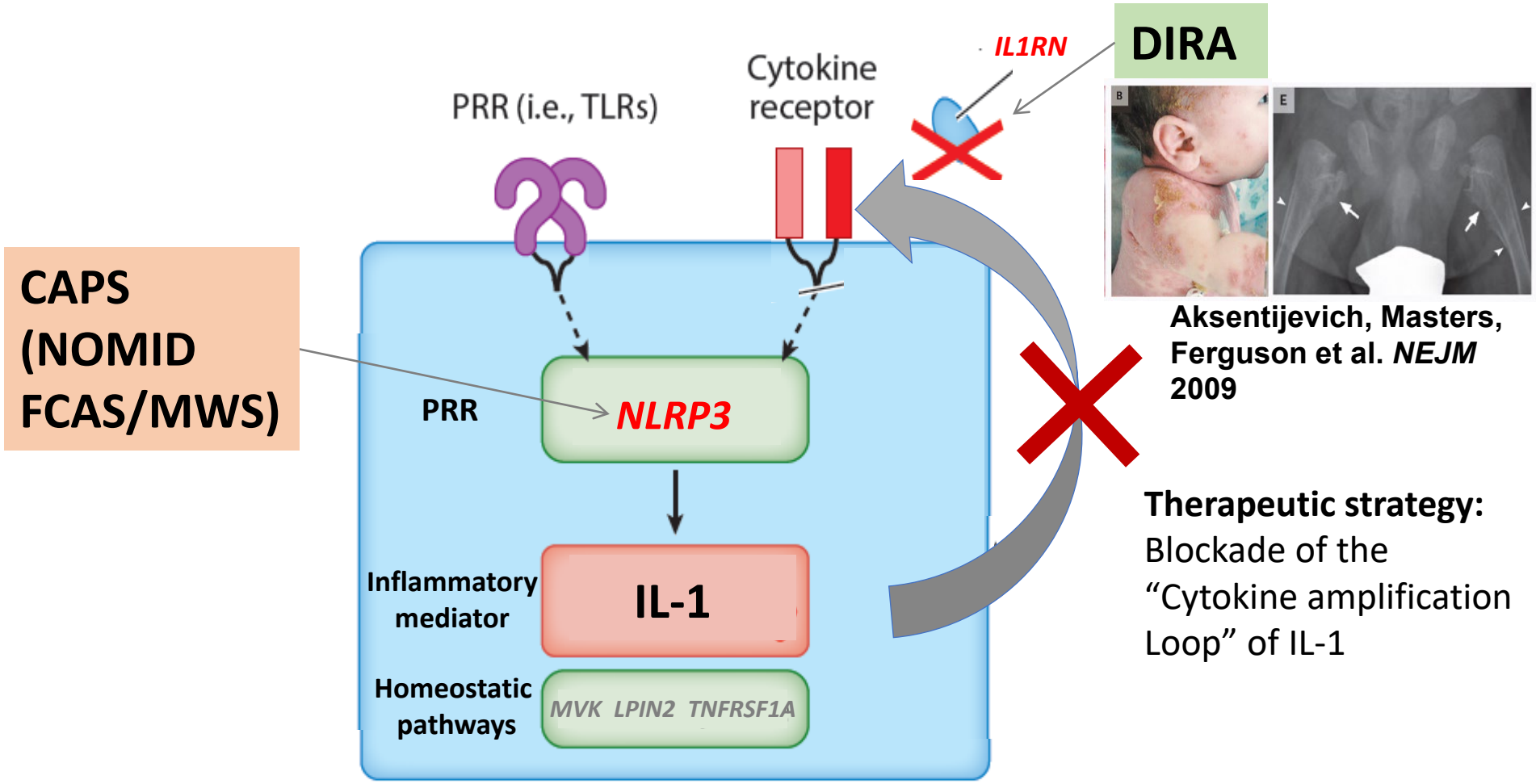
3 days post Rx initiation



7 days post Rx initiation



IL-1 amplification: Compelling mechanism of action



Aksentijevich, Masters, Ferguson et al. *NEJM* 2009

Therapeutic strategy:
Blockade of the "Cytokine amplification Loop" of IL-1

Genetic Approaches

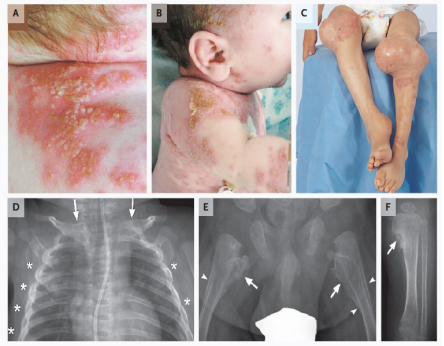
Targeted Therapeutics (Proof of Concept)

de Jesus & Goldbach-Mansky *Annu. Rev. Med.* 2014

Translational Research: DIRA (Deficiency of the IL-1 receptor antagonist)

13 year journey

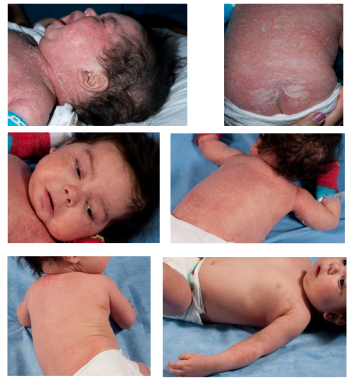
Late 2007 — **Empiric treatment with IL-1 inhibitor anakinra**



Aksentijevich I, Masters SL, Ferguson PJ et al. NEJM 2009 (description of genetic mutation and clinical improvement)

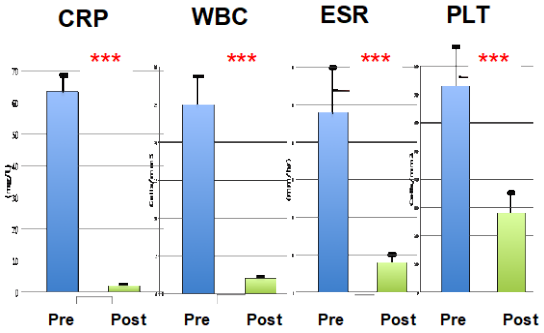
2008 — **Gene Discovery:** autosomal recessive loss of function mutations in *IL1RN*

2009 — **NH study 03-AR-0173: 9 DIRA pts on Anakinra treatment**



de Jesus AA et al. Arthritis Rheum 2012, Altiok E et al. Clin Immunol 2012 (description of novel genes causing DIRA)

March 2013 — **Translational Study: 13-AR-0086: A Pilot Open-Label Study of Rilonacept (Arcalyst®) in The Deficiency of the Receptor Antagonist (DIRA) Syndrome in 6 DIRA pts**
(**PI:** ***Gina Montealegre-Sanchez, Staff Clinician***)



Mendonca L.…de Jesus AA. JOCI 2017 novel DIRA mutation in Indian patient

Garg M.…Montealegre Sanchez GM. JCI Insight 2017 (benefit of rilonacept in maintaining long-term remission)

2014 — **Analysis of Safety and Efficacy data of Rilonacept in DIRA**

First Steps. The Journey begins….

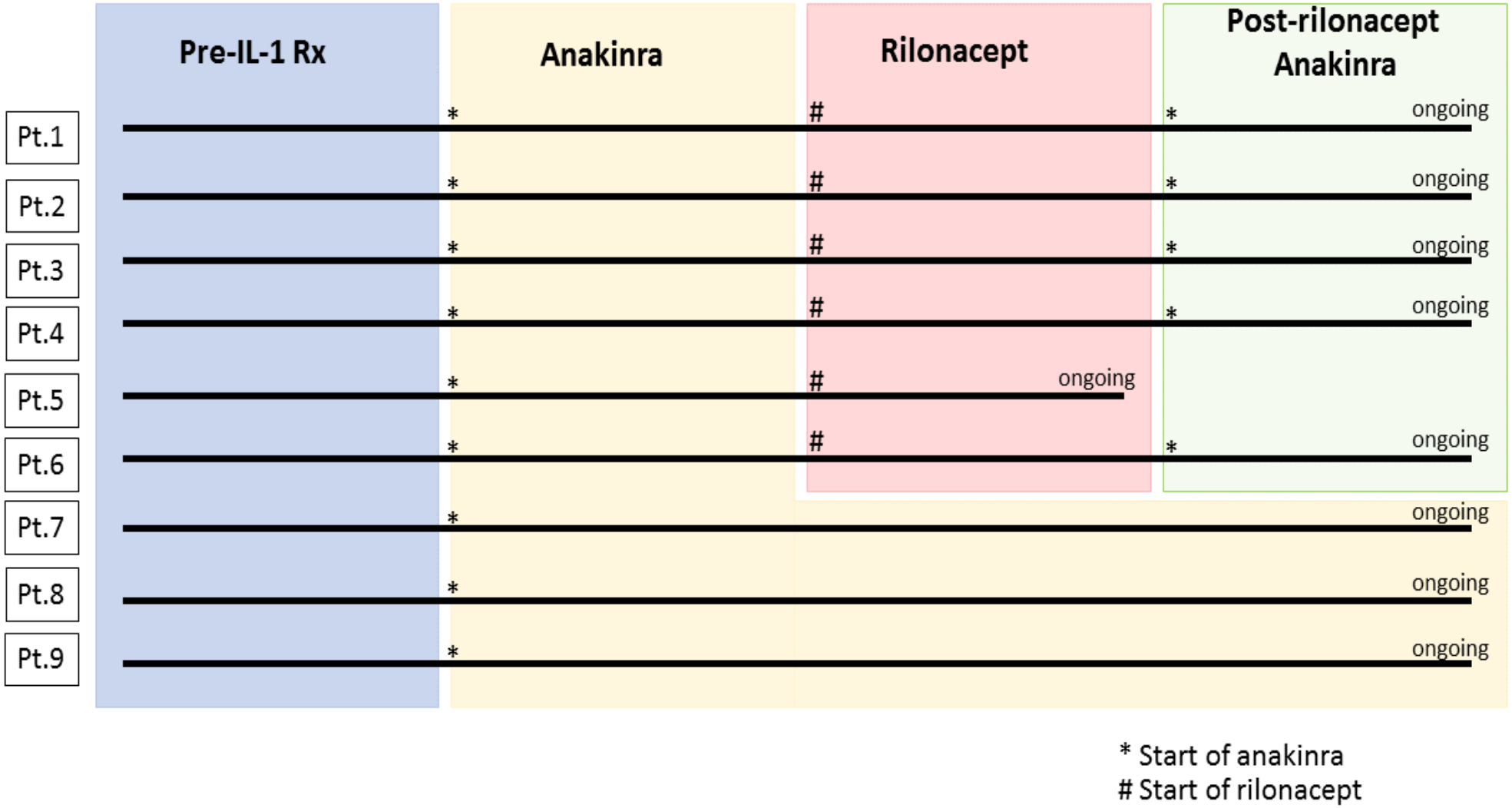
1. *July 2015* FDA informs Regeneron of opportunity to file sBLA for rilonacept for DIRA after hearing about the project.
2. *October 2016* Regeneron agrees to file sBLA for rilonacept in DIRA
   - Briefing book for meeting with FDA
   - Database with trial data
   - Clinical study report
3. *April 2017*, publication of DIRA anakinra and rilonacept data (Garg M et al. *JCI Insight*. 2017)
4. *January 2018*: FDA Type B meeting discussion rilonacept registration
   - FDA encourages co-filing of sBLA for anakinra and rilonacept
   - Regeneron endorses this plan

Next steps: The Journey continues….

5. *March 8th 2018*: 3-institutional TC (NIH-SOBI-Regeneron) discussing feasibility of co-submission
   - SOBI Attendees: *Annika Loftenius*, Program Director (project management), *Sue Crowley*, Medical Affairs North America, *Ola Sandborgh*, Global Commercial, *Karin Franck-Larsson*, Global Medical Affairs, *Matt Boyd*, Regulatory Affairs North America
   - Regeneron Attendees: *Scott Mellis*, Clinical Development, *Sara Benvin*, *Brian Walter*, Regulatory Affairs)

   Regeneron and ICON (CRO) complete final FDA submission documents
6. *May 14th 2018*: SOBI management unable to support DIRA co-submission due to insufficient resources
7. *May 29th 2018*: NIAID/NIH funds CRO – ICON to assist with filing
8. *June 4th 2018*: SOBI senior management endorses co-filing and commits to drafting the regulatory modules and draft label

Definition of: Study Subjects and Data Collection Periods



FDA Approval of IL-1 Blocking Drugs

for rare autoinflammatory diseases

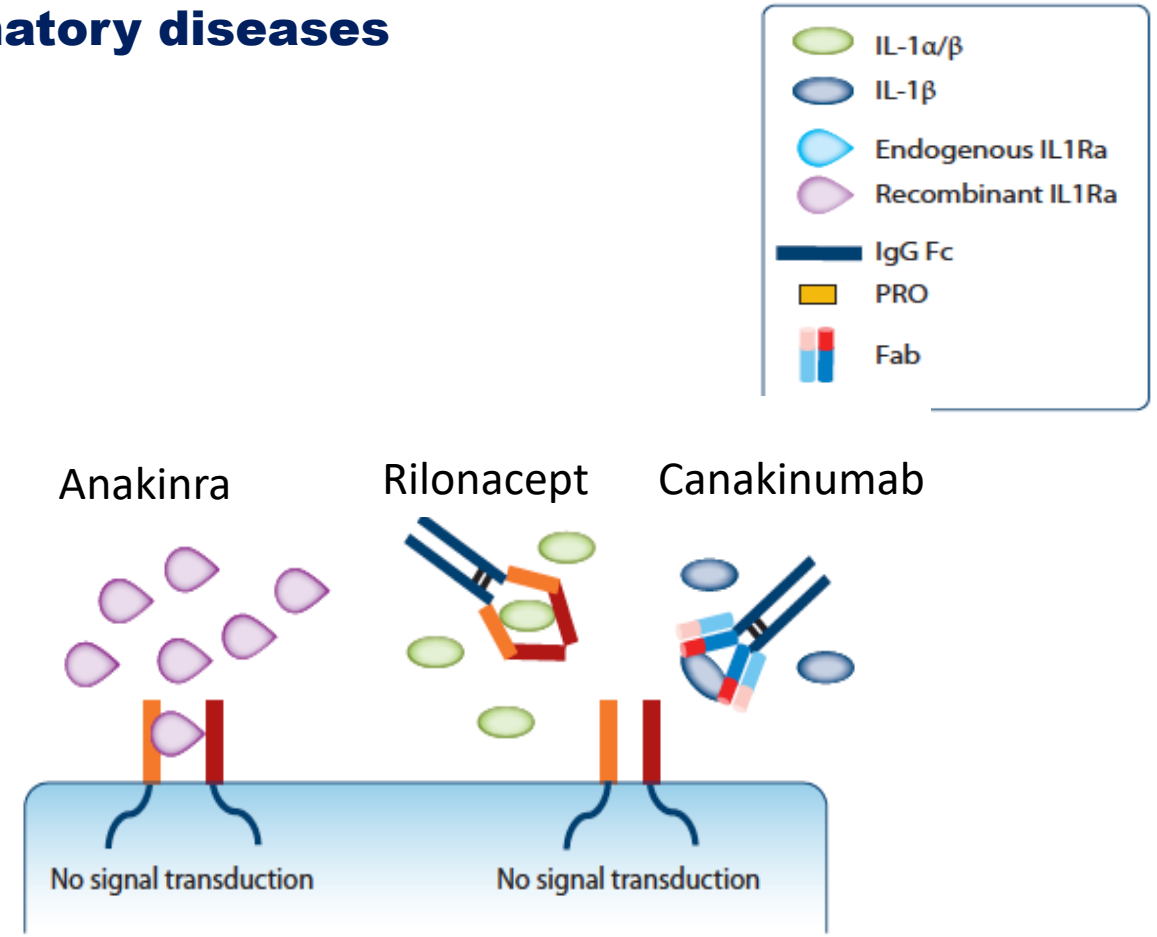
2008 — **FDA: rilonacept** for **FCAS and MWS**

2009 — FDA: canakinumab for FCAS and MWS

2012 — **FDA: anakinra for NOMID**

2016 — FDA: canakinumab for FMF, TRAPS and MVK

2020 — **FDA: anakinra and rilonacept** for **DIRA**



Romano M, Arici ZS, Piskin D et al. *Ann Rheum Dis*. and *Arthritis Rheum*. *2022*
Ozen S, et al. *Ann Rheum Dis* 2016

Working with CRO

DELIVERABLES:

- Monitoring of extracted data
- Statistical Analysis Plan (SAP).
- Clinical Study Report (CSR) and datasets
- Support sBLA summaries and draft labeling in support of a sBLA for anakinra (regulatory modules require company support, safety, dosing label)

Data extraction: Dr. Gina Montealegre, Jenna Wade, Gema Souto-Adeva, Kim Johnson

Statistical Analysis Plan

- No formal sample size and power calculation
- Remission rates and 95% confidence intervals using exact Binomial methods at following time windows:
  - Day 2 – 6 months, 6 – 12 months, 12 – 24 months, and >24 months and final NIH visit.
- Paired t-tests were used to compare baseline to the suggested time windows for:
  - laboratory values (WBC, ESR, Hgb, platelets, CRP)
  - height and weight z-scores
  - BMD z-scores
- Normalized Hospitalization rates in pre-, and post-treatment periods (i.e. days in hospital/days spent in this period).

- **Data included retrospective and prospective data**

Definition of Primary Endpoint: Remission

Measure	Anakinra Study	Rilonacept Study
Diary Scores	**NA**	Score <0.5
CRP	≤0.5 mg/dL (5.0 mg/L)	<0.5 mg/dL
Cutaneous manifestations	No pustulosis **NIH visit:** No objective skin rash determined by principal investigator or dermatology evaluation **Outside records**: explicit documentation of absence or presence of skin findings	No objective skin rash determined by principal investigator or dermatology evaluation
Bone disease	No Inflammatory bone disease, either: • No evidence of bone inflammation shown in imaging (bone scans, x-rays, or MRIs) such as osteomyelitis/periostitis [a] OR • No clinical evidence of bone pain or bone swelling (in which case no bone imaging was performed)	No radiological evidence of active bone lesions on x-ray[c]
Glucocorticosteroids	No glucocorticosteroids in use	**NA**

Definition of Efficacy: Secondary Endpoints

1. Glucocorticosteroid use
   - Ability to reduce glucocorticosteroids, and other DMARDs is an important endpoint in children with chronic rheumatic and inflammatory diseases.
2. Laboratory markers of systemic inflammation
   - Normalization or significant decrease of CRP, ESR, WBC, and PLT
   - Increase in Hgb level
3. Anthropometric and developmental outcomes
   - Normalization of Height, weight and BMD z-score compared to age matched controls.
4. Hospitalizations
   - Rate of hospitalizations summarized pre-anakinra, during anakinra, and post-rilonacept/anakinra periods
5. Patient reported outcomes
   - CHAQ Disability index
   - Disease burden/quality of life via the PedsQL Rheumatology module
   - Physician global, pain and global health evaluation (VAS) in the Anakinra Study only

Efficacy Conclusions:

- **All patients achieved inflammatory remission off glucocorticosteroids with anakinra treatment. Remission was maintained with rilonacept**.

- Patients received anakinra doses between 1.0 mg/kg/day to 5.2 mg/kg/day at the time of first documented remission and the maximum daily dose was 7.5 mg/kg.
- Normalization of inflammatory markers was achieved during anakinra treatment in all 9 patients as assessed by CRP. ESR normalized in all except one patient.
- WBC, ANC, and PLT decreased and normalized and Hgb increased and normalized on anakinra.
- On anakinra treatment, z-scores for weight and BMD (DEXA) improved and normalized in 8 of 9 children with DIRA, and the z-scores for height normalized in 7 out of 9 patients.

Efficacy Conclusions:

- Number and duration of hospitalizations were significantly reduced for all patients after anakinra.
  - The mean percentage of time spent in hospital:
    40.8% during pre-treatment to 0.6% during anakinra treatment
- Both CHAQ and PedsQL also showed improvement while on rilonacept.

<u>Safety</u>: **anakinra and rilonacept were well tolerated.**

Additional Documents: Natural history of the disease:

A Literature Review of the Natural History of Deficiency of Interleukin-1 Receptor Antagonist (DIRA)

- summarized 29 patients known worldwide, 9 (31%) had died prior to making a diagnosis
- out of 20 alive, 9 were followed at the NIH in the NH protocol 17-I-0016

Narratives generated on 9 patients summarizing pre-, and post-treatment data

Table of contents

Table of tables

Summary of FDA meetings and approval for treatment for DIRA

- August 2015 — **Teleconference between FDA and Regeneron** to encourage regulatory submission
- January 2018 — **Meeting between FDA, NIH and Regeneron** to discuss study results and submission package for sBLA for rilonacept → suggestion to co-submit
- March 2018 — **3-institutional TC (NIH-SOBI-Regeneron)** to discuss feasibility of co-submission
- November 2019 — **Pre sBLA meeting between FDA, NIH and Sobi and Regeneron**
- June 2020 — **Parallel sBLA submission to FDA :**
  rilonacept study data
  anakinra study data collected under natural history protocol
- December 2020 — **FDA Approval of:**
  1. anakinra (SOBI) for the treatment of DIRA
  2. rilonacept (Regeneron) for maintenance of remission of DIRA

FDA Approval of rilonacept and anakinra for treatment of DIRA

Rilonacept:

- Maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing 10 kg or more (healthy child: 6-9 mo age).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125249s049lbl.pdf

Anakinra:

- The recommended starting dose of KINERET is 1-2 mg/kg daily for patients with DIRA. The dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation. (2.3)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103950s5189lbl.pdf

Thank you!!

NIAID

Gina Montelegre
Gema Souto-Adeva
Jenna Wade
Lena Bichell

Christopher Constantini
Gilliam, Alyssa
Enugu, Sukanya
Holinka, Tara
Kent, Berneta
Voosala, Naveen
Ganupooru, Mahesh
Kaske, Alexander
Jensen, Erik
Poff, Dana
Sanford, Ben

Scott Mellis
Sara Benvin
Brian Walter

Annika Loftenius
Sofie Broberg
Sue Crowley
Ola Sandborgh
Karin Franck-Larsson
Matt Boyd

Patients and Parents

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases

National Institutes of Health

AUTOINFLAMMATORY ALLIANCE

Thank you!!

NIAID

Gina Montelegre
Gema Souto-Adeva
Jenna Wade
Lena Bichell

Patients and Parents

National Institutes of Health

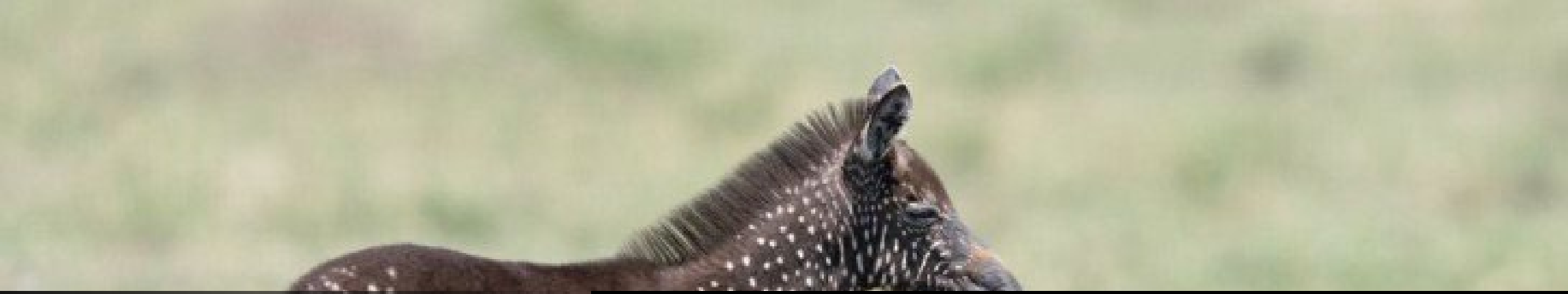
ICON

REGENERON
science to medicine™

sobi

NIH National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases

AUTOINFLAMMATORY ALLIANCE



Baricitinib in CANDLE Patients

(Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperatures)

Bita Shakoory, MD

Translational Autoinflammatory Diseases Section (TADS), NIAID/NIH

Outline

- Introducing CANDLE and Baricitinib
- Brief review of baricitinib study in CANDLE
  - Challenges, obstacles
- Lessons learned from communications and submissions to FDA
- Steps towards improving the result

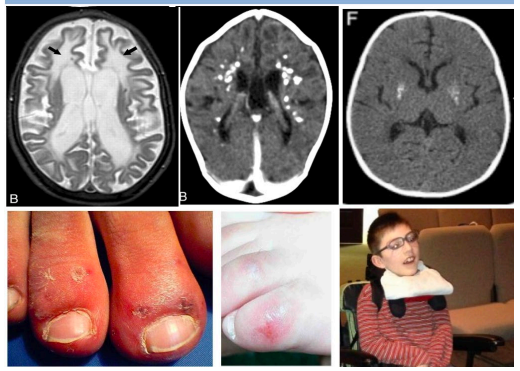
Autoinflammatory Interferonopathies

2006 ***TREX1*** **and** ***RNASEH2*** **causes AGS1-4**

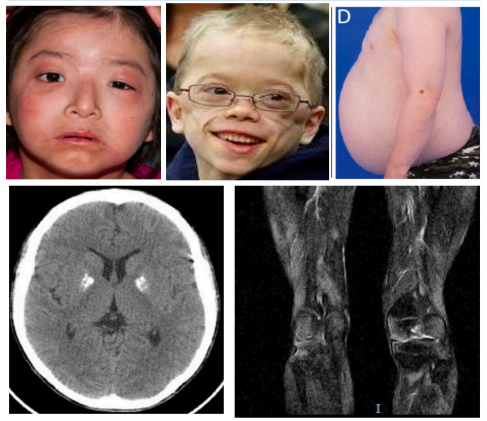
2010/ ***PSMB8***
2011 ***CANDLE/NNS/PRAAS***

2014 ***TMEM173/STING1*** **causes SAVI**

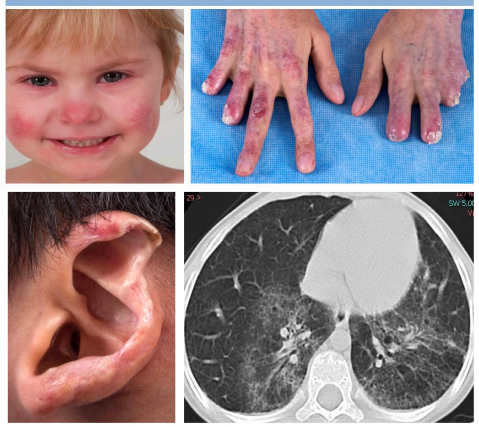
Aicardi Goutières Syndrome(AGS) 1-7

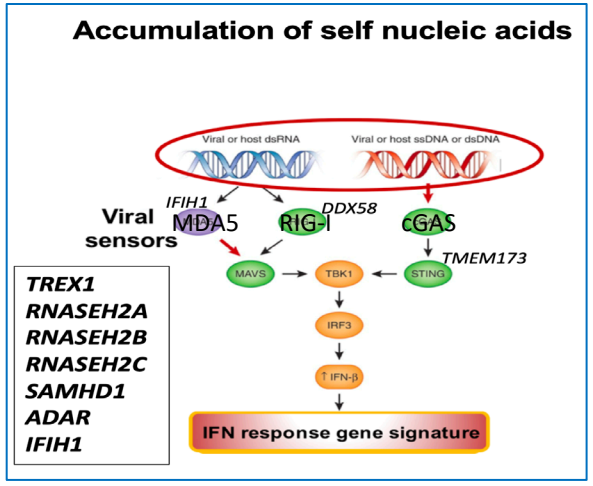


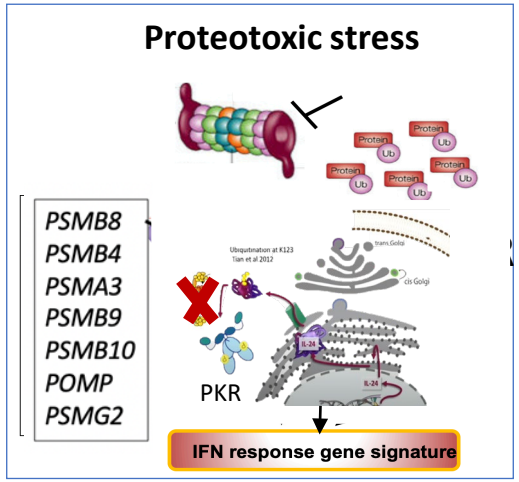
PRAAS/CANDLE

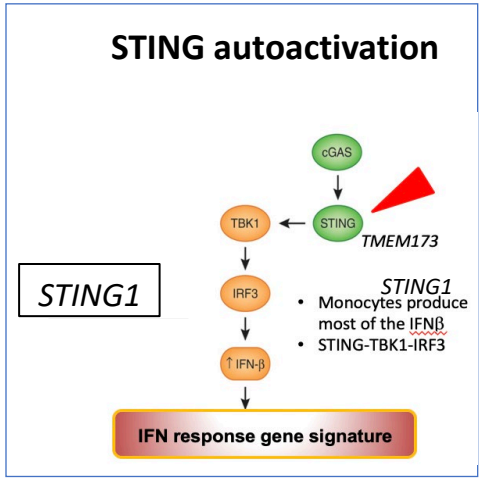


SAVI



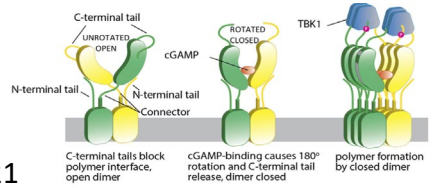






Crow, Y.J et al. *Nat Genet* 2006
Agarwal et al 2010, Arima et al *PNAS* 2011, Kitamura A *JCI* et al 2011,
Liu Y et al. *Arthritis Rheum* 2011
Liu Y et *NEJM* 2014 Jeremiah N et al. *JCI* 2014

Zhang C et al *Nature* 2019
Lin B et al. *Front. Immunol* 2021



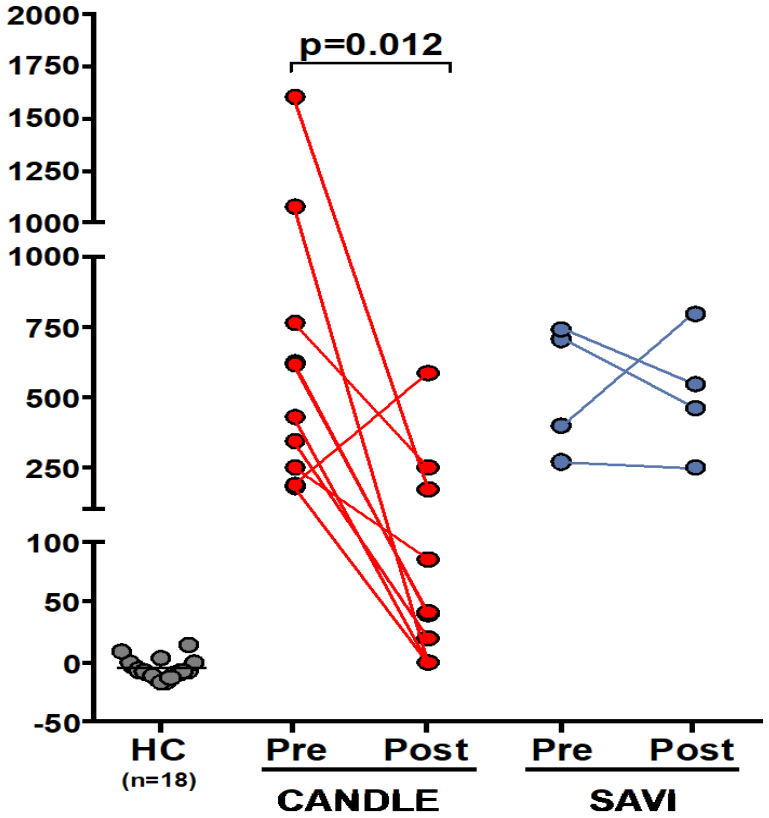
JAK inhibitor Baricitinib Compassionate use NIH protocol with Eli Lilly

- Oct 2011-Feb 2017
- Patients with genetically proven CANDLE and CANDLE-like phenotype
  - Later patients with SAVI and JDM were also included
- Patients: 10 patients with CANDLE*; 4 patients with SAVI and 4 patients with other interferonopathies
- Intervention: Open label baricitinib
- Dosing*:
  - No pediatric dosing, PK/PD data,
  - No template or precedence to guide dose adjustment
- Endpoints: Reductions in daily diary score, corticosteroid requirement. quality of life, organ inflammation, changes in IFN-induced biomarkers

Autoinflammatory Interferonopathies-Treatment

Remission in 50% of patients

Treatment JAKi:



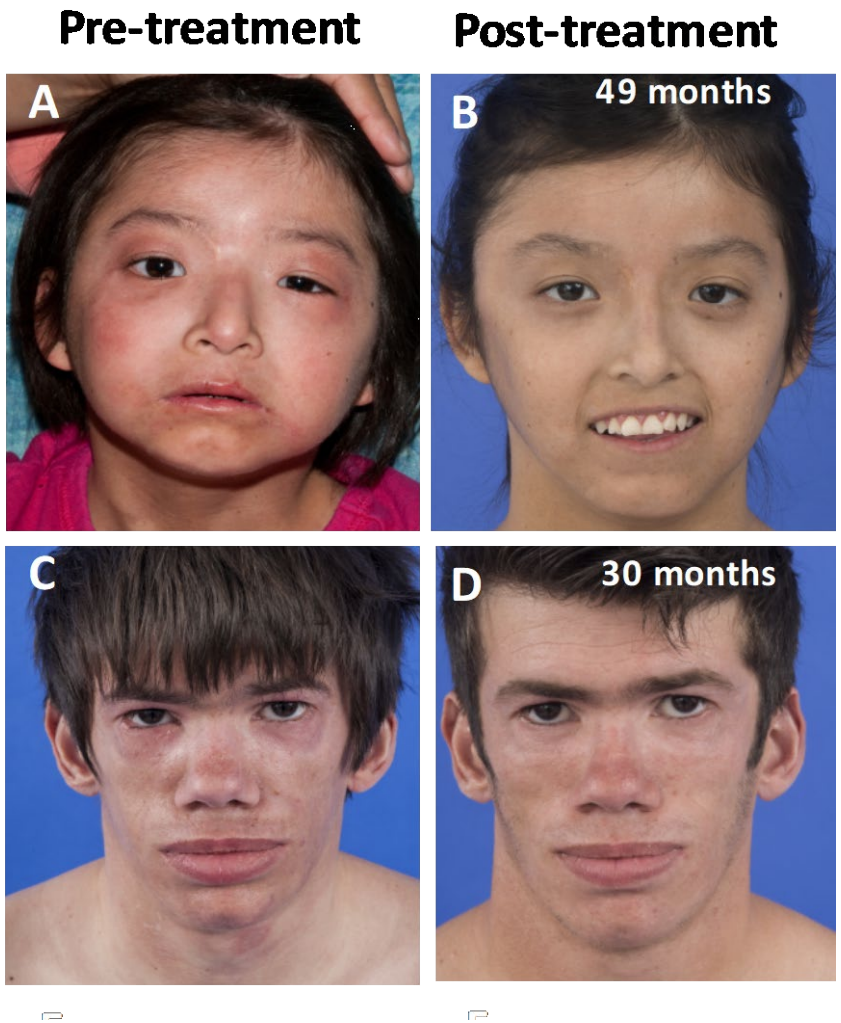
Improvement also

- Growth parameters (height and DEXA scan)
- Cytopenias

Safety

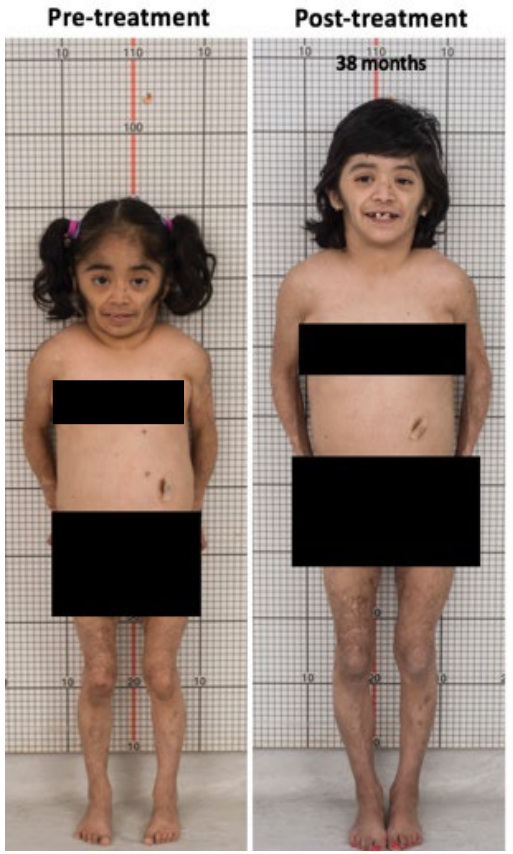
- Drug Exposure:~1.8 fold higher than RA at 4mg/d
- Reactivation of (BK, HZV)

Kim H et al. 2018
Sanchez et al. *JCI* 2019

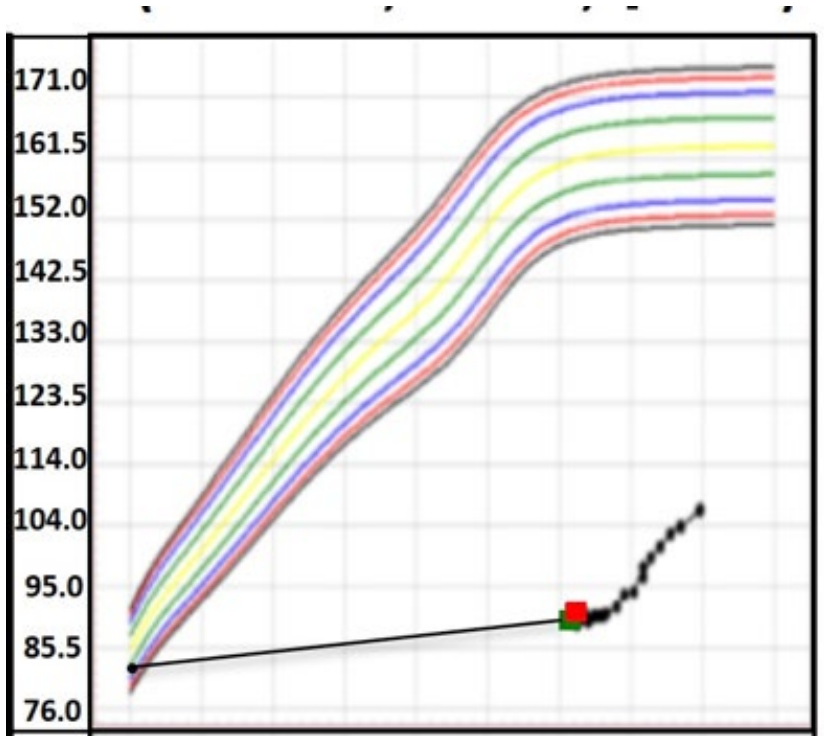


3'6"

Currently:
4'3"



14 yrs



Kim et al. *Clin Pharmacol Ther*. 2017
Montealegre GA et al. *J Clin Invest*. 2018

Translational Research: CANDLE

(*C*hronic *A*typical *N*eutrophilic *D*ermatosis with *L*ipodystrophy and *E*levated *T*emperatures)

2011-2017 **JAK inhibitor Baricitinib Compassionate use NIH protocol with Eli Lilly**

2017 **Persistent remission in 50% of CANDLE patients. Narrow therapeutic window does not allow higher doses**

2018 **Plan to file sBLA for CANDLE with FDA**

Jan 2020 **FDA canceled Pre-NDA Type C Meeting: inadequate data**

2016
Approved in **EU**
for **RA**

2017
FDA Rejected in **RA**

2018
FDA Approved
in **RA**

FDA Feedback

Criticism	Suggestion	NIH/Lilly
Limited data, small ”n”	Use comparable external or historic control	Rigorous data collection and documentation of historic data
	Use comparable Endpoints	Longitudinal integration of data from various physicians and hospitals
	Show Objective changes in core clinical outcomes (such as survival)	Defining flare based on withdrawal data
Limited data on safety		Detailed Safety Narratives and reports
Unblinded: Risk of bias	Randomized controlled trial	
Unclear impact of disease and age on PK	None- do not agree with higher dosing.	Detailed PK, PD, dose optimization data
Objective outcomes	Caution against use of proxy in diary reports. Caregivers should not report about unobservable symptoms known only to the patient (pain and fatigue)	Our daily diary is based on observer reported outcome and not proxy.

A Literature Review of the Natural History of Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE)/Proteasome Associated Autoinflammatory Syndrome (PRAAS).

Table of Contents

n=55 CANDLE/PRAAS patients

- 15 (27%) were seen and prospectively followed NIH
- 6 patients had detailed clinical descriptions, medical records and clinical updates were provided by the treating physician.
- 34 patients clinical and immunological data were extracted from the literature only.

13 (23.6%) of the 55 patients were deceased

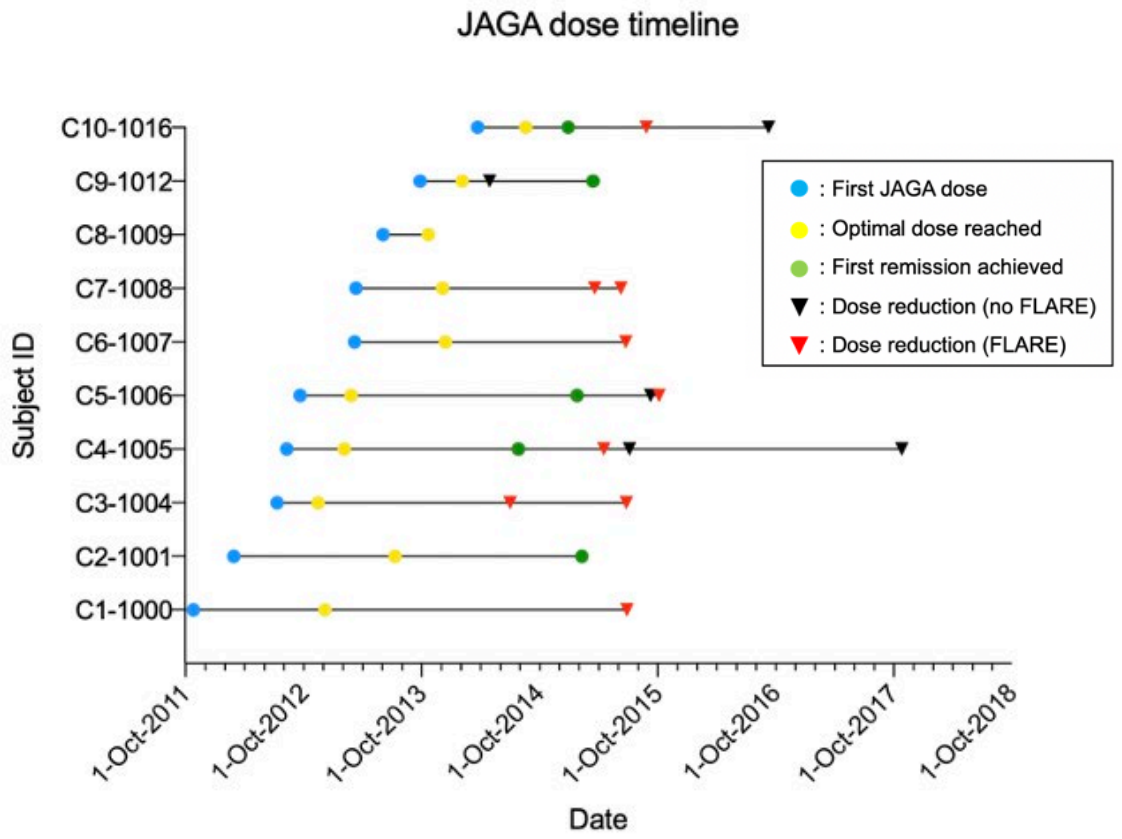
Sofia Torreggiani (ms. in preparation)

2. sNDA CANDLE

Retrospective Sub-Analysis of 8 Patients Who Experienced 13 Baricitinib Dose Reductions in JAGA

TABLE OF CONTENTS

LIST OF TABLES



Kader C Gedik (ms in preparation)
Grace Materne

Translational Research: 3. CANDLE

(*C*hronic *A*typical *N*eutrophilic *D*ermatosis with *L*ipodystrophy and *E*levated *T*emperatures)

Jan to Sep 2020 — **Enhanced Briefing package based on FDA Feedback**

Sep 2020 — **Briefing package and meeting request submitted to FDA**

Oct 2020 — **FDA Grants Pre-NDA Type C Guidance Meeting**

Jan 2021 — **Meeting with FDA to discuss sBLA (with Rare Disease Office representation in the meeting)**

2018-
Safety Concerns arise

2019
Safety study in **RA**

FDA Feedback from January 2021

Criticism/Suggestion Comment	Modifiable	Non-Modifiable
Inadequate data to support risk/benefit assessment. **(Randomized withdrawal study)**	Data presentation	Morbidity and mortality of CANDLE (Patients died of disease activity aftertreatment discontinuation per protocol
Endpoint based on daily diary score	Publishing the data in peer reviewed journals	Safety profile of JAK inhibitors
Review of published cases inadequate	Reference to FDA Rare Disease Guidance Document	Number of patients, length of historic data
Prospective endpoint data is inadequate	Expand patient cohort (collaboration)	Negative publicity associated with JAK-i
Historic data unclear: Disease variability and Treatment effect	Reference to other similar diseases	Negative data
Remission not sustained	Better define treatment response parameters	Barriers of multi-center studies
Biological plausibility: link between intervention and the pathogenesis		
Risk associated with higher dosing: Concern about risk of thromboembolic events and serious infections	Our daily diary is the patient reported outcome components of endpoints (along with reduction in steroid dose and disease specific improvements). See FDA guidance on patient reported outcomes (BMJ 2010;340:c2921).	

Translational Research: 3. CANDLE

(*C*hronic *A*typical *N*eutrophilic *D*ermatosis with *L*ipodystrophy and *E*levated *T*emperatures)

Jan to Sep 2020 — **Enhanced Briefing package based on FDA Feedback**

Sep 2020 — **Briefing package and meeting request submitted to FDA**

Oct 2020 — **FDA Grants Pre-NDA Type C Guidance Meeting**

Jan 2021 — **Meeting with FDA to discuss sBLA (with Rare Disease Office representation in the meeting)**

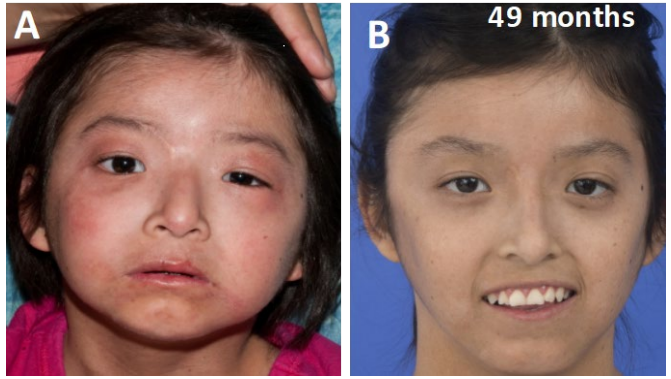
Summer 2021 — **After much discussion with Lilly, we decided not to pursue a withdrawal study**

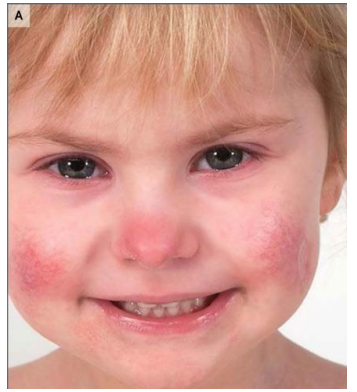
Sept 2021 — FDA Issues a **Black Box Warning** based on post-marketing safety data in tofacitinib (Xeljanz), baricitinib (Olumient), and upadacitinib (Rinvoq)

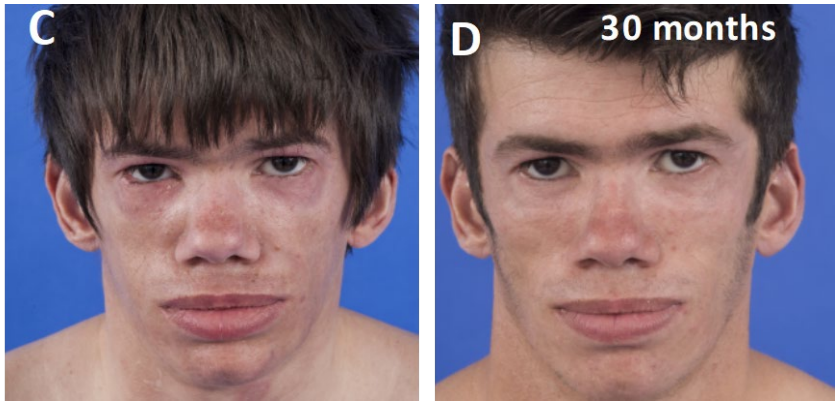
2018-
Safety Concerns arise

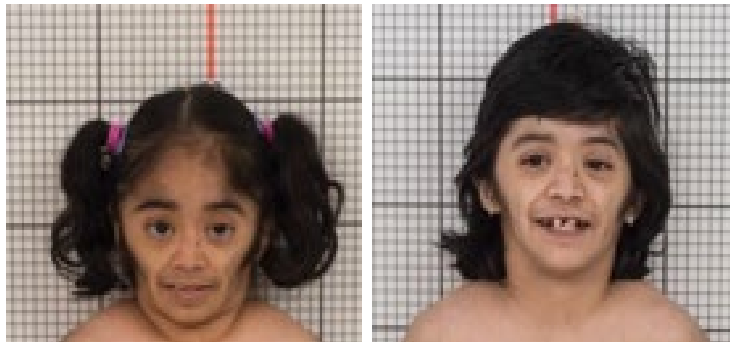
2019
Safety study in **RA**

We tried, but failed









Changing the result: investigator component

- Detailed documentation
  - Determining the best outcomes
  - Safety data
  - Flare and response criteria
  - Diligent statistical analysis
- Enrollment of international patients
- Collaboration with other major centers

- IRB approval and patient consent
  - Send-in sample collection
  - Sample storage (future analysis)
- Building the infrastructure:
  - Detailed databased software
  - Web-based data collection platforms
  - Clinical data collection software
  - Methodological innovation

Changing the result: drug component

- Collecting PK and PD data
- PK modeling and dose adjustment algorithms in place
- Biomarkers and metabolites

Changing the result: Protocol component

- Crossover design
- Withdrawal study
  - Patient/parent are not interested
  - Ethical concerns about holding off treatment in stable patients
- Novel trial designs:
  - Adaptive studies
  - Platform studies
- Statistical analysis methods for rare diseases
- Use of alternative approach if blinding of treatment is not possible

Dialogue with Regulatory Authorities

There is a need for shift in the current perspective towards clinical trials in rare diseases, in all of the involved parties

- Flexibility for rare disease discoveries
  - Innovative trial designs
  - Manageable regulatory requirements
- Differences between adults and kids:
  - Children are not small size adults
- Death is not the only poor outcome:

Thank You

SESSION 2: CASE STUDIES — AN ACADEMIC PERSPECTIVE

Moderator: Elizabeth A. Ottinger, Ph.D.,
Deputy Director of Programs &
Head of Project Management, DPI, NCATS, NIH

Lunch Break

SESSION 3: CORE PRINCIPLES FOR CLINICAL TRIALS

Moderator: Katie Donohue, M.D., M.Sc.,
Director, DRDMG, ORPURM, OND, CDER, FDA

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Dose Optimization for Rare Diseases

Jie (Jack) Wang, PhD

Division of Translational and Precision Medicine (DTPM)
Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS),
CDER, FDA

Disclaimer

Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

Throughout the talk, representative examples of commercial products may be given to illustrate a methodology or approach to problem solving. No commercial endorsement is implied or intended.

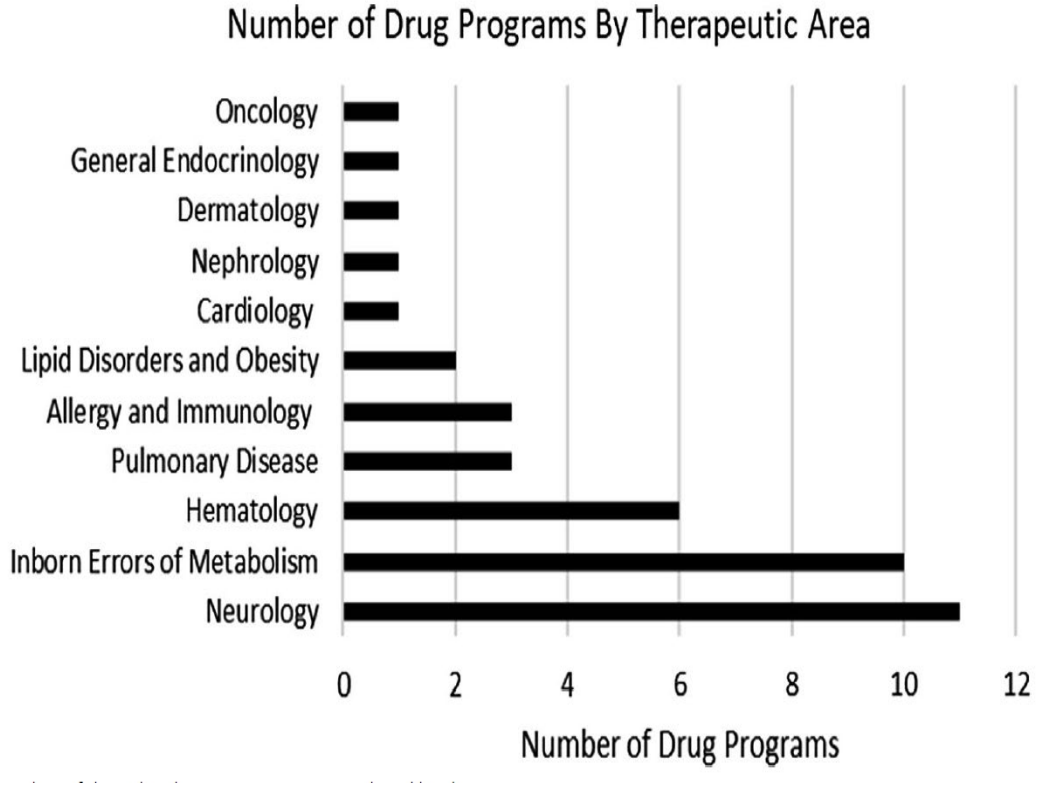
Why Are Dose Selection and Optimization Important?

- Failures in dose selection and uncertainty about the optimal dose were the leading cause for **non-approval** of NME drugs.
(*Sacks et al. JAMA, 2014*)

Table 1. First-Cycle Approval Rates by Medical Specialty

Medical Specialty	Total NMEs Submitted	Approved During First Review Cycle, No. (%)
Oncology	61	44 (72)
Metabolic diseases[a]	45	21 (47)
Neurology/psychiatry	42	14 (33)
Infectious diseases	39	23 (59)
Cardiology	22	7 (32)
Ophthalmology	15	7 (47)
Pulmonology/allergy	13	4 (31)
Gastroenterology	13	9 (69)
Urology	11	4 (36)
Reproductive medicine	10	4 (40)
Dermatology	9	3 (33)
Rheumatology/analgesia	7	3 (43)
Hematology/hemostasis	7	4 (57)
Other	8	4 (50)

- Among 40 NME drugs approved for rare genetic diseases from 2015 to 2020, 33 (82%) of the development programs had dose-finding studies/explorations.
(*Wang et al. Orphanet Journal of Rare Diseases, 2022*)



Outline

- Clinical pharmacology principles in dose optimization
- Role of biomarkers in dose selection/optimization and as confirmatory evidence of effectiveness
- Dose selection/optimization in an adaptive trial design
- Take-away messages (Part 1 & Part 2)

Dose Optimization: Goals to Achieve and Questions to Address

- **Goals:**
  - To maximize benefit-risk profile in individual patients; therapeutic individualization
  - Rs: right drug, right dosage form, right dose & dosing frequency, right route, right time, right patient, and right monitoring
- **Two key questions to address:**
  1) *Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?*
  2) *Is an alternative dosing regimen (or management strategy) needed for subpopulations based on intrinsic/extrinsic factors?*
- **Approaches:**
  - To investigate exposure-response relationships for efficacy and safety
  - To identify intrinsic and extrinsic factors that influence the disease, exposure, and response

Image from google

Clinical Pharmacology Studies To Support Dose Optimization and Individualization

Intrinsic Factors

- **Renal impairment**
  FDA guidance, September 2020
  https://www.fda.gov/media/78573/download
- **Hepatic impairment**
  FDA guidance, May 2003
  https://www.fda.gov/media/71311/download
- **Age**
- **Genotype**

  ….

Extrinsic Factors:

- **Drug-drug interactions**
  FDA guidances, January 2020
  https://www.fda.gov/media/134581/download
  https://www.fda.gov/media/134582/download
- **Food effect**
  FDA guidance, February 2019
  https://www.fda.gov/media/121313/download

  …

Other Factors:

- **Bioavailability studies**
  FDA guidance, April 2022
  https://www.fda.gov/media/121311/download
- **Immunogenicity**
  FDA guidances 2019 &2014
  https://www.fda.gov/media/119788/download
  https://www.fda.gov/media/85017/download
- **Bioanalytic method**
  FDA guidance, May 2018
  https://www.fda.gov/media/70858/download

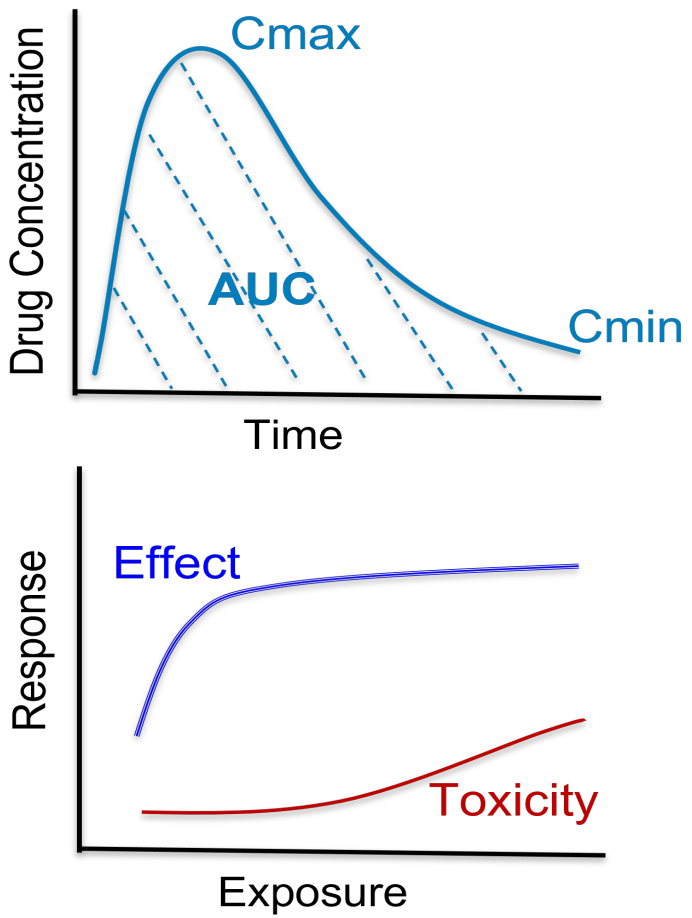
The sponsors may receive a list of standard comments in their early interaction (e.g., pre-IND) with FDA. Discuss with FDA of your specific drug development program for rare diseases:

1) *Which studies are needed?*
2) *When do you need these clinical pharmacology studies?*
3) *What are the potential alternative approaches?*

Exposure (E), Response (R), and E-R relationships

- Exposure: drug concentrations achieved following a dose administration
  - Dose, AUC, Cmax, Cmin (Ctrough)
- Response: desirable (efficacy) and undesirable (safety) drug effects
  - Clinical outcome/endpoints, pharmacodynamic (PD) biomarkers, adverse events
- Exposure-response relationships
  - Relating the drug concentrations (from various doses) to observed clinical response
  - Modeling approach has assumptions

An optimal dose is an effective and safe dose for an individual patient.



"Exposure-Response" In Regulatory Decision-Making

- **Guide dose selection through all phases of drug development**
  - ✓ *Exposure-response relationships (FDA guidance; April 2003)*
    https://www.fda.gov/media/71277/download
  - ✓ *Population pharmacokinetics (FDA guidance; February 2022)*
    https://www.fda.gov/media/128793/download
  - ✓ *Dose-response (ICH-E4)*
    https://database.ich.org/sites/default/files/E4_Guideline.pdf

- **Provide evidence of effectiveness**
  - ✓ *Demonstrating substantial evidence of effectiveness (Section IV.C; FDA guidance, December 2019)*
    https://www.fda.gov/media/133660/download
  - ✓ *Providing Clinical Evidence of Effectiveness (Section II.C.1, FDA guidance, May 1998)*
    https://www.fda.gov/media/71655/download

- **Recommend dosing in specific patient population**
  - ✓ *Clinical Pharmacology considerations for Pediatric studies (FDA guidance; December 2014)*
    https://www.fda.gov/media/90358/download

- **Assess special safety endpoint**
  - ✓ *QT/QTC guidance (ICH-E14)*
    https://www.fda.gov/media/71372/download

Dose-Finding in Rare Diseases: Current Experiences

- Among 40 NME NDA/BLA approved for rare genetic diseases from 2015 to 2020, 21 (53%) of the development programs conducted dedicated dose-finding studies.
- Population PK and exposure-response analyses are used in majority of the development programs regardless of whether dedicated dose-finding studies were conducted.

Type of Study or Analysis	All Drug Development Programs (n=40)	No Dedicated Dose-Finding Study (n=19)
Dedicated dose-finding study	21 (53%)	N/A
Population PK analysis	31 (78%)	13 (68%)
Exposure-response analysis	28 (70%)	11 (58%)

Reference: Wang et al. Orphanet Journal of Rare Diseases, 2022

Application of Population PK and E-R Approaches: Examples of DRDMG's Recent NME NDA/BLA Approvals

NDA/BLA#	**NDA 213969**	**NDA 214018**	**BLA 761194**
Drug name	Lonafarnib	Fosdenopterin	Avaglucosidase alfa-ngpt
Approval date	2020	2021	2021
Therapeutic area or indication	Hutchinson-Gilford Progeria Syndrome	Molybdenum cofactor deficiency (MoCD) Type A	Late-onset Pompe disease
Regulatory decision based on population PK, E-R, and other clin pharm approaches	• **Expanding the indication and dosing from 2 years of age and older to patients 12 months and older**	• **Dose adjustment in pediatric patients <12 months of age**	• **Expanding the indication and dosing from 16 years of age and older to 1 year of age and older** • **Body weight-tiered dosing regimens**

References: The product labeling and FDA's Integrated Reviews through Drugs@FDA
DRDMG: Division of Rare Diseases and Medical Genetics, FDA

Take-Away Messages (Part 1):

1. Conduct intrinsic factor studies (e.g., hepatic, renal impairment) based on PK properties of the drug and when these factors are involved in disease pathophysiology and progression; specify organ functions in inclusion/exclusion criteria of the trial design.
2. Conduct at least in vitro DDI studies before the first-in-human trial; update allowed/prohibited concomitant medications in clinical trials as DDI data evolves.
3. For oral drugs, investigate food effect early and specify food conditions in clinical trial design.
4. Include dose-ranging as part of drug development program and explore exposure-response relationships through all phases.
5. Other important reminders: validate PK/PD assays; and use the to-be-marketed drug product (formulation) in the efficacy/safety trial(s)!

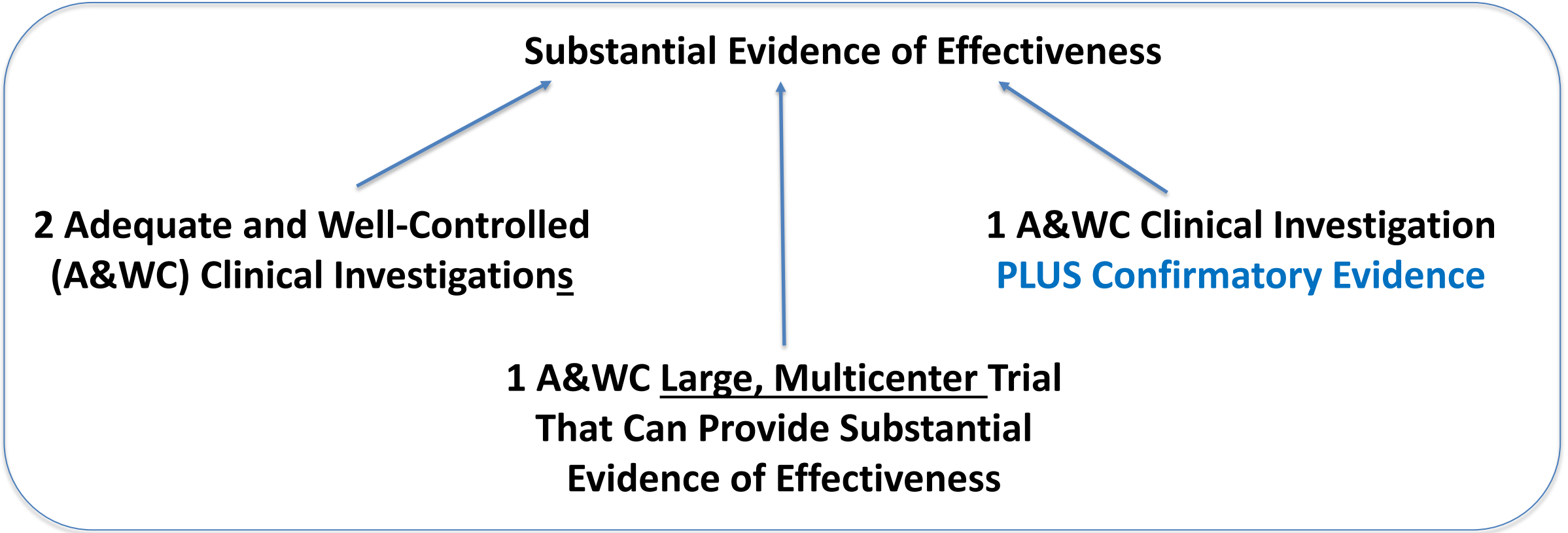
Challenges in Dose Optimization for Rare Diseases

	Challenges In Rare Diseases		
Example	**Limited number of patients**	**Heterogeneity in disease pathogenesis**	**Not-well-defined clinical endpoints**
A typical drug development program for inborn errors of metabolism (IEM)	<100 patients ➔**Low computational capacity**	Disease classes; subtypes; CRIM status; genotypes; phenotypes… ➔**Traditional intrinsic & extrinsic factors for PK less critical**	e.g., 6-minute walk ➔**E-R analysis less likely to inform dosing**

Opportunities and Perspectives:

- Exposure-response analyses and other model-based approaches are increasingly used in orphan NDA/BLA submissions to facilitate dose optimization (i.e., methodologies are available).
- Small number of patients in rare diseases ➔ High percentage of the total patient population already enrolled in clinical trials ➔ Trial results may be more generalizable to the target population.
- Not-well-defined clinical endpoints ➔ Potential use of PD biomarkers when appropriate ➔ Confirmatory Evidence of Effectiveness.
- Less informative of *post hoc* analysis in dose optimization ➔ Early-stage involvement; successes can be planned ➔ Dose-ranging in an adaptive trial.

Role of Confirmatory Evidence in Demonstration of Substantial Evidence of Effectiveness



Reference: Demonstrating substantial evidence of effectiveness (FDA guidance, December 2019)

Use of Biomarker Data as Confirmatory Evidence

- Selection of biomarker:
  - Should consider both the mechanism of action of the drug and well-understood disease pathophysiology;
  - Does not need to be validated as a surrogate endpoint that predict clinical outcomes.
- The biomarker data can be from earlier phase clinical trials.
- Demonstration of an exposure-response relationship of the PD biomarker data can strengthen its use as confirmatory evidence.
- Bioanalytical assays should be adequately validated.

If the sponsor plans to use data from one adequate and well-controlled clinical investigation plus confirmatory evidence to establish effectiveness, the sponsor is encouraged to discuss with the FDA early regarding what will comprise the confirmatory evidence.

Use of Pharmacodynamic Biomarkers in Dose-Finding

- Majority of the dose-finding studies for rare genetic diseases have used PD biomarkers as primary or secondary endpoints (*Orphanet Journal of Rare Diseases, 2022);*

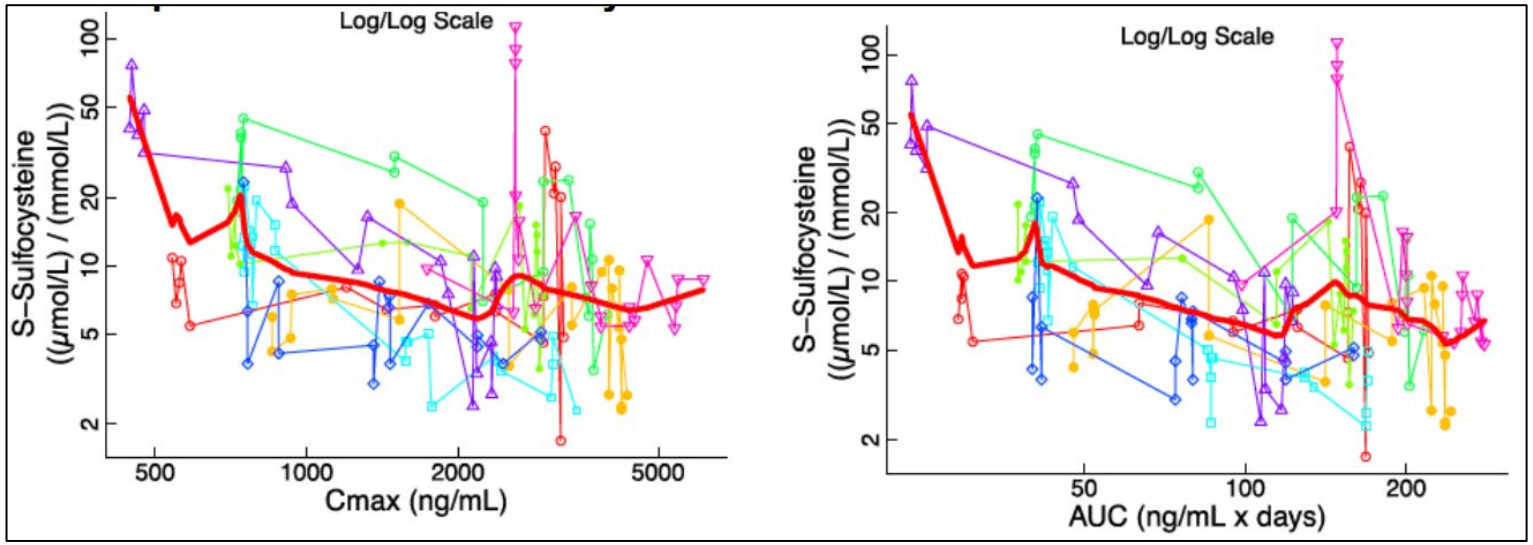
Category of Primary Endpoint	Number of Dedicated Dose-Finding Studies (n=13)
Biomarker	**10 (77%)**
Clinical Outcome	1 (8%)
Biomarker, Clinical Outcome Assessment	1 (8%)
Biomarker, Clinical Outcome	1 (8%)
Category of Secondary Endpoint	Number of Dedicated Dose-Finding Studies (n=22)
Biomarker	**14 (64%)**
Clinical Outcome	2 (9%)
Biomarker, Clinical Outcome Assessment	4 (18%)
Biomarker, Clinical Outcome Assessment, Clinical Outcome	1 (5%)
Clinical Outcome, Clinical Outcome Assessment	1 (5%)

- PD biomarkers are more sensitive to drug effects ➔ smaller number of patients and shorter treatment duration.

Use of Biomarker as Confirmatory Evidence: An Example

NDA 214018: Fosdenopterin for patients with molybdenum cofactor deficiency (MoCD) Type A; Approved 2021

- In MoCD Type A, the lack of effective sulfite oxidase (SOX) results in elevated levels of the neurotoxic sulfite, S-sulfocysteine (SSC).
- Treatment with fosdenopterin resulted in a reduction in the level of urinary SSC. Higher plasma fosdenopterin exposure was associated with lower urinary SSC.
- The exposure-response relationship supported the recommended dosing regimens and further strengthened the use of biomarker data as confirmatory evidence.

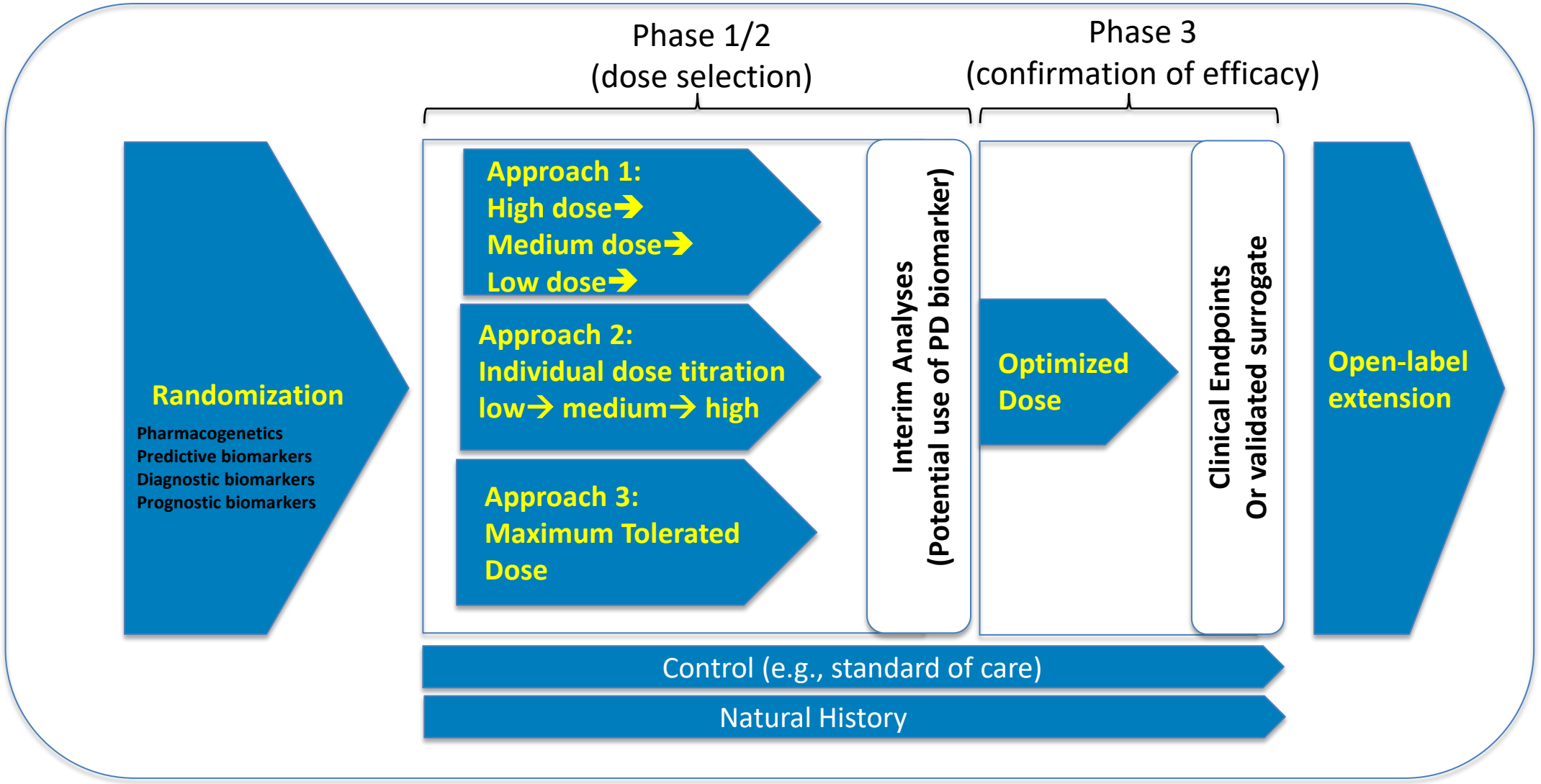


References: The product labeling and FDA's Integrated Review for NDA 214018 at Drugs@FDA

Exposure-Response and Clinical Trial Design

Study Design	**Pros**	**Cons**
Cross-over	• Provide both population and individual exposure-response	• Need reversible response endpoints; changes in baseline-comparability
Parallel	• Long-term treatment with chronic response	• Do not provide individual exposure-response • Need relatively large sample size
Titration	• Provide both population and individual exposure-response • Need relatively small sample size	• Potential carryover effect

Dose Optimization by Design: Adaptive Dose-Ranging Trial

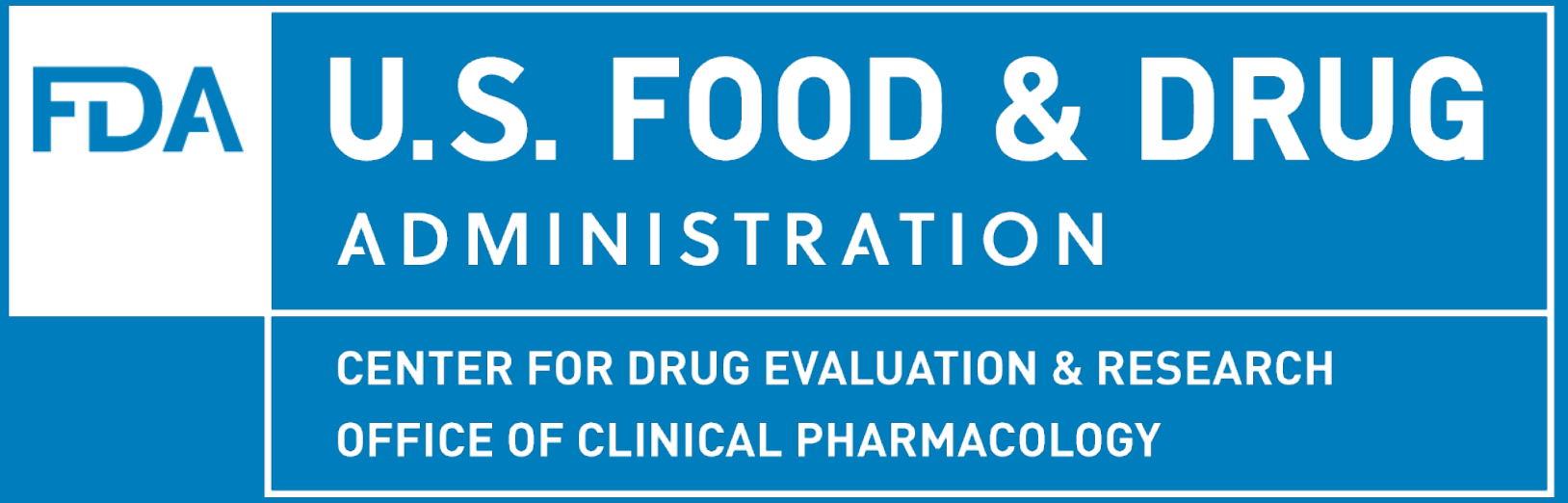


Take-Away Messages (Part 2):

1. Establish a comprehensive biomarker assessment plan in early phases of clinical development; validate bioanalytical assays for biomarker assessment;
2. Ensure adequate PK&PD sampling in all clinical trials to allow for E-R analyses for PD biomarkers;
3. Consider seamless designs that incorporate both dose selection and confirmation of efficacy of the selected dose, when dedicated dose-ranging trials are not feasible.

Acknowledgement

- DTPM and Office of Clinical Pharmacology
  - Nayeem Hossain
  - Travis Ready
  - Michelle Li
  - Oluseyi Adeniyi
  - Kate Drozda
  - Lian Ma
  - Lingshan Wang
  - Gilbert Burckart
  - Robert Schuck
  - Michael Pacanowski
- FDA review teams for the NDA/BLA case examples
- DRDMG


FDA
U.S. FOOD & DRUG
ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

CORE PRINCIPLES FOR CLINICAL TRIALS

Jie (Jack) Wang, Ph.D.
Clinical Pharmacology Team Leader, Division of Translational and Precision Medicine, Office of Clinical Pharmacology (OCP), OTS, CDER, FDA

Katie Donohue, M.D., M.Sc.
Director, DRDMG, ORPURM, OND, CDER, FDA

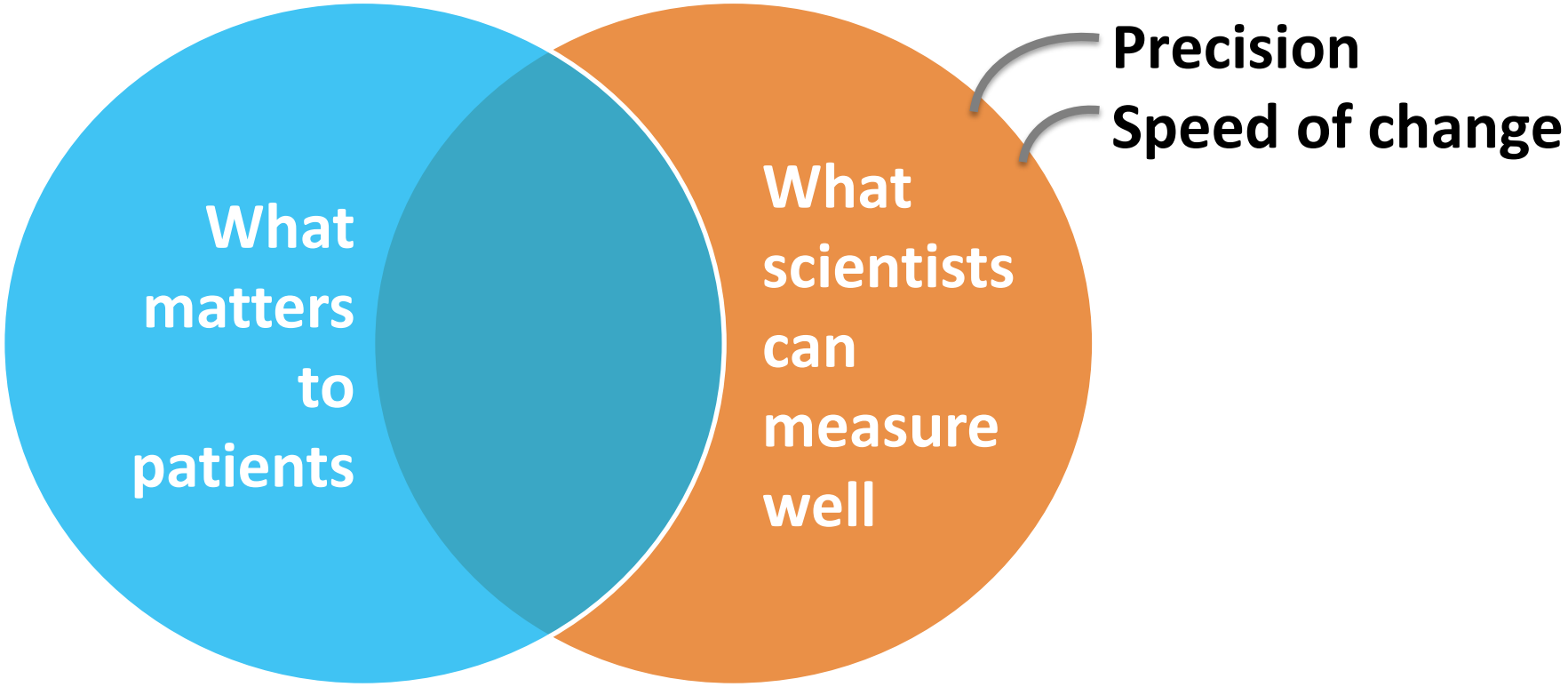
Yan Wang, Ph.D.,
Statistical Team Leader, Division of Biometrics IV, Office of Biostatistics (OB), Office of Translational Sciences (OTS), CDER, FDA

CDER-NCATS Rare Disease Workshop
May 16, 2022

Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies
- In this talk "drug" refers to both drugs and biologics

Endpoints


What matters to patients
What scientists can measure well
Precision
Speed of change

When can single arm trials work?

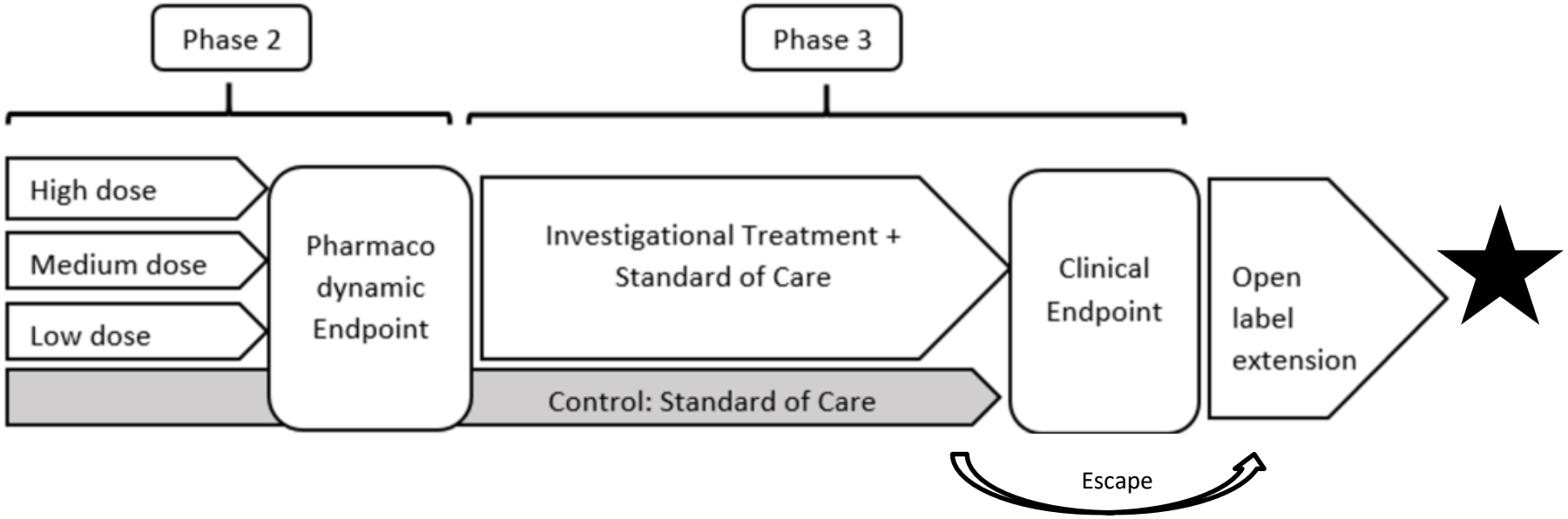
- Objective endpoints that predict clinical benefit – x-rays, blood tests
- Natural history stable over time
- Dramatically effective treatments

Nannenberg et al. Effect of Ascertainment Bias on Estimates of Patient Mortality in Inherited Cardiac Diseases. Circ Genom Precis Med. 2018 PMID: 30354299.

Randomize the first patient

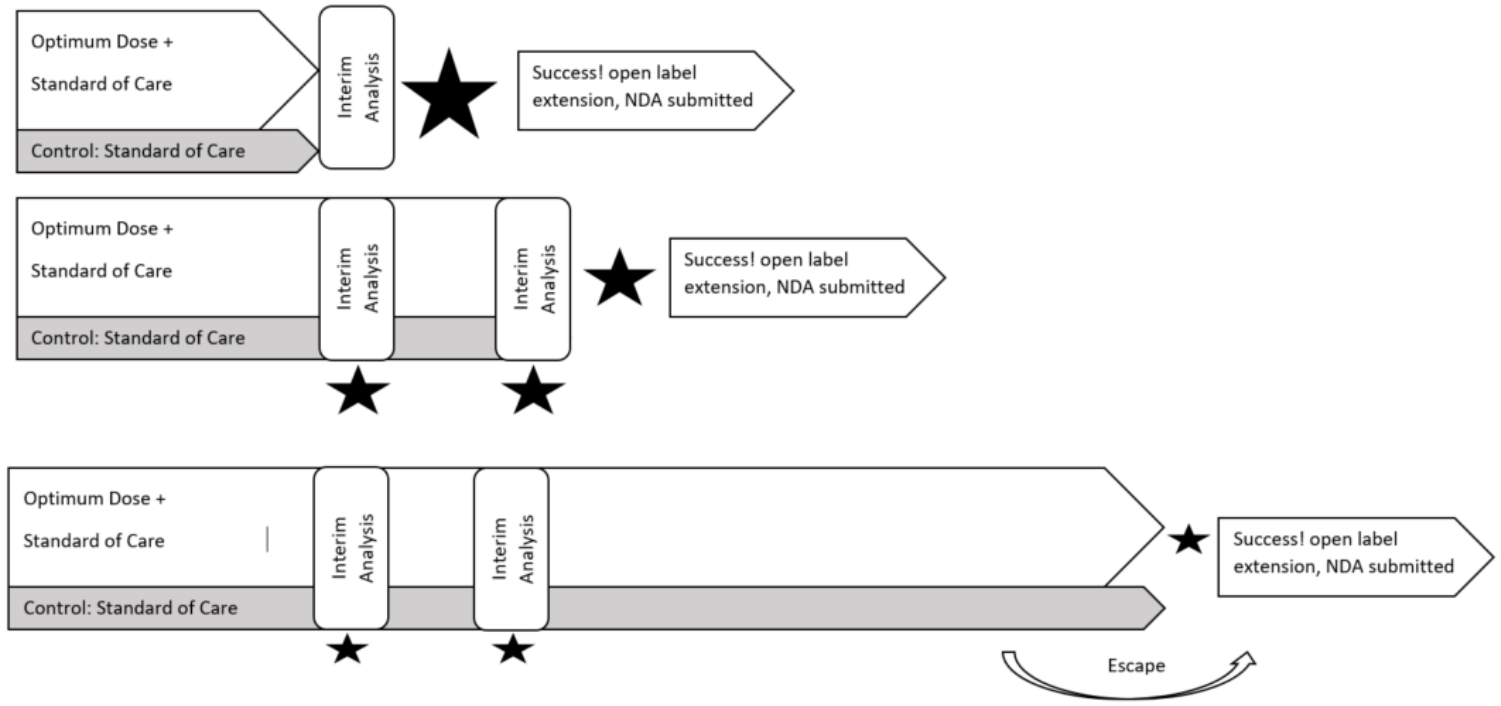
Be good stewards of *perception* of equipoise

Dose-ranging in rare diseases



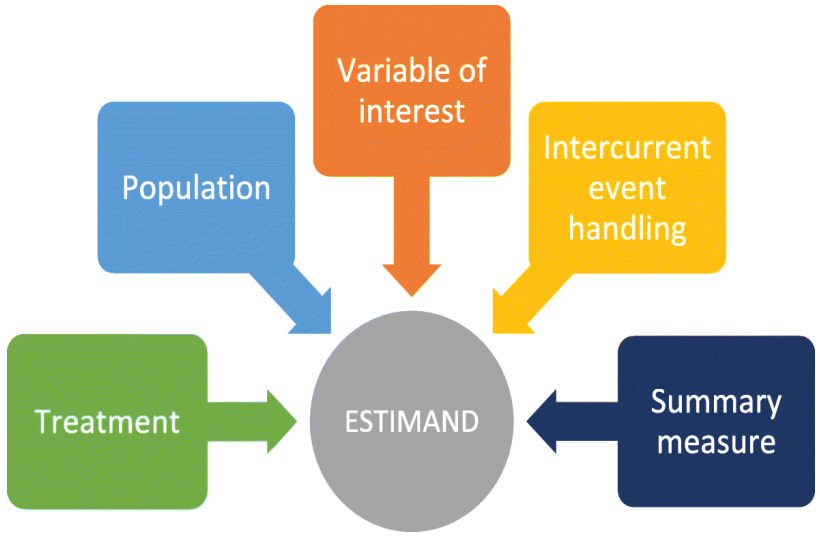
FDA Guidance: Adaptive Designs for Clinical Trials of Drugs and Biologics
https://www.fda.gov/media/78495/download

Adapting Trial Duration



www.fda.gov

Estimands



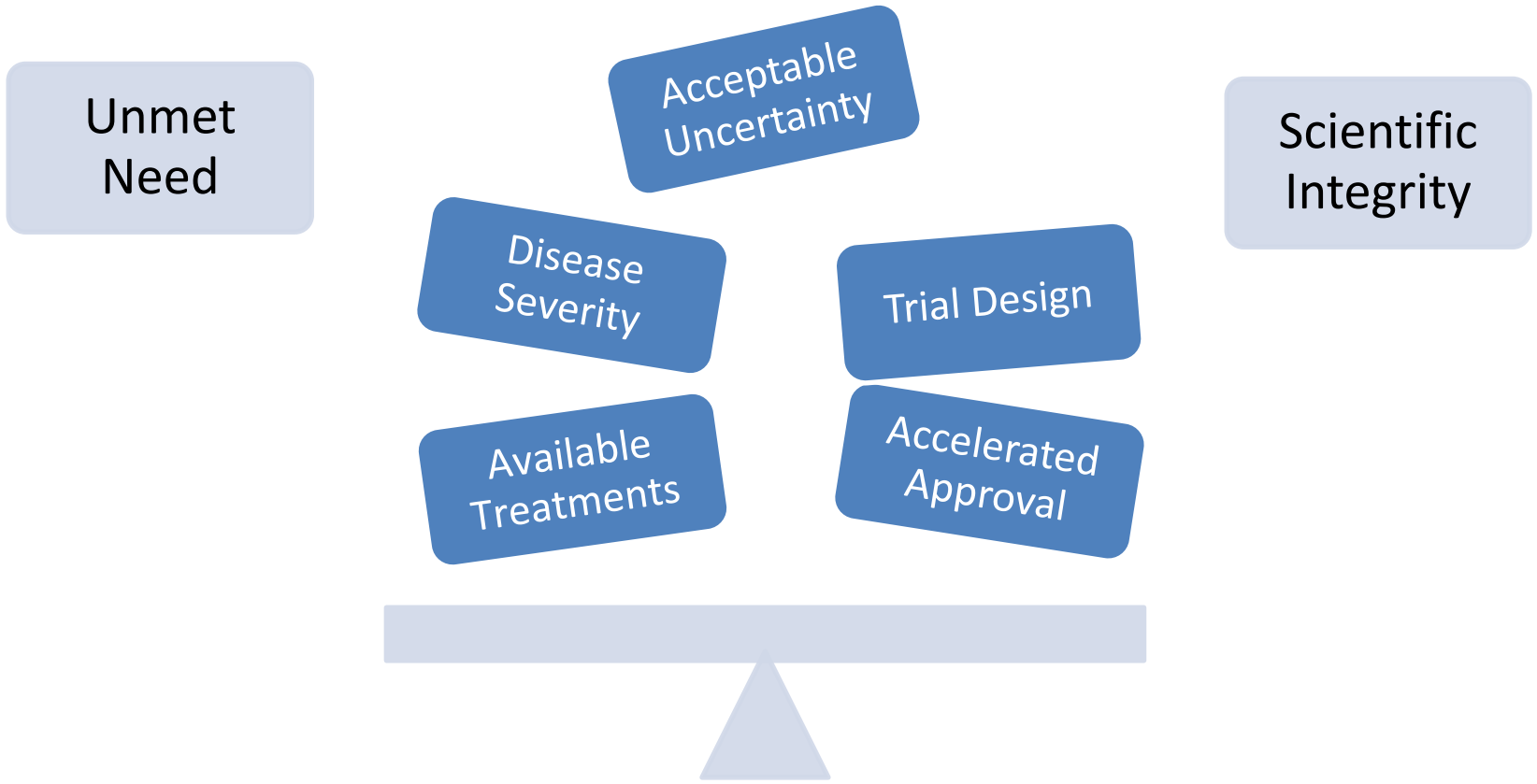
Intercurrent events – events that occur after treatment initiation and affect interpretation or existence of outcome measurement

e.g. discontinuation of treatment, switching between treatments, or use of an additional medication

Trial protocol should describe planned measures to encourage all study patients to remain in the trial for key efficacy and safety assessments even after prematurely discontinuing study treatment or experiencing other intercurrent events. ← we should obtain as much data as possible in small sized trials

ICH E9 (R1) Addendum
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

Regulatory Flexibility




FDA
U.S. FOOD & DRUG
ADMINISTRATION

Statistical Considerations in Rare Disease Clinical Trials

Yan Wang, Ph.D.
Statistical Team Leader, Division of Biometrics IV
Office of Biostatistics
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

CDER-NCATS Workshop: Regulatory Fitness in Rare Disease Clinical Trials
May 16, 2022

Disclaimer

This talk reflects the views of the author and should not be construed to represent FDA's views or policies

In this talk, "drug" refers to both drugs and biologics. Representative examples of commercial products may be given to illustrate a methodology or approach to problem solving. No commercial endorsement is implied or intended.

Outline

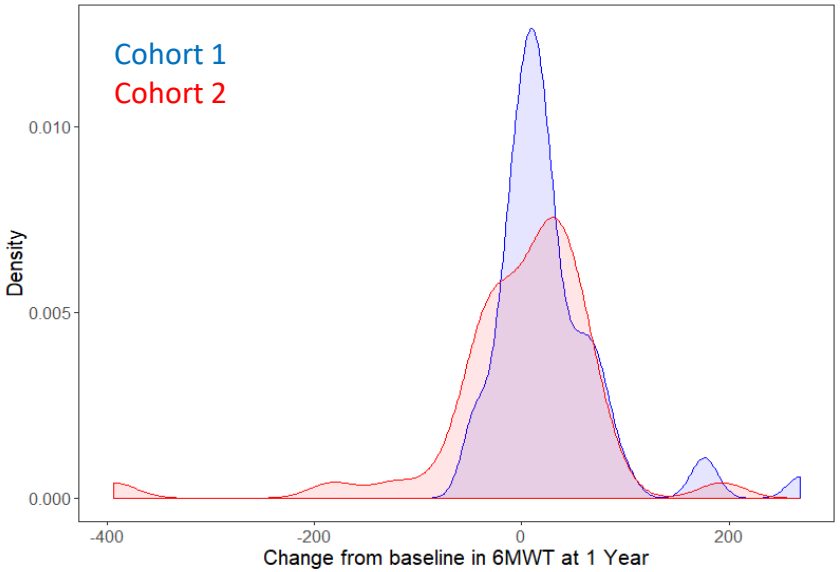
- Design, Endpoint, and Analysis
- Sample Size and Power Calculation
  - Sample size re-estimation
  - Treatment duration adaptation
  - Global tests for multiple endpoints
- Quality of Trial Conduct and Data Collection

Challenges in Drug Development for Rare Inborn Errors of Metabolism (IEM)

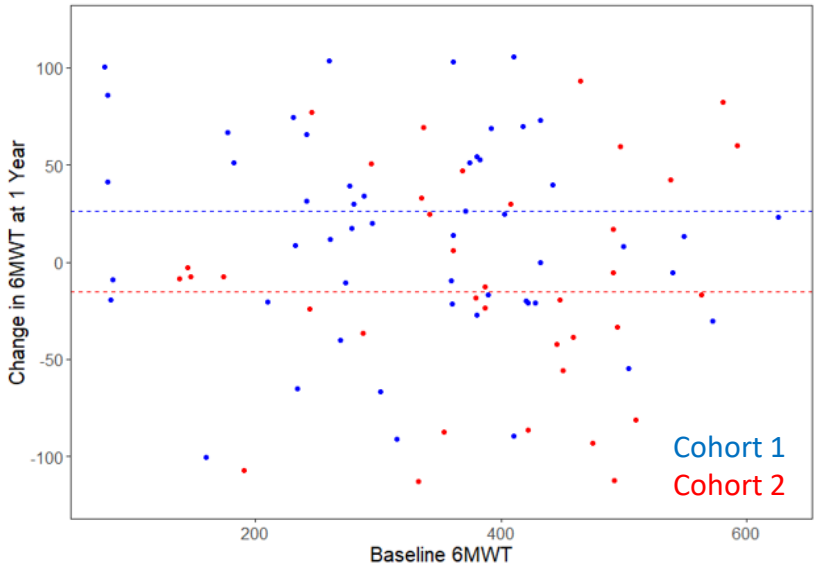
- Small and sometimes very small patient populations
  - Definition of a rare disease: fewer than 200, 000 patients
  - Many IEM have less than few thousands of patients
- Natural history often poorly understood
- Affect multiple organs and tissues and have heterogeneous clinical manifestations
- Lack of understanding and consensus on efficacy endpoints
- Difficulty for new drug development after the first approval (Non-inferiority trial is often infeasible)
- Efficacy outcome measurements usually have large variabilities

Example: large variabilities in distance walked during a 6-minute walk test (6MWT) for patients with late-onset Pompe disease (LOPD)

	Change from baseline in 6MWT at 1 year
Cohort 1 (N=57)	Mean = 27m & SD = 55m
Cohort 2 (N=43)	Mean = -2m & SD = 85m



Density functions estimated based on data from two clinical trials



Data were generated using the mean and SD estimated from two clinical trials

Example: large variabilities in 6MWT for patients with LOPD (cont.)

	Change from baseline in 6MWT at 1 year
Cohort 1 (N=57)	Mean = 27m & SD = 55m
Cohort 2 (N=43)	Mean = -2m & SD = 85m

- Two cohorts came from two different trials and patients in both cohorts received the same treatment
- Was the observed difference in the mean change from baseline due to chance alone, or due to difference in baseline disease severity, standard of care, or procedures for the 6MWT test? Was the studied treatment effective?

Need a randomized placebo-control trial to answer these questions!

Randomized, double-blinded, and placebo-controlled trial design is most commonly used

Most reliable design to determine effectiveness of a drug

- **Randomization**: unbiased assignment of patients to trial arms
- **Double-blinded:** assigned treatments are blinded to patients and investigators
- Minimize/eliminate potential biases caused by
  - Differences in baseline prognostic factors (known/unknown)
  - Placebo effect, observer effect, and differences in standard of care
- Placebo control does not imply that the control group is untreated → all patients receive standard of care → limit ethical concern

Primary Efficacy Endpoint (Variable)

- Provide primary evidence of efficacy for drug approval
- Directly measure how a patient feels, functions, or survives
- Can be validated surrogate endpoint or validated clinical outcome assessment (COA)
- Surrogate endpoint that is reasonably likely to predict clinical benefit can be used for accelerate approval
- **Composite endpoint:** integrate or combine multiple measurements into a single or "composite" variable
  - e.g., time to the first occurrence of death, renal, cardiovascular, and cerebrovascular events for Fabry disease
  - e.g., total Chorea score for 7 different parts of the body for Huntington disease (validated COA)
- **Multiple primary endpoints:** selected to cover the range of treatment effect
  - e.g., 6MWT and FVC (% predicted) for LOPD, MPS-I, MPS-II

Statistical Analysis

The principal features of the statistical analysis of the primary endpoint(s) should be described in the statistical section of the protocol

- Null and alternative hypotheses: the null hypothesis proposes that the test drug has no treatment effect.
  - For continuous outcomes: difference in means or medians
  - For binary outcomes: risk difference, relative risk, odds ratio
  - For time-to-event outcomes: difference in survival probabilities, restricted means or medians of survival time
- Methods for estimating and testing treatment effect
- Methods for controlling type I error rate at the pre-specified significance level
- Methods for handling missing data

Sample Size Determination

- Key question in designing a randomized controlled trial: how many patients should be enrolled?
- Should be large enough to provide a reliable answer to the question: Does the test drug have a treatment effect
- Protocol should clearly provide details on **the key elements impacting sample size calculation**
  - The null hypothesis and the method for testing this hypothesis
  - Significance level (type I error rate α): probability of erroneously rejecting the null hypothesis if it is true
    - The lower the significance level, the more likely it is to avoid a false positive claim and the more samples needed
    - Conventionally set at 0.025 for a 1-sided test
    - Larger α level may be used for ultra rare diseases

Key elements impacting sample size calculation (cont.)

- Power: probability of detecting a true treatment effect when it exists
  - The higher the power, the more likely it is to detect an effect when it exists, and the more samples needed
  - Conventionally set at 80% - 90%

- Effect Size: the magnitude of the treatment effect and its variability assumed under the alternative hypothesis. For a continuous endpoint,

$$\text{Effect Size} = \frac{\text{Treatment Effect}}{\text{Standard Deviation}} = \frac{\text{Mean}_T - \text{Mean}_C}{SD} = \frac{\Delta}{SD}$$

  - The larger the Δ, the easier it is to detect an effect and require fewer samples
  - The smaller the SD, the easier it is to detect an effect and require fewer samples

How to Estimate Effect Size in Sample Size Calculation?

- In principle, effect size should be estimated based on the minimal effect which has clinical relevance, or published data, or the results of earlier trials in similar settings
- For rare diseases without approved therapy, there are often limited or no data available to estimate effect size
- Rare disease trials are typically sized based on an assumed large effect size
- However, most drugs have a moderate effect size if it exits

Examples: Effect Sizes Estimated Based on Data from Randomized Placebo-Controlled Trials

	Aldurazyme (laronidase)	Elaprase (idursulfase)	Lumizyme (alglucosidase alfa)
Disease population	MPS-I	MPS-II	LOPD
Treatment duration	6 months	12 months	18 months
# of patients randomized	45	64	90
Effect Size			
6MWT	0.56	0.60	0.48
FVC (% predicted)	0.61	0.27	0.65

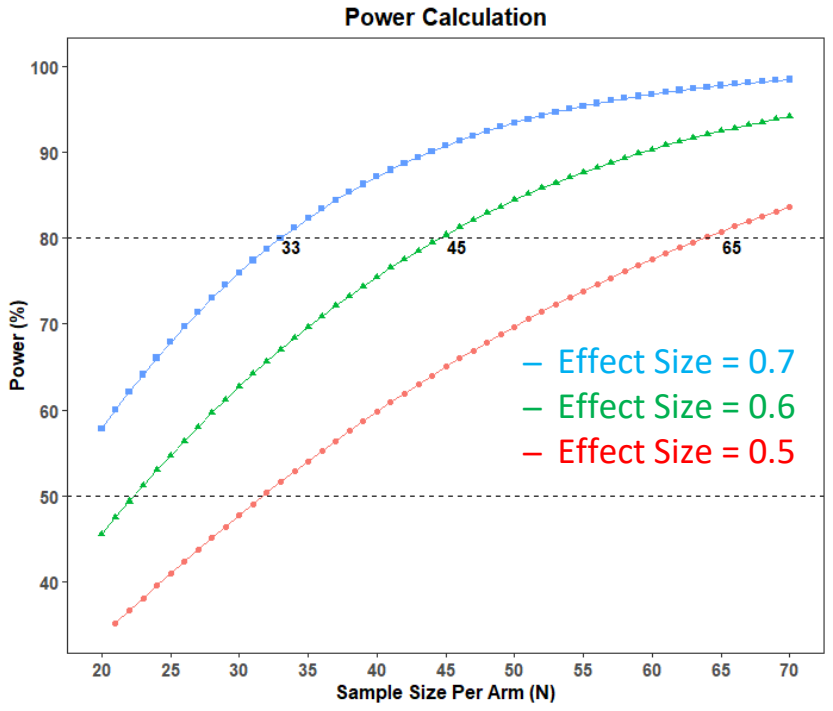
MPS: mucopolysaccharidosis
LOPD: late-onset Pompe disease
6MWT: distance walked in a 6-minut walk test
FVC: forced vital capacity

http://wayback.archive-it.org/7993/20170404044054/https://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4389s1-00-index.htm

Examples: Sample Size (SS) and Power Calculations

Setting: placebo-controlled trial with 1:1 randomization

- For an effect size = 0.7, **33 per arm** are needed to attain a power of 80%
- For an effect size = 0.6, **45 per arm** are needed to attain a power of 80%
- For an effect size = 0.5, **65 per arm** are needed to attain a power of 80%
- Most trials for rare IEM have a SS < **30 per arm** and thus are underpowered (< 50%) to detect a statistically significant treatment effect if the test drug has a moderate effect size (≤ 0.5)



α level = 0.05 for 2-sided test

Approaches to Increase Power (Chance of Success) in Detecting a Statistically Significant Treatment Effect

- Adaptive design: sample size re-estimation
- Adaptive design: treatment duration adaptation
- Global tests for multiple endpoints

Trial Design With Sample Size Re-estimation (SSR)

- Address the considerable uncertainty on the assumed effect size in sample size calculations for rare disease trials
- Based on interim data, SSR methods investigate the validity of the assumed effect size and increase the sample size if the conditional power is promising
- The conditional power is calculated based on the assumption that the future treatment effect will be the same as the one estimated from the interim data
  - if the conditional power is promising (e.g., 50%), the sample size can be increased to attain a higher power (e.g., 80%)
  - if the conditional power is favorable (e.g., >80%), the sample size will not be increased

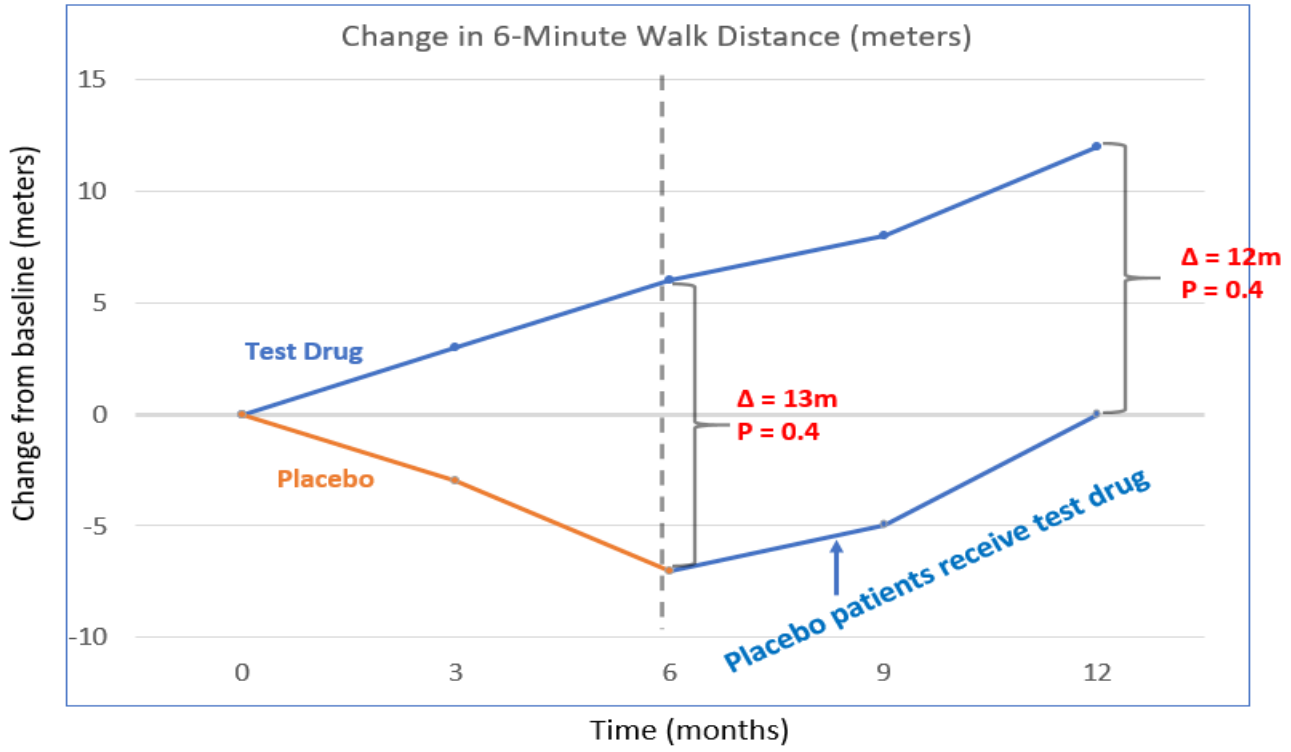
SSR: hypothetical example

- A trial with SSR: starts with a planned SS of 33 per arm based on an assumed effect size of **0.7** (6MWT: Δ=35m & SD=50m) to attain a power of 80% and plans to increase the SS up to 50 per arm if the pre-defined interim analysis is promising
- The interim analysis is run after the first 20 patients per arm
  - The estimated effect size is **0.55** (6MWT: Δ=30m & SD=55m)
  - The conditional power is 65% and promising
- SS is increased to 45 per arm (36% increase from 33) to attain a conditional power of 80%
- If the trial is designed with a fixed SS based on an effect size of 0.55, 54 per arm are needed to attain a power of 80% → a **20%** increase compared to the design with SSR (45 per arm)

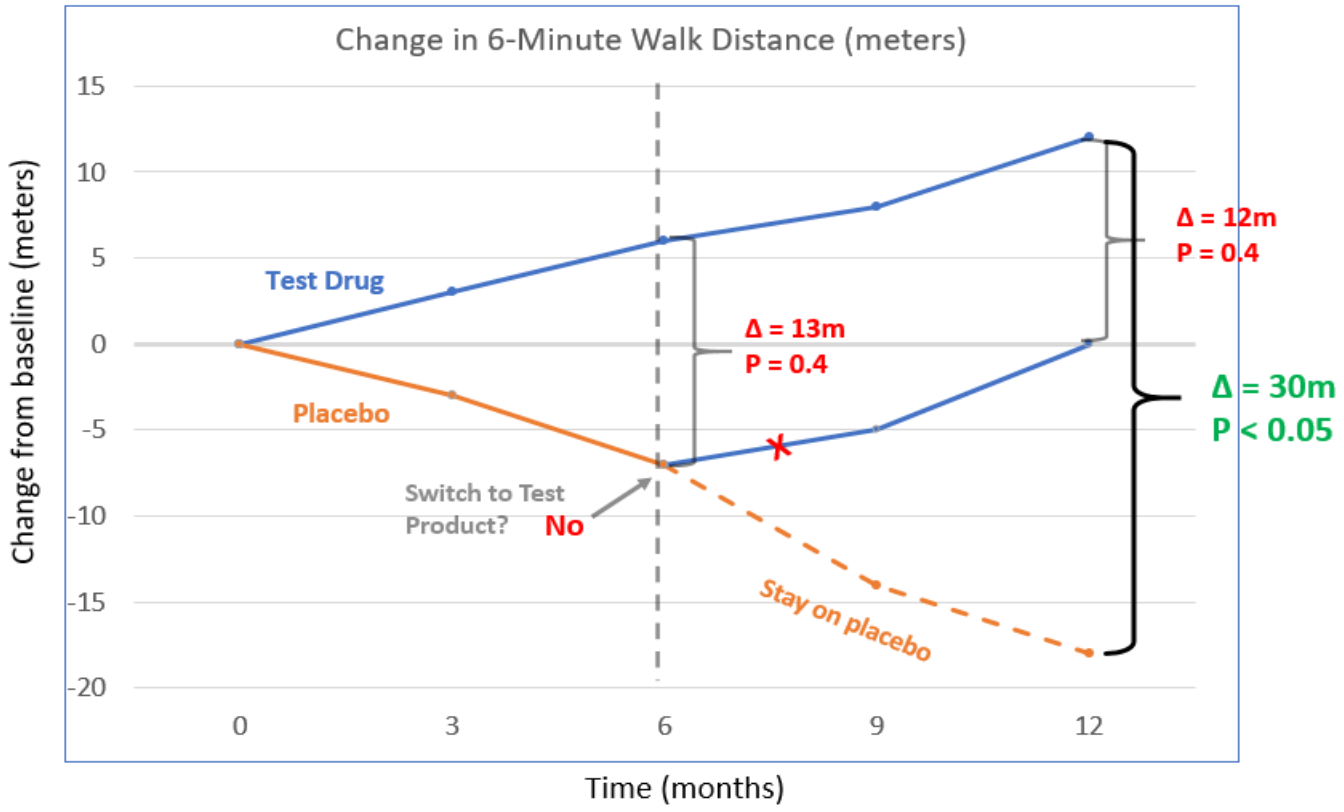
Trial Design With Treatment Duration Adaptation

- Address the considerable uncertainty on the treatment duration needed to demonstrate efficacy
- Adaptation is based on an analysis of the efficacy endpoint assessed at a pre-defined interim time point for **all patients**
  - If the analysis shows convincing efficacy, the randomized treatment can be stopped early prior to the pre-defined maximum time point T_{max}
  - If the analysis does not show convincing efficacy, all patients remain on their randomized treatment and the final efficacy analysis is based on the endpoint assessed at T_{max}
- In other words, this design consists of two efficacy endpoints -- one assessed at the interim time point and one at T_{max}, and the trial can stop early prior to T_{max} if the endpoint at the interim time point meets the pre-defined success criteria for efficacy

Trial Fails to Provide Conclusive Evidence of Efficacy Due to Inadequate Treatment Duration



Successful Trial with Treatment Duration Adaptation



Global Tests for Multiple Endpoints

When a test drug is anticipated to have effect on multiple endpoints in a small trial, it is desirable to perform a global test on the multiple endpoints so that one can make a single probability statement about the drug effect.

Hypothetical Trial

Change from baseline at 52 weeks	FVC%		6MWT (meter)	
	Placebo (N=24)	Drug (N=24)	Placebo (N=24)	Drug (N=24)
Mean (SD)	-0.1 (10)	3.5 (10)	13 (60)	40 (76)
Treatment Comparison				
Difference (95% CI)	3.6 (-2.1, 9.1)		27 (-11, 65)	
P-value				
ANCOVA	0.12		0.07	
Global Test				
O'Brien Rank-Sum		**0.03**		
Test-Statistics-Sum		**0.02**		

Drug is efficacious

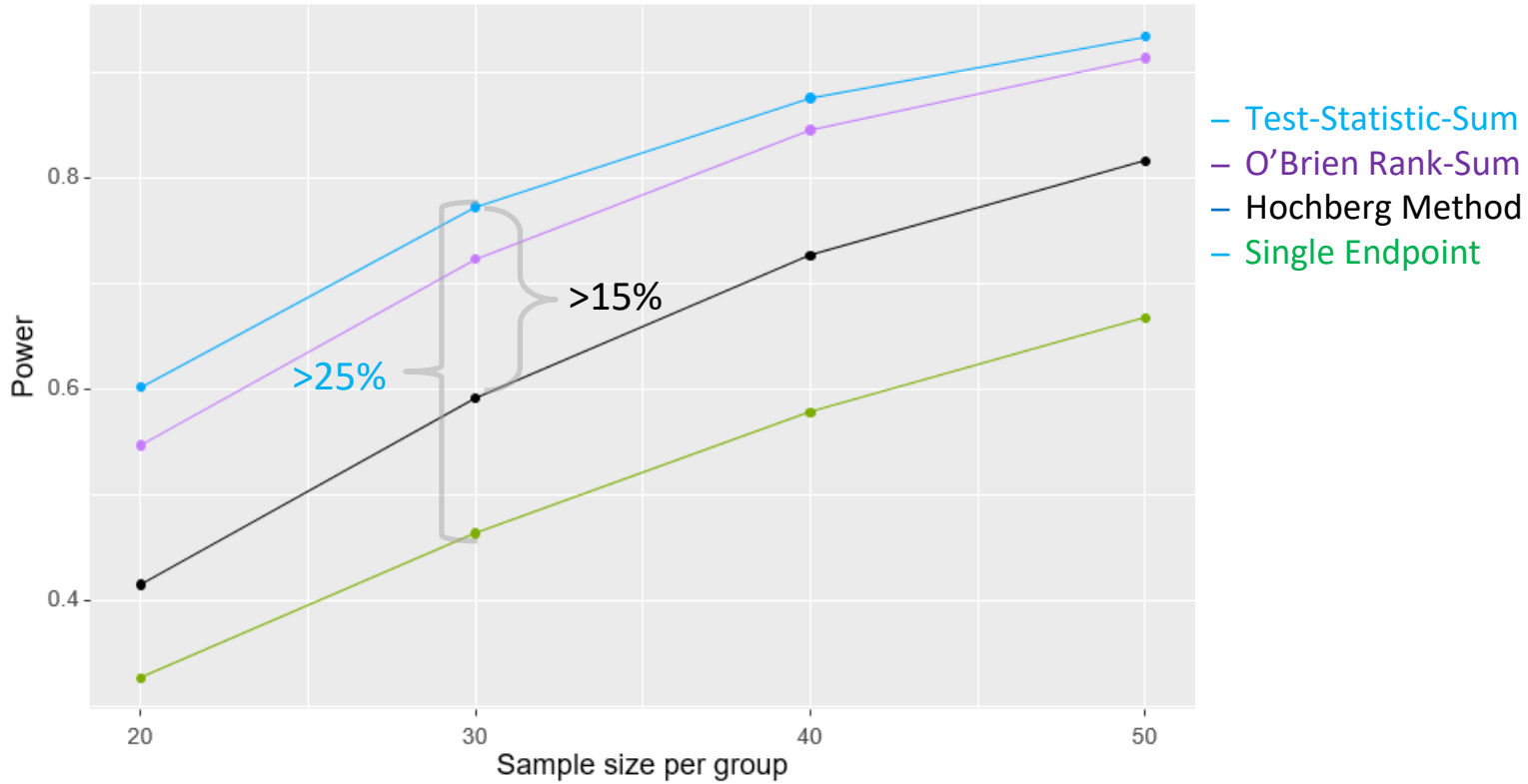
Global Tests Integrate Evidence from Multiple Endpoints

- **O'Brien Rank-Sum:** based on the sum of the ranks of data from the multiple endpoints for each patient
  - Combines data at patient-level
  - Typically used for continuous or ordinal endpoints

- **Test-Statistics-Sum:** based on the test statistics for treatment comparison for each endpoint
  - Combines test statistics at endpoint-level
  - Can be used for all types of endpoints, including binary endpoints and time-to-event endpoints

Global Tests: more powerful when a drug has effect on both endpoints

Simulation Study: Effect size = 0.5 for both endpoints



Data were generated using a normal distribution for each endpoint

High Quality of Trial Conduct and Data Collection Are Essential to Success of Rare disease Trials

- ICH E6(R2) Good Clinical Practice Guidelines

  "*The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).*"

  "*Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.*"

- Methods and procedures for outcome assessments should be standardized to reduce external variability → increase statistical power

Example 6MWT: Δ = 35m, SD = 60m, and N = 35 per arm (α=0.05)
10% Variability ↓ from 60m to 54m, **13%** power ↑ from 67% to 76%

Acknowledgement

Division of Biometrics IV/OB/OTS/CDER/FDA

Yared Gurmu, Ph.D.

Wonyul Lee, Ph.D.

Emily Morris, Ph.D.

Therri Usher, Ph.D.

Lei Nie, Ph.D.

References

1) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9-statistical-principles-clinical-trials
2) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical
3) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1
4) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products
5) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry
6) https://oir.nih.gov/sites/default/files/uploads/sourcebook/documents/ethical_conduct/data_quality_management-2015_05_15.pdf
7) Cyrus R. Mehta and Stuart J. Pocock: “Adaptive increase in sample size when interim results are promising: a practical guide with examples”, *Statistics in Medicine, Vol. 30, 2010*
8) O’Brien, P. C.: “Procedures for comparing samples with multiple endpoints”. *Biometrics, Vol. 40, No. 4: 1079-1087, 1984*
9) Ristl R. et al.: “Methods for the analysis of multiple endpoints in small populations: A review”. *Journal of Biopharmaceutical Statistics, 29:1, 1-29, 2018*

SESSION 3: CORE PRINCIPLES FOR CLINICAL TRIALS

Moderator: Katie Donohue, M.D., M.Sc.,
Director, DRDMG, ORPURM, OND, CDER, FDA

We'll be back after this short break...

SESSION 4: CASE STUDIES — REAL WORLD EXPERIENCES

Moderator: Tiina K. Urv, Ph.D.,
Program Director, DRDRI, NCATS, NIH

From biomarker to study to basket: trials and tribulations of advancing science from the bedside or bench to trials: two models in academia

Andrea Gropman, M.D., FAAP, FACMG, FANA

NIH National Center for Advancing Translational Sciences

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NIH National Institute of Diabetes and Digestive and Kidney Diseases

Urea Cycle Disorders Consortium

RARE DISEASES CLINICAL RESEARCH NETWORK

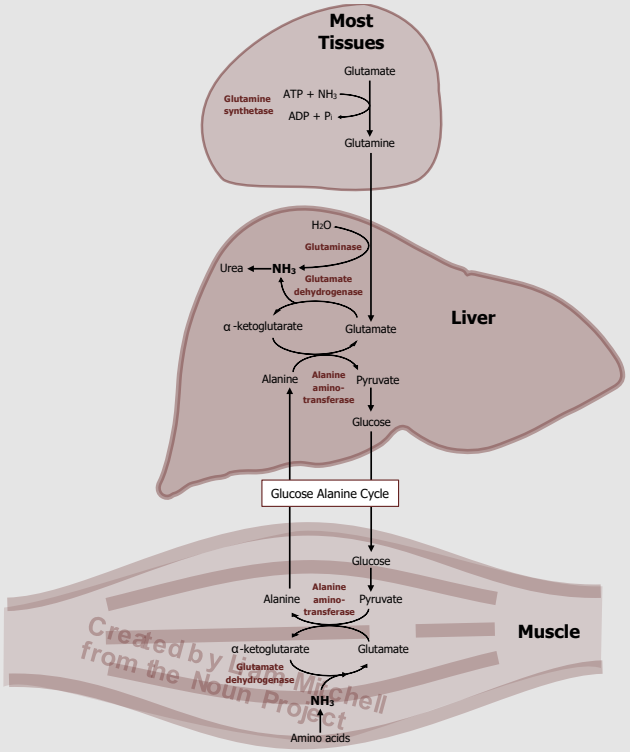
National Urea Cycle Disorders Foundation

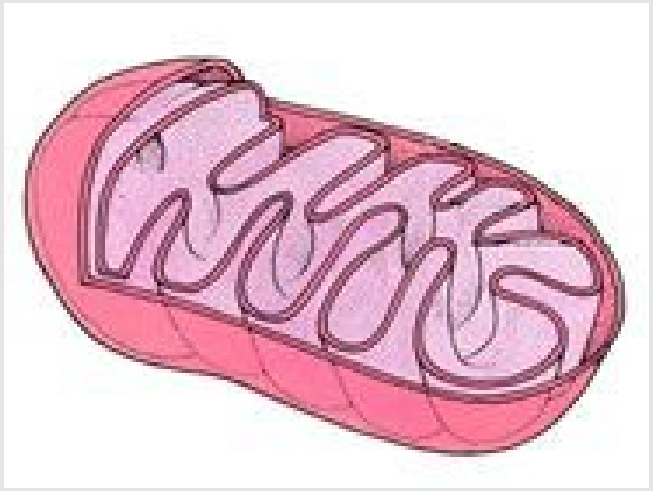
families research education support ... Hope

Disclosures

- I receive federal funding from NIH, NCATs, NIDDK, HRSA
- I receive funding from private foundations: O'Malley Family Foundation, Kettering Foundation
- Medical and Scientific Advisory boards: NUCDF, PRISMS, MSUD

Drug development in two classes of disease



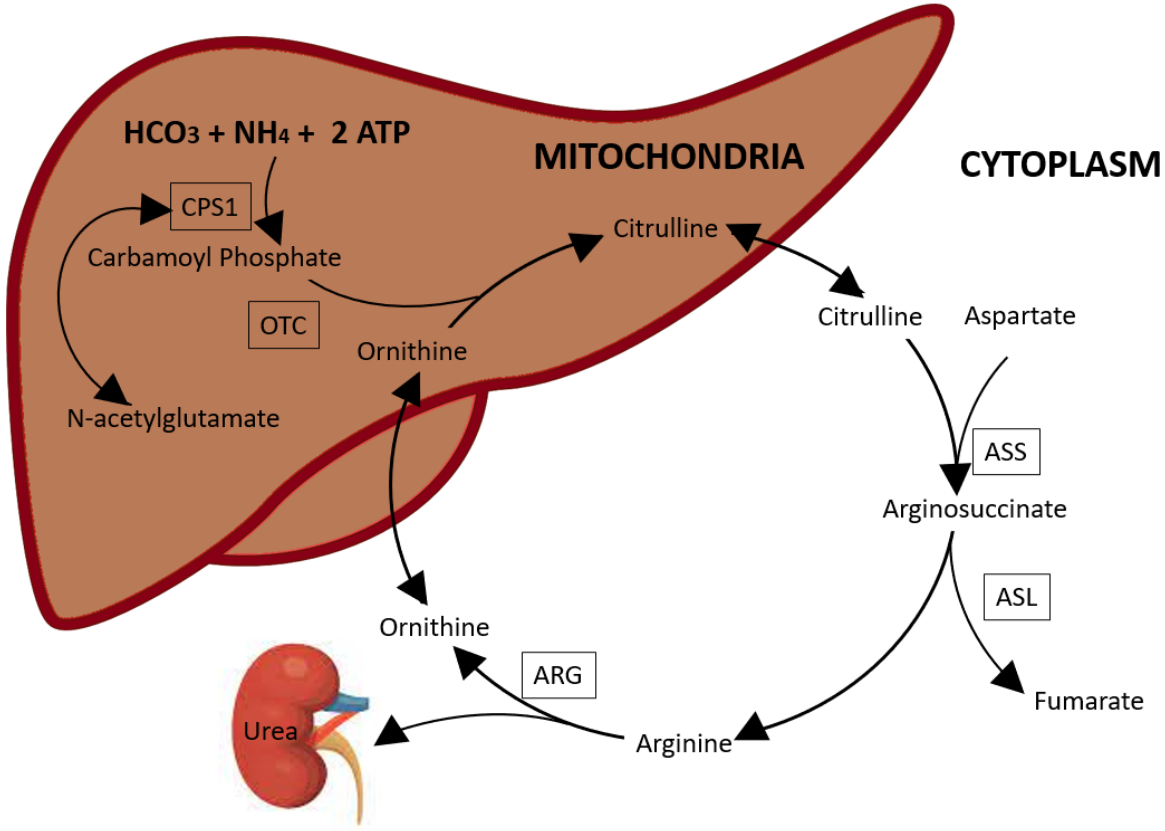


- Urea cycle disorders
- Mitochondrial disorders
  - LHON
  - MELAS

History of Drug development and UCDC

- Clinical Trial Readiness from the UCDC
  - Biomarker discovery
  - Preclinical studies to inform trial design
- UCDC expertise in developing a new therapy for UCDs
- UCDC Facilitated the phase IV studies for approved treatment for ultra rare UCDs

The Urea cycle disorders



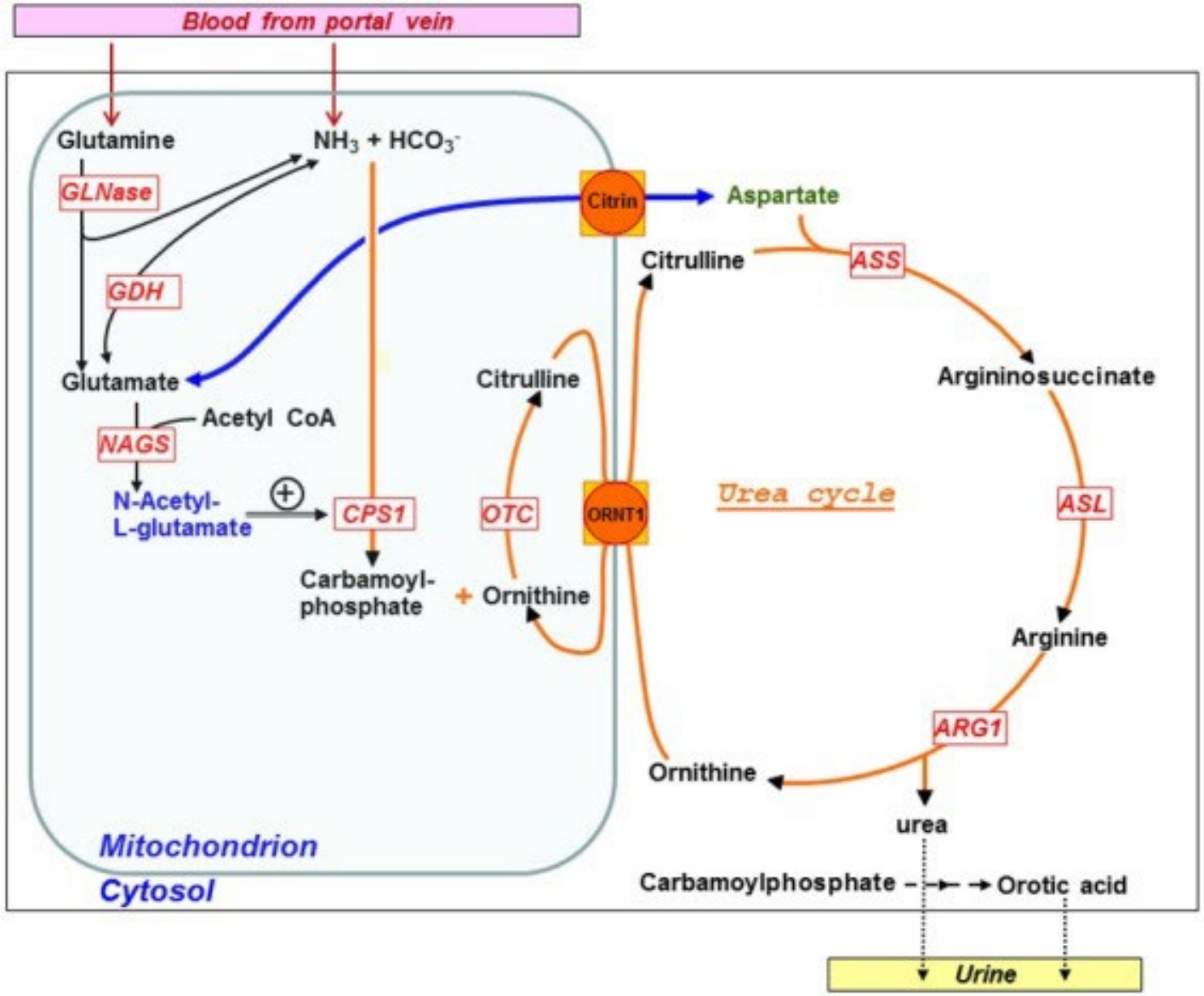
- The role of the urea cycle is the disposal of waste nitrogen via the conversion of ammonia to urea which is then excreted in the urine
  - Deficiencies of the enzymes or transporters responsible for converting ammonia to urea can result in the accumulation of toxic levels of ammonia in the blood and brain
  - The resulting encephalopathy can cause death or neurological impairment
- Long-term management of urea cycle disorders (UCDs)
  - low-protein diet, supplements of essential amino acids and other nutrients
  - ammonia lowering agents
  - emergency protocol for use during illness/acute hyperammonemia

Treatment options UCD

- Oral sodium benzoate (NaBz)
  - Conjugation with glycine and excretion as non-toxic hippuric acid in urine
- *Sodium phenylbutyrate/ Sodium phenylacetate*
  - Conjugation with glutamine and excretion as non-toxic phenylacetylglutamine in urine
- *Glycerol phenylbutyrate*
  - Conjugation with glutamine and excretion as non-toxic phenylacetylglutamine in urine; slower release and uptake than sodium PBA
- Arginine infusion

Treatment options UCD

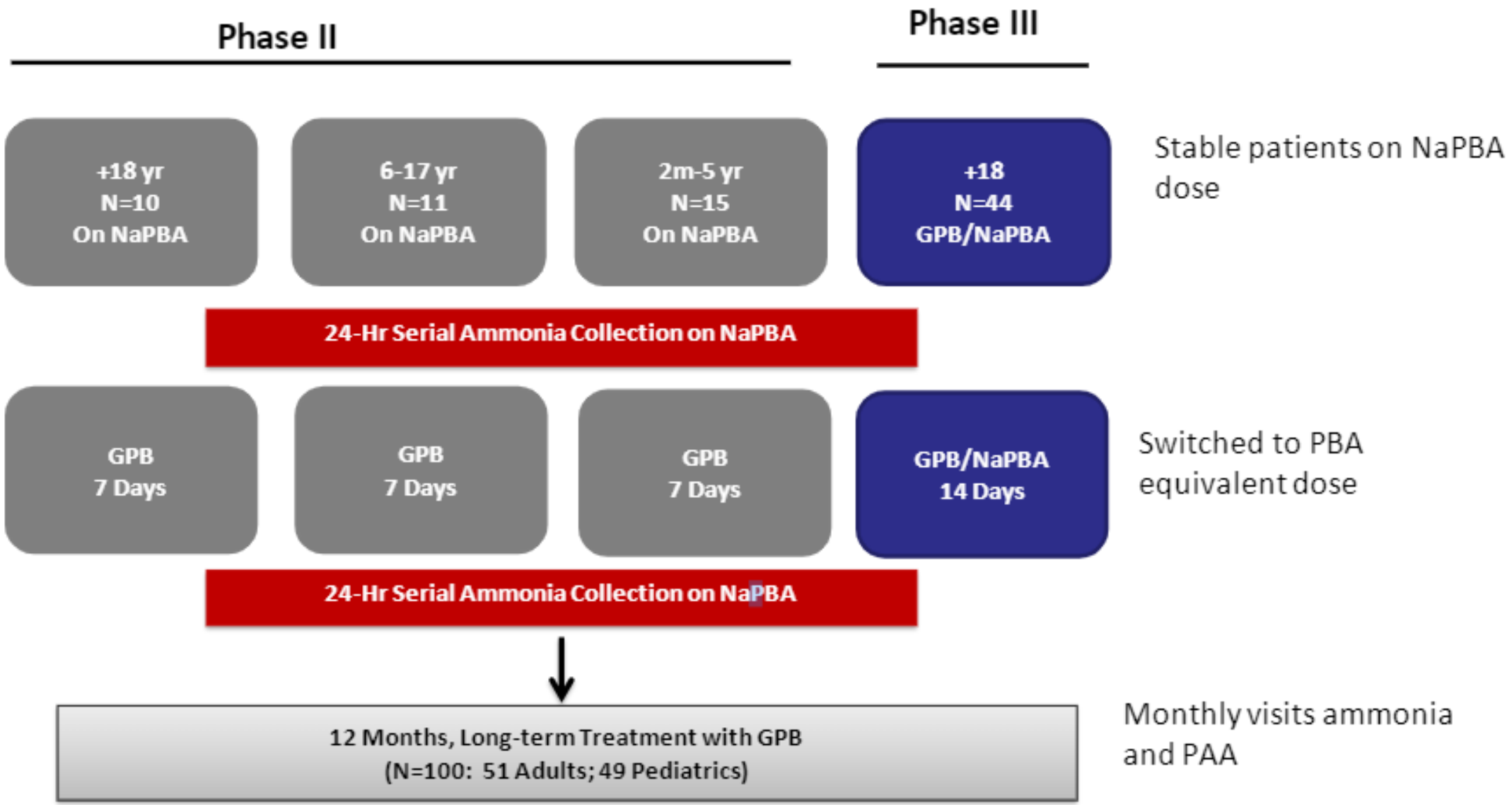
- NAGs
  - *N-carbamyl-glutamate*



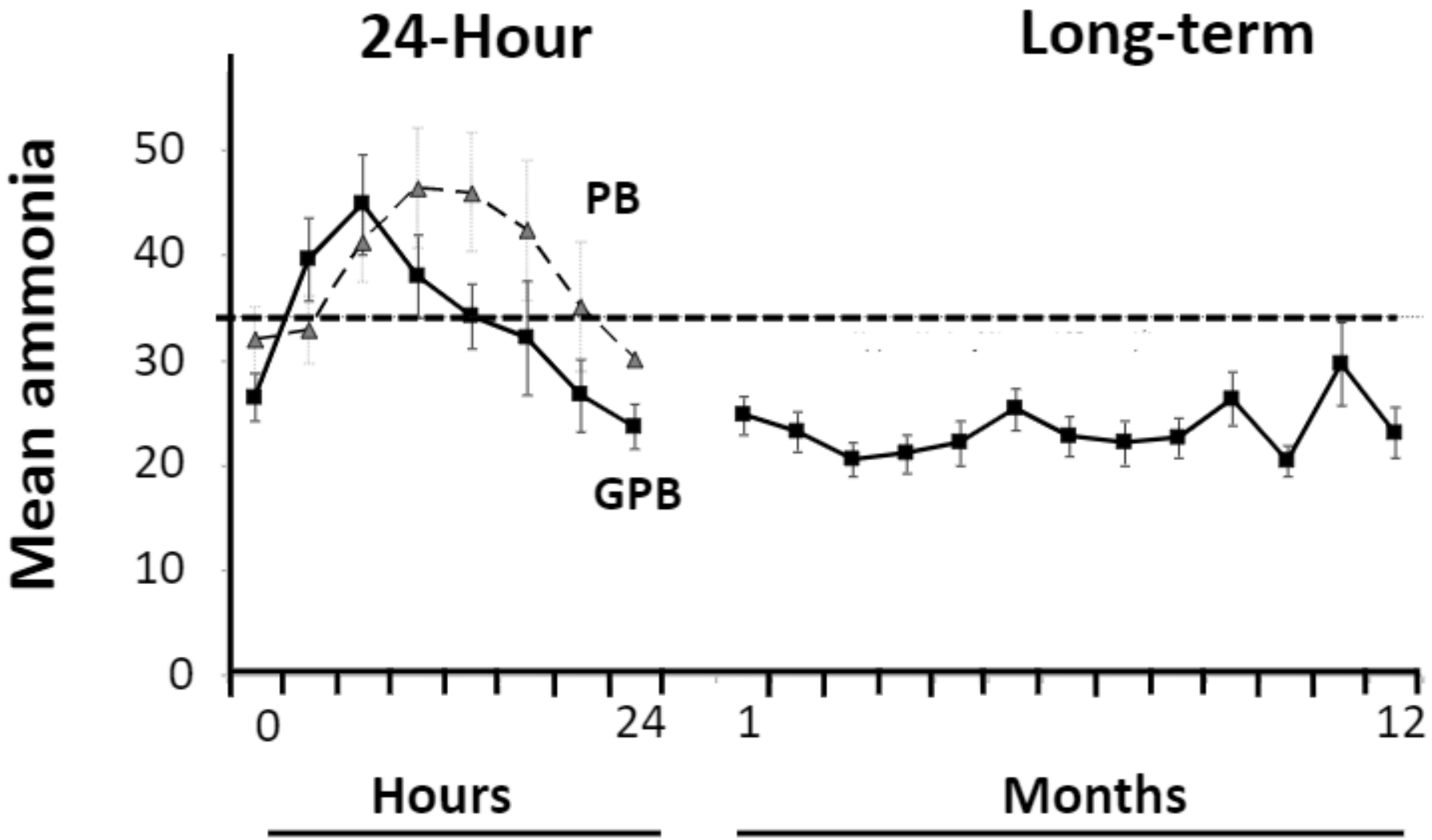
Protocol	Study	Status	Accrual
5101	Longitudinal study of UCDs	E	849
5102	RCT of low vs. high dose arginine in ASLD	C	12
5104	Neural injury in UCDs – neuroimaging study	C	46
5105	NCG for treatment of HA	C	48
5107	Brain nitrogen metabolism in OTCD	C	49
5110	NO flux in ASS1D	C	6
5111	Orphan Europe Carbaglu surveillance protocol	E	4
5113	Biomarkers of neurological injury and recovery	E	19
5114	NO supplementation in ASLD	C	12
5115	Manipulating gut microbiome in UCDs	C	4
5116	Sequencing as NBS for proximal UCDs	C	NA
5117	PCORI – liver transplant vs. conservative treatment	E	313
5118	Non-invasive assessment of chronic liver disease	C	28
5119	Prevalence of electrographic seizures in UCDs	ES 2021	
5120	Noninvasive Biomarkers of Hepatic Fibrosis in Urea Cycle Disorders	ES 2021	
5121	Comparison of Standard (Traditional) Neuropsychological Battery and NIH Toolbox	ES 2021	
5122	Hepatic Histopathology in UCD	ES 2021	

Company	Product	Purpose of Product	Dates of Involve-ment	Involvement
Orphan Europe (acquired by Recordati)	Carbaglu (N-carbamyl glutamate) FDA approval: 2010	Synthetic form of N-acetyl-glutamate (NAG)	2005 - ongoing	Conducting post marketing surveillance (RDCRN protocol 5111). UCDC showed that Carbaglu can be effective in a subset of patients with CPS1D but not effective OTCD (UCDC 5105). Through a subsequent R01 grant (R01-HD058567), Dr. Tuchman, emeritus PI assembled a multisite team of investigators (all but one are also part of the UCDC) who are conducting a double-blind placebo-controlled phase II trial of Carbaglu in hyperammonemia. Orphan Europe supplies the drug and placebo and reimbursement for enrollment in the trial, which is also supported by the O'Malley Family Foundation.
Horizon Pharma (formerly Hyperion Therapeutics)	Ravicti (glycerol phenylbutyrate) FDA approval: 2013	Nitrogen binding agent	2008 - ongoing	Provided de-identified aggregate LS data to inform Ravicti clinical trials and made introductions to UCDC investigators who served as consultants and performed clinical trials. Planning for the post-marketing surveillance study through the UCDC is currently under consideration
Aeglea Biotherapeutics	Pegzilarginase (AEB1102)	Enzyme therapies	2015-ongoing	The UCDC provided de-identified data on the ARGD participants enrolled in the LS to inform the clinical trial and introduced Aeglea to UCDC investigators to serve as expert consultants. Company now has an active phase I/II clinical trial of arginase enzyme replacement therapy.

Studies with Glycerolphenylbutyrate for UCDs



GPB Evaluated in a Randomized Control Study



Diaz et al. Hepatology 2013

Biomarkers for Clinical Investigation and Clinical Care

© American College of Medical Genetics and Genomics

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder

Brendan Lee, MD, PhD[1,2], George A. Diaz, MD[3], William Rhead, MD, PhD[4], Uta Lichter-Konecki, MD[5], Annette Feigenbaum, MD[6], Susan A. Berry, MD[7], Cindy Le Mons[8], James A. Bartley, MD[9], Nicola Longo, MD, PhD[10], Sandesh C. Nagamani, MD[1], William Berquist, MD[11], Renata Gallagher, MD, PhD[12], Dennis Bartholomew, MD[13], Cary O. Harding, MD[14], Mark S. Korson, MD[15], Shawn E. McCandless, MD[16], Wendy Smith, MD[17], Stephen Cederbaum, MD[18], Derek Wong, MD[18], J. Lawrence Merritt II, MD[19], Andreas Schulze, MD, PhD[6], Gerard Vockley, MD, PhD[20], David Kronn, MD[21], Roberto Zori, MD[22], Marshall Summar, MD[5], Douglas A. Milliken, MS[23], Miguel Marino, PhD[15], Dion F. Coakley, Pharm D[24], Masoud Mokhtarani, MD[24], the UCD Consortium and Bruce F. Scharschmidt, MD[24]

Plasma ammonia has become a standard and acceptable surrogate endpoint in clinical trials

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Glutamine and hyperammonemic crises in patients with urea cycle disorders☆,☆☆

B. Lee[a,*], G.A. Diaz[b], W. Rhead[c], U. Lichter-Konecki[d], A. Feigenbaum[e], S.A. Berry[f], C. Le Mons[g], J. Bartley[h], N. Longo[i], S.C. Nagamani[a], W. Berquist[j], R.C. Gallagher[k], C.O. Harding[l], S.E. McCandless[m], W. Smith[n], A. Schulze[o], M. Marino[j], R. Rowell[p], D.F. Coakley[q], M. Mokhtarani[q], B.F. Scharschmidt[q]

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

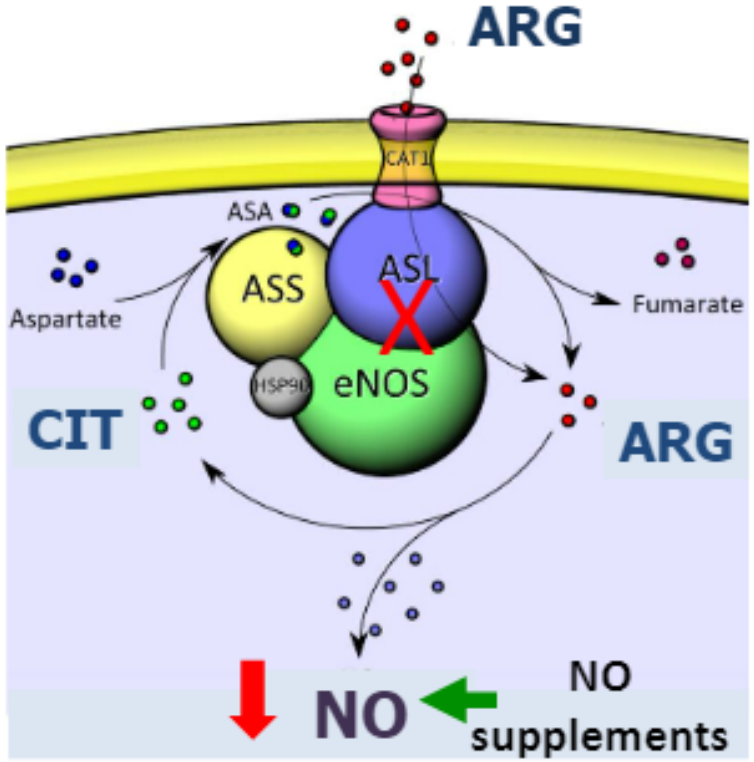
journal homepage: www.elsevier.com/locate/ymgme

Elevated phenylacetic acid levels do not correlate with adverse events in patients with urea cycle disorders or hepatic encephalopathy and can be predicted based on the plasma PAA to PAGN ratio☆

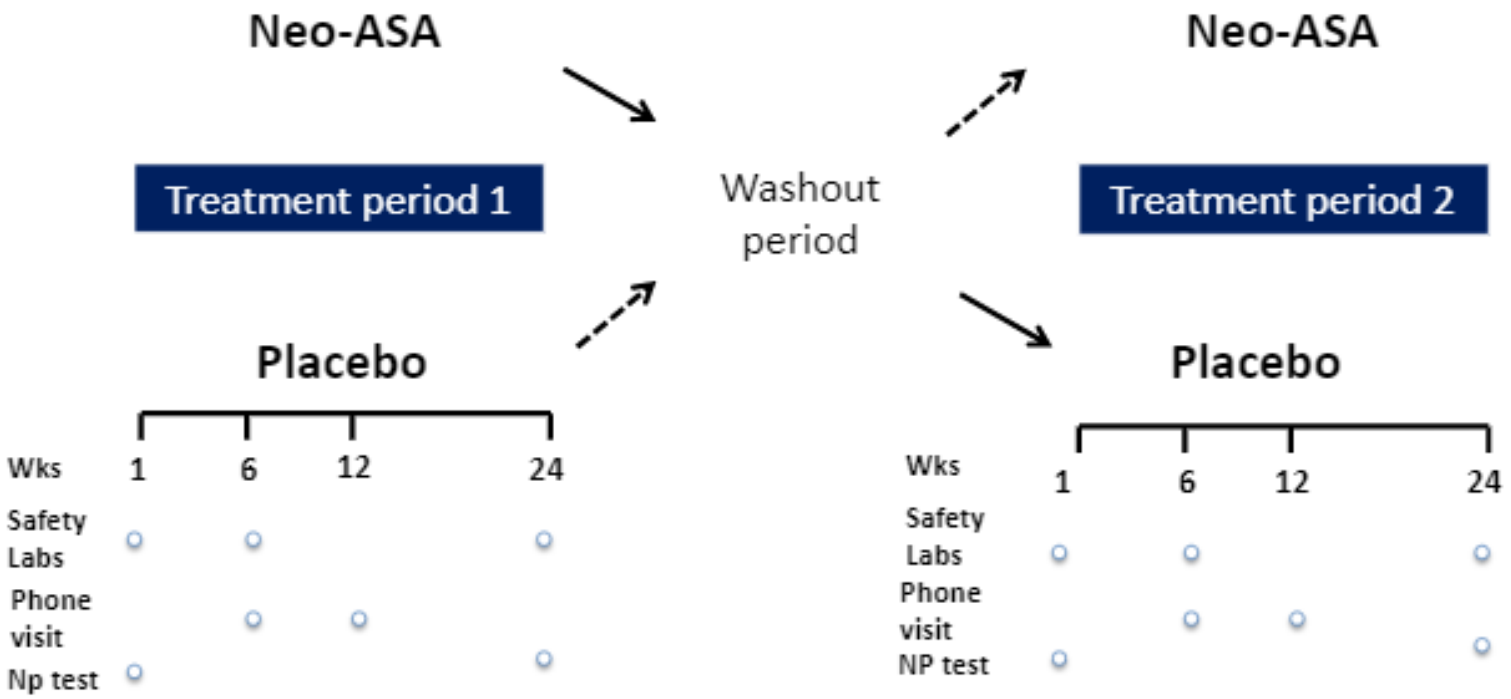
M. Mokhtarani[a,*], G.A. Diaz[b], W. Rhead[c], S.A. Berry[d], U. Lichter-Konecki[e], A. Feigenbaum[f], A. Schulze[f], N. Longo[g], J. Bartley[h], W. Berquist[i], R. Gallagher[j], W. Smith[k], S.E. McCandless[l], C. Harding[m], D.C. Rockey[n], J.M. Vierling[o], P. Mantry[p], M. Ghabril[q], R.S. Brown Jr.[r], K. Dickinson[a], T. Moors[a], C. Norris[a], D. Coakley[a], D.A. Milikien[s], S.C. Nagamani[t], C. LeMons[u], B. Lee[t], B.F. Scharschmidt[a]

LS Data to Power Clinical Trials in the UCDC

Brendan Lee Sandesh Nagamani

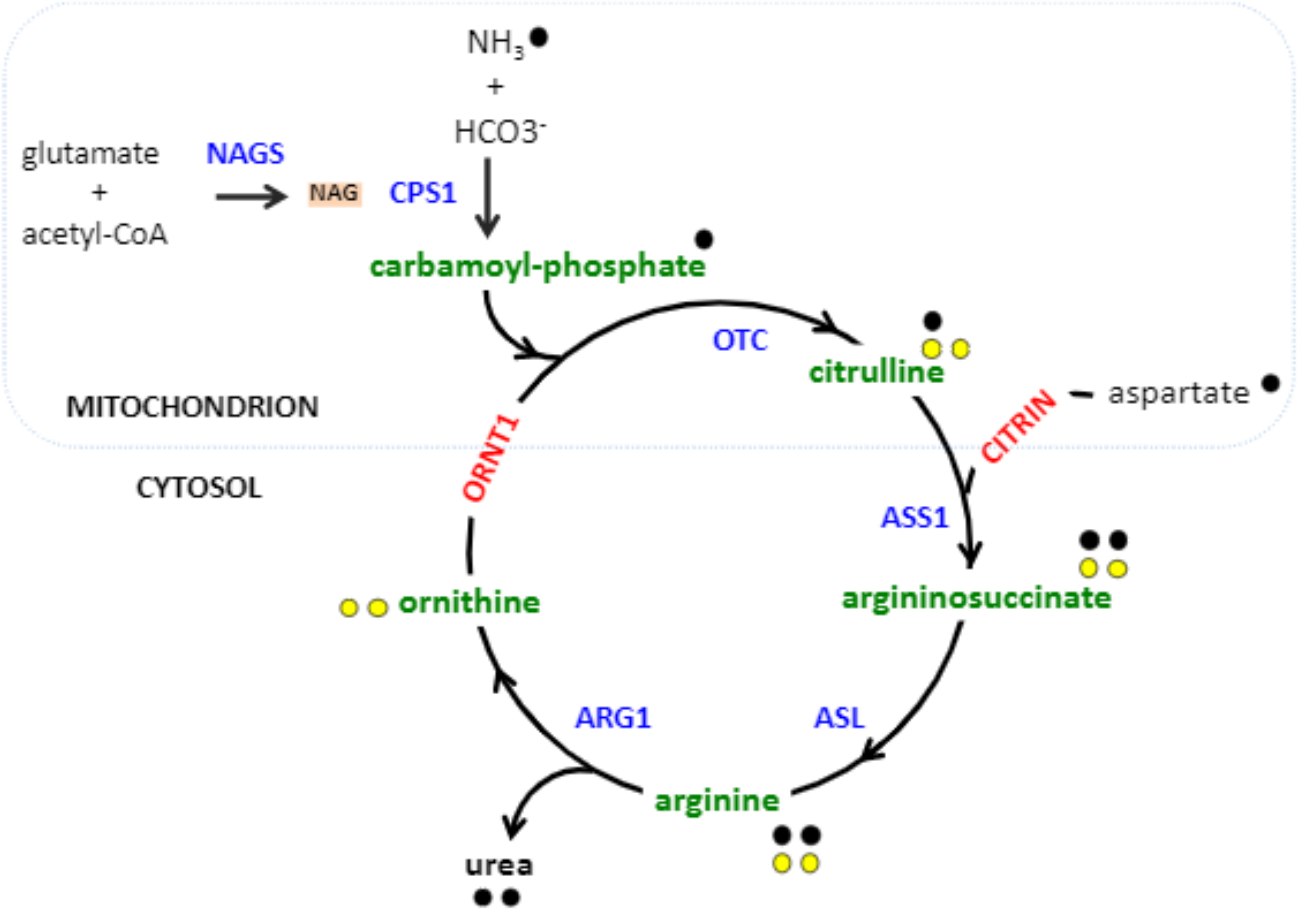


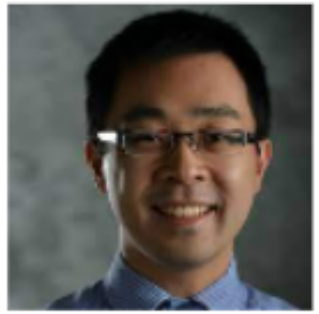
Effect of NO supplementation on neurocognitive functions in ASLD (UCDC 5114)



Sample size for primary neurocognitive outcome endpoints was powered using the data from neuropsychological assessments of the LS

UCDC and Phase IV studies





Nicholas Ah Mew, MD

- NAGS is a very rare UCD
- Carglumic acid approval (2010) based on uncontrolled studies
- Long-term safety data were unavailable
- **Carbaglu surveillance protocol of the UCDC leverages LS**
- Only surveillance protocol for this

Clinical studies and trials in the UCDC

Biomarkers identification

- Neuroimaging studies in UCDs (Gropman)

Comparative efficacy studies

RT of Bz vs. PB va. Bz+PB (Nagamani & Marini)

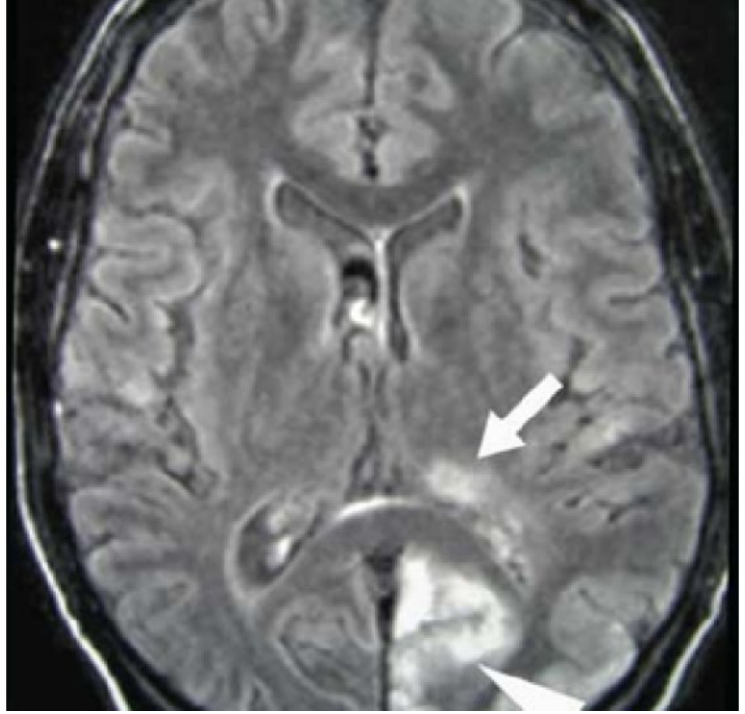
Liver transplantation vs. conservative treatment in UCDs (Ah Mew, LeMons, Tuchman)

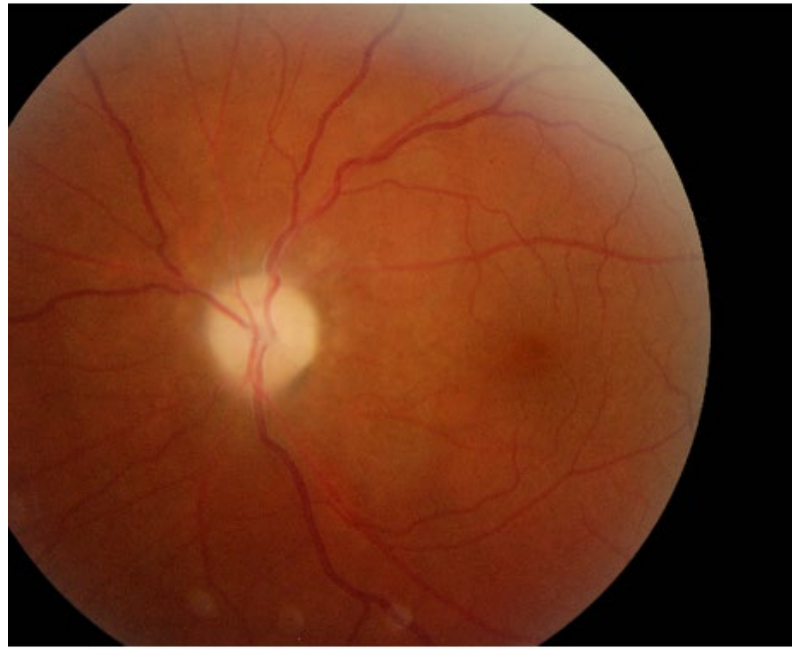
Evaluation of novel therapies

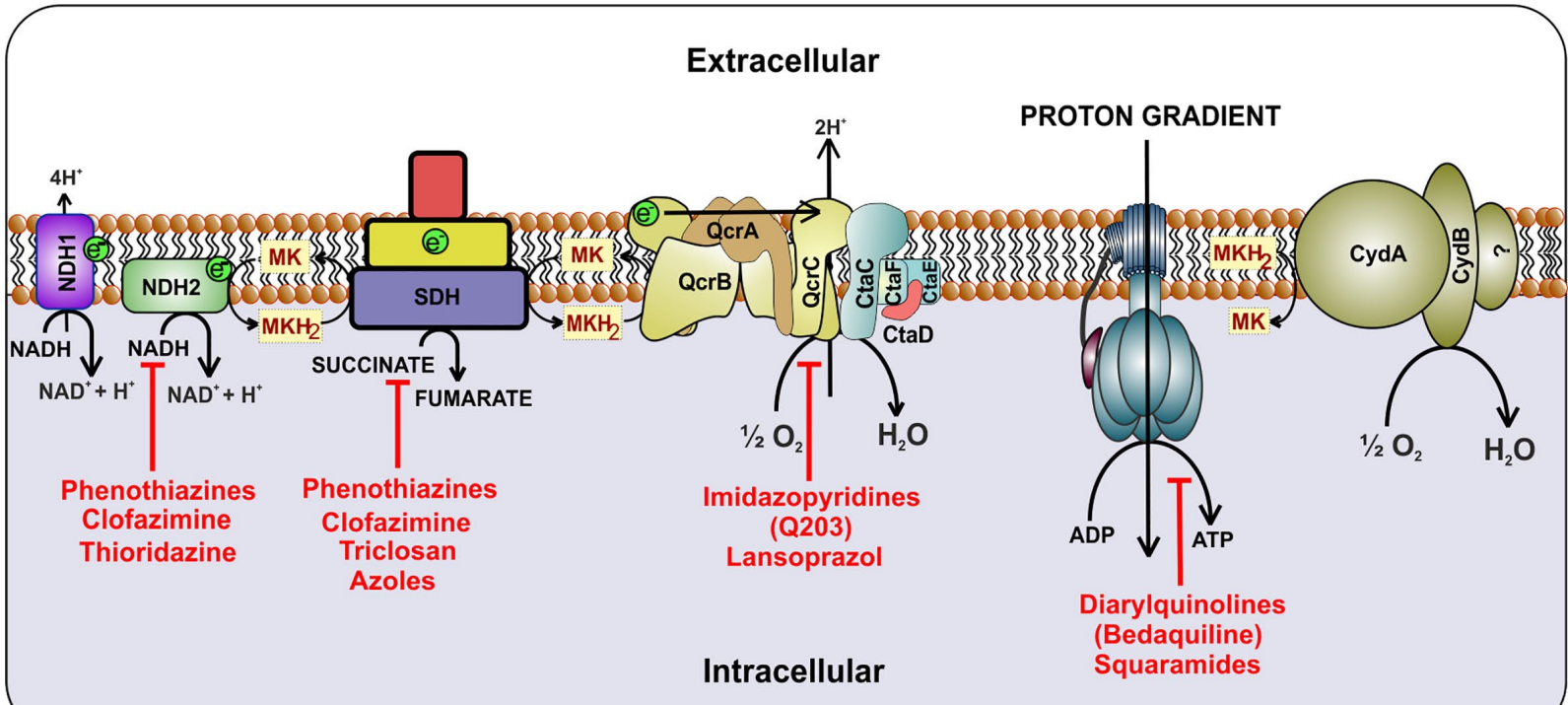
- NO supplementation in ASLD (Lee, Burrage, Nagamani)

Mitochondrial disorders

- LHON plus
- MELAS







Mitochondrial disorders

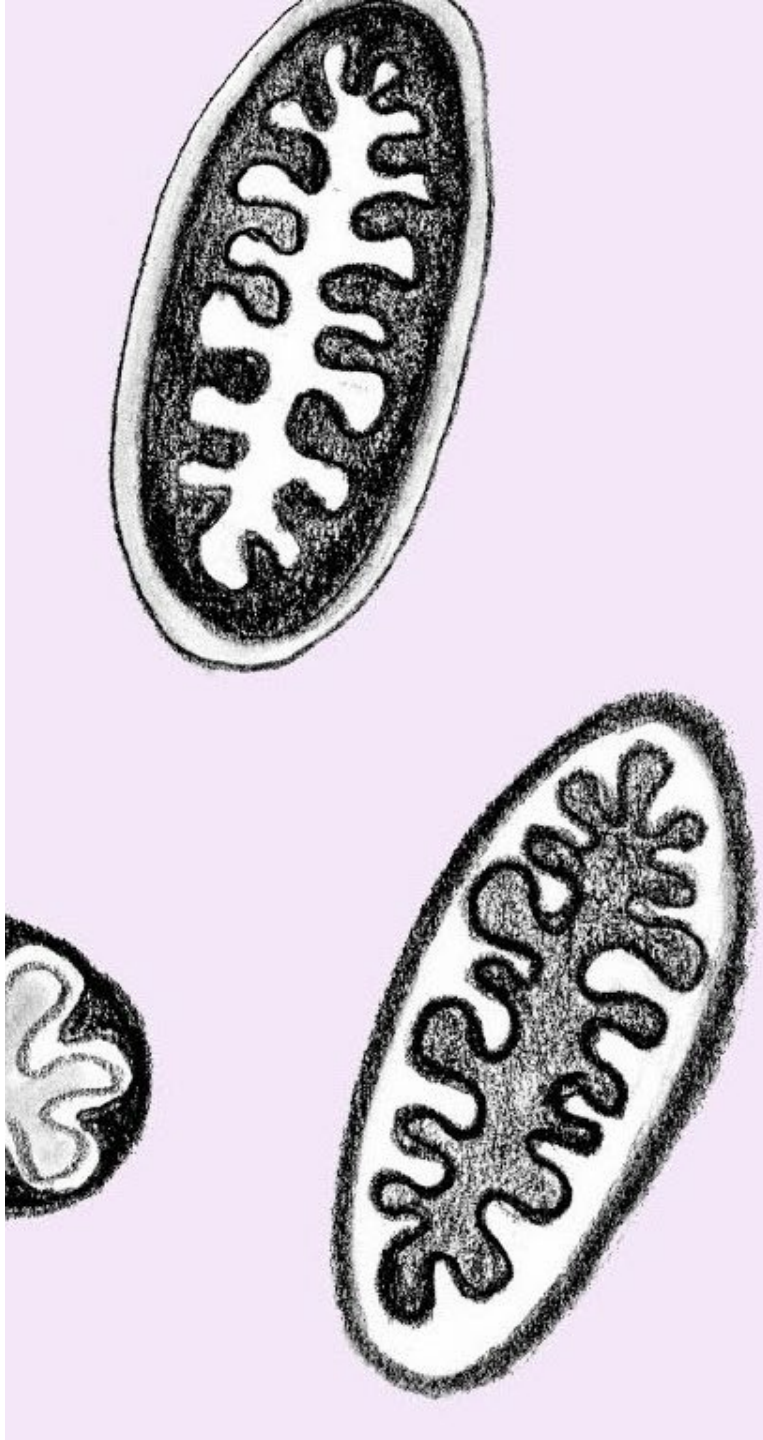
- MELAS (Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes) and LHON-Plus (Leber's hereditary optic neuropathy-Plus) are progressive neurodegenerative diseases
  - Some similar but other different clinical manifestations and broad clinical spectrum even in families
- maternally inherited pathogenic variants affecting the oxidative phosphorylation (OXPHOS) system
  - the LHON-Plus variants are near-homoplasmic, MELAS variants are heteroplasmic.

Preclinical work in MELAS fibroblasts

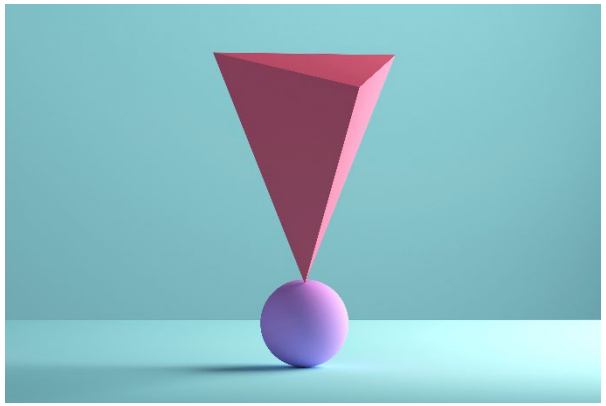
- To gain insights into the pathogenic signature of MELAS, Chairamello lab designed a comprehensive strategy integrating proteomics and metabolomics in patient-derived dermal fibroblasts harboring the ultra-rare MELAS pathogenic variant m.14453G>A
  - complex I
  - The Mito-EpiGen Program
    - The Mito-EpiGen Program | The Chiaramello Laboratory (gwu.edu)

Preclinical work in MELAS fibroblasts

- OXPHOS dysregulation with a predominant deficiency of complex I subunits
- Alterations in key bioenergetic pathways, glycolysis, tricarboxylic acid cycle, and fatty acid β-oxidation
- Model for precision medicine and testing compounds
- Downregulation of the arginine biosynthesis pathway



Challenges of clinical trials in academia

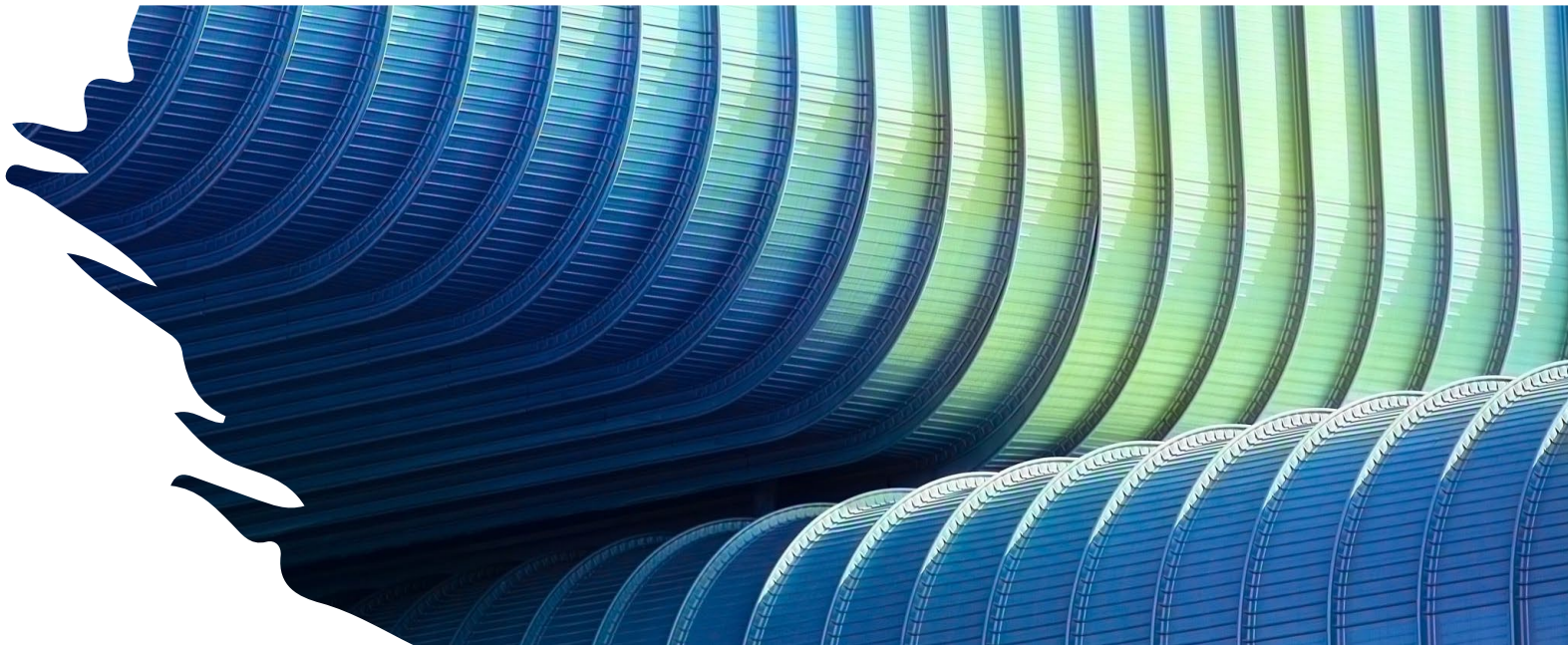


- Funding
- Responding to multiple review cycles
  - Obtaining Institutional Review Board (IRB) approvals
- Establishing clinical trial and material transfer agreements with sponsors and medical centers
  - Find the appropriate resources in the academic institution
- Patient recruitment
- Securing protected research time from medical school departments
- Large amounts of associated paperwork

Basket clinical trial

RFA-TR-20-031: Basket Clinical Trials of Drugs Targeting Shared Molecular Etiologies in Multiple Rare Diseases (UG3/UH3 Clinical Trial Required)

UG3/UH3 Exploratory/Developmental Phased Award Cooperative Agreement

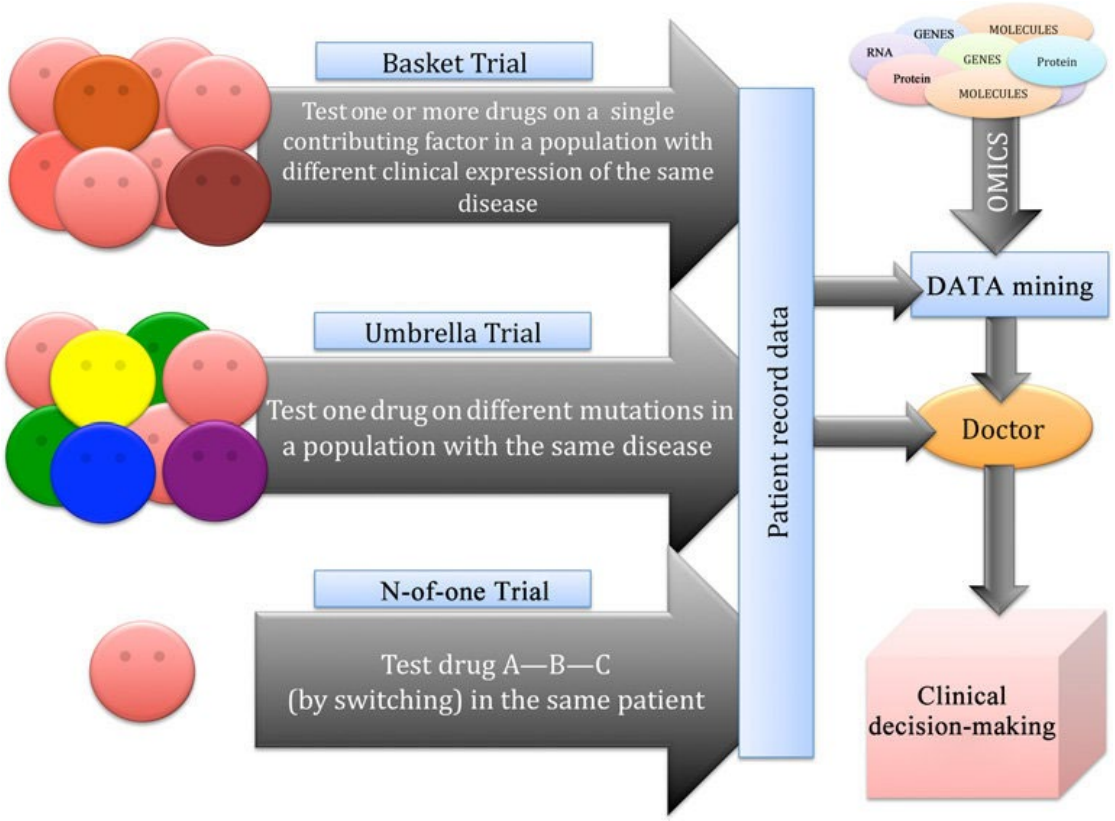


Rationale for basket trial in rare disease

- Multiple companies and investigators are developing drugs targeting shared molecular etiologies
- The standard approach in clinical trials is to focus on one disease at a time, with the choice of diseases often based on prevalence
- This approach inevitably results in clinical trials in only the most common rare diseases, with the exclusion of patients with the least common diseases, even though the scientific rationale for the use of the drug may be as strong, if not stronger, in the lower prevalence rare diseases

Rationale for basket trial in rare disease

- One potential solution to this problem is to adapt the basket trial approach that has been developed for tissue agnostic oncology drugs, i.e., for clinical trials of drugs that target molecular defects common to anatomically different cancers. Notably, this approach has already resulted in regulatory approvals from the US FDA (https://www.fda.gov/drugs/fda-approves-larotrectinib-solid-tumors-ntrk-gene-fusions). One potentially important difference between oncology and rare diseases however is the relative diversity of clinical outcome measures in rare diseases compared to cancer


Basket Trial
Test one or more drugs on a single contributing factor in a population with different clinical expression of the same disease
Umbrella Trial
Test one drug on different mutations in a population with the same disease
N-of-one Trial
Test drug A—B—C (by switching) in the same patient
Patient record data
GENES
MOLECULES
RNA
GENES
Protein
Protein
MOLECULES
OMICS
DATA mining
Doctor
Clinical decision-making


Condition #1
Condition #2
Condition #3
Condition #4
Condition #5

Rationale for basket trial in rare disease

The UG3 Phase

- All projects will have two phases. The UG3 component will support translational activities leading to submission of an IND to the FDA, whereas the UH3 will support the clinical trial itself.

Transition to the UH3 Phase

- The duration of the UG3 Phase will depend on the maturity of the project at entry. Only those UG3 projects that have met specific criteria (see below) will be eligible for transition to the UH3 phase after NIH administrative review

The UG3/UH3 cooperative agreement mechanism is milestone-driven and involves significant input from NIH program staff regarding project and milestone planning, monitoring of research progress, and go/no-go decision-making. NIH staff may also provide assistance to investigators in familiarizing them with the regulatory development process and the criteria needed to advance drugs targeting shared molecular etiologies in rare disease patients into clinical trials.

The UH3 Phase

- The UH3 phase will support a small clinical trial, involving at least two different diseases.
- As a cooperative agreement, NIH program staff will be involved in the planning and execution of the projects.

Conducting clinical trials in academia

- Complexity of Trials
- Regulations
- Costs/Budget
- Patient access
  - Link to RDCRN
  - Patient advocacy
- Staff roles and responsibilities
- Governance and oversight

Conducting clinical trials in academia

- Navigating the FDA web site for submission of Pre IND meeting
  - No pre-IND meeting request tab
  - Go into all the tabs
    - Research IND builder, the last tab
    - Several tabs for nonclinical studies
      - Default activation
    - Definition of sponsor
    - Institutional email encryption does not work with FDA system
      - Had to de encyrpt

Emerging therapeutic candidates for rare maternally inherited mitochondrial diseases with shared etiologies

- Focus on the two ultra-rare mitochondrial diseases, MELAS and LHON-Plus
- Studied by the Rare Diseases Clinical Research Network
  - Challenging to recruit adequate number of MELAS and LHON-Plus patients to clinical trials
  - Currently, these patients do not have access to effective treatments
- Repurposing a drug used in solid organ tumors
- Reactivate in studies in two new patient populations for a new indication: mitochondrial disease caused by a maternally inherited pathogenic mitochondrial variant causing Complex I deficiency and chronic energy deficit

Emerging therapeutic candidates for rare maternally inherited mitochondrial diseases with shared etiologies

- We don’t have an animal model
- We have preclinical studies in human fibroblasts
- Will studies establishing the preclinical efficacy of the active pharmacological ingredient butyrate and incorporated in the withdrawn IND along with the additional data provided in the briefing package support initiation of the proposed proof-of-concept studies in these two new populations?

Emerging therapeutic candidates for rare maternally inherited mitochondrial diseases with shared etiologies

- We plan to rely on the extensively published studies on the preclinical efficacy of butyrate and tributyrin using numerous cell lines
- Preclinical efficacy using three healthy neuronal paradigms
- Embryonic day 17.5 cortical neurons dissected from pregnant dams that were treated intraperitoneally at embryonic day 12.5
- Dissected embryonic day 17.5 hippocampal neurons
- Our engineered neuronal cell line behaving as neuronal progenitor

Acknowledgements

- Sandesh Nagamani
- Cindy LeMons
- UCDC PIs
- Patients and families
- Anne Chiaramello

Brittle Bone Disorders Consortium: Translating Discoveries to Therapy and Clinical Trial Readiness

Brendan Lee, M.D., Ph.D.

Department Molecular of Human Genetics

Baylor College of Medicine

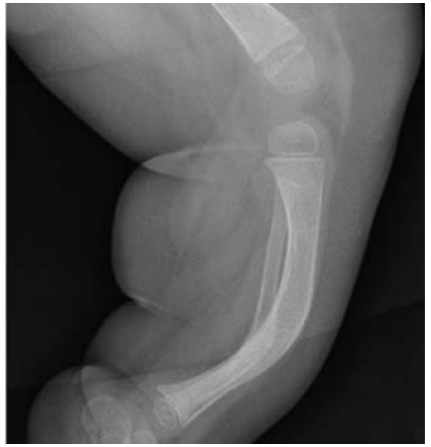
Houston, TX

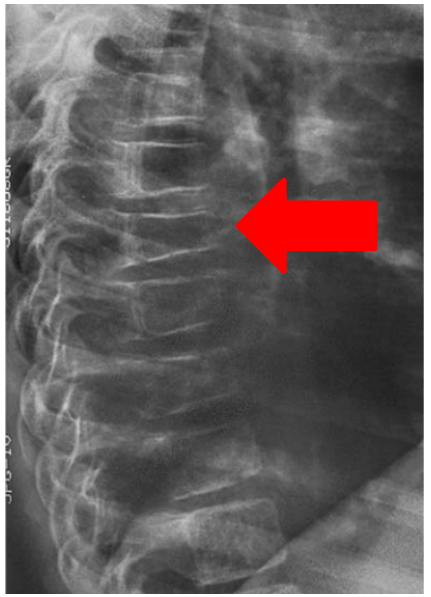
Disclosures

- Research funding from Sanofi in support of Fresolimumab trial of the NIH Brittle Bone Disorders Consortium
- Licensed gene therapy for osteoarthritis to Genequine Biotherapeutics and Flexion therapeutics
- Licensed small molecule therapy for MSUD to Acer Therapeutics
- Consultant for Biomarin – DSMB Vosoritide Trial
- SAB for Fresh Wind Biotechnologies, Ambys Medicines
- The Dept. of Molecular and Human Genetics receives support from our Baylor College of Medicine & H.U. Holdings joint venture laboratory Baylor Genetics

Osteogenesis Imperfecta

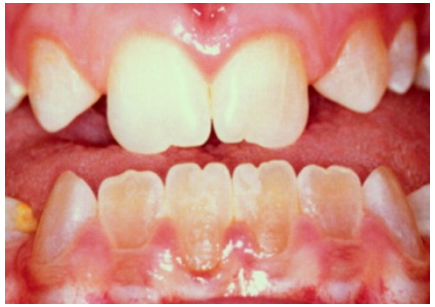
- Low bone mass
- Brittleness
- Bone deformities and fractures
- Extraskeletal manifestations



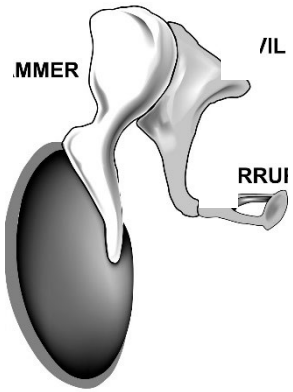


Rev Endocr Metab Disord 2008

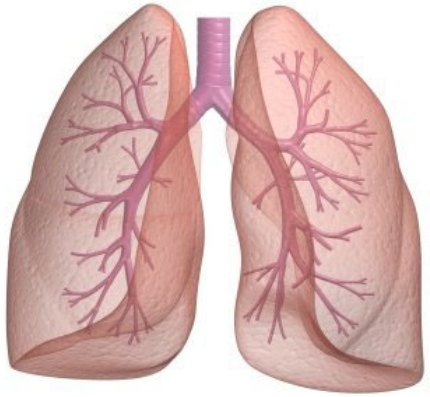
Dentinogenesis Imperfecta



Hearing loss



Lung problems



Lessons Learned from the Translation of Rare Bone Diseases

- The structural functions of the mouse and human skeleton has been remarkably conserved and supports strong clinical translation
- Clinical endpoints have suffered from enormous clinical heterogeneity that have reflected locus and allelic heterogeneity
- Early partnership and collaboration among NIH, industry, patient advocacy groups, and academic researchers key to identifying unmet (unknown) needs, accelerating research, natural history studies, powering endpoints, and accelerating early phase studies
- Leverage human experience (dosing and toxicity) for new (optimal) applications

Success of clinical Translation: Anabolic vs. Anti-Resorptive Treatment for Osteoporosis

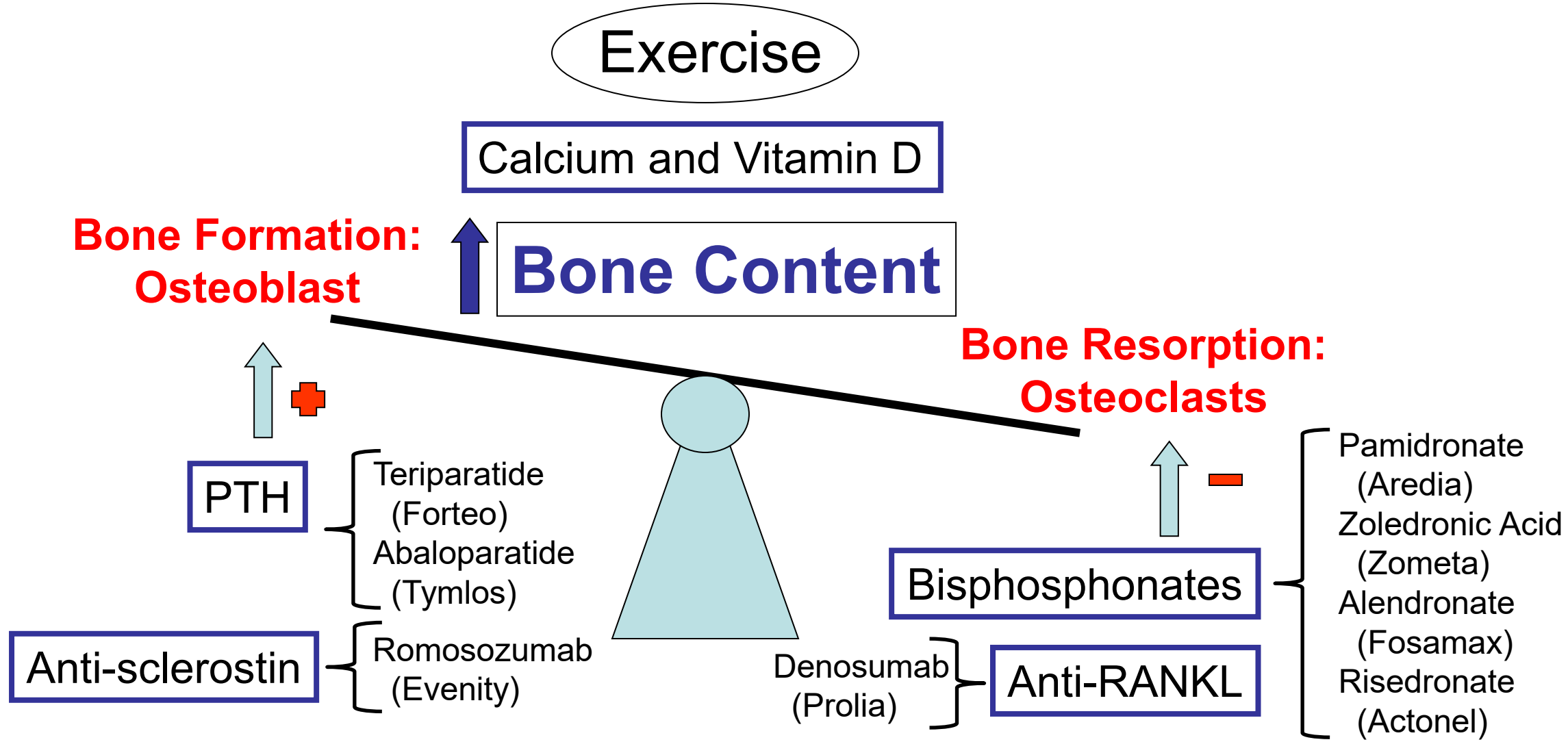


Table 1. Genetic classification of osteogenesis imperfecta types and main clinical features

OI type	Inheritance	Gene	Severity and unique clinical features
I	AD	*COL1A1*	Mild, normal or short stature; little or no deformities
II	AD AR (rare)	*COL1A1, COL1A2* AR genes below	Lethal, minimal calvarial mineralization, beaded ribs, long bone deformities
III	AD AR	*COL1A1, COL1A2* AR genes below	Severe, progressively deforming bones
IV	AD	*COL1A1, COL1A2*	Moderate severity with short stature
V	AD	*IFITM5*	Variable severity, calcification of interosseous membrane of the forearm, hyperplastic callus formation
VI	AR	*SERPINF1*	Moderate-to-severe, accumulation of un-mineralized osteoid; biopsy shows fish-scale pattern of the lamellae
VII	AR	*CRTAP*	Severe to lethal, rhizomelia
VIII	AR	*LEPRE1*	Severe to lethal, rhizomelia, coxa vara, popcorn metaphyses
IX	AR	*PPIB*	Severe, short bowed femurs with anterior bowing of the tibiae
X	AR	*SERPINH1*	Severe
XI	AR	*FKBP10*	Moderate-to-severe, joint contractures; biopsy shows distorted lamellar structure and a fish scale-like pattern
XII	AR	*SP7*	Moderate severity
XIII	AR	*BMP1*	Severe
XIV	AR	*TMEM38B*	Moderate-to-severe
XV	AR (AD causing osteoporosis)	*WNT1*	Moderate-to-severe, also have brain malformations
XVI	AR	*CREB3L1*	Severe, perinatal fractures, multiple fractured tubular bones with an accordion-like broadened appearance
XVII	AR	*SPARC*	Progressively severe
XVIII	AR	*FAM64A*	Moderate-to-severe, dysmorphic features, developmental delay
XIX	X-linked	*MBTPS2*	Moderate-to-severe, pectus deformity
Un-classified	AR	*PLOD2*	Moderate-to-severe, joint contractures
Un-classified	X-linked	*PLS3*	Osteoporosis with fractures, clinical overlap with OI

AD, autosomal-dominant; AR, autosomal-recessive; OI, osteogenesis imperfecta.

Rossi, Lee, Marom **Curr Opin Peds** 2019

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

[Intervention Review]

Bisphosphonate therapy for osteogenesis imperfecta

Kerry Dwan[1], Carrie A Phillipi[2], Robert D Steiner[3,4], Donald Basel[5]

- Bisphosphonates are de factor standard of care in OI especially in children with severe OI
- 14 trials reviewed using bisphosphonates
- “It is unclear whether oral or intravenous bisphosphonate treatment consistently decreases fractures, though multiple studies report this independently and no studies report an increased fracture rate with treatment.”
- “The studies included here do not show bisphosphonates conclusively improve clinical status (reduce pain; improve growth and functional mobility) in people with osteogenesis imperfecta.”

Brittle Bone Disorders Consortium

NIH National Center for Advancing Translational Sciences

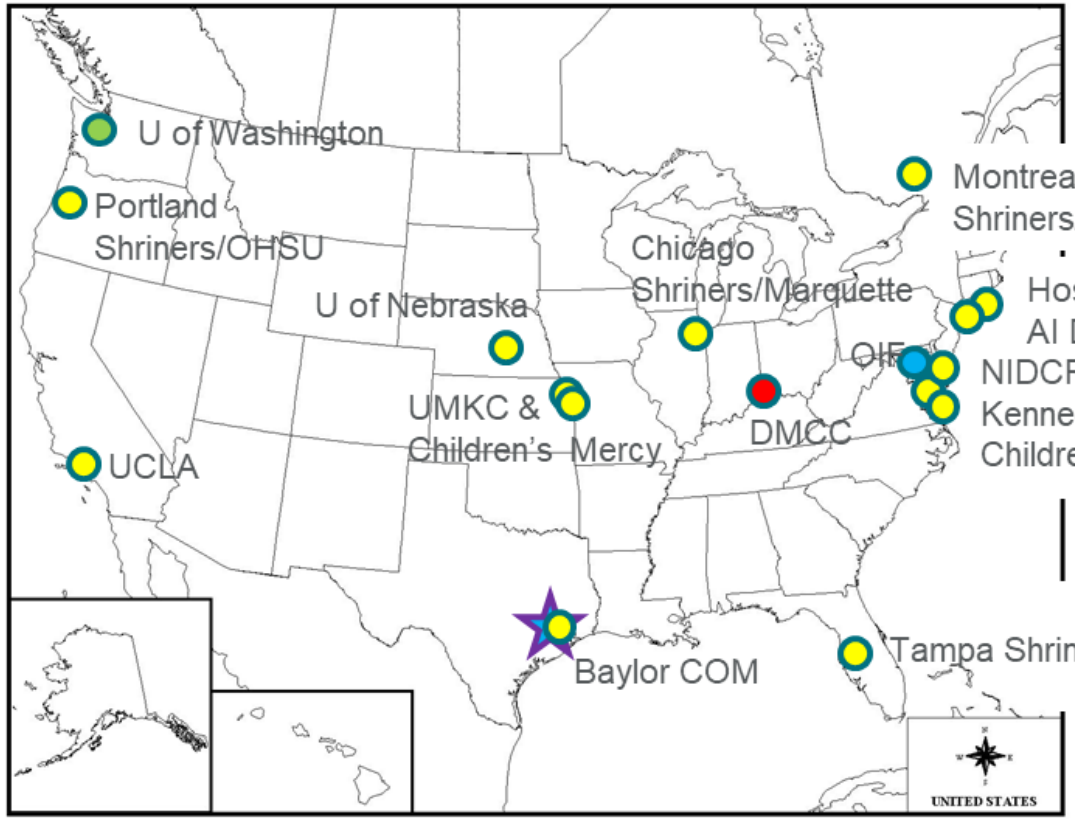
NIH National Institute of Dental and Craniofacial Research

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NIH National Institute of Mental Health

OSTEOGENESIS IMPERFECTA FOUNDATION



Administrative Core
Clinical Site

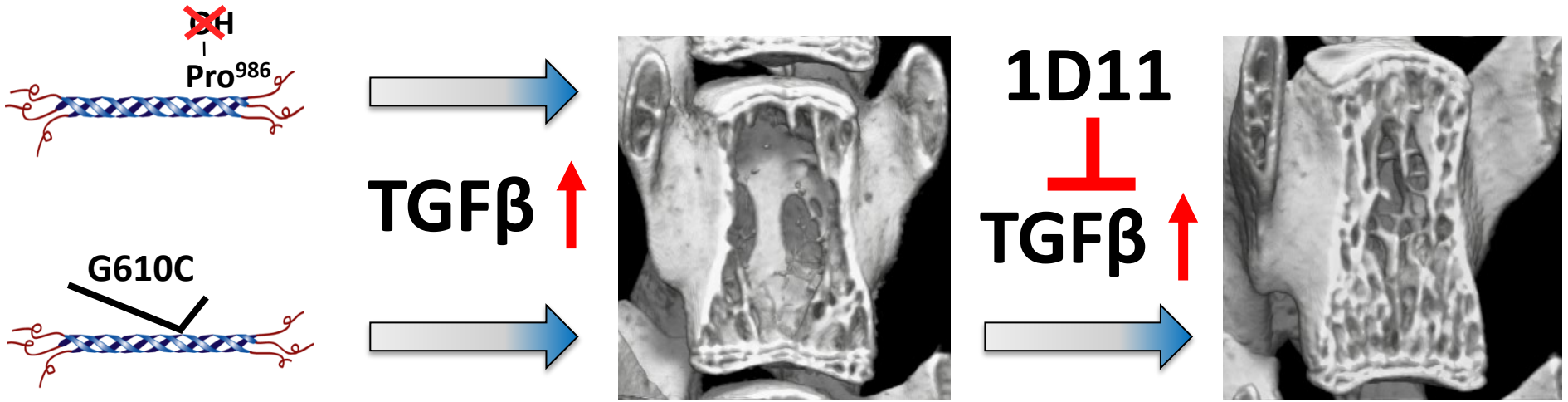
Biomarker Core
Data Management Center
Advocacy Partner

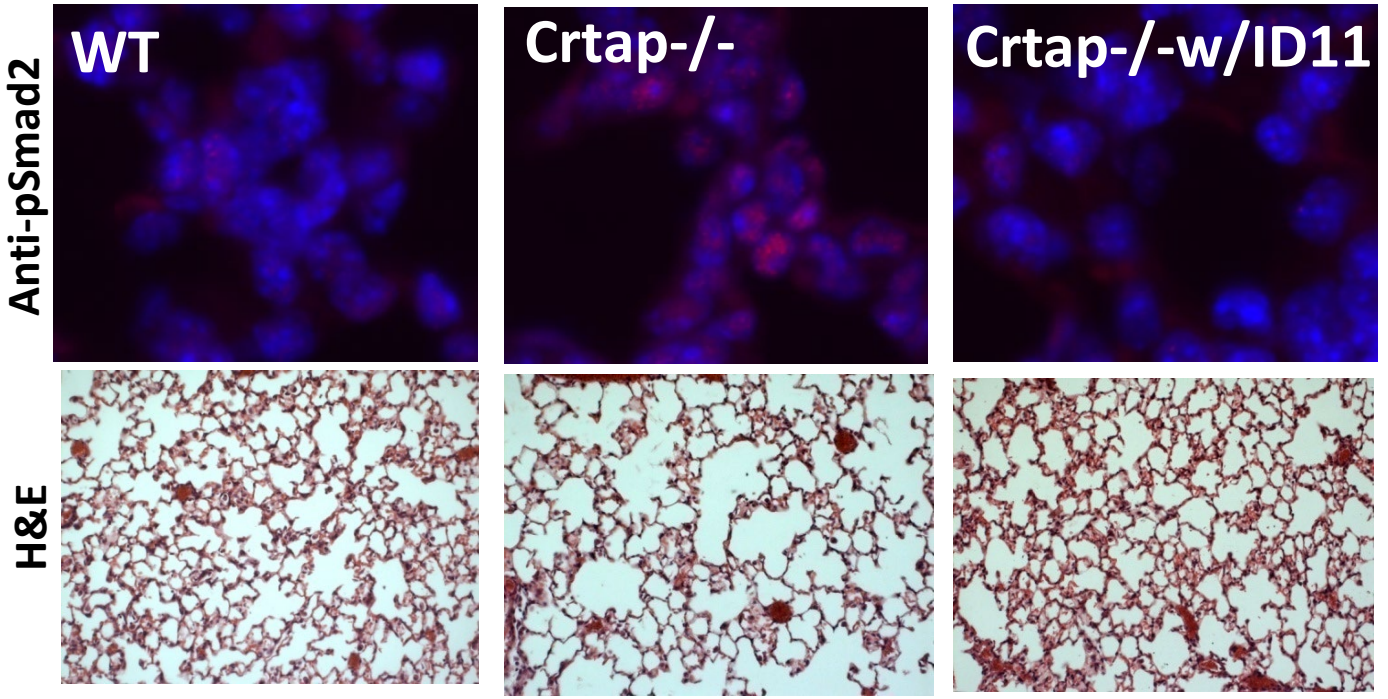
RARE DISEASES CLINICAL RESEARCH NETWORK

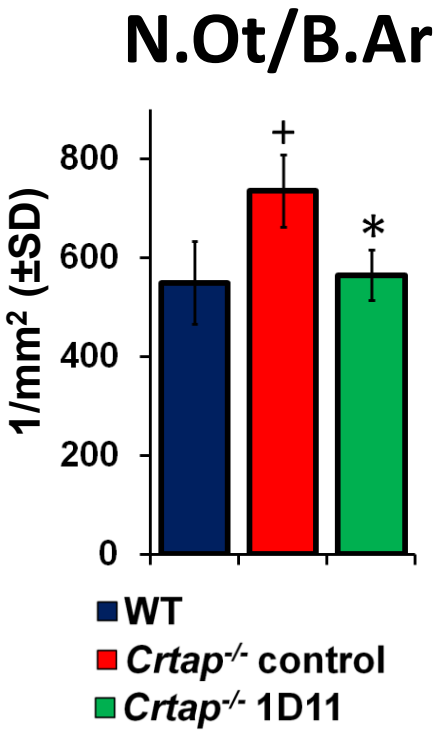
Brittle BONE DISORDERS CONSORTIUM

BBDC Achievements

- Largest sample sizes to date to inform clinical endpoints relevant to clinical trial readiness (~1000)
- Discover clinical signals not previously appreciated or studied
  - Postpartum hemorrhage, Pain and anxiety
- Effect sizes for different subtypes of OI (addresses variable expressivity that confounds sample size) – Growth, PFTs, Mobility, Hearing Loss, QOL, etc.
- Broad connective tissue targets beyond bone
- Basis for both academic and industry partners in clinical trial design and feasibility
  - BBDC Phase 1 Fresolimumab – Sanofi
  - Industry sponsored - Mereo/Ultragenix Phase 1 Sestrusumab

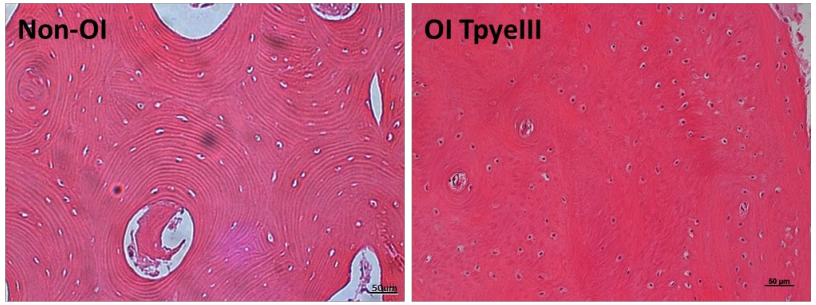


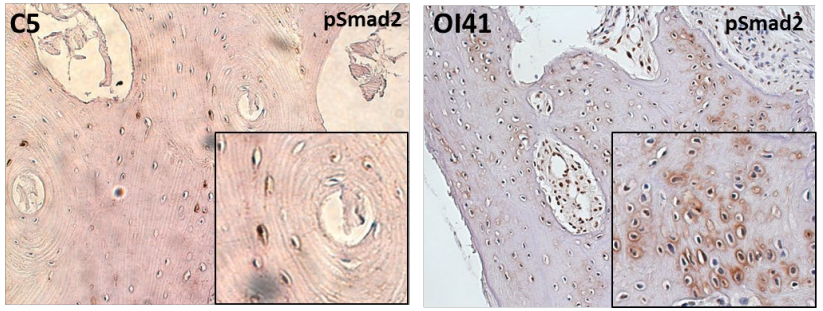


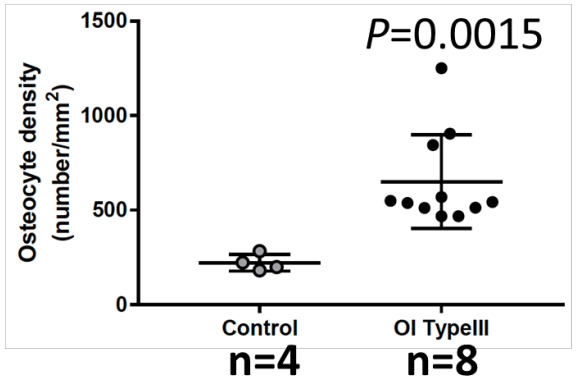


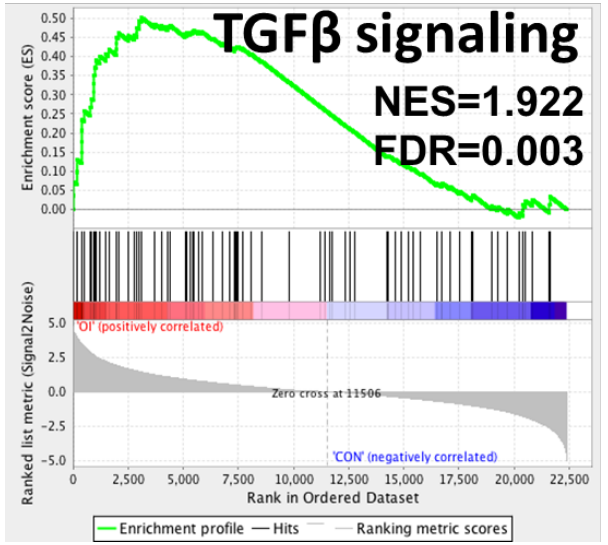
Grafe et al & **B Lee Nature Medicine,** 2014

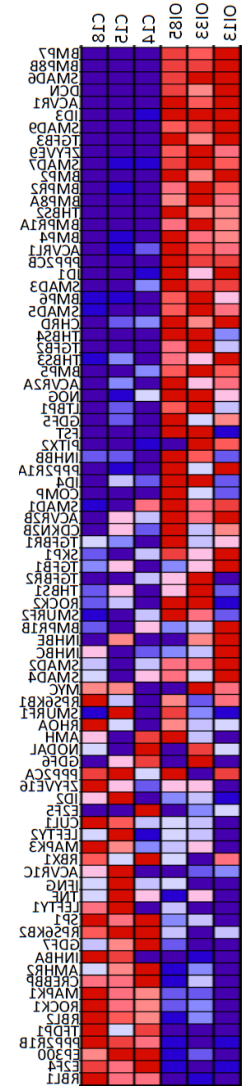
Increased TGFβ in human OI bone

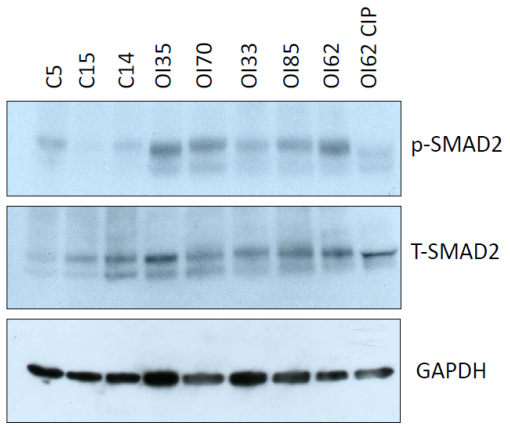


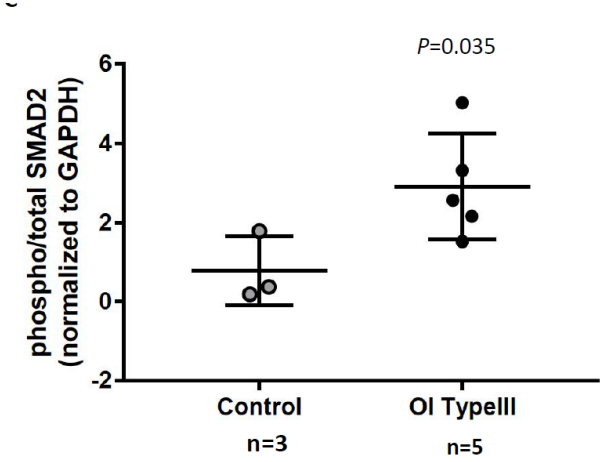












Song, Nagamani et al & B Lee, **Journal of Clinical Investigation** 2022

Fresolimumab (anti-TGF-β) in adult with OI (NCT03064074)

Stage 1 – single dose study

Group 1 — N=4 — **1 mg/kg single dose**

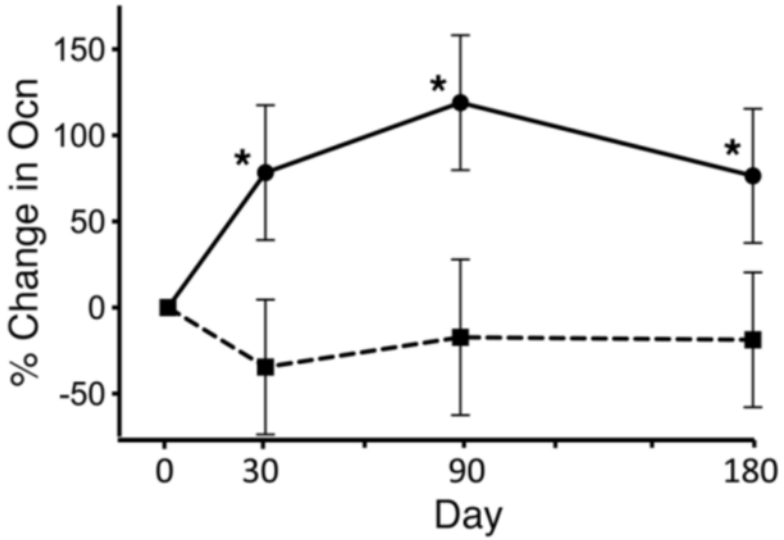
Group 2 — N=4 — **4 mg/kg single dose**

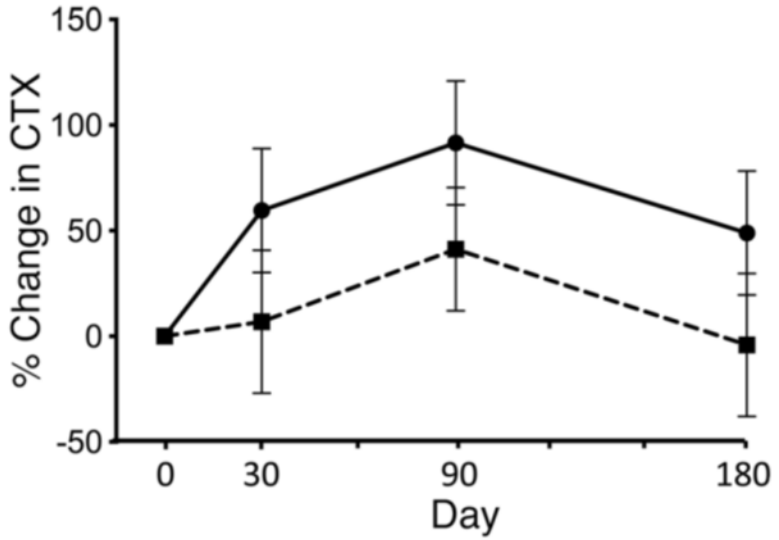
6 months

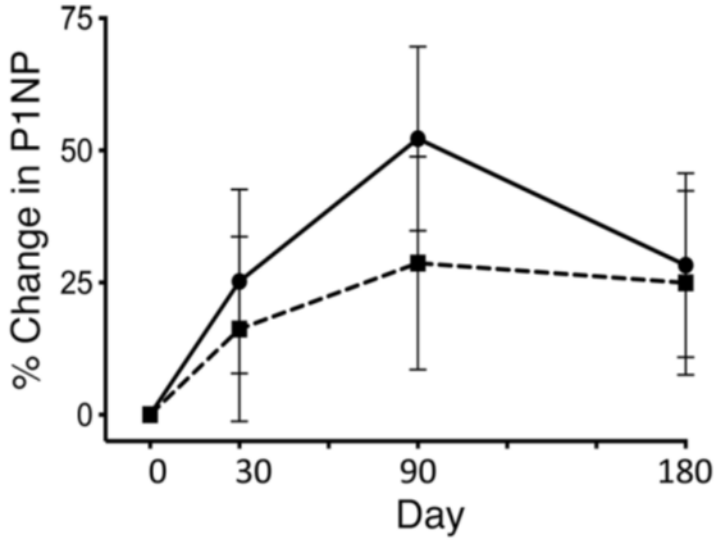
Primary objective:
Safety

Secondary objectives:

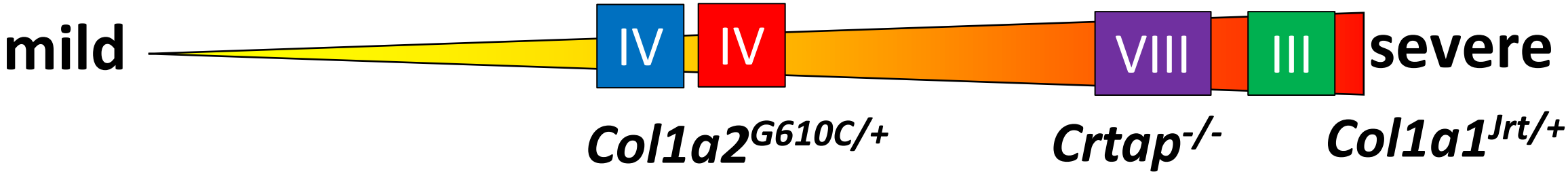
Bone remodeling markers: Ocn and CTX
Bone density: lumbar spine aBMD

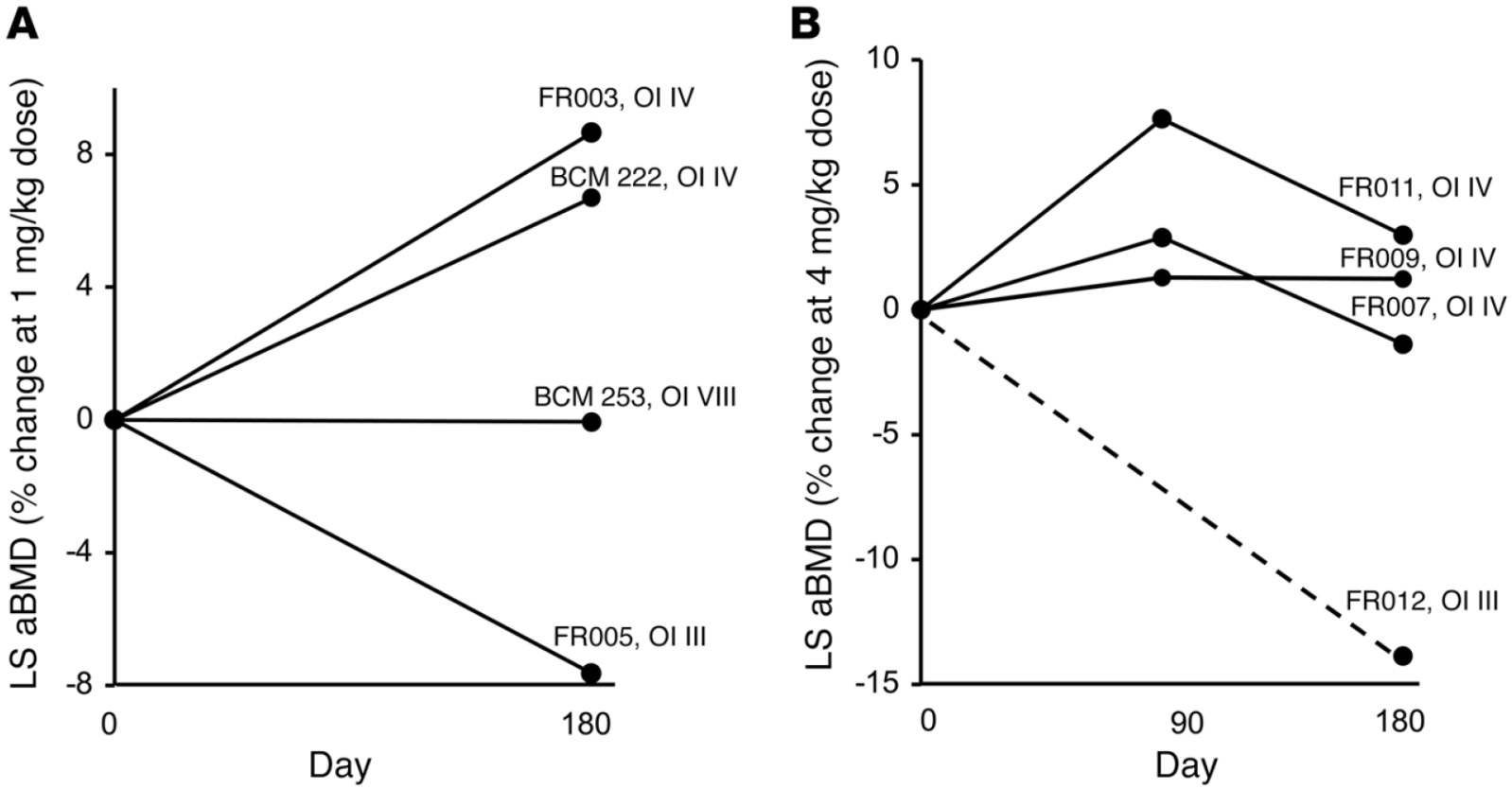






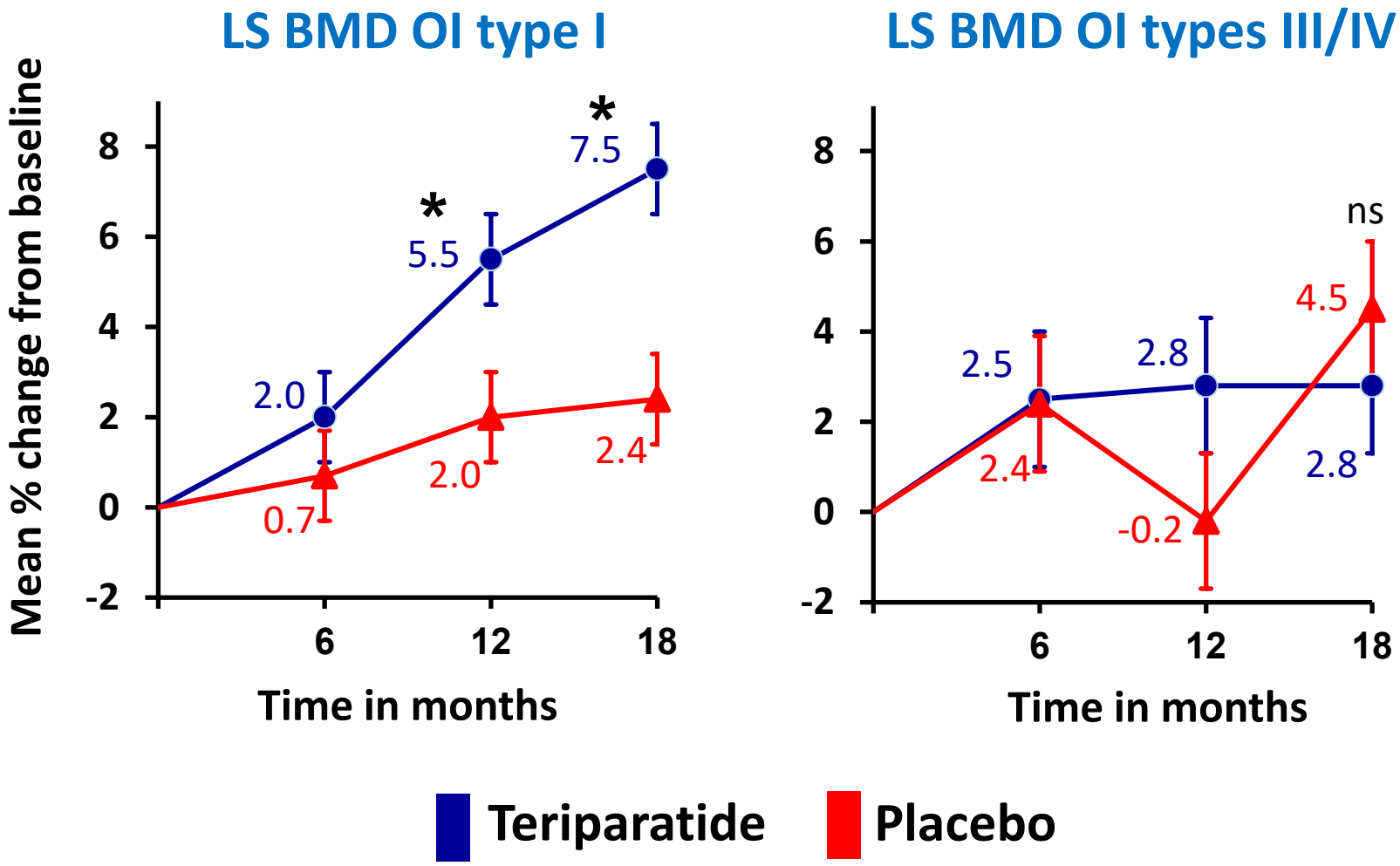
Anti-TGFβ: Dose response depending on severity?





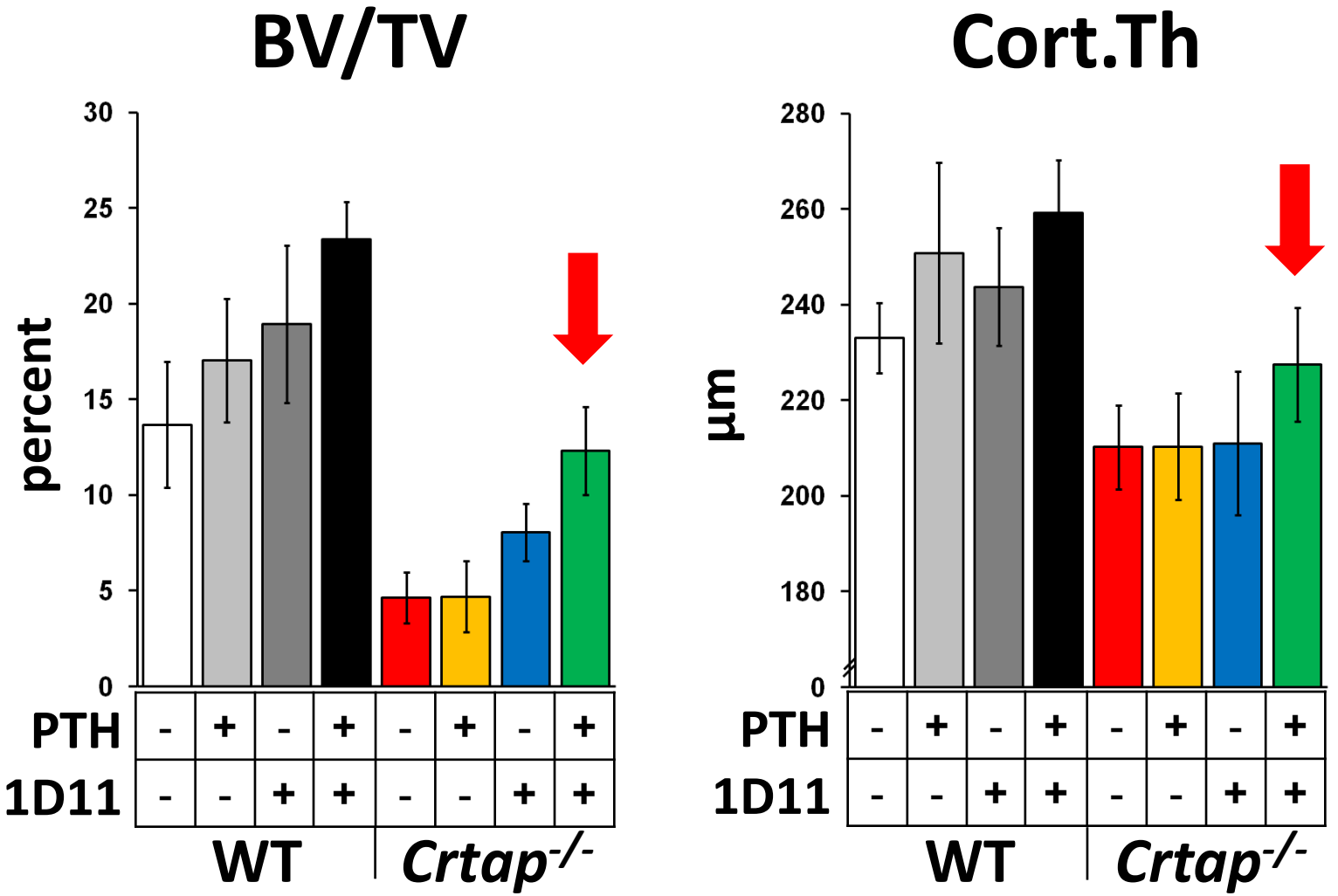
IW Song et al, & B Lee **Journal of Clinical Investigation** 2022

Placebo controlled RCT of Teriparatide in adults with OI (N=78) NCT00131469



E. Orwoll et al, S. Nagamani & et al, B. Lee **Journal of Clinical Investigation** 2014

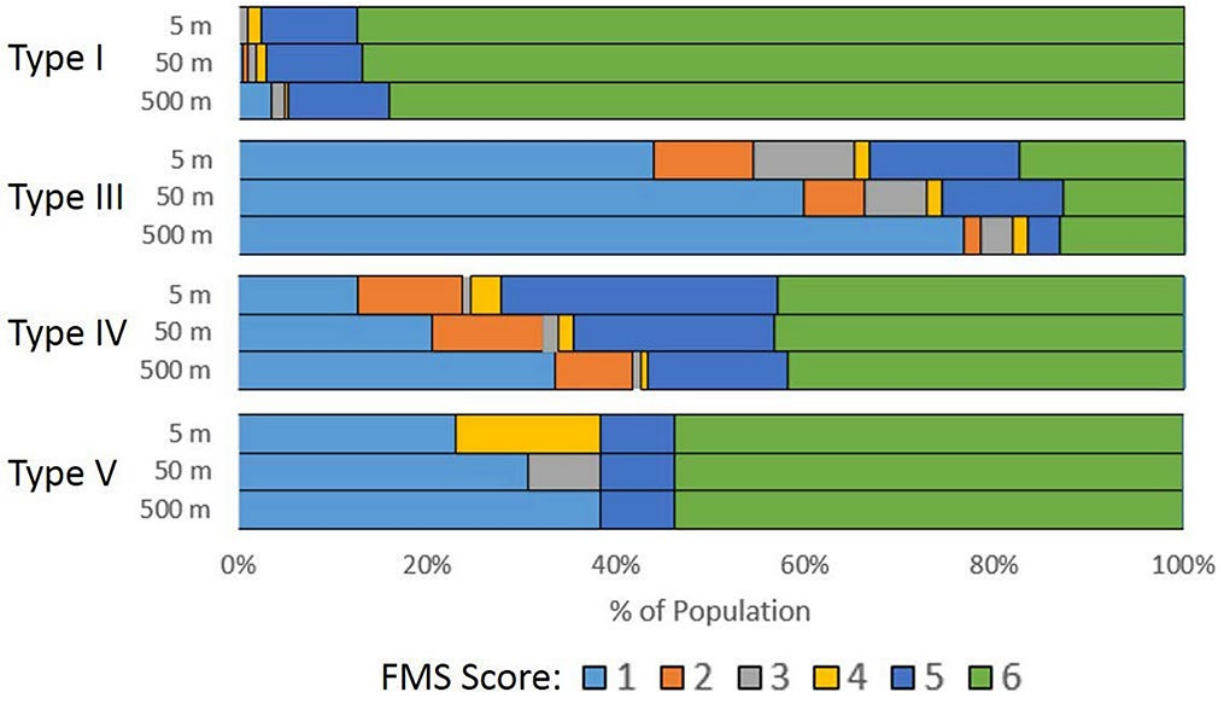
Low-dose TGFβ-inhibition (1D11) restores responsiveness to PTH in *Crtap*$^{-/-}$ mice

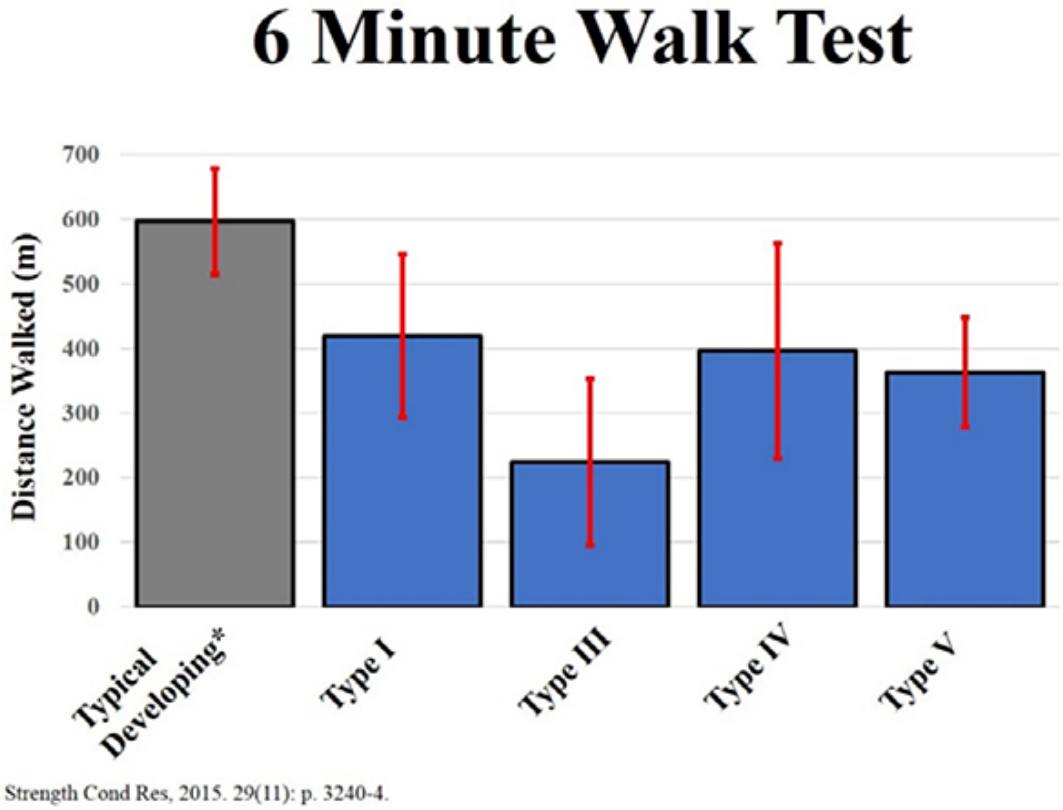


Ingo Grafe

microCT femurs, n=7/group

Mobility in OI: Kruger et al Genet Med 2019





*J Strength Cond Res, 2015. 29(11): p. 3240-4.

PODCI for Clinical Trial Readiness in OI

Murali et al Genet Med 2020

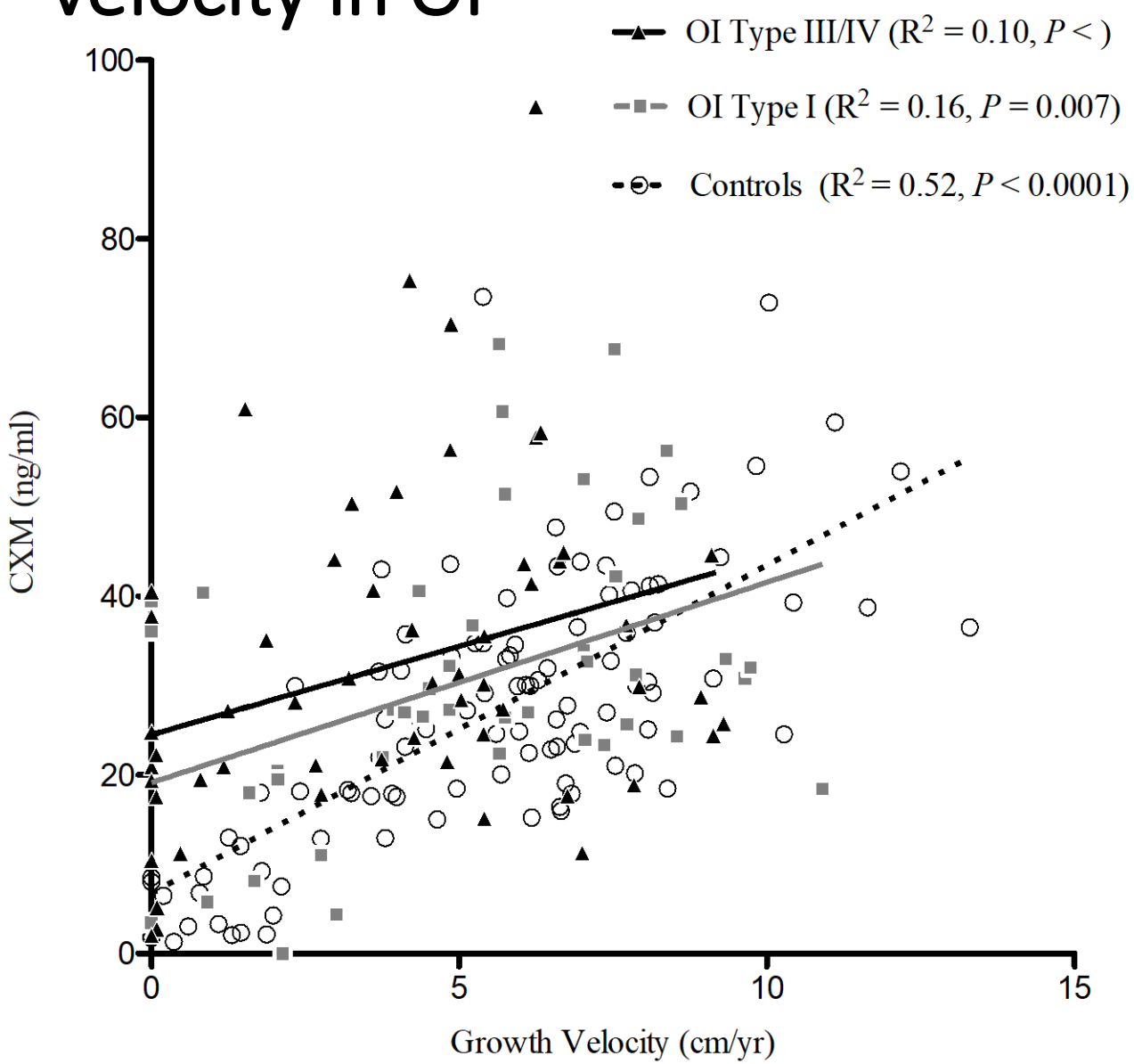
			Sample size required for a paired t test to detect a mean difference of			Sample size required for two group comparison to detect a mean difference of		
PODCI Core Scale	Mean score	SD	5	10	15	5	10	15
Upper Extremity and Physical Function								
Pediatric age group 2y – 10y11m	76.07	20.71	137	36	17	270	69	31
Adolescent age group 11y – 18y11m	93.07	11.59	45	13	7	85	23	11
Transfer and Basic Mobility								
Pediatric age group 2y – 10y11m	75.59	31.01	304	78	20	605	152	69
Adolescent age group 11y – 18y11m	86.06	22.14	156	41	20	309	78	36

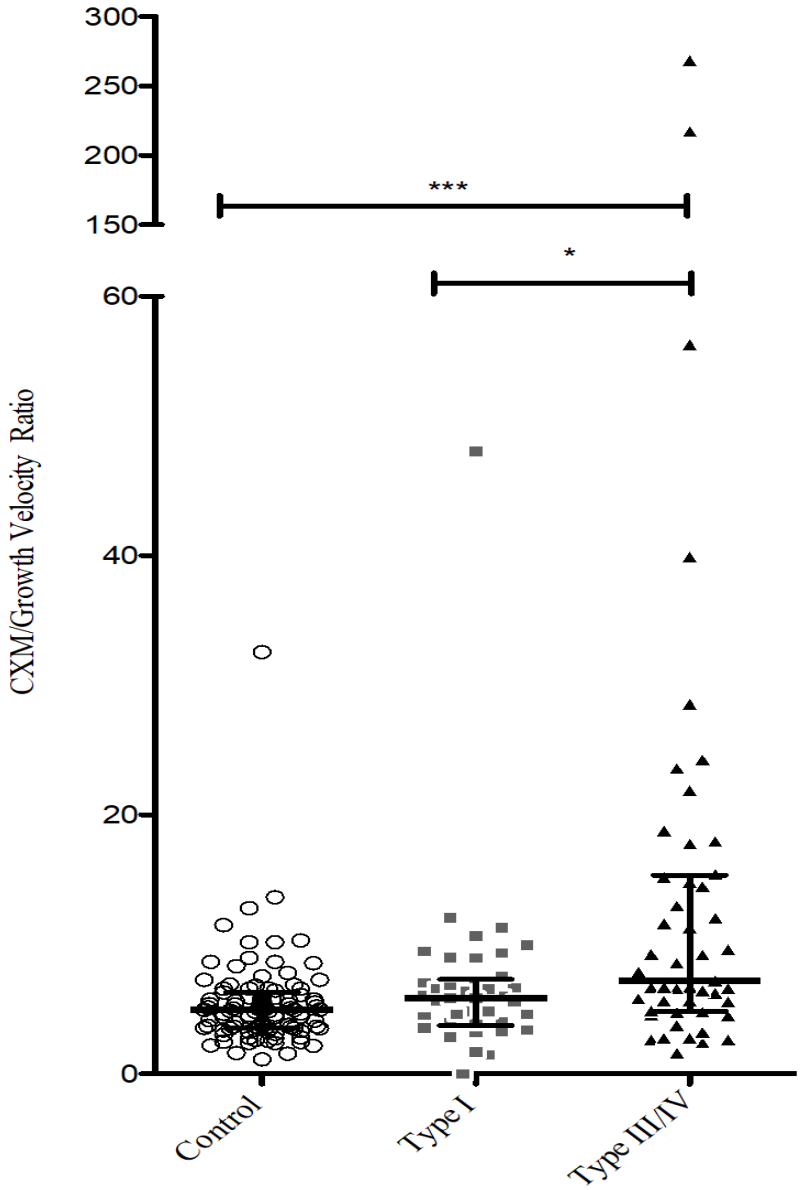
SF-12v2's Applicability to Clinical Trials

Murali et al Clin Genet 2021

	SF12v2		Sample size for parallel group design to detect diff. of			Sample size for crossover design to detect diff. of		
			2	5	10	2	5	10
	Mean score	SD						
OI types I, III, and IV								
PCS	44.8	10.1	824	136	36	55	11	6
OI type I								
PCS	46.4	10.6	926	152	40	55	11	6
OI Type III								
PCS	39.9	7.1	418	70	20	36	9	5
OI type IV								
PCS	44.3	9.5	744	122	34	44	10	5

Biomarker Discordance: High CXM levels with low growth velocity in OI





Leveraging the BBDC infrastructure, Expertise, and Community

- **Industry partnership to accelerate downstream studies towards FDA approval**
  - Sanofi and anti-TGFβ in OI
- **Industry engagement of investigators for development**
  - Ultragenyx/Mereo and anti-sclerostin in OI
- **Natural history and longitudinal data informing clinical trial design and sample sizes**
- **Expansion of patient advocacy networks and capacity**
  - PCORI and Rare Bone Disease Alliance

Acknowledgements

- V. Reid Sutton, Sandesh Nagamani, Dianne Nguyen, & Brendan Lee (BCM)
- Frank Rauch, Francis Glorieux (Montreal Shriners & McGill)
- Jean Marc Retrouvey, Eric Rush (UKMC & Mercy Children's)
- Janice Lee (NIDCR DIR)
- Eric Orwoll, Lindsey Nicol (OHSU and Portland Shriners)
- Deborah Krakow (UCLA)
- Mahim Jain (KKI & JHU)
- Laura Tosi (CNMC)
- Cathleen Raggio (HSS)
- Karen Kruger, Gerald Smith, Peter Smith (Chicago Shriners & Marquette)
- Paul Esposito, Meagan Wallace (University Neb)
- Michael Bober & Richard Kruse (Nemours)
- Danielle Gomez (USF)
- Pamela Smith (Phoenix Children's)
- Maurizio Macaluso (DMCC)
- Tracy Hart (OIF)

Resolving Disease Heterogeneity for Targeted Therapies in Rare Glomerular Disease:

From syndromic disease classes to precision medicine trials

M.Kretzler, University of Michigan

NEPHCURE Kidney International
Saving Kidneys • Saving Lives

NIH National Institute of Diabetes and Digestive and Kidney Diseases

RARE DISEASES CLINICAL RESEARCH NETWORK

Disclosures

- Current Employer: U. Michigan Medical School,, Ann Arbor, MI, USA
- Research Funding and Consulting as PI at U Michigan: NIH, EU IMI, JDRF, Chan Zuckerberg Initiative, amfAR, Astra-Zeneca, Boehringer-Ingelheim, Gilead, Goldfinch, Lilly, Angion, Astellas, Poxel, Certa, NovoNordisc, Jansen, Moderna, Chinook, RenalytixAI, Regeneron, Travere, Ionis.
- Advisory Board: NIH/NCATS council; Nephcure Kidney International.
- Patent: Biomarkers and methods for progression prediction for chronic kidney disease.

Molecular Definition of Rare Glomerular Disease: From syndromic classes to mechanistic categories

Tissue-centred Clinical & Molecular Phenotyping

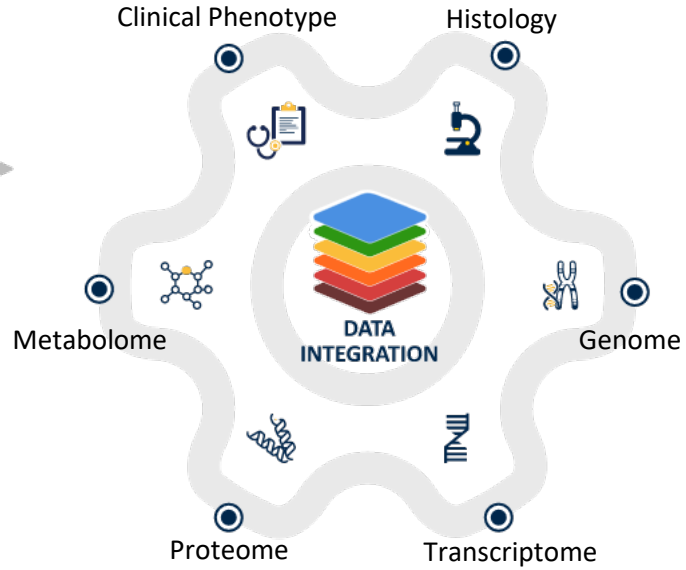
Prospective cohort studies

Molecular Definition of Rare Glomerular Disease: From syndromic classes to mechanistic categories

Tissue-centred Clinical & Molecular Phenotyping

Prospective cohort studies

Multiscalar Data Integration

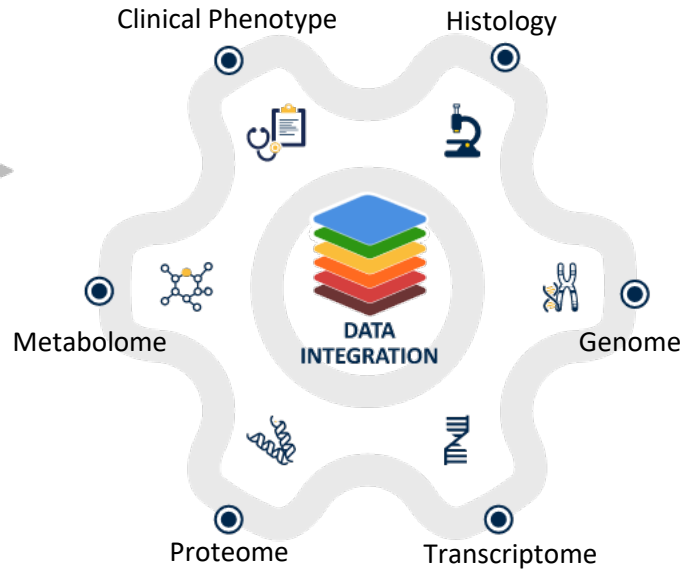


Molecular Definition of Rare Glomerular Disease: From syndromic classes to mechanistic categories

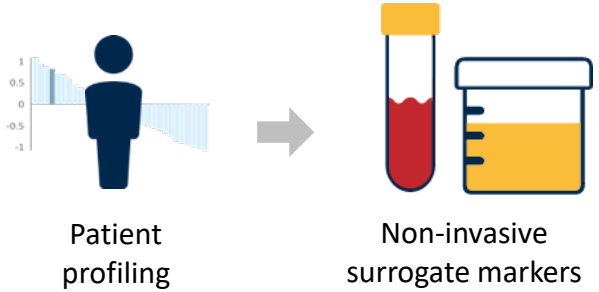
Tissue-centred Clinical & Molecular Phenotyping

Prospective cohort studies

Multiscalar Data Integration

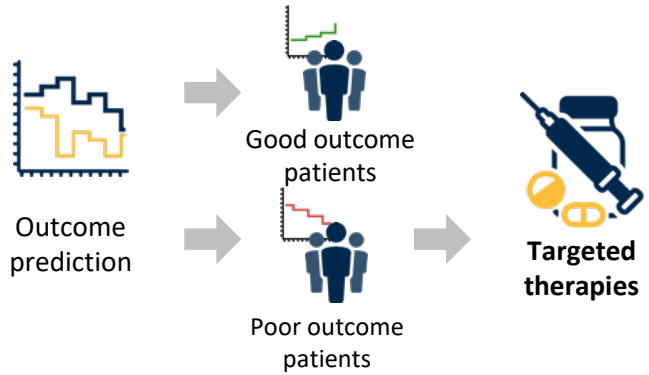


Patient-level Pathway Activity

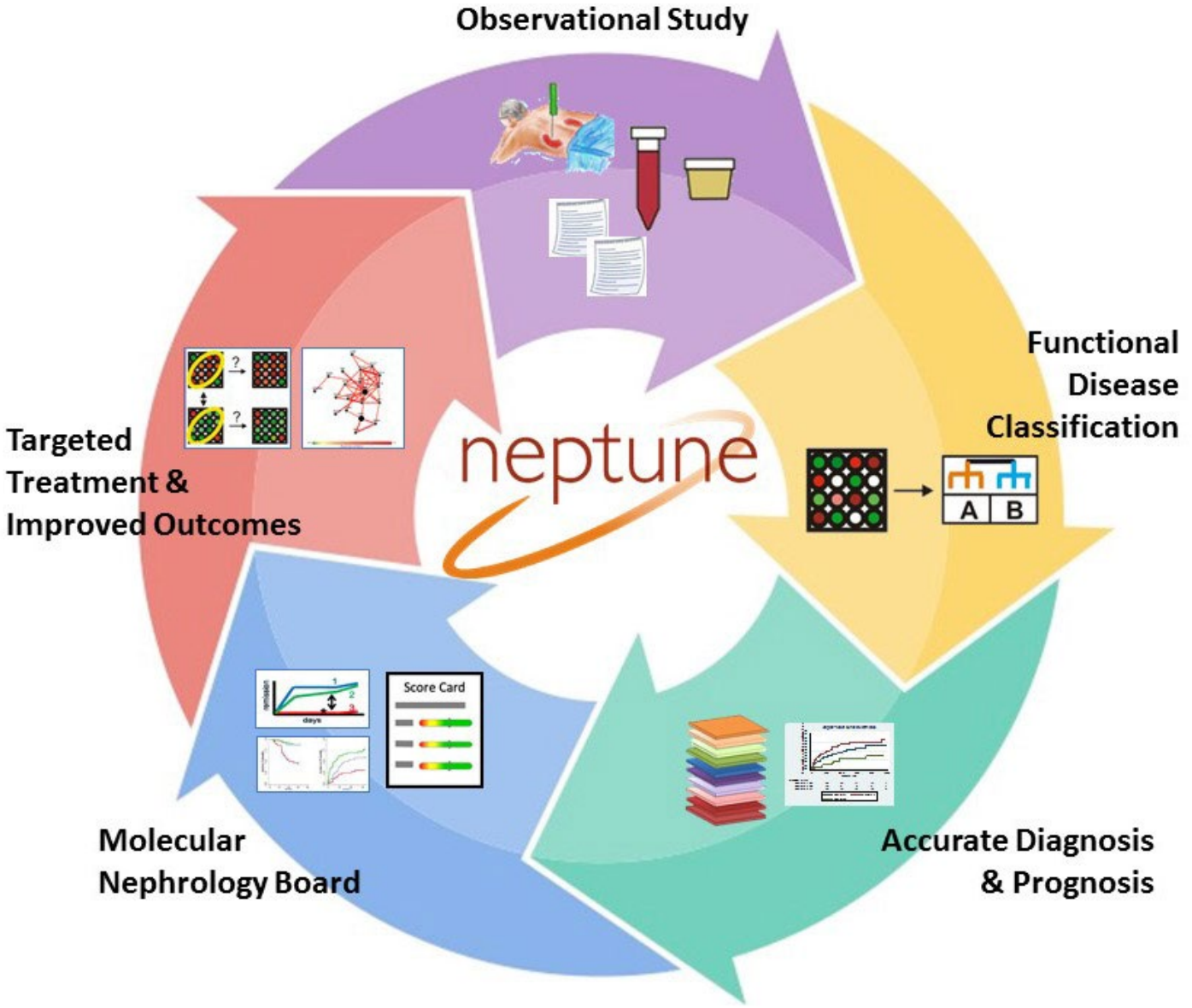


Patient profiling

Non-invasive surrogate markers



The Nephrotic Syndrome Study Network



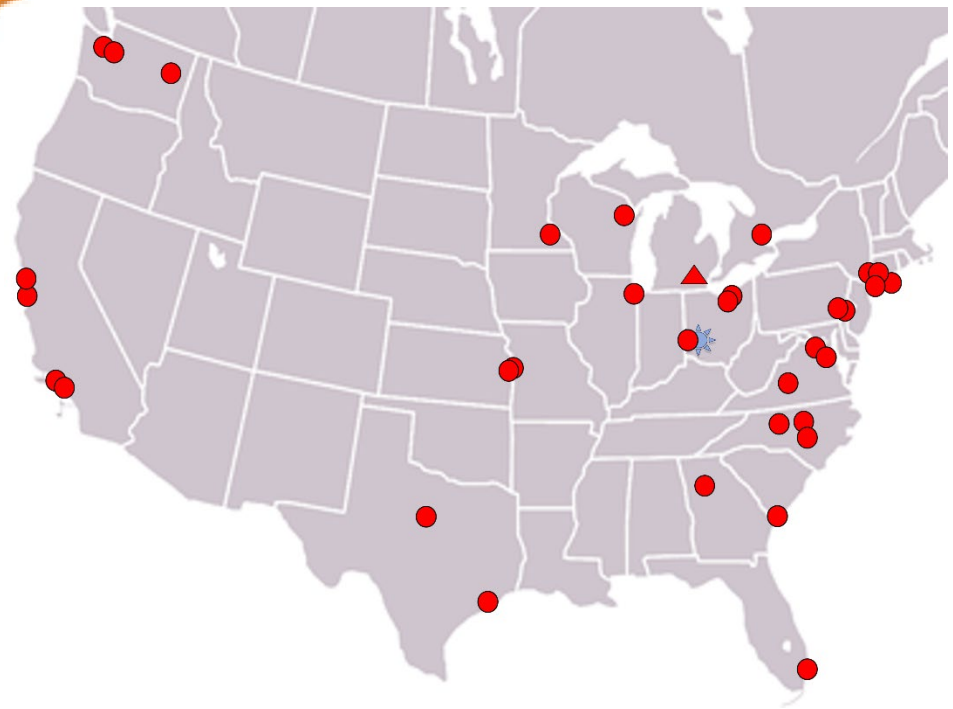
Identifying the right trial for the right patient at the right time.

NEPHCURE Kidney International
Saving Kidneys • Saving Lives

NIH National Institute of Diabetes and Digestive and Kidney Diseases

RARE DISEASES CLINICAL RESEARCH NETWORK

Precision Medicine for Nephrotic Syndrome



NEPTUNE provides a collaborative, investigational infrastructure across 27 North American sites for translational research in:

- Focal Segmental Glomerulosclerosis (FSGS)
- Minimal Change Disease (MCD)
- Membranous Nephropathy (MN)
- Pediatric Non-biopsy Cohort

Cleveland Clinic, Cleveland, OH
Cohen Children's Medical Center, Manhasset, NY
Children's Mercy Hospital, Kansas City, MO
Columbia University, New York, NY
Duke University, Raleigh, NC
Emory University, Atlanta, GA
Harbor UCLA Medical Center, Torrance, CA
Johns Hopkins Medical Institute, Baltimore, MD
John H. Stroger, Jr. Hospital of Cook County, Chicago, IL
Kansas University, Kansas City, KS
Levine Children Atrium Health, Charlotte NC
Medical University of South Carolina, Charleston, SC
Montefiore Medical Center, Bronx, NY
New York University School of Medicine, New York, NY
Providence Medical Research, Spokane, WA
Seattle Children's Hospital, Seattle, WA
Stanford University, Stanford, CA
The Mayo Clinic, Rochester, MN
The Ohio State University College of Medicine, Columbus, OH
Temple University, Philadelphia, PA
Texas Children Hospital, Baylor College of Medicine, Houston, TX University of California as San Francisco, San Francisco, CA
University Health Network, Toronto, Ontario, Canada
University of Miami Medical Center, Miami, FL
University of Michigan, Ann Arbor, MI
University of Minnesota, Minneapolis, MN
University of North Carolina at Chapel Hill, Chapel Hill, NC
University of Pennsylvania, Philadelphia, PA
University of Southern California, Children's Hospital of LA, CA
University of Texas Southwest Medical Center, Dallas, TX
University of Washington, Seattle, WA
Wake Forest, Winston-Salem, NC

RDCRN III DMCC – Cincinnati Children's Hospital, Cincinnati, OH
NEPTUNE DACC – University of Michigan, Ann Arbor, MI

Resource for translational and clinical studies in glomerular disease studies

- Patient partnerships
- Ancillary study projects & data sharing
- Pilot and career development program
- Robust public/private partnerships

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NEPHCURE Kidney International

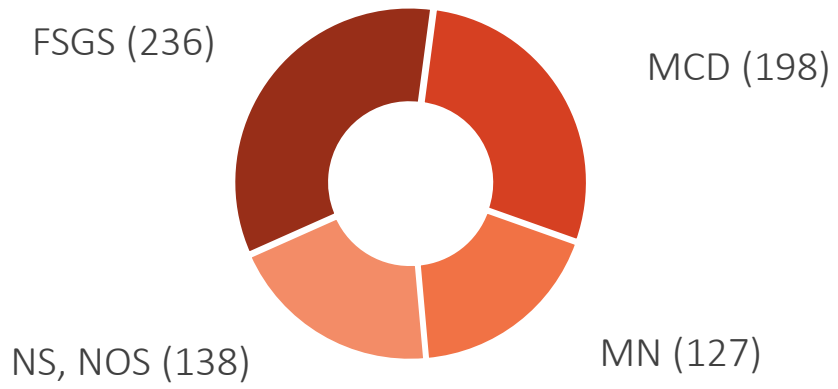
Saving Kidneys • Saving Lives

Longitudinal Cohorts

Biopsy:
Adults & children with FSGS, MCD, MN recruited at time of biopsy

Non-Biopsy:
Children with NS recruited at first presentation before diagnostic biopsy

NEPTUNE Cohort by Disease



Knowledge network of multi-scalar datasets and collaborative studies
Demographics
Clinical data with prospective outcomes
Patient-reported outcomes
Census tract links to neighborhood data
Whole genome sequencing
Morphometric analyses (IFTA, glom. Dimension)
Glomerular Pathology descriptors
EM Pathology descriptors
Glomerular & tubular gene expression
Biopsy single cell gene expression
Plasma and Urine Targeted proteomics
Urinary and blood biomarkers

Biorepositories	
Biospecimens:	Kidney tissue from biopsy Urine: spot; 24-hour Plasma, serum, DNA, RNA
Cell lines:	iPSC repository
Digital pathology:	Whole slide images 51 descriptors

Framework for Translational Research in Nephrotic Syndrome

neptune

http://neptune-study.org

NEPTUNE Knowledge Network

Clinical profile: clinical data

Morphologic profile: renal biopsy (first, initial, repeat Neptune)

Molecular profile: non-invasive biomarkers, gene expression maps, genetic analysis obtained and integrated

Predict

1 Response to standard of care

- Uni-scalar Prediction
- Multi-scalar Prediction

Identify

2 Target identification and development

- Define renal disease in mechanistic terms
- Match drugs with pathways in individual patients
- Identify targets for drug development

Target

3 Targeted Clinical Trial

- Molecular Patient Stratification for targeted therapy selection

Framework for Translational Research in Nephrotic Syndrome

neptune

http://neptune-study.org

NEPTUNE Knowledge Network

Clinical profile: clinical data

Morphologic profile: renal biopsy (first, initial, repeat Neptune)

Molecular profile: non-invasive biomarkers, gene expression, genetic analysis obtained and integrated

180

Ancillary Studies by International Glomerular Research Community

Predict

1 Response to standard of care

- Uni-scalar Prediction
- Multi-scalar Prediction

Identify

2 Target identification and development

- Define renal disease in mechanistic terms
- Match drugs with pathways in individual patients
- Identify targets for drug development

Treat

3 Targeted Clinical Trial

- Molecular Patient Stratification for targeted therapy selection

Defining Disease Subgroups for targeted treatment trials

neptune

http://neptune-study.org

NEPTUNE Knowledge Network

Clinical profile: clinical data

Morphologic profile: renal biopsy (first, initial, repeat Neptune)

Molecular profile: non-invasive biomarkers, gene expression maps, genetic analysis obtained and integrated

Predict

1 **Response to standard of care**

- Uni-scalar Prediction
- **Multi-scalar Prediction**

Identify

2 Target identification and development

- Define renal disease in mechanistic terms
- Match drugs with pathways in individual patients
- Identify targets for drug development

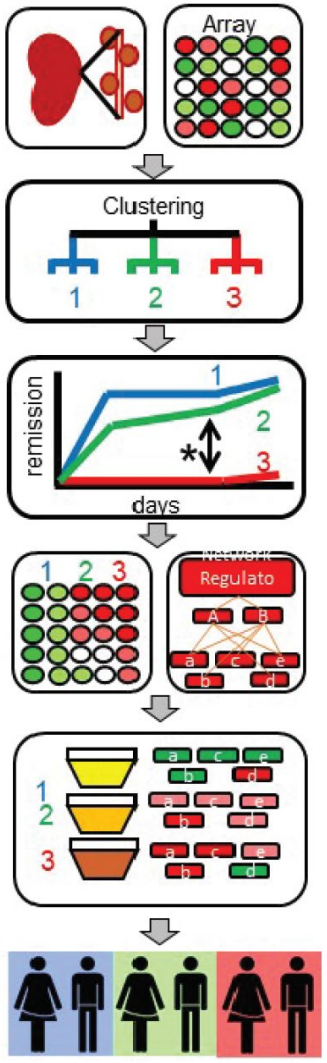
Target

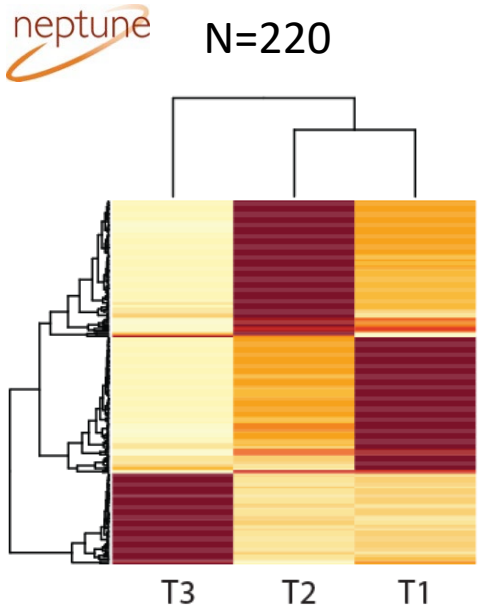
3 Targeted Clinical Trial

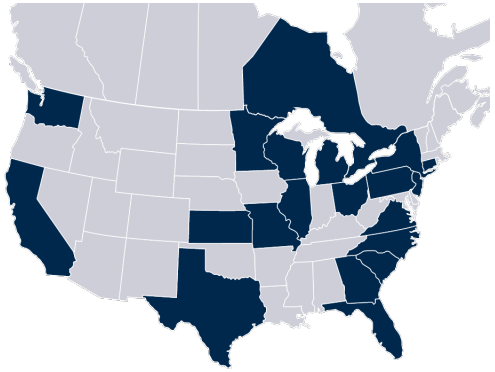
- Molecular Patient Stratification for targeted therapy selection

Identification of targetable pathways in FSGS subgroups for non-invasive disease stratification

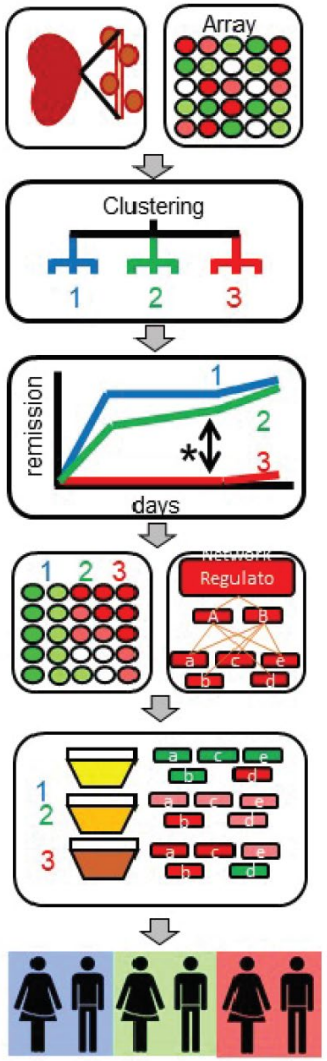
Tissue Gene Expression Identifies Molecular Subgroups in FSGS/MCD



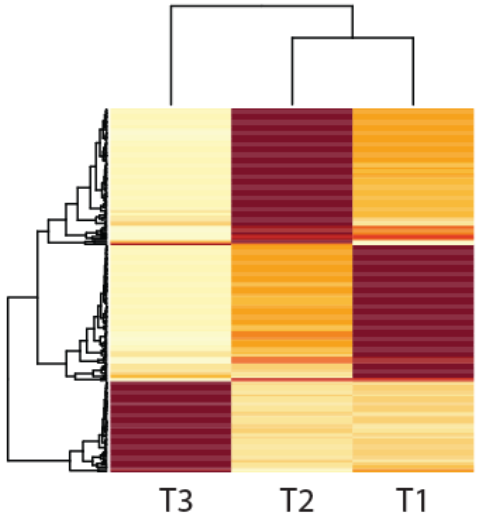


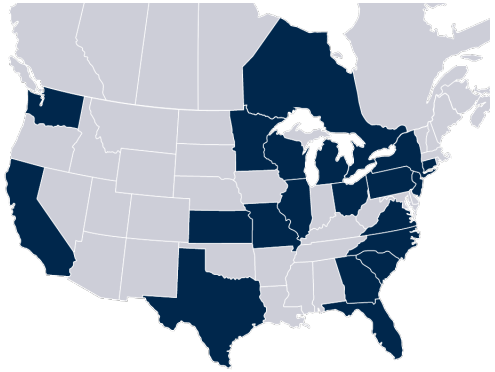


Tissue Gene Expression Identifies Molecular Subgroups in FSGS/MCD

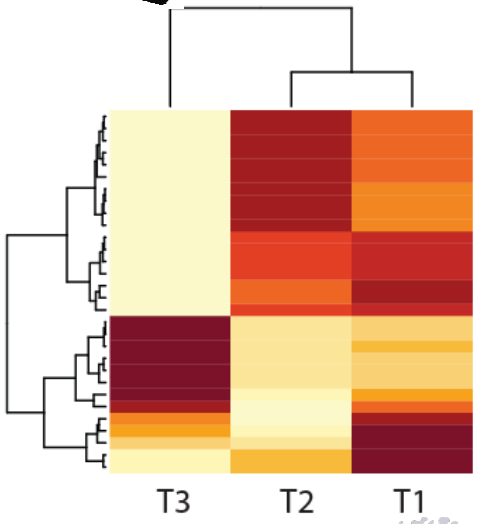


neptune N=220

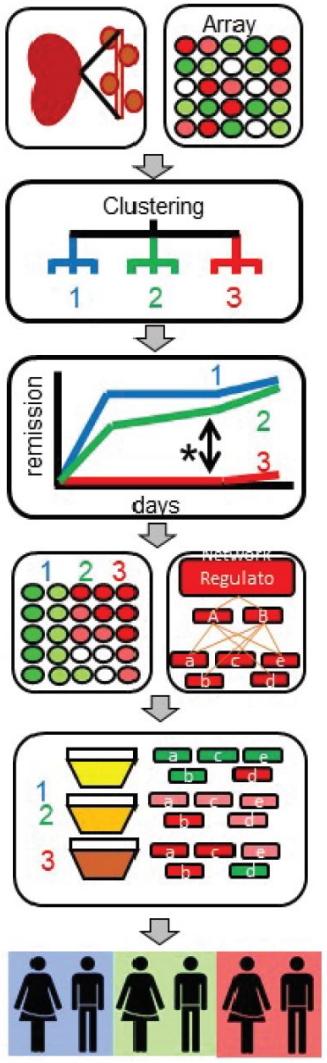




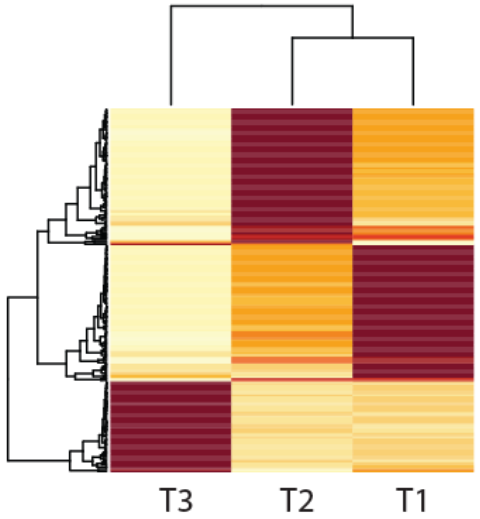
ERCB N=30

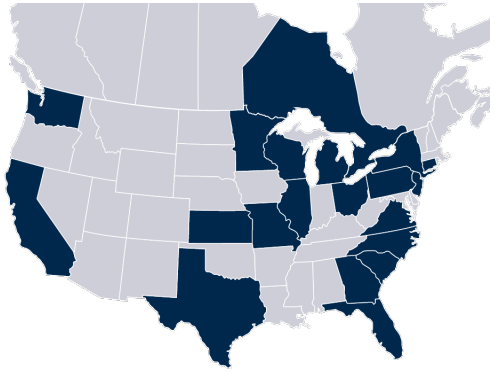


Tissue Gene Expression Identifies Molecular Subgroups in FSGS/MCD

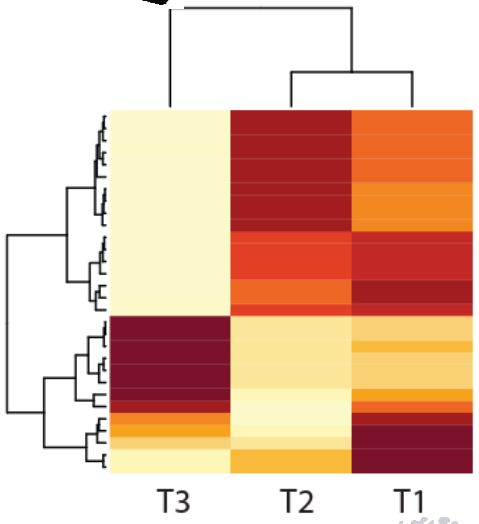



neptune N=220

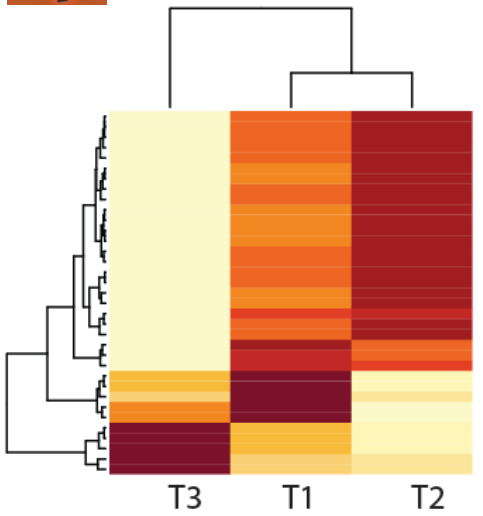




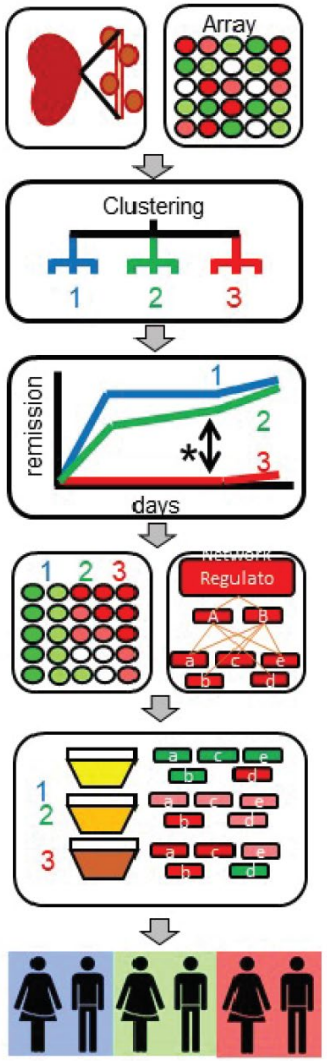
ERCB N=30



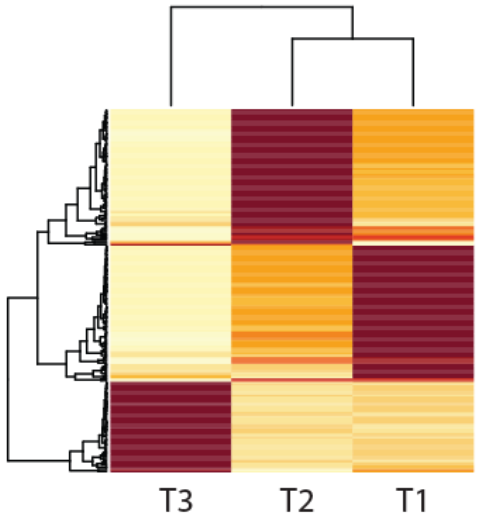
N=35



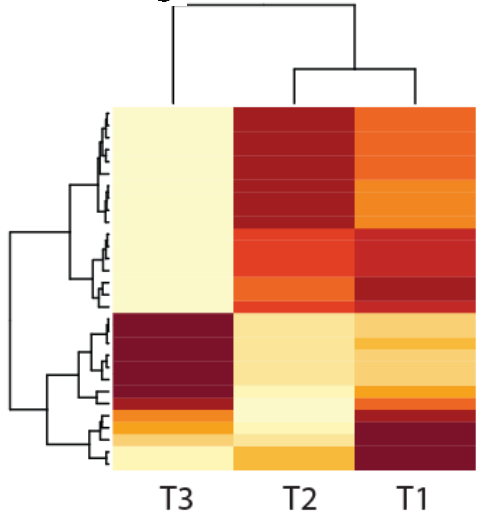
Tissue Gene Expression Identifies Molecular Subgroups in FSGS/MCD

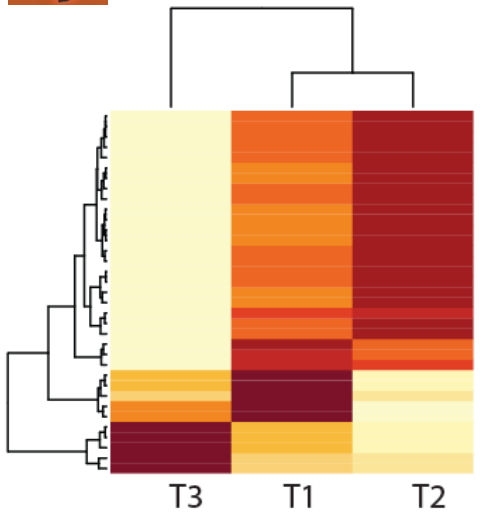
neptune N=220



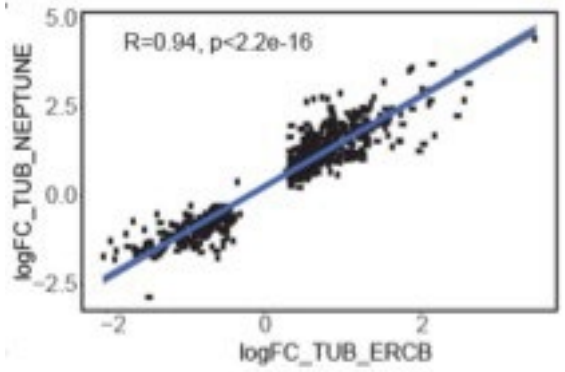
ERCB N=30

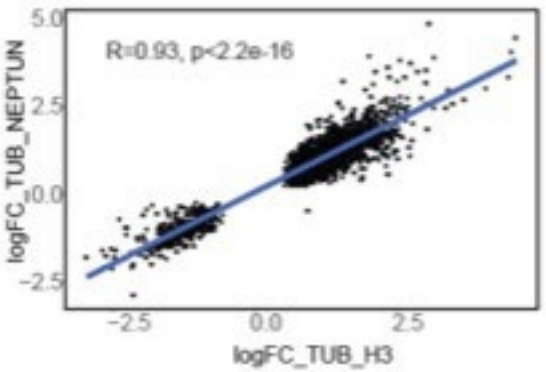


H3 N=35

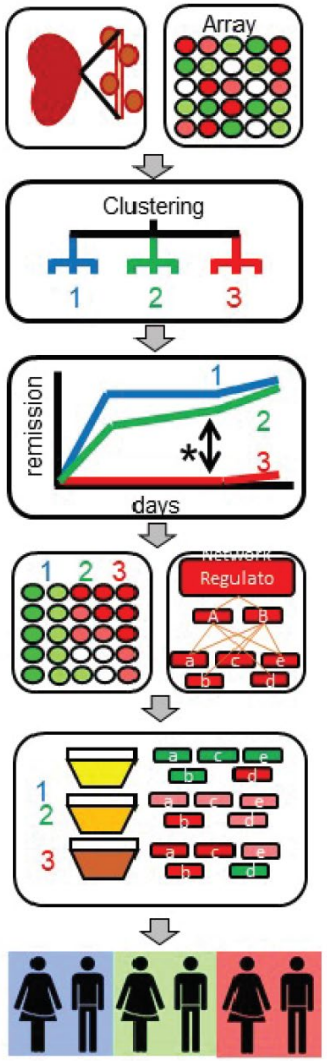


D. NEPTUNE (N=220)



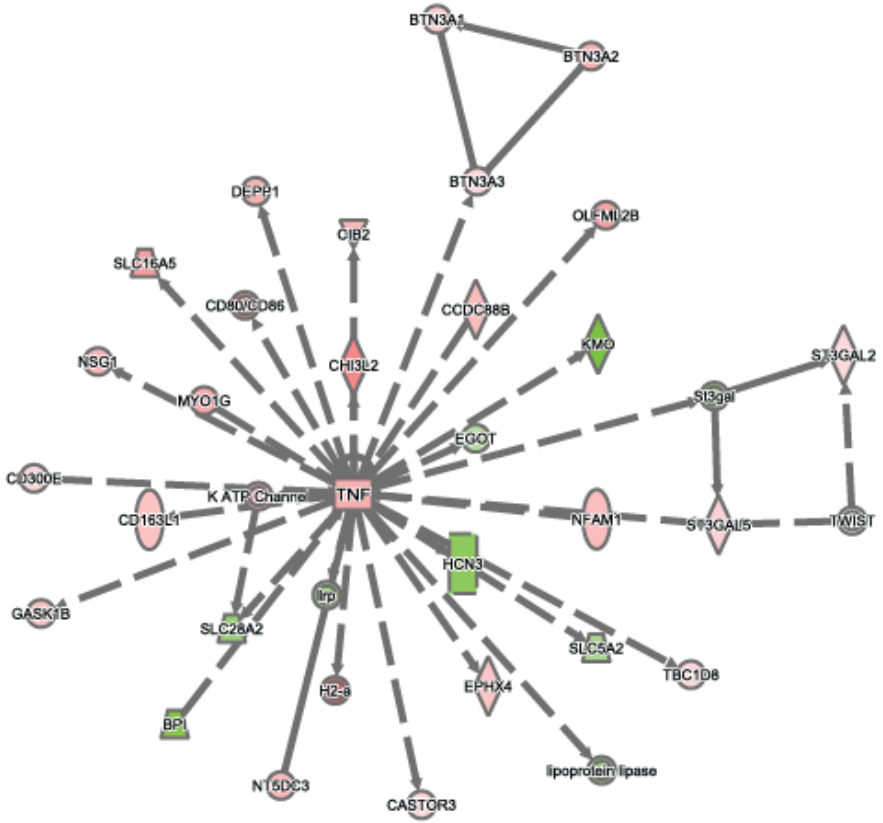


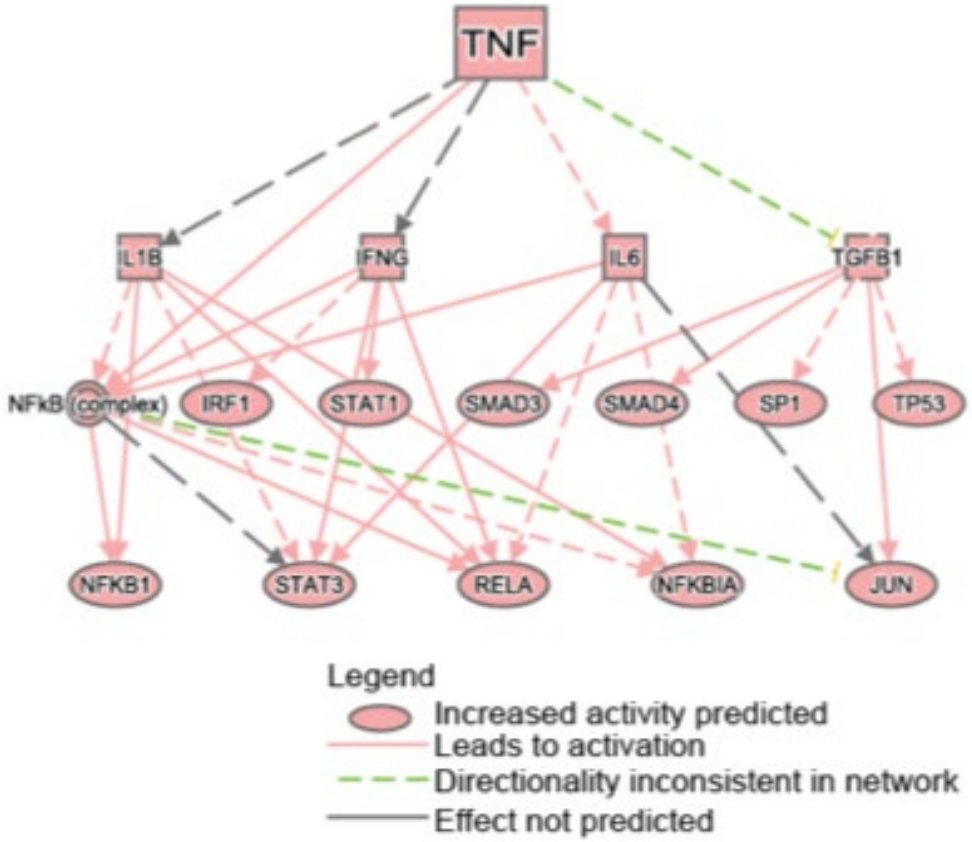
TNF as upstream regulator in poor outcome cluster 3



C.

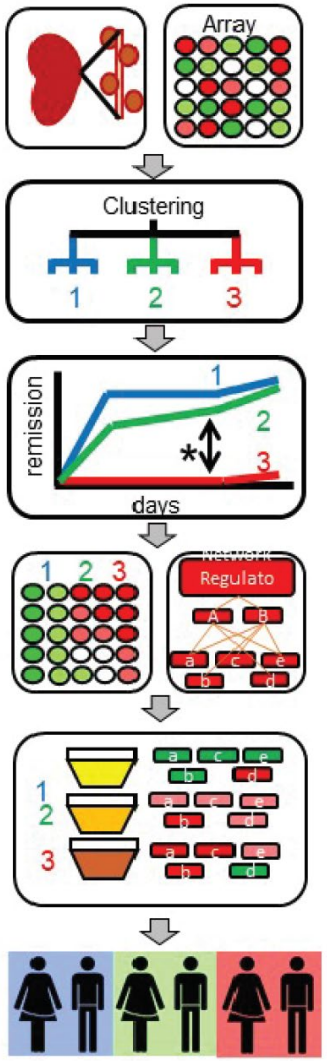
Differential Gene Expression in Cluster 3 vs. 1+2





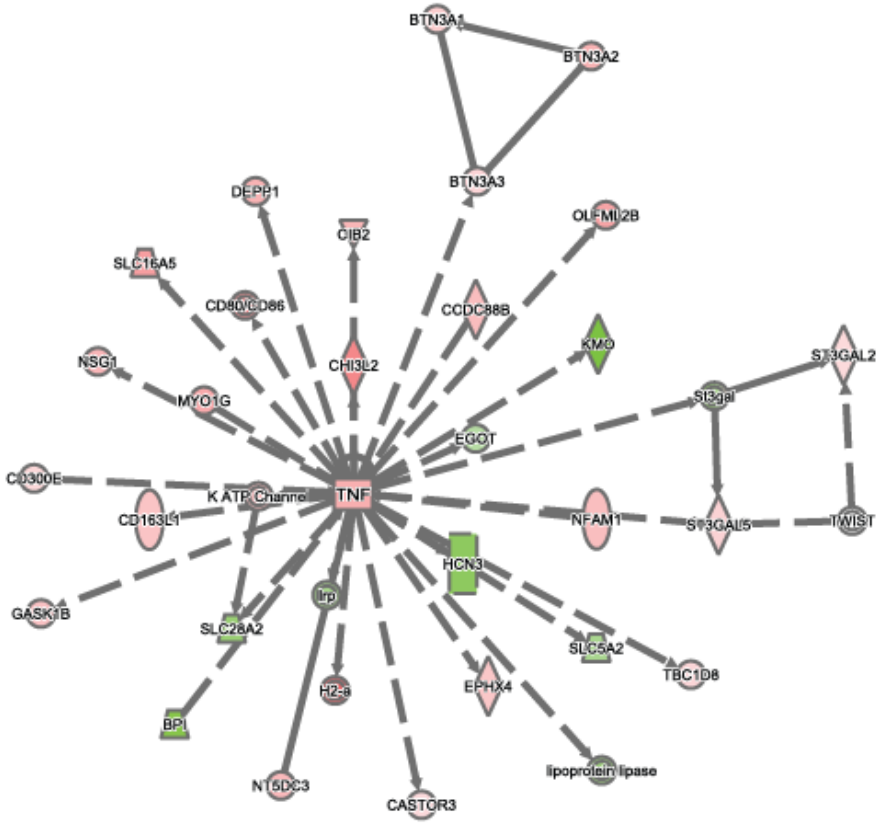
TNF inhibition induced response in subset of multidrug resistant FSGS in FONT2 (Trachtman et al. 2010)

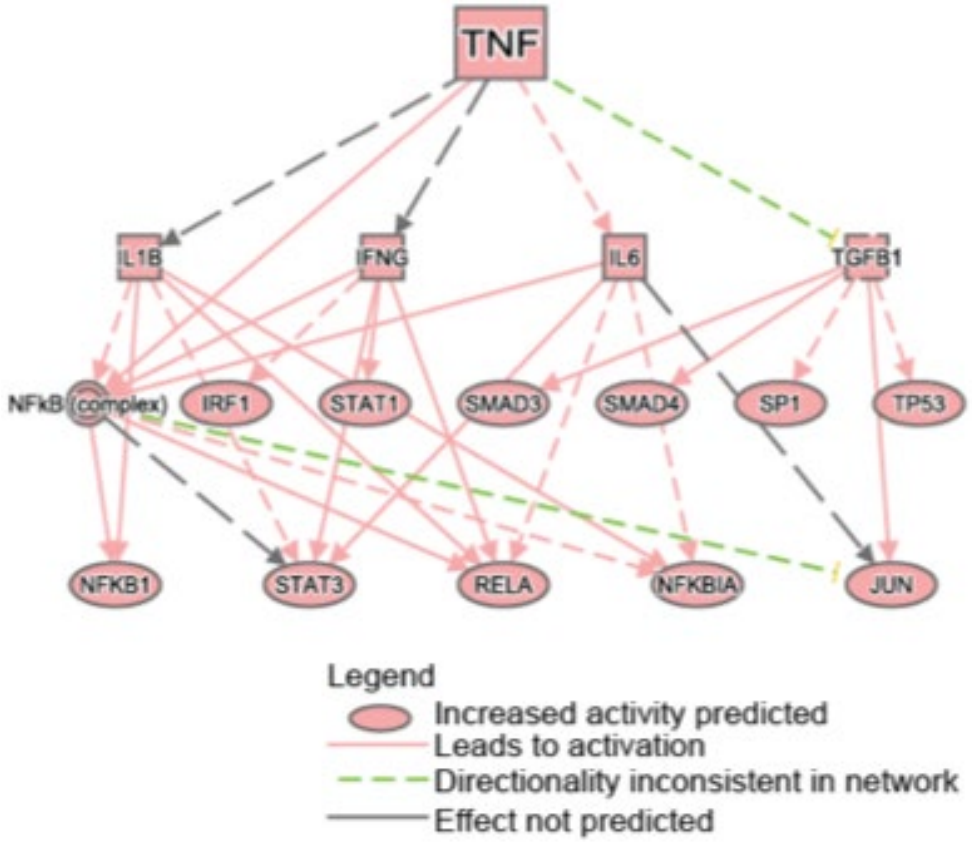
TNF as upstream regulator in poor outcome cluster 3



C.

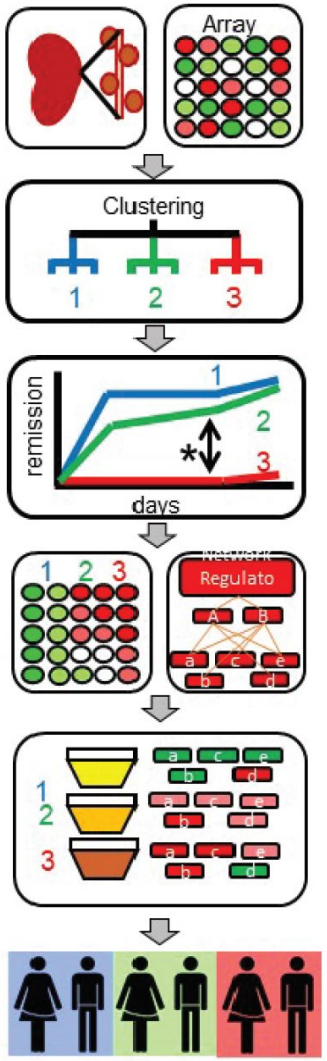
Differential Gene Expression in Cluster 3 vs. 1+2





TNF inhibition induced response in subset of multidrug resistant FSGS in FONT2 (Trachtman et al. 2010)

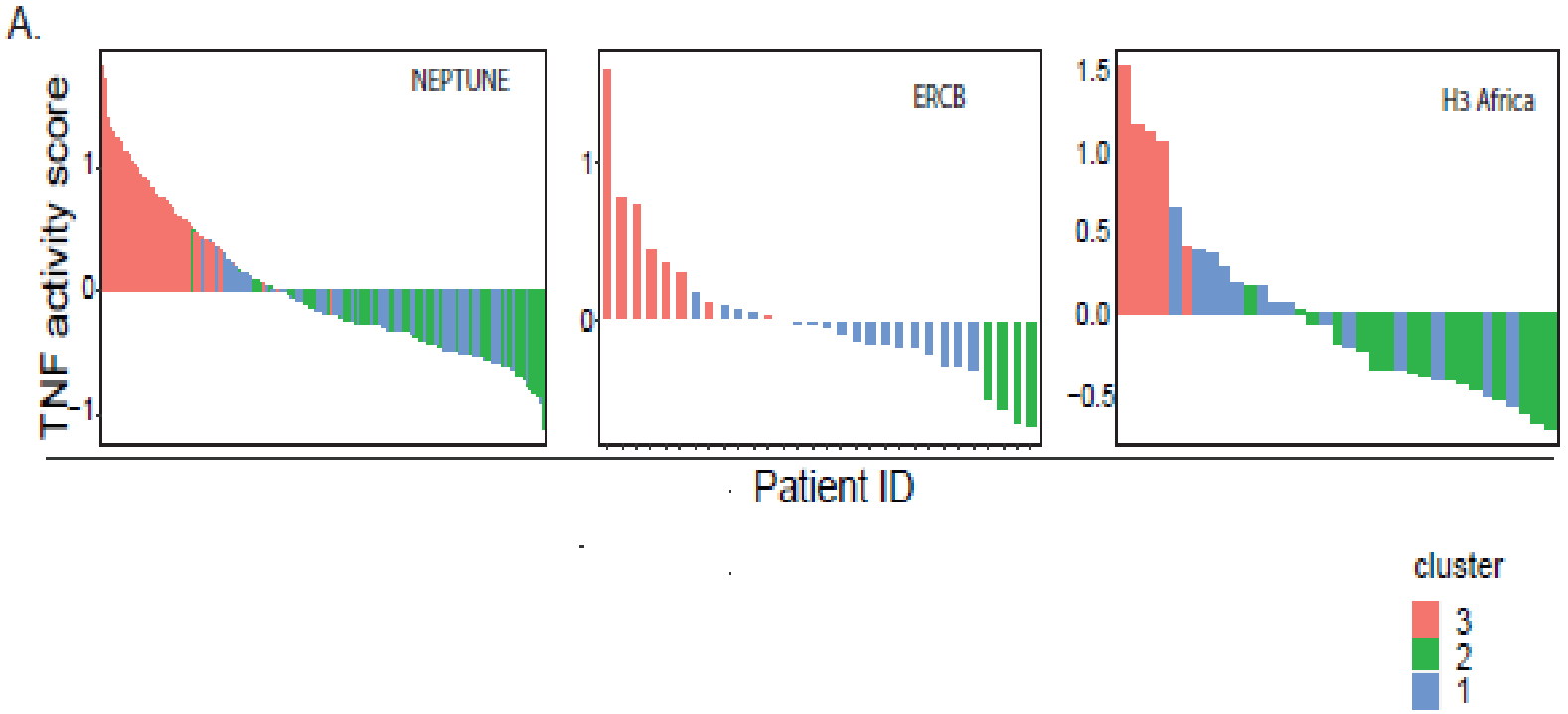
Patient-level TNF activation score linked to molecular subgroup across three continents



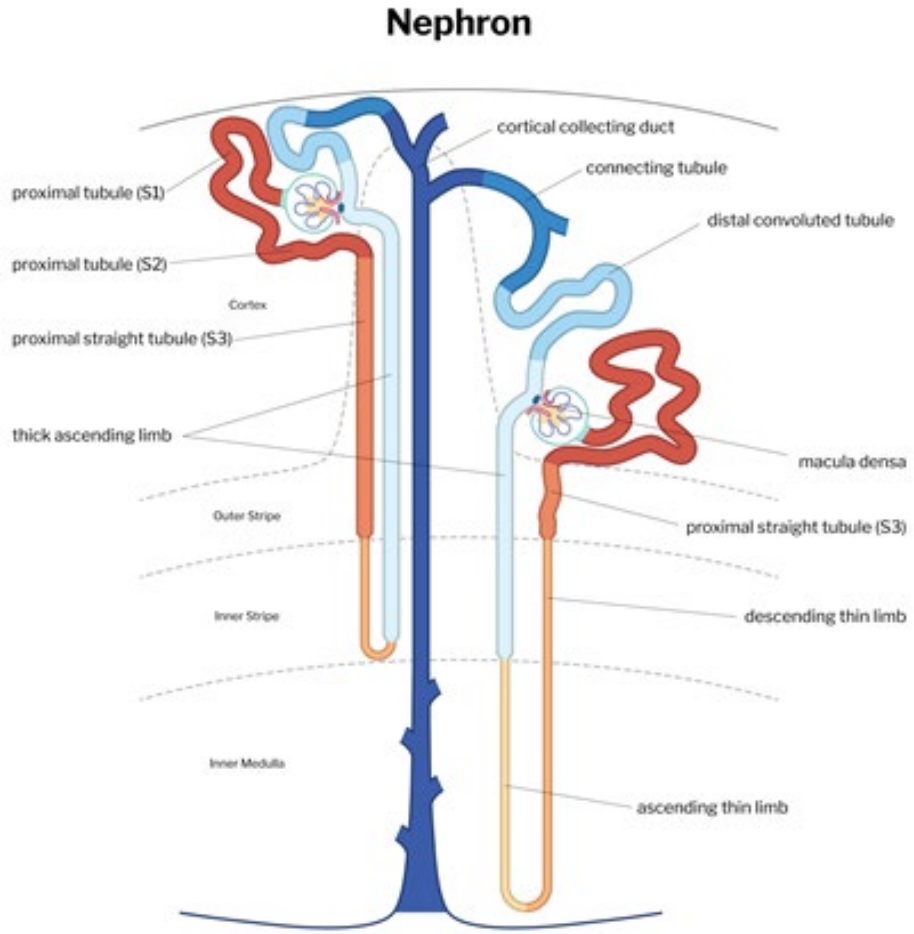
neptune

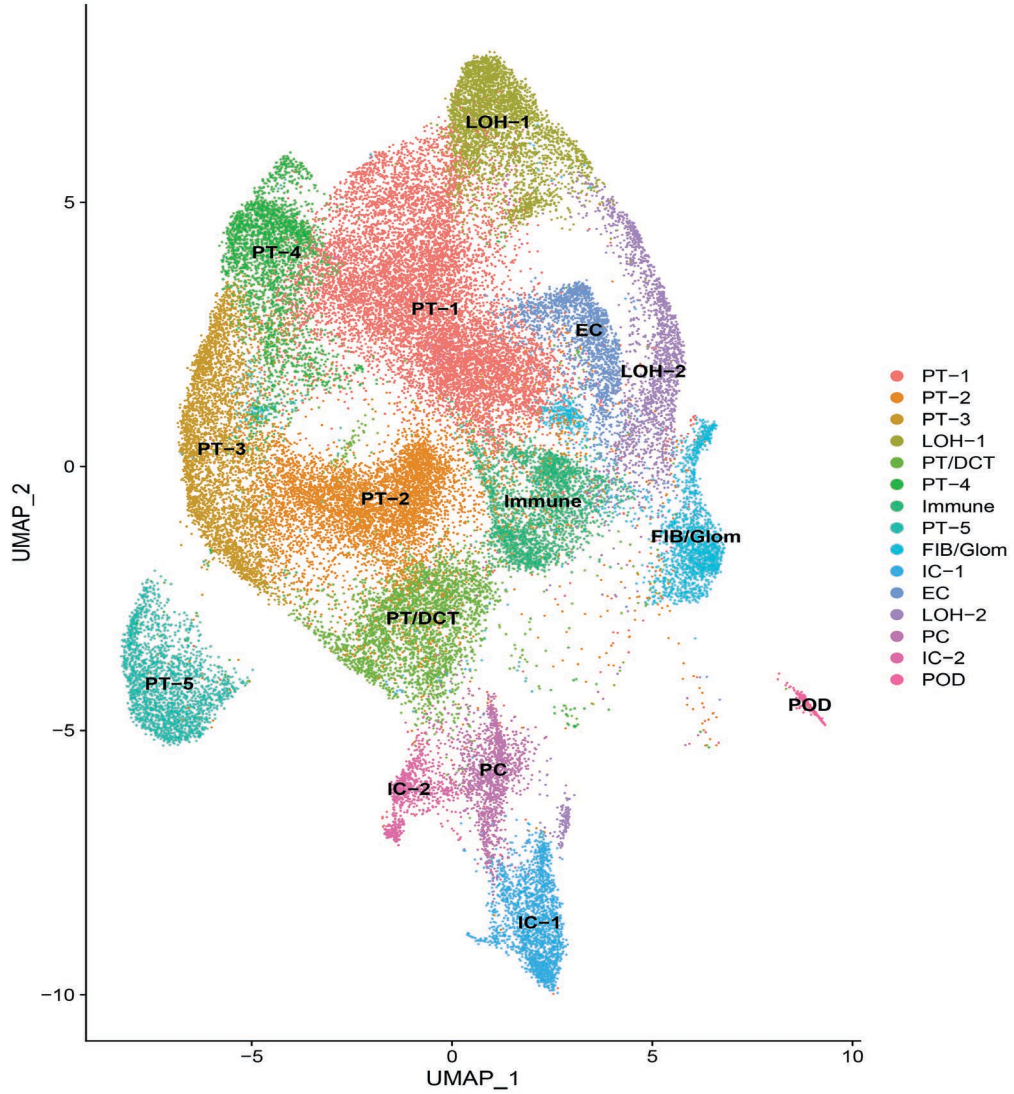
ERCB

H3

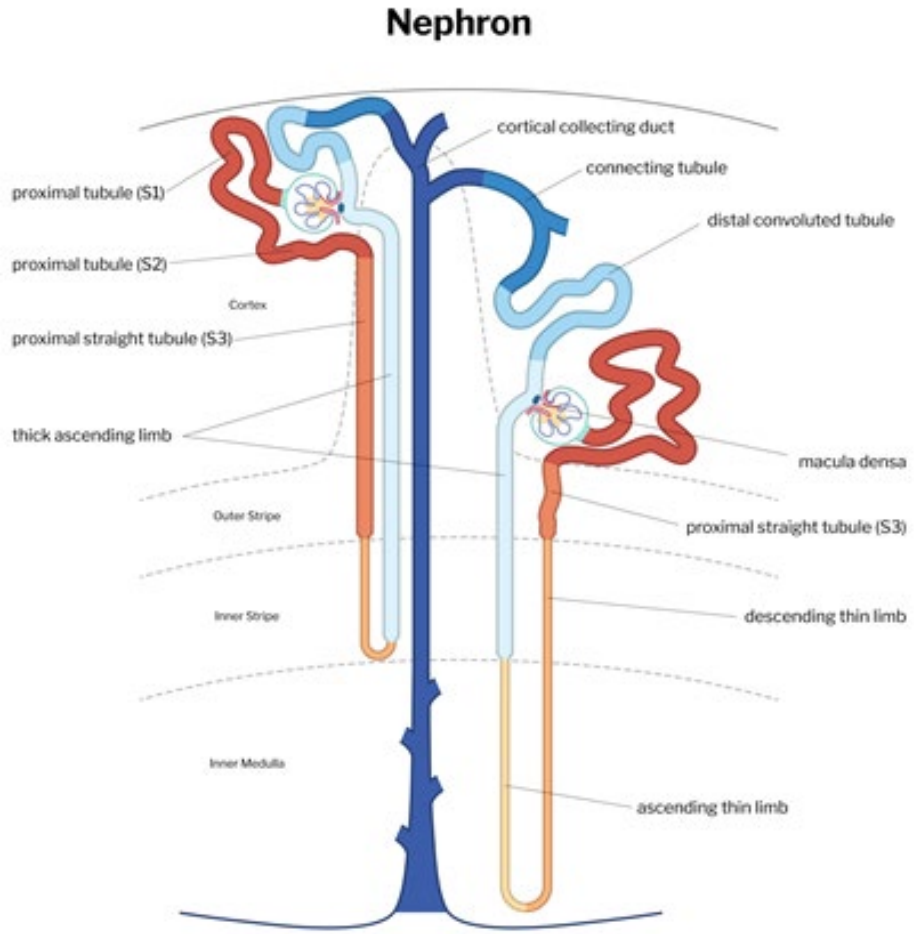


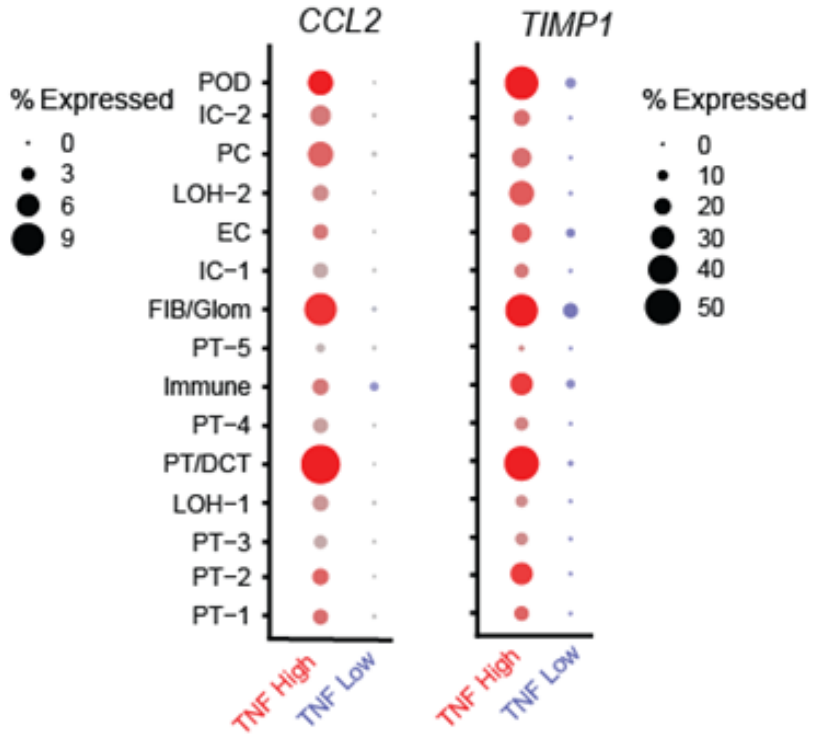
TNF-regulated transcripts associated with outcome demonstrated cell-selective expression





TNF-regulated transcripts associated with outcome demonstrated cell-selective expression



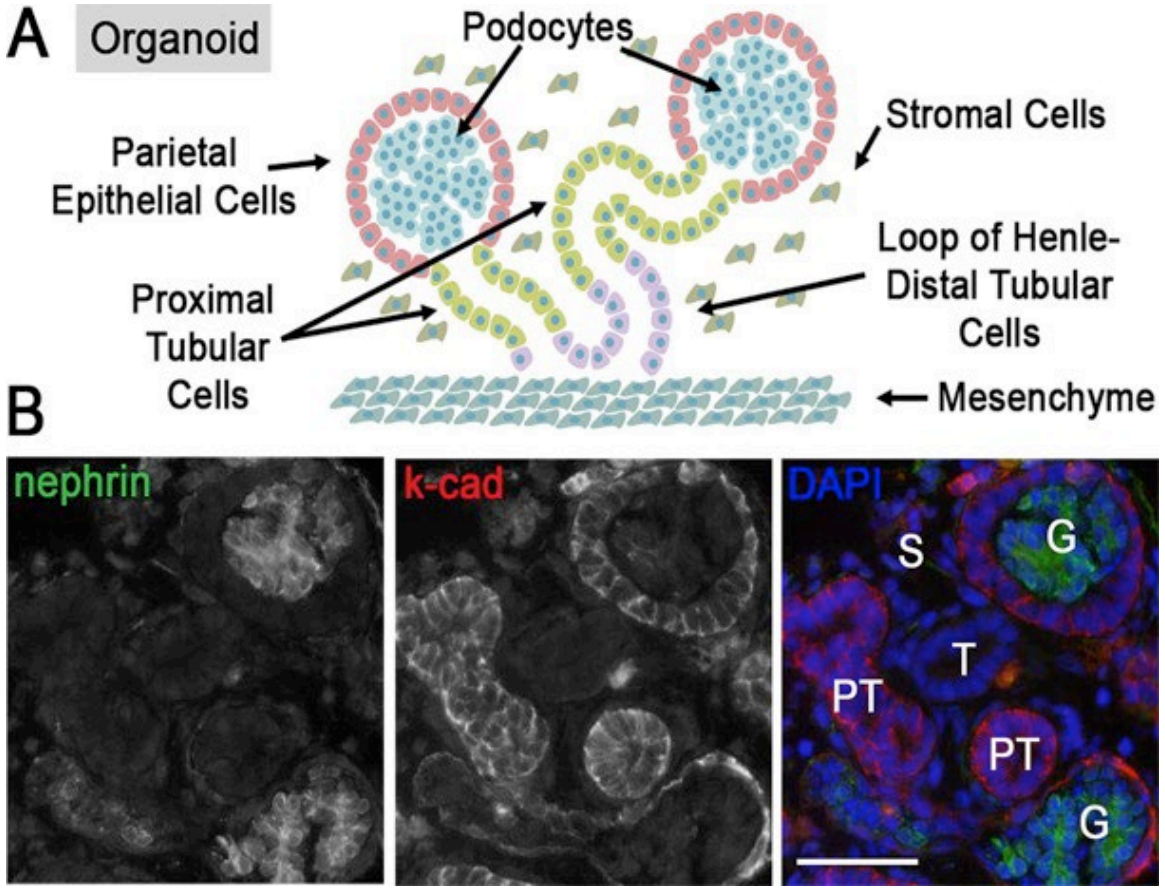


Neptune FSGS snRNAseq:

TNF High (n=5)

TNF Low (n=5)

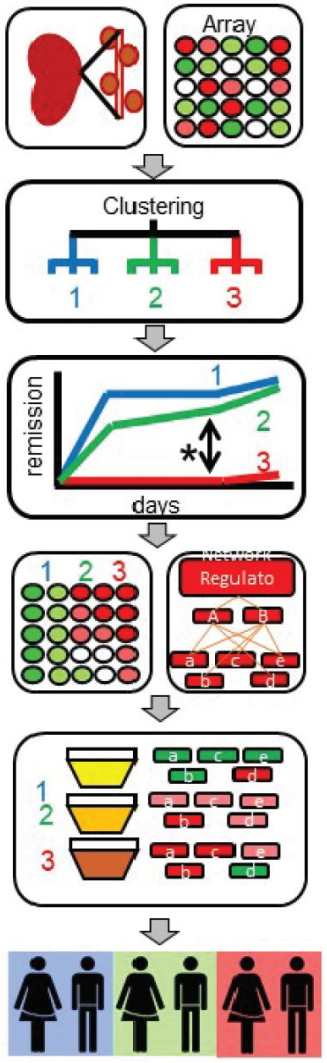
Evaluate therapeutic target response in human models: FSGS Organoid System



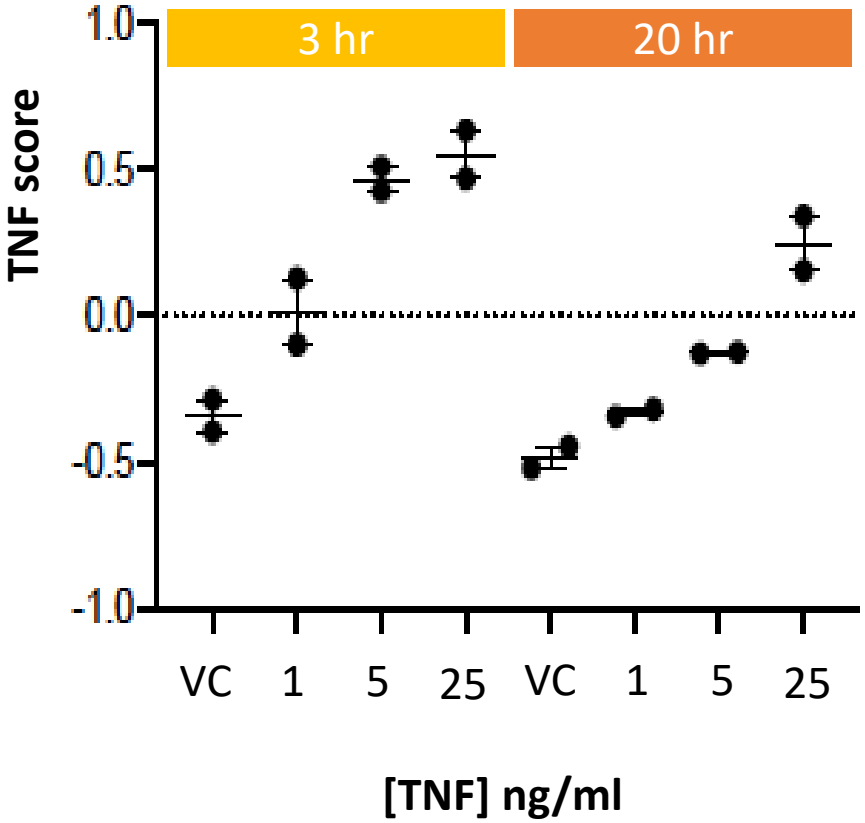
Organoids as a patient specific ex vivo model with NCATS Trial on a Chip program

Harder et al. JCI Insight 2019

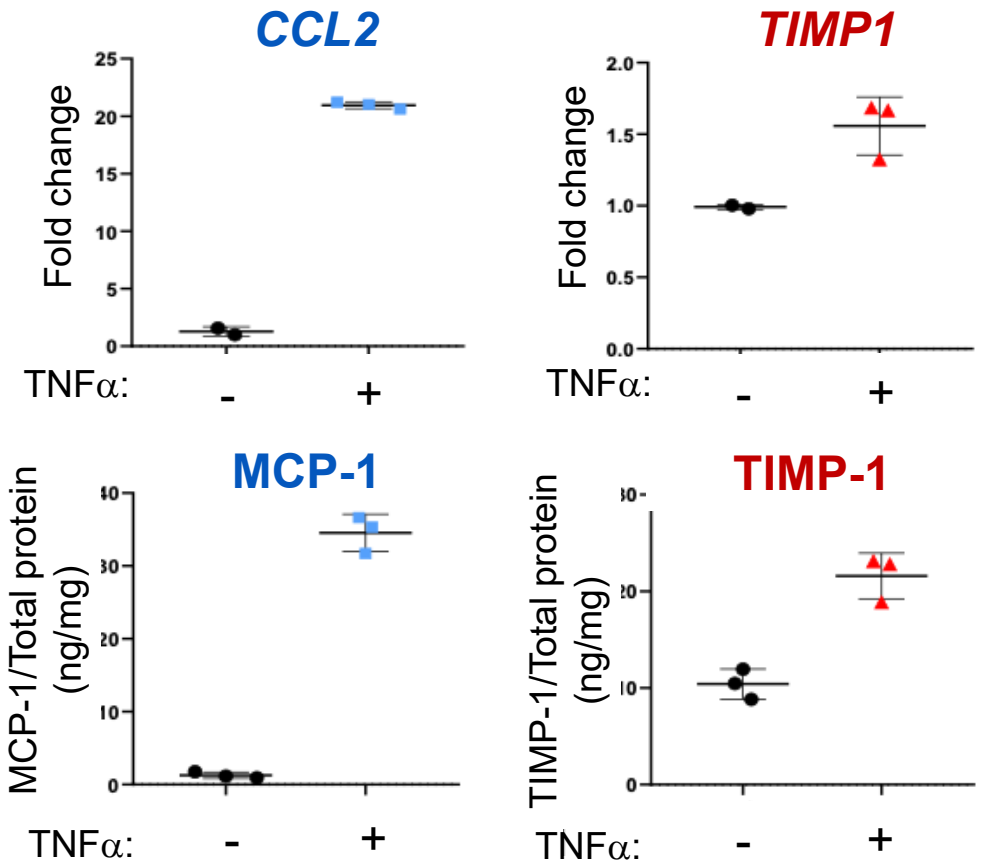
From association to causation:
Modelling TNF regulation of biomarkers in renal organoids



Organoid RNA-seq

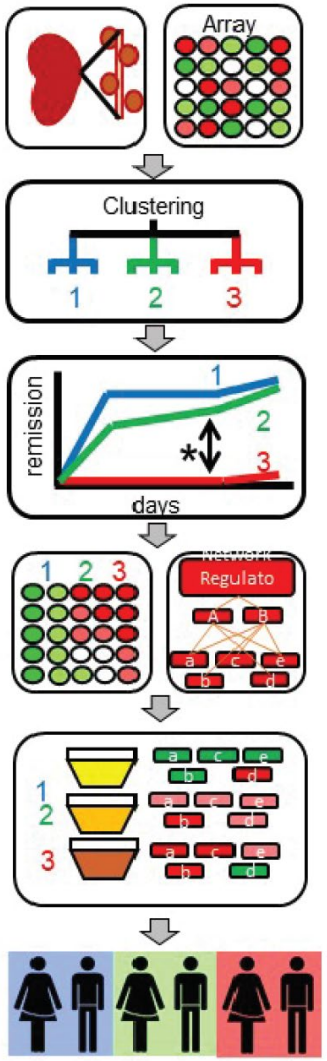


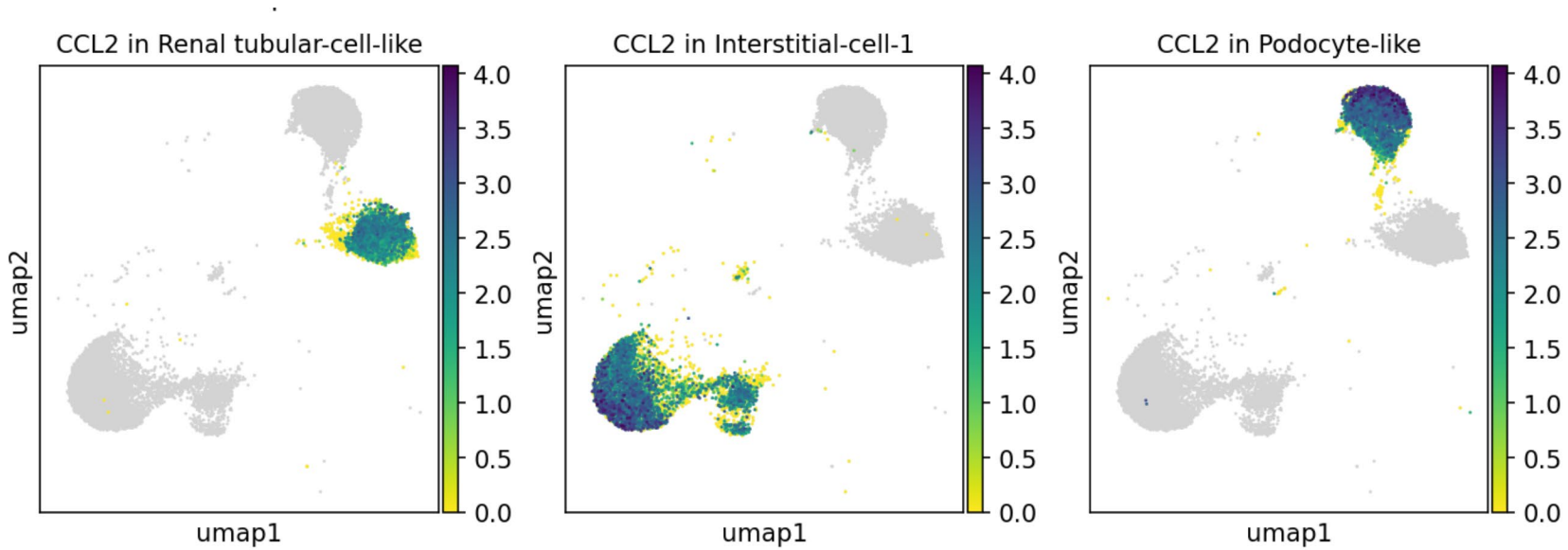
Transcript by qPCR

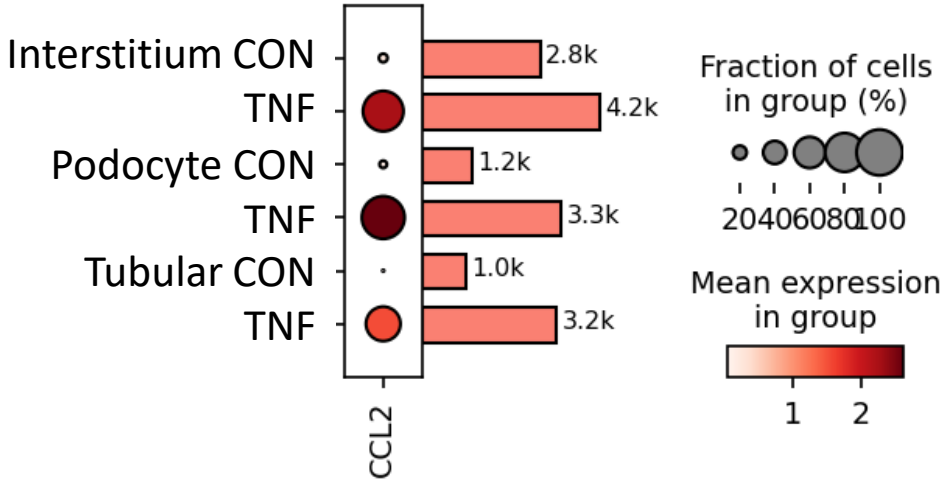


Supernatant Protein by ELISA

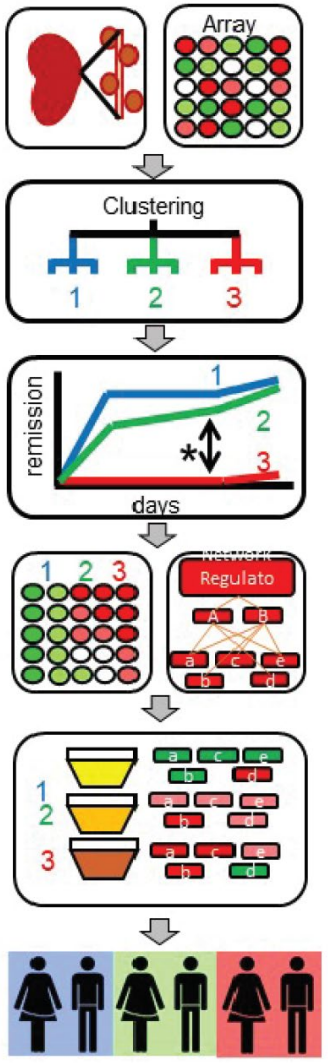
From association to causation:
Modelling TNF regulation of biomarkers in renal organoids

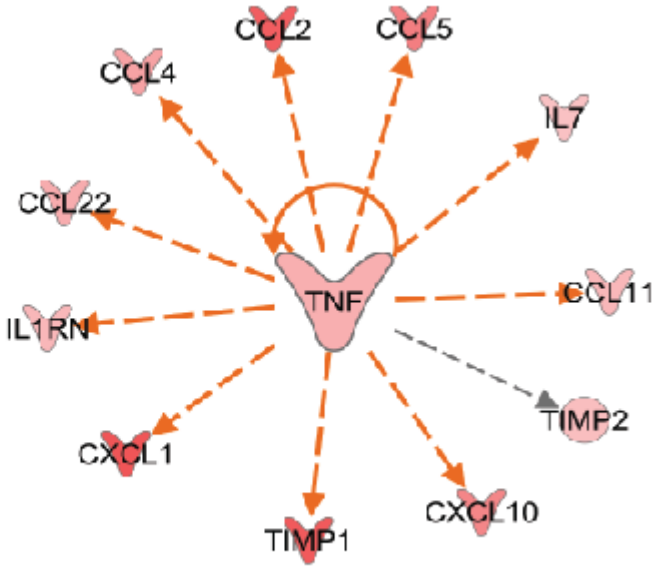






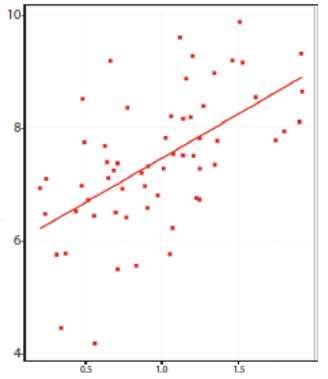
Urinary biomarkers as non-invasive surrogates of TNF activation





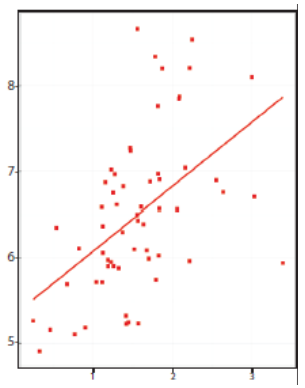
Intra-renal Transcript

CCL2



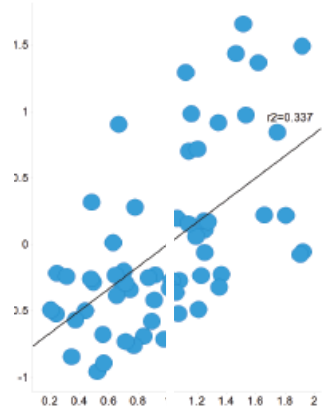
uMCP-1/uCr

TIMP1

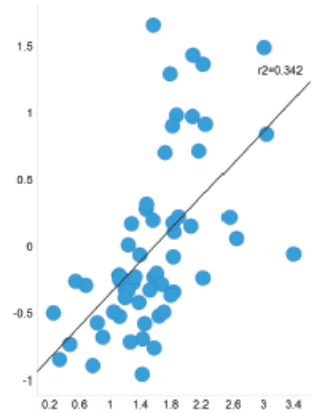


uTIMP-1/uCr

Tissue TNF activation score

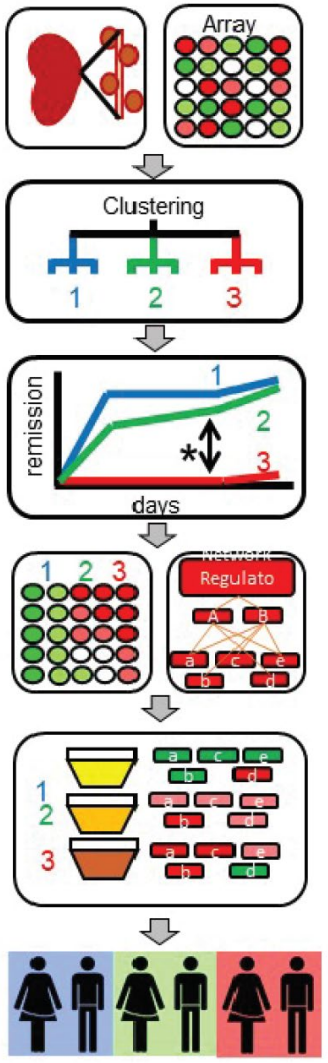


uMCP-1/uCr

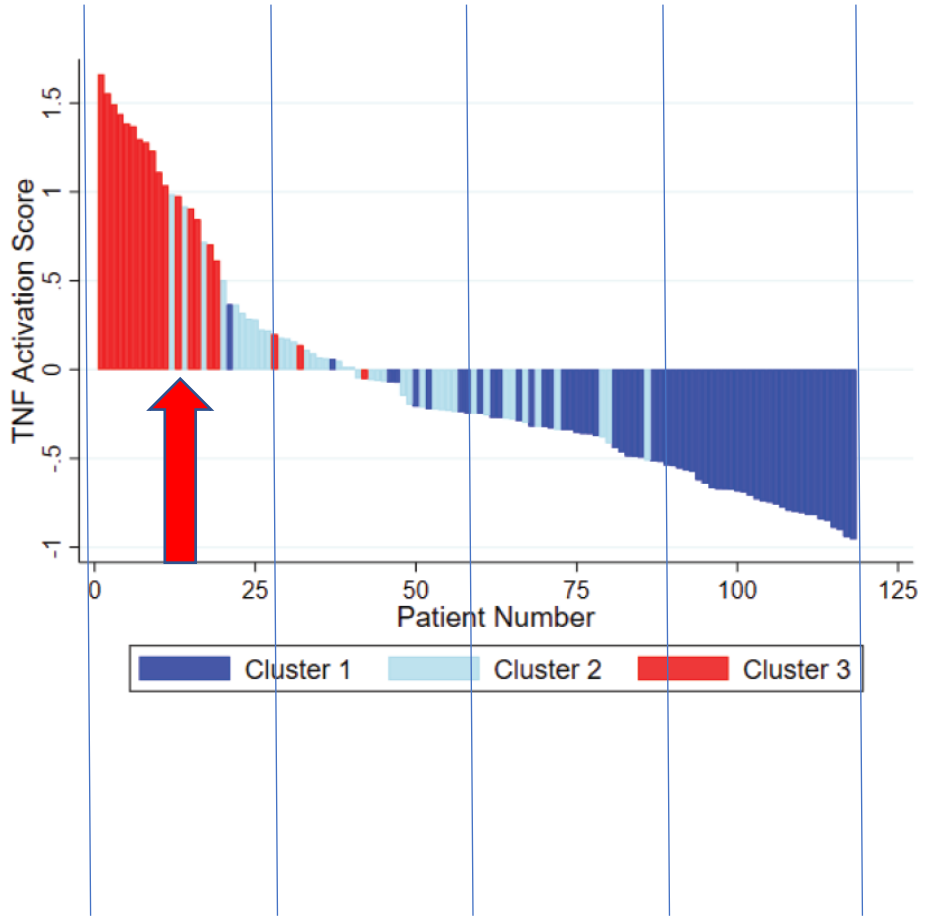


uTIMP-1/uCr

Assessing the intra-renal TNF Activity: Non-invasive patient stratification



- Measure urinary MCP1 and TIMP1
- Calculate predicted TNF Activation Score
- Compare to existing NEPTUNE Population



More of a Match

Less of a Match

Proof of concept trial:
FSGS patient stratification for TNF inhibition

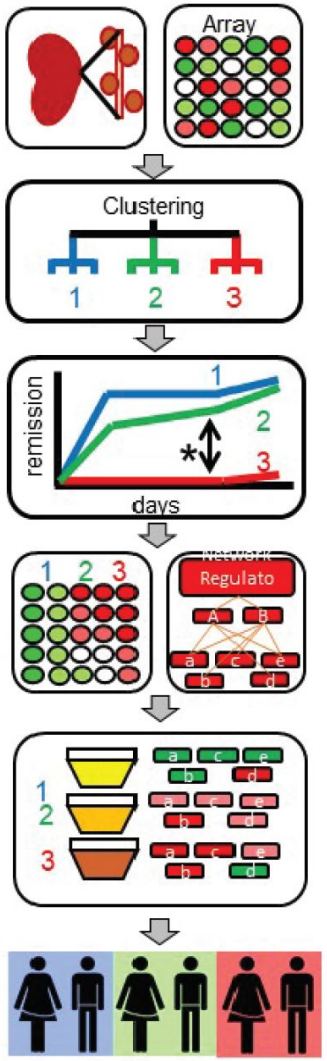
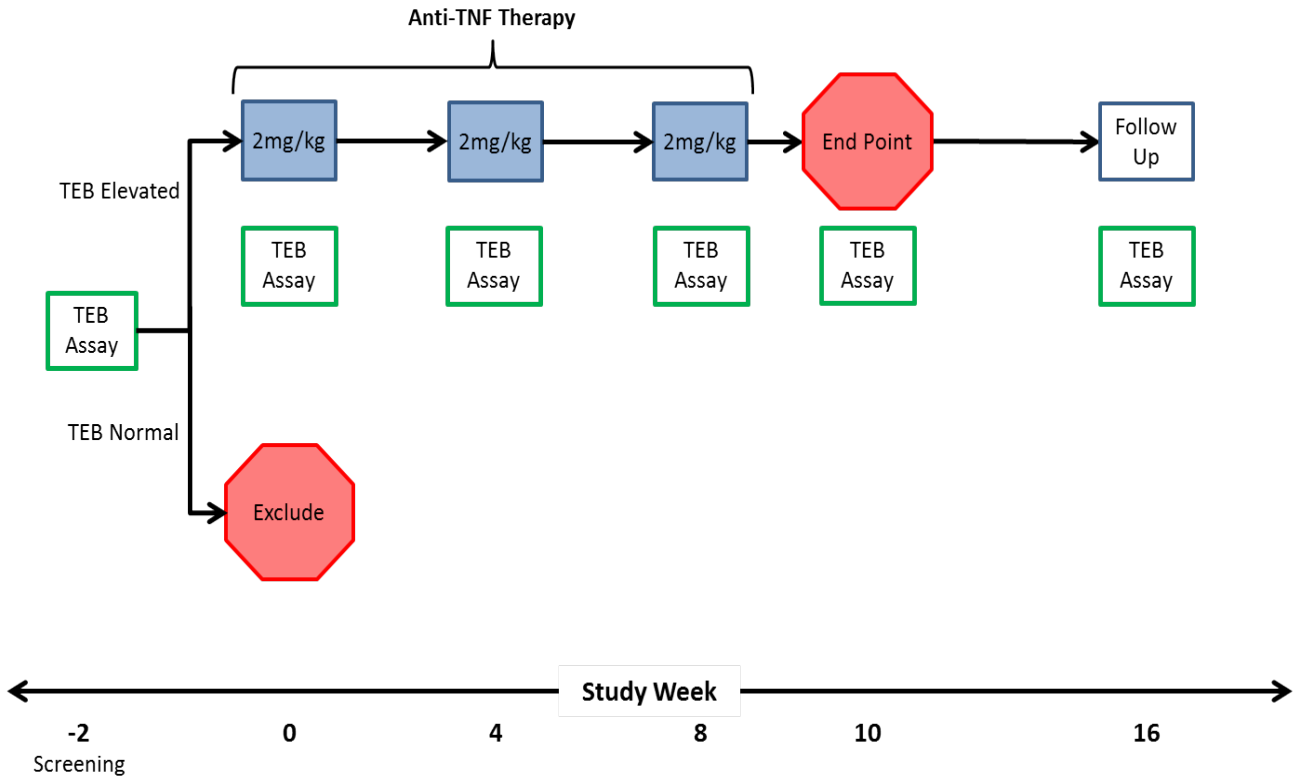


Figure 1. Schematic of Study Design



TEB = Target Engagement Biomarker
TEB levels will be assessed at study weeks -2, 0, 4, 8, 10 and 16

TEB: urinary TIMP1 and MCP1

clinicaltrials.gov:NCT04009668

NEPTUNE Match

Rare Clinical Diseases Research Network
Initiative of the National Center for Advancing Translational Sciences (NCATS)

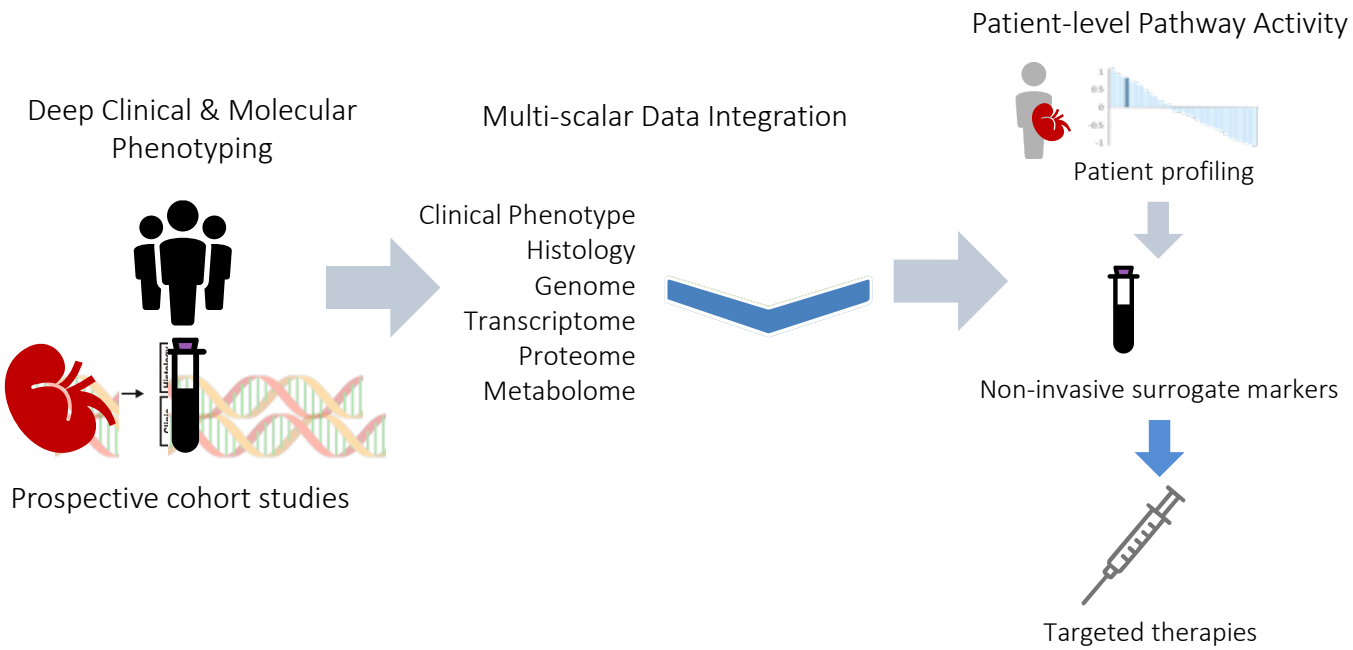
NIH National Institute of Diabetes and Digestive and Kidney Diseases

NEPHCURE Kidney International
Saving Kidneys • Saving Lives

NEPTUNE Match

Drug Develop Partnership with Pharma
Shared exploration of NEPTUNE resources
(ClinicalTrials.gov Identifier: NCT04571658)
Match individual patient's molecular disease mechanism with pathways targeted in independent, ongoing nephrotic syndrome clinical trials.

Right Trial for the Right Patient at the Right Time

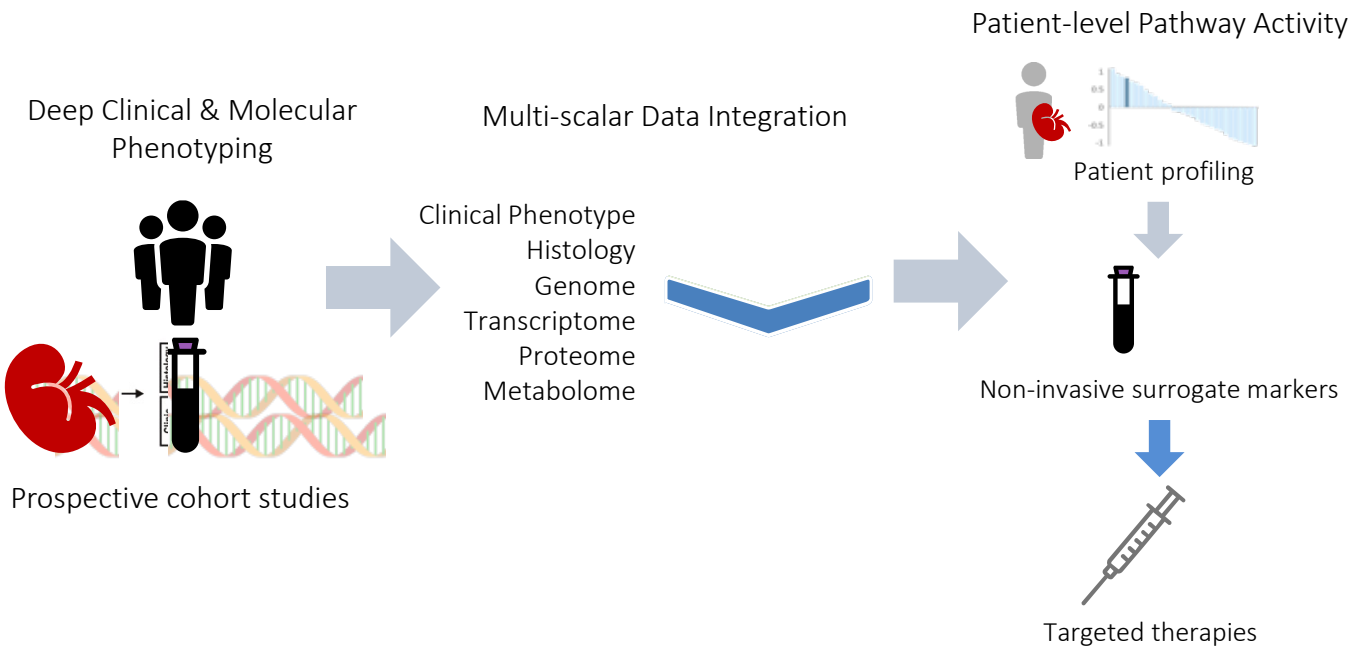


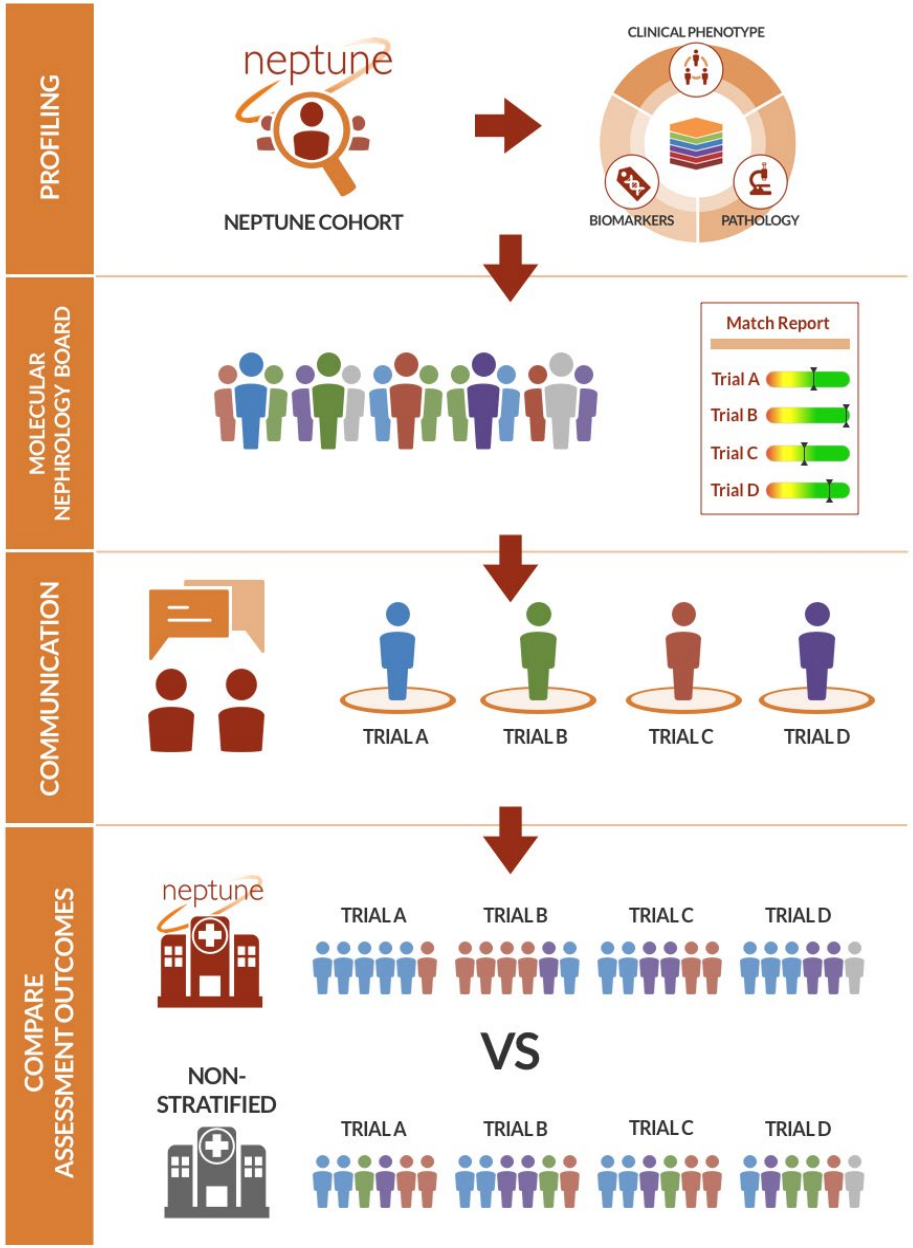
NEPTUNE Match

Drug Develop Partnership with Pharma
Shared exploration of NEPTUNE resources

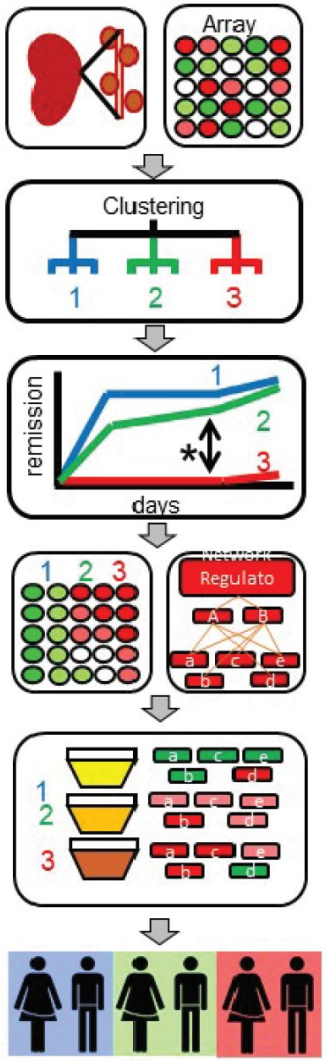
Match individual patient's molecular disease mechanism with pathways targeted in independent, ongoing nephrotic syndrome clinical trials.

Right Trial for the Right Patient at the Right Time



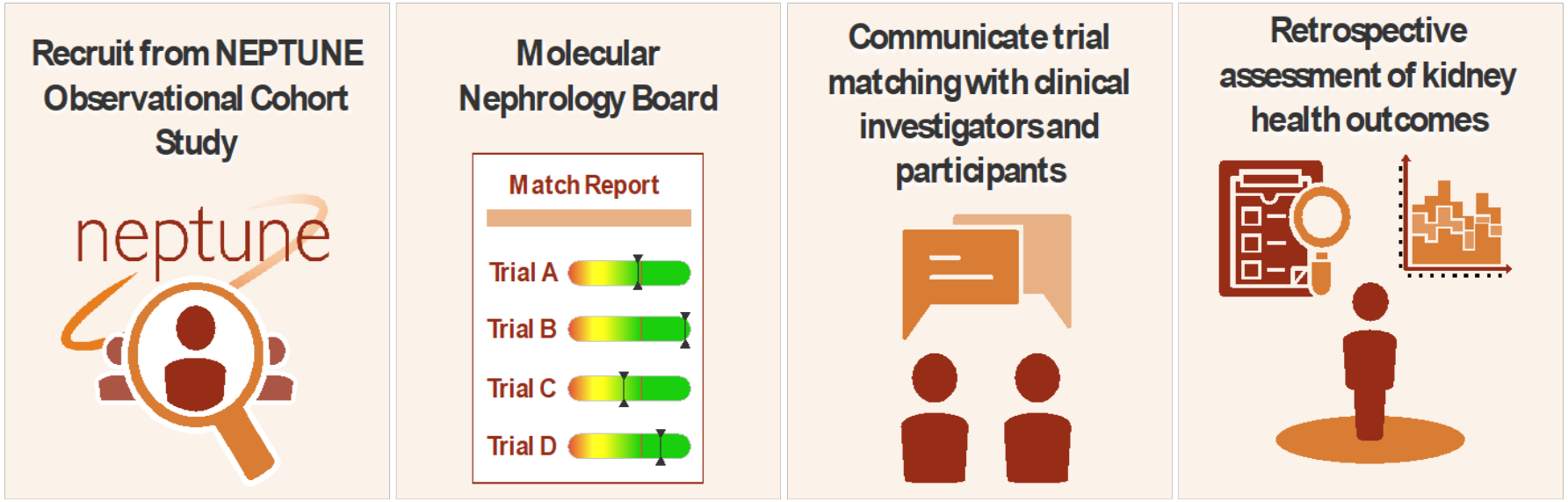


NEPTUNE Match



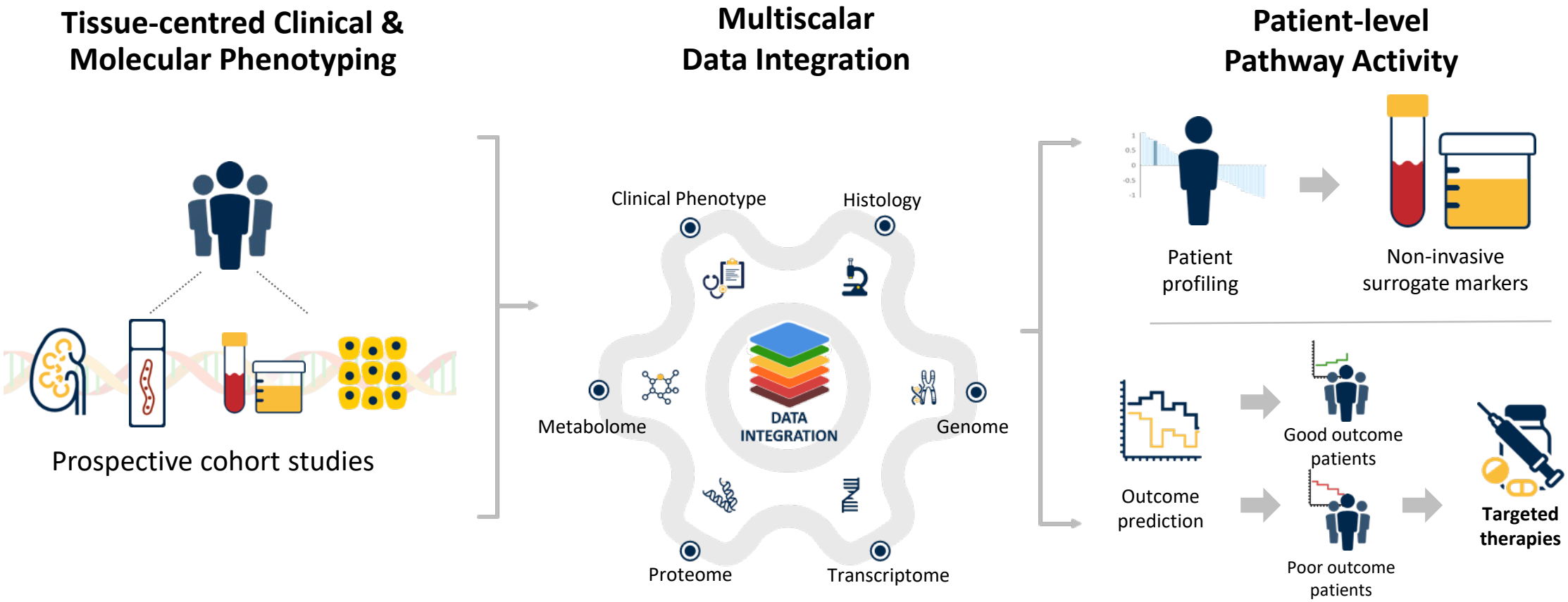
NEPTUNE Match is a prospective, open-label study testing a process to effectively communicate patient-specific clinical trial matching with kidney patients and clinician investigators.

Match four components:



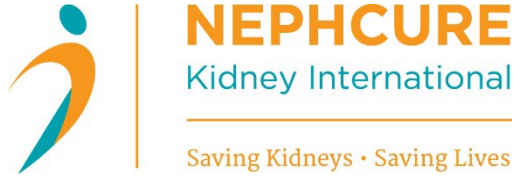
1. Recruiting
2. Matching
3. Communicating
4. Comparing

Molecular Definition of Rare Glomerular Disease: From syndromic classes to mechanistic categories



Drug Develop Partnership between Academica and Pharma active(ClinicalTrials.gov Identifier: NCT04571658). Three trials in progress matching individual patient's molecular disease mechanism with pathways targeted in independent, ongoing nephrotic syndrome clinical trials (NCT05003986, NCT04009668, NCT05213624).

Acknowledgements



The Nephrotic Syndrome Study Network (NEPTUNE), U54-DK-083912, is a part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), the National Center for Advancing Translational Sciences (NCATS) and the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK). Additional funding and/or programmatic support for this project has also been provided by the University of Michigan, NephCure Kidney International, and the Halpin Foundation.

neptune

The Nephrotic Syndrome Study Network (NEPTUNE), U54-DK-083912, is a part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), the National Center for Advancing Translational Sciences (NCATS) and the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK). Additional funding and/or programmatic support for this project has also been provided by the University of Michigan, NephCure Kidney International, and the Halpin Foundation.

MICHIGAN KIDNEY TRANSLATIONAL MEDICINE CORE

Team Science in Renal Research

Thanks to a **resilient team** in challenging times … still having fun

SESSION 4: CASE STUDIES — REAL WORLD EXPERIENCES

Moderator: Tiina K. Urv, Ph.D.,
Program Director, DRDRI, NCATS, NIH

ADJOURNMENT

REGULATORY FITNESS IN RARE DISEASE CLINICAL TRIALS

A Workshop by the
FDA's Center for Drug Evaluation & Research and
NIH's National Center for Advancing Translational Sciences

May 16-17, 2022