SaME Therapeutics : Groping Rare Disease Patients by Shared Molecular Etiology to Accelerate Clinical Trials

Philip J. Brooks, Ph.D.
Program Director
Division of Clinical Innovation and
Office of Rare Diseases Research
National Center for Advancing Translational Sciences (NCATS)
National Institutes of Health

NCATS

NAS workshop: Enabling Precision Medicine: The Role of Genetics in Clinical Drug Development, 3/8/2017

I have no conflicts of interest to disclose

The views expressed in this presentation are those of the author and do not reflect the official policy or position of the National Institutes of Health, the Department of Health & Human Services, or the US Government

NCATS Mission

To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

Human Conditions with Known Molecular Basis

Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome

Expanding rare disease drug trials based on shared molecular etiology

Philip J Brooks, Danilo A Tagle & Steve Groft

Nature Biotechnology 32, 515–518 (2014)
doi:10.1038/nbt.2924

NCATS

National Center for Advancing Translational Sciences

Precedent : Genomically Driven Oncology Basket Trials

Disease	ALK-	ALK +
Anaplastic large-cell lymphoma		N = 9
Non-small-cell lung cancer		N = 2
Neuroblastoma		N = 11
Inflammatory myofibroblastoma		N = 7

Key points :

Four different cancers affecting different organs

Subset of patients grouped by shared molecular etiology (activating ALK mutations)

Different # of subjects for each cancer

Small N s

Different outcome measures (scintography for neuroblastoma, CT for others)

One trial

Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study

Yael P Mossé, Megan S Lim, Stephan D Voss, Keith Wilner, Katherine Ruffner, Julie Laliberte, Delphine Rolland, Frank M Balis, John M Maris, Brenda J Weigel, Ashish M Ingle, Charlotte Ahern, Peter C Adamson, Susan M Blaney

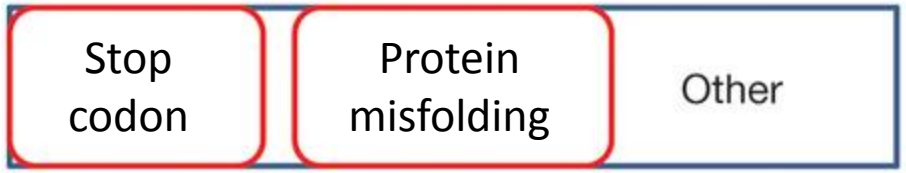
Lancet Oncol 2013; 14: 472–80

Thousands of Rare Diseases, but far fewer etiologies

- Two major types of genetic diseases
  - Dominant
    - Gain of function
  - Recessive
    - Loss of function
- Limited number of loss of function mutation types
- Nonsense mutations - premature stop codons

- Missense mutations → abnormal protein folding

Cystic Fibrosis



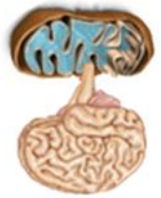
Gaucher

Tay-Sachs

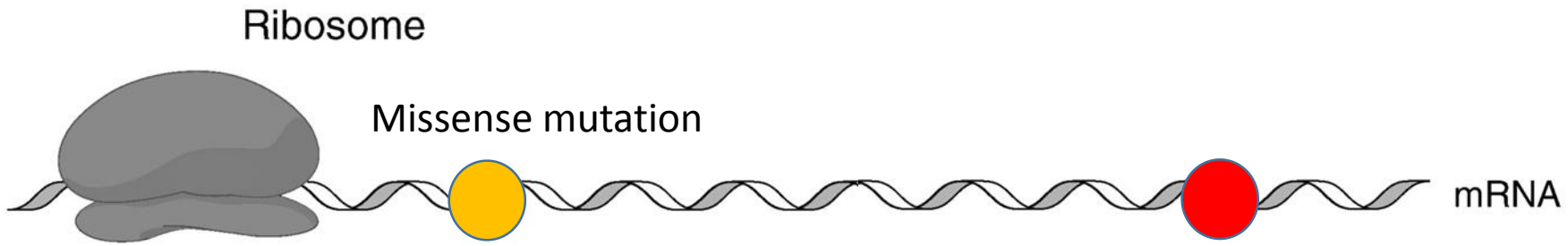
Premature stop codon disease

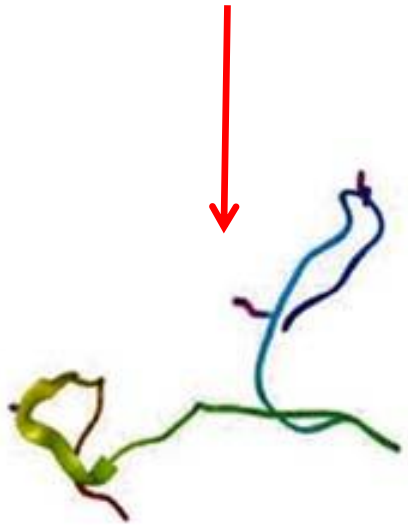
Rare Disease A	Stop codon	
Rare Disease B	Stop codon	
Rare Disease C	Stop codon	
Rare Disease D	Stop codon	
Rare Disease E	Stop codon	
Rare Disease X	Stop codon	
Rare Disease Y	Stop codon	
Rare Disease Z	Stop codon	

Protein misfolding disease

Rare Disease A	misfolding	
Rare Disease B	misfolding	
Rare Disease C	misfolding	
Rare Disease D	misfolding	
Rare Disease E	misfolding	
Rare Disease X	misfolding	
Rare Disease Y	misfolding	
Rare Disease Z	misfolding	

Some missense mutations can cause protein misfolding





Full length,
misfolded protein
non-functional

Therapeutic ?

Correctly folded
protein

Traditional approach: Single molecular target in an individual disease

- Pros:
  - Can be successful

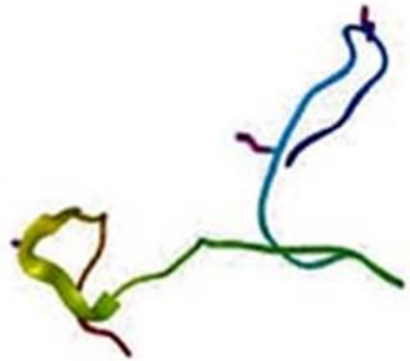
- Cons:
  - One disease at a time
    - Inefficient
    - Time-consuming
    - Not cost effective

Proteastasis: Protein Homeostasis

Proteostasis modifiers

Error-prone synthesis
Mutations
Polymorphisms
Post-translational modifications
Environmental stress
Physiological stress
Metabolic stress

→ **Disease**



Proteastasis Pathway Regulators

HSR (HSPA1A, DNAJ)
UPR (HSPA5, HSP90B1, CALR)
Oxidative stress response (GCLM, HO1, SOD1)
Autophagy (ATG)
UPS, ERAD (EDEM)
Organellar Ca^{2+}, HDAC

Curr Top Med Chem. Author manuscript; available in PMC 2014 Mar 15.
Published in final edited form as:
Curr Top Med Chem. 2012; 12(22): 2623–2640.
PMCID: PMC3955168
NIHMSID: NIHMS491049

Protein Homeostasis as a Therapeutic Target for Diseases of Protein Conformation[‡]

Barbara Calamini[1] and Richard I. Morimoto[2,*]

Proof of Concept Studies of Proteastasis Pathway Targeting in Multiple Misfolded Protein Diseases

Diseases Studied

Remodeling the Proteostasis Network to Rescue Glucocerebrosidase Variants by Inhibiting ER-Associated Degradation and Enhancing ER Folding

PLOS ONE

Fan Wang, Laura Segatori

Published: April 19, 2013 • http://dx.doi.org/10.1371/journal.pone.0061418

Gaucher,
Tay-Sachs

Partial Restoration of Mutant Enzyme Homeostasis in Three Distinct Lysosomal Storage Disease Cell Lines by Altering Calcium Homeostasis

PLOS BIOLOGY

Ting-Wei Mu, Douglas M Fowler, Jeffery W Kelly

Published: February 5, 2008 • http://dx.doi.org/10.1371/journal.pbio.0060026

Gaucher,
α-mannosidosis
mucopolysaccharidosis

Modulation of the Maladaptive Stress Response to Manage Diseases of Protein Folding

PLOS BIOLOGY

Daniela Martino Roth, Darren M. Hutt, Jiansong Tong, Marion Bouchecareilh, Ning Wang, Theo Seeley, Johanna F. Dekkers, Jeffrey M. Beekman, Dan Garza, Lawrence Drew, Eliezer Masliah, Richard I. Morimoto, William E. Balch

Published: November 18, 2014 • http://dx.doi.org/10.1371/journal.pbio.1001998

alpha-1-antitrypsin deficiency ,
Niemann-Pick type C1 ,
Alzheimer's disease,
cystic fibrosis

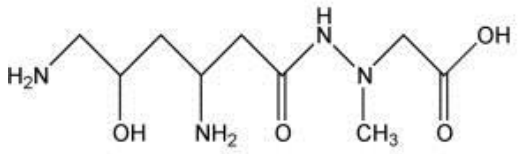
Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit

Science 10 Apr 2015:
Vol. 348, Issue 6231, pp. 239-242
DOI: 10.1126/science.aaa4484

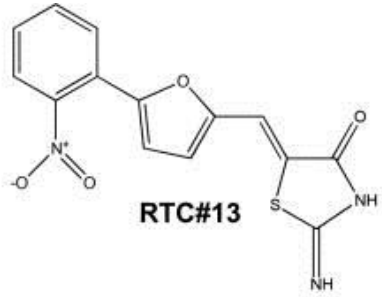
Indrajit Das[1], Agnieszka Krzyzosiak[1], Kim Schneider[1], Lawrence Wrabetz[2,*], Maurizio D'Antonio[2], Nicholas Barry[1], Anna Sigurdardottir[1], Anne Bertolotti[1,†]

ALS,
Charcot-Marie Tooth

Premature stop codon read-through drugs: Beyond PTC-124



Negamycin



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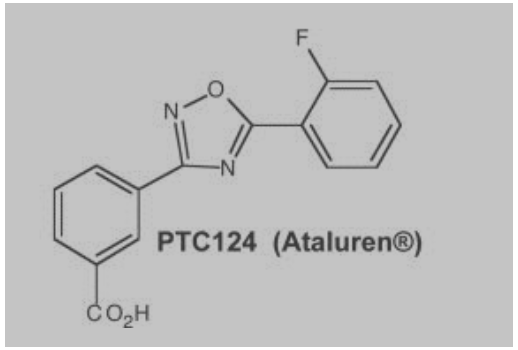
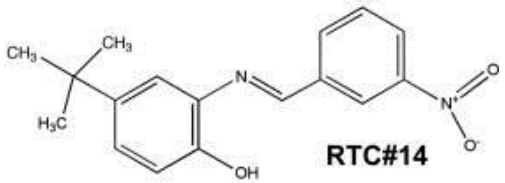


PTC124 (Ataluren®)



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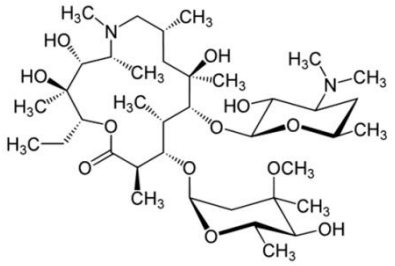
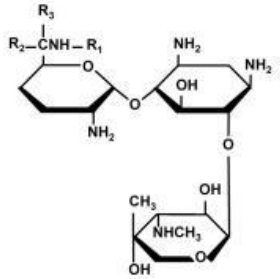


Azithromycin

Caspi et al
Journal of Molecular Medicine
2016, 94, pp 469–482

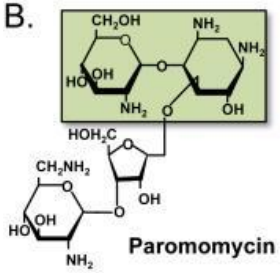
A.

Gentamicin

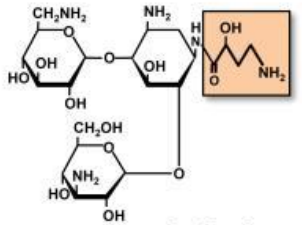


Isomer	R_1	R_2	R_3
C1	CH_3	CH_3	H
C1a	H	H	H
C2	H	CH_3	H
C2a	H	H	CH_3
C2b	CH_3	H	H

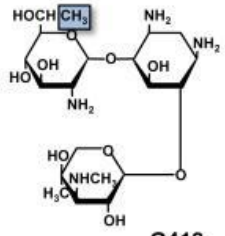
B.



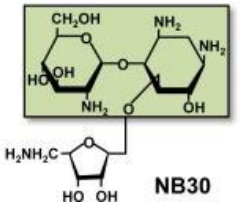
Paromomycin



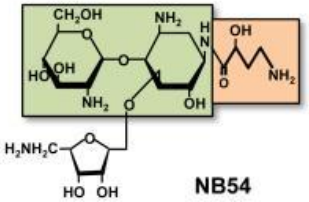
Amikacin



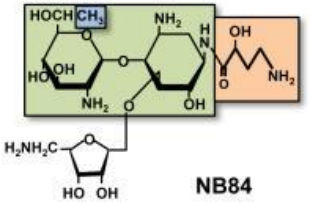
G418



NB30



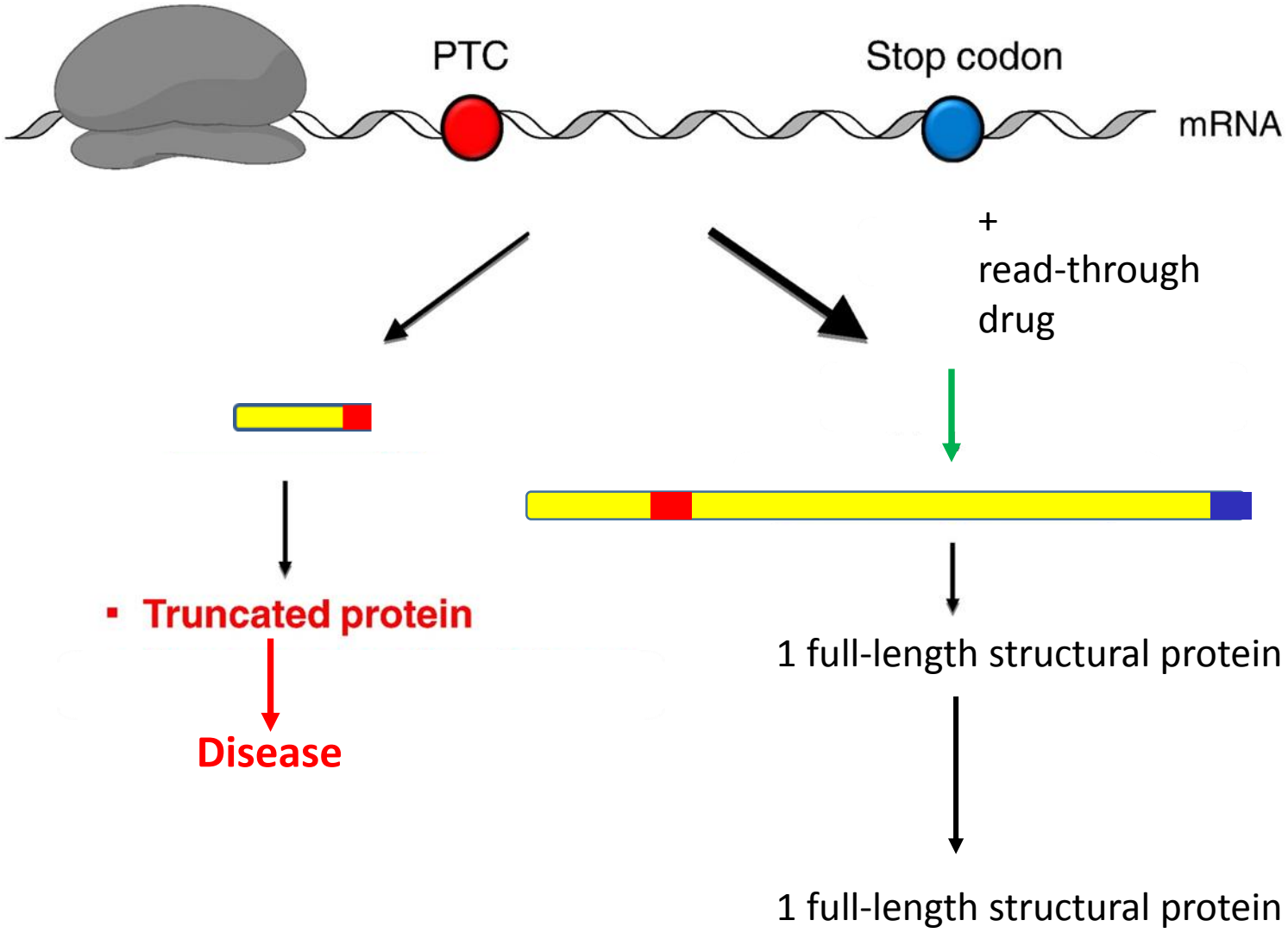
NB54



NB84

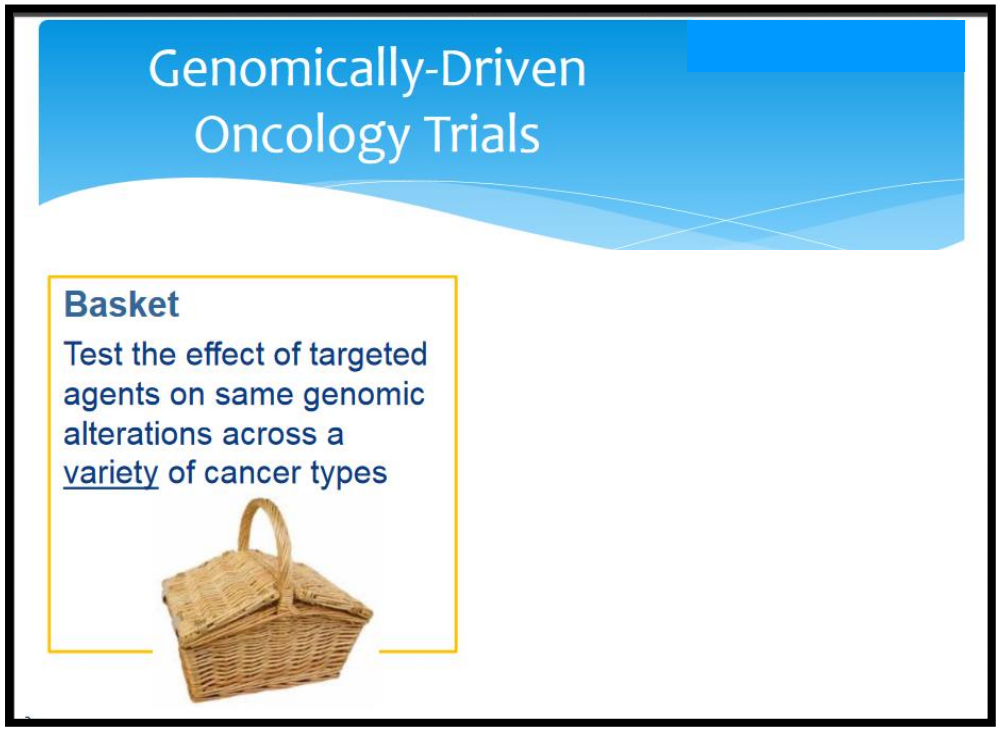
From Keeling and Bedwell, Crit Rev Biochem Mol Biol. 2012 47(5): 444–463.
doi: 10.3109/10409238.2012.694846

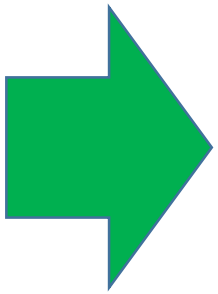
Effects of premature stop codon read-through depend on target

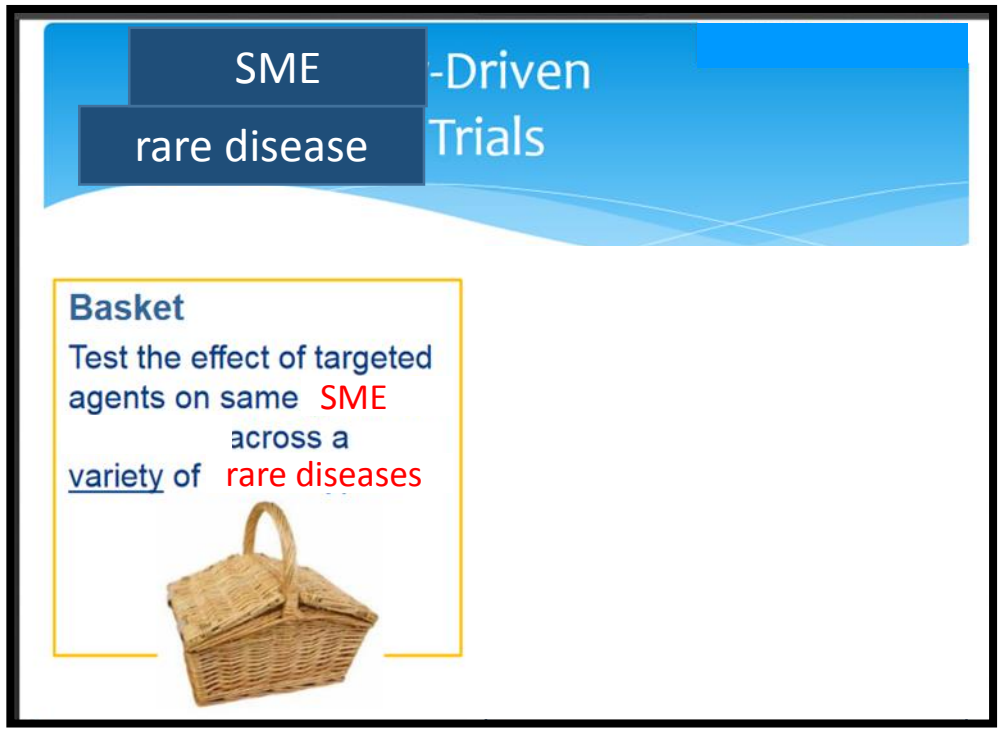


Thousands of Rare Genetic Diseases, or only a few ?

- Biochemical pathways as shared molecular etiologies
  - Epigenetic dysregulation diseases
    - HDAC inhibitors
  - “- opathies”
    - Tauopathies
    - shankopathies,
    - MTORopathies







Enrollment criteria

Endpoints

Enrollment Criteria

Oncology Basket Trial

Assay molecular marker
in tumor
Standardized tests
genotyping
immunostaining

If marker +

Assay Predictive Biomarker
in patient cells
disease-specific assays
cellular assays
biochemical measurements

Rare Disease SME Trial

Rare Disease Organization

Patient advocates
Clinical specialists
Laboratory scientists with
disease biology expertise

Identify possible patients for trial
Test patient cells for response to drug

If responder

Endpoints

Oncology Basket Trial

Outcome measure :
tumor growth/size

Outcome measure:
Pharmacodynamic/Response Biomarker

Clinical endpoint

Rare Disease SME Trial

Rare Disease Organization

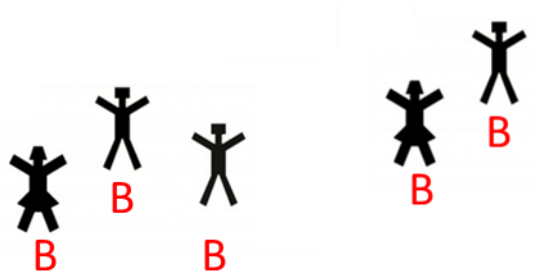
Patient advocates
Clinical specialists
Laboratory scientists with disease biology expertise

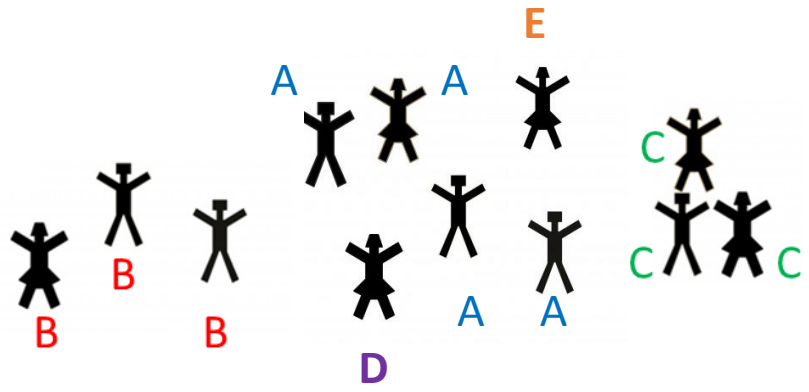
Identify and measure appropriate biomarkers and clinical endpoints

Key role for rare disease organizations in SME basket trials

Rare Disease B Organization

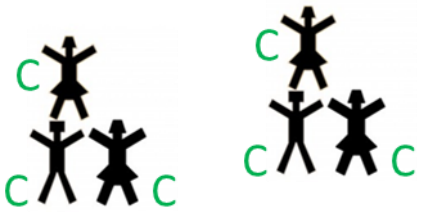
Patient advocates
Clinical specialists
Laboratory scientists with disease biology expertise





Rare Disease C Organization

Patient advocates
Clinical specialists
Laboratory scientists with disease biology expertise

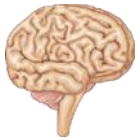


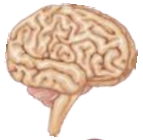
Rare disease SME basket trial

PD/Response endpoint

clinical endpoint


Rare Disease A


Rare Disease B


Rare Disease C


Rare Disease D


Rare Disease E


Rare Disease F

Traditional disease-specific registration trials

Rare Disease A

Rare Disease C

Rare Disease F

NCATS SaME Therapeutics Funding Opportunities

CTSA Collaborative Innovation Awards (PAR-15-172)

- Involve collaboration with investigators from at least 3 different CTSA hubs
- Develop new technology, method or approach to address roadblocks in translational science at any stage (T1-T4)

New Topic of Interest: Clinical trials of drugs targeting shared molecular etiologies underlying multiple diseases

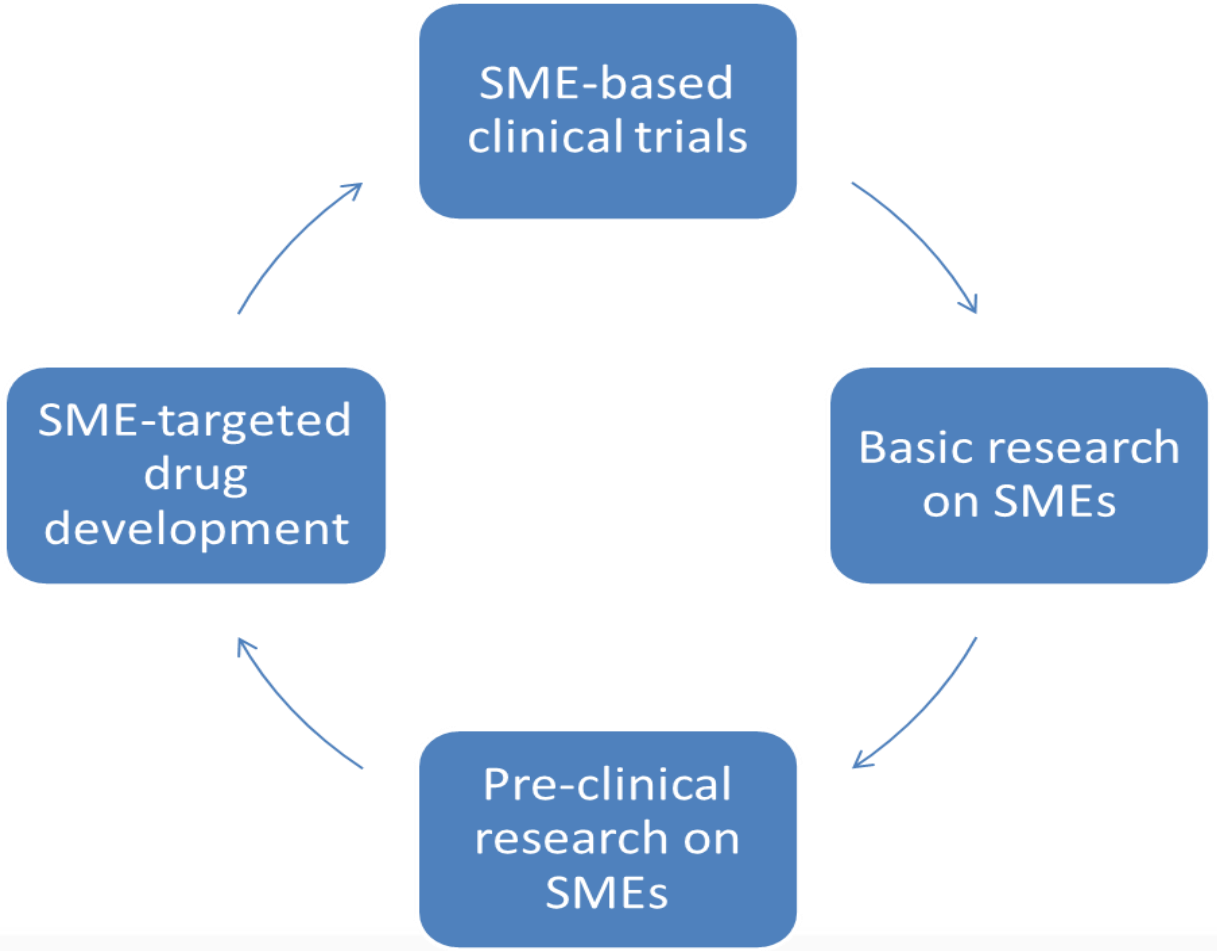
NCATS will give priority to applications for trials with rare diseases

https://grants.nih.gov/grants/guide/notice-files/NOT-TR-17-004.html

SBIR & STTR Research Priorities

- Interventions that target molecular pathways or mechanisms common to multiple diseases

Catalyzing a Virtuous Cycle



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