SaME Therapeutics: Grouping 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

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
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

~500 with therapy
Expanding rare disease drug trials based on shared molecular etiology

Philip J Brooks, Danilo A Tagle & Steve Groft

### Precedent: Genomically Driven Oncology Basket Trials

<table>
<thead>
<tr>
<th>Disease</th>
<th>ALK-</th>
<th>ALK +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic large-cell lymphoma</td>
<td>N = 9</td>
<td></td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>N = 2</td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>N = 11</td>
<td></td>
</tr>
<tr>
<td>Inflammatory myofibroblastoma</td>
<td>N = 7</td>
<td></td>
</tr>
</tbody>
</table>

- **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 Ns
  - Different outcome measures (scintography for neuroblastoma, CT for others)

---

**One trial**
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
  • stop codon read-through compounds

• Missense mutations → abnormal protein folding
  • proteostasis pathway modulators
Protein misfolding disease

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

Premature stop codon disease

Rare Disease A
Rare Disease B
Rare Disease C
Rare Disease D
Rare Disease E
Rare Disease X
Rare Disease Y
Rare Disease Z
Some missense mutations can cause protein misfolding.

- Full length, misfolded protein: non-functional
- Correctly folded protein

Therapeutic?
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

Proteostasis Pathway Regulators

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

- Gaucher
- Tay-Sachs
- α-mannosidosis
- Mucopolysaccharidosis
- Glucocerebrosidase variants
- α-1-antitrypsin deficiency
- Niemann-Pick type C1
- Alzheimer's disease
- Cystic fibrosis
- ALS
- Charcot-Marie Tooth
Premature stop codon read-through drugs: Beyond PTC-124

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

Effects of premature stop codon read-through depend on target

- Truncated protein → Disease
- 1 full-length structural protein
- 1 full-length structural protein
- 1 full-length enzyme

- millions of toxic molecules degraded
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
**Oncology Basket Trial**
- Assay molecular marker in tumor
- Standardized tests: genotyping, immunostaining

If marker +

**Rare Disease SME Trial**
- Assay Predictive Biomarker in patient cells
- Disease-specific assays: cellular assays, biochemical measurements

**Enrollment Criteria**

- 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

**NIH National Center for Advancing Translational Sciences**

**NCATS**
**Endpoints**

**Oncology Basket Trial**

Outcome measure: tumor growth/size

Clinical endpoint

**Rare Disease SME Trial**

Outcome measure:
Pharmacodynamic/Response Biomarker

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

Traditional disease-specific registration trials

Possible accelerated approval?  Possible conversion to full approval?

<table>
<thead>
<tr>
<th>PD/Response endpoint</th>
<th>clinical endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare Disease A</td>
<td>Rare Disease A</td>
</tr>
<tr>
<td>Rare Disease B</td>
<td></td>
</tr>
<tr>
<td>Rare Disease C</td>
<td>Rare Disease C</td>
</tr>
<tr>
<td>Rare Disease D</td>
<td></td>
</tr>
<tr>
<td>Rare Disease E</td>
<td>Rare Disease E</td>
</tr>
<tr>
<td>Rare Disease F</td>
<td>Rare Disease F</td>
</tr>
</tbody>
</table>
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


SBIR & STTR Research Priorities

• Interventions that target molecular pathways or mechanisms common to multiple diseases
Catalyzing a Virtuous Cycle

1. SME-based clinical trials
2. Basic research on SMEs
3. Pre-clinical research on SMEs
4. SME-targeted drug development
Learn More About NCATS

Website: www.ncats.nih.gov

Facebook: facebook.com/ncats.nih.gov

Twitter: twitter.com/ncats_nih_gov

YouTube: youtube.com/user/ncatsmedia


Email us! info@ncats.nih.gov