Infinite Possibilities: The Past, Present, and Future of Rare Disease Therapeutics

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RARE DISEASES by the NUMBERS

50% of the people affected by rare diseases are children

Approximately 7,000 rare diseases & disorders have been identified

30 MILLION people in the U.S. are living with rare diseases
30 MILLION people in Europe are living with rare diseases

#DYK: If all of the people with rare diseases lived in one country, it would be the world’s 3rd most populous country

PAST
12-year UK epidemiologic study of PIND, 147 different diagnoses were recorded in 1114 of 2636 patients <16 years.


Verity C, et al. *Arch Dis Child*. 2018
Neuronal Ceroid Lipofuscinosis – Historical Perspective

Otto Christian Stengel (1826)

1st description of NCL

Neuronal Ceroid Lipofuscinosis – Historical Perspective

- Otto Christian Stengel (1826) – 1st description of NCL
- Batten (1903) – 1st report with pathology
- Vogt (1905), Spielmeyer (1905)
- Jansky (1908), Bielschowsky (1913) – reported a similar late-infantile onset disorder
- Kufs (1925) – reported a similar adult-onset disorder
- Haltia and Santavuori (1973) – described infantile-onset form

Neuronal Ceroid Lipofuscinoses

- Group of lysosomal storage diseases
- Most prevalent neurodegenerative disorder of childhood, 1:12,500
- Unifying clinicopathologic features
  - clinical symptoms
  - progressive neuronal loss
  - autofluorescent storage material

A: GRODs
B: curvilinear profiles
C: fingerprint patterns
D: rectilinear profiles

Haltia et al, Biochim et Biophys Acta 2006; 1762: 850–856
<table>
<thead>
<tr>
<th>NCL type</th>
<th>Intervention</th>
<th>Indication</th>
<th>Sample size</th>
<th>Duration of follow-up</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNCL JNCL</td>
<td>Antioxidants</td>
<td>Disease modification</td>
<td>74</td>
<td>6-18 yrs</td>
<td>Inconclusive</td>
<td>Santavuori 1988</td>
</tr>
<tr>
<td>JNCL JNCL</td>
<td>Polyunsaturated fatty acids</td>
<td>Disease modification</td>
<td>5</td>
<td>1 yr</td>
<td>Inconclusive</td>
<td>Bennett 1988</td>
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<tr>
<td>LINCL, JNCL</td>
<td>Antioxidants</td>
<td>Disease modification</td>
<td>3</td>
<td>0.5 - 1.75 yrs</td>
<td>Inconclusive</td>
<td>Naidu 1988</td>
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<tr>
<td>JNCL JNCL</td>
<td>Polyunsaturated fatty acids</td>
<td>Disease modification</td>
<td>6</td>
<td>4 - 7 yrs</td>
<td>Possibly effective</td>
<td>Bennett 1994</td>
</tr>
<tr>
<td>JNCL JNCL</td>
<td>Antioxidants</td>
<td>Disease modification</td>
<td>43</td>
<td>8 yrs</td>
<td>Possibly effective</td>
<td>Santavuori 1989</td>
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<tr>
<td>JNCL JNCL</td>
<td>Antioxidants</td>
<td>Disease modification</td>
<td>46</td>
<td>Unknown</td>
<td>Possibly effective</td>
<td>Santavuori 1977</td>
</tr>
<tr>
<td>JNCL JNCL</td>
<td>Antioxidants</td>
<td>Disease modification</td>
<td>125</td>
<td>4 - 11 yrs</td>
<td>Partially effective</td>
<td>Santavuori 1985</td>
</tr>
</tbody>
</table>

**Case Series**

**Open label, single group clinical trials**

**Open label, historical control clinical trial**

**Open label, parallel group clinical trials**

**Randomized, placebo controlled, clinical trial**
PAST

Describing phenomenology, grouping characteristics, and linking to pathological findings
PRESENT
Average 5-7 years to diagnosis
40% have misdiagnosis
Up to 50% never achieve a specific disease diagnosis
Genetic discoveries

1952: Electrophoresis
1953: DNA double helix structure described
1958: Semi-conservative DNA replication shown
1966: Genetic code cracked
1972: Development of recombinant technology
1975: Southern blot, Sanger sequencing published
1977: First genome sequenced (FX174)
1980: RFLP concept
1982: Whole-genome shotgun
1983: First human disease gene mapped with DNA markers (HD)
1985: DNA fingerprinting, PCR invented
1987: Site-directed mutagenesis of the mouse genome
1990: Successful gene therapy
1995: Microarray technology
1998: Full-length cDNA technologies, RNAi
2001: Draft of human genome released
2005: Next-generation DNA sequencing
The Orphan Drug Act (ODA)

- Decade prior to 1983 – only ~1 drug/year independently developed by pharmaceutical sponsors
- Legislation needed to promote rare disease drug development
- The Orphan Drug Act signed into law on Jan. 4, 1983
Development for CNS disorders is rising

Number of Compounds in Clinical Development

- Anti-infectives (including vaccines)
- Cardiovascular
- Central nervous system
- Endocrine
- Gastrointestinal
- Genitourinary
- Hematology
- Oncology
- Immune system
- Musculoskeletal
- Respiratory

Year

JACC. Volume 64, Issue 5, August 2014
Higher rates of success for rare diseases

[Graph showing probability of success for rare diseases compared to other diseases across different phases of clinical development]

The Orphan Drug Act has had strong impact and rare disease approvals are on the rise

Source: FDA Law Blog
Orphan Drug Approval Characteristics Have Shifted Over Time

<table>
<thead>
<tr>
<th>Decade</th>
<th>Biologics</th>
<th>Small Molecule Drugs</th>
<th>Cancer</th>
<th>Metabolism and Endocrinology</th>
<th>Rare Genetic Disorder</th>
<th>Targeted Therapy</th>
<th>Not Targeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>77%</td>
<td>23%</td>
<td>12%</td>
<td>67%</td>
<td>21%</td>
<td>88%</td>
<td>100%</td>
</tr>
<tr>
<td>1990s</td>
<td>69%</td>
<td>31%</td>
<td>23%</td>
<td>59%</td>
<td>18%</td>
<td>86%</td>
<td>1%</td>
</tr>
<tr>
<td>2000s</td>
<td>66%</td>
<td>34%</td>
<td>31%</td>
<td>54%</td>
<td>15%</td>
<td>81%</td>
<td>8%</td>
</tr>
<tr>
<td>2010s</td>
<td>58%</td>
<td>42%</td>
<td>46%</td>
<td>41%</td>
<td>13%</td>
<td>81%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Legend:
- Biologics
- Small Molecule Drugs
- Cancer
- Metabolism and Endocrinology
- Rare Genetic Disorder
- Targeted Therapy
- Not Targeted
The # of recognized unique mutations and unique variants is rising 

OMIM Phenotypes for which the Molecular Basis is Known (2007 & 2013)

<table>
<thead>
<tr>
<th>Inheritance Pattern</th>
<th>January 2007</th>
<th>July 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal</td>
<td>1,851</td>
<td>3,525</td>
</tr>
<tr>
<td>X Linked</td>
<td>169</td>
<td>277</td>
</tr>
<tr>
<td>Y Linked</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>2,048</td>
<td>3,834</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Age at Onset</th>
<th>Chromosome</th>
<th>Protein</th>
<th>Ultrastructure</th>
</tr>
</thead>
</table>
| CLN1      | Infantile  
Late infantile, juvenile, and adult | 1p32       | PPT1                           | Granular Osmophilic deposits (GRODS)     |
| CLN2      | Late infantile  
Juvenile            | 11p15      | TPP1                           | Curvilinear profiles                     |
| CLN3      | Juvenile                                  | 16p12      | Transmembrane protein (lysosomal) | Fingerprint profiles                     |
| CLN4 (DNAJC5) | Adult (AD) (Parry)  | 20q13.33   | Cysteine string protein        | Rectilinear profiles                     |
| CLN5      | Late infantile (Finnish variant)          | 13q22      | Soluble protein (lysosomal)    | Rectilinear profiles, Curvilinear profiles, Fingerprint profiles |
| CLN6      | Late Infantile  
Adult (Kufs)          | 15q21      | Transmembrane protein (endoplasmic reticulum) | Rectilinear profiles, Curvilinear profiles, Fingerprint profiles |
| CLN7      | Late Infantile (Turkish variant)          | 4q28       | MFSD8, membrane protein (lysosomal) | Fingerprint profiles                     |
| CLN8      | Late infantile (Northern epilepsy)        | 8q23       | Transmembrane protein (endoplasmic reticulum) | Curvilinear profiles                     |
| CLN10     | Congenital                                 | 11p15      | Cathepsin D                    | GRODS                                    |
New Classification of NCL Disorders

According to GENES and CLINICAL TYPE

**Designation of disease**

<table>
<thead>
<tr>
<th>Genetic type</th>
<th>Mutated gene</th>
<th>Clinical type (age of onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CLNX</td>
<td>• CLNX disease</td>
<td>• Infantile (6–24 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Late infantile (2–5 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Juvenile (5–7 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adult</td>
</tr>
</tbody>
</table>

*Example*: CLN2 disease, late infantile

Rational Therapeutic Targets for NCLs

- **Correction of genetic information:**
  - Gene therapy
  - Stop codon read-through

- **Correction of secondary cellular abnormalities:**
  - Manipulation of autophagy

**Gene mutation**

**Degradation of Mutated protein**

**Endoplasmic reticulum**

**Golgi apparatus**

**Autophagic pathway**

**Secondary cellular abnormalities**

**Inhibition of substrate synthesis**

**Intra-lysosomal storage of undegraded substrate**

**Deficiency of lysosomal enzyme activities**

**Improving folding and stability of mutated enzymes**
  - Pharmacological chaperones
  - Proteostasis regulators

**Lysosomes**

**Enzyme therapies** (ERT)

**Increasing lysosomal exocytosis**

Clinical Presentation Of CLN2 Disease/TPP1 Deficiency

Adapted from: Kohlschütter A. Pediatr Endocrinol Rev 2016

**Early features (2-4 years):**
- Early language delay
- Seizures, often polymorphic
- Increasing developmental concerns
- Referral for diagnostic investigations
- Developmental stasis

**Rapidly Progressing (3-5 years):**
- Drug-resistant seizures
- Loss of milestones
- Progressive dementia
- Movement disorder
- Sleep disorder
- Worsening mobility
- Pain and irritability

**Prolonged Late stage:**
- Gastrostomy dependent
- Dysphagia
- Loss of communication
- Loss of voluntary movement
- Ongoing seizures and myoclonus
- Spasticity, contractures

**Age (years):**
- Birth
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- Death
## Motor & language function scoring (CLN2)

<table>
<thead>
<tr>
<th>Score</th>
<th>Motor Domain</th>
<th>Functional Description</th>
<th>Language Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Has grossly normal gait; no prominent ataxia, no pathologic falls</td>
<td>Has apparently normal language that is intelligible and grossly age-appropriate, with no decline noted</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Has independent gait as defined by ability to walk without support for 10 steps; obvious instability and possibly intermittent falls</td>
<td>Has language that has recognizable abnormalities but includes some intelligible words; may form short sentences to convey concepts, requests, or needs</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Requires external assistance to walk or can only crawl</td>
<td>Has language that is hard to understand with few intelligible words</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Can no longer walk or crawl</td>
<td>Has no intelligible words or vocalizations</td>
<td></td>
</tr>
</tbody>
</table>
CLN2 Natural History

First seizure: ~2.9 years
Walking: Normal
Language: Minor concerns

Rate of decline: 2.2 units/year (SD±1.1)

Age at diagnosis: ~5 years
No independent walking
Language: Unintelligible

N=58 subjects with CLN2 disease in the DEM-CHILD registry, a multinational NCL patient database.

Cerliponase alfa – approved for prevention of loss of ambulation in CLN2 disease (2017)

Spinal Muscular Atrophy (SMA)  
Leading Genetic Cause of Infant Mortality

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of Onset</th>
<th>Highest Function</th>
<th>Natural Age of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Prenatal</td>
<td>Respiratory support</td>
<td>&lt;1 mo</td>
</tr>
<tr>
<td>1</td>
<td>0–6 mo</td>
<td>Never sit</td>
<td>&lt;2 y</td>
</tr>
<tr>
<td>2</td>
<td>&lt;18 mo</td>
<td>Never stand</td>
<td>&gt;2 y</td>
</tr>
<tr>
<td>3</td>
<td>&gt;18 mo</td>
<td>Stand alone</td>
<td>Adult</td>
</tr>
<tr>
<td>3a</td>
<td>18 mo–3 y</td>
<td>Stand alone</td>
<td>Adult</td>
</tr>
<tr>
<td>3b</td>
<td>&gt;3 y</td>
<td>Stand alone</td>
<td>Adult</td>
</tr>
<tr>
<td>4</td>
<td>&gt;21 y</td>
<td>Stand alone</td>
<td>Adult</td>
</tr>
</tbody>
</table>
2017: 1st treatment for Spinal Muscular Atrophy

Nusinersen impacts survival for patients with SMA

Overall Survival

Probability of Survival (%)

Hazard ratio for death, 0.37 (95% CI, 0.18–0.77)
P=0.004

Week

No. at Risk
Nusinersen 80 71 58 41 28 23
Control 41 33 23 17 12 10

Gene replacement therapy for SMA (2019)

PRESENT: Translating knowledge to treatment

Model of CGRP-induced hypersensitivity
Expert Reviews in Molecular Medicine © 2011
Cambridge University Press
PRESENT

Describing phenomenology, grouping characteristics, linking to genetic diagnosis, accelerating development of new therapies
FUTURE
Rising Interest in Therapy Development for NCLs

- Pre-clinical models: Zebrafish, Xenopus, Mouse, Primate, Human cells

- Regulatory incentives

- Engaged families & foundations

- Natural history knowledge

- Clinician-Investigators

- Successful product approval
Small molecule approaches
  CLN1, CLN3

Gene replacement therapies (AAV9, various routes of administration)
  CLN1, CLN2, CLN3, CLN5, CLN6, CLN7

Enzyme replacement
  CLN1

Anti-sense oligonucleotide therapy
  CLN7
Emerging Therapeutic Strategies

![Graph showing disease progression and therapeutic strategies](http://www.sens.org)
Emerging Therapeutic Strategies

Fig. 4.1. Hypothetical patterns of growth and dementia in children.

EG Shapiro, et al 1994; http://www.sens.org
Classic Genotype-Phenotype Concordance

- Genotype
- Phenotype
- Trisomy 21
  - Down syndrome
Genetic Heterogeneity

Genotype 1
Genotype 2
Genotype 3
Genotype n

Phenotype

Phenotypic Pleiotropy

Genotype

Phenotype 1
Phenotype 2
Phenotype 3

Increasing recognition of links between rare and common disorders

- NCL and frontotemporal dementia
- Rare and common epilepsies
- Lysosomal storage disease and Parkinson Disease


*Figure 2: Primary model analysis of familial non-acquired focal epilepsy*
Pediatric approvals may be on the decline

7% annual decline (95%CI -9.8,-4.1) p<0.0001

Source: FDA Law Blog; Vermillion et al 2018
Rare Disease Barriers to Therapy Development

- Efficient diagnosis and recognition of disease
- Incomplete understanding of natural history
- Lack of robust, patient-relevant outcome measures
- Low statistical power for small sample sizes
- Challenges in recruitment
- Late phase compound failures

Emerging Questions – CLN2 disease

- Impact on lifespan, other key disease domains
- Emergence of systemic pathology
- Long-term tolerability and device duration
- Delivery optimization
- Need for combination approaches
- **Development of robust global disease endpoints**
Relative importance of gene expression level versus cell specificity

Adequacy of preclinical model translation to human benefit

Threshold age of intervention

Add-on therapy considerations

Competing trials in a small population
Challenges ahead

- Timely diagnosis for known disorders
- Defining unsolved diseases
- Approved treatments with quality data
- Treatment access
- Increasing total # of treatments
- Increasing rate of first treatments
- Future of the Orphan Drug Act
FDA News Release

FDA approves first treatment for a form of Batten disease

For Immediate Release

April 27, 2017
European Commission Approves Brineura™ (cerliponase alfa), the First Treatment for CLN2 Disease, a Form of Batten Disease and Ultra-Rare Brain Disorder in Children

Dosing includes all ages from birth for this fatal and rapid pediatric neurodegenerative condition. Brineura is among first therapies to go through European Medicine Agency’s new accelerated assessment process.

Jun 1, 2017
NICE deems Batten disease therapy too costly for NHS use

13th February 2018
FUTURE

Accelerating development of new therapies, defining precise and meaningful diagnosis, changing our concept of therapeutic treatment groups, early and multi-modal intervention
Systematically building clinical knowledge about rare diseases

Neuronal Ceroid Lipofuscinoses (Batten diseases)

Sequencing Symptom Onset

Quantifying Progression

Examining Sex Differences

https://www.urmc.rochester.edu/neurology/batten-disease-center.aspx
Next Steps – Batten Diseases

**Modeling Disease Trajectory**

![Graph showing disease trajectory over age](graph.png)

**Clinical Endpoint & Biomarker Qualification**

![Brain image](brain_image.png)

**Testing Novel Interventions**

![Diagram of gene therapy](gene_therapy_diagram.png)

Brain image courtesy A.Schulz
www.trnds.org – September 19, 2019
Batten Research Group & Collaborators

Jonathan Mink  Foxe Lab
Frederick Marshall  Singh Lab
Heather Adams  Weimer Lab
Amy Vierhile  Gray Lab
Christopher Beck  Giovanni Schifitto
Alyssa Thatcher  Jen Vermilion
Kris Bonafacio  Shannon Dean
Grace Zimmerman  Mina Chung

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