Cyclodextrin (HP-β-CD) for NPC1 Disease

Clinical Strategy

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Niemann-Pick C

- Autosomal Recessive
- Neurodegenerative disorder
- Neurovisceral lipid storage
  - Unesterified Cholesterol
  - Glycosphingolipids
- Estimated Incidence: 1/120,000 to 1/150,000
Niemann-Pick C locus heterogeneity

- **NPC1** (~95%) 18q11
- **NPC2** (~5%) 14q24.3

NPC2 binds cholesterol (side chain)

NPC1 binds cholesterol (3β-OH)

NPC1 Mutations

Millat et al. (2005)
Niemann-Pick C Clinical Phenotype
Variable Clinical Phenotype

- Neonatal systemic
- Early Infantile
  - <2 years old, ~20%
- Classical Disease: 2-15 years old (60-70%)
  - Late infantile (2-5 years)
  - Juvenile (5-16)
- Adolescent and adult

Vanier et al. (1988)
Macías-Vidal et al, 2011
# Niemann-Pick C Clinical Phenotypes

<table>
<thead>
<tr>
<th>Clinical Phenotype</th>
<th>Vanier et al. (n=70)(^1)</th>
<th>Spain (n=27)(^2)</th>
<th>NIH cohort (n=70)(^3)</th>
<th>UK (n=94)(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td></td>
<td>10%</td>
<td>1.5%</td>
<td>3%</td>
</tr>
<tr>
<td>Early infantile</td>
<td></td>
<td>33.3%</td>
<td>40%</td>
<td>35%</td>
</tr>
<tr>
<td>• No neurological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neurological</td>
<td></td>
<td>~ 20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classical disease</td>
<td>~ 60-70%</td>
<td>40%</td>
<td>50%</td>
<td>37%</td>
</tr>
<tr>
<td>• Late infantile</td>
<td></td>
<td>20%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>• Juvenile</td>
<td></td>
<td>20%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Adolescent/Adult</td>
<td></td>
<td>6.6%</td>
<td>7.1%</td>
<td>25%</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>10% unclassified</td>
<td>1.4% asymptomatic</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Vanier et al. (1988)  
\(^2\)Macías-Vidal et al. (2011)  
\(^3\)Unpublished data  
\(^4\)Imrie et al. (2007)
Niemann-Pick C Phenotypes

Neonatal

- Neonatal cholestasis with progressive hepatosplenomegaly
  - Resolves in most by 2-4 months
  - 10% fatal liver failure
  - NPC- 27% of idiopathic neonatal cholestasis and 8% cholestasis

- In utero signs (50%)
  - Hepatomegaly (most common)
  - In utero ascites or hydrops
  - Intrauterine growth retardation (IUGR)
  - Thrombocytopenia and anemia
  - Cholesterol accumulation in the placenta

- Siblings variability

Vanier et al. (2003)
Niemann-Pick C Phenotypes

Early Infantile (Onset <2 years)

- Isolated hepatosplenomegaly, or
- Severe infantile neurological onset form (~20%)
  - Hepatosplenomegaly is typical
  - Hypotonia
  - Developmental delay by 12–18 months (absence of walking)
  - Progressive loss of acquired motor skills
  - Pyramidal signs
  - Intention tremor
  - Rare supranuclear gaze palsy or seizures
  - MRI: leukodystrophy.
  - Survival <5 years.

Vanier et al. (2003)
Niemann-Pick C Phenotypes “Classical”

- Transient neonatal icterus or hepatosplenomegaly common
- Vertical supranuclear gaze palsy
- Progressive ataxia
- Intellectual impairment
- 10% no hepato/splenomegaly
- Seizures (50%)
- Gelastic cataplexy with or without narcolepsy (20%)
- Pyramidal signs
- Dysphagia
- Death mostly as teenager but some to young adulthood
Niemann-Pick C Phenotypes
Adolescent/Adult Presentation

- Neurological:
  - Insidious onset
  - Progressive dementia
  - Psychosis may be the initial manifestation
  - Movement disorders and extrapyramidal signs are more common
  - Hepato/splenomegaly (~50%)
Niemann-Pick C Diagnosis

- Filipin Staining
  - Variable staining
    - 80-85% “classical”
    - 10-15% “variant”
    - 3-5% questionable

- Delayed diagnosis
  - ~4.5 years

- Genetic testing

Filipin Staining

Control                      NPC

Jiang et al. (2011)
NIH/TRND NPC Team Goal

Collaboratively develop a safe, effective and FDA-approved therapy for patients with NPC1.
The pathway to NPC drug development


Selection compound

Dog Tox studies

HPBCD formulation

Regulatory

Bionalytical and Biomarker development

HPBCD Trial Preparation

NeuroNEXT

NCGC

Aug 2008–Feb 2009: Screening supported by APMRF

3 yrs

May 2011

Dog Tox studies

5/21/11: Regulatory Kick-off meeting
6/15/11: Collaboration meeting with J&J
8/11: Requested pre-IND meeting with FDA
Oct 2011: Package submission
11/1/2011: Meeting FDA #1
12/13/2011: Meeting FDA #2

02/2012: Response from FDA.
2/23/2012: Dog Toxicology Study (on-going)
7/25/2012: IRB Approval
10/30/2012 (tentative date): IND filing

IND

1 yr 2 yrs

Ph I Ph II

NeuroNEXT

May 2011
Niemann-Pick C Challenges

- Rare disease (1/120,000-150,000)
- Locus and allelic heterogeneity
- Variable phenotype
  - Randomization
- Delayed diagnosis: ~4.5 years
- Lack of defined outcome measures
  - NPC severity score
- Biomarkers
  - 24-HC
  - Oxysterols
  - Other

Candidate Compound: HP-β-CD
TRND pilot project
http://trnd.nih.gov
Niemann-Pick C Biomarkers

- **Oxysterols**: Nonenzymatically formed cholesterol oxidation products
  - Increased in the plasma of human NPC1 subjects:
    - 7-ketocholesterol (7-KC)
    - Cholestane-3β,5α,6β-triol (3β,5α,6β-triol)
  - Specific to NPC1 disease
  - Correlates with neurological severity.
  - Significant reduction in cyclodextrin-treated cats.

- **24(S)-HC**: Enzymatic oxidation of cholesterol in neurons by CYP46A
  - Plasma 24(S)-HC significantly lower than in age-matched controls.
  - Age-corrected 24(S)-HC concentrations show an inverse correlation with disease severity.

NPC Biomarkers
Plasma Oxysterols

- Nonenzymatically formed cholesterol oxidation products
- 97.3% sensitivity and 100% specificity

Jiang et al. 2011
Niemann-Pick C Biomarkers
Plasma Oxysterols

- Correlates with neurological severity.
- Significant reduction in cyclodextrin-treated cats.

Porter et al. (2010)
Niemann-Pick C Biomarkers
24(S)-HC

HPBCD Administration

Redistribute Lysosomal Cholesterol

Increase Cholesterol Esterification

Increase ER Cholesterol

Suppress Cholesterol Synthesis

LXR Activation

Stimulate 24-HC Synthesis

Promote sterol Efflux

Increase Plasma 24-HC

Plasma 24-HC post HPBCD ICV in NPC1 mice
Niemann-Pick C
Clinical Outcome measures

- Exploratory evaluation of potential clinical outcome measures.
  - Swallowing
  - Speech/language
  - Hearing evaluation
  - Spiral analysis
  - Ambulation/coordination
  - NPC1 Clinical Severity Scale
  - Patient and caregiver reported outcomes
Nieman-Pick C
Linear Rate of Progression

- Neurological progression
- Predicted rate = 1.87 ± 0.18 points / year
- Potentially useful as a longitudinal clinical outcome marker in therapeutic trials

Clinical Severity Score (NIH)

Yanjanin et al. (2010)
Shin et al. (2011)
8 children treated (5 in the US) under single-patient INDs:

- IV infusion up to 2900 mg/kg/day of HP-β-CD, 1-2 times per week, for up to 2 years in 2 of the patients.
- No drug related serious adverse effects have been reported; also no measurable clinical outcomes of efficacy
- Intrathecal or Ommaya reservoir up to 450 mg of HP-β-CD, once every 2 weeks
- No drug related serious adverse effects have been reported; also no measurable clinical outcomes of efficacy
Niemann-Pick C1 Cyclodextrin Phase I Trial

- Goal: To establish safe and effective dosing regimen for HP-β–CD treatment of human NPC1 subjects
  - Define a safe and biochemically effective dose
  - Utilize biomarkers to infer biochemical efficacy in a short-term trial
  - Determine the ability of HPBCD to impact clinical symptoms in a prolonged trial

- Design:
  - Intracerebroventricular (ICV) Administration via an Ommaya Reservoir
  - 3 dosing cohorts
Phase I Study Design

- Intracerebroventricular (ICV) Administration via an Ommaya Reservoir
- The dose escalation study will include 9 patients divided in 3 dosing cohorts.
- Safety
- Biochemical Response (24-HC)
Dose Level 1
≥2 monthly administrations

Biochemical Response/Well-Tolerated
Maintain Monthly Administrations

No Biochemical Response/Well-Tolerated
Increase Dose

Dose Level 2
≥2 monthly administrations

Biochemical Response/Well-Tolerated
Maintain Monthly Administrations

No Biochemical Response/Well-Tolerated
Increase Dose

Dose Level 3
≥2 monthly administrations

Well-Tolerated
Maintain Monthly Administrations

Poorly Tolerated

Halt Study
## Rationale for route of administration of HP-β-CD

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<tr>
<th></th>
<th>Peripheral administration</th>
<th>CNS administration</th>
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<tbody>
<tr>
<td><em>Npc1&lt;sup&gt;–/–&lt;/sup&gt;</em> mice ED&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</td>
<td>132,000 mg/kg&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>~ 0.5 mg/kg&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>Npc1&lt;sup&gt;–/–&lt;/sup&gt;</em> mice Half-life</td>
<td>6.5 hours&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><em>Npc1&lt;sup&gt;–/–&lt;/sup&gt;</em> mice Therapeutic effect</td>
<td>&gt; 7 days</td>
<td></td>
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</table>

<sup>a</sup> Ramirez et al, 2011  
<sup>b</sup> This dose is several times higher than those associated with toxicity in the feline model of NPC1 (Vite, unpublished data).  
<sup>c</sup> Aqul et al, 2011

- Murine ED<sub>50</sub> of ~0.5 mg/kg = Human ED<sub>50</sub> ~35 mg
ICV administration of HP-β-CD

- ICV has several potential advantages:
  - Better CSF distribution than LP
  - Leads to highest concentrations within the cerebral ventricles
  - Easy CSF sampling
ICV HP-β-CD for NPC1 Safety

- Safety data will be collected with each dose.
- Dose decisions made for each patient based on individual safety data.
- Cumulative safety of each dose level will be evaluated on an ongoing basis by the SRC.
- Vital Signs, Clinical and neurological evaluation
- Monitored by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.02.
- Hearing evaluation, including Auditory Brainstem Responses (ABR)
- Clinical Laboratory Tests: hematology, chemistry, urinalysis, coagulation, antiepileptic levels
Home

NeuroNEXT • Network for Excellence in Neuroscience Clinical Trials

The Network for Excellence in Neuroscience Clinical Trials, or NeuroNEXT, was created to conduct studies of treatments for neurological diseases through partnerships with academia, private foundations, and industry. The network is designed to expand the National Institute of Neurological Disorders and Stroke’s (NINDS) capability to test promising new therapies, increase the efficiency of clinical trials before embarking on larger studies, and respond quickly as new opportunities arise to test promising treatments for people with neurological disorders.

The NeuroNEXT program aims to:

• Provide a robust, standardized, and accessible infrastructure to facilitate rapid development and implementation of protocols in neurological disorders.

How do I access the form required to submit a proposal to NeuroNEXT?

Process for Solicitation and Review of Clinical Studies for NeuroNEXT

NeuroNEXT, a NINDS initiative to conduct Phase II trials in neurological conditions, receives proposals from academics, foundations and industry. All proposals...
NIH/TRND NPC Team
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- **Parent/Patient Support Organizations**