Therapeutic Development Strategy

- Patient population is generally refractory to pharmacological therapy
  - Viral delivery platform is appropriate
  - Surgical approaches are standard and established
- Biochemistry is well understood and deficiencies can be targeted
- Specific clinical outcome is measurable
  - Pre-clinical studies have indicated encouraging efficacy
  - Clinical testing can be conducted in a relatively small number of patients within a reasonably short time period
- Sustainable competitive advantage through IP positions
 NLX Technology Platform Overview

- Employ Adeno-Associated Virus (AAV)
  - Non-pathogenic, non-replicative
  - Ability to deliver a wide range of genes
    - Unique gene for each disease
  - Simpler and safer alternative to current surgical methods (standard of care)
    - Under local anesthesia
    - Novel catheter infusion system permits bedside infusion and bedside removal out of OR
    - No hardware left behind
# Product Pipeline

<table>
<thead>
<tr>
<th>Application</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td><strong>Gene Therapy</strong></td>
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<tr>
<td>Parkinson’s Disease</td>
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<td>(NLX-P101, GAD Gene)</td>
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<td>Epilepsy</td>
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<tr>
<td>(NPY Gene)</td>
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<td>Depression</td>
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<td>(P111 Gene)</td>
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<td>Huntington’s Disease</td>
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<td>(XIAP Gene)</td>
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Study Protocol

- CRO for study: Pharmanet
  - Randomization scheme, study monitoring and database maintenance and quality control, statistical analysis

Month

Blinded Phase

- All patients and raters remained blinded until final patient reached 6 months post-surgery
Assessed for Eligibility (N=66)

Randomized (N=45)

AAV-GAD (N=22)

Analyzed (N=16)
Excluded:
  Missed target (N=2)
  System Delivery Failure (N=1)
  Both (N=3)

Sham (N=23)

Analyzed (N=21)
Excluded:
  System Delivery Failure (N=2)

Screen Failures (N=21)
PET (11), Declined (4), Other (4)

Lost to Follow-up (N=0)
Discontinued (N=0)
## Survey Assessment of the Blind

### Patient Opinion On Post-Surgery Day 3

<table>
<thead>
<tr>
<th>Actual Group</th>
<th>Treated</th>
<th>Sham</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>9</td>
<td>5 (2 improved UPDRS and 3 changed opinion at 6 mo)</td>
<td>7</td>
</tr>
<tr>
<td>AAV-GAD</td>
<td>13</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>
Phase 2 Clinical Trial
Study Results-Primary Outcome Measure
Change in 6 Month UPDRS III From Baseline

GAD
n=16

Sham
n=21
Change in UPDRS III Over Time

Overall $P = 0.03$ (rmANOVA)

* $p < 0.05$, Fisher’s LSD
$x$ $p = 0.058$
Six Month UPDRS III for GAD/Sham and DBS/Best Medical Therapy

(Weaver, et. al. JAMA 2009, Follet, et. al. NEJM 2010)
Motor Fluctuation Impact

Consistent Medication Effect

Wearing Off

On-Off Fluctuations

Freezing
Blinded Catheter Tip Localization

Target Area Relative to Mid-Commissural Point:
X=9-14mm lateral
Y=2mm anterior-5mm posterior
Z=1mm dorsal-7mm ventral

(Standard DBS tip coordinates in postero-ventral STN:
X=12mm lateral, Y=3.5mm posterior, Z=4mm ventral)
6 Month Outcome vs. AP Location

R = 0.58

R = 0.24
6 Month Outcome vs. Depth

6 Month UPDRS Change vs. Right Z Relative to MCP

R = 0.55

6 Month Change in UPDRS vs. Left Z Relative to MCP

R = 0.18
Refractory Epilepsy – AAV-NPY

- Group of diseases associated with recurrent seizures
  - 3 million patients, U.S.
  - 50% of patients continue to have seizures despite drug therapy
- Neuropeptide Y (NPY) shown to dampen overactivity and prevent seizures in multiple epileptic models
  - Over 300 animals (rodents and non-human primates) treated with AAV-NPY
  - Gene delivered to hippocampus
  - Significant reduction in seizure frequency, duration and progression
  - No adverse events or safety issues
AAV-NPY in mTLE – Background & Rationale

- NPY is most abundant CNS neuropeptide with pleiotropic activity

- In the hippocampus, Y2 G protein-coupled presynaptic receptors on glutamatergic neurons inhibiting glutamate release predominate, particularly in the setting of epilepsy where they are upregulated in both animal models and resected human tissue (Y1 receptors downregulated)

- AAV-NPY is highly effective in multiple models of both acute seizures and chronic spontaneous epilepsy, including kindling, systemic, icv and intrahippocampal (ih) kainate and post sustained status epilepticus (SSE)

- Efficient transport of NPY in cell processes together with release of peptide influences physiology beyond immediate transduced cells. No change in Y2 receptors post gene transfer
AAV-NPY in mTLE – Background & Rationale (cont.)

- AAV1-NPY decreases ih kainate ictal time by 75%, AAV2 (less efficient) by 50%, hence even low level expression effective

- AAV1-in a kindling model alters AD threshold and retards kindling, and in an icv kainate model abolishes status epilepticus (more potent than transgenic NPY-overexpressing rats)

- AAV1-NPY reduces spontaneous seizures and progression in SSE model, whereas in a control AAV group none improve and 70% have a marked increase in seizures consistent with a anti-epileptogenesis effect in addition to seizure suppression

- AAV1-NPY has weak anxiolytic effects and mildly diminishes hippocampal LTP in naïve animals but with no impairment of behavior in epileptic models
Mechanism of NPY Anticonvulsant Activity


Reduction of Ca$^{2+}$ influx through several types of Ca$^{2+}$ channels
(Qian et al, J Neurosci, 1997)

Vezzani et al, Trends Neurosci, 1999

ü Y2 agonists have anticonvulsant properties
ü Y2 KO mice are more susceptible to seizures
Effect of Capsid Serotypes on Transgene Expression

rAAV-NSE-NPY
serotype 2

Vector spread: ~1.5 mm

NPY overexpression in interneurons

rAAV-NSE-NPY
chimeric serotype 1/2

Vector spread: ~2.5 mm

NPY overexpression: interneurons granule cells pyramidal cells subiculum

Richichi et al, J Neurosci, 2004
Kainic Acid-Induced Seizures

Intrahippocampal (40 ng)

Serotype 1/2 rAAV-NSE-NPY is more effective than serotype 2 to inhibit hippocampal seizures

Intraventricular (250 ng)

Richichi et al, J Neurosci, 2004
Is Gene Therapy Effective in Chronic Epileptic Brain?

Chronic epileptic tissue is characterized by the loss of neurons, synaptic and molecular rearrangements and phenotypic changes in parenchymal cells.

from Pitkanen and Sutula, 2002
Experimental Protocol

- **Spontaneous Seizures**
  - 3 Months
  - Latency

- **Video-EEG Recording**
  - 4 wks
  - 2 wks
  - 2 wks

- **SE**

- **Sustained Status Epilepticus**

- **rAAV1/2– CBA promoter**
  - 3 µl of 5x10^12 vg/ml
  - Bilateral Injection

- **rAAV-CBA-NPY**

- **rAAV-Empty**

- **Video-EEG Recording**
  - 2 wks
  - 2 wks
rAAV-NPY impairs the progression of spontaneous seizures
AAV-NPY Phase 1 Clinical Trial

- Open label, dose escalation in intractable subjects with mTLE and concordant data (EEG, imaging, WADA) who met criteria for temporal lobectomy

- Direct infusion of AAV-NPY into mid-hippocampal head (100µl of either $5 \times 10^{12}$ or $1 \times 10^{13}$ vg/ml)

- 6 month monitoring with option for temporal lobectomy at that time

- Clinical grade (GMP) vector packaged

- Protocol submitted at University of Auckland Hospital and GTAC (New Zealand’s FDA equivalent)