Development of a Galanin Receptor-2 Based Therapy

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Advantages of Developing Peptide-Based Therapeutics

Neuropeptides

Advantages:
- High Receptor Potency & Specificity
- Lower Potential Toxicity
- Mechanistically Novel Therapeutics
- CNS Bioavailability

Technical Challenges:
- Poor Metabolic Stability
- Poor CNS Bioavailability
Galanin Receptor-2 Targeted Therapy – Approach –

Native Galanin Sequence

Galanin: GWTLNSAGYLLGPHAVGNHRSFSDKNGLTS

Sar: WTLNSAGYLLGPKKK-NH₂
Galanin Receptor-2 Targeted Therapy
– Approach –

- **Lipidization**
  (Peripheral vs. CNS activity)

- **Cationization**
  (Increases bioavailability)

Chemical structure:

```
Sar-WTLNSAGYLLGHKKKKK-NH2
```
Galanin Receptor-2 Targeted Therapy

– Approach –

Cationization
(Increases bioavailability)

Lipidization
(Peripheral vs. CNS activity)

NAX 505-5

Prototype galanin-based analog

I. Potently active following systemic administration in models of epilepsy and pain

II. Potential galanin receptor-1 mediated liabilities

Sar-WTLNSAGYLLGHKKKKK-NH$_2$
Galanin Receptor-2 Targeted Therapy
– Approach –

Lipidization
(Peripheral vs. CNS activity)

Receptor selectivity hot-spot
(galanin receptor-2 vs. galanin receptor-1)

Cationization
(Increases bioavailability)
Galanin Receptor-2 Targeted Therapy

- NINDS U01 Translational Research Grant
  - Milestone driven funding to fully support preclinical development of a galanin receptor-2 targeting analog to IND filing

- Progress
  - 38 analogs targeting galanin receptor-2 were designed and synthesized then evaluated in the mouse 6 Hz seizure model
  - 3 lead compounds identified
  - NAX 810-2 extended profiling preformed in seizure and pain models
NAX 810-2
Galanin Receptor-2 Targeting Lead
– Potent Anticonvulsant Activity –

<table>
<thead>
<tr>
<th>Seizure Model</th>
<th>ED50 (mg/kg, i.p.)</th>
<th>NAX 810-2</th>
<th>NAX 505-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Hz Seizure (mouse)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>32 mA</td>
<td>2.5</td>
<td></td>
<td>0.8</td>
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<tr>
<td>44 mA</td>
<td>5.9</td>
<td></td>
<td>2.9</td>
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<tr>
<td>Fring’s Audiogenic (mouse)</td>
<td>9.2</td>
<td></td>
<td>3.2</td>
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<tr>
<td>Corneal Kindling (mouse)</td>
<td>7.4</td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>MES (mouse)</td>
<td>Inactive at 20</td>
<td>Inactive at 20</td>
<td></td>
</tr>
<tr>
<td>Binding Assays</td>
<td>Ki (nM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galanin Receptor 1</td>
<td>494</td>
<td></td>
<td>3.5</td>
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<tr>
<td>Galanin Receptor 2</td>
<td>32</td>
<td></td>
<td>52</td>
</tr>
</tbody>
</table>
NAX 810-2
Galanin Receptor-2 Targeting Lead – Potent Analgesic Activity –

<table>
<thead>
<tr>
<th>Pain Model</th>
<th>Analgesic Activity (ED50 or % of untreated control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse Carrageenan</td>
<td>ED50: 4.7 mg/kg, i.p.</td>
</tr>
<tr>
<td>Mouse Formalin</td>
<td></td>
</tr>
<tr>
<td>Acute Phase</td>
<td>46% at 8 mg/kg, i.p.</td>
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<tr>
<td>Chronic Phase</td>
<td>38% at 8 mg/kg, i.p.</td>
</tr>
<tr>
<td>Rat Sciatic Nerve Ligation</td>
<td>307% at 4 mg/kg, i.p. (% threshold increase compared to pre-drug)</td>
</tr>
</tbody>
</table>
Summary and Conclusions

- Proprietary technology enhances metabolic stability and, if desired, blood-brain-barrier penetration of neuropeptides; e.g., galanin (NPY, NPW & neurotensin - data not discussed)

- Through rational design galanin receptor preference was altered while maintaining metabolic stability and in vivo activity

- NAX 810-2 is a galanin receptor-2 targeting lead compound that demonstrates potent in vivo activity in rodent models of epilepsy and pain following systemic administration

- Technology platform provides first-in-class drug candidates for epilepsy and pain
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