**BACKGROUND**

- An ideal anti-seizure medicine would inhibit excitatory circuits while sparing inhibitory circuits.
- Voltage-gated sodium channel inhibitors (e.g. carbamazepine) are effective anti-seizure medicines but these drugs inhibit the sodium channels that drive inhibitory interneuron firing (Na\(_v\)1.1) as well as those primarily linked to excitatory neuron firing (Na\(_v\)1.2 & Na\(_v\)1.6).

**METHODS**

- We created inhibitors that target Na\(_v\)1.6 selectively (XPC-7224) or Na\(_v\)1.2 and Na\(_v\)1.6 (XPC-5462) while sparing Na\(_v\)1.1 and other voltage-gated sodium channels.

**RESULTS**

**Distinct Selectivity Profiles Enable Specific Targeting of Na\(_v\)1.1 and Na\(_v\)1.2**

<table>
<thead>
<tr>
<th>Selectivity Profile</th>
<th>Na(<em>v)1.1 IC(</em>{50}) (µM)</th>
<th>Na(<em>v)1.2 IC(</em>{50}) (µM)</th>
<th>Na(<em>v)1.6 IC(</em>{50}) (µM)</th>
<th>Selectivity Na(_v)1.1/Na(_v)1.2</th>
<th>Physiologic EP assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>XPC-7224</td>
<td>0.11</td>
<td>0.30</td>
<td>5.4</td>
<td>16</td>
<td>XPC-7224 0.11</td>
</tr>
<tr>
<td>XPC-5462</td>
<td>0.005</td>
<td>2.4</td>
<td>0.012</td>
<td>160</td>
<td>XPC-5462 0.005</td>
</tr>
</tbody>
</table>

Potency and Selectivity Profiles of Selective Inhibitor (XPC-7224), Dual Inhibitor (XPC-5462), and Nonselective Inhibitor (Carbamazepine)

- XPC-7224 is highly selective for Na\(_v\)1.6.
- XPC-5462 blocks both Na\(_v\)1.2 and Na\(_v\)1.6; spares Na\(_v\)1.1 and Na\(_v\)1.5.
- Carbamazepine is similarly potent on all Na\(_v\) isoforms.

**SELECTIVE INHIBITOR VS SELECTIVE INHIBITOR VS CARBAMAZEPINE**

- Selective Na\(_v\)1.1 Na\(_v\)1.2/1.6 inhibitors.
- Nonselective Na\(_v\)1.2/1.6 spike and prevent the simultaneous impairment of the activity of inhibitory interneurons.
- Carbamazepine reduced action potential firing of inhibitory interneurons to a significant and similar degree as in pyramidal neurons.

**CONCLUSIONS**

- Selectively targeting the specific sodium channel isoforms expressed in excitatory neurons, Na\(_v\)1.2, and Na\(_v\)1.6, enables selective reduction of action potential firing in those neurons, and prevents the simultaneous impairment of the activity of inhibitory interneurons.

- This profile provides a new, mechanistically differentiated, class of voltage-gated sodium channel inhibitors with the potential to provide improved seizure control and side effect profile for epilepsy patients.

Xenon Pharmaceuticals Inc., 3650 Gilmore Way, Burnaby, BC, Canada


**DISCLOSURE**

Neurocrine Biosciences, Inc. and other parties have submitted Na\(_v\)1.6 inhibitors and dual Na\(_v\)1.2/1.6 inhibitors. All trademarks are the property of their respective owners.