ION CHANNELS

OFFERING
Evotec’s world-class ion channel platform combines industry-driven expertise with state-of-the-art instrumentation. In routine use are multiple setups for manual patch clamp studies and all of the most popular automated patch clamp instruments. The automated patch clamps or FLIPRs can be used as entry points for HTS, and the manual and automated patch clamps enable on-going support of medicinal chemistry programmes progressing from HTS through hit expansion, hit-to-lead, lead optimisation but are also utilised for safety pharmacology.

OVERVIEW OF ION CHANNEL SCREENING AT EVOTEC
Evotec has a strong background in running hit identification campaigns against ion channel targets. On average more than 235,000 compounds per target are screened in singlicate at a fixed compound concentration. Campaigns resulted in “primary” hit rates in the range of 1% and confirmation rates are generally good (650%), underlining robust assay performance. Secondary assays using electrophysiology to confirm compound activity is part of the routine HTS follow-up and are key to the successful identification of relevant starting points for medicinal chemistry projects.

Stephen Hess
Research Leader Ion Channels

The electrophysiology platforms in place at Evotec

<table>
<thead>
<tr>
<th>PLATFORM</th>
<th>2</th>
<th>384-well</th>
<th>4,000-10,000</th>
<th>High-throughput screening, hit-to-lead</th>
</tr>
</thead>
<tbody>
<tr>
<td>IonWorks® Quattro™</td>
<td>2</td>
<td>48-well</td>
<td>150-450</td>
<td>Hit-to-lead, lead optimisation and early safety assessment</td>
</tr>
<tr>
<td>Q-patch HTX®</td>
<td>2</td>
<td>16-well</td>
<td>75-150</td>
<td>Hit-to-lead, lead optimisation and early safety assessment</td>
</tr>
<tr>
<td>PatchLiner®</td>
<td>2</td>
<td>1-well</td>
<td>25-50</td>
<td>Hit-to-Lead, Lead optimisation</td>
</tr>
<tr>
<td>Port-A-Patch®</td>
<td>2</td>
<td>1-well</td>
<td>1-25</td>
<td>Lead optimisation, safety pharmacology</td>
</tr>
<tr>
<td>Manual Electrophysiology (Dynflow® optional)</td>
<td>5</td>
<td>1-well</td>
<td>1-25</td>
<td>Lead optimisation, safety pharmacology</td>
</tr>
</tbody>
</table>

TRACK RECORD OF SUCCESS WITH A RANGE OF ION CHANNEL CLASSES
Evotec has electrophysiology and ion channel pharmacology expertise using transiently & stably-expressing cell lines or cells from primary tissues (e.g. DRGs, NDGs). In addition, we have capabilities and experience in the generation of transient and stable formats for ion channel targets.

- Voltage gated ion channels
  - Potassium ion channels: Kᵥ family
  - Calcium channels: Cav family
- Sodium channels: Nav family

- Additional potassium ion channels: Kᵥ family
- Inward rectifiers: Kir family
- Tandem pore domain: TREK, TASK family
- Ligand-gated ion channels: P₂X family
- Glutamate receptors: NMDA, AMPA family
- TRP family
- GABA-A
- Others: CRAC, Chloride channel (e.g. CFTR)

Electrophysiological recordings from primary cells provide additional mechanistic insight beyond that possible using recombinant cells. In this case we used neurons isolated from dorsal root and nodose ganglia. On the right is an example taken from our efforts using mouse nodose ganglion neurons:

- Voltage-gated sodium channels (Naᵥ) are expressed in neurons
- The selective Naᵥ blocker, TTX (300nM) inhibited Naᵥ signal in big diameter cells (arrows)

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