Ion Channel Drug Discovery

Computational Drug Discovery

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Ion Channel Drug Discovery

- Primary focus: Pentameric ligand gated ion channels
- $\text{GABA}_A$, Nicotine, Serotonin 5-HT$_3$ and Glycine receptors

- Multiple different subunits, complex assembly pattern, complex pharmacology
- Receptors assembled in different stoichiometric forms - “subtypes of subtypes”
- “Novel” interfaces represent novel opportunities for drug discovery

- Identification, characterization and de-orphanisation of novel drug binding sites
Allosteric Modulators – Benzodiazepine type modulation

\[
\begin{align*}
\alpha_4 & \quad \beta_2 \\
(\alpha_4)_3(\beta_2)_2
\end{align*}
\]

**Graph:**
- **Y-axis:** Log[ACh] % of maximal ACh
- **X-axis:** Log[ACh] µM
- **Data Points:**
  - ACh
  - ACh+NS9283 (31.6 µM)
- **EC50:** 3.2 µM

**Additional Information:**
- EC50: 0.11 µM
- EC50: 1.1 µM
- EC50: 93 µM
- EC50: 0.11 µM

**Molecule Structure:**
- Benzodiazepine site
- Agonist site

**Lindquist & Birnir, J. Neurochem. 2006**
Techniques

– Dry Lab
  – Computer aided drug design
  – SAR analysis
  – Homology modeling
  – Pharmacophore modeling
  – Docking, fragment docking
  – Scaffold hopping
  – Molecular dynamics
  – Free energy perturbation

– Wet Lab
  – Oocyte electrophysiology
  – Molecular biology
  – Assay development
  – Screening
  – Compound characterisation
  – Radioligand binding assays
Techniques – Docking – Molecular Dynamics
Oocyte electrophysiology
What we would like from DDI

– DDI PhD scholarships
– DDI seed funding

– Medium - High-through put screening capabilities

– Access/collaborations large scale protein expression + X-Ray crystallography/Cryo-EM
– Access/collaborations Medicinal chemistry

– Access/collaborations using slice electrophysiology
– Access/collaborations in other behavioral models

– Access to ADME
Ion Channel Drug Discovery Team