Ion Channel Drug Discovery

Computational Drug Discovery

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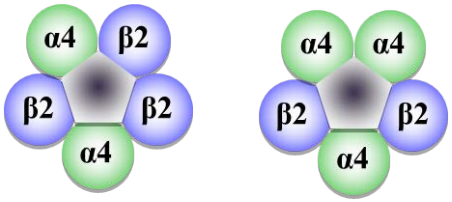
Ion Channel Drug Discovery

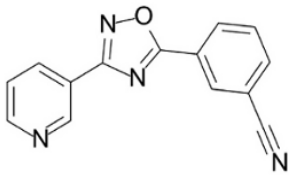
- Primary focus: Pentameric ligand gated ion channels
- $GABA_A$, Nicotine, Serotonin $5\text{-}HT_3$ and Glycine receptors

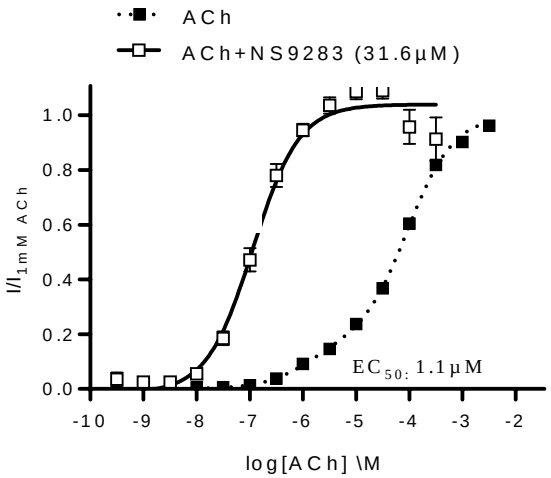
- Multiple different subunits, complex assembly pattern, complex pharmacology
- Receptors assembled in different stoichiometric forms - “subtypes of subtypes”
- “Novel” interfaces represent novel opportunities for drug discovery

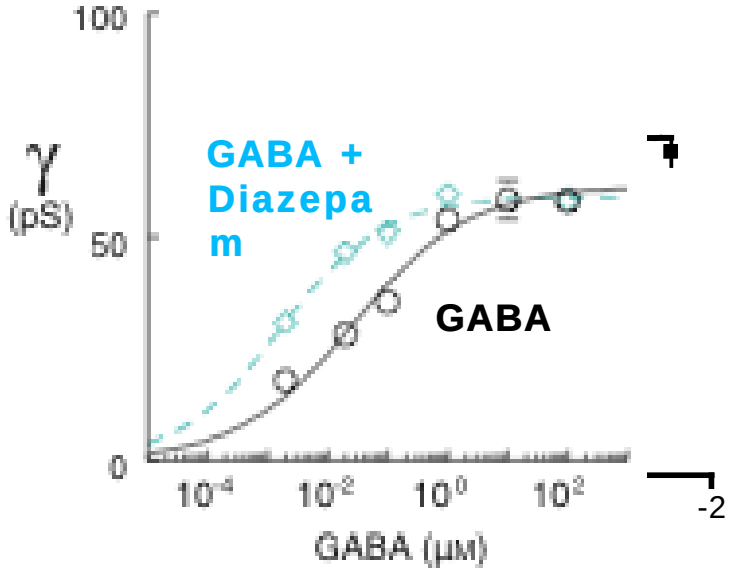
- Identification, characterization and de-orphanisation of novel drug binding sites

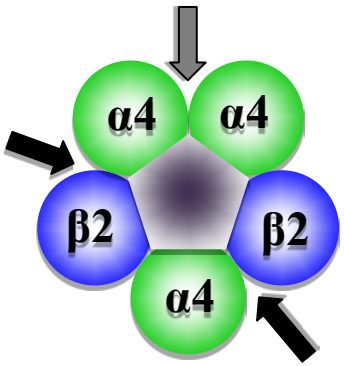


Allosteric Modulators – Benzodiazepine type modulation

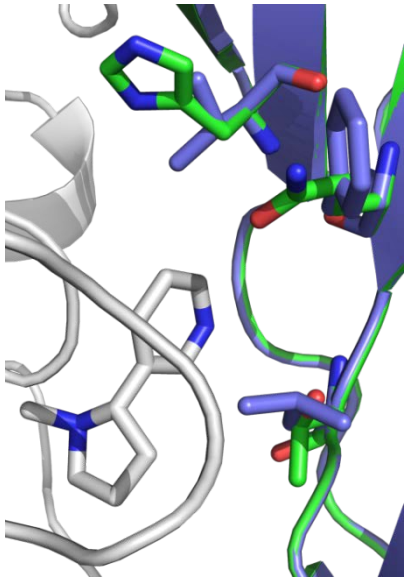


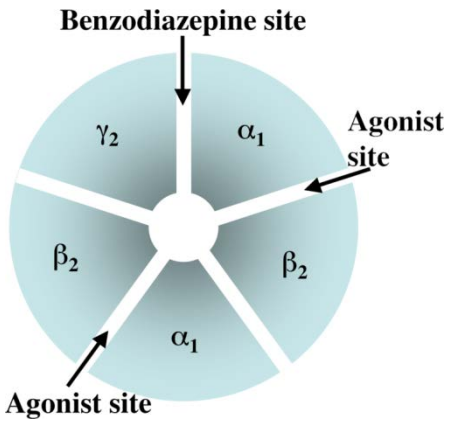






$(\alpha4)_3(\beta2)_2$



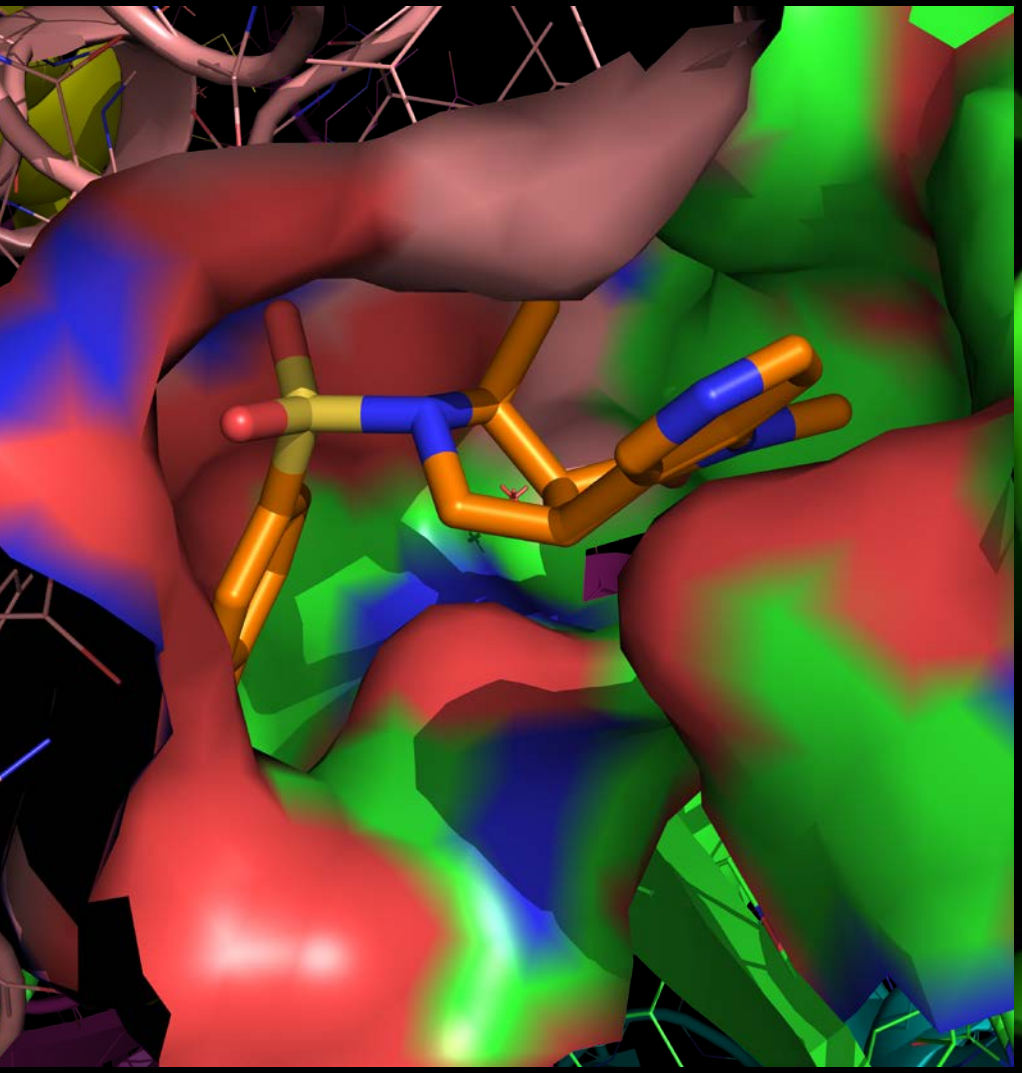


Lindquist & Birnir, J. Neurochem. 2006

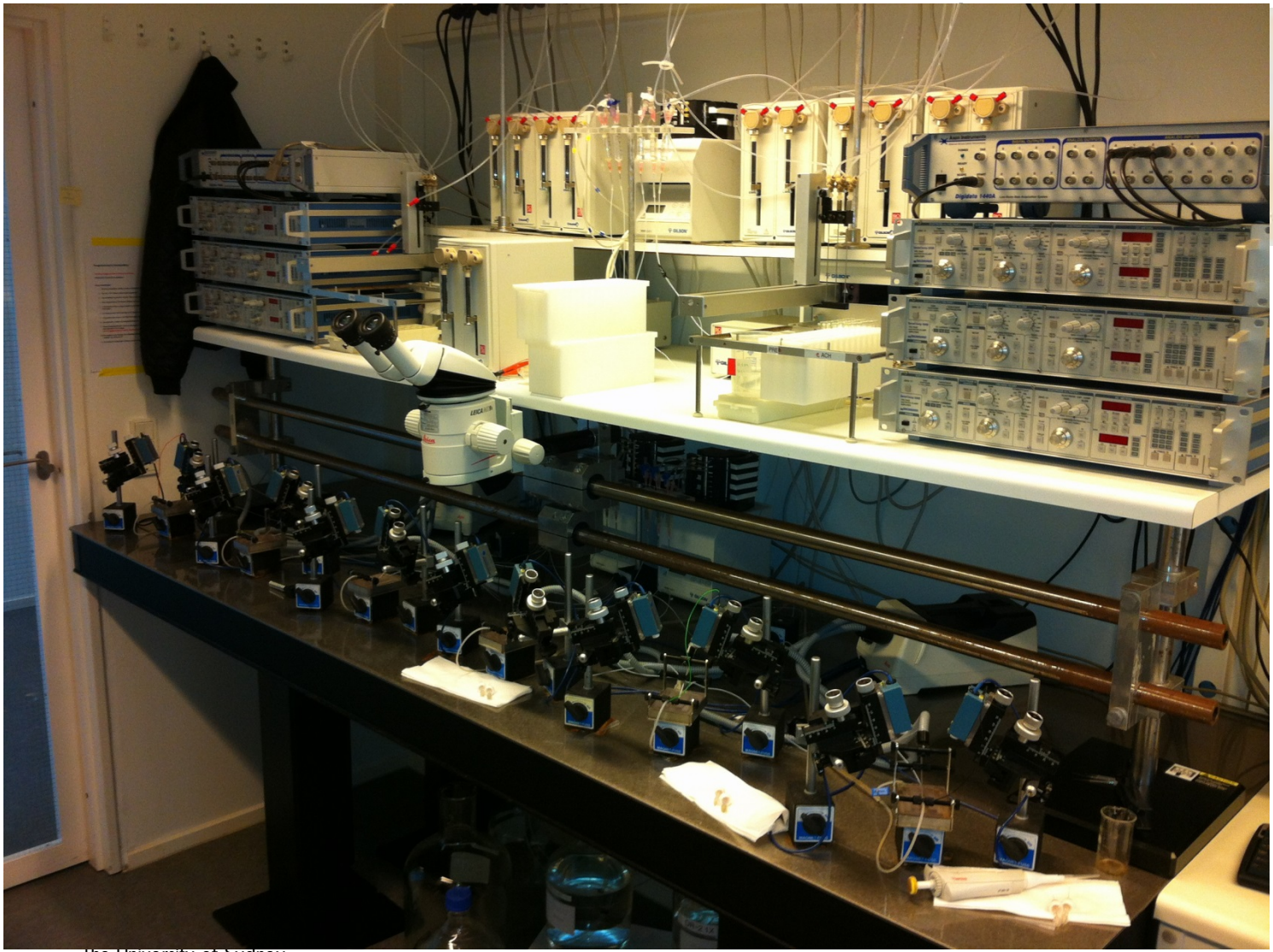
Techniques

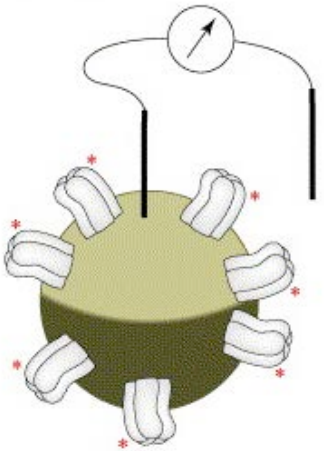
- **Dry Lab**
  - Computer aided drug design
  - SAR analysis
  - Homology modeling
  - Pharmacophore modeling
  - Docking, fragment docking
  - Scaffold hopping
  - Molecular dynamics
  - Free energy perturbation
- **Wet Lab**
  - Oocyte electrophysiology
  - Molecular biology
  - Assay development
  - 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

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Mary Collins

Thomas Balle

Australian Government
National Health and Medical Research Council

Australian Government
Australian Research Council