

## Pain Testing Models

TetraQ offers a range of techniques for investigating the effectiveness of potential pain drugs, with a focus on *in vivo* models. We are leaders in *in vivo* pain models and are continually expanding our offering to include new models.

### Nociceptive Pain (validated)

#### Tail flick & hotplate tests

- Behavioural endpoints: noxious thermal stimuli applied to tail & paws respectively
  - Highly predictive for strong opioid analgesics &  $\alpha_2$ -agonists

#### Formalin test

- Model of persistent nociceptive pain
- Behavioural endpoints: licking, biting & flinching –phases 1 & 2

#### Post-surgical pain model (Brennan model)

- Behavioural endpoints: mechanical allodynia & hyperalgesia

#### Inflammatory Pain (validated)

- FCA-rat model of inflammatory pain
- Behavioural endpoints: hyperalgesia & hindpaw inflammation

### Multiple Models of Neuropathic Pain (validated)

#### Chronic Constriction Injury of the Sciatic Nerve

- Behavioural endpoints: allodynia & hyperalgesia

#### Painful Diabetic Neuropathy

- Streptozotocin-induced diabetes in rats
- Zucker Diabetic Fatty (ZDF) rats
- Behavioural endpoints: allodynia & hyperalgesia

#### ddC-induced Neuropathy

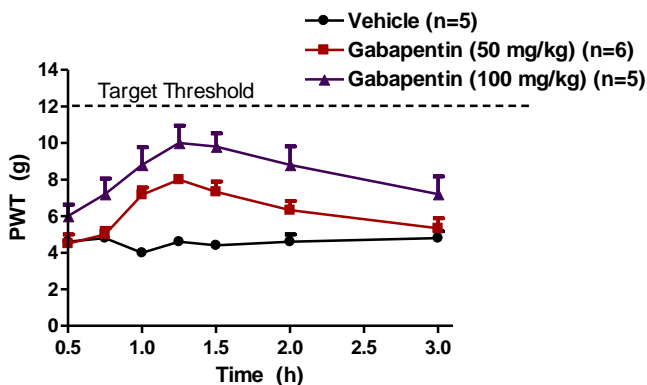
- Behavioural endpoints: mechanical allodynia & hyperalgesia

#### Chemotherapy (cisplatin)-induced Neuropathy

- Behavioural endpoints: mechanical allodynia & hyperalgesia

## Specialising in Pain Drug Development

### Cisplatin-induced Neuropathy in Rats



### Other Rodent Pain Models (validated)

- Capsaicin-induced hindpaw sensitivity
- EAE-mouse model of neuropathic pain
- Bone cancer pain
- Behavioural endpoints: mechanical allodynia & hyperalgesia

### Other Rodent Models of Persistent Pain Currently in Development

#### Varicella zoster virus (VZV)-induced neuropathy

- Human VZV isolates currently being cultured
- Behavioural endpoints: mechanical allodynia & thermal hyperalgesia; activity cage
- Aim to have validation completed in Q3 2011

TetraQ has experience with a variety of pain target classes and pain drug molecule classes. Additionally, TetraQ offers bioanalytical, toxicology and pharmaceuticals capabilities in support of pain drug development.

#### TetraQ Experience: *ex vivo* Assessments

- Real-time RT-PCR
- Immunohistochemistry
- Bioanalysis of plasma/CSF concentrations of test compounds – systemic exposure; identify targeted therapeutic plasma concentration for subsequent clinical studies
- Pharmacokinetics of test compounds

#### TetraQ Experience: Drug Target Classes

- GPCRs
  - Opioids
  - Others – *commercial-in-confidence*
- Transporters
  - Norepinephrine transporter (Mr1A, Xen2174)
- Ion Channels
  - N-type calcium channel blockers– (CVID, MVIIA)
  - $\alpha_2\delta_1$  subunit of  $Ca^{2+}$ -channel – (gabapentin)
  - Others - *commercial-in-confidence*
- Enzymes
  - Kinases - *commercial-in-confidence*

#### TetraQ Experience: Molecule Classes:

- Small Molecules
- Peptides
- Proteins
- siRNA

#### Drug Dosing Routes in Rodents

- Oral (by gavage)
- Intravenous
- Intraperitoneal
- Subcutaneous
- Intrathecal & epidural
- Intracerebroventricular & intracerebral
- Intradermal
  - Parenteral routes –via injection or continuous infusion
  - Infusion –via Culex machine or osmotic mini-pump

## Specialising in Pain Drug Development

#### Quantitative Assessment of the Following Side-Effects in *in vivo* Studies in Rats:

- Respiratory depression in awake freely moving rats using whole body plethysmography
- Constipation in rats (castor oil test & charcoal test)
- Motor impairment (rotarod)
- General activity (activity cage)

#### Bioanalysis Services – ADME

- GLP recognised & NATA ISO 17025, Research & Development Accredited
- Bioanalytical method development & sample analysis of drugs/metabolites in biological fluids, human and animal samples
- Validated bioanalytical methods
- in vitro* and *in vivo* bioavailability and pharmacokinetic studies
- Drug metabolism studies including metabolite identification
- Biodistribution and plasma protein binding studies
- Toxicokinetics

#### Toxicology

- GLP recognised
- Genotoxicity assays (Ames Test, Micronucleus, Mouse Lymphoma Assay)
- In vivo acute & repeat dose (chronic) toxicity studies
- In vivo safety pharmacology (including hERG, respiratory and CNS)
- Cytotoxicity assessment

#### Pharmaceutics

- Physicochemical characterization
- Formulation development
- Structure elucidation, solubility
- Stability trials & stability indicating method development
- Dissolution studies

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