

Mouse models for inflammatory, non-inflammatory and neuropathic pain

Species: mice

Fields of application: Inflammation

Nociceptive pain. This is the type of pain that all people have had at some point. It is caused by actual, or potential, damage to tissues. For example, a cut, a burn, an injury, pressure or force from outside the body, or pressure from inside the body (for example, from a tumor) can all cause nociceptive pain. The reason why we feel pain in these situations is because tiny nerve endings become activated or damaged by the injury, and this sends pain messages to the brain via nerves. Nociceptive pain tends to be sharp and/or aching. It also tends to be eased well by traditional pain medication such as paracetamol, anti-inflammatory painkillers, codeine and morphine.

Neuropathic pain. This type of pain is caused by a problem with one or more nerves themselves. The function of the nerve is affected in a way that it sends pain messages to the brain. Neuropathic pain is often described as burning, stabbing, shooting, aching, or similar to an electric shock. Neuropathic pain is less likely than nociceptive pain to be helped by traditional pain medication.

At IME-TMP, we have several animal models available for study of nociception and pain.

Inflammatory Pain Models

- Formalin test
- Ultraviolet light B (UVB)
- Injection into hindpaw of:
 - ✓ Carrageenan
 - ✓ Zymosan
 - ✓ Complete Freund's adjuvant (CFA)

Non-inflammatory Pain Models

- Thermal
 - ✓ Hot plate, Tail flick, Hargreaves
 - ✓ Cold allodynia*: Cold plate, Acetone test
- Mechanical allodynia* - Dynamic plantar von Frey fibre test

Neuropathic Pain Models

- Spared Nerve Injury (SNI): a model of peripheral neuropathic pain following partial denervation of the sciatic nerve by lesioning the tibial and common peroneal nerve branches, leaving the remaining sural nerve intact.
- Sciatic Nerve Crush: a method to crush the mouse sciatic nerve; resembles human neuropathy resulting from trauma of peripheral nerves, with some functional preservation of the innervation (nerve entrapment or compression).

- Chemotherapy (paclitaxel or oxaliplatin): peripheral neuropathy is a very frequent and severe side effect of chemotherapy and is often the limiting factor for achieving effective doses.

* Allodynia is a nociceptive response to a stimulus which does not normally provoke pain. Temperature or physical stimuli can provoke allodynia. This often occurs after tissue injury. Hyperalgesia, in contrast to allodynia, is a state of exaggerated sensitivity to a stimulus which is normally painful.

Endpoints/Outcome parameters: Our approach is not only to use standard readouts, but we also offer the possibility to study more subtle and objective readouts that potentially could have a higher translational value.

Readout parameters

Several animal models and readouts for pain rely solely on the measurement of reflexes. In addition to these, we assess other parameters as well, that may add translational value to the study of disease progression and drug efficacy.

More subtle and objective measurements of balance, motor coordination and muscle strength can be investigated using (semi) automated setups, rotarod, treadmills and the grip strength meter.

Pain can induce cognitive impairment which represents a major obstacle to daily activities and rehabilitation, especially in the patient suffering from chronic pain. Besides cognition, also mood and anxiety can modulate pain in human subjects. Therefore, these factors should also be taken into account when measuring pain in animals. We offer the opportunity to test effects of compounds on cognitive impairment in the neuropathic pain animal models using setups such as the Mouse Touch Screen Chambers (Campden Instruments Ltd.).

We additionally offer fluorescence-activated cell sorting (FACS) / immunohistochemistry (IHC) analysis of tissue and blood samples; analysis of cytokines / chemokines / lipid profile and microglia activation. In addition, in collaboration with the Institute of Clinical Pharmacology (Pharmazentrum Frankfurt/ZAFES, Frankfurt am Main) we offer the use of multi Epitope Ligand Cartography (MELC) which allows staining of the same tissue section with up to 100 fluorescent markers.

Pharmacokinetics and determination of drug concentrations by LC-MS/MS: PK/PD studies of drugs, including chiral compounds, in rodent models

Bioluminescent imaging: The IVIS Spectrum (Caliper Life Sciences) is used as optical imaging technology to facilitate non-invasive longitudinal monitoring of disease progression (e.g. inflammation), cell trafficking and gene expression patterns in living animals.

Optogenetics: Optogenetics is a technology that allows targeted, fast control of precisely defined events in biological systems as complex as freely moving mammals. We are currently exploring opportunities to use optogenetic activation and sensitization of pain pathways in freely moving mice.

Quality management and validation: The models have been validated with clinical reference compounds.

References: Lu, Ruirui; Bausch, Anne E.; Kallenborn-Gerhardt, Wiebke; Stoetzer, Carsten; de Bruin, Natasja; Ruth, Peter; Geisslinger, Gerd; Leffler, Andreas; Lukowski, Robert; Schmidtko, Achim (2015). Slack Channels Expressed in Sensory Neurons Control Neuropathic Pain in Mice. *The Journal of Neuroscience*, 35(3): 1125-1135; DOI: 10.1523/JNEUROSCI.2423-14.2015

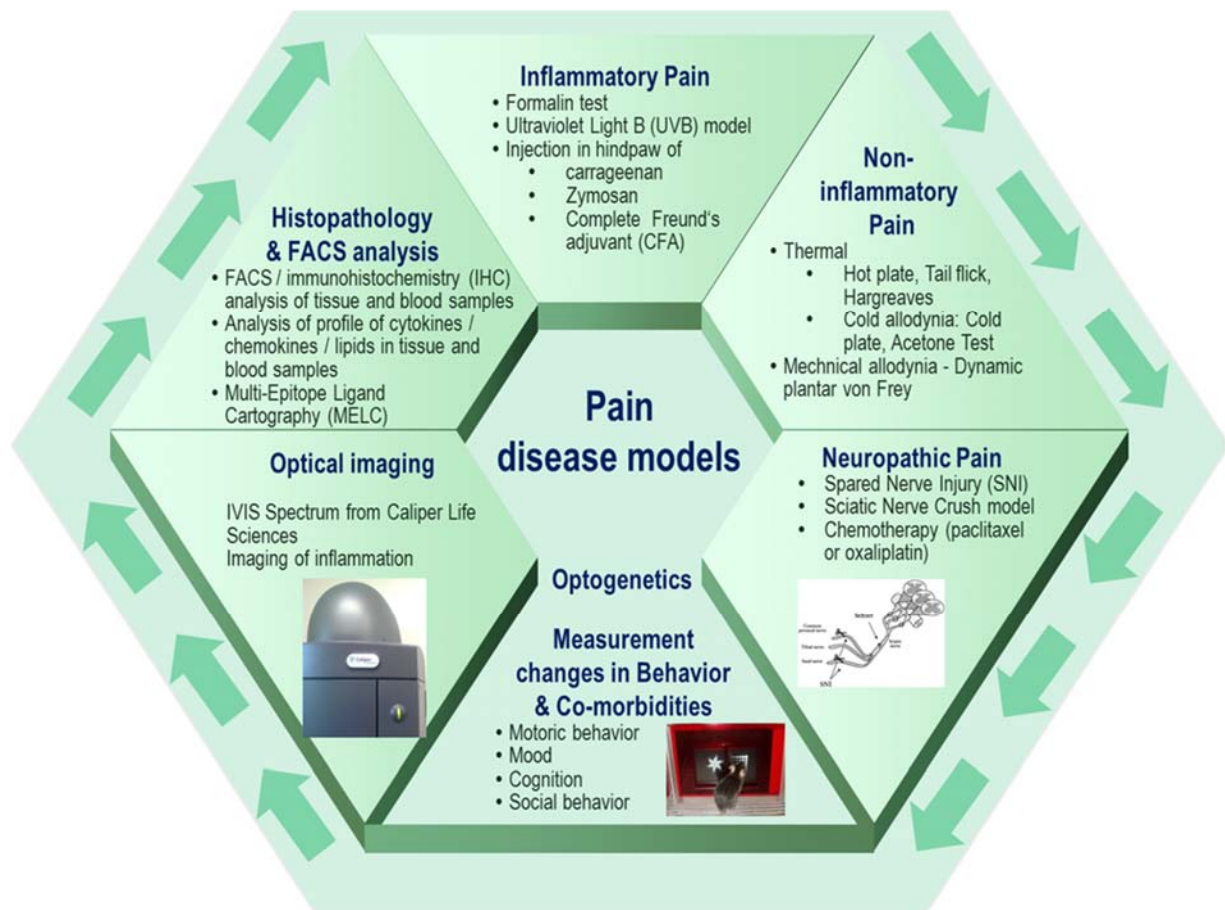


Figure: Various animal models for pain and relevant readouts at Fraunhofer-TMP

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