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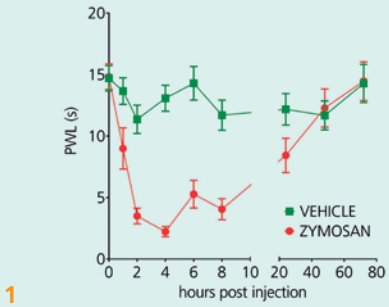

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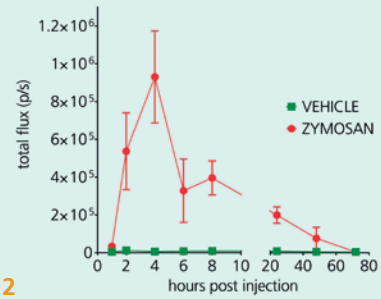

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1 *Hargreaves test: zymosan-induced hyperalgesia (paw withdrawal latency)*
2 *In vivo luminol-based bioluminescent imaging (BLI) following zymosan*
1 + 2 *© Fraunhofer IME / Olga Arne, Natasja de Bruin.*

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MOUSE MODELS FOR INFLAMMATORY, NON-INFLAMMATORY AND NEUROPATHIC PAIN

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 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 Fraunhofer IME Branch for Translational Medicine and Pharmacology, we have several animal models available for study of nociception and pain.

Animal models

Inflammatory Pain

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

Non-inflammatory Pain

- Thermal
  - Hot plate, Tail flick, Hargreaves
  - Cold allodynia*:
    Cold plate, Acetone test

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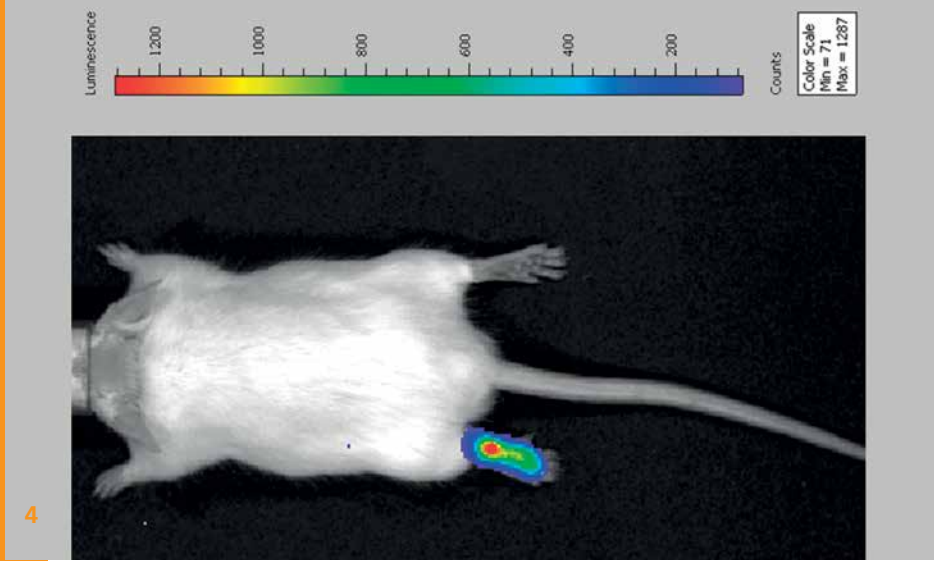

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- Mechanical allodynia*: Dynamic plantar von Frey fibre test

Neuropathic Pain

- 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.

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, threadmills 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, 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.).

Additional/complementing offers

- **Fluorescence-activated cell sorting** (FACS) / immunohistochemistry (IHC) analysis of tissue and blood samples; analysis of cytokines / chemokines / lipid profile and microglia activation
- in collaboration with the Institute of Clinical Pharmacology (Pharmazentrum Frankfurt/ZAFES, Frankfurt am Main) use of **Multi Epitope Ligand Cartho-graphy** (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:** allowing 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.

Selected publications

Zinn et al. (2017) The leukotriene B4 receptors BLT1 and BLT2 form an antagonistic sensitizing system in peripheral sensory neurons. J Biol Chem 292:6123–34. doi:10.1074/jbc.M116.769125.

Sisignano et al. (2016) Targeting CYP2J to reduce paclitaxel-induced peripheral neuropathic pain. PNAS 113:12544–9. doi:10.1073/pnas.1613246113.

Lu et al. (2015) Slack channels expressed in sensory neurons control neuropathic pain in mice. J Neurosci 35:1125–35. doi:10.1523/JNEUROSCI.2423-14.2015.54.

* 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.

3 *Optogenetic place preference setup for mice © Fraunhofer IME / Martine Hofmann.*

4 *Luminol–induced BLI in the IVIS following zymosan © Fraunhofer IME / Natasja de Bruin.*