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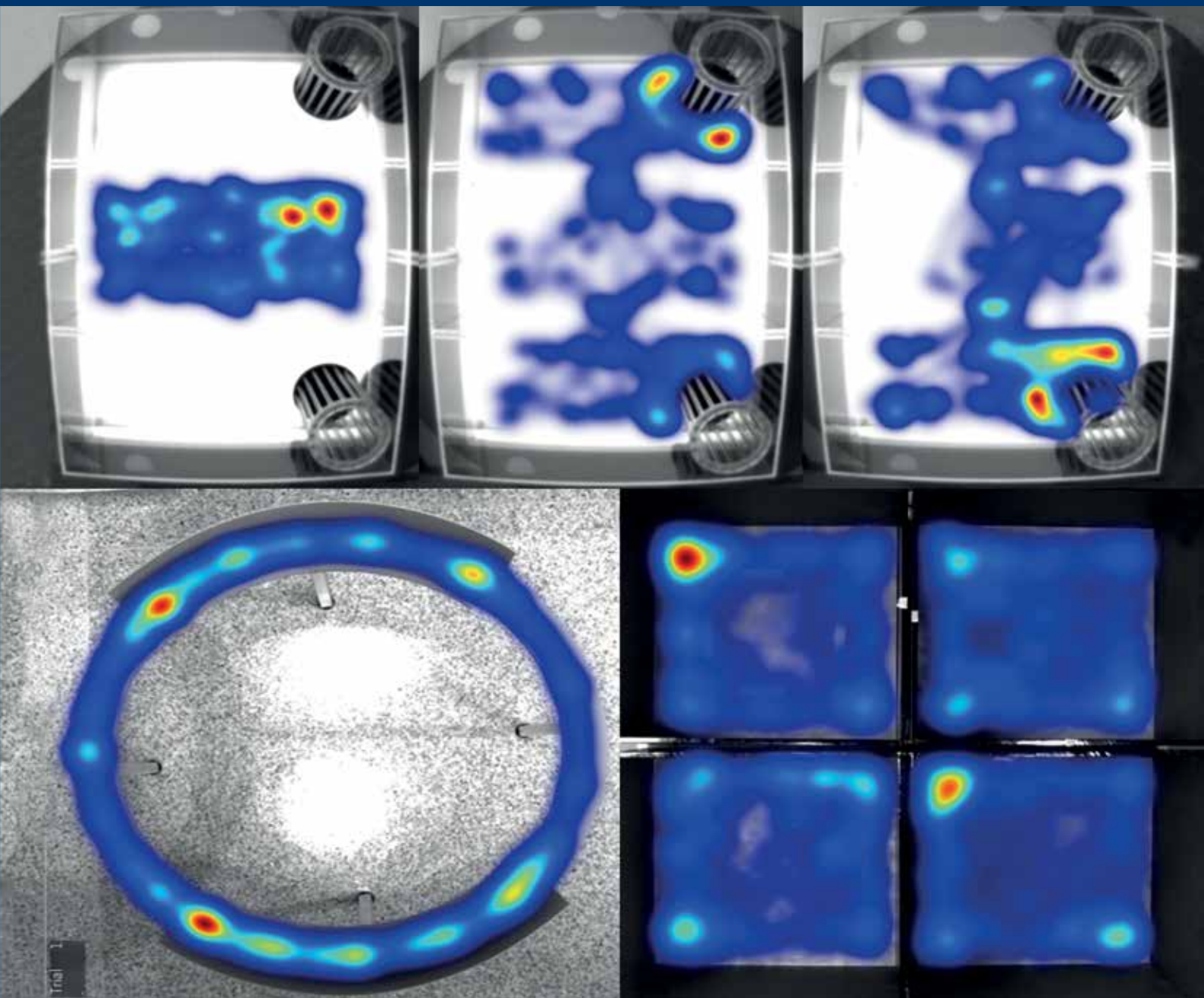
FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY IME

TRANSLATIONAL MEDICINE IN VIVO PHARMACOLOGY



TRANSLATIONAL DRUG VALIDATION PRECLINICAL DISEASE MODELS

Translational medicine contributes steadily and substantially to the development of new approaches for the diagnosis and treatment of diseases that are inadequately understood or controlled.

Translational Medicine and Pharmacology

Pharmaceutical research promotes the development of new drugs and enhances our understanding of how they work. However, R&D costs have increased exponentially whereas the number of new drug registrations has declined steadily over the last 10 years. One critical factor is that the identification of drug targets for inadequately understood diseases requires more extensive investment in discovery research but has a high attrition rate.

This reflects the lack of validated clinical models for efficacy and safety, and intensive efforts are currently underway to develop new disease models and preclinical/clinical biomarkers, allowing R&D projects to be translated into benefits for patients.

The research focus of the project group is drug research, development of predictive preclinical and clinical models of disease and clinical research.
The synergy generated by housing predictive preclinical and clinical models under one roof will make it easier to take early go/no-go project decisions.

The field of translational medicine spans the value chain, from target identification through active agent screening and translational preclinical validation to clinical trials.

Based on the internal expertise in the field of pathophysiological signalling pathways, we perform research on novel innovative therapeutic approaches (systems medicine). Drawing on cutting-edge research activities and intellectual property within both Fraunhofer IME and Goethe University Frankfurt, we apply the latest technology and research concepts to our collaborative projects, with pre-competitive research focusing on the treatment of chronic inflammatory joint disease, sepsis, multiple sclerosis, pain and neurodegenerative disorders.
One research focus is the repositioning of known active agents within the disease areas of pain, rheumatoid arthritis, sepsis, multiple sclerosis and inflammation.

Preclinical disease models

We offer a specialized spectrum of preclinical in vivo disease models.

We have developed validated disease models covering the fields of neurodegenerative and chronic inflammatory gastrointestinal diseases, acute inflammation and pain (inflammatory, neuropathic, oncological and post-operative), arthritic and skin disorders.

Variables determined include direct functional, imaging and behavioral analyses, as well as ex-vivo immunohistological, immunological, cellular (e.g. FACS), receptor, mediator generating, enzyme, signaling, proteomic and genomic processes. This detailed assessment allows for distinctive phenotyping of drug effects.

Environmental enrichment is an important aspect of laboratory animal husbandry.

AVAILABLE DISEASE MODELS

Some patients with acute and inflammatory pain pain do not achieve satisfactory pain relief with traditional analgesics.

Established animal models available within the Fraunhofer IME in Frankfurt am Main cover a range of inflammatory, autoimmune, pain and neurodegenerative indications.

ACUTE AND INFLAMMATORY 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.

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
- Mechanical allodynia: Dynamic plantar von Frey fibre test

Selected Publication

Zinn S, Sisignano M, Kern K, Pierre S, Tunaru S, Jordan H, Suo J, Treutlein EM, Angioni C, Ferreiros N, Leffler A, DeBruin N, Offermanns S, Geisslinger G, Scholich K (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.

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.

Spared Nerve Injury

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.

Selected Publications

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.

Chemotherapy-induced peripheral neuropathy is due to the toxicity of the chemotherapeutic drugs.

AVAILABLE DISEASE MODELS

It takes several years to develop a drug from an initial concept, test its safety and effectiveness in humans before a drug can be put onto the market.

DERMAL INFLAMMATION

Oxazolone-induced delayed-type-hypersensitivity

Dermatitis is a broad term covering a variety of different inflammatory skin diseases. Animal models of allergic contact dermatitis, such as the T-cell-mediated hypersensitivity reaction (Delayed Type Hypersensitivity or DTH Type IV), and associated responses are useful for testing new therapeutic compounds, but also provide a simple means to study skin inflammation and systemic immune responses.

Imiquimod model for psoriasis

Psoriasis is an autoimmune disorder in which cells multiply too quickly and form shiny scales on the skin's surface, psoriasis often occurs alongside arthritis or other joint diseases. The Imiquimod-induced psoriasis model develops skin pathology which highly correlates to that of human psoriasis.

Bleomycin model for systemic sclerosis

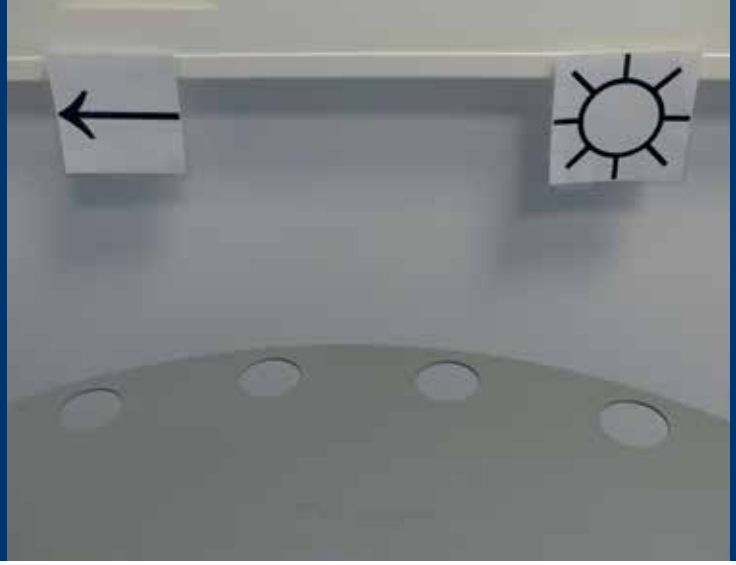
Systemic sclerosis or scleroderma is an inflammatory rheumatic connective tissue disease that is characterized by fibrosis of the skin and various internal organs. One of the animal models available for systemic sclerosis is the murine bleomycin-induced dermal fibrosis model.

Selected Publications

Hofmann MCJ., Schmidt M, Arne O, Geisslinger G, Parnham MJ, de Bruin NMWJ. Non-invasive bioluminescence imaging as a standardized assessment measure in mouse models of dermal inflammation. J Dermatol Sci. 2018; 91:153-63. doi: 10.1016/j.jdermsci.2018.04.013.

Pierre S, Linke B, Suo J, Tarighi N, Del Turco D, Thomas D, et al. GPVI and Thromboxane Receptor on Platelets Promote Proinflammatory Macrophage Phenotypes during Cutaneous Inflammation. J Invest Dermatol 2017;137:686–95. doi:10.1016/j.jid.2016.09.036.

Homann J, Suo J, Schmidt M, de Bruin N, Scholich K, Geisslinger G, et al. In Vivo Availability of Pro-Resolving Lipid Mediators in Oxazolone Induced Dermal Inflammation in the Mouse. PLoS One 2015;10:e0143141. doi:10.1371/journal.pone.0143141.



NEURODEGENERATIVE DISEASES

Cognition and behavioral assessments

Co-morbid symptoms such as cognitive impairment, fatigue and mood disturbances are often untreated and therefore represent potential therapeutic targets. Our aim is the identification of cognitive and behavioral deficits in various disease models and subsequently the in vivo testing of drugs for their ability to normalize cognitive and behavioral deficits in various disease models.Cognition can be measured in animals in a similar fashion to that in humans which offers the opportunity to investigate cognitive deficits in animal models mimicking aspects of neurological diseases. Also, other behavioral assessments are important, for example measurements of motor capabilities, anxiety, mood, arousal, social behavior and motivation. Objective, sensitive and specific readouts for locomotor impairment, recovery or improvement are available.

App NL-G-F knock-in mouse model of Alzheimer's disease

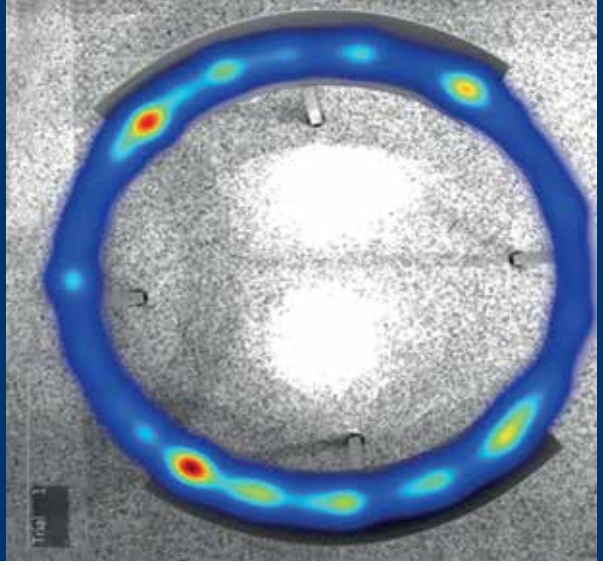
We have been working with an interesting novel knock-in mouse model of Alzheimer's disease available through Takaomi Saido (RIKEN Brain Science Institute, Wako-shi, Saitama, Japan).
Saito T, Matsuba Y, Mihira N, Takano J, Nilsson P, Itohara S, Iwata N, Saido TC (2014). Single App knock-in mouse models of Alzheimer's disease. Nature Neuroscience 2014;17:661–3. doi:10.1038/nn.3697.

Selected Publications

de Bruin NMWJ, Schmitz K, Schiffmann S, Tafferner N, Schmidt M, Jordan H, et al. Multiple rodent models and behavioral measures reveal unexpected responses to FTY720 and DMF in experimental autoimmune encephalomyelitis. Behav Brain Res 2016;300:160–74. doi:10.1016/j.bbr.2015.12.006.

de Bruin NMWJ, van Loevezijn A, Wicke KM, de Haan M, Venhorst J, Lange JHM, et al. The selective 5-HT6 receptor antagonist SLV has putative cognitive- and social interaction enhancing properties in rodent models of cognitive impairment. Neurobiol Learn Mem 2016;133:100–17. doi:10.1016/j.nlm.2016.06.020.

Barnes Maze for measurement of spatial learning and memory in mice.



AVAILABLE DISEASE MODELS

Elevated Zero Maze anxiety test in mice using Noldus EthoVision Videotracking.

MULTIPLE SCLEROSIS

Multiple sclerosis is a chronic demyelinating, inflammatory and degenerative neurological disease often occurring in early adulthood.

Experimental autoimmune encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) is a widely-used rodent model for MS, but a single model can hardly capture and adequately incorporate all features of MS. A number of different EAE models are available, resulting in different disease-progression patterns and clinical features. Dependent on the antigen and rodent strain used, the animals develop different disease processes.

- protracted- relapsing EAE (PR-EAE) in Dark Agouti rats
- chronic progressive EAE (CP-EAE) in C57BL/6 mice
- relapsing-remitting EAE (RR-EAE) in SJL mice
- monophasic EAE in Lewis rats.

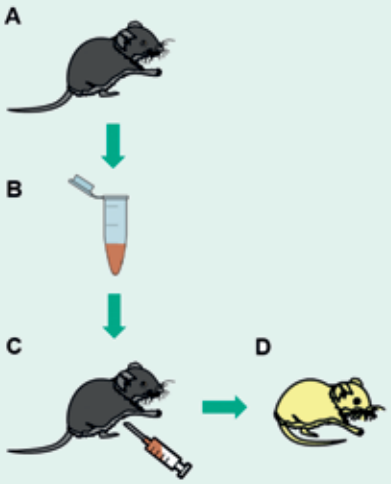
Cuprizone-induced demyelination of the corpus callosum in mice

All current drugs work by decreasing inflammation through modulation of the immune system and while they have been very efficient in reducing the rate of relapses, their impact on the chronic disease course is unknown. A current thought is that drugs that enhance remyelination may be more effective in reducing long-term disability.

Selected Publications

Schmitz K, Brunkhorst R, de Bruin N, Mayer CA, Häussler A, Ferreiros N, et al. Dysregulation of lysophosphatidic acids in multiple sclerosis and autoimmune encephalomyelitis. Acta Neuropathol Commun 2017;5:42. doi:10.1186/s40478-017-0446-4.

de Bruin NMWJ, Schmitz K, Schiffmann S, Tafferner N, Schmidt M, Jordan H, et al. Multiple rodent models and behavioral measures reveal unexpected responses to FTY720 and DMF in experimental autoimmune encephalomyelitis. Behav Brain Res 2016;300:160–74. doi:10.1016/j.bbr.2015.12.006.



SEPSIS AND VASCULAR INJURY

Systemic inflammation or sepsis is a reaction of the immune system to intensive and massive infections.

To study the pathophysiology of human sepsis, we use two animal models of polymicrobial septic peritonitis: **cecal ligation and puncture** and the **cecal slurry** model.
These are the most widely used animal models of the systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock, because they closely mimic the progression and characteristics of human sepsis.

Selected Publication

Knape T, Flesch D, Kuchler L, Sha LK, Giegerich AK, Labocha S, Ferreirós N, Schmid T, Wurglics M, Schubert-Zsilavecz M, Proschak E, Brüne B, Parnham MJ, von Knethen A. Identification and characterisation of a prototype for a new class of competitive PPARgamma antagonists. Eur J Pharmacol 2015;755:6–26 doi:10.1016/j.ejphar.2015.02.034.

IN DEVELOPMENT

- **Streptozotocin-induced type 1 diabetes**
  Streptozotocin is an antibiotic that produces pancreatic islet β-cell destruction and is widely used experimentally to produce a model of type 1 diabetes mellitus.
- **Animal models of tissue repair**
  In product development there is a need for translational research to obtain data that can lead to clinical trials and ultimately, improved wound care.
- **Adjuvant-, antigen- and collagen-induced arthritis**
  Arthritis can be induced in rodents in a variety of ways, and these models mimic human disease in some respects.
- **Telemetry system**
  In order to better understand pathophysiological changes in vital parameters during the course of diseases we are setting up a biometric animal telemetry system.

Experimental setup of the CS model. Harvesting of cecal slurry from a donor mouse (A) and preparation of stool suspension by adding sodium chloride 0.9% (B) followed by an i.p. injection of stool suspension in recipient mouse (C) for dose-dependent severity of sepsis (D).

Fraunhofer IME preclinical research laboratory located at Industriepark Höchst, Frankfurt.

WE ALSO OFFER

Optical imaging technology

The IVIS Spectrum (Caliper Life Sciences Inc.) can be used to facilitate non-invasive longitudinal monitoring of disease progression in living animals, applicable for example to inflammation, neurology, immunology and drug metabolism studies.
For drug discovery and translational purposes, it is important that disease processes can be tracked in vivo over a relatively long period of time. For example, in vivo bioluminescent imaging is a valuable and reliable method for in vivo measurement of dermal inflammation and for the assessment of changes during resolution of inflammation. While mirroring to some extent changes in classical readouts, dynamic, time-dependent changes are only detectable with in vivo bioluminescent imaging.

Pharmacokinetic studies

We offer the opportunity to do pharmacokinetic studies and determination of drug concentrations by LC-MS/MS: pharmacokinetic/pharmacodynamic studies of drugs, including chiral compounds, in rodent models.

Selected Publications

de Bruin N, Ferreirós N, Schmidt M, Hofmann M, Angioni C, Geisslinger G, et al. Mutual inversion of flurbiprofen enantiomers in various rat and mouse strains. Chirality 2018;35:28–50. doi:10.1002/chir.22826.

Beyer S, Xie L, Schmidt M, de Bruin N, Ashtikar M, Rüschenbaum S, et al. Optimizing novel implant formulations for the prolonged release of biopharmaceuticals using in vitro and in vivo imaging techniques. J Control Release 2016;235:352–64. doi:10.1016/j.jconrel.2016.06.013.

Villa Nova M, Janas C, Schmidt M, Ulshoefer T, Gräfe S, Schiffmann S, et al. Nanocarriers for photodynamic therapy—rational formulation design and medium-scale manufacture. Int J Pharm 2015;491:250–60. doi:10.1016/j.ijpharm.2015.06.024.

Sample storage at -80 °C.

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Editorial notes

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