

OVINE LARGE ANIMAL MODEL OF STROKE

Although rodent models are well established and reliable tools for the development of novel therapeutic strategies, all neuro-protective agents (successfully tested in rodent models) have so far failed in human clinical trials. This is most likely due to large inter-species differences and “up-scaling” difficulties between rat and human. Thus, the experts of the international STAIR committee strongly recommend the use of large animal models that more closely relate to the situation of human stroke patients. Available primate models are not only very expensive and ethically questionable, they mostly do not allow long term observation for efficacy and safety. These limitations are overcome by the unique ovine large animal model at Fraunhofer IZI.

Unique Feature

The ovine model is exclusively available at Fraunhofer IZI. The institute’s technical and logistical infrastructure and extensive knowledge in the fields of model system development, monitoring, pathology and imaging (together with partners) ensure a high-end methodological portfolio from one source.

Methods

Induction of cerebral ischemia is performed by a permanent occlusion of the middle cerebral artery in adult sheep. The size of lesion and functional impact can be controlled by surgical techniques. Additionally to surgical and microsurgical procedures also neuronavigation-assisted surgeries for specific issues (e. g. local application / transplantation, biopsy) are performed.

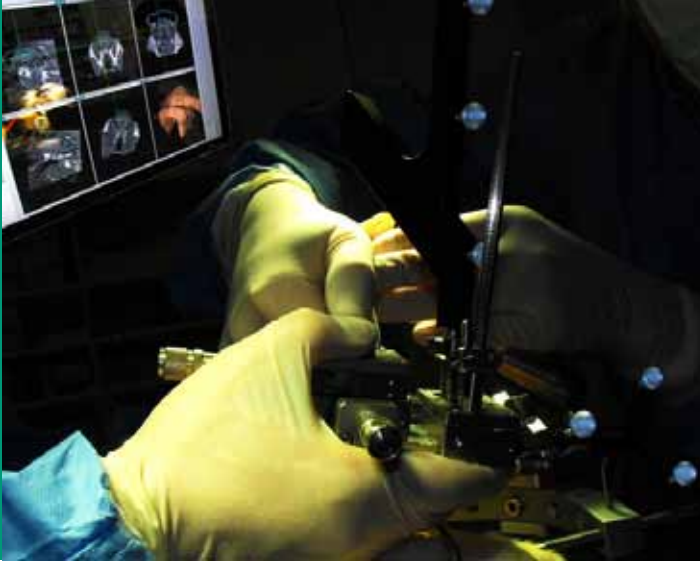
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Investigation Methods

In cooperation with our partners at the University of Leipzig, extensive state-of-the-art imaging procedures are used: additionally to 1.5 (Philips) or 3T (Siemens) MR imaging with extensive anatomical and functional sequences – functional metabolic processes are visualized using various hot-tracer in the PET. In both imaging facilities inhalative and perfusion anesthesia are established. Behavioural phenotyping to quantify sensorimotoric function and cognitive dysfunctions verify the clinical effect of an experimental therapy. Histology and immunohistology permit the verifying of therapeutic effect and the hypotheses of a possible underlying mechanism by morphological and morphometrical analysis. All investigations are conducted in a blinded examination.

Selected Applications

Preclinical evaluation of new treatment protocols under clinic-like and animal husbandry conditions can be carried out within acute- and long-term studies (safety and efficacy). The model is also suitable for further study of innovative combination therapies, and neurological intensive care procedures.

Due to the similar size and anatomy to human the model is extremely suitable for verifying and evaluation of novel diagnostic imaging tools (CT / MRI / PET). Additionally to extensive neuropathological investigations histologically characterizations of the therapeutic efficacy are performed in explorative and quantitative manner.

Reference Project

In a recent study a neuroprotective substance is tested under ambulatory clinic-like conditions. A permanent occlusion of the middle cerebral artery induced a focal cerebral ischemia in adult animals. Together with our partners a functional analysis of cerebral blood flow within 4.5 hours after acute stroke with and without therapy was performed using time elapsed PET-Scan with ^{15}O -H $_2\text{O}$. Subsequently magnetic resonance imaging (MRI) with routine sequences for stroke (t1, t2 *, T2 TSE, TOF, DWI, perfusion) completed the imaging procedure. Finally extensive pathohistological investigations were performed.