Fraunhofer
IZI

FRAUNHOFER INSTITUTE FOR CELL THERAPY AND IMMUNOLOGY IZI

CELL THERAPY SERVICES

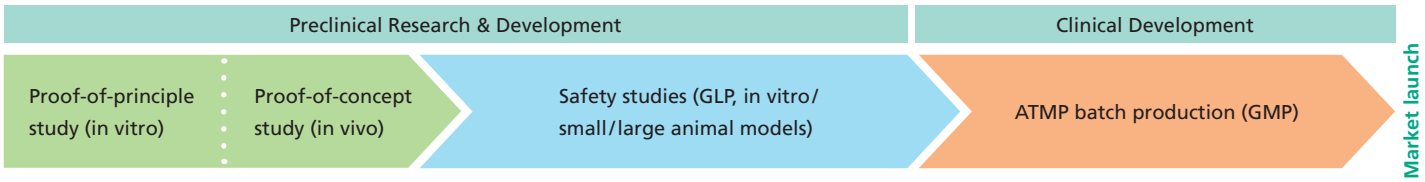
EFFICACY STUDIES | **SAFETY STUDIES** | **GMP MANUFACTURING**

FRAUNHOFER IZI

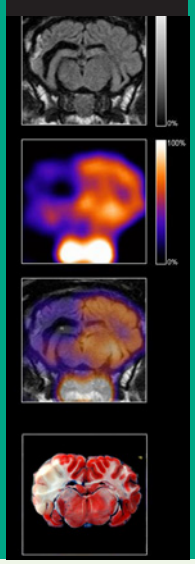
We at Fraunhofer are committed to provide our customers with services and products at the best possible rate. Under an economic-based approach, the Fraunhofer Institute for Cell Therapy and Immunology (IZI) finds solutions to specific problems at the interfaces between medicine, life sciences and engineering.

With core competencies in regenerative medicine, or more precisely in cell therapeutic methods of regenerating non-functioning tissue and organs, we lead the field in GMP-compliant manufacturing of cell therapy products including the assistance in obtaining manufacturing licenses and certifications.

The institute's expertise was already chosen by internationally renowned companies. **Be part of the Fraunhofer experience.**



CALIFORNIA'S STEM CELL AGENCY
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
NORTHWEST BIOTHERAPEUTICS
cytori
PRIMA BIOMED LTD
Australian Cancer Treatment Company
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN



EFFICACY STUDIES

The development of new therapeutic agents and strategies requires comprehensive preclinical studies from the generation of a hypothesis to the validation of safety and efficacy. For this purpose, we maintain a variety of model systems that enable the preclinical testing of novel concepts according to very strict quality criteria.

In order to demonstrate the benefit of new cellular therapeutics (Proof-of-Principle/ Proof-of-Concept), efficacy studies are performed with:

- clinical standards
- full implementation of STAIR criteria
- modular preclinical study design
- study monitoring and data management service
- concept reviewing and study evaluation service

Pathophysiology

To determine the underlying mechanisms of a disease and the corresponding mode of action of a therapeutic agent, we offer functional fate mapping of cells and clinical samples by:

- flow cytometric analysis of tissues and all body fluids
- identification of rare immune cells (e. g. antigen-specific T cells)
- functional analyses (e. g. apoptosis, chemokine expression & secretion)

Quality Assurance

Therapeutic agents might behave differently in experimental set-ups compared to real-life functioning. To ensure realistic results and outcomes of pre-clinical investigations we simulate true-to-life scenarios at the highest possible rate. Thereto:

- Comorbid animal models are used to mimic the impact of crossed disease activity (e. g. the influence of additional blood pressure).
- Extensive concomitant monitoring and analysis is performed. Due to the combination of PET and MRI imaging, morphological and functional imaging can be combined on a real-time scale.

Selected Models

- neuronal ischemia in vitro – identification of neuroprotective effects
- rodent stroke model – cell transplantation, behavioral phenotyping, MR imaging and histology
- ovine stroke model – long term investigation, use of adult autologous cell population, MRI
- a novel animal model of vascular dementia considering relevant comorbidities such as hypertension and enabling:
  - investigation of interaction between the CNS and the peripheral immune system
  - assessment of novel therapeutic strategies to counter vascular dementia with respect to underlying pathophysiological mechanisms

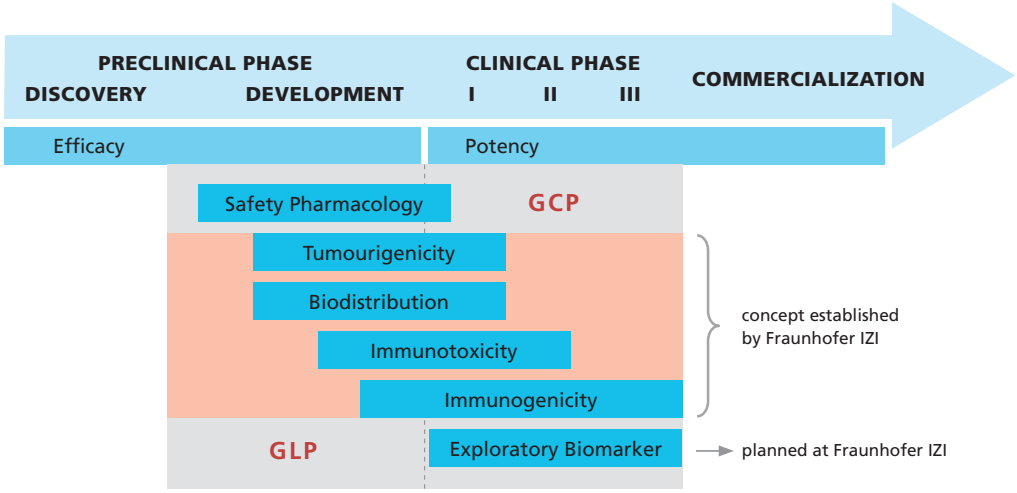
Indications

- neurodegenerative ischemia:
  - stroke
  - vascular dementia
- heart ischemia:
  - myocardial infarction
- cartilage and bone regeneration
- skin regeneration
- cancer vaccines

Reference Projects

- acute therapy of stroke using freshly isolated cells from adipose tissue (ADRCs)
  Cytori Therapeutics
- sustained investigation of recovery and immunological response after stroke using neural stem cells
  Stanford University, California Institute of Regenerative Medicine (CIRM), Translational Centre for Regenerative Medicine Leipzig
- improved homing of systematically ministered mesenchymal stem cells to the brain
  Johns Hopkins University

Contact:
Thomas Tradler, PhD, MBA
Head of Business Development/ Patent Management
thomas.tradler@izi.fraunhofer.de



SAFETY STUDIES

Our Good Laboratory Practice (GLP) unit focuses on planning and implementing of efficacy and safety studies in the context of the approval of new Advanced Therapy Medicinal Products (ATMP's). The concept and European requirements of non-clinical testing of ATMP's were established by Fraunhofer IZI. Accordingly, we are experts of non-clinical ATMP Testing. Safety testing of ATMP's covers all aspects of biodistribution, tumorigenicity, immunotoxicity and immunogenicity. Furthermore, we also develop, establish and validate individual test models for customers.

Certification

- area of expertise: "Immunotoxicological studies in vitro"
- official approval granted October 27, 2009 (test category 9)
- area of expertise: "Immunotoxicity/ immunogenicity studies in vivo" (including safety studies for ATMPs)
- official approval granted May 14, 2012 (test category 9)

Models

- sheep model for efficacy and safety testing
- mouse and NSG-mouse models for safety testing
- beagle dog for Immunogenicity testing

Tumourigenicity

- testing for tumourigenicity is performed in case of positive tumor findings after implantation and engraftment of ATMP's as well as in case of positive human cell retrieval in Biodistribution tests
- H/E staining
- IHC for tumour markers
- IHC for HLA-ABC
- pathohistological analysis

Biodistribution

- we test the desired as well as the undesired distribution of ATMP's
- PCR human DNA testing (can detect 5< cells in undesired sites)
- immunohistochemistry HLA-ABC testing

Immunotoxicology / Immunogenicity

- analysis of cytokine profiles of ATMP's
- analysis of the influence of ATMP's on differentiation and activation of human immune cells

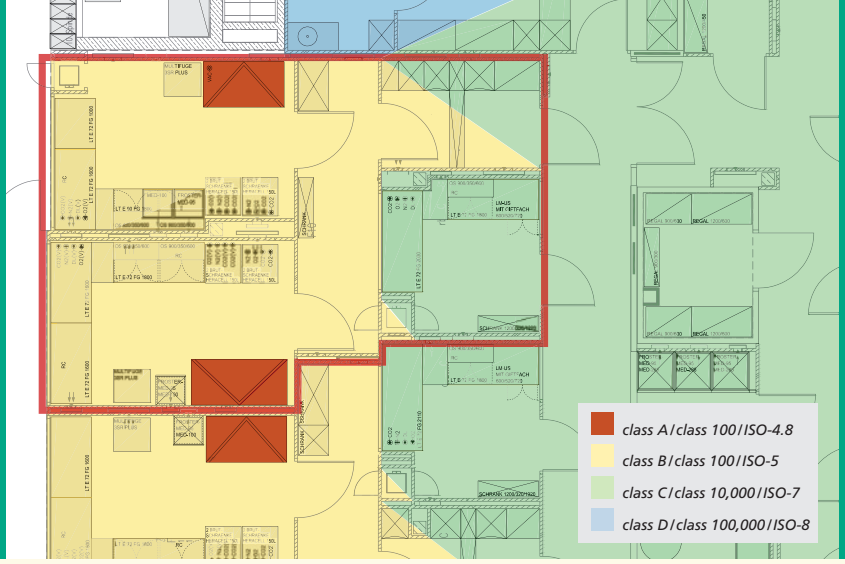
⇒ prediction of immunotoxicity/ immunogenicity

⇒ definition of endpoints for clinical study

Reference Projects

- immunogenicity of UVC-irridiated canine platelet concentrates
  Bombastus Werke AG
- safety study of human chondrocyte spheroids
  Co.don AG
- safety of a human/ovine mesenchymal stem-cell derived matrix-assistent cartilage transplant (MSC-MACT)
- efficacy and safety for cATMP's (combined ATMP/Medical Device), indication: decubitus, burn wounds
  Apraxon GmbH

Contact
Jörg Lehmann, PhD
Head of Cell Engineering/GLP
joerg.lehmann@izi.fraunhofer.de



GMP-COMPLIANT MANUFACTURING

Clinical trials using Advanced Therapy Medicinal Products (ATMP) require high quality investigational medicinal products manufactured according to European Good Manufacturing Practice (GMP, EC GMP guide), the "Guideline on human cell based medicinal products" of the European Medicines Agency (EMA), the German Drug Law (AMG) and the Ordinance for the manufacture of medicinal products and active pharmaceutical ingredients (AMWHV). Therefore, Fraunhofer IZI provides a highly qualified interdisciplinary team, a comprehensive quality assurance system, two pharmaceutical clean room facilities that adhere to the newest technical and regulatory standards and last, but not least, a well equipped quality control/tech-transfer laboratory.

Services

- manufacturing and quality control of autologous or allogeneic cell-based therapeutics for clinical trials and section 4b German Drug Law ("hospital exemption according regulation [EC] 1394/2007)
- support in set-up and validation of GMP-compliant manufacturing processes and quality control assays (process development)
- application for product-specific manufacturing authorizations according to section 13 of the German Drug Law
- application for tissue procurement permissions according to section 20b of the German Drug Law
- application for import permissions from countries outside of the European Union (e.g. for human derived materials used for manufacturing)
- support in regard to writing of Investigational Medicinal Product Dossier (IMPD)
- regulatory consultancy
- organization of the logistics of cellular starting materials and final products across Europe

Technical Data

- *facility no. 1:* 334 m² clean room area consisting of 4 clean room "suites" with altogether 8 clean room grade B manufacturing rooms (10 to 20 m²)
- *facility no. 2:* 410 m² clean room area consisting of 4 clean room "suites" with altogether 8 clean room grade B manufacturing rooms (15 m² each)
- each separate clean room "suite" possesses:
  - separate airlocks for material and staff from class C to B
  - a class C room for preparatory work (class 10,000/ISO-7)
  - 2 class B manufacturing rooms (class 100/ISO-5)
  - a laminar flow biological safety cabinet within each class B manufacturing room in order to establish a class A environment (class 100/ISO-4.8)
  - a separate ventilation of the class B manufacturing rooms and all other clean rooms

Additionally, a new clean room facility (222 m² clean room area with 5 clean room grade B manufacturing rooms) will be available in mid 2015.

Reference Projects

- autologous dendritic cell-based cancer vaccine DCVax®-L manufacturing for a pivotal phase III clinical trial for treatment of glioblastoma brain cancer
- autologous dendritic cell-based cancer vaccine Cvac™ manufacturing for two phase II clinical trials for treatment of ovarian cancer and pancreatic cancer
- process-transfer and application for a manufacturing authorization for autologous heart muscle derived CardAP Cells and subsequent manufacturing for a phase I/II clinical trial for treatment of chronic myocardial failure

Cognate BioServices, Inc
Northwest Biotherapeutics
Charité Universitätsmedizin Berlin
PRIMA BIOMED LTD Australian Cancer Treatment Company

Contact

Gerno Schmiedeknecht, PhD
Head of Cell Engineering Department
gerno.schmiedeknecht@izi.fraunhofer.de

Kati Kebbel, Dipl.-Ing.
Head of Cell Engineering/GMP
kati.kebbel@izi.fraunhofer.de