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FRAUNHOFER INSTITUTE FOR CELL THERAPY AND IMMUNOLOGY IZI

TOLERANCE AND TRANSPLANTATION MODELS

We are experts for hematopoietic stem cell transplantations in murine animal models for the following applications:

- Testing of pharmacologically active substances:
  - "Biologicals" (peptides, ligands, antibodies, growth factors, interleukins)
  - Cell therapeutics (e. g. MSCs [mesenchymal stem cells], regulatory T cells)
- Target:
  - Support of hematopoiesis after stem cell transplantation,
  - Minimising GvHD after stem cell transplantation
  - Induce of tolerance after organ- or stem cell transplantation
  - Development and testing of vaccination strategies
  - Development of therapeutic strategies for infectious, auto-immune, transplantation associated o inflammatory diseases

Testing of pharmacologically active substances in hematopoietic stem cell transplantations can be realized by the use of wild type mice (Balb/c, C57Bl/6) or transgenic mice (huCD4+, huHLA-DR3+, muCD4- with C57Bl/6 background). Conditioning of animals is carried out with chemotherapy or irradiation, depending on the disease model.

Test substances or cell therapeutics can be tested in in vivo and in vitro. Ex vivo pre-treatment of transplants is possible. In addition, we offer cultivation of supportive cells (Treg, MSC) for co-transplantations.

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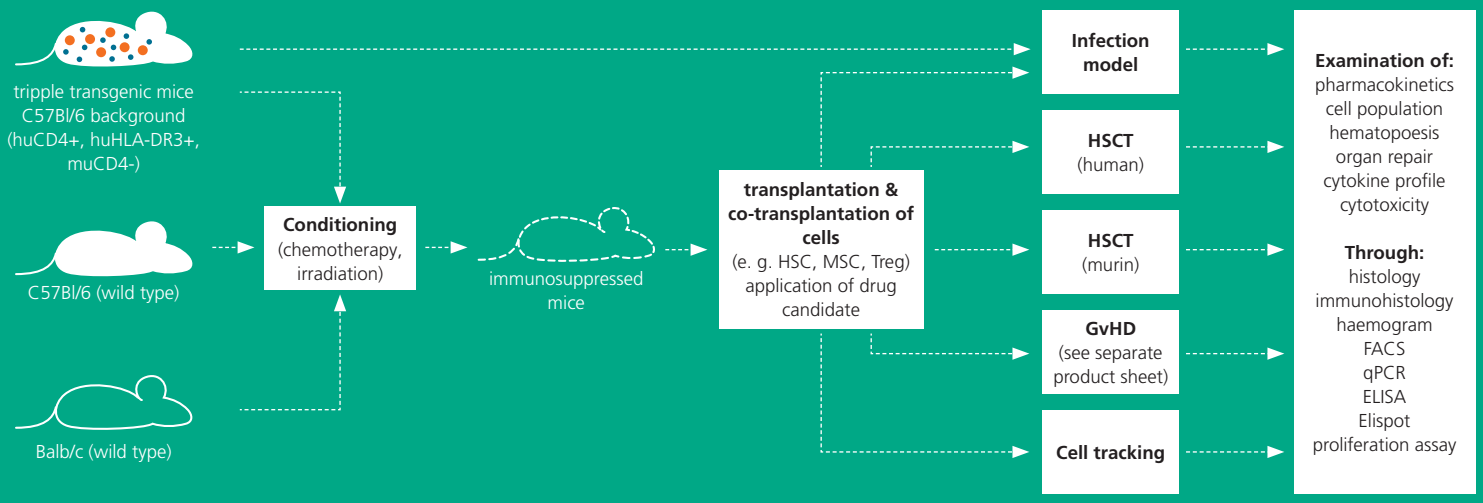

Equipment available at Fraunhofer IZI

- Radio isotope laboratory
- FACS (8 channels)
- Cell sorter
- AutoMACS for cell separations
- Fluorescence microscope (automated)
- Histology:
  - Automated infiltration system for dehydration automated staining system
  - Embedding center
  - Cryostat / microtome
- Access to animal facilities and surgery
- Access to irradiation facility
- LightCycler® 480 System for real time PCR
- Elispot
- Three part differential hematology analyzer
- Proliferation assays

Diagnostic support

Analysed parameters:

- Pharmacokinetics of compounds
- Composition of cell populations – organ repair
- Inflammatory markers
- Cytotoxicity
- Hematopoiesis
- Immune reaction markers

Animals used for transplantation models

Balb/c and C57Bl/6 wild type mice as well as transgenic mice (TTG) with C57Bl/6 background are used to establish different transplantation models.

Triple transgenic [TTG] mouse

The triple transgenic mouse expresses a human CD4 and HLA-DR (MHC-II) but no murine CD4. This unique mouse model is an ideal tool to study drugs interacting with these human proteins in vivo.

Triple transgenic [TTG] mouse treated with irradiation or chemotherapy

The unique genetic settings of this model allow fascinating insight into the fate of host and graft cells after transplantation of murine stem cell fractions, where the human CD4 and MHC-11 antigens are identifiers of the host's immune system. This allows identification and differentiation between the hematopoietic potential of host and graft immune system. Therefore this system is superior to other animal models for transplantation.

In vitro studies

Using standardized single or mixed lymphocyte cultures (mitogen- / cytokine-allogenic stimulated) we can characterize the effects of test substances (e. g. antibodies, cytokines, therapeutics, food ingredients etc.) on immune cells (B- and T-lymphocytes, NK-cells).

The lymphocyte cultures can be either of human or murine origin. Typical proliferation assays with these cells are measured in Fraunhofer IZI's own facilities by ^{3}H-thymidine incorporation. The Fraunhofer IZI has a radioisotope facility for such studies. Other analytic applications are, for example, FACS, ELISA, measurement of cytokine release (cytometric bead array, Elispot) and also the study of gene expression levels (real time PCR).

Tests with lymphocyte culture are a reliable, commonly used and economic alternative for preliminary studies of the immune system. Assay formats and the readouts can be adapted to needs of our partners.

Publications

- Fricke et al., PLoS One (2009) Jul 7;4(7):e6157.
- Fricke et al. Cell Mol Life Sci. (2010) Dec;67(23):4095-106.
- Fricke et al. Methods Mol Biol. (2011);690:315-32.
- Fricke et al. FlowCytometryPart A (2012); in press
- Fricke et al. Cytometry A. 2012 Apr 20. doi: 10.1002/cyto.a.22061. [Epub ahead of print]