Basic research is performed to understand. However, basic knowledge needs further development to finally become an instrument improving our lives. Concerning progress in clinical medicine, intense interactions between basic scientists and physicians are needed. Bench needs to meet bedside and bedside needs to communicate clinical observations back to the bench to guarantee a substantial flow of questions and knowledge.

To foster transition of the latest biomedical research results into preventive, diagnostic and therapeutic measures, GSF closely cooperates with both Munich Medical Schools (LMU and TUM), Max-Planck Institute of Psychiatry and Asklepios Lung Clinics. Cooperation is institutionalized by Clinical Cooperation Groups (CCG) which are selected on scientific excellence and flexibly organized. Their work aims at validation of promising results from basic research, further development of scientific concepts and performance of initial clinical trials, thereby guiding innovation into clinical practice. The working topics of CCGs reflect GSF’s engagement in environment associated and multifactorial diseases.

- Pathogenesis of Acute Myeloid Leukemia
- Molecular Oncology
- Osteosarcoma
- Molecular Neurogenetics
- Inflammatory Lung Diseases
- Environmental Dermatology and Allergology
- Immune Regulation in Childhood
- Hematopoietic Cell Transplants
- Tumor Therapy with Hyperthermia
- Antigen-Specific Immunotherapy
- Pediatric Tumor Immunology

Platform Technologies

- Immune Monitoring
- GMP-Facility
Pathogenesis of Acute Myeloid Leukemia

The group Pathogenesis of Acute Myeloid Leukemia aims to find out about the effects of known fusion proteins on the normal myeloid differentiation process and characterize mechanisms that lead to the deregulation of the normal proliferation and differentiation program of the earliest hematopoietic stem cells during malignant transformation.

Research focus is on

- Analysis of the effects of the CALM-AF10 fusion protein and other leukemogenic fusions on the development of leukemia using transgenic mouse models and bone marrow transplant models
- Analyzing the cellular function of leukemia-associated oncogenes
- Characterization of a model development for leukemic stem cells.

Further Information
http://www.gsf.de/neu/Forschung/Klinische_Kooperationsgruppen/paml/paml_index_en.php
Cancer cells produce specific proteins which differentiate them from healthy cells. Often patients do not exhibit an effective cellular immune response against these tumor antigens, because the tumor cells can suppress the activation of the immune system. Thus the development of new immunotherapies is of great clinical significance. One of the main aims of the Clinical Cooperation Group Molecular Oncology is the generation and characterization of tumor reactive immune cells for use in adoptive cell transfer.

Research focuses on the

■ Isolation and identification of tumor-associated antigens (TAAs) using AMIDA (Autoantibody Mediated IDentification of Antigens)

■ Validation and characterization of TAAs in vitro and in vivo

■ Molecular characterization of the TAA EpCAM (Epithelial Cell Adhesion Molecule)

■ Generation of TAA-specific cytotoxic T-lymphocytes (CTLs) using the EBV vector system

■ Adjuvant immunotherapy of EBV/CMV-associated diseases using antigen-specific CTLs

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**Further Information**

http://www.gsf.de/neu/Forschung/Klinische_Kooperationsgruppen/mo/mo_index_en.php

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**Osteosarcoma**

The Clinical Cooperation Group Osteosarcoma has two major scientific objectives

1. Identification of Tumor Suppressor Genes in Osteosarcoma: In a genome-wide allelic loss study of radiation-induced osteosarcoma in mice we have identified eleven candidate loci for tumor suppressor genes. For two of these mouse loci we have been able to identify two sections on chromosomes 6q14 and 15q21 which had not been described in humans before using a synteny comparison by mapping markers and genes in the mouse and human genomes. We could narrow down the gene locus on 6q14 to one candidate gene, TBX 18. Part of the project’s objective is the more accurate characterization of tbx18 with respect to its potential role in the development of osteosarcoma.

2. Identification of Susceptibility Genes in Osteosarcoma: Using a genetically defined animal model with radiation-induced osteosarcomas, the genes underlying a genetic predisposition can be mapped. Applying this strategy we have mapped 1 main locus and 5 secondary loci in the mouse.
Many neurological diseases (Parkinson’s, Alzheimer’s Disease) and psychiatric diseases (depression, schizophrenia) result from altered neurotransmitter (dopamine, serotonin, noradrenaline, and corticotropin) levels in the brain. To improve our understanding of the cause of these diseases at the Clinical Cooperation Group Molecular Neurogenetics, we investigate the development, the survival of the neurotransmitter-releasing neurons (dopaminergic, serotoninergic, noradrenergic and corticotropic neurons), and analyze the molecular signalling pathways that follow neurotransmitter-receptor interactions. Elucidation of these molecular interaction cascades and their modeling in animals will lead to a better understanding of the origin of these diseases and eventually to the development of novel therapeutic approaches.

Research focuses on
1. Neuronal differentiation and survival in the ventral midbrain and hindbrain
2. Differentiation of dopaminergic and serotonergic neurons in vitro and in vivo
3. Regulation of the stress hormone system
4. The impact of these neurotransmitters on animal behavior

**Molecular Neurogenetics**

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**Further Information**
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*Curious neighbours: The interaction between mice may provide clue to neurological disorders.*

Prof. Dr. Wolfgang Wurst
Inhaling a remedy makes treatment easier and more comfortable.

Dr. Marion Frankenberger

Inflammatoty Lung Diseases

Research in the Clinical Cooperation Group Inflammatory Lung Diseases focuses on inflammatory lung diseases, in particular environmentally-related chronic obstructive pulmonary disease (COPD). COPD includes both chronic obstructive bronchitis and emphysema. Diagnosis of COPD is difficult, and the disease can only be alleviated, not cured, by the forms of treatment currently available. The group has set itself the task of investigating the mechanisms of the pathogenesis of these inflammatory diseases and using the results to develop new methods for diagnosis and therapy. Aerosol techniques developed by the group and state-of-the-art molecular-biology and immunological methods are used. The group collaborates closely with the Asklepios Specialist Clinics in Munich-Gauting, Centre for Pneumology and Thorax Surgery.

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Further Information
http://www.gsf.de/neu/Forschung/Klinische_Kooperationsgruppen/am/am_index_en.php

Environmental Dermatology and Allergology

The scientific goal of the Clinical Cooperation Group Environmental Dermatology and Allergology is the investigation of biogenic and anthropogenic environmental factors influencing the development, the triggering, and the maintenance of allergic diseases and eczema. Research focuses on the

1. Relevance of pollen-associated lipid mediators in the initiation and maintenance of IgE-mediated allergic inflammation
2. Molecular biology of initial responses of anthropogenic and biogenic factors on epidermis and mucous membranes in atopic and healthy individuals
3. Pathomechanism of the adjuvant activity of polycyclic

Potent cause of allergies: Microscopic image of birch pollen.
Immune Regulation in Childhood

The aim of the Clinical Cooperation Group **Immune Regulation in Childhood** is to investigate how nutrition, the environment and allergies are linked together. The group focuses on

- **Prebiotic and probiotic substances**
  Results from epidemiological studies indicate that probiotic bacteria, for example Lactobacillus rhamnosus, can, under certain circumstances, prevent the emergence of allergic eczema. We test the effects of probiotic strains and selected bacterial signal molecules on dendritic cells and the T-cell immune response.

- **Fish oil**
  Oily fish is rich in n-3 polyunsaturated long-chain fatty acids (n-3-PUFA). There is a hypothesis that increased consumption of n-3-PUFA protects against allergies. We are investigating the effect of n-3-PUFA supplements during pregnancy on fetal immune parameters in a double-blind randomised European-wide study (NUHEAL, Nutraceuticals for a healthier life).

- **Farms**
  Several epidemiological studies have shown that children who grow up on working farms are better protected against allergies. The mechanisms of this allergy protection are unclear, however. Under the framework of an ongoing European Union study (PASTURE) we examine whether regulatory molecules of the immune system (ILT3, ILT4 and others) are expressed differently in farmer’s children than in other children living in rural areas.

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**Further Information**
http://www.gsf.de/neu/Forschung/Klinische_Kooperationsgruppen/uda/uda_index_en.php
Hematopoietic Cell Transplants

The aim of the Hematopoietic Cell Transplants Clinical Cooperation Group is the treatment of leukemias and other malignant hematopoietic diseases and solid tumors with allogenic stem cell transplants and the transfusion of immunocompetent cells from donors (adoptive immunotherapy). The aim of stem cell transplantation is to achieve immune tolerance between the patient and the transplant, which is the prerequisite for adoptive immunotherapy. The conditions for inducing tolerance to the transplant and the application of adoptive immunotherapy in chimaeras is investigated in dogs and then applied to humans.

Hyperthermia in Tumor Therapy

Hyperthermia combined with systemic chemotherapy or radio-chemotherapy is an innovative therapeutic concept in the specialist area of internal oncology. The scientific objectives of the group include clinical research on deep hyperthermia of solid tumors, biophysical investigation of non-invasive therapy monitoring, assessment of temperature-induced tissue changes, and especially biological research topics in the areas of immunology and cell biology.

Research of the Clinical Cooperation Group Hyperthermia in Tumor Therapy focuses on

- Clinical deep hyperthermia
- Combined chemotherapy studies
- Accompanying clinical-biology programme
- Research in the area of biophysical and medical technology: thermosensitive liposomes

Heating the tumor may help: The SIGMA_EYE_MR Applicator combines hyperthermia and nuclear magnetic resonance.
Antigen-Specific Immune Therapy

The Clinical Cooperation Group Antigen-Specific Immune Therapy is investigating new immunological methods for antigen-specific T-cell diagnosis and therapy in humans. A major goal is to establish novel strategies providing effective CD8+ T-cell responses especially in immune-compromised patients. This should be achieved by active immunization with particularly safe vector systems or by adoptive T-cell transfer.

The focus is on the:
1. Phenotypical analysis and isolation of antigen-reactive T-cells using MHC multimer reagents.
2. Development of culture-dependent and -independent methods for the generation of antigen-specific T-cell populations with defined specificity (suitable for GMP applications).
3. Production and immunological characterization of recombinant vector viruses based on the vaccinia virus strain MVA.
4. Evaluation of the applicability and immunogenicity of “passive” and “active” vaccination strategies in preclinical mouse models.
5. Immunity assessment for monitoring the progress and success of antigen-specific immune therapy in humans.
After binding of the Epstein-Barr virus (EBV) to CD21 expressed on the surface of B cells and subsequent endosomal processing of viral proteins, peptides of viral glycoproteins are presented on MHC class II molecules where they can be recognized by cytotoxic CD4(+) T-cells. These glycoprotein-specific T-cells eliminate newly EBV-infected cells before the cells become transformed by the virus and before viral replication takes place, thereby preventing the spreading of the virus and potentially reducing the risk of tumor outgrowth from EBV-infected B cells.
Immune Monitoring

The central goal of the Clinical Cooperation Group Immune Monitoring is to establish and apply a number of “state of the art” immune monitoring processes in ongoing clinical studies. The demanding nature of such tests necessitates their development, standardisation and validation in clinical applications under the supervision of qualified specialists. The fast technological developments result in an ongoing improvement of the immune monitoring processes and also contribute to our fundamental understanding of the cellular and molecular regulation of the human immune response in vivo.

Several immune monitoring methods were validated in two clinical studies on the Vaccination against HIV and Smallpox with MVA Vectors. Other methods are currently being applied in two ongoing clinical studies on Allogenic Tumor Cell Vaccines, in the process of which they will also be standardised and validated.

New technologies, e.g. for multi-parameter cell surface analysis, are being further developed in parallel. Methods for the analysis of viral proteins on the level of the individual cell in the absence of viral replication have already been established.

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Further Information
http://www.gsf.de/neu/Forschung/Klinische_Kooperationsgruppen/immunmonitoring/index.php

GMP Facility

One aim within the Clinical Cooperation Groups is the development of new therapeutic strategies on a cellular basis against viral or malignant diseases. To translate the results into clinically applicable protocols, the methods have to be adapted to GMP. The provisions of several laws have to be met: The production of sterile pharmaceuticals has to be performed under cleanroom conditions, the product must undergo sufficient quality control before approval and an adequate quality assurance system has to be implemented. The GSF is building a GMP facility with cleanroom and quality control to allow the transfer of research results in phase I/II studies. The first protocols to generate dendritic cells and specific cytotoxic T-cells are currently being established in a pre-GMP lab and will be transferred to the cleanroom after its construction. In parallel the methods for quality control are being established and validated.

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Good Manufacturing Practice Protocols require cleanroom conditions for the production of sterile pharmaceuticals.