




The Leibniz Institute for Age Research - Fritz Lipmann Institute is the first research institute in Germany entirely devoted to biomedical age research. Around 260 employees, mainly biologists, biochemists and physicians, conduct research on molecular mechanisms of ageing and age-related diseases. Organized in 20 interconnected research groups, they follow interdisciplinary approaches in two main areas.

Several research groups focussing on “Cellular and organismic ageing” examine, for instance, the stability and functional aspects of genes, genomes and telomeres. We analyse the role of candidate proteins in different processes of ageing. Mainly genomic approaches are used to analyse the epigenetic regulation of genes as well as to identify new genes involved in ageing. Research groups focussing on “Age-related diseases” study the mechanisms causing, for instance, protein folding diseases (e.g. Alzheimer’s and Huntington’s disease) and other neurodegenerative diseases. Furthermore, mechanisms causing cancer and age-related organ dysfunctions (such as kidney failure, osteoporosis, immunosenescence) are studied. FLI’s experimental methodology ranges from protein biochemistry to structural biology, from in vitro models (cell cultures) to primary patient material and animal models of disease.

RG Cornelis Calkhoven

Translational control of gene expression
The expression of important key proteins in eukaryotic cells is often regulated and controlled by mRNA translation. Mutations in genes of the translational control machinery lead to serious diseases, which illustrates the significance of this regulatory mechanisms. We plan to study the molecular mechanisms of translational control under normal physiological conditions in healthy cells as well as in diseased cells and organisms. For this purpose, we have established a translation control reporter system which is not only applicable for our basic research but also for pharmacological screening.




Projects

- Molecular mechanisms of uORF-mediated translational control
- C/EBP α -uORF and C/EBP β -uORF knockout mice
- Reporter systems for analysing translational control

RG Marcus Fändrich

Protein folding and conformation-related diseases
Conformation-related diseases are caused by incorrect three-dimensional folding of physiological peptide chains. A growing number of known diseases is assumed to be caused by peptide misfolding, with age-related diseases being amongst the best known examples, such as Alzheimer’s and Parkinson’s disease and the Creutzfeldt-Jacob syndrome. A subgroup of such diseases, the amyloidoses, is characterized by aggregation of peptide fibrils. Using cell-biological and biophysical techniques, we analyze mechanisms of fibrillar aggregation.

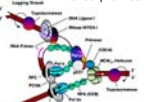


Projects

- Structure of amyloid fibrils
- Amyloid formation compared to protein folding
- Amyloid formation in vivo

RG Frank Große

Genomic instability, p53 & cellular ageing
Genomic instability is an important cause of cellular ageing and cancer. The tumor suppressor protein p53 helps to maintain the integrity of the genome. We are interested in studying how p53 influences basic mechanisms of the DNA and RNA metabolism, apart from its well-documented role as a transcription factor. p53 could directly influence the fidelity of DNA replication and DNA repair, e.g. as proofreader for DNA polymerase α . Additionally, p53 plays an important role in the regulation of DNA recombination, and in RNA processing and transport, presumably as partner of DNA helicase II.

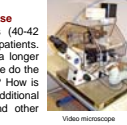


Projects

- DNA polymerases and replication initiation
- DNA helicases & DNA topoisomerases
- Protein analysis (2D gels, peptide sequencing, MS)

RG Christoph Käther

Membrane transport of genes involved in Alzheimer’s disease
Amyloid deposits consisting of accumulated short peptides (40-42 amino acids, A β) are typically found in the brain of Alzheimer’s patients. Two proteases, the beta- and gamma secretases, can cut a longer amyloid precursor protein (APP) into such short peptides. Where do the secretases meet the APP substrate to generate the peptides? How is this interaction regulated? Do secretases have other additional functions, for instance, during cellular transport of APP and other proteins of neuronal cells?




Projects

- Subcellular localisation of APP
- Molecular structure and transport of gamma secretases
- Confocal microscopy and videomicroscopy

RG Gabriele Schilling

Proteolysis and therapeutic approaches in Huntington’s disease
Huntington’s disease (HD) is caused by amplifications of glutamine (GLN) triplets in the Huntingtin gene (htt) generating more than 80 GLN sequences instead of the normal 18. The Huntingtin gene codes for a protein which is cleaved in the cell by a yet unknown protease. Cleaved huntingtin proteins containing abnormally extended GLN sequences are prone to aggregation, which is toxic for neuronal cells. We have generated animal models carrying different sized glutamine sequences in the Huntingtin gene. With increasing length of GLN repeats, neurodegenerative disorders develop in mice which are similar to Huntington’s disease in humans.

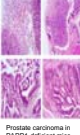


Projects

- Identification of the cleavage site in the Huntingtin protein
- Transgenic HD mouse models, without proteolytic recognition site
- Identification and possible inhibition of the responsible protease

RG Zhao-Qi Wang

Genomic stability
Cellular DNA damage responses include activation of DNA damage signalling, DNA repair, control of cell cycle and - if necessary - programmed cell death (apoptosis). Several already known proteins are involved in these processes whose functional deficiency in rare genetic diseases causes cancer, neurodegeneration and premature ageing. We analyse the functional deficiency of the respective genes in culture, in animal models and in tumor material of patients in order to identify the role of proteins encoded in these genes in tumorigenesis and in ageing.




Projects

- Role of specific DNA repair proteins in DNA repair pathways, tumorigenesis and tissue degeneration
- Biological function of molecules modulating poly-ADP ribosylation (PARP1, PAR2)
- Optimizing gene targeting and gene transfer methods

RG Stephan Diekmann

The nucleus of mammalian cells – the centromere/kinetochor-complex & PML-bodies
Important cellular functions are organised and controlled in the nucleus. Our research mainly focuses on the relation between structure and function of the centromere/ kinetochor complex. This complex is essential for correct chromosome segregation, by ensuring the attachment of chromosomes to the spindle apparatus during mitosis. Several essential multi-protein complexes can be found in the nucleus in PML-bodies whose function is still unknown. Induced by viral infections and in certain leukemic diseases, the structure of PML-bodies is often disrupted. We examine whether PML-bodies generally regulate transcription by RNA-Polymerase II and whether they play any role in the activation of specific genes.




Projects

- Cloning of kinetochor proteins / interaction studies in vitro and in vivo
- In vitro and in vivo analysis of the protein components of PML-bodies

RG Matthias Görlich

Structural relevance of molecular interactions for ageing and disease
Metabolic and regulatory processes pivotally depend on biomolecular recognition mechanisms. Disruption of recognition specificity can cause malfunctioning of biological processes and the development of diseases. We use NMR spectroscopy to analyse the structure of the recognition sequences of interacting molecules.




Projects

- Our research focuses increasingly on anti-oxidative proteins and their interaction with cellular substrates, or RNA-protein complexes and protein-protein complexes of cancer inducing viruses as well as on RNAs involved in the pathogenesis of neuromuscular diseases. Additionally, we constantly develop and improve solid-phase spectroscopy, which is considerably gaining importance

RG Peter Herrlich

DNA repair and genomic instability
We study the link between DNA repair, genomic instability and cellular ageing in mammalian cells, particularly in proteins and mechanisms involved in homologous recombination (HR).

Molecular mechanisms of cancerogenesis
Following an injury, the remaining cells proliferate until the wound is closed, until new cells contact other new cells. We examine the mechanisms of this contact-mediated inhibition. This mechanism blocks all stimulating signals, transferred from the cell surface to its interior, that control shape, mobility and proliferation of the cell. The contact-mediated inhibition is abrogated in cancer.




Projects

- Radiosensitivity of individual cancer patients and cells; HR genes
- Cell surface proteins: Inhibition of carcinogenesis in the colon
- Activation of the switch proteins Ras and Rac: by membrane-bound actin

RG Matthias Platzer

Genome analysis
In cooperation with clinical partners, we work on the detection and functional analysis of genetic and epigenetic variations in the human genome that determine the individual susceptibility to complex diseases, such as cancer, adiposity and inflammation. We also analyse and compare prokaryotic and eucaryotic genomes that are relevant for research on inflammation, on ageing and on evolution.




Projects (selected)

- Analysis of candidate genes for sarcoidosis
- Role of Defensin genes in prostate cancer
- Genomic variability of host factors in the macaque model of AIDS
- Identification of virulence genes in *Legionella* and *Borrelia*
- Comparative genome analysis (primates, fish, social amoebae)

RG Jürgen Sühnel

Structural bioinformatics and computational genome analysis
Knowledge of the three-dimensional structure of proteins and nucleic acids is in many cases a pivotal prerequisite for understanding biological functions. We are interested in identifying and analysing unusual structural motifs in order to increase our knowledge on structural principles of biological macromolecules. To do so, we apply quantum chemical techniques, molecular dynamics simulations as well as statistical analysis of large databases of experimental structures (structural bioinformatics) in our research. In collaboration with M. Platzer’s research group we develop new tools for analysing microbial genomes.




Projects

- Jena library of Biological Macromolecules (www.fli-leibniz.de/IMAGE.html)
- Structure of telomeric DNA
- Analysis of the conformation of amino acid backbones
- Comparative analyses of microbial genomes (pgv.fli-leibniz.de)

RG Falk Weih

NF κ B signal transduction pathways in development and immune system dysfunction
The RelN κ B transcription factor plays a pivotal role in the immune response, in inflammation, in the regulation of apoptosis and in cancer. Using genetically modified mouse models, we study RelN κ B signal pathways in normal development as well as in pathological alterations of the immune system. Our main goal is to understand the role of RelN κ B in age-related immunodeficiency and in diseases.




Projects

- Regulation of lymphoid organ development by RelN κ B
- Development and function of natural killer T-cells
- Regulating early T-cell development
- Role of RelN κ B in immunosenescence and age-related immunodeficiencies

RG Christoph Englert

Molecular basis of urogenital development
Many human disease genes play a pivotal role in the development of specific organs. For instance the Wilms tumour suppressor gene is essential for proper kidney and gonad development in humans, its mutant form however causes kidney cancer in children. To better understand how mutations in this and similar *Eya*, *Six* genes lead to malformations in humans, we want to decipher their molecular functions. Furthermore, we are interested in the regulation of the length of chromosome ends, the telomeres, which are gradually shortened during each mitosis and thus contribute to cellular ageing.




Projects

- Identification of WT1 target genes in gonad and kidney development
- Analysis of the Pax / Six / Eya networks in kidney development
- Telomerase regulation during development and tumorigenesis

RG Karl-Otto Greulich

Oncogenes, DNA repair and wound healing
There are surprisingly few genes overexpressed in all cancer tissues examined. Detecting groups of such genes will improve the general knowledge of cancer mechanisms. Some of those genes code for DNA repair proteins or for cell cycle proteins. We study their functions using laser-based methods and single cell assays (Comet assay).

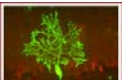


Projects

- Laser microprobes & microscopy
- Protein chips
- Comet FISH & DNA repair
- Single molecule techniques
- Tubulin / kinesin nanotechnology

RG Heike Heuer

Thyroid hormones and their functions in the brain
Thyroid hormones are essential for normal brain development as well as for a healthy metabolism of the organism. Thyroid hormone deficiency leads to dementia, neurological disorders and depression in adult patients. Untreated congenital thyroid deficiency causes irreversible brain damage. Surprisingly the underlying molecular causes are still ill understood. Our objective is to analyse thyroid hormone-regulated processes in the brain, in particular during development.




Projects

- Functions of thyroid hormones in brain development
- Physiological role of the thyroid hormone transporter MCT8

RG Aspasia Plioubidou

Virus-induced oncogenesis and the role of the cytoskeleton
Viral gene products of tumor viruses can cause cancer. In the course of viral carcinogenesis, alterations of the cytoskeleton play a crucial role in further tumor progression. We aim at understanding the underlying mechanisms of the modifications in order to suppress the tumorigenic potential of the viruses. Using appropriate virus-host-systems and Xenopus oocyte extracts, we analyse specific functions of the cytoskeleton, how it is used by the virus and the virus-induced modifications during tumor progression.




Projects

- In vivo systems of oncogenic virus transformation, modifications of the cytoskeleton
- Interaction of viral proteins with cytoskeleton components
- Changes of signalling pathways of virus induced cells
- Correlation: experimental oncogenesis - clinical tumours

RG Jan Peter Tuckermann

Tissue specific functions of steroid hormone receptors and their interaction partners in age-related diseases
Glucocorticoids (GC) belong to the steroid hormones. Upon binding to the nuclear glucocorticoid receptor, they have strong anti-inflammatory and immunosuppressive effects. Yet its widespread application in medical treatment is complicated by its severe side effects. To better understand the specific molecular and cellular mechanisms of steroid hormones, we examine the role of the GC receptor, of the estrogen receptor and of its interacting transcription factors in the immune system, in bone development and osteoporosis, as well as their influence on hematopoietic stem cells.




Projects

- Identification of steroid-responsive cells in cre-loxP mouse models
- Identification of GC receptor target genes in cell cultures and in vivo
- Interaction of the GC receptor with other proteins and signal pathways

RG Thomas Wilhelm

Theoretical systems biology
We are aiming at understanding complex cell functions by employing appropriate models on a cellular level. Based on this holistic approach we search for new static and dynamic structures in large-scale data sets. This involves analysing all levels of cellular regulation: the genomic level, proteomic level and transcriptomic level as well as comparing different levels with each other. We offer simple dynamic models for mechanistic explanations of the observed structures.



Projects

- Searching for new structures in large data sets
- Searching for statistically significant substructures
- Combination of data sets to discover e.g. new correlations
- Development of simple dynamic models to understand the observed structures