Institute of Pathology

Chair of General Pathology and Pathological Anatomy

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Research focus
- Diagnostic molecular pathology
- Experimental tumor pathology – gastrointestinal tumors
- Breast and gynecological tumors
- Tumors of the head and neck region
- Clinical and predictive molecular pathology of urogenital carcinomas
- Pathology of immune and inflammatory reactions

Structure of the Chair

Professorships: 6
Personnel: 80
- Doctors (of Medicine): 14
- Scientists: 4 (thereof funded externally: 4)
- Graduate students: 35

Clinical focus areas
Histopathology with specific expertise in
- Breast pathology
- Gynecological pathology
- Urogenital pathology
- Head and neck pathology
- Soft tissue pathology
- Molecular pathology

Research

The main research focus of the Institute of Pathology is the identification of molecular alterations in different malignant tumors. In different research groups, gastrointestinal tumors, breast cancer, gynecological tumors, tumors of the head and neck region, urological tumors, and sarcomas are investigated for both, diagnostic markers and new therapeutic targets. The aim is the integration of the identified molecular alterations into diagnostic molecular pathology. An additional focus is the characterization of immune and inflammatory cell infiltration in tumors and the importance of this immune response for tumor development and response prediction to immunotherapy.

Diagnostic molecular pathology
PI: Prof. Dr. F. Haller, Dr. E.A. Moskalev, Dr. L. Tögel, Prof. Dr. R. Stöhr
The aim of the group is the development and functional validation of novel genetic and epigenetic markers with diagnostic, prognostic, or predictive impact in solid tumors. The successful establishment of next-generation sequencing technology enabled the group to identify novel key molecular events in different salivary gland tumors and soft tissue neoplasms. Whole genome sequencing in collaboration with the German Cancer Research Center identified recurrent translocations in acinic cell carcinomas of the salivary glands. Another focus of the group is the massive parallel sequencing of multi-gene panels in lung cancer, soft tissue tumors, cancer of the urogenital tract, and head and neck cancer to correlate the presence of mutations among distinct genetic pathways with specific histomorphological subtypes, clinical behavior, and therapy response. The functional characterization of novel genetic or epigenetic aberrations in cell culture systems is another aim to develop the basis for future therapeutical options. Since 2016 the interdisciplinary molecular tumor board has been successfully installed which aims to detect genetic aberrations in patients with advanced cancer that can be used as therapeutic targets. Since 2018, patient samples presented in the molecular tumor board are analyzed in collaboration with the routine diagnostic molecular pathology group. Also since 2018, the Institute participates in the national network genomic medicine (nNGM) with a focus on providing state-of-the-art molecular diagnostic work-up of lung cancer samples.

Experimental tumor pathology – gastrointestinal tumors
PI: Prof. Dr. R. Schneider-Stock, Dr. K. Erlenbach-Wünsch, Dr. M. Eckstein, Dr. C. Geppert, Prof. Dr. A. Hartmann, Prof. Dr. A. Agaimy
The main focus of our group is the molecular and biochemical characterization of genetic and epigenetic alterations in tumors and preneoplasias of the gastrointestinal tract. Research projects on initiation and progression of colorectal tumors and their molecular subtypes are in focus. We aim at identifying new valid biomarkers for tumor transformation in colorectal carcinogenesis that could be of potential therapeutic interest. We are interested in tumor invasion front and thus in regulation of EMT and stemness to drive invasion and metastasis. For translation we are equipped with diverse tissue mircroarrays of CRC patients and immunostainings can be already digitally analyzed. A broad spectrum of 2D and 3D models, patient-derived 3D organoids, co-culture models of tumor cells and immune cells, and CRISPR-ko cell lines is established. The chorioallantoic membrane assay is used as an alternative *in vivo* test model. Novel experimental conditional ko mice were generated. Since many years we have been studying successfully the anti-cancer effects of novel plant-derived compounds for colorectal tumor cells especially in combination treatment with clinically used drugs.

Breast and gynecological tumors
PI: Prof. Dr. A. Hartmann, Dr. R. Erber
In collaboration with the Department of Gynecology and Obstetrics, we aim to analyze molecular-biological changes of breast cancer and gynecological tumors. Regarding breast cancer, identification of molecular prognostic and predictive biomarkers that can be used in the clinical-pathological differential diagnosis and therapeutical stratification of malignant breast cancer is the main focus. Therefore, we predominantly investigate tumor probes included in large multicentric therapy studies. Besides immunohistochemistry, molecular-pathological techniques like gene expression analyses and sequencing are deployed. Furthermore, we consider immun-oncological aspects. The second main focus of our working group includes investigation of molecular-biological features of malignant endometrial and ovarian cancer for potential therapy stratification.

Tumors of the head and neck region
PI: Prof. Dr. A. Agaimy, Prof. Dr. F. Haller
We investigate the molecular changes in tumors of the head and neck region in cooperation with the Departments of Otorhinolaryngology – Head and Neck Surgery and of Oral and Cranio-Maxillofacial Surgery. This research project has two objectives: One is to compile a molecularpathological and histopathological classification of salivary gland tumors with low and high risk of relapse and progression, the second is to identify early molecular markers to identify dysplastic changes as tumor precursors in the mucosa of the head and neck region.

Clinical and predictive molecular pathology of urogenital carcinomas
PI: Prof. Dr. A. Hartmann, Prof. Dr. Dr. R. Stöhr, PD Dr. Dr. C. Stöhr, PD Dr. S. Bertz, Dr. M. Eckstein, I. Polifka, V. Weyerer, Dr. E. Erlmeier
The group investigates the basic molecular principles of the development, progression, and sub-

typing of urothelial carcinoma of the urinary bladder, prostate cancer, squamous cell carcinoma of the penis, and renal cell carcinoma. There is a close cooperation with the Department of Urology, the Institute of Clinical and Molecular Virology and with numerous national and international cooperation partners. The objective is the identification of genomic and epigenetic changes in urothelial carcinomas of the urinary bladder and kidney tumors to identify new markers for early diagnosis and new therapeutic target molecules. In addition, gene expression analyses are used to establish a risk stratification of the tumors that should support the finding of the ideal treatment option for a patient in daily clinical routine. Another focus of the groups' work is the molecular investigation of patients with early-onset disease. These analyses should clarify if tumors in young patients have distinct molecular developmental pathways as compared with tumors from aged patients. Moreover, molecular investigation of tumors from patients with early-onset disease could allow the identification of predisposing factors and disease-initiating events helping to define individuals with high disease risk. In addition, the group is closely involved into the multi-institutional BRIDGE-Consortium, which main goal is the characterization and clinical implementation of new therapeutic targets for treatment of urothelial carcinoma of the bladder.

Selected main topics of the group are:

- Histologic and molecular characterization of rare subtypes of urothelial cancers
- Histologic and molecular characterization of urothelial cancers of the upper urinary tract in context of an EU-funded multi-institutional TRANSCAN project
- Identification of relevant therapeutic targets using retrospectively selected patient cohorts after adjuvant chemotherapy and multimodal therapies
- Identification of progression markers for bladder cancer using a whole-organ mapping approach on cystectomy specimens
- Analyses of urothelial tumors from patients with early-onset disease (≤ 45 years of age) to identify disease initiating and predisposing factors
- Histologic, immunohistochemical and molecular characterization of renal cell carcinomas with focus on non-clear cell subtypes, partly in cooperation with the German Network Renal Cell Carcinoma
- Improvement of the diagnostic discrimination between chromophobe renal cell carcinoma and renal oncocytoma
- Characterization of the immune cell infiltration and tumor cell metabolism of renal cell carcinoma (cooperative project with Prof. Dr. B. Seliger, Halle)
- Identification of molecular risk factors and prognostic relevant alterations of squamous cell carcinoma of the penis

Pathology of immune and inflammatory reactions

PI: Dr. M. Eckstein, Dr. C. Geppert, Prof. Dr. A. Hartmann,

This group focusses on the characterization of immunological interactions of different tumors (in particular: colon carcinoma, Barrett's carcinoma of the esophagus, muscle invasive urothelial carcinoma, squamous cell carcinoma of the head and neck) with their immunological microenvironment. There are numerous national and international cooperations.

In particular, the characterization of antitumorally active immune cell populations and their immunosuppressive antagonists are the focus. Based on differentially expressed immune cell populations and their activity status, which is largely controlled by immune-checkpoints, different immunophenotypes should be identified which potentially harbor both, prognostic and a predictive significance (for example with regard to a response to chemotherapies and/or immunotherapies). Another key topic is the establishment and harmonization of predictive diagnostic tools to predict immunotherapy response such as immuno-checkpoint protein expression (especially PD-L1) and other next generation immuno-oncological biomarkers (e.g. digital pathological assessment of cytotoxic immuncell-infiltrates). In connection with this, the group carries out biomarker programs in different retrospective and prospective clinical trials (e.g. CheckRad-study in the setting of HNSCC).

Teaching

The Institute of Pathology is involved in the compulsory and elective curricular teaching of Medicine and Dentistry and of the degree programs Molecular Medicine and Medical Process Management. Particularly noteworthy is the interdisciplinary teaching in the context of cross-cutting subjects Q5 and Q6 together with the Departments of Obstetrics and Gynecology, Medicine 1, Urology, Surgery, Nuclear Medicine, and the Institute of Radiology.

Bachelor's and Master's theses as well as MD and PhD theses are looked after.

Selected publications

Sikic D, Keck B, Wach S, Taubert H, Wullich B, Goebell PJ, Kahlmeyer A, Olbert P, Isfort P, Nimphius W, Hartmann A, Giedl J; Bridge Consortium. Immunohistochemical subtyping using CK20 and CK5 can identify urothelial carcinomas of the upper urinary tract with a poor prognosis. PLoS One. 2017 Jun 20;12(6):e0179602

Weyerer V et al. Immunohistochemical and molecular characterizations in urothelial carcinoma of bladder in patients less than 45 years. J Cancer. 2017 Feb 5;8(3):323-331

Bure I, Geer S, Knopf J, Roas M, Henze S, Ströbel P, Agaimy A, Wiemann S, Hoheisel JD, Hartmann A, Haller F, Moskalev EA. Long noncoding RNA HOTAIR is upregulated in an aggressive subgroup of gastrointestinal stromal tumors (GIST) and mediates the establishment of gene-specific DNA methylation patterns. Genes Chromosomes Cancer. 2018 Nov;57(11):584-597

Zinnall U, Weyerer V, Compérat E, Camparo P, Gaisa NT, Knuechel-Clarke R, Perren A, Lugli A, Toma M, Baretton G, Kristiansen G, Wirtz RM, Cheng L, Wullich B, Stoehr R, Hartmann A, Bertz S. Micropapillary urothelial carcinoma: evaluation of HER2 status and immunohistochemical characterization of the molecular subtype. Hum Pathol. 2018 Oct;80:55-64

Polifka I et al. High proliferation rate and TNM-stage but not histomorphological subtype are independent prognostic markers for overall survival in papillary renal cell carcinoma. Hum Pathol. 2018 Aug 16. pii: S0046-8177(18)30311-3

Maiuthed A, Ninsontia C, Erlenbach-Wuensch K, Ndreshkjana B, Muenzner JK, Caliskan A, Husayn AP, Chaotham C, Hartmann A, Vial Roehe A, Mahadevan V, Chanvorachote P, Schneider-Stock R. Cytoplasmic p21 Mediates 5-Fluorouracil Resistance by Inhibiting Pro-Apoptotic Chk2. Cancers (Basel). 2018 Oct 9;10(10). pii: E373

International cooperations

Prof. F. Real, Spanish National Cancer Research Centre, Madrid: Spain

Prof. J. Galon, French National Institute of Health and Medical Research, Paris: France

Prof. I. Nagtegaal, Radboud University Medical Centre Nijmegen, Nijmegen: The Netherlands

Dr. S. Castellví-Bel, IDIBAPS / CIBERehd / Hospital Clínic Centre Esther Koplowitz (CEK), Barcelona: Spain