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: 5
Personnel: 102
- Doctors (of Medicine): 18
- Scientists: 8 (thereof funded externally: 3)
- Graduate students: 20

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, PD Dr. E.A. Moskalev, Dr. L. Tögel, Dr. C. Schubart, 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 inter-disciplinary 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, >600 patient samples presented in the molecular tumor board are analyzed in collaboration with the routine diagnostic molecular pathology group.

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 initiation and progression of colorectal tumors. 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 immunoncological 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, e.g. investigation of fumarat hydratase deficient uterine leiomyomas and mismatch repair deficient/microsatellite instable endometrial cancer.

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 molecular-pathological and histopathological classify-cation 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, Dr. I. Polifka, Dr. V. Weyerer, Dr. E. Erlmeier, K. Bende, Dr. F Ferrazzi, M Angeloni
The group investigates the basic molecular principles of the development, progression, and subtyping 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 and disease initiating 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 (cooperative project with Prof. Dr. M Schwab, Stuttgart, partly in cooperation with the German Network Renal Cell Carcinoma).
- 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
- Digital pathology and development of diagnostic and predictive deep learning approaches

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. 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).

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 crosscutting 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

Eckstein M, Erben P, Kriegmair MC, Worst TS, Weiß CA, Wirtz RM, Wach S, Stoehr R, Sikic D, Geppert CI, Weyerer V, Bertz S, Breyer J, Otto W, Keck B, Burger M, Taubert H, Weichert W, Wullich B, Bolenz C, Hartmann A, Erlmeier F. Performance of the Food and Drug Administration/EMA-approved programmed cell death ligand-1 assays in urothelial carcinoma with emphasis on therapy stratification for first-line use of atezolizumab and pembrolizumab. Eur J Cancer. 2019 Jan;106:234-243

Haller F, Bieg M, Will R, Körner C, Weichenhan D, Bott A, Ishaque N, Lutsik P, Moskalev EA, Mueller SK, Bähr M, Woerner A, Kaiser B, Scherl C, Haderlein M, Kleinheinz K, Fietkau R, Iro H, Eils R, Hartmann A, Plass C, Wiemann S, Agaimy A. Enhancer hijacking activates oncogenic transcription factor NR4A3 in acinic cell carcinomas of the salivary glands. Nat Commun. 2019 Jan 21;10(1):368.

Fasching PA, Gass P, Häberle L, Volz B, Hein A, Hack CC, Lux MP, Jud SM, Hartmann A, Beckmann MW, Slamon DJ, Erber R. Prognostic effect of Ki-67 in common clinical subgroups of patients with HER2-negative, hormone receptor–positive early breast cancer. Breast Cancer Research and Treatment 2019 Jun;175(3):617-625. doi: 10.1007/s10549-019-05198-9.

Pfannstiel C, Strissel PL, Chiappinelli KB, Sikic D, Wach S, Wirtz R, Wullweber A, Taubert H, Breyer J, Otto W, Worst T, Burger M, Wullich B, Bolenz C, Fuhrich N, Geppert CI, Weyerer V, Stöhr R, Bertz S, Keck B, Erlmeier F, Erben P, Hartmann A, Strick R, Eckstein M The Tumor Immune Microenvironment Drives a Prognostic Relevance That Correlates with Bladder Cancer Subtypes Cancer Immunol Res. 2019; 7(6): 923-938.

Woerl AC, Eckstein M, Geiger J, Wagner DC, Daher T, Stenzel P, Fernandez A, Hartmann A, Wand M, Roth W, Foersch S Deep Learning Predicts Molecular Subtype of Muscle-invasive Bladder Cancer from Conventional Histopathological Slides. Eur Urol. 2020; 78(2): 256-264.

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