3.9 Department of Obstetrics and Gynaecology

Professor Dr. med. Johannes Dietl
(Head of the Department)

Josef-Schneider-Str. 4
97080 Würzburg
Tel.: 0931/201-25251
Fax: 0931/201-25406
E-mail: frauenklinik@mail.uni-wuerzburg.de
www.frauenklinik.uni-wuerzburg.de
Prof. Dr. med. Arnd Hönig
Tel.: 0931/201 25253

Mission and Structure

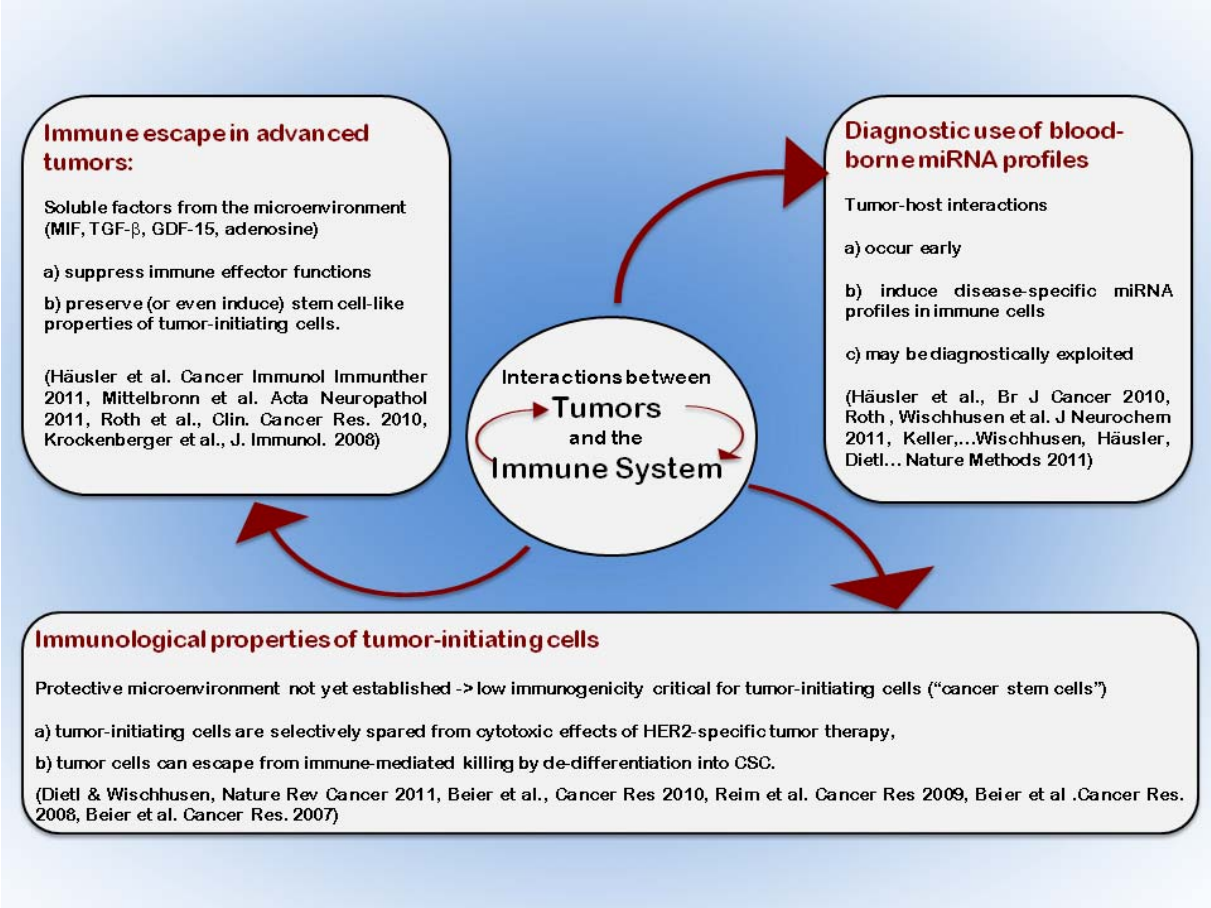
The Woman's Hospital (bed capacity of 84, 33 doctors, 102 nurses, 14,5 midwives, 6 assistant medical technicians) has two obstetrical and three gynecological wards, 5 labour and delivery rooms and a Level I Perinatal Centre with six neonatal intensive-care beds, three operating rooms of most modern standards, an operating room for caesarean sections, an intermediate-care unit, outpatient clinics for gynecology and obstetrics, gynaecological oncology, breast cancer, dysplasias of the cervix, child and adolescence gynecology, urogynecology, endocrinology and reproductive medicine, prenatal diagnostics. There are laboratories for endocrinology, cytology and reproductive medicine with andrology. Programs include a midwifery school. In the women's clinic are also department of the Clinic for Radiation Therapy (external radiation; brachytherapy) and the Institute of Radiology (mammography, vacuum biopsy) and the Department of Anaesthesiology (pain ambulance).

Per annum, approximately 2,500 operations, 1,600 deliveries, 5500 DRG cases, 25,000 outpatient therapies (of which 3500 were chemotherapies) have been performed. Centres of the clinic are: The interdisciplinary treatment of gynecological cancers, including breast (certified breast centre), the centre for hereditary breast and ovarian cancer, the treatment of urinary incontinence and pelvic floor dysfunction, care of risk pregnancies and infertility treatment including in vitro fertilisation.

Major Research Interests

Research Project „Tumour progression and immune escape“
(J. Wischhusen, S. Häusler, A. Chandran, M. Junker, A. Seida, V. Bruttel, I. Montalbàn del Barrio, K. Becker, I. Vögele, F. Grän, B. Fischer, E. Horn)

The research group investigates interactions between tumor cells and the immune system during different phases of tumor development (see Figure 1).



Particular emphasis is placed on

- immunological properties of tumor-initiating cells.

During early stages of tumor or metastasis formation, the tumor microenvironment has not yet been established. Thus, genetically altered cells are fully exposed to the immune system and its extrinsic tumor-suppressor functions. Accordingly, low immunogenicity could be a prerequisite for the survival of tumor-initiating cells (“cancer stem cells”). In this context we have found that

a) tumor-initiating cells are selectively spared from cytotoxic effects of HER2-specific tumor immune therapy,

b) tumor cells can escape from immune-mediated killing by de-differentiation into CSC.

- immune escape in advanced tumors, mediated by soluble factors from the microenvironment which

a) suppress effector functions of the innate and adaptive immune system and

b) preserve (or even induce) stem cell-like properties of tumor-initiating cells.

Certain members of the TGF-β family or the cytokine MIF apparently combine both these effects and might therefore be good and druggable therapeutic targets. Pharmacological intervention also appears possible in order to prevent the degradation of immune-stimulatory ATP (that is released from dying cells) to immunosuppressive adenosine.

- diagnostic potential of tumor-induced miRNA alterations in lymphocytes.

Using peripheral blood from afflicted patients, we could already show that ovarian cancer induces disease-specific miRNA profiles in immune cells These miRNA patterns most likely reflect tumor-host interactions which may occur long before a cancer is actually detected. As 14 different conditions were shown to be associated with distinct disease-specific patterns, we want to develop our original *proof-of-principle* study into a diagnostic test for the early detection of ovarian cancer.

The junior research group is funded (sponsored) by DFGF, IZKF, Graduate School of Life Sciences, Else-Kröner-Fresenius-Stiftung, Deutsche Krebshilfe, BMBF and others.

Die Nachwuchsforschergruppe wird von der DFG, IZKF, Graduate School of Life Sciences, Else-Kröner-Fresenius-Stiftung, Deutsche Krebshilfe, BMBF, und andere gefördert.

Investigation of impact and function of MIC-1 in human pregnancy decidua

(S. Segerer, U. Kämmerer, J. Dietl)

To date, the mechanisms which lead to the induction of tolerance against the semiallogenic fetus are not entirely resolved. However, several studies propose that a distinct composition of cytokines is essential for the establishment and maintenance of successful pregnancy. Macrophage inhibitory cytokine-1 (MIC-1), also named growth differentiation factor 15 (GDF15), is a member of the transforming growth factor-β (TGF-β) superfamily and is known to be expressed at high levels in human placenta. Women who subsequently miscarried or who had already miscarried exhibited significantly lower MIC-1 serum levels. As comparably low serum levels could even be detected three weeks before diagnosis of pregnancy failure, MIC-1 is thought to have a predictive role for pregnancy outcome.
So far, little is known about the decidual cell subsets producing MIC-1 and the effect of this cytokine on dendritic cells (DC), which are known to play a distinct role in the development of pro-fetal tolerance in pregnancy. We therefore investigate the impact and function of MIC-1 on DC (funded IZKF-project Z3/5 to S. Segerer).

Studies on function and prognostic value of LASP in the dissemination of breast and ovarian cancer

(A. Hönig, M. Kapp, U. Kämmerer)

LIM and SH3 domain protein (LASP) is an actin-binding protein that plays a role in cellular migration. In a study in collaboration with the institute of clinical biochemistry (E. Butt), we try to analyze the expression of LASP in breast cancer metastases in order to elucidate a possible significance of this protein in tumour progress. Cell culture studies investigate the function of LASP in the biology of tumour cells. The project is funded by the Deutsche Krebshilfe (No 107706).

New GnRH antagonists in the treatment of gynaecological malignancies and triple negative breast cancer

(J. Engel, A. Hönig)

GnRH seems to act as a local growth factor in a variety of tumours. GnRH antagonists show anti-tumour efficacy in vitro and in vivo, but it remains unclear whether atypical GnRH I- or GnRH II-receptors mediate these effects. „Peptidomimetic“-GnRH antagonists, whose advantage lies in the oral bioavailability, represent a new pharmacologic strategy. With the help of in vitro tumour models of endometrium, ovarian and tripel negative breast cancer, the

effect of these new non-peptidic GnRH antagonists in terms of their effectiveness and mechanism of action is investigated.

The AKT-pathway as a therapeutic target in gynecological and breast cancers
(J. Engel, A. Hönig)

The AKT-pathway is overactivate in various and seems to hold a key position in malignant transformation by regulating a multitude of actions, such as proliferation, resistance to apoptosis and chemotherapy and cell metabolism. Thus, proteins such as AKT in PI3K, which are in different positions in that pathway are highly promising targets in cancer therapy. In endometrial cancers for instance AKT is frequently overactivated by loss of its suppressor PTEN. In ovarian cancers overactivation of AKT is associated with resistance to chemotherapy. It could be demonstrated, that AKT-inhibitor perifosine displays substantial anti-tumor activity in models of human ovarian and endometrial cancers and shows additive effects with platinum derivatives. These results have been the basis for project which is fund by IZKF from January 2010, aiming at investigating the AKT-pathway in ovarian cancers with special regard to immunemodulatory effects (B-131-N).

Molecular analysis of gamete interaction and the influence of uropathogenic microbes on fertility
(C. Rennemeier, C. Albert)

Infertility in men and women is frequently associated with genital contaminations caused by various microorganisms. The molecular basis of this correlation remains still elusive, and little attention has been paid on potential direct influences of commensal or uropathogenic microbes on human gametes. Since many microorganisms are known to release distinct communication signalling molecules in substantial amounts, we raised the question whether such molecules can directly affect human gametes. Our studies revealed that signalling molecules employed by the opportunistic human pathogens Candida albicans and Pseudomonas aeruginosa elicit multiple detrimental effects on human spermatozoa. In a beginning project we investigated the interaction of uterine dendritic cells (DCs) with human spermatozoa and the influence of seminal plasma on this interaction.

Teaching
The curricular teaching in Obstetrics and Gynaecology consist of a main lecture (8th semester), seminars, clinical visits (9th semester) and a practical training (10th semester).

Additionally, a „Skills Laboratory“ focuses on practical aspects of the subject. With gynaecological models and case studies, students learn to deal with clinical situations and to handle diagnostic equipment. The training is complemented by a number of interdisciplinary subjects like ethics, preventive medicine, emergency medicine, infectious diseases, tumour biology and oncology. For doctors in private practice, we organize regular interdisciplinary conferences as part of the perinatal centre.

Selected Publications

1. **Dietl J**, and **Wischhusen J**. 2011. The forgotten fallopian tube. *Nature Rev Cancer* 11(3):227.

2. **Häusler SF, Montalbán Del Barrio I, Strohschein J, Chandran PA,** Engel JB, **Hönig A, Ossadnik M, Horn E, Fischer B, Krockenberger M, Heuer S, Seida AA, Junker M**, Kneitz H, Kloor D, Klotz KN, **Dietl J, and Wischhusen J**. 2011. Ectonucleotidases CD39 and CD73 on OvCA cells are potent adenosine-generating enzymes responsible for adenosine receptor 2A-dependent suppression of T cell function and NK cell cytotoxicity. *Cancer Immunol Immunother* 60(10):1405-1418.

3. Keller, A., P. Leidinger, A. Bauer, A. Elsharawy, J. Haas, C. Backes, A. Wendschlag, N. Giese, C. Tjaden, K. Ott, J. Werner, T. Hackert, K. Ruprecht, H. Huwer, J. Huebers, G. Jacobs, P. Rosenstiel, H. Dommisch, A. Schaefer, J. Müller-Quernheim, B. Wullich, B. Keck, N. Graf, J. Reichrath, B. Vogel, A. Nebel, S.U. Jäger, P. Staehler, I. Amarantos, V. Boisguerin, C. Staehler, M. Beier, M. Scheffler, M.W. Büchler, **J. Wischhusen**, **S.F. Haeusler, J. Dietl**, S. Hofmann, H.P. Lenhof, S. Schreiber, H.A. Katus, W. Rottbauer, B. Meder, J.D. Hoheisel, A. Franke, and E. Meese. Toward the blood-borne miRNome of human diseases. *Nat Methods* 8:841-843, 2011.

4. **Rennemeier** C., **Schwab** M., Lermann U., Albert C., **Kämmerer** U., **Frambach** T., Morschhäuser J, **Dietl** J., Staib P.
   Seminal plasma protects human spermatozoa and pathogenic yeasts from capture by dendritic cells. *Hum Reprod* 26: 987-999, 2011.

5. **S. E. Segerer**, L. Rieger , Y. Dombrowski, **J. Dietl and U. Kämmerer** (2011).
   MIC-1, a multifunctional modulator of dendritic cell phenotype and function is produced by decidual stromal cells and trophoblasts.
   Hum Reprod 2012 Jan;27(1):200-9. Epub 2011 Nov 6