The Team:
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Group Leaders/Postdocs: M. Cronauer, C. Maier
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Additional Members of Thesis Advisory Committees: K. Spindler (Ulm), B. Wullich (Erlangen)

Department of Urology

Research in Urology

Head: Mark Schrader

The Department of Urology has recently merged two long-established prostate cancer study groups – Molecular Endocrinology and the Familial Prostate Cancer Project – to form one newly created research laboratory. This affiliation in the vicinity of the Clinic will enrich traditional projects by incorporating novel scopes of translational research.

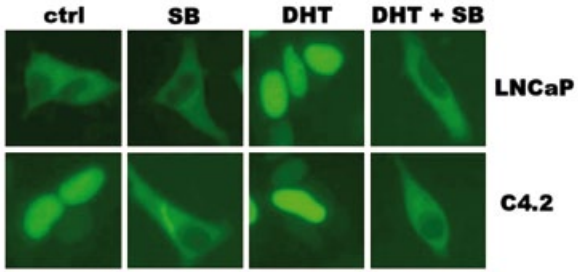
Molecular Endocrinology

Androgen receptor (AR) signaling plays a pivotal role in the development and growth of the prostate. The initial androgen-dependency of prostatic epithelial cells is the reason why most prostate cancer cells respond to androgen ablation therapy. However, during hormone ablation, the majority of prostate cancer cells progress to a state of the disease, known as Castration-Resistant Prostate Cancer (CPRC), where they can activate the AR under subphysiological levels of circulating androgens.

In order to generate genomic signals, the AR must be transported into the nucleus. The main focus of the Molecular Endocrinology Group consists of the analysis of factors involved in the nucleo-cytoplasmic shuttling of the AR. Identification and drug targeting of these factors may yield new strategies to diminish AR-signaling, especially in advanced CPRC.

Genetic Susceptibility of Prostate Cancer

Familial clustering of prostate cancer has long been recognized and the heritable component of this malignancy is expected to be stronger than for any other common cancer. Nevertheless, dissection of the responsible germline risk factors has proven difficult since it appears that a series of genes is involved where each one is hidden in a condition known as “complex inheritance”. In this context, two strategies seem promising for facilitating disease gene identification. The first entails collecting data from as many families as possible in order to strengthen the statistical power for capturing particular genes in approaches to genetic epidemiology. The second strategy aims at defining distinct subgroups of cancer, where the predisposing factors are hopefully more homogeneous.



Inhibition of GSK-3β by the maleimide SB216763 induces nuclear export of the AR in hormone-dependent LNCaP and castration-resistant C4.2 prostate cancer cells: (treatment: ctrl = untreated controls, SB = SB216763; DHT = dihydrotestosterone; DHT + SB = dihydrotestosterone + SB216763, detection by fluorescence microscopy of the AR).

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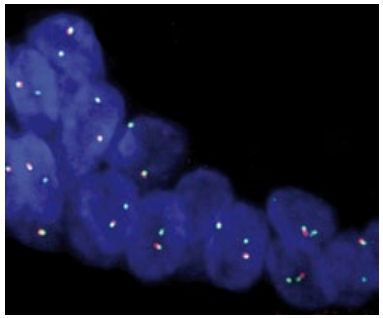
The "Familial Prostate Cancer Project" established by the Institute of Human Genetics and the Department of Urology at Ulm University has been engaged in both strategies: (1) For the generation of profound sample sizes, the unique German study cohort has been incorporated into large international prostate cancer consortia to conduct whole genome studies that include linkage, association and sequencing approaches. (2) Reducing heterogeneity by sample splitting is a special research focus pursued locally. For this purpose, the previously identified oncogene fusion *TMPRSS2-ERG* was introduced as a surrogate marker for a homogeneous pathomechanism to define a potentially distinct entity of prostate cancer. Within the PhD study of Manuel Lüdeke, candidate gene sequencing and association studies have revealed promising germline variants that appear to be substantially enriched in fusion positive prostate cancer cases. For the purpose of functional validation, an in vitro *TMPRSS2-ERG* induction assay has now been utilized to measure effects on fusion formation by knocking out the two candidate genes *POLI* (polymerase iota) and *ESCO1* (establishment of cohesion-1).



Genetic epidemiology on defined phenotype: *TMPRSS2-ERG* fusion positive prostate cancer. The dual color FISH break apart assay uses a green probe downstream of the *ERG* gene and a red probe mapping upstream towards the 3 Mb distant *TMPRSS2* gene at chromosome 21. Colocalization of the signals indicates an intact chromosome 21. Absence or separation of a red signal indicates deletion of the intergenic region, suggesting the fusion of *TMPRSS2* to *ERG*.

Selected Publications:

- *Christensen GB et al. (2010) Genome-wide linkage analysis of 1,233 prostate cancer pedigrees from the International Consortium for Prostate Cancer Genetics using novel sumLINK and sumLOD analyses, Prostate 70, 735-744.*
- *Schütz SV, Cronauer MV SV, Rinnab L (2010) Inhibition of glycogen synthase kinase-3β promotes nuclear export of the androgen receptor through a Crm1-dependent mechanism in prostate cancer cell lines, J Cell Biochem 109, 1192-1200.*
- *Luedeke M, Linnert CM, Hofer MD, Surowy HM, Rinckleb AE, Hoegel J, Kuefer R, Rubin MA, Vogel W, Maier C (2009) Predisposition for TMPRSS2-ERG fusion in prostate cancer by variants in DNA repair genes, Cancer Epidemiol Biomarkers Prev 18, 3030-3035.*
- *Hofer MD, Kuefer R, Maier C, Herkommer K, Perner S, Demichelis F, Paiss T, Vogel W, Rubin MA, Hoegel J (2009) Genome-wide linkage analysis of TMPRSS2-ERG fusion in familial prostate cancer, Cancer Res 69, 640-646.*
- *Eeles RA, and the PRACTICAL Consortium (2009) Identification of seven new prostate cancer susceptibility loci through a genome-wide association study, Nat Genet 41, 1116-1121.*
- *Rinnab L, Schütz SV, Jeannine Diesch J, Schmid E, Küfer R, Hautmann RE, Spindler KD, Cronauer MV (2008) Inhibiton of Glycogen-Synthase Kinase-3 (GSK) in Androgen Responsive Prostate Cancer Cell Lines - Are GSK-Inhibitors Therapeutically Useful? Neoplasia 10, 624-634.*