

## Meeting Report

### **DNA Repair 2006: 9th Biennial Meeting of the German Society for Research on DNA Repair**

(*DNA Repair 2006*, in press)

The 9<sup>th</sup> biennial meeting hosted by the Laboratory of Radiobiology and Experimental Radiation Oncology at the University of Hamburg stands in a now 18-year old tradition of German conferences on DNA repair inaugurated by Ulrich Hagen (Neuherberg-Munich) Friederike Eckart-Schupp and Marlis Frankenberg-Schwager. The first workshop in 1988 gathered about 40 researchers on DNA repair. Most of them were German radiobiologists. The organizers succeeded to attract scientists from other disciplines such as genetics, toxicology, oncology and immunology within only a few years. With the growing community, meetings started to circulate all over the country being hosted by various DNA repair groups. Since 1998 the number of participants was continuously growing reaching more than 170 scientists from 12 European and extra-European countries in 2006. The meeting comprised 6 plenary lecture sessions which were each embedded in extended poster viewing sessions, a well acknowledged feature of the German DNA repair conferences. These poster sessions were the basis of a most lively exchange between young and senior scientists. As an additional highlight, Errol C. Friedberg exquisitely entertained the campus audience in a public lecture about "The writing life of James D. Watson" referring to his newest book.

## **I Excision Repair**

In his keynote lecture **Errol C. Friedberg (University of Texas Southwestern Medical Center)** presented a comprehensive summary of the latest discoveries, which answer critical questions related to DNA damage tolerance by translesion DNA synthesis (TLS). In the first part of his talk, Friedberg outlined specific features of the different polymerases in the nucleotide insertion versus extension step during TLS and discussed discrepancies between *in vitro* and *in vivo* findings. Thus, in living cells Pol $\eta$  allows bypass past T-T(6-4) photoproducts and T-T CPDs, however, not past cisplatin adducts or 8-oxo-guanine. Interestingly, data from a knockout mouse model showed that Pol $\kappa$  supports *in vivo* TLS past benzo[a]pyrene and steroid, but not cisplatin adducts. pol $\kappa$ -/- mice resemble the human XP variant disease phenotype, are viable, fertile, but do not develop spontaneous cancer. When crossed with Big Blue mice they display a mutator phenotype in the germ line. A putative role of Pol $\kappa$  in mouse testes correlates with the expression of multiple transcripts of Pol $\kappa$ , but not of other polymerases, in this organ.

A series of extensive studies focusing on the REV1 protein revealed that this member of the Y family of eukaryotic DNA polymerases is engaged in multiple physical interactions and is involved in DNA damage-induced mutagenesis and growth regulation independently of its dCMP transferase activity. Thus, REV1 binds Pol $\kappa$ , Pol $\eta$  (via its C-terminus), and - like Pol $\kappa$  and Pol $\eta$  - also PCNA. Mutational analysis showed that the N-terminal BRCT domain of REV1 - which is unique among Y family of polymerases - is required for PCNA binding and for constitutive interactions of REV1 with replication factories. Similar to the situation with TLS polymerases such as Pol $\eta$ , monoubiquitylation of PCNA enhances REV1 interactions via an ubiquitin binding domain. These and further observations place PCNA in the center of the regulatory mechanisms promoting access of these low-fidelity polymerases to UV-inducible foci and enabling replicative bypass of UV-induced DNA damage.

**Bernd Kaina (University of Mainz)** explained his view on the O<sup>6</sup>-alkylguanine response pathway and MGMT dependent resistance mechanisms after treatment with chemotherapeutic

agents such as temozolomide (TMZ), DTIC, Zanosar, or Nimustin. O<sup>6</sup>-methylguanine is a highly recombinogenic lesion via DNA double strand break (DSB) formation as indicated by  $\gamma$ H2AX foci appearance and protection by DNA-PKcs. Interestingly, O<sup>6</sup>-methylguanine does not kill nonproliferating lymphocytes, whereas chlorinating agents such as fotemustine, which induce CG intrastrand links, do. Therefore, replication is absolutely essential for O<sup>6</sup>-methylguanine triggered apoptosis. Through the use of knockout cells homologous recombination (HR) was identified as the major repair pathways downstream of O<sup>6</sup>-methylguanine. Dissection of apoptosis pathways in human glioma cell lines showed that DSBs generated by TMZ treatment activate p53 and the downstream death receptor pathway. Altogether MGMT and p53 appear to be the most important predictive factors for TMZ therapy of gliomas. These findings have major implications for the newly established therapeutic approaches involving combined treatment with O<sup>6</sup>-alkylating agents and the sensitizing MGMT inhibitor O<sup>6</sup>-benzylguanine.

**Mathias Ziegler (University of Bergen)** reviewed the role of NAD<sup>+</sup> synthesis in DNA repair, signalling, and in energy transduction. Given that poly(ADP-ribosylation) by PARP-1 is the most active NAD-consuming pathway, many studies have more recently been dedicated to the analysis of NAD resynthesis pathways. Focusing on the key enzyme of NAD de novo and salvage synthesis, NMN adenylyl-transferase (NMNAT), Ziegler identified three human isoforms with localization of NMNAT-1 in the nucleus, NMNAT-2 in the Golgi, and NMNAT-3 in the mitochondria. PARP-1 automodification is stimulated by NAD and NMNAT-1. This nuclear isoform associates with the polymer but not with unmodified PARP-1. Both poly(ADP-ribose) association and PARP-1 stimulation are abolished by PKC mediated phosphorylation of NMAT-1. In the light of limited concentrations of free NAD in the nucleus and competing NAD-dependent processes such as protein deacetylation by Sirtuins, the interaction of NMAT-1 with the growing polymer could be central to the regulation of PARP-1 through direct substrate supply.

In the first proffered paper **Bernd Epe (University of Mainz)** described his results showing that PARP-1, CSB, XPA and XPG, but not CSA, XPC, or p53 are involved in a novel, OGG1-independent pathway for global repair of oxidative DNA base modifications. Experiments with  $\alpha$ -amanitin indicated that in this pathway PARP-1 is required to block transcription to signal for accelerated repair. In agreement with the existence of two repair pathways, the oxidative purine modifications, mutation frequencies, and carcinogen induced preneoplastic foci increased in double knockout mice approximately twofold. The next speaker **Agnieszka Gembka (University of Zürich)** reported on recent studies linking the Rad9-Rad1-Hus1 complex (9-1-1) to base excision repair (BER). Gembka provided biochemical evidence indicating that 9-1-1 can interact with and stimulate APE1 endonuclease and DNA polymerase  $\beta$  strand displacement activities in a single-enzyme assay and in the reconstituted long patch BER system, respectively. Therefore, 9-1-1 must be considered not only a DNA damage signalling component, but also a repair factor which connects both responses. **Markus Christmann (University of Mainz)** described a role of UV-induced c-Fos in the regulation of nucleotide excision repair (NER) and apoptosis. Thus, Christmann observed defects in SSB resealing and CPD removal in fos<sup>-/-</sup> mouse embryo fibroblasts after UV-C exposure. Concomitantly, expression of XPF and XPG transcripts was abrogated. Together with JNK inhibitor studies, his data indicate that JNK and c-fos protect against early apoptosis via DNA repair, whereas sustained JNK activation and upregulation of FasL upon repair failure are involved in apoptosis induction at later stages. **Simone Siehler (University of Ulm)** presented data from the systematic analysis of the role of MutL complexes in I-SceI triggered DSB repair. Application of pathway specific DNA substrates on a series of cell types differing in the MSH2, MLH1, PMS1, and PMS2 status revealed that

MutL counteracts HR independently of the primary mismatch repair complex MutS. Reducing the length of perfect homologies enhanced the anti-recombinogenic effect, suggesting a role of MutL in the fidelity control of HR.

## II Cell Cycle Regulation and Carcinogenesis

**Jiri Bartek (Institute of Cancer Biology, Copenhagen)** gave an overview of most recent insights into mechanisms and signalling cascades of DNA damage responses with emphasis on spatio-temporal control of protein localization and activation. Life cell imaging made clear that many posttranslational protein modifications and nuclear-cytoplasmic translocations after DNA damage occur within seconds rather than minutes or hours and thus likely escape from detection by conventional immunoprecipitation and western blotting procedures. Bartek showed that the ATR/ATRIP-driven signalling cascade requires TopBP1 and Claspin for proper phosphorylation of Chk1 targets but not for assembly at sites of DNA damage. This challenges the notion that recruitment to damaged sites is the critical event for ATR activation. One of the upstream events activating the ATR-dependent cascade towards DNA repair is the resection of double-stranded ends to 3' overhangs, for which the MRN complex is likely to be involved in mammalian cells. The signal mediator kinase Chk2 is required for ATM-dependent G1- and G2/M checkpoints in response to DNA damage. Interestingly, Chk2 null mice are radioresistant as specific pro-apoptotic p53-sites cannot be phosphorylated. Bartek also showed that the majority of human breast carcinomas express extremely low levels of Chk2, however, it appears to be constitutively phosphorylated at Thr68 and hence being activated in the tumor.

**Irene Dornreiter (Heinrich-Pette Institute, University of Hamburg)** introduced a novel splice variant of primate p53 (Delta-p53) which appears to be specifically involved in the intra-S-phase checkpoint by transactivating p21 and 14-3-3 but not pro-apoptotic p53 target genes. As a consequence, p21 activation inhibits the CyclinA/Cdk2 mediated DNA synthesis and delays replication after UV irradiation by about 4 hours. This pathway acts in addition to the short-term Chk1-Cdc25A-CyclinE/Cdk1-dependent inhibition of replication. The S-phase-specific delta-p53, therefore, complements the cell cycle function of full-length p53 which impacts upon G1- and G2- but not S-phase-checkpoints.

In the first preferred paper of this session **Raafat El-Awady (National Cancer Institute, University of Cairo)** presented evidence indicating that the XRCC3 protein is involved in homology-dependent recombination at DSBs but also in cell cycle delay after inhibition of topoisomerase I by topotecan. Thus, XRCC3 deficient cells not only displayed a repair defect but were also unable to activate the Chk1-dependent S-phase checkpoint. This could either hint at a cross-talk between HR and cell cycle regulation or reflect novel XRCC3 functions. **Rüdiger Greinert (Center of Dermatology, Buxtehude)** showed that not only UVB but also UVA radiation (95% of the solar light) is capable of inducing replication-independent DSBs as measured by  $\gamma$ -H2AX foci formation. These DSBs are likely to result from long-living reactive oxygen species. Remarkably slow kinetics of H2AX phosphorylation and dephosphorylation indicate different repair mechanisms for UVA/B- and IR-induced DSBs. Greinert's results suggest that sunlight-induced skin cancer may not only result from UVB but also from the UVA component. **Veronika Polakova (Inst. Experimental Medicine, Acad. Science, Prague)** reported on an association between changes in SSB repair rates and polymorphisms in the XRCC1 gene in 244 healthy donors. In particular, the homozygous R388Q polymorphism reduced impaired repair. Further reduction was observed upon combination with one or more other XRCC1 and APE1 SNPs which on their own did not

affect the repair capacity. So far, the underlying subtle changes in structure, function, or regulation have not been understood.

### III Repair proteins, Structure and Modification

**Stefan Jentsch (Max-Planck Institute, Martinsried)** comprehensively reported on posttranslational modification of repair proteins. Ubiquitylation and SUMOylation direct a single repair molecule to various pathways by exerting a variety of biochemical functions. Rad6/Rad18-dependent monoubiquitylation of PCNA at K63 promotes error-prone replication bypass, multiubiquitylation of the same residue by Rad5/Ubc13/Mms2 mediates error-free replication across the lesion. In contrast, Siz1 mediated SUMOylation of K164 downregulates a third alternative repair mode, namely Rad52-dependent recombination by attracting anti-recombinogenic Srs2 helicase. SUMOylation at K127 suppresses the PCNA-EcoI interaction required for sister chromatid cohesion. Jentsch further reported that poly-SUMOylation of Rad52, which interestingly depends upon functional MRX, occurs after irradiation and other types of DNA damage and promotes its repair function by sheltering from degradation.

**Thomas Carell (Ludwig-Maximilians University of Munich)** explained the geometry and binding energy of base pairing at prominent oxidative lesions during primer extension by high-resolution crystallography. While 8-OxodG strongly prefers dA pairing, FaPydG is perfectly fine with dC and dislikes dA partnership. FaPydG is, thus, not a principally mutagenic lesion. Carell further studied repair of UV damage at atomic resolution. He characterized the catalytic step of the bacterial photolyase (*A. nidulans*). The Glu 238 residue cleaves the pyrimidine dimer via proton transfer to the nucleotide radical anion.

Preferred papers: **Alfred Lammens (Ludwig-Maximilians University of Munich)** reported on bacterial transcription coupling of repair mediated by Mfd (mutation frequency decline). Mfd recruits UvrABC to sites where transcription meets damaged DNA. Crystallization revealed that Mfd resembles UvrB structurally with UvrA- and DNA-binding sites, but does not possess its catalytic activity. **Martin Digweed (Human Genetics, University of Berlin)** focussed on NBS in a clinical and molecular overview. Clinical symptoms reaching from mild to lethal clearly depend on allelic status and dosage of the mutated gene product. The few various known mutations differentially destabilize Nibrin but rarely abolish its function completely. One major function turns out to be enhancement of Chk2 phosphorylation and maintenance of G2/M block after DNA damage. Abrogation may contribute to the enhanced carcinogenesis associated with NBS. **Friederike Eckart-Schupp (GSF, Neuherberg)** addressed another feature of NBS, namely the apparent paradox of mutated cells being radiosensitive and repair proficient. In this context Eckart-Schupp found that NBS protects from death receptor (CD95) mediated apoptosis. Scavenging ROS decreased CD95 aggregation and rate of apoptosis in NBS<sup>-/-</sup> cells. From her data, inhibition of apoptosis by NBS is most likely due to stimulation of PI3-kinase thereby inhibiting ceramide-mediated CD95 clustering and caspase activation.

### IV Homologous Recombination

Given the frequent upregulation of AKT1 in sporadic breast cancer and AKT1 mediated phosphorylation of the HR surveillance factor BRCA1 in vitro, functional studies of the impact of AKT1 on HR are of particular interest. In this context, **Bernard Lopez**

**(Département de Radiobiologie et Radiopathologie, Fontenay-aux-Roses)** presented his intriguing results demonstrating that AKT1 represses HR indirectly via cytoplasmic sequestration of BRCA1 and RAD51. Mutating the residues 509 and 615 next to the BRCA1 NLS revealed that AKT1 mediated phosphorylation of BRCA1 is not required for this HR repression mechanism. Rather, from RNA interference experiments, the AKT1 effector and transcription factor FOXO1 turned out to be necessary; immunoprecipitation experiments showed physical interactions between FOXO1a and BRCA1. This has led to a model of AKT1 mediated phosphorylation of FOXO1, followed by complex formation with 14-3-3, and subsequent cytoplasmic BRCA1 retention together with RAD51. Importantly, first data from 25 breast carcinomas indicated a 70 % correlation between increased levels of activated AKT1 and cytoplasmic retention of BRCA1. The main conclusion from this work is that the PI3K/AKT signaling pathway, which involves well-known players such as PTEN, may play an unforeseen role in sporadic breast carcinogenesis via HR deregulation through BRCA1 and RAD51 inactivation.

**Lisa Wiesmüller (University of Ulm)** began by reviewing the large body of evidence originating from several groups and involving studies with mice models, cellular and *in vitro* systems, which made clear that p53 can regulate Rad51-dependent HR independently of transcriptional transactivation/repression, cell cycle arrest, or apoptosis induction, and that this function may contribute to tumor suppression. Describing elegant experiments using specifically designed SV40 and EGFP/I-SceI based test systems, Wiesmüller established that p53 counteracts homology-directed DSB repair between divergent sequences, i.e. low-fidelity processes. More recently, the same group discovered that in the absence of I-SceI triggered DSBs, spontaneous HR is enhanced by a pathway involving p53 and its interaction partner topoisomerase I, an observation that is interesting in the light of the proposed "gain-of-function" phenotype of mutant p53. In the last part of her talk, through mutational analysis and pharmacological inhibition, she explored the role of p53 phosphorylation in HR regulation. The results coordinate N- and C-terminal sites to inhibitory and stimulatory pathways, respectively, and shed light on possible switching mechanisms that orchestrate the multiple functions of p53 in recombinative DNA repair and apoptosis induction.

The first proffered paper by **Anke Schuerer (Leibniz Institute for Age Research, Jena)** presented data on the FancM homologues from yeast, which comprise the N-terminal helicase-like domain but lack the vertebrate-specific C-terminal XPF-like endonuclease domain. *S. pombe* spac9.05 and spac20H4.04 mutants showed similar phenotypes as *S. cerevisiae* mph1, particularly MMS and 4-NQO sensitivities. Epistasis analyses revealed that Spac9.05 is linked to HR and the BLM homologue rqh1+, but not to the branch of HR with epistasis to MPH1 which promotes error-free bypass of lesions at stalled replication forks. The relative distribution of NHEJ versus HR in DSB repair after treatment with ionising irradiation was the topic of **Andrea Beucher (University of Saarland, Homburg/Saar)**.  $\gamma$ -H2AX foci analysis in combination with cell cycle marker detection was applied to characterise repair in different cell cycle phases of NHEJ and HR mutant cells. NHEJ mutants showed a repair defect in G1 and G2 cells, HR mutants in G2 exclusively. In accord with previous findings ATM and Artemis were epistatic with DNA-PKcs in G1, but surprisingly with BRCA2 in G2 cells, suggesting an involvement of ATM and Artemis not only in NHEJ but also in HR. In his study, **Wael Y. Mansour (University of Hamburg)** addressed the interrelationship between NHEJ, HR, and SSA through the use of specific GFP-based reporter constructs stably integrated into the genome. Mansour made the interesting observation that - like NHEJ - the less prominent pathway of SSA can be used throughout the cell cycle. Analysis of xrs5 CHO cells revealed that Ku80 has little effect on NHEJ of DSBs after I-SceI-induced DSBs, however, antagonises HR and SSA. The last speaker in the session, **Horst-Werner**

**Stürzbecher (University of Lübeck)** focused on the key enzyme in HR, Rad51. To separate the multiple interactions of Rad51 with Rad54, Rad52, BRCA2, p53, and homologous recombination, Stürzbecher generated 20 Rad51 mutants and analysed subcellular localization. In MCF7 G variant cells, he found wild-type Rad51 in the cytoplasm, which was highly reminiscent of the observations made by the first speaker of the session. Expression of one specific mutant, which moved to the nucleus, correlated with p53-independent apoptosis induction, possibly indicating a dominant negative phenotype.

## V Modulation of Repair

**Andrea Hartwig (Technical University of Berlin)** reported on the impact of toxic metals and essential trace elements on p53 structure, function and redox control. Data was presented showing that metal compounds affect the integrity of the zinc-binding structure of p53. It was observed that water soluble as well as particulate cadmium compounds converted the correctly folded “wild type” conformation into a so-called “mutant” form with an unfolded zinc binding domain. Assessment of downstream events exerted diminished expression of the NER proteins XPC and p48, indicating the loss of p53 transcriptional activity. Similarly, UVC-induced wild-type p53 was unfolded in the presence of both cadmium compounds, inhibiting UVC-mediated repair gene expression. Remarkably, recent studies with extracts derived from cultured human cells demonstrate further an increased occurrence of “mutant” p53 after treatment with the reducible selenium compounds sodium selenite and phenylseleninic acid but not in case of fully reduced selenomethionine, which is likely due to an oxidation of cysteines involved in zinc complexation, indicating the redox sensitivity of the zinc binding structure. Further effects of selenite comprise changes in p53 phosphorylation patterns as detected by specific antibodies.

**H. Peter Rodemann (University of Tübingen)** reviewed the EGFR signaling as an important mechanism mediating resistance to exogenous stress factors, e.g. radiation. Radiation-induced activation of membrane bound EGFR results in two separate intracellular events: i) induction of signaling pathways, like PI3K-AKT and Ras-Raf-MAPK and ii) nuclear translocation of EGFR. PI3K-AKT- and Ras-Raf-MAPK pathways are known to regulate cell survival and proliferation respectively. Based on detailed analyses into EGFR dependent signaling pathways and nuclear translocation processes it was shown, that both mechanisms – most likely independent of each other - are involved in the regulation of DNA-double strand break repair in irradiated EGFR overexpressing and human tumor cell lines. Most interestingly, however, predominantly cell lines presenting a K-RAS mutation could be significantly radiosensitized by pre-irradiation treatment with selective inhibitors of EGFR-tyrosine kinase, PI3-kinase and AKT-kinase or the monoclonal antibody C225 directed against membrane bound EGFR. Both interventional strategies result in impaired repair of radiation-induced DNA-DSB through inhibition of DNA-PKcs. These data indicate a direct involvement EGFR-PI3K-AKT signaling as well as nuclear EGFR accumulation in the activation of DNA-PKcs and DNA-DSB repair in irradiated K-RAS mutated cells most likely through direct protein interactions of stimulated AKT and nuclear EGFR with DNA-PKcs.

In the proffered paper session **Claudia Keil (Free University of Berlin)** demonstrated that PARG, independently of its catalytic activity, can directly inhibit PARP-1 automodification reaction. PARG was also found to interact with the DNA repair factor XRCC1 which is recruited by DNA damage activated PARP-1. **Anja Rockstroh (University of Jena)** reported that a pronounced htopoI cleavage complex formation is a general feature of apoptosis, independent of the apoptotic stimulus and that cells show a diminished htopoI response after

treatment with DNA damaging agents, if the corresponding DNA repair pathway is impaired, by for example a p53, Mlh1 or Ogg1 deficiency. **Mahmoud Toulany (University of Tübingen)** found for A549 and FaDu cells that ionising radiation did not lead to an up-regulated expression of XRCC1 as observed by others. The expression of XRCC1 however was reduced, when EGFR or MEK were blocked or when cells are deficient in DNA PK. **Tanja Schwerdtle (Technical University of Berlin)** presented data showing that the effect of arsenic and cadmium on the assembly of NER is due to the impaired zinc-binding domain of XPA.

## VI Nonhomologous End-joining and Cancer Therapy

**George Iliakis (University of Duisburg-Essen)** reported on a Ku-independent back-up pathway of non-homologous end-joining. Biochemical and genetic studies support the view that the majority of DNA double strand breaks (DSB) induced in the genome of higher eukaryotes by ionizing radiation (IR) are removed by two pathways of nonhomologous end joining (NHEJ) termed D-NHEJ and B-NHEJ. While D-NHEJ depends on the activities of the DNA-dependent protein kinase (DNA-PK) and DNA ligase IV/XRCC4, components of B-NHEJ have not been identified. Using extract fractionation it was shown that the majority of DNA end joining activity in extracts of HeLa cells derives from DNA ligase III. DNA ligase III fractionates through two columns with the maximum in DNA end joining activity and its depletion from the extract causes loss of activity that can be recovered by the addition of purified enzyme. Furthermore knock down of DNA ligase III by RNAi in *LIG4<sup>-/-</sup>* cells reduces drastically intracellular end joining of a GFP reporter plasmid. These observations identify DNA ligase III as a candidate component for B-NHEJ and point to the PARP-1/XRCC1/DNA ligase III repair module as a backup component of NHEJ. Experiments with various mutants of D-NHEJ, as well as PARP-1 inhibitors and the expression of dominant negative protein fragments confirm a role for this module in DNA DSB repair.

**Bernard Salles (University of Toulouse)** reviewed the recruitment of DNA repair proteins to double-strand breaks. By monitoring protein assembly from human nuclear cell extracts on DNA ends in vitro, the order of proteins binding was determined and the role of DNA-PK dependent phosphorylation on the recruitment. Unexpectedly, under biochemical condition that handicap the DNA-PK-dependent NHEJ, PARP-1/XRCC1/ligase III/hPNK was found to be involved in end-joining. On the other hand, the choreography of the repair complex was followed by determining the mobilization of NHEJ proteins from a soluble nucleoplasmic compartment to a less extractable nuclear fraction. The recruited proteins co-immunoprecipitated, indicating that they had assembled into complexes. It was observed that Ku recruitment was not dependent on the co-recruitment of the other NHEJ proteins and that DNA-PKcs was physically required for the mobilization of the XRCC4-ligase IV complex and Artemis. In addition phosphorylation by DNA-PK was unnecessary for XRCC4 recruitment although it was necessary for Artemis recruitment. On the other hand, Ku70 was phosphorylated in vivo by DNA-PKcs in the presence of DSB. At last, DNA-PK localization is not restricted to the nucleus and the complex and/or each partner are involved in other processes such as cell invasion and hypoxia tolerance.

In her proffered paper session **Kirsten Dahm (University of Sussex)** reported that BRCA1 and MDC1 are involved in the Artemis dependent subpathway of NHEJ and facilitate the IR induced hyperphosphorylation of Artemis. **Johannes H. Schulte (University of Duisburg-Essen)** found that in SY5Y neuroblastoma cells the expression of the TrkA or TrkB receptor

tyrosine kinase alters the capacity of nonhomologous DNA end joining. **Kerstin Borgmann (University of Hamburg)** studied the impact of SNP's on the risk of late effects after radiotherapy. SNP's in TGF $\beta$  and XRCC1 were found to result in an enhanced risk, while SNP's in ATM and SOD2 were associated with a reduced risk. **Sabine Karl (University of Ulm)** demonstrated that the specific inhibition of NF- $\kappa$ B reduced TRAIL-induced apoptosis of glioblastoma cells while it had no effect on apoptosis induced by cytotoxic drugs.

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