**153** INVITED

**Communicating about illness: family nursing in oncology care**

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Cancer nursing includes not just assisting the patients but also their families to adjust and adapt to a life with cancer. The impact of both the illness and its treatment require individuals and their families to make changes to their lifestyles [1]. Cancer nursing practice is based on the notion of holism which includes the acceptance of cancer as a 'family illness' [2]. Also palliative care, which is often part of oncology care, emphasize the family in its definition 'the goal of palliative care is achievement of the best possible quality of life for patients and their families' [3]. The home is increasingly seen as the ideal place to dwell, even when ill, and a trend is that responsibility for the care of the ill will shift from the public sector to the family [4]. It has been suggested that family nursing enables nurses to work with the family in a supportive and more purposeful way, and family care has even been suggested to replace that of individual care [5]. Traditionally, the focus of nursing has been on the practice of nursing with individual patients [6]. If nurses involve families more in care, they need to modify their usual pattern of clinical practice [7]. Family nursing has evolved as a way of thinking about and working with families. Family nursing comprises a philosophy and a way of interacting with individuals and families that affect how nurses collect information, intervene with and advocate for patients/families [6]. For the family to have a chance to talk about issues such as hope and suffering in palliative care, both within the family and with the nurses, has been shown to be a healing experience. It gave them the opportunity to unburden themselves, as well as a way of learning and finding new strategies for managing daily life [8]. Family nursing could be an intervention where patients with cancer and their families are supported in identifying their own strengths and resources and also needs that require external resources [9]. This presentation will reflect on family nursing in oncology care.

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## *Scientific Symposium* (Tue, 22 Sep, 14:45−16:45)
## The DNA damage response in cancer: role in tumourigenesis and targeted therapy

**155** INVITED

**SMARCA5 links chromatin remodeling with the DNA damage response**

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Our genome is faced with DNA damage induced by endogenous (e.g. free radicals) and exogenous sources (e.g. ionizing radiation). Failure to repair DNA damage can lead to genomic instability, cancer development or cell death. Efficient repair of DNA lesions, however, is complicated by the fact that genomic DNA is packaged, through histone and non-histone proteins, into a condensed structure called chromatin. The DNA repair machinery has to circumvent this natural barrier to gain access to damaged DNA and repair DNA lesions. Our recent work in budding yeast demonstrated that ATP-dependent chromatin remodeling is a mechanism that cells use to alter chromatin structure at DNA lesions and promote DNA repair. However, the role of chromatin remodeling during DNA repair in mammalian cells remained largely unexplored. We performed a genome-wide RNA interference screen in the nematode *C.elegans* and identified *isw-1,* a SWI/SNF2-related chromatin remodeling factor, as a potential novel regulator of the DNA damage response. The human homologue of ISW-1*,* SMARCA5, rapidly accumulates at sites of laser-induced DNA damage, an event that is followed by the accumulation of different DNA damage response factors. Knockdown of SMARCA5 impaired the accumulation of these factors at sites of DNA damage, caused defects in checkpoint activation and DNA repair, and rendered cells hypersensitive to ionizing radiation. These results suggest that SMARCA5 chromatin remodeling protects genome integrity by modulating chromatin structure at DNA lesions to orchestrate the recruitment of DNA damage response factors. Moreover, SMARCA5 dysfunction may contribute to cancer development as defects in the DNA damage response have been linked to a number of genomic instability syndromes that are characterized by cancer predisposition.

**156** INVITED

**Exploiting cancer defects in targeted therapy**

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DNA repair and damage response pathways are activated as a tumour barrier at early stages during cancer development. Here, we show that oncogene-induced senescence is associated with signs of DNA replication stress, including prematurely terminated DNA replication forks and DNA double strand breaks. A new concept for cancer therapy is to amplify endogenous tumour-specific DNA lesions, to specifically kill tumour cells. Based on this concept we report that BRCA2 defective breast cancers can be specifically targeted using inhibitors of Poly(ADP-ribose) polymerase (PARP). We show that BRCA2 deficient cells, as a result of their recombination deficiency, are acutely sensitive to PARP inhibitors, presumably because resultant collapsed forks are no longer repaired. We exploit this requirement to specifically kill BRCA2 deficient tumours by PARP inhibition alone.
If replication forks stall, a multifaceted response including several DNA repair and cell cycle checkpoint pathways is activated to ensure faithful DNA replication. Here, we show that PARP1 binds to and is activated by stalled replication forks. PARP1 collaborates with Mre11 to promote replication fork restart following release from replication blocks, likely through Mre11-mediated resection of DNA. Both PARP1 and PARP2 are required for subsequent homologous recombination to promote cell survival following replication blocks. Our data suggest that PARP1 and PARP2 act as sensors of replication stress and are required for Mre11-mediated restart and recombination repair of stalled replication forks.

**157** INVITED

**Repair DNA polymerases as anticancer drug targets**

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Mammalian genomes are large and complex, thus requiring tightly regulated and coordinated processes to maintain the integrity of the genetic information, such as DNA replication, DNA repair, translesion DNA synthesis, involving the activity of multiple DNA polymerases (DNA pols). Several different DNA pols with different enzymatic properties (processivity, fidelity, substrate specificity) are acting in mammalian cells. Significant functional redundancy exists among certain DNA pols, while others appear to have unique functional roles. These enzymes are the only biological macromolecules able to duplicate the genetic information stored in the DNA and are absolutely required every time this information has to be copied, as during DNA replication or during DNA repair, when lost or damaged DNA sequences have to be replaced with "original" or "correct" copies. In each DNA repair pathway one or more specific DNA pols are required. A feature of mammalian DNA repair pathways is their redundancy. The failure of one of these pathways can be compensated by another one. However, several DNA lesions require a specific repair pathway for error free repair. In many tumors one or more DNA repair pathways are affected, leading to error prone repair of some kind of lesions by alternatives routes, causing accumulation of mutations and contributing to genomic instability, a common feauture of cancer cells. An overview of the different DNA pols

and their links to cancer, together with relevant examples of regulation of their functions, will be presented.

## *Scientific Symposium* (Tue, 22 Sep, 14:45–16:45)
## Investigating novel targets and anti-angiogenic agents in brain tumours

**158** INVITED

**Anti-EGFR and anti-angiogenic therapy – from mice to men**

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The development and clinical evaluation of therapeutic agents directed against the epidermal growth factor receptor (EGFR) or against tumor angiogenesis are two major strategies in targeting malignant gliomas. EGFR is overexpressed in approximately 60% of primary glioblastomas, frequently associated with *EGFR* gene amplification, and the constitutively active EGFRvIII variant is expressed in about half of the amplified cases. Specific EGFR targeting has been achieved using small molecule tyrosine kinase inhibitors (TKIs), such as erlotinib (Tarceva®) and gefitinib (Iressa®), as well as monoclonal antibodies (mAbs), such as cetuximab (Erbitux®). Erlotinib and gefitinib are the most well studied anti-EGFR agents. Xenograft studies in mice suggested that glioblastoma sensitivity to erlotinib is associated with the expresson of amplified and aberrant EGFR combined with wild-type PTEN. However, while two clinical studies found some evidence that a subset of patients with coexpression of EGFRvIII and wild-type PTEN or with high expression of wild-type EGFR and low levels of p-Akt respond to TKIs, a larger randomized EORTC trial detected no clinical benefit for erlotinib and no association with molecular markers. Using a highly invasive orthotopic mouse model with patient-derived xenografts, we found that response to local treatment with cetuximab depended on the presence of amplified and/or mutated EGFR, whereas the PTEN or p-Akt status was irrelevant. A recent phase II study showed that a small subgroup of patients with recurrent malignant glioma may benefit from cetuximab (administered i.v.), but response did not correlate with EGFR copy number. Promising results were recently reported for a vaccination approach, using a peptide that spans the EGFRvIII fusion junction. Phase I and II trials showed that this treatment led to T- and B-cell immunity in patients, eliminated tumor cells expressiong EGFRvIII, and caused an unexpectedly long patient survival.
Most anti-angiogenic strategies target the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) system, which is crucial to angiogenesis and edema formation in malignant gliomas. Xenograft studies showed that anti-VEGF and anti-VEGFR mAbs could strongly inhibit glioblastoma growth and prolong survival, however, treatment led to increased tumor invasion along the host vasculature. The most well studied anti-angiogenic compound is bevacizumab (Avastin®), a neutralizing mAb against VEGF. Bevacizumab has shown encouraging antitumor activity in combination with irinotecan, however this effect may be restricted to radiographic response and prolongation of progression-free survival, without prolongation of overall survival. Contrast-enhanced MRI can easily overestimate the effect of anti-angiogenic treatment, since it relies on extravasation of the contrast agent, which is impeded by the vascular permeabilty-reducing, anti-edematous effect of Bevacizumab. Nevertheless, strong subjective patient improvement and a steroid-sparing effect are clear benefits. Interestingly, tumor recurrence patterns after Bevacizumab treatment appear to confirm studies in rodents, since glioblastoma recurrences in humans are also more infiltrative. Ongoing larger randomized trials will show whether this represents a true increase in tumor cell invasiveness or a relative suppression of enhancing tumor growth, and they will further show whether Bevacizumab alone or in combination can prolong overall survival.

**159** INVITED

**PTEN and growth factor receptor targeting in glioblastoma**

I.K. Mellinghof[1]. [1]*Memorial Sloan-Kettering Cancer Center, Department of Neurology, New York, USA*

There is compelling evidence in a variety of human cancers that activating mutations in signal transduction pathways can result in tumor cell "dependence" on the mutant pathway and predict clinical response to pathway inhibition. In some of these diseases, clinical responses have been so consistent that the main challenge is no longer to achieve an initial treatment response, but to understand, overcome, and delay the emergence of acquired resistance to these agents. Progress with targeted cancer therapeutics has been slow in glioblastoma. When used as single therapy in molecularly unselected patient populations, most signal transduction inhibitors have produced radiographic responses in only a small fraction of patients. Mechanisms of resistance to specific signal transduction inhibitors in glioblastoma are largely unknown. My presentation will discuss molecular mechanisms of resistance to signal transduction inhibitors in glioblastoma, in particular PTEN-associated resistance to EGFR kinase inhibitors.

**161** INVITED

**Combining the adhesion pathway inhibition with radiotherapy – from the bench to the clinic**

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**Background:** Tumor response to radiotherapy is controlled by many intracellular tumoral factors whose deregulation leads to the modulation of the tumoral radiosensitivity, but also by micro-environmental factors such as hypoxia. These factors such as growth factors and their receptors and their downstream pathways can be intrinsically activated in some tumor cells leading to radioresistance, in particular via the inhibition of radiation-induced cellular deaths. These pathways are activated by irradiation, amplifying the phenomena of resistance by the activation of the radiation-induced DNA beaks repair, by the induction of tumoral repopulation, or stimulation of the migration pathways. Thus, irradiation activates receptors such as EGFR, FGFR, or avb3 and avb5 integrins involved in adhesion and angiogenesis, known to control tumor radioresistance via the induction of hypoxia, the control of tumor radiosensitivity via that of the endothelial cells, and its importance in the radioresistant tumor stem cells survival.
**Methods and Results:** We and other have shown that irradiation activates avb3/avb5 integrins, which are highly expressed in glioblastoma (GBM). Our lab has recently demonstrated that irradiation activates these integrins, which in turn control radioresistance in GBM cells via the integrin linked kinase (ILK) and RhoB under its farnesylated form, leading to the inhibition of the radiation induced mitotic death. These factors are moreover implicated in the control of the tumor micro-environment, particularly in angiogenesis and hypoxia. We have shown that the avb3/avb5 integrins, control intracellular radioresistance but also hypoxia *in vivo* and the regulation of HIF-1a via the focal adhesion kinase and RhoB, HIF-1a being a factor of radioresistance which is also activated by irradiation. Inhibition of this pathway leads to radiosensitization, normalization of hypoxia and angiogenesis. Moreover, we have shown in an other tumor that the co-expression of b3 integrin and FGF-2 was associated with a worse local control after radiochemotherapy, demonstrating the clinical relevance of this pathway in the control of the radiosensitivity.
Thus, one of the strategies to improve the radiosensitivity of radioresistant and hypoxic tumors as GBM consists in the association with the radiotherapy of inhibitors of these pathways. We and others have shown that the integrin inhibitor cilengitide induced a radiosensitization of GBM cells and xenografts. We have shown that inhibiting the farnesylation of RhoB led to radiosensitization, reoxygenation and normalization of the vasculature in GBM models. These results led us to design and conduce clinical phase I and II trials in GBM associating the farnesyltransferase inhibitor tipifarnib to radiotherapy showing good tolerance and encouraging results. An early phase trial associating cilengitide to radio-chemotherapy has shown promising results, in patients presenting the MGMT promoter methylation, probably due to a normalization of the vascularization obtained by cilengitide.
**Conclusions:** The optimal sequences of association between these targeted drugs and the radiotherapy remain incompletely elucidated and need to be studied. The precise study of the mechanisms of action of these therapies and of their interaction with radiotherapy, as well as the follow-up by metabolic imaging, of the patients accrued in such trials, will allow the determination of the optimal schedule of these promising combined treatments.

## *Scientific Symposium* (Tue, 22 Sep, 14:45–16:45)
## Clinical management of the elderly

**162** INVITED

**Geriatric assessment in oncology: a tool to provide better cancer care in the elderly**

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The aging population is characterized by an extreme diversity in terms of clinical, functional and social status. As a consequence, life expectancy in