nurses entering the workforce at present over half of the EU nursing workforce are over 45 years of age. As these staff approach retirement there needs to be sufficient numbers of younger recruits to replace them or an encouragement to entice staff to stay within the clinical setting.
The introduction of new therapies and improved survival of those diagnosed with cancer creates a longer term health care provision. The current success means that the numbers of people who have faced cancer is increasing by 2% a year requiring different ways of managing the volume of those who require future follow up, surveillance and after care. Oncology has focused on acute episodic care however these new developments require a shift to chronic illness models. Increasing complexity of treatment delivery requires broad skills from the nursing workforce and higher levels of proficiency and competence. Education is therefore fundamental in relation to increasing skills, keeping those nurses once trained and sustaining continuing professional development needs to be a future priority. Progress in recognising specialist cancer nursing across Europe is imperative for sustaining staff numbers and improving health outcomes. The importance of curriculum frameworks and standards across Europe will help in understanding the competence of cancer nurses. Part of this is through effective knowledge sharing through the exchange of good practice. Questions as to whether we can provide a workforce for future cancer care or what skill sets this workforce will require is important for us all. EONS aims to increase the visibility of the issues facing cancer nursing in the future.

Special Session (Thu, 24 Sep, 11:15−12:15)
Mouse models of cancer

336 INVITED

Identification of cancer genes and their collaborative networks by large-scale mutagenesis in tumour prone mice

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Insertional mutagenesis has proven to be a versatile tool to identify genes whose activation or inactivation can confer a selective advantage to cells in vitro or in vivo. The system has been exploited over the last 25 years successfully in the mouse to identify new oncogenes and tumor suppressor genes. With the availability of the complete mouse genome sequence and reliable PCR techniques this approach has become much more powerful. The insertional mutagenesis screen we performed to accelerate lymphomagenesis in mice illustrates this. Infection of newborn mice with replication-competent Moloney Murine Leukemia Virus gives rise to T and B cell lymphomas. The underlying mechanism is proviral activation of proto-oncogenes and inactivation of tumor suppressor genes. Retroviral insertional mutagenesis in over 1000 tumor-predisposed KO and control mice was performed. The largest specific cohort consisted of p53 and p19Arf KO mice. The resulting dataset with over 500 common insertion sites marking known and unknown proto-oncogenes, tumor suppressor genes, and microRNAs, also identified genotype-specific common insertion sites and highly significant co-occurrence of mutations and hits in tumor suppressor genes. The size of the dataset provided new information that could not have been extracted from smaller datasets collected previously, illustrating the “added value” of performing these studies on a large scale in defined genetic backgrounds. The approach is complementary to and can confirm the cancer-causing nature of genes identified by other approaches such as SNP analysis and high throughput sequencing of cancer genomes. Illustrating examples will be presented.

337 INVITED

Targeting DNA-repair deficiency in mouse models for BRCA-associated breast cancer

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Genetically engineered mouse (GEM) models of human cancer not only permit us to gain a detailed insight into the specific genetic changes that drive tumor initiation and progression [1], but also provide the tools to define the underlying mechanisms of drug response and acquired resistance. Once these processes are understood in sufficient detail it may be possible to design combination therapies that give rise to complete remissions, while at the same time eliminating remnant cells that might elicit recurrent disease.

Women carrying germline mutations in BRCA1 or BRCA2 are strongly predisposed to developing basal-like breast cancers, which frequently contain TP53 mutations. To study the role of BRCA1/2 loss-of-function in breast oncogenesis, we have generated conditional mouse models for BRCA1- and BRCA2-associated hereditary breast cancer based on combined inactivation of BRCA1/2 and p53 in epithelial tissues [2,3]. The mammary tumors that arise in our BRCA1 mouse model show strong similarity to BRCA1-associated breast cancer with respect to high tumor grade, expression of basal cell markers and high degree of genomic instability due to loss of homology-directed double-strand break (DSB) repair [3]. This model may therefore be helpful in predicting chemotherapeutic responses of human BRCA1-associated and BRCA1-like tumors. Indeed, preclinical intervention studies with conventional and targeted chemotherapeutics showed a selective sensitivity of BRCA1-deficient mouse mammary tumors towards agents that directly or indirectly cause DSBs, such as platinum drugs [4] or PARP inhibitors [5]. Treatment of tumor-bearing mice with the clinical PARP inhibitor olaparib (AZD2281) inhibited tumor growth without signs of toxicity, resulting in strongly increased survival. However, long-term treatment with olaparib resulted in the development of drug resistance, caused by up-regulation of P-glycoprotein drug efflux pumps. Indeed, acquired resistance could be effectively reversed by co-administration of olaparib and the P-glycoprotein inhibitor tariquidar.
BRCA1-deficient mouse mammary tumors become resistant to all drugs tested, with one exception: platinum-based chemotherapy drugs. Although tumors cannot be eradicated with cisplatin or carboplatin, the tumor recurrences invariably remain sensitive to retreatment with these drugs. These results data suggest that (partial) BRCA1 activity is required for induction of platinum resistance. Indeed, it has been reported that BRCA-associated hereditary ovarian cancers may become resistant to carboplatin by acquiring genetic reversion mutations in BRCA1/2, resulting in re-expression of BRCA1/2 and re-activation of homology-directed DSB repair [6,7]. In the mouse mammary tumors BRCA1 is inactivated by a large deletion in the Brca1 gene that cannot be reversed by any secondary mutation. To model chemotherapy resistance by genetic reversion, we have generated novel BRCA1-deficient mouse mammary tumor models mimicking defined human BRCA1 founder mutations (185-delAG and 5382-insC).

References

[1] Jonkers and Berns., Nat Rev Cancer 2002; 2:251−65.
[2] Jonkers et al., Nat Genet 2001; 29:418−25.
[3] Liu et al., Proc Natl Acad Sci USA 2007; 104:12111−6.
[4] Rottenberg et al. Proc Natl Acad Sci USA 2007; 104:12117−22.
[5] Rottenberg et al., Proc Natl Acad Sci USA 2008; 105:17079−84.
[6] Edwards et al., Nature. 2008; 451:1111−5.
[7] Sakai et al., Nature. 2008; 451:1116−20.

Special Session (Thu, 24 Sep, 11:15−12:15)
Clinical implications of new discoveries in cancer genetics

338 INVITED

Genetic susceptibility to breast cancer – new developments and clinical application

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Common cancers exhibit familial aggregation, consistent with substantial variation in inherited susceptibility. Over the past 25 years, the underlying genetic basis for this susceptibility has become increasingly understood. Three important classes of genetic loci have been identified: “high-penetrance” genes, such as *BRCA1* and *BRCA2*; “intermediate-penetrance” genes, such as *ATM* and *CHEK2*, in which mutations confer 2−3 fold risks; and “low-penetrance” loci (such as *FGFR2*), in which common polymorphisms confer more moderate risks, typically <1.5 fold. The high-penetrance loci are central in genetic counselling, but most genetic variation is explained by lower risk loci. While most if not all the important high-penetrance loci have been identified, identification of lower penetrance loci through genome-wide association studies is still in its infancy, and more further loci should be identifiable through genome scans and resequencing. Generally, genetic loci combine multiplicatively, consistent with multiple independent pathways.
Recent genome-wide association association studies have identified thirteen genetic loci with common susceptibility alleles. These loci include several plausible candidate genes, including *FGFR2*, *TNRC9*, *MAP3K1*, *LSP1* and *NEK10*, but also “gene deserts”. For the most part, the loci were not previously suspected to be related to carcinogenesis, and point to new disease mechanisms. While the risks conferred by the susceptibility