improvement program which is fully embraced by the European CanCer Organisation (ECCO). Initially, the focus will be on colorectal cancer. In the first period of 2 years the registration will make use of currently existing audit systems for colorectal cancer as in Norway, Sweden, Denmark, the United Kingdom, the Netherlands and Belgium, and start a benchmarking process. The national audit coordinators will provide access to their national databases and will form a multidisciplinary Steering Committee. The second period starts after the development of the European registration system. The data will be continuously used for benchmarking and internal feedback among participants. Afterwards, this experience will be used to extend the audit to other solid malignancies such as breast, gastric and oesophageal cancer. Data and experiences with colorectal audits will be discussed but indicate vast improvements of outcome.
Conclusion: Recent developments in quality assurance in surgical oncology have resulted in improvements that have a greater impact on survival than that of any of the adjuvant therapies currently under study. A European audit could advance future improvements and spread these to every cancer patient in Europe. The ECCO has recognised the importance of quality assurance and has created a framework to develop a European audit. As such, ECCO has established a strong, multidisciplinary organisation with a commitment to improve cancer care in Europe. All information about this project can be found on the website:
www.canceraudit.eu. Persons involved in the treatment of colorectal cancer and interested in joining or contributing to this European colorectal audit ECCO project can contact the authors at anytime.

137 INVITED

Quality Assurance of Radiotherapy

J. Bernier[1]. [1]*Genolier Swiss Medical Network, Department of Radiation Therapy, Genolier, Switzerland*

Objectives: In Radiation Oncology, QA systems are based on audits, which can be either internal or external to the Institution. Internal audits can, for instance, track intra-fraction and/or inter-fraction variations (e.g., variations in prostate position in function of rectum and bladder volumes). In this latter case, actions will be taken to match simulation and treatment settings, and random or systematic differences will be reported and recorded by the staff of the treatment unit. External audits can be national or international, performed on site or at QA review centers. They can be institutionally oriented, for instance, to check the accuracy of the beam calibration performed by the center. They can also be performed in the framework of prospective clinical studies, and conducted by experts of cooperative groups.
Material: In this case, the parameters requested and/or deviations investigated by the QA provider use to encompass: a) a definition of GTV, CTVs and PTVs; and b) an identification of isodose distributions underdosing GTVs, under/overdosing PTVs and/or overdosing critical organs such as, for instance in head and neck oncology, the spinal cord, brain stem, optic nerves and chiasm, etc.
Methods: At least two quality systems are essentially proposed to the investigators: the “dummy-run” and the “individual case review”, which were developed within EORTC. These procedures investigate both the compliance of individual institutions to the protocol guidelines and treatment accuracy. As regards the former one, in the very early phase of a trial activation, participating centers are given a number of reconstructed slices of the anatomical region of interest, including target volume contours, and asked to generate the irradiation plan them according to the protocol guidelines. As regards the latter one, it is based on the collection of images and data specific to individual cases treated in the framework of a given protocol. It generally includes diagnostic CT-scans, MRI and/or PET scans, planning CT-scans, treatment plans with dose distribution in target volumes. It is performed at the completion of the treatment (final review), but can also be “interventional” and scheduled at the very early phase of a trial activation.
Results: The clinical outcome of QA programs conducted in the framework of trials is not always easy to quantitate in terms of efficacy results or impact on quality of life. Examples of direct relationships between poor compliance to protocol guidelines and poor clinical results will be presented, especially as regards regimens combining radiation and drugs.
Conclusions: Among the main messages retrieved from a recent past, it can be shown that poor quality irradiation invalidates the scientific rationale of randomized trials of combined modality treatment, and centres enrolling only a few patients are the largest source of quality problems. Therefore sites involved in clinical research need to be rigorously credentialed prior to enrolling patients and interventional review should ideally be done before RT commences. At community level, doing well what we already know is more important than seeking incremental gains through new treatments.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00)
Novel Oncoproteomic Technology

138 INVITED

Label-Free Mass Spectrometry-Based Proteomics for Biomarker Discovery and Validation in Tissues and Biofluids

C.R. Jimenez[1], R.J.A. Fijneman[2], M. Wit[1], L. Bosch[2], S.R. Piersma[1], T.V. Pham[1], B. Carvalho[2], S. Mongera[2], H.M.W. Verheul[1], G.A. Meijer[2]. [1]*VU University Medical Center, OncoProteomics Laboratory Department Medical Oncology, Amsterdam,* [2]*VU University Medical Center, Tumour Profiling Unit Department Pathology, Amsterdam, The Netherlands*

Background: Colorectal cancer (CRC) is the second leading cause of cancer death in the Western world. Detection of CRC at an early stage of disease is associated with a much better prognosis for the patient, and is a realistic approach to reduce CRC mortality rates. Several randomised trials have shown that FOBT screening, ie detection of blood-derived haem in feces, reduces CRC mortality by ~16%. Nevertheless, the FOBT test performance is relatively poor, and it is commonly recognized that sensitivity and specificity of non-invasive CRC screening tests need to be improved, for which novel biomarkers are urgently needed.
Label-free mass spectrometry-based proteomics in (pre)-clinical samples and tumour proximal biofluids is emerging as a powerful, versatile approach for discovery of tissue-derived biomarkers with close association to the disease.
Aim: The aim of our studies is to identify novel protein biomarkers that can be used for development of a stool-based, blood-based, or molecular imaging-based screening test for early diagnosis of CRC.
Approach: Proteomics targeted to “biomarker-rich” compartments (proximal fluids, cell surface, nucleus) using a label-free GeLC-MS/MS workflow and spectral counting for protein quantitation. We have shown that this workflow is reproducible and outperforms other commonly used workflows in terms of the total number of identified proteins and the total number of reproducible identified proteins (Piersma et al., J.Proteome Res. 2010; Albrethsen et al., Mol. Cell. Prot., 2010).
Results: We have analyzed three different CRC model systems: 1) Proximal fluids of a mouse model for human sporadic CRC, which lacks variation due to genetic heterogeneity and allows to compare tumour-to matched control-samples; 2) Secretomes, exosomes and cell surface fractions of a panel of five human CRC cell lines; and 3) Proximal fluids and nuclear fractions of human colon adenoma and carcinoma tissues combined with patient-matched control tissues.
By combining proteome profiles of proximal fluids obtained from different CRC model systems we succeeded to identify tens of candidate biomarkers for stool-based or blood-based early detection of CRC. By combining cell surface proteomics with transcriptomics of adenomas and carcinomas we identified candidate biomarkers for molecular imaging of adenoma-to-carcinoma progression.
Outlook: We are currently validating these candidate biomarkers by IHC, ELISA and Selective Reaction Monitoring mass spectrometry using large series of clinical samples, in order to compose a *panel of biomarkers* with high sensitivity and specificity for CRC early detection and screening.
Acknowledgements: This work is supported by the VUmc Cancer Center Amsterdam and the Center for Translational Molecular Medicine that supports a national consortium ‘Decrease Colorectal cancer Deaths’ (DeCoDe).

139 INVITED

High Resolution Mass Spectrometry-Based Proteomics for Metabolism and Cancer Research

T. Walther[1]. [1]*Yale School of Medicine, Department of Cell Biology, New Haven, USA*

Recent Breakthroughs in mass spectrometry based proteomics enable the detection adn quantification of thousands of proteins in complex mixtures. In addition, these methodes allow for the quantification for global analysis of changes of posttranslational modifications, such as phosphorylation. The basic principles of the methodology will be discussed using examples of metablism and cancer research.

140 INVITED

Clinical Proteomics in the Early Detection of Breast Cancer

J. Celis[1]. [1]*Danish Cancer Society, Institute of Cancer Biology, Copenhagen, Denmark*

The completion of the human genome as well as the explosion of novel technologies within genomics, proteomics and functional genomics promise

to have a major impact on clinical practice, as these technologies are expected to accelerate the translation of basic discoveries to the clinical practice. In particular, proteomic technologies are likely to play a key role in the study and treatment of cancer, as they provide invaluable resources to define and characterize regulatory and functional networks, investigate the precise molecular defect in diseased tissues and biological fluids, and for developing specific reagents to precisely pinpoint a particular disease or stage of a disease.
Today, the application of novel technologies from proteomics and functional genomics to the study of cancer is rapidly shifting to the analysis of clinically relevant samples such as fresh biopsy specimens and biofluids. Being a patient-oriented organisation, The Danish Cancer Society catalysed in 2002 the creation of a multidisciplinary research environment, The Danish Center for Translational Breast Cancer Research (DCTB), to fight breast cancer. The direct access to and use of fresh patient material, as well as the close collaboration between basic researchers, surgeons, clinicians and pathologists is one of the unique features of the Centre.
Here I will present the proteomics strategies that we are currently been used to search for biomarkers for the early detection of breast cancer in the blood. Particular emphasis will be given to problems associated with tumour heterogeneity, clinical relevance of samples as well as marker validation.

141 INVITED

Protein Kinase Activity and Therapy Response

K. Røe[1]. [1]*Oslo University Hospital − The Norwegian Radium Hospital, Department of Radiation Biology Institute for Cancer Research, Oslo, Norway*

Of the human kinome, approximately half of the tyrosine kinase complement is implicated in cancer. Tyrosine kinases are thus important targets for therapeutic interventions and potential biomarkers for stratifying patients to individualized cancer therapy. To extract multiplex tyrosine kinase profiles, high-throughput methodologies are needed. One such method is based on simultaneous generation of phosphorylation signatures of 144 tyrosine kinase substrates by tissue samples using a 3D flow-through microarray technology (PamChip Arrays®). Examples on the use of this technology in the context of identification of functional biomarkers of disease aggressiveness and therapy response will be given.
First, a study characterizing tyrosine kinase signaling networks in prostate cancer is presented. In addition to their significant roles in tumour progression and therapy resistance, tyrosine kinases are major players in development of castration-resistant disease, still remaining the most apprehensive aspect in prostate cancer management, defying effective treatment. By analyzing samples from a preclinical model eliciting therapy-naïve, androgen-deprived, and castration-resistant disease, respective tyrosine kinases implicated in the different disease states were identified. Subsequently, clinical validation was achieved by analyzing paired normal and tumour tissue samples from prostatectomies of locally advanced disease or following androgen-deprivation.
Secondly, the method was used to assess the tyrosine kinase activity in 67 pre-treatment tumour biopsies from locally advanced rectal cancer, aiming to identify subsets of tyrosine kinases predicting the response to preoperative chemoradiotherapy (CRT). The tyrosine kinase activity profiles were shown to predict therapeutic response, as assessed by histomorphologic tumour regression grade of resected tumour specimens. Generally, baseline tyrosine kinase activities in tumours showing poor CRT response were significantly higher than in tumours with good CRT response. Specifically, many of the discriminating kinases represented signaling pathways implicated in radiation resistance.
In summary, novel analytic technologies enabling high-throughput tyrosine kinase profiling are imperative for providing further insights into the complex biology causing different cancers and their therapy responses. Future individualized cancer therapy may benefit from such technologies being developed into specific arrays containing biomarkers identifying aggressive disease and therapeutic response.

142 INVITED

Cancer Protein Biomarkers

Abstract not received

Keynote Lecture (Sun, 25 Sep, 11:30−12:15)
Do We Still Need to Understand the Cancer Genome?

143 INVITED

Evolution of the Cancer Genome

M. Stratton[1]. [1]*The Sanger Centre, Cancer Genome Project, Cambridge, United Kingdom*

All cancers carry somatically acquired changes in their genomes. Some, termed “driver” mutations, are causally implicated in cancer development. The remainder are “passengers”, and bear the imprints of mutational processes operative during cancer development. Following the advent of second generation sequencing technologies the provision of whole cancer genome sequences has become a reality. These sequences generate comprehensive catalogues of somatic mutations, including point mutations, rearrangements and copy number changes and provide insights into the evolutionary processes underlying the development of individual human cancers including the factors generating variation and the forces of selection. These insights will form the foundation of our understanding of cancer causation, prevention and treatment in the future.

Special Session (Sun, 25 Sep, 13:15−14:15)
Current Issues in the Management of Germ Cell Tumours

144 INVITED

Relapse and Prognostic Factors in Patients With Metastatic Germ-Cell Tumours

J. Beyer[1]. [1]*Vivantes Klinikum Am Urban, Department of Haematology and Oncology, Berlin, Germany*

In patients with metastatic germ-cell tumours (GCT) prognostic factors at initial diagnosis are universally accepted to guide treatment decisions *(IGCCCG, J Clin Oncol 1997)*. In patients who progress or relapse after first-line cisplatin-based chemotherapy, however, the issue of prognostic factors is far more complex. Salvage treatment can induce longterm remissions in a substantial proportion of patients using four cycles of conventional-dose chemotherapy (CDCT) with cisplatin, ifosfamide plus either etoposide, vinblastine or paclitaxel. In a recent large, international multicenter analysis, five clinical variables had been shown to strongly impact on the rate of longterm remissions: histology, extragonadal tumour location, response to first-line treatment, response duration, levels of serum tumour markers AFP and HCG as well as the presence of liver, bone or brain metastases at the time of salvage treatment. Depending on the presence or absence of these adverse prognostic factors, longterm remissions varied between near zero to close to 75% or more at two years using either CDCT or high-dose chemotherapy (HDCT). As a result, for the first time an universally accepted prognostic score could be established also for the first-salvage setting *(IPFSG J Clin Oncol 2010)*. Using the same database of 1594 patients the results after HDCT were compared to those after CDCT. With the limitations of a retrospective comparison, HDCT was superior to CDCT in all prognostic groups spuring once again the discussion about the optimal first-salvage treatment strategy *(Lorch, J Clin Oncol 2011)*. HDCT also represents a curative option for patients with second or subsequent relapses, although longterm remissions are less frequent compared to it’s ealier use *(Einhorn, N Engl J Med 2007; Lorch, Ann Oncol 2010)*. Options for third-line chemotherapy are oral etoposide, paclitaxel, gemcitabine, oxaliplatin or combinations of these agents usually given as palliative treatment. However, in individual patients even third-line combinations incorporating new agents and multimodality treatment can still result in longterm remissions or even cure *(Bokemeyer, Ann Oncol 2008)*. Surgical resecion of all residual lesions is an integral part of any salvage strategy. The rates of vital undifferentiated cancer or mature teratoma are higher in patients after salvage treatment as compared to patients after first-line chemotherapy *(Rick, J Clin Oncol 2004)*. Surgery should be scheduled as early as possible after completion of salvage chemotherapy. In patients with late relapse GCT more than two years after cisplatin-based first-line treatment, salvage surgery rather than salvage chemotherapy should be the initial approach, particularly in patients with a resectable single site and normal markers or elevations of AFP rather than HCG. In conclusion, salvage treatment may cure a substantial proportion of patients with GCT, but should be limited to centers exprienced in caring for this rare and complex patient cohort.