or by binding to the anchoring protein (RACK1), which leads to HIF-1α degradation.
Two HIF-1α chimeric reporter systems were developed that allowed us to investigate HIF-1α stabilization/degradation in different cell lines, both in culture and in xenografts. A comparison between HIF-1α/Fluc and HIF-1α(ΔODDD)/Fluc expression levels, as measured by bioluminescence imaging (BLI), demonstrate important differences between non-tumorigenic NIH3T3 and HEK293 reporter cells and tumorigenic PTEN-defective U87 cells. Non-tumorigenic NIH3T3 and HEK293 cells had low basal normoxic-levels of HIF-1α/FLuc expression that were readily detectable by BLI, but not by immunoblotting. In contrast, tumorigenic U87 reporter cells had high basal levels of HIF-1α/FLuc expression, and responded to hypoxia and hypoxia-mimetics as well. A significant reporter response was observed in animals bearing U87/HIF-1α/FLuc xenografts following an i.p. injection of $CoCl_2$, but not in animals bearing U87/HIF-1α(ΔODDD)/FLuc or native FLuc expressing (control) xenografts.
Immunofluorescence analysis of HIF-1α/FLuc subcellular localization and trafficking in reporter-transduced cell lines compared well with that of endogenous HIF-1α in wild-type cells. A bi-exponential BLI profile of HIF-1α/FLuc protein degradation was observed, indicating that both "rapid" and "slow" clearance mechanisms were operative. The half-time of the rapid clearance phase in these cells was ~3−6 min and consistent with the currently accepted half-life of HIF-1α (~5 min) under normal non-hypoxic conditions; a second slow clearance phase (~200 min) was newly identified. The immunofluorescence and kinetic profile analysis of HIF-1α/FLuc degradation suggests that the rapid and slow components of degradation are compartmentalized. Although the mechanism of HIF-1α shuttling between nucleus and cytoplasm is poorly understood, it is clear that HIF-1α subcellular distribution and degradation are regulated in a cell-specific manner, with significant differences between normal cells and cancer cells.

19 INVITED

Application of Hypoxia Imaging in Radiation Treatment Planning

U. Nestle[1], N. Wiedenmann[1], M. Hentschel[1], V. Jacob[1], S. Bucher[1], M. Mix[2], S. Adebahr[1], C. Offermann[1], W. Weber[2], A.L. Grosu[1]. *[1]University of Freiburg, Department of Radiation Oncology, Freiburg,[2]University of Freiburg, Department of Nuclear Medicine, Freiburg, Germany*

The appearance of tumour hypoxia is a common feature of solid tumours that is negatively correlated with prognosis and local control. Among other mechanisms, hypoxia-mediated radioresistance has been identified as a major obstacle for achieving permanent tumour control after radiotherapy. Derived from experimental studies, hypoxic mammalian cells are known to be up to 3 times less radiosensitive than euoxic cells. The elimination of tumour hypoxia has been a long standing therapeutic target. The PET tracers ^{18}F-fluoromisonidazole (F-MISO) and ^{18}F-fluoroazomycinarabinoside (FAZA) have been developed to provide a non-invasive tool for visualizing tumour hypoxia by positron emission tomography (PET). Accrdingly, tumour hypoxia assessed by PET has been found to be correlated with the risk of locoregional failure as well. Studies show F-MISO PET to be associated with a higher risk (HR 7) of locoregional failure after radiochemotherapy compared to non-hypoxic tumours [Rischin et al., JCO 2006]. One approach to target unfavorable tumour characteristics such as tumour hypoxia is the 'dose painting' concept. Thereby the radiation dose is selectively escalated within the most aggressive tumour areas. For hypoxia targeted radiation treatment hypoxic tumour subvolumes are derived from the hypoxia PET and treated with an increased radiation dose ('boost') using intensity modulated radiotherapy (IMRT) treatment planning. By selectively boosting hypoxic tumour cells the tumour control probability (TCP) is supposed to increase as shown by radiobiological considerations. Treatment planning may be based on baseline hypoxia as well as residual tumour hypoxia assessed at different timepoints during a timecourse of radiation treatment. However, radiation-induced tumour reoxygenation and dynamic changes in tumour oxygenation need to be considered. Data on the dynamics of tumour hypoxia during radiation treatment is scarce. Follow-up PET scans of tumour hypoxia during standard radiochemotherapy in locally advanced SCC of the head and neck will therefore be presented as well as examples and technical considerations for hypoxia besed treatment planning. While the role of hypoxia PET as a diagnostic tool is well established, the suitability and feasibility of a hypoxia based dose painting needs to be thoroughly discussed and addressed in clinical trials.

Scientific Symposium (Sat, 24 Sep, 11:15−13:15)
Long Term Follow Up in Childhood and Adolescent Cancer

20 INVITED

Pan-European Network for Care of Survivors After Childhood and Adolescent Cancer (PanCare)

L. Hjorth[1], J. Byrne[2], A. Georgiev[3], R. Haupt[4], L. Kremer[5], G. Levitt[6], P. Pisani[7], R. Skinner[8], E. Sugden[9]. *[1]Division of Paediatric Oncology & Haematology, Department of Paediatrics Lund Skåne University, Hospital Clinical Sciences Lund University, Lund, Sweden; [2]Boyne Research Institute, Drogheda, Ireland; [3]Law Firm Alexiev Georgiev Shalamanov, Sofia, Bulgaria; [4]Epidemiology and Biostatistics Section Scientific Directorate, Gaslini Children's Hospital, Genova, Italy; [5]Department of Paediatric Oncology, Emma Children's Hospital/AMC, Amsterdam, The Netherlands; [6]Department of Paediatric Oncology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; [7]Department of Epidemiology, Universitá di Torino, Torino, Italy; [8]Department of Paediatric and Adolescent Haematology/Oncology, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom; [9]Department of Paediatric and Adolescent Haematology/Oncology, Oxford Radcliffe Hospitals, Oxford, United Kingdom*

Background: Recognising the need for a voice in Europe for survivors with late complications of therapy for childhood and adolescent cancer, PanCare was founded to be the pan-European Network that addresses all aspects of childhood cancer survivorship.
Material and Methods: In March 2008, PanCare (Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer) was founded by 26 doctors and scientists from 14 European countries at a meeting in Lund, Sweden. The" Erice statement" was adopted as backbone of PanCare vision and mission.
Results: Seven meetings of the Network have so far been held. At present, PanCare has members from 26 European countries plus Canada and Japan. Most are paediatric oncologists; second most common are epidemiologists; followed by radiation oncologists; survivors psychologists; parent representatives; paediatric neurologists; paediatric and adult endocrinologists; nurses (too few!), medical students and one each being a lawyer and representative of a funding body. The PanCareSurFup consortium, based in PanCare, is a 5-year FP7 Health2010 Collaborative Project focusing on epidemiological studies on mortality, secondary malignancies and cardiac disease after treatment for childhood cancer, and on guidelines for survivors and dissemination of results. In addition to this, working groups within PanCare are currently establishing research projects on fertility, quality of life and ototoxicity. PanCare is also a partner in an FP7 funded Network of Excellence led by SIOPE.
Conclusions: PanCare is a multidisciplinary pan-European network of professionals, survivors and their families that aims to reduce the frequency, severity and impact of late side-effects of the treatment of children and adolescents with cancer. PanCare is working to achieve equity of access to care for childhood cancer survivors across Europe, to perform collaborative research and to act as a resource of research based information concerning all late side-effects of cancer treatment. An important aim of PanCare is to work with the European Community and other stakeholders to increase awareness and research about childhood cancer survivors all over Europe. The long-term strategic aim of PanCare is to ensure that every European survivor of childhood and adolescent cancer receives optimal long-term care.

21 INVITED

The Epidemiology of Childhood Cancer Survivors

R. Haupt[1], P. Pisani[2], S. Garwicz[3], M. Hawkins[4], R. Skinner[5], L. Hjorth[3]. *[1]Giannina Gaslini Children's Hospital, Epidemiology and Biostatistics Section, Genoa, [2]University of Turin, Childhood Cancer Registry of Piedmont, Turin, Italy; [3]Skåne University Hospital, Division of Paediatric Oncology & Haematology, Lund, Sweden; [4]University of Birmingham, Centre for Childhood Cancer Survivor Studies School of Health and Population Sciences, Birmingham, [5]Great North Children's Hospital Royal Victoria Infirmary, Department of Paediatric and Adolescent Haematology and Oncology and Children's BMT Unit, Newcastle upon Tyne, United Kingdom*

Background: As a result of the ever-increasing success rates achieved in recent decades in pediatric oncology, an increasing number of children and adolescents have successfully overcome their cancer experience and have reached or are entering adulthood.