in combination with cytotoxic agents. Unfortunately, in the clinic, anti-angiogenic therapy has not yet met initial expectations despite high radiological response rates. The direct anti-tumour effect of anti-angiogenic drugs is not clear and eventually all GBMs recur, indicating that the tumours develop escape mechanisms towards treatment.
In a series of preclinical studies using intracranial patient-derived xenografts, we have shown that such escape mechanisms are associated with a metabolic switch in the tumours towards glycolysis, as indicated by an up-regulation of the transcription factor HIF-1 (hypoxia inducible factor-1) and several metabolites associated with the glycolytic pathway (e.g. lactate). In conclusion, we have identified in a robust preclinical model system, specific biological escape mechanisms towards anti-angiogenic therapy, and based on this information novel therapeutic principles will be discussed.

273 INVITED

Targeting Angiogenesis in Glioma − Challenges and Pitfalls

R. Stupp[1], G. Tabatabai[2], M. Weller[2], C. Ruegg[3]. [1]*University Hospital Lausanne (CHUV), Department of Clinical Neurosciences, Lausanne,* [2]*University Hospital Zurich (USZ), Department of Neurologie, Zurich,* [3]*University of Fribourg, Department of Pathology, Fribourg, Switzerland*

Malignant gliomas, notably glioblastoma are among the most vascularized and angiogenic cancers, and microvascular proliferation is one of the hallmarks for the diagnosis of glioblastoma. Angiogenesis is regulated by a balance of pro- and antiangiogenic signals; overexpression of VEGF and activation of its receptors, most notable VEGFR-2 and -3, results in endothelial cell proliferation and leaky vasculature. Heterogeneous perfusion and oxygenation, peritumoral edema and increased interstitial pressure are the consequence. Both endothelial and tumour cells are strongly dependent on integrin-mediated adhesion for cell proliferation, survival, migration and invasion.
Strategies aiming at inhibition of cell signaling and angiogenesis, including integrin inhibitors, have been clinically investigated in gliomas over the last 5 years. Radiological responses, a decreased requirement of corticosteroids and temporary improvement in performance status have repeatedly been observed. Toxicity was mild-moderate and manageable, notably there was no evidence for a substantially increased incidence of intracranial bleeding. However definitive comparative (randomized !) investigation has failed to demonstrate improved outcome with single agent inhibition of EGFR, or PDGFR or VEGF/VEGFRs pathways in recurrent glioblastoma. Definitive phase III trials combining the anti-VEGF monoclonal antibody bevacizumab, or cilengitide, a peptidic integrin-inhibitor, together with temozolomide and radiotherapy are ongoing (accrual completed).
The integration of anti-angiogenic strategies in the management of malignant glioma also poses entirely new challenges in patient management: 1) Many agents are known for increasing the risk of thrombosis, embolism and intracranial bleeding. 2) Evaluation of treatment efficacy is difficult and new biomarkers of activity, including functional, metabolic or molecular imaging techniques are urgently needed. Normalization of vasculature leads to decrease in contrast enhancement without necessarily reflecting tumour shrinkage. Tumour heterogeneity, putative prognostic or predictive factors require early controlled trials, novel trial designs and endpoints. 3) Activation of alternate pathways and tumour escape mechanisms may require combination of multiple agents, which is often not feasible due to regulatory restrictions and potential complex toxicities. Emerging clinical and experimental evidence suggests that anti-angiogenic drugs might need to be combined with drugs targeting tumour adaptive mechanisms in addition to cytotoxic chemotherapy and irradiation for a maximal antitumour effect.

274 INVITED

Clinical

Abstract not received

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) **The Role of IGFs/IGF-1R Pathway in Paediatric Malignancies**

275 INVITED

Biology of IGF/IGFR Pathway in Sarcomas

Abstract not received

276 INVITED

IGF1R Inhibitors in the Treatment of Ewing Sarcomas

L. Helman[1], C. Yeung[1], X. Wan[1], L. Cao[1], L. Baker[2], A. Pappo[2], S. Patel[2]. [1]*National Cancer Institute, Center for Cancer Research, Bethesda MD,* [2]*Sarcoma Alliance for Research through Collaboration, Sarc, Ann Arbor MI, USA*

IGF signaling has been shown to play a role in a variety of pediatric sarcomas, including Ewing's sarcomas. While no genetic alterations in IGFIR have been identified, epigenetic changes in the form of loss of imprinting of the ligand, IGF-2, have been found in Ewing's sarcomas. These findings led to clinical studies testing a variety of IGFIR humanized antibodies in patients with recurrent Ewing's sarcomas. The Sarcoma Alliance for Research through Collaboration (SARC) initiated an international study utilizing the fully human IGFIR antibody R1507, in collaboration with Roche. We entered 132 unselected patients with recurrent Ewing's sarcoma from December 18, 2007 through April 4, 2010, and 115 patients were eligible for evaluation. Most patients were treated at a dose of 9 mg/kg as a weekly IV infusion, and five patients were treated with a dose of 27 mg/kg given every three weeks as an IV infusion when an amendment was included to test this dose at the end of the study. Overall, objective responses were seen in 19 patients for a RR of 16.5% including two CRs. Eight of the 19 responses lasted greater than 18 weeks, and 11 responses lasted less than 18 weeks. Most responses developed rapidly after initiating therapy, although there was at least one patient who developed a PR after more than 20 weeks of treatment. Patients tolerated therapy extremely well. The common Grade 3/4 toxicities observed included thrombocytopenia 7%, anemia 7% and hyperglycemia of 3%. We have created models to study the effects of IGFIR antibody treatment in mice and have identified factors that likely influence response. First, IGFIR density is quite variable in the surface of tumours, and tumours with very low density IGFIR do not respond to IGFIR Ab treatment. Second, similar to patients treated on this study, responding tumours eventually re-grow and this tumour re-growth corresponds with re-activation of pAKT, in the setting of continued IGFIR suppression. Thus we hypothesize that activation of "by pass" pathways leads to recurrence in responding patients. We still need to identify positive predictors of response and are engaged in analyzing patient samples treated on this study do so. Finally, we are using our preclinical models to identify combination therapy that might mitigate activation of "by pass pathways and these will be discussed.

277 INVITED

IGF1R Targeting in Non-sarcoma Pediatric Malignancies

B. Geoerger[1]. [1]*Institut Gustave Roussy, Department of Pediatrics and "Pharmacology and New Treatments in Cancer", Villejuif, France*

Insulin-like growth factors and their receptor insulin-like growth factor type 1 receptor (IGF-1R) are implicated in tumour growth, metastatic dissemination and drug resistance, and thus represent a promising therapeutic target in cancer. Physiological cell growth is widely regulated by growth factors such as IGF1 and IGF2, and normally down-regulated after growth. In multiple cancer cells, particularly pediatric cancers, this growth factor pathway is activated. Whereas *IGF-1R* gene mutations or gene amplification appear rarely, loss of imprinting of IGF2 (11p15) have been reported occurring in rhabdomyosarcoma, neuroblastoma, hepatoblastoma, nephroblastoma; elevated IGFBP-3 levels are found associated with EWS-FLI transfusion products in Ewing sarcoma. *MYCN* overexpression modulates IGF action through increased IGF-1R expression and decreased IGF-BP3 expression, resulting in increased tumorigenicity in neuroblastoma. In Wilms' tumours, mutations/deletions in WT1 result in overexpression of IGF-1R and IGF-II; the prior was found associated with relapsed disease. IGF-1R targeting using IGF1R antisense, different monoclonal antibodies or small molecule tyrosine kinase inhibitors has been explored preclinically in osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and neuroblastoma mostly showing anti-proliferative effects *in vitro* and growth inhibition in xenografts *in vivo*, Enhanced effects were observed when IGF1R targeting was combined with classical anticancer agents or other growth factor receptor or downstream pathway inhibitors such as PI3K, AKT or mTOR. The clinical evaluation

of IGF1R monoclonal antibodies was so far focused in patients with sarcoma, and studies are ongoing in children and adolescents evaluating the combination with chemotherapy or mTOR inhibition.

278 INVITED

The IGF1 Growth Hormone Axis in Human Development

J.M. Ricort[1]. [1]*University of Montpellier 2, Institut de Recherche pour le Développement, Montpellier, France*

Due to its major roles in initiation, progression and growth of tumours, the insulin-like growth factor (IGF) system, and more specifically the type I IGF receptor, has become a prime target for developing anti-tumour strategies. However, even if inhibiting this signaling pathway appears relevant to block tumour development, it may also affect the multiple physiological functions controlled by these secreted growth factors in particular during childhood and adolescence. In fact, IGFs are key elements that regulate growth and differentiation of many tissues and organs. Their complexity relies in particular on the fact that they are not only expressed in the liver, under the control of the somatotropic hypothalamic-pituitary axis, but also in all tissues where they played major autocrine and paracrine functions. Moreover, the strong homologies between the type I IGF receptor and the insulin one allows the constitution of hybrid receptors that need to be taken into account when developing therapeutic strategies. Studying human pathologies and animal models in which the IGF system is under- or over-regulated can shed lights on the main functions played by these growth factors during human development.

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) **Novel Radiation Technologies and Strategies**

279 INVITED

Adaptive Radiation Therapy − Technology and Strategies

Abstract not received

280 INVITED

Integrated MRI-Guided Advanced Radiotherapy

J.J.W. Lagendijk[1], B.W. Raaymakers[1], M. van Vulpen[1]. [1]*University Medical Center Utrecht, Department of Radiotherapy, Utrecht, The Netherlands*

In Utrecht a radiotherapy accelerator is being developed with MRI functionality. This system offers superb soft-tissue contrast imaging directly from the treatment table. The operator sees the actual beam according to the actual anatomy real time. Due to the dynamic capability of MRI a full inventory of motion, deformation and response can be assessed to minimise the margins for geometrical uncertainties in the tumour position. MRI does not only provide improved target localisation but also better target characterisation by means of functional MRI.
For treatment guidance, MRI can visualise the tumour without the need of surrogates, and can also visualise the surrounding organs at risk. This can be done not only once prior to each fraction but continuously during dose delivery, so also intra-fraction motion, e.g. breathing related motion, can be tracked and corrected for. This presentation will give an overview of the system being developed at the Radiotherapy Department of the UMC Utrecht, the Netherlands in collaboration with Elekta and Philips: a 6 MV accelerator with diagnostic quality 1.5 T MRI functionality. We expect that MRI guided Radiotherapy will become the new standard treatment machine. The moment we see what we do, on line, treatment improvements and dose optimisations are unavoidable. Dynamic on line MRI guidance can produce a breakthrough for difficult tumour sites like the kidney, liver, pancreas, rectum and oesophagus.
The MRI linac systems will be placed in a new Centre for Image guided Oncological Interventions, a close collaboration between Radiotherapy and Radiology. The equipment involved in this new Center and the intended patient categories will be discussed.

281 INVITED

Scanned Intensity − Modulated Proton Therapy

Abstract not received

282 INVITED

Laser-Accelerated Proton Therapy

W. Enghardt[1]. [1]*Technische Universität Dresden, OncoRay, Dresden, Germany*

Considering their interaction with matter beams of protons and light ions should have the potential for increasing the curing rate in radiotherapy. Their physical advantages over conventional therapeutic radiation modalities (ultrahard bremsstrahlung and electrons delivered by medical electron linear accelerators) lead to reduced normal tissue dose and to the possibility of dose escalation within the tumour volume. Additionally light ions show an increased relative biological effectiveness (RBE) at the end of their track, which can be confined to the tumour volume, if an appropriate beam delivery technique (pencil beam scanning) is applied. Up to now these advantages of particle beams could not be translated into improved cure rates for most of tumour species.
For this situation three reasons are relevant: (i) Treatment and quality assurance techniques applied to particle therapy have been adopted from conventional radiation therapy. This is not adequate, since the dose distributions of particle beams are much less robust against minor inaccuracies in the treatment workflow than those of photons. (ii) The number of patients treated worldwide at technological optimal devices in clinical studies of high quality is still low. (iii) The reasons outlined under (i) and (ii) are primarily caused by the high investment and operating costs of particle therapy facilities, which exceed those of conventional facilities by about one order of magnitude.
This situation has led to intensive research on compact acceleration and beam delivery concepts. These include superconducting, dielectric wall and laser driven accelerators. The latter may have the highest potential for miniaturizing particle therapy devices. However, before a clinical prototype will become realistic, several physical, technological and biomedical problems have to be solved requiring intensive research on: (i) high power lasers ($P > 1$ PW) of high repetition frequency ($f > 10$ Hz); (ii) radiator targets, which efficiently convert the laser light into high energy protons ($E > 200$ MeV); (iii) dedicated techniques of dosimetry and quality assurance, which fit to the unusual time structure and pulse dose rate of laser accelerated beams; (iv) comprehensive characterization of the RBE of this novel radiation type via in in-vitro and in-vivo experiments; (v) reduction of the overall size of the irradiation facilities by the combination of laser acceleration and compact beam deliveries.

Keynote Lecture (Mon, 26 Sep, 11:30−12:15) **How Registry Data Has Changed Rectal Cancer Treatment**

283 INVITED

How Registry Data Has Changed Rectal Cancer Treatment

Abstract not received

Special Session (Mon, 26 Sep, 13:15−14:15) **How Should We Treat Good Risk Prostate Cancer − Focally or Entirely?**

284 INVITED

Active Surveillance

Abstract not received

285 INVITED

Brachytherapy − High Dose Rate or I-125?

P.J. Hoskin[1]. [1]*Mount Vernon Hospital, Cancer Centre, Northwood Middlesex, United Kingdom*

Brachytherapy provides the ultimate tool for customising dose distributions within the prostate gland. Low dose rate (LDR) seed brachytherapy with I − 125 or Pd-103 is well established as an effective treatment for good risk prostate cancer with biochemical control rates and survival equivalent to that of the other major modalities of treatment in this setting. Currently high dose rate (HDR) brachytherapy is used to boost higher risk patients enabling dose escalation in that setting and does not have a established role in low risk patients, although there is increasing evidence that HDR monotherapy is an effective treatment with low toxicity in this group of patients.
The convention for both LDR and HDR is to define the clinical target volume by the capsule of the prostate gland and a variable margin encompass potential microscopic extra capsular extension, typically 3−5 mm. Focal treatment requires accurate definition of the dominate lesion or lesions to be ablated. This may be mapped using biopsies or using functional imaging.
Biopsy mapping can be used for LDR brachytherapy transposing the position of the dominant lesion onto the ultrasound images used for