inhibition in a clinical model. However, tumor pharmacodynamic studies may be better to explore the biologic effects of a selected agent than normal surrogate tissues, as tumor cells often respond in a different way to targeted drugs than normal cells. Therefore, the antineoplastic PD effect of a selected compound on the human tumor cells in the human host can only be evaluated when tumor biopsies are obtained before and during treatment. It has been also shown that the acquisition of sequential tumor biopsies before and on-treatment may be instrumental to elucidate mechanism of resistance to these targeted agents, either primary or secondary. We and others support PD studies with tumor biopsies from patients enrolled in clinical trials with new targeted therapies. These studies can not only evaluate the biologic effect of the drug in the tumor, but they may also identify the genomic and proteomic profile of the population with highest chances to benefit from treatment. In this presentation we will review the potential applications of these pharmacodynamic studies and give some examples validating this biomarker development approach.

161 INVITED

Function MRI – dynamic imaging of vascularity and diffusion imaging of cellularity

A.R. Padhani. *UK*

Abstract not received.

162 INVITED

PET scan

E. Aboagye. *UK*

Abstract not received.

Symposium (Wed, 26 Sep, 14:45−16:50)
Receptor signalling targets

163 INVITED

Introduction: The Rap1 signalling network in cell adhesion

J.L. Bos. *UMC Utrecht, Physiological Chemistry, Utrecht, The Netherlands*

Rap1 is molecular switch in a signaling network that regulates the integrity of cell layers, i.e. it stimulates integrin-mediated cell adhesion, inhibits migration, induces polarity and stabilizes cell-cell contacts. The network is activated by variety of different stimuli through a number of different guanine nucleotide exchange factors (GEFs), including the cAMP responsive Epac, the calcium responsive CalDAG-GEF, the PDZ-domain containing PDZ-GEF and C3G. Downstream from Rap1 a number of effectors have been assigned, including RapL and Riam in integrin-mediated cell adhesion, and Tiam and Vav in the control of the actin cytoskeleton. We will report on various aspects of this signaling network, including the differential usage of GEFs in the regulation of cell-cell junctions. Specifically, C3G is involved in the recruitment of E-cadherin to junctions, PDZ-GEF2 is involved in the maturation of junctions and Epac is involved in the regulation of the barrier function.

164 INVITED

mTOR-S6K1 signaling and cell growth control

J. Blenis, X. Ma, M. Holz, C. Richardson, R. Anjum. *Harvard Medical School, Department of Cell Biology, Boston, USA*

Background: Growth factor and oncogene-regulated PI3 kinase- and Ras-activated signaling pathways converge upon the nutrient- and energy-sensing mTOR pathway to modulate cell growth, survival and proliferation. In several human diseases, components of these pathways are often amplified or mutated resulting in inappropriate cell growth. The purpose of our research is to thoroughly define at a molecular and biochemical level how mTOR is regulated and signals, and how when improperly regulated this pathway contributes to carcinogenesis.
Materials and Methods: Multiple approaches including tandem affinity purifications, two-hybrid screens, proteomic screens, biochemical analysis and RNAi-based screens are being used to define this signaling system.
Results: The translation initiation factor eIF3, and the translation preinitiation complex (PIC), serve as scaffolds to promote growth factor- and nutrient-dependent initiation of mTOR-Raptor (mTORC1) signaling and phosphorylation of its two major effectors, the eIF4E binding proteins (4EBPs) and the S6 protein kinases (S6K1/2). Phosphorylation of these effectors results in their release from the PIC and promotes assembly of the translation initiation complex at the 5′ cap of mRNA. Once released from eIF3, S6K1 becomes activated and associates with the exon-junction complex of newly synthesized mRNA. Here the activated enzyme is positioned to phosphorylate targets involved in the pioneer round of translation. Thus, mTORC1 and S6K1 regulate assembly of the translational apparatus needed for pioneer and steady state translation, and connect growth factor signaling, nutrient availability and energy status to the energy consuming process of protein synthesis.
Conclusions: Rapamycin, a specific inhibitor of mTORC1, has emerged as a drug with potential therapeutic efficacy alone or in combination therapy. We are beginning to uncover the molecular basis of how mTORC1 and its effector, S6K1 are activated by multiple growth factor- and oncogene-regulated pathways, which in turn regulate cell growth through translation initiation and mRNA biogenesis. These studies are uncovering a basic mechanistic understanding of processes involved in regulating protein synthesis and are potentially revealing novel points of therapeutic intervention.

165 INVITED

Systems approach to growth factor signaling and to therapeutic intervention

Y. Yarden, I. Amit. *Weizmann Institute of Science, Department of Biological Regulation, Rehovot, Israel*

Growth factors and their transmembrane receptors contribute to all steps of tumor progression, from the initial phase of clonal expansion, through angiogenesis and metastasis. Hence, the information relay system involved in growth factor signaling provides potential sites for signal interception and tumor inhibition. A relevant example comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinase, namely ErbB-1/EGFR, which belongs to a prototype signaling module that drives carcinoma development. The extended module includes two autonomous receptors, EGFR and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor (ErbB-3). This signaling module is richly involved in human cancer and already serves as a target for several cancer drugs. Due to inherent complexity and a large amount of experimental data, we propose a systems approach to understanding ErbB signaling. EGF-to-ErbB signaling is envisioned as a bow-tie configured, evolvable network, sharing modularity, redundancy and control circuits with robust biological and engineered systems. My presentation will concentrate on system controls, a plethora of negative feedback loops, which include E3 ubiquitin ligases, receptor endocytosis and newly transcribed genes. Because network fragility is an inevitable tradeoff of robustness, systems level understanding is expected to identify therapeutic opportunities for targeting aberrant activation of the network in human pathologies. Specific examples will be discussed with an emphasis on gene expression and the control of metastsis.

166 INVITED

PKB-FoxO

B. Burgering. *University Medical Center Utrecht, Laboratory of Physiological Chemistry and Centre for Biomedical Genetics, Utrecht, The Netherlands*

The class O of Fox transcription factors (FoxO) has recently become a focus of interest, after it was shown that its C. elegans homologue DAF-16 is critical in determining organismal lifespan and stress resistance. In higher organisms FoxO transcription factors have important roles in metabolism, cellular proliferation, stress tolerance and probably also aging. The activity of FoxOs is tightly regulated by post-translational modifications (PTMs), including phosphorylation, acetylation and ubiquitination. We will discuss how these PTMs of Foxo are regulated and what their functional consequences are. Remarkably, the enzymes identified to be responsible for the regulation of these PTMs are often identical between FoxOs and p53, and our recent studies indicate that the interplay between FoxOs and p53 mediated by these PTM modifying enzymes might underlie a ‘trade-off’ between disease and lifespan, the principal hallmark of aging.

167 INVITED

Pre-clinical studies of BRAF signalling in cancer

R. Marais. *Institute of Cancer Research, Signal Transduction Team, London, United Kingdom*

BRAF is a protein kinase that is mutated in 7% of human cancer. Mutations are particularly common (50−70%) in melanoma, but are also reasonably frequent in thyroid, ovarian, colorectal and billiary tract cancers. The mutations activate BRAF by destabilizing an inactive conformation of the kinase domain and allowing the active conformation to prevail. Inhibitors of BRAF are being developed and preclinical studies suggest that inhibitors of HSP90 are also likely to be effective for the treatment of BRAF mutant

cancers. We have also shown that combinations of BRAF inhibitors with TNFα antagonists could provide an effective approach. We have developed mouse models of melanoma that are driven by oncogenic BRAF and the animals get melanoma following activation of BRAF from the endogenous gene, demonstrating that BRAF can be an initiating event in cancer. Finally, we have examined the downstream targets of BRAF and shown that critical to the ability of oncogenic BRAF to induce melanoma is its ability to induce transcription of the melanoma specific transcription factor M-MITF. Oncogenic BRAF regulates M-MITF through transcriptional regulation of the melanocytic factors BRN2 and PAX3. These data explain why BRAF is an addictive oncogene in melanoma.

Symposium (Wed, 26 Sep, 14:45−16:45)
Management and research issues in palliative care

168 INVITED

Neuropharmacology of cancer pain

A. Dickenson. *University College London, Pharmacology, London, United Kingdom*

Until recently, animal models of cancer-induced bone pain were based on the systemic injection of carcinoma cells, resulting in systemically unwell animals with multiple randomly sited bone metastases. This precluded systematic investigation of specific neuronal and pharmacological alterations that occur in cancer-induced bone pain. In 1999, Schwei et al. described a murine model of cancer-induced bone pain that paralleled the clinical condition in terms of pain development and bone destruction, but was confined to the mouse femur. This resulted in progressive bone destruction, elevated osteoclast activity and progressive and distinctive nocifensive behaviours (indicating the triad of ongoing, spontaneous and movement-induced hyperalgesia). In addition, cancer cells induce an inflammatory infiltrate and release growth factors, cytokines, interleukins, chemokines, prostanoids, and endothelins, resulting in a reduction of pH to below 5 and direct deformation of primary afferents. The osteoclast activity that destroys bone correlates with behavioural hypersensitivity suggestive of a neuropathic state. Bone marrow, mineralized bone and the periosteum are innervated by primary afferent fibres and it therefore follows that there would be primary afferent nerve destruction within the cancer laden bone. These peripheral changes, in turn, drive hypersensitivity of spinal cord sensory neurones, many of which project to the parts of the brain involved in the emotional response to pain. In turn, the ability of the painful messages from the spinal cord to impact upon mood, anxiety, the sleep cycle and central autonomic centres can explain some of the co-morbidities commonly observed in patients. Furthermore, these affective areas of the brain appear to drive descending excitations back to the spina lcord that enhance the pain statWithin the spinal cord, a unique neurochemical reorganization within segments of the dorsal horn of the spinal cord receiving nociceptive input from the sarcoma-injected bone has been described and includes an increased expression of the pro-hyperalgesic peptide dynorphin and massive astrocyte hypertrophy. However, changes in certain neurotransmitters as seen in pure neuropathy or inflammation are absent. The progressive nocifensive behaviour, bone destruction and the dorsal horn neurochemical markers all suggest that cancer-induced bone pain is a unique pain state with both elements of neuropathy and inflammation. This talk will consider the efficacy of a number of agents that include opioids and drugs used in neuropathic states based on the current knowledge of cancer induced pain.

169 INVITED

Recent research in opioid treated cancer pain

S. Kaasa. *Norway*

Abstract not received.

170 INVITED

Palliative sedation – its role in refractory symptoms

D. Schrijvers. *Ziekenhuisnetwerk Antwerpen-Middelheim, Department of Oncology, Antwerp, Belgium*

Palliative sedation (PS) is the use of sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in the patients' consciousness. A refractory symptom is defined as a symptom that is uncontrollable despite repeated efforts and various techniques. The appropriate drugs should be carefully titrated to obtain symptom relief. It is advisable to involve a palliative care specialist.

As all other decision at the end-of-life, PS should be discussed with the palliative care patient and his family beforehand and informed consent should be obtained before the initiation of PS. There should be a written procedure how to perform a PS.

PS is the cause of 2.5−8.5% of all deaths in Europe. In palliative care patients, it is used in 4−48% of patients depending on the care setting. The reasons for PS are incontrollable delirium, dyspnoea, pain and/or psychological stress.

Different medications (e.g. haloperidol, propophol) may be used to initiate a PS but midazolam is the treatment of choice. It can be given subcutaneously and should be titrated until the symptoms are controlled. All other medication except drugs for pain control may be stopped. In case of deep sedation, a bladder catheter should be inserted and complications such as pressure sores or eye ulcerations should be prevented by adequate care measures.

After deep PS, the median duration before death occurs is 1−5 days. During this period, it is essential to support the family and also the nursing staff since PS may cause a serious emotional burden.

PS is an essential part of palliative care and may be used in patients with refractory symptoms to improve the quality of life.

171 INVITED

Translational research in malignant bone pain – Impact on clinical practice

M. Fallon. *Western General Hospital, Palliative Care Team, Edinburgh, United Kingdom*

Cancer-induced bone pain (CIBP) is a major clinical problem with up to 85% of patients with bony metastases having pain. The last few years have seen a dramatic transformation in our knowledge of the mechanisms of CIBP and understanding of treatments. This has been largely the result of an appropriate animal model of CIBP and a more functional exchange of information between basic science and the clinic.

We have established a rat model of CIBP and shown that, like other chronic pain states, it relies on spinal NMDA receptor activation. However CIBP appears to be a unique pain state, bringing about a different profile of neurochemical changes in sensory nerves and spinal cord from those in other pain states, involving prominent glial activation.

In addition, the opioid-resistance of movement-associated bone pain may result from the greater sensory nerve activity/recruitment involved causing additional release of afferent transmitters to produce a sensitised state. By identifying the underlying molecular events in CIBP, it may be possible to develop novel and effective analgesics for this challenging clinical problem. Our clinical programme has fed into our basic science programme and vice versa.

Our clinical programme has characterised CIBP in patients attending a Regional Cancer Centre. In this study 50% of patients with CIBP had spontaneous pain. In 50% of cases (including both spontaneous pain or pain on movement) pain resolved in 15 minutes meaning standard oral opioid treatments are often irrelevant, simply leaving the patient drowsy. In addition, the single most important question to be identified to assess pain severity and impact on function was what has been your "worst pain in the last 24 hours".

Exploration of quantitative sensory testing supports peripheral and central sensitisation mechanisms in the clinic which support our basic science findings.

The threads of the clinical characteristics of CIBP, role of opioids and potential role of adjuvants based on basic science data will be woven together in this presentation.

Symposium (Wed, 26 Sep, 14:45−16:45)
New perspectives in melanoma therapy

172 INVITED

New developments in adjuvant therapy in melanoma

A. Eggermont. *Erasmus Medical Center Rotterdam, Daniel den Hoed Cancer Center/Department of Surgical Oncology, Rotterdam, The Netherlands*

The most important recent developments in adjuvant therapy are the outcome of the EORTC 18991 Trial comparing long term adjuvant therapy with Pegylated-IFN (PEG-IFN) versus Observation in stage III melanoma; the outcome of the Hellenic melanoma group trial comparing 4 weeks of iv HDI (high dose IFN) and the analyses of the importance of autoantibodies and S100 in the EORTC 18952 trial and the ECOG adjuvant trials.