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