Thursday 30 September 08:00–09:45

PLENARY SESSION 4

Proteasome inhibitors, antichaperone drugs, stress pathway inhibitors

238 INVITED

Oncogenic aberrations of SCF ubiquitin ligases

M. Pagano. *New York University Medical Center, Dept. of Pathology (Experimental) MSB 5 548, New York, USA*

Temporally coordinated destruction of cell cycle regulatory proteins by the ubiquitin-proteasome pathway represents an important regulatory mechanism that drives progression through the cell division cycle in a unidirectional and irreversible manner. There is increasing evidence that in addition to genetic alterations, aberrant proteolysis of cell cycle regulators contributes significantly to tumorigenesis, and is indeed found in many types of human cancer. I will discuss the role played in cancer by the F-box protein components of the SCF ubiquitin ligases and why these represent drugable targets in the therapy of cancer and other proliferative diseases.

239 INVITED

The proteasome and proteasome pathway inhibitors in cancer

A.J. Rivett. *University of Bristol, Department of Biochemistry, Bristol, UK*

Proteasomes are multicatalytic endopeptidase complexes that are responsible for a large proportion of intracellular protein degradation in eukaryotic cells. Among other functions, they play an essential role in cell cycle regulation and in the activation of the transcription factor NFkappaB. Proteasomes have an unusual catalytic mechanism with threonine residues acting as the catalytic nucleophile at each of their catalytic sites. Proteasome inhibitors include peptide aldehydes, boronic acids and vinyl sulphones and a number of unrelated compounds such as lactacystin and epoxomicin. These inhibitors have been useful for the characterization of catalytic components and in the elucidation of proteasome functions in animal cells. Perhaps surprisingly, they have also been found to be effective anti-cancer agents. Potent small peptide boronic acid inhibitors of proteasomes have been shown to be effective in a variety of animal models, and one (VELCADE) has been used successfully in clinical trials. Transformed cells are generally more sensitive to apoptosis induced by proteasome inhibitors than non-transformed cells. Also treatment of normal cells with proteasome inhibitors can lead to induction of a non-proliferative senescent phenotype. Understanding the mechanisms that underlie the anti-cancer effects of proteasome inhibitors will aid the design of better and more selective treatments. In particular, since the regulatory role of proteasomes often involves ubiquitin-dependent degradation of key substrates, studies are also underway to evaluate E3 ubiquitin ligases as novel targets for cancer therapy.

240 INVITED

Hsp90 and molecular chaperones as targets in cancer therapy

N. Rosen. *USA*

Abstract not received.

241 INVITED

Targeting the myeloma cell in its bone marrow microenvironment

K.C. Anderson. *Dana-Farber Cancer Institute, Jerome Lipper Myeloma Center/Department of Adult Oncology, Boston, USA*

We have developed both in vitro systems and in vivo animal models to characterize MM cell homing to BM, as well as factors promoting MM cell growth, survival, drug resistance, and migration in the BM milieu. These model systems have allowed for development of promising biologically-based therapies targeting the MM cell and the BM microenvironment including (thalidomide/revlimid, velcade, VEGF receptor inhibitor PTK787, histone deacetylase inhibitors SAHA); those targeting MM cells including heat shock protein 90 inhibitor 17 AAG and insulin growth factor receptor inhibitor; and those which target only the BM microenvironment including I_ B kinase and p38MAPK inhibitors. We have translated our laboratory studies to phase I, II, and III clinical trials to evaluate their clinical utility and toxicity, and to move them rapidly from the bench to the bedside. Velcade and Revlimid have already demonstrated marked clinical anti-MM activity even in patients with refractory relapsed MM, confirming the utility of our preclinical models to identify and validate novel therapeutics. Importantly, gene array and proteomic studies have helped to identify in vivo mechanisms of action and drug resistance, as well as aiding in their clinical application. For example, gene microarray profiling of Velcade treated MM cells reveals induction of heat shock protein 90 stress response, providing the rationale for the combined clinical use of Velcade and 17-AAG to enhance anti-MM activity. Protein profiling of Velcade treated MM cells demonstrated cleavage of DNA repair enzymes, providing the rationale for combining Velcade with DNA damaging agents to enhance sensitivity or overcome resistance to these conventional therapies. Correlative microarray studies of ongoing clinical protocols have demonstrated mechanisms of resistance, i.e. hsp 27 conferring resistance to Velcade, and suggested strategies to overcome resistance, i.e. P38MAPK inhibitors. Ongoing studies are using gene and protein profiling both to select cocktails of targeted therapies for specific patients, and to define targets of sensitivity and resistance in order to develop next generation, more potent and less toxic, therapeutics. Our studies have therefore demonstrated the critical role of host BM-tumor cell interactions both in MM pathogenesis and as targets for novel therapies. They have provided the framework for a new treatment paradigm targeting MM cell-host BM stromal cell interactions and their sequelae in the BM milieu to overcome drug resistance and improve patient outcome in MM

Thursday 30 September 10:15–12:00

PLENARY SESSION 5

Hypoxia as a target

242 INVITED

Imaging hypoxia in tumours

P.L. Olive. *BC Cancer Research Centre, Medical Biophysics, Vancouver, BC, Canada*

Hypoxia that develops in solid tumours is associated with a more aggressive tumour phenotype and poorer response to treatment. This appreciation has stimulated efforts to develop methods that could be used routinely to assess pretreatment tumour hypoxia as well as rates of reoxygenation during therapy. Hypoxic tumour cells, although a limitation to response, are also a recognized target for new therapeutic agents. Methods that can detect hypoxic cells could be used to identify patients likely to benefit from hypoxia-directed bioreductive cytotoxins like tirapazamine or gene therapy approaches like GDEPT that rely on activation of pro-drugs by hypoxic cells. Although non-invasive imaging would be preferable for many reasons, the dynamics of tumour hypoxia, both spatially and temporally, need to be better understood before we can have confidence in the imaging results that typically provide much lower resolution. Towards this end, chemical hypoxia markers like pimonidazole and EF5 can be administered to patients and then detected in tissue sections or fine needle aspirates using simple antibody labeling procedures. These are robust methods that provide information on the fraction of hypoxic cells as well as the degree of hypoxia. A technically simpler approach is to measure expression of endogenous hypoxia markers like the transcription factor HIF-1α and its downstream targets, carbonic anhydrase 9 and glucose transporter 1. Although often criticized as providing only a snapshot in time of what are undoubtedly very dynamic processes, it is possible to obtain kinetic information by analysis of a single tumour section. Staggering the delivery of two hypoxia or perfusion markers before biopsy can be used to identify regions of transient perfusion. Alternatively, by making use of the variability in the half time of hypoxia-inducible protein formation or loss in response to specific microenvironmental changes, dynamic changes can be identified in a single tumour biopsy. Tumour models that are thoroughly characterized using these quantitative techniques will be more useful for experimental therapeutic studies. Many of these approaches are already being applied to clinical biopsies.

243 INVITED

Clinical significance of tumour hypoxia

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Since the early seventies a number of clinical trials have been undertaken with the aim to modify tumor oxygenation. Some succeded and others