Friday 10 November 08:00–09:45

PLENARY SESSION 8

Novel imaging strategies and their impact on cancer biology and treatment

449 INVITED

Imaging angiogenesis using DCE-MRI

G. Jayson. *Christie Hospital and University of Manchester, Cancer Research UK Dept Medical Oncology, Manchester, United Kingdom*

Angiogenesis, the development of new blood vessels, is essential for tumour growth. The principal angiogenic cytokine, Vascular Endothelial Growth Factor (VEGF), has been the target of multiple anti-angiogenic drugs and has now been validated as a target in phase III clinical trials in colorectal, breast, lung and renal cancer. Despite this success there remains a critical need to define the population of patients who most benefit from this new class of drug as VEGF inhibitors are associated with toxicity and cost and imaging offers a strategy to achieve this.

The vessels formed during tumour angiogenesis are tortuous and highly permeable; the latter phenotype being mediated principally by VEGF. Because of this relationship, modelling of the passage of gadolinium contrast across the endothelium allows us to determine the level of activation of the VEGF pathway. This is usually achieved by acquiring Magnetic Resonance Images during administration of contrast in a method named Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI). Recent data have confirmed that anti-VEGF antibody-induced reductions in tumour VEGF R2 phosphorylation correlate with local reduction in vascular permeability, as measured by DCE-MRI.

DCE-MRI has been used to evaluate anti-VEGF antibodies and receptor tyrosine kinase inhibitors in phase I clinical trials, the rationale being that if the drugs are working as predicted then we should see local reductions in vascular permeability. Multiple trials have been conducted using this technology (but with a range of analytical techniques) and in general the data suggest that the magnitude of the reduction in vascular permeability correlates with the dose of the drug and that the magnitude of reduction is related to stabilisation of the disease.

There is a significant problem in the reporting of the DCE-MRI data to date. Typically data have been calculated as the median of the parameter under consideration, yet we know that tumour masses usually have a ring-enhancing pattern suggesting that there is considerable heterogeneity across a tumour. In recent studies we have shown that this heterogeneity is of clinical significance and therefore this will need to be taken into account in future studies.

We have also shown that the pre-treatment vascularised volume of tumours correlates with subsequent tumour growth and this offers a potential hypothesis to test as a biomarker for VEGF inhibitors. Thus imaging technology has been critical to the early phase development of VEGF inhibitors and now offers a potential strategy for identifying patients who might benefit from VEGF inhibitors.

450 INVITED

TGF beta pathway imaging in metastases

I. Serganova, R. Blasberg. *Memorial Sloan-Kettering Cancer Center, New York, USA*

The TGFβ family includes the TGFβs, activins and bone morphogenic proteins that have profound effects on many developmental processes, including cell proliferation, differentiation, cellular adhesion, skeletal development, hematopoiesis and inflammatory responses. TGFβ has opposing effects on many tumor cells. In the early stages of tumorigenesis, TGFβ suppresses the growth of pre-malignant lesions. As tumors progress to a more aggressive tumor phenotype, TGFβ ligands contribute to their metastatic potential, particularly in the case of breast cancer metastases to bone. Bone is one of a few places where TGFβ prevails in an active form and it is released by osteolytic resorption.

To study the spatial-temporal dynamics of TGFβ1 signal transduction activity during the development of breast carcinoma metastases, the SCP2 and SCP3 subpopulations of MDA-MB-231 cells (Minn et al., J Clin Invest, *115:* 44−55, 2005) were transduced with the herpes simplex virus one thymidine kinase and green fluorescent protein fusion reporter (HSV1-TK/GFP), controlled by multiple repeats of DNA binding motifs specific for Smads and Runx transcription factors (inducible *Cis*-TβRE reporter system), and by constitutively expressed red fluorescent protein (RFP) and Firefly luciferase (FLuc) genes. After intracardiac injection of 1×10^5 reporter-transduced SCP2T or SCP3T cells into mice, the localization and growth of metastatic lesions was assessed by bioluminescence imaging and CT. The spatial heterogeneity and temporal dynamics of TGFβ1 signaling in metastases was monitored by imaging HSV1-TK/GFP expression with [^{18}F]FEAU and PET. Reporter-transduced SCP2T cells produced predominantly bone metastases with high SMADs transcriptional activity. In contrast, reporter-transduced SCP3T cells developed more metastases in adrenal glands than in bone. The *Cis*-TβRE reporter system is responsive to the presence of active TGFβ ligands and can be used to non-invasively monitor the activity of the TGFβ signal transduction pathway in animals.

451 INVITED

Molecular imaging strategies to assess signal transduction and protein-protein interactions non invasively: real time imaging of drug target responses

D. Piwnica-Worms. *Washington University School of Medicine, Molecular Imaging Center, St Louis, USA*

Genetically-encoded imaging reporters introduced into cells and transgenic animals enable noninvasive, longitudinal studies of dynamic biological processes in intact cells and living animals. The most common reporters include firefly and click beetle luciferases (bioluminescence imaging), various green/red fluorescence proteins (fluorescence imaging), Herpes Simplex Virus-1 thymidine kinase (positron emission tomography) and variants with enhanced spectral and kinetic properties optimized for use *in vivo*. When cloned into promoter/enhancer sequences or engineered into fusion proteins, imaging reporters enable fundamental processes such as transcriptional regulation, signal transduction cascades, protein-protein interactions, oncogenic transformation, cell trafficking and targeted drug action to be temporally and spatially registered *in vivo*. Spying on cancer with genetically-encoded imaging reporters provides new insight into cancer-specific molecular and regulatory machinery within the contextual environment of the whole animal.

452 INVITED

Imaging probes for αvβ3 and CXCR4

H.J. Wester. *Germany*

Abstract not received.

Friday 10 November 10:15–12:00

PLENARY SESSION 9

Discovering novel targets and therapeutics for cancer

453 INVITED

Tumour stem cells – targeting the root of cancer

D. Bonnet. *London Research Institute, Lincoln's Inn Fields Laboratories, Haematopoietic Stem Cell Laboratory, London, United Kingdom*

Acute myeloid leukaemia (AML) is a clonal disorder defined by the accumulation of abnormally differentiated myeloid blasts. Because leukaemic blasts have very limited proliferative capacity, it is believed that leukaemic clone is maintain by a rare population of leukaemic stem cells (LSC) that have extensive proliferation and self-renewal capacities. Elucidating the nature of the target cell that undergoes leukaemic transformation and characterising the LSC is essential for both the understanding of the leukaemogenic process and for the design of effective therapies. The development of an in vivo model that replicates many aspects of human AML had provide a mean to identify leukaemic stem cells (termed the SCID-Leukaemia Initiating Cells, SL-IC). SL-IC is defined by the ability of that cell to initiate AML in NOD/SCID mice. This in vivo assay provides the foundation of an assay to define the biological and molecular properties of such leukaemic stem cells (LSC). Despite the clear importance of the LSC in the genesis and perpetuation of leukaemic disease, little is currently known about the biological and molecular properties that make LSCs distinct from normal haematopoietic stem cells. The presentation will summarise the work done using the xenograft system to characterise the nature of the leukaemic clone and will specifically highlights the advances made in phenotypically, molecularly and functionally defining LSC.