Scientific Symposium (Sun, 25 Sep, 09:00−11:00) **Tumour Microenvironment**

119 INVITED

Why Do We Get So Few Cancers?!

M. Bissell[1]. [1]*Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA*

Our work in the last three decades has provided much of the impetus for the current acceptance and recognition of the importance of context/microenvironment and extracellular matrix (ECM) in regulation of gene expression and underscored the plasticity of both the differentiated state and tumours. I will discuss how we use the normal mammary gland from both mice and humans to understand breast cancer and will present recent works, some as yet unpublished, shedding further light on the importance of tissue architecture on regulation of tissue-specificity, as well as the beginning of new models to understand metastasis, dormancy and the stem cell niche. I will also show recent data on the role of actin/laminin axis in the nucleus, the importance of MMPs, and kinetic imaging of how a unit of tissue function in the mammary gland (an acinus) is formed, destroyed in malignancy and reformed by controlling the microenvironment. These concepts and models have profound implication for prognosis and therapy of cancer.

120 INVITED

Monocyte and Macrophage Diversity Promotes Tumour Progression and Metastasis

J.W. Pollard[1]. [1]*Albert Einstein College of Medicine, Department of Developmental and Molecular Biology, Bronx, USA*

There is persuasive clinical and experimental evidence that macrophages promote cancer initiation and malignant progression. Macrophages enhance malignancy at the primary site by stimulating angiogenesis, inducing tumour cell migration, invasion and intravasation and by suppressing anti-tumour immunity. At metastatic sites macrophages promote tumour cell extravasation, survival and subsequent growth. Each of these activities is stimulated by a different population of macrophages whose unique signaling pathways might represent new therapeutic targets (Qian and Pollard, 2010).
Recent lineage tracing studies indicate that the primary and metastatic tumours recruit different populations of monocytes partially explaining the macrophage diversity. At the metastatic site the recruitment of CCR2 expressing monocytes requires tumour synthesized CCL2, the ligand for CCR2. Inhibition of CCL2 reduces this monocyte recruitment and subsequent differentiation into macrophages and this in turn reduces tumour cell extravasation and metastatic growth. This generation of macrophage diversity will be discussed in this presentation.
Qian BZ, Pollard JW (2010) Macrophage diversity enhances tumour progression and metastasis. Cell 141:39−51.

121 INVITED

Anticancer Approaches Based on Tumour Hypoxia and Metabolism

J. Pouyssegur[1], J. Chiche[1], R. Le Floch[1], D. Roux[1], M.P. Simon[1]. [1]*Centre Antoine Lacassagne, CNRS-UMR 6543, Nice, France*

It is well-established that cancer cells posses a metabolic profile that differs from non cancerous cells. The hypoxia-inducible transcription factor (HIF-1), in addition to genetic and epigenetic changes, that activate oncogenes (Myc, Ras) and inactivate tumours suppressors (pVHL, p53, pTEN, LKB1), are largely responsible for alterations in cell metabolism often exacerbated in hypoxic tumour cells. HIF-1 not only engages in cell proliferation through the metabolic shift to glycolysis and lactic acid production but also stimulates, in various ways, nutrient supply through adaptive survival mechanisms. These include epithelial-mesenchymal transition, angiogenesis, autophagy, synthesis and transient storage of glycogen and lipids. HIF-1 also ensures survival by correcting tumour acidosis *via* increased expression of carbonic anhydrases (CAIX) and lactate/H+ symporters (MCT4). A further understanding of the key alterations in cancer metabolism associated with pharmacological control of the energy-sensing AMP-kinase should offer novel therapeutic opportunities to treat multiple forms of cancer.
In this presentation we will demonstrate that targeting pHi-regulated processes severely restricts tumour growth, a process that entails glycolysis-generated ATP levels. We propose that membrane-bound carbonic anhydrases (CAIX, CAXII), monocarboxylate transporters (MCT1 and MCT4) as well as their chaperon Basigin/EMMPRIN/CD147), which are associated with exacerbated tumour metabolism represent new potential targets for anticancer therapy.

122 INVITED

Tumour − Stroma Interactions in Breast Cancer Metastasis

C.M. Isacke[1], N. Murugaesu[1], M. Iravani[1], D.A. Johnson[1], A. Ashworth[1], C.J. Lord[1]. [1]*The Institute of Cancer Research, Breakthrough Breast Cancer Research Centre, London, United Kingdom*

When breast carcinomas remain confined to breast tissue, cure rates exceed 90%. However, if the cancer disseminates through the body, long-term survival decreases depending upon the extent of, and the sites of, colonization. Metastases in visceral organs and the brain are the most life threatening, with five-year survival rates usually less than 20%. Genes that control the different stages of the metastatic process need to be identified to better delineate the mechanisms of disease progression, to aid in the development of metastatic biomarkers and to provide potential targets for the treatment of metastatic disease.
Genetic screens, such as those that exploit RNA interference, provide an unbiased approach to the identification of genes associated with a phenotype of interest. Although cell-based screens have been highly informative in identifying genes involved in tumour cell survival, migration and invasion, these *in vitro* approaches are largely unsuitable for interrogating the later stages of the metastatic process, in particular the processes of cell dissemination, tumour cell extravasation from the circulation and colonization of secondary sites. To overcome these limitations, we have developed an *in vivo* metastasis short hairpin (sh)RNA interference screen combined with massive parallel sequencing to identify novel determinants of the metastatic process. The implementation of this screen, the validation of the hits and the mechanistic analysis of a novel metastasis suppressor gene that modulates tumour cell intravasation at secondary sites will be discussed.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00) **The Application of Pharmacometrics in Oncology**

123 INVITED

Application of Population PK-PD Methods in Oncology

E. Chatelut[1], A. Schmitt[1], M. White-Koning[1], F. Thomas[1]. [1]*Institut Claudius-Regaud, EA4553, Toulouse, France*

The pharmacodynamic effects (PD) of anticancer drugs are multi-factorial. Administration of a drug either during clinical development or as standard chemotherapy generates a great amount of information. Nonlinear mixed effect approach represents a valuable tool to analyze PD by considering several patients' characteristics such as demographical, biological, pharmacokinetic (PK) parameters, administration of concomitant drugs ... After a general review of PK-PD methodologies used in the field of Oncology, two examples of analysis we have performed using population approaches will be presented. First, the results of a multicentric observational study of carboplatin given as standard chemotherapy for treatment of different cancer diseases allowed us to discriminate between PK covariates that should be considered for prediction of individual carboplatin clearance, and PD factors that should be taken into account for the choice of target Area Under the Curve of plasma concentrations vs. time [Schmitt et al, J Clin Oncol 2010]. For this study, neutrophil and thrombocyte counts versus time observed during the intercycle period after carboplatin administration were analyzed according to the semi-physiological PK-PD model proposed by Friberg et al [J Clin Oncol 2002]. The study revealed also that neither known polymorphisms of GSTP1 and ERCC1 nor age were significant PD covariates. However, age should be considered as PK covariate for carboplatin dosing in adults. In a second time, the results of PK-PD analysis of erlotinib data obtained in pediatric [Georger et al, Neuro Oncol 2011] and adult patients [Thomas et al, Eur J Cancer 2009] will be shown. Pharmacogenetic, biological, and demographical covariates have been identified as contributing to the interindividual PK variability. Erlotinib clearance expressed per kg was significantly higher in children in comparison with values observed in adults. However, the relationship observed between individual erlotinib plasma exposure and grade of skin toxicity was identical in children and in adults. Then, the higher Maximum Tolerated Dose in children (vs. in adults) is likely due to PK specificities rather than PD differences. In conclusion, these PK-PD analyses should be performed for registered drugs, but also during drug development.