will highlight the application of laser capture micro-dissection and high resolution MS for conducting proteomic investigations of formalin-fixed paraffin-embedded archival tissue for cancer biomarker discovery and validation.

SP156
New targets and cancer therapy: successes and failures

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In 1998, trastuzumab's approval for the treatment of HER2 postive metastatic breast cancer patients, successfully launched the era of targeted therapy and beginnings of the concept of personalized medicine. Within the decade additional successes have occurred: imatinib, initially approved in 2001 for the treatment of chronic myelogenous leukemia and since approved for the treatment of gastro-intestinal stromal tumours, systemic mastocytosis, idiopathic hypereosinophilic syndrome, dermatofibrosarcoma protuberans; the fall and rise of epidermal growth factor receptor inhibitors in lung, head and neck, and colorectal carcinoma, and vascular endothelial growth factor ligand and receptor inhibitors renal cell carcinoma. More recently, striking activity has been seen in early phase trials for inhibitors to PARP in BRCA deficient tumours and and triple negative breast cancer, to EML4-ALK translocations in NSCLC, to BRAF mutations in melanoma and to Hedgehog in multifocal, metastatic basal cell carcinoma, and to JAK2 in myelofibrosis. Swift drug development can occur when there is a successful linkage between a pharmacologically sound drug that effectively interacts with its target, target activation is a significant contributor to the malignancies of trial patients and that there is an accurate means for identifying such patients. Results with imatinib and trastuzumab, which has recently been shown to improve survival in HER2+ gastric carcinoma patients, suggest that activation due to mutations or amplification correlate with activity across histologies. Results from targeted agents also suggest that mutations within and between pathways are often mutually exclusive, activation of a specific target may correlate with activity for the target specific agent and resistance to other agents to targets that are upstream or in parallel pathways. Unfortunately, the simple linkage of good drug, good target and good test has remained elusive for many agents. Our challenge is narrow the gap between cancer biology, drug, and diagnostic test discovery and evaluation. Clinical trials and studies need to be conducted efficiently in rare tumours − to look for genetic links and activity across histologically and molecularly defined subsets. Further integration of activities in cancer target identification and validation, drug and diagnostic test development, is required for the efficient and ultimately successful cancer therapeutics.

SP147
Pharmacogenomics in pancreatic cancer

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Cancer of the pancreas is a relatively common malignancy and a leading cause of cancer related deaths. Progress in diagnosis and treatment has been disappointing but improvement in understanding of pathogenesis and of molecular changes may offer some ground for rational and etiological approach [1]. The first evidence about the benefit of targeting dysregulated pathways was provided by the study on the addition of the EGFR inhibitor erlotinib to gemcitabine. Since then, despite other numerous negative studies, various agents have been investigated in the preclinical and clinical setting and are currently through drug development pipeline. Advances in the understanding of pancreas cancer biology have been made over the past decade, including the discovery of critical mutations in oncogenes (i.e., K-Ras) as well as the loss of tumor suppressor genes, such as TP53 and p16(INK4). Other studies showed the dysregulation of the expression of proteins involved in the control of cell cycle, proliferation, apoptosis, and invasiveness, such as Bcl-2, Akt, mdm2, and epidermal growth factor receptor. These characteristics might contribute to the aggressive behavior of pancreatic cancer and influence response to treatment [2]. Indeed, the inactivation of p53 may explain the relative resistance to 5-fluorouracil, whereas Bcl-2 overexpression is associated with reduced sensitivity to gemcitabine. However, the future challenge of pancreas cancer chemotherapy relies on the identification of molecular markers that help in the selection of drugs best suited to the individual patient. Recent pharmacogenetic studies focused on genes encoding proteins directly involved in drug activity, showing the role of human equilibrative nucleoside transporter-1 as prognostic factor in gemcitabine-treated patients [3]. Finally, inhibitors of signal transduction and angiogenesis are under extensive investigation, and several prospective trials have been devoted to this area. Pharmacogenetics is likely to play a central role in the personalization of treatment, to stratify patients based on their likelihood of response to both standard and targeted treatments. Thus, molecular analysis should be implemented in the optimal management of the patient affected by pancreatic adenocarcinoma.

References

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SP157
Informed consent for future research: how much can/should we ask upfront & afterwards

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In cancer research, studies of biological samples hold great promise for identifying new targets, understanding mechanisms of action/resistance to therapy and, when linked with clinical data, prognostic and predictive factors for treatment selection. Issues related to informed consent for research on biological samples include: whether consent is required at all, the nature of research to be conducted, mechanisms for assuring confidentiality, how/if patients will receive results of the study(ies), withdrawal from the study, and oversight mechanisms for scientific and ethical review of research. There are variations in ethical guidelines and legal requirements from country to country that can affect the consent templates. This presentation will focus on tissue collections undertaken as part of a prospective research project (e.g. clinical trial or biobank) where a consent process will have taken place to address many of the key issues noted above. One problem that arises is how to handle the situation where research other than that initially agreed to by the patient is now proposed? In the biobanking situation this should be a rare phenomenon if the collection is obtained from patients appropriately consenting to a wide array of future research. However, many collections from clinical trials, particularly those from 5−10 years ago, obtained consent for an explicit research question and did not reference future use of tissue. In these circumstances, guidance must be sought not only from the legal regulations in the country(ies) from which the samples were obtained, but also from the ethical committee for the project. In some cases, the "new" project is simply an extension of the initial one; e.g. a patient has consented to EGFR expression studies in tissue and now FISH and mutational studies are proposed. In this example, re-consent is seldom required since the new project is in keeping with the original intent, and it carries no new risks to patients. If, however, the proposal is for genetic testing for cancer susceptibility genes, re-consent would be required in most jurisdictions. Interestingly, empiric studies of patients who have consented to tissue studies show most would agree to secondary research use provided confidentiality is maintained. Many now believe that, to avoid such problems, consent forms should state clearly the possible future uses for the collected samples and allow patients to authorize (or refuse) future research.

SP174
Gene signatures: Are we ready to change clinical management in cancer patient treatment?

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Introduction: Gene expression can be used to understand the biology and anticipate the clinical behavior of cancer. While effective for discovery, expression microarrays present significant challenges for clinical application.
Purpose: Review the approach to developing and validating gene signatures. Underscore specific successes and highlight their potential to improve cancer care. Discuss current trials and available tests that use gene expression signatures to guide therapy. Identify the important elements required for successful clinical application of gene signatures.
Main message: Successful application of gene signatures requires rigorous standards, meticulous execution, and the adoption of standard operating procedures so as to ensure robust and reproducible application to clinical samples.
Conclusions and Recommendations: While representing a significant challenge, gene signatures can be used to guide therapy. Development and application of gene signatures to guide clinical care requires a team approach and investigators with complementary expertise including oncology, molecular biology, pathology, laboratory medicine, and biostatistics.

SP168
Clinical relevance of circulating tumor cells (CTC) in primary and metastatic breast cancer

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A subclinical tumor cell spread can be assessed in breast patients with the detection of disseminated tumor cells (DTC) in bone marrow aspirates or