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.

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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

circulating tumor cells in the peripheral blood (CTC). Sequential peripheral blood analyses should be more acceptable than BM aspirations and many research groups are currently assessing in studies the clinical value of CTCs in primary and metastatic breast cancer. The purpose of this presentation is to give an overview of the clinical value of CTC.
Primary breast cancer: Depending on the detection technique used, CTC were revealed in 5−20% of patients with primary breast cancer. In contrast to metastatic breast cancer the role of CTC in primary breast cancer to predict prognosis is still under investigation and conclusive data have not yet be obtained. To monitor efficacy of therapy is of great clinical relevance especially in the adjuvant setting when no measurable tumor is present. In the SUCCESS-trial peripheral blood from 1,500 breast cancer patients before and after adjuvant taxane-based chemotherapy was examined for the presence of CTC. While the presence of CTC before systemic treatment did not show prognostic relevance, persistence of CTC after chemotherapy was a significant predictor for reduced disease free and overall survival. The aim of adjuvant therapy is to eliminate MRD reflected by CTC. Interestingly, the expression profile of therapeutic relevant markers differs between CTC and primary tumor indicating that adjuvant treatment strategies based on the expression profile of the primary tumor may not be efficient to eliminate minimal residual disease.
Metastatic breast cancer: The detection rates in metastatic breast cancer range from 40% to 80%. The prognostic significance of CTC in the metastatic setting has been clearly demonstrated by several large studies. Interestingly, CTC determinations seem to be superior over conventional imaging methods for therapy monitoring. In metastatic cancer the phenotype of metastatic disease is reflected by the phenotype of CTC. Therefore, characterization of CTCs may be useful to reassess therapeutic relevant markers (e.g. HER2, ER) particularly when a biopsy of the metastasis cannot be performed.
Conclusion: Based on current study results, circulating tumor cells have the potential to improve predicting prognosis, monitoring therapy and optimizing adjuvant treatment.

SP142
Molecular imaging

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Molecular Imaging (MI) using Positron Emission Tomography (PET) and tracers radiolabeled with positron emitting isotopes (Fluor-18, Gallium-68; Zirconium-89; Carbon-11; Copper-64, etc.) is increasingly studied as biomarkers in oncology. The strenght of the technology is based upon its unique nanomolar detection sensitivity (allowing a minimal amount of tracer to be administered, microdosing, without relevant pharmacologic effect) and by its capacity to perform rapid and semi-quantitative whole body imaging (allowing to quantitatively assess multiple lesions altogether in the same conditions, thus accounting for phenotypic heterogeneity), and to integrate molecular and structural information of cancer (hybrid PET-CT camera technology).
The PET biomarkers can be used for the selection of the patient for a specific drug (through the imaging of the expression of the molecular target, eg. HER2-neu receptor imaging, or physiologic state, eg. hypoxia), and for pharmacodynamic (PD) assessments (early changes of FDG uptake during therapy, or FLT, a surogate for proliferation, or apoptosis).
The lecture will deal with the rationale (how will MI contribute to a better cancer care), the technical principles (cameras and tracer) and the challenges (standardization and harmonization of MI in multicentric trials) of MI. Some ongoing multicentric clinical research projects incorporating MI will be discussed.

SP171
Prognostic and predictive signatures in breast cancer: update and future perspectives

N. Harbeck. *Universitaetskliniken Koeln, Germany*

In primary breast cancer, tumor-biology-based prognostic and predictive factors are urgently needed to optimize treatment decisions. The uPA/PAI-1 protein test and multigene assays, e.g. the Amsterdam 70-gene, the Rotterdam 76-gene or the 21-gene (recurrence score) signatures have been shown in retrospective studies to reliably predict patient outcome. Other promising factors include methlylation-based markers (e.g. PTIX2) or disseminated tumor cells in bone marrow or blood. Among prognostic factors, only uPA/PAI-1 has been validated by a prospective clinical trial at LOE I. For recurrence score and the 70-gene signature, large international trials are currently recruiting. The only tumor-biological predictive factors routinely used are HER2-status (trastuzumab) and hormone receptor status (endocrine therapy); but no factor can reliably identify the optimal chemotherapy. HER2 status has been suggested as a marker for anthracycline response yet high response rates with anthracycline and taxane containing neoadjuvant chemotherapy are seen in triple-negative disease. For topoisomerase 2, neither the biological role in anthracycline response nor the best determination method have been clarified. For endocrine therapy, CYP 2D6 mutation status has been suggested as a predictive factor based on decreased tamoxifen metabolism in mutation carriers. However, the lack of consistent predictive marker data is partly explained by hypothesis-generating data from small retrospective analyses lacking power for appropriate interaction and validation analyses. Individualizing adjuvant therapy decisions in primary breast cancer is already possible by protein or molecular markers. The challenge is to make these assays robust, quality-controlled, and applicable for clinical routine. Assays aimed at sparing patients from unnecessary therapy need to be thoroughly technically and clinically validated. Beside HER2 and hormone receptor status, no clinically validated biological predictive markers are currently available. We need assays that can help select chemotherapeutic and endocrine options that optimize therapeutic benefit and minimize side effects. Prognostic and predictive factors can only be prospectively validated in appropriately sized clinical trials with translational research programs. Pharmaco-economic data need to be generated to ensure appropriate pricing and benefit from these assays independent of the strength of national health budgets.

SP160
Targeted therapies directed against EML4-ALK translocations and BRAF mutations in patients with lung cancer

B. Johnson. *Dana-Farber Cancer Institute, USA*

Introduction: Prospective clinical trials have now shown non-small cell lung cancer NSCLC) patients with sensitizing mutations of the epidermal growth factor receptor EGFR) have 2 to 3 fold prolongation of progression-free survival when treated with gefitinib compared to those treated with chemotherapy. This led to the European Commission granting marketing authorization for gefitinib in patients with mutations in the EGFR in July of 2009.
Purpose: This presentation provides information on other potential genomic abnormalities that can be targeted with novel agents.
Main message: EML4-ALK translocations: Investigators discovered a chromosomal translocation in adenocarcinomas of the lung which could transform NIH 3T3 cells. The transforming gene was a fusion of the ALK gene with echinoderm microtubule-associated protein-like 4 (EML4) in Japanese NSCLCs. Further studies show the EML4-ALK translocation is present in NSCLCs arising in about 3% of patients from the United States and Europe. The translocated gene can now be detected by using fluorescence in situ hybridization in histologic sections of the tumor. The drugs directed against the ALK tyrosine kinase include TAE684 and PF2341066. PF2341066 has shown antitumor activity with a 50% response rate in phase I trials for NSCLC patients with the EML4-ALK translocation. A randomized phase III trial for patients with relapsed NSCLC and EM4-ALK translocation is planned.
BRAF mutations: Investigators have documented that BRAF mutations are common in melanoma and clinical trials have been developed for patients with melanoma where treatment is determined by the patients' BRAF mutations status. BRAF mutations are present in approximately 3% of patients with NSCLC. Trials have now been designed that include patients with NSCLC and BRAF mutations who are treated with MEK inhibitors.
Recommendations: Patients with advanced NSCLC should undergo genomic characterization for mutations in EGFR so they can initially be treated with gefitinib or erlotinib. The characterization of genomic changes should include additional genes so they can be allocated to appropriate genomically directed trials.
Conclusions: There are now two examples where genomic characterization of NSCLCs can lead to encouraging therapeutic outcomes (EGFR mutations and EML4-ALK translocation). Consistent characterization of other genomic changes will allow assessment of other targeted therapies in genomically defined NSCLC patient subsets.

SP164
Biomarker research: the patient perspective

P. Kim. *Translating Research Across Communities, USA*

Biomarkers and biospecimens hold the promise of helping patients and their healthcare teams improve in their goals of preventing, managing, treating, and curing disease.
Patients focus primarily on the opportunities and end products of biomarker research − translation: "How will this help me or my loved ones?"
Patients are not concerned with the challenges researchers face in arriving at the end products of biomarker research − translation: "Hurry up and figure this out so you can help me/us."