The consequence is poor performance in practice. However, one does not need all genes on the array. One can proceed in two steps, first reducing the number of genes to only a couple of signature genes using conventional test statistics, and then solving a low dimensional classification problem using standard linear discriminant analysis. While this strategy works, the resulting models have different properties on large-scale data, than they would have in a low dimensional setting. The large-scale setting imperatively requires a different kind of statistical thinking.

In this talk, I will point out the power and the limitations of conventional statistical methodology in large scale profiling. I will start with pointing out the specific statistical characteristics of microarray-based diagnosis. To this end, I will discuss, how to design a diagnostic microarray study, how to select marker genes, how to determine an appropriate number of marker genes, how to combine the expression levels of these genes to a diagnostic signature, how to evaluate the performance of a signature, and finally how to document a diagnostic signature for publication. In all steps I will choose statistical concepts, which are as conventional as possible for these tasks.

doi:10.1016/j.ejcsup.2006.04.019

S19. MOLECULAR MRI IMAGING OF GLIOBLASTOMA MODELS

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Conventional magnetic resonance imaging (MRI) in glioblastoma models concentrates on high resolution imaging, the description of pathophysiological changes by perfusion or diffusion weighted imaging and the characterization of metabolites with magnetic resonance spectroscopy.

With the advances in molecular biology and MRI there is rapidly growing interest in making radiological imaging techniques more sensitive and specific for monitoring, diagnosing, and differentiating biological processes.

The combination of information generated from molecular genetics, the large number of animal models of human diseases and new imaging techniques and contrast agents is the driving force of developments in molecular imaging. Major goals of molecular imaging by MRI are to image the presence of specific molecules with targeted contrast agents to track cell migration, follow changes in gene expression, and to develop strategies enabling MRI to monitor other specific biological processes. Encouraging results exist especially in the field of cell tracking and monitoring gene expression using the signal reduction caused by iron.

Problems encountered in the molecular imaging of glioblastomas include the creation of a highly specific imaging agent, access of the specific imaging agent to the molecular target (passage of the blood–brain barrier (BBB)) and an adequate imaging quality with strong specific signal. Translation of in vitro concepts to the in vivo application is often problematic. One major issue is the size of the specific compound hindering the imaging agent to pass the BBB or to pass even further to enter the cytoplasm. With this problem being unsolved further progress needs to be done before molecular imaging turns into a general imaging tool in animal models of glioblastoma.

doi:10.1016/j.ejcsup.2006.04.020

S20. MOLECULAR IMAGING CHANCES AND CHALLENGES

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Assessment of gene function following the completion of human genome sequencing may be done using radionuclide imaging procedures. These procedures are needed for the evaluation of genetically manipulated animals or new designed biomolecules which requires a thorough understanding of physiology, biochemistry and pharmacology. The experimental approaches will involve many new technologies including in vivo imaging with SPECT and PET. Nuclear medicine procedures may be applied for the determination of gene function and regulation using established and new tracers or using in vivo reporter genes such as genes encoding enzymes, receptors, antigens or transporters. Visualization of in vivo reporter gene expression can be done using radiolabeled substrates, antibodies or ligands. Combinations of specific promoters and in vivo reporter genes may deliver information about the regulation of the corresponding genes. Furthermore, protein–protein interactions and activation of signal transduction pathways may be visualized non-invasively. The role of radiolabeled antisense molecules for the analysis of mRNA content has to be investigated. However, possible applications are therapeutic intervention using triplex oligonucleotides with therapeutic isotopes which can be brought near to specific DNA sequences to induce DNA strand breaks at selected loci. Imaging of labeled siRNA's makes sense if these are used for therapeutic purposes in order to assess the delivery of these new drugs to their target tissue.

In gene therapy based on the transfer and expression of suicide genes usually genes coding for the non-mammalian enzymes, the Herpes simplex virus thymidine kinase (HSVtk) or the yeast and bacterial cytosine deaminase (CD), have been used. After infection of the tumor with the recombinant virus, a non-toxic prodrug is applied systemically, which is subsequently converted to a toxic metabolite by the recombinant gene product. Employing a radiolabeled prodrug and scintigraphic procedures it is possible to determine the functional activity of the recombinant enzyme in vivo. This information can be used to establish a therapeutic window of maximal gene expression and consecutive drug administration. If the gene therapy approach is based on the transduction of receptor genes, the recombinant gene expression in tumor cells is monitored using radiolabeled ligands. Transfer of transporter genes such as the sodium iodide transporter may also permit the visualization of transduction via accumulation of iodide or pertechnetate in the targeted tissue.

Pharmacogenomics will identify new surrogate markers for therapy monitoring which may represent potential new tracers for imaging. Also drug distribution studies for new therapeutic biomolecules are needed at least during preclinical stages of drug development. New treatment modalities such as gene therapy

with suicide genes will need procedures for therapy planning and monitoring. Finally, new biomolecules will be developed by bioengineering methods which may be used for isotope-based diagnosis and treatment of disease.

doi:10.1016/j.ejcsup.2006.04.021

S21. CURRENT STATUS ON MOLECULAR MARKERS AND TARGETS IN PANCREATIC DISEASE

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With an overall 5-year survival rate of approximately 4%, pancreatic ductal adenocarcinoma is one of the most aggressive human malignancies. Studies that aimed at the understanding of this exceptionally aggressive behavior discovered an increasing number of genetic and epigenetic alterations such as deregulated growth factor receptor/ligand systems, oncogenes, tumor suppressors, metastasis suppressors and related signal transduction pathways. Alterations of these genes and their respective proteins may occur throughout pancreatic carcinogenesis suggesting an adenoma-carcinoma model with an increasing number of molecular and cellular alterations. The most commonly mutated oncogene in pancreatic cancer is K-ras which induces cell proliferation via MAPK signaling. On the other hand, mutations in tumor suppressors such as p53, p16 and Smad4 also occur frequently. Besides, there are less common mutations in the tumor suppressor genes STK11, APC, FHIT, DCC, ARP, BRCA2, MKK4, TβR-I and TβR-II. Epigenetic alterations in growth promoting signaling pathways of the EGF, IGF and FGF family as well as autocrine or paracrine effects of their respective ligands have been shown to endow a growth advantage to pancreatic cancer cells. Concomitantly, it was shown that the important growth inhibitory pathway mediated by TGF-beta family members and their intracellular signal transduction molecules is lost in pancreatic cancer. Resistance to apoptotic cell death gives cancer cells a further growth advantage with downregulation of pro-apoptotic factors such as bak and bcl-2 or upregulation of anti-apoptotic bcl-X_L. Furthermore, aberrant expression of genes influencing invasion and metastasis is observed. Among those, heparanase, matrix metalloproteinases and galectins have been shown to mainly influence invasion while decreased expression of the metastasis suppressor KAI1 was associated with worse survival and an increased metastatic potential.

Identified alterations of signal transduction pathways can be used clinically as therapeutic targets, e.g. small-molecule tyrosine kinase inhibitors and other approaches show encouraging results in first clinical trials.

Thus, a translational research approach will be a promising way to slow down tumor progression and improve survival and quality of life of pancreatic cancer patients in the future.

doi:10.1016/j.ejcsup.2006.04.022

S22. NEW KEY MARKERS AND THERAPEUTIC SUBGROUPS IN BREAST CANCER RESULTING FROM MOLECULAR STAGING

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In breast cancer, tumor biological markers are urgently needed to individualize clinical decision making, particularly in order to avoid overtreatment in the increasing number of patients with small tumors. Urokinase-type plasminogen activator uPA and its inhibitor PAI-1 are the first novel markers validated at the highest level of evidence for their prognostic and predictive impact by a multicenter therapy trial (Chemo N_0) and a large EORTC-RBG pooled analysis. Their greatest clinical use so far is in node-negative (N_0) breast cancer where the test can be used to avoid adjuvant chemotherapy in patients with non-aggressive disease. In addition, in intermediate-risk patients as defined by the St. Gallen consensus, the test can be used to identify patients who should receive chemotherapy because their tumor has a more aggressive biology than classical pathological factors would otherwise lead to believe. The NNBC3 therapy trial (AGO, GBG, and EORTC PBG), which has already recruited almost 700 patients, compares risk assessment by uPA/PAI-1 to that by established prognostic factors and evaluates optimization of chemotherapy (FEC vs. FEC-DOC) in high-risk N0 patients. Other promising markers include methylation markers such as PITX2 for identification of patients with good outcome under adjuvant endocrine therapy, microarray signatures or multi-gene scores for risk group stratification. In addition to NNBC3, other large international therapy trials in N_0 breast cancer using gene signatures for risk group stratification will soon start recruitment. The current and future challenge is to integrate the most promising tumor biological factors into advanced decision support algorithms.

doi:10.1016/j.ejcsup.2006.04.023

S23. DNA-METHYLATION MARKERS AND YB-1 AS INDICATORS OF THERAPY RESPONSE IN BREAST CANCER

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Intrinsic or acquired resistance to chemotherapy is responsible for failure of current treatment regimens in breast cancer. For instance, transcription factor YB-1 regulates expression of P-glycoprotein gene *mdr*1 which plays a major role in the development of a multidrug-resistant tumor phenotype. High YB-1 protein expression in tumor tissue and surrounding benign epithelial cells is significantly associated with poor outcome in patients who received postoperative chemotherapy, indicating clinical drug resistance. Furthermore, in untreated patients, those with low YB-1 protein expression are still free of disease, whereas the 5-year relapse rate in those with elevated YB-1 is 30%.