

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.

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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.

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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