Award Lecture and Special Lecture

EACR Young Cancer Researchers Award

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From molecular changes to customized therapy

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Cancer is a disease caused by a series of mutations in tumor suppressor and oncogenes. Recently, some of the crucial pathways and major genes involved have been identified for certain tumor types. The possibilities for using this knowledge for improved diagnosis, treatment and survival are unlimited. While the practical applications of molecular profiling are still pending, some correlations already exist. For example, microsatellite instability, which is detected in a subset of colorectal cancer patients, has been shown to improve prognosis when adjuvant 5-fluorouracil is administered. With accumulating information on molecular prognostic indicators, genetic profiling of individual cancers could improve staging and help define the best treatment options for each pattern of mutations. It is likely, that instead of disease of organs (ie. colon cancer), patients will be treated according to mutation profile (ie. tumor with APC, RAS and p53 mutations with EGFR overexpression). Producing tumor genotypes is becoming less expensive and labor intensive as automated sequencers and microarrays provide high-throughput screening power.

Importantly, detecting differences between tumor and normal cells allows engineering tumor specific drugs. This approach has been recently validated with small molecule kinase inhibitors which have provided dramatic treatment results in previously highly resistant types of disease. Similar reports may become increasingly common, although curing diseases may require identification of gatekeepers and treatment of multiple steps of the malignant process.

Year 2000 was a breakthrough year for cancer gene therapy. For the first time it was unequivocally shown that genes can be delivered to target tissue for significant anti-tumor effect in heavily pretreated patients. This was achieved by using a conditionally replicating adenoviral agent which selectively replicates in cells harboring mutant p53, resulting in oncolytic killing of the cell and spread of viruses to surrounding cells. While these results are promising, there are numerous of possibilities for improving the activity and tumor selectivity of such agents. For instance, tumor or tissue specific promoters can restrict replication of the agent to tumor tissue and retargeting moieties can improve transduction of target tissues. These and other current approaches for improving the efficacy of cancer gene therapy will be presented.

Special Lecture

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Genomics - from complexity to simplicity ... a breast cancer experience

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Patients with the same diagnosis may have markedly different treatment responses and clinical outcome of disease. This variance might well be explained by the differences in the activation of genetic networks that underlie the biological behavior of the individual tumors. Recent developments in molecular biology and bio-informatics have opened a whole new era of global gene research, i.e., genomics, that can be used to unravel these networks.

Microarrays harboring upto 25.000 unique genes now enable us to explore the expression level of all known genes within a given tumor sample in one single experiment. Higher order mathematical analysis of these so-called expression profiles of a series of tumor samples is used to define signatures of expression for specific tumor (sub-)types that are otherwise indistinguishable. Thus, it is possible to identify signatures that predict treatment response, survival or the genetic predispostion of a patient.

In our own series of primary breast cancers of young patients we have established a gene expression signature indicative for a short interval to distant metastasis. This 'poor prognosis' signature was found to consist of genes that are involved in cell cycle, invasion and metastasis. The profile is a strong determinant of prognosis in a multivariate model ($p<0.001$) and patients with such a tumor expression profile have a 30-fold increased risk to develop a distant metastasis within five years.

Expression profiling demonstrates to be a powerful diagnostic tool and allows "array-guided" tailored therapy.