Symposia

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Polygenic inheritance of predisposition to lung cancer in experimental models

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Purpose: Dissection of genetics of the complex inheritance of susceptibility and resistance to lung cancer.

Methods: Genetic linkage experiments using crosses by mouse inbred strains with inherited predisposition ant resistance to lung cancer.

Results: We have previously mapped a major locus *(Pulmonary adenoma susceptibility 1, Pas1)* affecting inherited predisposition to lung cancer in mice on chromosome 6, near *Kras2* (*Nature Genet.*, 3: 132–136, 1993). Appropriate crosses that include *Pas1*/+ mice provide a model system for identifying loci that can modify the lung cancer predisposition phenotype caused by *Pas1*. Using this approach we have mapped, on mouse chromosome 11, the *Pulmonary adenoma resistance J (Par1)* locus that selectively inhibits lung tumor development in *Pas1*/+ animals and behaves, therefore, like a modulator gene of *Pas1* (*Nature Genet.*, 12: 455–457, 1996). More recently, we and another group mapped a second lung tumor resistance locus (*Par2*) on chromosome 18, near the *Dcc* gene.

Conclusion: Experimental models provide an essential tool for the mapping of lung cancer susceptibility/resistance genes and for the subsequent cloning of candidate genes.

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Molecular intervention in small cell lung cancer

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In vitro and *in vivo* studies suggest the epithelial glycoprotein-2 to be the optimal surface protein for the development of targeted therapy in small cell lung cancer (SCLC). A recombinant immunotoxin based on a single chain fragment of antibody MOC-31 and the domains II and IIII of *Pseudomonas* exotoxin was developed by rational engineering. The current results suggest this recombinant immunotoxin to be more efficient against SCLC cells than a chemical immunotoxin based on the entire antibody.

bcl-2 overexpression is prevalent in SCLC. For functional studies, a series of antisense oligonucleotides to *bcl-2* were synthesized. The oligonucleotide 2009 targeting the coding region of bcl-2 specifically reduced the viability of SCLC cell lines over 90% and acted synergistically with doxorubicin. Our results demonstrate that bcl-2 is a life sustaining factor for small cell lung cancer and suggest that antisense to bcl-2 may have a therapeutic potential for this tumor.

Human CD24 is a glycosylphosphatidylinositol-linked surface protein overexpressed in SCLC. It is involved in cellular adhesion (ligand of P-selectin) and signalling of SCLC cells. We investigated the 5′-flanking region of the human CD24 gene for its promoter activity in lung cancer cell lines using a luciferase reporter gene. Strong and selective activity under the CD24 promoter was seen in SCLC, but not in non-small cell lung cancer. The CD24 promoter might thus serve as tool for the cell type-specific expression of therapeutic genes in SCLC.

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Genetic susceptibility linked with rare HA-ras1 alleles and microsatellite alterations in non-small cell lung cancer (NSCLC)

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Purpose: Rare alleles of the H-ras1 minisatellite have been linked to increased susceptibilty to several neoplasms including NSCLC. We searched for rare H-ras1 alleles in peripheral blood lymphocyte DNA and in fresh tumors corresponding to 88 alleles from 44 resected NSCLC patients (pts) and 306 alleles from 153 healthy controls by PCR assay.

Method: Amplified products were electrophoresed through 40 cm long, 1.2% agarose gel. We also searched for the presence of microsatellite alterations using 3 dinucleotide markers on chromosome 3p (D3S1038, D3S1289, D3S1284) and one GAG trinucleotide on chomosome X.

Results: We found a higher number of rare alleles in NSCLC pts, 18/88 (20.4%) in contrast to the control group, 40/306 (13%). Among the rare alleles, al+4 was the most prevalent in 44% of NSCLCs. Loss of heterozygosity (LOH) was 31% and was more frequently observed (86%) in the NSCLC group with common Ha-ras1 alleles.

Conclusion: Rare Ha-ras1 alleles and LOH on chromosome 3p define divergent pathways in the development of NSCLC. Furthermore, rare Ha-ras1 alleles screened from blood DNA could plausibly represent an easy tool for use during the follow-up of resected NSCLC pts.

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The results of the accelarated fractionation scheme chart in the treatment of non-small cell lung cancer

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The knowledge that tumours have a potential for rapid cell proliferation has led to the hypothesis that tumours may repopulate during a course of radiotherapy. This led to the investigation of accelerated radiotherapy regimes. CHART (Continuous, Hyperfractionated Accelerated Radiotherapy) is the most accelerated regimen in clinical practice: 54Gy is given in 36 fractions of 1.5Gy treating three times per day for 12 consecutive days inclusive of the weekends.

A multicentre randomised controlled trial has been carried out under the auspices of the CHART Steering Committee comparing CHART to conventional radiotherapy 60Gy in 6 weeks in non-small cell carcinoma of the lung. A total of 563 patients were entered by 13 centre between April 1990 and March 1995. Patients with non-small cell lung cancer localised to the chest with a performance status of 0 or 1 were included.

The groups were well matched with regard to prognotic factors. Overall there was a 24% reduction in the relative risk of death equivalent to an absolute improvement in 2 year survival of 9% from 20 to 29% ($p = 0.004$). Likewise there was a significant improvement in local tumour control ($p = 0.027$).

CHART gave a significant improvement in survival in non-small cell lung cancer when compared to conventional radiotherapy. Further improvement may be achieved with dose escalation using conformal therapy, hypoxic cell radiosensitisation and/or by the addition of cytotoxic chemotherapy.

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Combined chemotherapy and radiation

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The efficacy of radiation in locally advanced NSCLC is limited. In a search for improving the outcome, particular attention has focused on the possibility of adding chemotherapy to radiation. The major expectation from this approach has been to increase the cure rate by either improved locoregional tumor control or by elimination of micrometastases outside the radiotherapy field. Two most frequently used strategies include chemotherapy preceding radiation and concurrent application of both modalities. The results of phase III trials comparing radiation alone to radiation combined with chemotherapy have been equivocal. Early studies utilizing chemotherapy not containing cisplatin were usually negative. More recent use of cisplatin-based regimens particularly if applied as *induction* treatment, has been found to produce modest, but significant survival benefit. The role of *concurrent* radiother-