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Methylation inactivates critical pathways in tumourgenesisJ. Herman¹, M. Esteller, P. Corn, S. Baylin. ¹ *Johns Hopkins University, Department of Oncology/Tumor Biology, Baltimore, United States*

Genetic alterations are a hallmark of human cancer. In addition to these genetic alterations, changes in DNA methylation, an epigenetic modification present in mammalian cells, are frequent in human cancer. The promoter regions of many genes contain CpG islands which, with the exception of genes on the inactive X chromosome and imprinted genes, are protected from methylation in normal cells. Work in the past several years has demonstrated that the silencing of tumor suppressor genes associated with promoter hypermethylation is a common feature in human cancer, and serves as an alternative mechanism for loss of tumor suppressor gene function, since promoter region hypermethylation leads to transcriptional repression. The genes targeted for this tumor specific change include genes important for tumor development and progression. For example, promoter region methylation inactivates genes regulating cell cycle control (Rb, p16, p15, p73) as well as those inhibiting invasion (E-cadherin) and apoptosis (DAP kinase), and genes involved in DNA repair (hMLH1, MGMT, GST-p). Patterns of inactivation for some of these genes have striking specificity, implicating particular importance to inactivation of these pathways in some tumors. This specificity is most striking for the inactivation of genes associated with inherited predisposition to cancer. Hypermethylation of these loci occurs in sporadic tumors of the same types as those which develop in the familial syndromes. The functional consequences of loss of function of these genes will be explored. In addition, promoter region hypermethylation is a promising new biomarker for early detection and disease monitoring in human cancer.

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RAS-oncogene interacting agentsJ. Verweij. *Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, 3075 EA Rotterdam, Netherlands*

The RAS supergene family is comprised of 21–29 Kd GTP-binding proteins, that play a central role in the integration of the regulatory signals that govern cell cycle and proliferation. In addition, they are involved in cellular differentiation, apoptosis, cytoskeletal re-arrangement and nuclear import of proteins. To function as such, RAS must localise to the plasma membrane and be activated. Mutations in the RAS gene leading to an almost continuous activation of RAS have been extensively reported in a wide variety of tumor types. Thus, interfering with RAS activation in theory would lead to inhibition of tumor cell proliferation. Recently, inhibitors of farnesylprotein transferase, the rate-limiting enzyme in the activation of RAS have entered clinical development. Although they have been developed as selective inhibitors, to a varying degree the FTase inhibitors suppress farnesylation of a number of proteins other than RAS. For an optimal efficacy it is likely that these agents will have to be administered in a continuous schedule. To date clinical experience has been reported for 3 FTIs, the peptidomimetic L778, 123 the tricyclic inhibitor SCH 66336, and finally R115777. H-RAS can also be targeted by antisense agents such as ISIS 2503. For all drugs it seems that at the recommended doses their toxicities are relatively minimal. The most recent findings will be discussed as well as issues on clinical trial design.

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Anti-angiogenesis drugsA.-R. Hanauske. *UZ Gasthuisberg, Leuven, Belgium*

Growth and survival of cancer cells beyond initial stages is critically dependent upon oxygenation and nutritional supply. Tumor-directed neoangiogenesis thus is an important step for tumor progression, invasion, and metastasis and involves the multifactorial development of an angiogenic phenotype characterized by overexpression of both stimulatory and inhibitory growth factors. Antitumor strategies targeting tumor-neoangiogenesis are worldwide actively pursued. Targets include angiogenic growth factors and their receptors (eg vascular endothelial growth factor ($\alpha_v\beta_5$ receptor), basic fibroblast growth factor ($\alpha_v\beta_3$ vitronectin receptor: EMD 121974, S 836)) as well as other components involved in angiogenesis. Strategies currently investigated comprise: 1. monoclonal antibodies (eg. against VEGF, VEGF receptors, endoglin), 2. ribozymes (eg. against VEGF receptors), 3. Antisense (eg. against mRNA of VEGF, VEGF re-

ceptors, angiogenin), 4. tyrosine kinase inhibition (eg. SU 5416, PD 166 285, PD 173074, CGP 79787), 5. antiangiogenic proteins (eg. angiostatin, endostatin), and 6. others (combretastatin-4, irsoglandine, fumagillin analogues). Since these compounds are not *prima* designed to directly cause tumor regression traditional endpoints of clinical shay design will have to be revisited. Supported by a grant from IND-Synergen Inc. and Verein z. Förderg. d. Krebsforschung e.V.

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Polymers and anti-cancer agentsJ. Cassidy¹. ¹ *Aberdeen University, Department of Medicine & Therapeutics, Aberdeen, United Kingdom*

Our inability to selectively target an anti-cancer drug to the tumour and away from the organs of toxicity has two major consequences. Firstly, non-selective cell killing severely limits the amount of drug we can give in total by the toxic effects on normal tissues, in other words, cytotoxics have a narrow therapeutic index. Secondly, in some cases, insufficient drug will reach the site of the tumour to allow for therapeutic effect. This can be present *de novo* or can be acquired and is termed "pharmacological resistance". As with other forms of resistance it is difficult to assess just how important this might be in each individual patient.

The general structure of polymers allows for maximum chance to engineer in characteristics that should be useful in targeting. Thus it is possible to manipulate molecular weight (and thus renal handling), charge, shape, lipophilicity, poly dispersion and other physico-chemical characteristics. Monomers may be introduced which have direct chemical bonding to cytotoxic moieties. More commonly "linker" substitutions can be introduced which not only allow for attachment of the cytotoxic component, but may in themselves be dependent on cleavage within specific cellular micro-environments. Thus leading to a further level of targeting.

The clinical application of polymer technology is limited at present. Gliadel wafers and slow release preparations of gonadotrophins are perhaps the most widely used at present. PK1 was jointly developed between the UK Cancer Research Campaign and Pharmacia Upjohn. Full results of phase 2 evaluations in colorectal, non-small cell lung and breast cancer are awaited. There are also a variety of agents which are in or about to enter phase 1 which show encouraging pharmacokinetic advantages in preclinical testing. The next generation will be polymers that can be tailor made with an intrinsic degradation and drug release profile, are non-immunogenic and completely biodegradable. This can be catalysed by the incorporation into the polymer of a fixed percentage of its own (non-mammalian) cleavage enzyme. These features are now achievable in the laboratory and urgently require translation into clinical practice.

If these systems eventually fulfill their promise it is conceivable that all cytotoxics would be administered as part of a selective delivery mechanism in future.

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Hemopoietic stem cell transplantation (HSCT) in EuropeA. Bacigalupo. *Department of hematology, Genova, Italy*

The European Group for Blood and Marrow Transplantation (EBMT) was founded in 1975 to bring together scientists involved in hemopoietic stem cell transplants (HSCT): originally there were less than 10 Centers performing 16 transplants/year, now we have 361 Centers from 31 Countries, who performed over 14.000 transplants in 1996. Of these 4369 (30%) were allogeneic and 9988 autologous (70%). Allogeneic stem cells can be obtained from different sources: in 1996 these were bone marrow in 74% and peripheral blood in 26%. A small number of cord blood transplants are also being performed at present. The donor was a family member in 3422 and an unrelated individual in 947.

Major indications were leukemias (34%), lymphomas (38%) and solid tumors (24%). Emerging indications now exist, like breast cancer.

The procedure has become rather sophisticated and its complexity is likely to increase in the future: we are slowly moving from unmanipulated