approximately 30 different growth factors, and through its potent coupling to the major control route of cell division, namely the Ras-MAP-kinase pathway, ErbB-2 efficiently delivers growth-regulatory signals to epithelial cells, the precursors of carcinomas. Successful blocking of ErbB-2 action may, therefore, prove beneficial in the clinics.

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Specific DNA sequences – A new target?

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Purpose: Agents now exist which can target both the type of damage, and particular DNA sequences with a far greater selectivity than conventional DNA damaging agents. Recent advances will be reviewed.

Methods: Novel DNA sequence selective agents have been rationally designed and synthesised. The novel technique of single strand ligation PCR (ssligPCR) now allows DNA damage by such agents to be mapped at the nucleotide level of single copy genes in intact cells.

Results: As examples oligopeptide based agents will be used to illustrate how sequence selective binding in the minor groove can be altered and enhanced and used to deliver selectively different types of reactive groups. The rational design of sequence selective interstrand crosslinking agents based on the pyrrolobenzodiazepine structure found in natural products such as anthramycin will also be illustrated. Until recently determination of sequence selective binding to DNA was only possible in cell-free systems using highly purified or synthetic DNA. Using ssligPCR binding of sequence selective agents to their target cellular gene sequence can be confirmed. In addition, the sequence selectivity of repair of individual lesions can be measured allowing more precisely the relationship between sequence selective binding and biological activity to be investigated.

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Vascular endothelial growth factors and receptors involved in angiogenesis and lymphangiogenesis

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Angiogenesis, the formation of new blood vessels from preexisting ones, and the permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two known receptors Flt1 (VEGFR-1) and KDR/Flk-1 (VEGFR-2). VEGFR-3 does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. We have purified the Flt4 ligand, *VEGF-C*. Transgenic mice expressing VEGF-C under a basal keratin promoter develop a hyperplastic lymphatic vessel network in the skin. VEGF-C is thus a novel regulator of lymphatic endothelia. As VEGF-C is also capable of stimulating VEGFR-2, its effects may extend beyond the lymphatic system, where VEGFR-3 is expressed. Another related novel growth factor, *VEGF-B* was also cloned in collaboration with Dr. Ulf Eriksson's group and found to be co-expressed with VEGF and VEGF-C in heart, muscles and less in other tissues.

Tie, one of the receptor tyrosine kinases we have cloned, is expressed in mouse hematopoietic stem cell fractions and in all studied fetal endothelial cells. Tie is required during embryonic development for the sprouting of new vessels, particularly in the regions undergoing angiogenic growth of capillaries, but it is not essential for vasculogenesis. Our results thus demonstrate an increased complexity of signalling for endothelial cell proliferation, migration, differentiation and survival.

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Functional and proliferative characteristics of neovasculature as potential targets in tumour therapy

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All solid tumours evoke a new network of capillaries. They are usually chaotic, thin walled, poorly innervated and lacking a corresponding lymphatic drainage system. The intercapillary distances are abnormally large and the blood contained within the vessels is nutritionally depleted. The endothelial cells are rapidly proliferating, immature, more procoagulant, sticky and leaky than in normal vessels. The vessels lack musculature and innervation.

As a consequence tumour cells are poorly supplied with nutrition and in large tumours extensive death due to starvation may almost balance the rapid production of new cells. Most tumour cells are totally dependent on a single capillary and have no access to an alternative collateral circulation if that vessel closes. Thus vessel occlusion or collapse can lead to an avalanche of secondary ischemic cell death. If the neovasculature is viewed as a target for anti-proliferative therapy, or for functional alteration e.g. of coagulation or permeability, the differences can be used to cause specific occlusion or destruction of newly formed vessels. This already happens sometimes with hyperthermia, photodynamic therapy, certain cytokines e.g. TNF and some cytotoxic drugs. However, little effort has been made to maximise the indirect effect mediated via vascular damage instead of direct killing of tumout cells. New approaches include targetted antibodies and inducible gene therapy using altered endothelial function to induce clots or blood stasis.

The changes in tissue architecture, especially nutrient gradients, also provide pathophysiological pO_2 and pH conditions which may be viewed as additional helpful factors in targetting either tumour endothelium or the tumour cells themselves.