Wednesday 8 November 10:15–12:00

WORKSHOP 4

New targets in angiogenesis

14 INVITED

Vascular targeting

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One avenue towards the development of more selective anti-cancer drugs consists in the targeted delivery of bioactive molecules (drugs, cytokines, procoagulant factors, photosensitizers, radionuclides, etc.) to the tumor environment by means of binding molecules (e.g., human antibodies) specific for tumor-associated markers.
The targeted delivery of therapeutic agents to newly-formed blood vessels ("vascular targeting") opens a broad palette of biomedical opportunities. Angiogenesis, i.e., the proliferation of new blood vessels from pre-existing ones, is an important process not only in cancer, but also in relevant diseases such as certain blinding ocular disorders and rheumatoid arthritis. The ability to selectively target and occlude neovasculature promises to be useful for the diagnosis and treatment of angiogenesis-related diseases.
In collaboration with Philogen SpA and with Luciano Zardi (Genova), my laboratory has developed human monoclonal antibodies, capable of selective targeting of neo-vascular structures in solid tumors and in a number of angiogenesis-related diseases. Three derivatives of these antibodies (i.e., two immunocytokines and a radiolabeled antibody) are currently being investigated in clinical trials.
The identification of novel vascular markers of pathology and the development of novel methodologies for the isolation of high-affinity small organic binding molecules are possibly the most pressing technological challenges for future developments in the field of vascular targeting. In the first research area, we have developed a novel chemical proteomic methodology based on the in vivo perfusion of tumor-bearing animals with reactive ester derivatives of biotin, followed by purification of the biotinylated vascular proteins in normal organs and tumors and by a comparative mass spectrometric analysis, for the identification of novel accessible markers of pathology. In the second research area, my laboratory has developed novel DNA-encoded chemical library technologies (e.g., encoded self-assembling chemical libraries), which allow the construction and screening of chemical libraries of unprecendented size.

References

D. Neri and R. Bicknell (2005). Vascular tumor targeting. Nature Rev. Cancer 5, 436–446.
S. Melkko, J. Scheuermann, C. Dumelin, D. Neri (2004). Encoded self-assembling chemical libraries. Nature Biotechnol. 22, 568–574.
J. Rybak, B. Kaissling, R. Giavazzi, D. Neri, G. Elia (2005). In vivo protein biotinylation for the identification of organ-specific antigens accessible from the vasculature. Nature Methods 2, 291–298.

15 INVITED

New hypoxia targets

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Hypoxia is common in human cancer and via hypoxia inducible factor 1 induces many proangiogenic cytokines, including VEGF, PDGF, TGFB3, adrenomedullin, leptin, endothelin 1, tie2. Receptors on endothelial cells are upregulated such as transferrin receptor, VEGF receptor 1, VEGF receptor 2, CXCR4 and Hepatocyte growth factor receptor. These already provide many targets for therapy. We discovered a novel endothelial pathway regulated by hypoxia, the expression of Delta4 and endothelial specific notch ligand, in human tumour vasculature and shown it is upregulated in bladder, breast and renal cancer endothelium. In vitro work indicates the important role of Delta4 in maintaining many endothelial functions necessary for angiogenesis and we are now investigating approaches to inhibit notch signalling in vivo.
Copper has been known for many years to be essential for angiogenesis although the mechanism has been unclear. Copper uptake is stimulated by hypoxia. We have carried out gene array analysis of endothelial cells and found that copper chelation induces free radical stress and inhibits Superoxide Dismutase 1 function. RNAi for Superoxide Dismutase inhibition also had similar effects, indicating this may be a key pathway controlling angiogenesis. Lysyl oxidase is another copper dependent hypoxia inducible enzyme critical for angiogenesis. We have therfore carried out a phase I trial of ATN224, an orally available copper chelator and shown it has effects on circulating endothelial cells and produced stable disease for a number of patients, at the highest dose in a phase I trial. Phase II trials are planned. Although VEGF inhibition has now shown marked effects in at least four major tumour types improving survival, clearly there are other pathways that interact or may synergise and amongst these are the notch pathway above and copper chelation. Combined approaches will be investigated in preclinical models initially.

16 INVITED

New drugs in early clinical development

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Tumours must develop and sustain a vascular network to grow beyond a few millimetres. Vascular endothelial growth factor (VEGF) is recognised as a pivotal stimulus of tumour angiogenesis and vascular permeability, and inhibition of VEGF/VEGF receptor signalling is considered to be an attractive therapeutic strategy. Indeed, recent clinical studies using the anti-VEGF-A monoclonal antibody bevacizumab in combination with certain chemotherapies have demonstrated the clinical value of targeting the VEGF signalling axis. An alternative anti-angiogenic approach is represented by the development of small-molecule inhibitors of VEGF receptor tyrosine kinase activity. Examples of this novel class of agent include AZD2171 and vandetanib (ZACTIMA™; ZD6474). AZD2171 is a highly potent inhibitor of VEGF signalling and angiogenesis. Early clinical data show that AZD2171 has encouraging antitumour activity across a broad range of tumours with a side effect profile that appears to be predictable and manageable. Vandetanib has potential for potent and broad antitumour activity by selectively targeting VEGFR and EGFR signalling, two clinically validated pathways in non-small-cell lung cancer. Vandetanib has additional activity against RET kinase, which is important for the growth and survival of certain types of thyroid cancer. Both agents have pharmacokinetic properties that support once-daily oral dosing. Data from the ongoing clinical development programmes for each agent will be presented at the meeting.
ZACTIMA is a trademark of the AstraZeneca group of companies.

17 INVITED

Metronomic antiangiogenic chemotherapy: recent preclinical and clinical advances

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"Metronomic" (antiangiogenic) chemotherapy refers to the close regular administration of low (non-toxic) conventional chemotherapy drugs, in the absence of any prolonged drug-free break periods, over long periods of time, even several years [1]. Unlike "dose-dense" and intensive chemotherapy it is minimally toxic and thus does not usually require supportive care drugs [1]. The preclinical anti-tumor effects of certain metronomic chemotherapy regimens can be surprisingly effective, especially when used in combination with concurrent administration with a targeted biologic antiangiogenic agent. It is thought that the anti-tumor basis of metronomic chemotherapy is mainly via antiangiogenic mechanisms as a result of the local targeting of dividing endothelial cells in the growing tumor neovasculature, and also the systemic targeting of bone marrow derived circulating endothelial progenitor cells (CEPs) [1]. Maximum tolerated dose (MTD) chemotherapy may, in some circumstances, also target CEPs but a hemopoiesis-like pro-angiogenic acute CEP 'rebound' can occur immediately afterwards which nullifies this potential antiangiogenic effect. Shortening or eliminating the drug-free break periods compromises this robust repair process. This CEP rebound phenomenon may also help explain the ability of certain antiangiogenic drugs such as bevacizumab (Avastin®) to enhance the efficacy of some conventional chemotherapy regimens, i.e., by preventing the systemic CEP rebound [2].
Several phase II metronomic chemotherapy clinical trials, some randomized, have been completed, most using daily low dose (e.g. 50 mg) oral cyclophosphamide, in conjunction with a targeted biologic agent such as bevacizumab or letrozole [3] for treatment of either advanced or early stage breast cancer, or celecoxib for advanced non Hodgkins lymphoma, with encouraging results despite the obvious drawback of the empiricism associated with metronomic dosing. However, advances, both preclinically and clinically are being made in the discovery of surrogate markers to monitor biologic activity of metronomic chemotherapy and help determine the optimal biologic dose. These markers include circulating apoptotic endothelial cells [1] and CEPs [4].

References

[1] R.S. Kerbel, B.A. Kamen. Nature Rev Cancer 2004; 4: 423.