antibodies specific to markers of angiogenesis have been generated either by antibody phage display or by iterative colony filter screening. In this lecture, I will present data on antibodies specific to splice isoforms of tenascin-C and of fibronectin. Human antibody derivatives which are currently in clinical trials have been produced in mammalian cell expression systems. RESULTS: The human antibodies F8, L19 and F16 (specific to the alternatively spliced EDA and EDB domain of fibronectin, and to the A1 domain of tenascin-C, respectively) have extensively proven their ability to efficiently and selectively localize around tumor blood vessels, following intravenous injection in tumor bearing mice. In the case of L19, its tumor targeting ability in patients with cancer has been extensively demonstrated using scintigraphic techniques, following antibody radioiodination. Five of the most promising antibody derivatives (L19-131I, L19-IL2, L19-TNF, F16, 131I, F16-IL2) are currently being investigated in over ten clinical trials, while three derivatives of the F8 antibody should enter clinical trials for the therapy of cancer by the end of 2008. In my lecture, I will provide an overview about the preclinical and clinical therapeutic performance of these products. CONCLUSIONS: Vascular targeting antibody derivatives represent a promising class of novel anti-cancer biopharmaceuticals. Five products of this type, developed in my lab and in the lab of Luciano Zardi in collaboration with Philogen SpA and with Bayer Schering AG, are currently being investigated in clinical trials in several European centers.

07 July 2008 09:00 - 09:45

PLENARY LECTURE

Metabolism

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Metabolism

No abstract received

07 July 2008 10:15 - 12:15

SYMPOSIUM

Invasion and metastasis

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Cell adhesion and signalling

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Cancer cell invasion and metastasis is a hallmark of the malignant phenotype that is responsible for most cancer deaths. Despite this, proteins involved in these processes are rarely considered as anti-cancer targets. One reason for this is the difficulty in devising optimal pre-clinical and clinical tests of the success of putative anti-invasive agents.

In recent years we have been devising ways of examining cancer cell invasion and metastasis in vitro and in vivo, and of testing the efficacy and mode of action of tyrosine kinase inhibitors that have anti-invasive activity and which are undergoing clinical evaluation. In particular, we are using genetically engineered mouse models of pancreatic and breast cancer, in which tumour cells arising also express GFP, to examine tumour development and progression in vivo by direct imaging. This is being done at the whole body- and single-cell levels in vivo.

Our results to date suggest that Src inhibitors might best be used as anti-invasive agents, and that invasion and metastasis is one role of both elevated Src itself and of focal adhesion kinase, Src's binding partner and substrate. This has implications for the use of these agents and for designing clinical trials that will examine their clinical usefuleness.

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Signaling mechanisms of tumor cell migration and metastasis

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Cell metastasis is a highly dynamic process that occurs in multiple steps that include cell invasion, intravasation, survival in the circulation, extravasation, and cell growth at the metastatic site. Understanding this process has been limited by the inability to visualize tumor cell behavior in real time using animal models. This is especially true in regards to the early events of metastasis which involve cell invasion and vessel wall penetration during intravasation. We have utilized translucent, GFP vascular transgenic zebrafish, and high resolution intravital confocal microscopy to study how human cancer cells expressing DsRed or CFP invade tissues, induce angiogenesis, and interact with newly formed vessels. The optical clarity and fluorescent vessels of this new xenograft model allowed us to visualize how the human metastatic gene RhoC promotes cell invasion and intravasation during the early events of cancer cell metastasis with unprecedented resolution. We find that RhoC expression induces a primitive amoeboid-like cell invasion characterized by the formation of dynamic membrane protrusions and blebs. Surprisingly, these structures penetrate the blood vessel wall exclusively at sites of vascular remodeling and not at regions of existing intact vessels. This process requires tumor cells to secrete VEGF which induces vascular openings, which in turn, serve as portholes allowing access of RhoC expressing cells to the blood system. Our results support a model in which the early steps in intravasation and metastasis require two independent events: 1) dynamic regulation of the actin/myosin cytoskeleton within the tumor cell to form protrusive structures and 2) loss of vessel wall integrity as a result of VEGF-induced permeability and vascular remodeling. The integration of zebrafish transgenic technology with human cancer biology may aid in the development of novel cancer models that target specific organs, tissues or cell types within the tumors. Zebrafish could also provide a cost effective means for the rapid development of therapeutic agents directed at blocking human cancer progression and tumor-induced angiogenesis.

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Individual and collective cancer cell invasion

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Cancer cell dissemination and metastasis in vivo result from a diverse set of migration strategies including individual cells and multicellular strands and clusters, referred to as collective invasion. Using 3D collagen lattices and in vivo intravital microscopy of cancer cell invasion, we have resonstructed at high resolution the subcellular location of pericellular proteolysis during the migration process, the resulting ECM remodeling, and invasion mechanism. Proteolytic microtracks generated by single cells are subsequently filled and widened by following cells that form collective stands moving along expanding macrotracks. Collective invasion in vitro was confirmed using in vivo xenografts monitored by intravital multiphoton microscopy. The findings show how cell invasion and proteolytic ECM remodeling form a functional unit of collective cell invasion and the generation of aligned tissue structures. Using molecular interference, including anti-integrin and protease-inhibitor-based inhibition, collective invasion is abrogated yet converted towards amoeboid single-cell scattering (collective-amoeboid transition), suggesting novel compensation strategies of cancer cell dissemination.

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Cell adhesion to the extra cellular matrix (ECM) in motility and metastasis

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The adhesive interactions of cells with their environment regulate a wide variety of cellular responses that affect multiple cellular features, including cell proliferation, survival, gene expression and migration. These signals are affected by a wide variety of environmental cues, including both chemical and physical properties of the adhesive surface. Thus, cells can differentially respond to different adhesive ligands, and can sense the geometry, rigidity, contractility and ligand density of the external surface. The complex information "gathered" by the cells via their matrix adhesion sites is processed and integrated, affecting a wide variety of cellular processes. Interestingly – this adhesion-mediated cross talk between the cells and the matrix is often perturbed in cancer cells, leading to many features of the transformed phenotype. In this lecture I will address the complex molecular interactions of cells with the extracellular matrix (ECM), focusing on the molecular complexity and diversity of the "integrin adhesome, and its multiple roles in regulating cell structure, migration and signaling. I will demonstrate that integrin adhesions can "sense" a wide variety of chemical and physical "environmental cues", including the nature