could be detected. This novel algorithm successfully designs and predicts efficiency of bifunctional siRNAs that can be used in the fight against NHL. A critical factor for any siRNA therapeutic is its effective and targeted delivery. Numerous B-cell malignancies show increased expression of BAFF receptor (BAFF-R). BAFF1 protein, a member of the tumor necrosis factor (TNF) family, trimerizes and binds to the BAFF-R on the cell surface where it is internalized by receptor mediated endocytosis (Lyu et al. 2007). This allows targeting of the BAFF-receptor for delivery purposes.

Non-Hodkin's Lymphoma cell lines such as Granta 519, Jeko-1, Rec-1, SUDHL4, Raji, Daudi and Z138 express BAFF receptor to different degrees. We produced BAFF receptor aptamers by using a nitrocellulose-filter based SELEX process. We chose two aptamers, designated as R1 and R14. Gel shift assays showed that the selected aptamers can specifically bind BAFF-R with nanomolar affinities (R1 $K_d = 47.12$ nM, R14 $K_d = 95.65$ nM). We have used live imaging confocal microscopy to visualize aptamers R1 and R14 selective binding and internalization in the B-cell lymphoma Jeko-1 cell line. Unlike the BAFF1 ligand, the aptamers do not enhance cell proliferation, and aptamer R1 is also able to block BAFF ligand mediated proliferation of these cells in MTS assays.

The ability of the aptamers to deliver functional siRNAs into B-cell lymphoma cells was examined using optimized R1 chimera-configurations to deliver an anti-Stat3 siRNA to Lymphoma cell lines. These aptamer siRNA chimeras internalize into Z138 and Jeko-1 cells and show target down-regulation.

248   INVITED
Targeting TRAIL receptors with genetically-engineered CD34+ stem cells

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Background: Preclinical studies demonstrating that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) exerts a potent and cancer cell-specific cytotoxic activity prompted clinical development of recombinant soluble TRAIL. Despite a good toxicity profile shown in phase I/II clinical studies, limited evidences of antitumor activity have emerged for soluble TRAIL. Stem/progenitor cell-mediated gene delivery of anticancer therapeutics might represent an innovative approach to overcome the limitations inherent to TRAIL receptor targeting, i.e., pharmacokinetic of soluble TRAIL, pattern of receptor expression, tumor cell resistance.
Methods: We have envisaged the use of CD34+ cells engineered by adenoviral transduction to express membrane-bound TRAIL (CD34-TRAIL+ cells).
Results: Transduced cells efficiently act as TRAIL-presenting vehicles and exert a potent tumor cell killing activity against a variety of hematopoietic (e.g., multiple myeloma, non-Hodgkin lymphoma) and nonhematopoietic (e.g., breast cancer) tumors, both in vitro and in vivo in xenograft models of human tumors. Following intravenous injection, CD34-TRAIL+ cells home in the tumor peaking at 48 hours after injection. Tumor homing of CD34-TRAIL+ cells is largely mediated by vascular cell adhesion molecule-1 (VCAM-1) and stromal cell-derived factor-1 (SDF-1). Computer-aided analysis of TUNEL-stained tumor sections demonstrates significantly greater effectiveness for CD34-TRAIL+ cells in increasing tumor cell apoptosis and necrosis over soluble TRAIL. Proteome array analysis indicates that CD34-TRAIL+ cells and soluble TRAIL activate similar apoptotic machinery. In vivo staining of tumor vasculature with sulfo-NHS-LC-biotin reveals that CD34-TRAIL+ cells but not soluble TRAIL target endothelial cells expressing TRAIL-R2, as shown by apoptosis of endothelial cells, appearance of hemorrhagic areas and marked reduction of vessel density.
Conclusions: Overall, these results demonstrate that CD34-TRAIL+ cells induce potent antitumor effects by targeting tumor cells and tumor vasculature. Phase I/II clinical trials to test the safety and activity of CD34-TRAIL+ cells in patients with advanced solid tumors are planned to exploit the anticancer potential of cell-based TRAIL delivery.

249   INVITED
The state of nanotechnology for targeted treatment delivery

A. Urtti. Finland

Abstract not received

250   INVITED
Targeted imaging and radionuclide therapy of somatostatin receptor positive tumours

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Targeted radionuclide therapy is a rapidly growing field in nuclear medicine. Some years ago only radioiodine was available for targeted radionu-clide therapy. Nowadays a number of approved radiopharmaceuticals

are available (e.g. MIBG, phosphonates, anti-CD-20-antibodies). Beside these commercially available radiopharmaceuticals, radiopeptides are of particular interest. G-protein coupled receptors are overexpressed on certain tumors and radiopeptides do have the capability to bind these receptors. Radiopeptides feature highly suitable pharmacokinetics (rapid targeting, high diffusibility and fast clearance) for radionuclide therapy.

Over the last years most experience was acquired with radiolabeled somatostatin analogues. The somatostatin analogues show exemplary the development of a radiopharmaceutical with its way from an imaging agent to a therapeutic drug and the efforts that are made to improve the therapy further.

The peptides that are used for therapy can be radiolabelled with gamma- or positron-emitting radionuclides which makes them suitable for imaging thus allowing a very precise prediction of the biodistribution of the radiopharmaceutical.

For therapy a number of different somatostatin analogues as well as different radionuclides have been used. Generally, objective response rates of approximately 30% can be achieved in patients suffering from metastatic, gastro-entero-pancreatic neuroendocrine tumors (GEP-NET). Recently a median time to progression of >36 months has been published for GEP-NET patients. Usually the treatment is tolerated very well with only limited short term side effects. In the long term mainly the kidneys and the bone marrow are at risk of radiation damage which makes these organs the dose limiting organs.

In summary, targeted radionuclide therapy with radiolabelled somatostatin analogues appears to be the most effective therapy for patients with meatsatic, somatostatin receptor positive GEP-NET. An overview of the current status as well as future developments in field of targeted imaging and therapy using radiopeptides will be given.

Thursday, 18 November 2010   14:05−14:45

Special Lecture

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251   INVITED
Lessons learnt of 20 years of targeted therapies

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Small molecule tyrosine kinase inhibitors and receptors-targeted antibodies have emerged over the last two decades as "revolutionary" anticancer drugs. The possibility of blocking specific targets overexpressed or mutated involved in carcinogenesis generated a great scientific enthusiasm. A high therapeutic efficacy with limited toxicity was expected due to the predicted selectivity of targeted drugs. The run for targeted therapy development led to important gains such as trastuzumab for breast cancer and imatinib for gastrointestinal stromal tumors. Nevertheless, an enormous amount of effort testing different targeted agents in large international studies turned to be negative or "marginally" positive.

Negative phase III clinical trials in diseases such as pancreatic cancer, non-small cell lung cancer and melanoma among others generated important informations: (1) The genetic complexity involved in carcinogenesis of solid tumors is a limiting factor for the identification of a unique target with the ability of blocking the oncogenic process − subpopulations are more likely to benefit. (2) Due to the "plasticity" of signaling pathways, pro-oncogenic signaling pathways can be unleashed upon blockade of a specific target − combination targeted therapy or multitargeted agents may be needed but "cumulative" side effects could be a limiting factor. (3) Defining the real implication of a specific target to the oncogenic process is needed − high throughput sequencing programs should be pursued to define the most important genetic abnormalities (e.g. mutations, translocations, . . .) for each tumor. A well performed preclinical and early clinical studies is a prerequisite step to predict the succes in the development of a new targeted agent.

Marginally positive phase III studies lead in limited circumstances to retrospective identification of subpopulations most likely to benefit or not from a given targeted agent. In advanced colorectal cancer, as an example, treatment with monoclonal antibodies targeting EGFR was restricted to a subpopulation known to be wild type KRAS after being studied in an unselected population. In fact, KRAS mutated tumors did not respond at all to this class of agent.

In the last years, the increasing sensibilisation towards upfront patient selection has already demonstrated strong positive results. In breast cancer, patients known to have defective DNA repair machinery due to BRCA gene mutation are particulary sensitive to PARP inhibitors. NSCLC patients with ALK gene rearrangements are highly senstitive to