SOMATOSTATIN BASED RECEPTOR TARGETING DRUG IN CANCER TREATMENT (Tel Hashomer)

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Abstract

Cancer has a tremendous impact on society and it is the second leading cause of death in the U.S.

Current cancer chemotherapy therapies are limited with respect to tumor cell targeting, therapeutic windows and the propensity to induce resistant tumor clones. One promising approach to overcome these problems is to use Targeted Drug Delivery (TDD) whereby a carrier that has a specific affinity to cancer cells is linked to an anticancer drug. While this strategy is being extensively investigated, the literature describes very limited range of conjugation methods mainly using mono-functional linkers for the coupling of drugs to carriers as enzymes, antibodies, peptides, and biodegradable polymers. The linkage of several and different drugs to a target specific carrier might improve the therapeutic efficacy of TDDs but this has yet to be achieved. Moreover, the possibility of engineering deviations in time release of different drug moieties from such a multi-conjugate suggests that employing a platform with multiple attachment and controlled release capabilities may represent a significantly improved architecture for drug multilinking - multi-released properties in TDD.

We target the somatostatin receptors: Somatostatin receptors (SSTr) is over expressed and found in neuro-endocrine tumors (NETs) such as lungs, brain, skin, adrenals, pancreas, liver and gastrointestinal tract. Somatostatin (SST) is a small cyclic peptides, secreted by the delta pancreatic cells and at the hypothalamic nerve endings. SST is involved in the regulation of diverse biological processes acting primarily as a negative regulator of a variety of different cell types, blocking processes such as insulin, glucagon and growth hormone secretion, cell growth and smooth muscle contraction. Each of the SST functions is initiated by the binding of the peptide to one or more of the five different receptor subtypes (SSTR1-5) which are expressed on the cell surface and belong to the G coupled protein receptor family. In normal tissues SSTRs present in endocrine and exocrine tissues, neuronal and immune cells, and have been identified in multiple sites throughout the nervous system, gastrointestinal tract, breast and pancreas. In various pathological conditions such as malignancies, autoimmune diseases, inflammation and others, SSTRs are significantly over-expressed in affected organs.

SST analogs: Native SST has a short half-life in vivo (2-3 minutes) due to

enzymatic activity. Somatostatin analogs are the first class of receptor binding peptides having gained clinical applications. Long-lasting synthetic somatostatin analogs have been developed and introduced into clinical practice. In addition, **Nuclear Medicine based on SSTR tumor targeting were developed as well**

The Need

Despite the progress in the development of SSTR analogs, there is still a need for improvement of the receptor targeting peptides by increasing the specific binding capacity to wider SSTR subtypes, prolonging binding and intracellular internalization processes and decreasing adverse effects on healthy tissues. These include the optimization of peptide analog properties e.g. receptor specificity and pharmacokinetics in order to obtain better selectivity of tumor and drug accumulation within tumor cells in comparison to normal tissues, especially to the critical organs such as liver, kidney and spleen. For example, the classical radioactive somatostatin analog DOTA-Tyr3-octreotide (DOTA-TOC) has relatively rapid clearance from the tumor and high uptake by kidney that makes it less safe and effective for radiotherapy.

The Technology

We have designed, tested and patented a novel family of SST analogs (PTR peptides) for tumor targeting applications using a proprietary backbone cyclization technology. A large number of derivatives were studied *in vitro* and *in vivo*, and one of them, (PTR 3207-86) labeled with a fluorescent moiety (FITC), showed very high tumor-targeting properties with no toxic effects. This leading compound displayed distinctive pharmacokinetic profile with clearance from the normal tissues while being accumulated in malignancies selectively. In mice xenografts models bearing human lung and colon carcinomas significant differences in fluorescence intensity between tumor and normal tissues were observed during the period from 24 to 72 hours after intravenous administration of the agent. Laser scanning microscopy revealed membrane binding with internalization of the agent into cancerous cells as well as in the peri- and intra-tumoral blood vessels.

We are developing the therapeutic platform for novel targeted chemotherapeutic conjugates for advanced cancer treatment based on somatostatin receptor specific drug delivery.

We have developed novel cancer targeting carriers - backbone cyclized somatostatin (SST) analogs (PTRs). A number of novel analogs were found to show

outstanding SST receptor specific binding *in vitro* and tumor accumulation *in vivo* with distinctively high and long-lasting tumor-to-normal tissue ratio (TNTR) compared to currently clinically used analogs. These preliminary results provide an excellent opportunity to use PTRs as specific carriers in TDD concept for advanced selective cancer therapy.

Our carrier is conjugated via unique chemical structure component to chemotherapy drug to enhance treatment selectivity, safety and clinical output .

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