

The Potential of Auger Endoradiotherapy

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Biologically targeted radiotherapy utilising tumour specific antibodies and peptides conjugated to therapeutic radionuclides is a promising treatment approach for the treatment of cancer. To date most biologically targeted radiotherapy has utilized beta emitting radionuclides as the therapeutic payload. However there is increasing interest in the use of high linear energy transfer (LET) radionuclides with a greater biological effect in order to enhance efficacy.

Peptide directed radiotherapy utilising Somatostatin analogues conjugated to beta emitting radionuclides has been proven over many years to be an effective treatment for patients suffering with neuroendocrine tumours. However Auger emitting radionuclides have several advantages as a therapeutic radionuclide including high LET and the potential for much higher conformality at a cellular level.

It has been suggested that a conjugate consisting of a DNA binding ligand labelled with an Auger emitter and a tumour specific biological, such as an antibody or peptide, could be exploited as a vehicle for the specific delivery of Auger emitters to the DNA of tumour cells via receptor mediated endocytosis.

Neuroendocrine tumours overexpressing somatostatin receptors can be selectively targeted using octreotide, a synthetic octapeptide that comprises a partial amino acid sequence of somatostatin and retains its receptor affinity.

We recently reported conjugation of a ¹²⁵I-labelled DNA minor groove binding ligand para-iodo Hoechst to the N-terminus of octreotate using an amide linker and investigated the affinity of the conjugate to somatostatin receptors (subtype 2, sst2) and its internalisation and nuclear localisation in a tumour cell line overexpressing sst2 receptors (A427, clone 7)¹. We also studied the biodistribution of the radioactive label following injection of A427-7 tumour bearing mice with the conjugate, ¹²⁵I-labelled (Tyr3)-octreotate or ¹²⁵I-labelled para-iodo Hoechst.

The results demonstrated that the conjugate retains affinity to sst2 receptors and showed enhanced uptake in A427-7 compared to the parent A427 cell line that lacks sst2 receptors. A substantially increased fraction of the cellular ¹²⁵I-activity following incubation with the radiolabelled conjugate was associated with nuclei compared to unconjugated para-iodo Hoechst. This nuclear localisation of para-iodo Hoechst was also demonstrated using fluorescence microscopy. Receptor mediated *in vivo* uptake of ¹²⁵I-activity in A427-7 tumours was observed following intravenous injection of radiolabelled conjugate. This uptake was blocked by co-injection of octreotate indicating that sst2 receptors are involved in the tumour uptake.

Although improved nuclear uptake of the conjugate was noted, once internalized into tumour cells the majority of the radiolabelled PIH remained within the cytosol, limiting the therapeutic potency of the agent. In ongoing work we are refining the structure of the conjugate aiming to improve its nuclear uptake in order to enhance its cytotoxicity.

[1] Lobachevsky P., Smith J, Denoyer D, Skene C, White J, Flynn B.L., Kerr, D.J., Hicks R.J., Martin R.F. Tumour targeting of Auger emitters using DNA ligands conjugated to octreotate. *International Journal of Radiation Biology* 2012; 88(12): 1009-1018.