^{166}Ho LABELLED COMPOUNDS FOR THE ENDORADIOTHERAPY

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Keywords: Holmium 166, macroaggregates, poly(L-lactic acid) microspheres, chitosan , biodistribution study

Aim : The purpose of this study was focused on the preparation Holmium-166 based agents for the radionuclide synovectomy (^{166}Ho-macroaggregates) and for the hepatic cancer therapy (^{166}Ho-chitosan complex). Radionuclide synovectomy (radiation synovectomy) is an alternative method, that cures patients with rheumatoid arthritis diseases without surgery. During treatment, the suspension of the radioactive particles is administrated via intra-articular injection into the target joint to destroy inflamed synovium. In case of hepatic tumour therapy treatment, ^{166}Ho-chitosan complex can be administrated either directly into the tumour, or via catheter into hepatic artery.
Materials and Methods: Isotope ^{166}Ho (E beta max = 1.84 MeV, half life = 26,8 hr) was prepared by the ^{165}Ho(n, gamma)^{166}Ho reaction at the neutron flux approximately 10^{14} $cm^{-2}s^{-1}$.

The Ho-macroaggregates (Ho-MA) were prepared by reacting the aqueous solution of $Ho(NO_3)_3$ with sodium borohydride solution in 0.2 M NaOH. The particle size distribution of the prepared Ho-MA was determined by the Laser Particle Size Analyser. Quality of the prepared Ho-MA particles was investigated by the electron microscope. The in-vitro stability studies were carried out by incubation ^{166}Ho-MA in 6 ml 0.9 % NaCl solution. The in-vivo stability studies of the ^{166}Ho-B-MA were done at 24 hours after administration of ^{166}Ho-MA into the knee joint of the rat (Wistar, 190-200g).

The Ho-poly(L-lactic acid) microspheres (Ho-PLA-MS), inactive samples were prepared. Samples were sonicated and the particle size distribution was inspected using the electron microscope and by the Laser Particle Size Analyser. Ho-PLA-MS were then irradiated. The in-vitro stability was studied after irradiation.

The ^{166}Ho-chitosan complex was prepared by reacting of $Ho(NO_3)_3.5H_2O$ with chitosan, which M.W. was from 150000 to 600000. The time dependence of ^{166}Ho-Chitosan viscosity was measured using Rheometer RC20-CPS (Rheotec). Radiochemical purity of ^{166}Ho-Chitosan complex was measured by radio TLC method.

Results: Studies carried out with ^{166}Ho-MA showed very good in-vitro stability prepared particles. The radioactivity leakage percentage was less then 5 % within approximately 190 hours of incubation. In-vivo studies showed very high retention of ^{166}Ho-MA in the target joint. The percentage of the activity retained in the knee joint was higher then 99.9 % at 24 hours after administration

Studies carried out with ^{166}Ho-chitosan complex proved relatively high radiochemical purity (more than 90%) within sufficient time period. However, ^{166}Ho-chitosan complex appears to be sensitive to the radiation degradation, heading for decreasing of the complex viscosity.
Conclusion : ^{166}Ho-Macroaggregates can be prospective agent for radionuclide synovectomy with respect to it's high in-vitro and in vivo stability. However, some disadvantages can be caused due to it's non-biodegradability.

^{166}Ho-chitosan complex is promising agent for the radiotherapy considering it's biocompatibility and biodegradability. It's quality though decreases with time and ^{166}Ho-chitosan usage immediately after synthesis will be probably highly required.

SYNTHESIS AND EVALUATION OF INDIUM-111-LABELED PEPTIDE DERIVATIVE TARGETED TO A CHEMOKINE RECEPTOR, CXCR4

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Keywords: CXCR4, peptide radiopharmaceutical, indium-111, metastatic tumor

A chemokine receptor, CXCR4 was identified as a coreceptor for the entry of T cell line-tropic HIV-1. Based on the structure-activity relationship study, specific CXCR4 inhibitors, T140 and its analogs (14-residue peptides) were developed as anti-HIV drugs (1). Recently, it was also reported that this receptor is highly expressed in tumor cells and plays an important role in tumor metastasis (2). The aim of this study is to develop a radiolabeled T140 derivative as a diagnostic agent for metastatic tumors. During T140 analogs, we selected Ac-TZ14011 as the mother compound because it shows high inhibitory activity and possesses a Lys residue for site-selective modification with diethylenetriaminepentaacetic acid (DTPA). By investigation of the antagonistic activity and *in vivo* behaviors of ^{111}In-DTPA-Ac-TZ14011, its applicability as radiopharmaceutical for tumor imaging was evaluated.

The protected peptide was synthesized using Fmoc-based solid-phase methodology, followed by trifluoroacetic acid treatment. The crude Cys(SH)-peptide was air-oxidized and its N-terminus was acetylated. Then, monoreactive DTPA (3) was attached to the side chain of D-Lys^8 that is distant from the indispensable residues for the antagonistic activity. DTPA-Ac-TZ14011 was reacted with $^{111}InCl_3$ for 30 min at room temperature. After purification by reversed phase HPLC, ^{111}In-DTPA-Ac-TZ14011 showed radiochemical purities of over 96%. Nonradioactive In-DTPA-Ac-TZ-14011 was prepared in the same way.

In-DTPA-Ac-TZ-14011 blocked the binding of a natural ligand, stromal cell-derived factor-1 (SDF-1), to CXCR4 in a concentration-dependent manner with IC_{50} of 7.9 nM. This value was slightly larger than that of Ac-TZ-14011 (1.2 nM). Furthermore, In-DTPA-Ac-TZ-14011 inhibited Ca^{2+} mobilization induced by SDF-1 stimulation through CXCR4.

Biodistribution study was performed on nude mice bearing CXCR4-expressed pancreatic carcinoma, AsPC-1 (4). ^{111}In-DTPA-Ac-TZ14011 showed higher accumulation in the tumor than those in the blood and muscle. By Ac-TZ14011 co-administration, the tumor-to-blood and tumor-to-muscle ratios were significantly reduced, suggesting CXCR4-mediated tumor accumulation.

In conclusion, we developed ^{111}In-labeled CXCR4 inhibitor, ^{111}In-DTPA-Ac-TZ14011, based on the structure-activity relationship. This compound demonstrated high antagonistic activity and specific accumulation in the CXCR4-expressed tumor. These findings suggested that ^{111}In-DTPA-Ac-TZ14011 would be useful for imaging of metastatic tumors.

T140 H-Arg-Arg-Nal-Cys-Tyr-Arg-Lys-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-OH
Ac-TZ14011 acetyl-Arg-Arg-Nal-Cys-Tyr-Cit-Arg-DLys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2

Figure 1 Amino acid sequences of T140 and Ac-TZ14011. A disulfide linkage is shown by a solid line. The indispensable residues for the antagonistic activity are underlined. Nal = L-3-(2-naphthyl)alanine, Cit = L-citrulline.

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SYNTHESIS, SEP-PAK PURIFICATION AND STABILITY OF THERAPEUTIC DOSES OF ^{131}IAZA, A CLINICALLY PROVEN HYPOXIA MARKER

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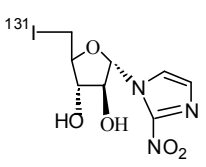

IAZA

Azomycin (2-nitroimidazole) nucleosides are highly diffusible radiosensitizers that readily permeate hypoxic tissues, where they are bio-reductively activated by single electron transfer and subsequently selectively bound as molecular adducts within viable hypoxic cells. The reversibility of this single electron reduction in the presence of oxygen limits adduct formation to cells that are pathologically hypoxic. This oxygen-dependent selectivity forms the basis for non-invasive (imaging) diagnosis of an hypoxic region with radiolabelled nitroimidazoles. A number of radio-iodinated azomycin -nucleosides have been synthesized and evaluated as hypoxia markers. Of these, l- -D-(5-deoxy-5-iodoarabinofuranosyl)-2-nitroimidazole (IAZA) has been used clinically as a marker for tissue hypoxia in a variety of pathologies involving tissue hypoxia.

This study describes the synthesis of high specific activity ^{131}IAZA in therapeutic doses (up to 3 GBq) by exchange technique and its purification by simple Sep-Pak technique. The radio-iodination was performed using 100 g of IAZA and Na[^{131}I]I in pivalic acid melt. Stability of Sep-Pak-purified ^{131}IAZA in 15% ethanol in saline at 4 C was monitored by HPLC. The product was stable for at least two weeks, with only ~8 % degradation over the storage period. Labelling yields, and chemical and radiochemical purity data will be presented.

SYNTHESIS AND IN VITRO EVALUATION OF BIOTIN NONAMERS FOR CROSS-LINKING OF MULTIPLE MOLECULES OF RADIOLABELED AVIDIN OR STREPTAVIDIN

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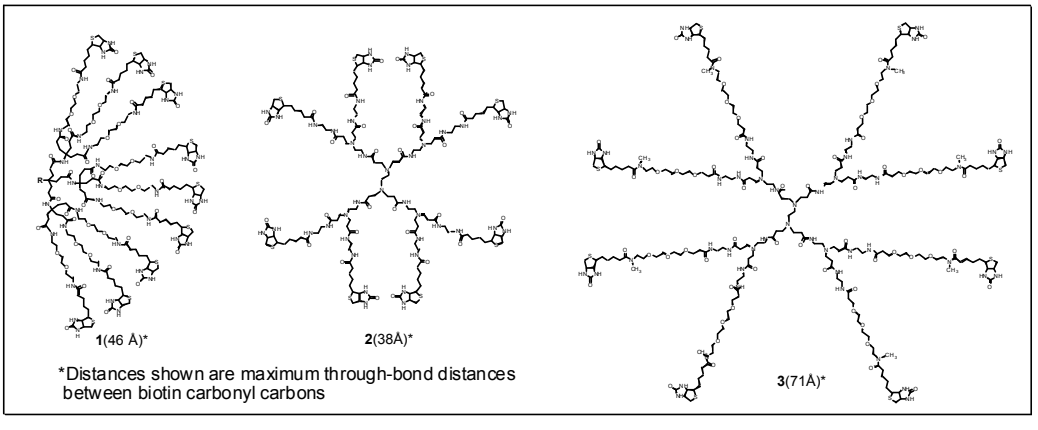
Keywords: biotin, dendrimer, streptavidin, pretargeting

In previous studies (*Bioconjugate Chem. 9*, 813-825, 1998), we investigated biotinylated starburst™ dendrimers (SBD) as reagents for increasing the amount of radioactivity on cancer cells. The concept is that pretargeted monoclonal antibodies (mAb) containing multiple biotins can bind multiple radiolabeled streptavidin (SAv) molecules, increasing the amount of radioactivity bound to a single tumor antigen. As conjugation of large numbers of biotin molecules to a single mAb will adversely affect its antigen binding, conjugation of biotin multimers is attractive. Our previous in vitro binding studies demonstrated that the polybiotin containing starburst dendrimers could increase the amount of radiolabeled SAv bound by up to 5x in a single administration. However, the starburst dendrimers have many positive charges and were found to concentrate in kidneys. Thus, the goal of this investigation was to prepare a biotin dendrimer for mAb conjugation that is water soluble and neutral in charge. The biotin nonamer, **1**, was chosen for synthesis and evaluation. A key consideration in the design of **1** was the longest distance between any two biotins. The distance between biotin binding pockets on a single face of SAv is 19-20Å, whereas, the distance from a biotin binding pocket on the opposite biotin-binding faces is >60Å. Thus, based on the structure of SAv, it was thought that the longest distance between biotin moieties should be kept to less than 60Å, allowing only two biotins to bind a single SAv molecule.

The biotin nonamer **1** (R=NO_2) was prepared via a multi-step synthesis from nitromethane tripropionic acid. Also, a nonamer with a N-phthalate protected polyethylene glycol side chain was prepared for conjugation with mAbs. Convergent syntheses were conducted where three units of trimer were combined with nitromethanetripropionic acid to form the nonamer. After synthesis, biotin nonamer **1** was evaluated for binding with radioiodine labeled SAv using SAv coated wells. As a comparison, biotinylated SBDs **2** and **3** were also evaluated. The in vitro binding results indicate that only two SAv molecules bound with **1** or **2**, whereas, three SAv molecules bound with biotinylated SBD **3**. It is apparent that spacers longer than 60 Å are required for maximum SAv binding. Additional studies are being conducted to synthesize longer spacers (60-85Å) between biotin moieties to determine the optimal length to bind the maximum number of SAv molecules (which should be five for a biotin nonamer).



TUMOR TARGETING PROPERTIES OF INDIUM-111 LABELED GENETICALLY ENGINEERED Fab' AND F(ab')$_2$ CONSTRUCTS OF chTNT-3

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Keywords: monoclonal antibody; tumor necrosis treatment; pharmacokinetics; biodistribution

Genetic engineering techniques have allowed the construction of Fab , and F(ab)$_2$ constructs of chTNT-3, a chimeric monoclonal antibody (MAb) which targets necrotic regions of solid tumors. The purpose of this study was to evaluate the *in vitro* and *in vivo* properties of Fab and F(ab)2 constructs radiolabeled with indium-111 using diethylentriaminepentacetic acid (DTPA) conjugation in order to compare their binding characteristics with parental chTNT-3. Optimization of the MAb to DTPA ratio showed that a 1:2 ratio gave the best immunoreactivity while providing good radiolabeling efficiency and high specific activity for all three DPTA conjugates. In addition, ^{111}In-labeled Fab and F(ab)$_2$ conjugates were found to have faster whole body clearance times and better biodistribution profiles compared to parental ^{111}In-labeled chTNT-3 in tumor-bearing mice. Although radiolabeled Fab and F(ab)$_2$ constructs showed lower tumor uptake than radiolabeled chTNT-3, biodistribution results showed that these constructs had significantly lower uptake in liver, spleen, and other normal organs (except the kidney) and therefore had higher tumor-to-organ ratios. In addition, a comparison of all derivatives showed that the F(ab)$_2$ reagent gave the best results in tumor imaging studies. These results demonstrate that stable, genetically engineered F(ab)$_2$ construct can be successfully radiolabeled with indium-111 in order to produce potential imaging reagents for the detection and monitoring of tumors.

ALPHA-IMMUNOTHERAPY WITH ^{213}BI-RITUXIMAB COMPARED TO EXTERNAL GAMMA IRRADIATION AND CHEMOTHERAPY IN B-CLL IN VITRO: CORRELATION WITH CLINICAL CHEMOTHERAPY SENSITIVITY

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Keywords: ^{213}Bi, Rituximab, immunotherapy

Aim: The natural course of disease in CLL is one of increasing resistance to chemo/radiotherapy, possibly related to deregulation of genes involved in apoptosis induction and DNA-repair. The aim of this study is to compare the apoptosis induced in B-CLL cells in vitro treated with ^{213}Bi conjugated antiCD20 in comparison to external gamma irradiation, to chlorambucil, fludarabine or methylprednisolone concentrations that are representative of pharmacologically obtained levels in vivo. These comparisons were made in patients with B-CLL and in vitro and in vivo sensitive (Chloram-S, n= 8), resistance (Chloramb-R, n= 8) to chlorambucil and untreated, stable disease (Chloramb-U, n= 5).

Material and Methods: B-CLL cells from patients (n= 21) were exposed while cultured in RPMI/10% FCS, to the following treatments: 2Gy ^{213}Bi anti-CD 20, 2Gy external ^{60}Co irradiation, 2,5 mM chlorambucil, 5 mM fludarabine and 5 mM methylprednisolone. Apoptosis was scored by flowcytometry staining with AnnexinV-FTIC and 7-AAD, gating on CD19+ cells.

Results: CLL cells from patients who had documented responses to chlorambucil and who were untreated had higher apoptosis scores after exposure to ^{213}Bi-Rituximab than after ^{60}Co irradiation. CLL cells from chlorambucil refractory patients were significantly hyporesponsive to all treatments when compared to the other groups. When comparing the treatment modalities within the refractory group no significant difference was observed in response. For all treatments chlorambucil sensitive patients scored higher than the non-treated and the refractory group.
There was no statistically significant difference between apoptosis induced by chlorambucil, fludarabine, methylprednisolone and gamma radiation. When comparing patients presenting with 11q- aberrations versus those without and the same was true for CD-38+ versus CD-38 negative CLL. The apoptosis induced by ^{213}Bi-Rituximab in patients with 11q- and in CD-38+ CLL, was significantly lower than the respective negative control groups ($p<0.05$).

Conclusions: Refractory patients scored lower apoptosis score to all treatments in comparison with the other groups and no significant difference was observed within the refractory group for the different treatments.

Apoptosis scores in % in vitro in CLL cells from patients who were responsive, refractory to chlorambucil or who were never treated.

	2Gy 213Bi-antiCD20	Chlorambucil 2,5mM	Fludara 5 mM	Methylprednisolone 5 mM	2 Gy 60-Co
Chloramb-S	28,6	16,0	28,8	23,8	22
ChloramB-U	20,8	11,2	19,0	20,5	10,6
ChloramB-R	11,8	5,2	9,0	14,1	11,8

DEVELOPMENT OF RADIOPHARMACEUTICAL USING ^{166}Ho-CHITOSAN COMPLEX (HC) FOR ANTICANCER AGENT

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Key words: ^{166}Ho-chitosan complex (HC), liver cancer

Radiation therapy has been used for the cancer treatment externally or internally. The external radiation therapy has been widely used, but for the lack of its selectivity it requires strong radiation dose causes the irritation and damage of the normal tissue or organ. So we investigates non-clinical and clinical studies of ^{166}Ho-chitosan complex (HC), in which chitosan is chelated with ^{166}Ho, as an anticancer agent for internal radiation therapy. Preparation and physicochemical properties, toxicity and biodistrbution of HC were performed as non-clinical studies. After that, clinical phase I and early phase II study were performed with 19 patients of liver cancer in 3 dose escalating steps [10mCi/cm (1step), 20mCi/cm (2step), 30mCi/cm (3step)], and late phase II study is being performed with 63 patients of liver cancer (dosage: 20mCi/cm). HC makes a clear solution under acidic conditions, but it converts to a gel under basic conditions. The pharmacokinetic study of intrahepatic or intratumoral administration of HC in rats revealed that 1) the effective biological half-life at the administration site is much longer than that at other tissues; 2) the administration site-to-tissue ratios are extremely high; and 3) the activity in the organs other than the administration site is very low. In case of clinical phase I study, the responses of the tumors to the treatments for 1, 2 and 3 step were 50.0, 85.7 and 66.7% respectively at CT imaging. And the response rates of clinical phase IIb study were 77.7%. Administered HC was well localized within tumors without distrbution to the other organs or tissues on gamma camera imaging. These results indicate strongly that HC can be a highly effective and safe new radiopharmaceutical agent for internal radiation therapy against liver cancer.

DEVELOPMENT OF A RADIOPHARMACEUTICAL USING ^{166}Ho-CHITOSAN COMPLEXES AGAINST PROSTATE CANCER

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Key words: ^{166}Ho-chitosan complex (HC), radiopharmaceutical, prostate cancer

^{166}Ho-chitosan complex (HC) is a new radiopharmaceutical approved in Korea for liver cancer. In these studies, therapeutic effect against prostate cancer and biodistribution of HC were evaluated in animal models using the technique of intraprostatic administration. For evaluation of the therapeutic effect, noble rats with AIT orthotopic or subcutaneous prostate cancer were used. In orthotopic model of prostate cancer, group 1 was a sham control, group 2 received 1 mCi of chitosan-free ^{166}Ho, group 3 received 0.5 mCi of HC and group 4 received 1.0 mCi of HC. In the meantime, the injection doses of HC were 10, 20 and 30 mCi in subcutaneous model. After 4 weeks post injection in subcutaneous model, inhibition rates of tumor growth in each group were 90.7, 96.9 and 82.9%, respectively. To determine the fate of HC, SD rats were used by studying its absorption, distribution and excretion after administration into the prostate gland. About 100 μCi of HC [0.1875 mg of $Ho(NO_3)_3 \cdot 5H_2O$ and 0.25 mg chitosan/head] was administered intraprostatically to male rats. Radioactive concentrations in blood, urinary and fecal excretion and radioactive distribution in tissues were examined. The radioactive concentrations in blood were not observed, and cumulative urinary and fecal excretions for 72hr were negligible. The radioactive concentrations in tissues and the whole body autoradiography images showed that most of the administered radioactivity was localized at the administration site (>98% at 144 hr post administration), and only slight radioactivity was distributed in the bone, liver, spleen and kidney.

These studies reveal that HC could be a safe and efficacious radiopharmaceutical candidate against prostate cancer.

CONVENIENT THERAPY WITH SPECIALLY DESIGNED RADIONUCLIDE, ^{166}Ho SKIN PATCH FOR SKIN CANCER

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Key words: ^{166}Ho patch, skin cancer

^{166}Ho, a ß-emitting radionuclide, was incorporated within polyurethane film for possible application for the therapy of skin cancers. The aim of this study was to investigate skin irritant after radiation with ^{166}Ho patch in rabbits and to estimate the efficacy of this therapy for skin cancer patients. Six NZW rabbits were used for skin irritant in this study. The dorsal hair of rabbits was removed with an electric clipper and blade. Three different radiation doses (control, 35Gy and 70Gy) were applied on skin of the shaved rabbit. Two weeks after radiation, desquamation, erythema or erosion developed in applied sites but these acute radiation reactions healed gradually.

For the evaluation of the efficacy of this therapy, 26 sites of Bowen's disease in 12 patients, 8 lesions of basal cell carcinoma in 8 patients, 3 lesions of squamous carcinoma in 3 patients and 18 lesions of Kaposi sarcoma in 4 patients were treated with ^{166}Ho patches (45-95 year old; 0.5-8 cm in size). The patches were applied to the surface of skin cancers for 30-60 min for a total radiation dose of 35 or 80 Gy according to the type of cancer. All of 26 lesions of Bowen's disease, 6 of 8 lesions of basal cell carcinoma, all of 3 lesions of squamous carcinoma and 17 of 18 lesions of Kaposi sarcoma showed complete response with single treatment. It was concluded from these studies that the ^{166}Ho patch is a safe, convenient, cosmetic and effective therapeutic modality without adverse effects on the surrounding normal tissue and bone.

153SM-EDTMP PLAYS MAJOR ROLE FOR THE PALLIATION OF PAINFUL BONE METASTASES

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AIM It is know that nearly 50% of patients with breast or prostate cancer will eventually develop bone metastases. A prominent symptom of these metastases is pain. Since control of metastatic bone pain is a clinical problem, an effective agent for palliation of bone metastases has been searched.

METHOD Question is that the radiopharmaceuticals containing samarium-153, strontium-89, rhenium-186, phosphorus-32 are effective, but we do not know which of these is the most efficacious or the safest. Toxicity includes mild-to-moderate pancytopenia and an occasional brief flare of pain, and treatment of patients with disseminated intravascular coagulation must be avoided because it may predispose the patient to severe thrombocytopenia.

RESULTS Post clinical study by means of Sm-153, Sr-89, Re-186 and P-32 for total 179 patients we can answer, that the earliest time interval to higher level of platelets after initial injection, shows samarium-153.

CONCLUSION Sm-153 injection is a safe and effective agent that, due to the complex of radioactive samarium and ethylene-diamino-tetarmethylene phosphonic acid (EDTMP) produced into Czech Republic via LACOMED Ltd., shows also an optimal outstanding affinity to the bone metastatic lesions. The clearence of the radiopharmaceutical is very short, the urine excretion is completed within 24 hours after administration. The elimination of drug is characterized by double-exponential curve with half times about 5 minutes and 1 hour. Two hours after administration there is only 5% of the activity applied in the blood.

RADIOLABELED J591 ANTIBODY SPECIFIC TO PROSTATE SPECIFIC MEMBRANE ANTIGEN (PSMA): COMPARISON OF INDIUM-111, YTTRIUM-90 AND LUTETIUM-177

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Keywords: Radiolabeled Antibody, PS , Radioimmunotherapy, Y-90, Lu-177

The emitters, ^{90}Y and lanthanide radiometals such as ^{177}Lu, ^{153}Sm and ^{166}Ho are potentially useful for radioimmunotherapy (RIT). J591 is a humanized monoclonal antibody (MAb) specific to the extracellular domain of PSMA. There is great interest in the development of radiometal labeled DOTA-J591 MAb for targeted RIT of prostate cancer. ^{111}In labeled antibodies and peptides have been routinely used as chemical and biological surrogates for ^{90}Y labeled therapeutic agents. Recent studies, however, have shown that there are significant differences in the biodistribution between ^{111}In and ^{90}Y labeled agents. While Y and Lu metals favor +3 oxidation state like In, there are minor differences in the solution and coordination chemistries among these metals (1,2). Since these metals form strong complexes with the macrocyclic chelator DOTA, we have optimized radiolabeling conditions using anti-PSMA J591 MAb. In addition, we have compared the pharmacokinetics and biodistribution of ^{111}In-DOTA-J591 with that of ^{177}Lu-DOTA-J591 in patients with prostate cancer.

MAb J591 was conjugated with 2-13 molecules of DOTA using DOTA-N-hydroxy-succinimidyl mono ester. The number of DOTAs per J591 IgG MAb molecule was determined using In/In-111 binding assay and the results were compared to the values obtained by two other methods; a fluorimetric assay using Eu^{3+} challenge and phenanthroline dicarboxylic acid (Eu-PDCA assay), and mass spectrometry. Radiolabeling of DOTA-J591 MAb with ^{111}In, ^{90}Y and ^{177}Lu chloride was optimized to obtain specific activities (SA) of 5-25 mCi/mg. Silica gel-ITLC with 5 mM DTPA solution was used to determine the free unbound radiometal.

The solubility and relative mobility of radiometal in ammonium acetate buffer is dependent upon pH and specific activity of radiometal. Compared to the other two metals, ^{111}In showed increased formation of (>50%) of non-mobile species in presence of carrier at pH >7.0. Similarly, ^{111}In showed greater apparent binding to antibody at higher pH, but challenge with 10mM DTPA resulted in greater free radiometal. The best labeling conditions for all 3 radionuclides is with 1 M ammonium acetate buffer at pH 6-7. Incubation at 37^{o}C for 15-30 min is optimal for routine labeling. Stability studies in presence of excess DTPA, serum or transferrin showed relatively insignificant amount of dissociation of metal over a period of 48-72 hours. Increasing the SA of radiolabeled J591 showed gradual reduction in the immunoreactivity. With ^{90}Y-DOTA-J591, 92% of the labeled antibody was immunoreactive at 1.0 mCi/mg compared to 77% at 25 mCi/mg.

Phase I dose-escalation studies in patients with prostate cancer were performed with ^{90}Y-DOTA-J591 (n=29) and ^{177}Lu-DOTA-J591 (n=25). Prior to ^{90}Y treatment dose, each patient had pharmacokinetic and imaging studies with ^{111}In-DOTA-J591 while these studies were performed with ^{177}Lu-DOTA-J591 following the treatment dose. There blood clearance kinetics of both ^{111}In ($T_{½}$ = 47±17 hr) and ^{177}Lu ($T_{½}$ = 43±15 hr) were similar. While the whole body retention of radioactivity was similar for these two agents, the liver uptake with ^{111}In (27.3± 2.2%) at 6-7 days was slightly higher compared to that with ^{177}Lu (21.7±7.0%). The radiation dosimetry estimates for ^{90}Y-DOTA-J591 based on ^{111}In or ^{177}Lu studies were similar.

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ANALYTICAL AND RADIOANALYTICAL QUALITY CONTROL OF PURITY AND STABILITY OF RADIOPHARMACEUTICAL [^{186}Re]HEDP FOR BONE METASTASES PAIN PALLIATION.

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Keywords: Quality Control, Radiopharmaceutical Stability, [^{186}Re]HEDP, Metastases, Pain Palliation

Rhenium-186 is used as labeling agent for radionuclide therapy due to its nuclear properties: short half-life (89.4 h) and emission of energetic beta particles at 1.07 MeV and 0.93 MeV.

The coordination compound [^{186}Re]HEDP (hydroxylethylidenediphosphonate disodium salt) has shown to be a suitable bone-seeking agent with efficient palliation of metastatic bone pain. Biodistribution studies showed a relevant in-vivo decomposition.

HPGe spectrometry was used for checking the radionuclidic purity of the radiopharmaceutical.

Chemical purity, specific activity of radiopharmaceutical and Re isotopic composition were determined by INAA.

For studying radiochemical purity and stability of radiopharmaceutical, two different paper radiochromatography methods were used. In the first one, free tetraoxorhenate(VII) anion was determined using Whatman 3MM paper as stationary phase and acetone as mobile phase. Re radiopharmaceutical and the hydrolysed Re(IV) species remain at the origin, while free tetraoxorhenate(VII) anion migrates with the solvent front. The second method is based on the use of Whatman 1 Chr paper as stationary phase and saline physiological solution as the mobile phase. The hydrolysed Re, remains at the starting point on the radiochromatogram, whereas both Re bound to HEDP and perrhenate(VII) anion move with different R_f values.

Stability with time, temperature and pH was studied both in-vitro and in-vivo.

LABELING ETHYLENEDICYSTEINE-METRONIDAZOLE WITH TECHENTIUM-99m AND RHENIUM-188 FOR DOSIMETRY AND INTERNAL TARGETED-RADIONUCLIDE THERAPY

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Keywords: metronidazole, radionuclide therapy, hypoxia, rhenium-188, technetium-99m

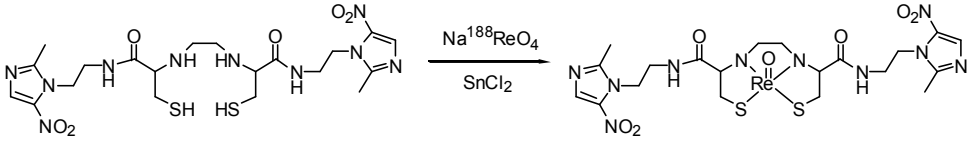
Purpose: Nitroimidazole derivatives can sensitize hypoxic tumor cells to the effects of ionizing radiation and are known to accumulate in hypoxic tissues due to increased levels of nitroreductase. Successful labeling of such derivatives can provide non-invasive imaging for monitoring tumor hypoxia, assessing functional changes within tumors pre- and post-therapy, and developing a predictive tool to determine the efficacy of internal radionuclide therapy. The aim of this study was to compare ^{188}Re-labeled metronidazole (MN), using ethylenedicysteine (EC) as a chelator, to ^{99m}Tc-EC-MN. Similarities between Tc-99m and Re-188 chemistry may allow for the use of Tc-99m labeled compounds to establish dosimetry data and aid in planning for internal radionuclide therapy with Re-188. The ability of Re-188 to emit both and particles allows patient monitoring following administration via scintigraphic imaging, and chelation to EC-MN may allow for a novel method of delivering internal targeted-radionuclide therapy to hypoxic tumors.

Methods: EC was conjugated to amino analogue of MN using N-hydroxysuccinimide and 1-ethyl-3-dimethylaminopropyl carbodiimide as coupling agents, yielding 55%. EC-MN was labeled with ^{99m}Tc- and ^{188}Re- in the presence of tin (II) chloride. *In vitro* cellular uptakes of ^{99m}Tc- and ^{188}Re-EC-MN (4 μCi/well) were obtained in human lung and rat mammary tumor cell lines at 0.5-4 hrs. Planar imaging (300 μCi/rat) and whole-body autoradiograms (100 μCi/rat) of ^{99m}Tc- and ^{188}Re-EC-MN were evaluated in breast tumor-bearing rats at 0.5, 2, and 4 hrs. To validate our tumor model, an oxygen probe was used to measure oxygen tension in the tumor tissue.

Results: Mass spectrometry and ^{1}H-NMR demonstrated the correct chemical structure of EC-MN. Heating and higher amounts of tin (II) chloride (10X) were needed for reduction/chelation of Re-188. Radiochemical purity of ^{188}Re-EC-MN (>93%) and ^{99m}Tc-EC-MN (>99%) was assessed using radio-TLC. ^{188}Re-EC-MN and ^{99m}Tc-EC-MN showed significantly higher uptake than controls in both cell lines evaluated. Planar imaging and autoradiography showed both agents can be used to localize tumors in murine animal models. Oxygen tension in tumor tissue was determined to be 6-10 mmHg compared to 40-50 mmHg in normal muscle tissue.

Conclusions: The results indicate that ^{99m}Tc-EC-MN and ^{188}Re-EC-MN can be efficiently synthesized and exhibit tumor uptake *in vitro* and *in vivo* due to hypoxia-based uptake as supported by the microprobe data. ^{99m}Tc-EC-MN may serve as an accurate marker for internal targeted-radionuclide therapy with ^{188}Re-EC-MN.

Structure:



^{99m}Tc DIRECT LABELLING AND BIODISTRIBUTION STUDIES ON HYALURONAN-BUTYRATE, A PROMISING ANTINEOPLASTIC AGENT

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Keywords: Hyaluronan, Butyrate, ^{99m}Tc-Direct Labelling, Biodistribution, YAP Camera

Sodium butyrate (But) is an histone deacetylase inhibitor, which has proved to have a relevant antineoplastic activity in a wide panel of human cancer cell lines including hepatocellular carcinoma. Unfortunately, the clinical application of But is limited by its very short half-life time. To overcome this disadvantage and to improve drug targeting, we developed a bioconjugate (HA-But) constituted by a hyaluronic acid backbone (HA) esterified with butyric acid residues. HA is an ubiquitous polysaccharide in human tissues, and its main characteristics is the high affinity for CD44, the specific membrane receptor for HA, which is overexpressed in most human cancers, including liver carcinomas.

Preliminary *in vitro* experiments with this agent confirmed an enhanced antiproliferative activity, with respect to the active principle, but showed that the *in vivo* antitumor activity is strongly dependent from the route of administration, and therefore from the biodistribution of the injected drug.

In the present study we labelled HA-But with ^{99m}Tc by a direct method. The optimised protocol afforded the labelled polymeric species in short time (2 hours), mild reaction conditions (pH = 4, 50 °C) and in high yield (>90 %). The labelled polymeric species has been easily purified by Gel Chromatography on Sephadex G25.

Then we investigated the polymeric species uptake in two human hepatocellular carcinoma cell lines, namely HepB3 and HepG2, characterized by a different percentage of CD44-positive cells (78% and 18%, for HepB3 and HepG2, respectively). The higher affinity *in vitro* of ^{99m}Tc-HA-But for HepB3 cells, compared to HepG2 cells, suggested for labelled hyaluronan derivatives a receptor mediated endocytotic uptake and therefore a promising use of HA as receptor-specific targeting agent for antitumour drugs.

The study of *in vivo* biodistribution of ^{99m}Tc-labelled HA-But, performed by the use of a YAP camera device, showed that after different routes of administration (i.v., i.p. and s.c.) the highest amount of HA-But is found in the liver. However, differences were observed in the timing of liver uptake of this compound: quite immediate after i.v. treatment and much slower after i.p. and s.c. treatment (at least 30 min are required). In order to test the pharmacological effect of HA-But on liver, we have settled a model of liver metastases, starting from intrasplenic injection of Lewis lung carcinoma cells. Treatment with i.p. administered HA-But markedly reduced liver metastases, and 87% of the treated animals were metastasis-free.

In conclusion this biodistribution study, performed with ^{99m}Tc-HA-But, showed the i.v. administration as the fastest route to deliver hyaluronan derivatives to the liver but suggested i.p. or s.c. administrations as preferential routes for a controlled delivery to hepatic carcinomas. The pharmacological *in vivo* results confirmed the usefulness of i.p. injected HA-But as antineoplastic agent for treating primary or metastatic liver tumours.

RESULTS OF RADICAL THERAPY OF EPIDERMOID LUNG CANCER WITH DYNAMIC FRACTIONATION DOSES

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Under supervision, there were 53 patients with epidermoid lung cancer who received radical therapy under the radical program (Muravskaja G. V. and co author 1998).

The purpose of work was to study results of radical treatment of epidermoid lung cancer under the radical program and some factors of the prognosis.

The diagnosis of epidermoid lungs cancer patients has been confirmed by morphology. All patients were under investigation for more than 1 year. The first group of 27 patients(51.0%) lived more than 1 year, 26 patients (the second group)- less than one year. The two year survival rate of patients of the first group was 15.1%. The three year survival rate - 11.3%. Results correspond to the literature(Bauman M.2001)with no relation to age. An analysis of distribution of patients on a degree of prevalence of a tumour established that in the first group it was observed:T2NO-4;T2N1-4;T2-3N2,T3NO-1-19. In the second group:T2 N0-3,T2N1-2;T2-3N2,T3N1-14;T2-3 N3-7. In both groups there was at least 111 degree of disease:in the first -70.9%,in the second 80.8%. But in the group of patients living less than one year, in 26.9% was observed metastatic spreading tumours in the lymphatic nodes, corresponding to category N3. In the second group also there was more often atelectasis. It was not possible to differentiate radiologically a shadow of a tumour from a shadow from atelectasis (58.0±9.7% and 30.0±8.8%,$p<0.05$). The frequency of full resorption of tumours observed in the first group was 37.0±9.3%, in the second 3.9±3.8%, almost 10 times less. The data show a direct correlation between the loco-regional control and lymphogenous distribution in epidermoid lung cancer in the presence of atelectasis. In the latter case, deterioration of results probably is caused by the impossibility, at the radiological level, to define the border of a tumour and atelectasis. These factors are important for planning the volume of irradiation. In this connection other methods of visualization are necessary for definition of a tumour with atelectasis.

TWO POTENTIAL TUMOR PET IMAGING AGENTS AND THERAPEUTIC AGENTS—Cu-SALICYLIDENE-TYROSINATO TERNARY COMPLEXES

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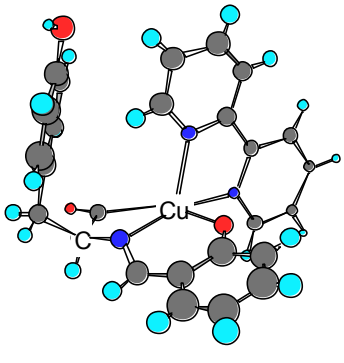
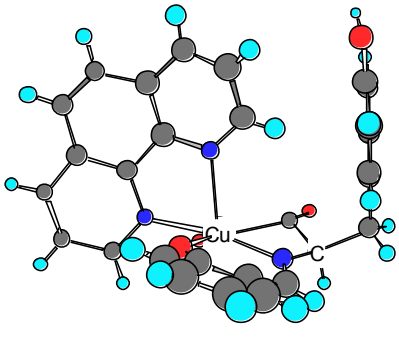
Keywords: Cu, Tumor Image and Therapy, Salicylaldehyde-amino Acid Schiff bases, Crystal Structure

Two ternary complexes, Cu(styr)L_1 and Cu(styr)L_2 (styr: N-salicylidene -tyrosinato; L_1 = phen: 1,10-phenathroline; L_2 = bipy: 2,2'-bipyridine), have been synthesized through in situ coordination and characterized by means of conventional methods. The crystal structure determination reveals that the Cu^{2+} ion is five coordinated in both complexes by one oxygen atom of carboxylate, the imine nitrogen atom and the salicylidene oxygen atom of the Schiff base as well as two nitrogen atoms of L_i, resulting in the distorted square pyramid coordination polyhedra. It is especially worth mention that the chiral carbon atom changed its configuration from S to R during the synthesis in Cu(styr)L_1 while it maintained the S configuration in Cu(styr)L_1. Their preliminary antitumor experiments unpon ICR mice (18~22 g, female) implanted with s-180 sarcoma show T/C ~45% for Cu(styr)L_1 and strong toxicity of Cu(styr)L_2. For the potential to be utilized as tumor PET imaging agents and therapeutic agents, the further animal experiments of the complexes and that of ^{64}Cu labled compounds as well as theoretic calculation are underway.



Cu(styr)L_1



Cu(styr)L_2

COMPARISON OF THE PHARMACOKINETICS OF ^{131}I-, ^{99m}TC- AND ^{188}RE-RITUXIMAB IN NMRI MICE

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Keywords: Rituximab, anti-CD20, pharmacokinetics, ^{188}Re

Introduction and aim: Low immunogenic chimeric anti-CD20 antibody Rituximab was labelled with 131I, 99mTc and 188Re for biodistribution studies in mice for the comparison of the pharmacokinetics.

Material and Methods: 131I-Rituximab was synthesized by the iodogen method. For the synthesis of 99mTc and 188Re-Rituximab the mAb was preliminary reduced with mercaptoethanol (1:2000 molar ratio). For the 99mTc-Ritxumab synthesis MDP was used as weak chelator in combination with Sn2+ as reductant, for the 188Re-Rituximab synthesis reduction of Re04- was performed with excess of Sn2+ in sodium acetate buffer with gluconate as weak chelator. After synthesis the labelled mAbs were purified with a PD-10 column (phosphate buffer pH 7.4). In vitro stability and r.c.y. were controlled by ITLC. Biodistribution studies were performed in NMRI Mice. 2 h prior the injection of the labelled rituximab, the animals were pre-treated with 100 µg of cold Rituximab. Immunoreactivity was controlled by the Lindmo assay.

Results: R.c.y. were respectively 75% for 131I and 95% for 99mTc and 188Re. After purification radiochemical purity was higher than 95% for all preparations. The 131I and 99mTc preparations were stable for more than 24h but to achieve a stability of more than 95% with 188Re gentisic acid was added to the preparation. Biodistribution studies in mice showed high uptake of activity in the blood (23.3, 27.7 and 34.5 % I.D./g organ for 131I, 99mTc and 188Re respectively at 1h p.i.). The biological half-life for the blood compartment was however significantly different for 99mTc and 188Re-Rituxmiab compared to 131I-Rituximab (16,4h, 1.85h and 3,22h). For 131I-Rituximab the uptake in other organs was low compared to 99mTc and 188Re where increased uptake was observed in kidneys (respectively 11.5 and 11.6 % I.D./g at 6 h p.i.). For 188Re-Rituximab increased uptake was also observed for the stomach (6.71 % I.D./g at 6 h p.i.).

Conclusion: This preliminary biodistribution study shows the importance of the choice of radionuclide and its reflection of the pharmacokinetics of the labelled mAb. For 99mTc and 188Re decreased biological half-life for the blood compartment and increased uptake in kidney liver and stomach were observed compared to 131I, probably a reflection of the oxidation of 99mTc and 188Re to the pertechnetate and perrhenate form.

THERAPEUTIC RADIOISOTOPES FROM THE HIGH FLUX ISOTOPE REACTOR (HFIR)

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Keywords: Reactor production, high specific activity, lutetium-177, platinum-195, tungsten-188

The high thermal flux of > 2 x 10^{15} neutrons/cm^2/s (85 MW) permits HFIR production of a variety of high specific activity therapeutic radioisotopes with applications for tumor, arthritis, and restenosis therapy, and for bone pain palliation and marrow ablation. High specific activity is often required for preparation of radiolabeled vectors such as peptides for targeting to limited binding sites. Compared to "direct" production (i.e. n, reactions), much higher specific activity, no-carrier-added (nca) products - and elimination of long-lived impurities - can often be obtained by alternative routes involving beta-decay of HFIR-produced isotopes or from generators using HFIR-produced parents.

Rhenium-188 is a key example of a generator-derived nca product, obtained from our W-188/Re-188 generator. The W-188 is produced by the W-186(n,)W-187(n,?)W-188 double-neutron-capture route (4-8 mCi/mg). The alumina-based W-188/Re-188 generator is a cost-effective source of nca Re-188, currently used for a wide variety of clinical research applications. We have optimized our production using enr iched W-186 oxide targets processed at 750 ^{o}C in an air stream which removes the Os-191 radiocontaminant that is introduced during irradiation. Our simple post-elution concentration technique provide very high specific volume solutions of Re-188 (>1–2 Ci/ml).

Lutetium-177 and Ho-166 are key lanthanide examples, which are produced either *via* direct neutron capture or, at the nca level, *via* "indirect" production by the Yb-176(n,)Yb-177( )Lu-177 and the Dy-164(n,)Dy-165(n,)Dy-166( )Ho-166 routes, respectively. Although high specific activity Lu-177 (50–80 Ci/mg of Lu-176 at saturation) and Ho-166 (> 10 Ci/mg of Ho-165 at saturation) are HFIR-produced by the direct (n,) reactions, Lu-177*m* ($T_{1/2}$ = 160 days) and Ho-166*m* ($T_{1/2}$ = 1200 y) are also produced, but are not formed by beta decay of Yb-177 and Ho-166, respectively. Extraction chromatographic separation of nca Lu-177 from Yb by acid elution of the Eichrom Ln resin provides nca Lu-177 free of Lu-177*m*. Higher-specific-activity Ho-166 is also obtained *via* the indirect route, without contamination with the long-lived Ho-166*m* impurity, and is expected to also be available from chromatography on the Ln resin.

Platinum-195*m* (Auger emitter) is traditionally reactor produced even at high thermal flux in only low specific activity (<1 mCi/mg), because of Pt-195*m* low production but high burn-up cross sections. We have recently demonstrated the feasibility of indirect production of Pt-195*m* *via* decay of Ir-195*m*, by the Ir-193(n,)Ir-194(n,)Ir-195*m*( )Pt-195*m* route, by HCl-thiourea elution of Dowex to separate the Pt(IV) from the Ir(IV)–thiourea complexes. Our initial data demonstrate significant expected increase of the specific activity of Pt-195*m* to 70–100 mCi/mg. Production level scale-up is planned. and this approach may offer for the first time higher specific-activity Pt-195*m* for evaluation of the therapeutic potential of this potent Auger emitter (33 electrons per decay) and for studies of Pt-based antitumor agents. This paper will discuss HFIR production capabilities, and processing technologies for these and other therapeutic radioisotopes.

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