DOE Award Number: ER60512-1003352-0000021

Project Title: "Preparation of Radiopharmaceuticals Labeled with Metal Radionuclides"

Project Director/Project Leader: Michael J. Welch

The overall goal of this project was to develop methods for the production of metal-based radionuclides, to develop metal-based radiopharmaceuticals and in a limited number of cases, to translate these agents to the clinical situation.

Initial work concentrated on the application of the radionuclides of Cu, Cu-60, Cu-61 and Cu-64, as well as application of Ga-68 radiopharmaceuticals. Initially Cu-64 was produced at the Missouri University Research Reactor and experiments carried out at Washington University. A limited number of studies were carried out utilizing Cu-62, a generator produced radionuclide produced by Mallinckrodt Inc. (now Covidien). In these studies, copper-62-labeled pyruvaldehyde Bis(N^4-methylthiosemicarbazonato)-copper(II) was studied as an agent for cerebral myocardial perfusion. A remote system for the production of this radiopharmaceutical was developed and a limited number of patient studies carried out with this agent. Various other copper radiopharmaceuticals were investigated, these included copper labeled blood imaging agents as well as Cu-64 labeled antibodies. Cu-64 labeled antibodies targeting colon cancer were translated to the human situation. Cu-64 was also used to label peptides (Cu-64 octriatide) and this is one of the first applications of a peptide radiolabeled with a positron emitting metal radionuclide.

Investigations were then pursued on the preparation of the copper radionuclides on a small biomedical cyclotron. A system for the production of high specific activity Cu-64 was developed and initially the Cu-64 was utilized to study the hypoxic imaging agent Cu-64 ATSM. Utilizing the same target system, other positron emitting metal radionuclides were produced, these were Y-86 and Ga-66. Radiopharmaceuticals were labeled utilizing both of these radionuclides. Many studies were carried out in animal models on the uptake of Cu-ATSM in hypoxic tissue. The hypothesis is that Cu-ATSM retention in vivo is dependent upon the oxygen retention of the tissue and the significantly greater retention amounting in hypoxic tissue. This hypothesis was confirmed in a series of animal studies.

Cu-64 can be used both as an imaging radionuclide and a therapeutic radionuclide. The therapeutic efficacy of Cu-64 ATSM was proven in hamsters bearing the CW39 human colorectal tumors. The administration of Cu-64 ATSM significantly increased the survival time of tumor-bearing animals with no acute toxicity. This copper agent therefore shows promise for radiotherapy. The flow tracer Cu-64 PTSM also demonstrates therapeutic potential by inhibiting cancer cells implanted in animal models. Again, this inhibition occurred at doses which showed no sign of toxicity to the animals. Cu-ATSM was translated to humans, under other support a series of tumors were investigated; these included head and neck cancer, non-small cell lung cancer, cervical cancer and renal cancer. Another radionuclide that was investigated was titanium 45. This radionuclide was successfully produced by radiation of a scandium foil with 15

MeV protons. The titanium 45 was processed and separated from residual scandium by high exchange chomotrophy. Titanium titanocene has been utilized as a therapeutic agent; this compound was prepared and studied in vitro and in vivo.

Another project was the preparation of cyclodextrin dimers as a new pre-targeting approach for tumor uptake. Beta-cyclodextradin and two other dimers were synthesized. These dimers were studied for the in vivo application. Work continued on the application of the radionuclide already discussed. Technetium 94m, a positron emitting radionuclide of the widely used 99m Tc nuclide was also prepared. This allows the quantification of the uptake of technetium radiopharmaceuticals. In collaboration with Professor David Piwnica-Worms, technetium 94m, sestamibi was studied in animal models and in a limited number of human subjects.

This project has resulted in several collaborations; one of these is a collaboration with Dr. Thomas Quinn at the University of Missouri-Columbia. We have evaluated a series of peptides targeted to melanoma. This has been carried out with both imaging and therapy and the peptide has been labeled with Cu-64, Y-86 and Ga-68. A major area of collaboration is with Dr. Karen L. Wooley and Dr. John Stephen Taylor of the Department of Chemistry at Washington University. In this collaboration, we initially carried out the evaluation of nanoparticles for cancer diagnosis and therapy, and showed that positron emitting labeled nanoparticles could be utilized to study the pharmacokinetics of nanoparticles in vivo. This preliminary work supported under this grant has led to major funding, both from the National Cancer Institute and the National Heart Lung and Blood Institute. The work on the preparation metal radionuclides has continued under the NIH grant “Research Resource in Radionuclide Research”. That this grant utilized the technology developed under DOE support to provide radionuclides such as Cu-64 and Y-86 to investigators at over 30 institutions. Collaborative research with other support has been carried out utilizing this Cu-64. The research carried out utilizing the Cu-64 produced in this manner has resulted in over 100 publications.

This DOE grant has resulted in the funding of several NIH grants; these fund both the clinical studies of agents developed under this grant and the production of the radionuclides utilizing technologies supported by this grant. This DOE grant has therefore been important to the widespread use of metal positron emitting radionuclides both in research and in patient studies.

Publications resulting from this work:

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