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CRADA Final Report
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USE OF REACTOR-PRODUCED RADIOISOTOPES FOR PREVENTION RESTENOSIS AFTER ANGIOPLASTY

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Use of Reactor-Produced Radioisotopes for Prevention Restenosis After Angioplasty

Energy Research Laboratory Technology Transfer Program
Oak Ridge National Laboratory
Cooperative Research and Development Agreement Project

Report Prepared as part of Cooperative Research and Development Agreement (CRADA) Between Oak Ridge National Laboratory (ORNL) and Mallinckrodt Medical, Inc.

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ABSTRACT

Coronary heart disease leads to myocardial infarction and is a major cause of death in the United States. Myocardial infarctions result from atherosclerotic plaque deposits in the coronary arteries, reducing blood flow through these arteries which supply oxygen and nutrients to the heart muscle. The two major approaches for restoring adequate blood flow are "coronary bypass graft surgery" and "coronary angioplasty". Angioplasty is a routinely used clinical procedure, where a deflated balloon attached to the end of a long catheter is inserted into an artery in the leg and then advanced through the aorta into the blocked regions of the coronary arteries. After positioning in the occluded region of the artery, the balloon is inflated with a pressurized saline solution which opens the artery restoring blood flow by pressing the atherosclerotic plaque into the vessel wall. Angioplasty is a widely performed procedure with the coronary arteries and is a much less expensive alternative to coronary bypass surgery. The best patients for angioplasty are those with single occlusions and this method is preferred over bypass grafting because of the significantly reduced expense. The reformation of plaque deposits in arteries (restenosis) following angioplasty, however, is a major clinical problem encountered in as high as 40 percent of patients. Because reduction of health care costs is a major national priority, development of effective new preventative methods for restenoses is an important national priority.

The biological response to such controlled vessel damage after angioplasty is the stimulation of accelerated growth of the smooth muscle cell layer which lines the artery with the resulting build up of additional plaque, thus leading to restenosis. A major current area of vascular biology is the development of methods to inhibit this restenosis after angioplasty. Although a variety of pharmacological approaches such as the use of corticosteroids, heparin, and other drugs are being

explored to inhibit restenosis after balloon angioplasty, ionizing radiation has been found to be one of the most efficient, easily performed procedures, and is expected to be a very cost effective and useful method for inhibiting arterial restenosis. Because the radiation must pass through the plastic balloon and penetrate the smooth muscle layer, a growing body of experimental data suggests that high energy beta particles (> 1 meV energy) are effective and safe for localized irradiation. One approach now in the initial stages of clinical evaluation uses small radioactive wires which can be threaded through the catheter line into the disease area of the artery before or after the balloon inflation angioplasty procedure. A unique alternative approach for such introvascular therapy would use a radioactive solution instead of a wire. In this approach the angioplasty balloon could be inflated with the radioactive solution for a predetermined period of time (two to four minutes), permitting irradiation of the smooth muscle cells at the same time of the angioplasty. Alternatively, a more conservative approach would involve low pressure re-inflation of the balloon with the radioactive solution following high pressure inflation with saline for opening the lumen.

OBJECTIVES

The objectives of this project were to evaluate the issues associated with the production and availability, suitability for routine use, and the biological endpoints associated with the usefulness of rhenium-186 and rhenium-188. Another objective of this project is for using these radioisotopes for the inhibition of coronary restenosis (re-closure) after vessels have been opened by balloon angioplasty. This multidisciplinary project encompassed expertise in radiochemistry, radioisotope preparation and vascular biology, and focused on developing and evaluating new approaches of inhibiting restenosis using ionizing radiation. Since beta particle emitting radioisotopes are usually neutron rich, essentially all of the radioisotopes that are expected to be useful for this application

are reactor-produced, and the Oak Ridge National Laboratory (ORNL) High Flux Isotope Reactor (HFIR) thus played a major role. This project exploited the unique capabilities of the ORNL HFIR, which has the highest steady state thermal neutron flux in the world and is an important resource for the high specific activity preparation of the medical radioisotopes for this proposed research.

The work at ORNL included providing the rhenium-186, rhenium-188, and tungsten-188/rhenium-188 generators for studies at Mallinckrodt, in conjunction with their collaborators, and evaluating the biokinetics and excretion characteristics of radioactive perrhenate in animal models to obtain data which could be used to project the possible dose consequences to humans in the unlikely event of balloon rupture. Since it had not yet been determined which reactor-produced radioisotopes are the most efficient, cost effective, and easy to use, the major goal of this project was the reactor production of these radioisotopes which would be provided to Mallinckrodt Medical for *in vitro* and *in vivo* evaluation. The avenues explored included the use of solutions of radioisotopes obtained in a clinical setting by elution radioisotope generator systems. Mallinckrodt performed systematic analytical and quality control testing on the radioisotopes received from ORNL to determine their acceptability for human use. ORNL also provided samples of radioisotopes to their testing sites for animals studies.

BENEFITS TO THE FUNDING OF DOE MISSION

This research involving the use of radioisotopes for the inhibition of restenosis after coronary angioplasty is consistent with the mission of the Department of Energy (DOE) in the peaceful use of nuclear technology for medical applications. Further, since the therapeutic radioisotopes investigated are all reactor-produced, the success of this technology in the clinical research and

commercial sectors is expected to develop a demand for HFIR-produced radioisotopes for these applications which benefit the contribution of the DOE to this important technology and establish a market for the DOE Isotope Production and Distribution Program (IPDP) services.

TECHNICAL DISCUSSION OF WORK PERFORMED

Work Performed at ORNL as Part of CRADA Project -

The ORNL group explored the development of the best target configuration and optimal irradiation conditions and then developed and optimized the most efficient processing methods and methods for providing radioisotopes to the industrial partner. Rhenium-186 was directly produced by irradiation of enriched rhenium-185. Carrier-free rhenium-188 was obtained by elution of a tungsten-188/rhenium-188 generator system fabricated and installed at ORNL. Tungsten-188/rhenium-188 generators were also provided for in-house elution of rhenium-188 at Mallinckrodt. Activities associated with providing these radioisotopes included obtaining the target material, target container, welding, leak testing, HFIR irradiation, transportation of irradiated targets, cell and process charge, and packaging and shipping.

Two shipments of samples of high specific activity rhenium-186 [10 Curies (Ci) per shipment] were provided to Mallinckrodt as well as two large scale, 0.50 Ci tungsten-188/rhenium-188 generators with guidance and procedures for generator bolus concentration. We also provided three samples of carrier-free rhenium-188 [200, 155, and 130 milliCurie (mCi)] and optimized our new tandem ion-exchange perrhenate concentration method and provided guidance and procedures to Mallinckrodt. In addition, we also assisted Mallinckrodt in dosimetry calculations which will complement the animal studies to correlate effective irradiation dose with inhibition of restenosis.

The ORNL group conducted tissue distribution and excretion, and the thyroid uptake, pre-blocking, and displacement with perchlorate of rhenium-188 perrhenate in female Fischer rats. These data were provided to Mallinckrodt. Tissue distribution data of rhenium-188 perrhenate in female Fischer rats were also determined. These studies were performed after local Animal Care and Use Committee (ACUC) approval. After intravenous administration of rhenium-188 sodium perrhenate which were obtained from the alumina-based tungsten-188/rhenium-188 generator, radioactivity is rapidly excreted *via* the urinary bladder with about 50 percent excreted in seven hours. Principal tissues showing residual rhenium-188 uptake were primarily the thyroid and intestinal tract (mucosa).

Data evaluating the effects of thyroid pre-blocking with sodium iodide and perchlorate displacement studies of thyroid localization of rhenium-188 perrhenate in rats were also provided. As expected, pre-administration of Lugol's solution had no effect on thyroid uptake of perrhenate. Pre-administration of perchlorate showed a significant decrease in thyroid uptake of subsequently administered perrhenate, but the timing was not studied to optimize pre-blocking. However, post-treatment with perchlorate [intravenous (i.v.)] showed a dramatic displacement of thyroid accumulation of perrhenate, as expected from the established ion channel mechanism. From these data, we recommended that protocols for introvascular irradiation using rhenium radioisotope-filled angioplasty balloons include precautions to have oral perchlorate available in the event of balloon rupture to minimize the thyroid dose.

In addition, compilations of data from studies conducted in a collaborative project between ORNL and investigators (Prof. J. Kotzerka, *et al.*) at the University of Ulm, Germany, evaluated the thyroid

uptake and displacement with perchlorate in two human subjects, in comparison with similar studies with technetium-99m pertechnetate in a group of 20 patients. Data from early human studies in which rhenium-188 perrhenate was orally administered to a human volunteer in a Oak Ridge Associated Universities (ORAU)/ORNL collaborative study between ORNL and the ORAU (study conducted in 1965) were provided.

The following information and summary data were also provided to Mallinckrodt: Copies of abstracts describing rat and swine studies from the *1997 and 1998 Society of Nuclear Medicine Meetings and 1997 American Heart Association Meeting; Draft* of paper describing perchlorate displacement studies of thyroid levels of rhenium-188-perrhenate in two human subjects comparing data from 20 patients with technetium-99m pertechnetate. This paper included the radiation dose estimates for rhenium-188-perrhenate before and after thyroid blocking. The ratio of thyroid rhenium-188 perrhenate uptake before and after perchlorate blocking is about 16:1, demonstrating that the thyroid dose can be reduced to about six percent of the dose without blocking in the unlikely event of angioplasty balloon rupture; Copies of abstracts describing human studies from the *1997 European Nuclear Medicine Congress and 1998 Society of Nuclear Medicine Meetings;* Copy of book chapter describing early rat studies and excretion kinetics of rhenium-188 perrhenate from a human volunteer. The human volunteer study was conducted in the Medical Department of the Oak Ridge Associated Universities before 1975.

Work Performed at Mallinckrodt as Part of CRADA Project -

A collaborative effort between ORNL and Mallinckrodt Medical, Inc., was initiated in 1997 in the formation of a CRADA. ORNL provided to Mallinckrodt Inc. several radioisotopes of interest for evaluation and testing in the research and development project for radiation treatment of arterial

restenosis, a cell proliferation disease induced in arteries following balloon angioplasty. Several radioisotopes were provided including rhenium-186, rhenium-188 and tungsten-188/rhenium-188 generators, which were used to produce a daily routine supply of the rhenium-188 radioisotope. The results of the analytical and quality control studies with these radioisotopes are summarized below.

Rhenium-186 (Re-186) - Multiple shipments of high radioactivity rhenium-186 solutions (10 Ci/shipment) were obtained from ORNL. These solutions were either tested as received or diluted with 0.9 percent sodium chloride (NaCl) solution and tested for solution appearance, radiochemical purity, and acidity (pH). These solutions were then normally diluted to a desired radioactivity concentration and used for a variety of physical or biological experiments. Chemical testing of rhenium-186 solutions from ORNL: Solution appearance clear and colorless; Radiochemical purity is greater than (>) 95 percent perrhenate ion; solution pH, between 3 to 5. Physical (Radiation dosimetry) Testing of rhenium-186 solutions from ORNL. Experimental measurements for Liquid - Filled Balloon Catheter (collaboration with Dr. S. Thomas, University of Cincinnati, OH). Dose : Distance profile for balloon catheter filled with solution of rhenium-186 (Reference: Advances in Cardiovascular Radiation Therapy II, March, 8-10, 1998, Washington, D.C., Abstract # 18). Biological Testing of Rhenium-186 Solutions from ORNL. Efficacy of Radiotherapy for Attenuation of *in vivo* Restenosis after Arterial Injury (collaboration with Dr. D. Abendschein, Washington University School of Medicine, St. Louis, MO). Preliminary study evaluating radiation treatment dose of between 0 to 14 Gray (Gy) for rhenium-186 filled balloon catheters in a swine coronary and carotid artery models. Dose: Range Study in Swine for Liquid-Filled Balloon Catheters (collaboration with Biosupport, Inc., Redmond, WA and Dr. K. Robinson, Emory University, Atlanta, GA). Effects of radiation dose range between 0 to 30 Gy for rhenium-186 filled balloon catheters

in a swine coronary artery model. (Reference: Advances in Cardiovascular Radiation Therapy II, March, 8-10, 1998, Washington, D.C., Abstract # 7). Biodistribution studies in swine for direct coronary injection of rhenium-186 solution (collaboration with Dr. K. Robinson, Emory University, Atlanta, GA). Clearance and relative distribution of rhenium-186 perrhenate ion from blood and selected organs in swine when a bolus of solution is injected directly into a coronary artery. Evaluation of Radiation Dose from a rhenium-186 Filled Balloon Catheter in Swine Coronary Model at 6-Month and 12-Month Follow-up Interval (collaboration with Dr. K. Robinson, Emory University, Atlanta, GA) Animal follow-up and evaluation in progress.

Rhenium-188 (Re-188)- Multiple shipments of rhenium-188 solutions (0.10 - 0.15 Ci) were obtained from ORNL. These solutions were either tested as received or diluted with 0.9% NaCl solution and tested for solution appearance, radiochemical purity, and pH. These solutions were normally diluted to a desired radioactivity concentration and used for a variety of chemical and physical experiments which are summarized below. Chemical Testing of rhenium-188 Solutions from ORNL: Radiochemical Purity > 95 percent perrhenate ion; solution pH, between 4.5 and 6.0 Physical (Radiation dosimetry) Testing of rhenium-188 Solutions from ORNL. Experimental measurements for Liquid-Filled Balloon Catheter (collaboration with Dr. S. Thomas, University of Cincinnati, OH). Dose: Distance profile for balloon catheter filled with solution of rhenium-188.

Tungsten (W-188)/Rhenium (Re-188) Generator - Tungsten-188/rhenium-188 (W-188/Re-188) generators were also obtained from ORNL. The function of this generator is to provide a routine supply of the radioisotope rhenium-188 in the chemical form, perrhenate ion. The generator was set up and eluded either daily or every other day with and with out the additional use of the concentrating technology (ion exchange methodology). Rhenium-188 solutions from the generator

was also tested for chemical and physical properties as the rhenium-188 solutions directly received from ORNL. In general, after the initial set up of the generator with the proper ion exchange cartridges for perrhenate ion concentrating and modification for the proper flow rates of elution, the generator delivered the anticipated quantity and concentration of rhenium-188 radioactivity. Chemical Testing of Rhenium-188 Solutions from ORNL Tungsten-188/Rhenium-188 Generator. Radiochemical Purity > 95 percent perrhenate ion; solution pH, between 4.5 and 6.0 Physical (Radiation dosimetry) Testing of Rhenium-188 Solutions from ORNL Tungsten-188/Rhenium-188 Generator. Experimental measurements for Liquid-Filled Balloon Catheter (collaboration with Dr. S. Thomas, University of Cincinnati, OH) Dose: Distance profile for balloon catheter filled with solution of rhenium-188. (Reference: Advances in Cardiovascular Radiation Therapy II, March, 8-10, 1998, Washington, D.C., Abstract # 18).

Animal studies were conducted with rhenium-186 and rhenium-188 to determine the effects of balloon catheters filled with radioactive solutions to prevent restenosis. The first study compared the effects of balloons filled with either saline or rhenium-186 to prevent restenosis of carotid arteries following a balloon overstretch injury. A second study determined the radiation dose-response relationship of rhenium-186 and/or rhenium-188 for preventing restenosis of porcine femoral vessels injured by a balloon overstretch injury. A third study determined the effects of two different doses of rhenium-186 or rhenium-188 radiation therapy for preventing neointimal hyperplasia of arterial-venous grafts implanted between the jugular vein and carotid artery of sheep. Finally, we have planned a comprehensive dose-response efficacy and safety study in pigs using a rhenium-186 solution.

INVENTIONS

No inventions resulted from work directly related to this project.

COMMERCIALIZATION POSSIBILITIES

Over 900,000 cases of myocardial infarction are documented in the United States annually resulting in over 225,000 immediate deaths. Of the remaining patients, over 400,000 coronary angioplasties are performed annually. Estimates from the American Heart Association (AHA) conservatively estimate a 25 to 30 percent incidence of restenoses. Thus, there are over 120,000 incidents of coronary restenoses in the United States annually. The costs associated with treatment of patients with restenoses after angioplasty are enormous and have been estimated by the Wall Street Journal (February 27, 1996) to represent over one billion dollars in additional health care costs per year. The availability of simple, readily available and cost effective procedures to inhibit restenoses would result in the savings of 100 million dollars in health care costs each year in the United States. This project promotes one mission of DOE in exploring their benefits of medical radioisotope technology.

Because of the high incidence of coronary artery disease in the United States and the significant costs associated with the treatment of restenosis after coronary angioplasty, this project has very high probability of identifying the best candidates for detailed clinical evaluation which would be expected to be further developed into important new clinical agents for therapy following the increasing use of angioplasty for the coronary arteries and atherosclerosis of other arterial systems. This project represents a unique opportunity to make an important contribution for an immensely important U.S. health care issue.

PLANS FOR FUTURE COLLABORATION

The possibility of further collaboration with Mallinckrodt on this project will depend upon the business decisions which Mallinckrodt will make concerning the further development, possibility of initiation of human trials, and the potential commercialization of this new technology using these radioisotopes.

CONCLUSIONS

These collaborative studies between ORNL and Mallinckrodt Medical, Inc., have demonstrated that HFIR-produced rhenium-186 and rhenium-188 can be obtained in suitable high purity for use for restenosis therapy. In addition, the tungsten-188/rhenium-188 generator is easy to use in a routine setting and has a long shelf life, indicating that use of rhenium-188 from this system will be cost effective on a commercial basis. Rhenium-186 and rhenium-188 radioisotopes (directly or from tungsten-188/rhenium-188 generators) solutions obtained from ORNL have been used for multiple chemical, physical, and biological studies in the development of the radiation treatment of restenosis in arteries. Both the rhenium-186 and the rhenium-188 radioisotopes are of great interest for this medical radiation treatment and potentially for many other radiopharmaceuticals in nuclear oncology. This CRADA between ORNL and Mallinckrodt Medical, Inc., permitted an effective collaboration between a national laboratory and a major radiopharmaceutical manufacturer and was very useful and fruitful in furthering Mallinckrodt's medical research and development interests.

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