FINAL REPORT SUMMARY	GRANT NUMBER DE-FG02-96ER62216
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR Anderson, Carolyn J.	PERIOD COVERED BY THIS REPORT FROM 4-1-00 THROUGH 3-31-01
APPLICANT ORGANIZATION Washington University	
TITLE OF PROJECT *(Repeat title shown in Item 1 on first page)* Radiation dosimetry of Cu-64-labeled radiotherapy agents using PET	

A. General Overview

This project began in 1996, and with no-cost extensions, was completed in July, 2001. The overall goals were to compare various methods of dosimetry of PET imaging agents, as well as develop more optimal methods. One of the major accomplishments of this grant was the human PET imaging studies of a positron-emitting radiopharmaceutical for somatostatin-receptor imaging, and subsequent dosimetry calculations resulting from this study. In addition, we collaborated with Darrell Fisher and Edmund Hui to develop a MIRD-hamster program for calculating hamster organ and tumor dosimetry in hamster models. Progress was made towards a point kernel approach to more accurately determining absorbed doses to normal organs, as well as towards co-registration of PET and MRI images. This report focuses on the progress made in the last 15 months of the grant, which in general is a summary of the progress over the 5 years the project was ongoing.

B. Specific Aims

1. Animal vs. human biodistributions

One of the goals of this grant was to compare absorbed doses based on calculations from rodent biodistribution studies to dosimetry estimates based on non-human primates and humans. This was accomplished with the somatostatin-receptor based imaging agent, ^{64}Cu-TETA-octreotide (^{64}Cu-TETA-OC). As shown in Table 1, the rat biodistribution data overestimates many tissues, such as the intestines and kidneys, while it underestimates the liver and spleen. Generally, it is a reasonable first assumption of absorbed dose of this particular radiopharmaceutical.

Table 1: Estimated human absorbed doses of ^{64}Cu-TETA-OC to normal organs using biodistribution data from CA20948 tumor-bearing Lewis rats, baboon and human PET data.

Tissue	Absorbed Dose (Rat Biodistribution) rads/mCi (mGy/MBq)	Absorbed Dose (Baboon PET) rads/mCi (mGy/MBq)	Absorbed Dose (Human PET) rads/mCi (mGy/MBq)
Bladder Wall	1.12 (0.30)#	0.62 (0.17)†	0.94 (0.25)† 0.23 (0.062)**
LLI* Wall	0.86 (0.23)	0.078 (0.021)	0.048 (0.013)
Kidneys	0.54 (0.15)	0.49 (0.13)	0.29 (0.078)
ULI* Wall	0.16 (0.043)	0.074 (0.020)	0.045 (0.012)
Pancreas	0.12 (0.032)	0.10 (0.027)	0.099 (0.027)
Liver	0.10 (0.027)	0.14 (0.039)	0.34 (0.091)
Marrow	0.07 (0.019)	0.071 (0.019)	0.047 (0.013)
Spleen	0.047 (0.013)	0.030 (0.0081)	0.26 (0.071)
Total Body	0.10 (0.027)	0.070 (0.019)	0.048 (0.013)

*ULI and LLI stand for upper large intestine and lower large intestine respectively.
#Assuming voids at 2 h and 5.5 h
†MIRDOSE 3 dynamic bladder model with a void at 4 h
**MIRDOSE 3 dynamic bladder model with a void at 1 h

For targeted radiotherapy studies in animal models, a program was developed by Darrell Fisher and Edmund Hui to determine the absorbed doses to both hamster normal organs and tumor. This program (MIRD Hamster) was developed for the evaluation of radiolabeled monoclonal antibodies (mAbs) in the GW39 human colorectal carcinoma bearing hamster model. Figure 1 shows the survival in the GW39 hamster model of ^{64}Cu vs ^{131}I-labeled mAb 1A3.

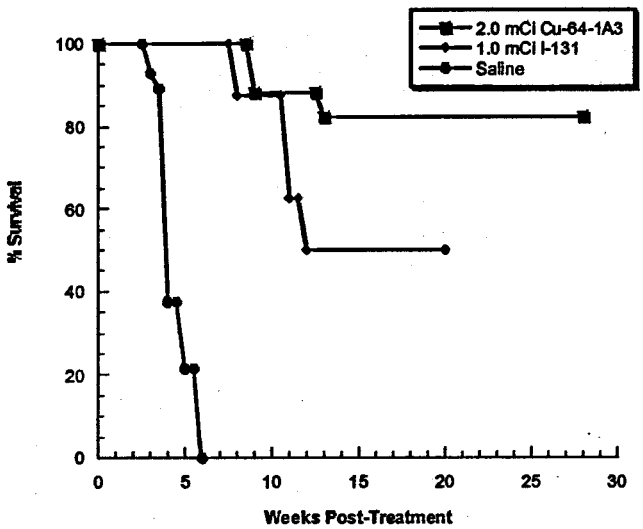

Figure 1: Survival of GW39 tumor-bearing hamsters administered either 2.0 mCi of ^{64}Cu-BAT-2IT-1A3 or ^{131}I-1A3. Hamsters administered saline were all euthanized by 5 weeks post-injection. Greater than 80% of hamsters administered 2 mCi ^{64}Cu-BAT-2IT-1A3 survived, while only 50% survival was observed in hamsters administered 1 mCi of ^{131}I-1A3.

Table 2 shows the hamster dosimetry data determined by MIRD Hamster. The data show that the absorbed doses for ^{64}Cu-BAT-2IT-1A3 are considerably lower than for ^{131}I-1A3. Greater than 80% survival was obtained for 2 mCi of ^{64}Cu-BAT-2IT-1A3, which corresponds to a tumor dose of 472 rad, while hamsters administered 1 mCi of ^{131}I-1A3, the absorbed dose to the tumor was 1308 rad, and only 50% survival was observed. In addition, the normal hamster tissue toxicity was significantly greater with ^{131}I-1A3, since 1 mCi gives a marrow dose of 960 rad, while 2 mCi of ^{64}Cu-BAT-2IT-1A3 provides a marrow dose of 258 rad. These data demonstrate the potential effectiveness of ^{64}Cu-labeled mAbs compared to radioiodinated mAbs.

Table 2: Absorbed doses for hamster normal organs and GW39 tumor for ^{131}I and ^{64}Cu-labeled 1A3.

Organ	Dose (rad/mCi) ^{131}I-1A3	Dose (rad/mCi) ^{64}Cu-BAT-2IT-1A3
Liver	387	106
Spleen	391	80
Kidneys	328	65
ULI	191	21
LLI	175	19
Tumor	1308	236
Marrow	960	129

2. Implement new image-based dosimetry methods

The second specific aim of this grant was to develop and validate a technique for parameterization of a series of whole-body, Cu-64 biodistribution images into 3-dimensional absorbed dose maps to replace the MIRD approach to tumor and organ dosimetry. This was achieved by means of a convolution with the known dose distribution "kernel" for Cu-64. By convolution with this kernel, biodistribution images

can be converted to absorbed dose-rate maps, from which doses to tumors and organs can be calculated with greater accuracy and specificity.

Table 2 compares the results of conventional MIRD dosimetry with the voxel-kernel approach averaged for the whole organ. There is general agreement between the two methods, but some organs, such as the kidney and spleen, differ significantly. In MIRD approach, the S-values are calculated for average standard organ sizes. This dosimetry was performed for a baboon imaged with a radiotracer labeled with ^{64}Cu. It is possible that some organ sizes differ by a factor 2 between primate and human. An advantage on the point-kernel approach is that it yields an absorbed dose distribution rather than a single value for each organ or tumor. But for a small organ like the gallbladder, the distribution is asymmetric and our determination of the average absorbed dose is strongly dependent on the size of the boundary we use to define the organ. This may also explain some of the discrepancy. Further animal studies are planned making use of this approach.

Table 2. Comparison of human absorbed dose determined by conventional MIRD schema and by point-kernel convolution for a ^{64}Cu labeled tracer.

Organ or Tissue	MIRD (rad)	Point Kernel (rad)
Lungs	0.71	0.74
Liver	2.28	2.18
Spleen	2.41	1.19
Kidneys	1.68	0.81

3. Improved calculation of tumor dosimetry in animal models

We proposed to tailor PET-based dosimetry methods to small animal imaging to more precisely determine the dose to tumors in laboratory animals. The accuracy of this determination and its relationship to tumor responsiveness will be critically important in the administration of therapeutic quantities of Cu-64-labeled agents to humans. In May, 2000 a microPET imaging scanner was purchased from Concorde Microsystems, and we are currently in the process of developing methods for determining absorbed dose calculations based on regions of interest.

4. Improved tumor and organ dosimetry with image registration

Since the installation of the microPET scanner, we have been working on methods for co-registering PET and MRI images. We have developed an animal support enabling the imaging of two mice in the microPET and MR scanner, which holds the mice in the same position for both instruments. The support can then be transported between the microPET and MRI facilities without removing the animals from the support. The methods for actual co-registration are currently being optimized.

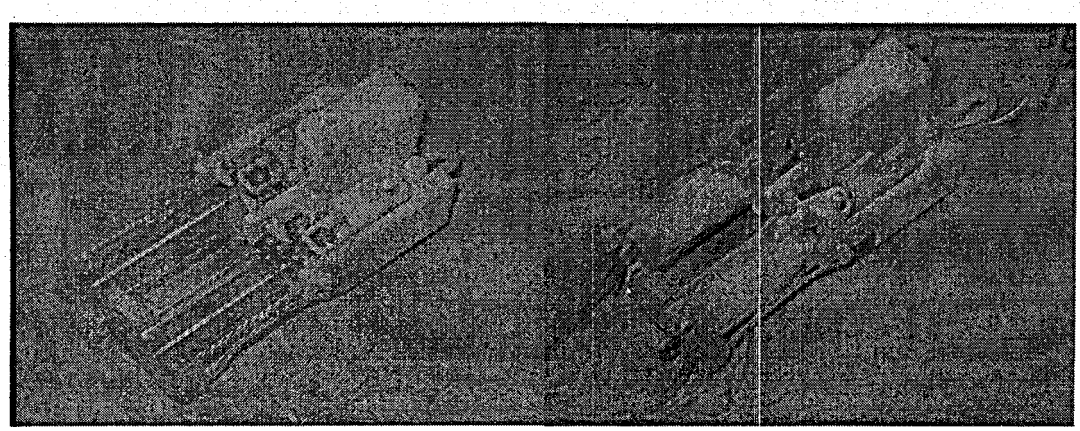

Figure 2: Holder for imaging mice by microPET and MRI without moving mice between imaging sessions.

C. Publications resulting from this work

Refereed manuscripts

1. Lewis JS, Laforest R, Lewis MR, Anderson CJ. Comparative dosimetry of copper-64 and yttrium-90-labeled somatostatin analogs in a tumor-bearing rat model. Cancer Biotherapy and Radiopharmaceuticals, 2000; 15:593-604.
2. Anderson CJ, Dehdashti F, Cutler PD, Schwarz SW, Laforest R, Bass LA, Lewis JS, McCarthy DW. Copper-64-TETA-octreotide as a PET imaging agent for patients with neuroendocrine tumors. Journal of Nuclear Medicine, 2001; 42:213-221.
3. Lewis JS, Wang M, Laforest R, Wang F, Erion JL, Bugaj JE, Srinivasan A, Anderson CJ. Toxicity and dosimetry of ^{177}Lu-DOTA-Y3-octreotate in a rat model. International Journal of Cancer, 2001; 94:873-877.
4. Lewis MR, Boswell CA, Laforest R, Buettner TL, Ye D, Connett JM, Anderson CJ. Conjugation of monoclonal antibodies with TETA using activated esters: biological comparison of ^{64}Cu-TETA-1A3 with ^{64}Cu-BAT-2IT-1A3. Cancer Biotherapy and Radiopharmaceuticals, 2001; 16: 483-494.

Abstracts

1. Laforest R, Lewis JS, Lewis MR, Morris MM, Wang M, Srinivasan A, Schmidt MA, Anderson CJ. Dosimetry comparisons of ^{90}Y- and ^{64}Cu-labeled somatostatin peptides in tumor-bearing rats. Journal of Nuclear Medicine 2000; 41:235P.
2. Anderson CJ, Radiolabeled somatostatin analogs for targeted radiotherapy of cancer. Metals in Medicine Workshop, NIH, Bethesda, MD, June, 2000.
3. Anderson CJ, Lewis JS, Lewis MR, Caruano AL, Dehdashti F. Copper-64-somatostatin analogs for cancer imaging and therapy. Midwest Regional ACS Meeting, St. Louis, MO October, 2000.
4. Anderson CJ, Lewis JS, Wang M, Wang F, Srinivasan A, Erion JL.Toxicity and Dosimetry of Lu-177-Y3-Octreotate. Pacifichem 2000; Honolulu, HI, December, 2000.