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DOSIMETRY AND QUANTITATIVE RADIONUCLIDE IMAGING IN RADIOIMMUNOTHERAPY

FINAL REPORT

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ABSTRACT

This final report under agreement No. DE-FG02-91ER61195 summarizes the overall progress in our research on the dosimetry and quantitative radionuclide imaging in radioimmunotherapy in the following areas:

1. Development of quantitative SPECT for high-energy photons (e.g. ^{87}Y, ^{19}F) and stability testing of ^{87}Y-labeled antibodies in the nude mouse model. This work has demonstrated the feasibility of using ^{87}Y-labeled antibodies for imaging prior to therapy with ^{90}Y-labeled antibodies.

2. Development of a unified approach to photon and beta particle dosimetry. The point-source kernel in this approach can be used for photons and beta particles for uniform and non-uniform activity distributions.

3. Quantitative SPECT for nonuniform attenuation. In a phantom study with non-uniform attenuation, differences between measured and computed activity concentrations were less than 6%.

4. Development of patient-specific dosimetry in radioimmunotherapy. Patient-specific dosimetry is based entirely on patients' quantitative SPECT studies and whole-body imaging and obviates the need for using "standard organs" in radiation dosimetry.

SUMMARY OF OVERALL PROGRESS

The results of our research have been published or have been accepted for publication in the open literature. Consistent with our previous reports, we therefore provide only brief summaries that describe the salient featrues of the approaches employed and the results obtained.

1. The use of ^{87}Y in radioimmunotherapy

In several clinical trials, ^{111}In-labeled antibodies were used for imaging and dosimetry prior to therapy with ^{90}Y-labeled antibodies. It is unlikely that the pharmacokinetics of ^{111}In- and ^{90}Y-labeled antibodies were exactly the same. Therefore, radiation dosimetry may have been compromised. To overcome this problem, we developed quantitative SPECT for ^{87}Y because ^{87}Y and ^{90}Y have the same chemical properties and chelation chemistry. Additionally, the in-vivo stability of ^{87}Y radioimmunoconjugates was determined by conjugating monoclonal antiferritin antibody to the chelator ITCB-DTPA and chelating with ^{87}Y. The results of these studies (see Publications 4 and 5) demonstrated that in a phantom study, ^{87}Y-containing fillable "organs" were imaged very well and that ^{87}Y activities in these organs were computed with a difference of less than 10% as compared to actual measurement. In tumor-bearing nude mice, tumor targetting and normal-organ distribution of ^{87}Y- and ^{90}Y-labeled antibodies were the same. The imaging results and animal data suggest that ^{87}Y-labeled antibodies could be used to reliably predict the pharmacokinetics of ^{90}Y-labeled antibodies and, hence, improve dosimetry in radioimmunotherapy.

In a subsequent investigation it was shown that the collimators used for imaging ^{87}Y photons also have potential application in ^{18}F (positron) imaging. A complete characterization of the collimators used is provided in Publication No. 21 (reprint enclosed).

2. A unified approach to photon and beta particle dosimetry

A complete description of this research is provided in Publiction No. 16; a reprint is enclosed.

The objective of this work was to develop a unified and practical method for photon and beta particle dosimetry. This was achieved by developing a point-source kernel that is equally valid for photons and beta particles. Explicit expressions were derived for the absorbed fraction within and outside of spheres containing a uniform distribution of activity. An important feature of the derivations is that absorbed-dose calculations can be

made analytically on the macroscopoic, cellular and subcellullar levels. As outlined below, the methodology employed and results obtained were subsequently utilized in patient-specific tumor and normal-organ dosimetry.

3. Quantitative SPECT for nonuniform attenuation

An important goal of our research was to develop and test quantitative SPECT for nonuniform attenuation with the circular harmonic transform (CHT) reconstruction algorithm developed by our group. Mathematically, this was achieved by developing a three-dimensional collimator filter model and employing the frequency-distance principle in CHT reconstructions.

Nonuniform attenuation is most pronounced in the thorax. Therefore, a phantom was constructed to simulate the different attenuations foud in this part of the body. A detailed description of this phantom was provided in Progress Report DOE/ER/61195-3, March 1994. As summarized in that report, the maximum difference between actual and computed redionuclide concentrations was approximately 6%.

4. Development of patient-specific dosimetry

The development of patient-specific dosimetry was the ultimate goal of our research in the dosimetry of administered radionuclides in general, and specifically, radiolabeled antibodies. A detailed description of the methodology uased and results obtained is provided in Publications 24 and 26.

Briefly, this approach to patient dosimetry is based on whole-body imaging and quantitative SPECT to generate time-activity curves for those tumors and normal organs which demonstrate significant uptake of radiolabeled antibodies. Additionally, tumor and normal organ volumes and the corresponding activity concentrations are determined from transverse SPECT slices. The absorbed doses corresponding to the activity concentrations are calculated using a three-dimensional discrete Fourier transform (3D-DFT). The 3D-DFT convolution method was validated in mathematical and physical phantoms by comparing it to Monte Carlo transport calculations which were carried out using the EGS4 system code. The root mean square error between the two methods was less than 0.1%. It was concluded that the 3D-DFT method which is computationally much more efficient than Monte Carlo tansport calculations is a precise tool for carrying out absorbed-dose calculations in clinical studies.

PUBLICATIONS ISSUED DURING THE TOTAL AGREEMENT PERIOD

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4. Leichner PK, Harvey EB, Holdeman KP, Harrison KIA, Hawkins WG, Kelly RF, Atcher RW, Lexa R, Valentino F, Dalrymple GV. SPECT imaging of Y-87 (485-keV) photons. Antibody Immunoconj Radiophar 5:355, 1992.

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12. Harrison KA, Dalrymple GV, Leichner PK, Tempero MA, Colcher DM, Augustine SC, Bierman PJ, Joshi SS, Holdeman KP, Quadri SM, Schneiderman MH, Jacobson DA. Clinical radiobiology of radiolabeled antibody therapy. Proceedgs 13th Annual Meeting of the Radiation Research Society, p.117, 1993.

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15. Hawkins WG, Links JM, Leichner PK. FFT interpolation for arbitrary factors: Application to cross-sectional imaging. Proceedgs 14th world congress on computational and applied mathematics 2:274-277, 1994.

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27. Akabani G, Hawkins WG, Leichner PK. Small-scale alpha dosimetry of red bone marrow using histological images. J Nucl Med 37:231P, 1996.

APPENDIX
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Reprints of two articles:

1. Leichner PK. A Unified Approach to Photon and Beta Particle Dosimetry. J Nucl Med 34:1721-1729, 1994.

2. Leichner PK, Morgan Ht, Holdeman KP, et al. SPECT Imaging of Fluorine-18. J Nucl Med 36:1472-1475, 1995.

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