The Present and Future Role of Monoclonal Antibodies in the Management of Cancer

24th Annual San Francisco Cancer Symposium, San Francisco, Calif., February 10–11, 1989

The Present and Future Role of Monoclonal Antibodies in the Management of Cancer

Volume Editors
Jerome M. Vaeth, San Francisco, Calif.
John L. Meyer, San Francisco, Calif.

56 figures, 1 color plate and 39 tables, 1990

KARGER

Basel · München · Paris · London · NewYork · New Delhi · Bangkok · Singapore · Tokyo · Sydney

Frontiers of Radiation Therapy and Oncology

Library of Congress Cataloging-in-Publication Data
San Francisco Cancer Symposium (24th: 1989)
The present and future role of monoclonal antibodies in the management of cancer/
24th Annual San Francisco Cancer Symposium, San Francisco, Calif.,
February 10–11, 1989; volume editors, Jerome M. Vaeth, John L. Meyer.
(Frontiers of radiation therapy and oncology; vol. 24)
Includes bibliographical references.
1. Monoclonal antibodies – Therapeutic use – Congresses.
2. Monoclonal antibodies – Diagnostic use – Congresses.
3. Cancer – Radioimmunotherapy – Congresses.
4. Cancer – Radioimmunoimaging – Congresses.
I. Vaeth, Jerome M., 1925– . II. Meyer, John L., 1949– . III. Title. IV. Series
[DNLM: 1. Antibodies, Monoclonal – therapeutic use – congresses.
2. Neoplasms – therapy – congresses.]
ISBN 3–8055–5029–4

Bibliographic Indices
This publication is listed in bibliographic services, including Current Contents® and Index Medicus.

Drug Dosage
The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

Printed in Switzerland by Thür AG Offsetdruck, Pratteln
ISBN 3–8055–5029–4

The Present and Future Role of
Monoclonal Antibodies in the Management of Cancer

Frontiers of Radiation Therapy and Oncology

Vol. 24

Series Editors
Jerome M. Vaeth, San Francisco, Calif.
John L. Meyer, San Francisco, Calif.

KARGER

Basel · München · Paris · London · NewYork · New Delhi · Bangkok · Singapore · Tokyo · Sydney

To my mentor and the
Patriarch of American Radiation Therapy **Dr. Juan A. del Regato**
on his 80th birthday

Jerome M. Vaeth

Acknowledgements

This year's Symposium was produced in association with the St. Mary's Foundation. The production of this Symposium, leading to the 24th volume of *Frontiers,* was assisted by the generosity of donations made by Computerized Medical Systems, Gammex Inc., Haynes Radiation Ltd., Janssen Pharmaceutica, Inc., Mallinckrodt, Inc., John Meyer, MD, NeoRx Corporation, Northern California Radiation Therapists Group, Inc., Oncogen, Schering Corporation, Siemens Corporation, and Varian Associates.

We are indebted to Cullyn Marie Vaeth, Aurore Vaeth, and Karen Freitas, who worked so tirelessly and devotedly to make possible this 24th Symposium.

Foreword

The subject 'The Present and Future Role of Monoclonal Antibodies in the Management of Cancer' was the theme of our 24th Annual San Francisco Cancer Symposium. There is a rapidly growing accumulation of basic and clinical information which has furthered the emergence of this exciting modality into today's oncological practice.

On February 10 and 11, 1989, some of the world's acknowledged authorities in labelled monoclonal antibodies joined us in San Francisco for this symposium. Their presentations blended the current basic physical, radiobiological and clinical information and formed the basis for this 24th volume of *Frontiers of Radiation Therapy and Oncology* published by S. Karger AG. We hope that this effort will update the information available to us today and will point the way to future frontiers of this exciting modality.

Jerome M. Vaeth, MD
Director, Radiation Oncology, St. Mary's Hospital and Medical Center, San Francisco
Clinical Professor of Radiology
University of California, Davis, Calif., USA

Contents

Dedication VII
Acknowledgements VIII
Foreword IX

Order, S.E. (Baltimore, Md.): Perspectives in Radioimmunoglobulin Therapy . . 1
Sinkovics, J.G. (Tampa, Fla./Houston, Tex.): The Earliest Concept of the 'Hybridoma Principle' Recognized in 1967–1968 18
Jain, R.K. (Pittsburgh, Pa.): Tumor Physiology and Antibody Delivery 32
Woo, D.V.; Derui, L.; Brady, L.W.; Emrich, J. (Philadelphia, Pa.); Mattis, J. (Malvern, Pa.); Steplewski, Z. (Philadelphia, Pa.): Auger Electron Damage Induced by Radioiodinated Iodine-125 Monoclonal Antibodies 47
Discussion 64
Steplewski, Z.; Fox, K.; Glick, J.; Koprowski, H. (Philadelphia, Pa.): Human Anti-mouse Antibody Response in Patients Treated with Multiple Infusions of Monoclonal Antibody CO17-1A 69
McGann, J.K (Menlo Park, Calif.); Langmuir, V.K. (Chicago, Ill.); Sutherland, R.M. (Menlo Park, Calif.): Modulators of Tumor Responsiveness to Radioimmunotherapy 73
Goldenberg, D.M. (Newark, N.J.): Cancer Imaging with Radiolabeled Antibodies 90
Dillehay, L.E.; Williams, J.R. (Baltimore, Md.): Radiobiology of Dose-Rate Patterns Achievable in Radioimmunoglobulin Therapy 96
Wessels, B.W.; Yorke, E.D.; Bradley, E.W. (Washington, D.C.): Dosimetry of Heterogeneous Uptake of Radiolabeled Antibody for Radioimmunotherapy . . . 104
Leichner, P.K.; Nai-Chuen, Y. (Baltimore, Md.); Wessels, B.W. (Washington, D.C.); Hawkins, W.G.; Order, S.E.; Klein, J.L. (Baltimore, Md.): Dosimetry and Treatment Planning in Radioimmunotherapy 109
Discussion 121
Macey, D.J.; DeNardo, G.L.; DeNardo, S.J. (Sacramento, Calif.): A Treatment for Radioimmunotherapy 123
Senter, P.D. (Seattle, Wash.): Antitumor Effects of Antibody Enzyme Conjugates in Combination with Prodrugs 132

DeNardo, S.J.; Deshpande, S.V.; Moi, M.K.; Adamas, G.P.; McCall, M.K.; DeNardo, G.L.; Meares, C.F. (Sacramento, Calif.): Today and Tomorrow: Radiochemistry for Radioimmunotherapy of Breast Cancer 142
Brady, L.W.; Markoe, A.M.; Woo, D.V.; Amendola, B.E.; Karlsson, U.L.; Rackover, M.A.; Koprowski, H.; Steplewski, Z.; Peyster, R.G. (Philadelphia, Pa.): Iodine-125 Labeled Anti-Epidermal Growth Factor Receptor-425 in the Treatment of Glioblastoma Multiforme: A Pilot Study 151
Discussion 161
Kemshead, J.T. (London); Coakham, H.B. (Bristol); Lashford, L.S. (London): Clinical Experience of Iodine-131 Monoclonal Antibodies in Treating Neural Tumours 166
Abrams, P.G. (Seattle, Wash.): Specific Targeting of Cancer with Monoclonal Antibodies. Diagnostic and Therapeutic Applications 182
Spitler, L.E. (Tiburon, Calif.): Monoclonal Antibodies in the Treatment of Malignant Melanoma 186
DeNardo, G.L.; DeNardo, S.J.; O'Grady, L.F.; Mills, S.L.; Lewis, J.P.; Macey, D.J. (Sacramento, Calif.): Radiation Treatment of B Cell Malignancies with Immunoconjugate 194
Discussion 202
Press, O.W.; Eary, J.F.; Badger, C.C.; Martin, P.J.; Appelbaum, F.R.; Nelp, W.B.; Krohn, K.A.; Fisher, D.; Porter, B.; Donnall Thomas, E.; Miller, R.; Brown, S.; Levy, R.; Bernstein, I.D. (Seattle, Wash.): High-Dose Radioimmunotherapy of B Cell Lymphomas 204
Markoe, A.M.; Brady, L.W.; Woo, D.; Amendola, B.; Karlsson, U.; Fisher, S.; Micaily, B.; Rackover, M.; Bulova, S.; Steplewski, Z.; Koprowski, H. (Philadelphia, Pa.): Treatment of Gastrointestinal Cancer Using Monoclonal Antibodies . . 214
Discussion 225
Wahl, R.L. (Ann Arbor, Mich.): Radiolabeled Monoclonal Antibodies for the Diagnosis and Treatment of Ovarian Carcinoma 228
Stickney, D.R. (Loma Linda, Calif.): Organization of a Monoclonal Antibody Clinical Unit 240
Brady, L.W.; Markoe, A.M.; Woo, D.V. (Philadelphia, Pa.): The Present and Future Role of Monoclonal Antibodies in the Management of Cancer. Summary . . 247

Subject Index 261

Vaeth JM, Meyer JL (eds): The Present and Future Role of Monoclonal Antibodies in the Management of Cancer. Front Radiat Ther Oncol. Basel, Karger, 1990, vol 24, pp 1–17

Perspectives in Radioimmunoglobulin Therapy

Stanley E. Order

Department of Radiation Oncology, The Johns Hopkins Oncology Center, Baltimore, Md., USA

Preclinical Studies

This review begins with some of the fundamental considerations for investigating and understanding radioimmunoglobulin therapy prior to clinical trials, since the requirements necessary for preclinical studies have not been clearly described in a general approach. In addition, the present state of the art in clinical trials is presented with a discussion of future perspectives for clinical advancement.

Antigen Specificity

'Specificity' is the fundamental basis of immunology, especially when considering the use of radioimmunoglobulins [1]. In early radioimmunoglobulin studies unique tumor-specific antigens were commonly held to be a requirement for radiolabeled antibody targeting. This is not, however, the case. Presently, anti-idiotypic monoclonal antibodies can recognize unique sites at the variable end of the immunoglobulin elaborated by B cells in non-Hodgkin's lymphomas [2]. Miller et al. [2], building on the original work of Kohler and Milstein, produced such monoclonal antibodies and achieved two complete remissions without radiolabeling. One of these remissions, of 6 years' duration, recurred following a traumatic accident. The recurrence was idiotypically identical to the original type, was treated with local irradiation, and was completely remitted. We must conclude from such an event that the new malignancy derived from resid-

ual clones of the original malignant cells which were not destroyed, and that other immunoregulatory events occurred to lead to the first complete remission. Other antigenic specificities not as unique, such as CEA [3, 4], colonic antigens [5], melanoma antigens [6] (96.5 antibody, etc.), and ferritin [7] have also been studied.

Normal Tissue Distribution

Early investigators had also considered cross-reactive antigens present in normal tissue and malignant tissue to be poor candidates for potential therapeutic trials. Ferritin, however, a cross-reactive protein debatable as to its degree of unique specificity (acid isoferritin, isoelectric focus, etc. [8]), is present in the normal spleen, muscle, heart, liver, etc. Ferritin will serve here to assess radiolabeled antibody distribution in normal tissue and malignant tissue, and to demonstrate factors limiting efficacy of therapeutic administration of radioimmunoglobulins [9–11].

Factors to consider in using a radiolabeled antibody as a therapeutic pharmaceutical, are antibody specificity, the rate of antibody biodegradation, the tightness of the isotope linkage and various characteristics of the isotope. Although very little consideration has been given to the species of origin from which the radiolabeled antibody is derived, our own investigations have demonstrated that monoclonal mouse antibodies are easily dehalogenated and biodegraded when ^{131}I is used as the isotope [12]. In contrast, polyclonal rabbit antibodies do not normally dehalogenate and their biodegradation occurs over a more prolonged time [12]. Both pig and baboon antibodies evidence similar prolonged biodegradation of 3–4 days with ^{131}I as the isotope [13].

Although ^{131}I antiferritin antibodies are highly specific for ferritin antigen, biodistribution studies reveal a high tumor to normal tissue ratio. Comparative studies using ^{131}I normal IgG and ^{131}I antiferritin show no difference in radioactive deposition in normal ferritin-bearing organs (fig. 1) [9–11]. Normal vasculature in ferritin-bearing organs likely prevents significant concentration of the ^{131}I antibody into the normal interstitium which has reduced ferritin concentrations for binding, while the more porous and less reactive tumor neovasculature allows easy transit of the radiolabeled antibody toward an interstitium containing a high ferritin concentration, thus accounting for the difference in targeting of tumor- and ferritin-bearing tissues.

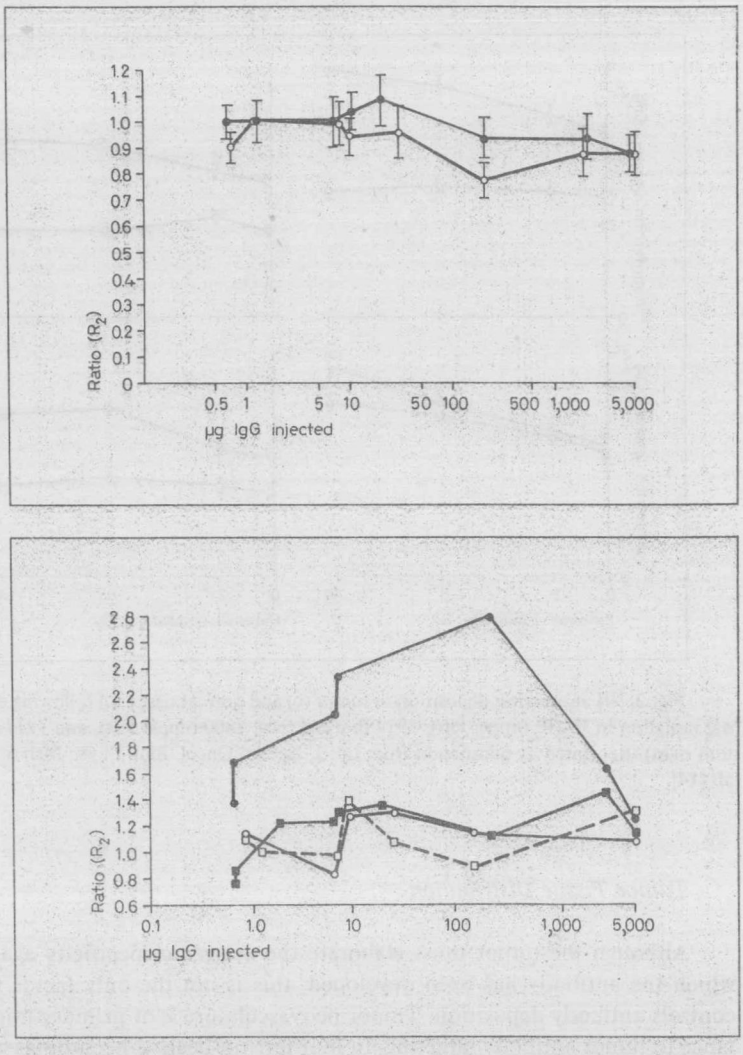


Fig. 1. a Quantitative similarity including standard deviations of ^{131}I normal IgG (○) and ^{131}I antiferritin IgG (●) as a function of injected protein and labeling ratio in ferritin-bearing organs. *b* Quantitative increase in ^{131}I antiferritin up to 100 µg IgG between tumor (●) and normal tissues (○). The normal organs were assessed by ^{131}I antiferritin (■) and ^{131}In IgG (□). Reprinted by permission from Am. J. clin. Oncol.; Rostock et al. [9].

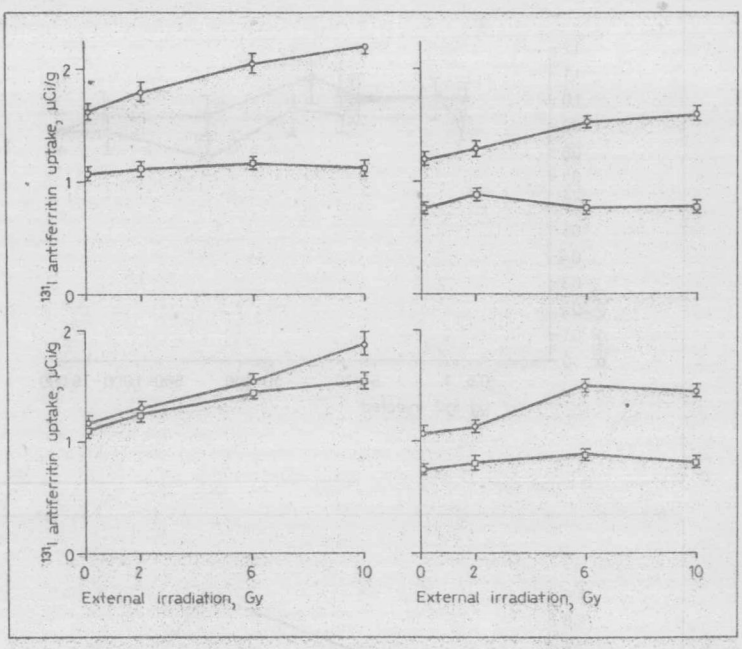


Fig. 2. ^{131}I antiferritin deposition in tumor (○) and normal tissue (□) following external radiation in H4IIE (upper left); 3924 (bottom left); 7800 (upper left), and 7777 (bottom right). Reprinted by permission from Int. J. Radiat. Oncol. Biol. Phys.; Msirikale et al. [14].

Tumor Tissue Distribution

Although the tumor must elaborate the antigenic specificity against which the antibody has been developed, this is not the only factor that controls antibody deposition. Tumor neovasculature is of primary importance to tumor antibody targeting. In four ferritin-bearing hepatomas having equal ferritin concentration, for example, equivalent 'tumor targeting' was not observed. Investigation of the neovascular content of the tumors demonstrated a direct correlation between neovascular content and radiolabeled antibody deposition. In addition, increasing neovascular pemeability with external irradiation also amplified radiolabeled antibody deposition without increasing normal tissue uptake [14] (fig. 2). In other experi-

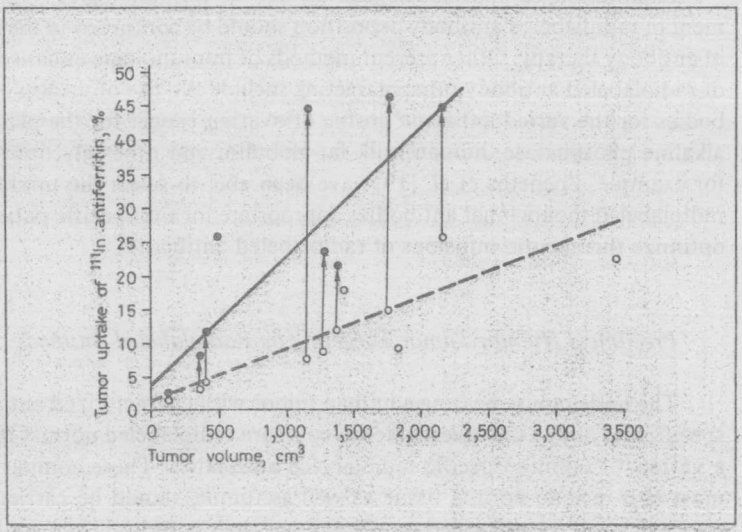


Fig. 3. Tumor uptake of ^{111}In antiferritin in percent of activity prior to (○) and following (●) 600–900 rad of external radiation. In 8 patients studied tumor localization increased (up arrow), 1.1- to 5.8 (mean 2.8)-fold following external radiation. Reprinted by permission from Int. J. Radiat. Oncol. Biol. Phys.; Leichner et al. [18].

mental models radiation and hyperthermia have also been shown to increase radiolabeled antibody uptake, although hyperthermia also enhanced normal tissue uptake of radiolabeled antibodies [15].

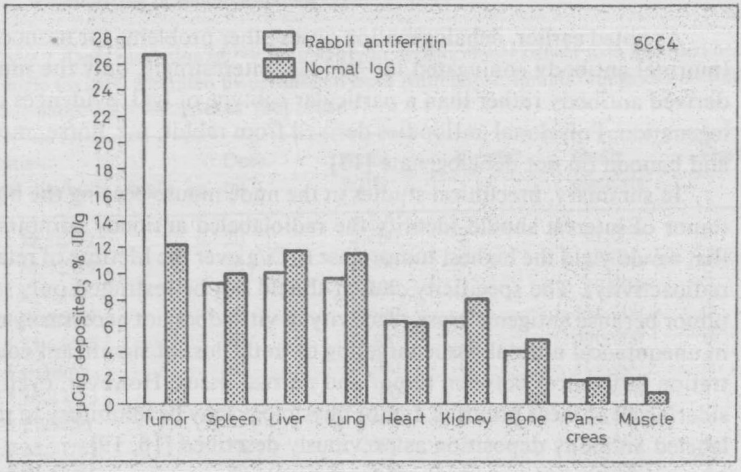
It should be appreciated that tumors have other characteristics which would both aid and impede radiolabeled (macromolecule) antibody transport. Hydraulic conductivity, large hydrophilic interstitial space, high interstitial diffusion, interstitial convection, interstitial flow, and the absence of lymphatics aid in radiolabeled antibody targeting of tumors, while increased interstitial pressure, low microvascular pressure, potential central hypoxia, low metabolic activity, and hypovascular tumor cores would all be counterproductive to radiolabeled antibody targeting [16, 17]. Thus, clinical application of radiolabeled antibody in nonirradiated patients is enhanced fivefold in tumor targeting when preceded by 600–900 rad when direct comparisons with ^{111}In antiferritin were carried out in the same patients [18] (fig. 3).

Exploration of pharmacological as well as immunological enhancement of radiolabeled antibody deposition should be continued in the study of antibody therapy. Other present methods of immunologic enhancement of radiolabeled antibody tumor targeting include the use of multiple antibodies for the varied antigenic profile of ovarian cancer for the placental alkaline phosphatase, human milk fat globulin, and other glycoproteins, for example, Epenetos et al. [19] have been able to select the mixture of radiolabeled monoclonal antibodies appropriate for the specific patient to optimize therapeutic infusions of radiolabeled antibodies.

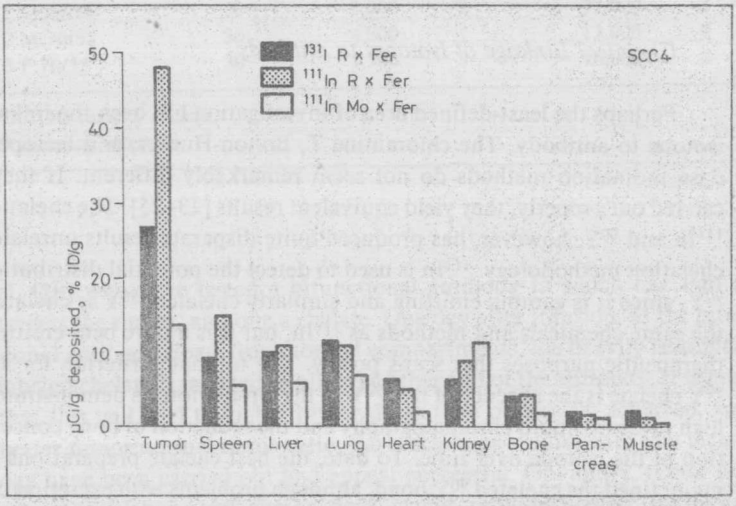
Preclinical Human Tumor Targeting by Radiolabeled Antibody

The nude mouse bearing a human tumor with characterized antigenic specificities allows the investigator to compare radiolabeled normal IgG to a variety of immunospecific radiolabeled antibodies. These comparisons must also include normal tissue as well as tumor, should be carried out over time, and are expressed in μCi/g rather than as ratios. Thus, multiple daily samples of normal tissue and tumor may be compared to determine the quantitative differences. If the antibodies tested are all derived from the same donor species, the effective half-life will be similar and only the dose deposited (μCi/g) will vary. This approach showed 96.5 radiolabeled antibody (melanoma-neuroectodermal antigen) to be superior to radiolabeled antiferritin in studies of glioblastoma, and ferritin to be superior to normal IgG in squamous cell cancers of the head and neck [20, 21] (fig. 4).

However, even methods of isotope linkage apparently make a difference, as demonstrated when we compared ^{111}In-chelated antiferritin with ^{131}I-labelled antiferritin [21] (fig. 5). We found that ^{111}In-chelated antiferritin did not target clinical hepatocellular cancer as well as ^{131}I-labeled antiferritin. As the nude mouse does not have normal human reticuloendothelium, it does not always demonstrate the different distributions that may occur in patients. In the case of ^{111}In, the chelate was so attracted to the hyperactive normal liver that the Fab end of the IgG molecule was not able to overcome this attraction. We have termed this phenomenon 'chelate domination'. In contrast, this same chelated antiferritin attached to ^{111}In targeted Hodgkin's tumor. Thus, when ^{90}Y, similarly chelated to antiferritin, was infused, the antibody performed quite well, leading to complete remission in the treatment of Hodgkin's disease [22].



4



5

Fig. 4. Quantitative comparison of ^{131}I antiferritin versus ^{131}I normal IgG in tumor and normal tissues. Reprinted with permission from Antibody, Immunoconjugates and Radiopharmaceuticals; Nguyen et al. [21].

Fig. 5. The effect of chelation on altering tumor deposition of radiolabeled antibodies is shown when comparing polyclonal ^{131}I antiferritin to ^{111}In polyclonal antiferritin, to ^{111}In monoclonal antiferritin. The ^{111}In makes the same polyclonal antiferritin 1.5 times more potent in radiolabeled antibody deposition. Reprinted by permission from Antibody, Immunoconjugates and Radiopharmaceuticals; Nguyen et al. [21].