Targeted Radionuclide Tumor Therapy

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Editors

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Biological Aspects

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Preface

The last three decades have provided opportunities to explore the potential of treating malignant diseases with antibodies or other targeting molecules labelled with nuclides. While considerable advances have been reported, there is still a significant amount of work left to accomplish before our ambitions can be achieved.

It now seems timely to review the accomplishments achieved to date and to clarify the challenges that remain. The choice of radionuclide, the conjugation procedure employed, and the selection of suitable targets were early issues that were faced by our field that still persist, however we can now tackle these obstacles with significantly better insight. The expanding array of new targeting molecules (recombinant antibodies, peptides and agents based upon alternate scaffolds) may increase the therapeutic efficacy or even modify the radiation sensitivity of the targeted tumor cell. The title of this book "Targeted Radionuclide Tumour Therapy – Biological Aspects" was selected to reinforce the concept that a major focus of this volume was devoted to understanding the biological effects of targeting and radiation. These important issues have not previously been the primary focus in this context. Furthermore, our rapidly expanding knowledge of different types of cell death and the increasingly likely existence of cancer stem cells suggests to us that even more efficient approaches in targeting might be possible in the future.

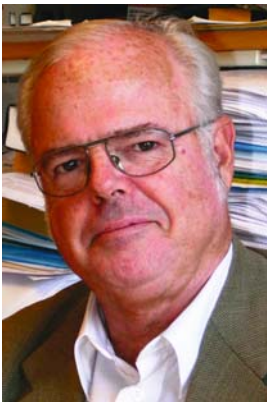
The development of targeted therapy is a true multidisciplinary enterprise involving physician scientists from the fields of nuclear medicine, radiation therapy, diagnostic radiology, surgery, gynaecology, pathology and medical oncology/haematology. It also involves many preclinical scientists working with experimental animal models, immunochemistry, recombinant antibody technologies, radiochemistry, radiation physics (dosimetry) and basic cell biology including the study of cell signalling pathways and the mechanisms of cellular death.

Certainly several challenges remain in bringing targeted therapy into mainstream of treatment modalities, but in many of the chapters significant improvements in targeting efficiency are observed and may indicate future efficacy and acceptance, maybe not as a single treatment modality, but in combination with other strategies.

It is the ambition of the editors to enable, with this volume, deeper insights in the process of improving targeted therapy for this diverse group of scientists. Clearly, some of the obstacles to gaining wider clinical acceptance might partly be related to this necessity of multidisciplinary collaborations. A number of disciplines,

many of them mentioned above, have to both collaborate and coordinate with each other in order to control the chain of judgement necessary for the treatment of each patient. All these requirements may not always be available or easy to accomplish. This is a management paradigm shift, which usually would take some time. However, we hope that the chapters in this book will convince you, the reader, that a critical mass of knowledge regarding how to effectively use targeted radionuclide therapy has been accumulated. We believe, and hope that you will agree, that the time now has come when targeted therapy can soon be added to standard oncology treatment regimens.

As editors we would also like to express our sincere gratitude to all the authors that contributed to this book.



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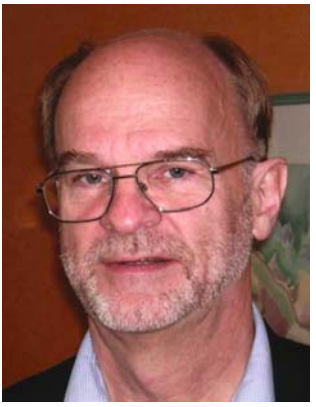

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Chapter 1
Introduction to Radionuclide Therapy

Jörgen Carlsson[1], Torgny Stigbrand[2], and Gregory P. Adams[3]

Summary This introductory chapter is written for those who are new to the field and desire a short overview of the present status of clinical and preclinical radionuclide therapy. In particular, this chapter provides an overview of the radiophysical concepts and key aspects of dosimetry and treatment planning that are beyond the scope of this book's focus on biological aspects of radionuclide therapy. Finally, a discussion on the choice of radionuclides and the availability of radiopharmaceuticals is provided.

The Editors View

The editors consider radionuclide therapy, to a large extent, as a potentially powerful method to eradicate disseminated tumor cells and small metastases. In contrast, bulky tumors and large metastases will likely have to be treated with surgery, external radiation therapy or chemotherapy before the remaining tumor cells might be reasonably treated with radionuclide therapy. The promising therapeutic results for hematological tumors [1], see also chapter 20, provide a reasonable expectation that radionuclide therapy will ultimately be effective for the treatment of disseminated cells from solid tumors.

Significant advances have recently been made in the characterization of new molecular target structures (chapters 2, 3, 7, 11, 18 and 20) and Fig. 1.1 schematically illustrates this. Furthermore, there is an increased knowledge in the pharmacokinetics, cellular processing and principles for modification of the radionuclide uptake for different types of targeting agents (chapters 4–8, 10, 11, 18 and 20).

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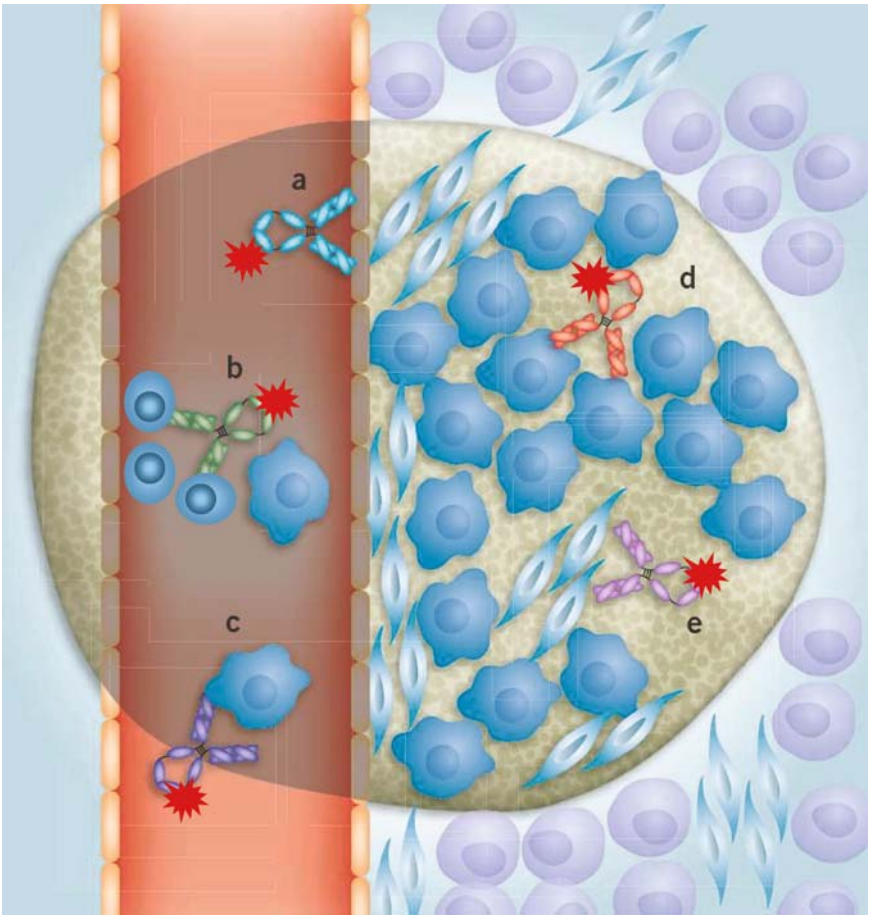

Fig. 1.1 Schematic drawing of potential targets for radionuclide therapy in a primary tumor or metastasis area. The radionuclide labelled targeting agents (e.g. monoclonal antibodies) can be used to target cancer-associated blood vessels (a), lymphoma or leukemia cell associated targets (e.g. CD20) in the blood flow (b), growth factor or other receptors on disseminated cells from a solid tumour (c) or on such cells that already have formed metastases (d). Also stroma cells and matrix components in the tumor area can be targets (e). The red stars indicate radioactive nuclides on the antibodies (Modified from [2]. With permission from the Nature Publishing Group)

There is also improved understanding of the factors of importance for the choice of appropriate radionuclides with respect to their decay properties and the therapeutic applications (chapters 7–11 and 20). Taken together, this suggests to the editors that this field is on the verge of experiencing major clinical advances.

However, we still need additional knowledge about the effects of low dose-rate (<1 Gy/h) radiation (chapter 16), programmed cell death (e.g. apoptosis) (chapter 12), cell cycle disturbances (chapter 14), bystander effects (chapter 17) and hyper

radiosensitivity (chapter 19) for various tumor cell types and for critical normal tissues exposed to targeted radionuclide therapy. Our knowledge in the area of tolerance doses for normal tissues when the radiation is delivered at low dose-rate is also very limited.

The disparate effects resulting from applying different qualities of radiation, e.g. low- versus high-LET, is also an interesting aspect that deserves further investigation (chapters 9–11). Furthermore, new concepts, such as the assumed existence of cancer stem cells (chapter 15) and possibilities to enhance the effects of targeted radionuclide therapy using various agents, such as chemotherapy agents and tyrosine kinase inhibitors (chapter 18), must be considered to better exploit the rapidly emerging knowledge of basic tumor biology. A striking example of that is the possibility for "double action" (chapter 13) or "autosensitization" (chapter 18) in which the targeting agent not only delivers therapeutically active radionuclides to tumor associated antigens and receptors, but also, simultaneously radiosensitizes the targeted tumor cells by triggering an intracellular signaling cascade (e.g. one that blocks radiation induced DNA-repair).

This book examines the topics mentioned above. This is important because in order for the field of radionuclide therapy to mature from one associated with palliation to one capable of curing patients with advanced malignancies it will be necessary to consider the basic biological factors that are believed to determine the outcome of radionuclide therapy.

Disseminated Tumor Cells and Radionuclide Therapy

As mentioned above, surgery and external radiation therapy are the major treatment modalities used for primary tumors and large metastases. Chemotherapy is used for disseminated disease and may be curative in cases of lymphomas, testicular tumors and tumors in the pediatric group or in solid tumors when used in combination with other modalities. However, in the vast majority of cases, there is no curative treatment available for the quantitatively large groups of patients with disseminated adenocarcinomas (e.g. breast, prostate, colorectal, lung and ovarian tumors) and squamous cell carcinomas (e.g. lung, esophagus and head-neck tumors). For most of these patients, a palliative effect and/or prolonged survival can at best be achieved with chemotherapy. This is also true for malignant gliomas and various other types of disseminated tumors, e.g. malignant melanomas and neuroendocrine tumors. Other, or complementary, treatment modalities seem therefore to be necessary to achieve considerable improvements in the treatment of the common types of disseminated malignant diseases, e.g. immunotherapy, anti-angiogenesis therapy, gene therapy or radionuclide therapy or possibly combinations of these (Fig. 1.2).

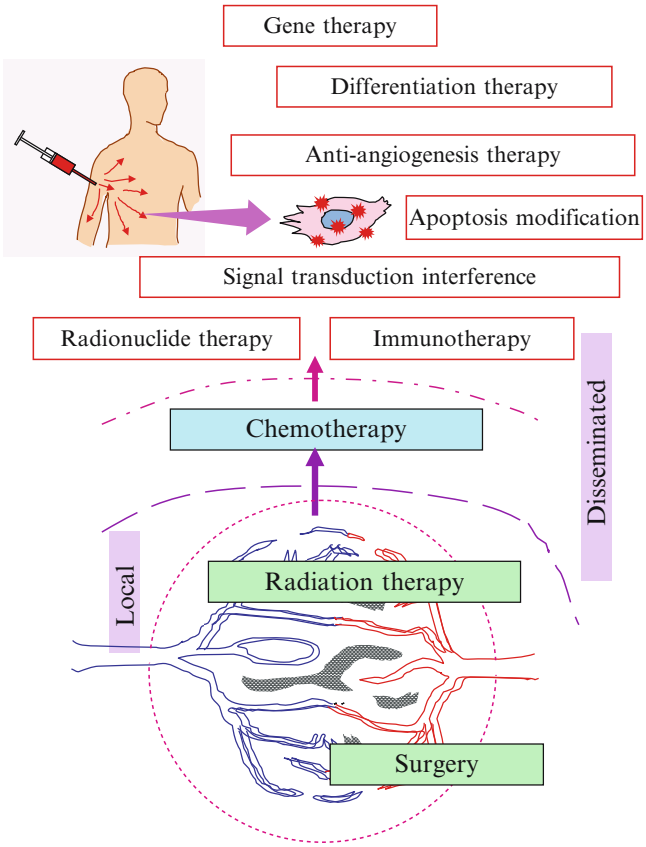

Fig. 1.2 Schematic illustration of strategies for tumor therapy. Surgery and external radiation therapy form the basis when locally growing tumor masses are treated. Chemotherapy in various forms is applied when there is tumor cell dissemination (symbolically shown above the dashed line). New therapy approaches (indicated with red frames above the dash-dotted line) will be tried when chemotherapy is not effective in its present forms. The new approaches are based on e.g. signal transduction interference with kinase inhibitors or modification of apoptotic processes. Some general and "biology-based" concepts are immunotherapy, differentiation therapy, anti-angiogenesis therapy and gene therapy. Radionuclide therapy is based on the same effect mechanism as external radiation therapy, namely induction of severe DNA-damage, and is therefore a form of radiotherapy. However, radionuclide therapy is placed among the new forms of "biology-based" therapies because it is dependent to a large extent on antigen and receptor expression and the biological factors regulating that (Modified from [45]. With permission from Elsevier Science Ltd.)

Present Status of Radionuclide Therapy

Chapter 20 in this book provides an in depth overview of the present status of clinical radionuclide therapy and we can also recommend recent reviews on the subject [2–6]. Although radionuclide therapy has been available for many years, few methods

are routinely used on a large scale. The exceptions are ^{131}I iodide, which has been used for a long time for therapy of thyroid cancer [5, 7, 8] and ^{32}P-orthophosphate for therapy of polycythemia and thrombocythemia [9, 10]. However, recently major successes have been achieved with the targeted radionuclide therapy of lymphomas (reviewed in chapter 20). Radiolabeled anti-CD20 antibodies Bexxar (^{131}I) and Zevalin (^{90}Y) provide significant improvement of response rate in comparison to use of the non-radiolabeled corresponding antibodies [1, 11], suggesting to us that this approach may soon experience more widespread use.

Other examples of recent successes with radiopharmaceuticals include ^{131}I or ^{125}I labeled MIBG (meta-iodobenzylguanidine) for treatment of pheochromocytoma and neuroblastoma [12–14] and the promising attempts to use ^{177}Lu labeled somatostatin analogues for treatment of neuroendocrine tumors [15–17] (see also chapter 7). Palliative treatments of skeletal metastases are routinely performed using radioactive calcium or phosphate analogues or other substances [18–20] and new approaches applying high-LET radiation have also been attempted as described in chapters 9 and 10.

In cases when the absorbed radiation dose to bone marrow stem cells is estimated to be too high, it has been necessary to prepare for stem cell transplantation prior to radionuclide therapy or combined chemo- and radionuclide therapy. This has, for example, been the case when large amounts of β-emitting radionuclides have been given for treatments of lymphomas and has been associated with favorable outcomes when stem cell transplantation was used in combination with high-dose chemotherapy and systemic radiotherapy [21, 22].

However, more research is necessary concerning advantages and disadvantages of stem cell transplantation in combination with radionuclide therapy. Actually, the need for stem cell transplantation will probably be much lower, or even eliminated, when short range α- and ß-emitters can be delivered with targeting agents that give a higher degree of specificity for tumor cell uptake.

Clinical Versus Preclinical Results

During the past two decades significant amounts of clinical and preclinical research have been devoted to targeted radionuclide therapy using radiolabeled monoclonal antibodies and receptor binding agents specific for CD antigens, somatostatin receptors, EGFR-family receptors and a range of other tumor-associated targets. Furthermore, various forms of antibody fragments, peptides and other molecules have also been employed (chapters 2–7 and 20). Only a few clinical studies have demonstrated a significant number of complete remissions. Thus, the potential for long-term cure has been limited. The best clinical results so far have been achieved for the treatment of lymphomas [1, 11].

However, there is enormous potential for improved clinical outcomes using radionuclide therapy [4]. Preclinical research has demonstrated the potential for cure of both primary and disseminated tumors [23–28] (see also references in

chapter 18) and such studies have enabled a selection of appropriate radionuclides and stimulated the development of a variety of new compounds. However the problem of a limited knowledge concerning the way to successfully transfer preclinical successes to the clinical setting remains.

Choice of Radionuclides

While it may not be oblivious to individuals not actively involved in the field of nuclear medicine, the choice of radionuclide is a very important consideration. Several types of radionuclides are suitable for therapy and these are well reviewed in chapter 8. The three major groups are β-particle emitting radionuclides (e.g. ^{67}Cu, ^{90}Y, ^{131}I, ^{177}Lu, ^{186}Re and ^{188}Re), Auger electron cascades (e.g. ^{111}In and ^{125}I) and α-particle emitting radionuclides (e.g. ^{211}At, ^{212}Bi, ^{213}Bi, ^{225}Ac and ^{227}Th). High-energy β-particles, such as ^{90}Y and ^{188}Re, are not efficient for killing single disseminated cells or small metastases, since only a small fraction of the electron energy will be deposited in such small targets. Most of the energy will instead travel beyond the tumor target to be absorbed in surrounding, often healthy, tissues. High-energy β particles might on the other hand be important for treatment in cases of non-uniform radioactivity distribution in large tumor areas. Irradiation from the targeted cells will then enable a more uniform dose-distribution and potentially elicit therapeutic effects on non-targeted tumor cells [29, 30]. In addition, it might be advantageous to use radionuclide cocktails to minimize the impact of heterogeneity [31].

Radionuclides emitting low energy β-particles such as ^{67}Cu, ^{131}I and ^{177}Lu and α particles (chapter 8) (or short-range electrons [32]) are options for treatment of small tumor deposits or even single disseminated tumor cells. However, a comparatively large amount of radionuclides per cell is needed when low energy β-particles (or low energy electrons) are used, thereby requiring a well-developed targeting process. By using α-particle emitting nuclides, or suitable Auger-electron emitters if nuclear localization is possible (chapter 11), fewer radionuclides per cell are needed. Recently, principles for local α-particle cascades were described whereby two or more α particles are emitted almost instantaneously and are therefore likely to contribute to the radiation dose in the vicinity of the site of the original decay (chapters 9 and 10).

The physical half-life of the radionuclides should preferably be in the same order of magnitude as the biological half-life of the radionuclide or the radionuclide conjugate. An overly long physical half-life increases the amount of radionuclides that must be delivered to the tumor cells to achieve therapeutic levels of decays before excretion. An extremely short physical half-life may not allow sufficient time for the tumor-targeting process to take place, resulting in the majority of the radioactive decays occurring in the vicinity of healthy, and often sensitive, tissues. It seems reasonable to assume that the most suitable physical half-lives range from a few hours up to a few days when targeting of disseminated cells is desired. Longer

physical half-lives (up to one or a few weeks) might be needed to achieve significant uptake in solid tumor masses.

Dosimetry and Treatment Planning

The radiophysical and technical aspects of targeted radionuclide therapy are important subjects but are not the focus of this book. Imaging techniques are briefly mentioned in a few chapters and dosimetry is not at all discussed. These subjects are instead covered by review articles [33] and other books [34–40]. However, as these are important considerations in radionuclide therapy a short overview of key aspects of dosimetry and treatment planning is provided below.

Tissue and organ level. Radionuclides associated with radiopharmaceuticals of therapeutic interest are taken up and excreted in a variety of ways in tumor cells and normal tissues. There is a continuous redistribution of radionuclides in the body and they are typically ultimately eliminated from the body, primarily by renal and faecal excretion. It is, of course, important to visualize and quantify the varying distributions.

The dosimetry used today is mainly based on conventional planar scintigraphy. It is highly desirable to improve the methods for quantification of radionuclide uptake in normal tissues and tumor areas and to use more quantitative methods. This can be achieved through the use of photon or positron emitting radionuclides suitable for SPECT [41] or PET [42, 43] imaging (SPECT = Single Photon Emission Computed Tomography, PET = Positron Emission Tomography), thereby making reliable dosimetry and radionuclide treatment planning possible. The PET technique is especially well suited for this.

For treatment planning, radionuclides intended for imaging should be used prior to radionuclide therapy. However, these radionuclides can also be used during therapy in order to allow calculations or corrections of achieved radiation doses. Suitable radionuclides for SPECT include ^{99m}Tc, ^{111}In and ^{123}I. ^{111}In and ^{123}I can also be used as SPECT-tracers in planning for therapy with radiometals and radiohalogens, respectively. Suitable radionuclides for PET include ^{18}F, ^{64}Cu, ^{68}Ga, ^{76}Br, ^{86}Y, ^{110}In and ^{124}I. The metals ^{64}Cu, ^{68}Ga, ^{86}Y and ^{110}In and the halogens ^{76}Br and ^{124}I can be used as PET-tracers in planning for therapy with radiometals and radiohalogens, respectively. There are also radionuclides, such as ^{177}Lu, that simultaneously deliver both therapeutically-relevant radiation doses through the emitted β-particles and photons capable of being monitored in a gamma camera.

The mean absorbed dose to normal tissues, primary tumors and large metastases can be estimated in this manner with reasonably high levels of accuracy and the results can be verified and supplemented, at least in experimental studies, using activity measurements taken on excised tissue samples. However, the dose to single disseminated tumor cells can only be roughly estimated. There is also a need for improved dosimetry, especially for determining the dose to bone marrow, which is often a critical dose-limiting organ in radionuclide therapy. The strategy with

targeted radionuclide therapy will be, as it is for external radiotherapy, to exploit the full tolerance radiation dose of critical normal tissues and thereby to maximize the amount given to the tumor cells.

The mean absorbed dose to large solid tumor masses and to critical normal tissues can be estimated reasonably well using the MIRD-formulation (MIRD = Medical Internal Radiation Dose) [34, 38, 44] using data from SPECT or PET studies. The amount of radionuclides excreted from the body can also be estimated by measurements of urine, faeces and, in some cases, by analyses of the remaining radioactivity in the body. Individual treatment planning should be routinely performed before radionuclide therapy to minimize the risk for under- or overdosing. However, it is necessary to consider that the kinetics of a radiopharmaceutical drug may in some cases be changed from the administration of a small test activity for treatment planning to the administration of larger amounts suitable for therapy.

It is possible that the absorbed dose to the tumor cells, in many cases, has been too low due to unfavorable pharmacokinetics of the therapeutic agent. Actually, the absorbed doses necessary for successful radionuclide therapy are not well known, nor are the tolerance doses for normal tissues. Studies regarding radiobiological effects have mainly been performed using external radiation generally with dose rates of about 1–2 Gy/min or more. In contrast, radionuclide therapy yields low dose rates, most often below 1 Gy/h (see chapter 16), making the use of external radiation derived absorbed dose values and tolerances questionable in these applications.

Cellular level. The radiation dose to single disseminated tumor cells can possibly only be estimated if representative samples of such cells are isolated from the body, e.g. by purification from the blood or by careful analysis of such cells from biopsies. Reasonable estimates of variations in dose at the cellular level can probably be achieved through computer calculations when the average amount of bound radionuclide is known. Knowledge of the subcellular radionuclide distribution will likely also be critical, especially for radionuclides emitting short-range particles.

For high-LET (LET = Linear Energy Transfer) particles, such as Auger electrons and α particles, microdosimetric concepts must be considered. Identical macroscopic radiation doses calculated with MIRD formalism can give quite different biological effects depending on the subcellular localization of the radionuclides.

Availability of Radiopharmaceuticals

An additional consideration that must be addressed is the potential reluctance of the pharmaceutical industry to produce radiopharmaceuticals. This is in part due to limited shelf life resulting from the physical half-life of the radionuclides and to complications associated with radiolysis during storage. It is our belief that these concerns may be solved in the future if the pharmaceutical industry focuses on producing non-radioactive substances designed for simple and effective radioactive labeling at the local hospital.

The substances could have a chelate coupled to them (chapter 8), as is presently the case for the somatostatin analogue octreoscan (chapter 7) and certain antibody preparations (chapter 4). This would allow them to be labeled with readily available metal radionuclides such as ^{177}Lu or ^{90}Y, different isotopes of indium or rhenium and potentially with short-lived α emitters such as ^{213}Bi. They could also be prefabricated to allow for halogen labeling with isotopes of iodine and the α-emitter ^{211}At, although such labelings would require a more complex procedure (see chapter 8).

The radionuclides could be produced locally at the nuclear medicine department with applied generators or accelerators or they could be bought from companies specializing in radionuclide production. It is important to note that the availability of radiopharmaceuticals will not be a severe problem if radionuclide therapy proves to be routinely effective in the clinical setting. Actually, radionuclide therapy might not be more complicated than chemotherapy combined with external radiotherapy provided that the non-radioactive substances prepared for radiolabeling are commercially available and that the radionuclides are available at the hospital [45].

References

1. Witzig TE (2006) Radioimmunotherapy for B-cell non-Hodgkin lymphoma. Best Pract Res Clin Haematol 19(4):655–68. Review.
2. Adams GP, Weiner LM (2005) Monoclonal antibody therapy of cancer. Nat Biotechnol 23(9):1147–57. Review.
3. Goldenberg DM, Sharkey RM (2006) Advances in cancer therapy with radiolabeled monoclonal antibodies. Q J Nucl Med Mol Imaging 50(4):248–64. Review.
4. DeNardo SJ, DeNardo GL (2006) Targeted radionuclide therapy for solid tumors: an overview. Int J Radiat Oncol Biol Phys 66(2 Suppl):S89–95. Review.
5. Oyen WJ, Bodei L, Giammarile F, Maecke HR, Tennvall J, Luster M, Brans B (2007) Targeted therapy in nuclear medicine–current status and future prospects. Ann Oncol 18(11):1782–92. Review.
6. Boerman OC, Koppe MJ, Postema EJ, Corstens FH, Oyen WJ (2007) Radionuclide therapy of cancer with radiolabeled antibodies. Anticancer Agents Med Chem 7(3):335–43. Review.
7. Pacini F, Schlumberger M, Harmer C, Berg GG, Cohen O, Duntas L, Jamar F, Jarzab B, Limbert E, Lind P, Reiners C, Sanchez Franco F, Smit J, Wiersinga W (2005) Post-surgical use of radioiodine ^{131}I in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. Eur J Endocrinol 153:651–9.
8. Woodrum DT, Gauger PG (2005) Role of ^{131}I in the treatment of well differentiated thyroid cancer. J Surg Oncol 89:114–21.
9. Berlin NI (2000) Treatment of the myeloproliferative disorders with 32P. Eur J Haematol 65(1):1–7. Review.
10. Berlin NI (2002) Polycythemia vera: diagnosis and treatment 2002. Expert Rev Anticancer Ther 2(3):330–6. Review.
11. Davis TA, Kaminski MS, Leonard JP, Hsu FJ, Wilkinson M, Zelenetz A, Wahl RL, Kroll S, Coleman M, Goris M, Levy R, Knox SJ (2004) The radioisotope contributes significantly to the activity of radioimmunotherapy. Clin Cancer Res 10:7792–7798.
12. Chrisoulidou A, Kaltsas G, Ilias I, Grossman AB (2007) The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr Relat Cancer 14(3):569–85. Review.
13. Howman-Giles R, Shaw PJ, Uren RF, Chung DK (2007) Neuroblastoma and other neuroendocrine tumors. Semin Nucl Med 37(4):286–302. Review.

14. Scholz T, Eisenhofer G, Pacak K, Dralle H, Lehnert H (2007) Clinical review: current treatment of malignant pheochromocytoma. J Clin Endocrinol Metab 92(4):1217–25. Review.
15. Kwekkeboom DJ, Mueller-Brand J, Paganelli G, Anthony LB, Pauwels S, Kvols LK, O'dorisio TM, Valkema R, Bodei L, Chinol M, Maecke HR, Krenning EP (2005) Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. J Nucl Med 46(Suppl 1):62S–66S.
16. Forrer F, Valkema R, Kwekkeboom DJ, de Jong M, Krenning EP (2007) Peptide receptor radionuclide therapy. Best Pract Res Clin Endocrinol Metab 21:111–29.
17. Van Essen M, Krenning EP, De Jong M, Valkema R, Kwekkeboom DJ (2007) Peptide Receptor Radionuclide Therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. Acta Oncol 46(6):723–34. Review.
18. Finlay IG, Mason MD, Shelley M (2005) Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol 6:392–400.
19. Bauman G, Charette M, Reid R, Sathya J (2005) Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radiother Oncol 75:258–270.
20. Lawrentschuk N, Davis ID, Bolton DM, Scott AM (2007) Diagnostic and therapeutic use of radioisotopes for bony disease in prostate cancer: current practice. Int J Urol 14:89–95.
21. Press OW, Eary JF, Gooley T, Gopal AK, Liu S, Rajendran JG, Maloney DG, Petersdorf S, Bush SA, Durack LD, Martin PJ, Fisher DR, Wood B, Borrow JW, Porter B, Smith JP, Matthews DC, Appelbaum FR, Bernstein ID (2000) A phase I/II trial of iodine-131 tositumomab (anti-CD20), etoposide, cyclophosphamide, and autologous stem cell transplantation for relapsed B-cell lymphomas. Blood 96:2934–42.
22. Molina A, Krishnan A, Fung H, Flinn IW, Inwards D, Winter JN, Nademanee A (2007) Use of radioimmunotherapy in stem cell transplantation and posttransplantation: focus on yttrium 90 ibritumomab tiuxetan. Curr Stem Cell Res Ther 2(3):239–48. Review.
23. Buchsbaum DJ (2000) Experimental radioimmunotherapy. Semin Radiat Oncol 10(2):156–67.
24. Behr TM, Blumenthal RD, Memtsoudis S, et al. (2000) Cure of metastatic human colonic cancer in mice with radiolabeled monoclonal antibody fragments. Clin Cancer Res 6(12):4900–7.
25. Barendswaard EC, Humm JL, O'Donoghue JA, et al. (2001) Relative therapeutic efficacy of (125)I- and (131)I-labeled monoclonal antibody A33 in a human colon cancer xenograft. J Nucl Med 42(8):1251–6.
26. de Jong M, Breeman WAP, Bernard BF, et al. (2001) [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate for somatostatin receptor-targeted radionuclide therapy. Int J Cancer 92:628–33.
27. Kassis AI, Adelstein SJ (2005) Radiobiologic principles in radionuclide therapy. J Nucl Med 46(Suppl 1):4S–12S. Review.
28. Murray D, McEwan AJ (2007) Radiobiology of systemic radiation therapy. Cancer Biother Radiopharm 22(1):1–23. Review.
29. O'Donoghue JA, Bardies M, Wheldon TE (1995) Relationships between tumor size and curability for uniformly targeted therapy with beta-emitting radionuclides. J Nucl Med 36(10):1902–09.
30. Hartman T, Lundqvist H, Westlin JE, Carlsson J (2000) Radiation doses to the cell nucleus in single cells and cells in micrometastases in targeted therapy with 131I labelled ligands or antibodies. Int J Radiat Oncol Biol Phys 46(4):1025–1036.
31. de Jong M, Breeman WA, Valkema R, Bernard BF, Krenning EP (2005) Combination radionuclide therapy using 177Lu- and 90Y-labeled somatostatin analogs. J Nucl Med 46(Suppl 1):13S–7S.
32. Bernhardt P, Forssell-Aronsson E, Jacobsson L, Skarnemark G (2001) Low-energy electron emitters for targeted radiotherapy of small tumours. Acta Oncol 40(5):602–8.
33. Wessels BW, Syh JH, Meredith RF (2006) Overview of dosimetry for Systemic Targeted Radionuclide Therapy (STaRT). Int J Radiat Oncol Biol Phys 66(2 Suppl):S39–45. Review.
34. Ell PJ, Gambhir S (2004) Nuclear Medicine in Clinical Diagnosis and Treatment. Elsevier Health Sciences, Edinburgh, UK (ISBN: 9780443073120).

35. Ramer K, Alavi A (2005) Nuclear Medicine Technology. Springer, New York (ISBN: 3540253742).
36. Schiepers C (2005) Diagnostic Nuclear Medicine. Springer, Germany (ISBN: 9783540423096).
37. Zaidi H (2005) Quantitative Analysis in Nuclear Medicine Imaging. Springer, New York (ISBN: 9780387238548).
38. Saha GB (2006) Physics and Radiobiology of Nuclear Medicine. Springer, New York (ISBN: 9780387307541).
39. Christian PE, Waterstram-Rich K (2007) Nuclear Medicine and Pet/Ct Technology and Techniques. Elsevier Health Sciences, St. Louis, MO (ISBN: 9780323043953).
40. Morton KA, Nance RW, Clark PB, Christensen CR, O'Malley JP, Blodgett TM, Waxman AD, Stevens JS, Drosten R, Chinn CA (2007) Nuclear Medicine. W.B. Saunders, Edinburgh, UK (ISBN: 9781416033394).
41. Evans ES, Hahn CA, Kocak Z, Zhou SM, Marks LB (2007) The role of functional imaging in the diagnosis and management of late normal tissue injury. Semin Radiat Oncol 17(2):72–80. Review.
42. Saleem A, Charnley N, Price P (2006) Clinical molecular imaging with positron emission tomography. Eur J Cancer 42(12):1720–7. Review.
43. Brans B, Bodei L, Giammarile F, Linden O, Luster M, Oyen WJ, Tennvall J (2007) Clinical radionuclide therapy dosimetry: the quest for the "Holy Gray". Eur J Nucl Med Mol Imaging 34(5):772–86. Review.
44. Thomas SR (2007) From the SNM MIRD committee. J Nucl Med 48(2):33N–34N.
45. Carlsson J, Forssell AE, Hietala SO, Stigbrand T, Tennvall J (2003) Tumour therapy with radionuclides; assessment of progress and problems. Radiother Oncol 66(2):107–17.

Chapter 2
Therapeutically Used Targeted Antigens in Radioimmunotherapy

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Summary Many antigens have been tested as targets for radioimmunotherapy with intact antibodies. Some of the early used targets have been found to be of decreasing interest due to low expression, extensive shedding or other reasons. Others have been found more useful due to their accessibility, amount available in the tumours, or the biological properties of the target antigen. In this chapter some of the most used antigens and their characteristics are presented.

Introduction

An increasing number of promising antigens on malignant cells for monitoring malignant diseases have recently been reviewed [1]. Several of the seventy markers in that review have also been investigated for putative use in radioimmunotherapy, and this chapter will focus on some of them.

The ideal antigen for targeting should be readily accessible, expressed mainly within the targeted tissue, if possible, and should be present in substantial amounts. In the early history of targeting experiments, many of the antigens referred to as "tumour markers" were employed and even secreted products were used for targeting. Several of these early secreted targets have turned obsolete today and have disappeared or are used in very limited extent (HCG, α-fetoprotein) and instead new aspects on the nature of the target have come into focus. Some of the major antigens in use will be presented here.

The amount available and accessibility of the antigen in combination of biological properties affect the outcome of targeting. The selectivity in tissue expression is also of importance. Some antigens may be regarded as disease specific for certain malignancies, while others are expressed in different type of tumours. Such ubiquitously

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expressed targets may have advantages at clinical radioimmunotherapy in a wider perspective. Several of the most used antigens today are expressed in several tumour tissues as for example, CEA, TAG-72, HER2/neu, EGFR and VEGF. CEA is expressed in colorectal, gastric, pancreatic, non-small cell lung and breast carcinomas. TAG-72 is similarly expressed in colorectal, gastric, pancreatic, ovarian, endometrial, breast, non-small cell lung cancer and prostate carcinomas. The expression of EGFR and HER2 is described in detail in chapter 3 but shortly described also below. In order to minimize hematopoietic toxicity at radioimmunotherapy, it is a significant advantage if the tissue expression is limited to the diseased tissue.

One aspect, today more in focus than earlier, is the metabolic behaviour of the targeted antigen. Some antigens, possible to target, may reside on the plasma membranes of the malignant cells, but also extracellularly located target molecules within the tumour tissue may be considered, if they are present in significant amounts, e.g. in the tumour stroma or tumour vasculature.

Many useful membrane antigens exert their biological role by recycling between the plasma membrane of the host cell and the interior of the same cell, providing a mechanism for internalization of antibodies by the targeted malignant cell. At the same time, however, the antibody will be exposed to the intracellular degradation machinery, including proteolytic cleavages of the labelled compound, with possibilities to separate the nuclide from its carrier. This causes a consecutive and continuous transport out of the cell of the nuclide as a low molecular weight compound, which will be subjected to urinary excretion.

Improved cellular retention can be achieved by the use radioactive metals (e.g. ^{90}Y or ^{177}Lu) which, after degradation of the targeting agent, bind to intracellular structures or by the use of residualizing reagents during coupling of radioactive halogens (e.g. ^{131}I or ^{211}At) to the targeting agent, see chapter 8 for more details.

Some of the antigens widely used are released or even secreted from the tumours and this causes appearance of circulating intact or degraded products of these antigens within the vasculature, which may interfere with the efficiency in the targeting by consuming the labelled antibodies with subsequent degradation within the reticuloendothelial system. Both CEA and TAG-72 appear in blood in soluble form in low amounts, and will compromise binding to the tumour, while for example CD20 is an excellent target because it is neither shed, nor internalized and furthermore expressed by almost all B-cell tumours. The properties of this antigen may be one of the important reasons for the positive outcome when treating different types of lymphomas.

Some of the most used antigens are presented below.

CEA

When the concept of oncofoetal antigens was introduced, following the discovery of CEA by Gold and Freeman [2], CEA was soon to be the very first antigen to be used both as a tumour marker and as target for intervention in the treatment of malignant diseases [3, 4].

The human CEA family has been fully characterized and comprises 29 genes, out of which 18 are expressed [5]. The CEA subgroup members are cell membrane associated and presents a complex expression pattern in normal and cancerous epithelial tissues. The form used as target is a heavily glycosylated single polypeptide chain of 180 kDa. CEA is an important tumour marker for colorectal cancer, but is expressed in many other tumours and regarded as a pancarcinoma marker.

Today CEA not only has become one of the most extensively used tumour markers, but also, due to its pronounced expression in many carcinomas, a widely used target antigen for radioimmunotherapy. Several interesting reports have been presented during the last years with this antigen and one trend is to use tailored constructs with several binding sites towards the antigen and the nuclides. Sharkey et al. generated a multivalent, bispecific antibody against CEA with a tenfold increase in uptake in a preclinical test with human colon xenografts and could reach tumour to non-tumour ratios up to 100 [6].

Similarly a streptavidin-conjugate of the chimeric antiCEAantibody T84.66 was also found to reach high ratios with an extremely rapid clearance from the blood and other organs [7]. This ^{90}Y-labelled antibody has also been tested on patients with uptake and radiation delivery to smaller nodal lesions [8].

An interesting new concept, the "dock-and-lock" approach to generate trivalent, bispecific antibodies against CEA was recently presented, with two binding sites for CEA and one for the nuclide. This construct displayed high specific targeting to pancreatic and colon cancer xenografts [9, 10]. A number of pretargeting reports furthermore support the usefulness of CEA as a target and improved localization has been reported, and provide experimental evidence for clinical application of radioimmunotherapy [11–15].

TAG-72

TAG-72 was initially identified 1985 as the target antigen of an antibody B72.3 raised against a membrane-enriched fraction of a metastatic breast carcinoma [16]. TAG-72 is a high molecular weight glycoprotein complex (240–400 kDa), which is also expressed on 80% of colorectal carcinomas, with very limited expression in normal tissues [17]. It should today also be regarded as a pancarcinoma antigen. A second generation of antibodies towards this antigen has been generated, CC49 being one of them [18, 19]. The TAG-72 antigen contains several carbohydrate epitopes and this CC49 antibody reacts with the sialyl-Tn and sialyl-T epitopes of the antigen. Since multiple epitopes can be present on a single target antigen, this may contribute to improved efficiency both when the antigen is the target or in monitoring assays.

The initial use of this antigen in radioimmunotherapy was limited, with sporadic positive effects and the murine antibody was highly immunogenic [20–23]. During the last years several reports have been presented, confirming TAG-72 over-expression in several tumour types [24]. Recombinant antibodies against TAG-72 have

demonstrated excellent pharmacokinetics and biodistribution targeting this antigen [25–28]. Furthermore, the heterogenous expression of some antigens in ovarian tumours have been compensated for by using several radiolabeled antibodies at the same time, one of them against TAG-72, a procedure which improved the targeting efficiency [29].

HER2/neu (c-erbB-2)

HER2 is a glycosylated protein with a molecular weight of 185 kDa. It has no known natural ligand. Instead it is activated via heterodimerization to other receptors in the EGFR-family. Activation leads to down-stream signalling to a large extent controlling cell proliferation and apoptosis (chapter 3).

HER2 is expressed, to a limited extent, in the epithelia of lung, bladder, pancreas and prostate. The ectodomain of this protein can, at least in experimental systems, be proteolytically cleaved off from the intact receptor and released in soluble form [30]. However, this seems not to occur, or at least only occur at a low level, in clinical cases since a constant strong tumour cell membrane associated overexpression of HER2 has been reported in an overwhelming number of cases (chapter 3).

Cell membrane associated HER2 overexpression has been studied mainly in breast cancer but has been observed also in several other malignancies such as prostate, ovarian and lung carcinomas [31–34]. HER2 is a potentially interesting target for radionuclide therapy, especially breast cancers that have primary or induced resistance to Herceptin treatment. Chapter 3 gives more detailed discussions about HER2 and other members of the EGFR-family as targets for radionuclide therapy.

EGFR

The epidermal growth factor receptor, EGFR, is a transmembrane glycoprotein that is activated by the binding of EGF, TGF-α and a few other ligands to the extracellular part of the receptor. Following activation, intracellular kinases are phosphorylated resulting in down-stream signalling controlling proliferation, differentiation, apoptosis and migration (chapter 3).

Elevated levels of the receptor (and often also of the ligands) have been observed in numerous cancer types, especially in various forms of squamous cell carcinomas, e.g. head & neck and non-small cell lung cancers, but a reasonably high expression has also been reported for adenocarcinomas such as breast, ovarian and colorectal cancers [35]. There are several recent reviews written on the expression of EGFR in various tumours and that is summarized in chapter 3 of this volume. EGFR expression has been studied as a potential target for intracavitary anti-EGFR radionuclide therapy of gliomas [36]. Genomic rearrangements can cause expression of modified receptors, which also can be considered for radioimmunotherapeutic trials [37].

A33

The A33 antigen has been extensively investigated. It is a transmembrane antigen which has lower molecular weight than e.g. EGFR and HER2, since the molecular weight for A33 is only 43 kDa. It belongs to the Ig superfamily and is expressed in normal gastrointestinal epithelia as well as in carcinomas of colon and rectum, where it is homogenously expressed in 95% of the tumours [38, 39]. Recently the antigen has been used for several radioimmunotherapeutic trials with excellent targeting, but only a few patients demonstrated stable disease while the others presented progressive disease [40–42].

MUC-1

MUC-1 belongs to the mucin family of proteins and is overexpressed in more than 90% of breast and other glandular epithelial cancers in a hypoglycosylated form. The core peptides of the extracellular domain are exposed, which is the structure employed for targeting [43]. Highly conserved repeats of 20 amino acids, VNTR, vary between 20 and 125 in the protein, depending on the allele. Each tandem repeat contains five potential glycosylation sites, which constitute the structure exploited for therapy. These core peptides in the repeats are masked in normal cells, but become exposed in tumour cells [43].

The major part of antibodies raised against this antigen reacts with carbohydrate epitopes within these repeats, as investigated in an ISOBM workshop with 56 monoclonal antibodies to this antigen [44]. In one report Nicholson et al. [45] were able to demonstrate that MUC-1 targeted radioimmunotherapy can be working. It was shown that out of 21 patients, with ovarian cancer with no remaining macroscopic disease after cytoreductive surgery, 16 were still alive ten years after radioimmunotherapy, which was significantly better than the median survival of less than four years in a control group.

VEGF

The vascular endothelial growth factor (VEGF) occupies a unique position in this context, since it is not expressed on the tumour cells, but was initially identified as a tumour-derived and excreted factor capable of increasing vascular permeability [46, 47]. In the embryo, VEGF and its isoforms are critical for normal vessel development and these peptide hormones can exert apoptotic, mitogenic and permeability-increasing activities specific for the vascular endothelium. A number of different isoforms of VEGF exist due to different splicing of a single gene with eight exons [48]. A family of peptides closely related to VEGF (VEGF-B – VEGF-E) are also known to stimulate angiogenesis.

VEGF and related factors have been demonstrated to increase in serum levels in various cancers and have been suggested to be used to monitor disease progress and response to treatment [49]. High levels have also been correlated to advanced stages or with a worse prognosis in tumours of the bladder, brain, breast, colon, lung, ovary, renal cell carcinoma, squamous cell carcinoma of the neck and neuroblastoma [50–58]. Recently in a preclinical investigation an ^{131}I-labeled antibody against VEGF was reported to cause growth retardation [59].

CD20

CD20 occupies a unique role in radioimmunotargeting by being widely used for the treatment of different lymphomas. It was initially discovered already 1981 by Nadler et al. [60]. It is a 33–36-kDa transmembrane phosphoprotein involved in the activation, proliferation and differentiation of B-lymphocytes [61]. The predicted amino acid sequence of the CD20 suggests four transmembrane-spanning regions with both the N- and C-terminals located intracellularly in the cytoplasm, which may contribute to the restricted mobility.

Activation of CD20 by binding of antibodies directed towards the extracellular domain of CD20 leads to tyrosine kinase pathway activation and modulation of cell cycle progression via interaction with src-related kinases. Binding of unlabeled humanized antibodies to this antigen can cause cell death via complement-dependant cellular cytotoxicity or antibody-dependant cellular cytotoxicity. Several investigators have documented variations in the surface intensity of the antigen of malignant B-cells in lymphoproliferative diseases, an observation which might affect the efficiency in therapeutic outcome [62].

The introduction of radioimmunotherapy and also the naked antibodies for haematological diseases has revolutionized the field of cancer treatment in the last decade. For recent reviews – see [63, 64] and chapter 20. Many positive reports on the efficiency of such treatments have been presented [65–67].

The Cytokeratins

The cytokeratins occupy a unique position within the group of antigens that can be targeted. These intermediate filaments are abundantly expressed intracellularily in all epithelial tissues in certain combinations. When released into the circulation they can be used as powerful tumour markers for several malignant diseases. Their unique repetitive structures, with comparatively low solubility, enable the cytokeratins to remain in place, within the tumour following cytotoxic therapy, and can by such mechanisms increase their level of antigen significantly by external radiotherapy or other cytotoxic drugs. (See also chapter 4) [68–70].

Conclusions

The targets for radioimmunotherapy and their impact on treatment results differ significantly, and the favourable properties of the well exposed CD20 partially contributes to the positive outcome when treating lymphomas, compared to solid tumours.

One of the reasons why the efficiency has so far been low at treating solid tumours might be that there is often too low amounts of specific target antigens. Exceptions might be targeting of EGFR and HER2 where we expect promising results when large scale clinical trials with strongly receptor expressing tumours start.

However, searching new antigens is still a needed activity. Release of antigens already within the tumour might be another possibility to increase targeting efficiency. External beam radiation, causing partial necrosis within the tumour, may cause significant exposure of intermediate filaments, which due to low solubility might remain within the tumour site and could be used as targets.

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References

1. Voorzanger-Rousselot N, Garnero P: Biochemical markers in oncology. Part I: Molecular basis. Part II: Clinical uses. Cancer Treat Rev 2007; 33:230–283.
2. Gold P, Freedman SO: Specific carcinoembryonic antigens of the human digestive system. J Exp Med 1965; 122:467–481.
3. Mach JP, Carrel S, Merenda C, Sordat B, Cerottini JC: In vivo localisation of radiolabelled antibodies to carcinoembryonic antigen in human colon carcinoma grafted into nude mice. Nature 1974; 248:704–706.
4. Goldenberg DM, DeLand F, Kim E, Bennett S, Primus FJ, van Nagell JR, Jr., Estes N, DeSimone P, Rayburn P: Use of radiolabeled antibodies to carcinoembryonic antigen for the detection and localization of diverse cancers by external photoscanning. N Engl J Med 1978; 298:1384–1386.
5. Hammarstrom S: The carcinoembryonic antigen (cea) family: Structures, suggested functions and expression in normal and malignant tissues. Semin Cancer Biol 1999; 9:67–81.
6. Sharkey RM, Cardillo TM, Rossi EA, Chang CH, Karacay H, McBride WJ, Hansen HJ, Horak ID, Goldenberg DM: Signal amplification in molecular imaging by pretargeting a multivalent, bispecific antibody. Nat Med 2005; 11:1250–1255.
7. Jia F, Shelton TD, Lewis MR: Preparation, characterization, and biological evaluation of a streptavidin-chimeric t84.66 conjugate for antibody pretargeting. Cancer Biother Radiopharm 2007; 22:654–664.
8. Wong JY, Chu DZ, Williams LE, Liu A, Zhan J, Yamauchi DM, Wilczynski S, Wu AM, Yazaki PJ, Shively JE, Leong L, Raubitschek AA: A phase I trial of (90)y-dota-anti-cea chimeric t84.66 (ct84.66) radioimmunotherapy in patients with metastatic cea-producing malignancies. Cancer Biother Radiopharm 2006; 21:88–100.

9. Goldenberg DM, Rossi EA, Sharkey RM, McBride WJ, Chang CH: Multifunctional antibodies by the dock-and-lock method for improved cancer imaging and therapy by pretargeting. J Nucl Med 2008; 49:158–163.
10. Sharkey RM, Karacay H, Vallabhajosula S, McBride WJ, Rossi EA, Chang CH, Goldsmith SJ, Goldenberg DM: Metastatic human colonic carcinoma: Molecular imaging with pretargeted spect and pet in a mouse model. Radiology 2008; 246:497–507.
11. Kraeber-Bodere F, Rousseau C, Bodet-Milin C, Ferrer L, Faivre-Chauvet A, Campion L, Vuillez JP, Devillers A, Chang CH, Goldenberg DM, Chatal JF, Barbet J: Targeting, toxicity, and efficacy of 2-step, pretargeted radioimmunotherapy using a chimeric bispecific antibody and 131i-labeled bivalent hapten in a phase I optimization clinical trial. J Nucl Med 2006; 47:247–255.
12. Lankester KJ, Maxwell RJ, Pedley RB, Dearling JL, Qureshi UA, El-Emir E, Hill SA, Tozer GM: Combretastatin a-4-phosphate effectively increases tumor retention of the therapeutic antibody, 131i-a5b7, even at doses that are sub-optimal for vascular shut-down. Int J Oncol 2007; 30:453–460.
13. Chatal JF, Campion L, Kraeber-Bodere F, Bardet S, Vuillez JP, Charbonnel B, Rohmer V, Chang CH, Sharkey RM, Goldenberg DM, Barbet J: Survival improvement in patients with medullary thyroid carcinoma who undergo pretargeted anti-carcinoembryonic-antigen radioimmunotherapy: A collaborative study with the french endocrine tumor group. J Clin Oncol 2006; 24:1705–1711.
14. Karacay H, Brard PY, Sharkey RM, Chang CH, Rossi EA, McBride WJ, Ragland DR, Horak ID, Goldenberg DM: Therapeutic advantage of pretargeted radioimmunotherapy using a recombinant bispecific antibody in a human colon cancer xenograft. Clin Cancer Res 2005; 11:7879–7885.
15. Li GP, Zhang H, Zhu CM, Zhang J, Jiang XF: Avidin-biotin system pretargeting radioimmunoimaging and radioimmunotherapy and its application in mouse model of human colon carcinoma. World J Gastroenterol 2005; 11:6288–6294.
16. Johnson VG, Schlom J, Paterson AJ, Bennett J, Magnani JL, Colcher D: Analysis of a human tumor-associated glycoprotein (tag-72) identified by monoclonal antibody b72.3. Cancer Res 1986; 46:850–857.
17. Thor A, Ohuchi N, Szpak CA, Johnston WW, Schlom J: Distribution of oncofetal antigen tumor-associated glycoprotein-72 defined by monoclonal antibody b72.3. Cancer Res 1986; 46:3118–3124.
18. Batra SK, Jain M, Wittel UA, Chauhan SC, Colcher D: Pharmacokinetics and biodistribution of genetically engineered antibodies. Curr Opin Biotechnol 2002; 13:603–608.
19. Meredith RF, Bueschen AJ, Khazaeli MB, Plott WE, Grizzle WE, Wheeler RH, Schlom J, Russell CD, Liu T, LoBuglio AF: Treatment of metastatic prostate carcinoma with radiolabeled antibody cc49. J Nucl Med 1994; 35:1017–1022.
20. Divgi CR, Scott AM, Dantis L, Capitelli P, Siler K, Hilton S, Finn RD, Kemeny N, Kelsen D, Kostakoglu L, et al.: Phase I radioimmunotherapy trial with iodine-131-cc49 in metastatic colon carcinoma. J Nucl Med 1995; 36:586–592.
21. Meredith RF, Khazaeli MB, Liu T, Plott G, Wheeler RH, Russell C, Colcher D, Schlom J, Shochat D, LoBuglio AF: Dose fractionation of radiolabeled antibodies in patients with metastatic colon cancer. J Nucl Med 1992; 33:1648–1653.
22. Meredith RF, Khazaeli MB, Plott WE, Grizzle WE, Liu T, Schlom J, Russell CD, Wheeler RH, LoBuglio AF: Phase II study of dual 131i-labeled monoclonal antibody therapy with interferon in patients with metastatic colorectal cancer. Clin Cancer Res 1996; 2:1811–1818.
23. Murray JL, Macey DJ, Kasi LP, Rieger P, Cunningham J, Bhadkamkar V, Zhang HZ, Schlom J, Rosenblum MG, Podoloff DA: Phase II radioimmunotherapy trial with 131i-cc49 in colorectal cancer. Cancer 1994; 73:1057–1066.
24. Ponnusamy MP, Venkatraman G, Singh AP, Chauhan SC, Johansson SL, Jain M, Smith L, Davis JS, Remmenga SW, Batra SK: Expression of tag-72 in ovarian cancer and its correlation with tumor stage and patient prognosis. Cancer Lett 2007; 251:247–257.