

Workshop Alpha-Emitters for Medical Therapy

**Denver, Colorado
May 30-31, 1996**

**Compiled and edited
by**

Ludwig E. Feinendegen and John J. McClure



Department of Energy

This report has been reproduced directly from the best available copy.

Available to DOE and DOE Contractors from the Office of Scientific and Technical Information, P.O. Box 62, Oak Ridge, TN 37831; prices available from (423) 576-8401.

Available to the public from the U.S. Department of Commerce, Technology Administration, National Technical Information Service, Springfield, VA 22161, (703) 487-4650.



Printed with soy ink on recycled paper

Workshop Alpha-Emitters for Medical Therapy

**Denver, Colorado
May 30-31, 1996**

Compiled and edited
by
Ludwig E. Feinendegen and John J. McClure

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED



kg
MASTER

**Department of Energy
Germantown, MD 20874-1290**

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

DISCLAIMER

**Portions of this document may be illegible
in electronic image products. Images are
produced from the best available original
document.**

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

Workshop

Alpha Emitters for Medical Therapy

Denver, Colorado

May 30-31

Introduction

The diagnosis and treatment of cancerous tumors in the human body increasingly use monoclonal antibodies and their molecular subunits in various forms as carriers for radionuclides. Other molecular carriers serve as specific ligands to receptors on or in tumor cells, or they are precursors in tumor cell metabolism.

When the radionuclides emit energetic photons, the labeled substrates are diagnostic tools for imaging the site and function of tumors in the patient's body. Radionuclides that emit short range charged particles are potent sources for irradiating tumors locally with minimal or no exposure of healthy tissue. Alpha particles deposit their energy over a short range within microscopic dimensions and are especially effective in damaging tumor cells locally.

In view of the expected demand for suitable alpha-particle emitting radionuclides for clinical therapy of malignant tumors and nonmalignant disabling diseases, a workshop on "Alpha-Emitters for Medical Therapy" was held by the Department of Energy (DOE) in Denver, Colorado, on May 30 and 31, 1996. The workshop was organized jointly by the Isotope Production and Distribution (IP&D) Program of the Office of Nuclear Energy, Science and Technology (NE) and by the Office of Health and Environmental Research (OHER) of the Office of Energy Research (ER).

The workshop was attended by 36 participants who are leading and internationally recognized experts in the following disciplines: Radiooncology, Nuclear Medicine, Immunotherapy, Radiobiology, Molecular Biology, Biochemistry, Radiopharmaceutical Chemistry, Dosimetry and Physics. The DOE was represented by 5 attendees.

The aim was to identify research goals and potential clinical needs for applying alpha-particle emitters, and to provide the DOE with sufficient information for future planning.

The agenda had 6 topics:

1. Clinical Potential and Need of Alpha-Emitters in Therapy
2. Alpha-Particle Dosimetry in Biologic Tissue
3. Production of Alpha-Particle Emitters and Generator Development
4. The Carrier Problem
5. Linking Alpha-Emitters to Carriers
6. Preclinical and Clinical Testing

Following short presentations of issues within the various topic areas, broad discussions informed all participants on the many aspects of this interdisciplinary task. The continuous open assessment in the plenary sessions of all topics generated useful recommendations. Short breakout sessions on the second day led to summaries of the discussions in each topic area. These were placed again before the general assembly by the session chairmen for final discussion prior to the conclusion of the workshop.

The presentations and discussion in each topic area were guided by designated individuals whose willingness to take on their assignment and whose contributions are gratefully acknowledged. The brief summaries given below for each topic area rely heavily on those prepared by the discussion leaders.

A major consensus was the need for focussing research and development on two promising alpha-emitters: astatine-211 (^{211}At) and bismuth-213 (^{213}Bi). The former has been successfully employed in a variety of research involving chemistry, radiopharmacology, biokinetics and efficacy in experimental tumor therapy; the latter is being currently supplied from abroad and has been linked to a specific monoclonal antibody against tumor cells being prepared for the first clinical trial, phase I, at the Memorial Sloan Kettering Cancer Center in New York, NY¹.

Workshop Summary Minutes

1. Clinical Potential and Need of Alpha-Emitters in Therapy

This session was opened by a *statement of goals* to be met for successful clinical therapy with α -emitters. The procedures should be relatively simple and straight forward. Biodistribution must be measured to calculate dosimetry for evaluating both toxicity and efficacy. At the same time one must ensure the safety of health workers and a high benefit/risk ratio. Alpha-emitters and carrier substrates should be commercially available at a cost that allows for competition with other therapies.

¹ This phase I trial has begun since the conclusion of the workshop.

Various β - and α -emitters have been approved for therapy; others are being developed. They were reviewed with emphasis on the sparsity of carrier substrates thus far available in the clinical setting.

The *spectrum of malignant diseases* that may be treated with α -emitters includes most common cancers and infectious diseases such as meningitis and even AIDS, when single cells or smaller clusters of cells are the potential target. Several clinical applications are envisaged in specific clinical situations, such as leukemia, in the relapsed patient, especially after a second remission. Local intracavitary administration holds promise, for example, treating metastases in the abdominal cavity following surgical resection of ovarian cancer. *Non-malignant applications* may include treatment of immune disorders and of rheumatoid and degenerating joint diseases. If clinical trials begin in the near future, results should be available in a year or two at most. It was recommended that clinical trials be started soon to take advantage of targeting experience in promising areas and in highly selected circumstances with agents that are available now.

The *labeled carrier substrate* must be chosen not only to treat the patient effectively but also with due consideration for the safety of health care workers preparing the agent. Also, the public must be properly protected from unwanted exposure to radiation.

Many opportunities exist for developing a wide range of suitable carriers, not only antibodies, but other agents such as peptides or small molecular metabolites. Thus, ample opportunities will allow selection of a carrier for given clinical applications. Antibodies can deliver agents intracellularly if they bind to internalizing cell-bound recognition sites as antigens. This will increase the probability that an α -emitter will kill the targeted cell. Internalization of an α -emitter may assure irradiation of the tumor cell as long as the radionuclide resides in the cell.

Preliminary dosimetry suggests that approximately 2 bismuth atoms are necessary on the target leukemia cell to achieve 50% cell kill. A therapeutic index of about 10 is seen in vitro. Human trials with other radionuclides show that saturation of target cells with up to 10,000 binding sites per cell can be achieved in one hour. Additional constructs under development include engineered antibodies capable of targeting breast cancer, prostate cancer, colon cancer, lymphoma, and cells infected with the human immunodeficiency virus (HIV).

Substrates labeled with an α -emitter may be administered in various ways. *Systemic targeting* by intravenous injection or by intracavitary or interstitial application will vary with the type of benign or malignant disorder and will depend on the nature of the carrier substrate.

Access of the α -emitter to the tumor is limited by diffusion kinetics and the best access is likely to be via blood vessels. Sufficient diffusion from the surface of peritoneal or pleural deposits seems unlikely. Success will, of course, also be limited by cell survival probabilities. If incomplete distribution of the α -emitter limits cell killing to 90% or 99%, the gains will not be great, equivalent on average to that from approximately 7 Gy and 14 Gy external beam therapy, respectively.

Application of short lived α -emitters to the *therapy of solid tumors* is a long-term challenge. Targeting the vascular space including the endothelial cells of these tumors may be efficient and rapid; efficacy of α -emitter therapy needs confirmation in different tumor systems. Since the α -emitter in this scenario does not attach directly to target tumor cells, the practical question of individual cell killing as a function of position of the α -emitter in real tumor situations needs to be addressed. Model systems with tumor cells adjacent to blood vessels can be used to give preliminary answers to these questions. One model uses animals with artificial pulmonary metastases that respond to α -emitters attached to a monoclonal antibody (MOAB) fragment binding to lung capillary endothelial cells. A large fraction of the injected amount of substrate is thus directed to the cells of the capillaries supplying the tumor. For optimizing this approach, the targeting agent must be highly specific for tumor blood vessels. One possibility is selecting random peptides displayed on bacteria phage libraries. While the details of structure of the target molecules may not be known, the selection system is designed to identify a peptide with suitable binding properties. Small peptides of restricted targeting specificity may prove to be the most efficient carriers for short-lived isotopes.

Alpha-emitters are particularly promising in the *treatment of micrometastases* in neoplastic diseases. Of the approximately one million new cases of cancer (excluding nonmelanoma skin cancer) that occur yearly in the United States, about 33% already have metastases, and about 67% initially appear with local disease. About 40% of these will subsequently develop distant metastases. It is especially this subset of patients with micrometastases who might benefit from adjuvant α -emitter therapy. The most common metastatic sites are lung, bone, brain, liver, and bone marrow. Hence, irrespective of the type of α -emitter chosen, various carrier substrates will probably be required.

Another example is the treatment of *ovarian carcinoma* that produces micrometastases throughout the peritoneal cavity. Radionuclides in the elemental or inorganic form such as ^{198}Au or $^{51}\text{CrPO}_4$ when administered intraperitoneally easily aggregate into microparticles that clearly do not specifically attack cancer cells in the peritoneal fluid and on surfaces. However, ^{212}Bi with its one hour half-life when injected into the peritoneal fluid in the form of $^{212}\text{BiOCl}$ remains evenly distributed for several hours; it uniformly exposes the cancer cells to α -particles emitted in the peritoneal fluid. In rabbits, lethal cell irradiation ensued with little or no serious toxic effects; less than 30% of the agent was lost from the peritoneal cavity mainly into the blood circulation. In mice, comparable amounts of $^{212}\text{BiOCl}$ left the peritoneum more rapidly and localized in the kidneys; this limits the potential for intraperitoneal cell killing in mice. Since the kinetics of $^{212}\text{BiOCl}$ in human peritoneal fluid are not known, they would be worth studying in preparation for clinical therapy trials.

A problem foreseen with α -emitters in clinical cancer therapy is likely the significant incidence of local recurrence. This is even seen with doses on the order of 70 Gy given as external beam therapy. It is unlikely that sufficient α -emitters could be targeted to a primary tumor within acceptable doses to normal tissue. Therefore the role of α -emitters in treatment of primary neoplasms would be as adjuvants or "*boost*" treatment following conventional radiation therapy,

chemotherapy, or surgery. Since local recurrence is an important cause of treatment failure, and no patient is cured without control of the primary tumor, the use of α -emitters in adjuvant treatment of primary disease appears highly attractive. But such applications will be extremely difficult to justify without prior experience in phase I trials in patients with established disease. This also holds for treating metastatic disease, since the number of tumor cells to be killed may often be lower than in primary disease.

Responses to treatment can be measured by regression in the case of primary tumors or clinically detectable metastases. In the case of micrometastases, efficacy may be determined by the decrease in the incidence of distant metastases; or by use of serum markers. A prolonged observation time demands ultimately randomized clinical trials.

With regards to α -emitters, optimal clinical application depends on a full understanding of both the advantage from their *physical characteristics* and the benefits and limitations conferred by their biologic effects. These must be compared with the benefits and limitations of β -emitters and of more conventional modes of therapy.

The ideal α -emitter should not emit high energy gamma-rays in its decay chain. The energy of the emitted α -particle should be such that its range in tissue covers several cell diameters. The half-life should be sufficiently long to allow for production, handling, distribution and radiopharmaceutical labeling, but sufficiently short to allow for patient treatment in a reasonable time with minimal risk from toxicity, including that from its daughter nuclides.

The *chemistry of the emitter* should be such that it can be stably incorporated into a variety of carriers under physiologic conditions. Finally, to be successful, an appropriately chosen α -emitter must be easily available and deliverable to the clinician on time. This demands the development of technologies that can be widely dispersed to all levels of the health care system. The application must be cost effective in terms of documented benefit in a clinical trial setting. The preparation of ^{212}Bi in a soluble form that is applicable in experimental therapy of ovarian cancer faces the problems of separation of radioactive daughter nuclides, of shielding, and of local transportation and distribution.

Over the next few years, three α -emitters may become readily available: ^{211}At , with a 7 hour half-life; ^{213}Bi , with a 45 minute half-life, and ^{212}Bi , with a 60 minute half-life. For targeting tumors with appropriately labeled carrier substrates giving optimum target to background ratios in patients, these half-lives are very short. Thus, major investments are needed for improving the syntheses of appropriately chosen carrier substrates. Various strategies, better than using whole immunoglobulins, embrace small molecular peptides and two-step avid-biotin type targeting approaches. Benefits should be seen within a few years in the treatment of common human tumors, perhaps even large ones. Selecting the right clinical setting for using α -emitters is important for cancer treatment.

Clinical trials with α -emitters will soon begin at Duke University Medical Center, Durham, NC. These trials involve ^{211}At - labeled chimeric 81C6 antibody that is administered intrathecally in patients with cystic gliomas. This application was chosen because of the compatibility of tumor geometry with α -particle range and of compartmental delivery which maximizes tumor exposure while minimizing normal tissue toxicity.

Presently, these tumors are treated with ^{131}I -labeled 81C6 (about 120 patients to date). The results of these studies serve as a valuable basis for seeking approval from the Food and Drug Administration (FDA) to use ^{211}At -labeled MOAB and, eventually, for evaluating the efficacy of its application. These studies will also foster the prediction of dosimetry on a macro-scale for ^{211}At . Also, toxicity of $[^{211}\text{At}]$ astatide, constituting the worst possible case scenario, and of the ^{211}At -labeled MOAB will be observed for one year in preparing for the approval from the FDA to use the new drug, by the registered Investigational New Drug (IND) holder.

The Memorial Sloan-Kettering Cancer Center group in New York focuses on the development of ^{213}Bi -CHX-A labeled antibodies². Proof of principle is expected from treatment trials involving patients with relapses of acute myelogenous leukemia (AML). For this, a genetically engineered humanized Anti-CD33 antibody (HuM195) has been chosen. Preclinical studies with ^{213}Bi have been completed using a 20 mCi actinium-bismuth generator from Karlsruhe, Germany produced from ^{229}Th recovered at a DOE facility.

In the long run, adjuvant clinical trials still to be developed may benefit patients with prostate cancer, colon cancer and breast cancer. These opportunities have a strong rationale, but the studies are likely to require large sample sizes and very long follow-ups which might not be available for 10-15 years. These clinical trials, on such a large scale, are probably going to be possible only after considerable further technical development to ensure appropriate guarantees of safety, cost-effectiveness, availability of labeled substrates and their distribution. These projects may be cooperatively supported with NCI/NIH type funding, taking advantage of NCI's experience in design and review of studies of this type.

For the purpose of *localizing the labeled carrier in patients*, surrogate γ -emitting nuclides should be found for those α -emitters that lack suitable γ -emissions for imaging. This also would produce the biodistribution data required for calculation of dosimetry. However, failure to find a suitable surrogate for tracing biodistribution should not negate the possibility of using an agent clinically. Preclinical studies generally allow one to quantify the uptake of agents, and clinical dose escalation studies will define acute toxicities associated with the agent. Chronic toxicity is usually predicted from preclinical studies.

² Clinical phase I studies have been initiated since the conclusion of the workshop.

The participants felt that the outcome of clinical trials that are now being prepared will decisively influence future applications. It was the opinion that the present symposium quite rightly explores the possible opportunities for major clinical benefit to U.S. citizens with serious diseases such as cancer. A more rapid development of α -emitters should be a national effort by the DOE. This demands *short-term actions for immediate development*, and longer term commitments over the next few years. DOE could provide absolutely essential support for the necessary basic research. This should include radionuclide availability for these projects, and the studies in radiobiology, radiochemistry, dosimetry and toxicity required for designing clinical trial protocols. Longer term research may well engage other appropriately experienced agencies, such as the National Cancer Institute (NCI) and National Institute of Health (NIH).

2. *Alpha-Particle Dosimetry in Biologic Tissue*

Based upon available *dosimetry* and upon radiobiologic and experimental evidence, α -particle emitters are believed to hold great promise for use in internal emitter therapy. The high linear energy transfer (LET) and short range of α -particles allow for very high potency and specificity. High potency is achieved because one to three tracks through the cell nucleus are sufficient to sterilize or kill the hit cell. Specificity arises due to the relatively short, 40 - 90 μm range of α -particles in tissue.

In general, that the range of the radiation approximates the dimensions of the *cell or group of cells being targeted* is an advantage. Since the range of α -particles is equivalent to a few cell diameters, α -emitters are ideal for small aggregates of cells or for thin layers of cells. Due to their high LET, α - particles are also ideal for sterilizing or killing individual cells. This applies to situations in which beta particles would be far less effective because of their lower LET and longer range.

With these physical characteristics in mind, initial *applications* should aim at targeting micrometastases and single tumor cells by intravenous administration. The targeting of compartmentalized disease by intracavitory administrations and, possibly, of solid tumors by intratumoral injections is also promising. Radiosynovectomy and specific immune-cell ablation are amenable to α -emitters. Most promising are situations in which targeting is rapid and single cell kill is needed for success.

Animal studies have been important in assessing *biodistribution* and in performing toxicologic studies. Detailed dosimetric evaluation of clinical applicability, efficacy and toxicity, however, will require human data. As much data as possible should be collected in the initial set of trials to assess the biologic basis for efficacy and normal tissue toxicity. The scope of detailed and specific data will depend upon the nuclide and its half-life as well as the carrier. Such measurements should include imaging and sampling of tissue and blood.

Imaging of radionuclide distribution is strongly recommended for the overall assessment of *biodistribution and dosimetry*. Imaging-based dosimetry can provide a macroscopic measure of absorbed dose to the tumor and to normal tissues. Depending upon the half-life of the radionuclide, imaging may allow a direct estimate of accumulated activity and residence time. Thus, repetitive imaging is needed over a duration that is long relative to the physical decay and/or biologic clearance rate of the labeled agent. This is the case with ^{213}Bi , for example, which has a half-life of 45.6 minutes. Further work to develop quantitative or semiquantitative imaging of α -particle emitters is recommended.

To determine the biologic relevance of macroscopic estimates of absorbed dose, the distribution of the labeled agent at the level of individual cells should be known. This is best obtained, for example, by directly sampling the pertinent tissue, which may be located by imaging. The distribution of the α -emitter at the cellular level within such samples may then be obtained by autoradiography.

In some cases tissue sampling and processing may not be feasible due to either the short half-life of the α -emitter or the inaccessibility of a particular tissue. In such cases, information on the expected distribution of the agent in the tissue may be helpful. This may be obtained from combining *modeling with blood clearance measurements*, with animal biodistribution data, and/or with measurements on isolated tissue samples.

The combination of data from various sources also promises usefulness for estimating the kinetics associated with cell-level distributions measured at a given time. Rapid techniques for assessing α -emitter distribution and for microdosimetric analyses should be further developed as α -emitters increasingly become clinical tools.

The *cell-level distribution* obtained from tissue sampling and the estimate of mean absorbed dose obtained from imaging may be used to evaluate the biologic relevance of the macroscopic mean dose. Such information should be converted with the help of tables into microdosimetric descriptors such as frequency and dose-weighted mean specific energy, its variance, and the fraction of cells receiving zero alpha-particle hits. These quantities should be obtained for several different α -particle energies and pertinent source-target geometries. Some appropriate geometries include: (a) cells exposed to a uniform distribution of α -particle emissions; (b) clusters of cells with α -emitters localized on the surface, within the cytoplasm, or cell nucleus; (c) a planar distribution of α -emitters with a target cell located at various distances from the plane; (d) an interface with uniform α -emitter distribution on one side and zero or different distribution on the other, with a target cell located at various distances from the interface; (e) geometries appropriate to bone marrow. Some of these parameters have already been calculated and simply need to be compiled in a standard format.

The combination of tissue sample analyses and *whole-body imaging* with tables that provide useful microdosimetric information will help reveal the biologic behavior of substrates that carry an α -emitter. These approaches also address the issues of heterogeneity and macro- vs. microdosimetry in a manner that affects clinical work.

Dosimetric data for red bone marrow may also be obtained by this approach. If the labeled substrate or radionuclide does not associate with cells of the peripheral blood and bone marrow, kinetics in bone marrow may be estimated from blood kinetics. When blood-forming tissue or micrometastases are being targeted, considerations that are not necessarily unique to α -emitters arise. For example, estimates of the fraction of tumor cells that are within the marrow and within cell clusters, as opposed to in suspension, are needed to properly estimate absorbed dose to red bone marrow. Once this information is available, for example from bone marrow sampling, peripheral blood counting and/or modeling, the approach described above may be applied.

Multiple modality treatment may include *simultaneous administration of β - and α -emitter-labeled substrates*. Alpha-emitters usually do not replace β -emitters or Auger-emitters in clinical therapy. The range of this approach should be investigated and defined. It may be important to re-evaluate β -emitters with concomitant use of α -emitters for possible targeting of single and small clusters of cells. Further studies are recommended of the therapeutic efficacy and potential toxicity of α - and β -emitter therapy both in vitro and in animal models.

In determining the initial schedule of administered activities for phase I clinical trials, values of *radiation quality or weighting factor*, as recommended for radiation protection, are inappropriate. Since acute radiation effects, rather than carcinogenesis, limit radiation dose in patients participating in phase I clinical trials, a relative biological effectiveness (RBE) should be used for such evaluations. The RBE should be based on a number of cell survival studies. For ^{213}Bi and ^{211}At , an RBE value of 5 is recommended, initially. This recommendation takes into account that the RBE often varies with target tissues. As clinical trials progress, a "clinical" RBE value for dose-limiting toxicity will be established that may be greater than or less than the starting value of 5.

3. Production of Alpha-Particle Emitters and Generator Development

Research and application of α -emitters in medicine cannot advance without a reliable, *reasonably priced supply* of suitable radionuclides. These must be provided in forms that can be conveniently used in hospitals for administration to patients. A list of candidate α -emitting radionuclides for medical application is provided in Table 1. Each final use α -emitter is linked to a generator system. Source radionuclides must be first produced and purified. Then a suitable generator for α -emitting radionuclide delivery must be produced.

Table 1: Candidate alpha emitters for medical applications

Source radioisotope (half-life)	Generator radioisotope (half-life)	Administered radioisotope (half-life)
^{228}Th (1.91 y)	^{224}Ra (3.66 d)	^{212}Bi (60 m)
^{229}Th (7340 y)	^{225}Ra (14.8 d)	^{225}Ac (10.0 d)
^{229}Th (7340 y)	^{225}Ra (14.8 d)	^{213}Bi (45.6 m)
^{227}Ac (22 y)	^{227}Th (18.7 d)	^{223}Ra (11.4 d)
-	^{255}Es (40 d)	^{256}Fm (20.1 h)
$^{209}\text{Bi}(\text{stable})[\alpha, 2n]$	Accelerator produced	^{211}At (7.21 h)
$^{232}\text{Th}[\text{p, spall}]$	^{211}Rn	^{211}At (7.21 h)
-	Accelerator produced	^{149}Tb (4.13 h)

Source α -emitters for research are currently in short supply, but proven techniques are available for production. For example, ^{229}Th may be currently obtained from two sources: (a) recovery of the radionuclide from the government stockpile of ^{233}U , and (b) irradiation of ^{226}Ra . Significant quantities of ^{229}Th exist in the ^{233}U stockpile in the DOE system and in Russia to support research and patient trials. The Oak Ridge National Laboratory (ORNL) has approximately 40 g of ^{229}Th in stored ^{233}U . Additional quantities of ^{233}U containing ^{229}Th are available at other DOE sites and in Russia³.

More ^{229}Th could be produced by irradiation of ^{226}Ra in a *nuclear reactor*. This yields a mixture of ^{227}Ac , ^{228}Th , and ^{229}Th . The quantities of each of these radionuclides depend on the irradiation time and also change with the reactor flux characteristics. ^{227}Ac , ^{228}Th , and ^{229}Th could be supplied by a proven method. In 1982, at ORNL ^{226}Ra was irradiated in the High Flux Isotope Reactor (HFIR) and ^{227}Ac was recovered from the target. Based on experience and calculated yields, the present capacity for processing ^{226}Ra targets is about 100 g per year; this assumes a supply of natural radium, as well as some investment in radon containment ventilation plus adequate manpower. Then, 8.4 g of ^{229}Th , about 1.8 Ci, along with 7500 Ci of ^{228}Th could be produced annually, not counting processing losses. Higher production rates would require some major new facilities. At the level of processing 100 g of ^{226}Ra per year, less than 20% of the HFIR's irradiation capacity would be utilized. Other DOE facilities could be selected for making ^{228}Th , ^{229}Th , and ^{227}Ac through the irradiation of ^{226}Ra , depending on their production capacity.

^{256}Fm can be obtained from reactor produced ^{255}Es which has a half-life of 40 days. About 25 Ci/y ^{253}Es with a half-life of 20 days are being produced in the transplutonium element production at ORNL. A small quantity of ^{255}Es is present as a contaminant in this material.

^{255}Fm having a half-life of 20-hours has been processed in the past. A monoclonal antibody has been labeled with ^{255}Fm for experimental use, but the quantities of ^{255}Fm available and the delivery schedules do not favor this α -emitter in medical practice.

^{211}At is a very promising α -emitter for therapeutic application. It is produced via the $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$ reaction, e.g., by bombarding natural bismuth targets with 28 MeV α -particles in an *accelerator*. Recently, an internal target system has increased production yields considerably. It is estimated that one accelerator run a week would be sufficient to supply 10 research laboratories with enough ^{211}At to pursue preclinical testing. The amount of ^{211}At needed for clinical investigations is difficult to predict because the individual demand per patient is not yet known. If one assumes that activities between 5 and 20 mCi will be used to treat 300 patients per week, then about 20 to 80 accelerator runs per week would be required. If ^{211}At -labeled substrates are demonstrated to be effective in patients, demands are likely to be met.

³ ^{229}Th has been recovered and purified at ORNL with DOE funding and is being used to produce generators for preclinical studies with ^{213}Bi since the conclusion of the workshop.

^{149}Tb , can be produced in small quantities of about 10 μCi using the ^{141}Pr (^{12}C , 4n) ^{149}Tb reaction at 70 MeV on a 10 MeV tandem accelerator. Another possibly higher yield reaction is ^{142}Nd (^{12}C , 5n) $^{149}\text{Dy} \rightarrow ^{149}\text{Tb}$ at 90 MeV. Quantities of about 30 mCi have been produced in the ISOLDE facility at the CERN spallation source. Four μA of 600 MeV protons from the synchrocyclotron bombarded a tantalum foil, 122 g cm^{-2} . Reaction products were ionized and accelerated from the source by means of a 60 kV potential. The 149 mass component was separated in a magnetic field and deposited for 75 min on an aluminum foil. ^{149}Dy decays by alpha emission (17%), positron emission (4%) and electron capture (79%). Subsequent decays are also by electron capture.

In summary, methods have been demonstrated for producing α -emitters that are source candidates in sufficient quantities for medical application with the exception of ^{255}Fm .

In order to provide the quantities of α -emitters required for research and therapy, it will be necessary for DOE and/or the Nation to invest a substantial amount of funds, the source of which has not yet been identified.

The second step in the successful application of α -emitters is the construction of reliable, *convenient generator systems* which will be used initially for research and later in the clinical setting.

The current generators for β - and γ -emitting radionuclides routinely utilize organic resins in ion exchange columns to absorb the parent radionuclide and elute, on demand, the desired daughter radionuclide for application. Although some success has been achieved in using organic resins for alpha-emitter generators, the generator shelf-life is very short due to radiolytic breakdown of the resin in the high α -radiation field. This also reduces yields of the desired radionuclide and results in higher concentrations of the undesirable parent radionuclides. Application of radiation resistant organic resins may improve generator performance. Newer developments eliminate the need for organic resins and the resulting problems of radiation damage. With improved techniques, reliable generators may be produced for clinical use.

Although useful α -emitters may be produced and radionuclide generator systems become available, demands for preclinical and clinical research are presently expected to exceed supplies. 1-3 mCi of ^{213}Bi , ^{223}Ra and ^{225}Ac , and 10-15 mCi of ^{212}Bi are currently available for research from DOE facilities ⁴. Multiple applications now require 20-50 mCi of ^{212}Bi , ^{213}Bi , ^{223}Ra , and ^{225}Ac for larger scale research and patient trials. The lack of an adequate supply of required radionuclides limits research and clinical application of α -emitters.

⁴ Since the end of the workshop, the DOE has funded the purification of an additional 45 mCi of ^{229}Th , which is also now available for the production of ^{225}Ac .

4. The Carrier Problem

Alpha-emitters may be widely applied to the treatment of cancerous and noncancerous disease. The range of applications largely depends on the proper *choice of the carrier substrate* with which the α -emitter is delivered to a chosen target. In cancer, targets may be single tumor cells, as in leukemia, micrometastases, minimal residual disease after other forms of therapy, intracavitory malignant tumors, and normal bone marrow prior to lethal irradiation in preparation for bone marrow transplantation. Noncancerous target cells may be in the vascular endothelium causing stenoses such as in the coronary arteries, in chronic inflammatory disease, and in the immune system for immunosuppression. The decision whether to explore the use of α -emitters in a particular clinical situation should be guided by knowledge of the physical and biologic properties of the available radionuclides and their carrier substrates.

General considerations of α -particle dosimetry, high relative biological effectiveness, short path length, and mostly short half-lives suggest that α -emitters would be best targeted against cells dispersed either singly or as small aggregates. The fact that the α -particles have a range greater than a single cell diameter means that bystander cells will be irradiated too; this increasingly occurs when more than approximately ten particles per cell are absorbed in the surrounding matrix. Such cross-fire effects will give some advantage to α -emitters when compared to targeted toxins and chemotherapeutic agents.

The potential advantage of α -emitters, however, may be negated in solid tumors by poor blood flow and other problems associated with carrier penetration of such masses. Penetration is a particular problem for α -particle delivery because of the need to achieve relatively close target cell proximity. Greater understanding of the physiologic barriers in solid tumors that restrict the absolute accumulation and rate of accumulation of carriers at chosen sites is needed before α -emitters can be fully exploited. On the other hand, micrometastases of rapidly proliferating, solid tumors may be more effectively treated with α -emitters than, for example, with current adjuvant chemotherapy, and with less associated systemic toxicity.

In some cases, simple physical methods may deliver the α -emitter, for example, for intra-compartmental therapy. Also, α -emitters bound to colloids, which will inhibit diffusion from the site of administration, might be injected into the cavity of joints for radiosynovectomy in the treatment of rheumatoid or degenerative arthritis. A converse carrier strategy would be to utilize α -emitters in a chemically inert form, for example, bound to a polymer which would assist diffusion through a tumor matrix. It may even be possible to use radon daughters as generator products infused into tumor blood vessels. Targeting would result from binding of hot atoms born from the radon daughters to cell surfaces by various physical and chemical mechanisms.

In a few cases, *chemical means* alone may help targeting. Astatide ions behave like iodide and could be used to treat hyperthyroidism or thyroid cancer. Similarly, radium, because it is a calcium analogue, could be used to target bone cancers, as could some of the bone-seeking actinide elements. A mixture of physical and chemical targeting has also been proposed, for

example, in the use of slow-release polymers to provide *in situ* radiation therapy of inoperable tumors or after incomplete tumor resection. A polymer containing an α -emitter could be inserted before the surgical site is closed, providing a long lasting source of α -emissions depending on the half-life of the radionuclide.

Although these chemical and physical approaches are interesting, *biologic targeting* has the greatest appeal because of its potential to seek out a target cell population and individual target cells. This allows exploitation of the short range of the α -particle while exposure of other non-targeted tissues is limited.

Many cellular targets may be identified through their specific recognition sites. They are both in normal tissues, for example as CD3, CD4 on lymphocytes for immune suppression, and in tumors, for example as tumor-associated antigens, mutated or over-expressed products of oncogenes and tumor suppressor genes, and as cytokines and cytokine receptors. The latter include Erb-B2, EGF-R, IL-2R, somatostatin R, transferrin R, and others. Specific cell adhesion molecules preferentially characterize blood vessel cells within tumors or tumor cells in metastases. The list of such recognition sites is growing fast as genome sequencing and molecular expression techniques identify new possible molecular targets.

It is often not clear what constitutes the optimal target for the carrier of an α -emitter. A high level of expression of cellular recognition sites in terms of specific surface molecules and their relatively long residence time are likely to be important. This applies foremost to α -emitters with their relatively short range and half-life; also, less α -emitters would need to be localized for cell killing in comparison with β -emitters for targeted therapy. At the level of the individual cell dosimetric modeling suggests that the efficiency of cell killing by α -emitters localized at membrane targets is only slightly less than it is for cytoplasmic or nuclear targets. Nevertheless, internalization of α -emitters appears superior and needs further research.

Attempts to target radionuclides to cells *in vivo* have focused primarily on the use of *monoclonal antibodies*. These are likely the carrier of choice in early trials with α -emitters. However, other approaches should also be explored. For example, purine or pyrimidine prodrug analogues are used as cytotoxic agents; if labeled with a suitable α -emitter they might allow a particularly potent combination therapy for cancer, especially if combined with tumor-targeted gene transfer to increase selective uptake. In the near future the range of peptide and oligonucleotide carriers with target specificity is likely to increase dramatically through the use of combinatorial chemistry techniques; this may give more flexibility in the choice of carrier. The smaller molecules such as physiologic metabolites may be labeled with an α -emitter. This will enhance tumor penetration as well as intracellular deposition, which will increase therapeutic efficiency.

For *in vivo targeting*, the short half-life of most α -emitters demands rapid labeling techniques and carriers that quickly and homogeneously distribute throughout the body. Perhaps one of the greatest disadvantages of monoclonal antibodies in targeting tumors is their lack of penetration of solid tumor masses. Their slow equilibration rate excludes their conventional use as carriers

of α -emitters for the therapy of many types of cancer. Antibody fragments such as Fv (25 kD) and Fab (50 kD) penetrate tumor tissue more easily and thus will distribute more homogeneously throughout the tumor. However, the fraction of injected carrier reaching the tumor is much less with the small molecular fragments that are rapidly excreted by the kidneys. Involvement of the kidneys in tubular resorption of these fragments raises concern for kidney toxicity.

One solution to the problem of efficiency of targeting is the use of *antibody pretargeting*. The antibody with an attached high affinity receptor, such as streptavidin, is allowed to target and accumulate at the tumor site. Residual circulating antibody conjugate is cleared; finally, the α -emitter is delivered attached to a small molecule such as biotin that specifically binds to streptavidin. In this context, ^{212}Bi with its half-life of 45 minutes may be useful, but the time for labeling of biotin and for its targeting may be too long for solid tumors. This short-lived α -emitter may be quite suitable for more accessible target cells, such as in leukemia or in the blood vessels of a tumor. The 7.2 hour half-life of ^{211}At appears more reasonable for applications in pretargeting solid tumor masses. The $^{212}\text{Pb}/^{212}\text{Bi}$ -system to generate ^{212}Bi *in vivo* appears promising, but eliminating the release of ^{212}Bi from the chelate conjugated antibody, due to the "hot atom effects" may be difficult.

In conclusion, it seems likely that the short path length, high relative biological effectiveness in cell killing, and short half-life of certain α -emitters can be exploited for therapeutic benefit. Also, these properties need to be considered in making decisions for selecting α -emitters according to disease, carrier, and target, in clinical research and practice.

5. *Linking Alpha-Emitters to Carriers*

Currently the most practical α -emitters with regard to their availability and radiochemical properties are ^{211}At , ^{212}Bi and ^{213}Bi with half-lives of 7.2 hours, 60.6 minutes and 45.6 minutes, respectively. The very nature of these radionuclides raises three critical issues when they are considered for therapeutic applications.

The first of these is the availability of a stable *attachment of the α -emitter to the carrier* molecule. Instability may not only compromise the therapeutic effectiveness of the α -emitter but also enhance damage to normal tissues through the presence of a radionuclide in the blood pool.

The second issue is similar and pertains to the *design of molecules*, which must bond or chelate with the α -emitter such that the labeled catabolic products of the carrier are rapidly excreted from the body via the renal system if the α -emitter has a long half-life. Given the short half-lives of many α -emitters, it is more important to develop carriers that do not localize to the kidneys.

The third issue arises from the short half-lives of generally suitable α -emitters. Short half-lives demand fast *procedures for labeling* the carrier molecules and for purifying the labeled product.

In order of existing priorities ^{211}At , ^{212}Bi and ^{213}Bi have received serious consideration and some investment of research resources based upon their *availability and radioactive decay properties*. The chemistry of the bismuth nuclides is reasonably well understood due to the availability of stable ^{209}Bi . On the other hand, the chemistry of the more useful ^{211}At is poorly understood and remains descriptive because of its 7.2 hour half-life and the lack of availability of the stable nuclide. However, as demonstrated in certain experiments with ^{211}At -labeled carrier, astatine resembles iodine.

It is recommended that the priorities of the α -emitters listed above be sustained in the foreseeable future. They are available and have properties allowing the *in vivo determination of efficacy* of targeted α -particle irradiation in animal models and selected clinical diseases. However, new chemical approaches to linker design may be required for broader application of these α -emitters, as discussed above. In addition, the usefulness of ^{211}At may be greatly improved by further exploration of its chemical properties as outlined below. Priority for ^{211}At is also supported by the recent demonstration of its improved production in an accelerator.

Previous research demonstrated the easy attachment of ^{211}At to antibodies by direct conjugation of astatinated reagents containing carbon-astatine bonds. Accumulated evidence also suggests that such bonds may be only marginally robust *in vivo*. This is largely due to a low At-C bond strength. In addition, it is possible that the astatine conjugation reagents, in which *At is believed to play the role of a halogen*, actually contain At in the oxidation state of +3, +5 or +7; this is commonly observed for iodine or metallic centers such as $-\text{TcO}^+$, $-\text{TcO}_2^+$, $-\text{TcO}_3^+$ and $-\text{TcO}_4^-$. Thus, the natural instability of the At-C bond could be exacerbated by the presence of $-\text{AtO}^+$, $-\text{AtO}_2^+$ or $-\text{AtO}_3^+$ groups attached to the aryl groups of conjugation reagents. Assuming that At may indeed be imbued with metallic oxidation states and thus form oxymetallate groups, it is not unreasonable to expect such oxyastatine centers to form stable chelates with polyfunctional chelation agents. If successful, this would provide a new method for binding ^{211}At to linker molecules. This would improve kinetic and thermodynamic stabilities and enhance *in vivo* performance of the linker-astatine array. This concept deserves immediate investigation.

Another approach to the chemical stabilization of ^{211}At uses astatine as an iodine-like substituent in polyhedral borane derivatives, which are themselves known to be useful substituents in linker molecules. Such derivatives would contain At-B bonds which are expected to be somewhat more stable than At-C bonds. Candidate conjugation reagents derived from boranes and carboranes are immediately available from DOE-supported research in boron neutron capture therapy. These materials should undergo simple astatination not unlike their known iodination reactions. This kind of exploratory astatination chemistry should receive a high priority among future research projects.

The *chelate chemistry of ^{212}Bi and ^{213}Bi* , as it applies to linker technology, is well developed and linkers for direct antibody conjugation are available. Future work should include the adaptation of bismuth chelation agents to biotin- or hapten-conjugated linkers with reduced or zero localization to kidneys for use in pretargeted carrier therapy. In addition, the design of new

chelation methods should be extended to include "inorganic" chelates in which bismuth is incorporated in a metal cluster species which, due to its structure, provides excellent kinetic stability. The success of therapy using bismuth radionuclides depends on the ability of the nuclide sequestering process to rapidly scavenge bismuth at very low metal-ion concentrations. The efficiency of this process could be improved. In one system this has been achieved with 85-90% efficiency within six minutes.

Selective tumor-targeted monoclonal antibodies that are capable of delivering therapeutic quantities of α -emitters are now available. It is, thus, possible to identify targeting proteins and peptides such as whole antibodies, antibody fragments or single chain antibodies as likely molecular carriers of α -emitters for research and clinical therapy. *Binding of the α -emitter to the carrier antibody* may be accomplished by (a) loading linker-antibody conjugate with radionuclide; (b) loading the linker with radionuclide followed by conjugation of the product of this reaction with antibody or (c) pretargeting the tumor. The latter may use an immunoprotein carrying a high-affinity receptor such as streptavidin, or a bispecific antibody; to either one, then, may be coupled *in vivo* the biotin- or hapten-bonded/chelated radionuclide, respectively.

Methods (a) and (b) rely on covalent chemical bond formation between the linker and the carrier while method (c) employs the very stable biotin-streptavidin or hapten-antibody complex to assure strong and accurately directed linkage of the α -emitter to the selected primary target. Thus, direct methods (a) and (b) differ from indirect method (c) only in the nature of the functional group used to bind the linker to carrier, for example, by an aminoreactive active ester for (a) and (b); a radio-labeled biotin or hapten molecule for (c). Method (c) has the advantage of labeling small molecules such as biotin and hapten. This may be done rapidly at elevated temperatures at specific conditions with appropriate pH. This helps avoid undue loss of radionuclide through radiation-induced decomposition or denaturation of the carrier molecule.

Goals to be met include the design and *synthesis of linker molecules*. This must consider the direct or indirect nature of targeting *in vivo* such as by carrier-linker-radionuclide, carrier-streptavidin-biotin-radionuclide or carrier with biospecificity for hapten-radionuclide. Also, all labeled catabolites should be rapidly excreted through the kidneys. Thirdly, the α -emitter must be complementary to the chemical and physical properties of the carrier molecule.

With respect to carrier and associated α -emitter delivery methods, the success of α -particle therapy will depend on employing *the most efficient available carrier* molecule that must be matched to the chosen type of malignancy. Thus, a whole antibody covalently linked to α -emitter may be useful for leukemias and highly vascularized tumor systems while smaller antibody fragments, engineered peptides and labeled biotin or hapten molecules for pretargeted delivery could be envisioned for use with solid tumors. When using these relatively small carrier molecules, renal blocking could be employed to extend circulation times and enhance tumor accretion. This wide range of possible approaches demands careful scrutiny and choice of priorities both for immediate research and preclinical testing before clinical trials may begin.

The use of α -emitters with relatively long half-lives are also under investigation as potential therapeutic agents. These are ^{223}Ra and ^{225}Ac with half-lives of 11.4 and 10 days, respectively. The longer half-lives of these isotopes could provide an advantage in matching the isotope decay time to the pharmacokinetics of carrier molecules in tumors. Pilot studies of chelation and linker chemistry of these nuclides are underway. Studies on in vitro stability of ^{223}Ra -labeled carrier molecules and their toxicity in animals will be completed in the near future. The priority for future preclinical research with ^{223}Ra and possibly other long-lived α -emitters depends largely on the outcome of these ongoing studies. However, this work is given a reduced priority at the present time.

Long-lived α -emitters may also be used for very localized and selective destruction of tissue and cells, which, for example may threaten physiologically vital functions. A case in point is localized arteriosclerosis impeding coronary blood flow. As an example, ^{148}Gd has a half-life of 75 years and emits a 3.2 MeV α -particle. Conceptually, this α -emitter could be firmly attached to an *applicator or probe* that is placed in contact with the targeted tissue and cells and is removed at will. The depth of burial of the α -emitter under the applicator surface could be used to "tune" the average kinetic energy of the α -particles released at the surface. Appropriate designs should be studied in view of possible approaches and methods for using such an α -emitting probe. Such an attractive project could begin immediately.

6. Preclinical and Clinical Testing

Preclinical and clinical testing should adhere to the applicability of the method under clinical conditions and should *promise therapeutic efficacy*. These prerequisites need to be established by basic and preclinical research.

The workshop identified a number of clinical situations in which α -emitters promise effective treatment. Many such clinical potentials have been cited throughout the workshop. In this session, various malignant and benign disorders were discussed on the basis of the *unique physical characteristics of α -emitters* and their possible use for directly and indirectly targeting single cells.

Clinicians expect therapy with α -emitters to be better than existing treatment modalities where limitations often exist partly because of systemic involvement with adverse effects. Therapy with α -emitters allows for better dose rates, efficiencies of cell killing, and safety to patients and personnel in comparison with some other presently used internal radiation emitters.

Some of the indications for clinical application of α -emitters are already being studied. Especially for tumors known to be resistant to conventional radiotherapy, *localized application of α -emitters*, perhaps also as adjuvant, may open new approaches and be effective *in routine clinical treatment*. Also, chemotherapy may be augmented by applying localized radiation

therapy with α -emitters. In this manner, toxicity of chemotherapy alone may be decreased, and the duration of such therapy may be shortened without compromising the therapeutic goal of tumor control. Selective irradiation from localized α -emitters may advance ablation of immune competent cells especially in serious immunological disorders.

Especially, various hematological disorders and intracavitory malignancies appear to be excellent candidates for preclinical and clinical testing according to the outcome of on-going preclinical research. Particular attention is aimed at solving the challenges in patient *preparation for bone marrow transplantation*. Here, the goal is the elimination of residual tumor cells and immune competent cells in the bone marrow to be transplanted. Another urgent clinical challenge is the treatment of ovarian cancer with metastases in the peritoneal cavity. The proper application of α -emitters may be the best treatment modality. The participants also encouraged the development of solid devices such as small probes or catheters containing α -emitters to be introduced into blood vessels for local irradiation of endothelial cells in the treatment of coronary artery disease.

Two clinical trials with α -emitters will soon begin. At Duke University Medical Center, Durham, NC., ^{211}At -labeled chimeric 81C6 antibody will be administered intrathecally in patients with cystic gliomas. The other trial at the Memorial Sloan-Kettering Cancer Center in New York focuses on the development of ^{213}Bi -CHX-A labeled antibodies for treating patients with relapsed acute myelogenous leukemia (AML).⁵

The time to enter clinical studies has come for these diseases. The lack of availability of α -emitters would essentially terminate these projects. Patients would seek alternative treatment and, also, might decide for treatment with α -emitters in other countries.

Alpha-emitters for clinical use appear timely, indeed. Many hurdles for therapy with α -emitters have been overcome as discussed at this workshop. Paramount is the understanding of nuclide chemistry; target identification; selection, production and chemistry of carrier molecules; linker chemistry; and availability of biologic models preparing for use in humans.

For assuring the best possible development of treatment modalities with α -emitters, *protocols for preclinical and clinical trials* should be compared and, when needed, adjusted in concordance with the Food and Drug Administration (FDA) and local Institutional Review Boards (IRB). Statistical analyses must eventually justify continuation, amendment or new designs of protocols. Interinstitutional contacts will support optimal progress in introducing these advanced treatments for identified malignant and benign diseases.

⁵ These clinical trials have been initiated since the conclusion of the workshop.

Workshop Participants

Dr. Robert W. Atcher
University of Alabama

Dr. J. E. Bigelow
Oak Ridge National Laboratory

Dr. Les Braby
Texas A&M University

Dr. Martin W. Brechbiel
National Institute of Health

Dr. Dean Cole
U.S. Department of Energy

Dr. William C. Eckelman
National Institute of Health

Dr. Ludwig Feinendegen
U.S. Department of Energy

Dr. Alan R. Fritzberg
NeoRX Corporation

Dr. Thomas Griffin
University of Washington Medical Center

Dr. Paul Harper
University of Chicago

Professor M. Frederick Hawthorne
(Chairman, Session 5)
University of California, Los Angeles

Dr. Robert E. Henkin
Loyola University Medical Center

Dr. John L. Humm
Memorial Sloan Kettering Cancer Center

Dr. Amin I. Kassis
Harvard Medical School

Dr. Steve Kennel
Oak Ridge National Laboratory

Dr. George L. Laramore
University of Washington Medical Center

Dr. Steven M. Larson
Memorial Sloan Kettering Cancer Center

Dr. Peter K. Leichner
University of Nebraska Medical Center

Mr. Owen W. Lowe
U.S. Department of Energy

Dr. Roger Macklis
The Cleveland Clinic Foundation

Dr. William H. McBride
(Chairman, Session 4)
UCLA Medical Center

Dr. John J. McClure
U.S. Department of Energy

Dr. Saed Mirzadeh
Oak Ridge National Laboratory

Mr. Brad D. Patton
(Chairman, Session 3)
Oak Ridge National Laboratory

Workshop Participants

Ms. Ana Ramirez Isotope Products Laboratory, Inc.	Dr. Robert Sharkey Center for Molecular Medicine and Immunology
Dr. John C. Roeske University of Chicago	Dr. Rainer Storb (Chairman, Session 6) Fred Hutchinson Cancer Research Center
Dr. Howard Sands Sparta Pharmaceutical Company	Dr. T. S. Tenforde Pacific Northwest National Laboratory
Dr. Stanley Satz BIO-Nucleonics, Inc.	Ms. Julie Turner U.S. Department of Energy
Dr. David Scheinberg Memorial Sloan Kettering Cancer Center	Dr. H. Rodney Whithers University of California, Los Angeles
Dr. Robert E. Schenter Pacific Northwest National Laboratory	Dr. Scott D. Wilbur University of Washington Medical Center
Dr. Jeffrey L. Schwartz University of Washington	Dr. Michael Zalutsky Duke University Medical Center
Dr. Aldo N. Serafini (Chairman, Session 1) University of Miami School of Medicine	Dr. Brian Zimmerman National Institute of Standards and Technology
Dr. George Sgouros (Chairman Session 2) Memorial Sloan Kettering Cancer Center	