Radiopharmaceutical Development and the Office of Science

April 2004

Prepared by a Subcommittee of the Biological and Environmental Research Advisory Committee

Radiopharmaceutical Development and the Office of Science

Radiopharmaceutical science in the U.S. has sprung from government-sponsored programs that began shortly after the 2nd world war under the Atomic Energy Commission and has continued to the present day, largely through support from the Office of Science/Biological and Environmental Research (BER) program within the Department of Energy (DOE). Today we can point to many practical human benefits that are derived directly from innovative research from these programs, including the development of modern nuclear medicine, which has improved health care around the world. More that 20 million nuclear medicine patient procedures are performed each year in the U.S. alone. The majority of instrumentation and radiopharmaceutical based inventions and discoveries in nuclear medicine have occurred, and continue to occur, through BER/DOE support!

It is clear that the sequencing of the human genome and the explosion of knowledge in proteomics, systems biology and pathogenesis of human disease offers unprecedented opportunity for medical science, including the further development of molecular imaging with nuclear medicine in the area of radiopharmaceutical science. In recognition of this time of opportunity, Dr. Raymond Orbach, Director of the Office of Science, charged BERAC to review the status of Radiopharmaceutical (RDP) Research. He asked how BER might support research and development in order to best translate scientific development into routine medical care. The charge consisted of four distinct but related questions (Charge, Appendix B).

This report draws from input from leading experts in Nuclear Medicine and Radiopharmaceutical Science including recent working groups convened by DOE, especially the February 11-12, 2003, BERAC subcommittee working group meeting on Radiopharmaceuticals. (Participants, Appendix A).

1. "Assess future needs for RDP development in the era of "molecular medicine"…

Radiotracers have applications in biologic research, drug discovery, diagnosis of human disease and molecular therapeutics for a wide variety of medical conditions. As we look to the future, we see rich promise for the development of novel radiotracers for imaging the molecular basis of specific biological processes by exploiting the rapid progress made in the technology of molecular imaging. Our understanding of the molecular basis of normal cellular functions, and our knowledge of how genetic programmed transformation of normal cells into diseased cells occurs is rapidly evolving. This rich knowledge base for the development of molecular radiopharmaceuticals complements that of molecular therapeutics through the development of molecular imaging diagnostics, together these advances characterize the era of "Molecular Medicine".

Components of radiopharmaceutical development include: a) chemical precursors and radionuclides used to construct radiotracers that are then used as molecular imaging probes; b) small radiolabeled molecules that target key molecular components of normal and diseased tissues (RNA, DNA and proteins); c) cellular based radiotracers (e.g.,

immune cells, progenitor cells, etc.); and d) radiolabeled macromolecules including peptides, antibodies, "minibodies", etc. These and other molecular probes can be used to target receptors and enzymes, RNA and DNA (in their normal and mutated forms), molecular machines and molecular modules, and signaling protein cascades. The expression of many genes can now be imaged using special reporter radiotracer systems. Important ancillary developments include specialized instrumentation, screening systems, such as "chemical biology", and in vivo biological screening and targeting systems.

Many radiotracers used as molecular imaging probes are labeled analogs of drugs. This provides a resource for new molecular imaging probes and also builds an important relationship to the pharmaceutical discovery process because these molecular imaging probes can also be used to study the pharmacokinetics of drugs and guide the drug discovery process in vivo from mouse to patient. All large pharmaceutical companies today either have small animal and human PET scanners (e.g., Merck has 5 PET scanners) or relationships with academic and other PET programs that provide these unique scientific tools.

Molecular therapeutics and molecular diagnostics share a common molecular disease target. The diagnostic agent images the target molecule with tracer amounts of the molecular probe to provide biological and pharmacokinetic information. The therapeutic drug is used in high mass amounts of the probe (or analog of the probe) to modify or eliminate the target molecule. The tracer approach provides the means to examine biological processes or pharmacokinetics without mass disturbances because of the non pharmacologic mass amounts used. This provides a safe and sensitive measurement indirectly in humans (e.g., in over 2 million PET studies with FDG, there is not one reported complication.)

In the decade ahead, there is a vision to create many more radiotracers, highly specific in nature that can serve as tools for advanced laboratory research as well as clinical applications. A new paradigm that integrates fast track development of radiotracers must be developed to match not only the needs of the pharmaceutical research and companies, but also the fast pace of post-genomic development that seeks to understand the systems biology of disease. Although much research will be performed in vitro, systems biology must be understood in the living mammalian organism, including patients, which are the only true model of human disease. Rapid progression and translation from mice to man is an urgent need of current radiotracer development.

DOE can remain in the forefront of these developments by promoting RDP research at the basic level, as well as fostering translational research. DOE can take advantage of its long-standing experience to support directly promising investigators and to create centers of excellence, which would serve as a resource for research scientists from many disciplines. Furthermore, a concerted effort should be made to link RDP research with DOE's "big science" programs related to Genomics:GTL, proteomics and nanotechnology developments. A close tie to these programs will enable more rapid identification of the critical disease targets and design of molecular imaging probes for these targets; also, in some cases this link will aid in the construction of "micro labs on

large scale integrated microfluidic chips" containing nanotechnology tool sets, molecular libraries and chemistry labs for constructing and biological screening of molecular probes within the context of the systems biology of normal cellular function and disease. In the future, the molecular imaging probes that are developed will help translate in vitro system biology into the in vivo setting to study systems biology within living mammalian models of disease, and from this will come the foundations of translational research in molecular imaging diagnostics in individual patients as a basis for both research advances and improved clinical care.

2. "Evaluate Impact of the reported shortage in highly trained radiochemistry…"

There is a consensus that there is a critical shortage of trained chemists (including pharmaceutical chemists, organic chemists, inorganic chemists and peptide and protein chemists) with interest and ability in the design and synthesis of molecular imaging and targeted radiotherapy probes. In a survey of 20 leading institutions, an average of 2-3 positions per institution went unfilled because of a lack of qualified applicants. We need to attract, recruit and train first rate scientists to drive the development of the radiotracers of the future. Basically we are now all competing for trained chemists from a small pool that is far below the needs of the BER programs, and this is definitely retarding progress.

3. "Complementary Role of Agencies…"

DOE's experience and unique capabilities in instrumentation development, radionuclide production, radiobiology and the physical sciences provides an important foundation for governmental support of radiopharmaceutical development. DOE has been the historical sponsor for Radiopharmaceutical Chemistry and related sciences. With the increasingly central role of radiotracers for non-invasive imaging of animal models and human research, other agencies are likely to have a growing interest in development of radiopharmaceutical science. In particular, NIH will have a role in clinical evaluation of molecular imaging targeted therapy technologies and procedures developed and applied to translational research applications within DOE funded laboratories. For example, NCI just released a pathway vision from its Director, Dr. Andy Von Eschenbach, that featured molecular imaging as one of the three key technologies. Moreover, NIH Director Elias Zerhouni has called for new strategies to speed the translation of new discoveries in the research sector to the clinic along with a thrust to advance the drug discovery process. These are both areas that will need advances in molecular imaging to probe drug behavior on the whole organism level including imaging in humans as part of the translational process. Pharmaceutical company partnerships should also be encouraged to promote the rapid development of useful drugs by exploiting radiotracer technology in drug discovery while also appreciating the need to protect intellectual property. DOE could play an additional role in supporting technologic developments that will facilitate such drug discovery, including applications that may be derived from the Genomics:GTL program, and the application of nanotechnology in drug and molecular probe development and screening.

4. “Impediments”

Current FDA regulations for approval of human use of new radiotracers were designed for drugs with pharmacologic action and side effects, and are inappropriate when applied to radiopharmaceuticals. More specifically, radiotracers are administered in tracer chemical quantities with non pharmacologic effects in a small number of doses, in contrast to pharmaceuticals that are taken every day for extended periods and, of course, in mass amounts. Regulations should be modified and confined to demonstrations of safety and radiotracer efficacy, at the same time recognizing the difference between a drug and a tracer. There is a sound scientific foundation and extensive experience that supports this distinction. Current regulatory hurdles inhibit translation of new discoveries into clinical research tools that can improve the human condition, even though there is no scientific foundation for such complex regulation. The artificial barriers should be removed, leaving only those that are scientifically justifiable. Other major impediments are the lack of bulk synthesis facilities, validated in vitro testing facilities, access to toxicology-pathology studies, access to gene-manipulated mice models, and state of the art lead structures from pharmaceutical companies. Facilities for these processes should be set up as a core facility available to investigators or support provided for partnerships to provide access to these resources. These should be collaborative efforts between other institutions and within DOE itself to minimize the need for new facilities. For example, NIMH of NIH has set up an in vitro testing facility, both NCI and NIMH of NIH have set up toxicology-pathology blanket contracts, gene-manipulated mice are being produced at the DOE facility in Oak Ridge, and collaborations with pharmaceutical companies will be a source of leads for new radiolabeled molecular imaging probes and will guarantee an important use of the radiotracers in the drug development process.

Summary Recommendations

1. Establish 5-6 regional centers of excellence, through freely competed peer review, whose purpose is to expand support for radiopharmaceutical development, by emphasizing new approaches to the molecular imaging probe discovery process. These centers can originate from modernization of existing BER funded programs or from new investigators. The Centers should include translational research, from the in vitro level in cells and tissues, to in vivo studies in mice and patients. Specifically, these centers should provide dedicated expertise and state of the art facilities that are designed for discovery, production and advanced applications of radiotracers as molecular imaging probes. Technologies should include advanced nanotechnologies, integrated microfluidics chips, biotechnologies and molecular imaging techniques including multi-modality imaging. There should be an emphasis on bringing chemistry, physics and biology together in the probe discovery process. Development should include both diagnostic and therapeutic molecular discovery that are linked together. These centers will relate to a network of specialized facilities, which will provide leadership and support for key ancillary capabilities such as mouse model consortia, unique imaging facilities, screening capabilities, toxicology-pathology, model infrastructures for translation to humans, etc., that are now impediments to rapid development of radiopharmaceuticals. Tens of millions per annum will ultimately be needed to establish and maintain the 5-6 regional centers and the specialized facilities. This investment will markedly increase the number of compounds available for basic and translational research, and would provide-training environments for radiochemists and allied personnel in the construction of molecular imaging probes with biologic and medical relevance as part of the growth in the scientific foundation of molecular medicine.

2. Expand training program support in radiopharmaceutical chemistry and allied chemical disciplines, including pharmaceutical chemistry, cyclotron (target) radiochemistry, organic chemistry, peptide and protein chemistry, and chemical biology, for those with interest in molecular targeting with radiotracers. Three to four million dollars of incremental funding should be used for training stipends, perhaps as “matching funds” with sister agencies, such as NIBIB and other NIH institutes (see below). U.S. colleges and universities are beacons to students from around the world and we should seize this opportunity to recruit talented young scientists to careers in radiotracer chemistry, and tracer assay development to build the future scientists of our discipline and through them what the discipline will become.

3. Create a master plan to foster more optimal development of radiotracers for biologic research and medical care by working with sister governmental agencies. An initial step would be for DOE to take a leadership role in establishing conjoint working groups to define a road map for sharing of support responsibilities. DOE, NIH, NRC and FDA should work together on common planning for maximizing safe and rapid progress.

4. Lead an effort involving FDA, NIH, United States Pharmacopea, professional societies and industry to create regulations and a process that recognizes the unique nature of radiotracers as “generally safe and effective” based on sound scientific principles. This would facilitate translation of promising radiotracers to human studies by demonstrating their proof of principle as well as their utility as scientific or clinical molecular diagnostic tools.

Appendix A

Participants

DOE BERAC Subcommittee Workshop
February 11-12, 2003
The American Geophysical Union
2000 Florida Avenue, NW
Washington, DC 20009

Steven M. Larson, M.D. (Chair, BERAC Subcommittee, BERAC Member)
Chief, Nuclear Medicine Service
Memorial Sloan Kettering Cancer Center
New York, NY

Nora Volkow, M.D. (Co-chair, BERAC Subcommittee, BERAC Member)
Associate Laboratory Director for Life Science Medical Department
Brookhaven National Laboratory
Upton, NY

S. James Adelstein, M.D. (BERAC Member)
Harvard Medical School
Boston, MA

Thomas Budinger, M.D., Ph.D.
Chairman, Department of Bioengineering, U.C. Berkeley
Head, Functional Imaging
Lawrence Berkeley National Laboratory
Berkeley, CA

William Eckelman, Ph.D.
Chief of PET Department
National Institutes of Health
Bethesda, MD

Juri Gelovani (a.k.a. Tjuvajev), M.D., Ph.D.
Associate Attending, Associate Professor,
Departments of Neurology and Radiology, K923
Memorial Sloan Kettering Cancer Center
and Sloan Kettering Institute
New York, NY

Joanna Fowler, Ph.D.
Senior Chemist
Chemistry Department
Brookhaven National Laboratory
Upton, NY

Kirk A. Frey, M.D., Ph.D.
Professor of Radiology and Neurology
Senior Research Scientist and Director
Neuropharmacology Section
University of Michigan Hospital
Ann Arbor, MI

Sanjiv Sam Gambhir M.D., Ph.D.
Director, Crump Institute for Molecular Imaging
Associate Professor
Dept. of Molecular & Medical Pharmacology
Residency Director for Nuclear Medicine
UCLA School of Medicine
Los Angeles, CA

Michael R. Kilbourn, Ph.D.
Professor of Radiology
Dept. of Radiology
University of Michigan Medical School
Ann Arbor, MI

Roger O. McClellan, DVM (BERAC Member)
Advisor, Toxicology and Human Health Risk Analysis
Albuquerque, NM

Michael E. Phelps, Ph.D.
Norton Simon Professor
Chair, Dept. of Molecular & Medical
Pharmacology
Dir., Crump Inst. for Molecular Imaging
Chief, Division of Nuclear Medicine
Los Angeles, CA

David Piwnica-Worms, M.D., Ph.D.
Professor of Radiology
Prof. of Molecular Biology & Pharmacology
Director, Molecular Imaging Center
Washington University School of Medicine
St. Louis, MO

Henry F. VanBrocklin, Ph.D.
Head, Radiopharmaceutical Chemistry
Center for Functional Imaging
Lawrence Berkeley National Laboratory
Berkeley, CA

Henry N. Wagner, M.D.
Director, Division of Radiation and Health Science
Johns Hopkins University
Department of Radiological Sciences
Baltimore, MD

Richard L. Wahl, M.D.
Johns Hopkins Medical Institute
Baltimore, MD

Michael J. Welch, Ph.D.
Professor of Radiology
Co-Director, Division of Radiological Sciences
Department of Radiology
Washington University School of Medicine
St. Louis, MO

Department of Energy
Washington, DC 20585

December 4, 2002

Dr. Keith O. Hodgson
Chair, Biological and Environmental
Research Advisory Committee
Department of Chemistry
Stanford University
Stanford, California 94305

Dear Dr. Hodgson:

For over 50 years, the Office of Biological and Environmental Research (BER) has successfully leveraged advances in the physical sciences to support highly productive technological advances in Nuclear Medicine. Notable examples of medically important BER supported advances include the development and refinement of nearly all clinical imaging devices for the radioisotopic diagnosis and characterization of disease, the evolution of positron emission tomography (PET) as today's most powerful tool for the staging of human cancers, and the development of many key radiopharmaceuticals that are used by nuclear medicine physicians today to characterize the biochemical and metabolic abnormalities produced by disease.

Advances in diagnosis and treatment in Nuclear Medicine are dependent on the synthesis of highly specific radiopharmaceuticals that target biological processes in normal and diseased tissues. The DOE, through BER supported research in universities and in the National Laboratories, occupies a critical and unique niche in the field of radiopharmaceutical research. The NIH relies on our basic research to enable them to initiate clinical trials. Industry has played only a minor role in radiopharmaceutical research and development. In view of this, the time has come to re-assess how BER research support might best stimulate directions in radiopharmaceutical research that are most likely to find translation into routine medical care in the coming decades.

To address this need, I am asking the Biological and Environmental Research Advisory Committee to create a subcommittee whose charge would be to evaluate how BER might optimize the scope of its Radiopharmaceutical Research Program. More specifically, the subcommittee should

1) Assess future needs for radiopharmaceutical development in the era of "molecular medicine" and how BER can remain in the forefront of fundamental science in this field;

2) Evaluate the impact of the reported shortage in highly trained radiochemists and determine if BER has a role in short and long range approaches to alleviate this shortage;

3) Assess the complimentary role of agencies, which support fundamental radiochemical sciences (DOE, BER), clinical imaging (NIH), and industry in facilitating the emergence in innovative radiopharmaceuticals into clinical practice;

4) Identify current national impediments to the efficient entry of promising new compounds into clinical feasibility studies and suggest ways for facilitating this translation of basic research into clinical practice.

I look forward to your findings and recommendations. I would appreciate receiving a preliminary report by April 15, 2003.

Sincerely,

Raymond L. Orbach
Director
Office of Science