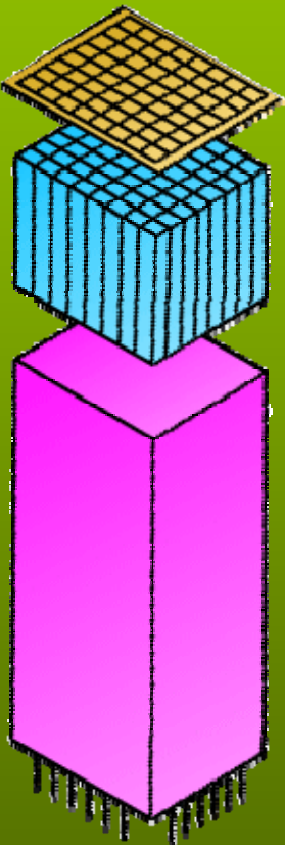


New Frontiers of Science: DOE Fueling the Future of Nuclear Medicine



Hyatt Regency
575 Memorial Drive
Cambridge, MA
617-492-1234
September 10-11, 2007



Workshop will focus on defining the radionuclide/radiopharmaceutical chemistry and instrumentation research problems, and science and technology needs for fueling the future of nuclear medicine within the scope of DOE Science Mission.

Life and Medical Sciences Division
Biological and Environmental Research
Office of Science
U.S. Department of Energy



*Preliminary Agenda
New Frontiers of Science
DOE Fueling the Future of Nuclear Medicine
Hyatt Regency
575 Memorial Drive
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Monday, September 10

8:00 a.m. - 8:45 a.m. Continental Breakfast and Registration (Charles View Foyer)

Workshop (Charles View Ball Room)

8:45a.m. - 8:50a.m. Welcome, Introduction
Prem Srivastava, DOE

8:50a.m. - 9:00a.m. Opening Remarks & Expectations from Workshop
Michael Viola, DOE

Workshop Session I: Overview (Michael Viola, Session Chair)

9:00a.m. - 9:15a.m. *“PET’s role in bridging the disconnect: preclinical and clinical science”*
Nora D. Volkow, M.D., NIH/NIDA

9:15a.m. - 9:30a.m. *“Technical Challenges in Radiopharmaceuticals”*
Michael J. Welch, Ph.D., Washington University

9:30a.m. - 9:45a.m. *“DOE Funding of Tracer Development: High Risk, High Benefit Research, No Warranty Necessary”*
Mark Goodman, Ph.D., Emory University

9:45a.m. - 10:15a.m. Roundtable Discussion *“Overview Session”* (Discussion Leaders include Session Speakers, and Michael Viola)

10:15a.m. - 10:30a.m. Break

10:30a.m. - 10:45a.m. *“BERAC subcommittee on Radiopharmaceutical Research. Final recommendations”*
Steven M. Larson, M.D.

10:45a.m. - 11:00 a.m. Roundtable Discussion, *“BERAC Subcommittee Report”* (Discussion Leaders include Larson, Fowler, Welch, Derenzo, and Viola)

Workshop Session II: Radionuclide Chemistry (Robert Atcher and Prem Srivastava, *Co-Chairs*)

- 11:00a.m. - 11:10a.m. *“Is there a role for off-line isotope separators in the production of radionuclides for therapy?”*
Thomas J. Ruth, Ph.D., TRIUMF/UBC, Canada
- 11:10a.m. - 11:15a.m. *“Compact Accelerators for the Production of Positron-Emitting Isotopes”*
James P. O'Neil, Ph.D., LBNL
- 11:15a.m. - 11:20a.m. *“Radionuclide generators for future applications”*
Eugene Peterson, Ph.D., LANL
- 11:20a.m. - 11:25a.m. *“Isotopes and Nanoparticle Carriers for the Future of Nuclear Medicine”*
Leonard Mausner, Ph.D. BNL
- 11:25a.m. - 12:00p.m. Roundtable Discussion , *“Critically Important Radionuclide Chemistry Research Technologies for the Future”* (Discussion Leaders include: Session Speakers, Atcher and Srivastava)
- 12:00p.m. - 1:00p.m. Working Lunch
- Workshop Session III:** Radiopharmaceutical Chemistry (Prem Srivastava, *Session Chair*)
- 1:00p.m. - 1:05 p.m. *“Prospects and Challenges in Targeted Radionuclide Therapy”*
Wynn Volkert, Ph.D., U.MO. Columbia
- 1:05p.m. - 1:10 p.m. *“Actinium Radiopharmaceuticals”*
Jon Fitzsimmons, Ph.D., LANL
- 1:10p.m. - 1:15 p.m. *“Nanoparticles as carriers for imaging agents and therapeutics”*
Adam Randinone, Ph.D., ORNL
- 1:15p.m. - 1:45 p.m. Roundtable Discussion, *“Critically Important Radionuclide Chemistries Pushing the Limits of Radiopharmaceutical Research Technologies for the Future”* (Discussion Leaders include: Session Speakers, Prem Srivastava)
- 1:45p.m. - 1:50p.m. *“Arsenic radiopharmaceuticals”*
Robert W. Atcher, Ph.D., LANL
- 1:50p.m. – 1:55p.m. *“Expanding Radiopharmaceutical Opportunities through New Methods for Radiochemical Syntheses”*
Michael R. Kilbourn, Ph.D., U. MI, Ann Arbor
- 1:55p.m. - 2:00p.m. *“Challenges in Radiotracer Chemistry and Targeting”*
Joanna S. Fowler, Ph.D., BNL

- 2:00p.m. - 2:30p.m. Roundtable Discussion, “*PET Radiotracer Technologies for the Future*” (Discussion Leaders include: Session Speakers, and Prem Srivastava)
- 2:30p.m. - 2:45p.m. Break
- Workshop Session IV:** Special Presentations (Michael Welch and Kirk Frey, Co-Chairs)
- 2:45p.m. - 3:00p.m. “*Metabolome-directed nuclear imaging of cancer*”
Joseph Ippolito, M.D., Ph.D., Washington University
- 3:00p.m. - 3:15p.m. Roundtable Discussion
- 3:15p.m. - 3:30p.m. “*Human Scale PET MRI*”
Bruce Rosen, M.D., Ph.D., MGH
- 3:30p.m. - 3:45p.m. Roundtable Discussion
- Workshop Session V:** Summary of Radionuclide and Radiopharmaceutical Chemistry
- 3:45p.m. - 4:30 p.m. “First Day Presentations Summary Synthesis”
(Atcher, Fowler and Welch with First Day Speakers)

Tuesday, September 11

- 7:30a.m. - 8:30a.m. Continental Breakfast (Charles View Foyer)

Workshop Sessions (Charles View Ball Room)

- Workshop Session VI:** Overview (Peter Kirchner, Session Chair)

- 8:30a.m. - 8:45a.m. “*DOE Strengths and Opportunities in Nuclear Medical Imaging Instrumentation*”
William W. Moses, Ph.D., LBNL

- 8:45a.m. - 9:00a.m. Roundtable Discussion

- Workshop Session VII:** “New Detector Technologies” (Peter Kirchner and Dean Cole, Co-Chairs)

- 9:00a.m. - 9:10 a.m. “*DOE Strengths and Opportunities for Developing Improved Detector Materials for Nuclear Medical Imaging*”
Stephen E. Derenzo, Ph.D., LBNL

- 9:10a.m. - 9:15 a.m. “*Prospects for New Photodetectors and Scintillators in Nuclear Medicine*”
Kanai Shah, Ph.D., RMD, Watertown, MA

- 9:15a.m. - 9:20 a.m. *“High Resolution 3D Semiconductor Small Animal PET”*
Feng Zhang, Ph.D., U.MI, Ann Arbor
- 9:20a.m. - 9:25 a.m *“Silicon Photomultiplier Tubes: An Example of the Technical Role of DOE National Laboratories in the Implementation of New Detector Technology for Biomedical Imaging”*
Drew Weisenberger, Ph.D., T.J. Lab
- 9:25a.m. - 10:00a.m. Roundtable Discussion *“New Detector Technologies”* (Discussion Leaders include: Session Speakers, Peter Kirchner and Dean Cole)
- 10:00a.m. - 10:15a.m. Break
- Workshop Session VII:** *“New PET Technologies”* (Stephen Derenzo and Peter Kirchner, Co-chairs)
- 10:15a.m. - 10:20a.m. *“Research towards improved time-of-flight PET”*
Joel Karp, Ph.D., U. Penn.
- 10:20a.m. - 10:25a.m. *“Virtual Pinhole PET and Its Applications”*
Yuan-Chuan Tai, Ph.D., Washington University
- 10:25a.m. - 11:00a.m. Roundtable Discussion *“New PET Technologies”* (Discussion Leaders include: Session Speakers, Stephen Derenzo and Peter Kirchner)
- Workshop Session VIII:** *“New Multimodality Imaging Technologies,”* (William Moses and Dean Cole)
- 11:00a.m. - 11:05a.m. *“Prospects for SPECT/MR in small-animal imaging”*
Todd E. Peterson, Vanderbilt University
- 11:05 a.m. - 11:10a.m. *“Multi-modality Imaging and Probes”*
David Schlyer, Ph.D., BNL
- 11:10a.m. - 12:00p.m. Roundtable Discussion, *“New Multimodality Imaging Technologies”* (Discussion Leaders include: Session Speakers, William Moses and Dean Cole)
- 12:00p.m. - 1:30p.m. Working Lunch
- Workshop Session IX:** Special Presentation (Fritz Henn, BNL, Session Chair)
- 1:30p.m. - 1:40p.m *“The Future of Functional Neuroimaging”*
Robert H. Kraus, Jr., Ph.D., LANL
- 1:40p.m. - 1:55p.m. Roundtable Discussion
- Workshop Session X:** Summary of Instrumentation Sessions

1:55p.m. - 2:30p.m.

“2nd Day Presentations Summary Synthesis”
(Moses with 2nd Day Speakers)

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REPORT*

Needs in Basic Nuclear Imaging Research and Training

Applications of nuclear medicine have expanded steadily since the field began after World War II. Many of the developments in the field resulted from activity funded by the Department of Energy and predecessor agencies. Considering the state of medicine today, there are several areas of potential advancement that remain unexplored with the potential to improve the utility of imaging and targeted therapy in health care. These areas have basic science components necessary for the rapid translation of more nuclear imaging and therapy techniques to the clinic.

There are four broad areas where DOE needs to play a leadership role in order to advance the development of nuclear medicine technology and to improve research techniques and health care in the US. They draw on DOE's strengths at the interface of the physical and biological sciences that reside in no other place. These four areas are:

- Radionuclide Research
- Radiotracers and radiopharmaceutical chemistry
- Instrumentation
- Training the next generation of chemists and other imaging scientists

Radiochemistry

Maximizing Specific Activity of Radiotracers: One of the most striking advantages of nuclear medicine techniques, when compared to other imaging modalities such as magnetic resonance imaging or X-ray computed tomography, is the sensitivity of the technique. Radiolabeled probes can be detected at concentrations up to 1000-fold lower than those labeled with other contrast agents. In order to best utilize this capability, there are requirements that must be met. One of these requirements is to maximize the specific activity of the radionuclide that is used to radiolabel the probe of interest. In many cases, the biomarker under investigation is not present in high concentration. Thus, the potential for saturating the biomarker with unlabeled material is high. Development energy is required to design accelerator targetry that will optimize the specific activity of the radionuclide produced to enable the synthesis of clinically useful radiopharmaceuticals. This is a fundamental requirement for improving the utility of nuclear medicine imaging. To label biological molecules with the radionuclides currently available, new labeling techniques for the high yield incorporation of the radionuclides need to be developed. This includes advances in labeling with both organic and inorganic nuclides.

Another way to increase the specific activity of a radionuclide, and subsequently a radiopharmaceutical, is to utilize a radionuclide generator. In this approach, a radioactive isotope decays into a shorter lived daughter radioactive isotope. If handled properly, one minimizes or eliminates the introduction of any stable forms of the daughter isotope thereby maximizing the specific activity of the daughter. There are several examples of systems that require development that have potential for use in medical imaging and therapy.

SPECT Radiotracers: The advent of the hybrid imaging instrument (PET/CT, PET/MRI and SPECT/CT) has increased the information generated by imaging. Being able to combine anatomic information with metabolic, physiologic or other biologic information at the same time is invaluable. While the initial work in this area was done with PET imaging, the more recent introduction of single photon hybrid instruments has opened up new possibilities. In particular, there is a distinct advantage when imaging probes that have long lifetimes in vivo, such as monoclonal antibodies, to using a single photon emitter rather than a positron emitter for the study. Most critical is the reduced radiation dose to the patient. An added benefit is the larger number of radionuclides that are available for single photon imaging when compared with positron emitters. Continued research efforts should be applied to developing SPECT agents for imaging. The higher resolution of SPECT in small animal imaging is also a driver for continued development of these agents. The fact that the positron has a finite path length reduces the resolution of a PET agent in small animals, resulting in less clear images.

Advances in Labeling Chemistry: Continued interest in therapeutic applications of radionuclides also requires advances in labeling chemistry. There are several issues to address. First, the concept of the in vivo generator in which a long lived radionuclide decays into a short lived one with the desired therapeutic potential has become reality. The need for superior conjugation chemistry is clear as the need to hold two different radionuclides with different chemical characteristics. Another challenge is the radiation chemistry occurring in the final product. The degradation of the agent by radiation effects is an important consideration in the synthesis and storage of the final product. The problem can increase as the specific activity of the product increases which is critical if targeting a structure of low concentration.

Dosimetry: Finally, one challenge related to both imaging and therapy is determining the dosimetry of the therapeutic construct. Ideally, one would like to identify a radionuclide with ideal imaging characteristics for the dosimetry study that is of the same element as that used for therapy. Yttrium-86 as an imaging agent to study Y-90 dosimetry is one example that is currently being pursued. Given the current state of the art of both SPECT and PET imaging, one could use either a positron emitter or a single photon emitter for this purpose. As noted above, SPECT radionuclides that would be used for dosimetry of longer lifetime probes such as monoclonal antibodies would be preferable from the standpoint of the radiation dose to the patient for the imaging study.

Instrumentation

There are many unmet instrumentation needs in nuclear medical imaging. Although there are several large manufacturers of nuclear medical imaging instruments for clinical use, there are countless applications for specialized instruments that are beyond the current state of the art. Examples of such applications are imaging neurological development in children and imaging gene expression without genomic alterations. These instruments would be invaluable tools to investigators doing fundamental research, but the worldwide market for them would be relatively small, and so there is no commercial incentive to develop them. There are other types of instruments that may have potential in clinical applications (such as PET insert devices for locally enhancing images) but require extensive technical development before their value can be determined. Thus, it is reasonable to develop these tools using federal funds.

All potential instrumentation improvements require some combination of increased sensitivity (efficiency), increased spatial resolution, larger field of view, multi-modality imaging, and lower cost. Virtually all potential designs rely on the same fundamental components, which are

radiation sensors (scintillators, photodetectors, and solid-state detectors), electronics, and computational tools. It is often these fundamental detector components that limit the performance of current instruments. Many of these novel applications are not within the tolerable risk level for federal agencies such as NIH or poorly match NIH's funding mechanisms. They do lie within the mission of the DOE for the range of research it supports.

Algorithms that Improve the Quantitative Accuracy of Image Data: There is yet another important area of nuclear medical imaging that is often overlooked and under-funded. Nuclear medical imaging is considered the most practical way to bring molecular imaging to human applications. Many preclinical developments rely on quantitative accuracy of the images in order to test and establish biological models. Algorithms that improve the quantitative accuracy and image quality, whether they are for image reconstruction or corrections for physical attributes such as organ motion or differences in attenuation, are as important to the images as the instruments themselves. Yet, this type of research is often under funded by NIH. One example is that there are no widely accepted instruments nor algorithms for extracting blood input function from mouse imaging studies. This parameter is essential for quantification in preclinical imaging studies. Similarly, development of more sophisticated models where kinetic and binding parameters can be extracted is a key for quantification in nuclear medical imaging, yet it is probably one of the least funded areas. DOE can certainly contribute and direct the future of this physical research aimed at biological problems.

DOE has extensive expertise and unique capabilities in the development of these fundamental detector components which are cornerstones of both imaging and therapeutic applications. They are critical to many DOE programs, including subatomic particle physics, nuclear physics, and nuclear non-proliferation. The DOE supports research in an extensive infrastructure that develops these technologies. This, too, is a logical area for support which is within the DOE mission space.

Development of algorithms and modeling are often part of research conducted in DOE and academic labs where nuclear medical imaging researches take place. It is important to promote the continuous development of these important techniques. Even more important is to make these algorithms and models widely available to the entire nuclear medical imaging community.

Fundamental Components of Imaging Instruments: Given this background, the recommendation is that within the field of nuclear medical instrumentation research, DOE support should emphasize the development of fundamental components, which are radiation sensors (scintillators, photodetectors, and solid-state detectors), electronics, and computational tools. Detector module and camera development needs additional funding particularly for projects that are on a larger scale and higher level of complexity than NIH typically supports. Academic and national lab researchers that have similar goals (through a competitive system and preferably to form regional centers of excellence) and industry (through the SBIR program) should be funded in this area. For algorithms and modeling development, funding can be used to support core development groups in these areas with the understanding that results need to be shared with the nuclear medical imaging community using a system similar to that developed by NIH for research it funds. It is also noted that DOE has played a major role in training young people in the skills necessary to do nuclear medical imaging (instrumentation and algorithms development), and that this should continue to be a priority.

Recommendations

Funding of Centers of Excellence: One important way to address all the areas of research discussed above is to establish regional centers of excellence to carry out the interdisciplinary basic science; a core of individuals with different scientific backgrounds need to work together. These centers of excellence would have state of the art facilities with research in physics, chemistry, biology, imaging, mathematics, instrumentation, and nanomaterials. As recommended in a recent NAS report, coordination between DOE and NIH programs that utilize nuclear medicine would ensure that there is translation from the DOE funded research and clinical applications. These centers would carry out translational research where basic advances in instrumentation and radiochemistry could be demonstrated in limited preclinical studies. The centers would cover a broad spectrum of disciplines and it is critical that there be a strong collaboration with biological areas. Research centers are needed where quantification is important and given high priority. The future of nuclear imaging lies in part in the ability to quantify results and use these numbers to make diagnoses, to plan and evaluate radionuclide therapies and to promote new clinical evaluations.

The future of nuclear imaging also relies in part on the cross-disciplinary training that can be given to the next generation of scientists in such centers. Thus, a critical part of these centers would be training programs in radionuclide production, radiochemistry, radiotracer development and design, instrumentation development including advanced detectors, electronics and software for image analysis, scanner development including multimodality imaging, and image data quantification. All of these are very important areas for future diagnostic and therapeutic applications of radiopharmaceuticals.

A master plan needs to be developed to foster more optimal development of radiotracers for biological research. The minimal core for a center of excellence would be a facility for radiotracer development including a staff of organic, inorganic and medicinal chemists, a facility where SPECT and PET scans can be done with an emphasis on quantification and access to a biologic research or medical facility where ideas for new tracers may be spawned.

*“Report prepared by Michael Welch, Robert Atcher, William Moses, Dave Schlyer and Joanna Fowler,” October 22, 2007.