WORKSHOP WHITE PAPER (FINAL DRAFT 12-20-07)

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OVERVIEW

The New Mexico Center for Isotopes and Medicine (NMCIM), in partnership with the UNM Cancer Research and Treatment Center (CRTC) and the Los Alamos National Laboratory Isotope Production Facility (IPF), recently hosted the "New Mexico Isotopes and Imaging Workshop." The workshop was held at the Embassy Suites Hotel and Conference Center in Albuquerque and was attended by 100 of the top isotopes and imaging scientists in the United States, along with medical residents, graduate and PharmD students. A major grant from the New Mexico Consortium's (NMC) Institute of Advanced Studies (IAS) and a gift from GE Healthcare supported the workshop.

The workshop was organized by Dr. Scott Burchiel, director of NMCIM and professor at the UNM College of Pharmacy, and by Dr. Robert Atcher, a scientist at LANL and a UNM-LANL professor in Radiopharmacy. Representatives of Congresswoman Heather Wilson and Stephan Helgesen, a key adviser for Governor Richardson's office of economic development, also attended the workshop.

The purpose of the work was to bring together collaborators and future partners of NMCIM, including GE Healthcare, Molecular Insights Pharma, Bioscan, Advanced Molecular Imaging/Gamma Medica, Genetech, Pfizer, IBA, Avid Pharma, Cell Cyte and others. Scientists from several University of California campuses that have institute affiliations with LANL (UCSD, UC Davis, UC Santa Barbara) and Dr. Henry van Brocklin from UCSF also attended the workshop. Two internationally renowned scientists, Dr. Bill Eckelman (UCSD Dept of Radiology) and Dr. Michael Welch (Washington University St Louis) gave keynote addresses.

Two consensus issues emerged from the workshop:

1. **There are many new opportunities to develop novel radiopharmaceuticals and cancer therapeutics. There needs to be renewed investment in the development of medically useful radiotracers for imaging and therapeutic applications.**

2. **In the U.S. and elsewhere in the world, there is an inadequate pipeline of qualified technicians and professionals to meet future needs for medical isotope production, research, and development. There needs to be a renewed commitment to the training of workers, scientists, and clinicians in the area of medical isotopes production and Research and development leading to new nuclear imaging and therapeutic agents.**

WELCOME AND INTRODUCTION TO WORKSHOP

SCOTT W. BURCHIEL, PHD, PROFESSOR AND ASSOCIATE VP FOR ADVANCED STUDIES, UNM IAS LEADER, DIRECTOR NM CENTER FOR ISOTOPES IN MEDICINE

ROBERT ATCHER, PHD, MBA, SENIOR STAFF MEMBER LOS ALAMOS NATIONAL LABORATORY, UNM LANL PROFESSOR OF RADIOPHARMACY, LEADER, IAS EMERGING MEDICAL TECHNOLOGIES

"WHO WE ARE" [NOTE: ATTENDEES COMPLETE LISTING IN APPENDIX 2]

- New Mexico Consortium (NMC) Institute of Advanced Studies (IAS) -UNM (COP, CRTC, SOM, UNMH), NMT, NMSU; faculty, staff, students (undergrads, grad, post docs, residents), admin
- Los Alamos National Laboratory – Director's Office, Institutes, Chemistry Div, Biosciences Div, Physics Division
- Academic Partners and Invited Speakers (U Arizona, UCD, UCSB, UCSD, UCSF, U Missouri, Emory, Washington U St Louis)
- Industry Partners and Attendees- GE Healthcare, Advanced Molecular Imaging, Bioscan, Molecular Insights Pharma, Genentech, Avid Radiopharmaceuticals, Pfizer, IBA, Cell Cyte, Radiochemistry Solutions, Gamma Medica, Biotage
- NM State Government - Gov's Office of Science and Tech, Office of Economic Development
- Federal Government – 1st Congressional District Office (Wilson) and DOE

WORKSHOP GOALS

Goal 1: To identify needs for medical isotope production and radiopharmaceutical development to support cancer imaging and therapy

Goal 2: To build collaborations between UNM, LANL, IAS, and various academic and industrial partners in radiopharmaceutical development, preclinical, and clinical imaging and radiotherapy

Goal 3: To define a process for strategic planning to take advantage of unique opportunities

PROGRAM EXERPTS AND HIGHLIGHTS

CHERYL WILMAN, MD – THE MAURICE AND MARGUERITE LIBERMAN CHAIR IN CANCER RESEARCH, PROFESSOR OF MEDICINE AND PATHOLOGY, DIRECTOR AND CEO, UNM CANCER RESEARCH & TREATMENT CENTER

TITLE: "UNM CANCER CENTER VISION FOR THE WORKSHOP"

The University of New Mexico Cancer Research & Treatment Center

- **The Official Cancer Center of the State of New Mexico**
- **A National Cancer Institute-Designated Center**

"Delivering State of the Art Patient Care and Community Outreach Through World Class Research"

MISSION – REQUIREMENTS OF NCI CENTERS

- To assure that *all* New Mexicans have access to world-class cancer treatment and benefit from advances in cancer research.

- *The University of New Mexico Cancer Center will* provide outstanding, expert, multidisciplinary cancer treatment; conduct world-class research to discover the causes and the cures for cancer, particularly those affecting New Mexicans; train the next generation of cancer healthcare professionals; and overcome New Mexico's significant cancer health disparities through community-based outreach programs.

GOALS : RESEARCH

1. To conduct world-class cancer research in our laboratories, clinics, and communities by building on unique institutional strengths and partnerships with the Lovelace Respiratory Research Institute, Sandia and Los Alamos National Laboratories, New Mexico's Universities, and industry.

110 Program Members Supported by Over $50 Million in Annual Funding From Federal, Private, and Industry Sources

2. To determine the genetic, environmental, social, and behavioral factors which contribute to the distinct patterns of cancer incidence and mortality in the multiethnic populations of New Mexico.

Research Partnerships with Sandia National Labs

- <u>High Performance Computing</u>: UNM/Sandia Center for Spatiotemporal modeling; Molecular modeling & drug design; Computational analysis of large genomic datasets
- <u>Nanoprobes and Sensors</u>: Ceramic Fluorescence Nanoprobes; Biologic Ligand-based Biosensors; Integrated Networks of Sensors; Titanium-based Nanotherapies
- <u>Innovative Imaging</u>: Dynamic Modeling of Membranes AFM imaging

Discovery: Novel Breast Cancer Target

- GPR30: A new type of estrogen receptor recently identified and characterized at the UNM CRTC in collaboration with NMSU (Prossnitz, Arterburn, Sklar, Leslie); *Science 307:1625; March 11, 2005*

New Cancer Drugs: The NM Libraries Screening Center

- GPR30: Using novel cheminformatic and high throughput flow cytometric screening technologies at the UNM
- CRTC Molecular Libraries Screening Center, a new drug to GPR30 was recently discovered (Prossnitz, Sklar, Arterburn, Oprea), *Nature Chem Bio 2(4):207; April, 2006*

New Imaging Agents and Radiotherapeutics: New Mexico Center for Isotopes in Medicine

- Partnership with the UNM College of Pharmacy and the Los Alamos National Lab

New Cancer Center: $90M; 190,000 Sq. Ft.; 5 Stories Completion: 2/2009

- Radiation Oncology
- Radiosurgery
- Cyclotron
- Radiopharmacy
- Research Space
- First Floor: State of the Art Cancer Imaging Suite
- North: Room for Medium Range Cyclotron Expansion

UNM CRTC Goals for the Workshop

- To develop a collaborative model between UNM, other Academic Institutions / NCI Cancer Centers, DOE Laboratories, and Industry to translate novel isotopes into cancer imaging and therapeutic agents
- To identify specific isotopes for focused development
- Future Goals:
- To develop an integrated research program spanning from novel isotope development to animal modeling and imaging to human testing in clinical trials
- To identify commercial partners for continued program development
- To identify joint funding sources for continued program development

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MARY NEU, PHD – ASSOCIATE DIRECTOR FOR CHEMISTRY, LIFE, AND EARTH SCIENCES

TITLE: "LOS ALAMOS ISOTOPE PRODUCTION FACILITY AND PLANS"

Isotope science has been, is, and will be an important part of LANL's mission

- Building upon history of production and research.
- Supported by unique expertise, facilities, and capabilities.
- Committed to isotope science, technology and applications.

Our vision is to serve the nation through our core national security mission and emerging mission areas, including energy and health security.

- The new $23 M 100 MeV Isotope Production Facility (IPF) at the Los Alamos Neutron Science Center (LANSCE)
- The TA-48, RC-1 hot cell facility (for 100 MeV IPF irradiated targets).
- The newly proposed 800 MeV Materials Test Station (MTS) at LANSCE.
- The CMR, wing-9 hot cell facility (for MTS irradiated targets)
- The TA-50 and TA-54 radioactive liquid and solid waste handling facilities Isotope production and distribution
- Research isotope revitalization
- Synthesis, characterization, and evaluation of radio-pharmaceutical molecules
- New Mexico Center for Isotopes in Medicine in collaboration with UNM and UC
- Industry partnerships for isotope production and R&D
- Isotope availability for national security and homeland defense programs.

LANL goals for the Workshop build on these

- Achieve better understanding of how LANL's current capabilities meet current needs locally/nationally. Identify gaps and develop strategy for the future.
- Strengthen existing partnerships within NMCIM network. Build bridges in the medical community regionally and nationally.
- Identify new opportunities that capitalize on LANL's strengths in production, research, and distribution.
- Look to new opportunities, paradigms. Develop facilities that can address current production gaps?

<u>KEYNOTE SPEAKER:</u> BILL ECKELMAN, PHD, ADJUNCT PROFESSOR, UNIVERSITY OF CALIFORNIA AT SAN DIEGO, DEPT OF RADIOLOGY

TITLE: "LINKING TARGETED IMAGING TO PHARMACEUTICAL DEVELOPMENT AND CLINICAL IMPACT"

New Mexico Isotopes and Imaging Workshop
Goal 1: To identify needs for … radiopharmaceutical development to support cancer imaging and therapy

Application of Imaging to Drug Discovery and Development

Why is Targeted Imaging becoming more important in Drug Development?

- As the pharmaceutical industry turns to targeted drugs, targeted imaging is well positioned to "biomark" the drug potential.
- Target identification is dependent upon clinical research, i.e., "humanomics" should be the approach of choice.

Radiotracers Have an Advantage in Targeted Imaging, especially for Low Density Sites (<20 nM)

Molecular Probe Design
• Develop Molecular Imaging Probes that target a protein that changes early in the disease.
• Develop molecular tracers that are based on a reductionist concept where the drug-organism interplay can be reduced to a drug-target interplay.
• Within or in collaborate with the pharmaceutical and radiopharmaceutical companies.

Drivers for Targeted Imaging
• Expansion of SPECT/CT complementing the continued expansion of PET/CT.
• Development of the parallel field of small animal imaging.
• The pharmaceutical company's need to increase their success rate from 17% for established targets and 3% for post-genomic targets.
• The FDA's need to encourage biomarker development, especially for human use.

Magnitude of the opportunities
• Failures in Phase II or Phase III are often due to newly identified toxicity or absence of targeting.

• 2000 drugs have failed to target sufficiently and are accumulating at a rate of 150-200 per year.

Efficient “Molecular Targeting” Discovery & Development

• Streamlining drug discovery: finding the right drug against the right target to treat the right disease.
• For Targeted Imaging probes: finding the right molecular probe against the right target to monitor the right disease.

A Major Challenge: Measuring Targeting with Imaging for targets of differing density

•In Vitro B/F = Bmax/Ki
Imaging requires B/F ratio ~3, Drugs do not
• High Specific Activity

Cancer is not a single gene disease, yet …..

• Imatinib (Gleevec)-effective in GIST and CML. Mutants appeared, but further TK inhibitors have high affinity for all mutants.
• Trastuzumab (Herceptin)-best in high expressors of HER2.
• Gefitinib (Iressa)-EGFR TK.
    – Shrinks tumor, but no change in survival in NSCLC. Population specific.
    – Erlotinib (Tarceva) & Cetuximab (Erbitux)-MAb (DDT 2004:9:1042-1044 Golsteyn RM. DDT 2005 10(6):381)

Targeting Proteins: The Magic Bullet

- Paul Ehrlich used the English expression “magic bullet” for the first time in his Harben Lectures.
- The German word “Zauberkugel” appears earlier in his thoughts and publications, based on his view of “sidechains”, the precursor of our concept of receptors, and on the desirable property of drugs that must not harm the host, but attach the parasitic invader.

(Royal Institute of Public Health (London:Lewis, 1908), Experimental Researches on Specific therapy. On immunity with special references to the relationship between distribution and action of antigens, 107.)

The Magic Bullet without imaging & a target

• Ehrlich’s first magic bullet was Salvarsan or arsphenamine, discovered in 1909, which provided the only cure for syphilis.
• Ehrlich also thought of attaching toxins to antibodies whereby the antibody would carry the deadly freight to the site of the invading parasite. His idea lives on in the development of immunotoxins.

The Target Space

Enzyme/Receptor Targeting

- How many radiotracers have changed clinical care?
- How many have been used in the development of pharmaceuticals?

Continuum of Cancer Intervention - Can radiopharmaceuticals help?

- Disease Recurrence
- Response to Therapy
- Tumor Characterization & Disease Prognosis

- Detection & Localization
- Serum biomarkers Whole Body Imaging
- Risk Assessment (personalized medicine)
- Genomics Proteomics Imaging
- Non-invasive screening for early disease, no symptoms
- Health burden, high sensitivity & specificity, low cost

(Hartwell, Mankoff, Paulovich et al. Nature Biotech 2006)

Imaging & "Molecular Targeting"
• Interactions between a probe and a protein target using pre-genomic techniques.
    – "Biochemical probes" such as iodide (~50 years), receptor binding radiotracers and monoclonal antibodies (~25 years) from autopsy, linkage and drug efficacy, etc.
• Interactions between a probe and a protein target using post-genomic techniques.
    – Molecular biology, proteomics, genomics, antisense, reporter genes, protein-protein interactions. More targets (500 2000-3000)

Sensitivity/Identifiability for Drug Changes
- Measuring endogenous transmitter changes

Targeted Drugs and Targeted Imaging
• Trastuzumab for HER2 (aka ErbB2 & Neu)
    – A cell surface glycoprotein with TK activity
    – HER2 amplification/over-expression is predictive for response in breast cancer.
    – Overexpression became an entry criteria and higher objective response was related to level of
    overexpression.

Imaging HER2 Receptor in response to HSp90 Inhibitors
• 17-allylaminogeldanamycin (17-AAG) is the first Hsp90 inhibitor to be tested in a clinical trial.
• 17-AAG induces proteasomal degradation of
HER2 by binding to Hsp90 chaperone protein.
• Image Ga-68 with the F(ab')2 of the anti-HER2 antibody Herceptin.

Smith-Jones et al. Nat Biotech 2004

Herceptin after surgical resection of primary breast cancer
• For those eligible for Herceptin treatment, the use of Herceptin after std. chemotherapy reduces the risk of recurrence by 52%.
• Trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women with surgically removed HER2-positive breast cancer.

(N Engl J Med 2005:353:1659-1672 & 1673-1684.)

Detection and Localization - Carl Hoh of UCSD on FDG:
1. Are there competing tests?
2. Is there a cost effective role in the clinical management?
3. Is the interpretation of the imaging study easy?

• Conclusion: whole body imaging on melanoma re- occurrence meets these criteria.

Biomarkers

• General Properties that lead to drug resistance.
  – Hypoxia
  – Drug efflux transporter (MDR, etc)
  – Liver metabolism

Current Individualized Medicine

•Metastatic pheochromocytoma (Pheo) can be detected using [123I]MIBG or [131I]MIBG prior to therapy with [131I]MIBG.
  – The mechanism of localization is based on the neuroendocrine character of this disease.

•Up to 73% of Pheo cells in vitro express somatostatin receptors so patients with Pheo have been assessed using somatostatin receptor imaging and therapy.

Current Individualized Medicine Protecting Normal Tissue

• The American College of Radiology has recently set practice guidelines for [90Y]ibritumomab tiuxetan (Zevalin) and [131I]tositumomab (Bexxar)
• Approved by the FDA for radioimmunotherapy of non-Hodgkin's lymphoma.
• A preliminary imaging studies to determine dosimetry or assess biodistribution is required before the radiotherapeutic is administered.

Targeted Drugs Targeted Imaging

• Imatinib is an inhibitor of BCR-ABL TK.
• The Philadelphia chromosome and BCR-ABL have prognostic significance for chronic myeloid leukemia (CML).
• Also, inhibits TK of the oncogene c-KIT in GIST.
• Imatinib-resistant mutants led to BMS 354825.

Targeted Drugs and Targeted Imaging

• The EGF receptor is overexpressed in many cancers.
• Both TK inhibitors, e.g., gefitinib & erlotinib and the antibody cetuximab have been studied.
• Gefitinib was studied in NSCLC
– Shrinks tumor, but no change in survival in NSCLC. Population specific.
• Glucose metabolic activity closely reflects response to gefitinib therapy. FDG-PET may be a valuable clinical predictor, early in the course of treatment, for therapeutic responses to EGFR kinase inhibitors (Su et al. 2006).

(Golsteyn RM. DDT 2005 10(6):381.)

Relationship of FDG to TK inhibition?

• Immunoblots showed the translocation of glucose transporters (GLUT3) from the plasma membrane to the cytosol; glucose transport rates were reduced 2.6-fold at this time. There was also a modest reduction of hexokinase activity. Su et al. (J Nucl Med 2006.)
• Consistent with tumour-specific reduction in FDG uptake on PET, a striking reduction in Glut1 staining intensity was observed in CI-1033-treated tumour sections compared to controls.

(Dorow et al. EJNM 2006.)

Goal: To identify needs for radiopharmaceutical development

• Ideal Properties of a Targeted Radiotracer
  – In vitro In vivo & high specific activity

• Source of Leads: pre or post genomic era.
• Develop molecular tracers that are based on a reductionist concept
• Goal of Clinical Impact.
    – Non-invasive screening
    – Risk Assessment
    – Detection & Localization
    – Disease Prognosis
    – Response to Therapy
    – Disease Recurrence

JOHN PANTALEO, PHD, PROGRAM DIRECTOR ISOTOPE PROGRAM, OFFICE OF NUCLEAR ENERGY

TITLE: OVERVIEW OF THE DEPARTMENT OF ENERGY'S ISOTOPE PRODUCTION CAPABILITIES

Mission

- The **Isotope Program** produces and sells radioactive and stable isotopes, byproducts, surplus materials, and related isotope services worldwide.
- **Annual appropriation** is used to maintain critical nuclear facilities in a safe, environmentally compliant and cost-effective manner to assure continued reliable isotope production. No Radiological Facilities Management funds are expended on the development or production of isotopes.
- DOE has unique facilities, such as large reactors, accelerators, and isotope processing hot cells, not available elsewhere.
- DOE is the only source for many of these isotopes used for medical, national security, and industrial applications

Program Background

- Since the 1940's, substantial dependency has been built around the use of DOE isotopes. Authority: Atomic Energy Act of 1954.
- In 1989, the Department requested and Congress established the Isotope Program as a single point at DOE headquarters for oversight of the Department's isotope activities.
- Public Law 101-101, as modified by Public Law 103-316 created the Isotope Production and Distribution Program Fund (a revolving fund) and allow prices charged for products and services to be based on production costs, market value, U.S. research needs and other factors.
- The annual appropriation and revenues from isotope sales are deposited in the fund. Isotopes are priced such that the research customers pay cost of production and commercial isotopes are sold at full-cost recovery.

Short Term Goals

To meet the growing isotope demand, the Isotope Program will:

- Continue to maintain isotope processing facilities;
- Revise procedures to meet the FDA's requirements for current Good Manufacturing
- Practices (CGMP) needed for the processing of medical isotopes at BNL, LANL, and ORNL;
- Work with MURR and other private sector isotope producers to increase research isotope availability;
- Develop at least two new isotope processing techniques as requested by researchers;

- Enhance target design to improve yields and radio purity;
- Continue to import irradiated targets from foreign suppliers to enhance supply;
- Continue sales from large inventories – stable isotopes, long-lived radioisotopes such as curium-244; and
- Address the recommendations of the National Institutes of Health study on the "State of Nuclear Medicine".

Long Term Goals

- For the long term, the Isotope Program will:
- Upgrade or expand isotope production capability to support year round availability of short-lived isotopes;
- Continue to work with other private sector isotope producers to increase research isotope availability and commercialize DOE isotope production/activities;
- Seek to replenish long-lived radioisotope and stable isotope inventory where needed;
- Develop backup supply agreements with other isotope suppliers;
- Upgrade or expand current facilities and processing capacity; and
- Purchase needed equipment including shipping containers.

Brookhaven Linac Isotope Producer (BLIP)
Brookhaven National Laboratory

Major Medical Isotopes and Their Applications

- Copper-67 Antibody labeling for cancer therapy
- Germanium-68 Calibration sources for Positron Emission Tomography equipment, antibody labeling
- Strontium-82/ Cardiac imaging
- Rubidium-82
- Advantages of BLIP for isotope production
- High energy beam with flexible access
- Well-equipped hot cell facility
- Target insertion and retrieval

Isotope Production Facility (IPF) Los Alamos- Medical Isotopes and Their Applications

- Germanium-68 Calibration sources for Positron Emission
- Tomography equipment, antibody labeling
- Arsenic-73 Biomedical Tracer for Arsenic Uptake
- Strontium-82/ Cardiac imaging
- Rubidium-82
- Advantages of IPF for isotope production
- High energy beam – not available in the private sector State-of-the-art facility – target insertion and retrieval
- Well-equipped and staffed Hot Cell Facility
- Available 30-40 weeks per year
- Will enhance short-lived isotope supply

High Flux Isotope Reactor (HFIR) *Oak Ridge National Laboratory*
Medical Isotopes and Their Applications

- Californium-252 Cancer therapy
- Nickel-63 Gas sensing devices
- Tungsten-188/Rhenium-188 Prevention of arterial restenosis, Bone pain from cancer
- Selenium-75 GAMMA Radiography sources

- Advantages of HFIR for isotope production
- High neutron concentration
- Easy access through hydraulic tubes
- Several hot cell facilities

Future

- o Capacity exists to produce many more isotopes
- o Chemical and Materials Laboratories

Oak Ridge National Laboratory- Stable Isotope Services

- o Chemical physical forms Metal and ceramic powder Pyrochemical conversion – Wire rolling/swaging oxides to high purity metal (hot or cold)
- o Drop casting Target fabrication
- o These laboratories are available to provide unique stable services and dispense over 200 different isotopes in a wide variety of chemical and physical forms.

A Few Key Isotopes Shipped

- Californium-252 2.645 yr alpha .02 Ci Reactor Neutron sources
- cancer therapy
- Cadmium-109 32.2 yr gamma 27 Ci Both reactor X-ray instrument
- accelerator calibration
- Cobalt-60 5.27 yr gamma 10.8 Ci Reactor Sterilization
- Strontium-82 25-day positron 5.41 Ci Accelerator Cardiac imaging
- Tungsten-188 69-day beta-gamma 5.41 Ci Reactor Cancer treatment
- Germanium-68 271-day positron 8.11 Ci Accelerator PET calibration

Isotope Newsletter

- The Isotope Newsletter will be reestablished in 2007 as a form to communicate the Department of Energy's isotope activities along with activities of the isotope community.
- We encourage you to submit articles on your isotope activities, upcoming events, regulatory changes, or any related newsworthy items regarding the use or application of isotopes.
- www.ornl.gov/isotopes/catalog.html

For Isotope Information

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WYNN A. VOLKERT, PH.D, DIRECTOR, RADIOPHARMACEUTICAL SCIENCES INSTITUTE, PROFESSOR [EMERITUS] OF RADIOLOGY, UNIVERSITY OF MISSOURI, COLUMBIA, MISSOURI

TITLE: "UTILIZATION OF RADIOMETALS FOR SPECT IMAGING AND TARGETED THERAPEUTIC APPLICATIONS"

SPECT Imaging in Cancer Applications

Three general uses of single photon emitting radionuclide labeled biomolecules for SPECT.

- For purely diagnostic applications
- As surrogates for targeted radiotherapeutic radionuclides that have low or no imagable photons
- For imaging the therapeutic radionuclide, itself, that emits sufficient levels of imagable protons in addition to the particulate emissions.

SPECT Radionuclides Readily Available for Formulation of Cancer Specific Radiolabeled Biomolecules

- Relatively few radionuclides for routine use in human SPECT imaging are available as FDA approved reagents (e.g., 99mTc, 111In, 123I and 261Tl).
- The two most widely used to formulate most molecular imaging agents are 99mTc and 111In. The chemical properties of the radiometals are not similar and require different synthetic approaches for preparation of radiolabeled bioconjugates.

99mTc/186/188Re "Matched Pairs"

- 99mTc can be used effectively as a surrogate for 188Re.
- The 99mTc- and 188Re-chelation chemistry and geometry often correspond well.
- Depending upon the chelator structure and the Tc and Re oxidation states and cores, chelation chemistry may not be the same.
- For example, Re is more susceptible to oxidation to ReO-4, leading to some 188Re-complexes with lower *in vivo* stability than the corresponding 99mTc-complexes

Tc/Re(I) Tricarbonyls

- Pioneered by the work of R. Alberto, and co-workers.
- Produce six-coordinate complexes containing the fac-M(CO)3 core [M= Tc and Re] that are kinetically inert, low-spin, d6 complexes.
- Radiochemical syntheses of the [99mTc(CO)3(OH2)3]+ synthon is straight-forward via a commercial kit.

ISOLINK

- First Kit for the Preparation of [99mTc(H2O)3(CO)3]+
- Utilizes Na2/K2[H3BCO2] as a source of reducing agent and CO to minimize risks to radiation worker or technician during formulation of the 99mTc-precursor (i.e., No toxic, gaseous CO is used; presence of highly reactive reducing agents not an issue).
- Available as <u>Isolink</u> from Covidien

111In is often used as a pseudo-surrogate for several therapeutic radiometals, including 90Y, radiolanthanides (e.g., 149Pm, 177Lu and 166Ho), and other radiometals

- 111In does not have the same chelation chemistry or geometry as these other radiometals. Thus, the physico-chemical properties of the respective radiometalled chelate moiety may be sufficiently different to create substantial alternatives in the tumor uptake/retention and pharmacokinetics of the radiolabeled bioconjugate. As with 111In, 68Ga may also not be an optimal surrogate for radiometals used for TRT

Pre-targeting Strategies for Molecular Imaging and TRT Applications

- Pioneered by C. Meares and D. Goodwin. Recent work by C. Meares et al., demonstrates the potential for using small radiometal chelate moieties as the imaging or TRT radiotracers.

- A novel example of using phage conjugates in a pre-targeting approach being studied by S. Deutscher, et al. is outlined on the following slides.

Retention and Clearance of Radioactivity from Tumors and Normal Tissues/Organs is a Major Issue Requiring Increased Research Emphasis

- SPECT imaging following *in vivo* administration of radiometal bioconjugates is effective in providing critical information about the pharmacokinetics and retention characteristics.
- Efficient clearance from the blood and normal tissues (e.g., kidneys) is important, particularly for TRT.
- Long-term retention of radioactivity in the tumor relative to normal tissues maximizes diagnostic and therapeutic efficacy.

Conclusions

- SPECT imaging of existing and new radiolabeled cancer specific molecular imaging radiotracers is and will continue to play an important role in diagnostic applications in human cancer patients.
- Single photon emitting radiometals make invaluable contributions in the development and applications of targeted radiotherapeutic (TRT) radiopharmaceuticals. For example, SPECT imaging radionuclides can be utilized:
  - As diagnostic surrogates/analogs for the corresponding TRT agents in basic and applied research studies.
  - For performing radiation dosimetry in animal and patient specific translational research, clinical trials and clinical applications of TRT radiotracers.

MARK M. GOODMAN, PHD, DEPARTMENT OF RADIOLOGY, DEPARTMENT OF HEMATOLOGY AND ONCOLOGY, DEPARTMENT OF PSYCHIATRY, EMORY UNIVERSITY, ATLANTA, GA

TITLE: FLUORINE-18 RADIOPHARMACEUTICALS FOR CANCER IMAGING

Emission Tomography Permits Noninvasive Quantitative Imaging of Tissues

- Amenable to repeated measurements
- Can probe different biochemical pathways in tumor masses using appropriate radiotracer
- Radiosynthetic methods are available for preparation a appropriate metabolic radiotracer

Radionuclidicand Chemical Properties Make 18F the Most Attractive Radioisotope for the Development of Tracers for PET Imaging

- 110 Minute half half-life to follow kinetics to equilibrium
- Lowest energy ββ++--emitter (2emitter 2--4mm range)
- Available in curie amounts as F F- by 18 18O(p,n) O(18 18F with F low energy (12 MeV MeV) cyclotrons
- Theoretical 1700 Ci per μμmole high specific activitymole activity
- Metabolically stable carbon fluorine bond
- Fluorine is a bioisostere for H or OH

F-18 FDG is the Most Widely Used Agent for Imaging Tumors with PET

- Retention is function of :Glucose transportGlucose transport
- Glucose metabolism by hexokinasehexokinase
- Degree of uptake is function of :Increased nonoxidativenonoxidativeglycolysisglyco

FDG Has Been Shown to Be Useful in the Diagnosis of Several Types of Cancer

- Lymphoma
- Lung
- Breast
- Colorectal

F-18 FDG Tumor Imaging Has Certain Limitations

- FDG images confounded by factors that increase glycolysis
- Tissue hypoxia
- Infiltration of inflammatory cells
- FDG images of brain tumors difficult to interpret
- High metabolic activity in surrounding brain tissue
- Results in relatively " low low" tumor to brain ratios (contrast)
- High levels of urinary excretion makes very difficult tumor visualization of the
- Kidney
- Ureter
- Bladder
- Pelvis

A Number of Fluorine-18 Agents Have Been Developed to Compliment 2-FDG in Tumor Diagnosis and to Predict and Monitor Response to Therapy

- Amino Acids
- Protein synthesis
- Transport
- Nucleosides
- Cell proliferation
- DNA synthesis
- Nitroimidazoles
- Hypoxia
- Steroids
- Receptor expression
- Choline
- Phosphatidylcholine synthesis

This Presentation Will Focus on Some Promising [18F] Tumor Imaging Agents

- Amino Acids
- 1-Amino Amino-3-[18 18F]fluorocyclobutane F]fluorocyclobutane-1-carboxylic acid (FACBC)
- Nucleosides
- 3'-deoxy deoxy-3' -[18 18F]fluorothymidine (FLT)
- Nitroimidazoles
- FMISO
- FAZA
- Steroids
- FES
- FDHT
- Choline analogs
- [18 18F]Fluoromethyldimethyl F]Fluoromethyldimethyl-(2 (2-hydroxyethyl)ammonium chloride (FCH)

RadiolabeledSynthetic Non-Naturally Occurring Amino Acids Will Be Better Than 2-18FDG for Imaging Human Tumors

- Kinetic studies indicate that transport not protein synthesis is the dominant tumor accumulation process
- Not metabolized or incorporated into protein
- No or few radiolabeled metabolites to confound image
- Low background of radioactivity

[18F]FACBC: Mechanism of Action

- Amino acids enter cells via specific membrane carrier proteins
- A-type amino acid transport
- Transports small neutral amino acids (e.g. alanine)
- Na Na+ and energy dependent
- Not present at normal blood blood-brain barrier
- L-type amino acid transport
- Transports large neutral amino acids (e.g. leucine)
- Na Na+ and energy independent
- Active at normal brain barrier

Studies in human tumor cells demonstrate that anti anti-[18 18F]FACBC F]has L L-type transporter specificity

- Both A A- and L L-types of transport are upregulated in tumor cells
- Ideal Characteristics of a Nucleoside Tumor Imaging Agent
- Rapidly incorporated into DNA
- Unidirectional capture by DNA synthetic pathway to provide relative measure of cell proliferation
- Minimal generation of labeled metabolites
- Uptake and retention in tumor after successful therapy declines more rapidly than FDG

Recent Studies Have Shown That 3'-deoxy-3'-fluorothymidine (FLT) Is a Promising Nucleoside for Measuring Cell Proliferation

- FLT is phosphorylated by the enzyme TK1 to FLT monophosphate and trapped in cells
- TK1 activity increases 10 10-fold in cellular DNA synthesis

Why F-18 Nitroimidazoles?

- A variety of tumors show oxygen deficiency (hypoxia)
- Rapid growth
- Insufficient angiogenesis
- Hypoxia accelerates malignant progression of primary tumors
- Hypoxia provides signaling pathways (HIF-1α) for tumor cells to increase growth and survival
- Resistance to anticancer drugs and radiotherapy

Why F-18 Steroids?

- All prostate and breast cancers show evidence of steroidal gene expression
- Prostate –androgen receptor
- Breast –estrogen receptor (ER) and progesterone (PR)
- Status of AR and ER are important prognosis factors
- ER positive tumors are less aggressive and respond to hormonal therapy
- Develop probes to assess steroid receptor expression and functionality

- Assess treatments that target AR and ER

Why F-18 Fluorocholine?

- Certain tumors show increased levels of phosphatidylcholine a biosynthetic product of choline
- In 1997-1998, Hara et al., reported C-11 cholinePET imaging of prostate cancer, bone cancer and brain tumors
- An F-18 radiolabel is needed for widespread use in clinical PET
- [18F]fluoromethylcholine (FCH) may be a close mimic of C-11 choline (DeGradoet al., 2000, 2001)

Summary

- [18F]FACBC is a promising new amino acid for imaging prostate bone metastases, and brain tumors
- [18F]FLT is a promising nucleoside for imaging lung cancer and has the potential to be more sensitive than FDG for determining response to therapy
- [18F]FMISO is an established nitroimidazolefor imaging hypoxic tumor volume
- [18F]FES is an established ER+ steroid for imaging breast cancer and metastasis
- [18F]FDHT is a promising new steroid for imaging prostate cancer metastasis
- [18F]FCH is a promising new analog of choline for imaging bone metastases, brain, prostate

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<u>KEYNOTE SPEAKER:</u> MICHAEL J. WELCH, PHD, MALLINCKRODT INSTITUTE OF RADIOLOGY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, AND SITEMAN CANCER CENTER

TITLE: PET IMAGING USING NONSTANDARD RADIONUCLIDES

NON STANDARD NUCLIDES SELECTED FOR PRODUCTION

- Cu-60, Cu-61, Cu-64 - wide range of t1/2
  Cu-64 has the potential for diagnosis and therapy
- I-124, Br-76, Br-77 - PET and therapeutic isotopes nuclides applicable to a wide range of compounds
- Tc-94m - PET Tc-nuclide
- Ga-66 - t1/2 between Ga-68 and Ga-67
- Y-86 - potentially useful for dosimetry prior to Y-90 therapy

Hypoxia Imaging and Consequences of Hypoxia

⇒ Hypoxia is related to:

(1) Expression of many genes
 Vascular endothelial growth factor (VEGF)
 Genes responsible for resistance to chemotherapy

(2) Increase in metastatic potential
 Soft tissue tumors (Brizel et al., 1996)
 Cervical cancers (Schwickert et al., 1995, Höckel et al., 1996)
 Head and neck cancers (Walenta et al., 1997)

(3) Increase in tumor aggressiveness
 Cervical cancers (Höckel et al., 1995 and 1996)

Why Image Hypoxia?

⇒ Hypoxia influences response to treatment:

(1) Radiotherapy - hypoxic cells are protected from lethal effects of conventional ionizing radiation therapy
(2) Chemotherapy - effect of hypoxia on special genes and drug delivery
⇒ Imaging of hypoxia is required in order to predict response to traditional therapies
⇒ Imaging of hypoxia in the brain, heart and cancer have been explored

Measurement of Tumor Hypoxia

- O_2 electrodes (Gatenby et al., IJROBP 1997, Hockel et al., Cancer Res 1996)
    - Observed correlation between pre-therapy oxygen measures and outcome of radiation therapy in some types of tumors
    - Invasive, technically demanding to use
    - Requires accessible tumors
    - May be subject to sampling errors
- Luminescence-based optical sensors (Collingridge et al., Radiat Res 1997)
- Ex vivo (biopsy) methods
- Ex vivo (biopsy) methods
    - DNA Comet assay (Olive et al., Radiat Res 1990)
    - Immunohistochemistry with antibodies (Koch et al., Br J Cancer 1990)
    - Hemoglobin-O_2 cryospectrophotometry (Fenton et al., Am J Physiol., 1990)

PET Imaging of Tumor Hypoxia

- Imaging by PET
    - Typically analogs of the nitroimidazole radiosensitizer misonidazole
    - Non-invasive
    - Entire tumor sampled
    - Repeated measurements possible
- 18F-Fluoromisonidazole (FMISO) (Rasey et al., Radiat Res 1990 and IJORBP 1989 & 1996)
    - FMISO undergoes bioreduction in hypoxic cells and remains within the cell
    - FMISO has been characterized as a probe for hypoxia *in vitro* and *in vivo*
    - Imaging hypoxic cells in human tumors (21 NSCLC, 7 head & neck cancer, 4 prostate and 5 others) (Rasey et al., IJORBP 1996)

Cu-ATSM in Cancer

- Preclinical studies demonstrated:
    - Selective and rapid uptake of Cu-ATSM in hypoxic tumor tissue
    - Likely superior to FMISO
        - Greater hypoxic/normoxic tissue activity ratio, likely reflecting the greater membrane permeability
        - More rapid blood clearance

Cu-ATSM - Clinical Studies

- To evaluate the feasibility of imaging with 60Cu-ATSM-PET in human tumors
    - Patients with non-small-cell lung cancer (NSCLC)
- To assess if the uptake of 60Cu-ATSM is predictive of response to therapy and/or outcome
    - Patients with NSCLC or advanced cervical cancer

Comparison of 60Cu- and 64Cu-ATSM

- T1/2 of 60Cu (23.7 min) limits widespread clinical use – requires on-site cyclotron
- T1/2 of 64Cu-ATSM (12.7 hrs) allows for regional distribution and possible delayed imaging
- Image blurring increases with positron energy
  - Better spatial resolution with 64Cu than 60Cu (4.7 vs. 6.3 mm)
- 64Cu-ATSM has potential as a therapeutic agent
- Laforest et al. Eur J Nucl Med Mol Imaging 2005; 32:1473-80

Cu-ATSM in Humans (IND 62,675)

- NCI-funded DCIDE grant (J. S. Lewis, PI) supported preclinical studies for IND application
  - Mutagenicity assays (*in vitro* Salmonella Reverse Mutation Plate Incorporation Assay; in vitro L5178Y/TK+/- mouse lymphoma mutation assay; in vivo micronucleus assay in rats
  - Cardiovascular and pulmonary safety testing in Beagles (750-fold dosing)
  - Neurological safety assessment in rats
  - 14-day toxicity study in rats (two target doses once a day; 110-fold daily dose basis; 1500-fold total dose)
  - 14-day toxicity study in rabbits (two target doses twice a day; 90-fold daily dose basis; 1200-fold total dose)

Comparison of 60Cu-ATSM and 64Cu-ATSM (IND 62,675)

- Assessed quality of 60Cu- and 64Cu-ATSM PET images
- Crossover study of 10 patients with Ib2-IVa cervical CA
  - Subjective – comparable; but, 64Cu-ATSM images less noisy
    - Similar quality in 8 patients
    - 64Cu-ATSM better than 60Cu-ATSM in 2 patients
  - T/M evaluation
    - Generally better target to background ratio (tumors seen more clearly on 64Cu-ATSM-PET in most cases)

64Cu and 86Y LABELING AND EVALUATION OF DOTA-ReCCMSH(Arg11), A CYCLIZED α-MSH ANALOGUE

64Cu vs. 86Y-DOTA-ReCCMSH(Arg11) microPET

- 86Y analog showed superior tumor uptake, organ ratios and low background compared with 64Cu

- Recently acquired new derivative with CB-TE2A chelate instead of DOTA to improve biodistribution. Work by Carolyn Anderson *et al* has demonstrated this to be a superior Cu-chelate.

Bromine-76 Labeled Antibodies

64Cu-Radiolabeled Nanoparticles: Nano-constructs for Molecular Imaging (NHLBI-PEN)

- Radiolabeled with medium-lived radionuclides such as Cu-64, Y-86, Br-76, I-124

HENRY F. VAN BROCKLIN, PHD, CENTER FOR MOLECULAR AND FUNCTIONAL IMAGING DEPARTMENT OF RADIOLOGY UC SAN FRANCISCO; PRESIDENT, SOCIETY OF NON-INVASIVE IMAGING IN DRUG DEVELOPMENT, AMI

TITLE: "ACADEMIC-INDUSTRIAL PARTNERSHIPS: PROSPECTS AND CHALLENGES IN RADIOPROBE AND DRUG DEVELOPMENT"

Nuclear Imaging Future: Challenges / Solutions

- Biomarker Validation
- Tracer Validation
- Microdosing
- Increase Specific Activity
- Miniaturization of Chemistry
- Cost of Tracer Development
- Regulations
- High-throughput Technologies

Solutions for Reducing the Cost

- Decrease cost of development
  - Apply therapeutic drug discovery
  - Academic institutions / public funding
  - Shared development amongst Pharma
  - Clinical phase represents largest cost
  - Regulatory changes
- Decrease cost per dose << $1000/dose
- Increase market size
- Diagnostic/ prognostic/ treatment monitoring
- Use for drug development (but not alone)

JULIE SUTCLIFFE PH.D, UC DAVIS, ASSISTANT PROFESSOR, DIRECTOR, CYCLOTRON AND RADIOCHEMISTRY FACILTY

TITLE: TARGETED MOLECULAR IMAGING WITH RADIOLABELED PEPTIDES: A RATIONAL AND RANDOM APPROACH

Goals

- Find peptide ligands *specific* for cell surface receptors expressed on cancer cell (a*v*β*6*integrin)α
- Use these ligands to develop new targeted imaging agents
- Two approaches (rational design and random design) α *v*β*6 :*

Rational approach

Foot and mouth disease virus Jackson T, et al, Vir Res 2003; 91: 33

- Identify (natural) ligand
- Determine binding site

- Synthesize Test
- *in-vitro*
- Test *in-vivo*

FMDV loop Logan D, et al, Nature 1993; 362: 566-568

Imaging (microPET)

- "A20FMDV2" Fragment (20 residues)
- FMDV loop YNGECRYSRNAVPNLRGDLQVLAQKVARTLP
- A20FMDV2 ~~~~~~~~~NAVPNLRGDLQVLAQKVART~~
- ELISA A20FMDV2 binding to immobilized αv β6

What is known?

- *No*X-ray structure of αvβ6binding site
- FMDV binds to αvβ6*via* VP1 loop
- VP1 X-ray structure

Logan D, et al, Nature 1993; 362: 566-568
Lea S. et al. Structure 1995; 3: 571-580

***Peptide synthesis* A20FMDV2: H2 N-NAVPNLRGDLQVLAQKVART-C(O)NH2**

- Standard Solid Phase Peptide Synthesis (SPPS)
- Preparation
- Labelling
- Cleavage
- Purification

F-18 peptides

- Selective coupling to N-terminus or NεLys of protected peptide on solid phase
- 4 steps, 120 –150 minutes
- Automated18F18FOOHOHO[18F]FBA[18F]FPAH-Peptide-TFA[18F]FBA-Peptide[18F]FBA,HATU[18F]FPA,HATUTFA[18F]FPA-Peptide[18F]FPA-Peptide-[18F]FBA-Peptide-

Peptide synthesis II

A20FMDV2: H2 N-NAVPNLRGDLQVLAQKVART-C(O)NH2
FMDV loop YNGECRYSRNAVPNLRGDLQVLAQKVARTLP
A20FMDV2 ~~~~~~~~~NAVPNLRGDLQVLAQKVART~~X = FBA FPA DOTA
Alexa680FOFONNNNCOOHHOOCHOOCOA20FMDV2FmocA20FMDV2H2NA20FMDV2HNXC(O)NH2A20FMDV2HNXFmoc
Removal Coupling (label X)1)
Cleavage (TFA)2)
Purification (HPLC)

In-vitro evaluation: ELISA

N-terminally labeled A20FMDV2 evaluated in competitive binding assay:

- Immobilized integrins (e.g.: αv β6) on 96 well plate
- A20FMDV2 competing with Fibronectin/ Vitronectin for binding

- High selectivity -(RGDy(Me)K)- shown for comparison:
- Low selectivity High affinity (~2-3 nM)

In-vivo study: mouse model

4-[18F]FBA-A20FMDV2 imaging in mouse model: Male nu/nu mice (n=20)
Paired xenografts (human cancer cell lines) on opposite flanks:

Prepare combinatorial libraries
One bead, one compound approach produce millions of unique compounds on insoluble beads

Evaluate performance
- *in vivo*
- microPET
- Sequencing
- Identify peptide sequences
- Cell-bead assay
- prepare identified peptides on mg scale

Random approach

<u>One Bead One Compound</u>
- single bead displaying only one compound
- up to 1013identical copies on a single bead (100 mm diameter)
- about 750,000 beads/mL (aqueous suspension)
- Spatially separable
- Individual compounds (beads) can be sequenced by Edman degradation and allows for on-bead assay

Lam, KS, et al., Nature 1991; 354: 82 *Molecular Libraries OBOC*

Library screening Cell-bead assay

1. Incubate cells with OBOC library
2. Pick the cell-covered beads
3. Remove cells
4. Identify the compound generate 6 peptide libraries using one-bead-one-compound strategy: 8-mer peptide libraries synthesized on TentagelKXDLXXLE
    - KXXXXXXE
    - XXDLXXLX
    - XXXXXXXX
    - CXDLXXLC
    - CXXXXXXC

3 libraries contain DLXXL motif all natural L amino acids used cysteine only included when disulfide bonds were desirable

High-throughput microPET

- 43 peptides radiolabeled with 18F and evaluated *in vivo*using microPET on 11 consecutive days
- 42 peptides identified from library + A20FMDV2 (control)

- 4 peptides radiolabeled per day
- 2 mice scanned simultaneously per peptide
- scan protocol: 60 min dynamic scan immediately following injection and 15 min static scan at 180 min time point

Conclusions

- synthesized and screened >106compounds to target the αvβ6 integrin using OBOC and cell-based screening methods
- *in vitro*assays identified 42 peptides that had significant affinity and/or selectivity
- peptides radiolabeled with F-18 and evaluated *in vivo* using microPET
    - 43 peptides evaluated *in vivo* on 11 consecutive days
    - no radiochemical, mechanical or biological failures that resulted in delays
    - 4 most promising compounds identified *in vivo* did not correspond to most promising compounds *in vitro*
- feasibility of using microPET for high-throughput screening of new molecular imaging agents demonstrated

***Conclusion* 4-FBA-A20FMDV2**

- *In vitro*: + αv β6 affinity, selectivity *In vivo:* + αv β6 affinity, selectivity
- rapid uptake, good retention
- renal clearance, rapid metabolism
- Promising 1stgeneration αvβ6*in vivo* imaging probe

JEFFREY P. NORENBERG, MS, PHARMD, UNM COLLEGE OF PHARMACY, ASSOCIATE PROFESSOR AND, DIRECTOR, RADIOPHARMACEUTICAL SCIENCES

TITLE: THE UNM COLLEGE OF PHARMACY RADIPHARMACEUTICAL SCIENCES PROGRAM: THE PRACTICE AND SCIENCE OF RADIOPHARMACY

UNM Radiopharmaceutical Sciences Program

• Education, Research, and Clinical Service
• First University-based Radiopharmacy Education and Training Program – 1972
• First Commercial Nuclear Pharmacy – 1971-1992
• DOE ANMI Nuclear Medicine Education Award for Graduate Radiopharmacy Education $100,000/yr 2001-2004
• New Mexico Center for Isotopes in Medicine - UNM-Los Alamos National Laboratory established 12/2005

Radiopharmaceutical Sciences Education Program Summary

- ASHP accredited in 1982; **Plan I and II programs; ***Distance program w/UAMS
- 1990 PhD Biomedical Sciences 3 NA
- 5/2007 Radiation Safety*** 40
- 5/2007 Department of Transportation*** >600
- 7/2006 MD Nuclear Cardiology*** 120
- 7/2004 Nuclear Pharmacy Technicians*** >300
- 2001 Authorized Users (Non-Pharmacist)*** 75
- 2001 Nuclear Education Online (NEO)*** 260
- 1986 MS Pharmaceutical Sciences ** 31
- 1977 to 1992 Post-graduate Radiopharmacy Residency* 31

o 1972 Authorized Nuclear Pharmacist (ANP) 187

Authorized Nuclear Pharmacist Program
• 1972 – Present
• 187 Graduates
• Professional Radiopharmacists
• ANP Certification
– 10 CFR 35.980
– APhA Syllabus for Nuclear Pharmacist Education and Training
– 250 Hours Didactic Education
• Physics and Instrumentation
• Radiochemistry
• Radiation Biology
• Radiation Safety
• Mathematics
• Clinical Clerkships
– 500 Hours Structured, Supervised Experiential Training

Nuclear Pharmacy Residency
• 1977 – 1992
• 31 Graduates
• Advanced Clinical Practice
• ASHP Accredited
Radiopharmaceutical Sciences
Graduate Program
• 1986 – Present
• MS Pharmaceutical Sciences (Radiopharmacy)
• 31 Graduates
• Focus on Applied and Translational Research
• Pharmaceutical Scientists
• Advanced Clinical Practitioners
• DOE ANMI NMEA $300,000 2001-2004

Nuclear Education Online (NEO)
www.nuclearonline.org
• Best Resources for Education
• Expert Faculty
• Advantages of Distance Education
– Anytime
– Anywhere
– Any pace
– Any base
• Active Learning using Problem- Based Learning (PBL)
• Consortium UAMS/UNM
• Authorized Nuclear Pharmacist 2001
– Goal 80 Students/Year
– 260 Graduates 2001-2007
• Authorized Users
– 75 Students 2001-2007
• Nuclear Pharmacy Technicians
– 300 Students 7/2004-2007

• Nuclear Cardiology Physicians
– 120 Students 7/2006
• DOT Training
– 800 Students 5/2007
• Radiation Safety
– 30 Students 5/2007
• Curriculum Licensed to Universities
– U of Oklahoma, MUSC

Future Directions At UNM New Mexico Center for Isotopes in Medicine Translational Radiopharmaceutical Sciences Program

- o Radiochemistry & Radiopharmacology
- o Experimental
- o Therapeutic
- o Radiopharmaceuticals
- o KUSAIR
- o KECK-UNM
- o Small Animal
- o Imaging Resource
- o Radiolabeled Compounds in Drug Discovery
- o First-in-Man Studies
- o PK/PD - Phase I
- o Surrogate Endpoints
- o Novel Isotopes/Radiopharmaceuticals
- o Small Animal Imaging Resource
- o Radioactive Animal Research Facility
- o Gamma Spectroscopy Facility

UNM Capabilities

• NMCIM = UNM + LANL + NMSU
• Radiopharmaceuticals
• Discovery, Development, and Translation
• cGMP Manufacturing and Formulation Support for Clinical Trials
• Small-Animal Imaging
• NanoSPECT/CT and PET
• Image-based Metrology
• Los Alamos National Laboratory
• Isotope Production Facility
• Chemistry Division

Radiolabeled Small Molecule Imaging Agent for Lymphoma LFA-1 *R-DOTA-butylamino-NorBIRT

1. over-expressed in lymphomas/leukemia
2. non-hematopoietic cells do not express LFA-1 ***R-DOTA-butylamino-NorBIRT *Patent Pending***
1. Specific allosteric inhibitor of LFA-1
2. Locks the receptor in bent low affinity state

Characterization of Radiolabeled DOTA-butylamino-NorBIRT

- o 100% radionuclide incorporation
- o Specific activity ~ 15MBq / µg

- Radionuclide Incorporation Yield by Instant Thin Layer Chromatography
- 177Lu-DOTA-213Bi-DOTA-butylamino-NorBIRT butylamino-NorBIRT Free (213Bi-DTPA)
- Radiolabeling does not hinder binding of butylamino-NorBIRT to LFA-1 receptors

Cell Binding of Radiolabeled butylamino-NorBIRT on HL-60 Cells
- Competition Binding of “Cold“ Lutetium Labeled DOTA-Total binding butylamino-NorBIRT
- Non-specific binding
- Specific binding
- Kd = 286
- The [FBA-NorBIRT] used is ≈50% of binding affinity Kd,
- the EC50 [DOTA-butylamino-NorBIRT] ≈50% Kd
- Kd = 286 nM for 177Lu-DOTA-butylamino-NorBIRT
- EC50 = 143 nM for Lu--DOTA-butylamino-NorBIRT

Somatostatin Receptor (SSTr) Activity
• Somatostatin
– pancreas, intestinal tract and regions of the central nervous system.
• Two forms of somatostatin are synthesized
– SS-14 and SS-28, reflecting their amino acid chain length.
• 5 subtypes identified
– SSTr2 and 5 over expressed in tumors
• Inhibits tumor growth
– Mechanisms and pathways like the MAPK
•Cell trafficking and internalization
– ligand binding Human SS-14
(adapted from Reubi JC, Endocr Rev. 2003; 24(4):389-427).

213Bi-DOTATOC
• DOTA provides extraordinary *in vivo* stability with high LET radionuclides
• Rapidly internalized and transported to the lysosomal compartments of the cell
• Radiometals are “permanently” localized with the cell

213Bi-DOTATOC PRRT in CA20948 Model
Conclusions:
•STTr-targeted and dose-related antiprolifereative effects
•Minimal nephrotoxicity
•No other acute or chronic toxicity

Evaluation of estrogen-receptor targeted 99mTc(I)-estradiol derivative
(A) Chemical structures of Re-pyridin-2-yl hydrazine derivatives with different linkage, (B) relative binding affinities and (C) cell permeability measured by Ca++ functional assay in transfected Cos-7 cells

(A) Saturation binding studies with MCF-7 cells using 99mTc-2 (n=3),
(B) competition binding studies with MCF-7 cells using Re-2
Tapan Nayak1, Helen Hathaway1, T. Anderson1, Jeffrey Arterburn2, Eric Prossnitz1,

What do we want? *In Vivo* Molecular Imaging
- PK and PD studies - QUANTITATION

- o Surrogate Markers of Drug Action or
- o Biomarkers
- o Limiting
- o Resolution
- o Depth of
- o Penetration

Meikle et al., Phys. Med. Biol. 50 (2005) R45-R61

KUSAIR - Keck-UNM Small Animal Imaging Resource
• Shared CRTC/COP Resource
• State of the Art Equipment
– Bioscan NanoSPECT/CT
– AMI LabPET8.0
• Expert Staff
– Imaging Scientists
– Radiopharmacologists
– Support Personnel
• High Throughput Capacity
– Special Shielding
– Integrated Anesthesia
– Surgical Procedure Stations
– Animal Staging Areas
• Proximity to Other Critical Resources
– Radiochemistry Laboratory
– Animal Housing

LabPET 8.0 Scanner
• 8-pixel, quad-APD detector module
• Parallel signal processing
• High count rate, negligible deadtime
• Ergonomic design
• Proven reliability (>10 years)
• Resolution ~1.1 mm (intrinsic)
• Efficiency ~ 3%
• Peak NEC > 2500 kcps
LabPET = Unique Technology
APD Scintillator

ECG-Gated Myocardium PET Study in Rat
Ventricular function
Cardiac viability
250 g Rat injected with 2,2 mCi of FDG, scanned for 40min

LANL 100 MeV Isotope Production Facility
• First protons were delivered to the facility on 12/23/2003.
• The facility was successfully commissioned January through April 2004.
– All commissioning objectives were met.
– The facility design goals were all achieved.
• Routine operations began February 2005.

IPF-Produced Medical Isotopes

- 82Sr: Parent of 82Rb used in cardiac perfusion studies with PET.
- 68Ge: Positron emitter used in calibration sources for every PET scanner in clinical use.
- 67Cu: Research isotope that shows promise in cancer detection and treatment.
- 186Re: In high specific activity this research isotope could be a potent cancer cell killer.
- 72As/76As: Use this research isotope pair in PET diagnosis and treatment in oncology.
- 77Br: Halogen isotopes are very versatile tracer labels (e.g., 18F) with diverse chemistry.
- Lanthanide isotopes: Show great potential in medical and biomedical applications.
- 88Y: A tracer surrogate for 90Y in oncological biodistribution studies.

BREAKOUT GROUPS

Group 1: Radioisotope Production and Needs
Objectives

This working group will examine the radioisotopes that are currently not commercially available but that should be considered for production by DOE. Specific topics to be discussed are: Current and future demands of isotopes for nuclear medicine applications, processes to obtain critical information to prioritize isotope development, and how to overcome current obstacles in obtaining isotopes for experiments and clinical trials. Discussions will also focus on identifying future research areas and needs of certain types of isotopes (i.e. Auger emitters, PET isotopes or isotopes for alpha-immunotherapy) in order to assist programs and production sites to plan their investments to meet future isotope demands and to avoid a shortage of supply. The list of isotopes developed by DOE in March 2007 is following:

Lu-177, Ho-166, Sn-117m (reactor), Pm-147, Ac-225 (from separation), W-188 /Re-188 Generator, Sn-117m (accelerator), Ra-223, Ti-44, Si-32, Cu-67, Zn/Cu-62 generator, Pt-195m, Ba/La-140 Generator, Mg-28, Y-86, Co-55, As-72 generator, Ac-225 (accelerator, reactor), Zr-89.

Questions for Discussion
(Group 1: Radioisotope Production and Needs)

1. Do we think the list of isotopes developed by DOE represents the isotopes needed for future research and clinical trials? If not, what isotopes are missing? How frequently would a user need these isotopes?

2. What are the ideal criteria to rank isotopes? What are suitable approaches to produce cost-effective isotopes to meet the research budgets?

3. Who are the customers, what is/are the proper funding mechanism(s), and how to obtain feedback and input from a broad stakeholder community? What is the strategy to develop advocacy for isotope production development?

General Discussion Points: This working group examined the radioisotopes that are currently not commercially available but should be considered for production by DOE. The primary topics discussed were:
- Current and future demand of isotopes for nuclear medicine application,
- Processes to obtain critical information to prioritize isotope development, and
- Facility needs to meet the future market demand.

This working group examined the radioisotopes that are currently not commercially available but that should be considered for production by DOE. The U.S. Department of Energy's Isotope Program has developed a list of radioisotopes that may be in demand for future nuclear medicine applications. The isotopes were prioritized based on mainly cost, and existing capability and existing or anticipated market demand. This raised the question: What are the criteria that can assist in determining which isotopes are critically needed and should be produced at DOE facilities? It was recognized that the task to prioritize isotope demand can be very difficult. A thorough market analysis should be performed in order to evaluate the market demand or potential future applications of isotopes recommended by individual researchers.

Issues related to targetry, such as enrichment, recycling of target material and availability of enriched material, must be considered for cost analysis.

The list of isotopes developed by DOE in March 2007 is following: Lu-177, Ho-166, Sn-117m (reactor), Pm-147, Ac-225 (from separation), W-188 /Re-188 Generator, Sn-117m (accelerator), Ra-223, Ti-44, Si-32, Cu-67, Zn/Cu-62 generator, Pt-195m, Ba/La-140 Generator, Mg-28, Y-86, Co-55, As-72 generator, Ac-225 (accelerator, reactor), Zr-89. This list was used as a starting point to discuss radioisotopes in need. The following is a brief summary of comments exchanged for isotopes discussed:

Re-186: Produced via a (p,n) reaction with low yield and large impurities that cause problems; not recommended for production by DOE.

Ac-225: this isotope is currently not produced by DOE, but is in high demand; received high recommendation for production by DOE; the different options for production, separation from existing stock materials or production in accelerator or reactor was briefly discussed.

Ti-44: this isotope made the list and is not used for nuclear medicine applications.

I-isotopes: Research is relying on the isotopes I-123, -124 and –125. These isotopes are commercially available; IBA is producing I-124 for sales; UC Davis is trying to revitalize I-125 production at the McClellan reactor facility.

Br-isotopes: production of Br-77 was recommended to DOE as a research isotope since it is actively needed in research activities.

Y-86: research isotopes that was featured during the oral presentations; production generates low yield; MURR is producing Y-86; alternative production of this isotope was recommended to be investigated by DOE; some development activities for Y-86 production are ongoing at BNL and LANL.

Ra-223: Apparently some institutions in Europe make this isotope available; this isotope was not recommended to the DOE for production.

Cu-isotopes: Significant research has been performed using Cu-67 and Cu64 isotropes indicating promising applications in therapy and diagnostics. Cu-64 is available at Washigton University and Dr. Welch has distributed Cu-64 to the research community; Cu-64 and -67 has been available from TRACE Life Sciences in Texas, but more production capacity for this isotope may be needed in the future; the copper isotopes were recommended to DOE for production and to provide back-up capacity.

Pb-isotopes: Pb-203 and Pb-212 were discussed; Pb-203 is a SPECT isotope and could be used for imaging purposes; Pb-212 is a alpha-emitter and could be used for alpha-immunotherapy in the future; the group did not feel strongly about these isotopes.

Other isotopes: The list of isotopes provided by DOE and also this breakout session focused strongly on isotopes with nuclear medicine applications. During the discussion other areas of isotope applications were discussed. As an example, radiotracers could be used in many environment-related sciences. Magnesium-28. sulfur-isotopes and Si-32 are isotopes used and demanded for research activities in agriculture, toxicology and oceanography research. It was recommended to DOE not to focus only on nuclear medicine applications, but to branch out and develop markets in other science areas, including homeland defense. These recommendations will be provided to DOE's Isotope programs to assist in prioritizing their isotope development activities.

In summary four isotopes were recommended for production at DOE facilities:

Ac-225, Cu-67(64) as a backup, Br-77 and Y-86.

Concerns were raised regarding the high costs of research isotopes, which make them too expensive for research activities. John Pantaleo, DOE/NE, explained that the production of commercial isotopes requires full cost recovery, while the research isotopes require batch cost recovery. DOE is working on revising their policies related to the costs of research isotopes to increase their availability.

The outcome of the discussion during this break-out session resonates very well with the recommendations obtained from the Council for radiopharmaceuticals. The council was asked by the DOE to review the list of isotopes and provide feedback from the user community. The Council recommended Cu-67, Y-86, Ac-225 and W-188 for the W-188/Re-188 generator.

The group also discussed briefly the infrastructure available for isotope production. Clearly, the DOE is providing unique facilities, such as reactors and accelerators, at National Laboratories. These facilities are currently used for generating the isotopes for the DOE's portfolio. However, concerns were raised regarding the uncertainty of the operation schedule of these facilities. Interruptions of isotope production can have devastating consequences ranging from delay of research activities, to missing milestones and deliverables to the sponsor and to cancellations of clinical trials. The DOE's Isotope programs has recognized these problems and tested concepts to enlarge production capacilty and availability of production facilities. It was recognized by the group that isotope production at DOE facilities has been considered less important to the main missions. However, DOE has made some efforts to enhance their production capacity by producing isotopes in a dedicated mode at LANL and BNL in FY 2007. The group also recommended strongly in investing in new production facilities that will enhance the DOE's infrastructure and that are certainly needed to meet future market demand. The group endorsed a new 70 MeV Cyclotron dedicated to produce isotopes for nuclear medicine and other research areas. The Material Test Station at LANSCE will be another opportunity for growing the DOE's isotope production capacity. The new 800 MeV beam at The MTS will provide additional opportunities to produce new isotopes. This facility is planned to operate in 2012. The DOE should maintain a footprint for isotope production, including a target removal ("rabbit") system for short-lived isotopes.

Participant List (Group 1)

Name	Affiliation
Stuart Adelman	Accurad
Moe Boussoufi	UC Davis
Daniel Conatser	Radiochemistry Solutions
Russel Dilts	UNM CRTC
Rob Duncan	IAS
Michael Fassbender	LANL
Jonathan Fitzsimmons	LANL
Ben Gershman	UNM COP
Jim Kronauge	Molecular Insight Pharmaceutical

Manuel Lagunas-Solar	UC Davis
Yubin Miao	UNM COP
Meiring Nortier	LANL
John Pantaleo	DOE Headquarter
Pawan Rastogi	LANL
Wolfgang Runde	LANL
Mark Soffing	IBA
Graham Timmins	UNM COP
Wynn Volkert	University of Missouri
David Wilk	Gamma Medica
Jim De Zetter	UNM Radiation Safety

Group II: Design and Synthesis of Radiopharmaceuticals - Jeff Arterburn (NMSU) and Eric Prossnitz (UNM)

The receptor-targeted approach offers great promise for the development of new diagnostic and therapeutic radiopharmaceuticals. In principle, this approach is feasible using a wide variety of radiolabeled receptor ligands, ranging from proteins and antibodies to small molecules. Applications involving intracellular receptor targets must overcome significant challenges to meet the requirements for optimal radiolabeling efficiency, chemical and biological stability, pharmacokinetics, receptor mediated uptake, and medical physics to produce the desired imaging or therapeutic effect.

Attendees:
Jeff Arterburn, Eric Prossnitz, Kelvin Hammond, Ritwik Burai, Heuman Fekrazad, Scot Burchiel, Craig Marcus, Jasmine Hunt, Michaelann Tartis, Tapan Nayak, Sudath Hapuarachchige, Julie Sutcliffe, Helen Hathaway, Haixun Guo, Naline Shenoy, Joanna Fair,
Hans Jueng, Mike Welch, Shannon Sheehan, Lars Furenlid.

Two participants identified that their research area directly involved isotope production and radiochemistry, six individuals identified their primary research area involved work with biological targets.

Questions to be Addressed by Group II:

1. What are the interests, expertise and facilities available for the production and radiochemistry of isotopes suitable for receptor targeted imaging and/or therapeutic applications in nuclear medicine.

> **Feedback:** The value of isotopes suitable for positron emission tomography (PET) was stated, particularly considering the example set by industry, where the major emphasis (~70-80%.) is focused on the development of isotopes for PET. The inherent time-dependent limitations of F-18 production was identified as a significant problem, since increased demand results in the need for around-the-clock availability that can not be met with singular production units. Major technical and distribution challenges face applications based on C-11. There is a need and opportunities for targeted PET applications that employ non-standard radionuclides including halogens and metals PET radionuclides such as ^{76}Br, ^{77}Br, ^{124}I, ^{86}Y, ^{94m}Tc, ^{66}Ga, ^{60}Cu, ^{61}Cu, ^{64}Cu. The group consensus from the discussion favored following the recommended isotopes from the National Cancer Institute (NCI). Many current studies report 15-20% radiochemical yields, that are not practical for viable production. There is a need for efforts focused on the optimization of radiochemical yields, however, limited sources of funding for this type of optimization are available.The NM Center for Isotopes in Medicine is well positioned to explore targeted imaging and therapeutic applications using radionuclide-labeled small molecules, building on expertise and facilities for high throughput screening and chemical libraries the exist in the NIH funded NM Molecular Libraries Screening Center.

2. What classes of biological targets are of interest for human health related imaging and therapeutic interventions employing radiopharmaceuticals.

Feedback: In the selection of appropriate biological targets for targeted radiopharmaceuticals, emphasis must be placed on their pathological relevance. The ideal "easy" case would involve an extracellular target, with a high affinity ligand, and well-defined structural binding model. The targeted approach is also feasible for intracellular targets, although additional characterization of uptake mechanism is important (e.g. distinguishing endocytosis). There is high clinical value in the development of agents that enable the prediction of individual patient response to convential radiation and chemotherapy, monitoring disease status, and improving the characterization of staging. The identification of responsive patients and targeted populations will be a major emphasis in the next generation of drug development. There is a real need for alternatives to 18F-fluorodeoxyglucose (FDG), considering the problems using FDG in patients who exhibit inflammation. Additional opportunities exist for targeted imaging of cell-death, including the characterization of apoptosis vs. necrosis, and would have broad implications for improving clinical care.

3. What are potential opportunities to merge existing strengths and interests in isotope production, radiochemistry, synthesis, biology, pharmacology, and nuclear medicine to develop new targeted radiopharmaceuticals?

Feedback: Significant barriers to the translation of diagnostic and therapeutic radiopharmaceuticals to clinical oncology exist, beyond the ever-present considerations of intellectual property. Previous experience has shown a reluctance of clinicians/specialists to use radionuclide agents that have shown promise in successful small-scale trials. In contrast, cardiologists have generally been more appreciative of the value of diagnostic agents, and more receptive to including imaging agents in care. The focus of radiopharmaceutical development must be on improving patient care. Individual concern was expressed that emphasis on specific technologies can potentially distract from the focus on patient care, and may also divert the interest of clinicians. This point was countered by other individuals who noted that significant technological improvements in image acquisition and processing have provided real opportunities for advancing the field, and increased the value of the results for clinicians. To achieve a balance between the costs associated with new technology vs. benefits to patient care, it was emphasized that the design of radiopharmaceutical studies must pursue valid scientific guiding principles. There is an additional need to consider the market for product development, and a recommendation for a minimal cost return for investment >$200K units per year was stated. The group consensus opinion was that greater acceptance and translation of radionuclide diagnostics and therapeutics can be achieved by focusing on improving patient care, combined with organizational top down influence and incentives for clinicians to interact with the basic researchers.

Invited Speaker Resources: Mike Welch (Wash U) and Julie Sutcliffe (UC Davis)

Group III: Translational Radiopharmaceutical Development - David Vera (UCSD) and Jan Marik (Genentech)

This group will discuss strategies to move radiopharmaceuticals from early phase development into preclinical and clinical trials.

Attendees:
Philip Kuehl, Mark Goodman, Henry VanBrocklin, Jean Luc VanderHeyen, Raj Manchandra, Mark Tengowski, Saeid Taheri, Andreas Kalmes, Tamara Anderson, BJ Bryant, Larry Sklar

Questions to be Addressed by Group III:

1. The exploratory-IND allows the use sub-pharmacological quantities (microdose) of drug candidates to be evaluated in humans. However, the toxicology data has to be provided to justify the dosing. How do such requirements apply to imaging agents based on protein therapeutics? Does a radiolabeled protein have to be subjected to toxicology studies if the toxicology data of the parent protein are known? How about peptide and small molecule based radiodiagnostics?

> **Feedback:** If high specific activity reagents are used to radiolabel proteins only a minute amount of the protein is modified with the radiolabel. Due to the large molecular weight of proteins the separation of the precursor from the radio-labeled protein is not possible. Therefore the toxicology studies should be performed using the major components of the final mixture or using the “decayed” material.

2. The cGMP requires full finished-product testing of every batch or process verification to ensure that PET drug meets all specifications. Regarding the cGMP requirements, is a manual synthesis followed by full finished-product testing any better than the automation of the synthetic procedure and process verification?

> **Feedback:** The automated synthetic procedure is always preferred to ensure reproducibility and to minimize human error.

3. Is there a context in which the FDA should approve a new radiopharmaceutical if it demonstrates equivalency to a currently approved agent? For example, if a minor change in structure demonstrates a more favorable dosimetry compared to a currently approved agent, should the FDA grant approval if the new agent demonstrated equivalent safety and efficacy?

> **Feedback:** [inadequate time to discuss]

Invited Speaker Resources: Henry Van Brocklin (UCSF) and Mark Goodman (Emory)

Group IV: Radiopharmaceutical Sciences Education and Training - Jeff Norenberg (UNM) and Rob Atcher (LANL)

This group will discuss the specialty training needs and the recent ACS and NAS Manpower needs surveys. The group may propose a model curriculum for training.

Attendees:
Steve Buelou, Robert Atcher, JP Norenberg, Lou Herrera, Gene Peterson, Melanie Bergeron (grad student from Canada), Daniel Irwin (student / Jeff's lab), Jeremy Howard (Jeff's Lab), Lourdes Rodriquez, C Eleanor Carbett (CoP student/Jeff's lab), KM Wittstrom

Questions to be Addressed by Group IV:

1. What are the manpower needs for Radiopharmaceutical Scientists in the US? Radiopharmacists? Radiochemists? Nuclear Chemists? Biologists? Radiobiologists? Physicists? Imaging Scientists?

Feedback:
Concern with graying of current professionals 10-15 years majority will need to be replaced. Needs include many skills and levels:

Radiopharmacists ~100/year
Radiochemists Biologists: *radiobiology; PK PD; molecular biologist*
Physicists: *health, imaging, dosimetry, shielding etc*
Translational physicians. , Regulatory experts; radiation safety experts;
Technician/technologists for support (*animal care, routine testing)* technical support: Accelerator operators; Instrumentation engineers.

2. What are the unique competencies and skills of Radiopharmaceutical Scientists? "Straw man" exercise.

Feedback:
Combination of multiple fields/discipline understandings: *chemistry, physics, biology, medicine.*
Ability to multi-task; creative thinkers; high intensity: *drive, follow through, tenacity*
Collaborative: *success depends on others*
Demonstrate strong leadership skills. Tolerate (even appreciate) non-standard working conditions (hours, length of hours, environment, hazards, etc)
Can deal with regulatory constraints without losing sight of target. Includes issues of chemistry, radiation, biological . Qc and QA
Able to tolerate and flourish in a field that is subject to constant change at many levels: Information, regulatory; product availability etc.

3. What are the necessary elements of a didactic curriculum and/or experiential training program?

Feedback:
Mentorship #1 Need to be refereed through choice of projects, the scientific methods, lots of feedback.
Maintain current information; keep course content dynamic; Require some prior training in the hard sciences; Utilize an internal review of curricula; Focus on the practical aspects, the

experiential; i.e. theory has to be inked to reality; Include statistical rigor; Study design both clinical and preclinical.

4. What are the advantages and disadvantages of various degree and training programs? i.e. Master of Science, Doctor of Philosophy, Post-graduate training.

Feedback:

Technicians: need definition of ideal training
Technologist: need training in research methods
Scientists: Post degree choices/options; Finding a mentor and undergoing the training to be a successful scientist.

5. How can students be effectively recruited and retained?

Feedback:
Radiochemistry summer schools- more program needed and inherent problems there.
Student awareness of opportunities in science research; Undergraduate outreach programs; National lab programs; need to be multi-disciplinary; Funding needed for training and for R&D

Infrastructure of paramount importance.

Invited Speaker Resource: Bill Eckelman (UCSD) and John Pieper (UNM)

APPENDIX 1: FINAL PROGRAM

NEW MEXICO CENTER FOR ISOTOPES IN MEDICINE

John A. Pieper, PharmD
Chair, Executive Advisory Board
Dean, UNM College of Pharmacy
Vice President for Research,
UNM Health Sciences Center

Scott W. Burchiel, PhD
Director
Professor & Associate Dean for Research,
UNM College of Pharmacy

Jeffrey P. Norenberg, PharmD
Associate Director
Associate Professor & Director
Radiopharmaceutical Sciences,
UNM College of Pharmacy

Robert Atcher, MBA, PhD
DHHS Program Manager,
Los Alamos National Laboratory
Leader, Emerging Medical Technologies,
NM Institute for Advanced Studies
UNM-LANL Professor

Duncan McBranch, PhD
Leader, Technology Transfer Division,
Los Alamos National Laboratory

Eugene Peterson, PhD
Division Leader, Chemistry Division,
Los Alamos National Laboratory

Robert Rubin, PhD
President & CEO,
Lovelace Respiratory Research Institute

Cheryl L. Willman, MD
Director & CEO,
UNM Cancer Research & Treatment Center

NEW MEXICO ISOTOPES AND IMAGING WORKSHOP*
EMBASSY SUITES HOTEL – ALBUQUERQUE, NM
AUGUST 2-4, 2007

Goal 1: To identify needs for medical isotope production and radiopharmaceutical development to support cancer imaging and therapy

Goal 2: To build collaborations between UNM, LANL, IAS, and various academic and industrial partners in radiopharmaceutical development, preclinical, and clinical imaging and radiotherapy

Goal 3: To define a process for strategic planning to take advantage of unique opportunities.

Day 1: Thursday 8/2/07

7:00PM	Poster Session and Reception

Day 2: Friday 8/3/07

7:45 AM	Continental Breakfast
8:30-8:40	WELCOME AND INTRODUCTIONS – John Pieper, PharmD
8:40-8:50	WORKSHOP "WHO WE ARE" AND "GOALS" – Scott Burchiel, PhD and Robert Atcher, PhD
8:50-9:00	UNM CANCER CENTER VISION FOR THE WORKSHOP – Cheryl Willman, MD
9:00-9:15	"LANL ISOTOPE PRODUCTION FACILITY AND PLANS" – Mary Neu, PhD, Associate Director for Chemistry, Life and Earth Sciences, (CLES)
9:15-10:00	**Keynote Speaker: Bill Eckelman, PhD, UCSD -** "LINKING TARGETED IMAGING TO PHARMACEUTICAL DEVELOPMENT"
10:00-10:15	Break
10:15 AM	**SESSION I: MEDICAL ISOTOPE PRODUCTION, RADIOPHARMACEUTICAL NEEDS AND OPPORTUNITIES**
10:15-10:45	Invited Speaker: John Pantaleo, PhD, DOE "OVERVIEW OF THE DEPARTMENT OF ENERGY'S ISOTOPE PRODUCTION CAPABILITIES"
10:45-11:15	**Invited Speaker:** Wynn A. Volkert, PhD - University of Missouri, Radiopharmaceutical Sciences Inst. "ADVANCES IN SPECT RADIOCHEMISTRY"
11:15-11:45	**Invited Speaker**: - Mark Goodman, PhD - Emory University "FLUORINE-18 RADIOPHARMACEUTICALS FOR CANCER IMAGING"
11:45 AM	**Lunch**

New Mexico Center for Isotopes in Medicine, College of Pharmacy, MSC09 5360, University of New Mexico, Albuquerque, NM 87131-0001
Phone: 505.272.8101 fax: 505.272.0704 email: sburchiel@salud.unm.edu http://hsc.unm.edu/pharmacy/isotope

1:00 PM **Session II: PET Translational Imaging Research and University-Based Cyclotrons**

1:00-1:30 **Keynote Speaker: Michael Welch, PhD, Washington University, St Louis** "PET IMAGING WITH NON-STANDARD PET NUCLIDES"

1:30-2:00 **Invited Speaker:** Henry Van Brocklin, PhD UCSF - "ACADEMIC-INDUSTRIAL PARTNERSHIPS - PROSPECTS AND CHALLENGES IN RADIOPROBE AND DRUG DEVELOPMENT"

2:00-2:30 **Invited Speaker:** Julie Sutcliffe, PhD, UC Davis - "TARGETED MOLECULAR IMAGING: A RANDOM AND RATIONAL APPROACH"

2:30-3:00 **Invited Speaker:** Jeff Norenberg, PharmD, UNM - "THE UNM COP RADIOPHARMACEUTICAL SCIENCES PROGRAM: THE PRACTICE AND SCIENCE OF RADIOPHARMACY"

3:00 PM **Session III: Break-Out Groups**

Group I: Radioisotope Production and Needs - Yubin Miao (UNM) and Wolfgang Runde (LANL)

This group will examine the current radioisotopes that are not commercially available that should be consider for production by DOE and LANL. This group will discuss the current DOE survey of isotopes and will provide feedback.

Suggested Invited Speaker Resources: John Pantaleo (DOE) and Wynn Volkert (U Missouri)

Group II: Design and Synthesis of Radiopharmaceuticals - Jeff Arterburn (NMSU) and Eric Prossnitz (UNM)

This group will discuss current rationale approaches to targeted radiopharmaceutical design and synthesis for targeted approaches.

Suggested Invited Speaker Resources: Mike Welch (Wash U) and Julie Sutcliffe (UC Davis)

Group III: Translational Radiopharmaceutical Development - David Vera (UCSD) and Jan Marik (Genentech)

This group will discuss strategies to move radiopharmaceuticals from early phase development into preclinical and clinical trials. Paradigm for high throughput evaluation of agents and overcoming regulatory obstacles will be discussed.

Suggested Invited Speaker Resources: Henry Van Brocklin (UCSF) and Mark Goodman (Emory)

Group IV: Radiopharmaceutical Sciences Education and Training - Jeff Norenberg (UNM)

Suggested Invited Speaker Resource: Bill Eckelman (UCSD) and John Pieper (UNM)

This group will discuss the specialty training needs and the recent ACS and NAS Manpower needs surveys. The group may propose a model curriculum for training.

4:00PM **Break-out group reports**

5:00 PM **Adjourn**

7:00PM **Dinner**

Day 3: Saturday 8/4/07

8:30AM	Continental Breakfast
9:00 AM	**SESSION IV: UNIVERSITY – INDUSTRY PARTNERSHIPS TO DEVELOP NOVEL CANCER IMAGING AGENTS**
9:00-9:20	**Invited Speaker:** Jean-Luc Vanderheyden, PhD, GE HealthCare - "MOLECULAR IMAGING: A CRITICAL STEP TO EARLY HEALTH"
9:20-9:40	**Invited Speaker:** John Babich, PhD, Molecular Insight Pharmaceuticals, Inc. - "INNOVATIONS IN MOLECULAR IMAGING"
9:40-10:00	**Invited Speaker:** Mark Soffing, PhD, IBA Molecular - "GETTING AGENTS TO PATIENTS REGULATORY ISSUES AFFECTING TRACER AVAILABILITY"
10:20-10:40	**Invited Speaker:** Jan Marik, PhD, Genentech "RADIONUCLIDE IMAGING IN THE DEVELOPMENT OF TARGETED THERAPEUTICS AT GENENTECH"
10:40- 11:00	Break
11:00	**WRAP UP AND FUTURE PLANS**
	Adjourn

THIS WORKSHOP IS SUPPORTED BY A MAJOR GRANT FROM THE NEW MEXICO CONSORTIUM'S INSTITUTE FOR ADVANCED STUDIES www.nmcias.org , GE HEALTHCARE, UNM CANCER AND RESEARCH CENTER, AND the UNM COLLEGE OF PHARMACY

New Mexico Consortium's

IAS

Institute *for* Advanced Studies

at Los Alamos National Laboratory

APPENDIX 2: LIST OF ATTENDEES

Name	Affiliation
Adelman, Stuart Lee	Accurad
Anderson, Tamara	UNM
Arterburn, Jeff	NMSU
Atcher, Rob	LANL-IAS
Babich, John	Invited Speaker-Molec Insight Pharma
Bergeron, Melanie	AMI - U Sherbrooke
Boussoufi, Moe	UC Davis
Buchanan, James	Phillips
Buelow, Steve	LANL-IAS
Bryant, BJ	NMSU Post Doc
Burai, Ritwik	NMSU Grad student
Burchiel, Scott	UNM-IAS
Carbett, Cher	UNM - PharmD student
Conatser, Daniel	Radiochemistry Solutions
Dai, Donghai	UNM CRTC
De Zetter, James	UNM Rad Safety
Dilts, Russell	UNM CRTC
Duncan, Rob	IAS
Eckelman, Bill	Invited Speaker - UCSD
Fair, Joanna	UNM Radiol Resident
Fassbender, Michael	LANL
Fekrazad, M. Houman	UNM Hem/Onc Fellow
Fitzsimmons, Jonathan	LANL
Furenlid, Lars	U Arizona
Garcia, John	UNM VPRED
Gershman, Ben	UNM
Goodman, Mark	Emory
Guo, Haixun	UNM - Post Doc
Hammond, Kelvin	Biotage
Hapuarachchige, Sudath	NMSU- grad student
Hathaway, Helen	UNM CRTC
Hawkins, Andrea	Congesswoman Wilson's Staff
Helgesen, Stephan	State Econ Develop
Heintz, Phil	UNM SOM Radiology
Herrera, Lou	Biotech
Howard, Jeremy	UNM
Hunt, Jasmine	UCSB
Irwin, Daniel	UNM
Jueng, Hans	UNM Student
Kalmes, Andreas	CellCyte
Kuehl, Phil	LRRI
Lagunas-Solar, Manuel	UC Davis MNRC

Liu, Jim	UNM COP
Luan, Shuang	UNM
Manchanda, Rajesh	Avid Radiopharmaceuticals
Marcus, Craig	UNM COP
Marik, Jan	Invited Speaker-Genentech
McBranch, Duncan	LANL
McIver, Jack	UNM VPRED
Miao, Yubin	UNM COP
Nayak, Tapan	UNM - grad student
Neighbour, Andrew	TRC
Neu, Mary	LANL
Norenberg, Jeff	UNM COP
Nortier, Meiring	LANL
Paden, Rae Ann	UNM CRTC
Pantaleo, John	Invited Speaker-DOE
Pesiri, David	LANL
Peterson, Gene	LANL
Pieper, John	UNM COP
Prossnitz, Eric	UNM CRTC
Rastogi, Pawan	LANL - summer student
Rivera, Natalie	LANL-IAS
Rodriguez, Lourdes	UNM COP/UAEM
Runde, Wolfgang	LANL
Sauer, Nan	LANL
Schmidt, David	LANL
Shenoy, Nalini	UNM Post Doc
Sklar, Larry	UNM CRTC
Smyth, Hugh	UNM COP
Soffing, Mark	IBA
Suttcliffe, Julie	UC Davis
Tengowski, Mark	Pfizer
Taheri, Saeid	UNM SOM Resident
Tartis, Michaelann	NMT
Tchiprout, Victor	Bioscan
Thompson, Todd	UNM COP
Timmins, Graham	UNM COP
Van Brocklin, Henry	Invited Speaker-UCSF
VanderHeyden, Jean Luc	Invited Speaker-GE Healthcare
Vera, David	UCSD
Volkert, Wynn	Invited Speaker- U Missouri
Wagenaar, Douglas	Gamma Medica
Wagner-Jones, Bridgette	UNM Conf Staff
Walker, Mary	UNM COP
Welch, Michael	Invited Speaker- Wash U St Louis
Willman, Cheryl	UNM CRTC
Wittstrom, Kristina	UNM

APPENDIX 3: DOE ISOTOPE PRODUCTION RANKING DISCUSSION DOCUMENT 5-23-07

Item	Process Chemistry Development	Target	Waste & ESH Costs	Current Capability	# of near-term users	Long-term societal benefits	Production or Unit Costs
Lu-177	1	1	1	3	3	1	1
Ho-166	1	1	1	1	4	2	1
Sn-117m (reac)	1	1	1	3	3	2	2
Pm-147	3	2	2	2	2	2	2
Ac-225 (from sep.)	1	1	3	3	1	1	4
W-188 /Re-188 Gen.	1	2	1	3	2	2	3
Sn-117m (acc)	3	3	1	1	4	2	3
Ra-223	1	1	4	2	4	2	3
Ti-44	1	1	1	3	3	2	5
Si-32	1	1	1	3	4	4	3
Cu-67	4	5	1	2	2	2	5
Zn/Cu-62 Gen.	3	3	1	5	3	2	3
Pt-195m	5	3	3	3	3	1	4
Ba/La 140 Gen.	3	2	2	4	3	3	3
Mg-28	2	1	1	2	5	4	4
Y-86	3	5	1	3	3	3	4
Co-55	3	4	1	2	5	3	4
As-72 Gen.	5	5	3	3	4	2	3
Ac-225 (acc, reac)	5	5	5	5	1	1	5
Zr-89	4	5	1	3	4	4	4

1= easy, or good; 5= expensive, or bad

CA = Commercially available

3* Currently there is great need and no commercial production. There is potential production on many cyclotrons throughout US, and potential commercial production IBA?

4* commercially available at Trace, minimum order = 100 mCi @ $100/mCi or $10,000. Cost prohibitive?

Definitions:

Process Chemistry Development: assessment of the in-house expertise and/or the difficulty of the chemical separation steps needed to separate the desired radioisotope from bulk target and impurities.

Target Development: assessment of difficulty to fabricate the target. This includes factors such as target design, engineering, impurities in target material, enrichment and availability of enriched material, target resistance towards chemical/radiological corrosion, pressure and irradiation effects.

Waste and ESH costs: assessment of the needs to implement specific waste disposal procedures, including safety and environmental impact.

Current (Infrastructure) capability: Assessment if the National Isotope Program has access to the infrastructure needed to irradiate and process the target, and to safely distribute the isotope in sufficient quantities and quality to support R&D and clinical trials.

Number of near-term users: assessment of immediate demand and evaluation of currently interested scientists and institutions.

Long-term societal benefits: assessment of the importance and impact of the radioisotope for applications in medicine, homeland defense, etc.

Production or unit costs: assessment of production costs (including costs for target material, target fabrication, beam time, processing, analysis and shipments) per unit of radioactivity produced.

APPENDIX 4: POSTER PRESENTATIONS

New Mexico Isotopes and Imaging Workshop
Thursday Night 7PM – August 2, 2007
Embassy Suites – Albuquerque, NM

1) EVALUATION OF ESTROGEN-RECEPTOR TARGETED ^{99M}TC (I)-ESTRADIOL DERIVATIVES FOR BREAST CANCER IMAGING. Nayak, TK, Hathaway, H, Anderson, TL, Arterburn, JB, Prossnitz, ER, Norenberg, JP. University of New Mexico, Health Sciences Center; New Mexico State University

2) ENHANCEMENT OF SOMATOSTATIN-RECEPTOR TARGETED RADIONUCLIDE THERAPY BY GEMCITABINE PRE-TREATMENT MEDIATED RECEPTOR UP-REGULATION AND CELL CYCLE MODULATIONS. Nayak TK, Norenberg, JP, Prossnitz, ER, Atcher, RW. University of New Mexico, Health Sciences Center; New Mexico State University; Los Alamos National Laboratory

3) IN VIVO IMAGING OF A ^{111}IN-RADIOLABELED SMALL MOLECULE TARGETING LFA-1 EXPRESSION IN LYMPHOMA. Carbett E, Anderson T, Gershman B, Erion J, Hathaway H, Wagner C, Aterburn J, Sklar L, Larson R, Norenberg J. University of New Mexico, Health Sciences Center; Department of Radiology, University of Pennsylvania; Biosynthema Inc.; Medicinal Chemistry, University of Minnesota; New Mexico State University

4) THE UNM RADIOPHARMACY PROGRAM: CELEBRATING 30 YEARS. Wittstrom K, Norenberg JP. College of Pharmacy, University of New Mexico, Health Sciences Center

5) RADIATION ABSORBED DOSE ESTIMATES FOR INTRAVENOUSLY INJECTED ^{213}BISMUTH-[DOTA]TYR3,OCTREOTIDE IN PEPTIDE RECEPTOR RADIONUCLIDE THERAPY. Norenberg JP, Ringer RJ, Krenning BJ, Konings IR, Bigman GH, Atcher RW, Garmestani K, Brechbeil M, de Jong M, Kvols LK. University of New Mexico, Health Sciences Center; Erasmus Medical Center; Los Alamos National Laboratory; National Institute of Health

6) A COMPARISON OF HIGH- VERSUS LOW-LINEAR ENERGY TRANSFER SOMATOSTATIN RECEPTOR TARGETED RADIONUCLIDE THERAPY IN VITRO. Norenberg JP, Nayak TK, Stabin MG, Atcher RW. University of New Mexico, Health Sciences Center; Vanderbilt University; Los Alamos National Laboratory

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