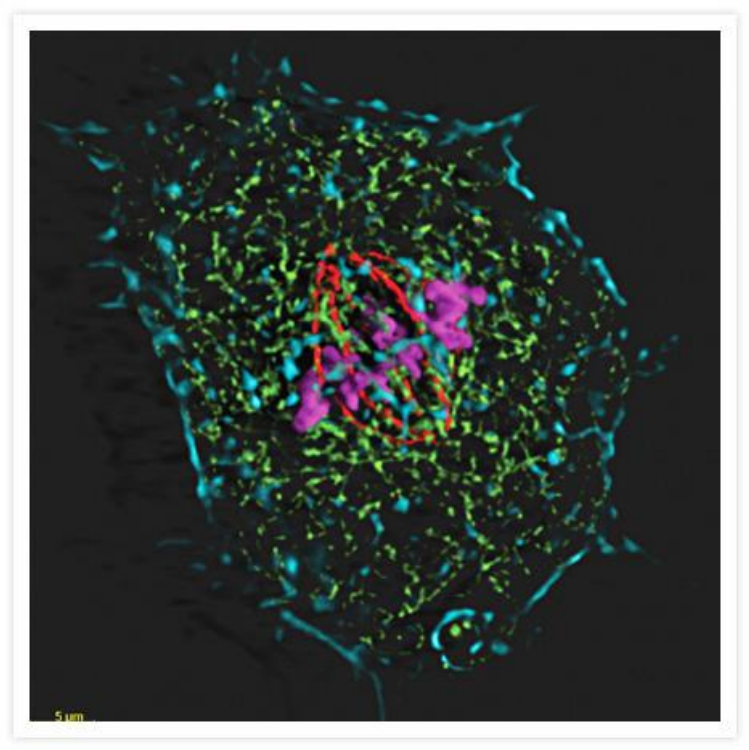
BIOMEDICAL IMAGING AT THE NATIONAL INSTITUTES OF HEALTH

Gary L. Griffiths, Ph.D.

Director, Imaging Probe Development Center, NHLBI

Molecular Imaging: *from intracellular to clinical scales*

Fluorescent



Intracellular Fluorescent Probes:
Four-color staining of a muntjac cell with probes for cytoskeletal, nuclear and mitochondrial proteins.
Invitrogen Corp.

Positron Emission Tomography

Sept 8, 2008

PET for Neuroimaging:

- Quantitation of uptake
- Drug tracking
- Occupancy & receptor studies
- Early diagnosis
- Guide for therapy
- Alzheimer's and other neurological diseases

NIH Institutes with Major Imaging Interests

Major Interests:	Others:
NCI	NIDDK
NIAID	NICHD
NHLBI	NIDA
NINDS	NHGRI
NIMH	NIA
NIBIB	NIEHS
& Clinical Center	NICDR

Modalities: Flourescence, ultrasound, magnetic resonance, positron emission tomography, single photon emission tomography & others

Disciplines: chemistry, physics, biology & medicine; & more

An aerial view of the NIH Clinical Center complex with the Mark O. Hatfield Clinical Research Center in the foreground

NIH Radiology and Imaging Sciences Department

Patient activities encompass clinical care and research support in the areas of Body Imaging, Interventional Radiology, Neuroradiology and Nuclear Medicine.

State-of-the-art equipment includes:

Three GE Advance whole body scanners ('93, '97, '01), Resolution 5-7 mm

Human brain and body; large animals

High Resolution Research Tomograph (HRRT, '04), Resolution 2.5 mm

Human and monkey brain; small animals

Diagnostic services in ultrasound, digital mammography, PET/CT, and nuclear medicine

Advanced processing capabilities for 3D and functional studies

PET Imaging, primarily for neuroscience

PET Department, CC

The PET Department functions as a core facility for the intramural research program

- Perform PET scans in humans under IRB-approved clinical research protocols
  - using IND radiopharmaceuticals manufactured in-house
- Perform research scans in large and small animals
- Provide shipments of cyclotron-produced radionuclides and radiopharmaceuticals

Three medical cyclotrons

PET Resources – Radiochemistry

- 10 hot cells for synthesis of radiopharmaceuticals
- Von Gahlen hot cells (6; 1985) and mini hot cells (4; 2005)
- Labs for radiopharmaceutical QC and dispensing

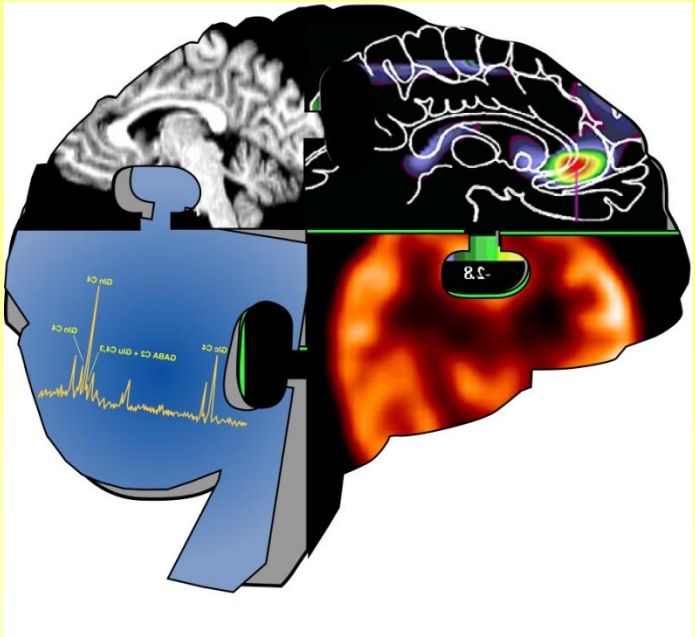
PET Radiopharmaceutical Sciences Section (PRSS)

The PRSS within MIB has as its primary mission the development of novel radiotracers for PET brain imaging for neuropsychiatric research

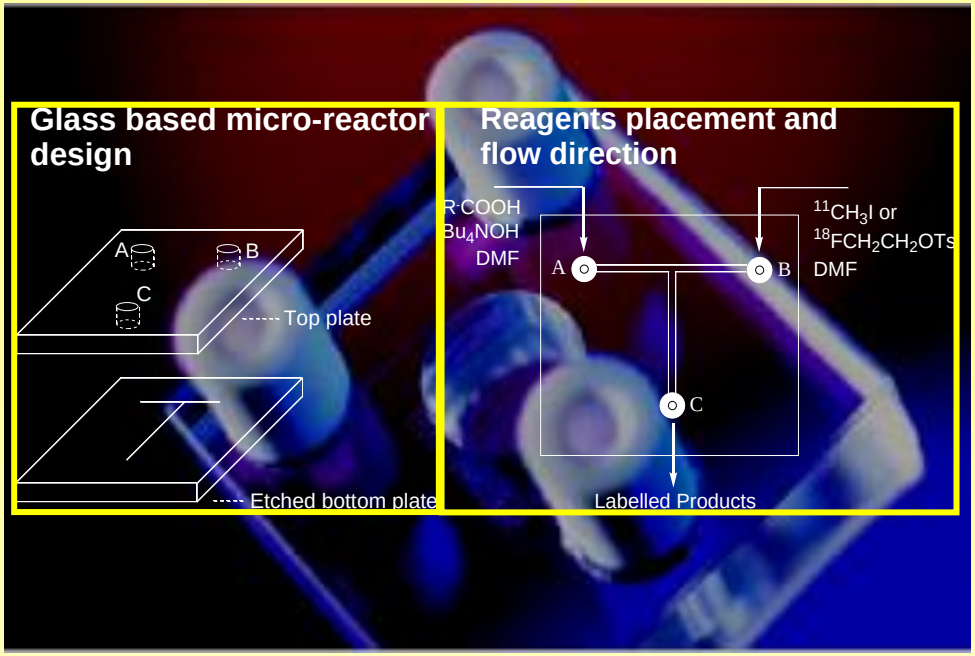
and, also produces a range of 'literature' PET radiotracers of interest to the NIMH/MIB molecular imaging program

12 literature radiotracers for use by NIMH investigators

- 1 RDRC, 4 IND and 2 eIND approvals
- New methodology for PET radiopharmaceutical sciences
- > 250 ligands and candidate ligands for various targets
- Including Promising new radiotracers for 5-HT_{1A}, NET, PBR, mGluR5 and CB_1 targets



Miniaturization of Radiochemistry



Advion a microfluidic system developed with support from NIH

Radiosyntheses of ^{11}C- and ^{18}F-esters, including a candidate ^{11}C-labeled PBR radiotracer. Lu *et al.*, *Lab on Chip* (2004) 4, 523–525.

The ATLAS System for PET Scanning, Developed at NIH

Enabling Technologies

NIH ATLAS small animal PET scanner circa 2001, one of the first dedicated laboratory animal PET imaging systems. Collaboration between intra and extra-mural partners, NIH shop facility on Bethesda campus.

GE eXplore VISTA small animal PET scanner circa 2009 marketed worldwide by GE and by SEDECAL (Spain) as ARGUS PET.

"Resolution Uniformity and Sensitivity of the NIH ATLAS Small Animal PET Scanner: Comparison to Simulated LSO Scanners without Depth-of-Interaction Capability". J. Seidel, J.J. Vaquero and M.V. Green. IEEE Transactions on Nuclear Science (50) No.5: pp. 1347-1350, October, 2003.

The New MONICA System for Small Animal SPECT Scanning

MONICA: A Portable Dual Gamma Camera System for Small Animal Projection Imaging

"**MO**bile **N**uclear **I**maging **CA**meras".

NIH/NCI MONICA portable dual (yellow arrows) gamma camera system circa 2009 for whole body single photon mouse imaging in support of pre-clinical development of cancer diagnostic and therapeutic drugs. Collaboration between intra and extra-mural partners, NIH shop facility on the Bethesda campus. Commercial potential unknown.

More information: <greenmich@mail.nih.gov>

Molecular Imaging Program (MIP) of the Center for Cancer Research at NCI

Vision: *To speed cancer therapy development using imaging biomarkers to guide therapy and patient selection*
Mission: *To develop and test targeted tumor imaging agents for human cancers*

Facilities: Extensive chemistry and biology. Clinical and preclinical imaging center

MRI Research:

Development of new targeted and non-targeted Gd-dendrimer-based imaging agents for use as lymphatic markers, angiogenic markers and surrogate markers for drugs

Dynamic contrast enhanced (DCE) MRI to evaluate patients on anti-angiogenesis drugs. Prostate MRI imaging using both DCE MRI and MR spectroscopy

Optical Imaging:

Use as a guide for surgery and endoscopy

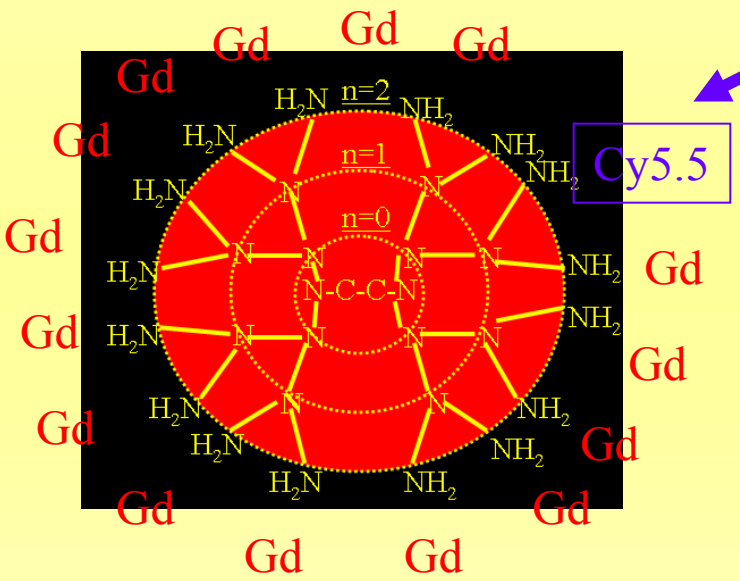
Targeted activatable fluorescent molecules as potential guides during surgery and endoscopy

Radionuclide/PET imaging:

Radiolabeled antibodies, peptides and other drugs

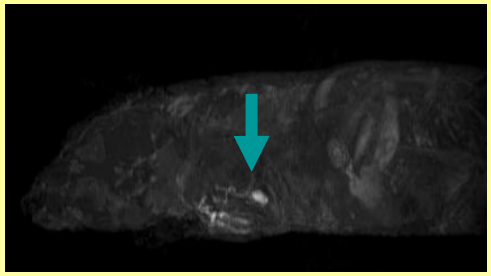
Dual labeling Reagents

- Pre-operative planning: Gd-Dendrimer
- Intra-operative guidance: Optical-Dendrimer

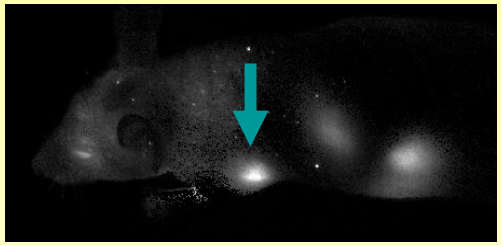


G6-Cy5.5 dual probe

MRI



Fluorescence



The Cancer Imaging Program at NCI

Mission:

To promote and support:

Cancer-related basic, translational and clinical research in imaging sciences and technology

Integration and application of these imaging discoveries and developments to the understanding of cancer biology and to the clinical management of cancer and cancer risk.

Sponsors a number of programs for specific purposes:

In-Vivo Cellular & Molecular Imaging Centers (ICMICs),
Small Animal Imaging Resource Program (SAIRP),
Development of Preclinical Drugs and Enhancers (DCIDE) program, and
Network for Translational Research: Optical Imaging (NTROI).

The Interagency Council on Biomedical Imaging in Oncology (ICBIO) was developed as a means for developers of new imaging techniques to seek advice on the best way to proceed to commercialize their ideas.

The Cancer Imaging Program at NCI

Interagency Council on Biomedical Imaging in Oncology (ICBIO)

The ICBIO brings together representatives of the Federal Government and technology developers to expedite the process of bringing new products to market.

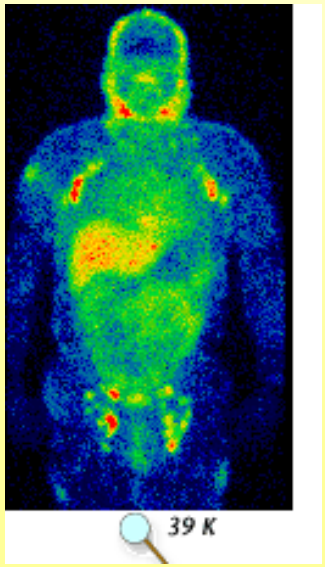
Government officials on the Council represent three Department of Health and Human Services agencies:

National Cancer Institute (NCI)
Food and Drug Administration (FDA)
Centers for Medicare and Medicaid Services (CMS)

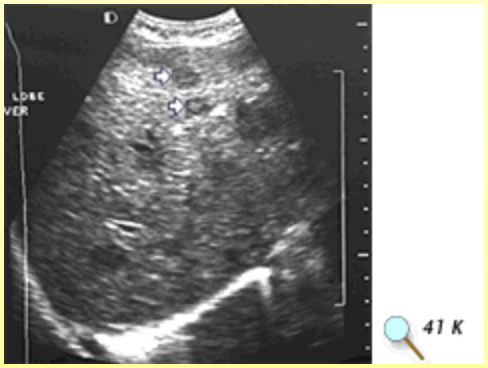
Technologies presented in the past have included: Computed tomography (CT) and combination instrumentation, Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), Ultrasound, Optical imaging, Nuclear medicine both single photon and PET, Molecular imaging agents, Image guided therapy FDA approval pathways, CMS approval and funding

***imaging**.cancer.gov/programsandresources/.../ICBIO*

The Cancer Imaging Program at NCI

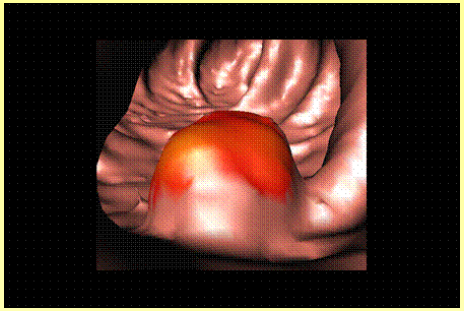


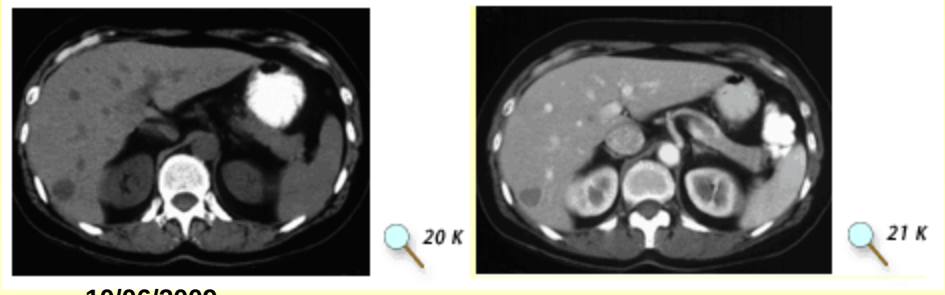
SPECT scan. High levels of antibody in pelvis and axilla (red) and uptake in skin of the thigh and right shoulder (green) showing areas of cutaneous T-cell lymphoma. Image from Dr. J. Carrasquillo, Nuclear Medicine Department, CCr, NIH.



Ultrasound image of the liver; dark areas by arrows show possible tumors. Image from Dr.T. Shawker, NCI.

Virtual colonoscopy image of the inside of a colon. The red colored area indicates a polyp detected by computer-aided detection (CAD). Image from Dr. R. Summers, Diagnostic Radiology Dept, CC, NIH.





Conventional CT scan without contrast (left) showing possible tumor in the liver. CT scan of the same patient using contrast (right). Images from Dr. Peter Choyke, Department of Radiology, CC, NIH.

NCI at Frederick, MD

Advanced Technology Partnerships Initiative (ATPI)

www.ncifcrf.gov/atpi/

An NCI initiative to speed translation of research into new treatments for patients with cancer and AIDS.

The ATPI establishes effective partnerships with academic institutions, industry, and nonprofit organizations.

Partnerships through the Federally Funded Research and Development Center (FFRDC) in Frederick, Md., - a government-owned, contractor-operated national laboratory.

Designed to meet special long-term R&D needs

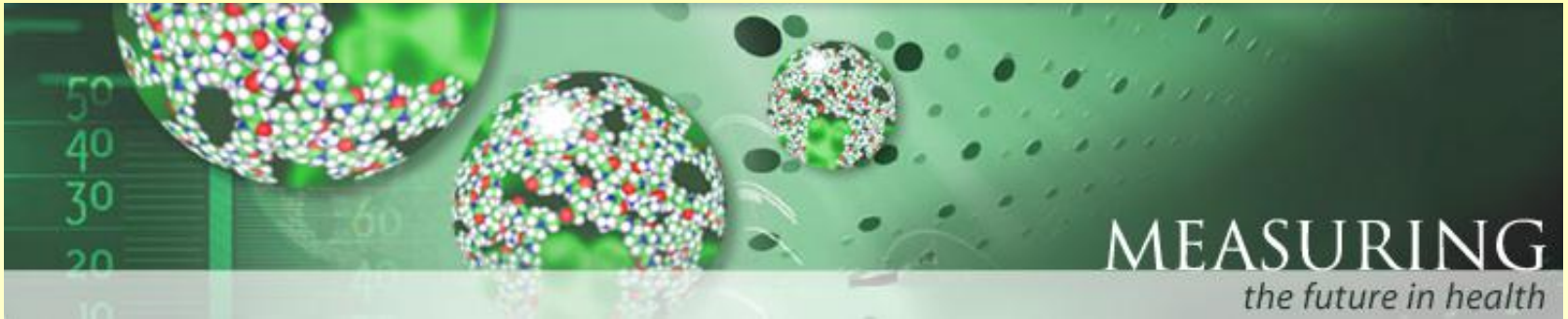
The FFRDC, has a wide range of state-of-the-art advanced technologies that support NCI's mission.

These include:
- genetics and genomics
- proteins and proteomics
- **nanotechnology characterization**
- **advanced biomedical imaging & high-performance biomedical computing**

NCI will use these resources in developing partnerships to identify the most promising diagnostic and therapeutic candidates and move them efficiently through R&D and into preclinical and clinical studies.

NCI Nanotechnology Characterization Laboratory (NCL)

- Characterization of physical properties of nanoparticles
- Pre-clinical efficacy
- Toxicity testing of nanoparticles intended for cancer therapy, imaging and diagnostics
- http://ncl.cancer.gov/working_application-process.asp



NIH MRI Research Facilities (NMRF)

www.lfmi.ninds.nih.gov/ ***&*** ***fmrif.nimh.nih.gov***

A shared, intramural resource for human MR imaging studies:

- Supported by all Institutes at NIH
- Resides within NINDS with NMR Center Steering Committee oversight
- Provides intellectual, technical and material support for investigators

In addition to LFMI, the NIH NMR Center contains active research programs from:

Laboratory of Cardiac Energetics, NHLBI

Laboratory of Diagnostic Radiology Research, CC

Laboratory of Brain and Cognition, NIMH

Stroke Diagnostic and Therapeutics Section of the Stroke Branch, NINDS

Animal MRI/Imaging Core Facilities

Laboratory of Functional and Molecular Imaging: http://www.lfmi.ninds.nih.gov/

A resource for magnetic resonance imaging of rodents
Equipment includes a 11.7T Animal MRI Scanner and a 7T Human MRI Scanner

7T/20 cm Animal MRI System at MIF

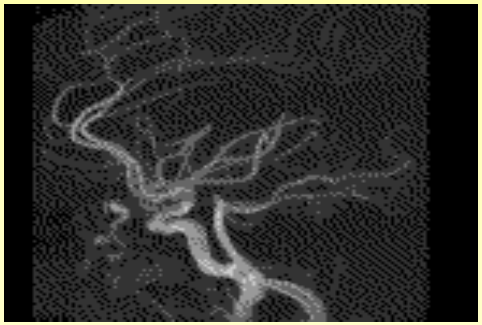
Selected Other Equipment:

MicroCat II CT System

Bioluminescence Imaging System

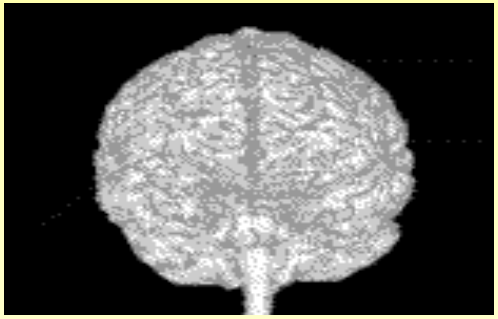
4.7 T / 40 cm Animal MRI System

7T Vertical Microimaging MRI System



Vascular imaging

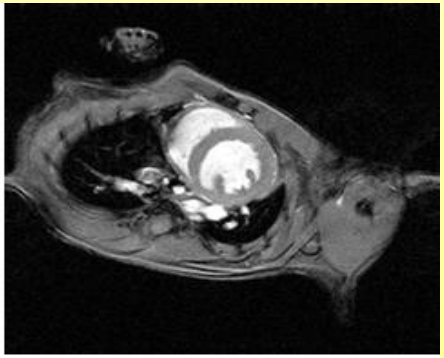
Functional MRI for brain imaging



Animal MRI/Imaging Core Facility (AMRI) at NHLBI

Develops and optimizes MRI methods for cardiovascular imaging of mice and rats
http://dir-intranet.nhlbi.nih.gov/amri/

Can also incorporate additional imaging Modalities that may be relevant such as computed tomography, ultrasound and bioluminescence



Examples of studies @ NHLBI:

- Cardiac imaging for ejection fraction
- High resolution imaging of myocardium for identification of infarct
- Imaging vessels in live mice and rats
- Imaging atherosclerotic plaque
- Perfusion of skeletal muscle
- Cellular imaging: magnetic labeling and tracking cell transplants
- Targeted MRI contrast agent research
- High resolution imaging of embryos
- High resolution imaging of fixed tissue

The Light Microscopy Core Facility in NHLBI

Provides state of the art equipment and image processing capabilities to assist researchers in experiments involving light microscopy.

Equipment:

Several types of confocal microscopes

A two-photon microscope

A standard epi-fluorescence wide-field microscope.

Capabilities:

Live cell imaging

Deep tissue-level imaging

Video-rate confocal imaging

Spectral imaging

Wide-field fluorescence and bright-field imaging of slides

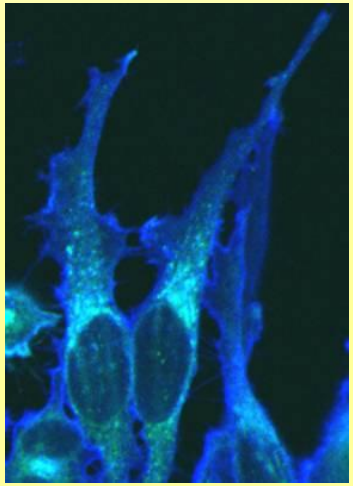
Image processing capabilities including deconvolution and 3D reconstruction as well as a custom in-house image processing

The Light Microscopy Core Facility in NHLBI

(http://dir-intranet.nhlbi.nih.gov/lmf/image-gallery/)

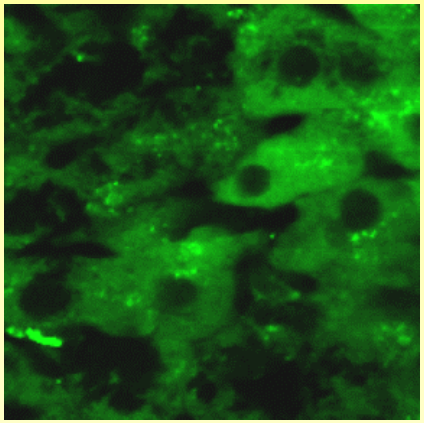
Rhodamine labeled blood vessels imaged deep in an intact mouse brain.

Distribution of GFP-tagged human ABCG1 transporter (green), and, cholesterol (blue) using cholesterol-specific cytochemical staining with filipin, in HeLa cells.



Drosophila embryo (200 microns thick) with cells labeled with Alexa 594.

2 photon image of autofluorescence from an intact mouse liver. This image was acquired approximately 50 microns into the tissue at a wavelength of 900 nm.



NIH Roadmap Initiatives

http://nihroadmap.nih.gov/

New Pathways to Discovery

- Building blocks, biological pathways and networks
- ➢ *Molecular libraries and imaging*
- Structural biology
- Bioinformatics and computational biology
- Nanomedicine

Research teams of the future

- High risk research
- Interdisciplinary research
- Public-private partnerships

Re-engineering the clinical research enterprise

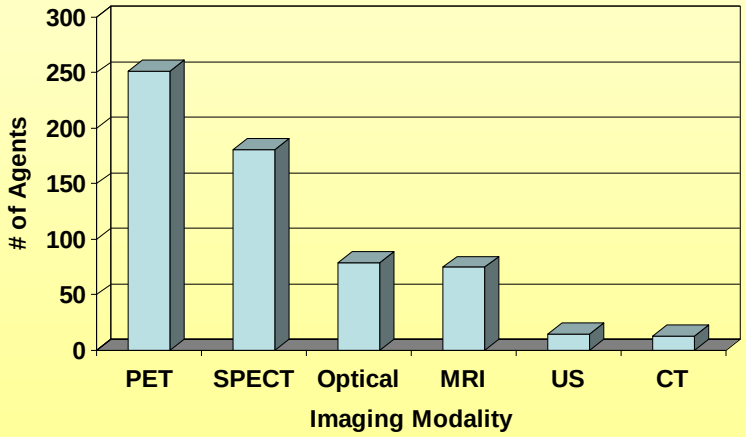
Molecular Libraries/Molecular Imaging Initiatives

- Molecular Libraries
  - Screening Centers
  - PubChem
  - Technology Development
- Molecular Imaging
  - Imaging Probe Database (MICAD)
  - Development of New Imaging Probes
  - *IPDC Core Synthesis Facility*

MICAD –Molecular Imaging and Contrast Database

http://micad.nih.gov

- MICAD - comprehensive, cumulative info. on ALL published *in vivo* imaging
- “Chapters” organized in 5 sections: background, synthesis, *in vitro*, animal and human studies
- Structures stored in PubChem and hyperlinked to “chapters”



NIBIB

National Institute of Biomedical Imaging and Bioengineering

Devel. of new imaging probes

http://www.nibib.nih.gov/HomePage

http://www.nibib.nih.gov/publicPage.cfm?section=gallery&action=view&page=1

NIBIB Intramural Program Activities

PET Radiochemistry Group:

- Molecular Imaging Probe Toolbox Group
- Theranostic Nanomedicine Group
- Radiochemistry Group
- Biological Molecular Imaging Group

Laboratory of Bioengineering and Physical Science:

- Drug Delivery and Kinetics
- Biomedical Instrumentation and Multiscale Imaging
- Ultramicro Immunodiagnostics
- Dynamics of Macromolecular Assembly
- Supramolecular Structure and Function

The Imaging Probe Development Center (IPDC)

www.ipdc.nih.gov

IPDC is a core synthesis facility producing commercially unavailable imaging probes as well as new probes for biomedical research and clinical applications

This may Include:

Any imaging modality: PET, SPECT, MRI, CT, fluorescence, ultrasound

Application of emerging technologies: Molecular modeling, microwave & solid phase syntheses, microfluidic reactors

Any type of composition: Nanoparticles & nanotubes, polymers, biologicals, new probes from drug screening efforts such as the libraries initiative

Improving known processes and developing novel syntheses

Operating from *in vitro* use, through *in vivo* studies, to clinical development

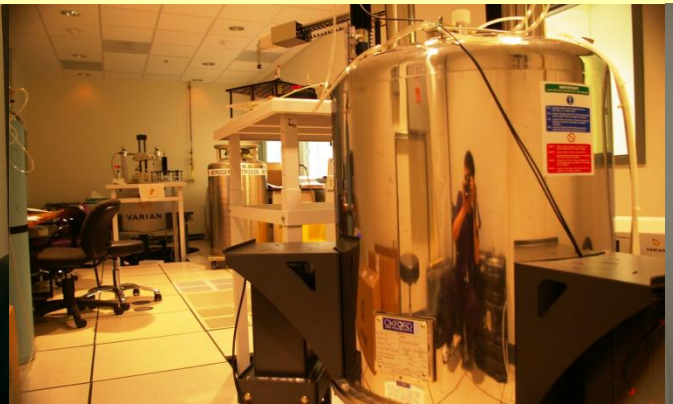
Fluorescent Dyes

- Modern and Classical synthetic dyes
- Structural modification of dyes to enhance targeting, physical properties or clearance characteristics
- Conjugates of targeting agent and dyes
- Activatable dye conjugates
- Application and development of specific linking strategies for dyes; e.g. cleavable compounds
- Advanced delivery techniques; e.g. multivalency, reactivity, permeability and binary targeting strategies



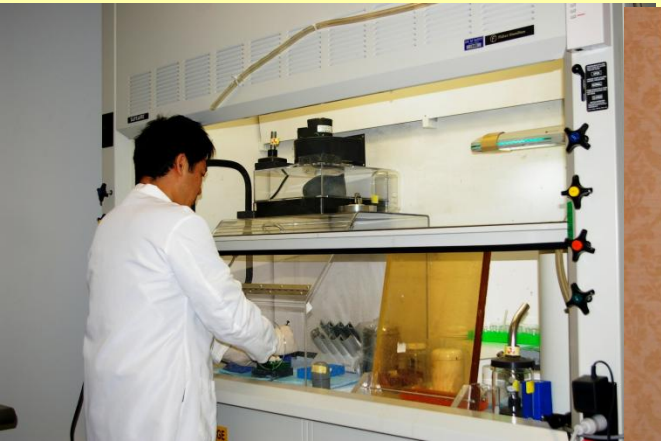
MRI Agents

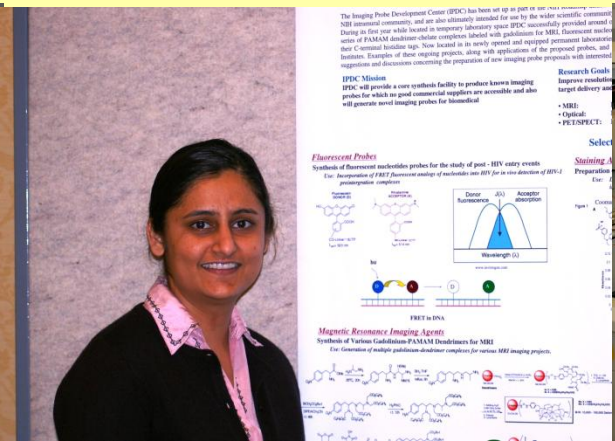
- Enhancement of metal (e.g. Gd) delivery and clearance
- Encapsulation techniques
- Targeted delivery of MRI agents
- Cleavable and binary delivery
- Polymeric systems such as dendrimers
- Particulate delivery systems such as iron oxides
- New techniques; e.g. hyperpolarization


PET/SPECT Agents

- Synthesis of precursors and standards
- Development of new radiolabeled targeting agents for PET/SPECT imaging
- Optimization of known preparation methods for PET/SPECT agents
- Improvements in specific activity
- Novel radionuclides for PET/SPECT detection
- Automated methods development





COLLABORATIONS

- **Many NIH Researchers Collaborate with Outside Entities**
  - **NIH internal research specializes in basic science**
  - **We need to pass the resulting technologies to those able to bring benefits to public health**
  - **This can be achieved through:**
    - **Licensing an NIH technology**
      - http://ott.od.nih.gov/Technologies/AbsSearchBox.aspx
    - **Cooperative Research and Development Agreement (CRADA)**
    - **Research Collaboration Agreement (RCA)**
    - **Exchange of Material or Information (MTA, CDA)**
  - **Contacting the TDC for the Institute concerned:**
    - http://ott.od.nih.gov/nih_staff/tdc.aspx

What are Cooperative Research Development Agreements? (CRADAs)

- A true collaborative effort with intellectual input from all parties
- Research Plan in-line with NIH's research mission
- Federal laboratory may provide personnel, services, facilities, equipment or other resources
- Collaborator may provide funds, personnel, services, facilities, equipment or other resources
- Provide option to exclusive license in specified field of use

Benefits:

Time and expertise of Federal researchers
Access to Federally owned materials, equipment and facilities
Select services such as animal toxicity studies or clinical trials
Paid access to existing Federally owned IP,
Background IP rights (via a royalty-bearing license)
CRADA Subject Inventions via an option to a royalty-bearing exclusive license)

NIH Technology Transfer Activities FY 2008

Invention Disclosures	402
New U.S. Patent Applications Filed	176
Total U.S. Patent Applications Filed	343
Issued U.S. Patents	88
Executed Licenses	259
Royalties ($ in millions)	$97.2

Standard CRADAs	33
Material CRADAs	39
Total Executed CRADAs	72

Source: http://www.ott.nih.gov/about_nih/statistics.aspx

NIH-OTT Licensing Opportunities – Cancer Diagnostics

8/14/2009	E-063-2008/1	**Nanoparticles for Imaging and Treatment of Brain Tumors**
8/12/2009	E-118-2009/0	Novel Diagnostic and Therapeutic Biomarkers for Squamous Cell Carcinomas
8/11/2009	E-058-2009/0	Development of a New Carbohydrate Antibody to GalNac1-3Gal
8/11/2009	E-207-2009/0	**Superior Method of Preparing Dendrimers for Use as Magnetic Resonance Imaging (MRI) Contrast Agents**
7/2/2009	E-042-2009/0	Immunogenic Peptide from NGEP Protein for Developing Prostate Cancer Vaccines
6/11/2009	E-086-2007/0	**An Imaging Radiotracer for the Noninvasive Detection of HER2-positive Tumors**
5/28/2009	E-340-2008/0	Methods for Identifying Breast Cancer Patients for Therapy with mTOR Inhibitors
5/28/2009	E-053-2009/0	Diagnostic Markers for Melanoma
5/28/2009	E-023-2009/0	Genomics-based Diagnostic Assay for Cancer
5/5/2009	E-179-2008/0	Salcut-NH2: A Novel Target for Development of Anti-Tumorigenic, Anti-Angiogenic Therapeutics and Diagnostics
5/4/2009	E-154-2004/0	Creation and Characterization of Carcinogen-Altered Mouse Epidermal Cell Lines
5/4/2009	E-257-2004/0	Modulating Expression of the Metastasis Suppressor MxA
5/4/2009	E-223-2006/1	Small-Molecule TSH Receptor Modulators for Diagnosis and Treatment of Thyroid Disease and Cancer

Summary

- Imaging sciences have a long and distinguished history at NIH
- Current NIH investments in imaging technologies are extensive and future investments in all aspects of molecular imaging will remain an important part of the NIH research portfolio
- Molecular imaging is complementary to and synergistic with other important NIH programs such as small molecule drug discovery, high resolution imaging research, and the application of biological targeting agents and nanotechnology
- Multiple opportunities are present for collaborative work under various agreements and across a wide range of these technologies