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.*

PET for Neuroimaging:
Quantitation of uptake
Drug tracking
Occupancy & receptor studies
Early diagnosis
Guide for therapy
Alzheimer’s and other neurological diseases

Sept 8, 2008
**NIH Institutes with Major Imaging Interests**

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<th>Major Interests:</th>
<th>Others:</th>
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<td>NCI</td>
<td>NIDDK</td>
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<td>NIAID</td>
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<td>NHLBI</td>
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<td>NINDS</td>
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<td>NIMH</td>
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<td>NIBIB</td>
<td>NIEHS</td>
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<td>&amp; Clinical Center</td>
<td>NICDR</td>
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**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*
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
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.
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.

The New MONICA System for Small Animal SPECT Scanning

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

“MOible Nuclear Imaging CAmeras”.

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

Fluorescent dye

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.
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](http://ncl.cancer.gov/working_application-process.asp)
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


A resource for magnetic resonance imaging of rodents

Equipment includes a 11.7T Animal MRI Scanner and a 7T Human MRI Scanner

Selected Other Equipment:

- MicroCat II CT System
- Bioluminescence Imaging System
- 4.7 T / 40 cm Animal MRI System
- 7T Vertical Microimaging MRI System

Functional MRI for brain imaging

Vascular imaging
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
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.
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

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

NIBIB Intramural Program Activities

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:
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

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
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<tbody>
<tr>
<td>Invention Disclosures</td>
<td>402</td>
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<tr>
<td>New U.S. Patent Applications Filed</td>
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<tr>
<td>Total U.S. Patent Applications Filed</td>
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<tr>
<td>Issued U.S. Patents</td>
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<tr>
<td>Executed Licenses</td>
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<td>Royalties ($ in millions)</td>
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<td>Standard CRADAs</td>
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<tr>
<td>Material CRADAs</td>
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<tr>
<td>Total Executed CRADAs</td>
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<tr>
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<th>Code</th>
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<tr>
<td>8/14/2009</td>
<td>E-063-2008/1</td>
<td>Nanoparticles for Imaging and Treatment of Brain Tumors</td>
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<tr>
<td>8/12/2009</td>
<td>E-118-2009/0</td>
<td>Novel Diagnostic and Therapeutic Biomarkers for Squamous Cell Carcinomas</td>
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<tr>
<td>8/11/2009</td>
<td>E-058-2009/0</td>
<td>Development of a New Carbohydrate Antibody to GalNac1-3Gal</td>
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<td>7/2/2009</td>
<td>E-042-2009/0</td>
<td>Immunogenic Peptide from NGEP Protein for Developing Prostate Cancer Vaccines</td>
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<td>5/28/2009</td>
<td>E-340-2008/0</td>
<td>Methods for Identifying Breast Cancer Patients for Therapy with mTOR Inhibitors</td>
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<td>5/28/2009</td>
<td>E-053-2009/0</td>
<td>Diagnostic Markers for Melanoma</td>
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<td>5/4/2009</td>
<td>E-257-2004/0</td>
<td>Modulating Expression of the Metastasis Suppressor MxA</td>
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<tr>
<td>5/4/2009</td>
<td>E-223-2006/1</td>
<td>Small-Molecule TSH Receptor Modulators for Diagnosis and Treatment of Thyroid Disease and Cancer</td>
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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