Advances in Cancer Imaging

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Beth Israel Deaconess Medical Center

Professor of Medicine
Professor of Radiology
Harvard Medical School
# Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Employment</td>
<td>No conflict of interest to disclose</td>
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<td>Research support</td>
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<td>Scientific advisory board</td>
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<td>Speakers bureau</td>
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<tr>
<td>Major stockholder</td>
<td>Curadel, Curadel ResVet Imaging, Curadel Surgical Innovations</td>
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<td>Patents</td>
<td>FLARE™ Imaging Systems and Contrast Agents</td>
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<td>Honoraria</td>
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<td>Travel support</td>
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<tr>
<td>Other</td>
<td>This talk describes the off-label use of indocyanine green and methylene blue, two NIR fluorophores that are FDA-approved for other indications. The FLARE™ imaging system is investigational only and not approved for the indications shown.</td>
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</table>
Outline

I. What is cancer imaging? And how is it performed?

II. State-of-the-Art in Screening

III. State-of-the-Art in Staging

IV. State-of-the-Art in Treatment and Monitoring

V. Reading the Tea Leaves
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V. Reading the Tea Leaves
The “Big Picture” in Cancer

Number of Cells

\[10^{12}\]

\[10^9\]

\[10^6\]

\[10^3\]

Time

Death of Patient

Frangioni JV. “New technologies for human cancer imaging.”
The Cancer Detection Problem (Cont.)

Untreated, how many net cell divisions between clinical detection and death of the patient?

\[ 2^x = 1000 \]

\[ x \approx 10 \]

How long does this take?

- Burkitt’s Lymphoma \((t_D 24 \text{ hr})\): 10 days
- Metastatic Solid Tumors \((t_D 30-45 \text{ d})\): 9 - 15 mo
The Cancer Detection Problem (Cont.)

A Revised Definition of Remission:

There is somewhere between zero (cure) and one billion cancer cells in the body, but we just can’t say how many, or where

Implications for Chemotherapy:

Solid tumors are being treated during lag, rather than log, phase of growth
Imaging in Cancer Care

- **Screening**
  - Do they have it?

- **Staging**
  - How much & where?

- **Treatment**
  - Kill malignant cells
# Current State of the Art in Cancer Imaging

<table>
<thead>
<tr>
<th>Modality</th>
<th>3-D</th>
<th>3-D Specific</th>
<th>Full Exogenous</th>
<th>Limit of Cell Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>CT</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>MRI</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>SPECT</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>$\approx 10^9$ cells/cm³</td>
</tr>
<tr>
<td>PET</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>$\approx 10^8$-$10^9$ cells/cm³</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>Optical (2-D)</td>
<td>-</td>
<td>+</td>
<td></td>
<td>$\approx 10^1$-$10^4$ cells/cm²</td>
</tr>
</tbody>
</table>

**Typical Doses of Intravenously Administered Diagnostic Agents and Radiotracers from High (CT) to Low (PET)**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Human dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>75 cc of 930 mM solution ($\approx 800$ Da) = 56 g</td>
</tr>
<tr>
<td>MRI</td>
<td>15 cc of 500 mM solution ($\approx 940$ Da) = 7 g</td>
</tr>
<tr>
<td>Optical</td>
<td>$\approx 10$ cc of 1 mM solution ($\approx 1,000$ Da) = 10 mg</td>
</tr>
<tr>
<td>SPECT</td>
<td>20 mCi (10,000 Ci/mmol; $\approx 500$ Da) = 1 $\mu$g</td>
</tr>
<tr>
<td>PET</td>
<td>20 mCi (10,000 Ci/mmol; $\approx 500$ Da) = 1 $\mu$g</td>
</tr>
</tbody>
</table>

2 regular-strength acetaminophen (bioavailable dose) = 600 mg

FDA definition of “micro-dosing” = 100 $\mu$g

## Bayes’ Theorem Applied to Cancer Imaging

Consider 100 subjects given a cancer imaging test having a sensitivity of 90% and a specificity of 90%:

<table>
<thead>
<tr>
<th>Incidence</th>
<th>True Positives</th>
<th>False Positives</th>
<th>True Negatives</th>
<th>False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>1</td>
<td>10</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>10%</td>
<td>9</td>
<td>9</td>
<td>81</td>
<td>1</td>
</tr>
<tr>
<td>50%</td>
<td>45</td>
<td>5</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>90%</td>
<td>81</td>
<td>1</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>
Other Confounding Issues

- **Lead Time Bias**: Overestimation of survival and treatment efficacy.

- **Length Bias**: Slower growing tumors are more easily detected, and typically at a lower stage.

- **Stage Migration**: A.k.a., The Will Rogers’ Effect. More sensitive detection or accurate staging improves the outcome at any given stage.

- **Over-Treatment**: For example, prostate cancer.

- **Cost**: New technology is expensive.
Contrast Generation at the Level of the Cell

Diameter: \( \approx 10-20 \ \mu m \)

Volume: \( \approx 1-2 \ \text{pL} \ (1 \times 10^{-12} \ \text{L}) \)

Cell Surface Receptors: Average \( 10^3-10^4/\text{cell} \)

<table>
<thead>
<tr>
<th>Total per cell:</th>
<th>( 10^7 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSMA or ErbB2:</td>
<td>( 10^5-10^6 )</td>
</tr>
<tr>
<td>Melatonin Receptor:</td>
<td>( 4 \times 10^4 )</td>
</tr>
<tr>
<td>Monocyte FcR:</td>
<td>( 2 \times 10^4 )</td>
</tr>
<tr>
<td>Epo Receptor:</td>
<td>( 8 \times 10^2 )</td>
</tr>
<tr>
<td>Type I IFN Receptor:</td>
<td>( 7 \times 10^2 )</td>
</tr>
<tr>
<td>TPO Receptor (c-MPL)</td>
<td>( 6 \times 10^1 )</td>
</tr>
</tbody>
</table>
### Binding Sites vs. Contrast Agent or Radiotracer Concentration

<table>
<thead>
<tr>
<th>Receptors/Epitopes/Ligands</th>
<th>Moles</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^0$</td>
<td>$1.7 \times 10^{-24}$</td>
<td>1.7 pM</td>
</tr>
<tr>
<td>$10^1$</td>
<td>$1.7 \times 10^{-23}$</td>
<td>17 pM</td>
</tr>
<tr>
<td>$10^2$</td>
<td>$1.7 \times 10^{-22}$</td>
<td>170 pM</td>
</tr>
<tr>
<td>$10^3$</td>
<td>$1.7 \times 10^{-21}$</td>
<td>1.7 nM</td>
</tr>
<tr>
<td>$10^4$</td>
<td>$1.7 \times 10^{-20}$</td>
<td>17 nM</td>
</tr>
<tr>
<td>$10^5$</td>
<td>$1.7 \times 10^{-19}$</td>
<td>170 nM</td>
</tr>
<tr>
<td>$10^6$</td>
<td>$1.7 \times 10^{-18}$</td>
<td>1.7 µM</td>
</tr>
</tbody>
</table>
# Binding Sites vs. Contrast Agent or Radiotracer Concentration

<table>
<thead>
<tr>
<th>Receptors/Epitopes/Ligands/</th>
<th>Moles</th>
<th>Cell Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound 10^0</td>
<td>1.7 x 10^{-24}</td>
<td>1.7 pM</td>
</tr>
<tr>
<td>PET 10^1</td>
<td>1.7 x 10^{-23}</td>
<td>17 pM</td>
</tr>
<tr>
<td>SPECT 10^2</td>
<td>1.7 x 10^{-22}</td>
<td>170 pM</td>
</tr>
<tr>
<td>Optical 10^3</td>
<td>1.7 x 10^{-21}</td>
<td>1.7 nM</td>
</tr>
<tr>
<td>10^4</td>
<td>1.7 x 10^{-20}</td>
<td>17 nM</td>
</tr>
<tr>
<td>10^5</td>
<td>1.7 x 10^{-19}</td>
<td>170 nM</td>
</tr>
<tr>
<td>10^6</td>
<td>1.7 x 10^{-18}</td>
<td>1.7 µM</td>
</tr>
<tr>
<td>MRI CT</td>
<td>Highest Achievable Likely 800 nM</td>
<td></td>
</tr>
</tbody>
</table>
Contrast Generation at the Level of the Organism

SBR for a Targeted Exogenous Fluorophore

Introduction

SBR \approx 1

Biodistribution

SBR \approx 1

Clearance

SBR High
Contrast Generation at the Level of the Organism

Adapted from J. E. Riviere, “Comparative Pharmacokinetics”, Iowa State Press (Ames, IA) 1999

Most of “Molecular Imaging”
Additional Barriers to *In Vivo* Imaging with IV Contrast

1) **Plasma**: Inhibition and/or competition with ligand

2) **Endothelium**: Effective pore size $\leq 40,000$ Da ($\leq 5$ nm HD)

3) **Blood-Brain Barrier (Specialized Endothelium)**: Restricted to small, uncharged, hydrophobic molecules

4) **Basement Membrane**: Present in all epithelia. Pre-invasive cancers not readily accessible to bloodstream

5) **Tumor Itself**: High hydrostatic pressure, leaky lymphatics, charge, mucous

6) **Clearance**: Kidney (Renal): $\leq 40,000$ Da ($\leq 5$ nm HD) cleared, rest remains in blood

   Liver (Hepatic): $\geq 10$ nm HD
Factors Impacting the SBR of Diagnostic Agents

A Complex, Three-Dimensional Technical Problem

1) Improved chemistry (affinity and specificity)
2) Improved chemistry (better clearance and reduced background)
3) Improved chemistry/physics (improved sensitivity)

Outline

I. What is cancer imaging? And how is it performed?

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V. Reading the Tea Leaves
Screening of the “Big 4”

Remember Bayes’ Theorem

- Breast
- Lung
- Colon
- Prostate
Breast Cancer Screening

1) **Tomosynthesis plus Digital Mammography:**

   • Tomosynthesis reduces recall rate but has no impact on cancer detection.

   • Digital mammography compared to screening film mammography only improves cancer detection rates in women <50 yo.

But, average sensitivity is only ≈ 40% and although specificity is ≈ 95%, accuracy is only ≈ 70-75% and PPV is only 11%. In young women with large fatty breasts, accuracy can be as low as 50% (flip of a coin).
Breast Cancer Screening

2) Ultrasound-Based Elastography:

- Secondary evaluation of fatty breasts and a negative mammogram.
- Images stress and strain of the tissue in the FOV.
- Extremely dependent on device and software algorithms: sensitivity 35-100%, specificity 35-100% in the literature.
Breast Cancer Screening

3) MRI with Contrast:

- Increases sensitivity to 73% and specificity to 88% for accuracy ≈ 80%.

- No evidence to date that 3.0T vs. 1.5T improves imaging.

- Screening currently limited to high-risk populations due to cost and complexity.

- Can be combined with gadolinium-based DCE-MRI for improved accuracy.

Breast Cancer Screening

4) Positron Emission Mammography (PEM):

- Currently only $^{18}$F-FDG available and used at relatively high dose.
- Currently only large bore clinical scanners or parallel plate detectors.
- Initial results from pendant breasts in small bores are promising (2 mm resolution):

Lung Cancer Screening

1) Low-Dose CT (LDCT):
   - Sensitivity ranges from 80% to 100%. Specificity ranges from 28% to 100%.
   - Efficacy limited to smokers.
   - False-positives requiring rescan is common.
   - Harms include radiation exposure and over-diagnosis.

2) PET:
   - Currently unpublished study at Sumitomo Corporation in Japan on every worker at the company.
Colon Cancer Screening

1) Lumenography:

- Non-invasive imaging of body lumens and virtual “oscopies” but prep is currently still the same!
- Virtual reality interrogation of the entire lumen.
- CT- or MRI-based. CT methods are more advanced but necessitate radiation exposure. Shortage of experienced readers in the US.
- CMS and US PSTF argue that there is not enough evidence to assess colonography as a screening tool for colorectal cancer.

www.medicalphysics.uchicago.edu
2) Optical Coherence Tomography (OCT):

- Think of it as ultrasound using light. Complements fiberoscopy.
- Micron (single cell) resolution at mm depths.
- Recent advances in frequency-domain methods permit rapid interrogation of large 3D volumes in the GI tract:

Prostate Cancer Screening

None.
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Staging and the All-Important Decision about “Curative Intent”

**PET/MRI**

**PET**: High sensitivity and (potentially) specificity

**MRI**: High resolution anatomy

*** Success is completely dependent on the affinity, biodistribution, clearance, and radioisotope of the radiotracer.

At the present time, only $^{18}$F-FDG is widely available
Positron Emission Tomography (PET)

Notes: Detection via coincident counting with fixed ring of detectors
Blurring due to annihilation distance (≈ 1 - 10 mm)
Positronium formation (lung is less dense - less matter - lower resolution)
Some isotopes emit prompt (contaminating) gamma rays
Current clinical scanners have a zero background sensitivity of ≈ 1,000 cells!
PET/MRI

Breast cancer metastatic to bone (bone scan negative)

PET/MRI

Right leg melanoma metastatic to inguinal and iliac nodes

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Treatment Monitoring

- $^{18}$F-FDG for assessing cytotoxic treatment efficacy in a variety of diseases

- Ion beam therapy-induced PET imaging

- Image-guided cancer surgery using invisible near-infrared fluorescent light
Ion Beam-Induced PET Imaging

*In vivo* dose and range verification for proton or carbon ions (Either in-beam or post-Rx PET)

Proton ($\approx 250$ MeV) or carbon ($\approx 400$ MeV) ion beams create nuclear reactions in tissues that produce positrons of endogenous atoms ($^{15}$O, $^{13}$N, $^{11}$C), which can be imaged by PET.

NIR Fluorescence for Image-Guided Surgery

Because of 4 physical principles:
1) Photon absorption is minimal
2) Photon scatter is minimal
3) Autofluorescence is minimal
4) NIR light is invisible to the human eye

Benefits are:
• High contrast: “Bright stars on a black sky”
• No change to the look of the surgical field
• Any object can be potentially be highlighted
• Real-time intraoperative imaging
• Millimeter, instead of micron, depth detection
1) Photon Absorption is Minimal in the NIR

2) Photon Scatter is Minimal in the NIR

**Skin** (Rayleigh-Type, i.e. Wavelength-Dependent Scatter)

**Breast** (Mie-Type, i.e., Non-Wavelength-Dependent Scatter)
3) Autofluorescence is Minimal in the NIR


4) NIR Light is Invisible to the Human Eye

The visible spectrum ranges from approximately 400 nm (violet) to 700 nm (red). Beyond 700 nm, the wavelength is considered near-infrared (NIR). The NIR window, which is the range of wavelengths that are optimal for imaging, typically includes 700 nm to 900 nm. This is because the sensitivity of Phototopic vision, which is the ability to see in bright light, decreases sharply below 700 nm, while Scotopic vision, which is the ability to see in dim light, remains relatively constant. Therefore, NIR light is invisible to the human eye due to its location in the spectrum where the human visual system ceases to function effectively.
Typical Imaging System Setup

Form Factors
Open surgery
Fiberoscopy

Key Parameters
Fluence rate adjusted for laser Class 3R
Fluence rate adjusted below photobleaching
NIR-compatible optics
Real-time acquisition and display

NIR Contrast: “Bright Stars on a Black Sky” **

** Provided that optimal imaging systems and contrast agents are available.
So, Why all the Excitement?

- Sensitive, real-time, high-resolution tumor margin detection (deposits as small as 10 cells wide)
- Avoidance of blood vessels, nerves, ureters, bile ducts, and other vital structures during tumor resection
- Rapid identification of sentinel lymph nodes and other sub-surface structures without the need for ionizing radiation
- Reduced anesthesia time
- Lower patient morbidity from damage to vital structures
- Increase surgeon and OR throughput (raise income)
- Improved surgical outcomes lead to lower healthcare costs
Clinically-Available NIR Fluorophores

500+ patients studied to date at 6 clinical trial sites in 4 countries on 3 continents

700 nm Fluorescence

**Methylene Blue**

- Ureter imaging
- Bile duct imaging
- Cardiac perfusion imaging
- Insulinoma

M.W. 320

800 nm Fluorescence

**Indocyanine Green**

- Sentinel lymph node mapping
- NIR angiography
- Perforator flap mapping
- Intraluminal imaging

M.W. 776
ICG: Breast Cancer

- Exposed Axilla
- Exposed SLNs
- Resected SLNs

ICG: Colon Cancer Hepatic Metastases

van der Vorst et al., Cancer. 2013; 119: 3411-3418.

Real-time identification of colorectal liver metastases in 22 patients undergoing liver resection.

NIR fluorescence imaging was performed 24 or 48 h after administration of 10 or 20 mg ICG.

5 of 40 small, superficial metastases not detectable by ultrasound or palpation
Methylene Blue: Parathyroid Tumor Imaging

van der Vorst et al., Head and Neck. 2013; In Press
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# The History of Clinical Translation in Imaging

“What we learn from history is that people don't learn from history.” Warren Buffett

<table>
<thead>
<tr>
<th>Modality</th>
<th>First Patient</th>
<th>Clinical Acceptance</th>
<th>Lag</th>
<th>Mean (yr)</th>
<th>Median (yr)</th>
</tr>
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<tbody>
<tr>
<td>PET</td>
<td>1953</td>
<td>≈ 2003</td>
<td>≈50 years</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Plain Films (X-rays)</td>
<td>1895</td>
<td>≈ 1920s</td>
<td>≈ 25 years</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>SPECT</td>
<td>≈1963</td>
<td>≈ 1985</td>
<td>≈23 years</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>≈1940s</td>
<td>≈ 1960s</td>
<td>≈ 20 years</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>1970</td>
<td>≈ 1985</td>
<td>≈15 years</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>1967</td>
<td>≈ 1975</td>
<td>≈ 7 years</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>NIR Fluorescence</td>
<td>1999</td>
<td>? ?</td>
<td>14+ years</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

Frangioni Laboratory

www.centerformolecularimaging.org
The Critical Objective Test for New Medical Technology

Will it improve patient management?

Not... Is there a clinical need?
...necessary but not sufficient
Is it possible to do?
Is it exciting to do?
Does it represent state-of-the-art engineering and/or chemistry?
Predictions for the Next Decade

Screening

• Optical coherence tomography (OCT) and/or NIR light (with or without contrast) will enable more sensitive and specific fiberscopic screening (endoscopy, colonoscopy, colposcopy, etc.)

• But, because of GPU and other technical advances, virtual lumenography will replace fiberoscopy for some clinical applications

• PET/MRI will be accepted as standard of care for breast cancer screening after advances in radiotracers and detectors reduce dose to 10-100X lower than today and dedicated instruments are developed
Predictions for the Next Decade

Staging

• The imaging signature for “aggressive” prostate cancer will be found thus enabling improved screening and staging

• PET/MRI will replace CT in most cancer staging once improved radiotracers are developed and hybrid imaging systems are refined - improved confidence in the decision for “curative intent”

• Sentinel lymph node mapping will be performed either non-invasively using PET/MRI or invasively without the need for radioactivity
Predictions for the Next Decade

Treatment

- NIR fluorescence-guided surgery will lower anesthesia time, lower margin positivity rates, reduce morbidity from damage to normal structures, and/or permit aggressive metastasectomies

- Spectrally unmixed photoacoustic imaging of deoxy- and oxy-hemoglobin will be used routinely for real-time monitoring radiofrequency ablation and radiotherapy

- Targeted contrast agents will morph into targeted cytotoxic agents thus eliminating the need for cancer imaging altogether!

Seeing is Curing™
The BIDMC Translational Cancer Imaging Facility (TCIF)

Slosberg-Landay Basement
The BIDMC Translational Cancer Imaging Facility (TCIF)

Table 1 – Functional Organization of the BIDMC Translational Cancer Imaging Facility (TCIF)

<table>
<thead>
<tr>
<th>Figure 1</th>
<th>Category</th>
<th>Agency/Board</th>
<th>Regulation(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Standard Operating Procedures (SOPs)</td>
<td>All</td>
<td>All</td>
<td>Preparation of written documentation and templates</td>
</tr>
<tr>
<td>B</td>
<td>Radiation Safety</td>
<td>Radiation Safety, MA Dept of Public Health</td>
<td>MA-CMR-105, NRC, ALARA</td>
<td>Nuclear regulatory permitting for the handling and disposal of radioisotopes</td>
</tr>
<tr>
<td>C</td>
<td>First-in-Human</td>
<td>FDA</td>
<td>eIND/IND</td>
<td>Investigational new drug application approval prior to IRB</td>
</tr>
<tr>
<td>D</td>
<td>Clinical Trial</td>
<td>IRB</td>
<td>45 CFR 46 and 21 CFR 50</td>
<td>Institutional Review Board approval for clinical trial</td>
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<tr>
<td>E</td>
<td>cGMP Synthesis</td>
<td>FDA</td>
<td>21 CFR 210/211, USP &lt;823&gt;</td>
<td>PET radiotracer cGMP</td>
</tr>
<tr>
<td>F</td>
<td>Sterile Compounding</td>
<td>MA Board of Pharmacy</td>
<td>MA-CMR-247, USP &lt;797&gt;</td>
<td>Sterile compounding of API</td>
</tr>
<tr>
<td>G</td>
<td>QA/QC</td>
<td>FDA</td>
<td>USP 467, etc.</td>
<td>Quality assurance/quality control</td>
</tr>
</tbody>
</table>
The BIDMC Translational Cancer Imaging Facility (TCIF)

BYOD (Bring Your Own Drug) - We Provide the Rest

- cGMP manufacture of small molecules, proteins, and cells under ISO-7
- Radiolabeling of APIs for SPECT or PET (FDA-mandated BioD and PK)
- Aseptic fill-finish of non-radioactive or radioactive APIs
- Longwood Small Animal Imaging Facility (Longwood SAIF) for rodent validation, biodistribution, and pharmacokinetics
- Dedicated and experienced staff to assist with process validation and regulatory documentation (BYO Drug)
FLARE™ Imaging Network

Beth Israel Deaconess Medical Center, Boston
Bernard Lee, M.D.  Samuel Lin, M.D.  Adam Tobias, M.S.

Brigham & Women’s Hospital, Boston
Yolonda Colson, M.D., Ph.D.

Dana-Farber Cancer Institute, Boston
Susan Troyan, M.D.

Leiden University Medical Center, The Netherlands
Alex Vahrmeijer M.D.
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Acknowledgements (Presented Data)

Frangioni Laboratory (BIDMC):
- Yoshimoto Ashitate
- Hak Soo Choi
- Sylvain Gioux
- Lorissa Moffitt

BIDMC: Bernie Lee
- Samuel Lin
- Adam Tobias

DFCI: Susan Troyan

Leiden University Medical Center:
- Alex Vahrmeijer
- Merlijn Hutteman
- Cornelis van de Velde
- Joost van der Vorst
Acknowledgements (Funding)

R01-CA-115296 (BRP)
R01-EB-005805
R01-EB-001022
R01-EB-011523
R01-CA-134493
R21/R33-EB-000673
R21/R33-CA-88245
R21-CA-110185
DOE DE-FG02-01ER63188
CIMIT Awards (4)
Doris Duke Charitable Foundation
CaPCURE
Relevant Reviews


You are all invited to continue this conversation!

Focus on clinical translation

www.advancedmolecularimaging.org
The Critical Path Initiative

Basic Research
Prototype Design or Discovery
Preclinical Development
Clinical Development
FDA Filing/Approval & Launch Preparation

Marketing and Patient Availability

Logarithmic Scale in Terms of Time, Money, and Effort

Basic Research through First-in-Human Trial (Translation)

Everything Else (Commercialization)

Linear Scale in Terms of Time, Money, and Effort
The “Risk Conundrum” for First-in-Human Device Trials

The FDA IND Process for First-in-Human Drug Trials

Research Grade
- Diagnostic Agent Development
- Previous Preclinical Research Data

QA/QC
- Facilities
- Personnel
- Reagent Sourcing/Controls
- cGMP Processes
- cGMP Manufacturing
- Sterile Compounding
- SOP Documentation

cGMP Development
- Scale Up: cGMP-Compatible Synthetic Scheme Development

cGMP Synthesis & Validation
- cGMP Process Validation
- cGMP Synthesis

Toxicology/Safety
- Toxicology
- Mutagenicity
- Genotoxicity
- Toxikinetics

Manufacturing
- Sterile Compounding
- Drug Release

Clinical Grade
- Previous Relevant Clinical Data
- Protocol Planning
- Clinical Protocol

Documentation
- Agent Development
- cGMP Development
- Preclinical Data
- Toxicology Data
- Manufacturing Data

Clinical Studies
- Protocol Plan

Clinical Trial
- eIND/IND Application
- IRB Application
- Approval

The FDA IND Process for First-in-Human Drug Trials
<table>
<thead>
<tr>
<th>Contribution</th>
<th>Barrier</th>
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<tbody>
<tr>
<td>5%</td>
<td>Science and engineering</td>
</tr>
<tr>
<td>5%</td>
<td>Pre-clinical and first-in-human studies</td>
</tr>
<tr>
<td>35%</td>
<td>Economic:</td>
</tr>
<tr>
<td></td>
<td>Market size</td>
</tr>
<tr>
<td></td>
<td>Cost of approval process</td>
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<tr>
<td></td>
<td>Cost of “time”</td>
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<tr>
<td>35%</td>
<td>Regulatory:</td>
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<td>ISO 13485 (Devices)</td>
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<td>ICH Q10 (Contrast Agents)</td>
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<td></td>
<td>Institutional Review Board (IRB)</td>
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<td>Food &amp; Drug Administration (FDA)</td>
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<td>European Medicines Agency (EMEA)</td>
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<tr>
<td>20%</td>
<td>Integration into clinical workflow:</td>
</tr>
<tr>
<td></td>
<td>Physicians and Surgeons</td>
</tr>
<tr>
<td></td>
<td>Nursing and Allied Health Professionals</td>
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Why are Diagnostic Agent Approvals so Rare?

**Time and Money (Per Agent)**

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Approx. Cost</th>
<th>Approx. Time</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>$0.3-1M</td>
<td>6-12 months</td>
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<tr>
<td>Phase II</td>
<td>$5-10M</td>
<td>1-2 years</td>
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<tr>
<td>Phase III</td>
<td>$30-50M</td>
<td>2-3 years</td>
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</tbody>
</table>

**Total: $35-61M ** 3.5-6 years

** As high as $200M for high-dose MRI/CT agents