Cancer Imaging
Methods and Applications

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Do any of these images look familiar? Can you identify them?
• Diagnosis/staging of disease at the time of presentation
• Assess response to therapy
• Surveillance tool (wait and watch)
• Screening tool for clinically occult cancers
Radiation Oncology

• Identification of tumors to be irradiated
• Accurate delivery of radiation to the target (tumor)

Goals
Delineation of patient anatomy (desired radiation target) and organs at risk that should be spared from radiation dose.

Identified volumes are then used to compute an optimal radiation treatment strategy.

Durante & Loeffler, Nat Rev Clin Oncol
Drug Discovery and Development

- Target expressed and functional?
- Relative efficacy of different agents
- Species variation
- Biodistribution, pharmacokinetics
- Toxicity, safety
- Validate imaging for subsequent clinical use
- Efficacy
- Safety
- Human pharmacokinetics
- Dose adjustment
- Availability
- Efficacy
- Dose adjustment
- Presence of target

Target identification
Compound screening
Preclinical testing of lead compound
Phase 1-2 trials
Phase 3 trials
Sales

Genomics and proteomics
Drug discovery
Drug development
Clinical use

Metabonomics

Rudin and Weissleder, Nature Rev 2003
RECIST: Response Evaluation Criteria In Solid Tumors

RECIST criteria are a voluntary, international standard, and are not an NCI standard. They are based on a simplification of former methods (WHO, ECOG) and based on measurable disease, i.e., the presence of at least one measurable lesion.

RECIST criteria offer a simplified, conservative, extraction of imaging data for wide application in clinical trials. They presume that linear measures are an adequate substitute for 2-D methods and registers four response categories:

- CR (complete response) = disappearance of all target lesions
- PR (partial response) = 30% decrease in the sum of the longest diameter of target lesions
- PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions
- SD (stable disease) = small changes that do not meet above criteria

☑ Simple ruler measurements
☑ Common language of efficacy

Great!! So what is the problem?

The Changing Landscape of Medicine

Medicine has gone molecular...

Hanahan and Weinberg, Cell 2011
Problems: Patient selection, biological end point assessment

Hanahan and Weinberg, Cell 2011
Is RECIST good enough?

Traditional **cytotoxics** vs. modern **cytostatics**

Does not account for morphologic complexity; tumor heterogeneity

Tumor shrinkage alone may not be a sensitive measure of biological activity

Volumetric change is a late, non-specific end point

**Need: Functional response indicators**
Molecular Imaging

Visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems. (includes 2D and 3D imaging and quantification over time)
So what can we see?

- Evading apoptosis
- Self sufficiency in growth signals
- Insensitivity to anti-growth signals
- Limitless replication potential
- Abnormal glucose uptake & metabolism
- Resistance to acid-mediated toxicity
- Tissue invasion and metastasis
- Sustained angiogenesis
- Avoidance of immune surveillance
### Table 1. Characteristics of imaging modalities used in the clinic

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Spatial resolution</th>
<th>Limit for depth of imaging</th>
<th>Sensitivity estimates</th>
<th>Agent/probe used</th>
<th>Amount of agent&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>1–2 mm</td>
<td>No</td>
<td>$10^{-11}–10^{-12}$ M</td>
<td>Radiolabel (e.g. $^{18}$F)</td>
<td>Nanograms</td>
</tr>
<tr>
<td>SPECT</td>
<td>1–2 mm</td>
<td>No</td>
<td>$10^{-10}–10^{-11}$ M</td>
<td>Radiolabel (e.g. $^{99m}$Tc)</td>
<td>Micrograms</td>
</tr>
<tr>
<td>Optical/fluorescence</td>
<td>~1/10 of depth of imaging</td>
<td>Up to 10 cm&lt;sup&gt;b&lt;/sup&gt;</td>
<td>$10^{-9}–10^{-11}$ M</td>
<td>Fluorescence</td>
<td>Micrograms to milligrams</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>50–500 μm</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Gas-filled bubbles</td>
<td>Micrograms to milligrams</td>
</tr>
<tr>
<td>MRI</td>
<td>25–100 μm</td>
<td>No</td>
<td>$10^{-3}–10^{-5}$ M&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Paramagnetic or ferromagnetic iodine&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Milligrams to grams</td>
</tr>
<tr>
<td>CT</td>
<td>50–200 μm</td>
<td>No</td>
<td>$10^{-2}–10^{-3}$ M&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>Grams</td>
</tr>
</tbody>
</table>

<sup>a</sup> Estimates of the amounts needed to be injected into humans.

<sup>b</sup> Less than 1 cm for reflectance imaging; up to approximately 10 cm with fluorescence tomographic technique.

<sup>c</sup> Reduced signals from deep tissues, depending upon the frequency used.

<sup>d</sup> Depends very much on bubble size and structure, and the frequency used; single bubbles may be detected.

<sup>e</sup> Cells labeled with SPIO may have sensitivity close to SPECT.

<sup>f</sup> Not well characterized; less sensitive than MRI; not sensitive enough for MI.

<sup>g</sup> So far mostly iodine used; other heavy atoms can theoretically be used.
Magnetic Resonance Imaging (MRI)
Basics of MRI

Nuclear spin – Hydrogen nuclei (protons)

Magnetization

Radiofrequency

Image contrast in MRI

Acquisition parameters (T1 or T2-weighted images)
Proton density
Physical/chemical environment of the protons
(biological states of water)
*Contrast-enhancing agents: DCE-MRI

www.lahey.org/.../MRI_CommonTypes_Brain.asp

E-MRI.org
Contrast sensitivity

- Ability to produce an image that can distinguish different objects or tissues

Contrast in MRI can be affected by acquisition parameters, tissue properties, and using contrast-enhancing agents.
Applications of MRI

Anatomic Imaging

T1W                      T2W

Ca - Floor of the Mouth (Axial) M – soft tissue mass; Arrow - genioglossus

✓ Simple anatomic imaging
✓ Extent of tumor (delineation of margins)

Rumboldt et al., Oral Oncol 2006
Typically involves repeated (dynamic) T1/T2-weighted imaging of tissues before and after administration of the contrast agent (contrast-enhanced).

Relates enhancement pattern of tissues to underlying physiological parameters (perfusion, permeability) by analyzing time-dependent tracer concentration.
DCE-MRI of Nodal Metastases

$K_{\text{trans}}$ \quad $V_e$

$K_{\text{trans}}$ – permeability constant; $V_e$ – volume fraction of EES
Top – solid composition; Bottom – cystic or necrotic

Kim et al., JMRI 2007
SPIO-enhanced MRI of Lymph Nodes

Darkening on T2W images due to susceptibility artifacts from iron

(SPIO - super paramagnetic iron oxide based contrast agents)
Molecular MRI using Gd-nanoparticles

Folate overexpressing tumors

Folate-targeted Gd nanoparticles for MRI

Swanson et al., Int J Nanomed 2008
Positron Emission Tomography (PET)
A compound labeled with a positron-emitting radionuclide is introduced into the body, usually by intravenous injection.

When one of the radionuclide atoms decays, a positron is emitted, travels a very short distance in tissue (typically $0^{-1} - 10^0$ mm for radionuclides of interest), and annihilates with an electron in the tissue.

The mass of the two particles is converted into energy, which is emitted in the form of two back-to-back 511 keV gamma rays.
## Basics of PET

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Label</th>
<th>Half-life (hours)</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choline</td>
<td>$^{11}$C</td>
<td>0.34</td>
<td>Choline metabolism</td>
</tr>
<tr>
<td>Acetate</td>
<td>$^{11}$C</td>
<td>0.34</td>
<td>Fatty acid/sterol metabolism</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>$^{11}$C</td>
<td>0.34</td>
<td>Amino acid metabolism</td>
</tr>
<tr>
<td>Methionine</td>
<td>$^{11}$C</td>
<td>0.34</td>
<td>Amino acid metabolism</td>
</tr>
<tr>
<td>Ammonia</td>
<td>$^{13}$N</td>
<td>0.17</td>
<td>Vascular perfusion</td>
</tr>
<tr>
<td>Water</td>
<td>$^{15}$O</td>
<td>0.03</td>
<td>Vascular perfusion</td>
</tr>
<tr>
<td>FDG</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Glucose metabolism</td>
</tr>
<tr>
<td>FLT</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Cellular proliferation</td>
</tr>
<tr>
<td>FHBG</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Gene expression</td>
</tr>
<tr>
<td>FIAU</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Gene expression</td>
</tr>
<tr>
<td>Galacto-RGD</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>Dimeric-RGD</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>FMISO</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>FAZA</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>EF5</td>
<td>$^{18}$F</td>
<td>1.83</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Cu-ATSM</td>
<td>$^{64}$Cu</td>
<td>12.70</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Cu-PTSM</td>
<td>$^{64}$Cu</td>
<td>12.70</td>
<td>Vascular perfusion</td>
</tr>
</tbody>
</table>

FDG, ($^{18}$F)fluoro-2-deoxyglucose; FLT, ($^{18}$F)fluorothymidine; FHBG, $^{18}$F-9-[4-fluoro-3-(hydroxymethyl)butyl]guanine; FIAU, $^{18}$F-2'-fluoro-2'-deoxy-1-$^{18}$F-D-arabinofuranosyl-5-iodouracil; RGD, arginine-glycine-aspartic acid; FMISO, ($^{18}$F)fluoromisonidazole; FAZA, ($^{18}$F)fluorozomycin-arabinoside; EF5, 2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3-($^{18}$F)pentaffluoropropyl)-acetamide; Cu-ATSM: Cu(II)-diacetyl-bis(N(4)-methylthiosemicarbazone); Cu-PTSM: Cu(II)-pyruvaldehyde-bis(N(4)-methylthiosemicarbazone).
$^{18}$FDG is taken up in facilitated transport by metabolically active cells via glucose transporters (Glut) in cell membrane. In cell cytoplasm, $^{18}$FFDG undergoes phosphorylation to form FDG-6-phosphate (FDG-6-P) that, unlike glucose, cannot undergo further metabolism and becomes trapped in cell with only negligible amount of FDG-6P diffusing from cells.
Figure 1: A 61-year-old man with nasopharyngeal SCC and bilateral cervical lymph node metastases underwent PET/CT for staging. Axial PET, CT, PET/CT, and maximum intensity projection (MIP) images are shown. PET/CT revealed focal FDG uptake in the right liver lobe indicating liver metastasis (black, white arrows). PET/CT also revealed multiple focal FDG uptakes in the lumbar spine, sternum, and ribs indicating multiple bone metastases (red arrows). PET/CT was valuable for detection distant metastases.
18F-30deoxy-30-fluorothymidine (FLT), which can measure tumor cell proliferation noninvasively.

FLT is retained inside the cell by thymidine kinase 1 and is considered a marker of the S-phase.
18 F-16b-Fluoro-5a-Dihydrotestosterone

**Figure 2.** Monitoring the pharmacodynamics of antiandrogen therapies with the radioligand 18F-FDHT. **A,** a schematic representation of how the radioligand 18F-FDHT is applied in man to assess AR expression levels and receptor occupancy by drug. In the context of CRPC, pathologic activation of AR often occurs despite low circulating levels of androgens, allowing the radiotracer 18F-FDHT to bind AR in prostate cancer lesions. When applied post-antiandrogen therapy, the absence of 18F-FDHT binding can indicate that AR is effectively engaged by drug. **B,** a pilot study showing that 18F-FDHT can be used to interpret dose selection of antiandrogens in man. Patients were scanned with 18F-FDHT before enrolling in the phase I/II trial, and after 4 weeks of therapy, were scanned again to assess receptor blockade by MDV3100. Although 18F-FDG SUV$_{\text{max}}$ values almost uniformly declined in this cohort—pointing to effective engagement of AR by MDV3100—percent changes in serum PSA or 18F-FDG SUV$_{\text{max}}$ values did not overlay in an interpretable fashion with these 18F-FDHT “responses,” further pointing to a need for imaging agents that measure AR pathway signaling output directly.
Opto-Acoustic Imaging Techniques
Optical Imaging systems

10 excitation filters

Multi-modality imaging

Bioluminescence PC3M-luc

Fluorescent Conjugate – Antibody

Fluorescent protein – GFP
RipTAG model of pancreatic cancer

- Expression of firefly luciferase in addition to the SV40 T antigen enables visualization of tumor growth by bioluminescence imaging

Zumsteg et al, Carcinogenesis 2010
Optical Imaging of Tumor Response to Rx

Byrne et al, 2013
Snoeks et al, 2010
Optical Imaging-guided surgery

Fig. 1. Cetuximab is labeled with Cy5.5 fluorescent probe. Cetuximab is an antiepidermal growth factor antibody approved for use in treatment of head and neck cancer. Antibody was conjugated to fluorescent probe, Cy5.5, that is chemically similar to indocyanine green and can be detected in near infrared range.

Ntziachristos et al., 2003
Rosenthal et al., 2006
Folate receptor targeting in ovarian cancer

Van Dam et al., 2011
A transmitter produces a train of short pulses of high frequency oscillations, which are transformed by a transducer into high frequency mechanical oscillations. The vibrational energy of the mechanical oscillations is directed into the scanned object and swept back and forth. The return of an echo depends mainly on the type of scanned object/tissue and penetration depth. Echoes are detected by the transducer and transformed into electrical signals that are processed by a receiver to create an image.”
Contrast-enhanced US

VEGFR2 targeted microbubbles

Fig. 2. In vivo evidence for reduction in rBV following G6-31. A, percentage change in rBV and rBF in control and treated groups after 48 h of anti-VEGF treatment. B, representative ultrasound perfusion blood volume maps for each treatment group pretreatment and at 48 h posttreatment.
Nanotechnology & Cancer Imaging
Nanocarriers for Cancer Imaging and Rx

Image 1. Schematic of a multifunctional nanoparticle with imaging probes and/or anticancer drugs encapsulated inside and tumor-specific ligands and/or antibodies presenting on the surface.

Figure 1. Relative sizes of nanoparticles (NPs): hydrodynamic diameter ranges for nanoscale materials useful for biomedical imaging (top row) and naturally occurring materials (bottom row). QD = quantum dot.
Nanocarriers for Cancer Imaging and Rx

Ideal characteristics

A. The nanoparticle carrier must bind or contain the desired chemotherapeutic drug(s).
B. The nanoparticle-drug complex must remain stable in the serum to allow for the systemic delivery of the drug.
C. The nanoparticle-drug complex must be delivered only to tumor cells.
D. The nanoparticle must be able to release the drug once at the site of the tumor.
E. After drug delivery, the residual nanoparticle carrier must be safely degraded.

Thakor and Gambhir, 2013
**TABLE 1. Examples of Nanoparticles Used in Cancer Therapy**

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>DESCRIPTION OF NANOPARTICLE</th>
<th>CANCER TARGETED BY THE NANOPARTICLE</th>
<th>PHASE OF DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraxane</td>
<td>Albumin-bound paclitaxel</td>
<td>Metastatic breast cancer&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>Doxil</td>
<td>Liposomal doxorubicin</td>
<td>HIV-related Kaposi sarcoma, metastatic breast and ovarian cancer&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>DaunoXome</td>
<td>Liposomal daunorubicin</td>
<td>HIV-related Kaposi sarcoma&lt;sup&gt;26,27&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>Myocet</td>
<td>Liposomal doxorubicin</td>
<td>EGFR2-positive metastatic breast cancer&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>DepoCyt</td>
<td>Liposomal cytarabine</td>
<td>Intrathecal lymphomatous meningitis&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>Marqibo</td>
<td>Liposomal vincristine sulphate</td>
<td>Acute lymphoblastic leukemia&lt;sup&gt;30,31&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>Oncaspar</td>
<td>Polymeric PEG-L-asparaginase</td>
<td>Acute lymphoblastic leukemia&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>Zinostatin stimalamer</td>
<td>Copolymer styrene maleic acid-conjugated neocarzinostatin</td>
<td>Unresectable hepatocellular carcinoma&lt;sup&gt;33,34&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>Resovist</td>
<td>Carboxydextran-coated SPIO</td>
<td>MRI contrast agent for imaging hepatocellular carcinoma&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>Genexol-PM</td>
<td>Polymeric methoxy-PEG-poly(D,L-lactide) paclitaxel</td>
<td>Metastatic breast cancer&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>NanoTherm</td>
<td>Aminosilane-coated SPIO</td>
<td>Local ablation of glioblastoma multiform&lt;sup&gt;37,38&lt;/sup&gt;</td>
<td>Approved</td>
</tr>
<tr>
<td>Xyotax</td>
<td>Poly-L-glutamic acid (poliglumex) conjugate with paclitaxel</td>
<td>Ovarian cancer and NSCLC&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Phase 3</td>
</tr>
<tr>
<td>NKTR-102</td>
<td>PEG micelle with irinotecan</td>
<td>Breast and colorectal cancer&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
### TABLE 2. Examples of Nanoparticles Used in Cancer Imaging

<table>
<thead>
<tr>
<th>IMAGING MODALITY</th>
<th>DESCRIPTION OF NANOPARTICLE</th>
<th>CANCER IMAGED BY THE NANOPARTICLE</th>
<th>STAGE OF DEVELOPMENT/CLINICAL TRIAL NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Superparamagnetic iron oxide nanoparticles</td>
<td>Liver tumors (ie, hepatocellular carcinoma, liver metastases)</td>
<td>Currently used in clinical practice(^{142})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High-grade glioma</td>
<td>NCT00769093</td>
</tr>
<tr>
<td></td>
<td>Ultrasmall superparamagnetic iron oxide nanoparticle</td>
<td>Preoperative staging of pancreatic cancer</td>
<td>NCT00920023</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelvic lymph node metastases from prostate, bladder, or other GU cancers</td>
<td>NCT00147238</td>
</tr>
<tr>
<td>CT</td>
<td>Heavy metal (ie, gold, lanthanide, and tantalum) nanoparticles</td>
<td>Solid organ tumors</td>
<td>Preclinical stage of development(^{143})</td>
</tr>
<tr>
<td>SPECT</td>
<td>TC-99m sulfur colloid nanoparticles</td>
<td>Sentinel lymph node mapping in invasive breast cancer</td>
<td>NCT00438477</td>
</tr>
<tr>
<td>PET</td>
<td>(^{124})I-labeled cRGDY silica nanoparticles</td>
<td>Melanoma and malignant brain tumors</td>
<td>NCT01266096</td>
</tr>
<tr>
<td>Optical</td>
<td>Surface-enhanced Raman scattering nanoparticles</td>
<td>Colorectal cancer</td>
<td>Preclinical stage of development(^{57})</td>
</tr>
<tr>
<td>Photoacoustic</td>
<td>Single-walled carbon nanotubes</td>
<td>Solid organ tumors</td>
<td>Preclinical stage of development(^{144})</td>
</tr>
</tbody>
</table>

MRI indicates magnetic resonance imaging; NCT, National Clinical Trial; GU, genitourinary; CT, computed tomography; SPECT, single-photon emission computed tomography; TC-99m, technetium-99m; PET, positron emission tomography; \(^{124}\)I, iodine-124; cRGDY, cyclic Arg-Gly-Asp-Tyr.
PET imaging of EGFR expression

PET detection of epidermal growth factor receptor (EGFR) in colorectal cancer xenografts

Table 4. Main characteristics of the ideal positron emission tomography probe

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Well known</td>
</tr>
<tr>
<td></td>
<td>Highly expressed in tumours</td>
</tr>
<tr>
<td></td>
<td>Differentially expressed in comparison to the nonpathological tissues</td>
</tr>
<tr>
<td>Tracer</td>
<td>Good target binding affinity</td>
</tr>
<tr>
<td></td>
<td>Good target binding selectivity</td>
</tr>
<tr>
<td></td>
<td>Ideal chemical properties (lipophilicity or solubility depending on the cellular site)</td>
</tr>
<tr>
<td>Stability</td>
<td>Slow washout from the tumour</td>
</tr>
<tr>
<td></td>
<td>Not long half-life limiting serial images in human studies</td>
</tr>
<tr>
<td></td>
<td>Low hepatic excretion in order to visualise liver metastases</td>
</tr>
<tr>
<td>Labelling</td>
<td>Adequate half-life for human studies</td>
</tr>
</tbody>
</table>

Pantaleo et al., Ann Oncol 2009
Nanoparticle-mediated drug delivery

PSMA-targeted Docetaxel nanoparticle

Targeting moiety:
2-[3-[5-amino-1-carboxypentyl]-ureido]-pentanedioic acid (ACUPA) – a PSMA substrate analog inhibitor

Fig. 6. PK and efficacy of DTXL-TNP in humans. (A) PK in patients with advanced solid tumors of DTXL-TNP at a dose of 30 mg/m² (n = 3) compared to published sb-DTXL data at the same dose (n = 3). Data are means ± SD. (B) PK profiles over the first 8 hours after single-dose administration of DTXL-TNP (3.5 to 75 mg/m²), n = 1 patient per dose level at 3.5 and 7 mg/m², n = 2 at 15 and 75 mg/m², and n = 3 at 30 and 60 mg/m². Cₘₐₓ versus dose $r^2 = 0.87$; AUC versus dose $r^2 = 0.79$. (C) Axial images from contrast-enhanced CT scans obtained from a 51-year-old male cholangiocarcinoma patient with lung metastases at baseline and at day 42 after two treatment cycles of DTXL-TNP (15 mg/m²). Red circles indicate locations of metastatic lesions observed in the baseline scan. (D) Coronal images from contrast-enhanced CT scans obtained from a 63-year-old male patient with tonsillar cancer at baseline and at day 42 after two treatment cycles of DTXL-TNP (30 mg/m²). Target tonsillar lesion is outlined in red.
Take home message

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity of detection in MRI</th>
<th>Spatial resolution \textit{in vivo}</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>500 micromolar (Gd-DTPA)–low millimolar (iodine) range</td>
<td>$&gt;10 \mu m$</td>
<td>High spatial resolution</td>
<td>Patients are exposed to radiation</td>
</tr>
<tr>
<td>MRI</td>
<td>$T_2$-contrast, iron oxide nano-particles: nanomolar–micromolar range</td>
<td>$4 \mu m$ (experimental MRI), $250 \mu m$ in plane (clinical MRI)</td>
<td>High spatial resolution</td>
<td>Particle size is often large, which restricts \textit{in vivo} delivery</td>
</tr>
<tr>
<td>MRI</td>
<td>$T_1$-contrast, multilabeled targeted Gd-DTPA macromolecules: $&gt;10 \mu M$</td>
<td>$4 \mu m$ (experimental MRI), $250 \mu m$ in plane (clinical MRI)</td>
<td>High spatial resolution</td>
<td>Particle size of contrast agent or reporters is relatively large</td>
</tr>
<tr>
<td>MRS</td>
<td>Millimolar range ($^1H$ at 4.7–11 Tesla)</td>
<td>$\geq0.5 \text{ cm (3 Tesla), 0.7 cm (1.5 Tesla)}$</td>
<td>Detection of endogenous metabolites</td>
<td>Low sensitivity results in low spatial resolution</td>
</tr>
<tr>
<td>Optical</td>
<td>Nanomolar range: $\geq50$ cells (fluorescence); $\geq1000$ cells (bioluminescence)</td>
<td>$&gt;25 \mu m$, intravital microscopy: 1–15 $\mu m$</td>
<td>High sensitivity, high spatial resolution</td>
<td>Restricted depth detection</td>
</tr>
<tr>
<td>PET</td>
<td>Picomolar range</td>
<td>$\geq1 \text{ mm (microPET), } \sim4–5 \text{ mm (clinical PET)}$</td>
<td>High sensitivity, short-lived isotopes</td>
<td>Low spatial resolution, cyclotron required for generating some isotopes</td>
</tr>
<tr>
<td>SPECT</td>
<td>Picomolar range</td>
<td>$\geq1 \text{ mm (microSPECT), } \geq3 \text{ mm (clinical SPECT)}$</td>
<td>High sensitivity</td>
<td>Low spatial resolution, long-lived isotopes</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>$&gt;10^6$ microbubbles per ml blood</td>
<td>$&gt;40 \mu m$</td>
<td>High spatial resolution, cost effective</td>
<td>Few probes available</td>
</tr>
</tbody>
</table>

Glunde et al, Trends in Mol Medicine
Integration of Radiology & Pathology

Kuo, Radiogenomics
Pop Quiz revisited
Photodynamic Therapy

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Feb 25, 2014
Photodynamic Therapy (PDT)

- Food and Drug Administration (FDA) approved treatment for a variety of oncologic and non-oncologic conditions originally developed at Roswell Park (Dougherty, 1974).

- Involves photoactivation of a tissue-localized drug by light of a specific wavelength.

T.J. Dougherty (1974)@Roswell
Photo-destruction of cells in vitro by fluorescein

While using a technique called “vital staining” to test the toxicity of an ionizing sensitizer he had made, Dougherty accidentally discovered that when cancer cells that contained the vital stain (fluorescein diacetate) were exposed to room light, they died.
Basic principles of PDT

- Administration of a drug (sensitizer)
- Localized activation (excitation) of the sensitizer in tissue by light of a specific wavelength
- Generation of highly reactive free radicals
- Oxidization of biological substrates causing cytotoxic effects within the illuminated tissue.

Agostinis et al., CA Cancer J Clin 2011
Photodynamic Triad

**Sensitizer**
- Administration
- Tissue concentration
- Localization

**Light**
- Wavelength
- Light sources
- Fluence/Fluence rate

**Oxygenation**
- Tissue distribution
- Vascular perfusion
- Rate of diffusion

**Photochemistry**

**Photophysics**

**Photobiology**
# Photochemistry

<table>
<thead>
<tr>
<th>PHOTOSENSITIZER</th>
<th>STRUCTURE</th>
<th>WAVELENGTH, nm</th>
<th>APPROVED</th>
<th>TRIALS</th>
<th>CANCER TYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porfimer sodium (Photofrin) (HPD)</td>
<td>Porphyrin</td>
<td>630</td>
<td>Worldwide</td>
<td></td>
<td>Lung, esophagus, bile duct, bladder, brain, ovarian</td>
</tr>
<tr>
<td>ALA</td>
<td>Porphyrin precursor</td>
<td>635</td>
<td>Worldwide</td>
<td></td>
<td>Skin, bladder, brain, esophagus</td>
</tr>
<tr>
<td>ALA esters</td>
<td>Porphyrin precursor</td>
<td>635</td>
<td>Europe</td>
<td></td>
<td>Skin, bladder</td>
</tr>
<tr>
<td>Temoporfin (Foscan) (mTHPC)</td>
<td>Chlorine</td>
<td>652</td>
<td>Europe</td>
<td>United States</td>
<td>Head and neck, lung, brain, skin, bile duct</td>
</tr>
<tr>
<td>Verteporfin</td>
<td>Chlorine</td>
<td>690</td>
<td>Worldwide (AMD)</td>
<td>United Kingdom</td>
<td>Ophthalmic, pancreatic, skin</td>
</tr>
<tr>
<td>HPPH</td>
<td>Chlorin</td>
<td>665</td>
<td>United States</td>
<td></td>
<td>Head and neck, esophagus, lung</td>
</tr>
<tr>
<td>SnEt2 (Purlytin)</td>
<td>Chlorin</td>
<td>660</td>
<td>United States</td>
<td></td>
<td>Skin, breast</td>
</tr>
<tr>
<td>Talaporfin (LS11, MACE, NPe6)</td>
<td>Chlorin</td>
<td>660</td>
<td>United States</td>
<td></td>
<td>Liver, colon, brain</td>
</tr>
<tr>
<td>Ce6-PVP (Fotolon), Ce6 derivatives (Radachlorin, Photodithazine)</td>
<td>Chlorin</td>
<td>660</td>
<td>Belarus, Russia</td>
<td></td>
<td>Nasopharyngeal, sarcoma, brain</td>
</tr>
<tr>
<td>Silicon phthalocyanine (Pc4)</td>
<td>Phthalocyanine</td>
<td>675</td>
<td>United States</td>
<td></td>
<td>Cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>Padoporfin (TOOKAD)</td>
<td>Bacteriochlorin</td>
<td>762</td>
<td>United States</td>
<td></td>
<td>Prostate</td>
</tr>
<tr>
<td>Motexafin lutetium (Lutex)</td>
<td>Texaphyrin</td>
<td>732</td>
<td>United States</td>
<td></td>
<td>Breast</td>
</tr>
</tbody>
</table>

Abbreviations: ALA, 5-aminolevulinic acid; AMD, age-related macular degeneration; Ce6-PVP, chlorin e6-polyvinpyrrolidone; HPD, hematoporphyrin derivative; HPPH, 2- (1-hexyloxyethyl)-2-devinyl pyropheophorbide-a; MACE, mono-(L)-aspartylchlorin-e6; mTHPC, m-tetrahydroxyphenylchlorin; nm indicates nanometers; SnEt2, tin ethyl etiopurpurin.
Photochemistry

- **Porphydrins**
  - Useful sensitizers, high singlet oxygen yield, absorption in the visible spectrum

**Photofrin®**
- combination of monomers, dimers & oligomers derived from chemical manipulation of Hp, 630 nm absorption

Allison *et al*, 2004
Photofrin

- 1st photosensitizer to be approved by the FDA
- Approved indications in endobronchial and lung cancers, Barrett’s esophagus
- **Limitation**: Prolonged cutaneous sensitivity
Photosensitizer: HPPH
2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) (665 nm)

- Chlorin-based sensitizer - Pandey et al., (1991)
- Significantly decreased photosensitivity than Photofrin in patients
- Currently undergoing clinical evaluation in head and neck and lung cancers
Photochlor

**Study**
45 patients
• 3, 4, 5 or 6 mg/m^2 HPPH
• Up to 133 J/cm^2 solar-spectrum light (SSL) on 3 consecutive days after HPPH

**Results**
18% had *no reaction* to SSL
• 16% had strongest reaction obtained in the study—*erythema w/o edema or blistering*
• Response appears to be related to HPPH-dose

---

**Skin phototoxicity (HPPH)**

Photochlor, at clinically effective antitumor doses, causes only mild skin photosensitivity that declines rapidly over a few days.

*Bellnier et al.*, 2006
Guidelines for ‘ideal’ photosensitizers

- Toxicity
- Activation
- High singlet oxygen yield
- Ease of administration
- Elimination
- Cost-effective

Increased interest in developing targeted photosensitizers

Table 2 Photosensitizer families.

<table>
<thead>
<tr>
<th>Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyrin platform</td>
</tr>
<tr>
<td>HpD (hematoporphyrin derivative)</td>
</tr>
<tr>
<td>HpD-based</td>
</tr>
<tr>
<td>BPD (benzoporphyrin derivative)</td>
</tr>
<tr>
<td>ALA (5-aminolevulinic acid)</td>
</tr>
<tr>
<td>Texaphyrins</td>
</tr>
<tr>
<td>Chlorophyll platform</td>
</tr>
<tr>
<td>Chlorins</td>
</tr>
<tr>
<td>Purpurins</td>
</tr>
<tr>
<td>Bacteriochlorins</td>
</tr>
<tr>
<td>Dyes</td>
</tr>
<tr>
<td>Phthalocyanine</td>
</tr>
<tr>
<td>Napthalocyanine</td>
</tr>
</tbody>
</table>

Allison et al, 2004
Nanoparticles in PDT

Made from biodegradable material (PLA or PLGA) or non–polymer-based materials such as ceramic and metallic nanoparticles.

Encapsulating sensitizers within nanoparticles for increasing intracellular uptake.

Polymer matrix can be optimized for controlled degradation and release of photosensitizer.

FIGURE 3. Nanoparticles in Photodynamic Therapy. Nanoparticles can deliver light-activatable chemicals, known as photosensitizer molecules, to tumor cells for use in photodynamic therapy. After the absorption of light, photosensitizer molecules can generate cytotoxic oxygen-based reactive species, which can subsequently cause cellular damage and cell death via oxidative stress.
Laser source is used to deliver monochromatic light through optical fibers.

- Wavelength of activation generally corresponds to the absorbance maxima of the sensitizer used.

- Longer wavelength sensitizers (~800 nm) are preferred

- Light sources – pumped dye lasers (bulky, inefficient), diode lasers (compact, portable, cost-effective)
Blue light penetrates least efficiently through tissue, whereas red and infrared radiations penetrate more deeply.

600-1200 nm (tissue optical window)

Beyond 800 nm, there is insufficient energy for initiation of photodynamic reaction

Agostinis et al., CA Cancer J Clin 2011
Light delivery

No single light source is ideal for all PDT applications even with the same PS

Choice of light source/delivery fiber depends on the disease site (location, size of lesions, access, tissue characteristics)
Light Dosimetry

- Defined by the fluence and fluence rate

- **Fluence**: Total amount of light dose delivered (J/cm²).
- **Fluence rate**: Rate at which the light dose is delivered (mW/cm²).

- The photochemical process associated with singlet oxygen generation is also oxygen-consuming.

- Biological response to PDT is critically dependent on the regimen employed
The biological effects of PDT are a consequence of a dynamic interaction between the PS, light and tissue/molecular oxygen.
Biological response to PDT

- Complex
- Combination of direct cytotoxicity, vascular damage and the induction of immune/inflammatory responses
- The efficacy of the photodynamic reaction depends on several parameters:
  - PS used
  - Light treatment conditions
  - Tissue oxygenation

Unlike tissue factors (vascularity/oxygenation), light treatment conditions are under the direct control of the clinician

Castano et al, Nature Reviews Cancer 2006
Vascular response to PDT

- Increased vascular permeability
- Hemorrhaging
- Loss of perfusion (shutdown)

Depending on sensitizer and treatment conditions

Chen et al, 2006
Immune/inflammatory response to PDT

- Prostaglandins
- Cytokines
- Chemokines
- Inflammatory cell infiltration (neutrophils and macrophages)
Emerging as a viable clinical treatment for nearly every histological type/site.

- Head and neck cancers (Biel et al., 1998)
- Skin cancers (Oseroff et al., 2005).
- Intra-abdominal sarcomas (Hahn et al., 2006).

**Off-label use** Brain, bladder, head and neck, prostate, breast.

Table 2. Approved photodynamic-therapy drugs for oncological indications

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>Generic name</th>
<th>Date and country of approval</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematoporphyrin derivative, polyhaematoporphyrin</td>
<td>Porphimer sodium</td>
<td>First approved in 1995; now approved in more than 40 countries</td>
<td>Advanced and early lung cancer, superficial gastric cancer, oesophageal adenocarcinoma, cervical cancer, and bladder cancer</td>
</tr>
<tr>
<td>Methyl-tetrahydroxyphenyl chlorin</td>
<td>Temoporfin</td>
<td>Approved in 2001 in European Union, Norway, and Iceland</td>
<td>Palliative head and neck cancer</td>
</tr>
<tr>
<td>5-aminolevulinic acid</td>
<td>Aminolevulinic acid</td>
<td>Approved in 1999 in USA</td>
<td>Actinic keratosis</td>
</tr>
<tr>
<td>Methyl 5-aminolevulinate</td>
<td>Methyl aminolevulinate</td>
<td>Approved in 2001 in Europe</td>
<td>Actinic keratosis, superficial basal-cell carcinoma, and basal-cell carcinoma</td>
</tr>
</tbody>
</table>
Clinical PDT

Advantages

✓ Equivalent or greater efficacy compared to standard therapies
✓ Reduced morbidity/disfigurement
✓ Can be repeated for large bulky tumors – interstitial PDT
✓ Use of PDT is not precluded by prior/subsequent surgery or chemotherapy
✓ Excellent cosmetic outcome – skin lesions, HNC
✓ PDT as an adjunct could eliminate residual disease
Clinical PDT

- Prevention
- Transplant
- Hematologic Blood Cancers
  - Lymphoma
  - Hodgkins
  - Non-Hodgkins
  - Multiple Myeloma
  - Chronic Lymphocytic Leukemia
  - Leukemia
  - Myelodysplastic Syndrome
- Phase 1 Studies
  - "Advanced Solid Tumors"
- Melanoma/Sarcoma
- Pediatric
- PhotoDynamic Studies
- Infectious Disease
- Radiation
- Other
- Male Cancers
  - Prostate
  - Testicular
- GYN Cancers
  - Ovarian
  - Uterine
  - Cervical
  - Vaginal
  - Vulvar
  - Endometrial
- Brain
- Head & Neck
- Esophagus
- Skin
- Kidney
- Breast
- Gall Bladder
- Lung
- Liver
- Stomach
- Bladder
- Pancreas
- Colorectal
- Peritoneal

http://www.roswellpark.org/Patient_Care/What_Is_a_Clinical_Trial/ClinicalTrialsOnlineSearch
Head and neck cancers

- Management often requires aggressive surgical intervention
- Morbidity issues – speech, appearance and function
- **Alternative Rx:**
  - PDT – could be of potential benefit
    - non-invasive
    - excellent cosmetic results
    - single/adjunct
Oral cancer

Photofrin-PDT (75 J@150 mW)

Pretreatment

1 week post

Pretreatment

3 weeks post

Courtesy of Nestor Rigual, MD
Photodynamic Therapy with 3-(1'-Hexyloxyethyl) Pyropheophorbide a for Cancer of the Oral Cavity

Figure 1. A, high grade dysplasia with microinvasion (within the ellipse) before therapy. B, response to PDT at 7 days posttreatment. C, complete clinical disappearance of the target lesion at 9 months after PDT.
The FDA-approved sensitizer Photofrin® is associated with prolonged and sometimes severe cutaneous sensitivity in patients lasting for 1-2 months.

Develop newer sensitizers with decreased phototoxicity

Improve therapeutic efficacy

Combination strategies?

Develop methods for detection/monitoring efficacy or activity

How can imaging help in treatment planning/monitoring?
PDT as an intraoperative adjuvant

Original Investigation

Adjuvant Intraoperative Photodynamic Therapy in Head and Neck Cancer

OBJECTIVES To determine the safety of photodynamic therapy with 2-(1-hexylloxyethyl)-2-devinyl pyropheophorbide-a (HPPH) in combination with surgery in patients with head and neck squamous cell carcinoma.

DESIGN, SETTING, AND PARTICIPANTS Nonrandomized, single-arm, single-site, phase 1 study at a comprehensive cancer center among 16 adult patients (median age, 65 years) with biopsy-proved primary or recurrent resectable head and neck squamous cell carcinoma.

INTERVENTIONS Intravenous injection of HPPH (4.0 mg/m²), followed by activation with 665-nm laser light in the surgical bed immediately after tumor resection.

MAIN OUTCOMES AND MEASURES Adverse events and highest laser light dose.

RESULTS Fifteen patients received the full course of treatment, and 1 patient received HPPH without intraoperative laser light because of an unrelated myocardial infarction. Disease sites included larynx (7 patients), oral cavity (6 patients), skin (1 patient), ear canal (1 patient), and oropharynx (1 patient, who received HPPH only). The most frequent adverse events related to photodynamic therapy were mild to moderate edema (9 patients) and pain (3 patients). One patient developed a grade 3 fistula after salvage laryngectomy, and another patient developed a grade 3 wound infection and mandibular fracture. Phototoxicity reactions included 1 moderate photophobia and 2 mild to moderate skin burns (2 due to operating room spotlights and 1 due to the pulse oximeter). The highest laser light dose was 75 J/cm².

CONCLUSIONS AND RELEVANCE The adjuvant use of HPPH-photodynamic therapy and surgery for head and neck squamous cell carcinoma seems safe and deserves further study.

Rigual et al., 2013
Combination strategies

<table>
<thead>
<tr>
<th>DRUG OR TREATMENT MODALITY</th>
<th>OUTCOME/RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHEMOTHERAPEUTICS AND NOVEL ANTICANCER DRUGS</strong></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Doxorubicin improves PDT-mediated tumor growth control in mice^{103}</td>
</tr>
<tr>
<td>Platinum compounds</td>
<td>Cisplatin potentiates antitumor activity of PDT in mice^{103}</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Methotrexate enhances in vitro cytotoxicity of PDT with ALA by upregulation of protoporphyrin IX production^{104}</td>
</tr>
<tr>
<td>Microtubule inhibitors</td>
<td>Vincristine administered prior to or immediately after PDT improves its antitumor activity in mice^{105}</td>
</tr>
<tr>
<td>DNA methyltransferase inhibitors</td>
<td>S-azadeoxyctydine prolongs survival of PDT-treated animals and improves tumor growth control^{106}</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib enhances PDT-mediated ER stress in cancer cells in vitro and significantly delays post-PDT tumor regrowth in mice^{48}</td>
</tr>
<tr>
<td><strong>RADIOThERAPY</strong></td>
<td></td>
</tr>
<tr>
<td>Two-way enhancement of antitumor effects: PDT sensitizes cancer cells to radiotherapy^{107} and radiotherapy increases anticancer efficacy of PDT,^{108} prolonged tumor growth control induced by combined treatment^{109}</td>
<td></td>
</tr>
<tr>
<td><strong>DRUGS MODULATING ARACHIDONIC ACID CASCADE</strong></td>
<td></td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td>COX-2 inhibitors (such as NS-398^{110}, nimesulide^{111} or celecoxib^{112}) potentiate antitumor effects of PDT, possibly through indirect angiogenic effects</td>
</tr>
<tr>
<td>LOX inhibitors</td>
<td>MK-886, which also serves as a FLAP inhibitor, sensitizes tumor cells to PDT-mediated killing^{113}</td>
</tr>
<tr>
<td><strong>AGENTS INCREASING PS ACCUMULATION IN TUMOR CELLS</strong></td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Increases ALA-induced protoporphyrin IX accumulation and thus potentiates PDT cytotoxicity in vitro^{114}</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Increases intracellular accumulation of second-generation PSs and thus potentiates PDT cytotoxicity in vitro and in vivo^{115}</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>Lovastatin, a HMG-CoA reductase inhibitor, improves in vitro LDL binding and perfimer sodium uptake by cancer cells^{116}</td>
</tr>
<tr>
<td>Salicylate and related drugs</td>
<td>Enhancement of PDT efficacy in vitro via increased PS uptake by tumor cells^{117}</td>
</tr>
<tr>
<td><strong>APPROACHES INCREASING OXYGEN DELIVERY TO TUMOR CELLS</strong></td>
<td></td>
</tr>
<tr>
<td>EPO</td>
<td>EPO improves chemotherapy-induced anemia and restores antitumor efficacy of PDT in mice^{118}, however, EPO might also inhibit direct PDT-mediated cytotoxicity toward certain cancer cells^{119}</td>
</tr>
</tbody>
</table>

Agostinis et al., 2011
The Vascular Disrupting Agent 5,6-Dimethylxanthenone-4-Acetic Acid Improves the Antitumor Efficacy and Shortens Treatment Time Associated with Photochlor-sensitized Photodynamic Therapy In Vivo

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2 Preclinical Imaging Resource (Department of Cancer Biology), Roswell Park Cancer Institute, Buffalo, NY

Received 4 March 2008, accepted 5 May 2008, DOI: 10.1111/j.1751-1097.2008.00395.x
Combination strategies

Photodynamic therapy augments the efficacy of oncolytic vaccinia virus against primary and metastatic tumours in mice

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Gil et al., 2011
Image guidance in PDT

Image-guidance interstitial PDT

Sajisevi et al., 2014 In press

Jerges et al., 2008
CT-guided interstitial PDT
Imaging-based monitoring of PDT efficacy

Real-time monitoring of PDT efficacy using blood oxygenation level dependent MRI

Seshadri et al., 2008
Concluding remarks

Understand basic principles
Basic components:
Photo-physics/chemistry
Biological response
Clinical indications/applications

PDT is a multidisciplinary endeavor
(scientists, physicists, surgeons, radiologists, nurses)