Multimodality Molecular Imaging

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• Philips Healthcare (Equipment support)
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Using dual-contrast agents to improve image registration, e.g., CT with MR

Liposomes resuspended in iohexol and gadoteridol, extruded, and dialyzed

Multi-modality Hybrid Imaging
(Nuclear/CT soon PET/MR)

SPECT/CT

PET/CT

www.Philips.com

www.hermesmedical.com

medicalphysics.duke.edu

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Multimodality molecular imaging with combined optical and SPECT/PET modalities (small molecule)


Multimodal Molecular Imaging
For Targeting Validation

MRI
(Paramagnetic or Superparamagnetic)

Fluorescence Microscopy

(Bimodal)


Laurent S, et al. In vitro characterization of the gd complex of \([2,6\text{-}\text{pyridinediy}l\text{bis(methylene nitrito)}]\) tetraacetic acid (PMN-tetraacetic acid) and of its Eu analogue, suitable bimodal contrast agents for MRI and optical imaging. Bioorganic and Medicinal Chemistry Letters. 2007;17(22):6230-3.


Bimodal (MRI - Fluorescence) RGD Liposomes

Color Mapped 2D MRI Slice Showing Paramagnetic Contrast In and Around Mouse Tumor

Microscopic Images of Rhodamine Fluorescent Signal from Lipid Surfactant

Perfluorocarbon Nanoparticles

Target Ligand to
Fibrin (Ab, Fab, peptides)
Integrins (Ab, peptidomimetics, peptides)
Tissue Factor (Ab)
Necl2 (Receptor)
Robo4 (Ab)
Selectins, Notch (Ab)

Lipid coat
Dyes (Rhodamine, Cypate, FITC, AlexaFluor)
Drugs (Fumagillin, Rapamycin, Doxorubicin)
Cytolytic Peptides (Mellitin)
Fibrinolytic enzymes

Metal Chelates of
\( \text{Gd}^{3+} \)
\( ^{111}\text{In} \)
\( ^{99m}\text{Tc} \)
\( ^{177}\text{Lu} \)
\( \text{Eu}^{3+} \)
Liquid Fluorocarbon Core

MRI

Ultrasound

Thrombus (in dogs)

Before Contrast

Gd$^{3+}$

After Contrast

Vx2 Carcinoma in Rabbits

$^{19}$F Gd$^{3+}$

Anti-fibrin PFC Paramagnetic NP (3T)

$\alpha v \beta 3$

Thrombus

Anode

19F

SNM 2008 Annual Meeting

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$^{19}$F Imaging Can Confirm, Quantify and Differentiate Targeted Nanoparticles

Confirm

Quantify

Differentiate

Proton  Fluorine

Clot

Number of NP x $10^{10}$

R$^2 = 0.946$

$y = 0.95x - 7.77$

Crown Ether Content (%)
Anti-Angiogenesis with anti-VEGF Therapy is Significant Element in the Treatment of Breast, Lung, and Colon Cancer

3 FDA approved drugs for treatment of patients with specific cancers in conjunction with current chemo or radiation therapy:
- bevacizumab (Avastins)
- sunitinib malate (Sutents, SU11248)
- sorafenib (Nexavars, BAY 43-9006)

All inhibit VEGF signalling by blocking VEGF ligand or VEGF receptor. Sunitinib and sorafenib inhibit PDGFR and other tyrosine kinases.

Cost: $20,000 / 8-week course, $100,000/year

Side effects: Renal disease, Hypertension, Thrombosis, GI perforation

Optimal benefits accrue to only a small fraction of eligible patients.

Unmet need: Rational patient stratification
Angiogenesis in the Rabbit Vx-2 Model Using $\alpha\nu\beta3$-Paramagnetic PFC Nanoparticles

MRI and histology correlate with each other
High Field (3T) CMR Allows Characterization of Neovasculature with $\alpha_\nu\beta_3$-Paramagnetic Nanoparticles

2D Slices to 3D Maps

3D Neovascular Map
Constrained Vascular Targeting of $\alpha_5\beta_1(\alpha_v\beta_3)$-targeted Nanoparticles Prevents Binding to Intratumoral Integrin

Co-localization of $\alpha_5\beta_1(\alpha_v\beta_3)$-NP and vasculature observed in peripheral tumor ‘growth front’, but rarely in tumor core
Temporal-Spatial evolution of neovasculature assessed with $\alpha_v\beta_3$-Paramagnetic Nanoparticles in the VX2

Aggressive Angiogenic Phenotype

Individual Rabbit

Group Changes

% Area of periphery enhancing in VX2 tumors

Targeted Treatment Nontargeted

8d 14d 16d
Comparison of MR Contrast Enhanced Images presented as 2D Slice and 3D Volume

Fumagillin Treated
30µg/kg x3
10,000-fold
Less than clinical TNP-470

Control

High Sensitivity – High Resolution SPECT-CT / MR
Molecular Imaging of Angiogenesis in the Vx2 Model

Lijowski, M et al. submitted to Invest. Radiol. 2008
High Sensitivity – High Resolution Dual-Modality Molecular Imaging of Angiogenesis

$^{99m}$Tc-NP
SPECT/CT

$^{99m}$Tc-Gd$^{3+}$-NP
SPECT/CT/MRI

Lijowski, M et al. submitted to Invest. Radiol. 2008
Summary

1) Multimodality molecular imaging has different forms for different purposes in preclinical and clinical research:
   - Hybrid imaging (SPECT/CT; PET/CT)
   - Bimodal and dual modality imaging: (validation of signal, functional imaging, or high-sensitivity - high resolution protocols)

2) Bimodal molecular imaging agents for preclinical studies: (Nuclear-optical [small molecule] and MR-optical [nanoparticle])

3) Dual $^{99m}$Tc/Gd$^{3+}$ high-sensitivity - high resolution protocol for sensitive nuclear detection and high resolution MR characterization

Nanomedicine strategies are developed to provide tools to detect early disease, risk stratify patients to optimal therapy, and longitudinally follow and manage response.