

1. **Quantum dot imaging for embryonic stem cells.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17925032

Lin S, Xie X, Patel MR, et al.

BMC Biotechnol. 2007;7:67.(Oct 9).

ABSTRACT: BACKGROUND: Semiconductor quantum dots (QDs) hold growing potential for cellular imaging both in vitro and in vivo. In this report, we aimed to evaluate the in vivo multiplex and long-term imaging of mouse embryonic stem (ES) cells labeled with Qtracker delivered quantum dots (QDs). RESULTS: Murine ES cells were labeled with six different QDs delivered by Qtracker. ES cell viability, proliferation, and differentiation were not adversely affected by QDs compared with non-labeled control cells (P=NS). Afterward, labeled ES cells were injected separately and subcutaneously onto the back of athymic nude mice. These labeled ES cells can be imaged with good contrast with one single excitation wavelength. With the same excitation wavelength, the signal intensity, defined as (total signal-background)/exposure time in millisecond is 11+/-2 for cells labeled with QD 525, 12+/-9 for QD 565, 176+/-81 for QD 605, 176+/-136 for QD 655, 167+/-104 for QD 705, and 1,713+/-482 for QD 800. Finally, we have shown that QD 800 offers greater fluorescent intensity than the other QDs tested. CONCLUSIONS: This is the first demonstration of in vivo multiplex imaging of mouse ES cells labeled QDs. Upon further improvements, QDs will demonstrate greater utility for the long-term tracking of stem cells deep within deeper tissues. These results provide a promising, innovative tool for imaging stem cell therapy non-invasively in vivo.

2. **Human reporter genes: potential use in clinical studies.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17921031

Serganova I, Ponomarev V, Blasberg R.

Nucl Med Biol. 2007;34:791-807.(Oct).

The clinical application of positron-emission-tomography-based reporter gene imaging will expand over the next several years. The translation of reporter gene imaging technology into clinical applications is the focus of this review, with emphasis on the development and use of human reporter genes. Human reporter genes will play an increasingly more important role in this development, and it is likely that one or more reporter systems (human gene and complimentary radiopharmaceutical) will take leading roles. Three classes of human reporter genes are discussed and compared: receptors, transporters and enzymes. Examples of highly expressed cell membrane receptors include specific membrane somatostatin receptors (hSSTRs). The transporter group includes the sodium iodide symporter (hNIS) and the norepinephrine transporter (hNET). The endogenous enzyme classification includes human mitochondrial thymidine kinase 2 (hTK2). In addition, we also discuss the nonhuman dopamine 2 receptor and two viral reporter genes, the wild-type herpes simplex virus 1 thymidine kinase (HSV1-tk) gene and the HSV1-tk mutant (HSV1-sr39tk). Initial applications of reporter gene imaging in patients will be developed within two

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different clinical disciplines: (a) gene therapy and (b) adoptive cell-based therapies. These studies will benefit from the availability of efficient human reporter systems that can provide critical monitoring information for adenoviral-based, retroviral-based and lentiviral-based gene therapies, oncolytic bacterial and viral therapies, and adoptive cell-based therapies. Translational applications of noninvasive in vivo reporter gene imaging are likely to include: (a) quantitative monitoring of gene therapy vectors for targeting and transduction efficacy in clinical protocols by imaging the location, extent and duration of transgene expression; (b) monitoring of cell trafficking, targeting, replication and activation in adoptive T-cell and stem/progenitor cell therapies; (c) and assessments of endogenous molecular events using different inducible reporter gene imaging systems.

3. **Development of radioimmunotherapeutic and diagnostic antibodies: an inside-out view.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17921028

Boswell CA, Brechbiel MW.

Nucl Med Biol. 2007;34:757-778.(Oct).

Only a handful of radiolabeled antibodies (Abs) have gained US Food and Drug Administration (FDA) approval for use in clinical oncology, including four immunodiagnostic agents and two targeted radioimmunotherapeutic agents. Despite the advent of nonimmunogenic Abs and the availability of a diverse library of radionuclides, progress beyond early Phase II radioimmunotherapy (RIT) studies in solid tumors has been marginal. Furthermore, [(18F)]fluorodeoxyglucose continues to dominate the molecular imaging domain, underscored by a decade-long absence of any newly approved Ab-based imaging agent (none since 1996). Why has the development of clinically successful Abs for RIT been limited to lymphoma? What obstacles must be overcome to allow the FDA approval of immuno-positron emission tomography (immuno-PET) imaging agents? How can we address the unique challenges that have thus far prevented the introduction of Ab-based imaging agents and therapeutics for solid tumors? Many poor decisions have been made regarding radiolabeled Abs, but useful insight can be gained from these mistakes. The following review addresses the physical, chemical, biological, clinical, regulatory and financial limitations that impede the progress of this increasingly important class of drugs.

4. **Non-invasive in vivo imaging of calcium signaling in mice.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17912353

Rogers KL, Picaud S, Roncali E, et al.

PLoS ONE. 2007;2:e974.

Rapid and transient elevations of Ca(2+) within cellular microdomains play a critical role in the regulation of many signal transduction pathways. Described here is a genetic approach for non-invasive detection of localized Ca(2+)

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concentration ([Ca(2+)]) rises in live animals using bioluminescence imaging (BLI). Transgenic mice conditionally expressing the Ca(2+)-sensitive bioluminescent reporter GFP-aequorin targeted to the mitochondrial matrix were studied in several experimental paradigms. Rapid [Ca(2+)] rises inside the mitochondrial matrix could be readily detected during single-twitch muscle contractions. Whole body patterns of [Ca(2+)] were monitored in freely moving mice and during epileptic seizures. Furthermore, variations in mitochondrial [Ca(2+)] correlated to behavioral components of the sleep/wake cycle were observed during prolonged whole body recordings of newborn mice. This non-invasive imaging technique opens new avenues for the analysis of Ca(2+) signaling whenever whole body information in freely moving animals is desired, in particular during behavioral and developmental studies.

5. **In vivo imaging of the systemic recruitment of fibroblasts to the angiogenic rim of ovarian carcinoma tumors.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17909023

Granot D, Addadi Y, Kalchenko V, et al.
Cancer Res. 2007;67:9180-9189.(Oct 1).

Tumor-associated stroma, in general, and tumor fibroblasts and myofibroblasts, in particular, play a role in tumor progression. We previously reported that myofibroblast infiltration into implanted ovarian carcinoma spheroids marked the exit of tumors from dormancy and that these cells contributed to vascular stabilization in ovarian tumors by expression of angiopoietin-1 and angiopoietin-2. Ex vivo labeling of fibroblasts with either magnetic resonance or optical probes rendered them detectable for in vivo imaging. Thus, magnetic resonance imaging (MRI) follow-up was feasible by biotin-bovine serum albumin-gadolinium diethylenetriaminepentaacetic acid or iron oxide particles, whereas labeling with near-IR and fluorescent vital stains enabled in vivo visualization by near-IR imaging and two-photon microscopy. Using this approach, we show here that prelabeled fibroblasts given i.p. to CD-1 nude mice can be followed in vivo by MRI and optical imaging over several days, revealing their extensive recruitment into the stroma of remote s.c. MSL human epithelial ovarian carcinoma tumors. Two-photon microscopy revealed the alignment of these invading fibroblasts in the outer rim of the tumor, colocalizing with the angiogenic neovasculature. Such angiogenic vessels remained confined to the stroma tracks within the tumor and did not penetrate the tumor nodules. These results provide dynamic evidence for the role of tumor fibroblasts in maintenance of functional tumor vasculature and offer means for image-guided targeting of these abundant stroma cells to the tumor as a possible mechanism for cellular cancer therapy.

6. **Nanoparticulate carrier containing water-insoluble iodinated oil as a multifunctional contrast agent for computed tomography imaging.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17904632

Ho Kong W, Jae Lee W, Yun Cui Z, et al.

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Biomaterials. 2007;(Sep 27).

Contrast-enhanced computed tomography (CT) imaging is a valuable and routine strategy for the clinical diagnosis of various diseases. However, all current CT contrast agents are liquids, so they flow through the blood vessels and disappear very quickly by extravasation. If it were possible to make a blood-compatible particulate contrast agent, we could highlight a particular tissue by either passive or active targeting. In this work, Pluronic F127 and a naturally iodinated compound, Lipiodol, were used to form radiopaque nanoreservoir structures. The resultant nanoparticles have a stable structure at high concentrations, sufficient X-ray absorption, a safety profile similar to or better than that of Iopromide, and a longer circulation time than commercial iodinated preparations. The utility of the resultant radiopaque nanoparticles as a contrast agent was tested using micro-SPECT/CT imaging in vivo. Together with the very good solubility of hydrophobic drugs (e.g., Taxol) in Lipiodol, these results suggest the possibility that these particulate structures and their bioconjugates could become functional CT contrast agents that could deliver therapeutic agents to a particular tissue.

7. **Conjugated Polymer Dots for Multiphoton Fluorescence Imaging.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17918941

Wu C, Szymanski C, Cain Z, et al.
J Am Chem Soc. 2007;(Oct 6).

We report on the two-photon excited fluorescence of conjugated polymer dots (CPdots). As a new class of two-photon fluorescent probes, CPdots exhibit two-photon action cross sections as high as 2.0×10^5 GM, to our knowledge, the largest reported thus far for a nanoparticle. The cross section values are 3-4 orders of magnitude higher than those of conventional fluorescent dyes and an order of magnitude higher than those of inorganic quantum dots. Single particle fluorescence imaging was achieved using relatively low laser power.

8. **Fluorine-19 MRI for visualization and quantification of cell migration in a diabetes model.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17899609

Srinivas M, Morel PA, Ernst LA, et al.
Magn Reson Med. 2007;58:725-734.(Oct).

This article describes an in vivo imaging method for visualizing and quantifying a specific cell population. Cells are labeled ex vivo with a perfluoropolyether nanoparticle tracer agent and then detected in vivo using (^{19}F) MRI following cell transfer. (^{19}F) MRI selectively visualizes only the labeled cells with no background, and a conventional (^1H) image taken in the same imaging session provides anatomical context. Using the nonobese diabetic mouse, an established model of type 1 diabetes, (^{19}F) MRI data were acquired showing the early homing behavior of diabetogenic T cells to the pancreas. A computational algorithm provided T cell counts in the pancreas. Approximately 2% of the transferred cells homed to the pancreas after 48 hr. The technique allows for

both unambiguous detection of labeled cells and quantification directly from the in vivo images. The in vivo quantification and cell trafficking patterns were verified using (^{19}F) spectroscopy and fluorescence microscopy in excised pancreata. The labeling procedure did not affect T-cell migration in vivo. This imaging platform is applicable to many cell types and disease models and can potentially be used for monitoring the trafficking of cellular therapeutics. *Magn Reson Med* 58:725-734, 2007. (c) 2007 Wiley-Liss, Inc.

9. Optical probes to identify the glucocorticoid receptor ligands in living cells.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17897691

Awais M, Sato M, Umezawa Y.
Steroids. 2007;(Aug 22).

Glucocorticoids act through glucocorticoid receptor (GR) and are used for the treatment of several diseases. Ligand-induced recruitment of coregulator protein(s), coactivator/corepressor, to GR is an initial step in transcriptional activation/inhibition of GR. We describe herein genetically encoded fluorescent probes for screening of glucocorticoids, natural and synthetic, in single living cells. The GR ligand binding domain was connected to the GR interacting peptide sequence from coactivator or corepressor protein via a flexible linker sequence. This fusion protein was sandwiched between cyan and yellow fluorescent proteins (CFP and YFP, respectively) to complete the construct of the probe. This construct functions as an optical probe for imaging ligand-induced interaction between the glucocorticoid receptor and the coregulator protein (GLUCOCOR) in live cells. The interaction between GR LBD and coregulator peptide within GLUCOCOR brings CFP in close proximity of YFP to induce fluorescence resonance energy transfer from CFP to YFP. The GLUCOCORs can identify functionally active GR ligands, rapidly and conveniently, in a high-throughput screen; and are capable of distinguishing GR agonists, antagonists, and selective GR modulators in intact living cells. Therefore, the present method may play a significant role in developing new glucocorticoids for clinical use.

10. Magnetic nanoparticle labeling of mesenchymal stem cells without transfection agent: Cellular behavior and capability of detection with clinical 1.5 T magnetic resonance at the single cell level.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17899592

Hsiao JK, Tai MF, Chu HH, et al.
Magn Reson Med. 2007;58:717-724.(Oct).

The purpose of this work was to evaluate the efficacy of labeling human mesenchymal stem cells (hMSCs) by ionic superparamagnetic iron oxide (SPIO) without a transfection agent and verifying its capability to be detected with clinical 1.5 T magnetic resonance (MR) at the single-cell level. Human hMSCs were incubated for 24 h with an ionic SPIO, Ferucarbotran. The labeling efficiency of hMSCs was determined by iron content measurement spectrophotometrically, and the influence of labeling on cell behavior was ascertained by examination of

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cell viability using the trypan blue exclusion method, cell proliferation analysis using MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, mitochondrial membrane potential (MMP) change, differentiation capacity, and reactive oxygen species (ROS) production measured by dichlorofluorescein diacetate (DCFDA) fluorescent probe. Labeled hMSCs were scanned under 1.5 T MRI with three-dimensional (3D) and two-dimensional (2D) T(2)-weighted gradient echo (GRE) pulse sequences. Human hMSC labeling without transfection agent was efficient. The iron content in hMSCs was 23.4 pg Fe/cell. No significant change was found in viability, proliferation, MMP change, ROS production, or differentiation capacity. About 45.2% of the hMSCs could be detected using 1.5 T MRI at the single cell level with 3D GRE and four repetitions. *Magn Reson Med* 58:717-724, 2007. (c) 2007 Wiley-Liss, Inc.