Tracking cells after administration: Imaging modalities and probes

Brooke Helfer, PhD

Celsense, Inc. Pittsburgh PA, United States

HESI CT-TRACS Point of Administration Co-chair

Conflict of Interest

- I am an employee of Celsense, Inc. the manufacturer and provider of the fluorine based imaging agent mentioned herein.

A Fundamental Question

If there is no clinical response, did the cell product not work, or did the cell product not reach and/or persist at the site of action?

Cell Therapy: Technology and Markets, Jain Pharmabiotech August 2008

Cell Trafficking Questions

- How many cells were delivered?
- How many cells migrate?
  - Site of action?
  - Off target?
- How many cells persist?
  - Site of administration?
  - Site of action?
- Strategies that affect cell trafficking?

Cell Trafficking Biomarkers

- Does cell trafficking data support hypothesized mechanism of action?
- Does cell trafficking data correlate with efficacy and safety endpoints?
- Is cell trafficking data a predictor of efficacy and safety?
- Can cell trafficking data guide dosage and/or repeat administration?

Requirements for an imaging agent

- Imaging reagents need to be:
  - Non toxic to cells
  - Not alter the phenotype and function of the cells
  - Non toxic to surrounding tissues
  - Indicates the location, migration and quantity of labeled cells
  - Allow for repeated, non-invasive detection
  - Accurately reflects the behavior of labeled cells

* adapted from Frangioni *et al* 2004 *Circulation*

Modality	EM Spectrum	Advantages	Disadvantages
Positron emission tomography (PET)	High energy gamma rays	High sensitivity; isotopes can substitute for naturally occurring atoms; quantitative; translational research, targeted, multiple probes	PET cyclotron or generator needed; relatively low spatial resolution; ionizing radiation
Single photon emission computed tomography (SPECT)	Lower energy gamma rays	Many molecular probes; can image multiple probes simultaneously; adaptable to clinical imaging systems	Relatively low spatial resolution; ionizing radiation
Optical bioluminescence imaging	Visible light	Highest sensitivity; quick, easy, low cost and relatively high throughput, multiple probes	Low spatial resolution; relatively surface weighted
Optical fluorescence imaging	Visible light or near-infrared	High sensitivity; detect fluorochrome in live and dead cells, low cost, high throughput, multiple probes	Low spatial resolution; 2D imaging only; relatively surface weighted; limited translational research
Magnetic resonance imaging (MRI)	Radio waves	Highest spatial resolution; combines morphologic and functional imaging	Relatively low sensitivity; long scan and post processing time, mass quantity of probe may be needed
Computed tomography (CT)	X-rays	Bone and tumor imaging; anatomic imaging	Limited molecular applications; limited soft tissue resolution, ionizing radiation
Ultrasound	High frequency sound	Real time; low cost	Limited spatial resolution; mostly morphologic.
Photoacoustics	near-infrared stimulation/sound wave detection	low cost; moderate spatial resolution; tomographic image	limited penetration depth

* CT-TRACS adapted from *Gambhir S,* 2007 *mi gateway*

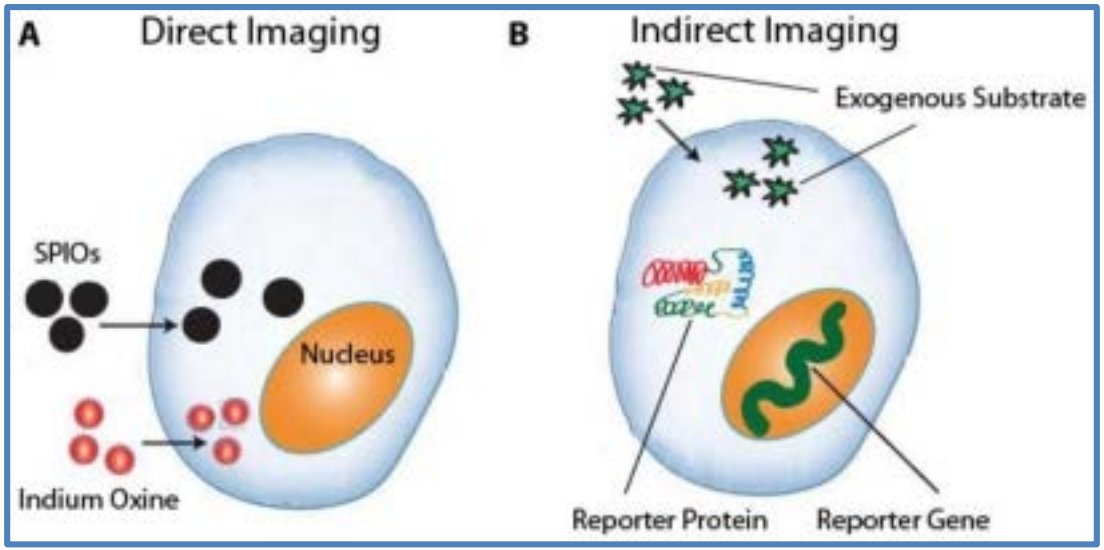
Multiple Modalities Different Approaches

Direct Labeling

- Where the label is applied to cells prior to administration – directly linking the cells and the label

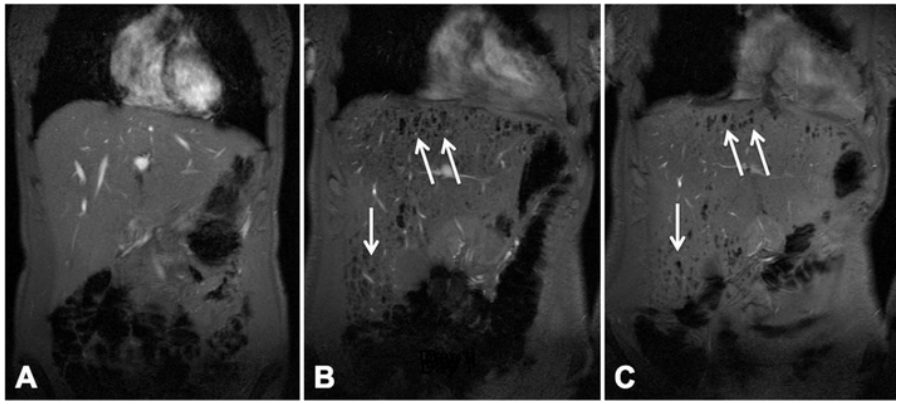
Indirect Labeling / Reporter Genes

- Where the cells either create the label, or the label binds to a receptor which the cell creates

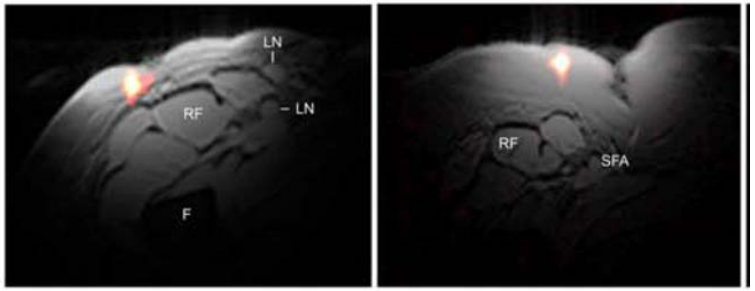


E. Gu et.al. 2012 *Theranostics*

Magnetic Resonance Imaging



F Saudek et al 2010 *Transplantation*



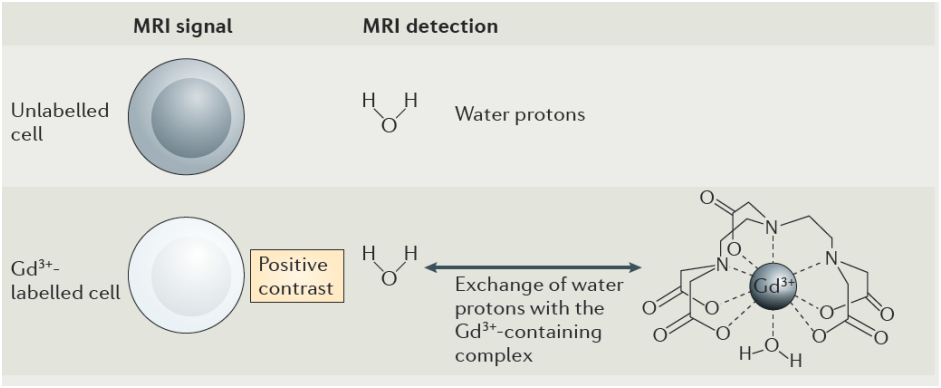
Ahrens et al 2014 *Mag Res Med*

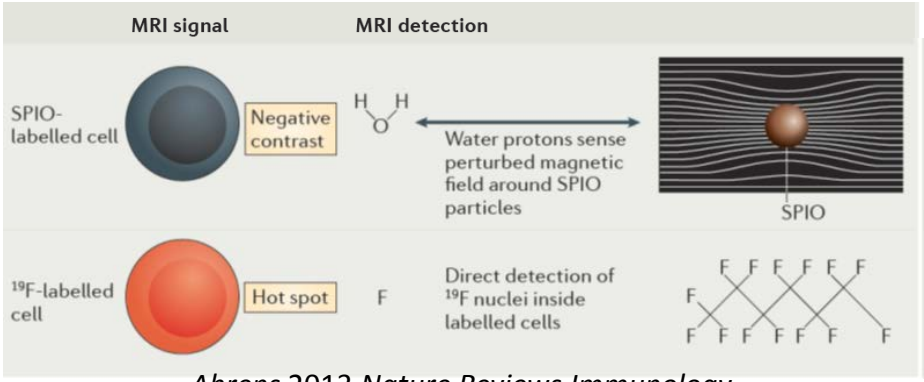
Pros

- Highest spatial resolution
- Combines morphologic and functional imaging
- Quantitative

Cons

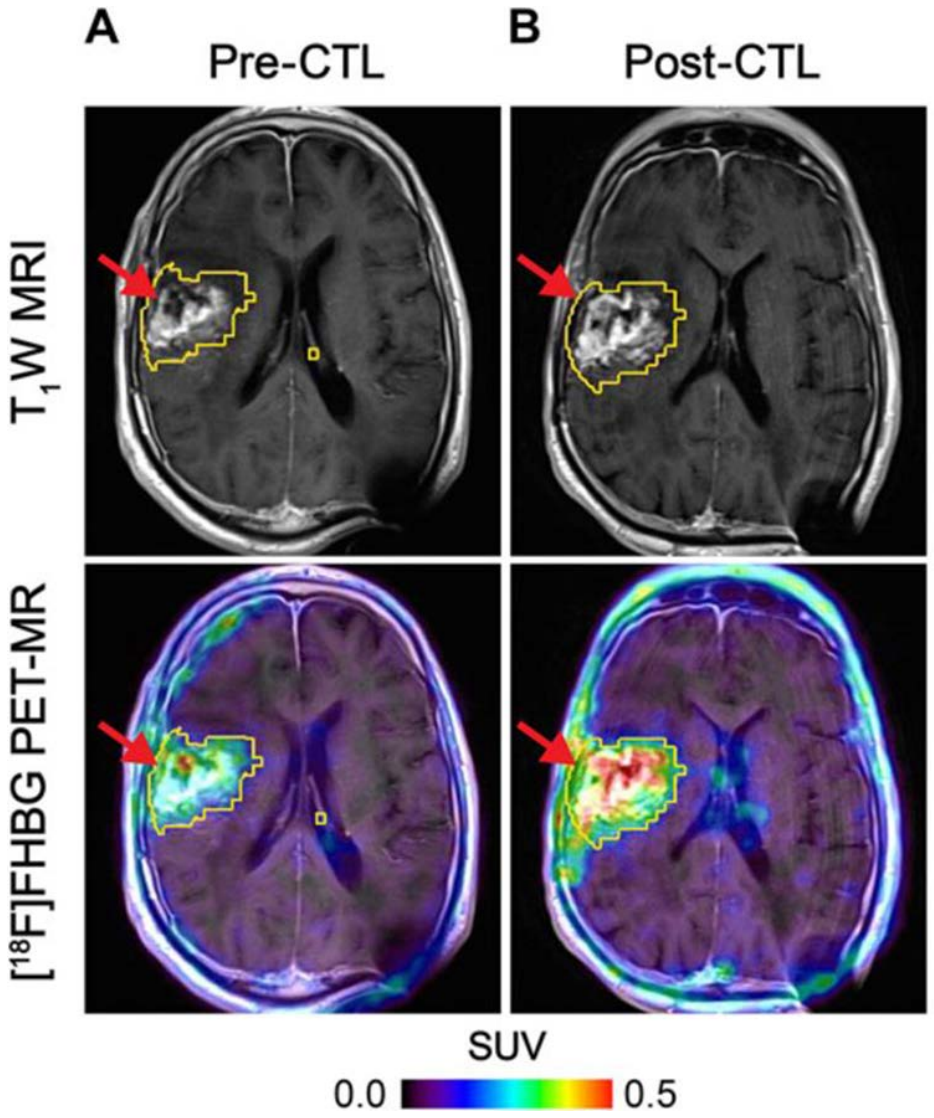
- Low sensitivity
- Potentially long scan and post processing time
- Mass quantity of probe may be needed





Ahrens 2013 *Nature Reviews Immunology*

Positron Emission Tomography



Keu 2017 *Science Translational Med*

Pros

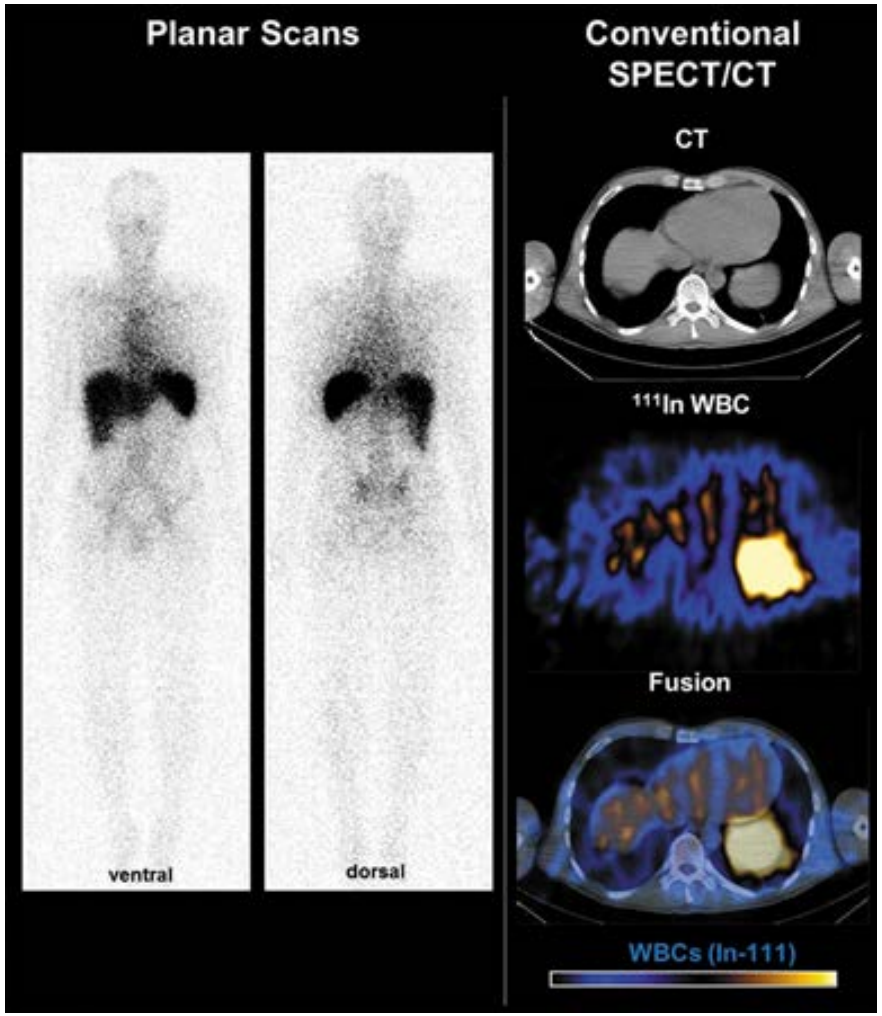
- High sensitive
- Isotopes can substitute for naturally occurring atoms
- Targeted
- Multiple probes
- Quantitative
- Cell survival
- Proliferation

Probes:
Zirconium-89
Fludeoxyglucose (F18)
Reporter genes

Cons

- PET cyclotron or generator needed
- Low spatial resolution
- Ionizing radiation
- Half-life decay
- Cytotoxicity
- Translation barriers

Single **P**hoton **E**mission **C**omputed **T**omography



Caobelli et al. 2017 *Eur Heart J*

Pros

- Many molecular probes
- Can image multiple probes simultaneously
- Adaptable to clinical imaging systems

Cons

- Low spatial resolution
- Ionizing radiation
- Half-life decay
- Cytotoxicity
- Translation barriers

Probes:
Indium 111
Technetium 99

Optical

Pros

- Sensitivity
- Low cost
- High throughput
- Multiple probes
- Quantitative
- Cell survival
- Proliferation
- Well established preclinically

Cons

- Low spatial resolution
- Surface weighted
- Limited to 2D imaging
- Toxicity
- Mostly preclinical
- Translation barriers

Photoacoustic

Pros

- Low cost
- Moderate spatial resolution
- Tomographic image

Cons

- Limited Penetration Depth

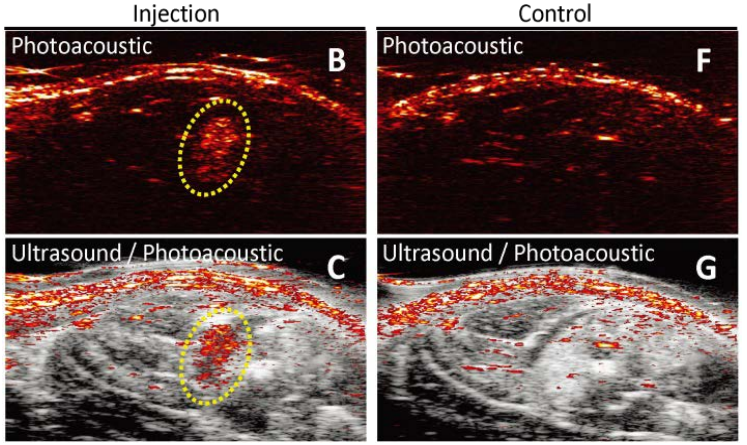
Ultrasound

Pros

- Low cost
- Real time

Cons

- Low spatial resolution
- Surface weighted



SY Nam et al. 2012 *PLOS*

Potential benefits of imaging

- Visualize delivery, homing, and persistence
- Ability to answer unsolved questions:
  - Do transferred cells migrate to sites of disease or off-target sites?
  - Is migration correlated with clinical effectiveness
  - Can outcomes be improved by modifying migration/delivery/homing?
- Preclinical rodent models may not be predictive to activity in humans

Administration vs. Misadministration

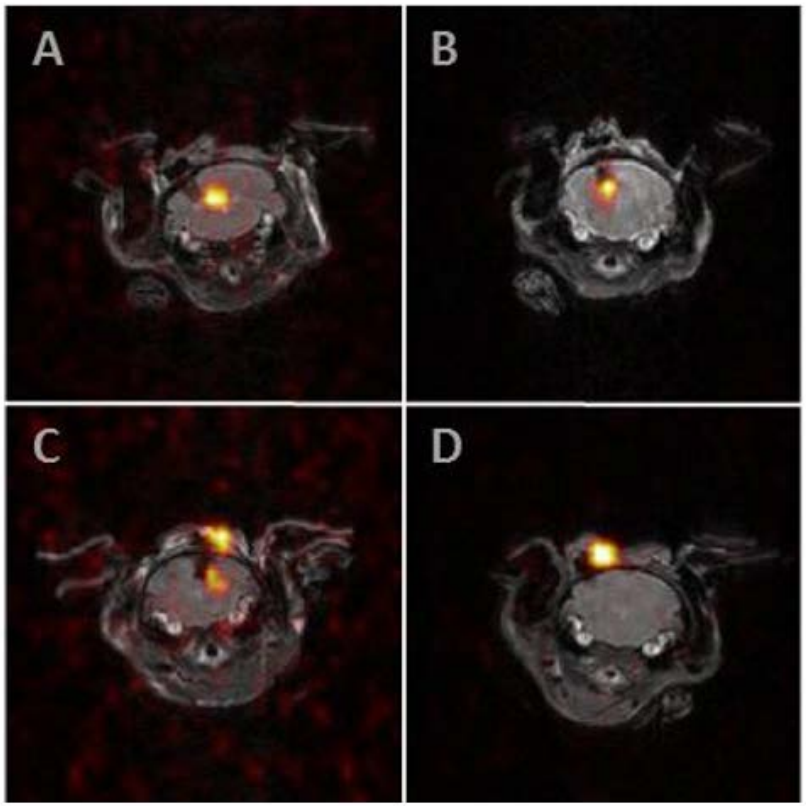


Figure 3: Visualization of success (A,B), partial success (C), and failure (D) in delivery of labeled NK cells.

Dean Lee Innate Killer Summit 2016 Presentation
Kennes 2019 Journal Neuro-oncology

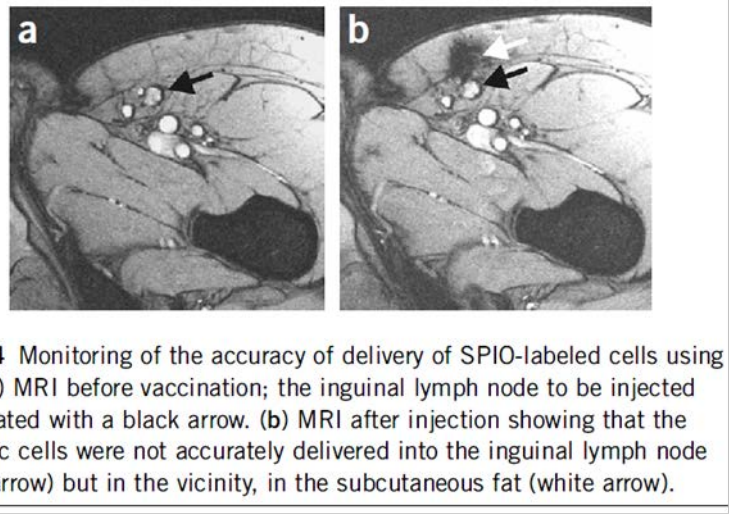


Figure 4 Monitoring of the accuracy of delivery of SPIO-labeled cells using MRI. (**a**) MRI before vaccination; the inguinal lymph node to be injected is indicated with a black arrow. (**b**) MRI after injection showing that the dendritic cells were not accurately delivered into the inguinal lymph node (black arrow) but in the vicinity, in the subcutaneous fat (white arrow).

de Vries 2005 *Nature Biotechnology*

Are there imaging trade offs?

- Toxicity versus information
- Sensitivity versus spatial resolution
- Complexity versus translatability
- Quantitation
- Cost

Acknowledgements:

The CT-TRACS subcommittee on Biodistribution and Point of Administration Monitoring

Coauthors on pending review manuscript "Options for imaging cellular therapeutics *in vivo*: a multi-stakeholder perspective"

Colleagues at Celsense