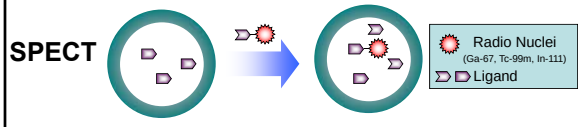
Imaging of targeted and activatable particles

Katherine Ferrara

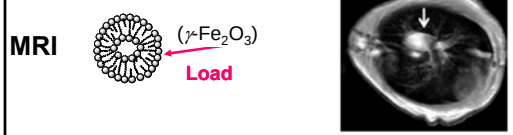
Imaging of targeted and activatable particles

- How?
- Why?
- Recent results

Entrapment of the label in the particle



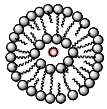
Philips WT, et al. Nucl Med Biol 1992; 19:539. Bao A, et al. J Pharm Sci 2003; 92:1983. Bao A, et al. J Pharmacol Exp Ther 2004; 308:419



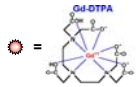
Martina M-S & Lesieur S. et al. J Am Chem Soc 2005; 127:10676

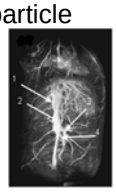
Entrapment of the label in the particle

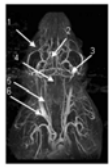
MRI



DTPA
(diethylenetriamine pentaacetate)

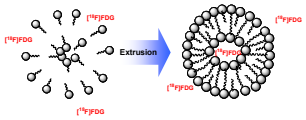






Ayyagari AL & Bellamkonda RV et al.
Magnetic Resonance in Medicine 2006; 55:1023

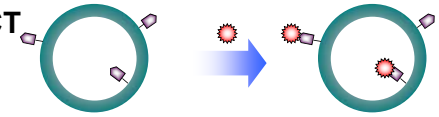
PET



Oku N, et al. Biochim Biophys Acta 1995; 1238: 86. Kondo M, et al. Int J Cancer 2004; 108:301.

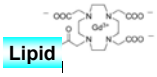
Surface chelation

SPECT

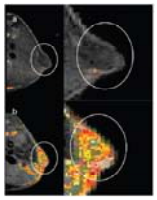


Tilcock C, et al. Nucl Med Biol 1994; 21:89. Laverman P. et al. J Nucl Med 1999; 40:192

MRI



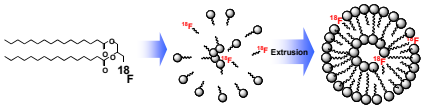
Lipid

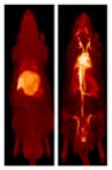


Kamaly N & Miller AD. et al. Bioconjugate Chem 2007 ASAP

Inclusion of the tracer in the shell

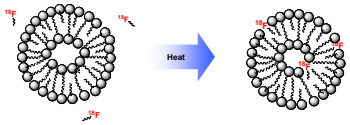
1) Directly label the lipid, preinsert





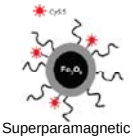
Marik J, et al. Nucl Med Biol 2007; 34: 165

2) Post-Insertion method

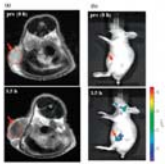


Urakami T, et al. J Med Chem 2007; 50:6454

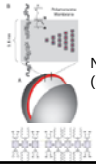
Inclusion of tracer within the shell
NIR Optical Imaging



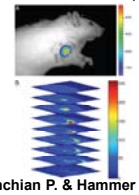
Superparamagnetic iron oxide nanoparticles (**SPION**)



Lee H. & Jon S. et al, J AM CHEM SOC 2007; 129:12739



NIR fluorophores (**NIRF**s)

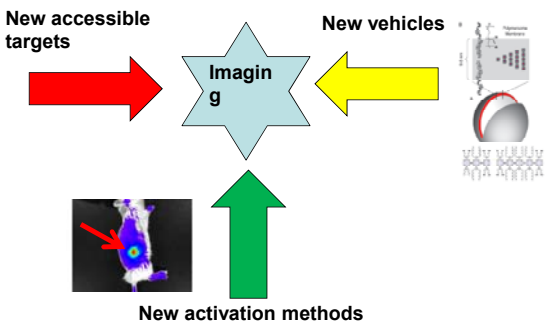


Peter Ghoroghchian P. & Hammer DA et al. PNAS 2005; 102:2922

Imaging of targeted and activatable particles

- How?
- **Why?**
- Recent results

Why?



What to image?

- Circulation & targeting

Quantitative, high time and spatial resolution

- Activation

High time resolution, need change with pH, heat, etc.

- Metabolism & clearance of vehicle

Circulation and targeting: Vascular Targeting

Receptors: RGD	Janssen, M. L. et al. Cancer Res 2002;62:6146-6151.
Aminopeptidase N	Garde, S.V., et al., Anti-Cancer Drugs, 2007; 18:1189-1200.
Aminopeptidase P	Essler M, et. al., Proc Natl Acad Sci U S A 2002; 99:2252-2257.
Neuropilin-1	Starzec A. et. al. Life Sci 2006; 79:2370-2381.
Nucleolin	Christian S. et. al. J Cell Biol 2003;163:871-878. Porkka, K. et. al. Proc. Natl. Acad. Sci. USA. 2002; 99:7444–7449.
PSMA	Foss CA et. al., Clin Cancer Res 2005;11:4022-4028.
Organ specific	Zhang, Circulation, 112, 1601, 2005.

First use heart targeting as model system

Why?

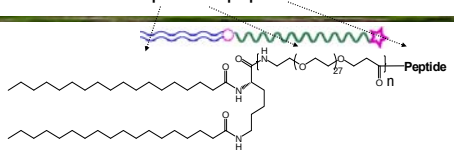
Want to separate enhanced permeability and retention (EPR) effect from molecular targeting to optimize particles

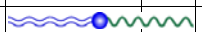
No EPR effect in heart

**Zhang et al, Biomaterials, 2008, in press

Methods

Lipo-PEG-peptides

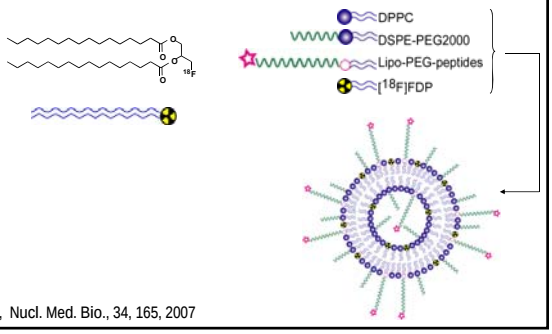


	peptide	n	Mw (PEG)
CRPPR-3	CRPPR*	3	3600
CRPPR-2	CRPPR	2	2400
CRPPR-1	CRPPR	1	1200
DSPE-PEG2K			2000

**Zhang et al, Biomaterials, 2008, in press

Methods

[^{18}F]FDP

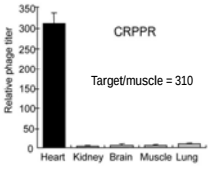


Marik, Nucl. Med. Bio., 34, 165, 2007

Results

Organ specificity – well counts

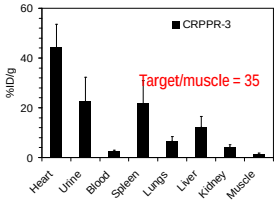
Peptide phage*



Specificity to CRIP-2 protein shown by antibody blocking

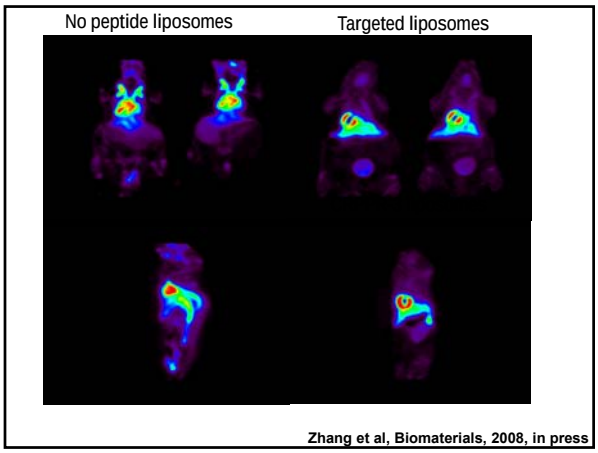
* Zhang, Circulation, 112, 1601, 1601, 2005

Peptidyl liposomes**

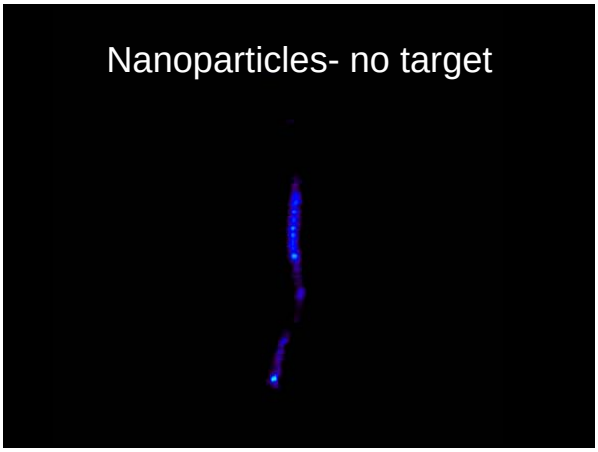


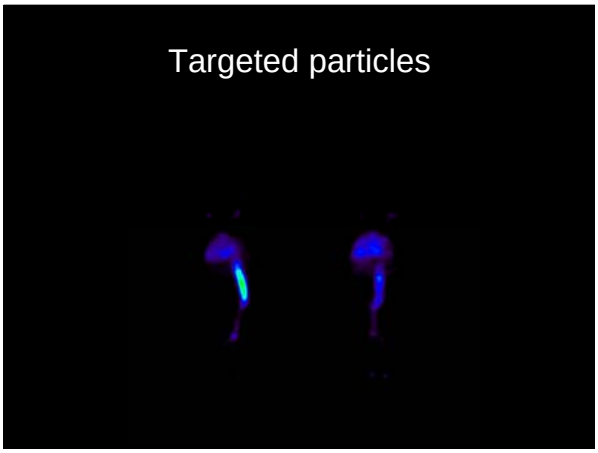
LPP:DSPE-PEG2K:DPPC = 6:6:88 (mol/mol), 90min after injection.

**Zhang et al, Biomaterials, 2008, in press



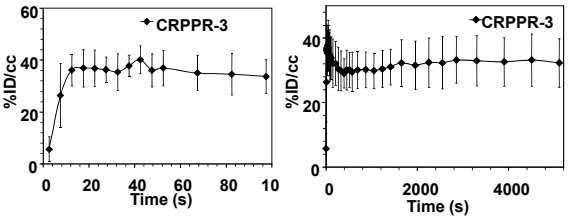
Zhang et al, Biomaterials, 2008, in press





Results

Pharmacokinetics – heart muscle

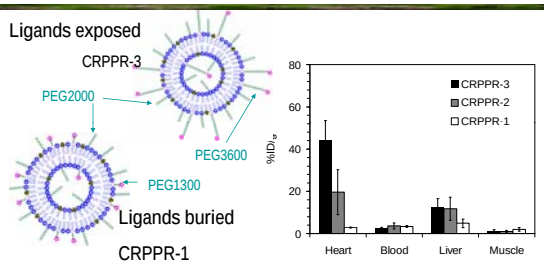


Targeted liposomes bind to heart within 100 seconds and stay stably.

Zhang et al, Biomaterials, 2008, in press

Results

Surface architecture – length of PEG spacer



Ligands must be exposed (not buried) to bind to heart.

Zhang et al, Biomaterials, 2008, in press

Why vehicle activation?

Protection of vehicles during circulation ≠ **Bioavailability at target**

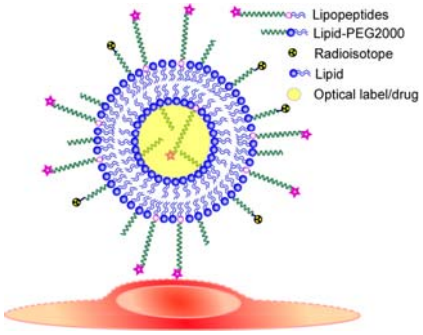
Why activatable imaging probe?

Assessment of enzyme activity
Cellular internalization
Assessment of vehicle stability & metabolism

UCDAVIS

CENTER FOR MOLECULAR AND GENOMIC IMAGING
DEPARTMENT OF BIOMEDICAL ENGINEERING

Multi-modal particles

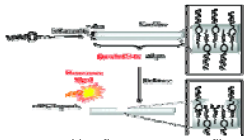


Why? Show local particle activation

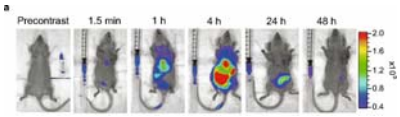
Why? Show stability
Stable liposomes

Unstable liposomes

Particles, degradation and activation

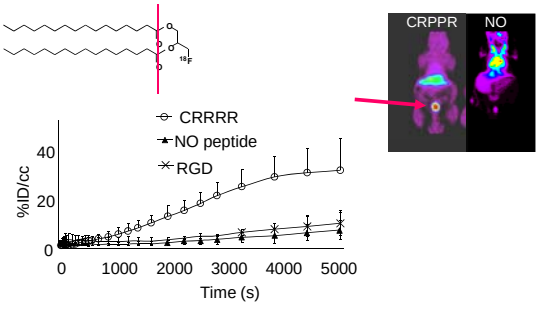


Law B, et al. Protease-sensitive fluorescent nanofibers. Bioconjug Chem. 2007 Nov -Dec;18(6):1701-4.



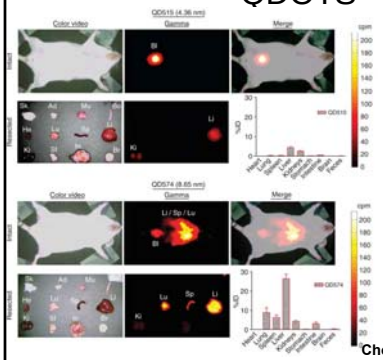
Melancon MP, et al. A novel method for imaging in vivo degradation of poly(L-glutamic acid), a biodegradable drug carrier. Pharm Res. 2007 Jun;24(6):1217-24.

Kinetics of metabolism- bladder



**Zhang et al, Biomaterials, 2008, in press

Clearance of intact particle-QDOTS



4.36 nm

8.65 nm

Choi, HS, *Nature Biotechnology* 25, 1165 - 1170 (2007)

Conclusion

- New imaging tools under development to assess pharmacokinetics of vehicles with MRI, SPECT,PET, optical imaging.
- Kinetics of targeted vehicles can vary greatly.
- Activatable vehicles require new imaging approaches. Optical imaging and MRI are obvious choices.
- *In vivo* imaging of vehicle metabolism and clearance also require new approaches. Nuclear medicine techniques are feasible.