Novel Metalloporphyrins as Molecular MR Contrast Agents

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Introduction: To date, no imaging methodology exists which can image prostate cancer *in vivo* with sufficient sensitivity and specificity for diagnostic utility. As a consequence, urological surgeons and oncologists proceed with treatment strategies based on 'blind' biopsy tissue specimens and limited diagnostic evaluations using conventional MRI and ultrasound. In these experiments, we have investigated a new class of therapeutic metalloporphyrins for their potential as molecular MR imaging probes for prostate cancer detection. Mn(III)TE-2-Pyp^{5+} (meso-tetrakis(N-ethyl-2-prydil)porphyrin) and Mn(III)TnHex-2-PYP^{5+} (meso-terakis(N-n-hexyl-2-pyridyl)porphyrin are powerful superoxide dismutase mimics with low toxicity and antineoplastic activity [1]. In phantom experiments, we observe unusually high T1 relaxivity with these compounds that is several-fold greater than commercially available gadolinium chelates (Magnevist, Prohance.) Observable detection limits are in the low micromolar range at 7 Tesla. *In vivo*, we observe selective accumulation of these probes in prostate tumor xenografts following a single dose of either compound. Relaxation changes in prostate tumors is 10-11 fold greater than in normal prostate gland, suggesting these compounds may be particularly effective at selectively detecting multifocal disease in situ.

Methods: MR imaging experiments were performed at 7.0T on a Bruker Biospec horizontal bore scanner. *In vitro* experiments were done on varying concentrations of porphyrins , magnevist, ProHance and MultiHance in ringers solution. All *in vivo* experiments were performed on C57 black mice implanted with human prostate cancer cells on the hind-limb location. 10 mg/kg of MnTn-Hex-2-PyP (n=4) and 2 mg/kg MnTE-2-PyP (n=3) were given i.p in a single dose. Experiments were performed before and after 60 or 120 minutes following injection. T2 images were collected using a RARE based sequence, with a TE/TR = 12/4200, thickness =1 mm, FOV = 4cm X 4cm, RARE factor = 2. T1 maps were performed with a variable TR RARE sequence. TE = 9.7 ms. TR's = 300ms, 800ms, 1800 ms, 3000 ms, 5000 ms, 7500 ms . All the images were collected using a volumevolume coil. The images are processed using Paravision 4.0.

Results and Discussion: T1-weighted imaging of MnTE-2-PyP in phantoms is shown in the Figure 1. Both Mn porphryins were detectable at concentrations as low as 1 µM. Relaxivities were compared to gadolinium based chelates and showed relaxivities at least 2-3 times higher than commercially available contrast agents (Table 1). Figure 2 shows superposition of T1 shortening merged onto T2 anatomical images. Figure 2A and 2B are before and at 120 minutes after i.p injection of MnTE-2-PyP. Table 1 shows comparison of observed Tumor/Tissue contrast for MnTnHex-2-PyP and MnTE-2-PyP.

References: [1]. Spasojevic, I *et al* Free Radical biology & Medicine 45(2008) 943-949.

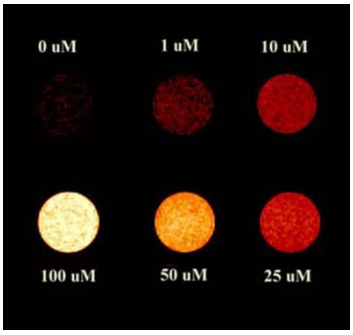

Figure 1 T1 weighted images of MnTE-2-PyP at different concentrations

Table1: T1 Relaxivity of different contrast agents at 7T

Compound	Relaxivity ($mM^{-1}S^{-1}$)
Magnevist	2.85
ProHance	2.37
MultiHance	3.19
MnTE-2-PyP	5.09
MnTnHex-2-PyP	5.34

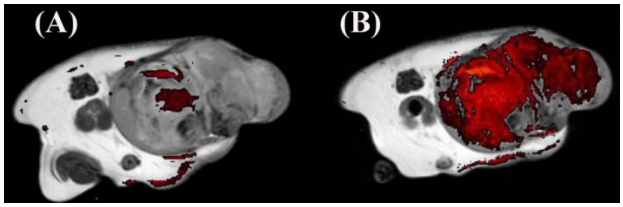

Figure 2 Before (A) and after (B) i.p injection of MnTE-2-PyP. Significant T1 shortening observed

Table 2:

Prostate		**Tumor T1 map(msec)**		**Muscle T1 map(msec)**		**%Drop**		**Tum/Pros**
DRUG		Before	After	Before	After	Tumor	Tissue	
MnTE-2-PyP		3653±120	3288±275	4313±200	4117±300	10.1	4.6	10.0
		NormalProstate T1(msec)		**Tissue T1 map(msec)**		**%Drop**		
MnTE-2PyP		3201±77	3165±72	3317±70	3275±90	1.1	1.2	