Development of Dual-Modality Nanoparticles for PET/MR

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Abstract:

Behind strong medical treatments lie accurate diagnostics that commonly involve imaging—such as magnetic resonance imaging (MRI) and positron emission tomography (PET). Recently, to overcome limitations of each individual modality, PET and MRI are combined into a more efficient and accurate procedure for functional evaluation of imaging agent uptake with high resolution anatomy. However, this new technique requires new contrast agents enabling the dual-modality assessment. To date, numerous nanoparticles have been researched, but many require chelators for conjugation of radioisotopes to the nanoparticle surface. This raises concerns of radiolabeling stability and diagnostic accuracy. To address these issues, our project aimed at developing new PET/MR dual-modality nanoparticles by doping MRI contrast agents such as iron oxide (IO) and gadolinium oxide (GdO) with positron-emitter ^{64}Cu. We first focused on the synthesis of nanoparticles through one-step reduction, copper doping efficiency, size and shape uniformity, contrast magnitude, structural stability, and surface modification. We then successfully incorporated ^{64}Cu into IO with ~ 30% incorporation of total radioactivity and achieved high specific activity for sensitive PET detection. Further, phantom studies and *in vivo* pharmacokinetic evaluations suggested potential applications of this particle for PET/MR. We will continue the optimization for further *in vivo* animal PET/MRI studies.

Introduction:

With MRI we are able to achieve excellent soft tissue and soft organ contrast providing images with high anatomical accuracy. This can be helpful in locating a patient's specific medical condition such as a tumor. However, it cannot provide functional information such as tissue growth rate and metabolism. In order to collect this information a patient might have to undergo additional imaging techniques. A common approach is PET imaging, which offers the needed sensitivity through detection of extremely minute amounts of radioactive labeled agents.

When these imaging techniques are combined we then need dual-modality agents. In our research, nanoparticle systems were exploited because of their multifunctionality capability. Specifically, we combined two detection elements, radionuclides and MRI agents, but future work could involve additional components used for targeting and therapeutic payloads. Operating on the nanoscale also offers enhanced *in vivo* stability, efficacy, and reduced toxicity. With such potential it is no surprise that six nanoparticle delivery systems for cancer are already on the market and numerous others in clinical development [1].

Experimental Procedure:

Cu-IO Synthesis. Iron oxide particles were synthesized following a modified one-step copper incorporation thermal decomposition procedure [2]. To study effects of copper incorporation on particle characteristics we varied the percentage of copper in the reaction medium (0%, 2% and 10%) through addition of copper chloride dihydrate.

Cu-GdO Synthesis. Gadolinium oxide particles were synthesized following a modified one-step copper incorporation polyol process [3]. Similarly to IO we studied the effects of copper incorporation by varying the presence of copper in the reaction medium (0% and 5%).

Surface Modification. Before conducting any *in vivo* study, particle surfaces first needed to be modified for stable aqueous dispersion. This was achieved through the exchange of initial hydrophobic coatings, a product of synthesis reagents, with polyethylene glycol (PEG) through a modified PEGylation process [2]. Particles were first synthesized with non-radioactive copper and studied via transmission electron microscope (TEM) in order to characterize size and shape. Copper incorporation was then confirmed with inductively coupled plasma mass spectrometry (ICP-MS). Finally, after successful surface modification for stable aqueous dispersion the synthesis was repeated except with the use of ^{64}Cu. Further studies were then conducted on structural stability via thin layer chromatography (TLC), contrast magnitude via PET and MR phantom, and pharmacokinetic properties via mouse biodistributions.

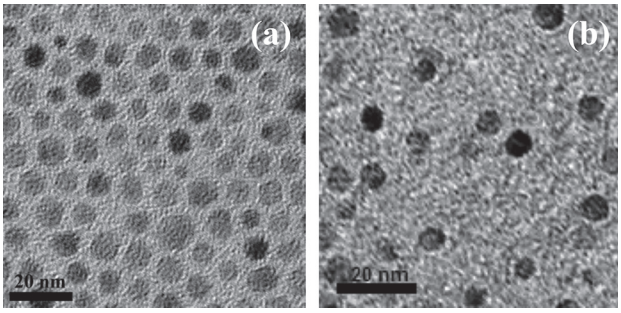

Figure 1: TEM images of (a) IO-0% Cu and (b) GdO-0% Cu with 20 nm scale bars.

Target	Measured Cu	TEM size
IO	--	7.0 ± 1.2 nm
IO-2% Cu	1.4%	8.2 ± 1.0 nm
IO-10% Cu	1.8%	9.6 ± 1.4 nm
GdO	--	6.3 ± 1.6 nm
GdO-5% Cu	0.23%	4.6 ± 0.9 nm

Figure 2: Particle diameters via TEM and measured copper percentage via ICP-MS.

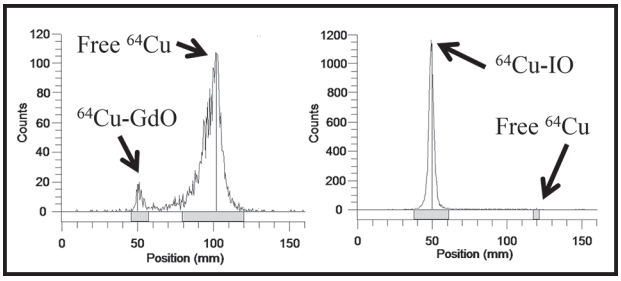

Figure 3: Radio-TLC plots showing 64Cu incorporation into (left) GdO and (right) IO.

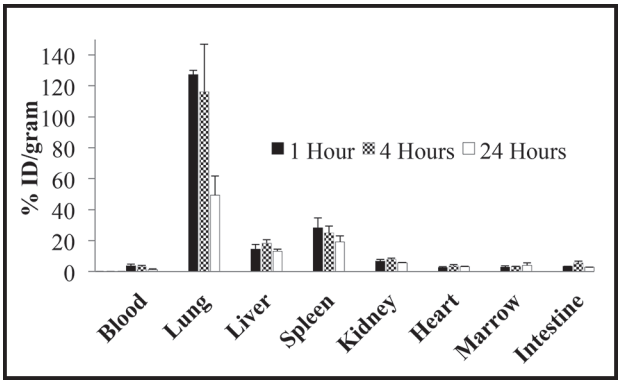

Figure 4: Mouse biodistribution study of 64Cu-IO.

Results and Conclusions:

Synthetic procedures produced particles monodisperse in size and shape for both IO and GdO as seen in Figure 1 and 2. It can also be seen that there were only slight changes in particle diameters as the percentage of copper increased. This consistency and stability is beneficial as it allows for the variable tuning of copper incorporation without significant changes to other features such as PET and MR contrast magnitude; confirmed via phantom studies. Further, we were able to confirm the presence of copper by ICP-MS. While the actual values are lower than amounts present during synthesis we were successful nonetheless as the high sensitivity of PET is capable of detecting such minute amounts of ^{64}Cu.

When particles were synthesized with ^{64}Cu we measured radiolabeling stability by observing how much ^{64}Cu remained intact versus how much broke free from the main particle system; seen in Figure 3. For both IO and GdO we saw that ^{64}Cu remained intact, but in the case of GdO there was also detachment; signified by the "Free ^{64}Cu" peak.

Since current progress with IO showed greater radiolabeling success we then studied pharmacokinetic properties of ^{64}Cu-IO via mouse biodistributions. As seen in Figure 4, particle concentration in the lungs was greater than any other organ. While this suggests a potential application for drug delivery to the lungs further studies are needed to explore the underlying mechanism behind the accumulation.

Future Work:

While this preliminary work was successful in using IO, GdO, and ^{64}Cu for the development of dual-modality particles, we hope to increase radiolabeling incorporation and stability though synthetic procedure modifications. After optimization of both IO and GdO systems we can then continue with PET/MR imaging and exploration of *in vivo* particle accumulation.

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References:

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