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Tungsten and Bismuth Nanoparticles for X-ray Computed Tomography

Vishwas N. Joshi[1].

[1.] Nanoprobes, Inc., 95 Horseblock Road, Unit 1; Yaphank, NY.

Nanoparticles (NPs) are playing a progressively more significant role in multimodal and multifunctional imaging [1]. NPs have been used as contrast agents (CAs) for magnetic resonance and optical imaging studies [2]. More recently, X-ray computed tomography (CT) CAs based on heavy metal NPs of gold, tantalum and bismuth have been reported [3]. We herein report tungsten (z = 74) oxide (WO_3), zero valent bismuth (z = 83) ZV-Bi NPs stabilized and biocompatibilized with organic ligands for *in vivo* use as CT contrast agents.

Uniformly sized WO_3 NPs (2-80 nm dia.) were prepared by water-in-oil (w/o) emulsion method [4]. The particles were then coated with a mixture of tetraethyl orthosilicate (TEOS) and 2-[methoxy(polyethyleneoxy) 9-12 propyl] trimethoxysilane (PEG-silane) to make them dispersible in water by adding TEOS/PEG-silane mixture to the emulsion containing nanoparticles, followed by ammonium hydroxide to hydrolyze TEOS or PEG-silane and deposit SiO_2 layer(s) [5]. Particles were isolated by breaking the emulsion with excess of acetone. It was difficult to achieve narrow size distribution and uniform silica coating for bigger particles (Fig. 1), and the particles had surfactant entrapped in the silica layer. Also, it is difficult to produce WO_3 NPs on a large scale by this method.

Direct reduction of Bi(III) salts in water a with large excess of strong reducing agent like sodium borohydride (BH_4^{1-}, it is unstable under acidic conditions) in the presence of thiols and acetic acid (to keep thiols protonated) (Fig. 2) resulted in ligand stabilized ZV-BiNPs. The thiol B (Fig. 2) gave 1-4 nm NPs and thiol D gave 4-13 nm NPs. Under basic conditions unique 30-70 nm long nanoassemblies (Bi-NAs), of ZV-BiNPs (5.21±0.6 nm) were formed with hydroxy terminated thiols (Fig. 3C). We attribute the formation of BiNAs to ligand hydrophobicity and the interaction of terminal -OH groups based on the estimated ligand lengths and average width of the BiNAs. The HR-TEM confirms crystalline nature of both WO_3- and ZVBi-NPs (Fig. 1B and 3D).

The WO_3-NPs with a thin SiO_2 coating were toxic, probably due to release of tungstate under physiological conditions, while Bi-NPs were oxidatively unstable and aggregated in isotonic buffers (change of color from black to gray-white). Therefore, we prepared WO_3- and ZVBi-silica hybrid NPs by TEOS hydrolysis method (Fig. 4). Although, the WO_3- and ZVBi-silica hybrid particles are useful blood pool agents their long-term whole body retention is a main concern for their *in vivo* use.

The new NPs can be functionalized a mixture of silanes A and A' (Fig. 2; 75% to 25% surface coverage) for further cross-linking to other CAs agents for multimodal and for attachment to targeting agents for molecular imaging [1-3] [6].

References:

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[6] This work was supported by NIH 1 R43 EB015845 SBIR grant.

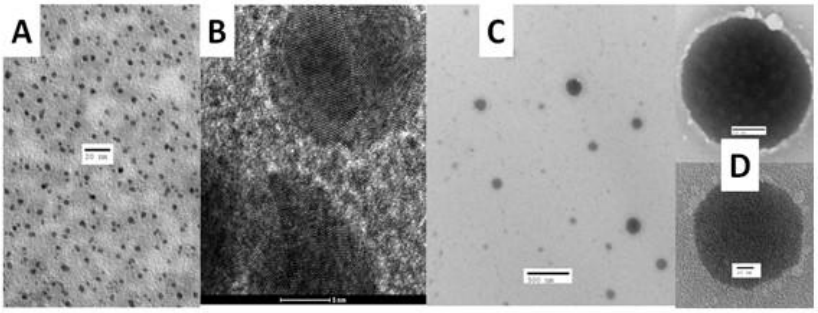

Figure 1. **A**) TEM of uniformly-sized WO_3-NPs coated with silica; **B**) their HR-TEM; **C**) TEM of larger NPs - note their size distribution and; **D**) non-uniform silica layers.

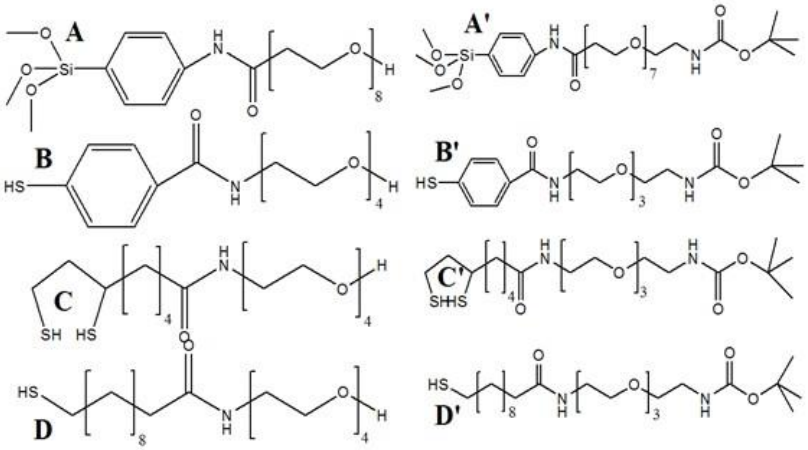

Figure 2. Hydroxy- and t-Boc-amine-terminated silanes and thiols.

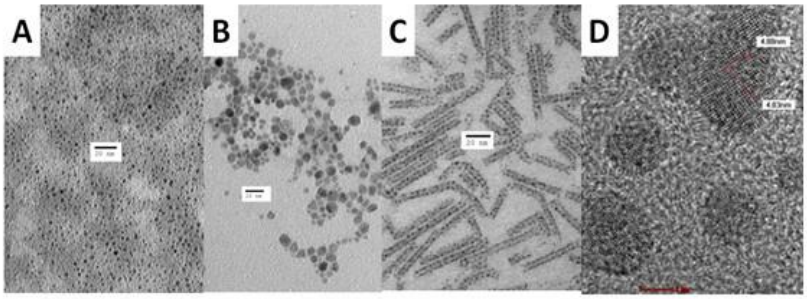

Figure 3. TEM of ZV-BiNPs: **A**) stabilized with ligand **B** (**Fig. 2**); **B**) with ligand **D** (**Fig. 2**); **C**) **Bi-NAs** stabilized with ligand **B** (**Fig. 2**); HR-TEM of ZV-BiNPs shown in **A**).

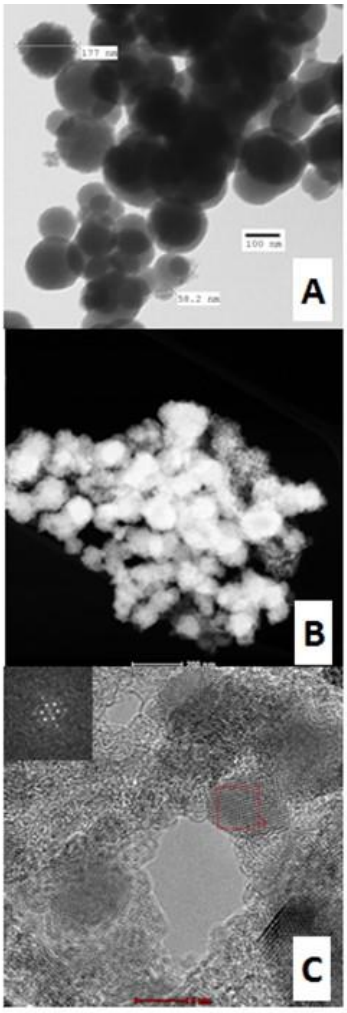

Figure 4. A) TEM of WO_3-SiO_2; **B**) STEM-HAADF of ZVBi-SiO_2; and **C**) HR-TEM of ZVBi-SiO_2 hybrid NPs

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