Molecular Engineering of Gold Nanorod Surfaces: Towards Improved Physical Properties and Understanding Nanoparticle-Cell Interactions

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Gold nanorods have unique optical properties and promising applications in chemical sensing, biological imaging, drug delivery, and cancer treatment.[1] Wet chemical synthesis of gold nanorods is the most popular route to prepare these nanomaterials and it requires the use of cetyltrimethylammonium bromide (CTAB) as shape-directing surfactant, which form a bilayer on the surfaces of gold nanorods.[2-3] CTAB molecules in the bilayer are held via weak hydrophobic forces and thus tend to desorb, resulting in nanorod aggregation and toxicity to cultured cells.[4] Herein, three surface-engineering approaches to "fix" CTAB molecules in the bilayer have been examined (Figure 1): 1) *an electrostatic approach* via overcoating gold nanorods with polyelectrolytes;[4b] 2) *a covalent approach* via surfactant polymerization;[4b,c] 3) and *a hydrophobic approach* via cholesterol insertion into the bilayer. Stabilization of the CTAB bilayer was found to enhance gold nanorod biocompatibility and colloidal physical stability against aggregation in both aqueous and organic media.[4]

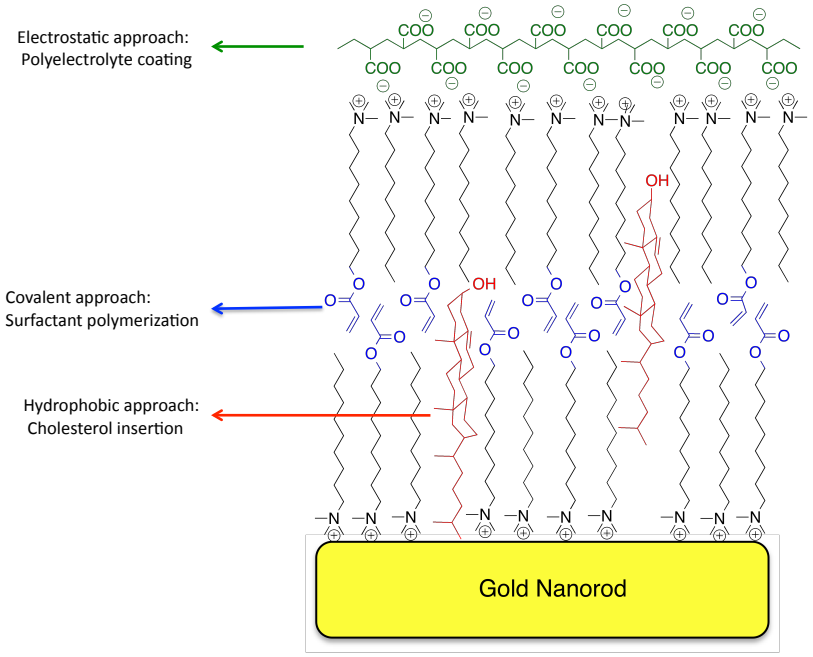

Figure 1. Cartoon demonstrating the approaches to stabilize the CTAB bilayer on gold nanorods: electrostatic, hydrophobic, and covalent.

Layer-by-layer coating has been used to overcoat CTAB-capped nanorods with both negatively and positively charged polyelectrolytes.[5] Compared to CTAB-capped nanorods, polyelectrolyte-coated gold nanorods showed improved stability against aggregation in culture

media and enhanced biocompatibility to cultured cells.[4a] While gold nanorods themselves were found to be not toxic at certain doses, the apparent toxicity of CTAB-capped gold nanorod solutions was assigned quantitatively to free CTAB molecules, which originate from inadequate purification and desorption of CTAB from nanorod surfaces.[4a] Coating the CTAB bilayer with polyelectrolytes significantly reduces cytotoxicity of gold nanorods. Similar biocompatibility profiles for both cationic and anionic coated-gold nanorods were observed, which disagree with the general notion that cationic nanoparticles are "more toxic" than anionic ones, due to their ability to disrupt negatively charged cell membranes.[4a] In our case, the explanation as to the similar toxicity of both cationic and anionic nanorods was extracted from nanorods-growth medium interaction studies.[4a] Using FTIR, UV-Vis, and surface charge analysis, spontaneous protein adsorption from the growth media was confirmed on both cationic and anionic nanorods, and thus all examined nanoparticles (cationic and anionic) had similar negative surface charges to the media proteins itself. Where both cationic and anionic coated gold nanorods found not toxic to the tested cell line, different cellular uptake profiles were observed as evident from transmission electron microscopy, dark field microscopy, and inductively-coupled plasma mass spectrometry analysis.[4a]

In addition to the enhanced biocompatibility and aqueous stability, stabilization of the CTAB bilayer on the surface of gold nanorods has allowed for suspending gold nanorods in organic solvents without aggregation. The suspendability of coated-gold nanorods in polar organic solvents facilitates the incorporation of these nanomaterials into hydrophobic polymers and thus fabrication of thin films that contain uniform gold nanorod dispersions (Figure 2).

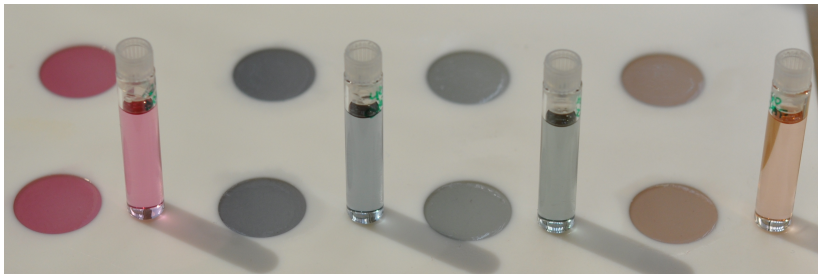

Figure 2. Photograph of polyelectrolyte-coated gold nanorods in DMF and PDMS films prepared from the corresponding solutions. An identical color of each solution and its corresponding film is indicative of uniform dispersion of gold nanorods in the film. DMF: dimethylformamide; PDMS: polydimethylsiloxane; Aspect ratio of gold nanorods (length to width) increases from left to right and results in different solution/film colors.

Our covalent approach to stabilize CTAB bilayer on the surface of gold nanorods relies on synthesizing a polymerizable version of the CTAB (the acrylate moiety in Figure 1). A polymerizable CTAB version was used to prepare gold nanoparticles (both spheres and rods) with excellent size and shape control.[4b,c] Surfactant polymerization on the surface of gold nanoparticles were monitored using FTIR and NMR analysis, and was found to retard surfactant desorption and thus enhance both aqueous stability against aggregation and biocompatibility of these nanomaterials.[4b,c]

The hydrophobic approach to stabilize the CTAB bilayer on gold nanorods relies on using a bilayer-condensing agent such as cholesterol to increase the total hydrophobic interactions (Figure 1). Cholesterol is known to consist of up to 50% of the total lipids in mammalian cell membranes and have stabilization effects via condensing the phospholipid molecules and increasing the total hydrophobic interactions.[6] Borrowing the idea from nature and using a cholesterol-rich growth medium, we have prepared gold nanorods with excellent size and shape distribution as evident from transmission electron microscopy and UV-Vis spectroscopy analysis. The prepared gold nanorods in the presence of cholesterol have a significantly higher surface charge (zeta potential) and exhibit superior stability aqueous against aggregation compared to the nanorods prepared without cholesterol.

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