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Review

# Functionalized gold nanorods for nanomedicine: Past, present and future

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ABSTRACT

Gold nanorods (GNRs) have been on the forefront in biophotonics due to their extremely attractive optical properties and their use in a variety of applications in biosensing and nanomedicine. In this review, we first present the synthesis and functionalization approaches and then describe the extraordinary optical properties of GNRs. Thereafter, we elaborate on the recent research advances in the use of GNRs for sensing, and highlight the increasing use of GNRs for *in vitro* and *in vivo* diagnostics and therapeutic applications. We also discuss the toxicity effects of GNRs on the body and environment and present an evaluation on the role of surface modifications in affecting the toxicity in biological systems. Finally, we provide concluding perspectives on the overall current status, challenges, and future directions for the use of GNRs in research and clinical applications.



**Contents**



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## 1. History and background of GNRs

The application of colloidal gold nanoparticles has a long history dating back to the fourth century A.D. when they were used for decorating Roman vessels known as "*cage cups*". The famous example is the Lycurgus Cup, which displayed a greenish-yellow color under direct light and promptly changed to ruby color when light shone through (Fig. 1) [1]. However, the complete understanding of this unusual dichroic effect was not realized for centuries [2]. In the beginning of 17th century, Francisci Antonii, a philosopher and medical doctor, published the first book on the medical use of colloidal gold particles [3]. Michael Faraday was the first scientist to methodically study the color effects of colloidal gold and suggested that the intense ruby color came from the "*exceedingly fine particles*" of gold [4]. Although the size of the colloidal gold had been speculated to be invisible to the human eye [2,5], it is unlikely that people had ever realized how small these "*fine particles*" really were before the 20th century. In the early 20th century, Mie developed a theory explaining the optical characteristics of colloidal metal solutions and people started to realize that the average diameter of those mystery gold particles was in fact much smaller than the wavelength of visible light [6]. The direct observation of gold nanoparticles was possible after the invention of electron microscopy in the 1930s [7]. Since then, the evolution of electron microscopy over the years has provided us a means to understand the structure and composition of gold nanoparticles. To date, many advanced microscopic and spectroscopic equipment have been developed that enable us to study these gold nanoparticles in a greater detail (e.g. characterization of their size, shape, crystalline structure, etc.) and these fundamental studies help us to exploit their unique features for various applications.

Intense research efforts had begun to be put toward the development of anisotropic gold nanoparticles in the late 1990s [8,9]. At that time, scientists were curious about the effects of differently shaped gold nanoparticles on their optical properties. In 1997, Yu et al. made a breakthrough when he successfully synthesized GNRs by an electrochemical method in the presence of a cationic surfactant cetyltrimethylammoniumbromide (CTAB) in the reaction solution [10]. The GNRs were then characterized using a UV–Vis spectrometer and the absorption profile showed two distinguishable absorption bands: the first band was usually centered between 520 and 540 nm and the second band generally appeared in the longer wavelength range (600–1600 nm) and the second band could be tuned by manipulating the GNR aspect ratio. The optical properties of GNRs are discussed in detail in Section 3. Ever since the discovery of this unique optical property from GNRs, this nanomaterial has attracted great attention in the past decade. Another breakthrough in GNR synthesis was made by Murphy's group [11]. They developed seed-mediated growth method to prepare GNRs and the method was further improved by El-sayed's group [12]. Since then, this approach has become the most popular method to produce GNRs with excellent monodispersity and high yield. In 2012, Murray's group reported the use of aromatic additives to improve the monodispersity of GNRs through seed-mediated growth method [13]. The authors demonstrated that monodispersed GNRs with negligible shape impurities (<1% of the total number of particles) are obtained by introducing aromatic additives into the growth solution and the longitudinal surface plasmon resonance peak can be systematically tuned from 630 nm to over 1246 nm by adjusting the types of aromatic additives in the reaction solution (Fig. 2).

Since the first discovery of GNRs in 1991, GNRs were applied only in a few research areas until 2005, including GNR assembly [14,15], surface enhanced Raman scattering (SERS) [16,17], template synthesis of hollow nanotube [18], biosensing [19,20], fabrication of novel electrode [21] and gene delivery [22]. More recently, GNRs were introduced as plasmonic scattering probes for dark-field imaging applications. The earliest dark-field images of GNRs in the literature were reported by Sönnichsen et al. in 2002 [23]. They studied the drastic reduction of plasmon damping in GNRs. In dark-field microscopy, the light source is completely blocked by the condenser. The bright spots of different colors appearing in the "dark field" correspond to strong scattering from the gold nanoparticles (Fig. 3). Huang et al. first demonstrated the

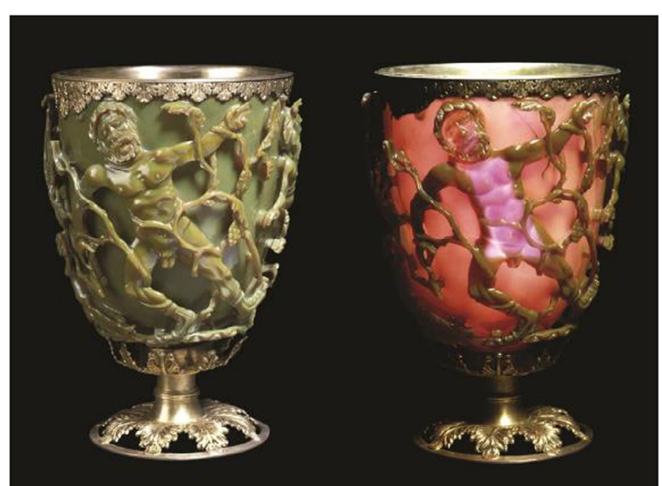

**Fig. 1.** Pictures of the *Lycurgus Cup* (British Museum; AD fourth century) in different optical illumination. Left: direct light illumination and right: transmitted light illumination. Reprinted from www.britishmuseum.org/. THE TRUSTEES OF THE BRITISH MUSEUM.