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# 上转换与钯基多功能纳米颗粒的合成及在光动力/光热治疗方面的应用

# Preparation of Upconversion/Palladium Multifunctional Nanoparticles for Photodynamic/Photothermal Therapy

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# Preparation of Upconversion/Palladium Multifunctional Nanoparticles for Photodynamic/Photothermal Therapy

A Dissertation Submitted for the Degree of Master of Philosophy

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# 摘 要

癌症已成为危害人类健康的主要杀手，实现癌症的有效诊断和治疗已成为当代社会迫切需要解决的重要课题之一。近年来，具有特定功能的纳米材料在癌症的成像诊断和治疗中发挥着重要的作用。本论文针对纳米材料在肿瘤的光动力学治疗和光热治疗方面的应用主要开展了两方面的研究工作：(1) 以稀土上转换发光纳米颗粒作为光敏剂的载体开展近红外光诱导光动力学治疗研究；(2) 设计并合成钯纳米片/光敏剂复合纳米颗粒，用于肿瘤细胞的单激光激发下的光热-光动力联合治疗。具体内容如下：

第一章：针对纳米材料在癌症治疗中的应用，简要综述了稀土上转换纳米颗粒在光动力学治疗，光热纳米材料在光热治疗及多功能纳米材料在癌症联合治疗中的应用进展，并且阐明本论文的研究内容和意义。

第二章包括以下三部分：

(1) 通过热注射法代替传统热分解法合成 $NaGdF_4$:Yb,Er@$NaGdF_4$(UCNP)核壳上转换纳米颗粒，利用反相胶束法在油溶性的 UCNP 表面包覆 $SiO_2$ 的同时将光敏剂($AlC_4Pc$)共价结合在硅壳中。制备的 UCNP@$SiO_2$($AlC_4Pc$)复合纳米颗粒尺寸均一可控，光敏剂不易泄露，在近红外光照射下具有高效的单线态氧产生能力。体外细胞实验结果表明，当用 0.5 W/$cm^2$ 的 980 nm 近红外激光照射纳米颗粒孵育的细胞 5 分钟，可杀死 40%的细胞。并且，这些纳米颗粒在水溶液及细胞内均具有良好的磁共振对比效果。

(2) 用热分解法合成了具有多重发射(539, 654 和 802 nm)的 $NaYF_4$:Yb,Tm@$NaYF_4$:Yb,Er 核壳上转换纳米颗粒(UCNP)，经 980 nm 激光照射，发射较强的可见及近红外光。将其表面修饰 PEG-磷脂(PEG-PP)后与光敏剂(Ce6)物理吸附制备 UCNP@PP-Ce6 复合纳米颗粒，可用于深组织近红外光学成像和光动力学治疗。实验结果表明，该复合纳米颗粒具有良好的水溶性，均一可控的尺寸(31 nm)，高效的近红外-近红外上转换效率以及光动力学治疗能力。

(3) 为了有效地调控上转换发光以及考察贵金属 Pd 纳米片对其发光的影响，我们设计了不同厚度 $SiO_2$ 包覆的上转换纳米颗粒并与小钯片相结合

$NaGdF_4$:Yb,Tm,Er@$NaGdF_4$@$SiO_2$-$NH_2$-Pd (UCNP@$SiO_2$-$NH_2$-Pd)。我们详细探讨了 $SiO_2$ 层的厚度、不同 Pd 量以及温度对其上转换发光的影响。

第三章包括以下两部分：

(1) 以中空介孔 $SiO_2$ 为载体使 Pd 纳米片与光敏剂有机结合(*hm*-$SiO_2$($AlC_4Pc$)@Pd)，实现光动力学与光热的联合治疗。体外细胞实验结果表明，当用 0.5 W/$cm^2$, 660 nm 的激光照射 200 ppm *hm*-$SiO_2$($AlC_4Pc$)@Pd 孵育的细胞 10 分钟，治疗效果明显优于单独的 *hm*-$SiO_2$($AlC_4Pc$)以及 Pd 纳米片的治疗效果。

(2) 由于上述 *hm*-$SiO_2$($AlC_4Pc$)@Pd 复合纳米颗粒粒径较大，不利于活体的光热光动力联合治疗，我们设计了小 Pd 表面直接负载光敏剂的复合纳米颗粒(Pd@PEI-Ce6)。结果表明，该复合纳米颗粒整合了光敏剂和钯纳米片各自的特点，具有粒径小、单线态氧产生能力强和光热转换效率高等优点。当用 0.5 W/$cm^2$，660 nm 激光照射仅有 50 ppm Pd@PEI-Ce6 孵育的细胞 5 分钟，就可以杀死 50%细胞，联合治疗效果高。

**关键词：** 稀土上转换纳米颗粒 光敏剂 小钯片 光动力学治疗 光动力学-光热联合治疗

# Abstract

Cancer has become the main killer of human's health. In recent years, nanoparticles with unique functions have played an important role in cancer imaging and therapeutics. Aiming at the application of nanoparticles in cancer photodynamic therpy and photothermal therpy, this thesis mainly carries out two parts of study: (1) Application of lanthanide ion doped upconversion nanoparticles as photosensitizer carrier to develop near-infrared light- induced photodynamic therapy; (2) Design and synthesis of small Pd nanoplate/photosensitizer composites to be used for photothermal-photodynamic combined treatment of cancer cells with single laser. The detailed research work and major results are as follows:

**Chapter 1.** From the point of view of the application of nanomaterials in therapy, we brief review and summarize the research progress on the rare-earth upconversion nanoparticles in photodynamic therapy, photothermal nanomaterials in photothermal therapy and some multifunctional nanomaterials in combined cancer therapy. We also demonstrated that the main contents and significance of the dissertation.

**Chapter 2.** It includes three parts:

(1) Upconversion $NaGdF_4$:Yb,Er@$NaGdF_4$ (UCNPs) nanocrystals were prepared by hot-injection approach instead of thermal decomposition. The as-prepared hydrophobic UCNPs were then coated with a layer of silica to form UCNP@$SiO_2$ nanoparticles by using a reverse-micelle method, meanwhile, the photosensitizer molecules ($AlC_4Pc$) were covalently incorporated inside the silica shell. These UCNP@$SiO_2$($AlC_4Pc$) were uniform in size, stable against leakage of $AlC_4Pc$ from the nanoparticles and could effectively produce reactive oxygen species when were excited with a 980 nm laser. In vitro results indicated that cancer cells incubated with UCNP@$SiO_2$($AlC_4Pc$) nanoparticles after exposure to the 980 nm laser (0.5 W/$cm^2$), nearly 40% cells were killed after 5 minutes of irradiation. Moreover, the good $t_1$ and $t_2$ relaxivity capabilities of UCNPs were also demonstrated in cell MRI imaging.

(2) The preparation, characterization and application of $NaYF_4$:Yb,Tm@$NaYF_4$:Yb,Er core–shell upconversion nanocrystals (UCNPs) with multiple emission peaks (e.g. 539, 654 and 802 nm) have been demonstrated in this work. The monodisperse nanocrystals were prepared via a modified thermal decomposition synthesis. The resulting UCNPs were about 31 nm in diameter with the lanthanide ions $Tm^{3+}$and $Er^{3+}$ doped in the core and the shell, respectively. Under the laser diode excitation at 980 nm, these core–shell nanocrystals give strong upconversion emissions from the visible to near-infrared (NIR) region. By coating a PEG–phospholipid (PP) layer on the surface of the nanocrystals, the as-prepared UCNPs were favorably endowed with good water solubility for the potential biological applications. Here, a photosensitizer drug of Chlorin e6 (Ce6), which has maximum absorption that overlaps with the red emission of UCNPs, was loaded on these PP-coated UCNPs (UCNP@PP) by physical adsorption. The activity of the Ce6-loaded UCNP@PP (UCNP@PP–Ce6) in photodynamic therapy of cancer cells in vitro has been fully investigated in this work. Our results indicated that these multifunctional UCNP@PP–Ce6 nanoparticles have efficient NIR-to-NIR upconversion luminescence and photodynamic therapy capabilities, which could be potentially employed as a theranostic platform for cancer treatment.

(3) In order to investigate the effect of noble metal on the luminescence intensity of upconversition nanoparticles and efficiently adjust their luminescence, we prepared different thicknesses of silica coated $NaGdF_4$:Yb,Tm,Er@$NaGdF_4$ nanoparticles and then attached small Pd sheets by both electrostatic attraction and coordination(UCNP@$SiO_2$-$NH_2$@Pd). The effect of thicknesses of silica, quantity of Pd nanosheets and temperature on the fluorescence intensity of upconversition nanoparticles were detailly investigated.

**Chapter 3. It includes two** parts**:**

(1) The hollow mesoporous silica nanoparticles were used as nanocarries of photosensitizer and Pd nanosheets (*hm*-$SiO_2$($AlC_4Pc$)@Pd) to combine photodynamic therapy with photothermal therapy. In vitro (Cancer cells were incubated with 200