Journal of Photochemistry and Photobiology C: Photochemistry Reviews 20 (2014) 71–96

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology C: Photochemistry Reviews

journal homepage: www.elsevier.com/locate/jphotochemrev

Review

Engineering lanthanide-based materials for nanomedicine

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ARTICLE INFO

Article history:
Received 1 November 2013
Received in revised form 23 June 2014
Accepted 27 June 2014
Available online 8 July 2014

Keywords:
Lanthanide
Nanoparticles
Diagnostics
Therapeutics
Upconversion
Magnetic
Toxicity

ABSTRACT

Multifunctional lanthanide-based nanomaterials are envisioned to create a huge impact in nanomedicine through improved diagnosis and treatment of diseases. This review focuses on the opportunities and advantages afforded by "designer" lanthanide-based nanomaterials in medical application in the recent 5 years. We begin with a brief overview of the unique properties of lanthanide nanomaterials and then move onto their synthesis, surface modification and bioconjugation strategies, which help one in the design of promising agents for imaging and therapeutic applications. We discuss approaches to fabricate down-conversion, up-conversion and persistent luminescent probes for optical imaging. We present the recent development of lanthanide-based nanoprobes in T_1 and T_2 magnetic resonance imaging, which show superior performances over currently used commercials agents. The potential benefits of multifunctional lanthanide-based nanomaterials in multimodal diagnostics are also highlighted. An important feature of lanthanide-based nanomaterials is the external controllability of light emission from UV to NIR wavelengths. This unique capability makes this class of nanomaterials useful for not only controlled/triggered release of drugs and gene delivery but also photodynamic or photothermal therapy at targeted sites. Finally, we discuss recent efforts to address concerns of short-term and long-term toxicity of lanthanide materials. The wide range of unique features of lanthanide-based nanomaterials accentuates their promise as efficient platforms for nanomedicine.

Contents

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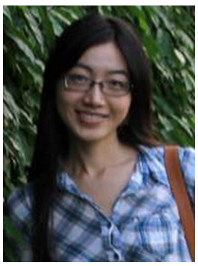
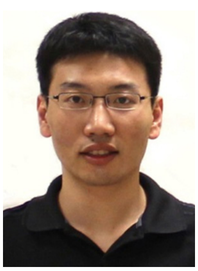
http://dx.doi.org/10.1016/j.jphotochemrev.2014.06.001
1389-5567/



Dr Yan Zhang received her bachelor degree from Tianjin University, China in 2007. She obtained her Ph.D. degree in 2012 under the supervision of Prof. Timothy Tan. Since 2012, she has been continuously working in the area of tailoring multifunctional lanthanide nanomaterials for nanomedicine.



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1. Introduction

The quest for diagnostics, therapeutics or theranostics of enhanced performances has spurred greater research efforts in nanomedicine. With well-defined physicochemical properties such as size, shape, composition and surface chemistry, nanomaterials can be engineered with imaging/detection/therapeutic functionalities. The resulting nanosystems, capable of simultaneous detection, diagnosis and treatment of disease, have shown superior performances such as enhanced permeation and retention (EPR) in the circulatory system, greater imaging contrasts and specific delivery of drugs to target sites. Therefore, nanomedicine is expected to play a significant role in the dawning era of personalized medicine [1].

Of various types of nanomaterials, such as iron oxide nanoparticles (NPs) [2,3], quantum dots (QDs) [4], carbon nanotubes (CNT) [5], gold NPs [6] and silica NPs [7] that have been investigated, lanthanide nanomaterials emerge as superior candidates in nanomedicine due to their unique optical and magnetic properties, and low toxicity characteristics. Nanomaterials that can response to light offer a unique opportunity in diagnostic and image-guided drug/gene delivery. However, many nanomaterials engineered for drug delivery lack of optical properties (such as fluorescence and photothermal response) and therefore, their trafficking in the biological system is only possible when they are labeled with optical or contrast moieties. The luminescence of lanthanide materials, in this context, is helpful and superior over the traditional organic dyes, green fluorescent protein (GFP) or even QDs as lanthanide elements possess abundant metastable energy levels and rather long-lived excited states in their 4f orbitals. Lanthanide ions have the ground state electronic configuration [Xe]4f^n (n = 0–14). Shielded by the outer 5s and 5p orbitals, 4f electrons do not directly participate in bonding. Therefore, lanthanides exhibit narrow bands, intense luminescence ranging from ultraviolet (UV) to visible and near-infrared (NIR). Multicolor emissions can be achieved by simply varying the dopant ions. Furthermore, as 4f–4f transitions in lanthanides are electric dipole 'forced' and normally forbidden or at a low possibility of occurring, the excited state lifetimes tend to be very long, in the order of micro- to milliseconds [8,9]. They have been used in living systems to monitor cell-related process, recognize pathogen or detect tumor, and enable drug delivery and therapy. The delivery kinetics and treatment efficiency can be monitored at the same time, which is significant in view of therapeutic mechanism and possible toxicity evaluation. In addition to their unique optical properties, certain lanthanide ions, such as gadolinium (Gd^{3+}), dysprosium (Dy^{3+}) and holmium (Ho^{3+}) are useful as contrast agents in magnetic resonance imaging (MRI). MRI is particularly useful to visualize internal structures of the body in detail, especially soft tissues, such as the brain, muscle, heart. Gd-DTPA (Magnevist®) was the first clinically approved contrast agents, and is by far the most commonly used agent [10]. It can increase the conspicuousness of cells and facilitate easy tracking of cells in low-signal tissues. More than 10 million MRI studies performed worldwide are using Gd^{3+}-based contrast agents every year [10]. And finally, multiple functions can be readily integrated into the lanthanide nanomaterials to achieve multimodal imaging and therapy. For example, Gd-based or doped NPs have shown strong potential as contrast agents in both MRI and optical imaging, which can generate more accurate and reliable data. By combining with photosensitizers (PSs), they can be applied in photodynamic therapy (PDT), which is especially useful for treatment of deep-seeded tumors. They can even be engineered to trigger cell death by the generation of reactive oxygen species (ROS), and used as