Upconversion nanoparticles: on the way from diagnostics to theranostics

Alla Generalova[1,2,*], *Kristina* Mironova[1,2], *Natalya* Sholina[3], *Vasylina* Rocheva[2], *Andrey* Nechaev[4], *Ekaterina* Grebenik[3,5], *Anna* Guller[5], *Andrey* Zvyagin[5], *Sergey* Deyev[1], *Vitaly* Zubov[1], and *Evgeny* Khaydukov[2,3]

[1]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS, 117997, Moscow, Russia
[2]Scientific Research Centre "Crystallography and Photonics" RAS, 119333, Moscow, Russia
[3]Sechenov First Moscow State Medical University, 119991 Moscow, Russia
[4]Institute of Fine Chemical Technologies, 119571, Moscow Russia
[5]Macquarie University, Sydney, NSW 2109, Australia

Abstract. We report of surface modification approaches of nanoparticles with anti-Stokes luminescence, known as upconversion nanoparicles (UCNPs), comprised of inorganic host $NaYF_4$ codoped with Yb^{3+} and Er^{3+}or Tm^{3+}. These approaches enabled the facile, lossless preparation of hybrid polymer-encapsulated UCNPs suitable for bioassays. These probes inherited UCNP properties, such as excellent photoluminescence under excitation with NIR light from the biotissue "transparency window", as well as they were dispersible in aqueous media and physiological buffers, exhibiting chemical stability. The feasibility of the hybrid UCNPs was demonstrated for *in vitro* bioassay and *in vivo* optical whole animal imaging using a home-built epi-luminescence imaging system.

1 Introduction

Lanthanide-doped upconversion nanoparticles (UCNPs) represents a flexible platform, where various surface moieties can be attached enabling targeting, bioimaging and therapy in a broad physiological context. UCNPs are characterized by sharp emission, high conversion efficiency, long lifetimes, low cytotoxicity, negligible photobleaching, and high spatial-temporal resolution during bioimaging. The efficient conversion of near-infrared (NIR) excitation at the wavelength of 980 nm into the shorter-wavelength IR, visible and UV spectral range emission (known as "upconversion") represents its most acclaimed property. Under the NIR excitation of UCNPs the excitation of tissue autofluorescence is almost negligible. Additionally, the excitation light penetration in biological tissue is greater in comparison with visible light, up to one centimeter. Generally, the UCNPs are based on efficient host matrix $NaYF_4$, which produces anti-Stokes luminescence, co-doped with lanthanide ions: Yb^{3+} as a sensitizer, and Er^{3+} or Tm^{3+} as activator.

* Corresponding author: a-generalova@yandex.ru

2 Results and Discussion

Typically, UCNPs are synthesized in organic solvents, resulting in UCNPs stabilized with hydrophobic oleic acid ligand. This fact limits their biological applications. Therefore, surface modification of UCNPs is a crucial step in an effort to create the water-dispersible and biocompatible UCNP probes.

Modification method using amphiphilic polymer poly(maleic anhydride-*alt*-1-octadecene) have been developed, which made it possible to create target-based UCNP hybrid nanocomplexes for *in vitro* labeling the HER2 / neu cancer-specific marker (Fig.1, way 1) [1]. We exploited the original design of UCNP nanocomplexes, where a "corona" was obtained from chemically bound PEG molecules, in order to increase the circulation time in the blood system *in vivo* and deliver UCNPs to the tumor (Fig.1, way 2) [2]. UCNP encapsulation into polyacrolein particles in the course of radical heterophase polymerization was the basis for production the reagents capable to study the particle biodistribution by organs at intravenous injection (Fig.1, way 3) [3]. Unique optical properties of UCNPs enabled formation of hybrid nanocomplexes with riboflavin (Rf) responsible for generating active oxygen forms under the NIR-radiation through the realization of FRET effect. Hybrid nanocomplexes were successfully applied for photodynamic therapy and showed tumor regression in mice, following the Rf-UCNPs peritumoural injection and near-infrared light photodynamic treatment of the lesions (Fig.1, way4) [4].

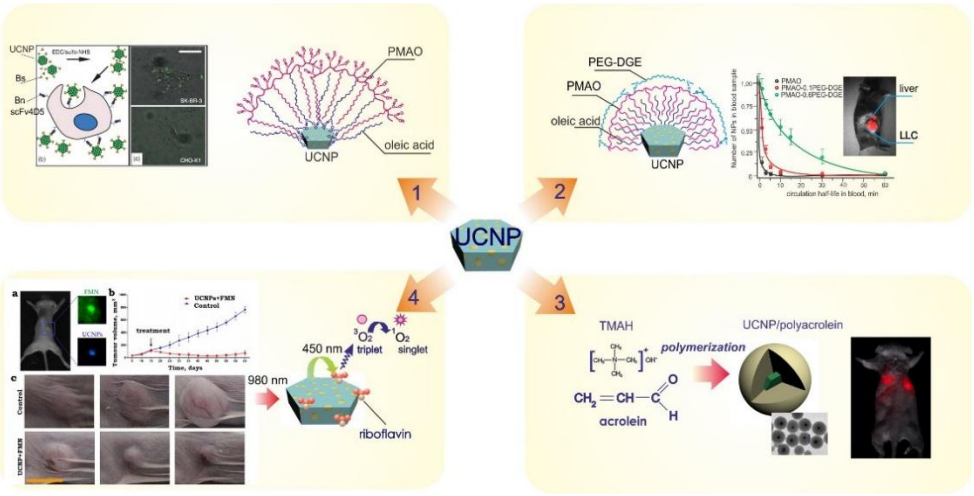

Fig. 1. Approaches of UCNP surface modification for various bioapplications.

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