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(Summary)

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（要 旨）

This thesis entitled, “Research on lanthanide doped upconversion nanoparticles for photodynamic therapy,” deals with the synthetic studies of sugar-coated lanthanide nanoparticles and their applications to photodynamic therapy (PDT) in combination with 5-aminolevulinic acid (ALA). The thesis is composed of the following five chapters.

The first chapter, “Introduction,” explains the fundamentals of upconversion process, upconversion nanoparticles (UCLNP), and ALA-based PDT. It states that the problem in the ALA-based PDT was the low penetrative blue incident lights required for the sensitization of protoporphyrin IX (PPIX), a product of ALA selectively accumulated in cancer cells. Accordingly, it proposes the use of near-infrared (NIR) as the incident light, which are converted to blue and green lights via UCLNP in cancer tissues, allowing PDT for the cancers deep under the skin. This study aims at the application of sugar-attached UCLNPs to PDT, in which the sugar was incorporated to gain biocompatibility of UCLNPs and to target tumor-associated macrophages with sugar-binding lectins.

In the second chapter, “Synthesis of various lanthanide doped upconversion nanoparticles,” the author attempted to synthesize UCLNP with the structure, $NaYF_4$:Yb/Er and stronger luminescence intensities at 540 and 655 nm than previously reported UCLNPs by adding some dopants as $B(OH)_3$, ethylenediaminetetraacetic acid, and metal ions. He found that the addition of $B(OH)_3$ to UCLNP and annealing of it produced a UCLNP with very strong emission intensity, while the other attempts ended in deterioration of the luminescence. He also discovered that the luminescence of LNPs decreased in the order, D_2O > DMSO > EtOH > H_2O, and it was ascribed to the de-excitation of the excited states by H-O vibrations and also to the absorption of NIR light itself by water. He also obtained some important pieces of information regarding the factors changing the property of UCLNPs.

The third chapter, “Sugar-attached upconversion lanthanide nanoparticles,” explains his study on the attachment of sugar on UCLNP and its application to lectin and macrophage assays. He succeeded in the attachment of mannose and galactose on polyethyleneimine (PEI)- and olieic acid (OA)-coated UCLNPs. He found that glutaric acid linker showed an efficient result for PEI-coated UCLNP in emission intensity whereas the attachment of a sugar severely deteriorated the luminescence. On the other hand, it was found that the oxidation of the olefinic group in OA-UCLNP into carboxylic acid and coupling with sugar scarcely affected the emission of OA-UCLNP. Using sugar-OA-UCLNP, he demonstrated that these UCLNPs were a potential tool for high throughput screening of lectins and macrophage cells with lectins on the surface. That is,

sugar-UCLNPs were aggregated with the lectins of a corresponding sugar specificity and the aggregates generated strong emission by irradiation with an NIR laser, enabling a quick estimation of lectin specificities or inhibitor structures.

In the fourth chapter, "Using synthesized UCLNP in PDT experiments," he used boric acid doped $NaYF_4$:Yb/Er (18/2 mol%) nanoparticles in PDT experiment in vitro. NIR-irradiation of MKN45 stomach cancer cells pretreated with UCLNP and ALA demonstrated that over 40% of cells were killed, thus encouraging the use of the NIR-UCLNP-ALA protocol for the treatment of the cancers deep under skin. He also showed that the UCLNPs, in the dispersed solution used in PDT study, were non-toxic to the cancer cells.

In the fifth chapter, "Conclusion," he proposed that the lanthanide doped upconversion nanoparticles could be used in photodynamic therapy to overcome the shortcoming of low penetration depth by using NIR (980 nm) light source.

In summary, this thesis demonstrates the potential of NIR-UCLNP-ALA protocol for the treatment of the cancers deep under skin, contributing to a large extent to medical science and engineering.