INTRODUCTION TO BIOMEDICAL APPLICATIONS

UPCONVERSION NANOPARTICLES

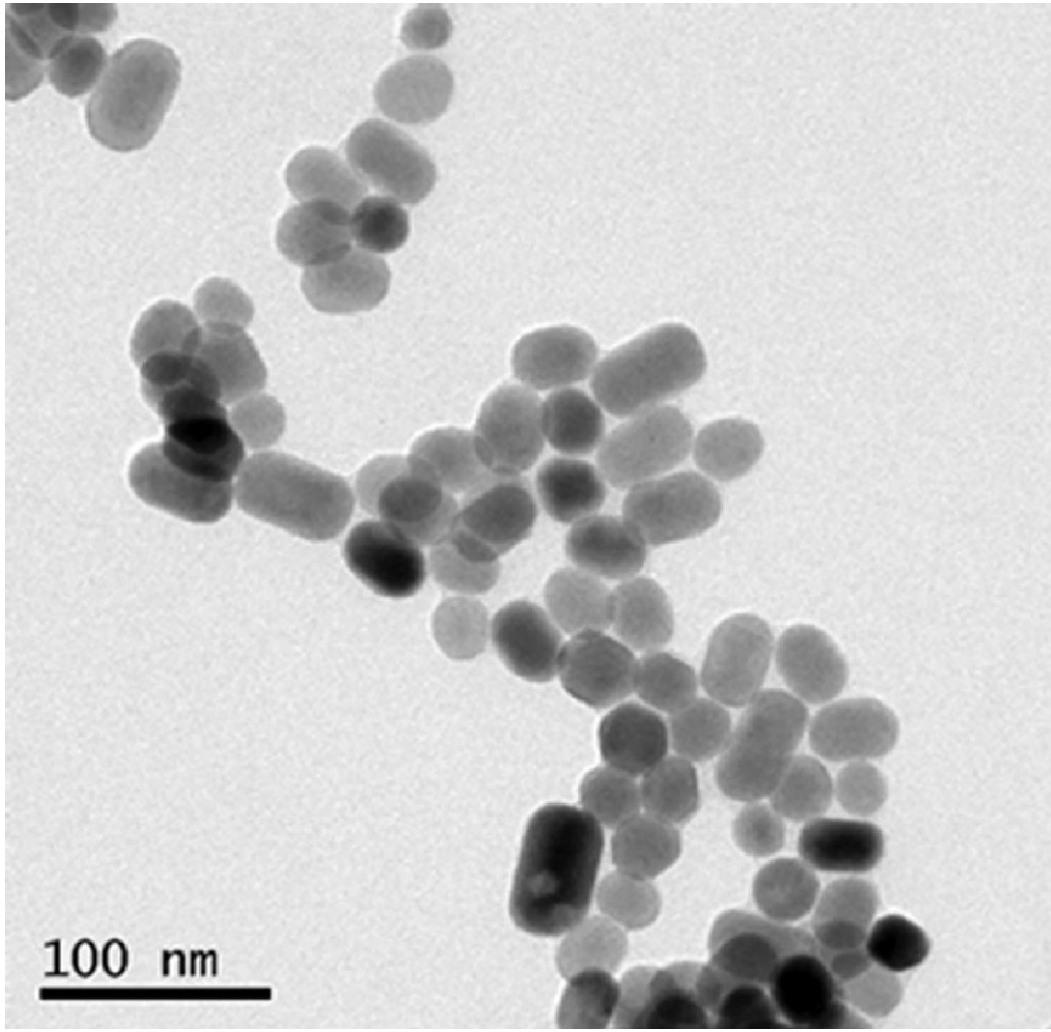
Most of the UCNPs are highly crystalline materials. Unlike conventional luminescence, upconversion processes involve multiple intermediate states to accommodate low energy excitation photons.

UCNPs consist of inorganic host and lanthanide dopant ions embedded in the host lattice. They depend on the ladder like arrangement of energy levels of lanthanide dopant ions.

The crystal structure and optical property of host materials play prominent role. The host materials absorb excited energy of the dopant ions through lattice vibrations.

When the crystal structure of host material changes, the crystal field around dopant ions varies, attributing to different optical properties of UCNPs.

Highly crystalline UCNPs exert strong crystal field around dopant ions and minimize energy loss of dopant ions arising from crystal defects [4].



- In case of lanthanides, the 4f electrons are completely shielded by 5s and 5p subshells and hence they don't interact with host lattice. Therefore, the absorption and emission spectra of lanthanide-doped UCNPs depict sharp lines, which are spectroscopic fingerprints.

- The chemical composition of the host material does not affect the emission peak. The colors emitted by UCNPs can be varied by changing the dopant concentration.

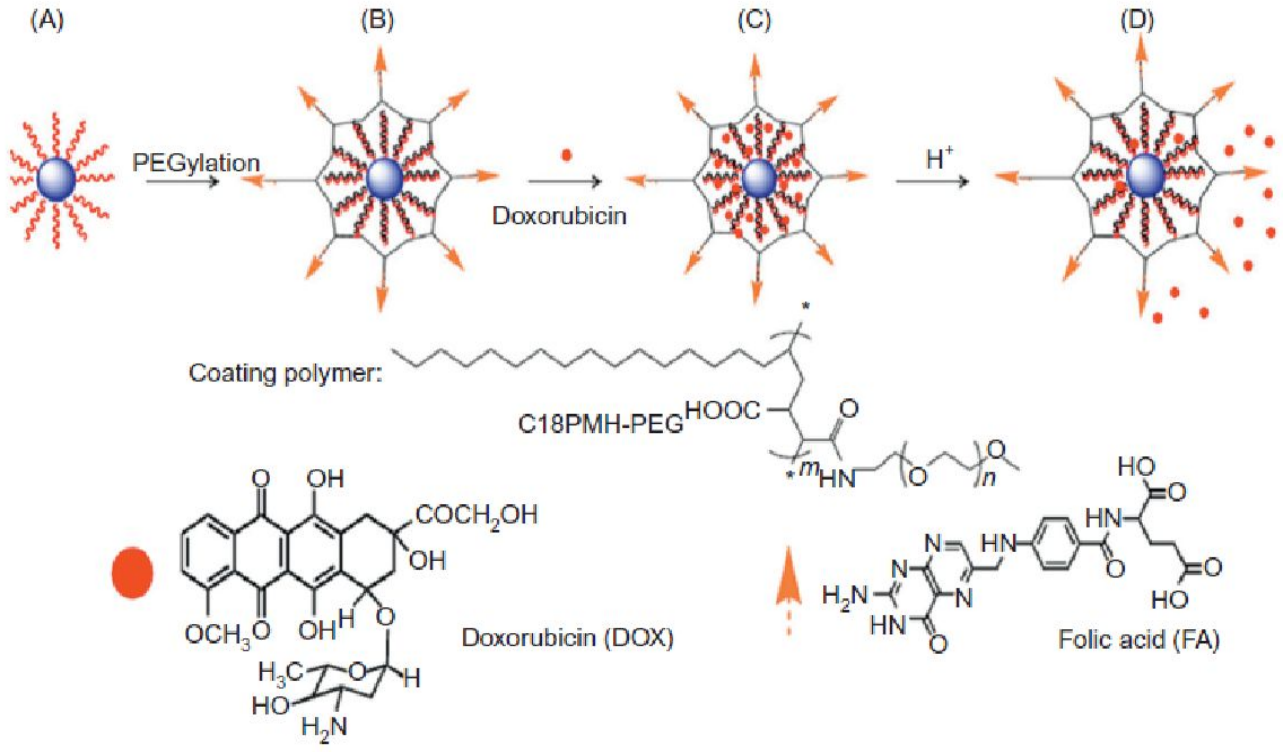
- These emissions do not involve chemical bond breakage and are thus stable against photobleaching. Surface functionalization of UCNPs is necessary to improve aqueous solubility and biological functions.

- Some of the functionalization techniques include surface silanization, ligand exchange, ligand attraction, oxidation, and electrostatic layer by layer assembly.

- Among them, silanization has gained lot of importance as silica coating is applicable to both hydrophilic and hydrophobic materials. Besides these, nonsilane reagents like polyethyleneimine are also used for surface modification.

APPLICATIONS IN DRUG DELIVERY

The main goal of targeted drug delivery is to deliver drug to diseased cells and spare the normal cells [6,7]. Wang et al. functionalized UCNPs with PEG-grafted amphiphilic polymer. They were loaded with a chemotherapy drug like doxorubicin by simple adsorption for intracellular drug delivery.



- The release of doxorubicin was pH controlled with an increased drug dissociation rate in acidic environment. It was observed that DOX was shuttled into cells by UCNPs and released in cells by endocytosis.

- The nanoparticles were conjugated with folic acid so that they can target cancer cells (Figure 13.2) [3]. Yang et al. formulated doxorubicin-loaded ultra-small sized BaGdF6Yb31/Tm31- based UCNPs. The drug was released by cleavage of hydrazine bonds in acidic environment.

- The nanoparticles proved to be toxic to anticancer cell lines (HeLa cells). Around 10 mg/kg of UCNPs were injected in mice which survived for 40 days without any adverse health effects [8].

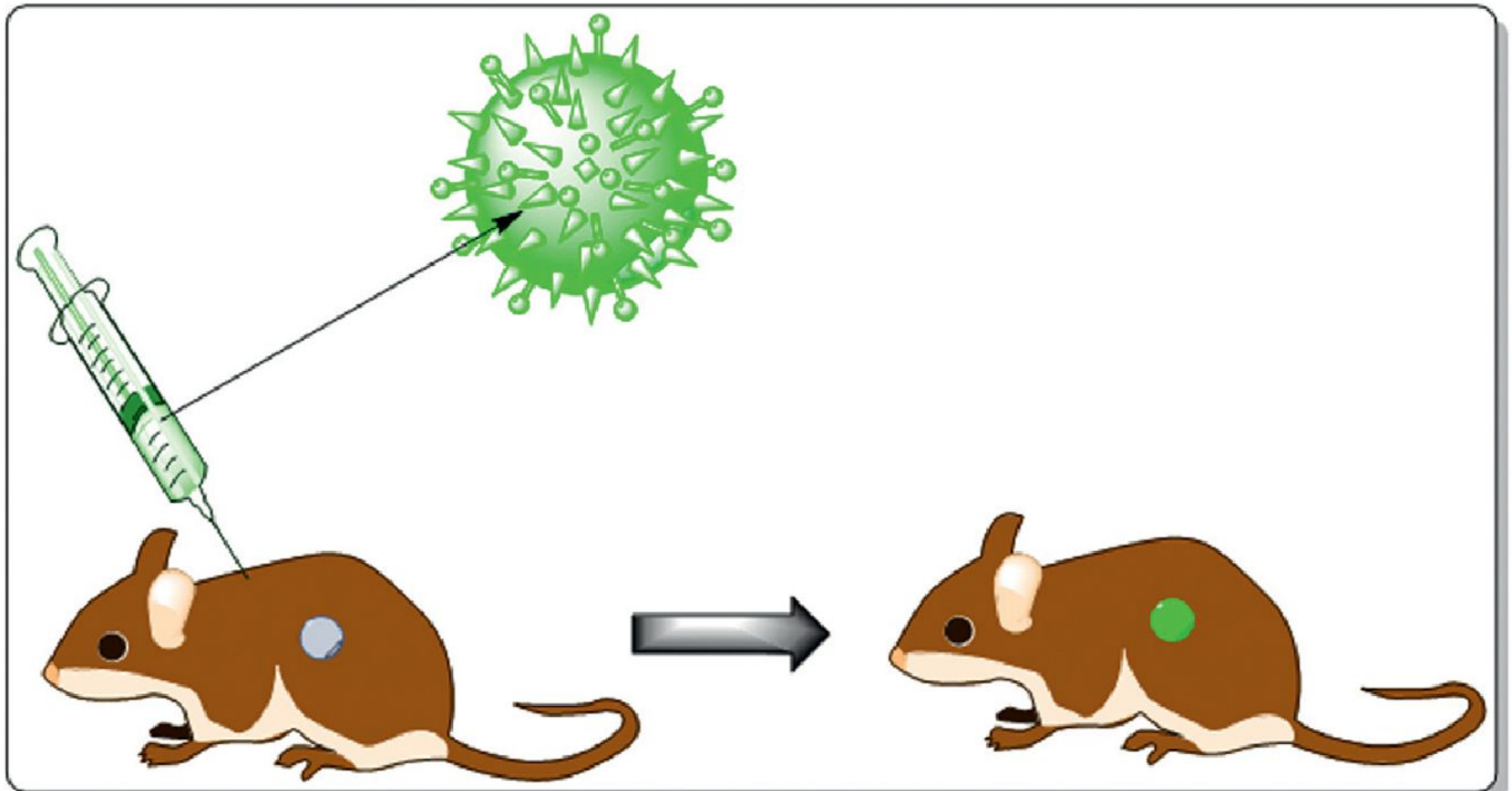
- Xu et al. have encapsulated hydrophobic UCNPs along with iron oxide nanoparticles using amphiphilic block polymer by microemulsion method. They were loaded with doxorubicin and fluorescent dye and were found to be cytotoxic on HeLa cells [9].

- Liu et al. reported on the development of multifunctional UCNPs that can target cancer cell nuclei and deliver anticancer drug to the nuclear region. The nanoparticles were made of Er/Yb-doped NaYF4 core and NaGdF4 shell and enhanced the efficacy of

APPLICATIONS IN BIOLOGICAL IMAGING

- Biological imaging is a technique developed that allows noninvasive study of biological processes in small lab animals [11,12]. UCNPs are gaining lot of attention in biological imaging due to their photostability, deep tissue reaching, and autofluorescence (Figure 13.3).

- A number of articles have reported the use of UCNPs as bioimaging agents. Chromophoric ruthenium complexes based nanophosphors were synthesized as highly selective water-soluble probes for upconversion



- luminescence sensing of intracellular mercury ions. This nanoprobe could detect lower levels of mercury (1.95 ppb) in drinking water. The maximum level of mercury was 2 ppb, as set by US EPA. It could detect changes in the distribution of mercury in living cells [13]. Chen et al. developed biocompatible core/shell (NaYbF4:Tm31)/CaF2-based UCNPs for high contrast and deep imaging. These particles emitted photoluminescence at 800 nm, when they are excited at 980 nm.

- Around 700 pmol/kg of UCNPs were intravenously injected into BALB/c mice. High contrast images were obtained by using a nanoparticle-loaded synthetic fibrous mesh wrapped around the femoral bone of rat [14].

- Zhou et al. prepared multihydroxy dendritic UCNPs with enhanced water dispersibility and surface functionality for bioimaging. They mainly consist of multihydroxy hyperbranched polyglycerol shell. They showed low cytotoxicity, deep light penetration depth, and high luminescent contrast [15].

- Yi et al. synthesized dual model nanoprobes for synergistic upconversion luminescence and X-ray imaging in a single system functionalized by amine. These water-soluble UCNPs produced green and dominant red emissions.

- High contrast images of HeLa cells labeled by these particles were obtained. The ex vivo upconversion images showed that UCNPs traveled from lungs into liver. Both upconversion and X-ray images were obtained at the same region of nude

APPLICATIONS IN BIOLOGICAL DETECTION

- UCNPs assist in biological detection through two mechanisms namely, fluorescence resonance energy transfer (FRET) and non-FRET.

- In FRET process, energy is transferred between donor and acceptor at a distance of 10 nm, through Coulombic interactions. Li et al. developed an ultrasensitive FRET aptasensor for detection of kanamycin using UCNPs as the energy donor and graphene as the energy acceptor [16].

- UCNPs were modified using oleic acid and synthesized via hydrothermal process followed by ligand exchange with hexanedioic acid. UCNPs were tagged with kanamycin aptamer through EDC-NHS procedure.

- The aptamer and graphene were brought closer by ππ interaction which initiated FRET process leading to quenching of UCNPs fluorescence.

- When kanamycin was added to UCNPsaptamergraphene complex, energy transfer was blocked by the conformation change of aptamer into a hairpin structure. The UCNP-based aptasensor showed good specificity towards kanamycin without getting disturbed by other antibiotics. Another FRET system was designed for determining thrombin, using NaYF4:Yb,Er UCNPs as donor and gold nanorods as acceptor [17].

- The UCNPs were carboxyl functionalized and conjugated with thrombin aptamers. The fluorescence emission band of
- UCNPs overlapped with absorption band of gold nanorods. The fluorescence quenching efficiency increased with concentration of thrombin and the aptasensor was successful in measuring thrombin in blood plasma.

- For non-FRET based detection, UCNPs were used as luminescent reporter and luminescence from these nanoparticles were observed directly. Zhang et al. synthesized lanthanide-doped upconverting phosphors for detecting glutathione.

- Their unique NIR excitation nature can overcome interferences from complex samples [18]. Upconverting phosphors and dopamine quinone are linked through hydrogen bonding and electrostatic interaction.

- Dopamine quinone quenched upconverting fluorescence while glutathione reduced dopamine quinone tuning on fluorescence. This fluorescence method broadened the scope of UCNPs in complex biological detection.