Figure S1

HRTEM images of UNCs showing nanoparticle with a mean size of 20 nm. The inset shows the selected area electron diffraction pattern of UNCs particles confirm the crystalline nature and fluorite structure. A(111), B(200), C(220) and D(311) in SAED correspond to the different lattice planes of UNC fluorite crystal structure.

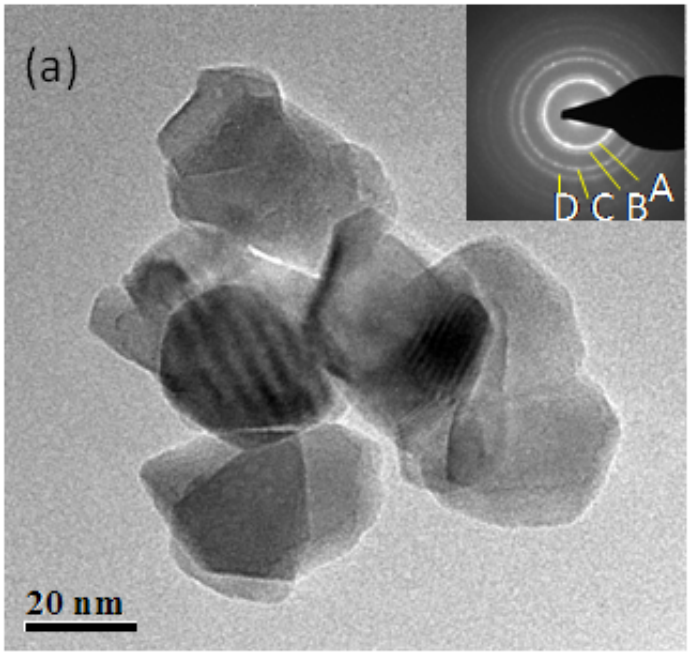
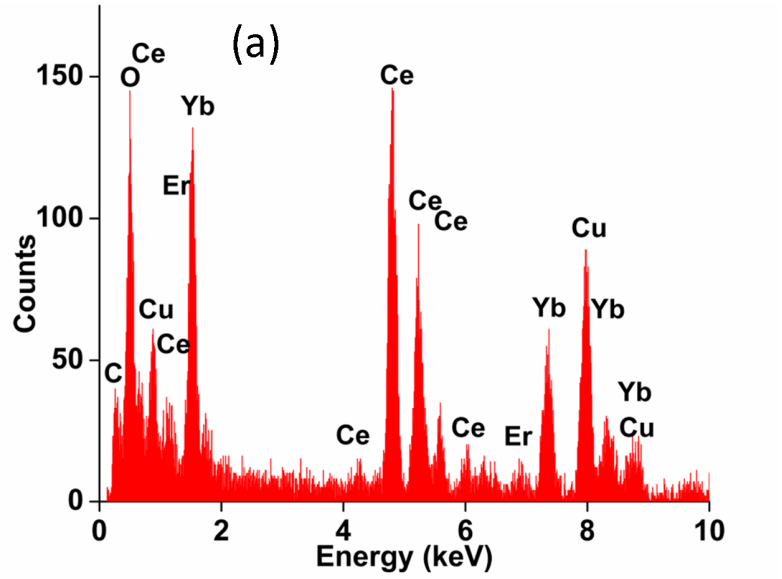


Figure S2

(a) Energy dispersive X-ray analysis of doped cerium oxide powder illustrates the elemental composition corroborating the presence of Yb, Er, in cerium oxide. Presence of Cu is from copper TEM grid.

b) X-ray diffraction pattern indicates a fluorite structure formation of doped cerium oxide and ascertain that dopant do not present as a separate oxide phase and it can be concluded that Yb^{3+} and Er^{3+} were doped into the matrix of cerium oxide.



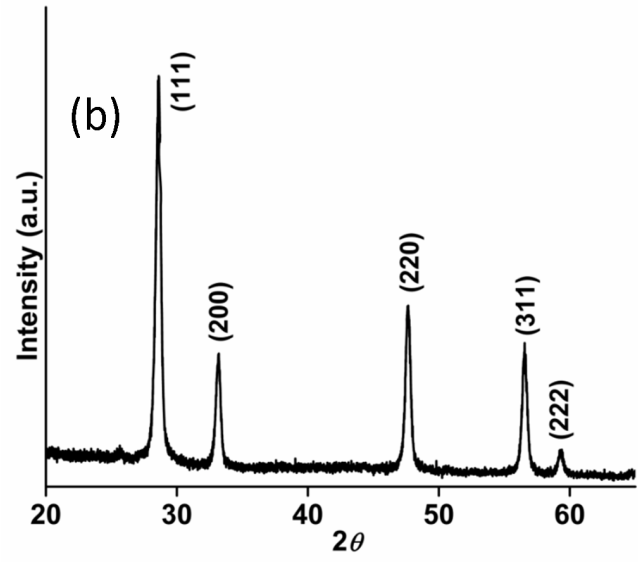


Figure 3S

Emission spectra of the CeO_2, 20% Yb, 5%Tm

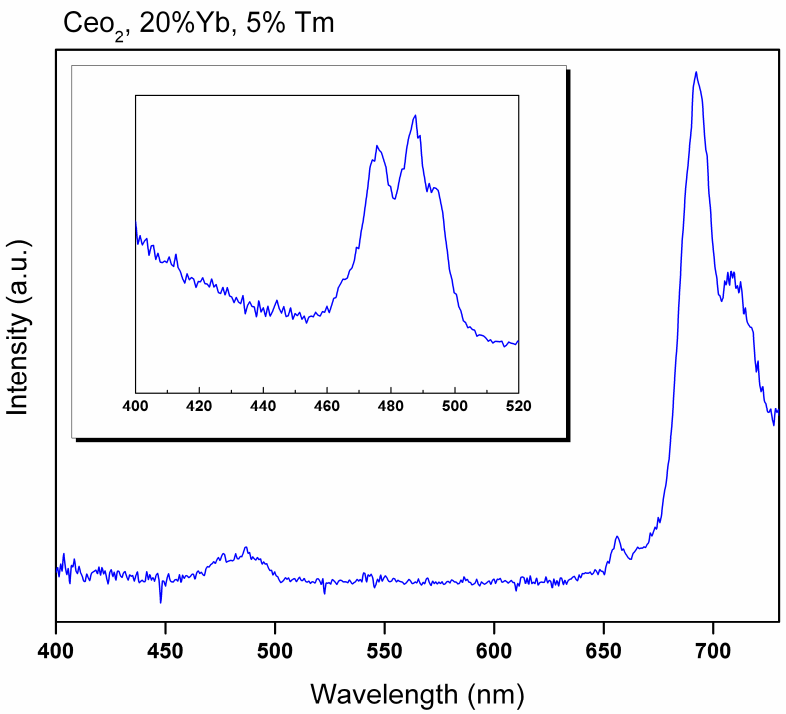
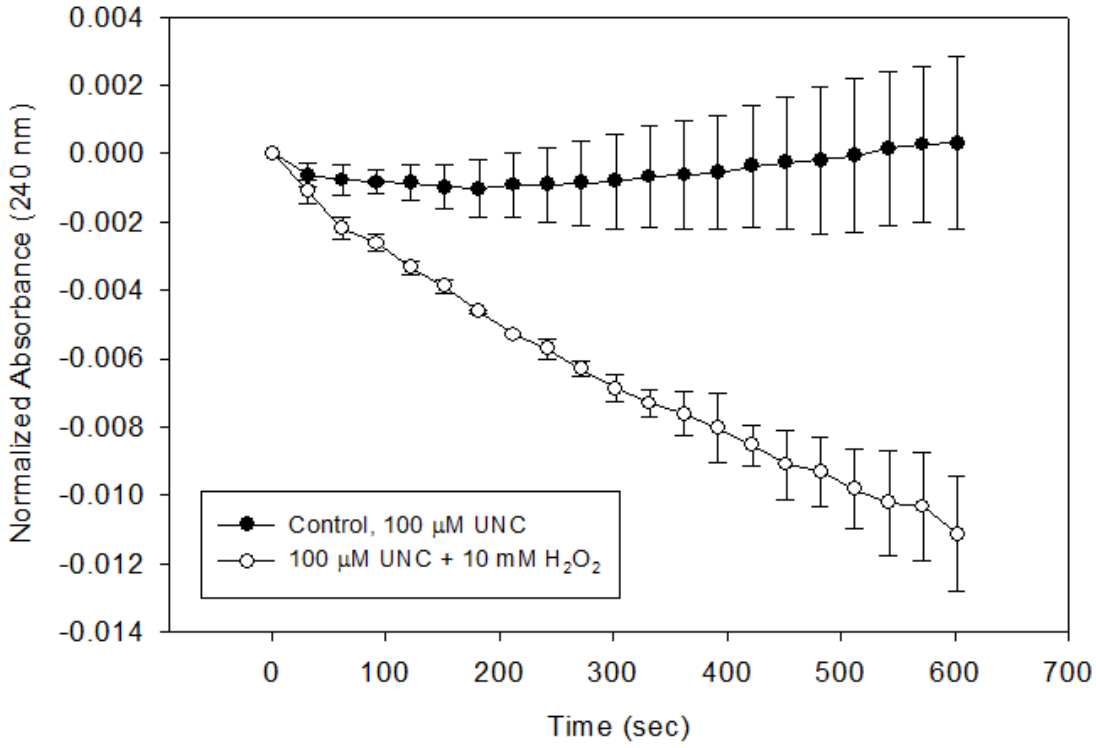


Figure S4

Catalase mimetic activity of UNCs; the conversion of hydrogen peroxide to oxygen was followed by measuring decrease in hydrogen peroxide levels at 240 nm. Data plotted represent the mean of at least three samples and the error plotted is the standard deviation of the mean.



Experimental details

Synthesis of co-doped CNPs and characterization

Analytical grade nitrates of Ce, Yb, Er, Ho and Tm from Sigma-Aldrich Chemical Inc. were used. To aqueous nitrate solutions of Ce^{3+} (0.1 M), Yb^{3+} (20%) and Er^{3+} (2%), ammonia solution (1N Alfa Aesar) was added to maintain the pH above 10. The resultant upconversion nano cerium oxide (referred as UNC, hereafter) precipitate was washed, annealed at 900°C for 2 hours and filtered through 100 nm membrane filter [22]. A similar procedure was used to synthesize CeO_2:20%Yb,2%Ho and CeO_2:20Yb%,0.5%Tm. To evaluate the size and morphology high resolution transmission electron microscopy (HRTEM) studies were carried out with FEI Tecnai F30 having an energy dispersive X-ray (EDX) analyzer. Powder X-ray diffraction (XRD) was performed with monochromatized CuKα radiation. Subsequent to the powder characterization, UNCs were tested by cell viability assay, imaging under NIR excitation and cancer cell proliferation assay.

Catalase mimetic activity

All spectrophotometric data was collected using a 40 µL quartz cuvette with a 1 cm path length in a Hewlett-Packard diode array UV-visible 8453 spectrophotometer. Reactions were carried out in assay buffer containing 50 mM Tris, pH 7.5 and 1 mM diethylenetriaminepentacetic acid (DTPA) to chelate any possible adventitious metal. Hydrogen peroxide (Acros Organics) was added to start the reaction and samples were analyzed for a total of 600 seconds with a cycle time (time point) of 0.5 seconds at a wavelength of 240 nm. UNC preparations were reconstituted in H_2O to initial concentration of 10 mM and ultrasonicated for 45 min before use. Experiments were carried with at least three independent samples preparations and each of the preparation was tested two times.

Cell Culture

WI-38 and CRL-5803 were obtained from American Type Culture Collection (Manassa, VA, USA) and Human Umbilical Vascular Endothelial Cells (HUVEC) cells were obtained from Lonza Walkersville, Inc. (Walkersville, MD, USA). CRL-5803 cells were cultured in Dulbecco's modification of Eagle's medium (DMEM) (Mediatech, Inc, Manassa, VA, USA) supplemented with 10% fetal bovine serum (FBS) (Equi-tech Bio, Kerrville, TX, USA) and 100 IU mL^{-1} penicillin (Mediatech, Inc, Manassa, VA, USA). WI-38 cells were cultured in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% FBS and 100 IU mL^{-1} penicillin. HUVEC cells were cultured in Endothelial Cell Medium (ECM) (ScienceCell, San Diego, CA, USA) supplemented with 5% FBS and 100 IU mL^{-1} penicillin. All cultures were maintained at 37°C in a humidified incubator under a 5% atmosphere of CO_2.

Optical Imaging

For microscopic analysis, cells were grown to approximately 60-70% confluence. After 24 hour treatment with various UNC concentrations, cells were washed two times in appropriate saline (for WI-38, Dulbeccos's Phosphate Buffered Saline from Mediatech,

Inc, Manassa, VA, USA while for HUVEC, Hepes Buffered Saline without Phenol Red from Lonza Walkersville, Inc., Walkersville, MD, USA), trypsinized and transferred to glass coverslips. After a further 24 hour growth, cells were washed two times in appropriate saline, fixed in cold (-20°C) methanol for 10 min at RT then washed two times with sterile water. A diode laser emitting at 975 nm with a 4 ns pulse rate, 10 Hz pulse repeat rate and a pump power of 170 mW was used for optical imaging.

MTT and LDH cell viability assay

Cells were cultured in 96-well culture dishes using appropriate media conditions and treated with UNCs in varying concentrations; 0, 50, 250, 500, 750, 1000 μM and incubated for 24 hour at 37°C. MTT dye (3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) from Amresco (Solon, OH, USA) was added to a final 1.2 mM concentration and cells were incubated for another 4 hours at 37°C. To solubulize the dye, cells were lysed (10% SDS, 0.01 M HCl) and incubated overnight at 37°C. Absorbance was measured at 570 nm using a SpectraMax 190 spectrophometer (Molecular Devices, Sunnyvale, CA, USA). Cell proliferation was determined by dividing the absorbance of treated samples to untreated controls and reported as a percentage. Lactate dehydrogenase (LDH) release was measured in presence of UNC using Cytotoxicity Detection Kit^{PLUS} (LDH) (Roche Diagnostics, Germany). In short, supernatants from each well was collected and spun to remove cell cellular debris. Freshly prepared reaction mixture was added, incubated for 15 min at room temperature protected from light. Stop solution was added and absorbance was measured at 490 nm. LDH release was determined as percentage of untreated control samples.

Cancer cell proliferation studies

Lung cancer cells CRL-5803 were seeded as per the procedure reported earlier [16]. After 24 hour incubation, the media was aspirated and replaced with fresh media containing various nanoparticle concentrations (0, 0.01 nM, 0.1 nM, 1 nM, 10 nM, 100 nM). Post 24 hour treatment, cell viability was determined by the Cell Titer-Glo® Luminescent Cell Viability and Proliferation Assay (Promega; Madison, WI) and activation of apoptosis was determined by measuring the activation of caspase-3/7 via the Caspase-Glo® 3/7 Assay (Promega; Madison, WI). A direct relationship exists between Caspase-Glo®3/7 luminescence and caspase-3/7 activation. Since activation of caspase-3/7 plays a key role in mammalian cell apoptosis, the Caspase-Glo®3/7 luminescence is directly proportional to the amount of apoptosis activation. The caspase-3/7 activity was normalized by dividing relative luminescence by the number of viable cells. The relative luminescence (RLU) was measured by an Optima Fluor Star Luminometer (BMG Labtech; Durham, NC).