Engineered Therapeutic Nanoparticles as Catalytic Antioxidants

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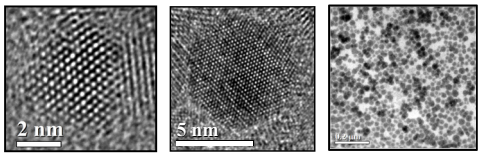
Rare Earth Nano oxides as Nanomedicine

- 13-14 million cases of loss of vision due to retinal diseases
- Rare earth oxide nanomaterials can prevent retinal degeneration
- Nano cerium oxide with its multiple valence oxidation states can treat diseases caused by the reactive oxygen intermediates (ROI)

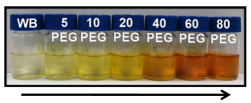
Objectives of Current Research

1. Engineering of surface active nano cerium oxide in various biologically compatible and active media
2. Accurate theoretical description of cerium mixed valence states (+3 and +4) and interaction of vacancies with ROI
3. Evaluation and confirmation of theoretical prediction with redox chemistry using spectrophotometric assays
4. In vivo studies to validate the therapeutic effects of nanoceria based on rat photoreceptor cells
5. Utilize nanotechnology as a tool for better advancement of science, technology, healthcare and education
6. Education and outreach of nanotechnology

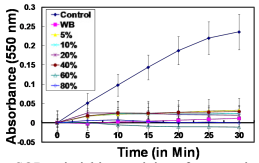
Controlled Engineering: Synthesis, Handling and Storage of Nanomaterials - PEGylated Nanoceria



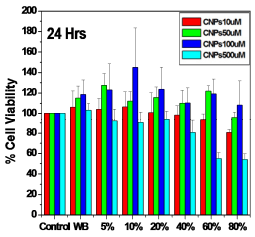
Nanoceria synthesized in varying molecular weight of PEG (a) 300 MW b) 1000 MW c) 6000 MW) shows the ability to tune the particle size and control the aggregation behavior of nanoparticles

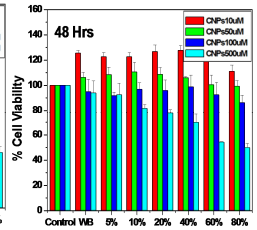


Nanoceria synthesized in varying concentration of 600 MW PEG shows the ability to scavenge CNPs and tune the oxidation state of CNPs to contain tailored amount of Ce^{3+}/Ce^{4+} oxidation state



SOD mimicking activity of nanoceria synthesized in varying concentration of 600 MW PEG

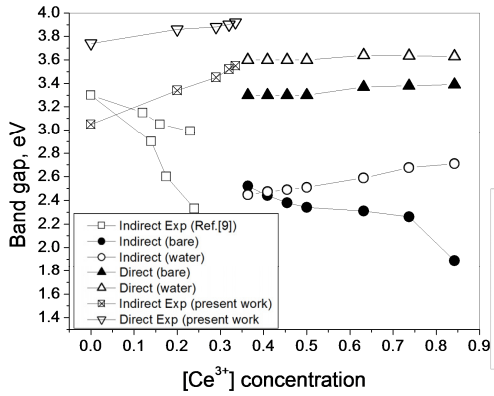


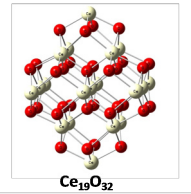


- Highly dispersed nanoparticles synthesized in biocompatible mediums such as poly(ethylene) glycol and dextran
- Tunable properties can be achieved using PEGylation
- PEGylated nanoceria can scavenge both superoxide and peroxide

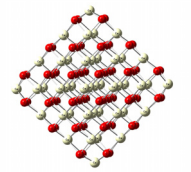
Theoretical Modeling (Density Functional Theory) – Understanding Origin of Reactivity and Role of Surfaces

- Simulation performed using $Ce_{19}O_{32}$ and $Ce_{44}O_{80}$
- Performed density functional theory (DFT) calculations using plane-wave based Vienna *ab initio* simulation package (VASP 4.8)
- Study the effect of water on the properties of nanoceria – adsorption of water causes a blue shift in optical spectra
- Energetics of regeneration of active oxidation state of nanoceria under calculation
- Electron transfer occurs from Ce in cerium oxide nanoparticles to adsorbed superoxide and oxygen causing a change in spin state of adsorbed oxygen





$Ce_{19}O_{32}$

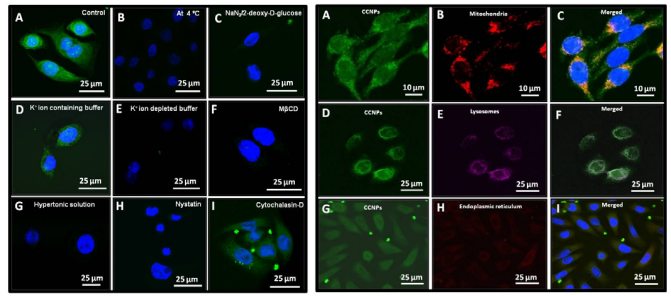


$Ce_{44}O_{80}$

Adsorption of water strongly affects the optical properties of nanoceria. A strong blue shift is observed upon adsorption of water as compared to bare nanoceria. Indirect band gap shows a Ce3+ concentraiton dependent blue shift while the direct band gap shows a blue shift which is independent of Ce3+ concentration. Adsorbed water molecules destabilize f-band with increase in the number of electrons occupying this band

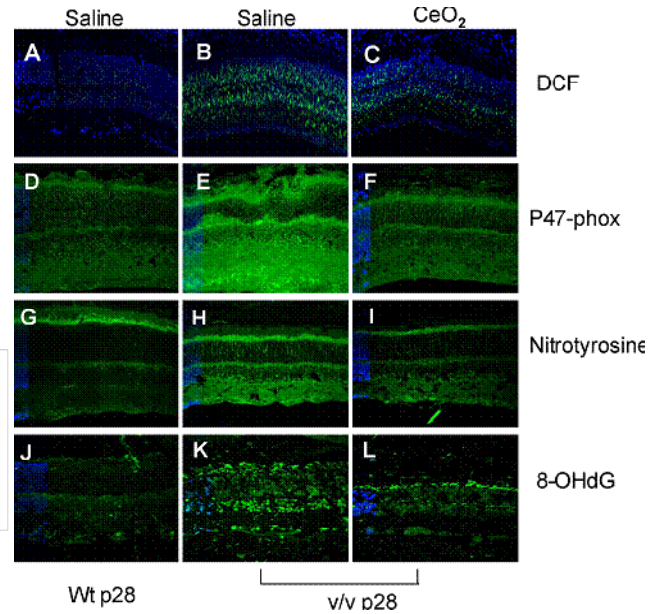
Uptake and Sub-Cellular Localization of Nanoceria in Cells

- Nanoceria particles were tagged with carboxyfluroscein to understand the uptake and sub cellular localization using simple wet chemistry methods
  - Nanoceria was incubated for 1, 3, 6, 9 and 12 hrs and analyzed for uptake
  - Maximum uptake occurred within 3 hrs of incubation



Uptake of CCNPs is mediated by energy, clathrin and caveolae dependent pathways: Confocal fluorescent images of the HaCat cells incubated with CCNPs at 37 ºC (A), 4 ºC (B) and cells pre-incubated with NaN_3/2-deoxy-D-glucose, ATP depleting drugs (C). Cells pre-treated with K^+ ion containing buffer (D) showed uptake of CCNPs whereas cells pretreated with K^+ ion depleting buffer (E) and hypertonic sucrose solution (G) completely blocked the uptake. Pretreatment with MβCD (F), and Nystatin (H) again blocked the uptake while cytochalesin-D (I) did not impose any alteration in uptake. **Sub cellular distribution of CCNPs:** Subcellular distribution of CCNPs (A, D and G) was studied by mito-tracker dye (B), lyso-tracker dye (E) and ER-tracker dye (H). These organelle specific dyes showed partial overlapping with CCNPs when merged.

Nanomedicine Trials – Oxidative Stress Indicators and Treatment



Indicators of oxidative stress are much higher in the Vldlr retina than in the normal wild type retina and injection of Nanoceria inhibits these increases.

Education Outreach and Dissemination – Training and Learning

Personal Training: Post Doc - Dr. Talgat Inerbaev (UCF), Dr. S. Babu (UCF), Dr. X. Yu (OU), Dr. X. Zhou (OU), L. Wong (Instructor), S. Sezate (Technician) , Dr. S. Singh (UCF)
Graduate Students: Ms. Shruba Gangopadhayay (F), A. Karakoti (M), A. Kumar (M), A. Vincent (M), E.. Heckert (M) (completed Master's), J. Dowding (F), Workalemahu Mikre (M)
Undergraduates: Mr. Andrew Teblum (UG), Jessica King (F), Andrew Teblum, Stephanie Locks (high school), Jarrod Spring (NARCH Program), Jessie Smith (F)
Publications:6 peer reviewed journal publication in each 2008 and 2009, *REU student:**1)** Karakoti, A., Singh, S., Kumar, A., Malinska, M., Kuchibhatla, S., Wozniak, K., Self, W., and S. Seal (2009) PEGylated Nanoceria as Radical Scavenger with Tunable Redox Chemistry, **J. Amer. Chem. Soc**. 131 (40): 14144–14145. **2)** Vincent, A., Babu, S, Heckert, E., Dowding, J., Hirst, S. M., Inerbaev, T. M., Self, W. T., Reilly, C. M., Masunov, A. M., and Sudipta Seal (2009) Protonated nanoparticle surface governing ligand tethering and cellular targeting. **ACS Nano**. 3 (5): 1203-1211. **3)** Seal, S., Self, W. T., McGinnis, J. and A.S. Karakoti. (2009) "Nanoparticles for Novel Healthcare Therapeutics" **in New Materials and Technologies for Healthcare**, Edited by Larry L. Hench and Julian R. Jones, Imperial College Press, London and Singapore **4)** Schanen, B. C., Karakoti, A. S., Seal, S., Drake, D. R., Warren, W. L. and W. T. Self (2009) Exposure to Titanium Dioxide Nanomaterials Provokes Inflammation of an in Vitro Human Immune Construct. **ACS Nano**. 3 (9): 2523-2532.. **5)** Babu, S., Thanneeru, R., Inerbaev, T. A., Day, R., Masunov, A. E, Schulte, A. and Seal,* S. Dopant mediated oxygen vacancy tuning in ceria nanoparticle. **Nanotechnology** 20 (8); 085713, 2009 **6)** S.V.N.T. Kuchibhatla, A.s. Karakoti, D.C. Sayle, H. Heinrich and S. Seal (2009), Symmetry-Driven Spontaneous Self-Assembly of Nanoscale Ceria Building Blocks to Fractal Superoctahedra, **J. Crystal Growth & Design**, 9 (3), 1614-1620
Invited talks 5, and **Conference** presentations 14
Patents : 2 pending and 1 new filed
Collaboration: with EMSL- PNNL
High School Outreach – Using Boing Boing Bionic Cat model in collaboration with Prof L. Hench to introduce nanotechnology and medicine to school kids
Major awards: Dr. S. Seal – Fellow of American Association for advancement of Science, Talib Pir won 3rd prize in NanoFlorida Orlando, Florida, Sept. 25-26th
Cover Page article in J. Crystal Growth and Design, Research Highlight in EMSL, PNNL news
Transformatory Research: The technology lead to a patent between UCF and OU and lead to a company creation NTIOX at OU incubator by Prof. McGinnis