Development of Quantitative Structure-Activity Relationship for Prediction of Biological Effects of Nanoparticles Associated with Semiconductor Industries *(Task Number: 425.025)*

PIs:

- **Yongsheng Chen, Environmental Engineering, Georgia Institute of Technology (GIT)**
  Email: yongsheng.chen@ce.gatech.edu

Graduate Students:

- **Kungang Li, PhD student, Environmental Engineering, GIT**

Other Researchers:

- **Wen Zhang, Postdoctoral Fellow, Environmental Engineering, GIT**
- **Yang Li, Visiting Ph.D. student, Department of Science and Environmental Engineering at Beijing Normal University**

Cost Share (other than core ERC funding):

- **$25 k start-up fund from ASU;**
- **60k start-up for consumables and $152k funds from GIT for AFM and other lab instrument purchase**

Objectives

Develop a quantitative structure-activity relationships (QSARs) model for prediction of the biological effects of engineered nanoparticles (NPs) associated with semiconductor industries. To pursue this goal, our approach mainly includes:

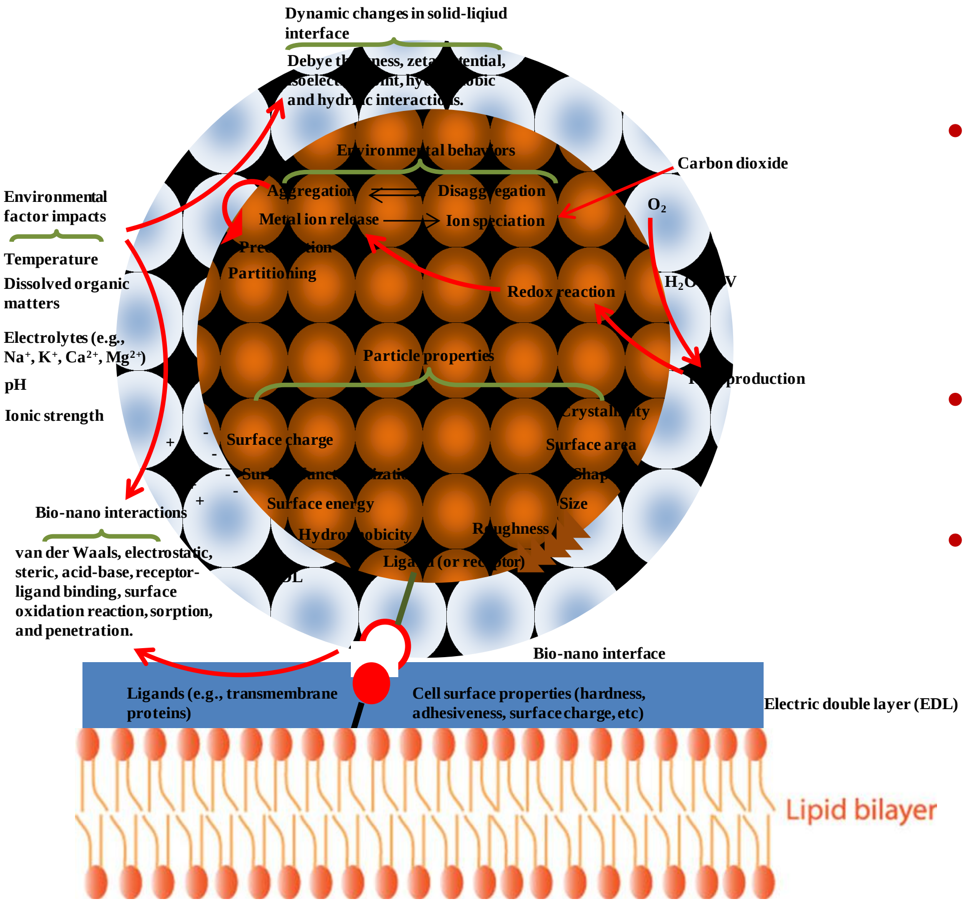
- **Establish a comprehensive understanding of relevant physiochemical properties of semiconductor nanomaterials that govern their fate, transport and biological interactions.**
- **Collect sufficient experimental and theoretical data showing the environmental behaviors and the associated biological consequences.**

ESH Metrics and Impact

1. **Our work aims at development of fundamental understanding of cytotoxicity of semiconductor NPs to human health and provides a comprehensive database and clear definition of ESH-problematic manufactured nanomaterials.**

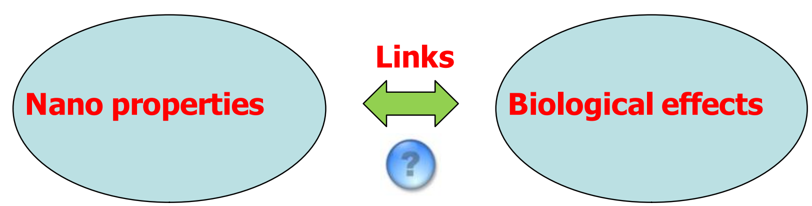
2. **Based on the quantitative structure-activity relationship (QSAR) model we plan to establish, problematic nanomateirals from industrial manufacturers could be predicted, identified, and effectively modified to produce environmental benign semiconductor nanomaterials.**

Motivation



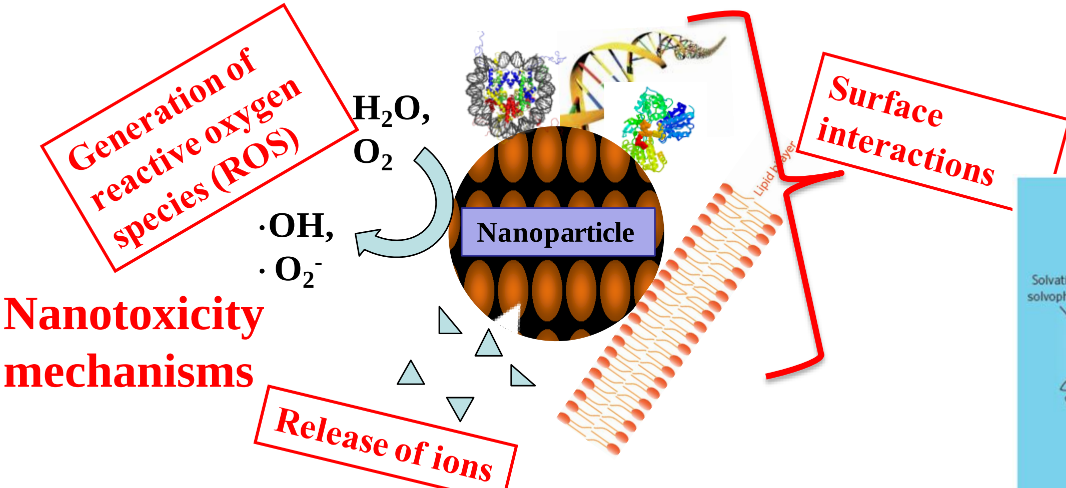
Cited from Wen Zhang, PhD dissertation, 2011, Georgia Tech

- Insufficient knowledge of the environmental fate, transport, transformation, and biological interactions;
- Lack of nanotoxicity data on new model biosystems;
- New criteria that are used to categorize and prioritize nanomaterials and their relevant properties.

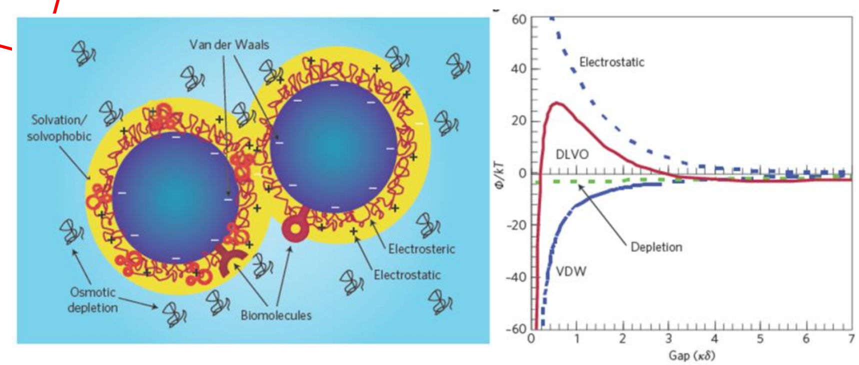


Method of Approach

ROS generation mechanism: band gap



Derjaguin–Landau–Verwey–Overbeek (DLVO) and extended DLVO (EDLVO) theories describe surface interactions



Modeling … Ag NPs) on … ere collision t…

Dynamic, owing to aggregation, dissolution, and polymer adsorption

Input parameters required by EDLVO		
Size	Roughness and porosity	Ionic strength
Surface charge or surface potential	Shape	Electrolyte type
Ligands	Composition	Temperature
Hydrophobicity or hydrophilicity	Concentration	pH

Wen Zhang, Ying Yao, Nicole Sullivan, and Yongsheng Chen. *ES&T*, 2011
Andre Nel, et al. *Nature Materials*, 2009

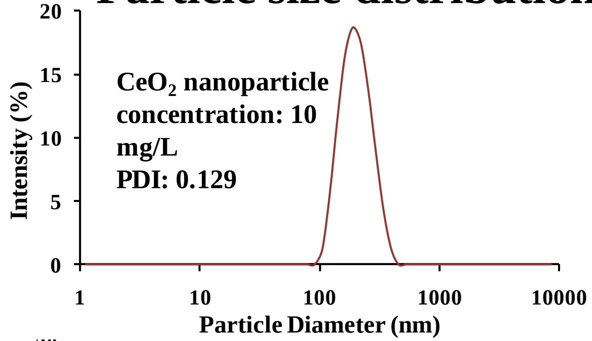
Highlight of Results

1. **Aggregation kinetics of NPs in aqueous solution;**
2. **ROS generation by NPs and underlying mechanisms**
3. **Acute toxicity of ten engineered NPs to *paramecium* and development of an indicator for pre-evaluating the toxicity of NPs**

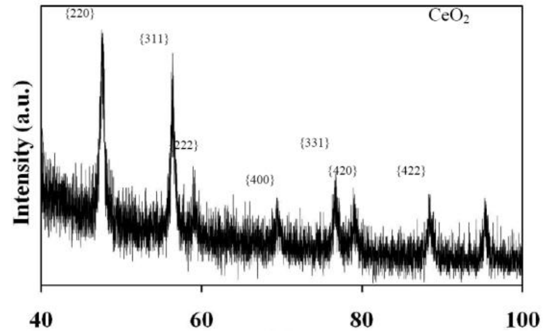
1.1. Aggregation kinetics of NPs in aqueous solution

CeO_2 NP characterizations

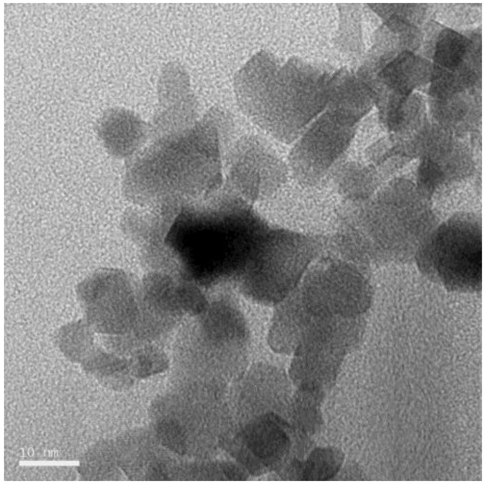
Particle size distribution

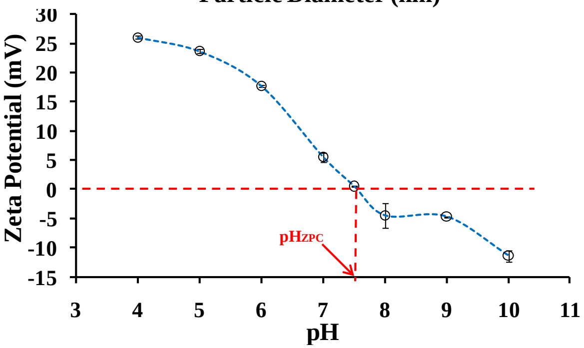


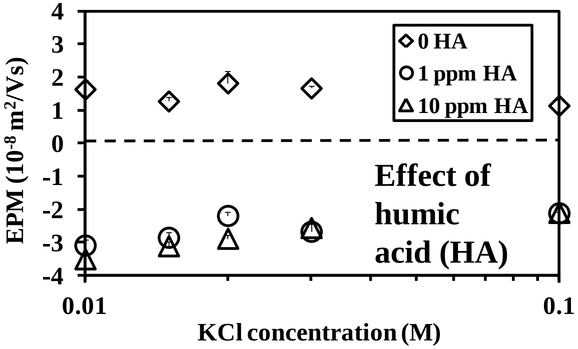
XRD

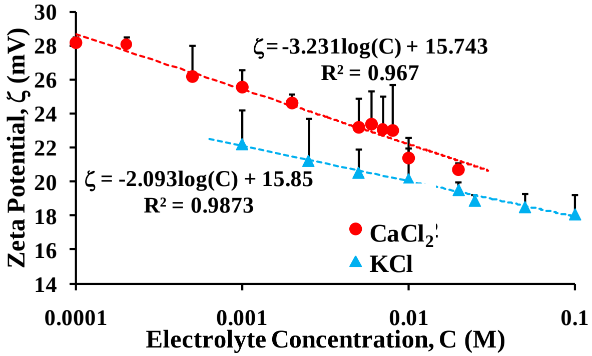


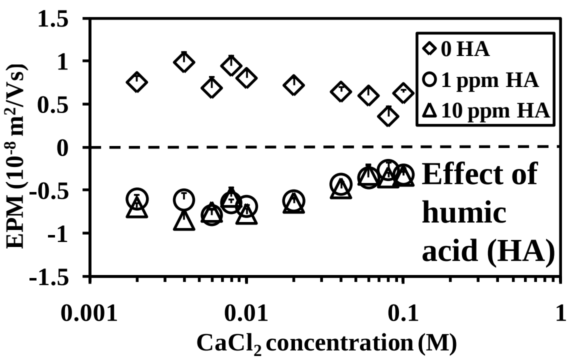
TEM

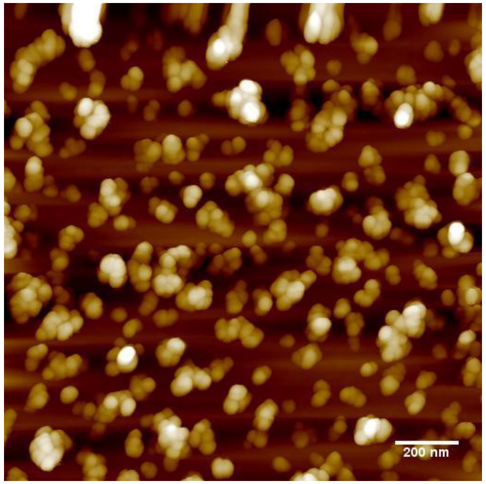










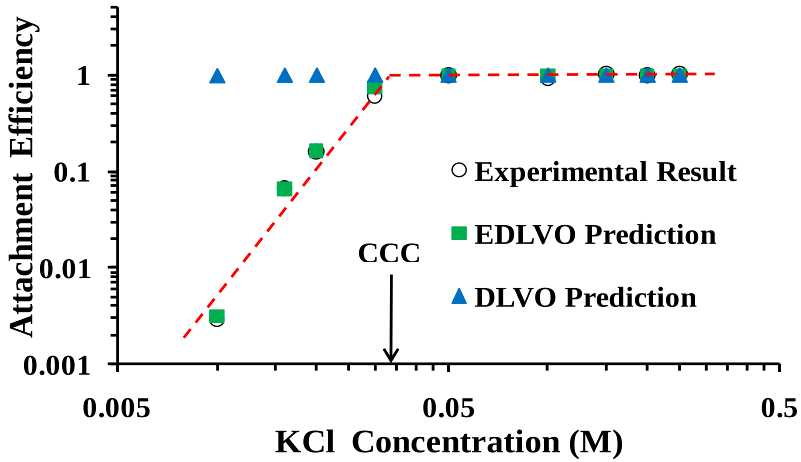


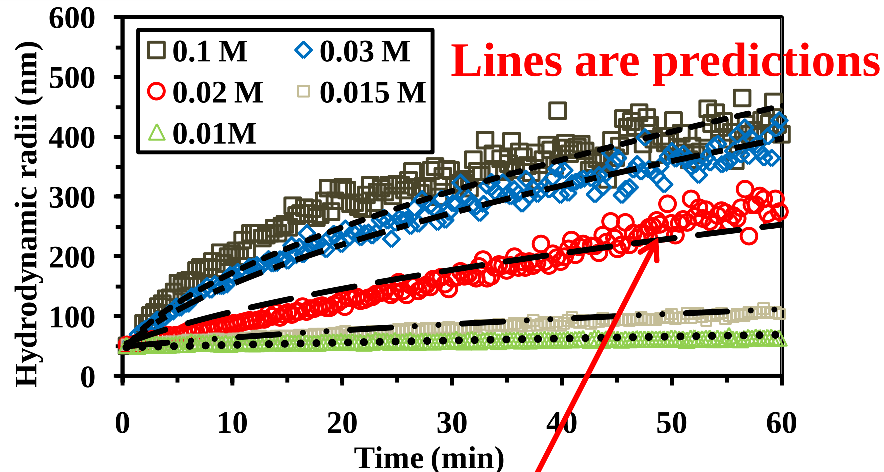
AFM

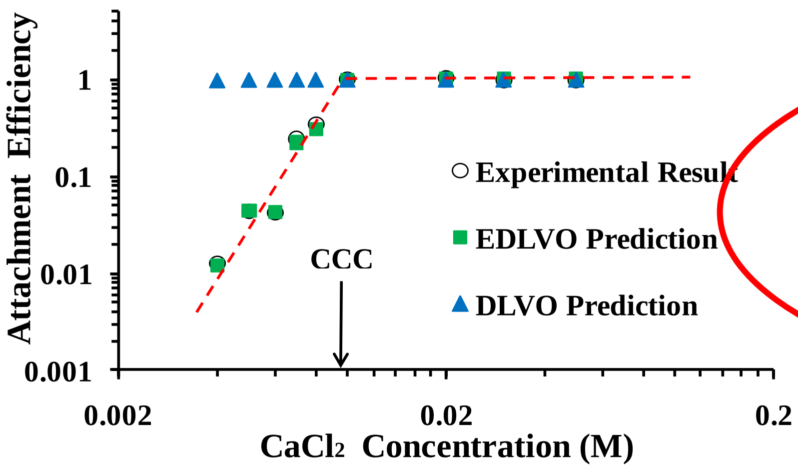
Surface potential

1.2. Aggregation kinetics of NPs in aqueous solution

Ionic strength effect







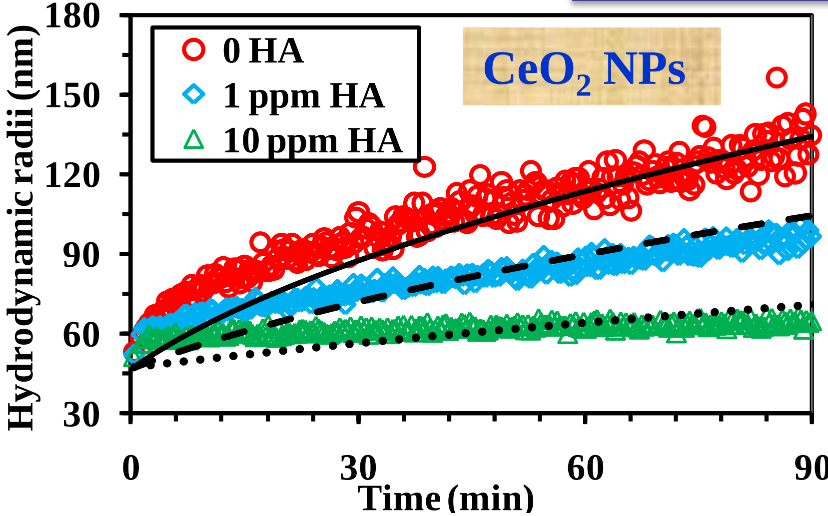
$$r = a \cdot \left\{ 1 + \frac{4k_B T n_0}{3\mu W} t \right\}^{1/d_F}$$

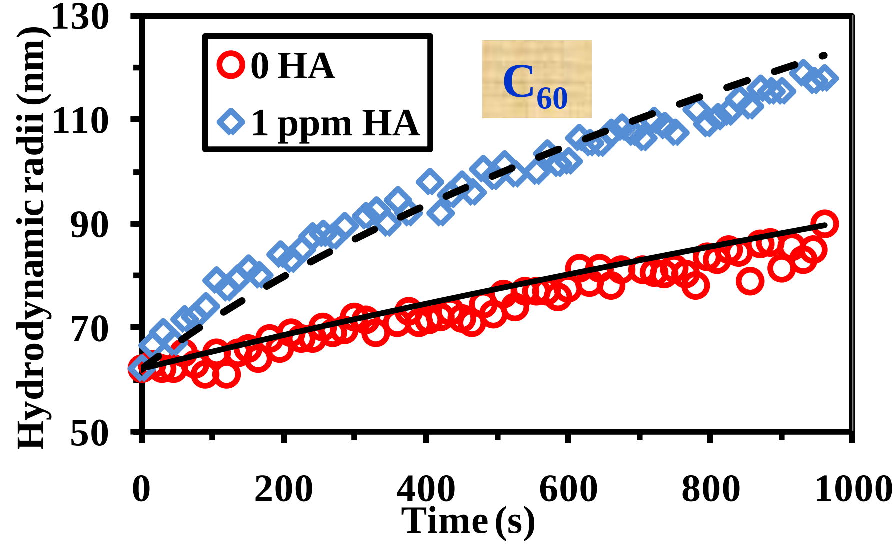
$$W = \left[\int_0^\infty \lambda(u) \frac{\exp\left(V_T(u)/kT\right)}{(2+u)^2} du \right] \cdot \left[\int_0^\infty \lambda(u) \frac{\exp\left(V_A(u)/kT\right)}{(2+u)^2} du \right]^{-1}$$

Kungang Li, Wen Zhang, Ying Huang, Yongsheng Chen. *J. Nanoparticle. Res*. 2011

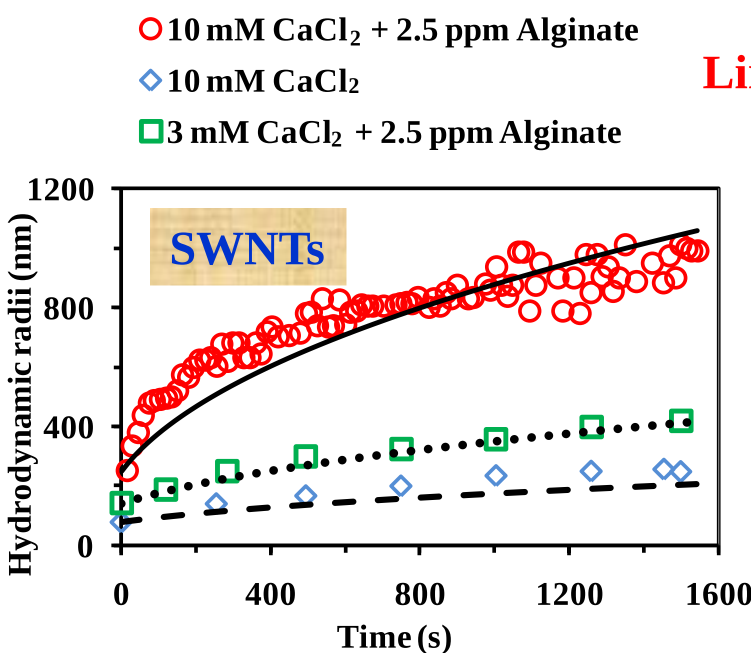
1.3. Aggregation kinetics of NPs in aqueous solution

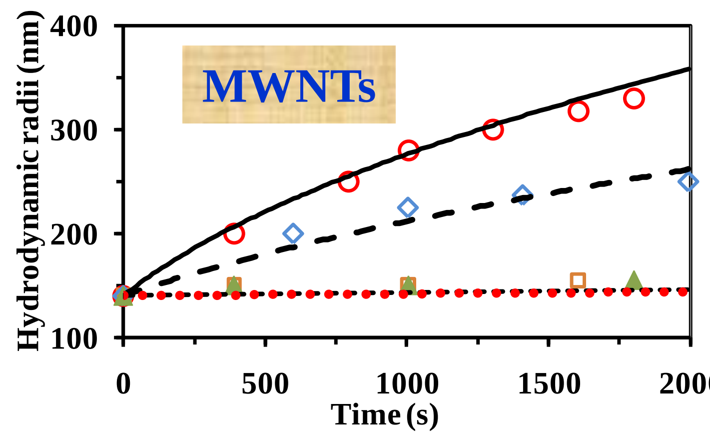
Natural organic matter (NOM) effect





Lines are predictions!





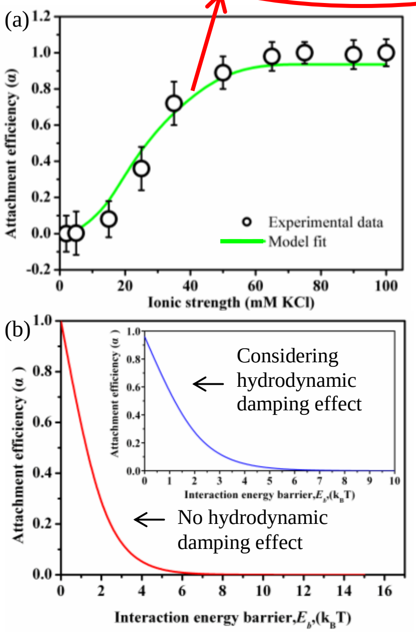
Kungang Li and Yongsheng Chen. *J. Hazard. Mater*. 2012

1.4. Aggregation kinetics of NPs in aqueous solution

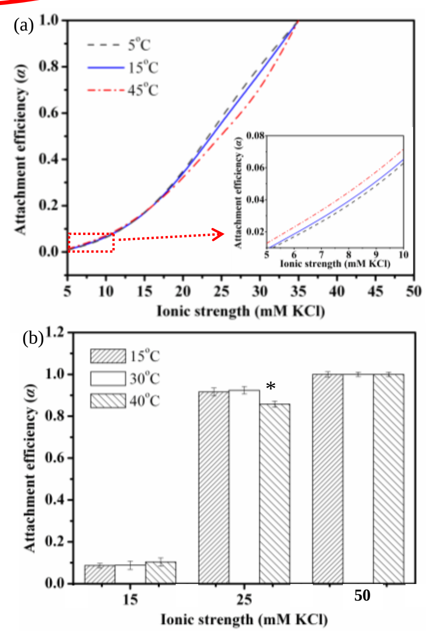
Attachment efficiency model on the basis of Maxwell-Boltzmann distribution

$$\frac{\Delta N_{E_b\to\infty}}{N_{0\to\infty}} = \frac{\int_{v^C}^{\infty} 4\pi\left(\frac{m}{2\pi k_B T}\right)^{3/2} e^{-\frac{mv^2}{2k_BT}} v^2 dv}{\int_{0}^{\infty} 4\pi\left(\frac{m}{2\pi k_B T}\right)^{3/2} e^{-\frac{mv^2}{2k_BT}} v^2 dv} = \frac{\int_{E_b}^{\infty} e^{-E}E^{1/2}dE}{\int_{0}^{\infty} e^{-E}E^{1/2}dE}$$

$$\alpha_m = \delta\cdot\frac{\Delta N}{N} = \delta\cdot\int_{E_b}^{\infty} e^{-E}E^{1/2}dE$$

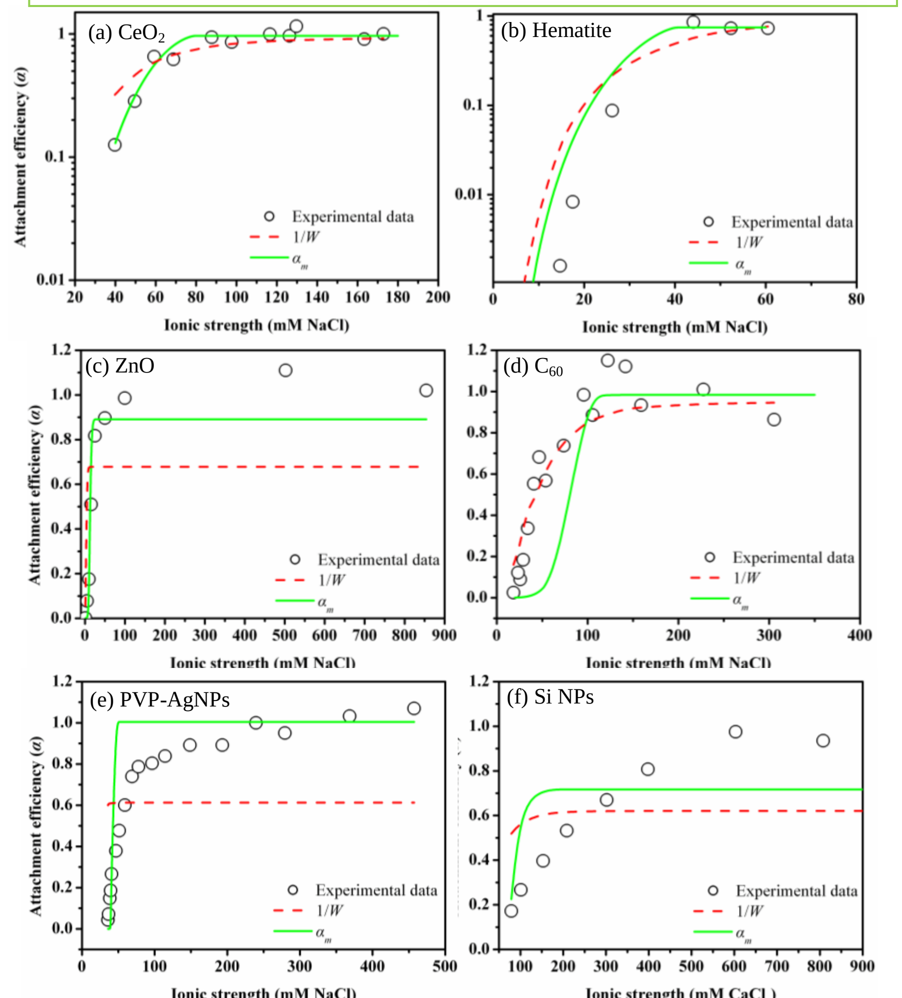


Ionic strength effect



Temperature effect

Green lines are new model predictions



Wen Zhang, John Crittenden, Kungang Li, Yongsheng Chen. *ES&T* 2012

2.1. ROS generation by NPs and underlying mechanisms: Cytotoxic implication

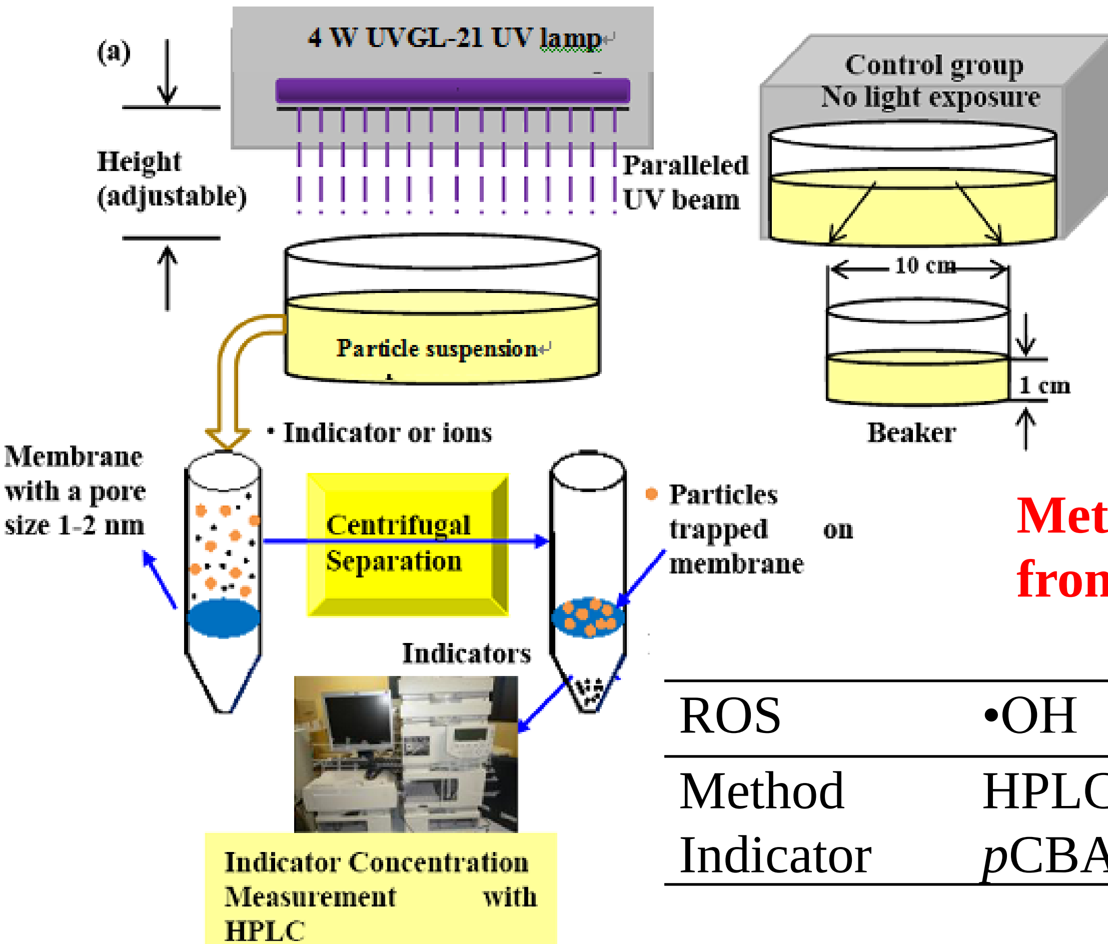
- High surface area of NPs provides more reactive sites for ROS production
- ROS formed in NP suspension usually consist of superoxide radical ($O_2^{\bullet-}$), hydroxyl radicals ($\bullet OH$), and singlet oxygen ($^1O_2$)
- Representative reaction stochiometry (TiO_2 as an example):

$$TiO_2 \xrightarrow{h\nu} TiO_2(h_{vb}^+ + e_{cb}^-)$$
$$O_2 + e_{cb}^- \rightarrow O_2\bullet^-$$
$$O_2\bullet^- + e_{cb}^- + 2\,H^+ \rightarrow H_2O_2$$
$$O_2\bullet^- + H_2O_2 \rightarrow \bullet OH + OH^- + O_2$$
$$e_{cb}^- + H_2O_2 \rightarrow \bullet OH + OH^-$$
$$h_{vb}^+ + OH^- \rightarrow \bullet OH$$
$$h_{vb}^+ + H_2O \rightarrow H^+ \bullet OH$$
$$2\bullet OH \rightarrow H_2O_2$$

Implications:

Oxidant injury of cells, lipid peroxidation, enzyme or protein oxidation, membrane pitting, changes in membrane permeability, etc.

2.2. ROS generation by NPs and underlying mechanisms: ROS measurement using indicator method

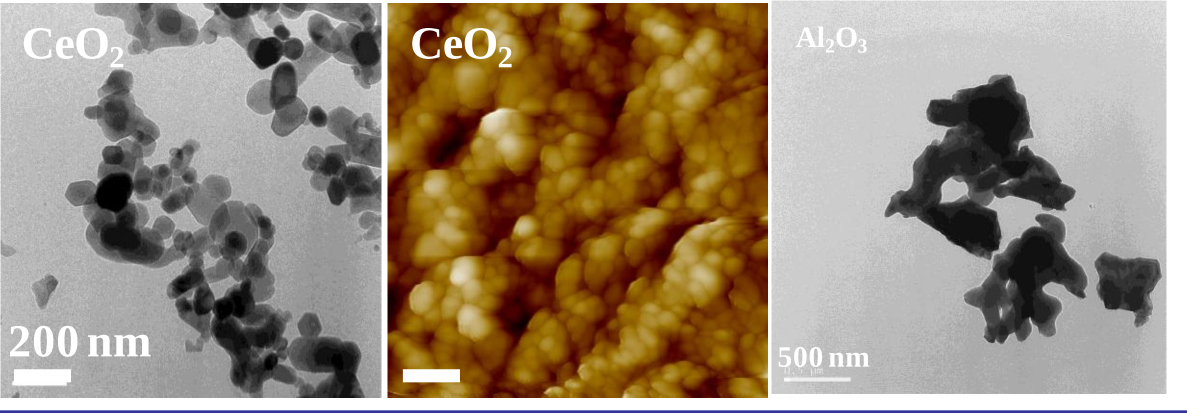


Methods of probing ROS generation from different types of NPs

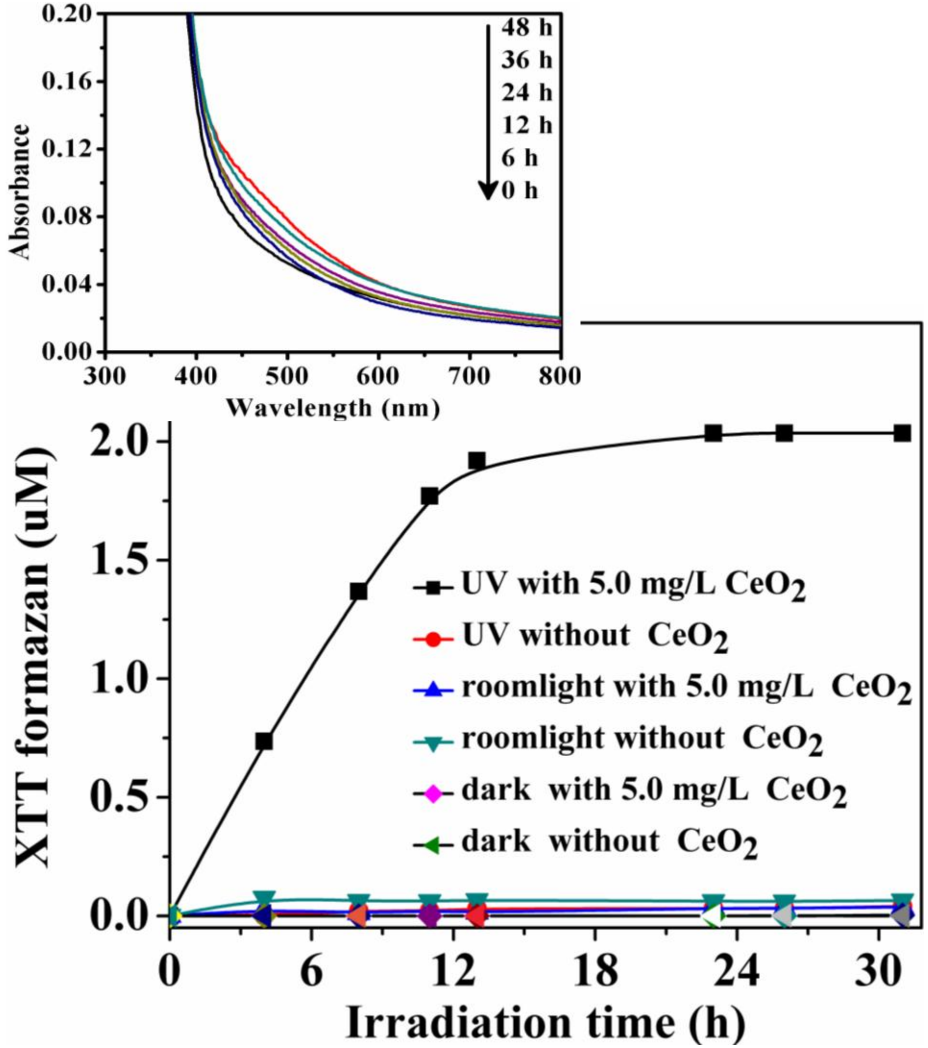
ROS	•OH	$^1O_2$	$O_2^{\bullet-}$
Method	HPLC	HPLC	UV-Vis (430 nm)
Indicator	*p*CBA	FFA	XTT

2.3. ROS generation by NPs and underlying mechanisms: Characterization of CeO_2 and Al_2O_3 NPs

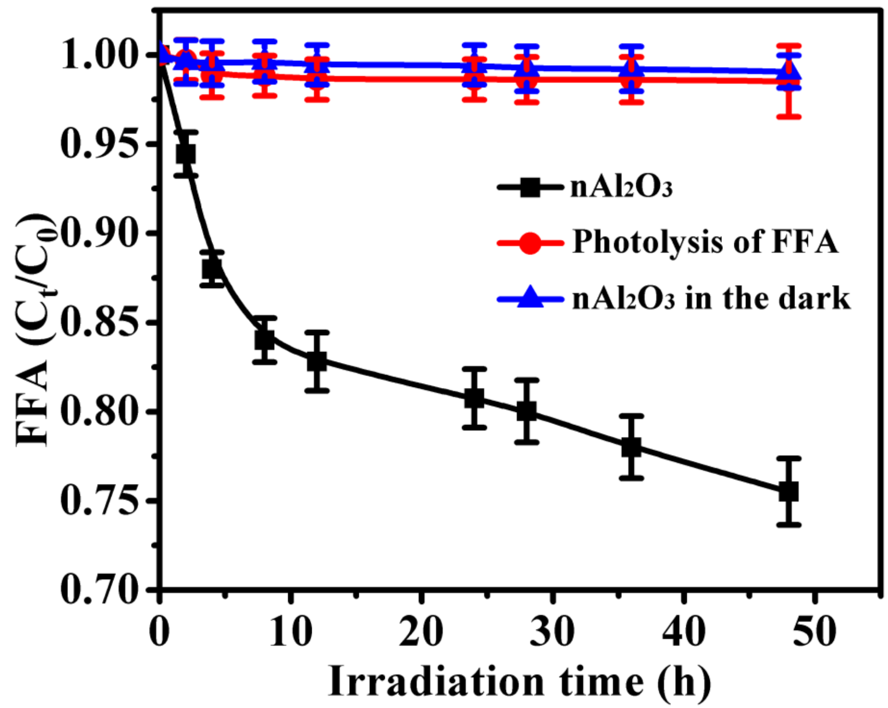
Particles	Nominal TEM diameter (nm)	Hydrodynamic radius (nm)	Zeta potential (mV)	Purity (%)	Type	Vendor /Catelog number
nCeO_2	25	94±4	20±5	99.95	Cubic Fluorite	Sigma-Aldrich (product. No. 643009)
nAl_2O_3	<50	637±245	38±3	99.9	Gamma phase	Sigma-Aldrich (product. No. 544833)



2.4. ROS generation by NPs and underlying mechanisms: ROS measurement results



➢CeO_2 NPs were found to produce $O_2^{\bullet-}$ only.



➢Al_2O_3 NPs were found to produce $^1O_2$ only.

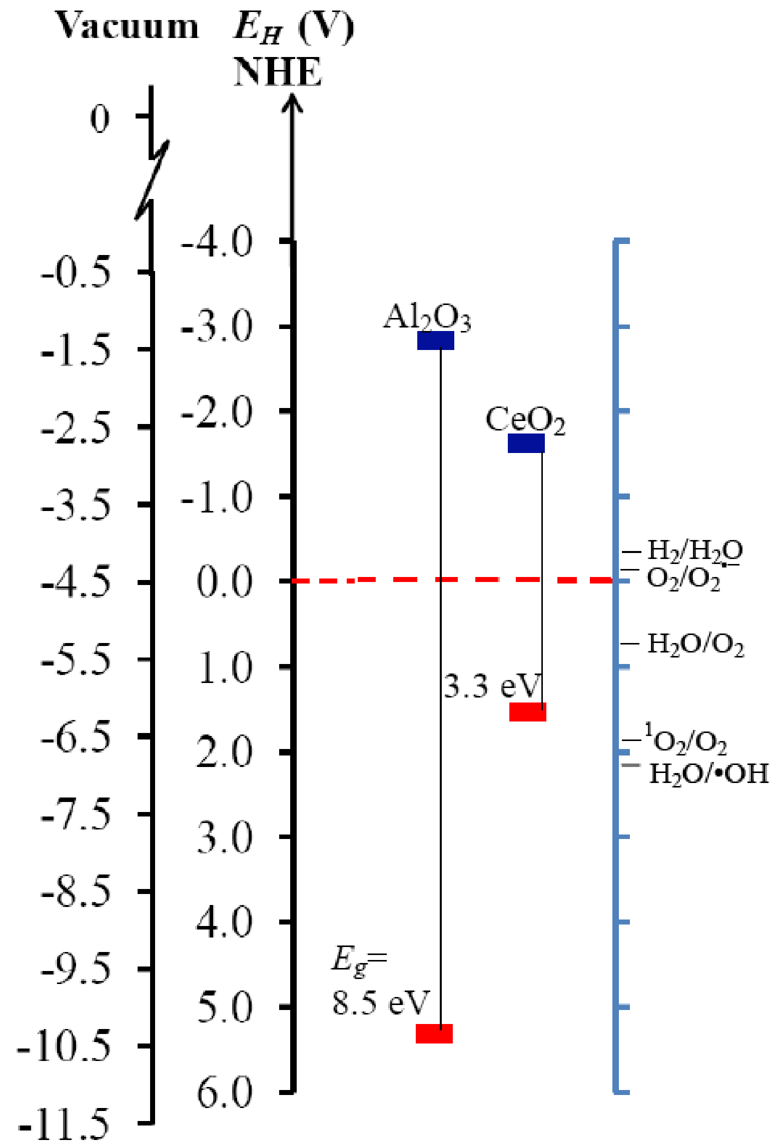
Yang Li, Wen Zhang, Junfeng Niu, and Yongsheng Chen. Mechanism of Photogenerated Reactive Oxygen Species and Correlation with Antibacterial Properties of Engineered Metal Oxide Nanoparticles. *In preparation*.

2.5. ROS generation by NPs and underlying mechanisms: ROS generation mechanism

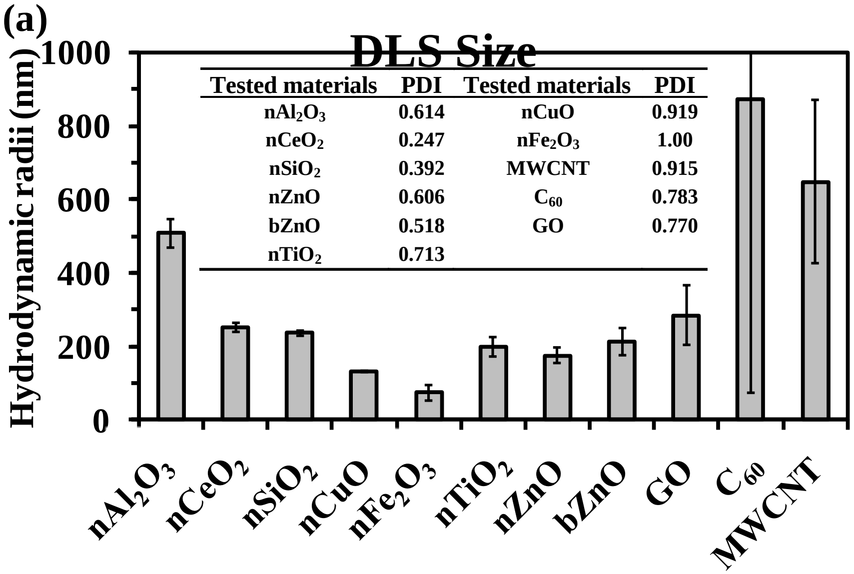
The band edge positions of CeO_2 and Al_2O_3 NPs in contact with the water solution at pH 5.6. The lower edge of E_C (blue color) and upper edge of E_V (red color) are presented along with the band gap in eV. The energy scale is indicated either the normal hydrogen electrode (NHE) or the absolute vacuum scale (AVS) as a reference. On the right side the redox potentials of ROS redox couples are presented.

The photon energy is approximately 3.4 eV for the 365-nm wavelength of incident UV.

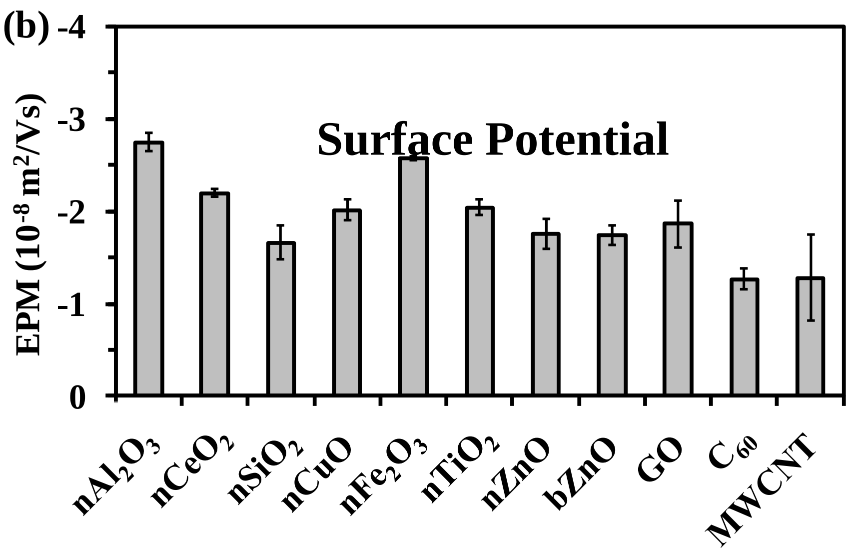
Yang Li, Wen Zhang, Junfeng Niu, and Yongsheng Chen. Mechanism of Photogenerated Reactive Oxygen Species and Correlation with Antibacterial Properties of Engineered Metal Oxide Nanoparticles. *In preparation*.

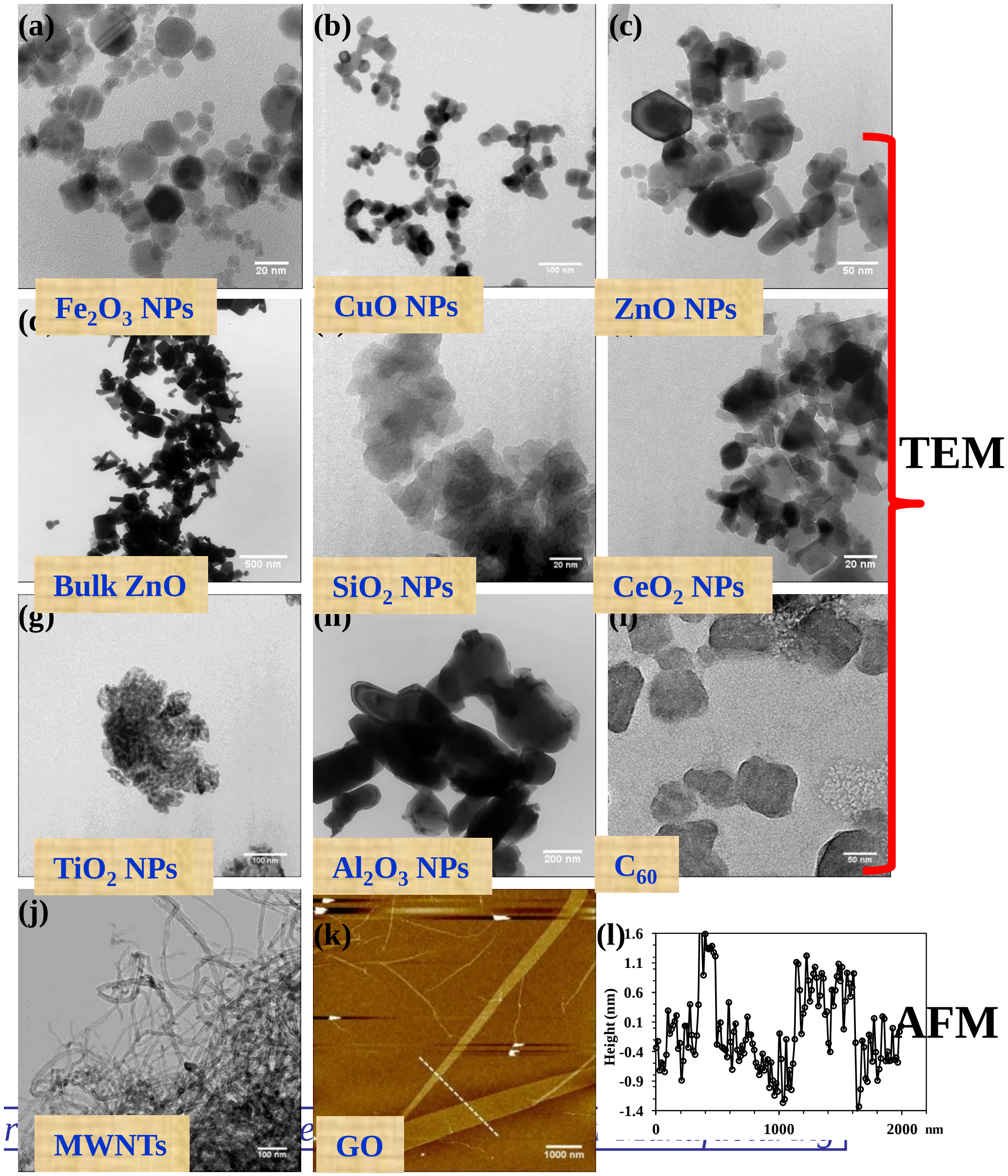


3.1. Preliminary indicator development for acute toxicity of ten engineered NPs to *paramecium*



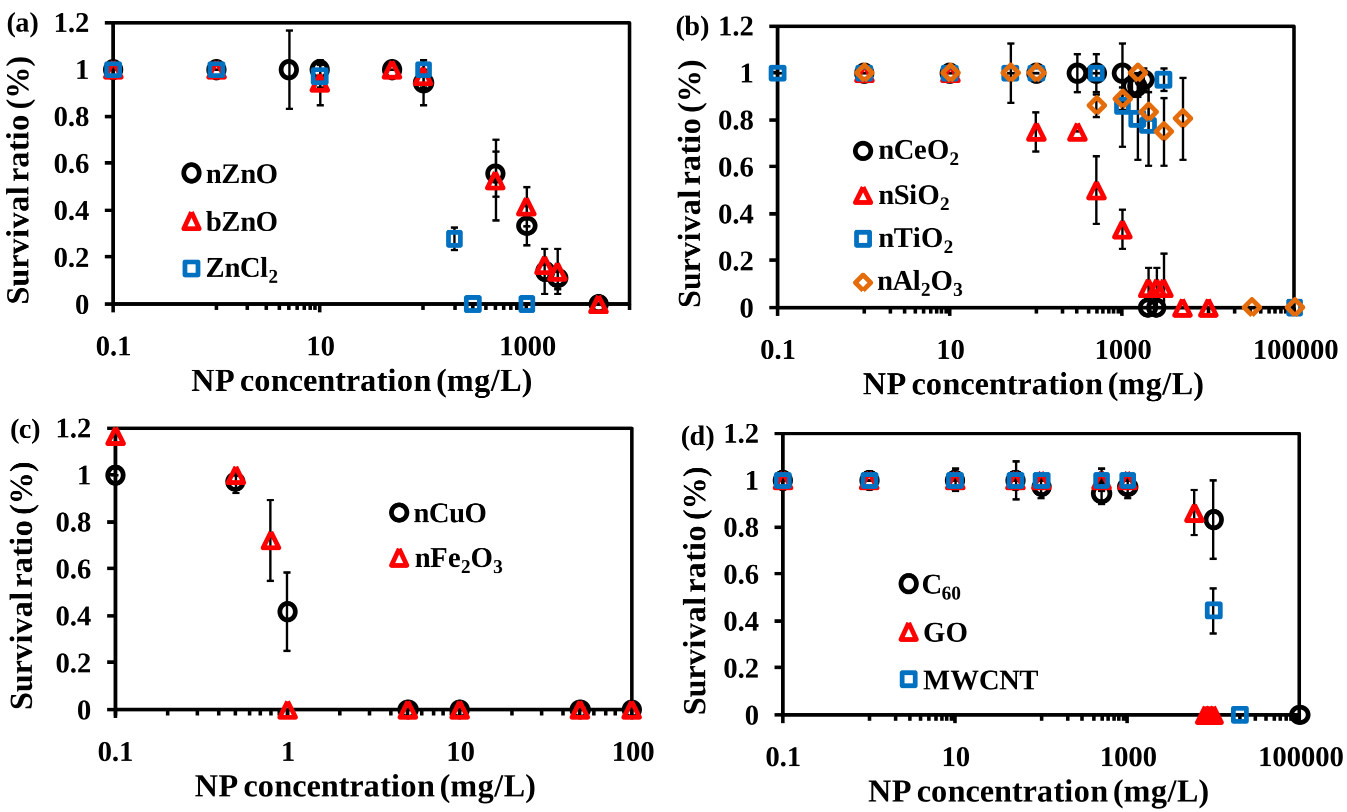
Tested materials	PDI	Tested materials	PDI
nAl_2O_3	0.614	nCuO	0.919
$nCeO_2$	0.247	nFe_2O_3	1.00
$nSiO_2$	0.392	MWCNT	0.915
nZnO	0.606	C_{60}	0.783
bZnO	0.518	GO	0.770
$nTiO_2$	0.713		

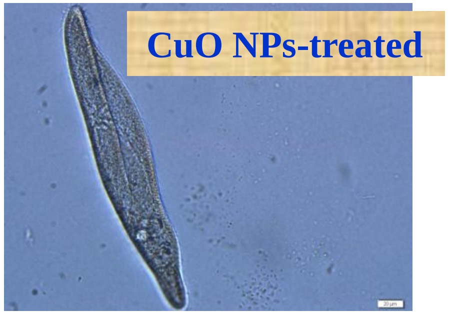


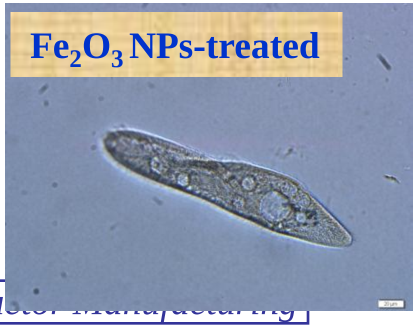


3.2. Preliminary indicator development for acute toxicity of ten engineered NPs to *paramecium*

48-h LC_{50} acute toxicity test results







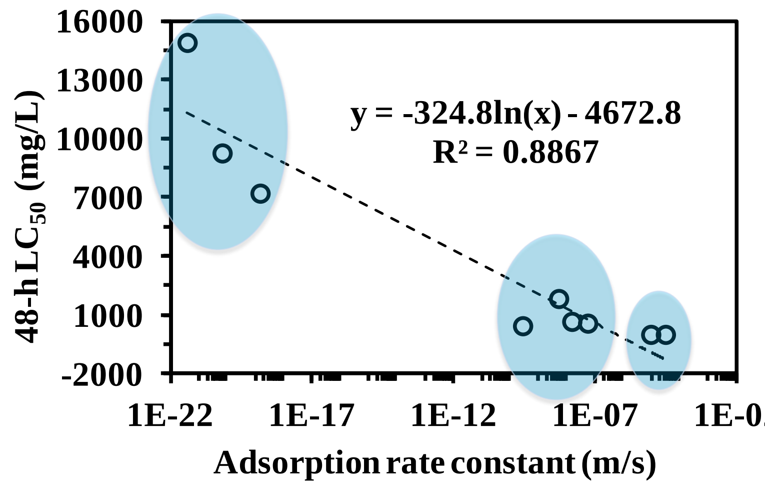
3.3. Preliminary indicator development for acute toxicity of ten engineered NPs to *paramecium*

$$\frac{d\Gamma}{dt} = k_a C_w \qquad k_a = \frac{D_\infty}{\int_{h=h_0}^{h=\delta_{IFBL}} \left[(1+R_H/h) \exp\left(V^{TOT}(h)/kT\right) - 1 \right] dh}$$

Tested materials	48-h LC_{50} (mg/L)	95% confidence intervals (mg/L)	Adsorption rate constant (m/s)	Energy barrier (kT)
nAl_2O_3	9269.2	4783.1–35409.6	6.62×10^{-21}	33.9
$nCeO_2$	1832.5	1739.9–1925.1	5.15×10^{-9}	7.81
$nSiO_2$	442.6	337.0–559.8	2.75×10^{-10}	10.9
nZnO	573.8	448.6–707.9	5.46×10^{-8}	5.71
bZnO	663.7	581.6–745.7	1.50×10^{-8}	6.75
nCuO	0.98	0.84–1.25	9.26×10^{-6}	1.61
nFe_2O_3	0.81	0.60–1.09	3.05×10^{-5}	1.36
$nTiO_2$	7215.2	3730.1–38142.7	1.45×10^{-19}	31.8
C_{60}	14918.3	3965.9–42272.1	3.84×10^{-22}	54.4
MWCNT	8708.0	5686.2–15449.8	N.A.	N.A.
GO	6562.6	6304.7–7109.7	N.A.	N.A.
$ZnCl_2$	175.2	147.7–191.3	N.A.	N.A.

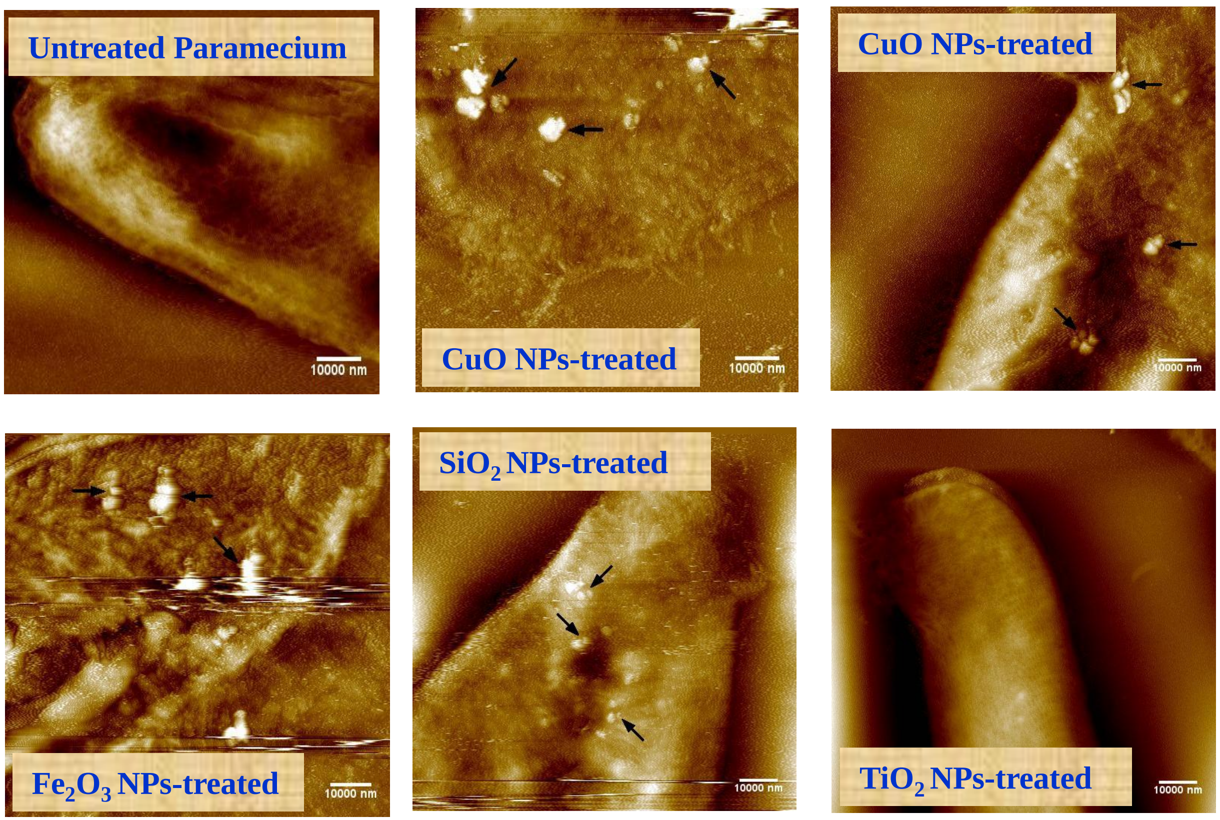
Tested NPs	Ion release ratio (%)
nAl_2O_3	0
$nCeO_2$	0
$nSiO_2$	0
nZnO	22.89 ± 0.07
bZnO	19.91 ± 0.23
nCuO	0.36 ± 0.04
nFe_2O_3	0
$nTiO_2$	0

Ion release may not govern the nanotoxicity

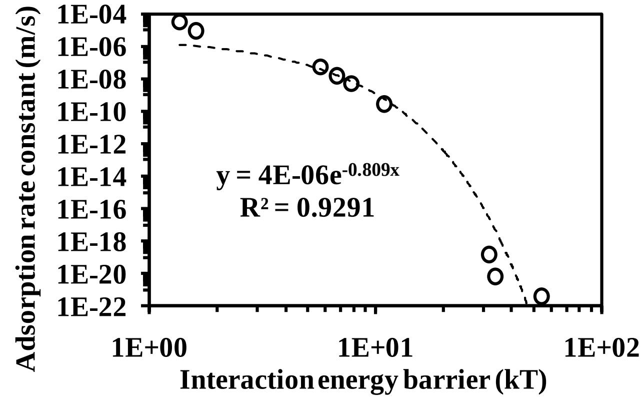


Adsorption rate constant of NPs to cell membrane may be used to pre-evaluate the toxicity of NPs

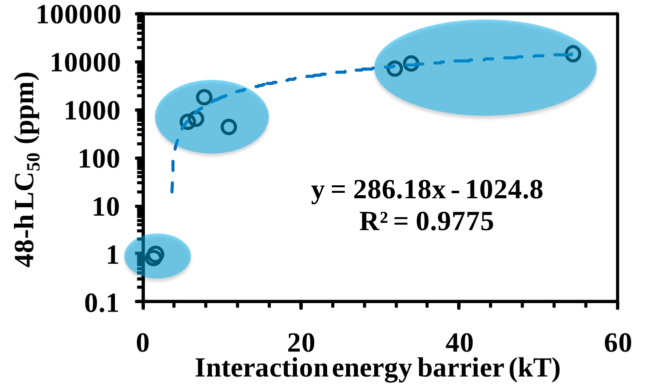
3.4. Preliminary indicator development for acute toxicity of ten engineered NPs to *paramecium*



Kungang Li, et al. *Environ. Toxicol. Chem.* Under review



Interaction energy barrier could be a substitution for adsorption rate constant



Interaction energy barrier is well related with the acute toxicity data

Industrial Interactions and Technology Transfer

- **Collect toxicity data of a variety of nanomaterials**
- **Develop models to evaluate and predict the toxicity of nanomaterials, which saves time and money that are invested on expensive conventional toxicity experiments**
- **Guide academia and industry to produce envionmental benign semiconductor nanomaterials, on the basis of analyzing physicochemical properties of nanomaterials**

Future Plans

Next Year Plans

- Continue toxicity tests with various typical cells (e.g., *bacteria and paramecium*) and semiconductor nanoparticles of high interest;
- Investigate the entry route of nanoparticles into cell, and evaluate the role of endocytosis and direct penetration
- Develop AFM-based imaging tools for assessing the genotoxicity of nanoparticles (e.g., the inhibition of DNA transcription by nanoparticles)

Long-Term Plans

- Accumulating sufficient data to categorize and prioritize relevant nanoparticles and their characteristics that are used for establishing robust and accurate predictive QSAR models.
- Provide fundamental information for manufacturing environmental benign semiconductor nanomaterials for industries.

Publications, Presentations, and Recognitions/Awards

Publications (Total 12: 8 published, 2 accept, and 2 submitted)

1. Kungang Li, Wen Zhang, Ying Huang, Yongsheng Chen. Aggregation kinetics of CeO_2 nanoparticles in KCl and $CaCl_2$ solutions: Measurements and modeling. *Journal of Nanoparticle Research.* 2011, 13, 6483
2. Kungang Li and Yongsheng Chen. Effect of natural organic matter on the aggregation kinetics of CeO_2 nanoparticles in KCl and $CaCl_2$ solutions: Measurements and modeling. *Journal of Hazardous Materials.* DOI: 10.1016/j.jhazmat.2012.01.013.
3. Wen Zhang, Ying Yao, Kungang Li, Ying Huang, Yongsheng Chen, "Influence of dissolved oxygen on aggregation kinetics of citrate-coated silver nanoparticles", *Environmental Pollution* , (2011), doi:10.1016/j.envpol.2011.07.013
4. Wen Zhang, Ying Yao, Nicole Sullivan, Yongsheng Chen,"Modeling the primary size effects of citrate-coated silver nanoparticles on their ion release kinetics", *Environmental Science and Technology*, 45(2011):4422-4428
5. Wen, Zhang, Bruce Rittman, and Yongsheng Chen, "Size effects on adsorption of hematite nanoparticles on Ecoli cells.", *Environmental Science and Technology*, 45 (2011): 2172–2178
6. Wen Zhang, Ying Yao, and Yongsheng Chen, "Imaging and Quantifying the Morphology and Nanoelectrical Properties of Quantum Dot Nanoparticles Interacting with DNA", *J. Phys. Chem. C*, 15 (2011): 599–606
7. Wen Zhang, Andrew G. Stack, and Yongsheng Chen,"Interaction Force Measurement between E. coli Cells and Nanoparticles Immobilized Surfaces with Using AFM", *Colloids and Surfaces B: Biointerfaces*, 82 (2011) 316–324
8. Wen Zhang, Madhavi Kalive, David G Capco, and Yongsheng Chen, "Adsorption of Hematite Nanoparticles onto Caco-2 Cells and the Cellular Impairments: effect of particle size", *Nanotechnology*, 21 (2010): 355103-35512
9. Wen Zhang, John Crittenden, Kungang Li, Yongsheng Chen. Attachment efficiency of nanoparticle aggregation in aqueous dispersions: Modeling and experimental validation. *Environmental Science and Technology.* Accepted.
10. Li, Yang; Zhang, Wen; Li, Kungang; Yao, Ying; Niu, Junfeng; Chen, Yongsheng, " Oxidative Dissolution of Polymer-Coated CdSe/ZnS Quantum Dots under UV Irradiation: Mechanisms and Kinetics ", *Environmental Pollution*, (2011), accept
11. Kungang Li, Ying Chen, Wen Zhang, Zhichao Pu, Lin Jiang, Yongsheng Chen. Preliminary indicator development for acute toxicity of ten engineered nanoparticles to *paramecium*. *Environmental Toxicology and Chemistry.* submitted.
12. Wen Zhang, Joseph Hughes, and Yongsheng Chen, "Impacts of Hematite Nanoparticle Exposure on Biomechanical and Surface Electrical Properties of E. coli Cells", *Applied and Environmental Microbiology*, (2011), submitted

Presentation

During year 2008-2010, Wen Zhang attended and made oral presentations in 8 national conferences, including ASM, ACS, USEPA grantees meetings, ICEIN, SRC, IENC, and etc.

Award

Wen Zhang, Recipient of Simon Karecki Award 2011