Nanomagnetism and Magnetic Nanoparticles for Biomedical Application

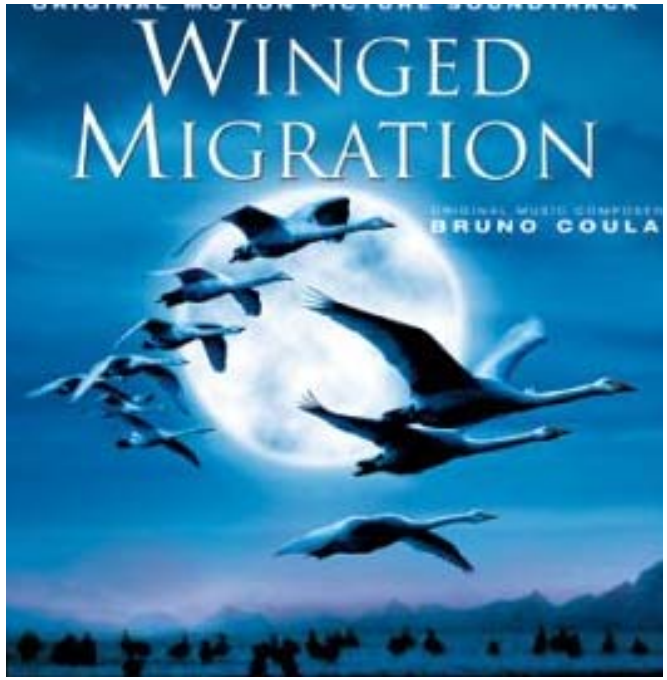
You Qiang*, Amit Sharma, Jiji Antony, Alan McConnaughey, Ryan Souza and Yufeng Tian

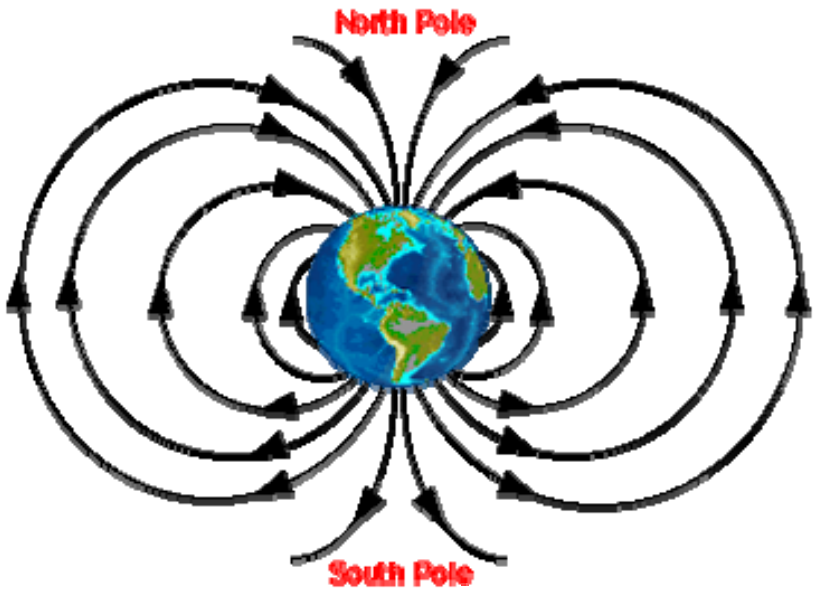
Department of Physics,
University of Idaho, Moscow, ID 83844-0903

**Corresponding author: E-mail: youqiang@uidaho.edu,*
Telephone: (208) 885-7558, Fax: (208) 885-4055

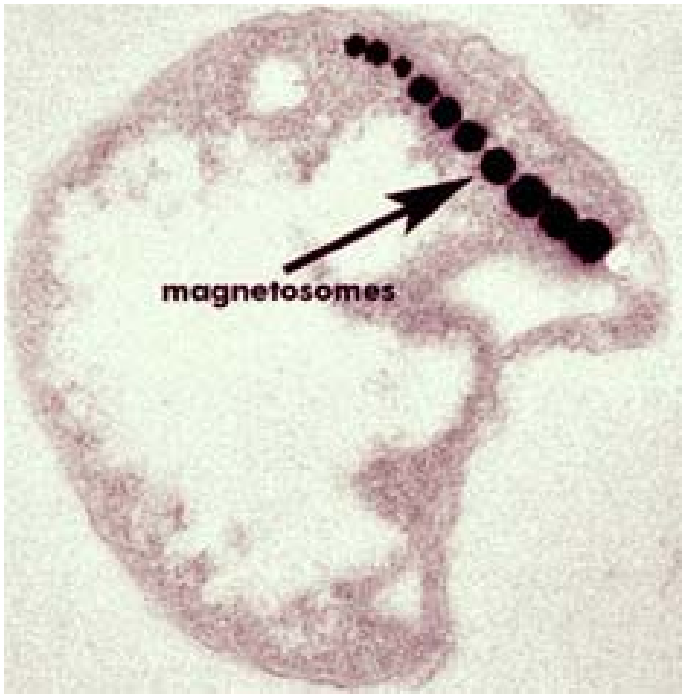
IMR Shenyang Summer School July 9-10, 2008

University of Idaho
Tradition. Change. Excellence.

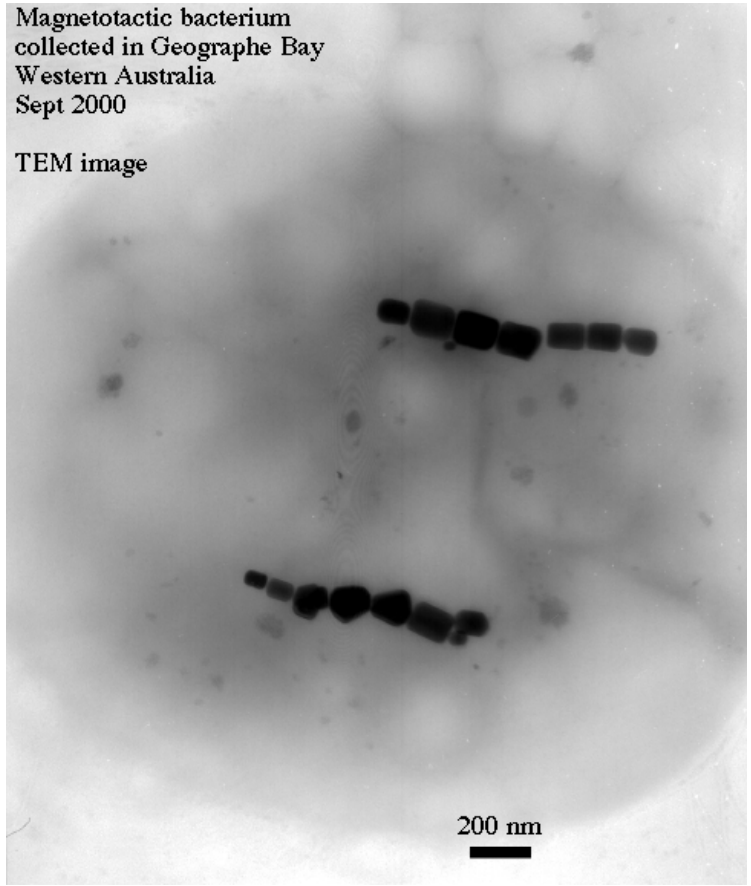




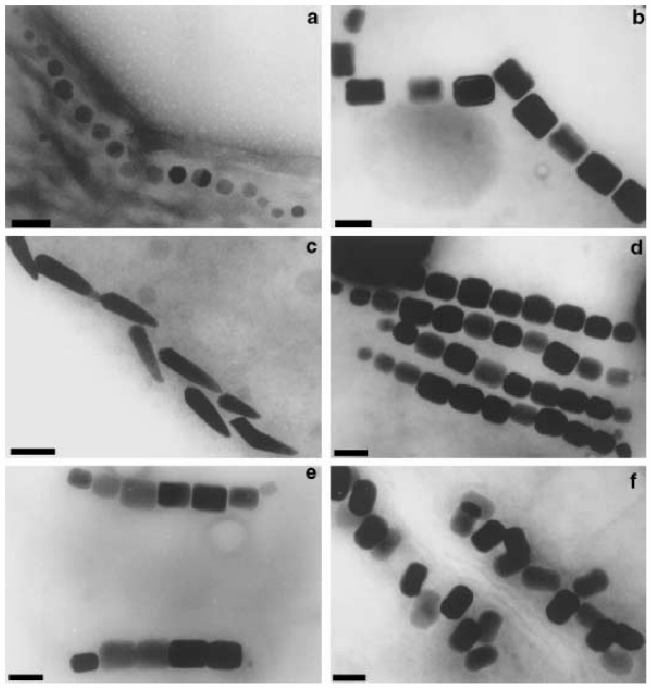
University of Idaho
Tradition. Change. Excellence.



Magnetococcus-MC-1



University of Idaho
Tradition. Change. Excellence.


a
b
c
d
e
f


3 J's Loft
"Silverado"
CU 32567/98
Sire of BK 310
7th Le Tour 1999

Table 1. Examples of organisms synthesizing magnetic nanoparticles (MNP)

Type of organism	General name	Latin name	Localisation of MNP	Type of MNP
Micro-organisms	Magnetotactic bacteria	*Magnetospirillum sp.*	magnetosomes	Fe_3O_4
			magnetosomes	Fe_3S_4
	Algae		cells	Fe_3O_4
Protozoa			cells	Fe_3O_4
Insect	Honeybee	*Apis mellifera*	abdomen	Fe_3O_4
	Migratory ant	*Pachycondyla marginata*	abdomen	Fe_3O_4
	Termites	*Nasutitermes exitiosus*	thorax, abdomen	Fe_3O_4
		Amitermes meridionalis	thorax, abdomen	Fe_3O_4
Fish	Atlantic salmon	*Salmo salar*	lateral line	Fe_3O_4
	Sockeye salmon	*Oncorhynchus nerka*	skull	Fe_3O_4
	Rainbow trout	*Oncorhynchus mykiss*	olfactory lamellae	Fe_3O_4
	Chum salmon	*Oncorhynchus keta*	head	Fe_3O_4
Amphibians	Eastern red-spotted newt	*Notophthalmus viridescens*	whole body	Fe_3O_4
Birds	Bobolink	*Dolichonyx oryzivorus*	upper beak	Fe_3O_4
	Homing pigeon	*Columba livia*	upper-beak skin	Fe_3O_4
Mammals	Common Pacific dolphin	*Delphinus delphis*	dura mater	Fe_3O_4
	Human	*Homo sapiens*	brain, heart	Fe_3O_4

Magnetite

MNPs for biomedical applications

1. Biological labels
2. Drug and gene delivery
3. Bio detection of pathogens
4. Detection of proteins
5. DNA Probing
6. Tumor destruction via heating (hyperthermia)
7. Separation and purification of molecules and cells
8. MRI contrast enhancement

University of Idaho
Tradition. Change. Excellence.

Bio-Magnetism

- **These applications require that MNPs be superparamagnetic at room temperature, high magnetic moment and monodispersive.**
- **Most magnetic particles or beads used in biomedical applications are based on ferromagnetic iron oxides with low magnetic moment (20 to 50 emu/g), and polydispersive.**
- **Our newly developed nanocluster source can synthesize monodispersive, high magnetic moment core-shell structured nanoparticles for biomedical applications.**

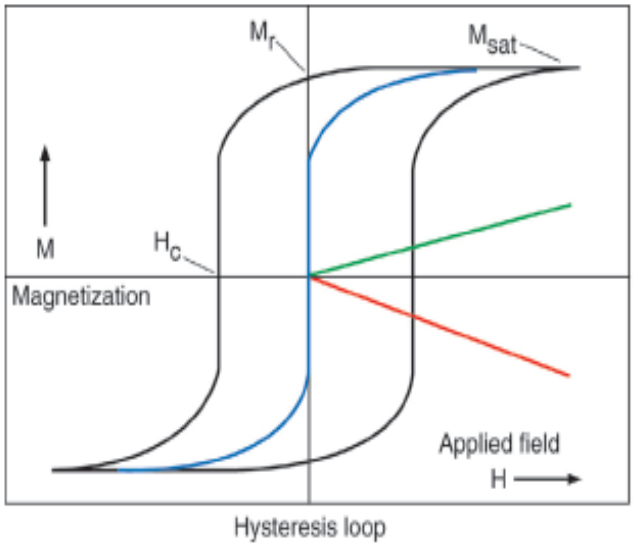
Table 2. Examples of commercially available biocompatible magnetic nanoparticles

Product name	Composition	Particle size (nm)	Application	Manufacturer or supplier
Combidex	Magnetic iron oxides – dextran	17–20	Magnetic resonance contrast agent	Advanced Magnetics, USA
Endorem[a]/ Feridex[b]	Magnetic iron oxides – dextran	100–250	Magnetic resonance contrast agent	Advanced Magnetics, USA
MicroBeads	Magnetic iron oxides – dextran	50	Separation and labelling of cells and molecules	Miltenyi Biotec, Germany
Nanomag	Magnetic iron oxides – dextran	100	Magnetic labelling	Micromod Partikeltechnologie, Germany
Resovist	Magnetic iron oxides – dextran	57	Magnetic resonance contrast agent	Schering AG, Germany

[a] Commercial product name in Europe; [b] commercial product name in the United States

Problem:

- **Small specific magnetic moment (m_s) < 50 *emu/g*,**
- **Large size distribution**
- **Aggregation in solutions**



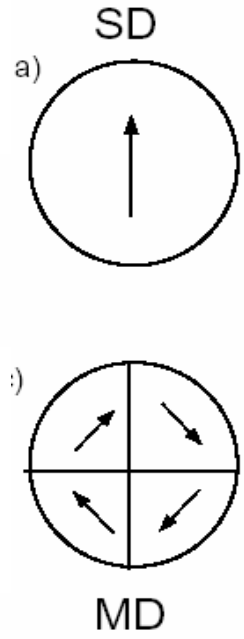
M_{sat} = Saturation magnetization

M_r = Remanence magnetization

H_C = Coercive field

— Ferromagnetism
— Diamagnetism
— Paramagnetism
— Superparamagnetism

$$D_c = \frac{9\gamma}{2\pi M_s^2} \cong 1.44\frac{\gamma}{M_s^2}$$



For Co and Fe nanoparticles:
$D_c \sim 30$ nm
$D_{sp} \sim 8$ - 12 nm

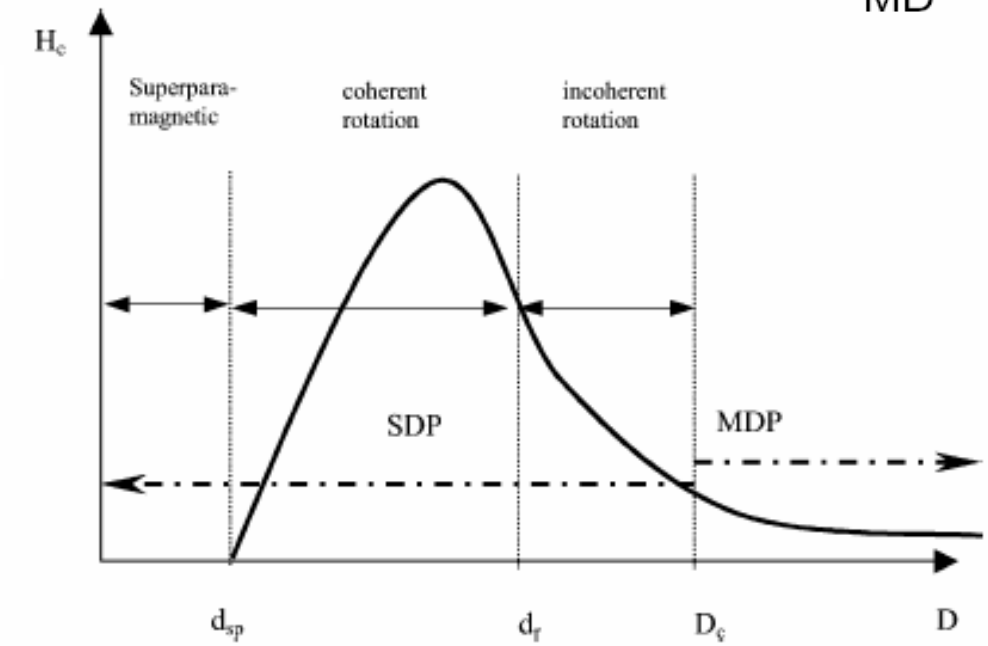
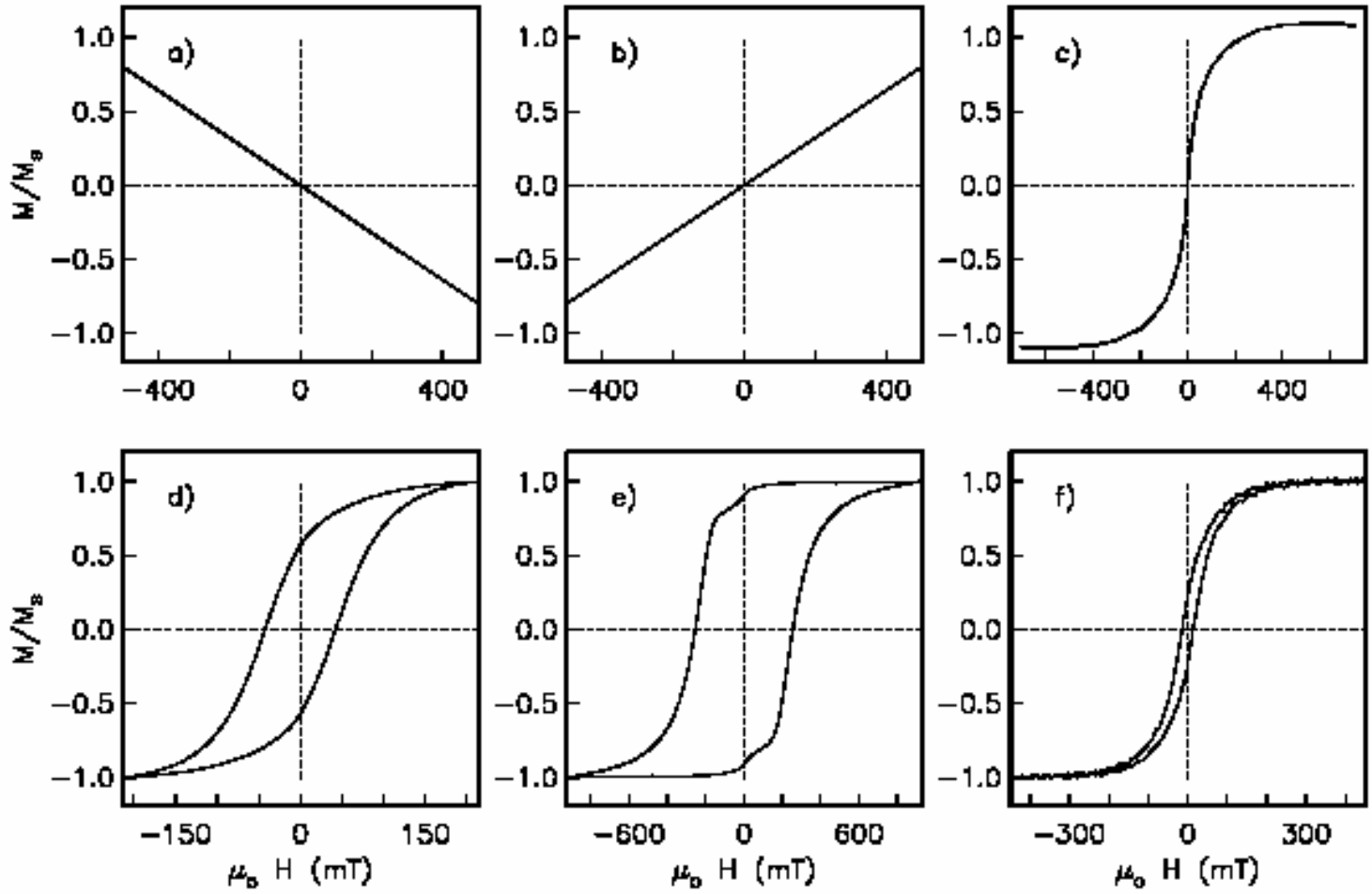
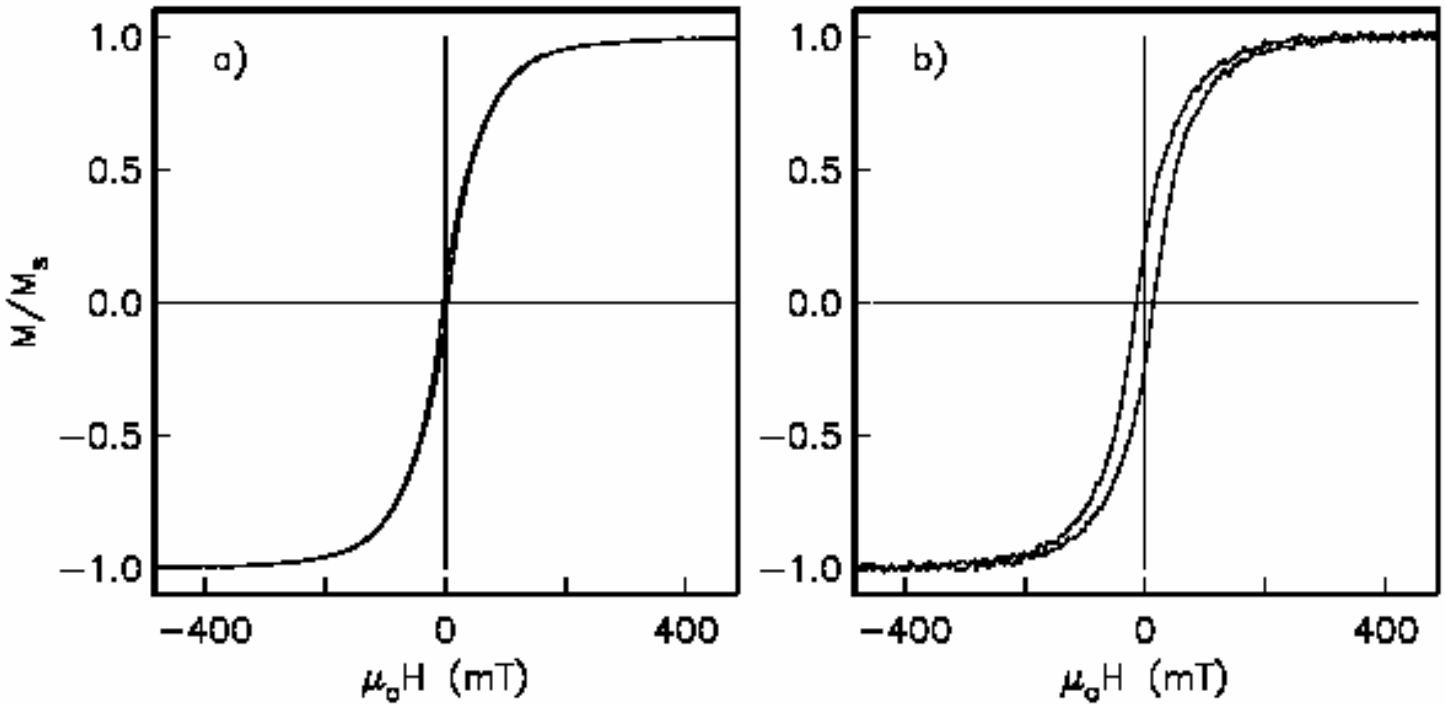


Fig. 1. A schematic qualitative relation between the coercivity and the magnetic grain size.



Diamagnetic, Paramagnetic, and Ferromagnetic Materials

University of Idaho
Tradition. Change. Excellence.



$T > T_b$, $H_c = 0$ $\quad\quad$ $T < T_b$

Superparamagnetic behavior

University of Idaho
Tradition. Change. Excellence.

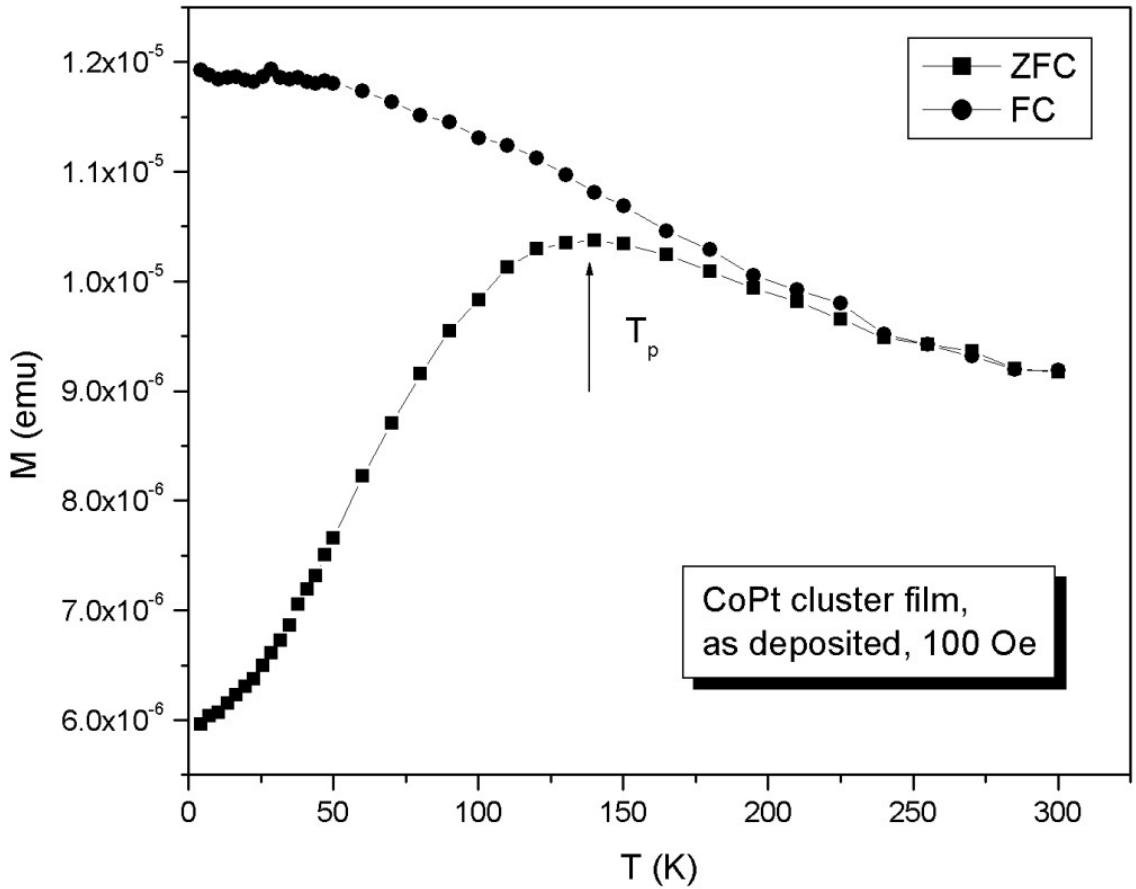
MPMS XL7 SQUID System, Quantum Design Inc

- **Magnetic field: 7 T**
- **Temperature: 1.5 – 400 K**
- **Sensitivity: 1 x 10^{-8} emu**

Supported by NSF Idaho-EPSCoR

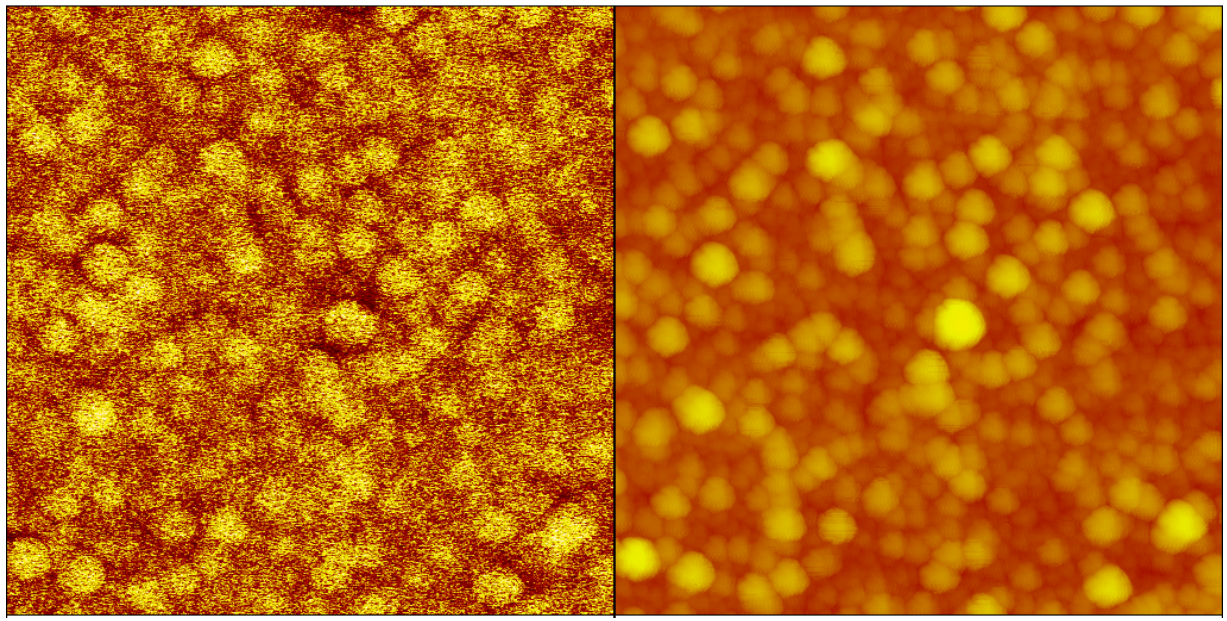
University of Idaho
Tradition. Change. Excellence.

ZFC and FC measurements



University of Idaho
Tradition. Change. Excellence.

MFM AFM

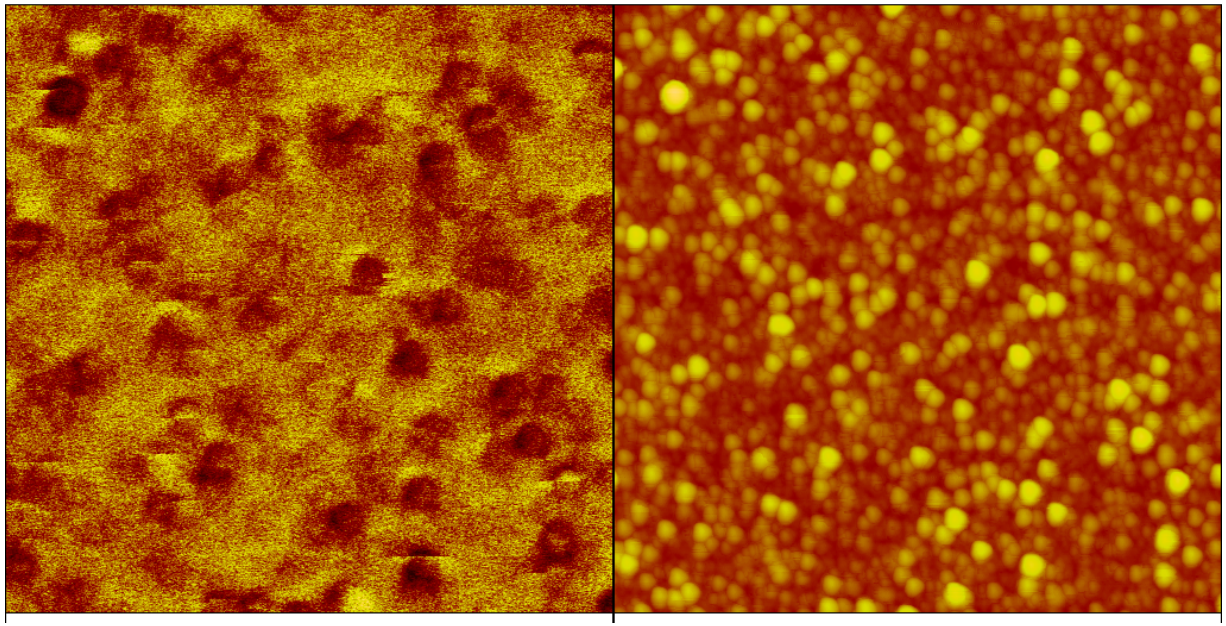


0 500 nm

As deposited

University of Idaho
Tradition. Change. Excellence.

MFM AFM

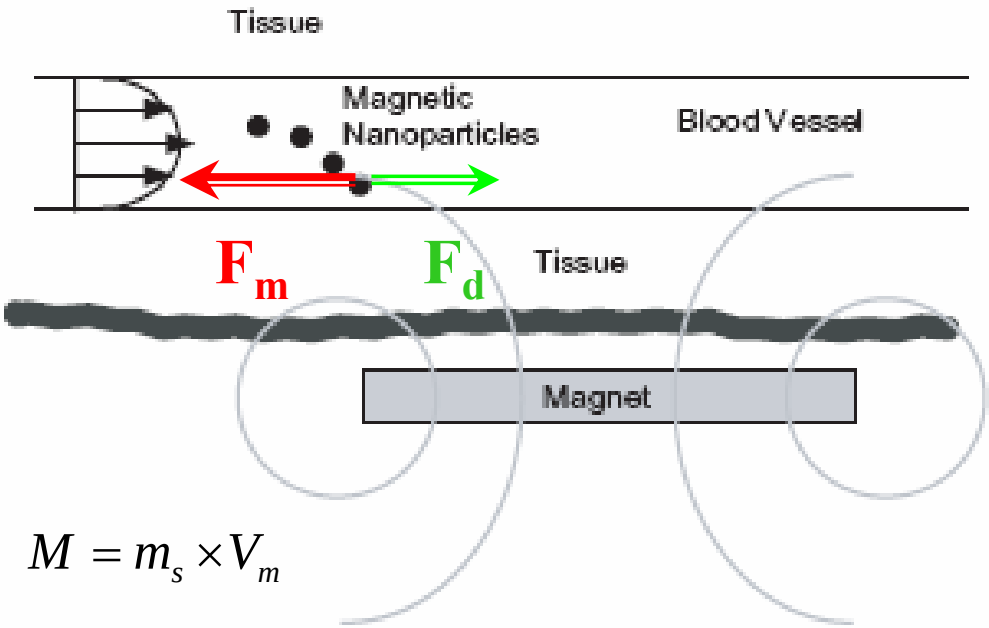


0 1000 nm

After magnetization, 10 kOe, in plane

University of Idaho
Tradition. Change. Excellence.

Magnetic Drug Delivery



$M = m_s \times V_m$

F_m (magnetic force) >> F_d (drag force)

$M = m_s \times V_m$

$F_m \sim f(M \text{ and } \Delta B)$
$= f(m_s, V_m \text{ and } \Delta B)$

V_m and ΔB as small as possible, m_s as large as possible

$F_d \sim f(\eta, V_m \text{ and } \Delta v)$

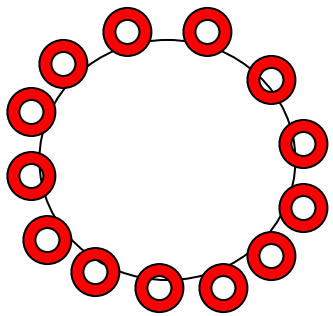
University of Idaho
Tradition. Change. Excellence.

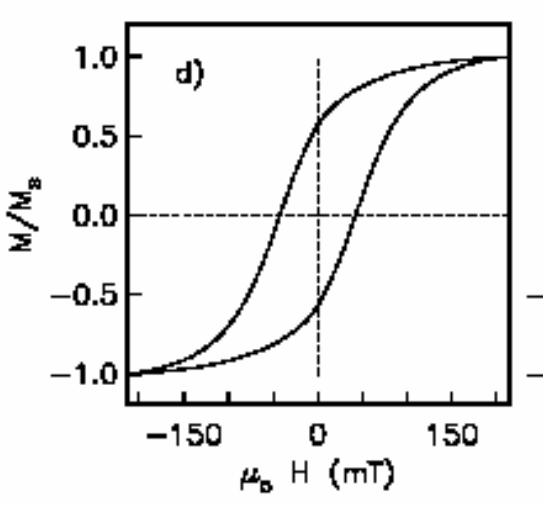
Hyperthermia

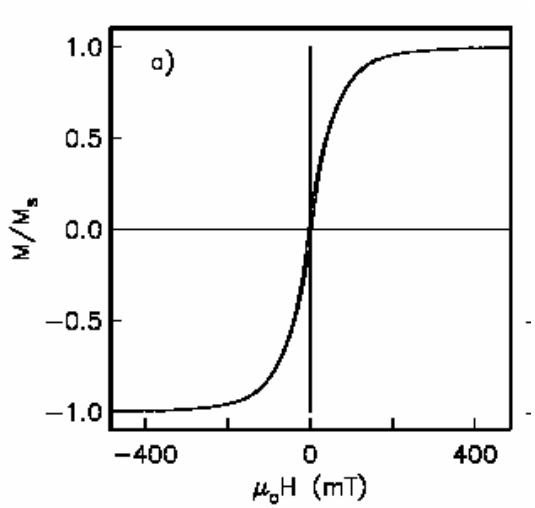
A new way to treat cancer

The amount of heat generated per unit volume in NP is given by:

$$P_{FM} = \mu_0 f \oint H dM \qquad P_{SPM} = \mu_0 \pi f \chi'' H^2$$







Frequency and magnetic moment dependence

University of Idaho
Tradition. Change. Excellence.

Fe is not stable in many environments. What is new at the nanoscale?

Nanoparticles

Properties vary with:

- **Size**
- **Shape**
- **Impurity**
- **Time (stability)**
- **Environment**

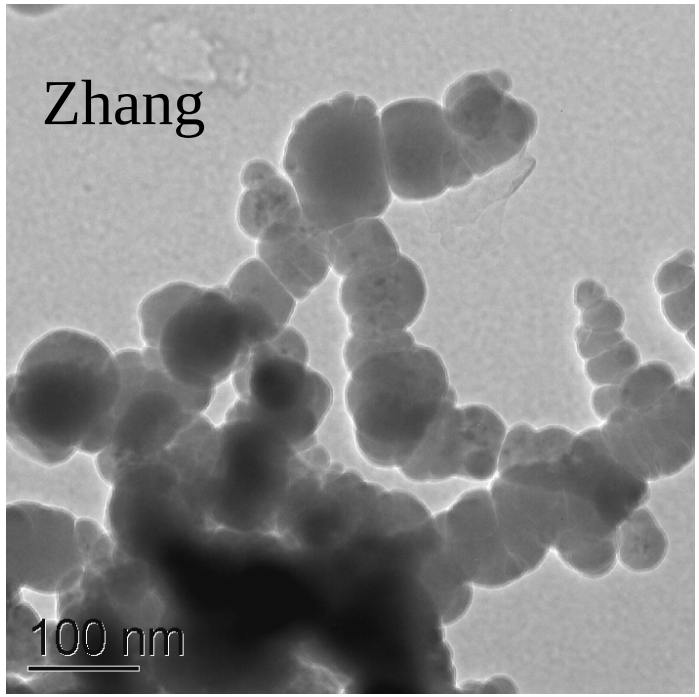
Nanoparticle Synthesis

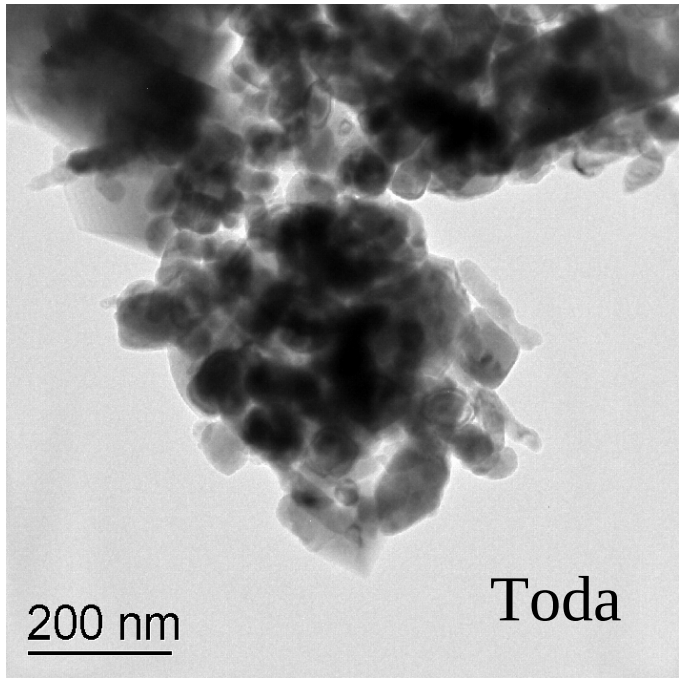
a) **Sol-Gel : gelation, precipitation, and hydrothermal treatment**
   - *i. Borohydride reduction (Zhang Nano Fe)*
   - ii. Inverted micelles
   - iii. Polymer matrix architecture, block copolymers, Polymer blends
   - iv. Porous glasses
   - v. Ex-situ particle capping

b) **Gas phase : nucleation and growth**
   - i. combustion flame
   - ii. plasma
   - iii. laser ablation
   - iv. chemical vapor condensation
   - v. spray pyrolysis, Electrospray, plasma spray

c) **Other Synthesis Strategies**
   - *i. Sonochemical (Toda)*
   - ii. Cavitation
   - iii. Microemulsion
   - iv. High energy ball milling

Two Fe nanoparticles used in remediation testing





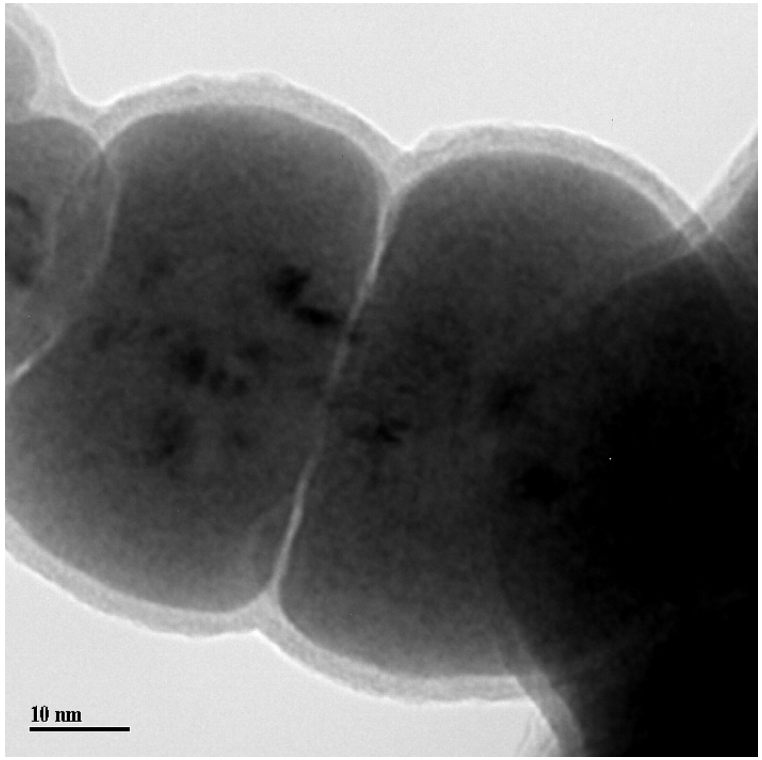
1: From W. Zhang, Lehigh University

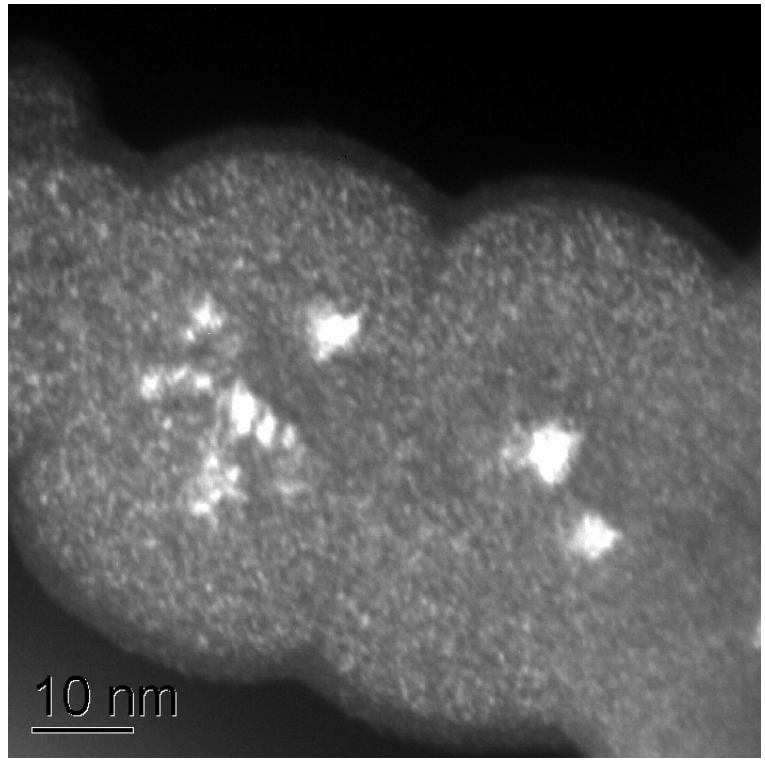
Borohydride reduction

1.6 M $NaBH_4$ (aq) to 1.0 M $FeCl_3*6H_2O$ solution.

2: From Toda Kogyo Inc, NIZ 100 Reactive Nanoscale Iron Particles.

Sonochemical processing, Ferrous ion precipitated with NaOH?





Zhang-. Bright- and dark field images. Note the core-shell Structure as well internal structures

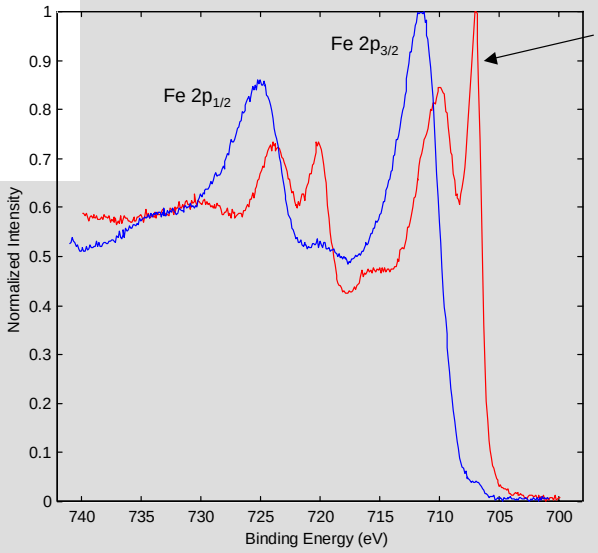
Each particle is composed of ordered atom clusters!

XPS Analysis	B1s	C1s	O1s	Na1s	S2p	Fe2p
Atomic %	14.31	10.35	44.03	12.94	0.46	17.92

University of Idaho
Tradition. Change. Excellence.

Instability

XPS photoemission spectra of the Fe 2p region
Zhang Fe nano-particles

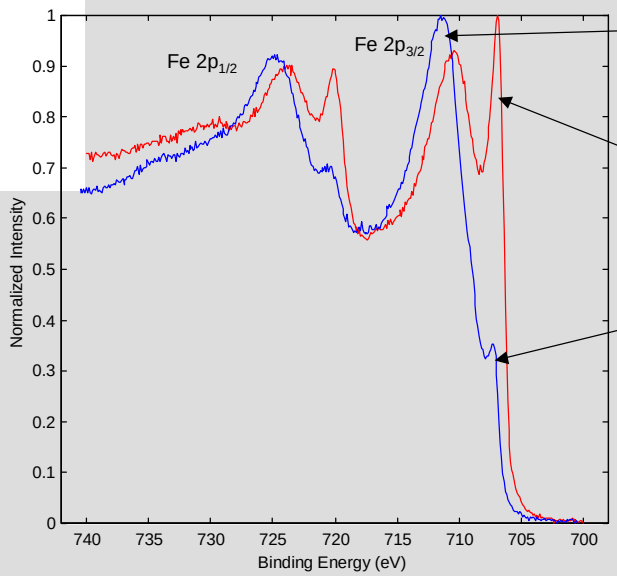


Red: Fe^0 @ 707 eV
Glove bag mounted specimen <30 ppm O_2

Blue: 711.6 eV
Air exposed for <5 minutes.

Carbon 1s reference at 285.4 eV for the oxidized sample

XPS photoemission spectra of the Fe 2p region
Toda Fe nano-particles



Blue: 711.4 eV
Air exposed for <5 minutes.

Red: Fe^0 @ 706.9 eV
Glove bag mounted specimen <30 ppm O_2

Blue: Fe^0 707.3 eV
Air exposed for <5 minutes.

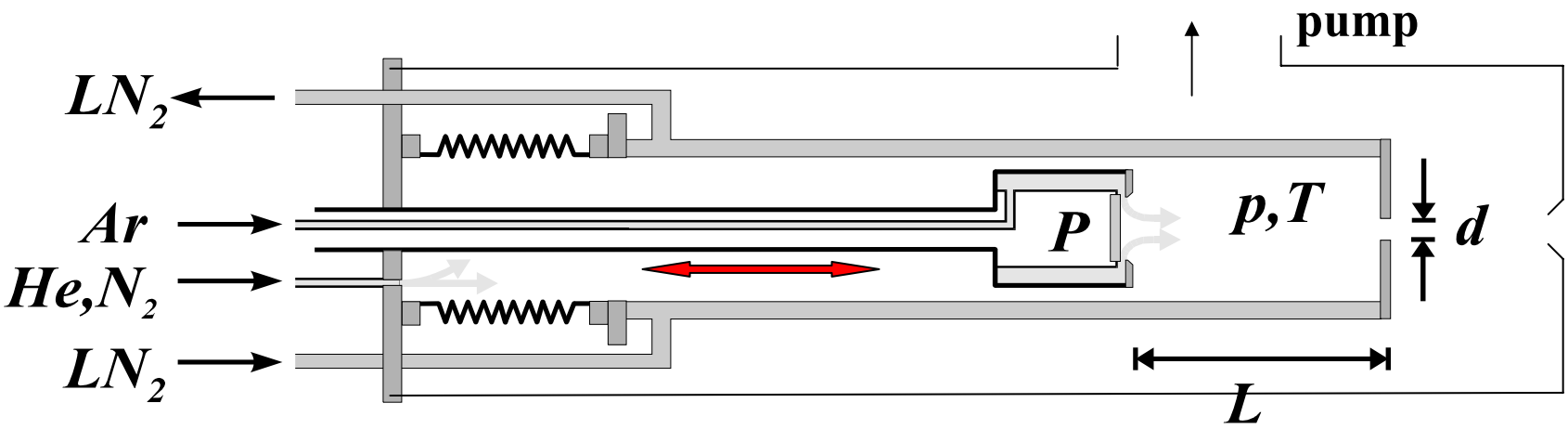
Carbon 1s reference at 285.4 eV for the oxidized sample

Zhang: the disappearing of the surface layer with time under electron beam for ~ 10 min in vacuum and 5 min in air.

Toda: Oxide shells disappeared in air about 5 min.

University of Idaho
Tradition. Change. Excellence.

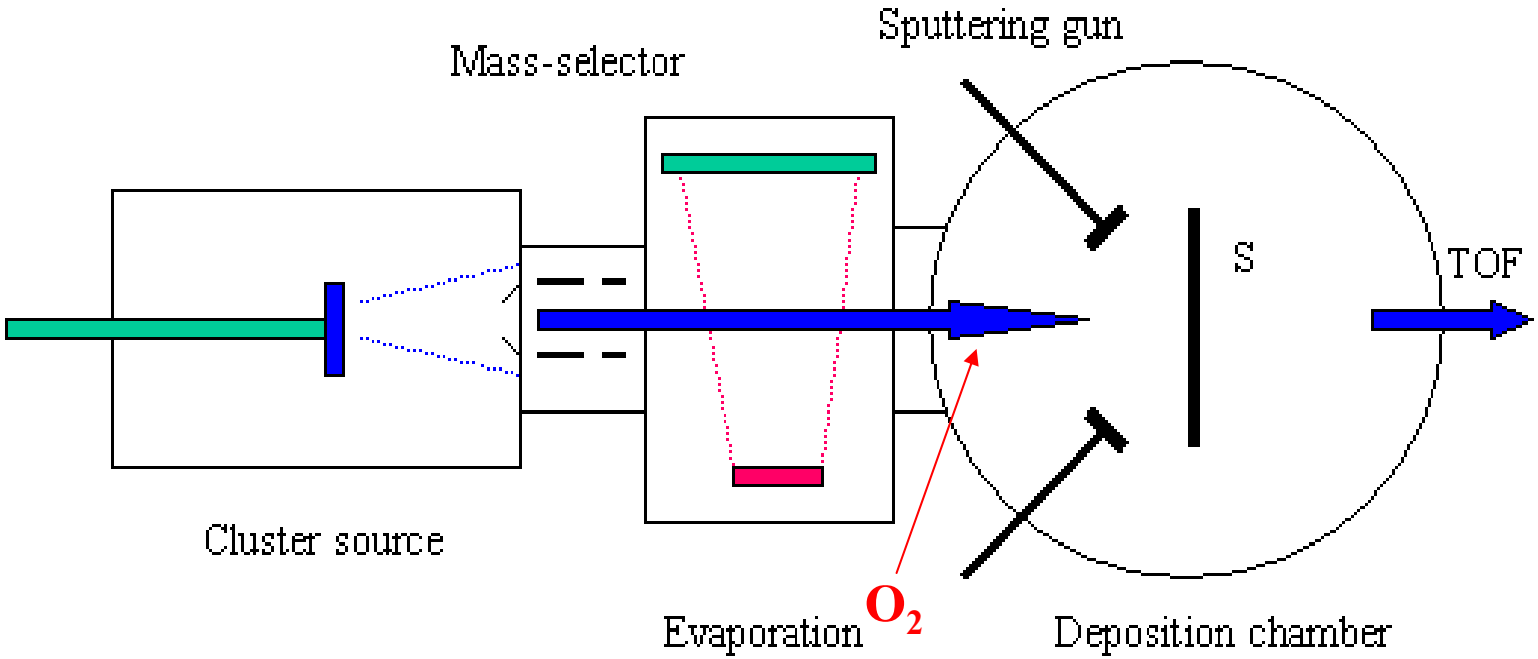
Sputtering-Gas-Aggregation Source



- Deposition rate > 5 Å/s,
- Ionization rate > 60%, (35% positive charged ion, 30% negative charged ion for Cu clusters),
- Controlled size range 1 to 100 nm

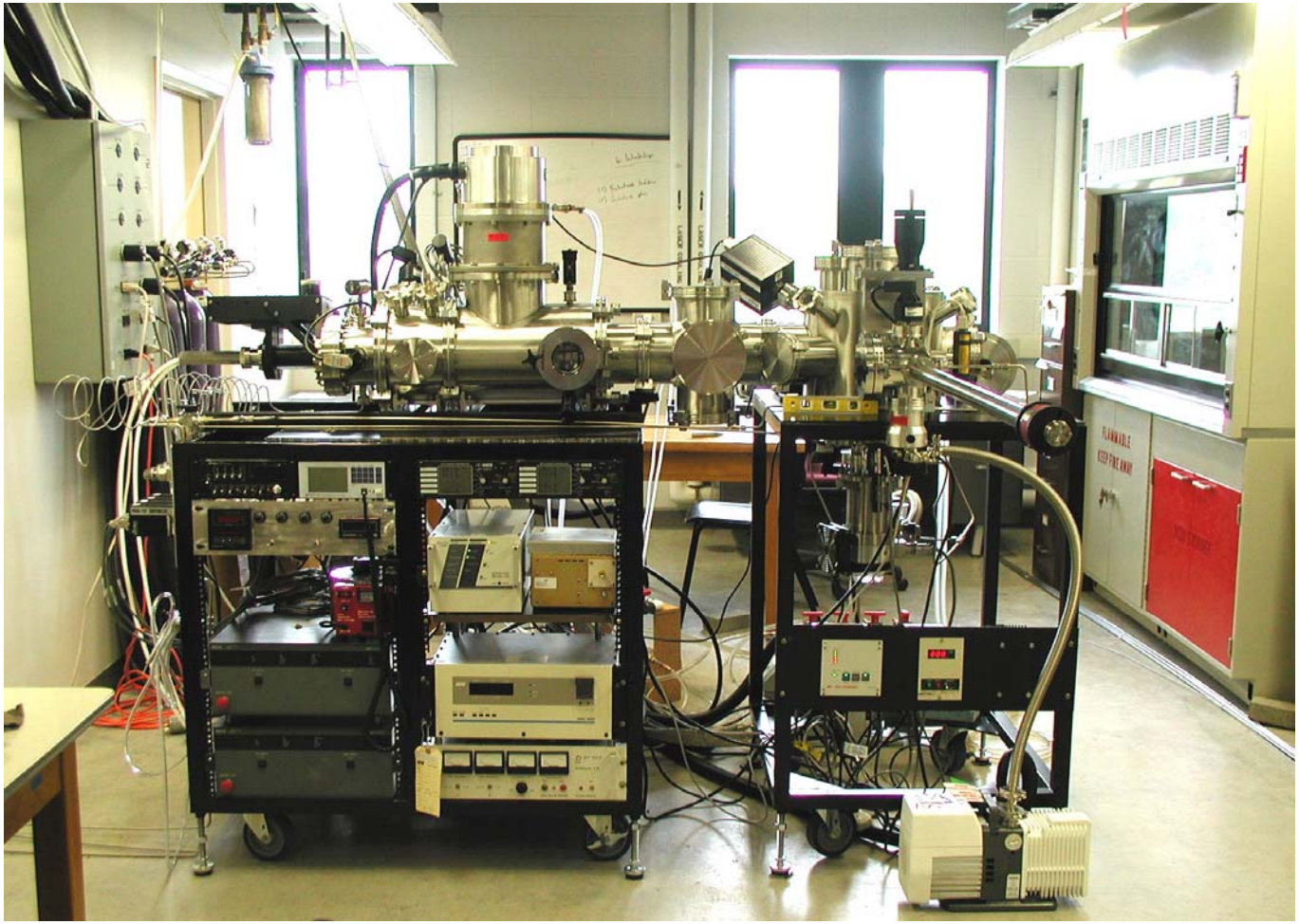
University of Idaho
Tradition. Change. Excellence.

Cluster Deposition System

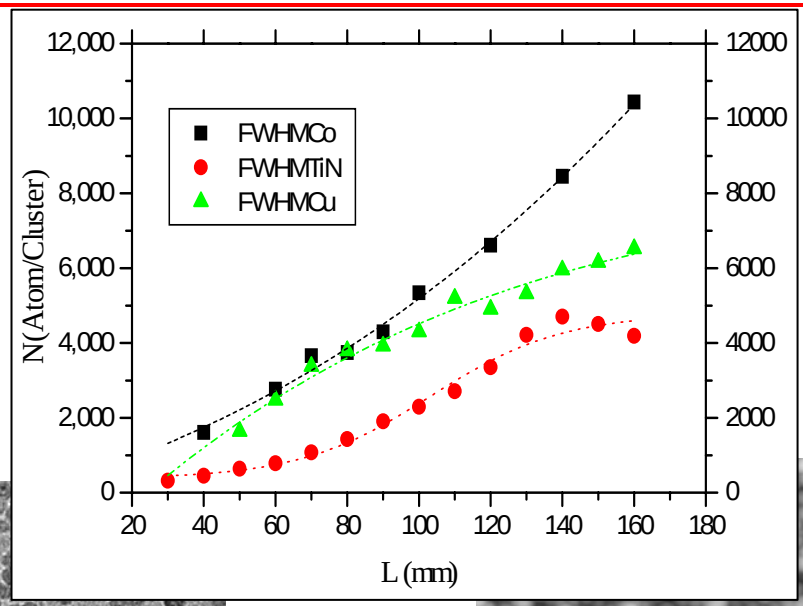


- Cluster size: D = 1 to 100 nm
- Materials: Co, Fe, Ni, Ag, Al, Cu, Mg, Mo, ZnO
  Si, Ti, CoPt, FePt, TiN, TiAlN, Al_2O_3

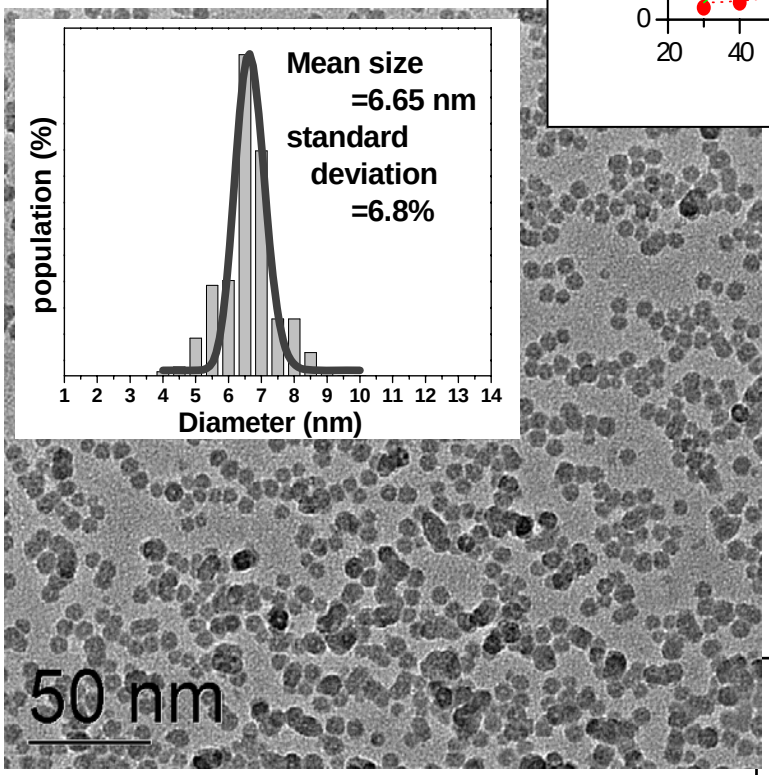
Cluster Deposition System



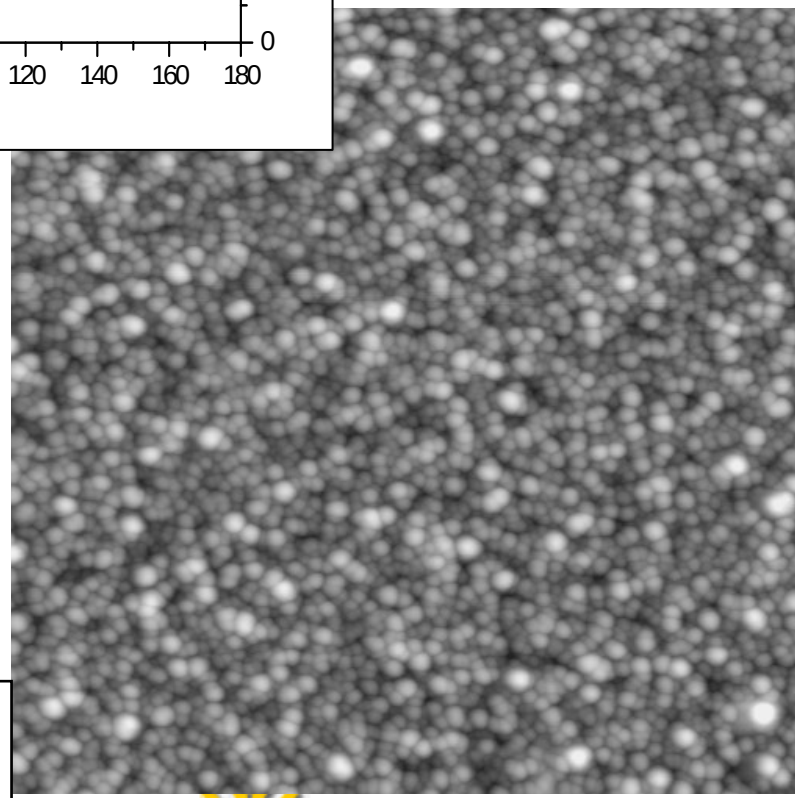
Nanoclusters and Size Distribution



TEM



AFM



Iron-iron oxide NPs

History of SGA Cluster Source

1st **generation, University of Freiburg, 1994, ~ 0.1 mg/h**

2nd **generation, University of Nebraska-Lincoln, 2000, ~ 1 mg/h**

3rd **generation, University of Idaho, 2002, ~20 mg/h**

4th **generation (testing), University of Idaho, 2007, ~2 g/h**

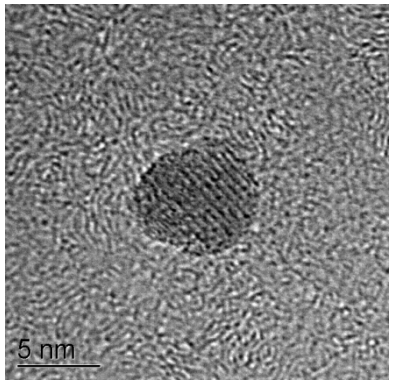
.

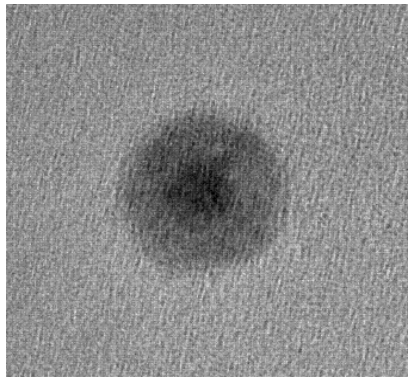
.

.

Nth **generation, 200?, up to kg/h**

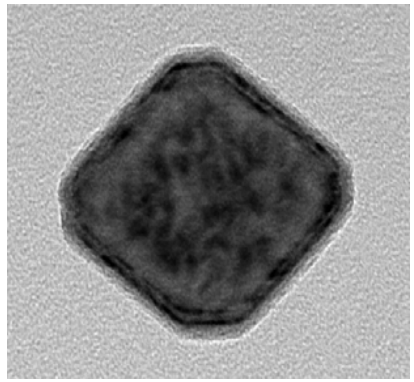
Core-Shell (Fe/Fe Oxide) Nanoparticles





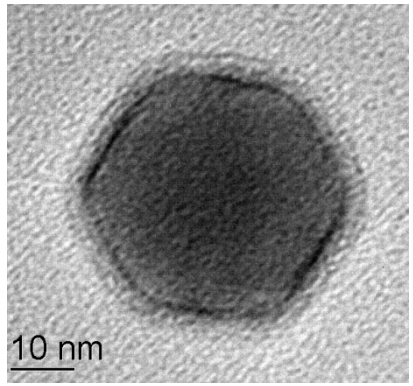
sphere

5 nm



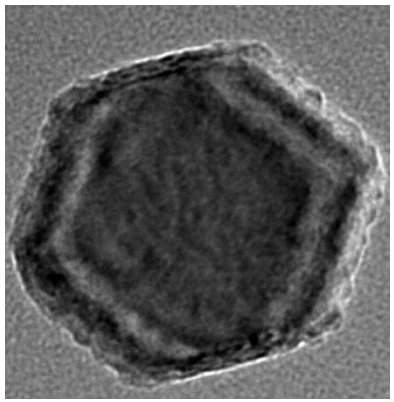
tetrahedron

25 nm

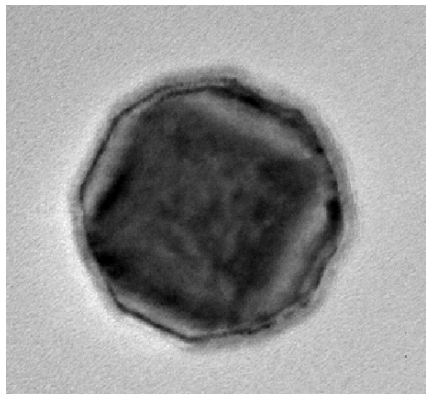


hexahedron

35 nm

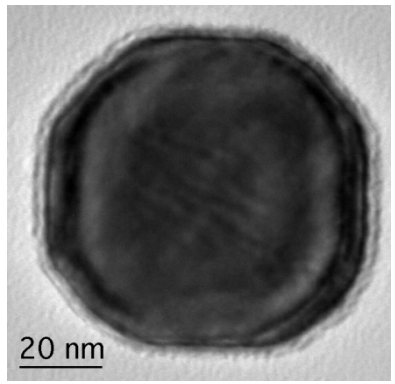


50 nm



octahedron

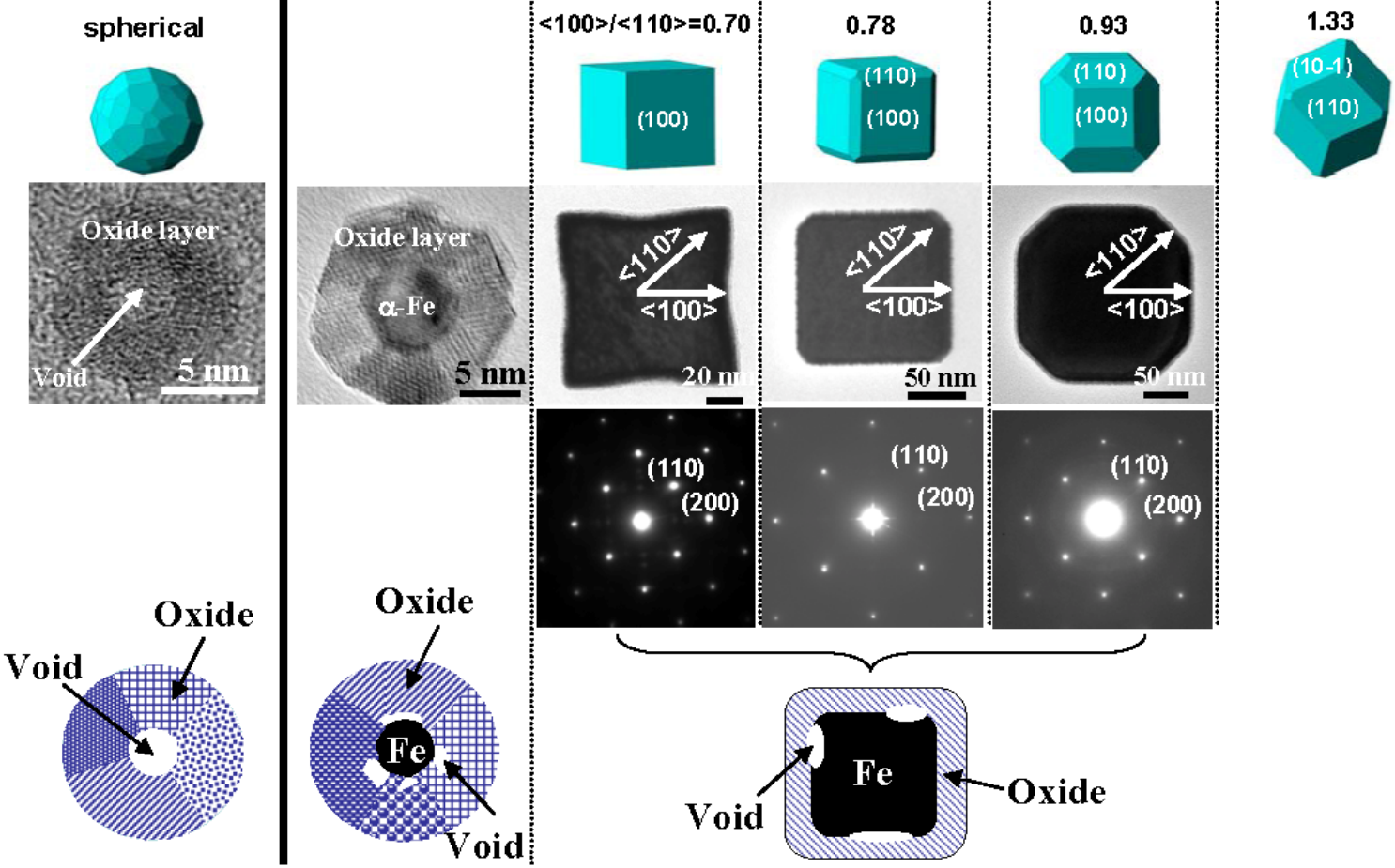
70 nm



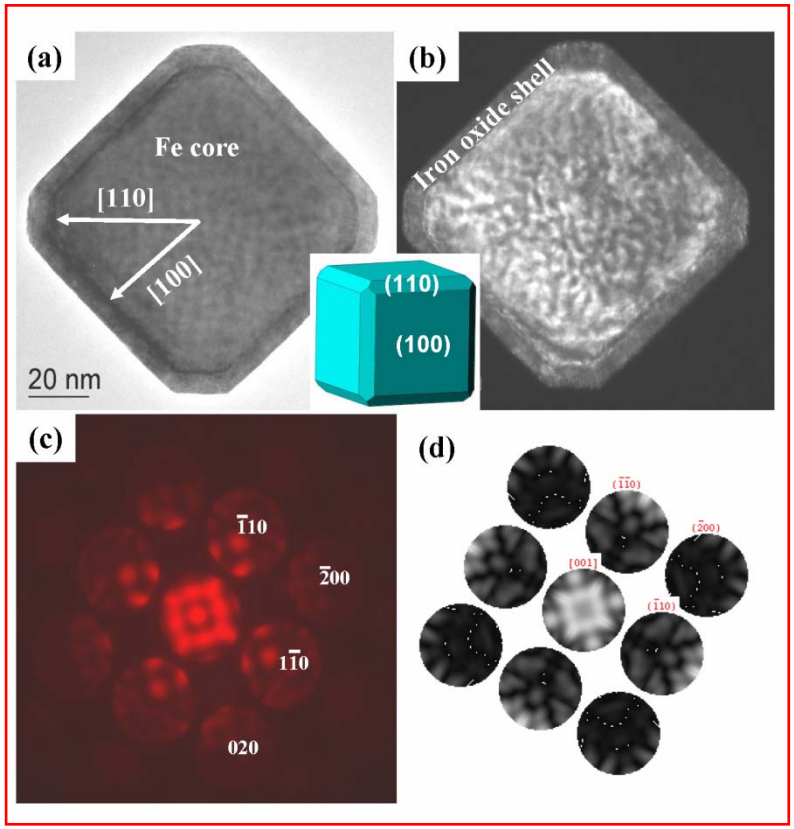
81 nm

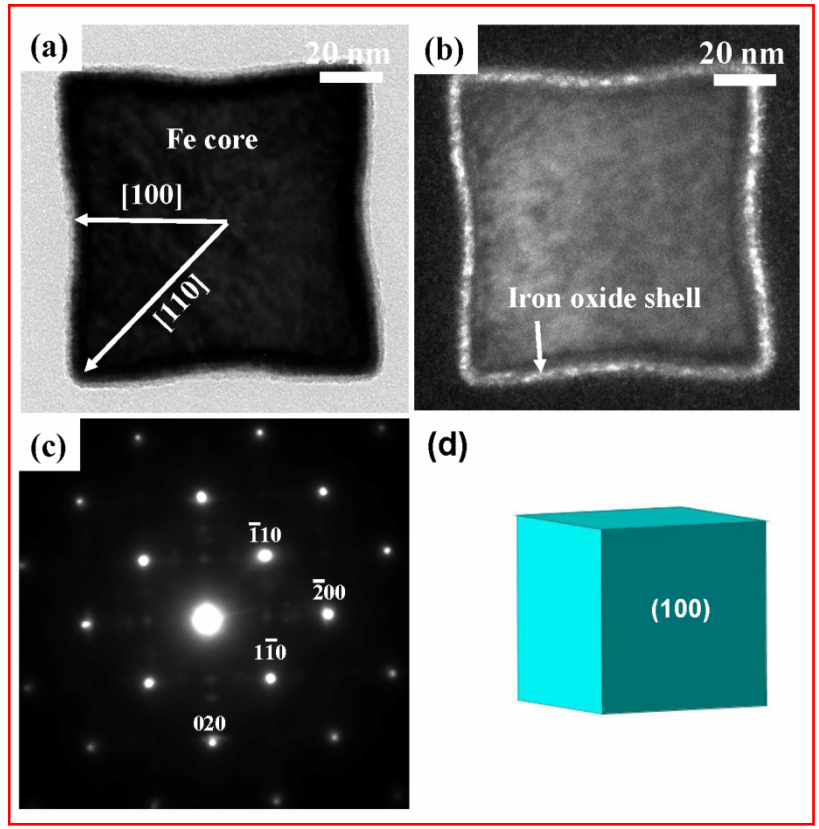
University of Idaho
Tradition. Change. Excellence.

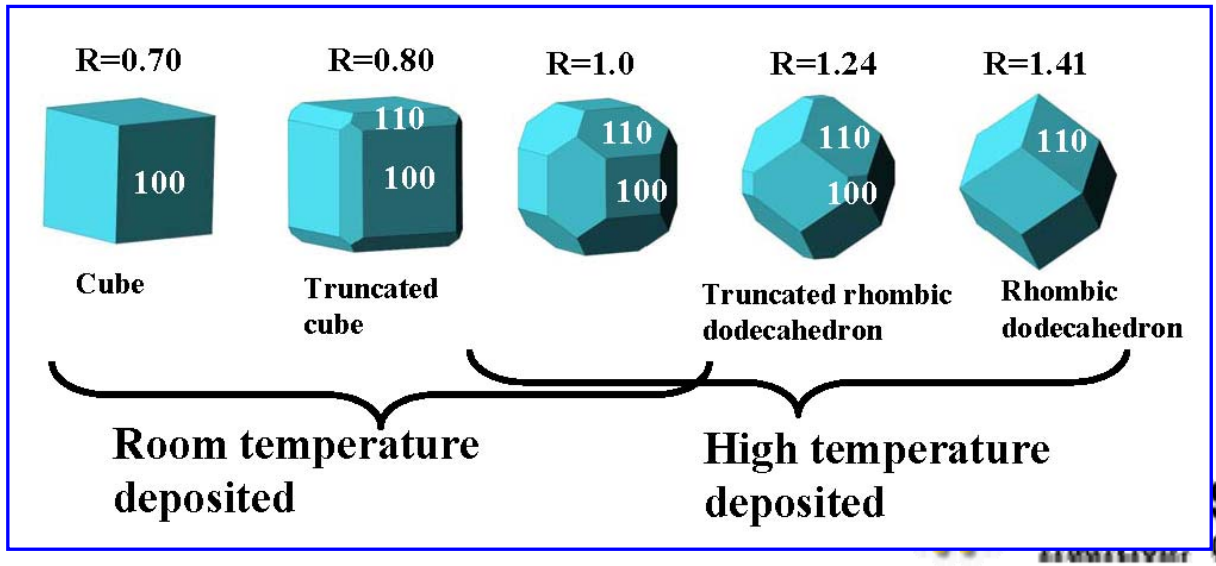
Size < ~ 8 nm Fully oxidized	Size > ~ 8 nm Forming core-shell structure with the oxide shell thickness ~ 3 nm Faceted at {100} and {110} planes



University of Idaho
Tradition. Change. Excellence.

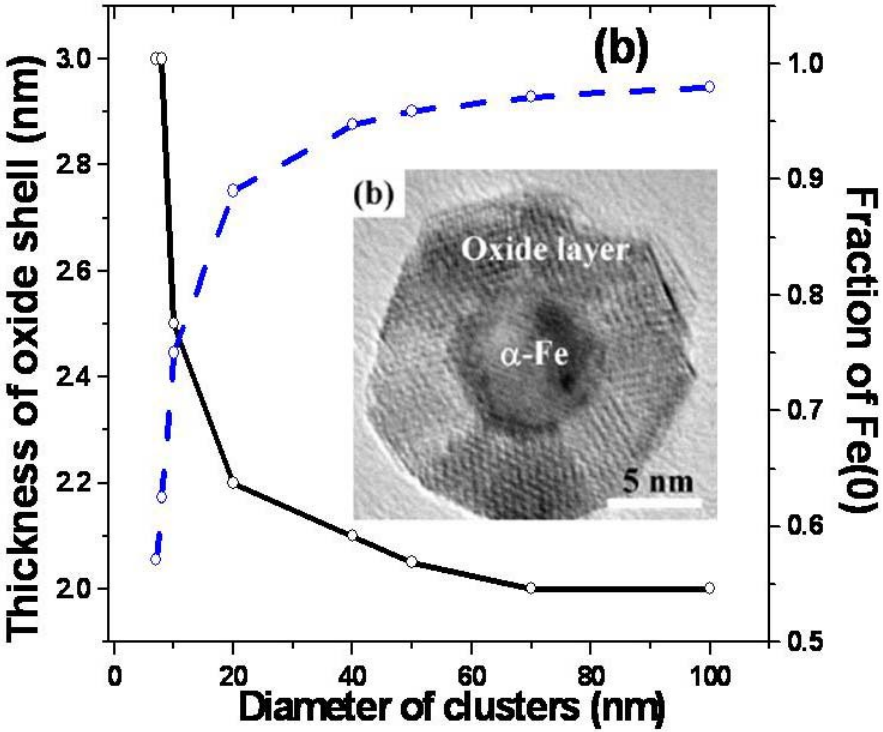


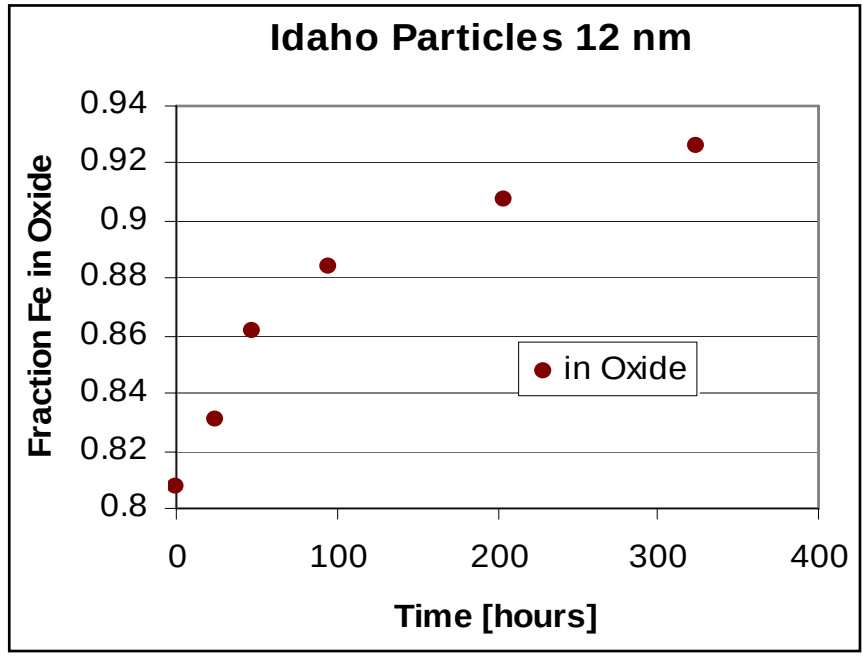




sity of Idaho
Change. Excellence.

Nanoparticle Stability and Aging

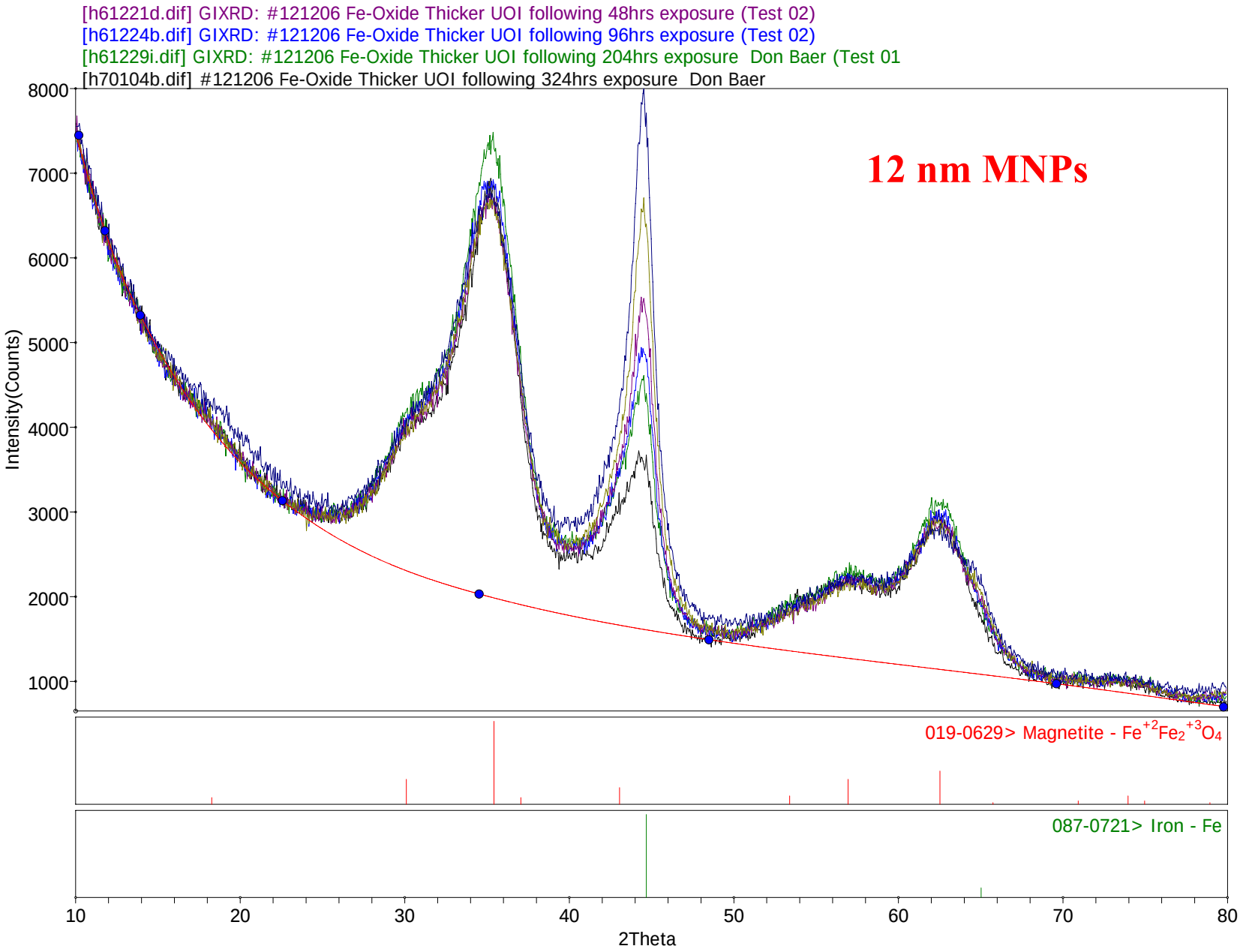




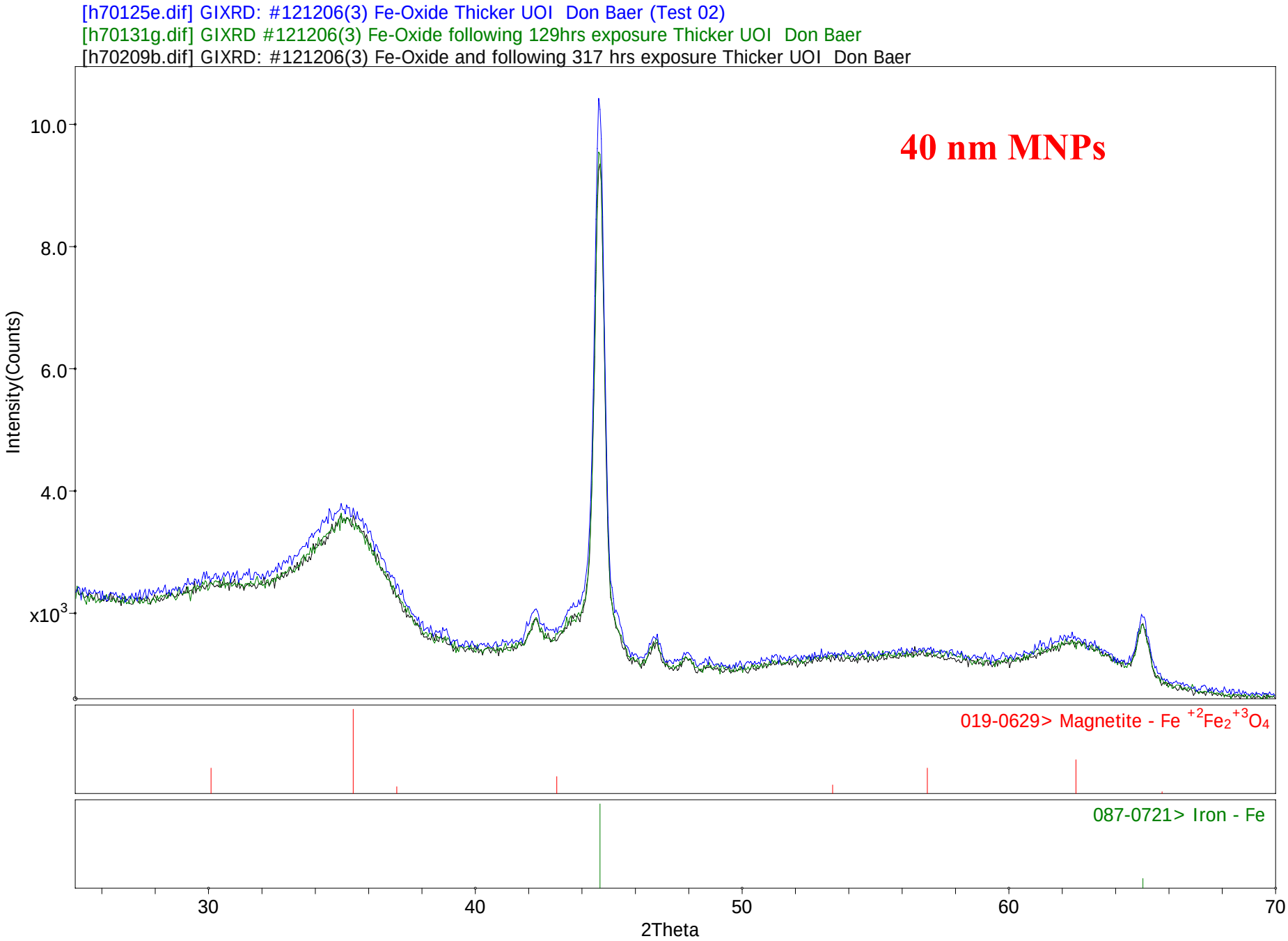
Oxide shell thickness increases for small nanoparticles. no pure Fe core for d < 6 nm. No change in air about 6 months.

Aging process of Core-shell Fe NPs exposed in water measured by XRD. 15 time slower than that of Toda NPs (50 nm).

University of Idaho
Tradition. Change. Excellence.



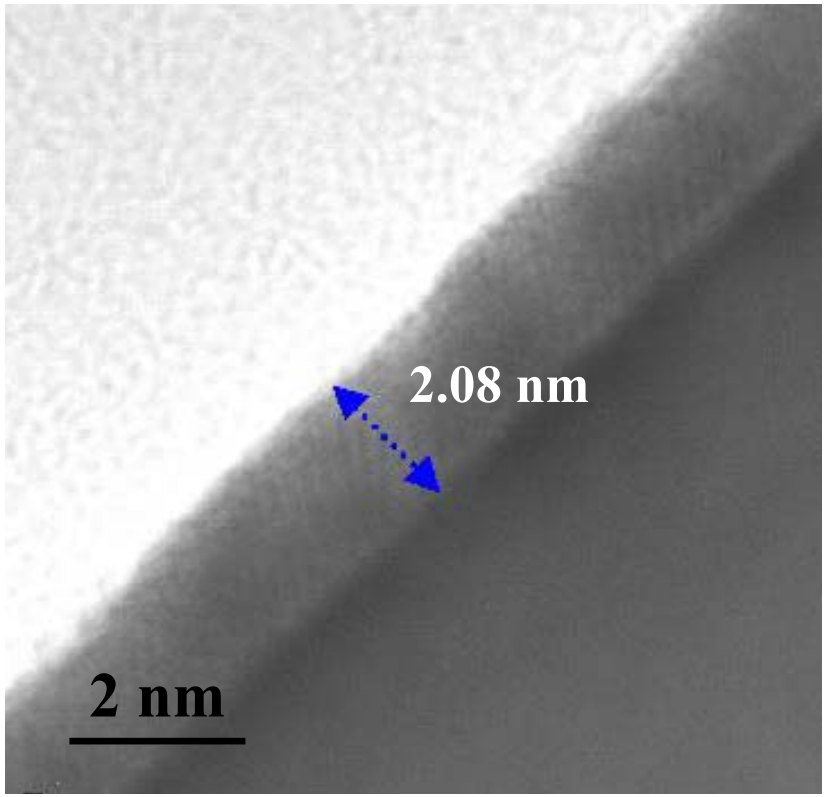
University of Idaho
Tradition. Change. Excellence.

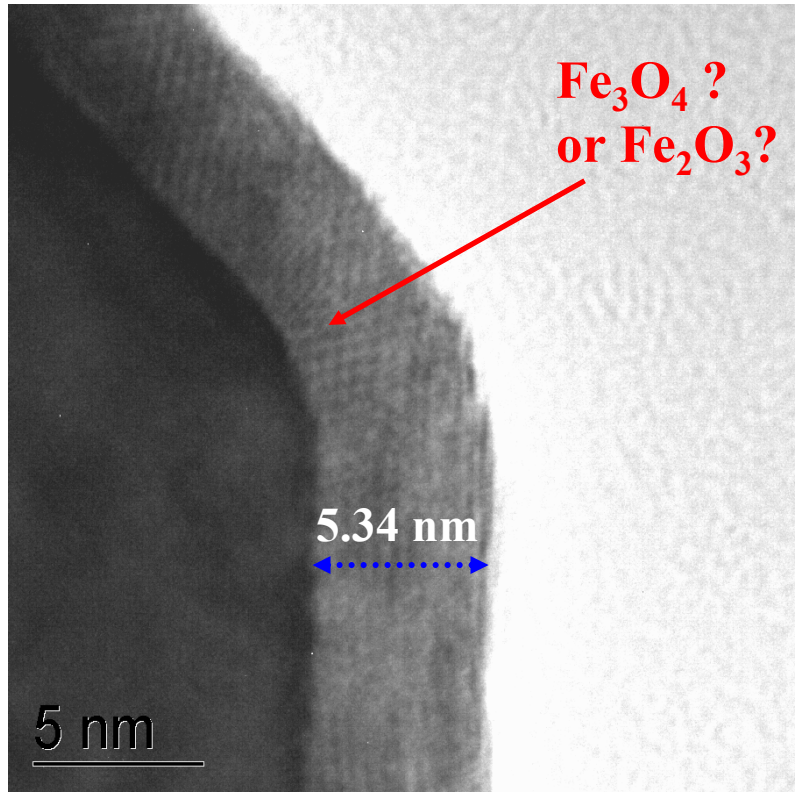

[h70125e.dif] GIXRD: #121206(3) Fe-Oxide Thicker UOI Don Baer (Test 02)
[h70131g.dif] GIXRD #121206(3) Fe-Oxide following 129hrs exposure Thicker UOI Don Baer
[h70209b.dif] GIXRD: #121206(3) Fe-Oxide and following 317 hrs exposure Thicker UOI Don Baer
40 nm MNPs
Intensity(Counts)
10.0
8.0
6.0
4.0
x10^3
019-0629> Magnetite - Fe +2Fe2 +3O4
087-0721> Iron - Fe
30
40
50
60
70
2Theta

HRTEM showing shell is a crystalline phase

As deposited

Annealing at 250 C, 3 hrs in air



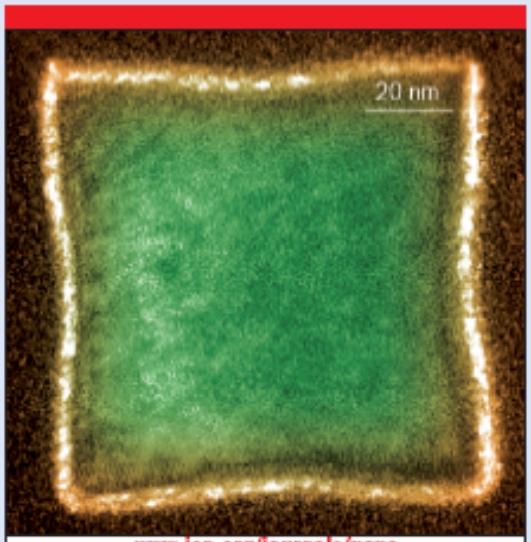


University of Idaho
Tradition. Change. Excellence.

ISSN 0957-4484

NANOTECHNOLOGY

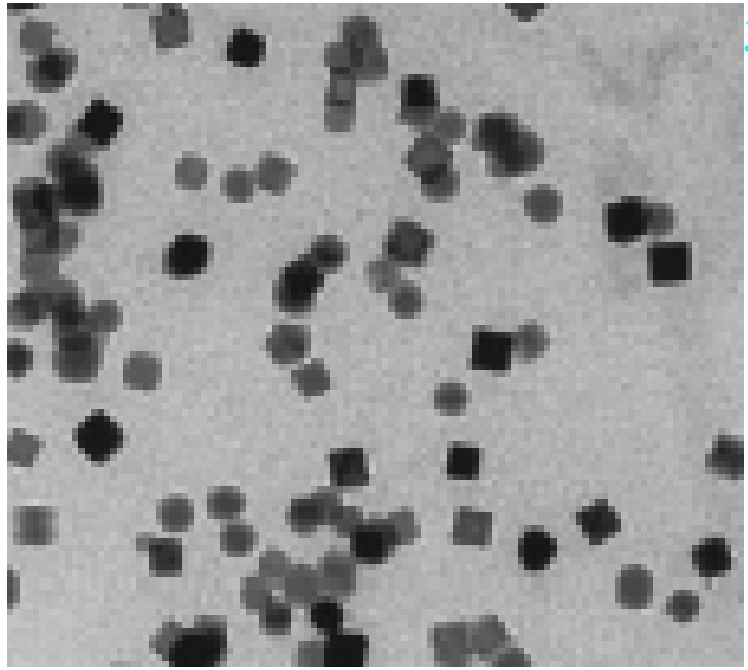
VOLUME 18 NUMBER 25 27 JUNE 2007



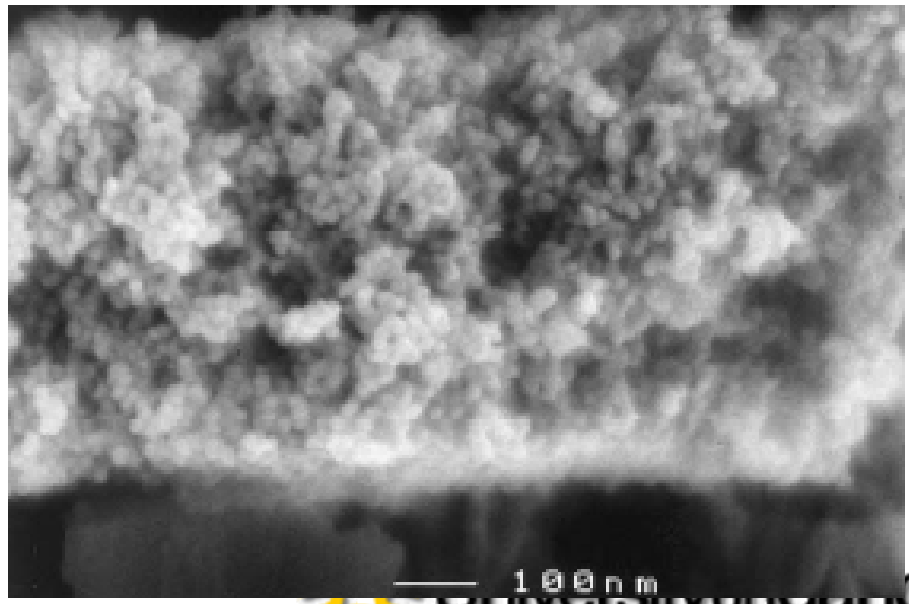
www.iop.org/journals/nano

Featured article:
Morphology and oxide shell structure of iron nanoparticles grown by sputter-gas-aggregation
C M Wang, D R Baer, J E Amonette, M H Engelhard, Y Qiang and J Antony

IOP Publishing

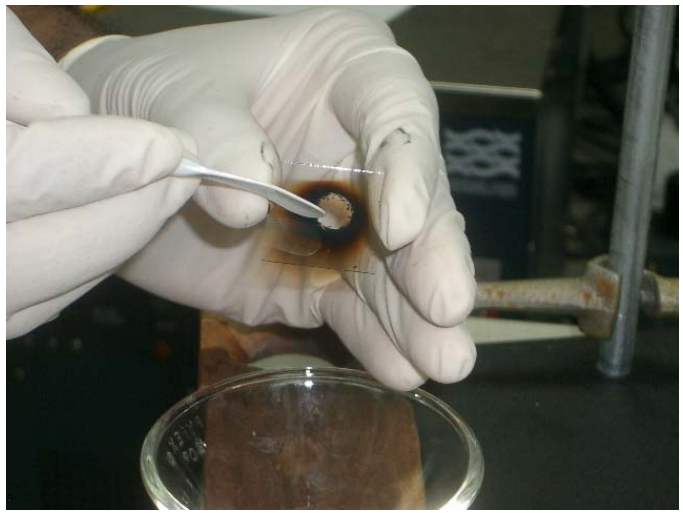


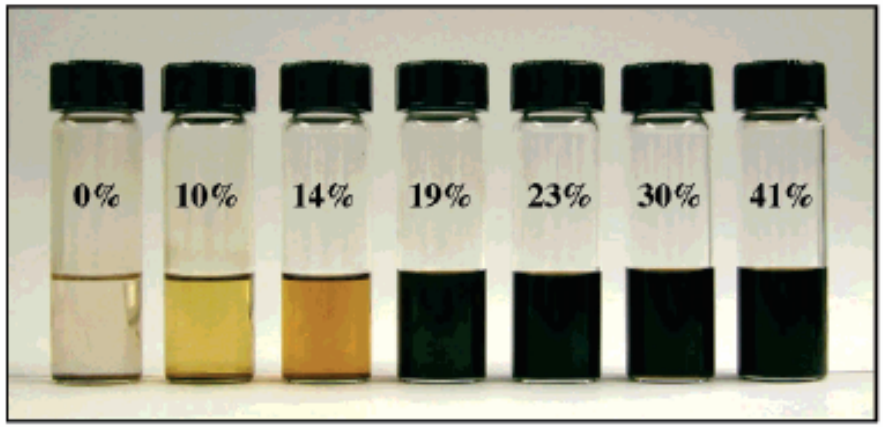
soft landing Fe nanoclusters

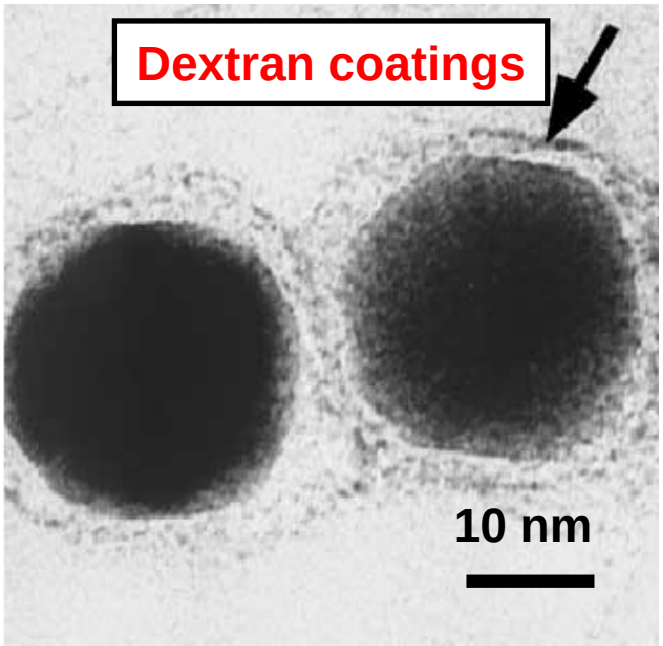


University of Idaho
Tradition. Change. Excellence.

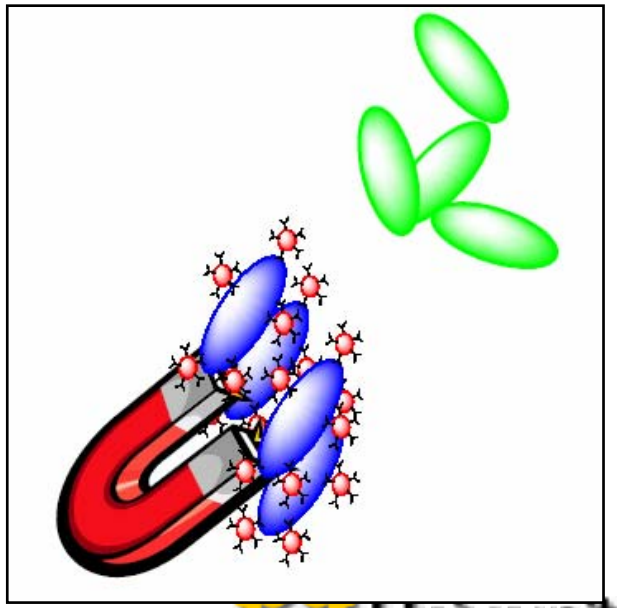
Nanoclusters disperse in solution uniformly w/o surface stabilizer



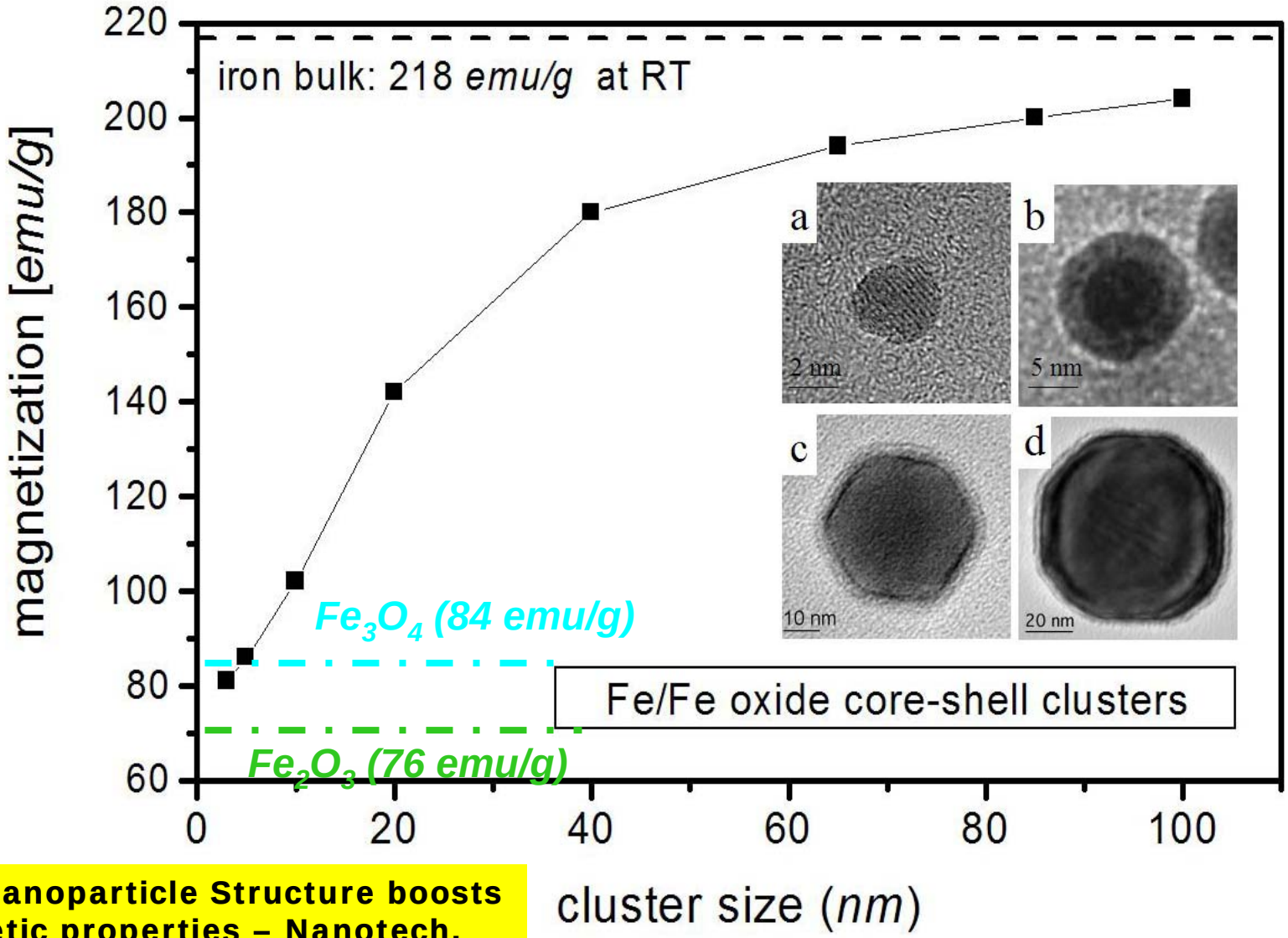




Magnetic separation

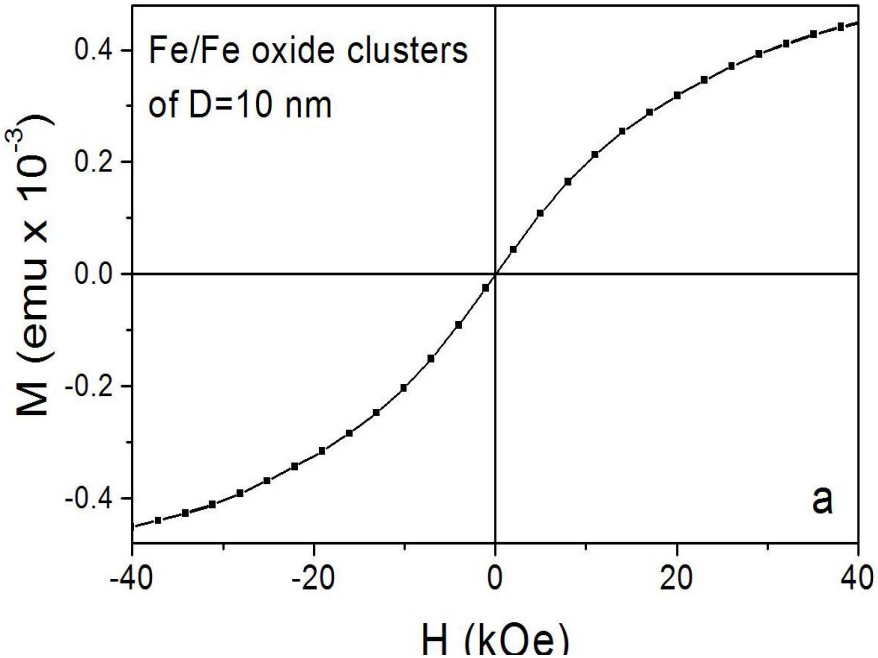


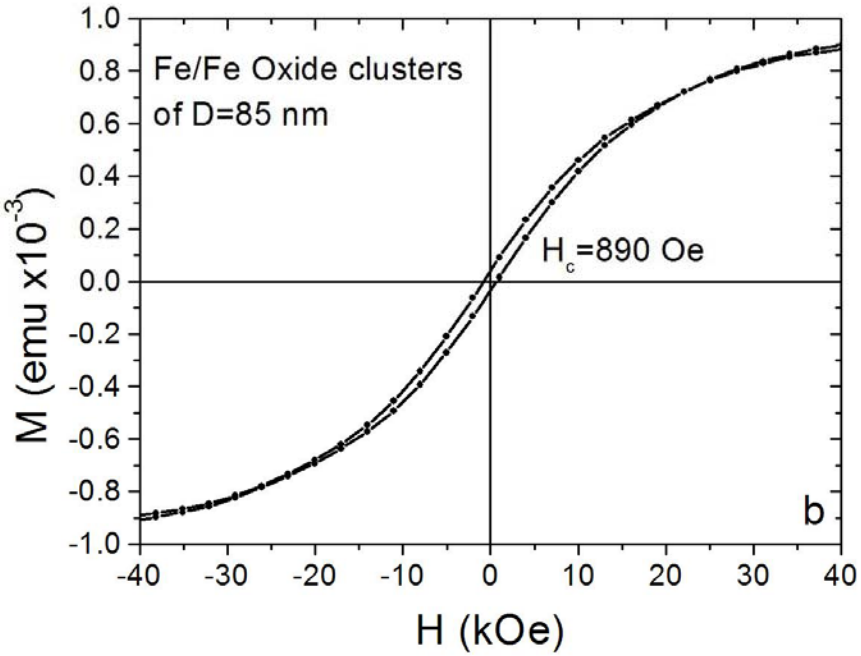
Specific Magnetic Moment of Core-Shell Nanoclusters



New Nanoparticle Structure boosts magnetic properties – Nanotech. Breaking News from National Cancer Institute, 12/19/2005

University of Idaho
Tradition. Change. Excellence.



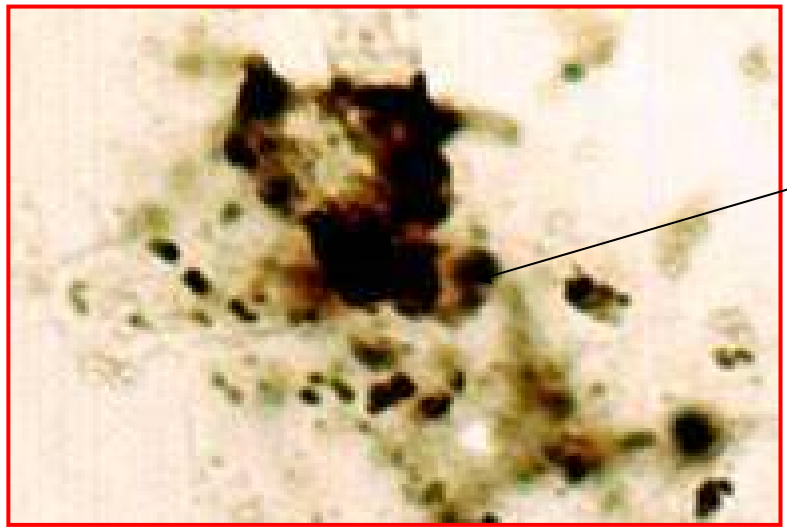


Superparamagnetic when the size less than 15 nm!

MNPs are uptaken by cancer cells

- Uniform dextrin coated and uncoated our iron-iron oxide core-shell NPs are incubated with LX-1 small cell lung cancer (SCLC) cells in rats without protamine.
- Commercially produced nanoparticles namely Feridex was also incubated with cancer cells with protamine.
- Protamine was added to Feridex samples to prevent the coagulation of cells.

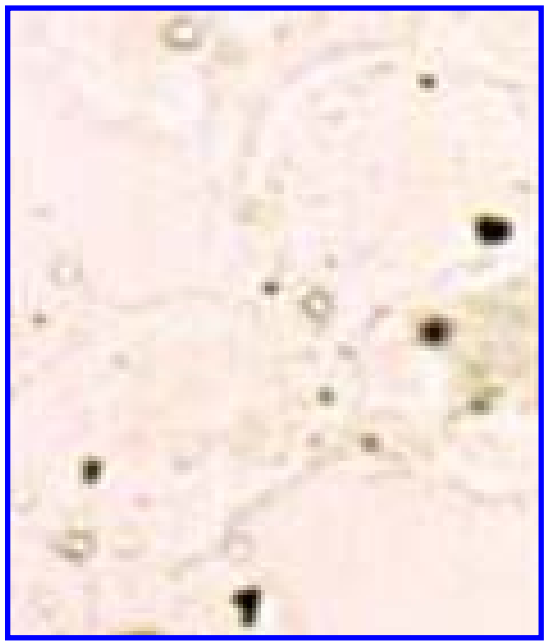
University of Idaho
Tradition. Change. Excellence.



Feridex MNPs with 10 µg protamine

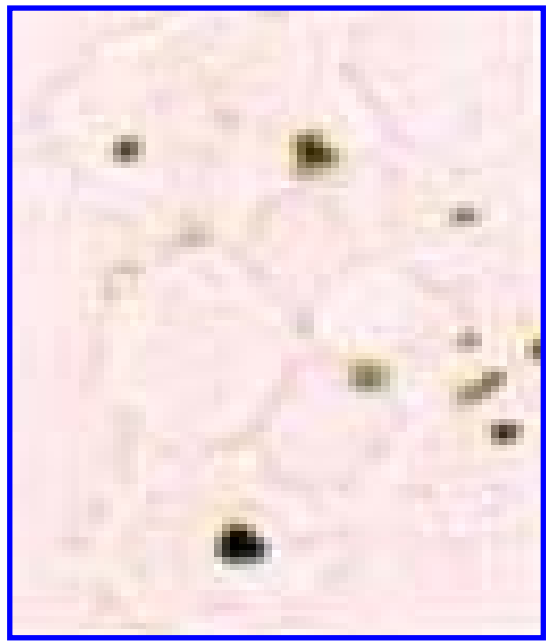
Feridex a well known aqueous colloid of superparamagnetic iron oxide associated with dextrin for intravenous administration was used to label the uncontrolled sample. Feridex was incubated with cancer cells and was used as a standard to compare with MNP's produced in our lab incubated with cancer cells. Protamine sulfate was used to prevent the coagulation of cells. The results of all the samples were compared with the controlled samples. Control samples are the samples which used as a standard reference for samples treated with nanoparticles. This helps in verifying the consistency of the experiment. We tested the noncoated and coated MNP's for toxicity and uptake.

Results



250µl pure core-shell NPs
incubated by the
LX-1 SCLC cancer cells

No Protamine



250µl dextrin coated
Core-shell NPs
incubated by the
LX-1 SCLC cancer cells

No Protamine

250µl Feridex
incubated by the
LX-1 SCLC cancer cells

10 microgram protamine

University of Idaho
Tradition. Change. Excellence.

Magnetic Resonace Imaging

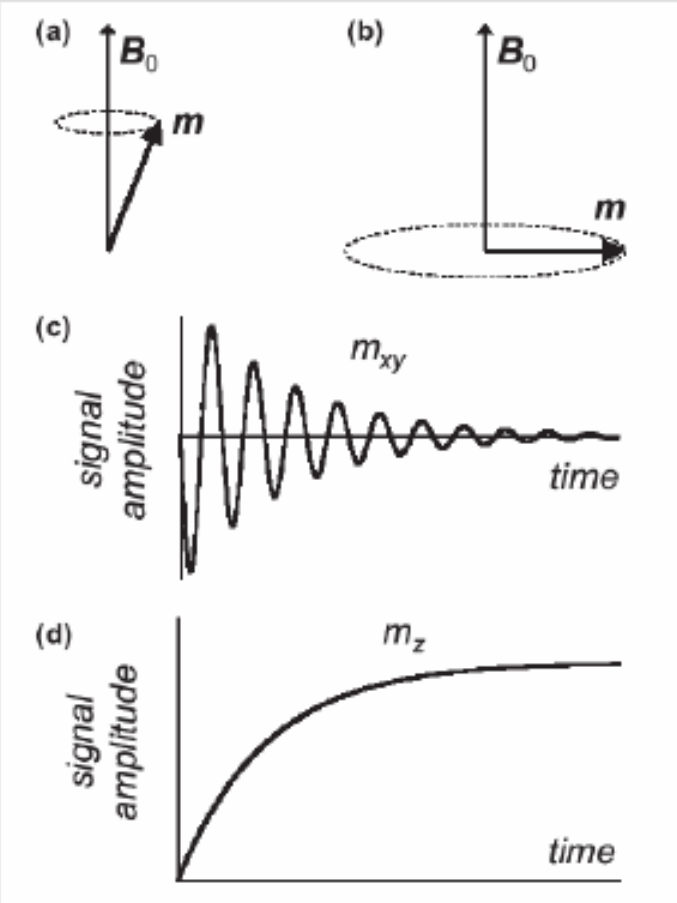


Illustration of magnetic resonance for a large ensemble of protons with net magnetic moment ***m*** in the presence of a external magnetic field $\boldsymbol{B}_0$.

In (*a*) the net moment precesses around $\boldsymbol{B}_0$ at the characteristic Larmor frequency, ω_0.

In (*b*) a second external field is applied, perpendicular to $\boldsymbol{B}_0$, oscillating at ω_0. Despite being much weaker than $\boldsymbol{B}_0$, this has the effect of resonantly exciting the moment precession into the plane perpendicular to $\boldsymbol{B}_0$.

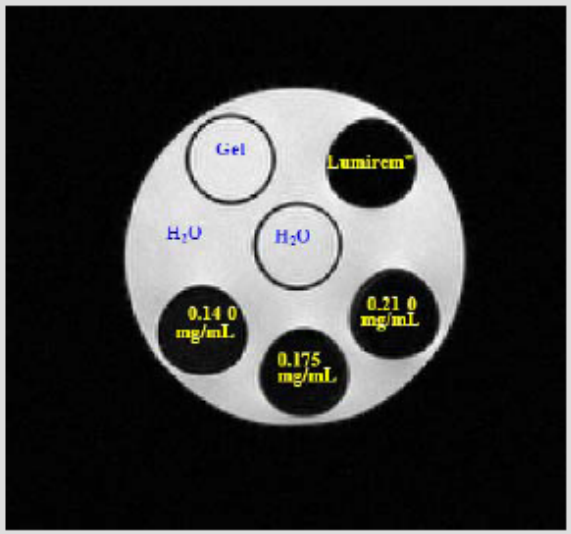
In (*c*) and (*d*) the oscillating field is removed at time zero, and the in-plane (*c*) and longitudinal (*d*) moment amplitudes relax back to their initial values.

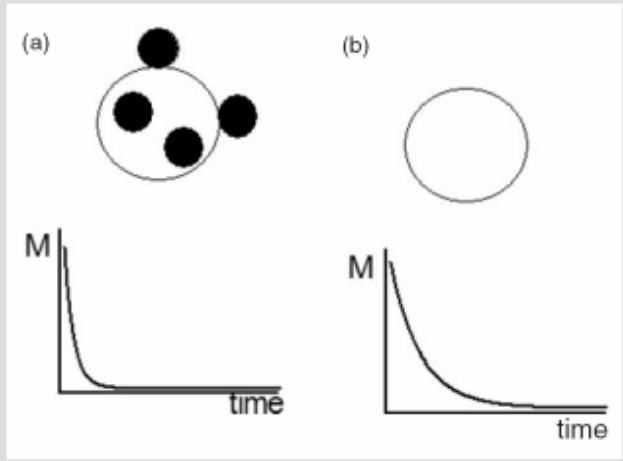
Punkhurst et al. J.Phys.D.36 (2003) R167.

University of Idaho
Tradition. Change. Excellence.

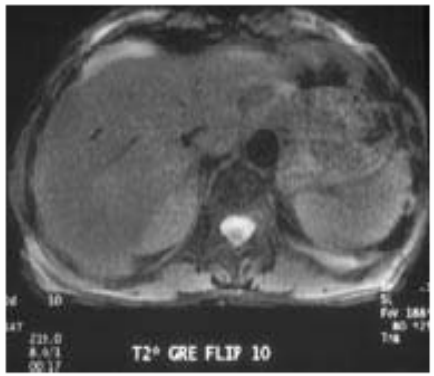
$$m_z = m(1 - e^{-t/T_1})$$

$$m_{x,y} = m \sin(\omega_0 t + \phi) e^{-t/T_2}$$

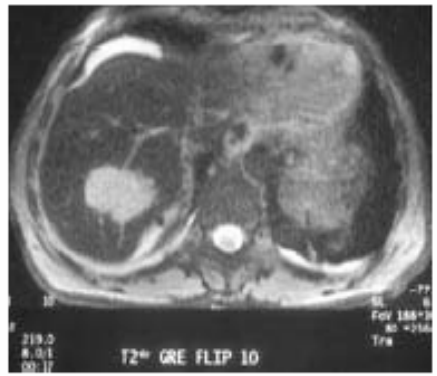




The relaxation time T_2



Without NP Contrast agents



With NP Contrast Agents.

University of Idaho
Tradition. Change. Excellence.

Magnetic attraction force **Hydrodynamic drag force**

$$F_m = \frac{\chi V}{2\mu_0}\nabla B^2 \qquad F_d = 6\pi R\eta\nabla v$$

$$\left|F_m\right| \geq \left|F_d\right| \Rightarrow \nabla B \geq 30T/meter$$

χ is the MNP's susceptibility; R is MNP's radius (10 nm);
η – the medium viscosity; v is the streamline velocity

University of Idaho
Tradition. Change. Excellence.

Acknowledgment

***Collaborators*:**

- **Dr. Donald R. Baer,** *Pacific Northwest National Laboratory*
- **Dr. C. M. Wang** *Pacific Northwest National Laboratory*
- ***Prof. Leslie Muldoon,*** *OHSU, Medical School*

Financial supported by:

- *NIH-INBRE (P20RR016454),*
- *DOE-BES (DE-FG02-06ER15777),*
- *Murdock Charitable Foundation*
- *Battelle/PNNL*

University of Idaho
Tradition. Change. Excellence.

Selected Publications:

1. Jiji Antony, You Qiang, Donald R. Baer and Chongmin Wang, "Synthesis and Characterization of Stable Iron-Iron Oxide Core-Shell Nanoclusters for Environmental Applications" J. of Nanoscience and Nanotechnology, 6 (2006) 568-572
2. You Qiang, Jiji Antony, Amit Sharma, Joseph Nutting, Daniel Sikes and Daniel Meyer, "Iron/iron Oxide Core-Shell Nanoclusters for Biomedical Applications", *J. of Nanoparticle Research, (2006) 8: 489-496*
3. Wang, CM, DR Baer, LE Thomas, JE Amonette, J Anthony, Y Qiang, and G Duscher. "Observations of Cation Diffusion and Void Formation during Early Stages of Passivation: Initial Oxidation of Iron Nanoparticles at Room Temperature", J. of Applied Physics 98 (2005) 094308.
4. Joseph Nutting, Jiji Antony, Daniel Meyer, Amit Sharma, and You Qiang, "The effect of particle size distribution on the usage of the AC susceptibility in biosensors", J. of Applied Physics, 99, 08B319 (2006)
5. Amit Sharma, You Qiang, Pawel Karnacki, Andrzej Paszczynski, Daniel Meyer, Joseph Nutting, and Jiji Antony, "Dramatic increase in stability and longevity of enzymes attached to monodispersive iron nanoparticles", IEEE Transactions on Magnetics, 43 (2007) 2418.
6. Leslie L. Muldoon, You Qiang, Edward A. Neuwelt, et, al. "Imaging and nanomedicine for diagnosis and therapy in the CNS: Report of the eleventh annual blood-brain barrier disruption consortium meeting", American Journal of Neuroradiology, 27:715-721, March 2006.
7. Amit Sharma, You Qiang, Daniel Meyer, Ryan Souza, Alan Mcconnaughoy, Leslie Muldoon, and Donald Baer, "Biocompatible core-shell magnetic nanoparticles for cancer treatment", J. of Appl. Phys, 103 (2008) 07A308.

THE END

University of Idaho
Tradition. Change. Excellence.