nanomaterial–biological interactions

NBI KNOWLEDGEBASE

An EZ Metric for Defining the A in nanoSARs

OSU Oregon State University

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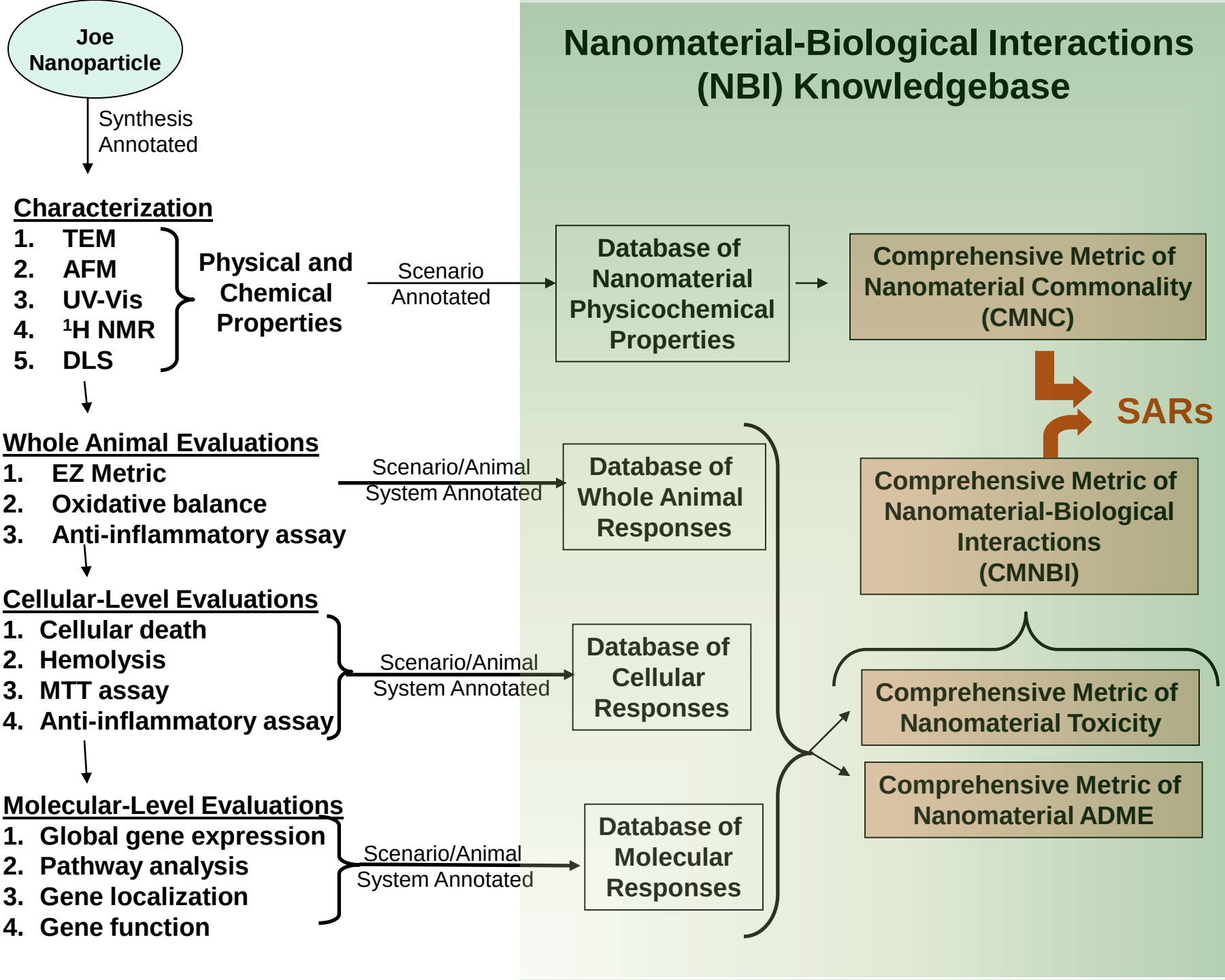
Environmental and Molecular Toxicology
Chemical, Biological and Environmental Engineering

Nanomaterial-Biological Interactions (NBI) Knowledgebase



Model Organism

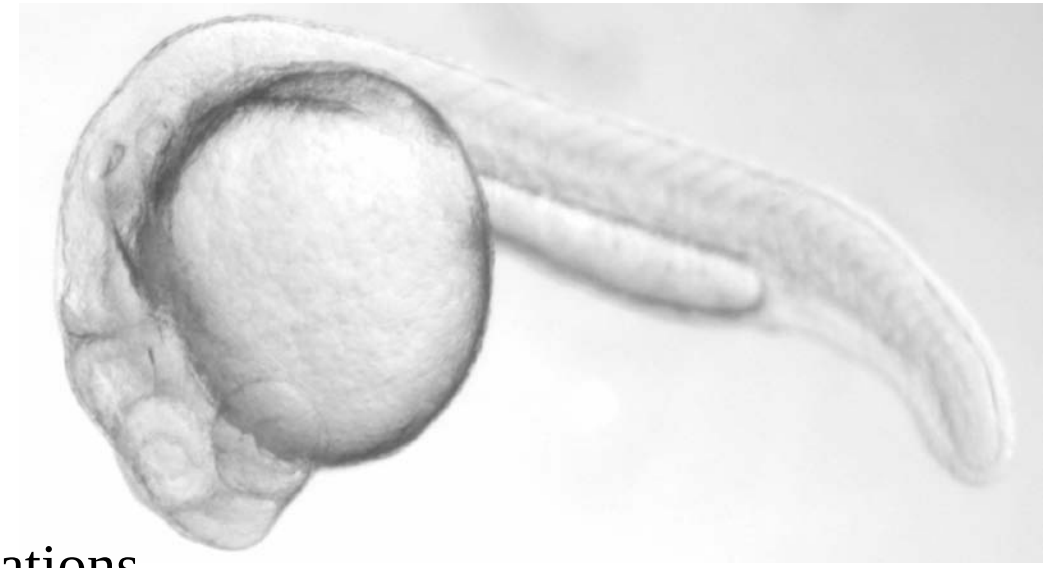
Embryonic Zebrafish Model

General Attributes

Share molecular, cellular and physiological characteristics with other vertebrates

Develop rapidly

Easy to maintain



Toxicity Evaluation

Large sample sizes

Many routes of exposure

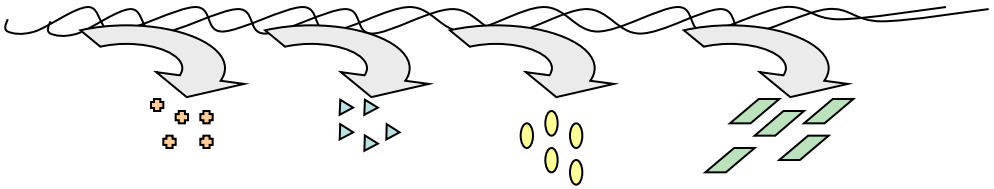
Transparent - non-invasive evaluations

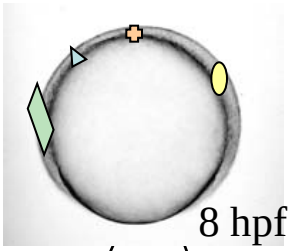
Amenable to mechanistic evaluations

Investigate genomic → whole animal responses in same organism

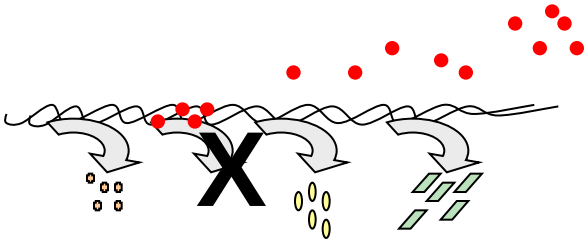
Full suite of molecular signaling necessary and active early in development

Molecular Signaling



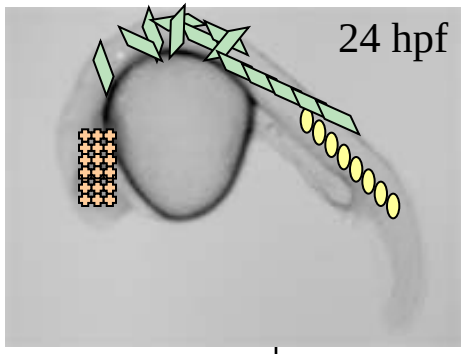


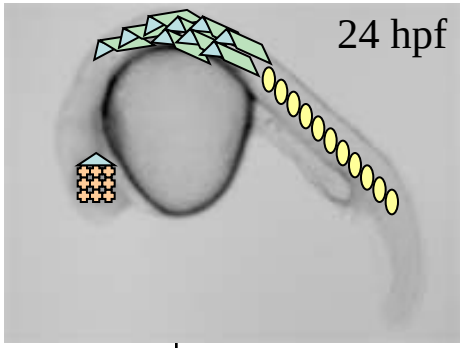
Nanomaterial Interference

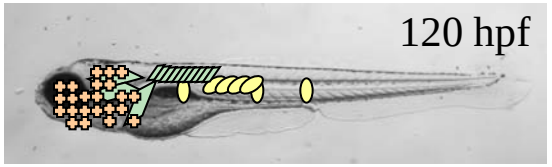


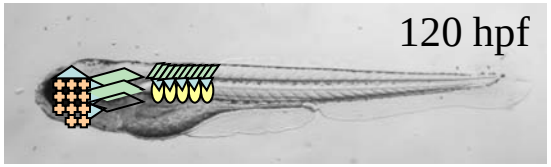
Exposed

Control



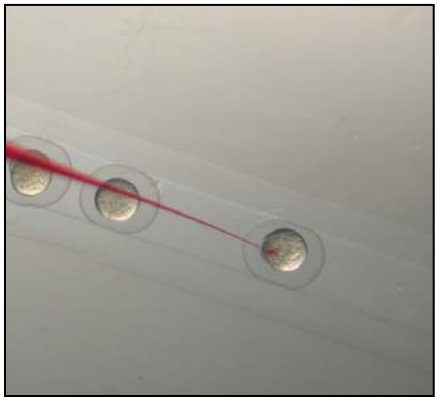


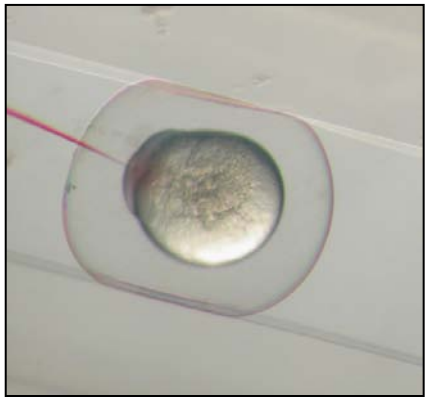




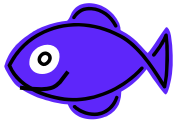
Toxicity Screening

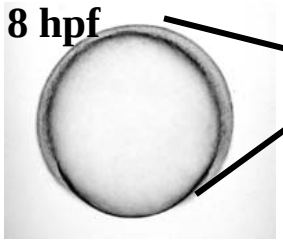
microinjection of nanoparticles





male **female**

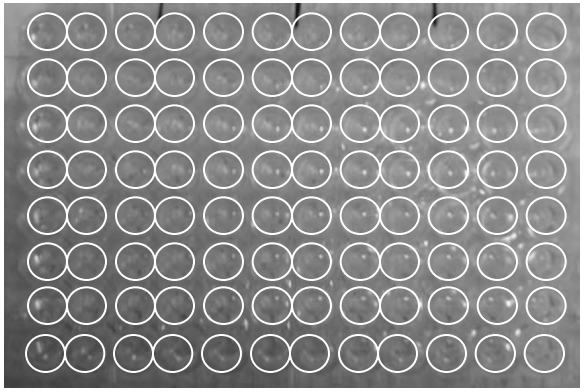




8 hpf

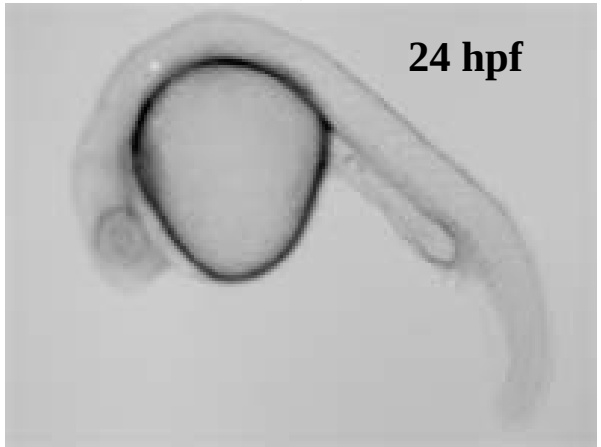
embryos

add 1 embryo/well



add nanoparticles

Evaluations



24 hpf

Evaluations

TOXICITY EVALUATIONS

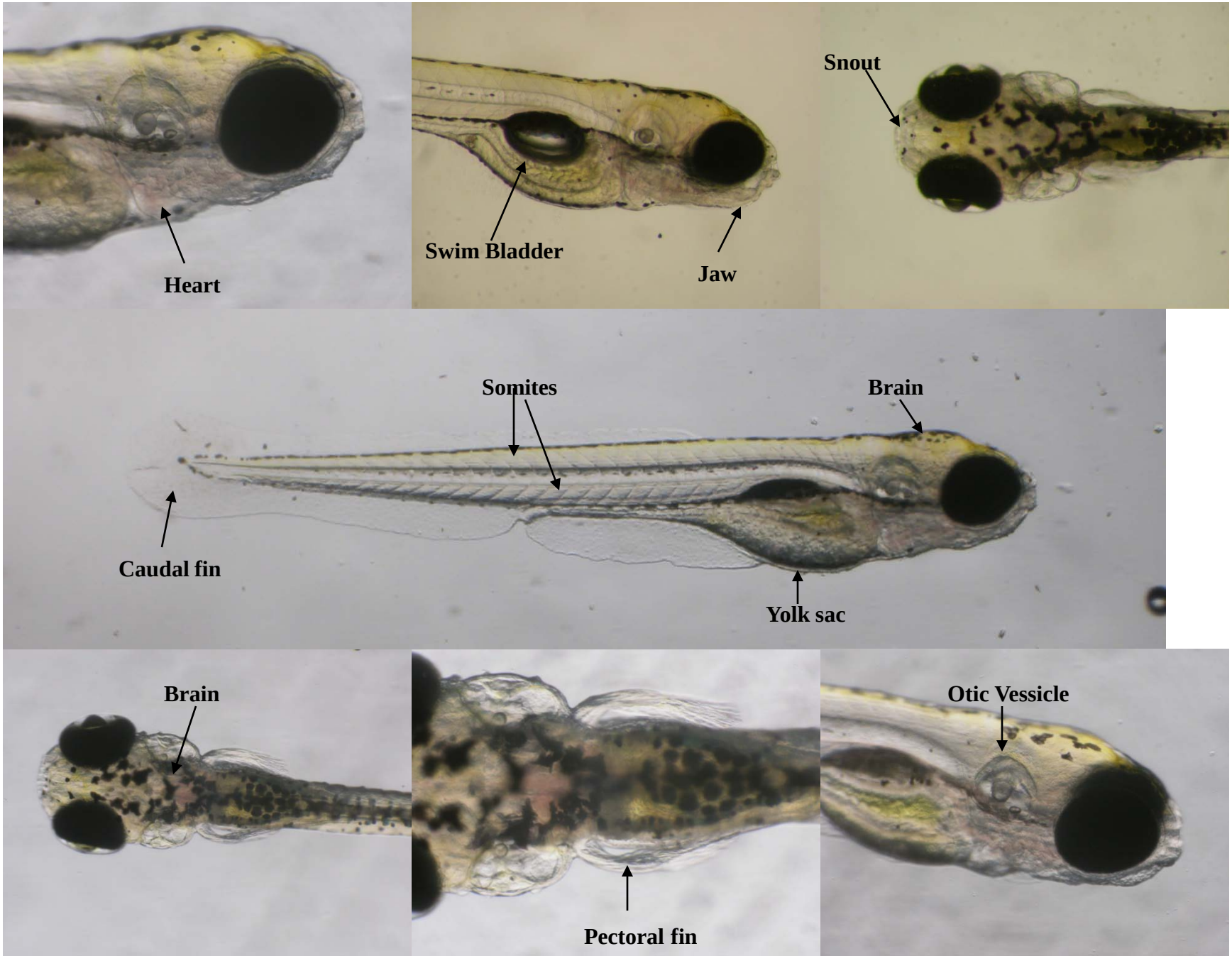
24 hpf evaluations

- Mortality (**mort**)
- Developmental progression (**dp**)
- Spontaneous movement (**sm**)
- Notochord (**nc**)

120 hpf evaluations

- Mortality (**mort**)
- Yolk sac edema (**YSE**)
- Body axis (**axis**)
- Eye
- Snout
- Jaw
- Otic vessicle (**otic**)
- Pericardial edema (**PE**)
- Brain
- Somites
- Pectoral fin (**pfin**)
- Caudal fin (**cfin**)
- Pigmentation (**pig**)
- Circulation (**circ**)
- Trunk
- Swim bladder (**swim**)
- Motility (touch response, **tr**)

Controls


Heart
Swim Bladder
Jaw
Snout
Somites
Brain
Caudal fin
Yolk sac
Brain
Pectoral fin
Otic Vessicle


Pectoral Fin Malformation

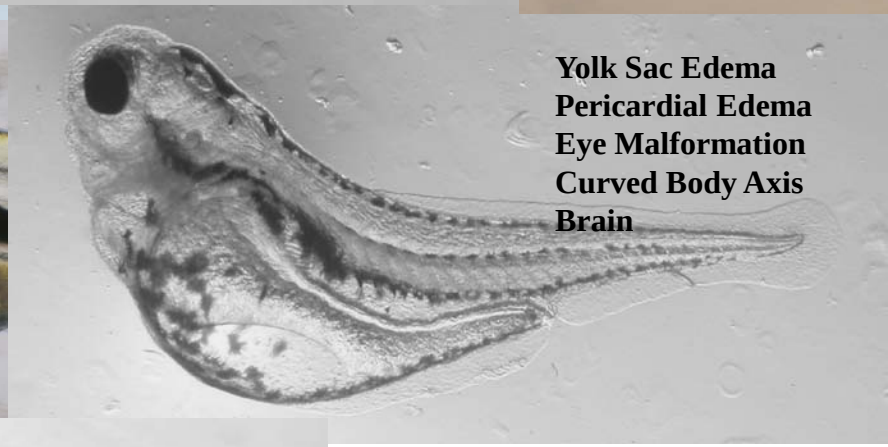

Pectoral Fin Malformation
No pectoral fins

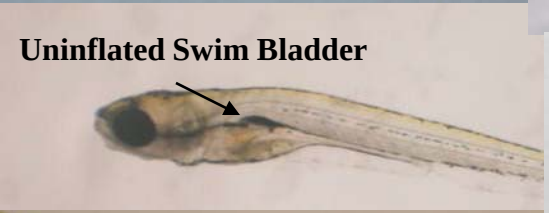

Pectoral Fin Malf.


Otic vessicle

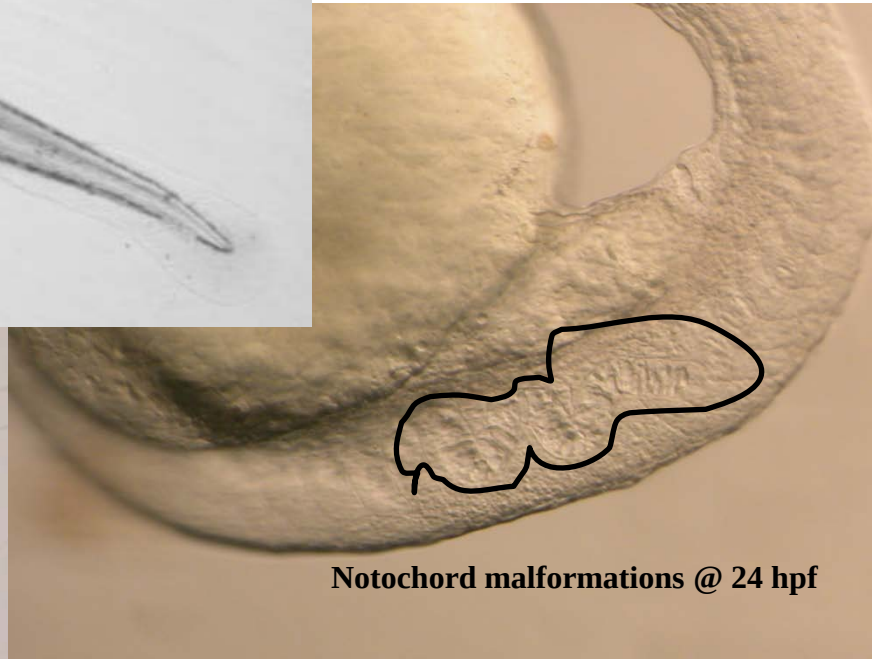

Curved Body Axis


Jaw Malf.
Snout

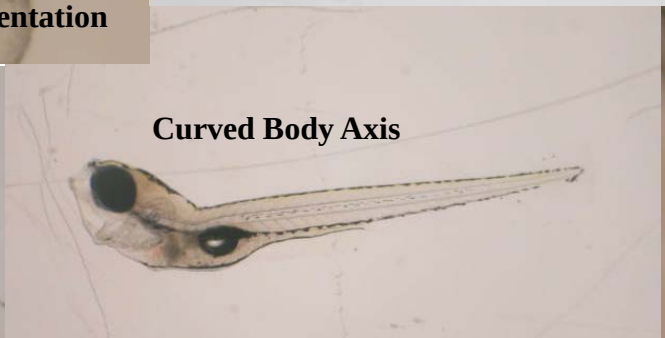

Yolk Sac Edema
Pericardial Edema
Eye Malformation
Curved Body Axis
Brain

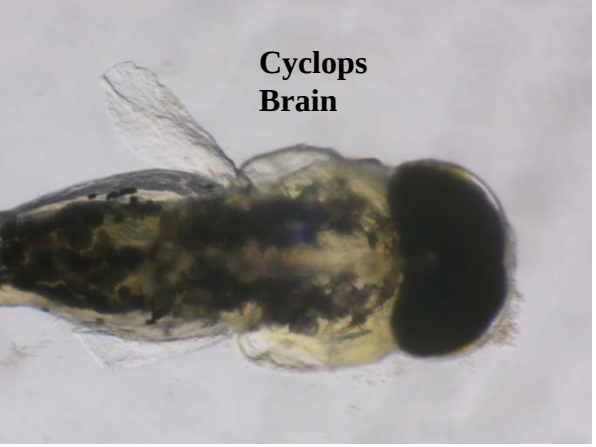

Uninflated Swim Bladder

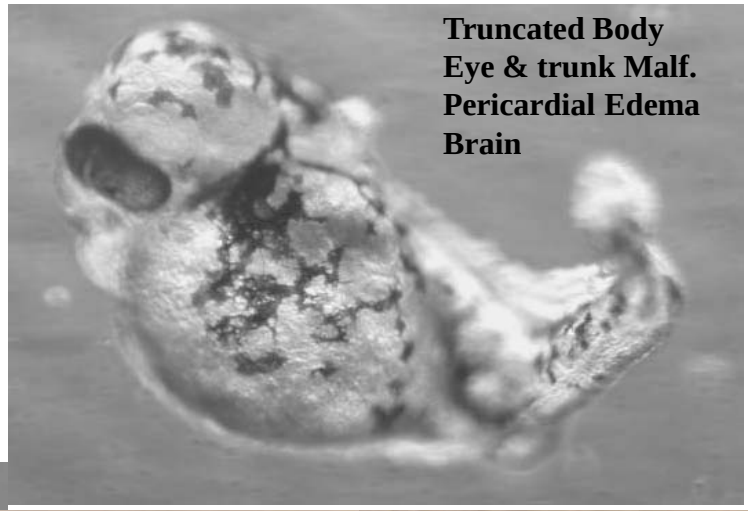

No pigmentation

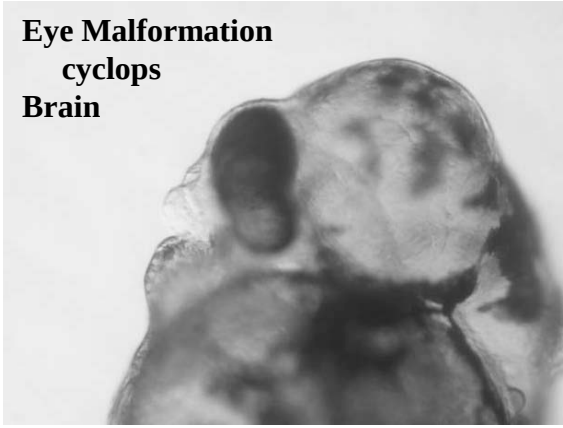

Notochord malformations @ 24 hpf

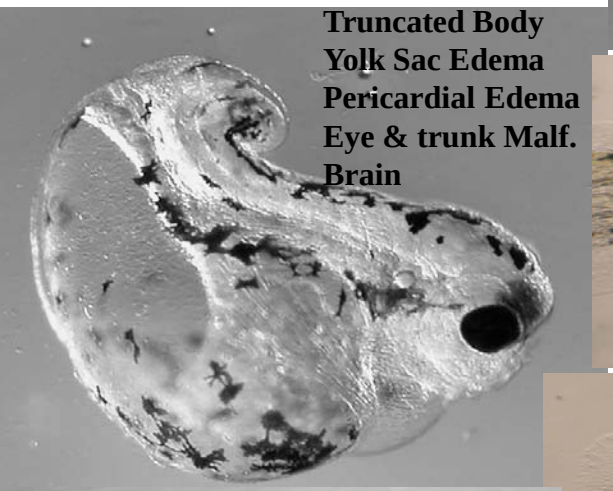

Curved Body Axis


Curved Body Axis


Cyclops
Brain


Truncated Body
Eye & trunk Malf.
Pericardial Edema
Brain


Eye Malformation
cyclops
Brain


Truncated Body
Yolk Sac Edema
Pericardial Edema
Eye & trunk Malf.
Brain


Mass on trunk

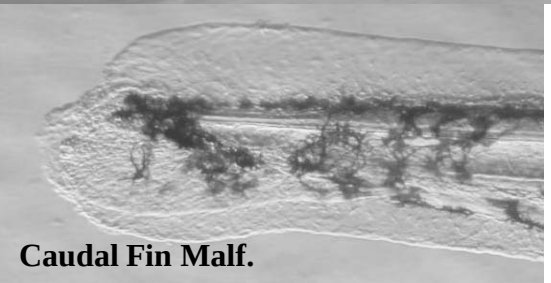

Mass on trunk
Somites


Eye Malformation
no eyes
Brain


Mass on trunk
Jaw malf.


Eyes
Snout


Pericardial Edema


Caudal Fin Malf.


Caudal Fin Malf.
Delayed Dev.


Caudal fin Malformation

What is the EZ Metric?

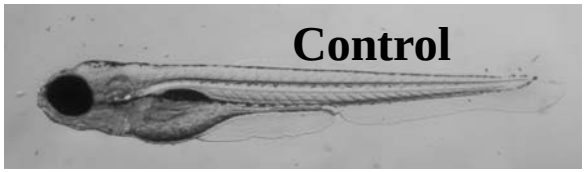
nanomaterial–biological interactions

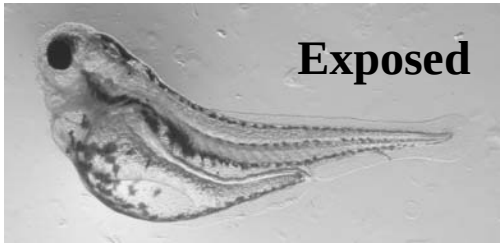
Method of Data Compression:

A single metric representative of adverse effects (toxicity) in embryonic zebrafish screening-level assay

- 23 endpoints for each animal (N = at least 24)
- 7 exposure concentrations + control
- over 200 nanomaterials evaluated
- needed summary of overall effects
- consider mortality and morbidity

EZ Metrics for Nanomaterial Toxicity





Developed using OSU's

NANOMATERIAL–BIOLOGICAL INTERACTIONS KNOWLEDGEBASE

frequency of effect
x hierarchical ranking
EZ Metric

Normalized to scale 0-24; *additive and weighted metrics*

EZ Metric	toxic potential	interpretation
≤ 5	low	likely benign
5 to 15	moderate	suspect nanomaterial
> 15	high	requires further testing

Analytical Hierarchical Process For Weighted EZ Metrics

nanomaterial–biological interactions

Web-based system to capture multiple expert opinions on weight of effects

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
1		0.33		5	5	5	5	5	7	7	9	7	7	7	9	1	120hr mortality
2	3		5	5	5	7	9	9	9	9	9	9	9	9	9	2	24 hr mortality
3	0.33	.2		3	1	3	3	5	5	5	9	5	7	7	9	3	24hr dev prog
4	0.2	.2	0.33		1	1	1	1	3	3	7	5	7	7	7	4	axis
5	0.2	.2	1	1		5		5	5	7	7	7	7	9	9	5	brain
6	0.2	14	0.33		.2		9		5	5	5	7	7	14	9	6	eye
7	0.2	11	0.33		1	11		7	7		0.2	0.11		9	9	7	heart
8	0.2	11	0.2		.2	33	14		3	1	3	1	1	1	3	8	jaw
9	0.14	11	0.2	33	.2	.2	14	33		1	3	1	1	1	3	9	notochord
10	0.14	11	0.2	33	14	.2	1	1	1		3	1	1	1	3	10	otic
11	0.11	11	.11	14	14	.2	5	33	33	33		0.33	3	0.33		11	pectoral fin
12	0.14	11	0.2	2	14	14	9	1	1	1	3		0.33	1	33	12	snout
13	0.14	11	14	14	14	14	11	1	1	1	3	3		1	1	13	somite
14	0.14	11	14	14	11	7	11	1	1	1	3	9	1		3	14	trunk
15	0.11	11	11	14	11	11	11	33	33	33	1	3	1	33		15	trunk fin

6	12
eye	snout

Importance of eye over

1/9 1/7 1/5 1/3 1 3

Up

Back Next

Down

AHP Calculation

Expert Opinion Documentation

nanomaterial–biological interactions

NBI KNOWLEDGEBASE

Oregon State University
Oregon Nanoscience and Microtechnologies Institute
Corvallis, Oregon 97331
Ph: 541-737-2791
Fax: 541-737-7966
www.oregonstate.edu/nbi

EXPERT OPINION DOCUMENTATION

Date: _____ Submit by Email

Contact Information

Name: _____
Position: _____
Affiliation: _____
Address: _____
City/State: _____
Zip Code: _____

Qualifications

Institution and location	Degree	Year	Field of Study

Area of Specialty:

Experience with Zebrafish:

Prioritization Considerations (e.g. developmental effects focused, considered long-term impacts on survivability):

Can we list your documentation on the NBI knowledgebase website? Yes ☐ No ☐

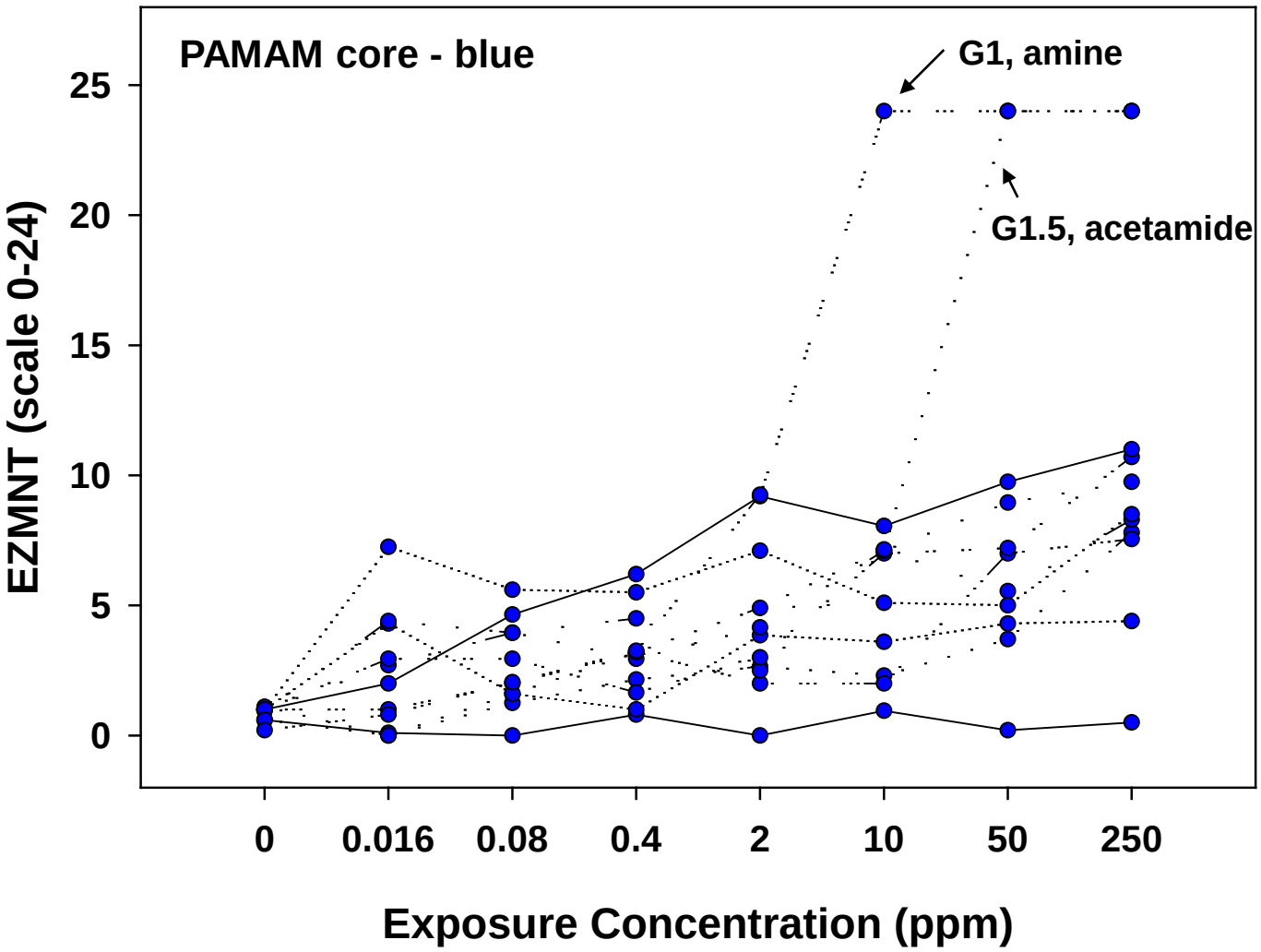
May we contact you for further comment regarding prioritization of effects? Yes ☐ No ☐

Gain consensus on relative weight of effects

Captures experience with model system and considerations for ranking

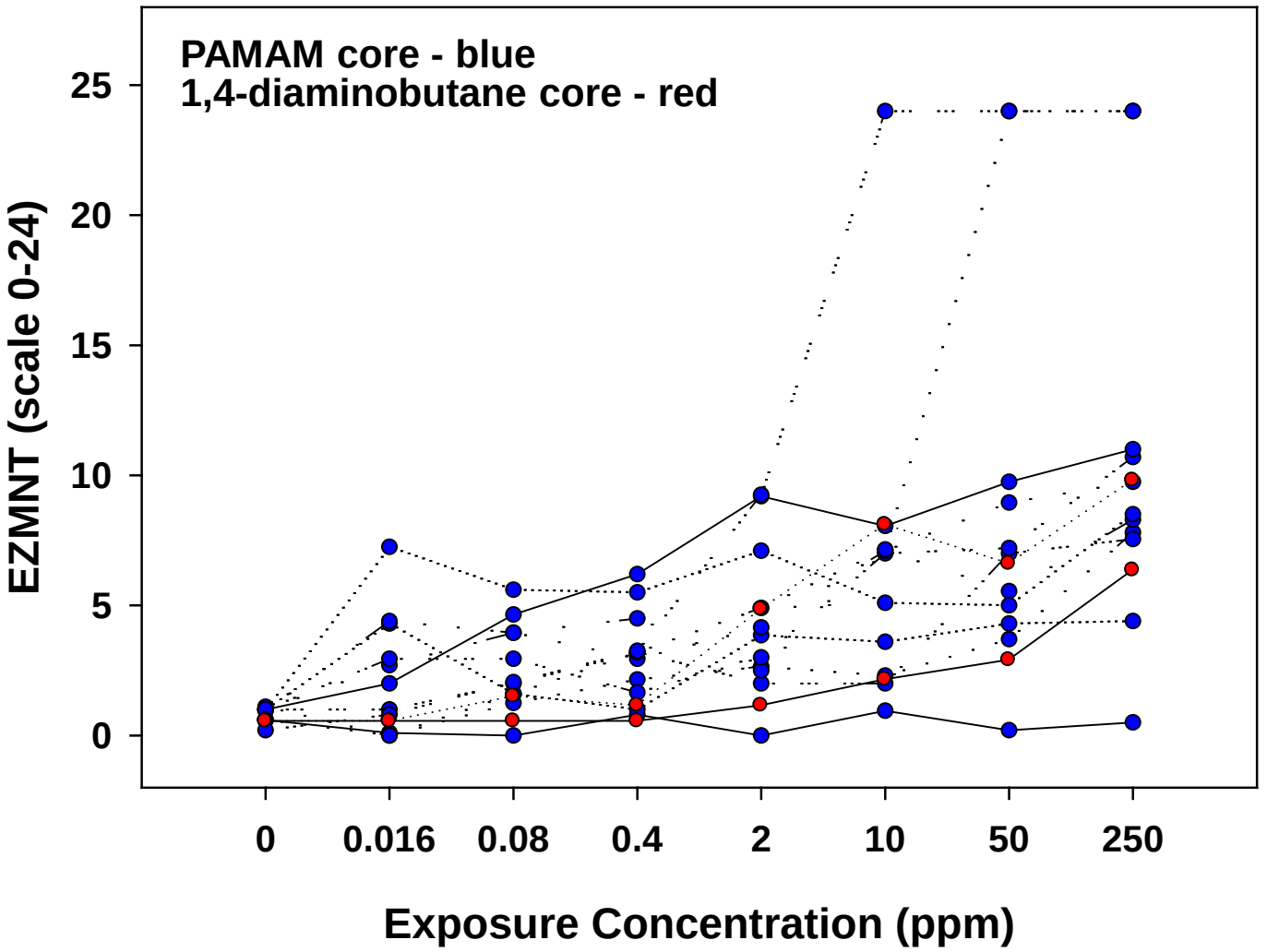
Useful to understand variability

EZ Metric - Dendrimers



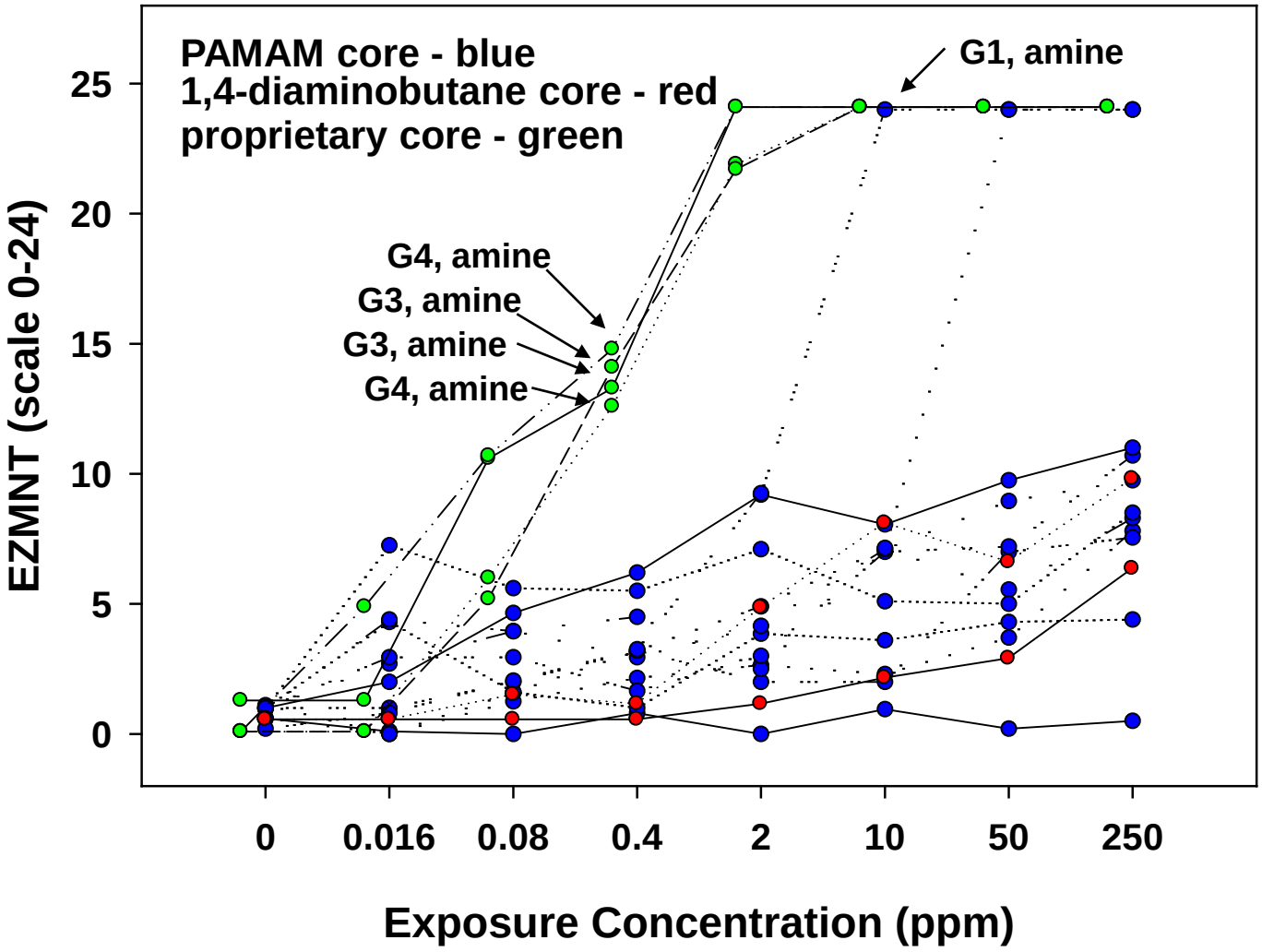
nanomaterial–biological interactions

EZ Metrics - Dendrimers



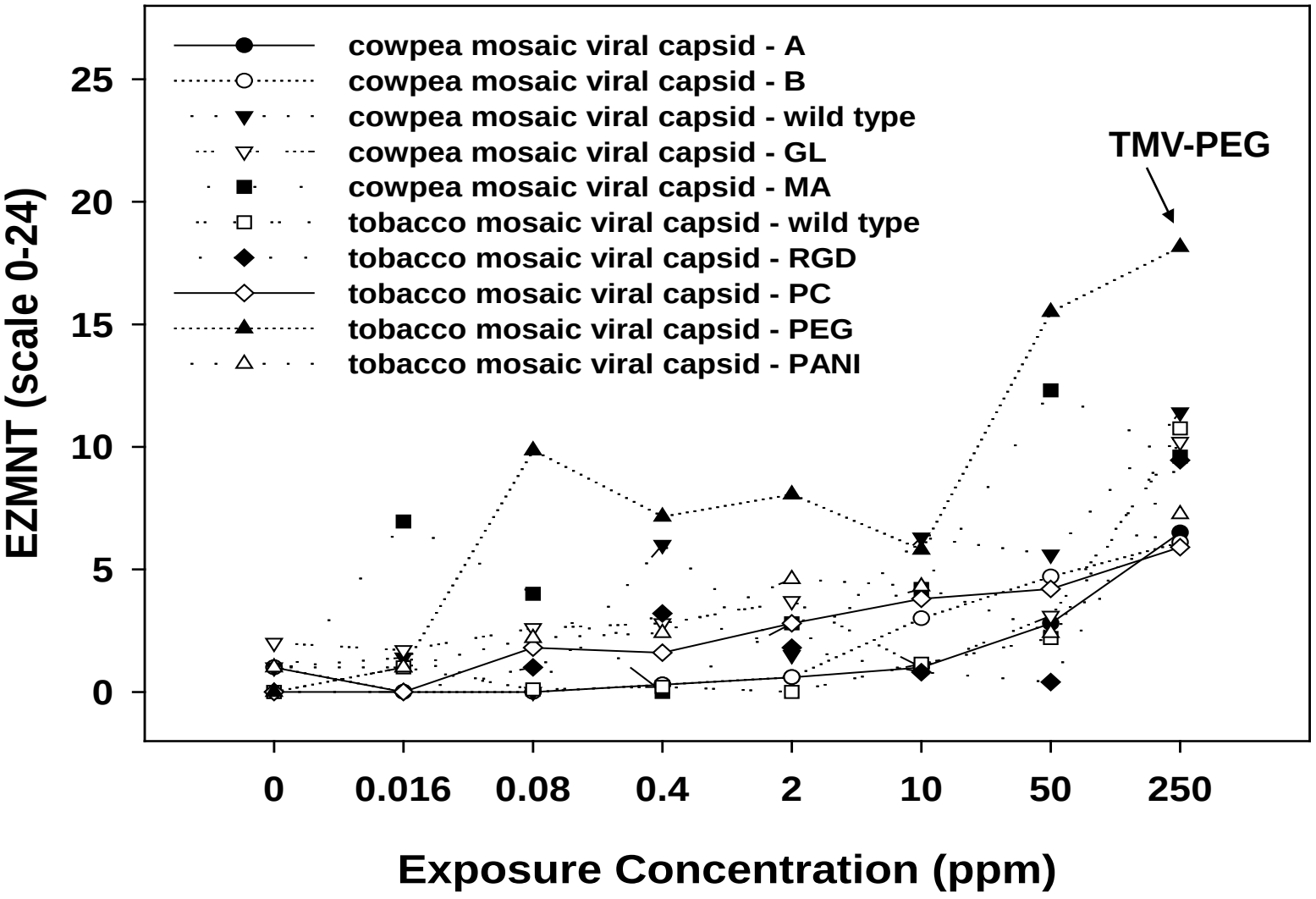
nanomaterial–biological interactions

EZ Metrics - Dendrimers



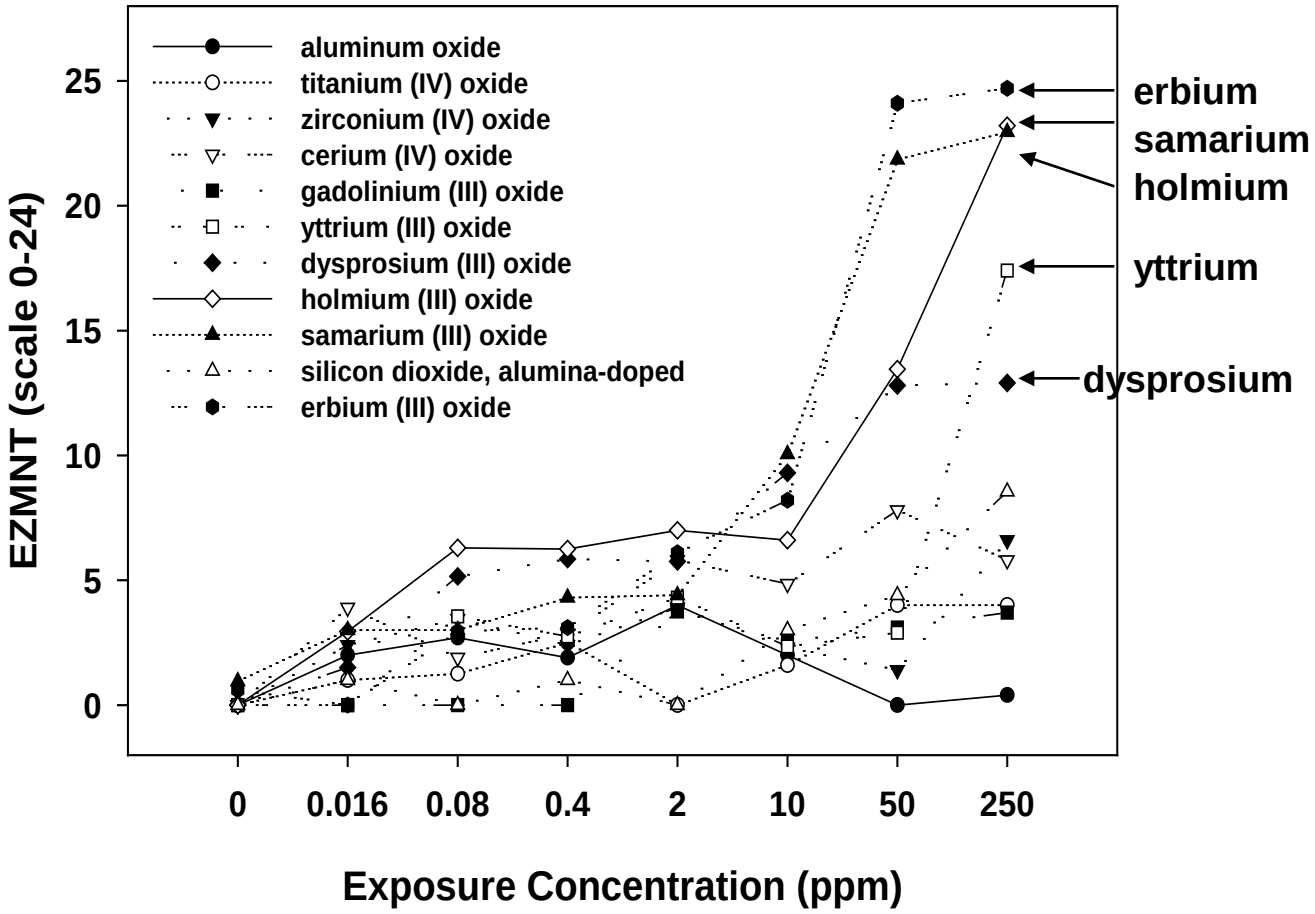
nanomaterial–biological interactions

EZ Metrics – Viral Nanoparticles



nanomaterial–biological interactions

EZ Metrics – Nanoparticulate Metal Oxides

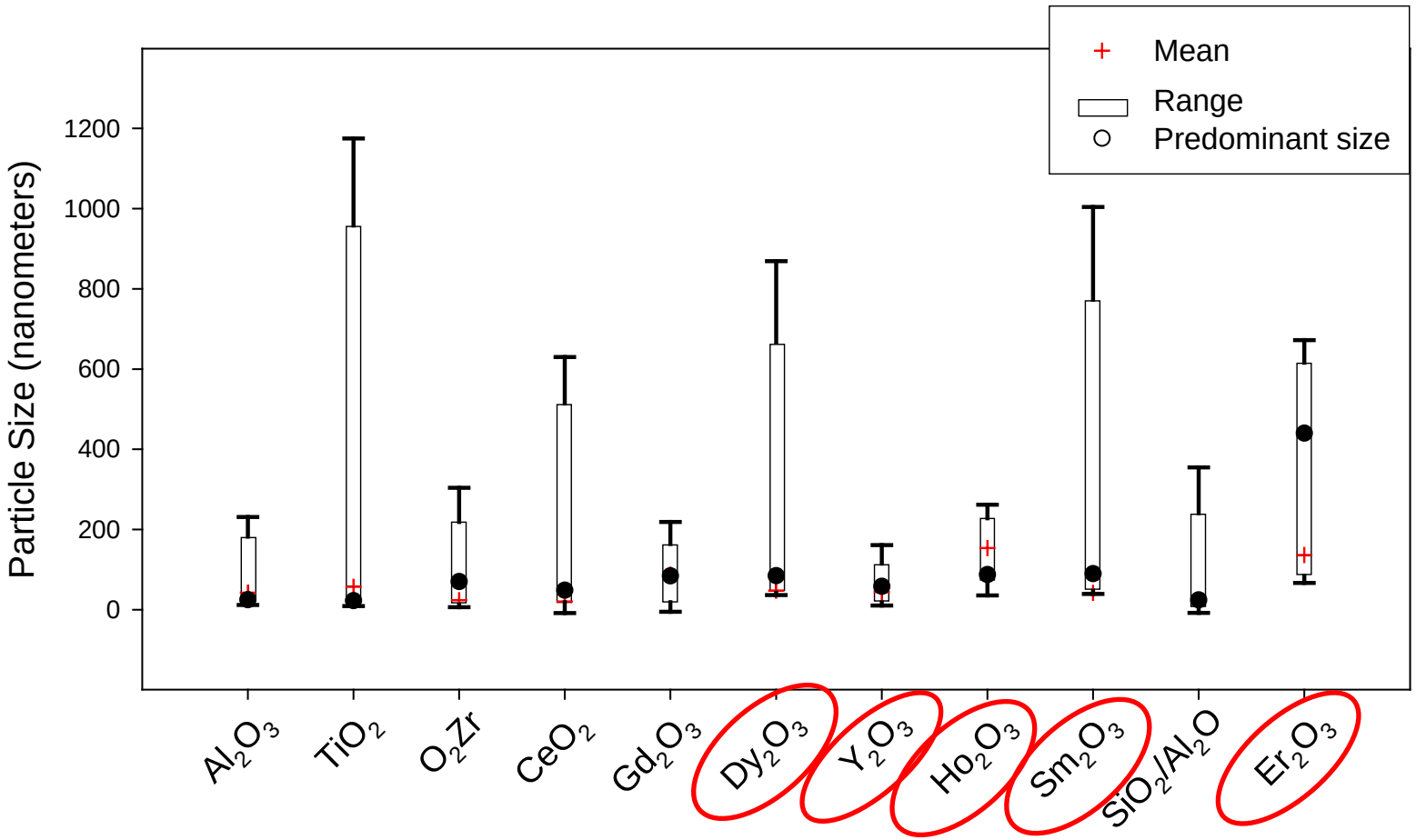


nanomaterial–biological interactions

EZ Metrics – Nanoparticulate Metal Oxides

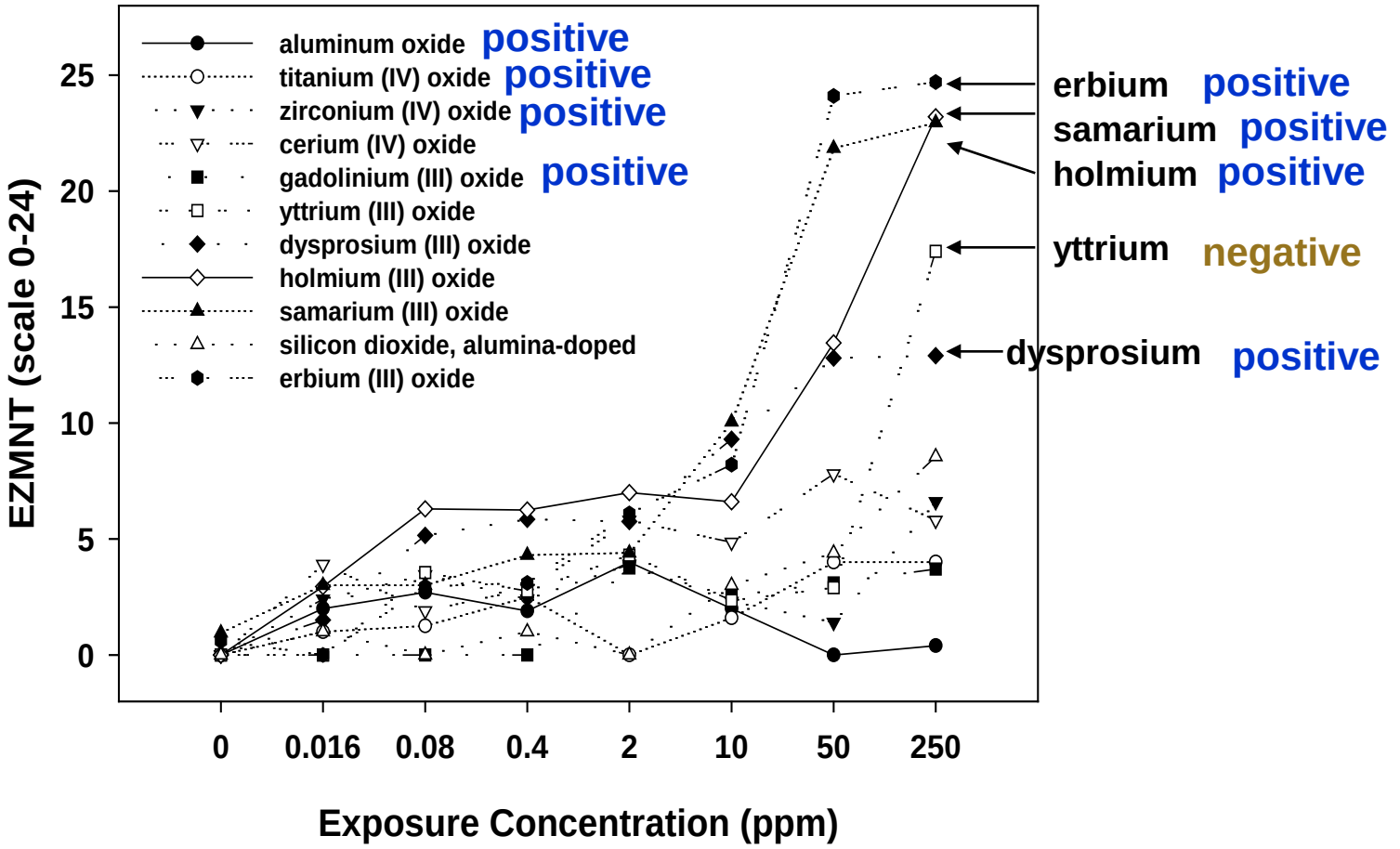
nanomaterial–biological interactions

Effect of Size



EZ Metrics – Nanoparticulate Metal Oxides

Effect of Charge

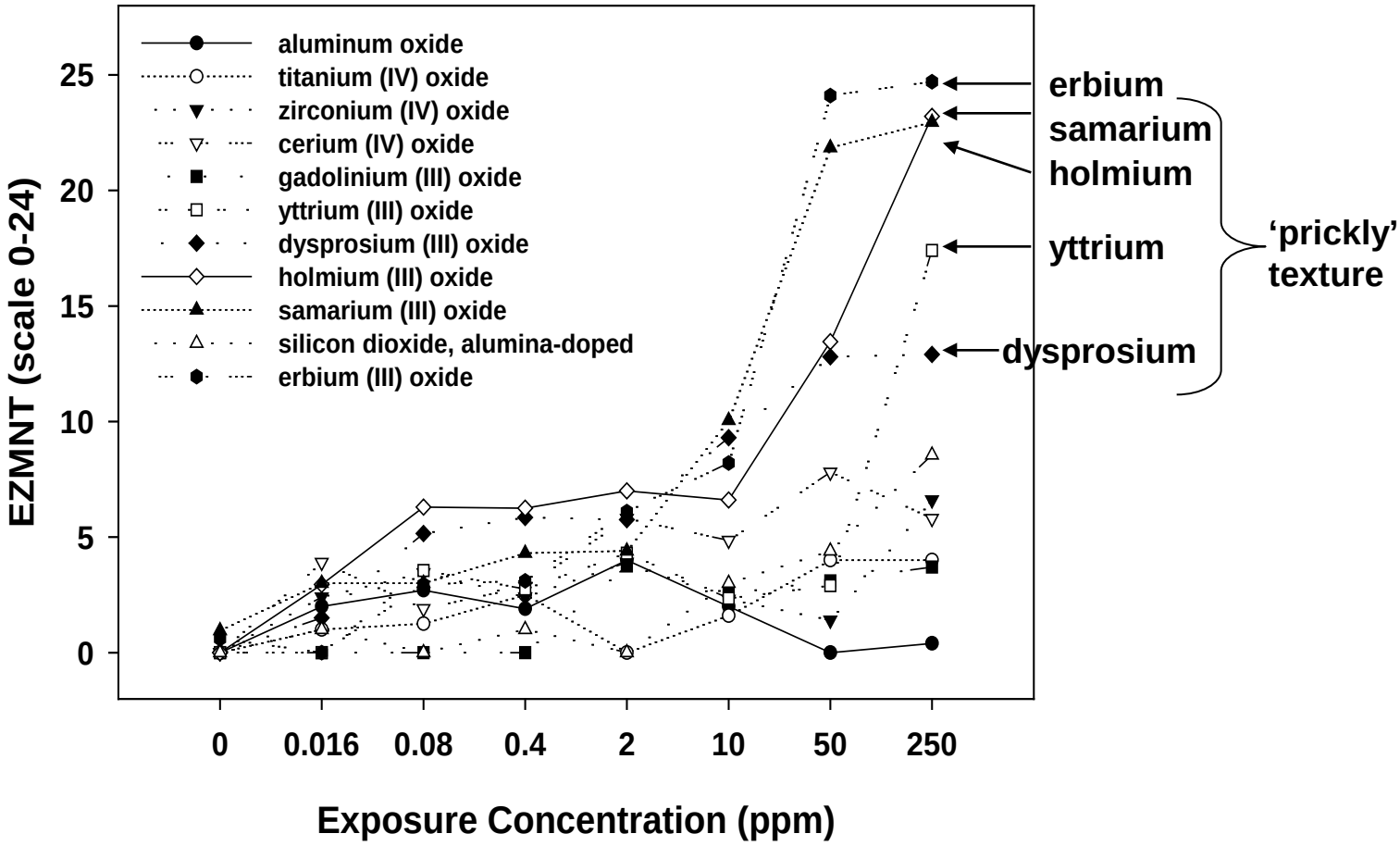


nanomaterial–biological interactions

EZ Metrics – Nanoparticulate Metal Oxides

nanomaterial–biological interactions

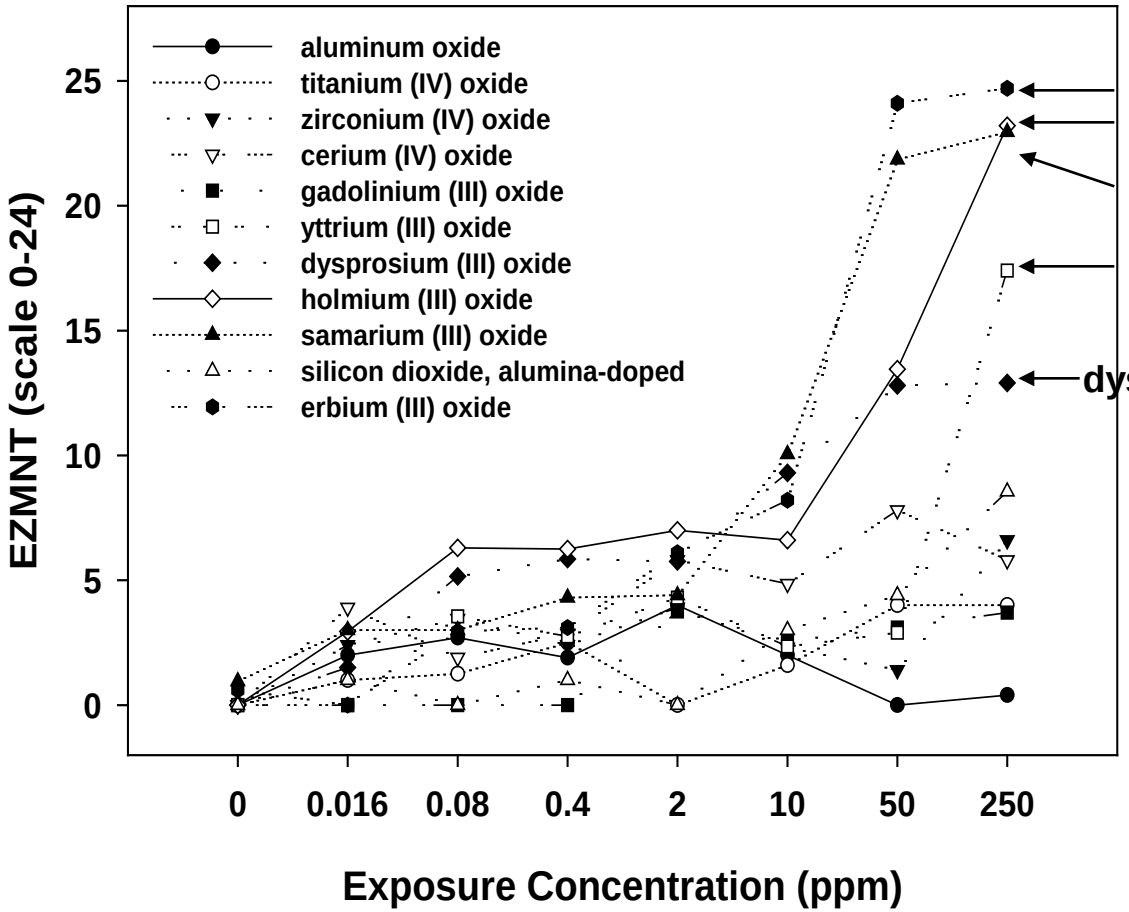
Effect of Shape

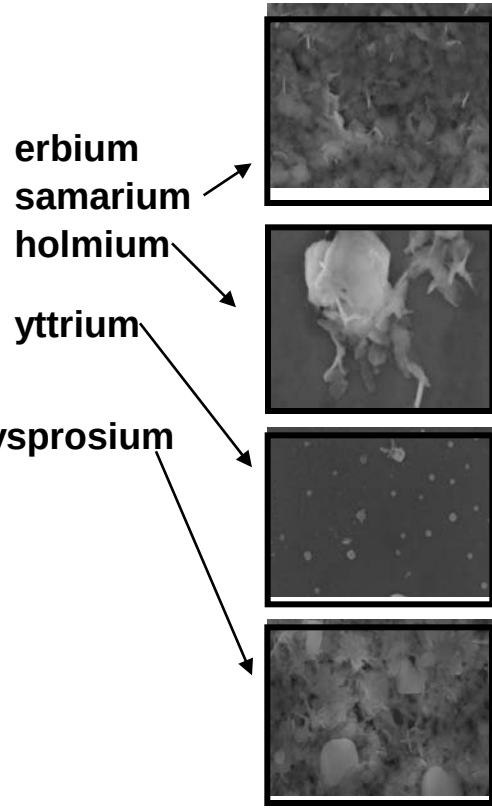


EZ Metrics – Nanoparticulate Metal Oxides

nanomaterial–biological interactions

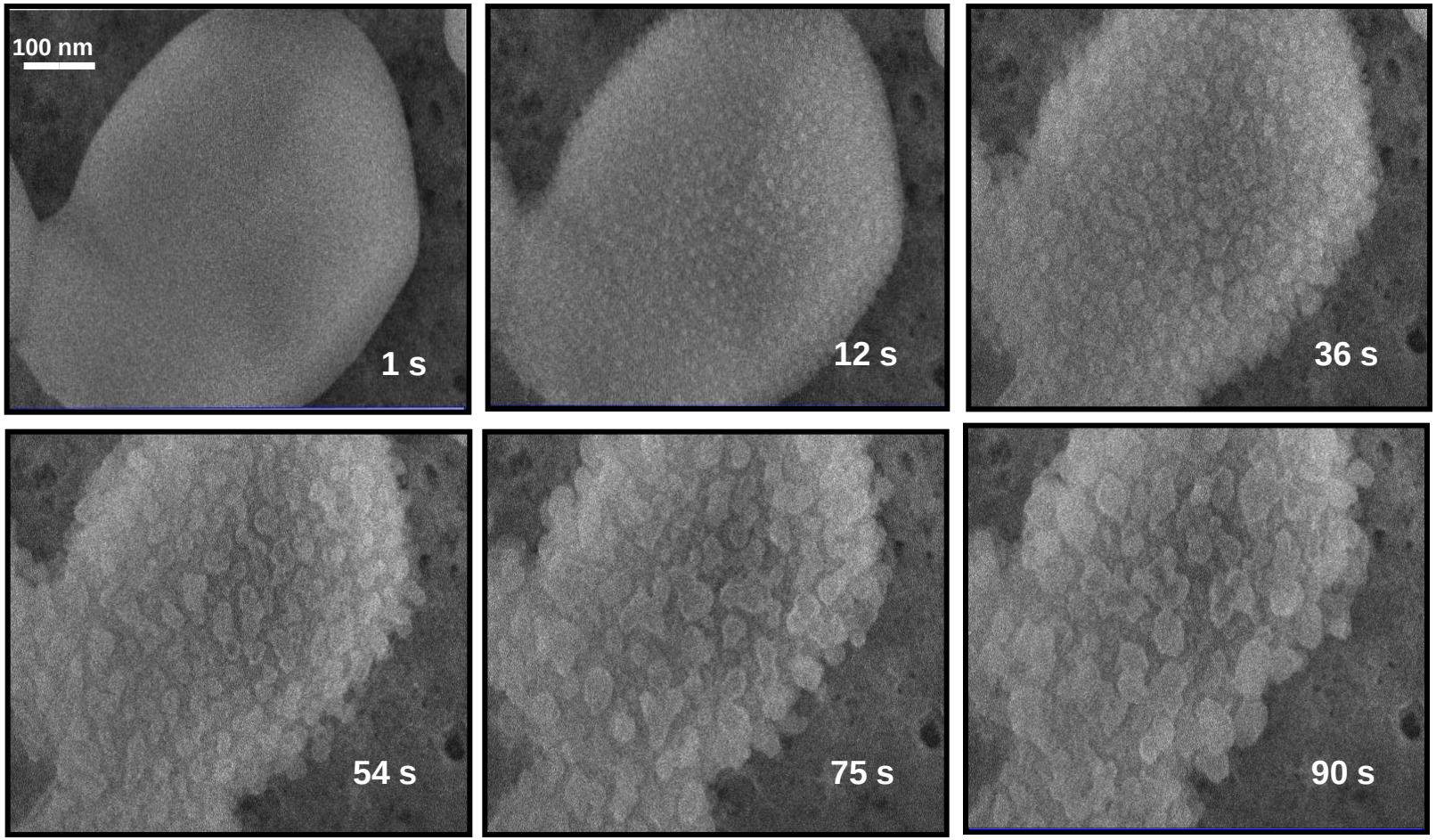
Effect of Shape





Erbium (III) Oxide Reactivity

nanomaterial–biological interactions



SEM analysis performed at CAMCOR

Comparative Nanotoxicology – EZ Metric

nanomaterial–biological interactions

EZ metric provides accurate, rapid indication of toxic potential of nanomaterials and nanomaterial solutions

EZ metric was consistent with other statistical evaluations

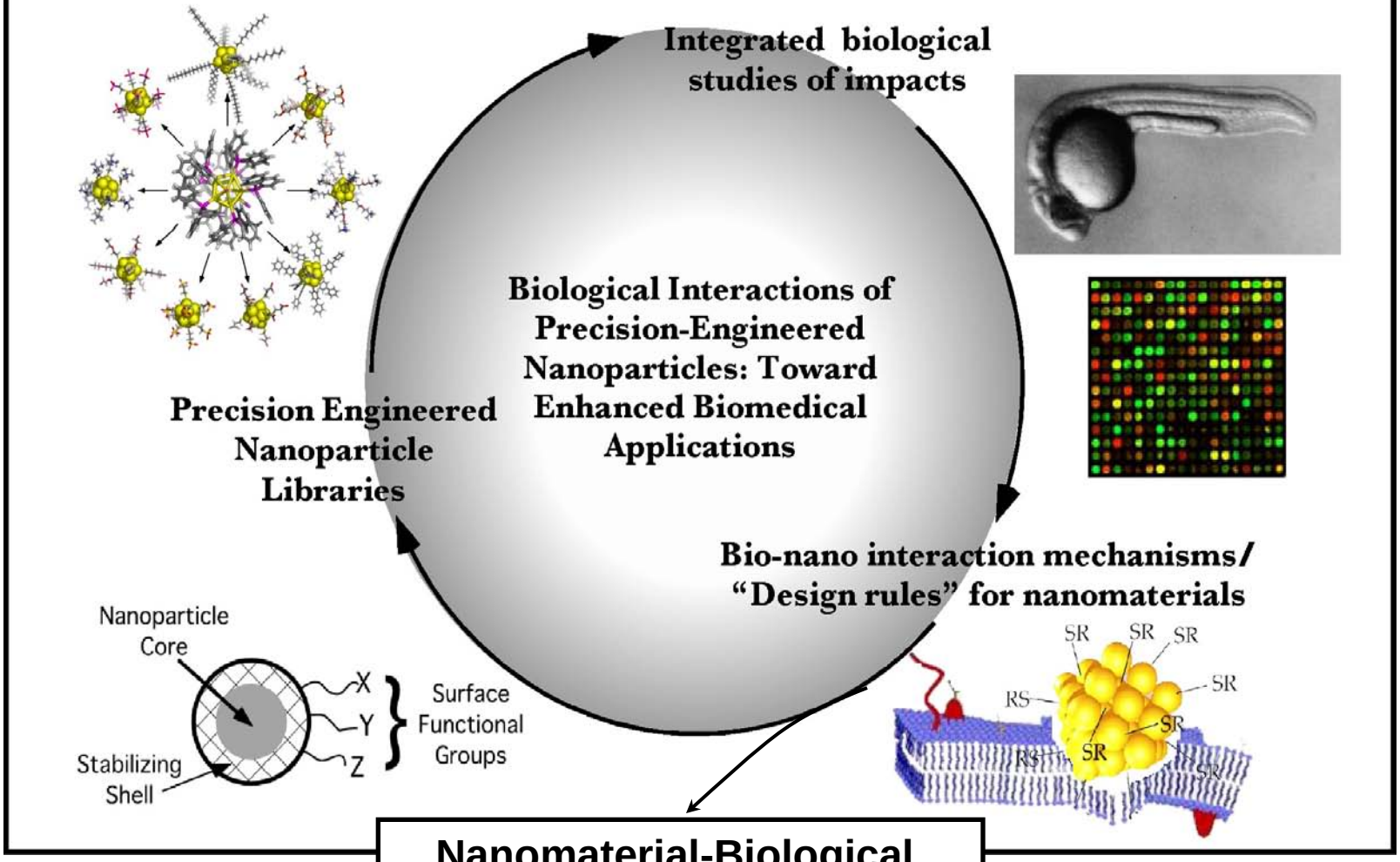
No biological response from vast majority of dendrimers, amine groups concerning

Viral capsids elicited minimal biological response

Toxicity of metal oxide nanoparticles dependent on composition, reactivity or shape, not charge or size distribution

Iterative Testing to Inform Nanomaterial Design

nanomaterial–biological interactions



Nanomaterial-Biological Interactions Knowledgebase

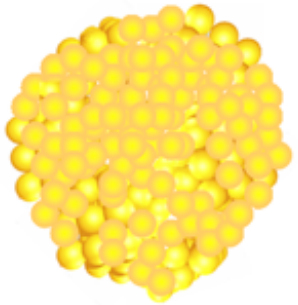
Precisely Engineered AuNPs

Harper, S.L., J.L. Carriere, J.M. Miller, J.E. Hutchison, B.L.S. Maddux and R.L. Tanguay. 2011. Systematic evaluation of nanomaterial toxicity: utility of standardized materials and rapid assays. ACS Nano 10.1021/nn200546k.

Core Size:

0.8 nm
11 Au Atoms
10 ligands

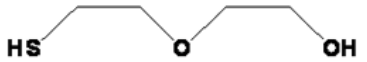
1.5 nm
101 Au Atoms
30-35 ligands



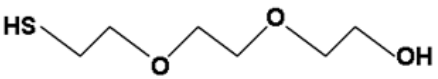
10 nm
37,000 Au Atoms
1400 ligands

Surface Functionalization:

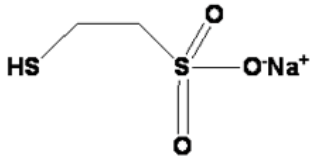
Neutral: 2-(2-mercaptoethoxy)ethanol (MEE)
0.8 and 1.5 nm
AuNPs



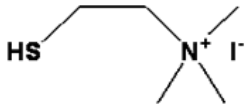
Neutral: 2,2,2-[mercaptoethoxy(ethoxy)]ethanol (MEEE)
0.8, and 1.5 nm AuNPs



Anionic: 2-mercaptoethanesulfonate (MES)
0.8 and 1.5 nm AuNPs



Cationic: N,N,N-trimethylammoniumethanethiol (TMAT)
0.8, 1.5 and 10 nm AuNPs



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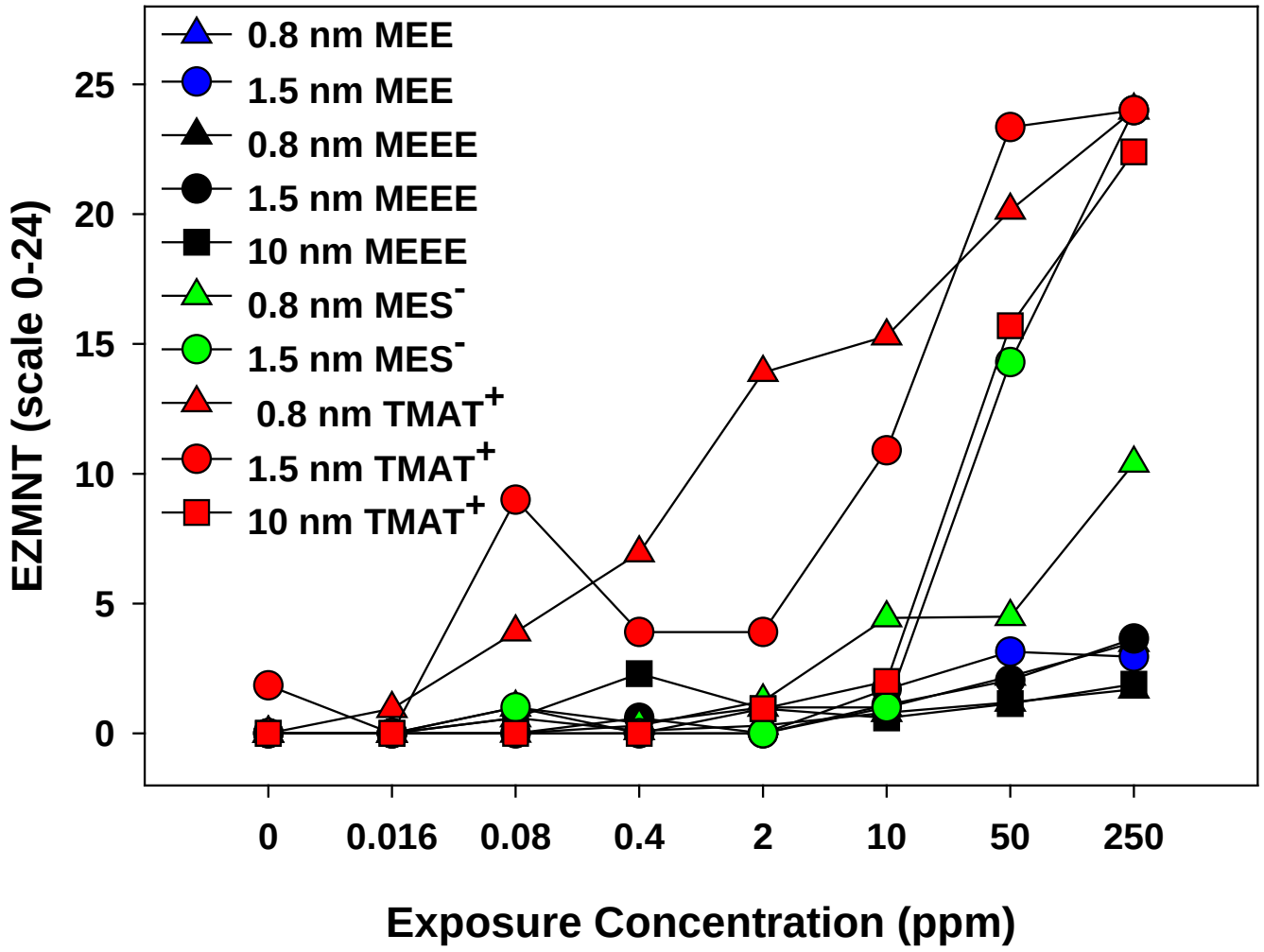
EZ Metrics – AuNP Exposure



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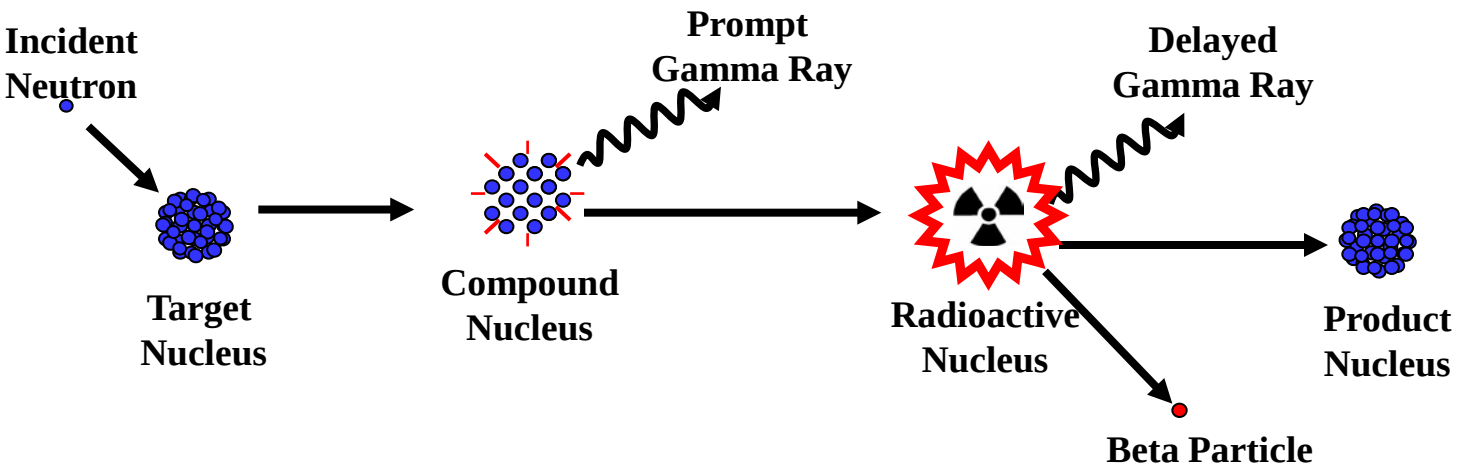
Quantification of AuNP Dose

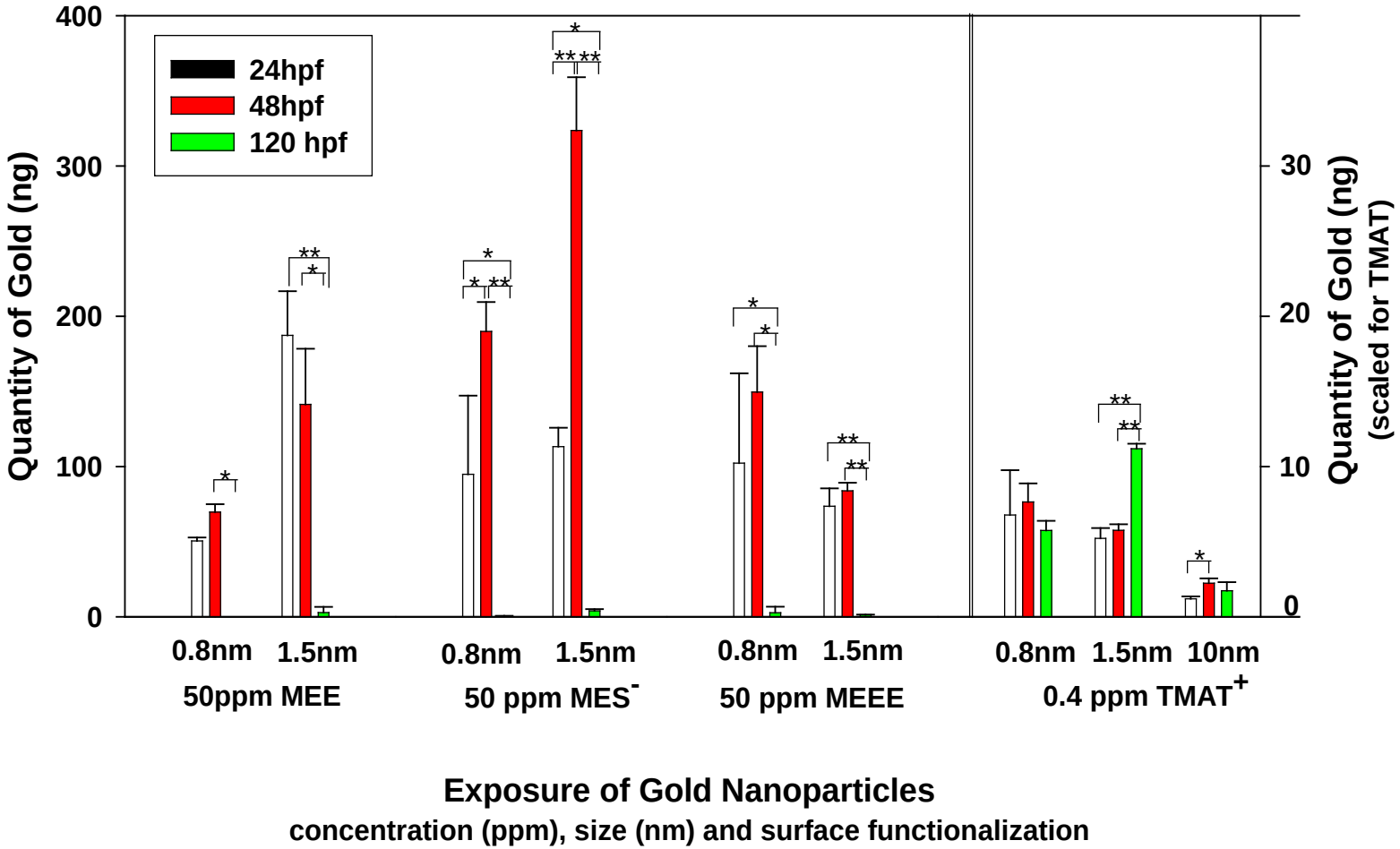
Instrument Neutron Activation Analyses



Neutron activation → excited state

Unique half-life of the radioactive nucleus → identify and precisely quantify original elements.

Quantification of Au in Individual Embryos



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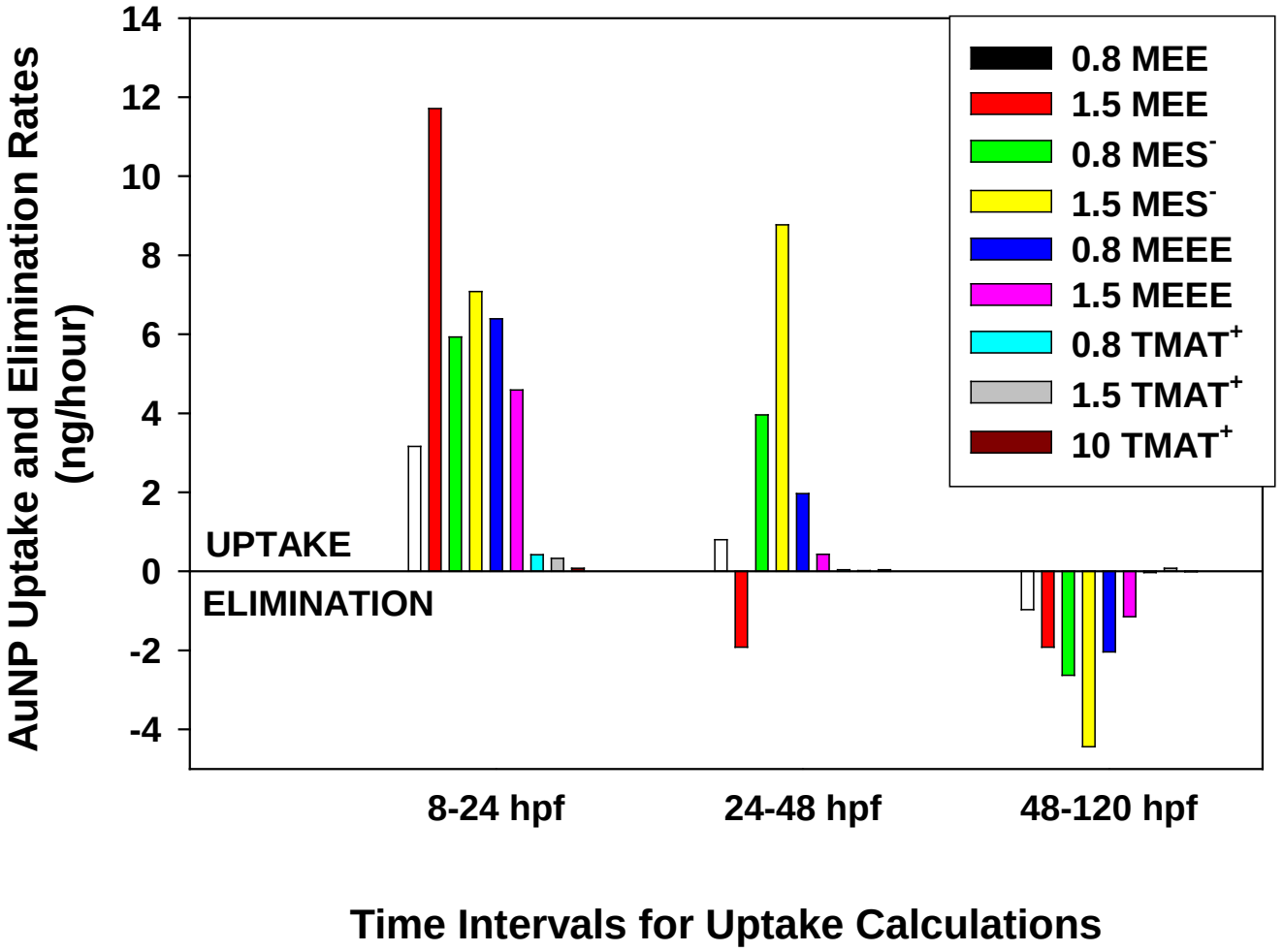
Uptake and Elimination Rates



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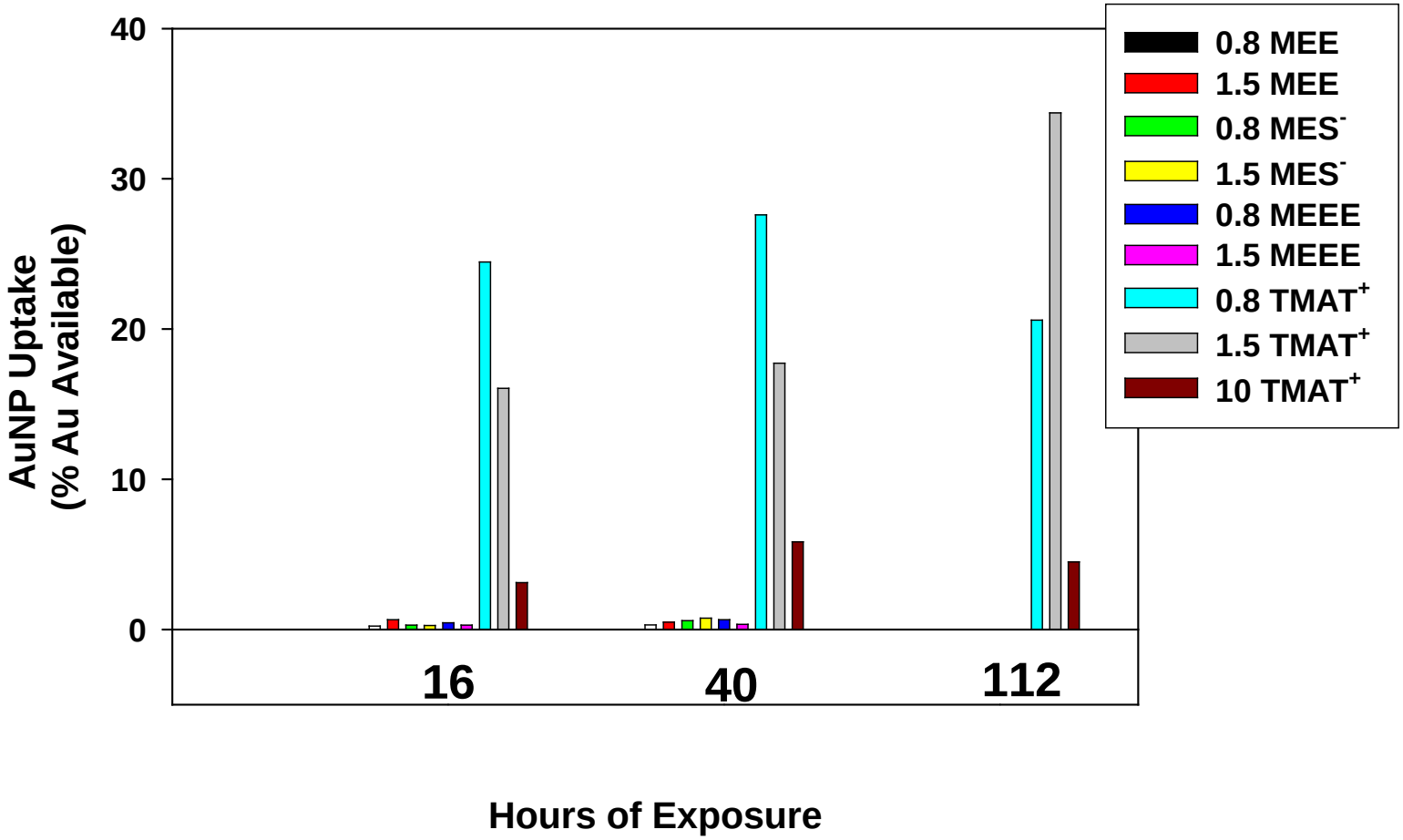
Uptake of AuNPs



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Comparative Nanotoxicology - EZ Metric

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Core size, charge and purity affect biological response to AuNPs

- Positively-charged ($TMAT^{+}$) had higher toxic potential than negative or neutral
- Positively-charged taken up more readily
- Positively-charged remained in animals longer

AuNPs provide a good platform to define nanoSARs

- Precisely engineered
- Large library (congeneric series)
- Green synthesis and purification
- Quantification with INAA

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NBI KNOWLEDGEBASE

INFORMATION | INTRODUCTION | PROJECTS | RESEARCH | NOTICE & PRESS | COLLABORATIONS | KNOWLEDGEBASE

nbi.oregonstate.edu

Nanomaterial -Biological Interactions Knowledgebase

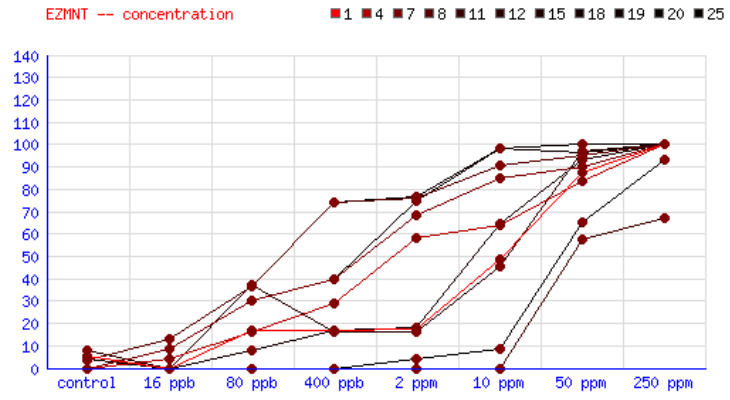
Knowledgebase

- Nanomaterial Library
- Analysis
- Prediction
- AHP Administration

Analysis — Knowledgebase >> Analysis

nanomaterial							EZMNT							
famly	core	structure	shape	size	charge	purity	concentration type	concentration						
metal	Au	TMAT		1.5		Ultra Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								5.32	0.00	16.88	16.67	17.29	48.48	87.29	100.00
metal	Au	TMAT		0.8		Ultra Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								0.00	3.96	16.25	28.96	57.92	83.75	83.96	100.00
metal	Au	TMAT		1.5		Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								0.00	8.75	30.21	39.58	68.33	84.79	90.21	100.00
metal	Au	TMAT		1.5		Dirty	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								3.33	12.92	36.46	74.38	75.83	90.42	95.00	100.00
metal	Au	TMAT		10		Ultra Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								0.00	0.00	0.00	0.00	0.00	0.00	57.50	67.42
metal	Au	TMAT	sphere	1.5	+	Ultra Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								7.71	0.00	37.50	16.25	16.25	45.42	97.29	100.00
metal	Au	TMAT	sphere	0.8	+	Ultra Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								0.00	3.96	16.25	28.96	57.92	83.75	83.96	100.00
metal	Au	TMAT	sphere	1.5	+	Ultra Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								3.96	0.00	7.92	17.08	18.33	64.38	93.54	100.00
metal	Au	TMAT	sphere	1.5	+	Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								0.00	8.75	30.21	39.58	75.00	98.54	98.46	100.00
metal	Au	TMAT	sphere	1.5	+	Dirty	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								3.33	12.92	36.46	74.38	76.67	98.33	100.00	100.00
metal	Au	TMAT	sphere	10	+	Ultra Pure	ppm	control	16 ppb	80 ppb	400 ppb	2 ppm	10 ppm	50 ppm	250 ppm
								0.00	0.00	0.00	0.00	3.96	8.33	85.42	93.33

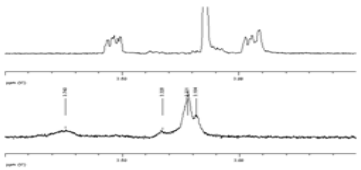
Graphs | Color Codes

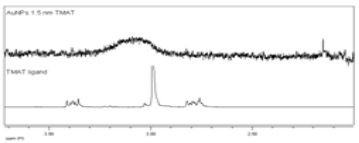


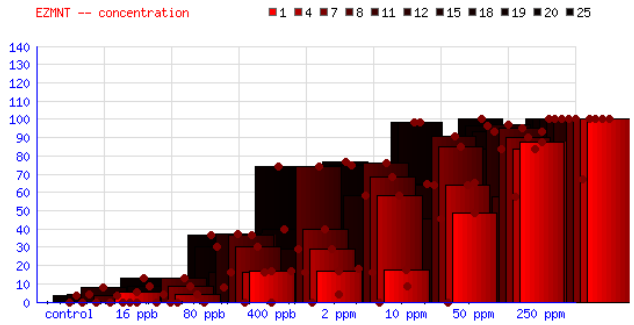
Family: metal
Core: Au
Structure: TMAT

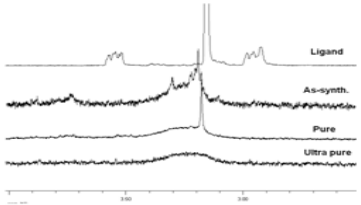
Description: TMAT-functionalized AuNPs have N,N,N-trimethylammoniumethanethiol surface groups. They are positively charged and spherical in shape.

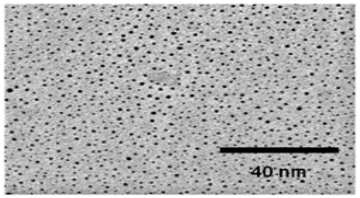
Related Links:
NIOSH
InterNano
http://ncl.cancer.gov/
http://www.nanohub.org/home
ICON
SAFENANO











Thank you for your attention

"I'm on board for microbrews, but nanopizza is taking technology a step too far."

Balbus et al. (2005) Issues in Science and Technology

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