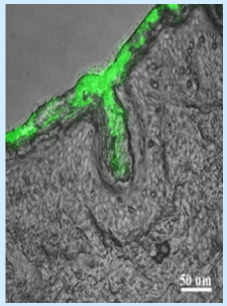
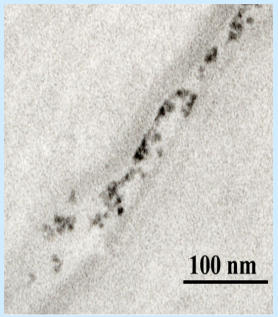
Perspectives on a Nano Career





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&

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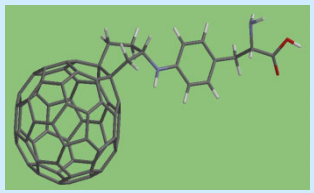
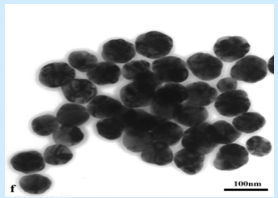
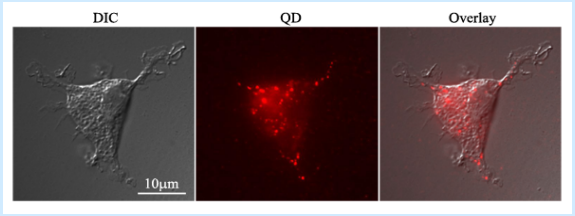
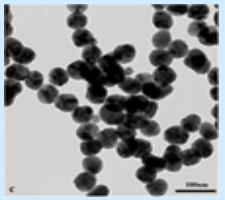
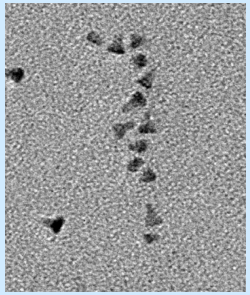






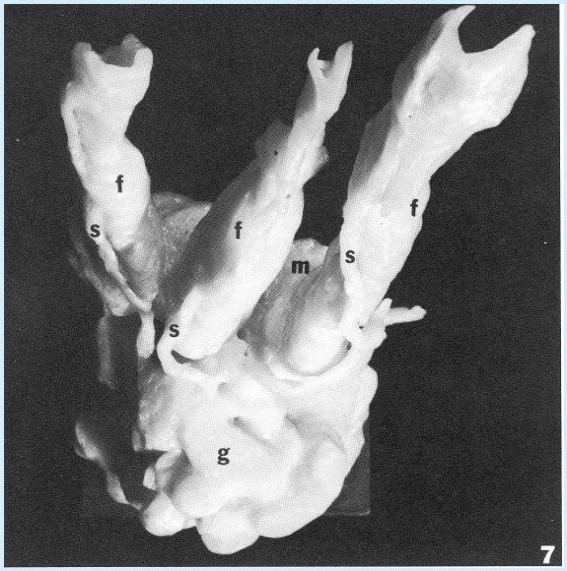


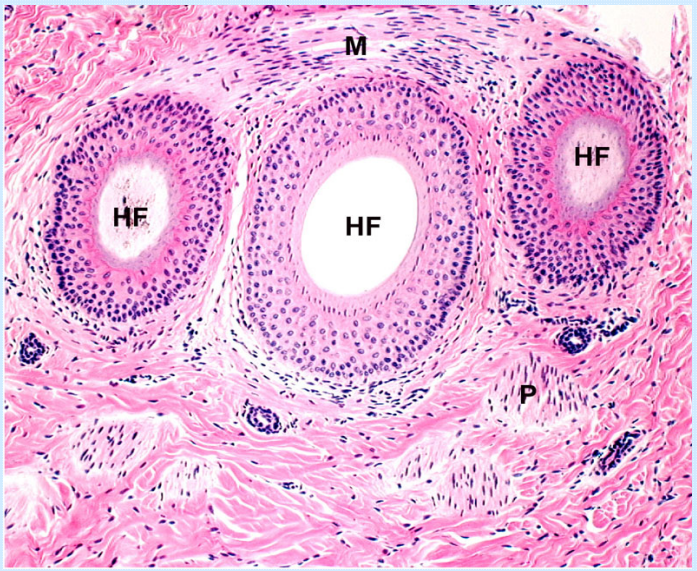


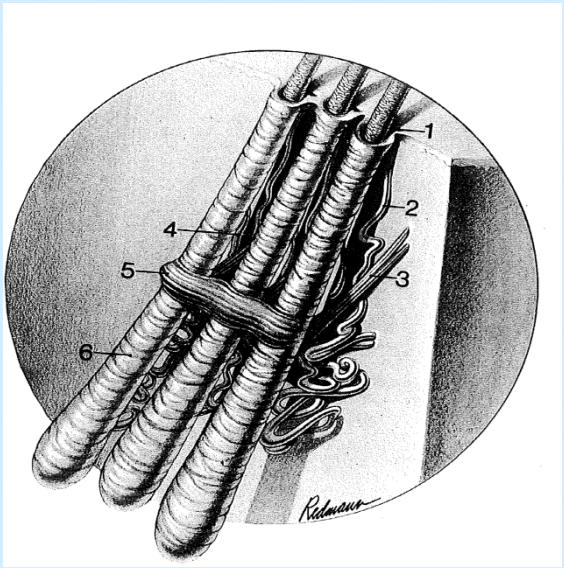
Background

- PhD in ultrastructural anatomy and cell biology (Skin)-Purdue University, West Lafayette, Indiana My Goal: "Best Comparative Anatomist”

Interfollicular smooth muscle in skin



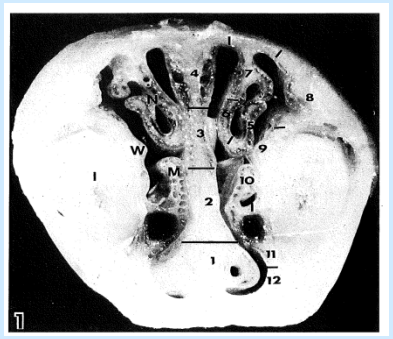


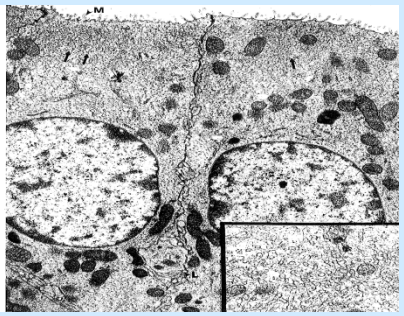


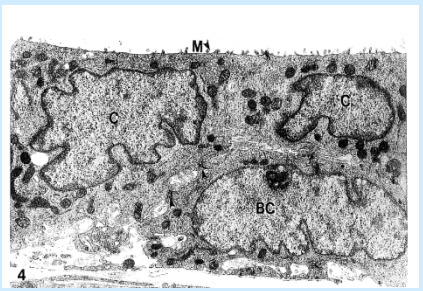
Anatomical Record 201: 455-462, 1981

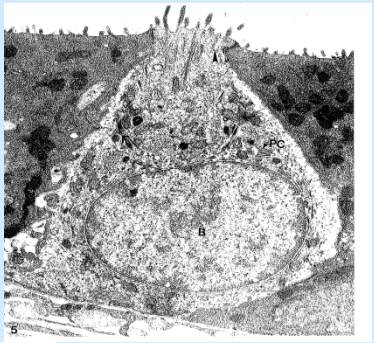
Background

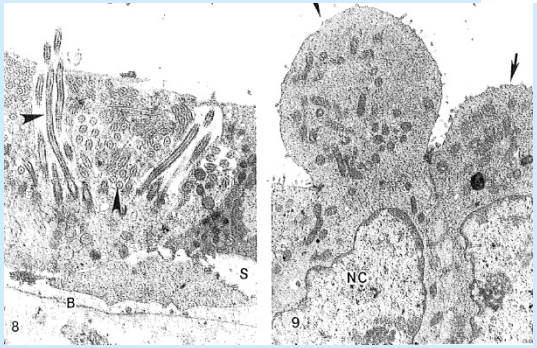
- Postdoctoral Fellowship in Toxicologic Pathology at the Chemical Industry Institute of Toxicology (CIIT), Research Triangle Park, NC (Formaldehyde inhalation)
- Discovered 3 new cell types in rat nasal mucosa: nonciliated columnar, cuboidal and brush cells.











Monteiro-Riviere NA and Popp JA. Ultrastructural characterization of the nasal respiratory epithelium in the rat. *American Journal of Anatomy* 169:31-43, 1984.

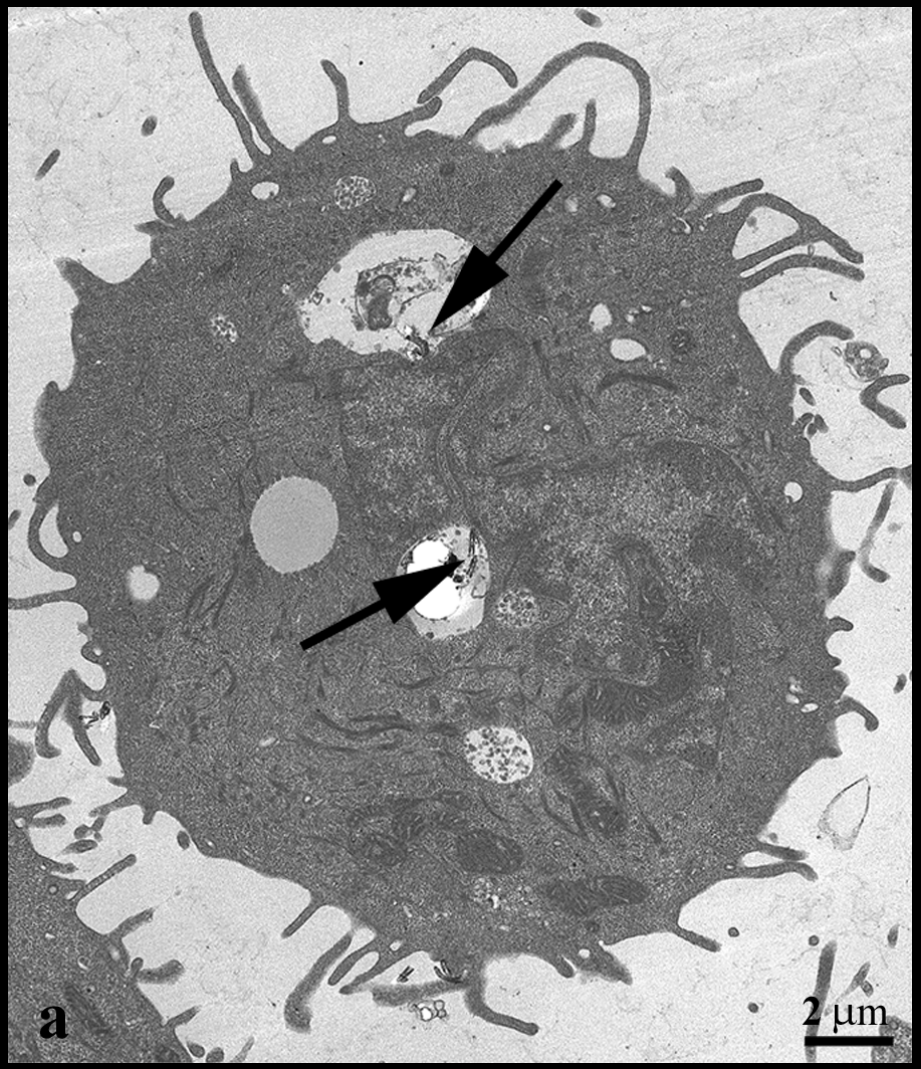
Ultrastructural evaluation of acute nasal toxicity in the rat respiratory epithelium in response to formaldehyde gas. *Fundamental Applied Toxicology* 6:251-262, 1986.

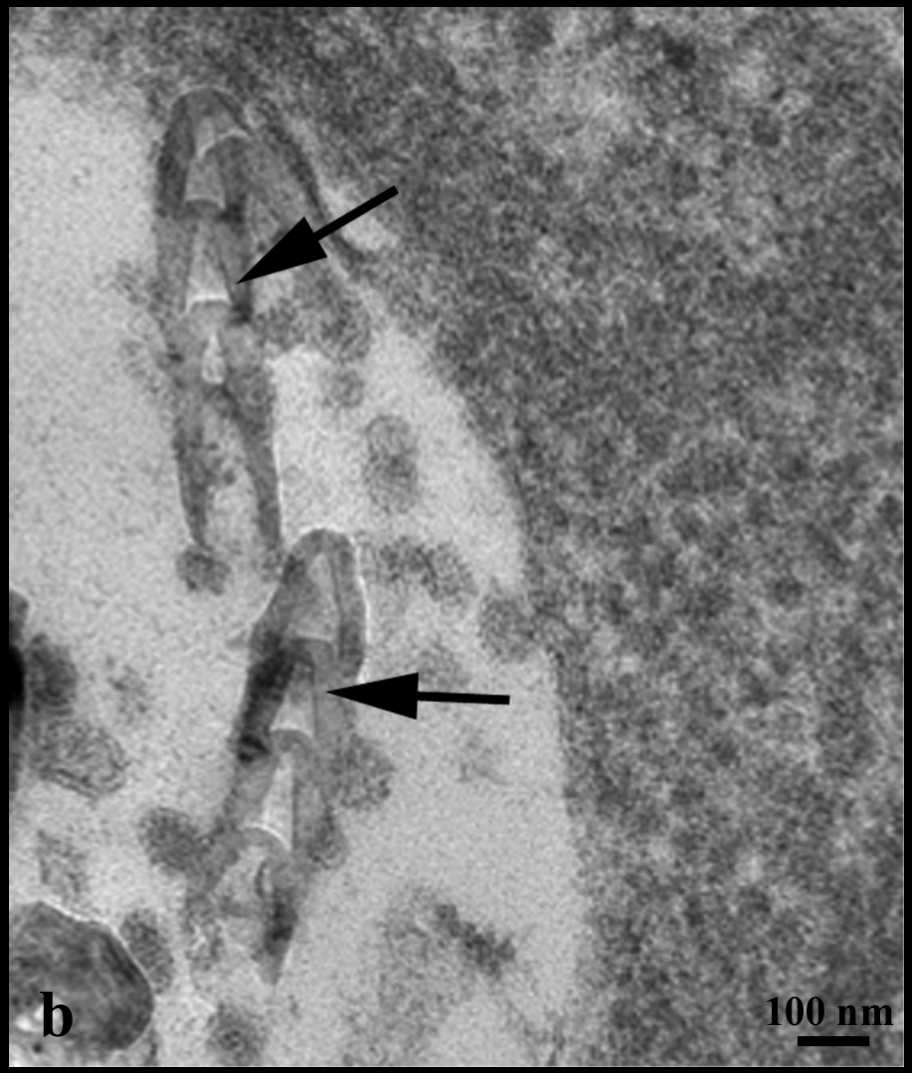
Background

- Assistant, Associate and Full Professor of Investigative Dermatology and Toxicology at North Carolina State University, Department of Clinical Sciences & Joint UNC/NCSU Biomedical Engineering for 28 years. Appointment at UNC Chapel Hill School of Medicine in Dermatology

- Research focus: skin absorption & toxicity - in vivo and in vitro models, in vitro models-cell culture, diffusion cells, IPPSF. Studied cutaneous toxicants ranging from chemical warfare agents, vesicants, iontophoresis, transdermal drug delivery systems, microneedle delivery.

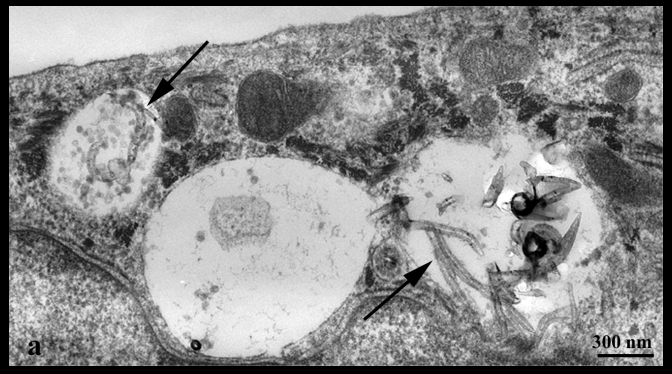
- Research funded by NIEHS, NIOSH, DoD-USAMRDC,US-AFOSR,EPA Star and numerous drug companies and industries.

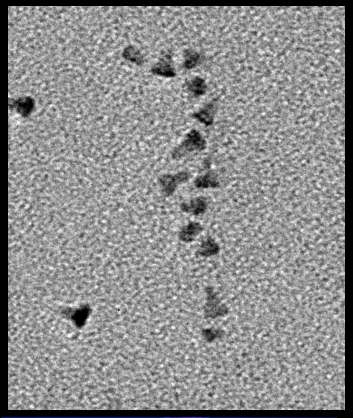


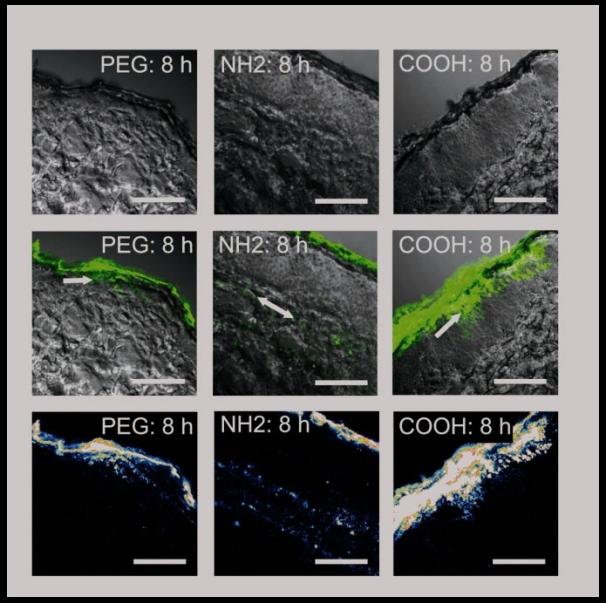


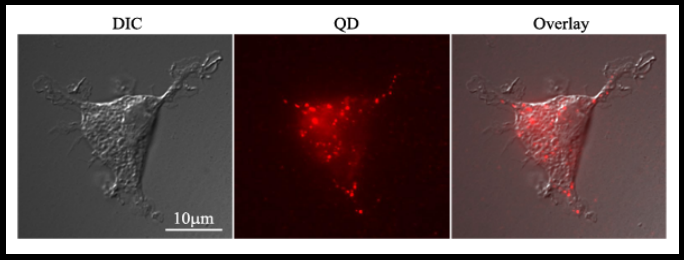
Monteiro-Riviere et al., *Science*, 306,p. 2164, 2004

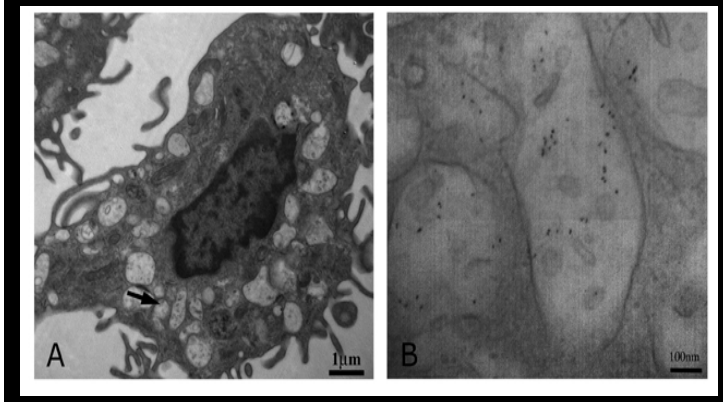
Monteiro-Riviere NA, Nemanich RJ, Inman AO, Wang YY, Riviere JE: Multi-walled carbon nanotube interactions with human epidermal keratinocytes. *Toxicology Letters* 155:377-384, 2005

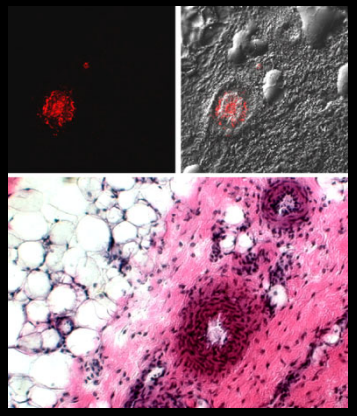


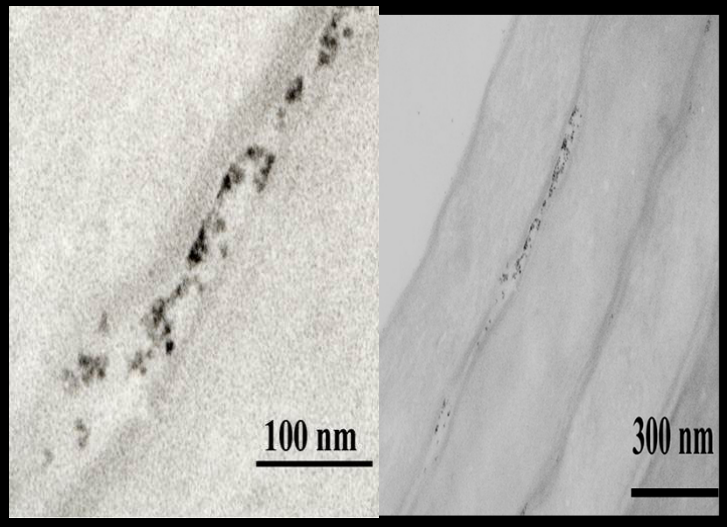






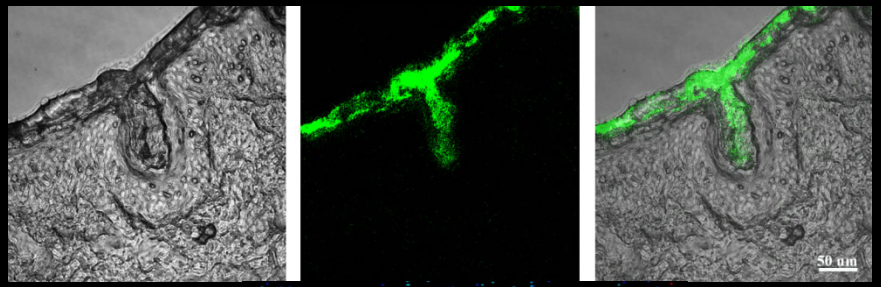


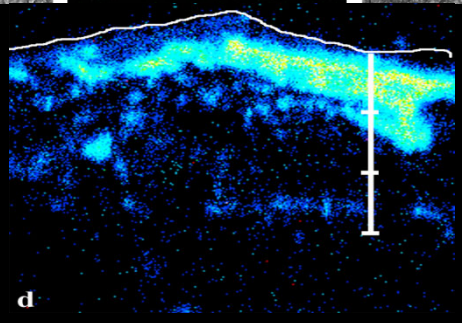




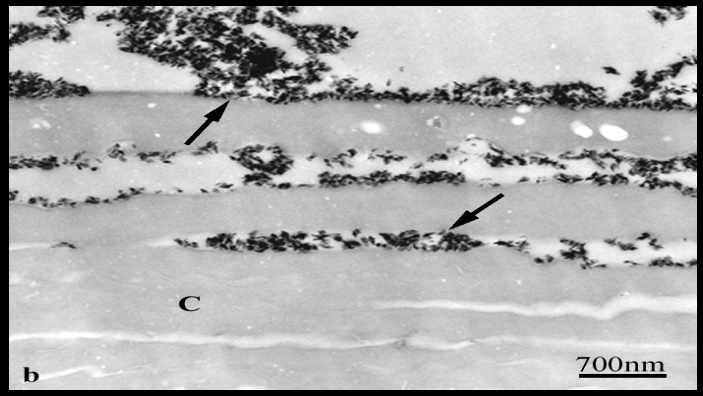
QD 565, 655, 621,

Topical skin : occupational and consumer products



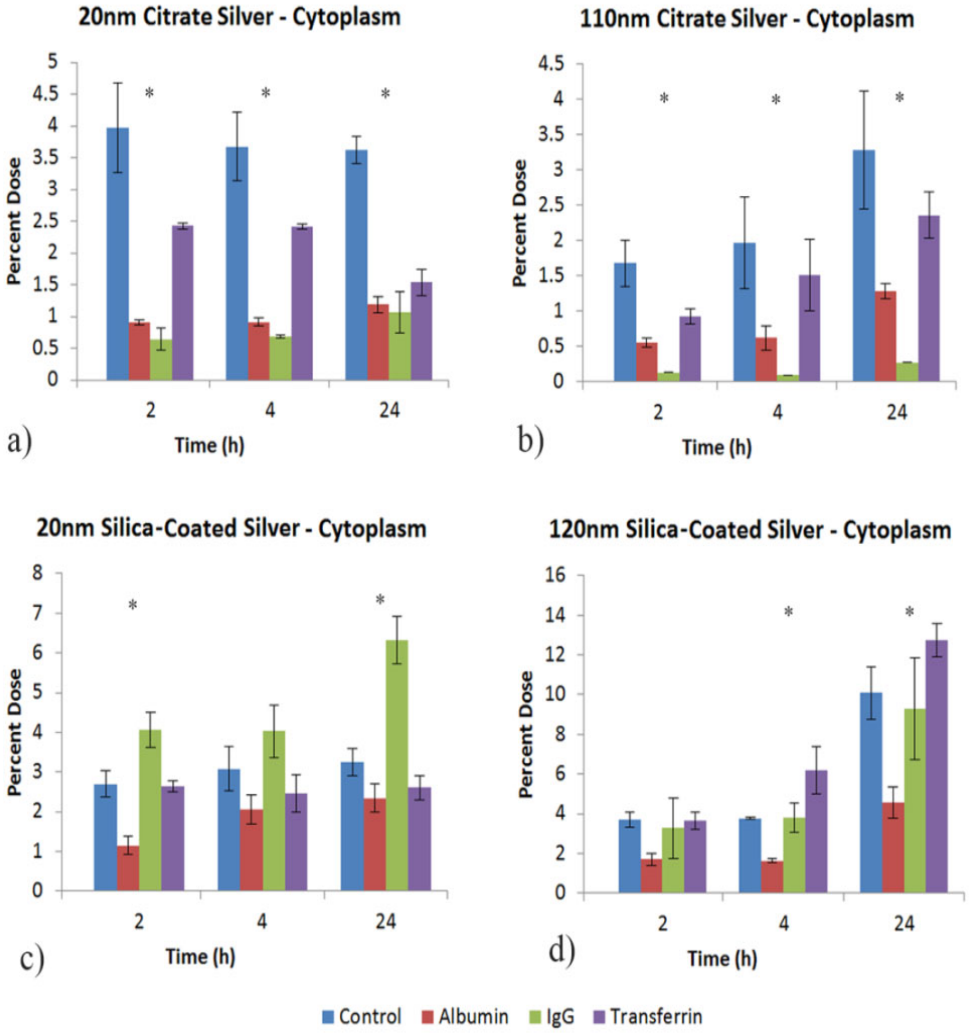


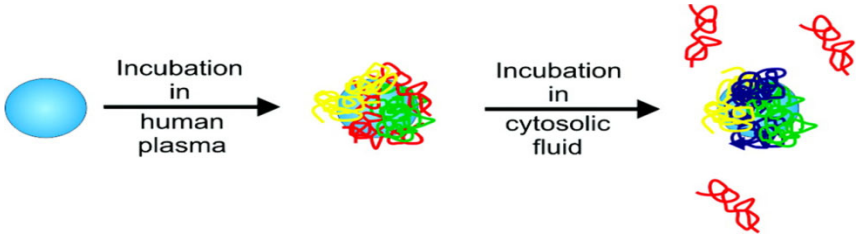
Time of Flight SIMS



Monteiro-Riviere, Wiench, Landsiedel, Schulte, Inman, Riviere. Safety evaluations of sunscreen formulations containing titanium dioxide nanoparticles in UVB sunburned skin: An in vitro and in vivo study. ***Toxicological Sciences*** **123:264-280, 2011.**

Biocoronas modulate cellular uptake of AgNP with two coatings pre-incubated with three different proteins





Monteiro-Riviere, et al., Protein binding modulates the cellular uptake of silver nanoparticles into human cells: Implications for in vitro to in vivo extrapolations? ***Toxicology Letters*** 220:286-293, 2013.

40 nm PC-BPEI (39/59)	80 nm PC-BPEI (36/59)	40 nm PC-LA (54/59)	80 nm PC-LA (54/59)	40 nm PC-PEG (51/59)	80 nm PC-PEG (54/59)
Human serum albumin (164)	***Human serum albumin (154)***	***Human serum albumin (154)***	***Human serum albumin (198)***	***Human serum albumin (105)***	***Human serum albumin (130)***
Fibrinogen beta chain (110)	***Fibrinogen alpha chain (151)***	***Talin-1 (104)***	Myosin-9 (96)	***Talin-1 (66)***	***Talin-1 (120)***
Fibrinogen alpha chain (100)	Fibrinogen beta chain (139)	Myosin-9 (74)	***Talin-1 (91)***	Myosin-9 (51)	Myosin 9 (114)
Fibrinogen gamma chain (82)	***Fibrinogen gamma chain (93)***	Filamin-A (72)	Filamin-A (81)	Filamin-A (50)	Filamin A (109)
Serotransferrin (35)	Plasminogen (55)	Integrin alpha IIb (59)	Integrin alpha IIb (55)	Integrin alpha IIb (40)	***Actin, cytoplasmic 1 (76)***
Actin, cytoplasmic 1 (34)	***Actin, cytoplasmic 1 (31)***	***Actin, cytoplasmic 1 (52)***	***Actin, cytoplasmic 1 (47)***	Vinculin (20)	Integrin alpha IIb (59)
Ig kappa chain C region (33)	Ig kappa chain C region (29)	Vinculin (38)	Vinculin (44)	Serotransferrin (24)	Alpha-actinin-1 (47)
Apolipoprotein A-I (30)	***Apolipoprotein A-I (26)***	Keratin, type II cytoskeletal 1 (36)	***Apolipoprotein A-I (40)***	***Actin, cytoplasmic 1 (23)***	Vinculin (43)
Ig gamma-1 chain C region (24)	***Ig gamma-1 chain C region (24)***	Integrin beta-3 (28)	Integrin beta-3 (36)	Integrin beta-3 (22)	Integrin beta-3 (36)
Talin-1 (23)	***Talin-1 (22)***	***Fibrinogen gamma chain (26)***	Serotransferrin (34)	***Fibrinogen gamma chain (21)***	***Fibrinogen gamma chain (30)***
Haptoglobin (21)	Haptoglobin (17)	Vitronectin (24)	Fibrinogen beta chain (33)	Ig kappa chain C region (20)	14-3-3 protein zeta/delta (29)
Ig mu chain C region (13)	Ig mu chain C region (16)	Alpha-actinin-1 (21)	***Fibrinogen alpha chain (32)***	***Apolipoprotein A-I (17)***	***Fibrinogen alpha chain (28)***
Ig alpha-1 chain C region (13)	Prothrombin (15)	Ig kappa chain C region (20)	***Ig gamma-1 chain C region (24)***	***Fibrinogen alpha chain (17)***	***Apolipoprotein A-I (25)***
Complement C3 (11)	Ig gamma-2 chain C region (13)	***Apolipoprotein A-I (20)***	***Fibrinogen gamma chain (23)***	***Ig gamma-1 chain C region (16)***	Ig kappa chain C region (23)
Ig gamma-2 chain C region (11)	Alpha-1 antitrypsin (13)	**Ig gamma-1 chain C region (20)**	14-3-3 protein zeta/delta (20)	Complement C4-B (17)	Complement C4-B (21)
Apolipoprotein E (11)	Serotransferrin (12)	***Fibrinogen alpha chain (18)***	Haptoglobin (19)	Ig mu chain C region (14)	***Ig gamma-1 chain C region (17)***
Alpha-2 macroglobulin (10)	Ig alpha-1 chain C region (10)	Fibrinogen beta chain (16)	Alpha-actinin-1 (19)	Haptoglobin (13)	Haptoglobin (17)
Alpha-1 antitrypsin (10)	Ig lambda-2 chain C region (10)	Keratin, type I cytoskeletal (16)	Keratin, type II cytoskeletal 1 (17)	Alpha-actinin-1 (13)	Clusterin (16)
Integrin alpha-IIb (8)	Clusterin (9)	Ig mu chain C region (15)	Vitronectin (17)	Keratin, type II cytoskeletal 1 (13)	Gelsolin (15)
Clusterin (8)	Complement C3 (8)	Serotransferrin (15)	Complement C3 (16)	Fibrinogen beta chain (11)	Ig mu chain C region (14)

Table 1. Top 20 most abundant hard corona proteins detected in the adsorbomes of 40 and 80 nm BPEI, LA and PEG AuNP after 1h of plasma exposure out of 59 proteins. Red italicized: most abundant protein in all AuNP coronas; Black italicized: proteins that are common to all AuNP coronas, within the abundant 20 proteins. Numbers within parentheses after each protein represents their respective spectral counts.

Gene Expression

126 genes for bare and plasma corona at nontoxic and toxic dose were affected out of 370 genes

25 µg/ml 40 nm BPEI AuNP

Bare

↓ 27 ↑ 3 = 30 genes changed

8/30 DNA Damage & Repair pathway (27%)
6/30 Heat Shock Response (20%)

Plasma Corona

↓ 1 ↑ 3 = 4 genes changed

- No major pathways were involved

75 µg/ml 40 nm BPEI AuNP

Bare

↓ 66 ↑ 14 = 80 genes changed

16/80 DNA Damage & Repair (20%)
14/80 Heat Shock Response (18%)
8/80 Mitochondrial energy metabolism (10%)

Plasma Corona

↓ 2 ↑ 47 = 49 genes changed

10/49 Phospholipidosis (20%),7/49 Apoptosis (14%), 6/49 Immunotoxicity (12%), 5/49 Cholestasis (10%),

Chandran,Riviere,Monteiro-Riviere.Surface chemistry of gold NP determines the biocorona composition impacting cellular uptake, toxicity, and gene expression profiles in human endothelial cells. ***Nanotoxicology*** *11:4, 507-519, 2017.*

Assessment of Nine Different Viability Methods with Five Different Types of Nanomaterials in a Human Cell Line

- Dye-based assays used to determine cell viability may produce invalid results due to the interactions of carbon nanomaterials (CNM) with the dye and/or CNM adsorption of the dye/dye products. Also, true for cytokines, essential nutrients, etc.

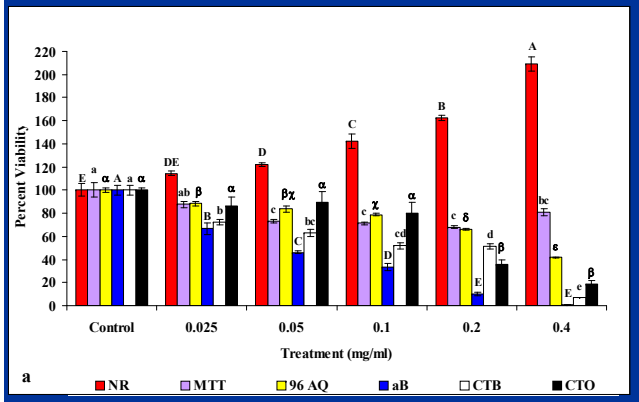
- To evaluate & compare 9 different viability assays on HEK cells treated with 5 NM (carbon and non-carbon based) to determine the best assay that would provide accurate results to elucidate the mechanism of toxicity.

Monteiro-Riviere NA, Inman AO: Challenges for assessing carbon nanomaterial toxicity to the skin. *Carbon* 44:1070-1078, 2006.

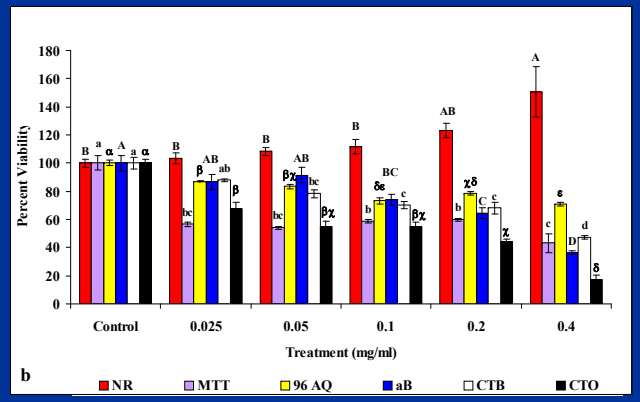
Zhang L, Zeng L, Barron AR, Monteiro-Riviere NA: Biological interaction of functionalized single-walled carbon nanotubes in human keratinocytes. *International Journal of Toxicology* 26:103-113, 2007.

Monteiro-Riviere NA, Inman AO, Zhang LW. Limitations and relative utility of screening assays to assess engineered nanoparticle toxicity in a human cell line. *Toxicology & Applied Pharmacology* 234:222-235, 2009.

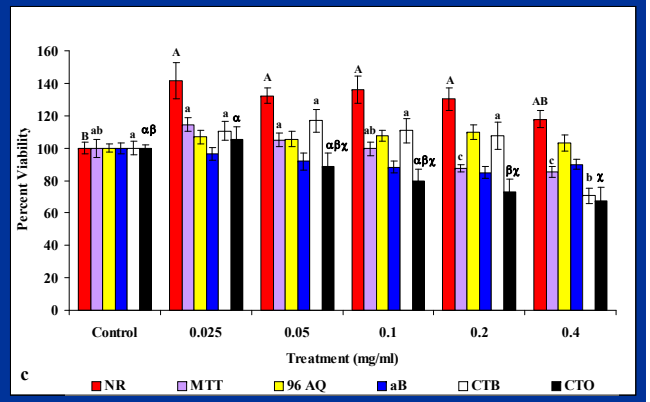
Nanomaterials Interfere with Viability Assays



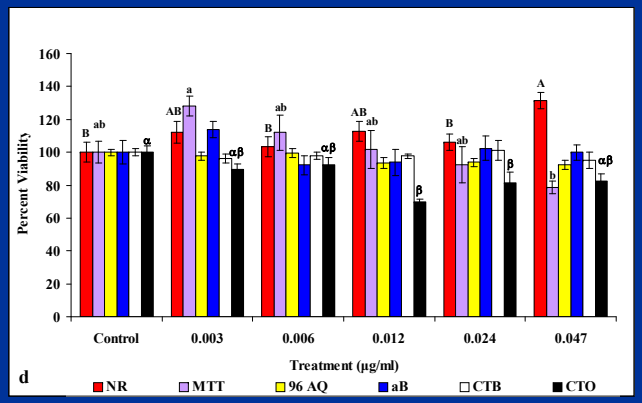
Carbon Black



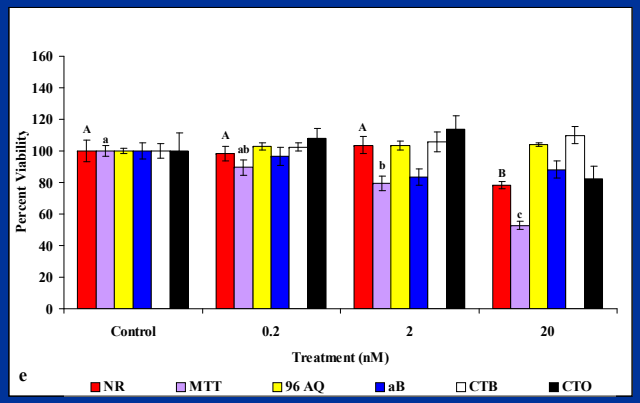
SWCNT



C60



nC60



QD655

Monteiro-Riviere NA, Inman AO, Zhang LW. Limitations and relative utility of screening assays to assess engineered nanoparticle toxicity in a human cell line. *Toxicology & Applied Pharmacology* 234:222-235, 2009.

Perspectives

- I got involved in nanotoxicology based on my background in EM and skin uptake and toxicity research after attending the National Academy of Sciences Keck Future Initiatives Conference on "*Designing Nanostructures at the Interface between Biomedical and Physical Systems*" in June 2004.
- This one meeting established a network of interdisciplinary collaborators that persist to this day and even provided seed funding to foster our collaborative research ideas.

Perspectives

- I made every effort to attend nanoscience meetings to learn about this emerging field and to expand my network of collaborators.
- As my research continued and became recognized, I was invited to numerous workshops and served on numerous national and international nanotoxicology related panels.
- We all learned that there are unique issues in studying nanotoxicology versus small molecule toxicology (physical chemical characterization, protein coronas, assay interference, etc).

The Future

- Despite our experience, senior scientists need to make room for new young investigators.
- We can take on new roles by offering valuable contributions and advice on research directions and career pathways.
- Young investigators have to make the effort to contact and interact with those with theoretical and practical experience in the field.


THANK YOU