

16 April 2009

ERC TeleSeminar Series



Accelerating the next technology revolution.



# Challenges in Assessing the Potential Toxicity of Carbon Nanotubes

**Paul Pantano, Ph.D.**

**Associate Professor of Chemistry**



# UT-Dallas Bionanosciences Group

est. 2002

- **Gregg R. Dieckmann**
  - Associate Professor of Chemistry
- **Rockford K. Draper**
  - Professor of Chemistry and Molecular & Cell Biology
- **Inga Holl Musselman**
  - Associate Professor of Chemistry
- **Steven O. Nielsen**
  - Assistant Professor of Chemistry
- **>12 other Researchers from the UTD Departments of:**  
Chemistry, Molecular & Cell Biology, Physics, Neuroscience, and  
Electrical Engineering & Computer Sciences
- **Bob Helms**
  - Professor of Electrical Engineering

# Collaborators

- **Ray H. Baughman**

- Department of Chemistry

- **Anvar Zakhidov**

- Department of Physics



- **Harold 'Skip' Garner**

- Division for Translational Research

- **Christopher Gilpin**

- Molecular & Cellular Imaging Facility

- **Ellen S. Vitetta**

- Cancer Immunobiology Center



- **Ara Phillipossian**

- School of Engineering



# Support



Collaborative  
Research  
Program



Accelerating the next technology revolution.



❖ Radu Marches

❖ Carole Mikoryak

❖ Ru-Hung Wang

❖ Makda T. Araya

❖ J. Gary Sinclair

❖ Austin D. Swafford

❖ Danielle A. Victor

❖ E. Kate Walker

❖ Morgan Black

❖ Chris Liu

❖ Robert N. Azad

❖ Pooja Baja

❖ Eric Becraft

❖ Pavitra Chakravarty

❖ Shook-Fong Chin

❖ Chi-Cheng Chiu

❖ Meredith C. Daigrepoint

❖ Will Kaberle

❖ Jane Nguyen

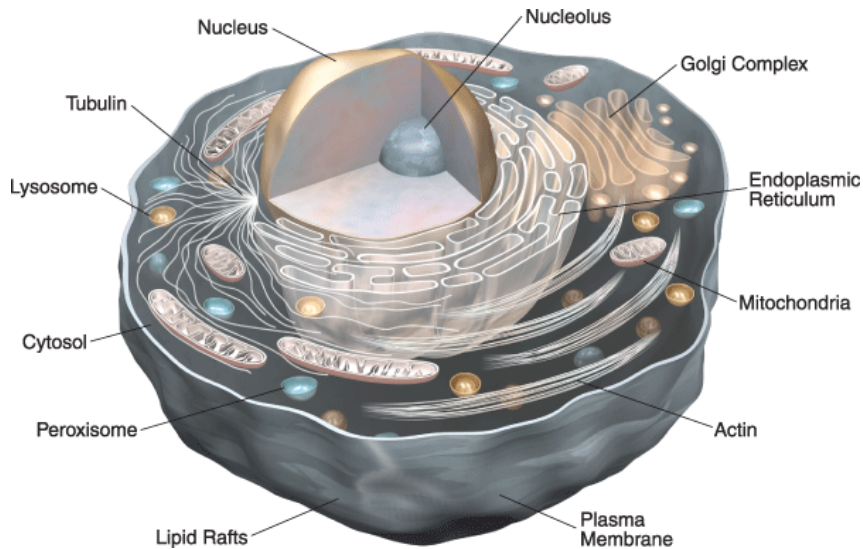
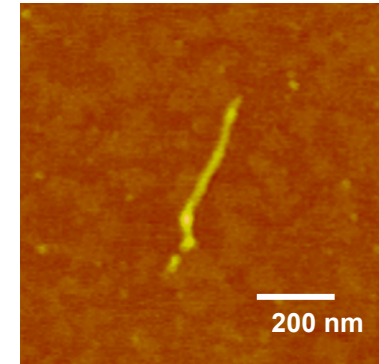
❖ Vasiliki Z. Poenitzsch

❖ Matthew N. Wallack

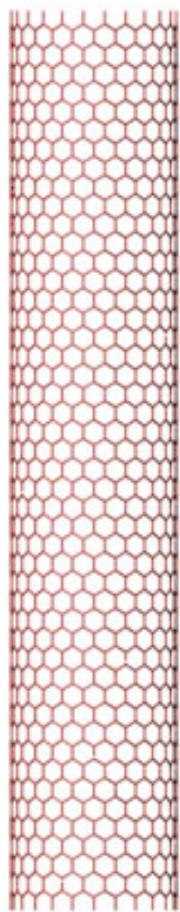
❖ Hadi N. Yehia

# Interactions of SWNTs with Cells

- Short, dispersed SWNTs coated with peptides or proteins
- What coatings ↑ SWNT uptake?

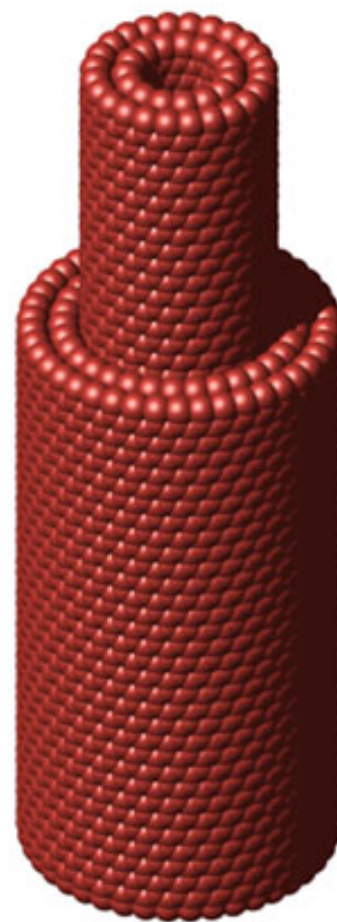


- What are the SWNT Uptake Mechanisms?
- Where do the SWNTs go?
- How do Cells respond?



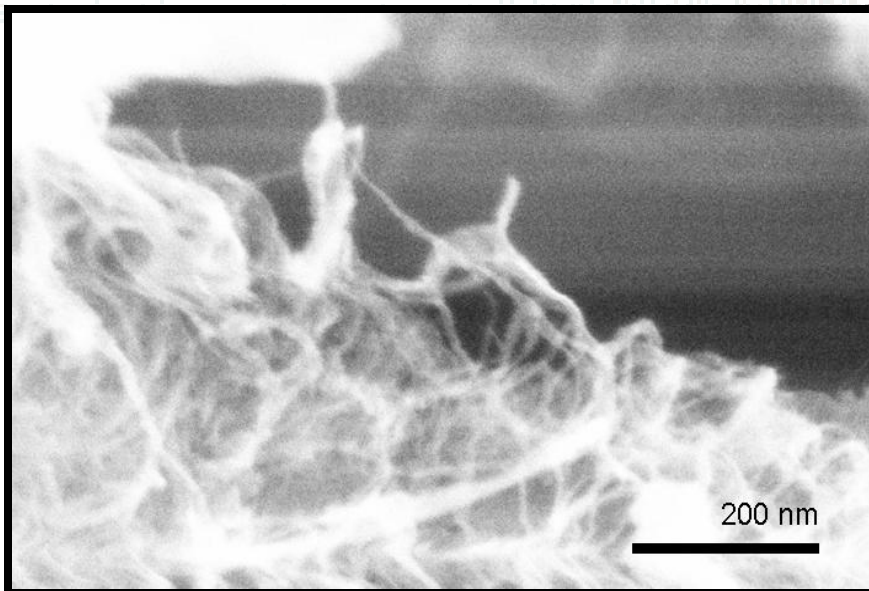
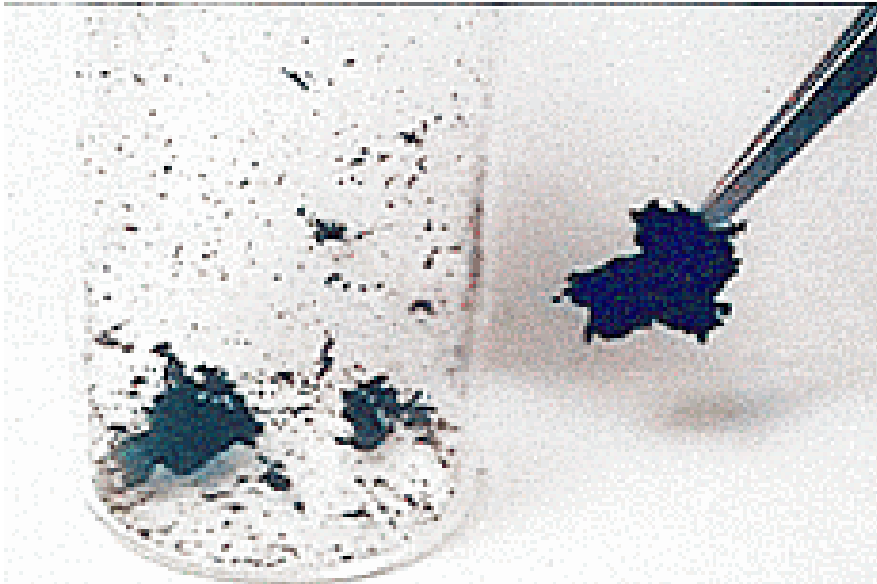
Single-walled  
nanotube

***Are CNTs  
Inherently  
Cytotoxic ?***

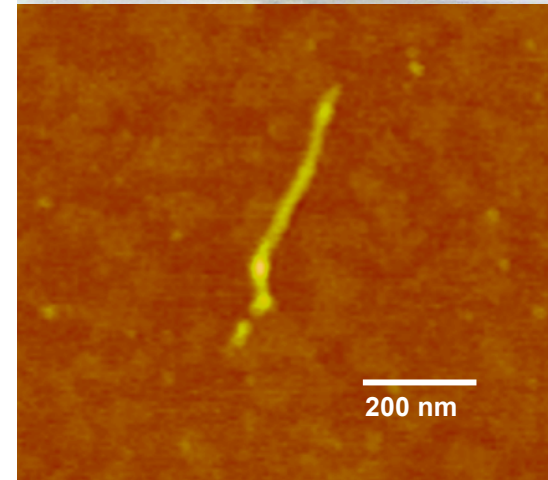


Multi-walled  
nanotube

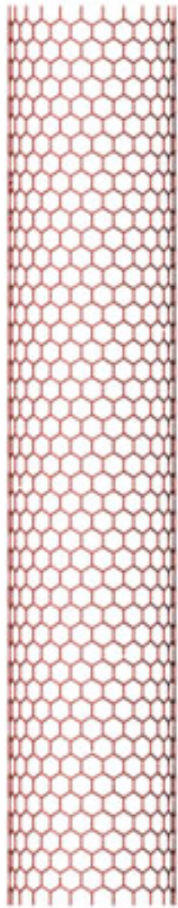
## Unprocessed powders



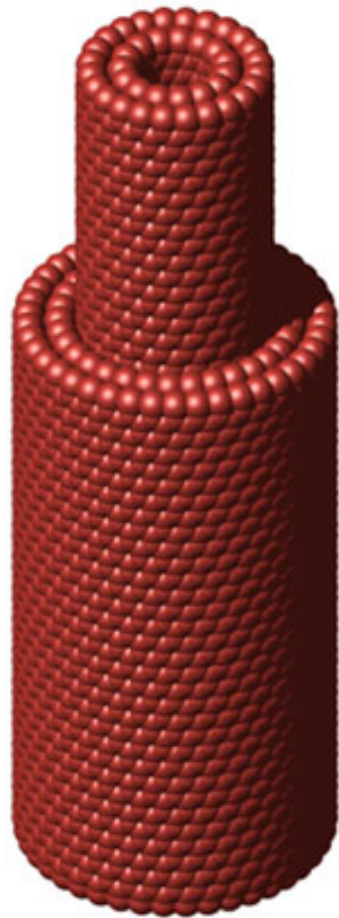
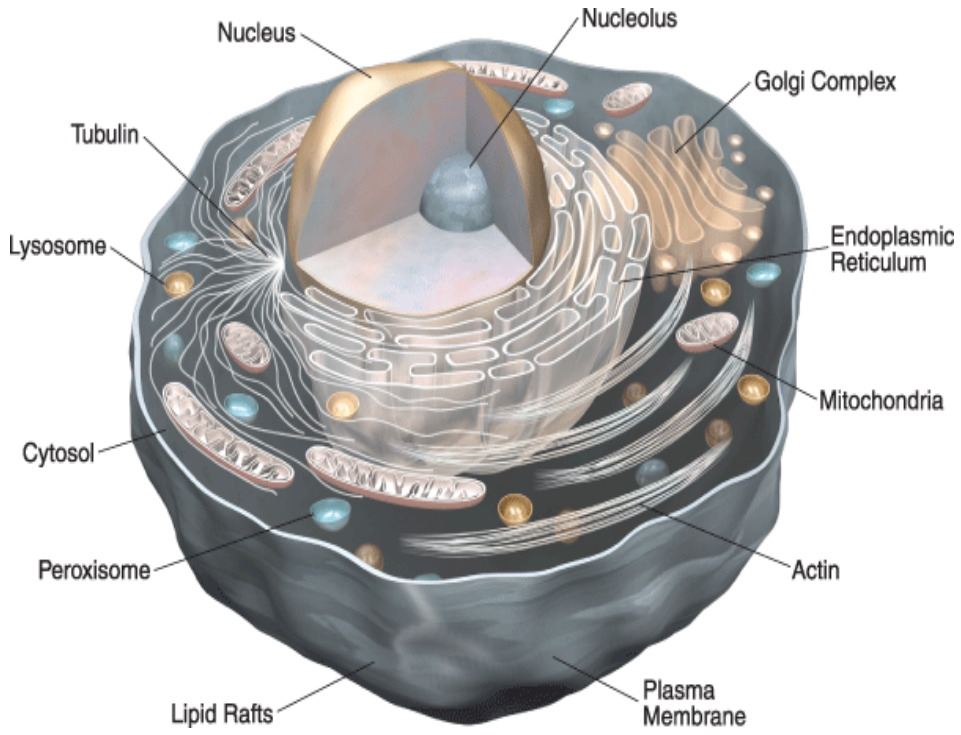
## Purified aqueous dispersions







Single-walled nanotube



Multi-walled nanotube

# Masses of 0.8-nm dia SWNTs with different lengths

25 nm  $\sim 84,000$  amu

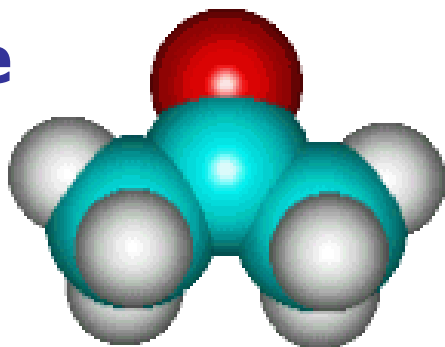
50 nm

100 nm

$\sim 678,000$  amu

200 nm

Acetone



$\geq 99.9\%$  purity

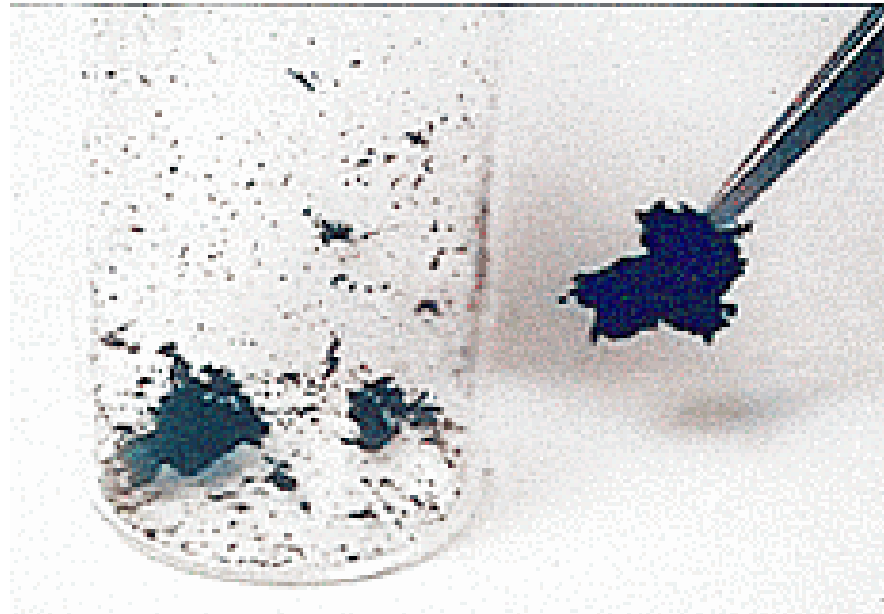
Molecular Weight: 58 g/mole

Kinematic Diameter:  $\sim 5$  Å

# *as-received* SWNT-containing powders

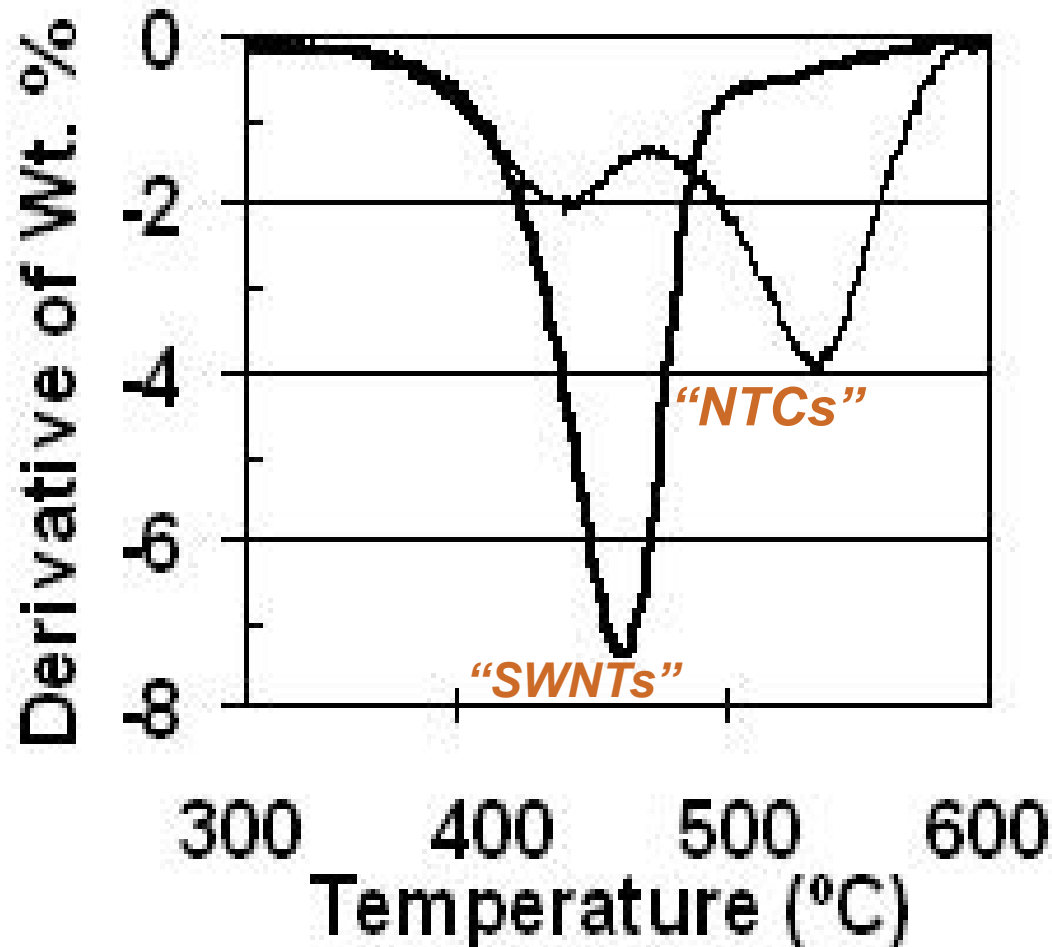
*What's  
Potentially  
Inside?*

- SWNTs
- Metal Catalysts
- Non-Tubular Carbon (NTC) species
  - amorphous carbons
  - graphitic nanoparticles
  - carbides
  - fullerenes



**TGA, SEM, XPS, Raman**

**TGA of two lots of the same product  
received 4 months apart  
from the same supplier**

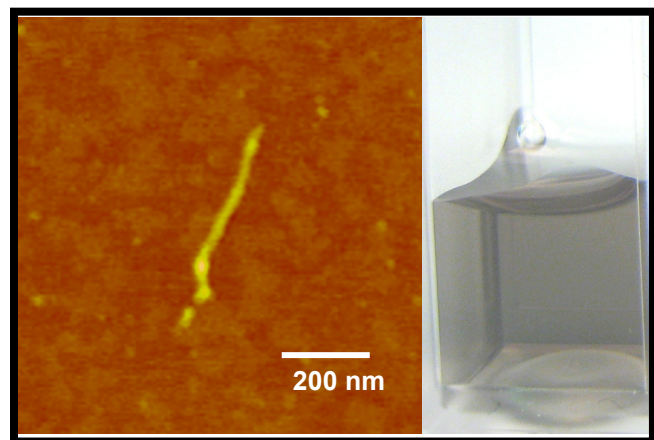
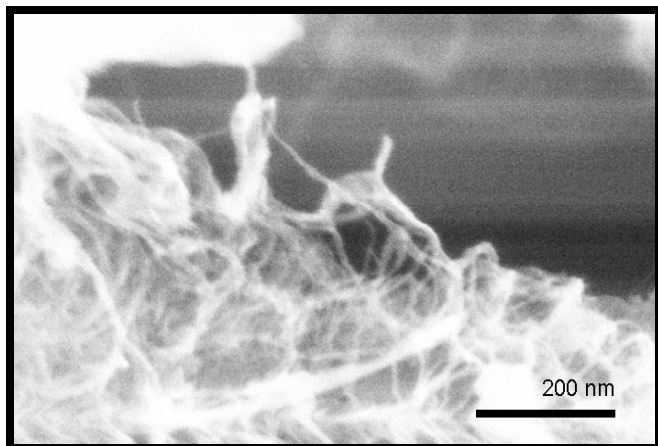


# SWNT-containing powders\*

	<u>weight percents</u>
<b>SWNTs</b>	<b>26 – 82 %</b>
<b>NTC species</b>	<b>5 – 44 %</b>
<b>Metals</b>	<b>10 – 32 %</b>

\*from a variety of sources/suppliers and SWNT manufacturing processes

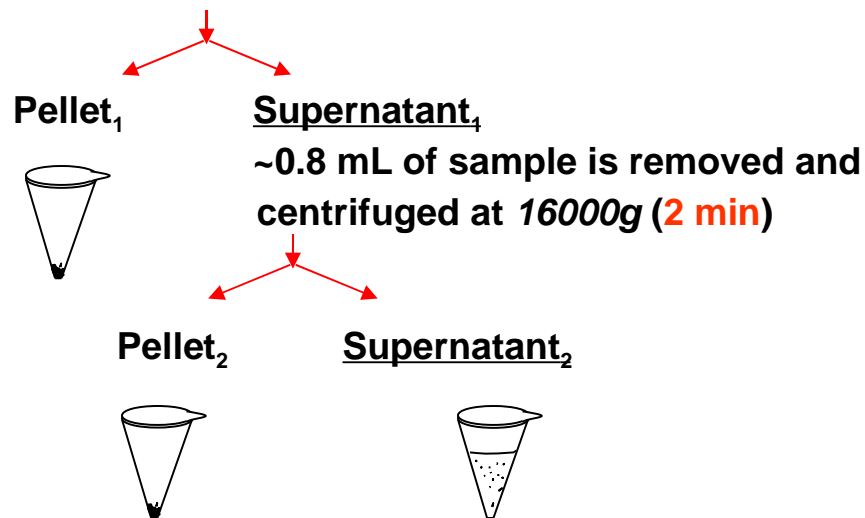
## Sonication/Centrifugation Protocol to debundle SWNTs and to minimize impurities from the SWNT-containing powder



1 mL of peptide or protein + 1 mg of SWNT-powder

Sonicate for **10 min** (using a 3-mm probe tip)

The 1-mL solution is centrifuged at **16000g (2 min)**

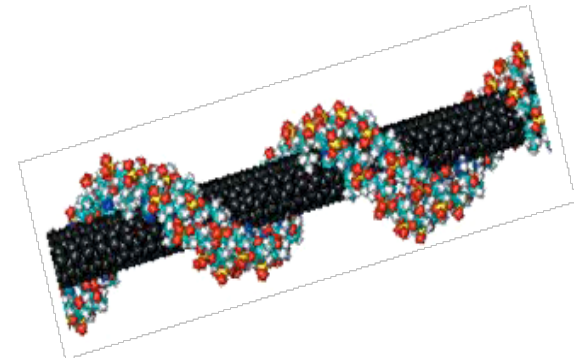


# 1<sup>st</sup> twenty pubs concerning cells being exposed to aqueous CNT dispersions (red rows = significant toxicity observed)

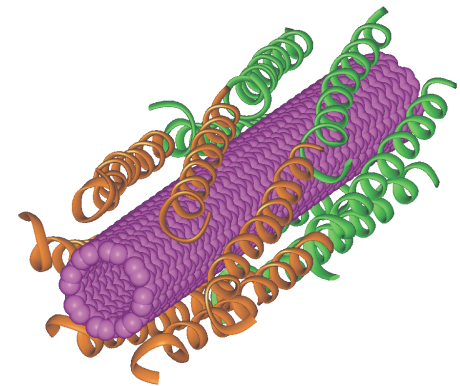
ID #	Cell Line	CNT type	Coating	mg/mL	Exposure	Cytotoxicity Assay	Sonic.	Cent.	EA
1	HEK	MWCNT	KGM media	0.1	24 h	Neutral red + IL-8	5 min	No	Yes- TEM slices
2	AM macrophage	S&MWCNT	RPMI media	1.41 ug/cm2	6 h	MTT (% cytotoxicity)	20 min	No	
3	HaCat	SWNT	KGM media	0.06	18 h	AlmarBlue + ESR	3 min	No	
4	HEK293	SWNT	Essential media	0.0125	24 h	MTT (% viability)	No	No	
5	HeLa	f-SWNT	SA	0.025	2 h-1,2,3 d	CellTiter96	Yes	Yes	
6	HL60	f-SWNT	SA	0.05	1 h -2 d	PI staining	Yes	Yes	
7	MCF7	SWNT	RPMI and RNA	0.4	72 h	Cell growth -MTS	90 min	0.45 filter	
8	HeLa	f-S-MWCNT	biological media	5.0-10.0	6 h	FACS	NA	NA	
9	3T3	f-SWNT	peptide	5 uM	1 h	PI and Annexin	Yes	Yes	
10	HaCaT	SWNT	DMF	0.01	12 h	MTT (% viability)	No	No	
11	H9c2	SWNT	DMEM	0.2	1,2,3 d	PI and Annexin	2x15 min	No	
12	HeLa	SWNT	DNA/PL-PEG	0.025	12 h	--	45 min	22000 g	
13	A549	f-SWNT	growth media	0.05	1,2,3,4 d	MTT, WST-1, LDH, MMP	6x30 sec	Yes	Acid Treatments
	ECV	f-SWNT	growth media	0.05	1,2,3,4 d	MTT, WST-1, LDH, MMP	6x30 sec	Yes	Acid Treatments
	NR8383	f-SWNT	growth media	0.05	1,2,3,4 d	MTT, WST-1, LDH, MMP	6x30 sec	Yes	Acid Treatments
14	Jurkat	f-MWCNT	Amb-FTIC	0.04	1 h	Yes	Yes	Yes	
15	fibroblasts	MWCNT		0.0006	48 h	microsc.: YO-PRO1	No	No	
16	fibroblasts	f-SWNT	pluronic F108	0.002 - 2	48 h	MTT	No	No	
17	macrophage	SWNT	purified and unp.	0.12	1-2 h	EPR-free radical	3x30 sec	No	26% vs 0.23% Fe
18	HUVEC	f-CNT	IMDM media	0.0006	Ref-18	Neutral red & MTT	not clear	No	
19	H596 lung tumor	f-MWCNT	Gelatin	0.02-02 ug/ml	1,2,3,4 d	MTT	not clear	not clear	
20	CHO	f-CNT	HPA-lipid C18	0.08	3 d	PDT (+ or - coating)	Yes & ?	Yes & ?	
21	fibroblasts	MWCNT	polysulfone		7 d	CellTiter96 - MTS	not clear	not clear	
UTD-1	HeLa	SWNT	Nano-1	100 ug/mL	6 d	PDT (+ or - coating)	10 min	10 min	Yes - Fe: 1-2 ppm
UTD-2	HeLa	SWNT	FBS/DMEM	50 ug/mL	6 d	PDT + MitoSOX	10 min	2 min	Yes - Mo: 3-6 ppm

# Cultured Cells exposed to CNTs

- Cell line
- CNT type
- CNT coating
- Dispersal procedure
- CNT concentrations
- Exposure times
- Viability tests
- % carbonaceous impurities
- % metal impurities



DNA-wrapped SWNT



Peptide-wrapped SWNT



# How many tested for the presence of metals in their samples?

ID #	Cell Line	CNT type	Coating	mg/mL	Exposure	Cytotoxicity Assay	Sonic.	Cent.	EA
1	HEK	MWCNT	KGM media	0.1	24 h	Neutral red + IL-8	5 min	No	Yes- TEM slices
2	AM macrophage	S&MWCNT	RPMI media	1.41 ug/cm2	6 h	MTT (% cytotoxicity)	20 min	No	
3	HaCat	SWNT	KGM media	0.06	18 h	AlmarBlue + ESR	3 min	No	
4	HEK293	SWNT	Essential media	0.0125	24 h	MTT (% viability)	No	No	
5	HeLa	f-SWNT	SA	0.025	2 h-1,2,3 d	CellTiter96	Yes	Yes	
6	HL60	f-SWNT	SA	0.05	1 h -2 d	PI staining	Yes	Yes	
7	MCF7	SWNT	RPMI and RNA	0.4	72 h	Cell growth -MTS	90 min	0.45 filter	
8	HeLa	f-S-MWCNT	biological media	5.0-10.0	6 h	FACS	NA	NA	
9	3T3	f-SWNT	peptide	5 uM	1 h	PI and Annexin	Yes	Yes	
10	HaCaT	SWNT	DMF	0.01	12 h	MTT (% viability)	No	No	
11	H9c2	SWNT	DMEM	0.2	1,2,3 d	PI and Annexin	2x15 min	No	
12	HeLa	SWNT	DNA/PL-PEG	0.025	12 h	--	45 min	22000 g	
13	A549	f-SWNT	growth media	0.05	1,2,3,4 d	MTT, WST-1, LDH, MMP	6x30 sec	Yes	Acid Treatments
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14	Jurkat	f-MWCNT	Amb-FTIC	0.04	1 h	Yes	Yes	Yes	
15	fibroblasts	MWCNT		0.0006	48 h	microsc.: YO-PRO1	No	No	
16	fibroblasts	f-SWNT	pluronic F108	0.002 - 2	48 h	MTT	No	No	
17	macrophage	SWNT	purified and unp.	0.12	1-2 h	EPR-free radical	3x30 sec	No	26% vs 0.23% Fe
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20	CHO	f-CNT	HPA-lipid C18	0.08	3 d	PDT (+ or - coating)	Yes & ?	Yes & ?	
21	fibroblasts	MWCNT	polysulfone		7 d	CellTiter96 - MTS	not clear	not clear	
UTD-1	HeLa	SWNT	Nano-1	100 ug/mL	6 d	PDT (+ or - coating)	10 min	10 min	Yes - Fe: 1-2 ppm
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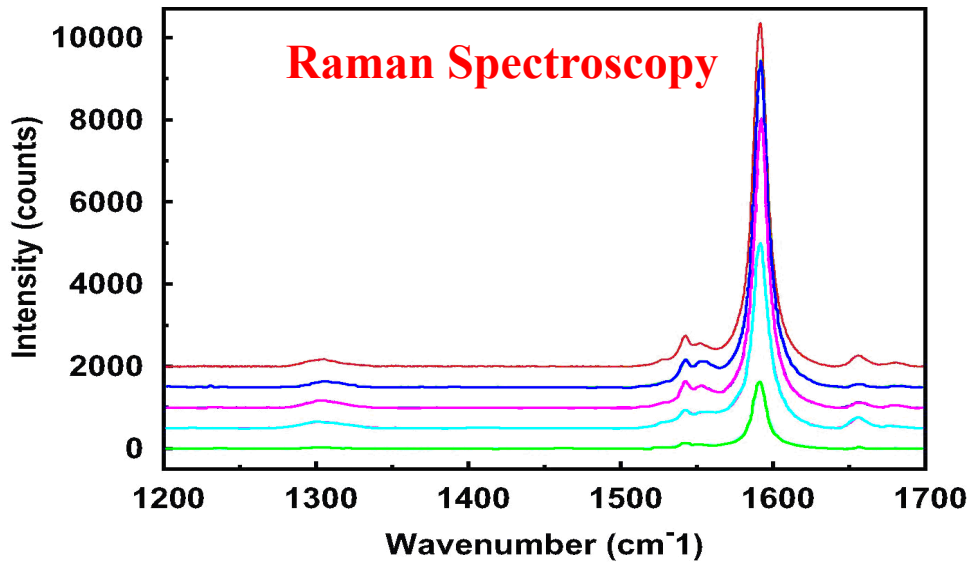
**Nanoparticle toxicity assessments must be accompanied by thorough material characterizations!**

## **Elemental Analyses of SWNT Powders and Dispersions**

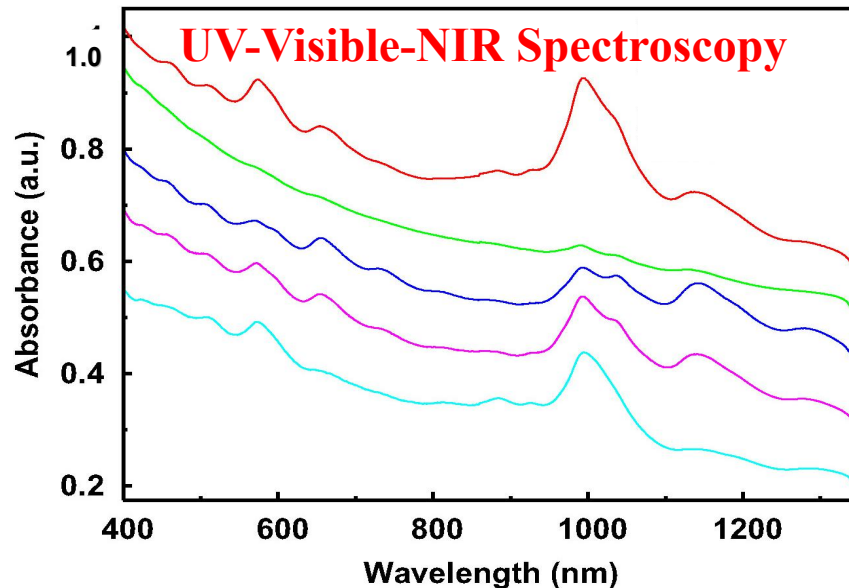
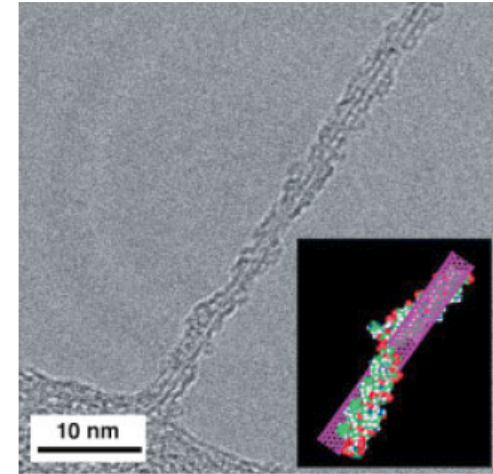
	<b>Metals (ppm)</b>	<b>Ti (ppm)</b>
<b>SWNT powder</b>	<b>~18,000</b>	<b>--</b>
<b>SWNT dispersion</b>	<b>~8</b>	<b>0.15</b>

**Our CNT sample preparation protocol  
effectively removes residual metal catalyst.**

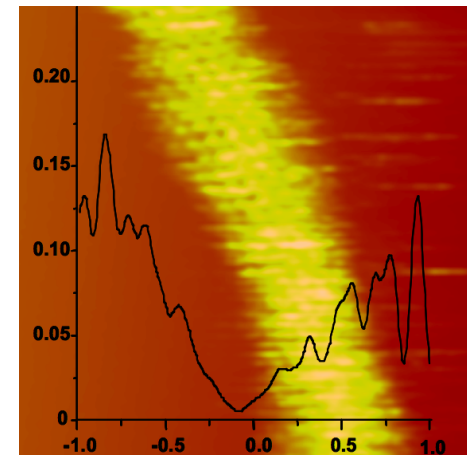
# Characterizations of SWNT dispersions



**Transmission Electron Microscopy**



**Scanning Tunneling Spectroscopy**



# Next Issue: the use of fluorescent dye-based assays of cell viability in the presence of CNTs

**Oops They Did It Again!  
Carbon Nanotubes Hoax Scientists in Viability Assays**

**J. M. Worle-Knirsch, K. Pulskamp, and H. F. Krug\*  
Nano Letters (2006) 6: 1261-1268**

*"Data from A549 cells incubated with carbon nanotubes fake a strong cytotoxic effect within the MTT assay after 24 h that reaches roughly 50%, whereas the same treatment with SWCNTs, but detection with WST-1, reveals no cytotoxicity."*

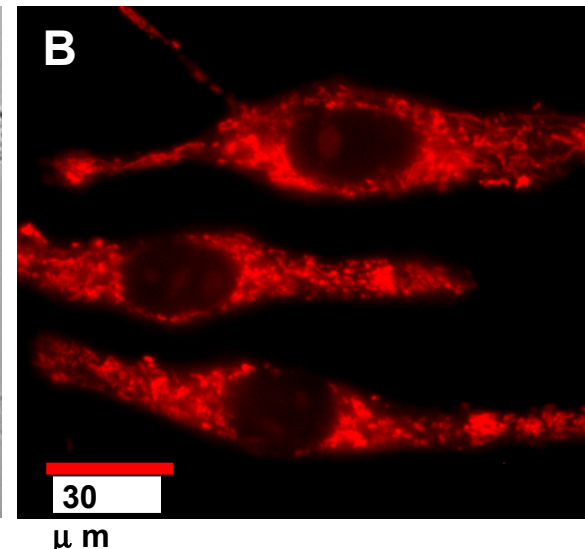
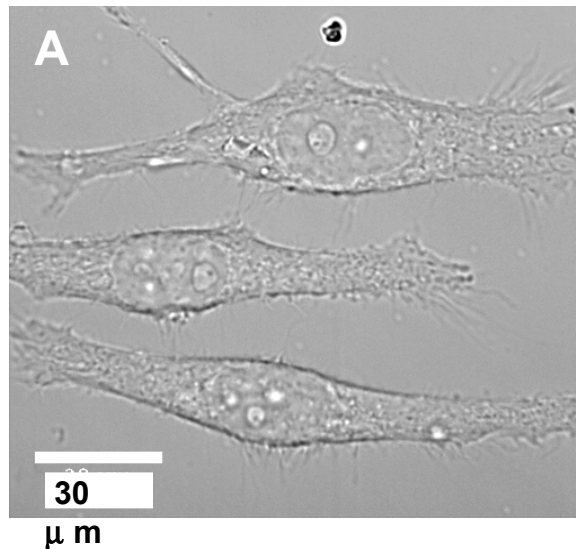
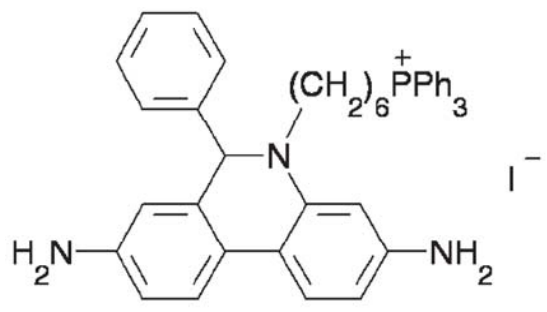
**Now, there are publications that indicate problems with WST-1.**

# How many used fluorescence-based assays of cell health without running the appropriate controls?

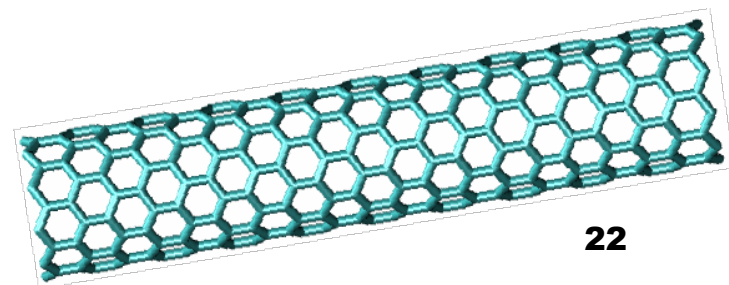
ID #	Cell Line	CNT type	Coating	mg/mL	Exposure	Cytotoxicity Assay	Sonic.	Cent.	EA
1	HEK	MWCNT	KGM media	0.1	24 h	Neutral red + IL-8	5 min	No	Yes- TEM slices
2	AM macrophage	S&MWCNT	RPMI media	1.41 ug/cm2	6 h	MTT (% cytotoxicity)	20 min	No	
3	HaCat	SWNT	KGM media	0.06	18 h	AlmarBlue + ESR	3 min	No	
4	HEK293	SWNT	Essential media	0.0125	24 h	MTT (% viability)	No	No	
5	HeLa	f-SWNT	SA	0.025	2 h-1,2,3 d	CellTiter96	Yes	Yes	
6	HL60	f-SWNT	SA	0.05	1 h -2 d	PI staining	Yes	Yes	
7	MCF7	SWNT	RPMI and RNA	0.4	72 h	Cell growth -MTS	90 min	0.45 filter	
8	HeLa	f-S-MWCNT	biological media	5.0-10.0	6 h	FACS	NA	NA	
9	3T3	f-SWNT	peptide	5 uM	1 h	PI and Annexin	Yes	Yes	
10	HaCaT	SWNT	DMF	0.01	12 h	MTT (% viability)	No	No	
11	H9c2	SWNT	DMEM	0.2	1,2,3 d	PI and Annexin	2x15 min	No	
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20	CHO	f-CNT	HPA-lipid C18	0.08	3 d	PDT (+ or - coating)	Yes & ?	Yes & ?	
21	fibroblasts	MWCNT	polysulfone		7 d	CellTiter96 - MTS	not clear	not clear	
UTD-1	HeLa	SWNT	Nano-1	100 ug/mL	6 d	PDT (+ or - coating)	10 min	10 min	Yes - Fe: 1-2 ppm
UTD-2	HeLa	SWNT	FBS/DMEM	50 ug/mL	6 d	PDT + MitoSOX	10 min	2 min	Yes - Mo: 3-6 ppm

# Reactive Oxygen Species Dynamics

## MitoSOX Red - a Superoxide Selective Dye

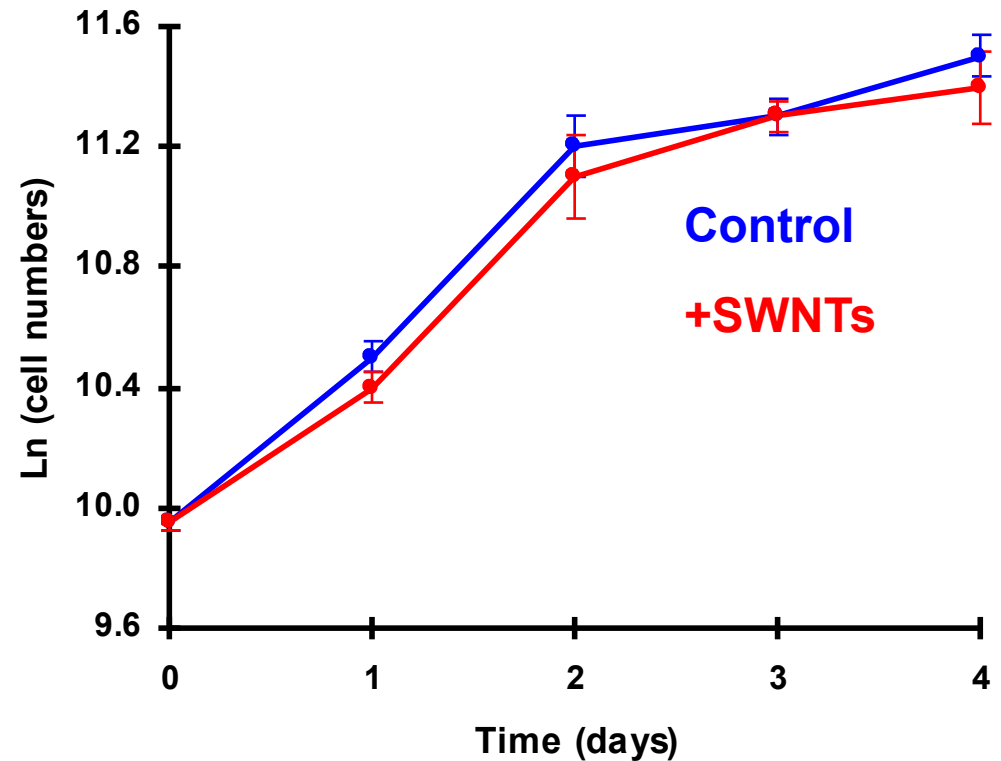
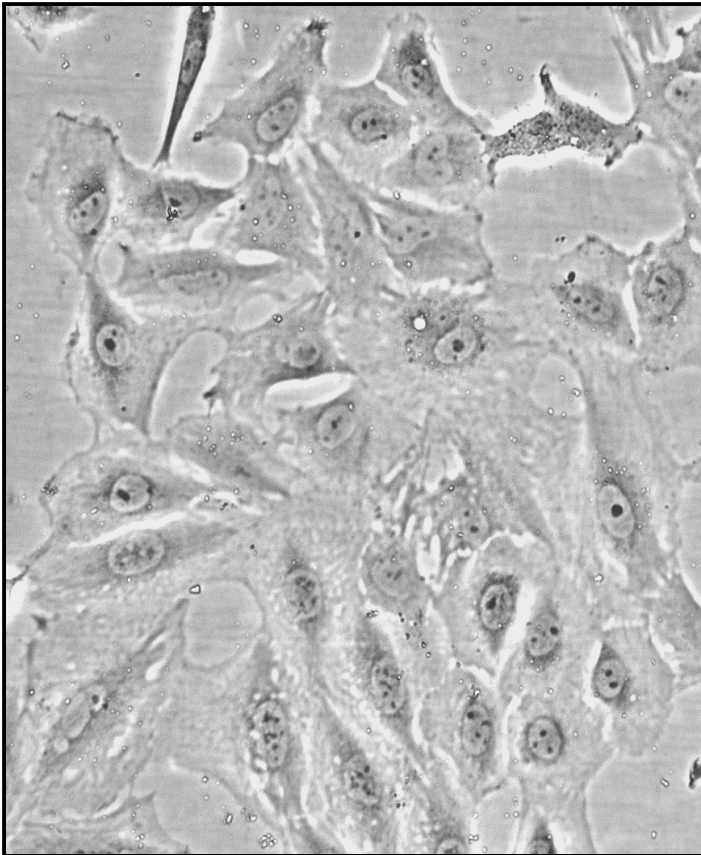


- **DIC (A) and fluorescence (B) images of MitoSOX Red-treated cells**
- **$I_{\text{Fluorescence}}$  increases as  $[\text{O}_2^{\bullet -}]$  increases**

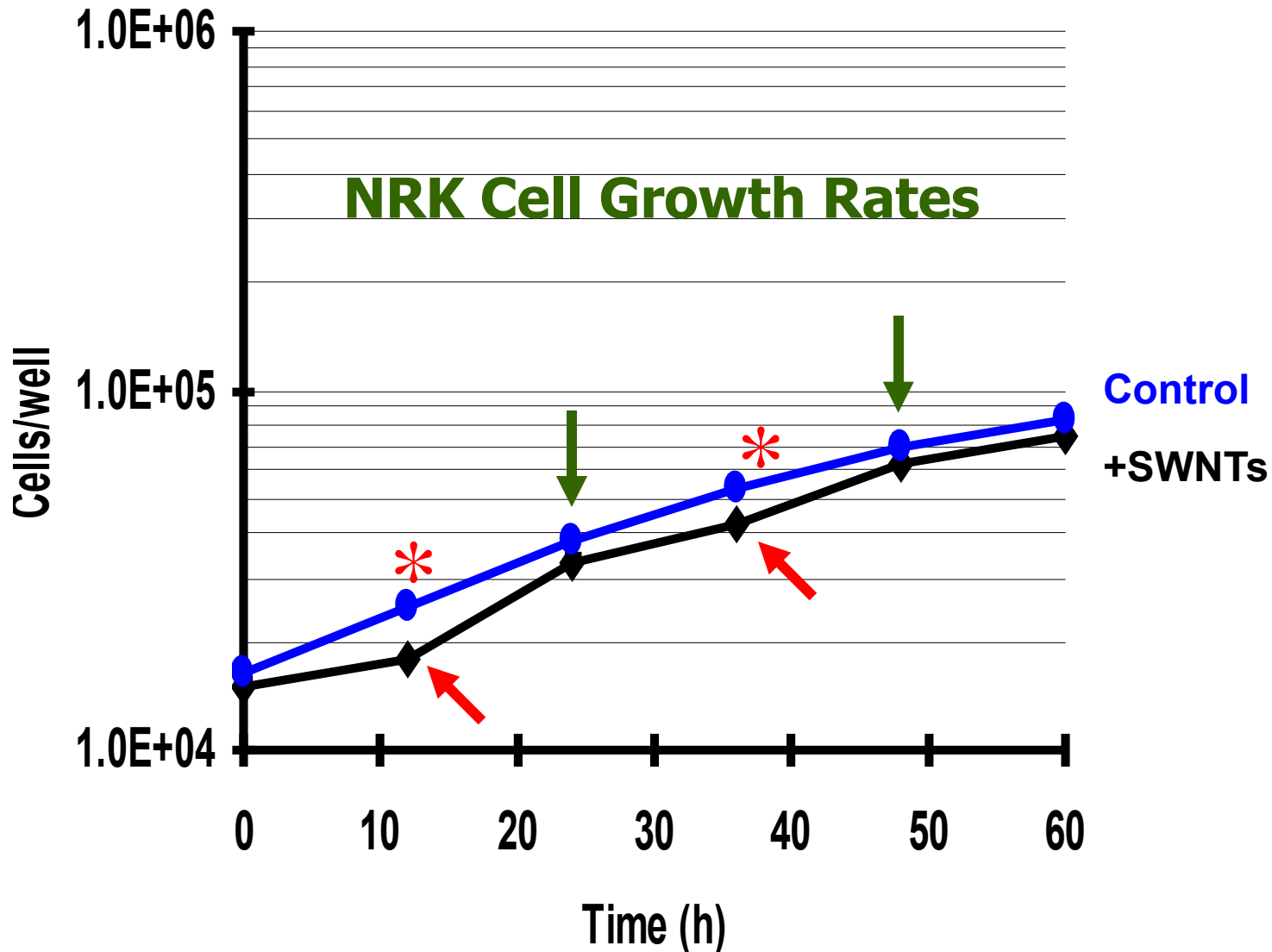


# Next Issue: CNTs can sequester essential growth media components

## HeLa Cell Growth Rates



# Next Issue: CNTs can sequester essential growth media components





**It makes perfect sense:  
many proteins have hydrophobic pockets  
and CNTs are hydrophobic**

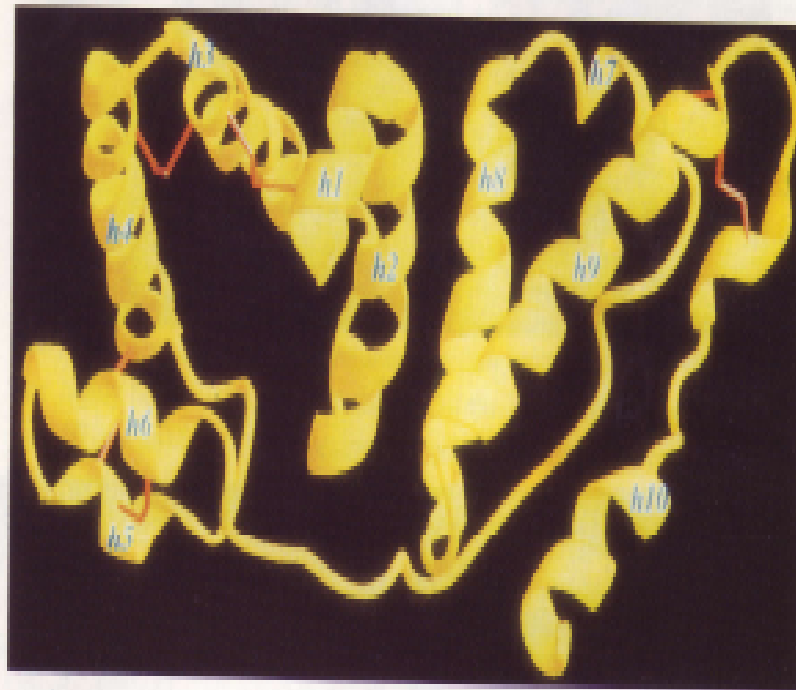
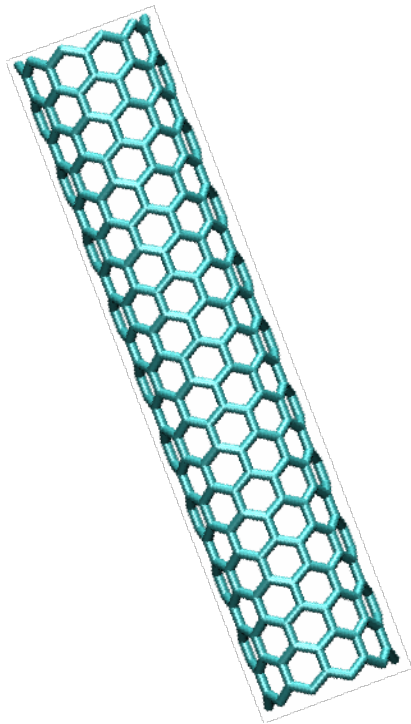
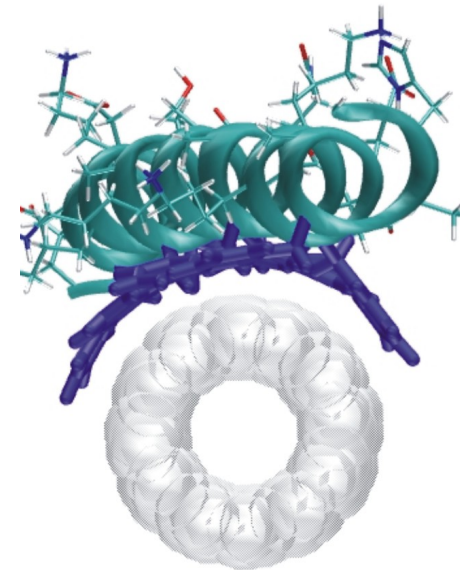


Fig. 2-11.

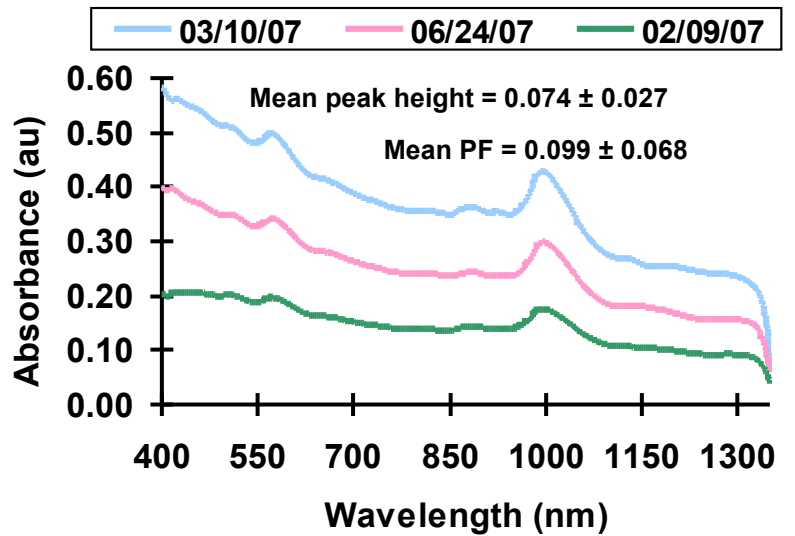
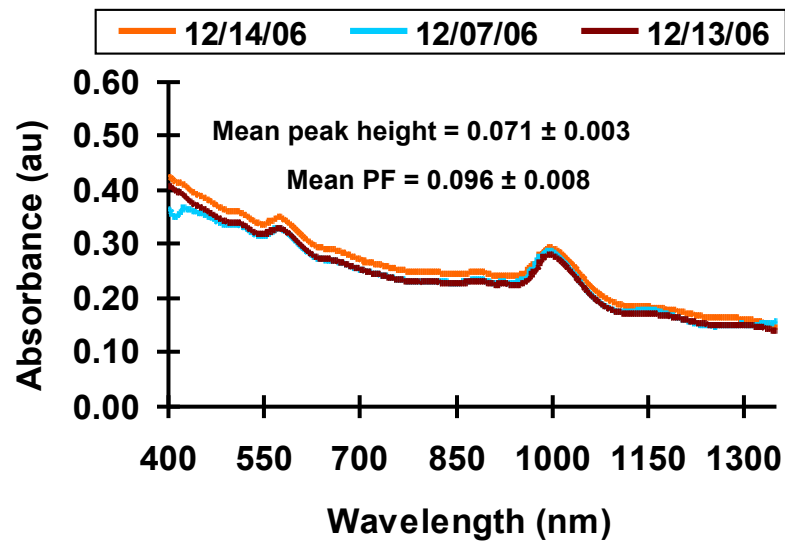
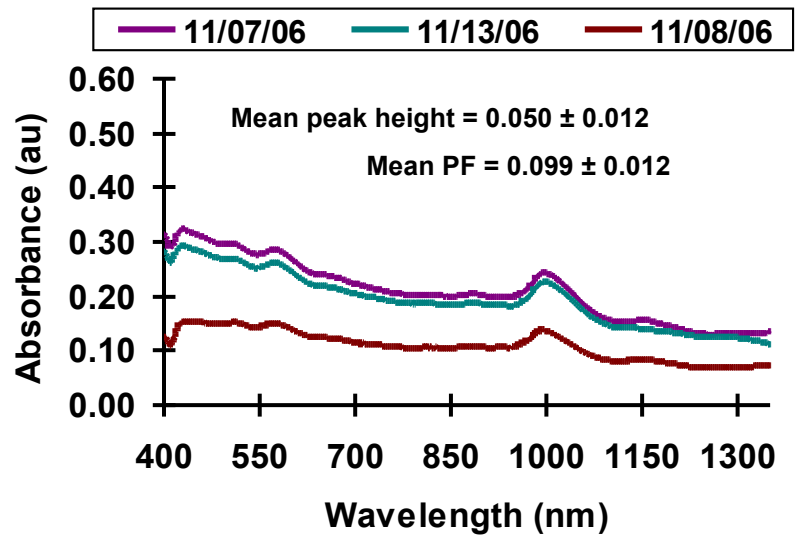
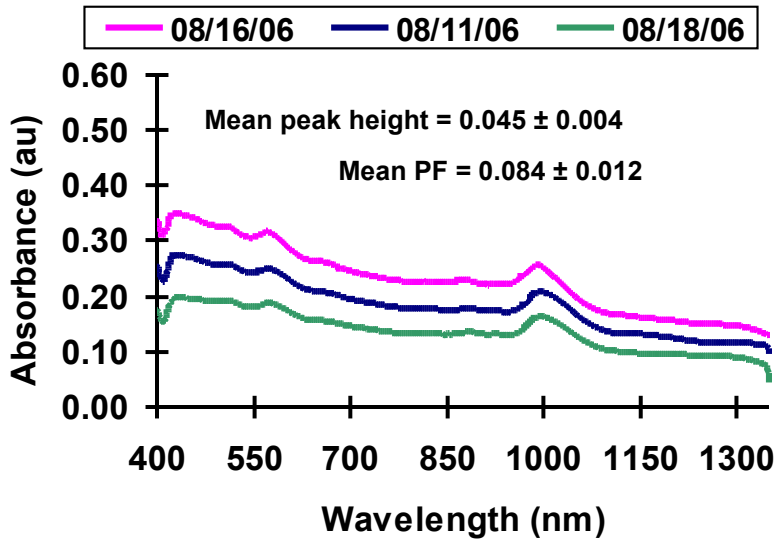


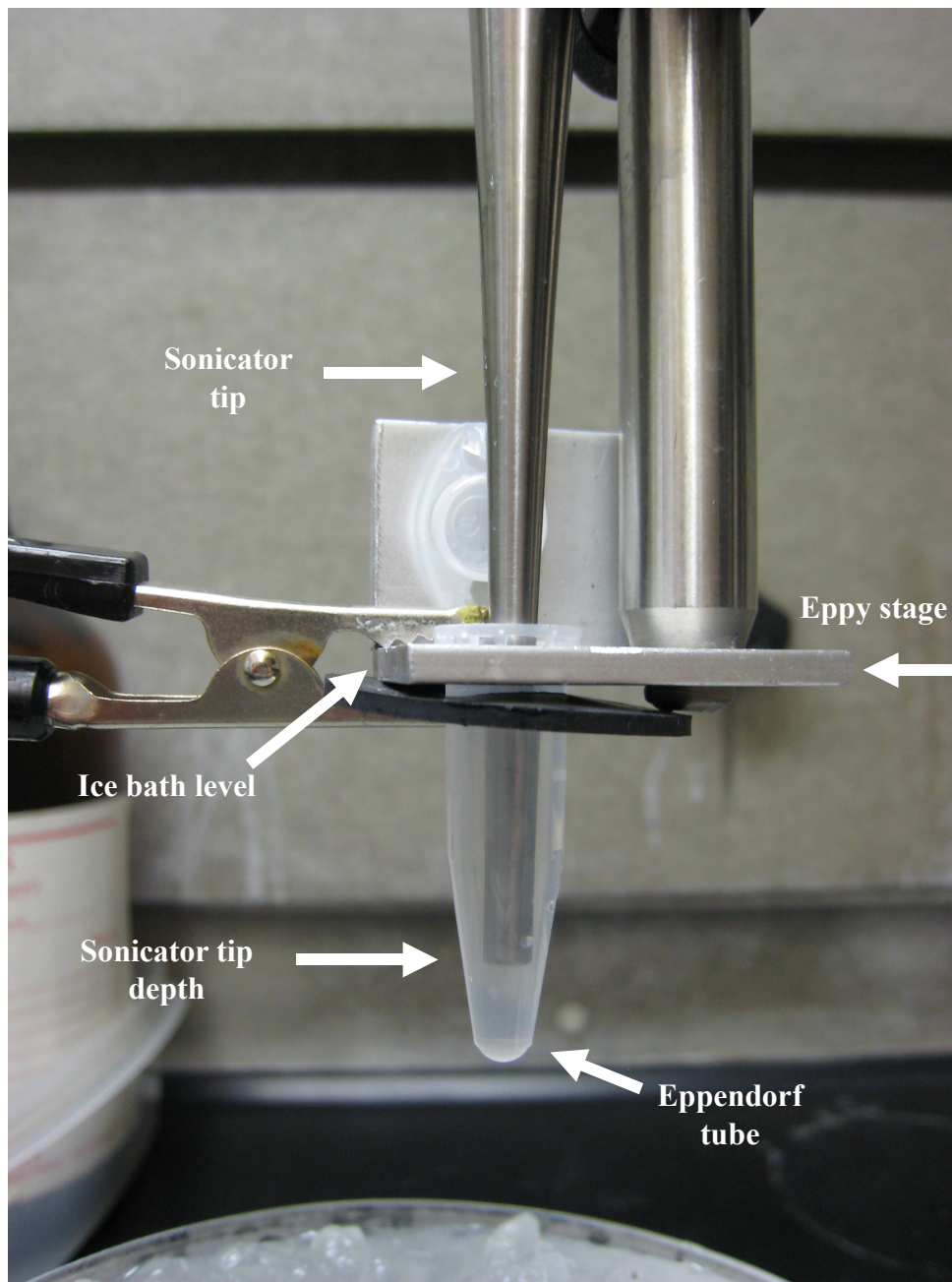
# (How many of these 1<sup>st</sup> twenty pubs that reported significant cytotoxicity were inaccurate???)

ID #	Cell Line	CNT type	Coating	mg/mL	Exposure	Cytotoxicity Assay	Sonic.	Cent.	EA
1	HEK	MWCNT	KGM media	0.1	24 h	Neutral red + IL-8	5 min	No	Yes- TEM slices
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5	HeLa	f-SWNT	SA	0.025	2 h-1,2,3 d	CellTiter96	Yes	Yes	
6	HL60	f-SWNT	SA	0.05	1 h -2 d	PI staining	Yes	Yes	
7	MCF7	SWNT	RPMI and RNA	0.4	72 h	Cell growth -MTS	90 min	0.45 filter	
8	HeLa	f-S-MWCNT	biological media	5.0-10.0	6 h	FACS	NA	NA	
9	3T3	f-SWNT	peptide	5 uM	1 h	PI and Annexin	Yes	Yes	
10	HaCaT	SWNT	DMF	0.01	12 h	MTT (% viability)	No	No	
11	H9c2	SWNT	DMEM	0.2	1,2,3 d	PI and Annexin	2x15 min	No	
12	HeLa	SWNT	DNA/PL-PEG	0.025	12 h	--	45 min	22000 g	
13	A549	f-SWNT	growth media	0.05	1,2,3,4 d	MTT, WST-1, LDH, MMP	6x30 sec	Yes	Acid Treatments
	ECV	f-SWNT	growth media	0.05	1,2,3,4 d	MTT, WST-1, LDH, MMP	6x30 sec	Yes	Acid Treatments
	NR8383	f-SWNT	growth media	0.05	1,2,3,4 d	MTT, WST-1, LDH, MMP	6x30 sec	Yes	Acid Treatments
14	Jurkat	f-MWCNT	Amb-FTIC	0.04	1 h	Yes	Yes	Yes	
15	fibroblasts	MWCNT		0.0006	48 h	microsc.: YO-PRO1	No	No	
16	fibroblasts	f-SWNT	pluronic F108	0.002 - 2	48 h	MTT	No	No	
17	macrophage	SWNT	purified and unp.	0.12	1-2 h	EPR-free radical	3x30 sec	No	26% vs 0.23% Fe
18	HUVEC	f-CNT	IMDM media	0.0006	Ref-18	Neutral red & MTT	not clear	No	
19	H596 lung tumor	f-MWCNT	Gelatin	0.02-02 ug/ml	1,2,3,4 d	MTT	not clear	not clear	
20	CHO	f-CNT	HPA-lipid C18	0.08	3 d	PDT (+ or - coating)	Yes & ?	Yes & ?	
21	fibroblasts	MWCNT	polysulfone		7 d	CellTiter96 - MTS	not clear	not clear	
UTD-1	HeLa	SWNT	Nano-1	100 ug/mL	6 d	PDT (+ or - coating)	10 min	10 min	Yes - Fe: 1-2 ppm
UTD-2	HeLa	SWNT	FBS/DMEM	50 ug/mL	6 d	PDT + MitoSOX	10 min	2 min	Yes - Mo: 3-6 ppm

**So what does the  
UT Dallas Bionano Group do?**

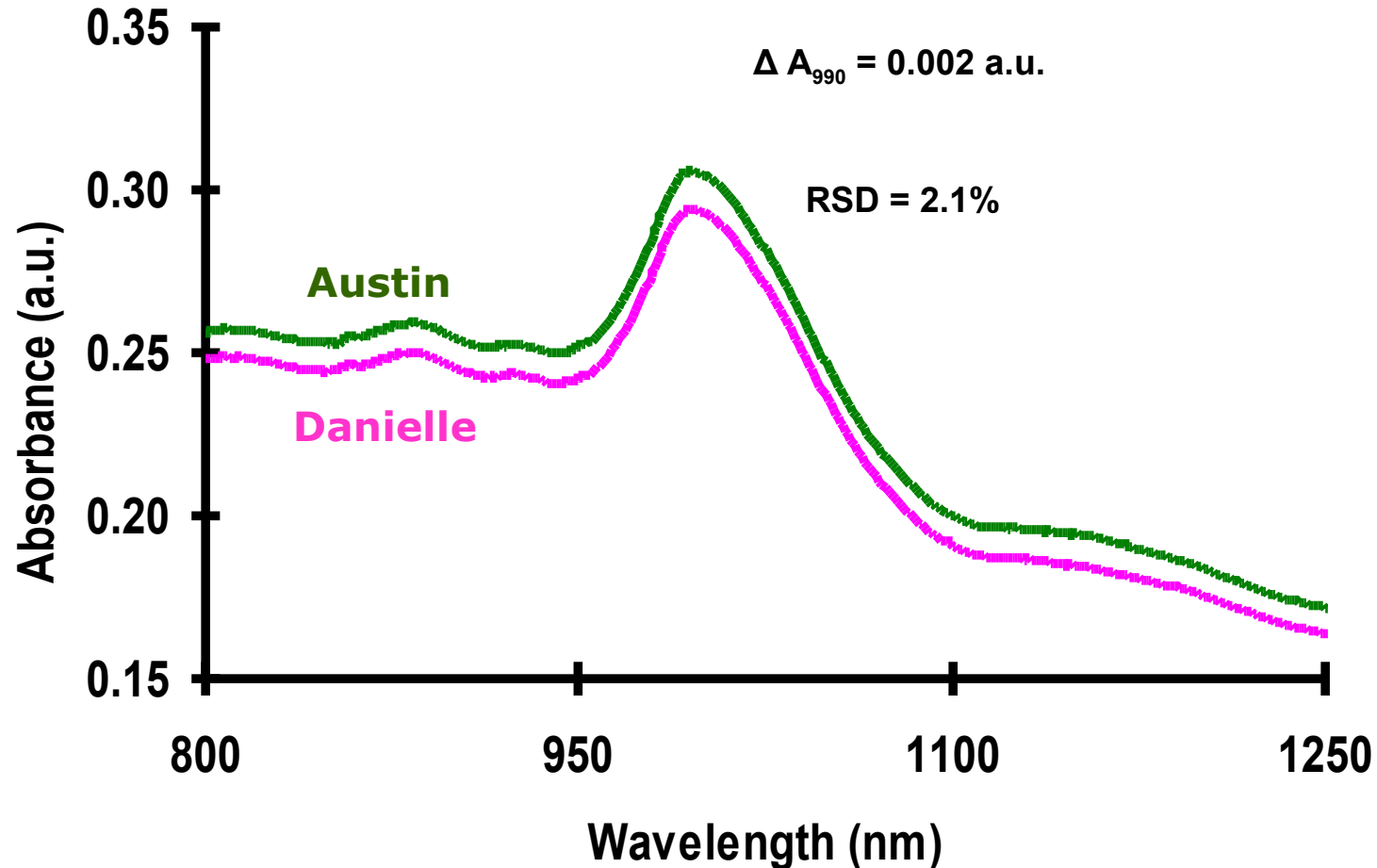
**Well, it first starts with protocols  
for the reproducible preparation of  
purified CNT dispersions**



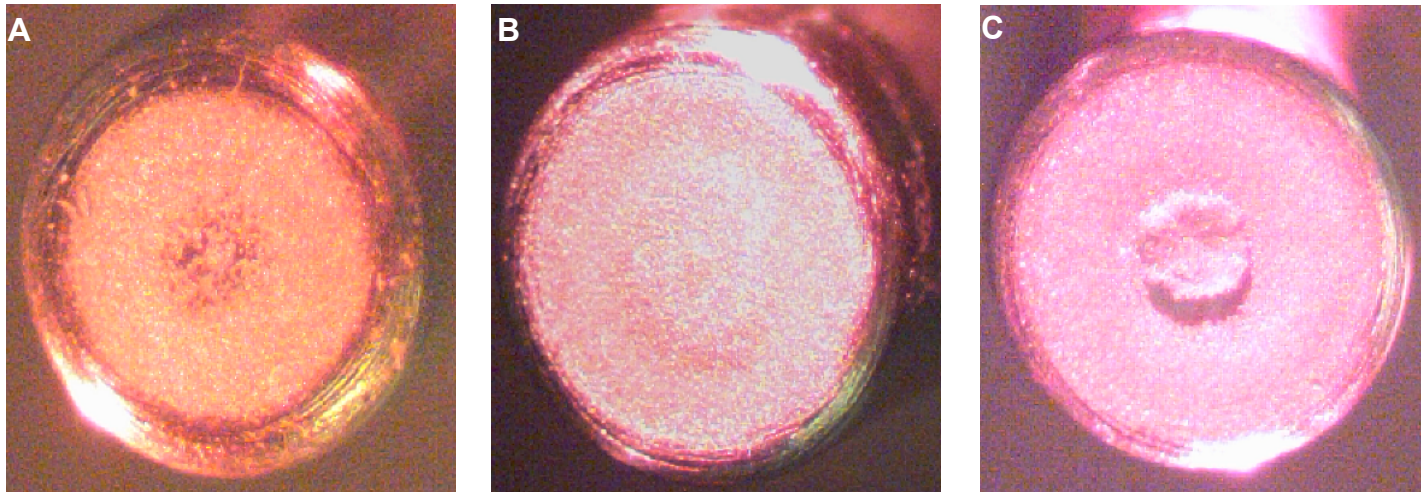


**Photograph showing the position of the sonicator tip in the eppendorf tube and the ice bath level.**

# Standard protocols for making and quantitating CNT dispersions

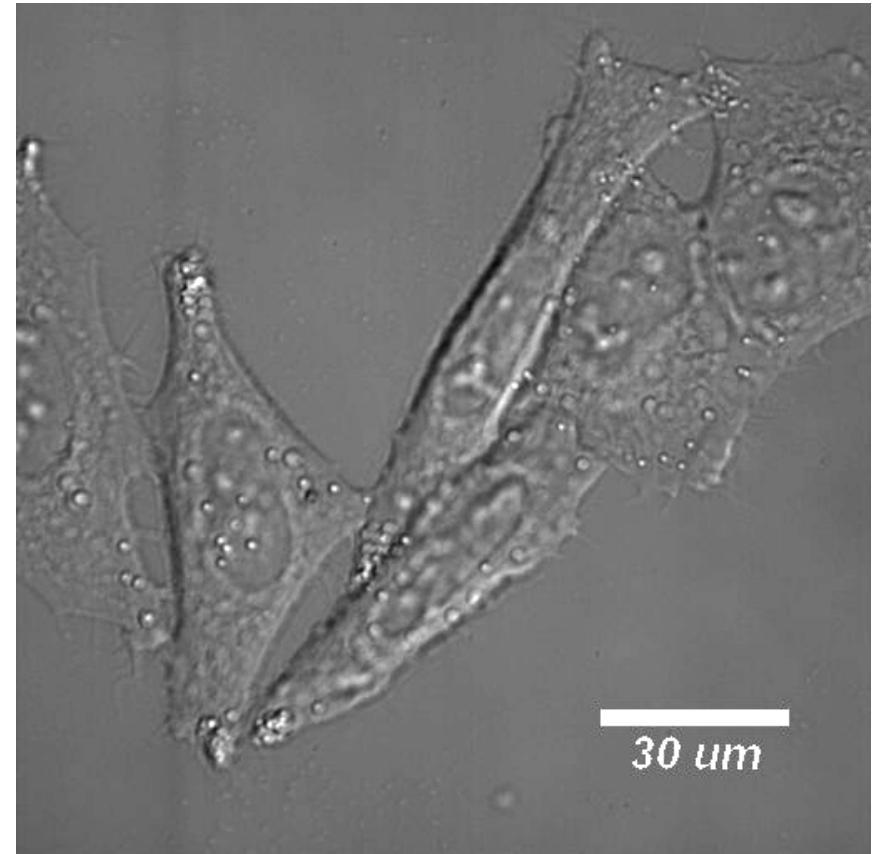
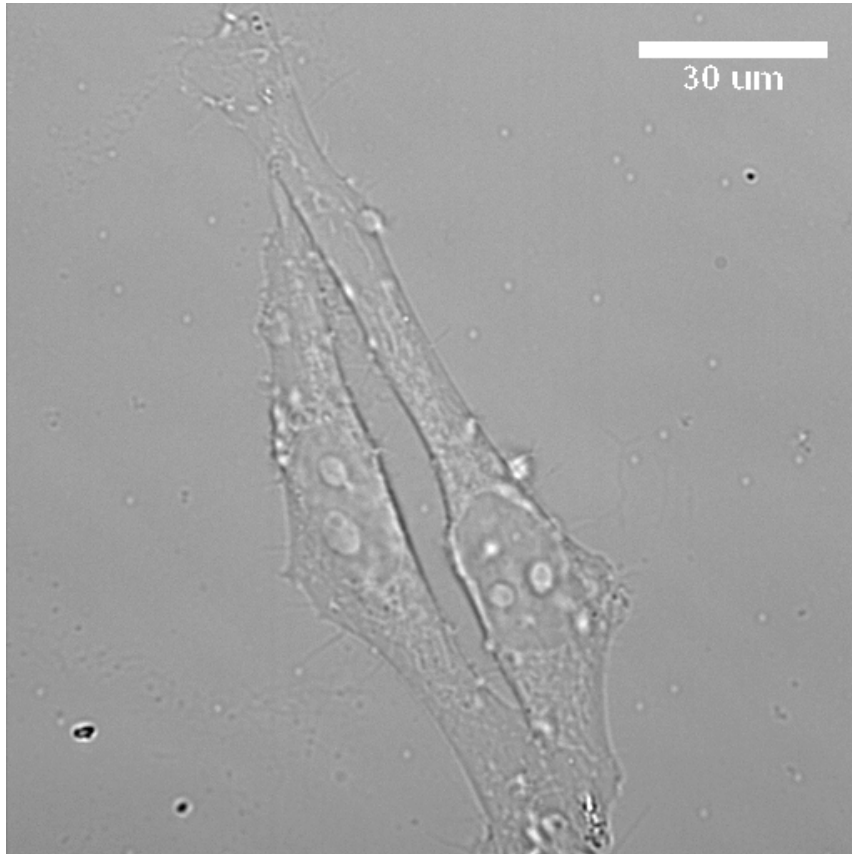


# Sonicator probe tips can introduce metals into CNT samples



	240 min	980 min	1670 min
Fe (ppb)	278	448	566
Ti (ppb)	249	312	393

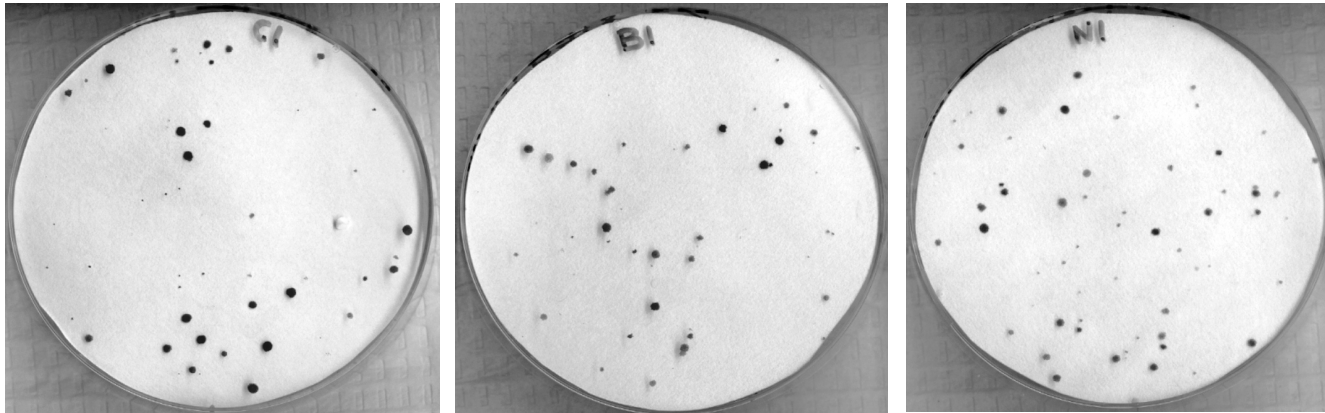
# So what does the UT Dallas Bionano Group do?



**HeLa Cells  $\pm$  SWNTs (3 days)**



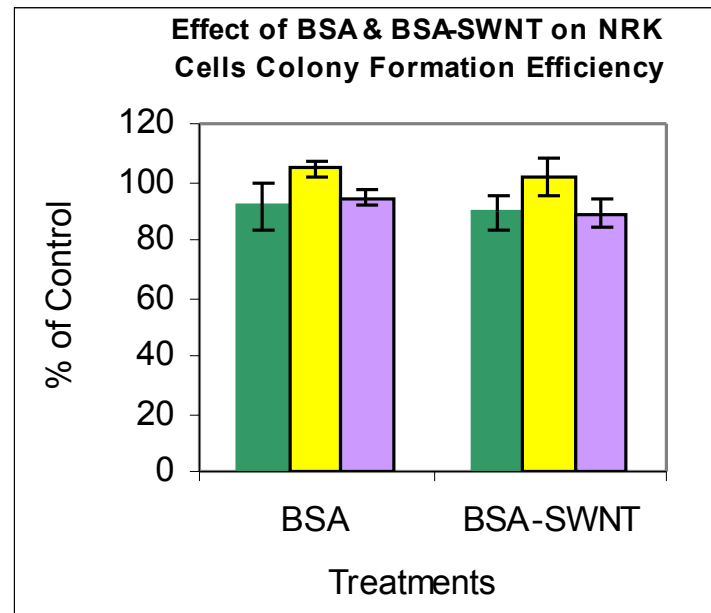
# NRK Cells: Fluorescent-dye Free Cell Colony Formation Assays



Control

BSA

BSA-SWNT



# Are CNTs Inherently Cytotoxic?

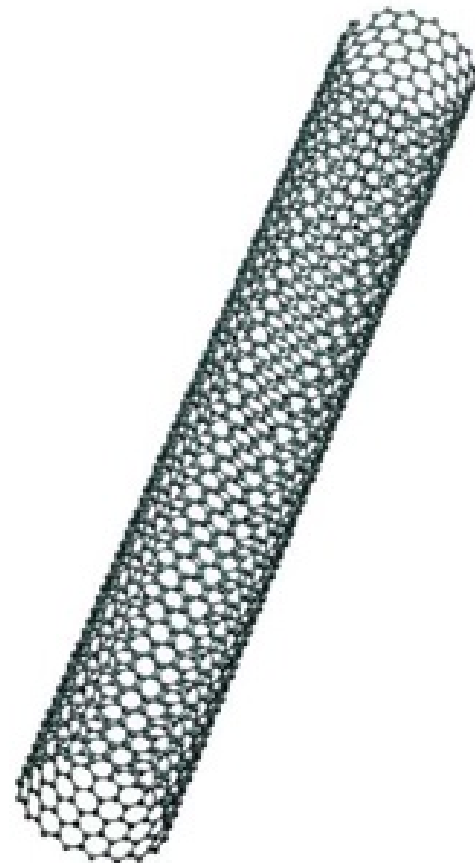
**The importance of thoroughly characterizing NP materials and developing/following standardized label-free protocols before cytotoxicity assessments are offered.**

**There are examples of certain:**

- **CNT types and chiralities**
- **CNT lengths**
- **CNT coatings**
- **Impurity levels**

**That are "OK" with certain:**

- **Cell lines**
- **CNT concentrations**
- **Exposure times**



# Biomedical Applications of CNTs

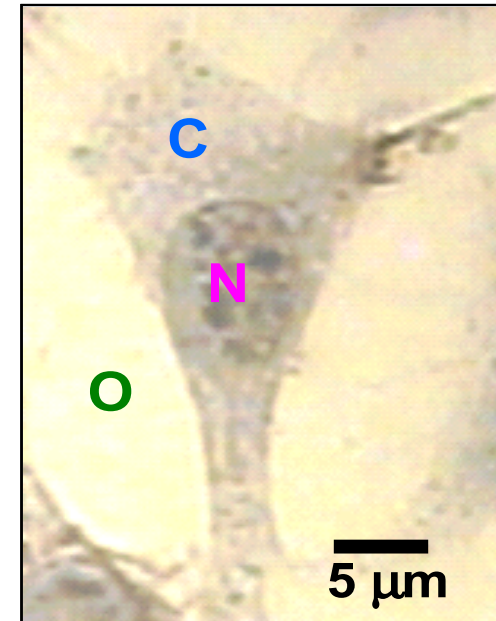
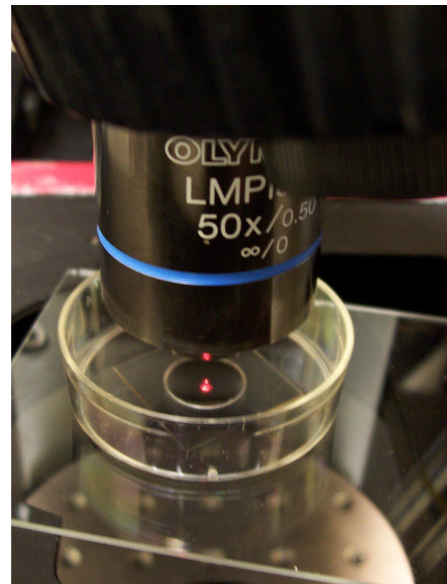
Concerning the biodistribution of chemically modified CNTs injected into mice and rabbits ...

... the groups of **Dai / Weisman / Bianco** are showing that CNTs are rapidly cleared from the animals with no evidence of toxicity.

**However, and in addition to standardized protocols, there still remains the need for standardized CNT reference materials and characterization methods ...**

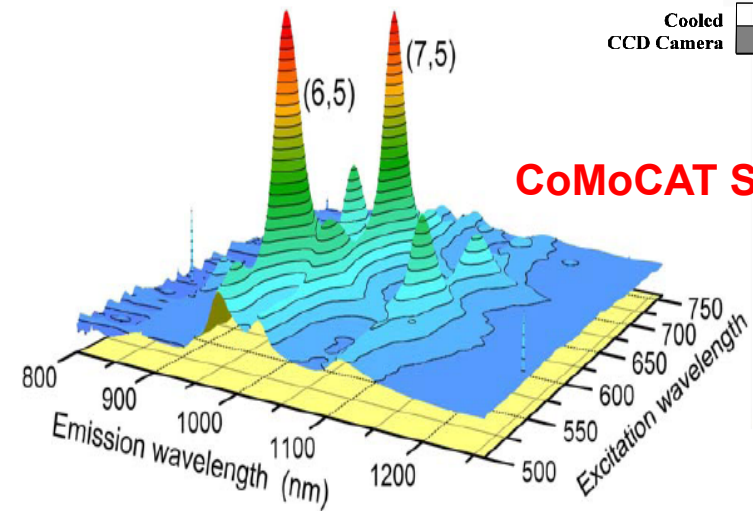
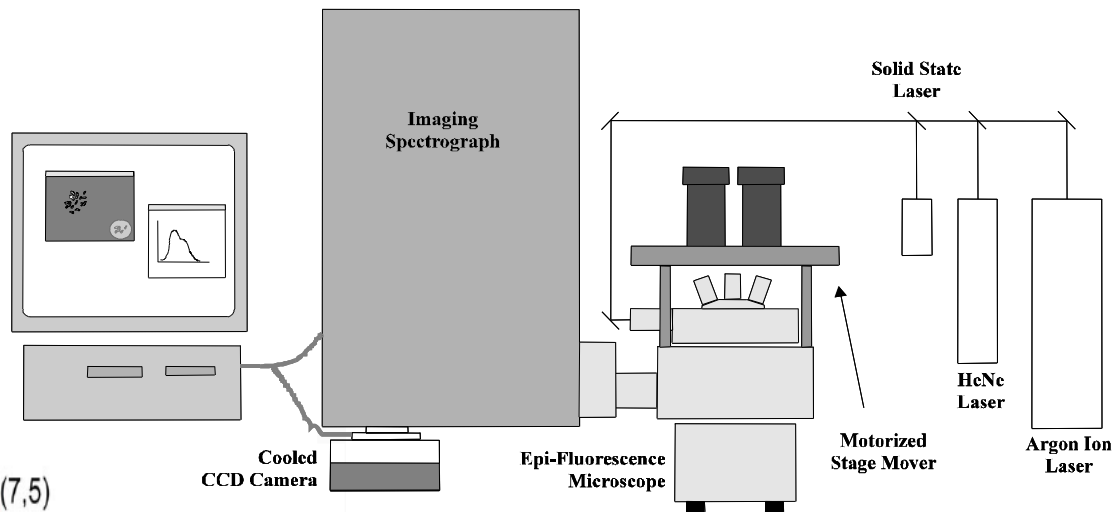
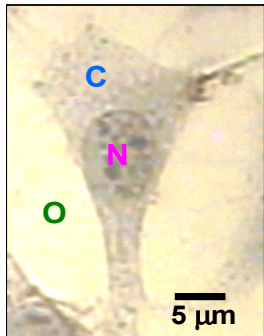
**... to provide society, legislators, investors, & scientists with better *in vitro* and *in vivo* data sets !**

# Improved Cell Viability Data

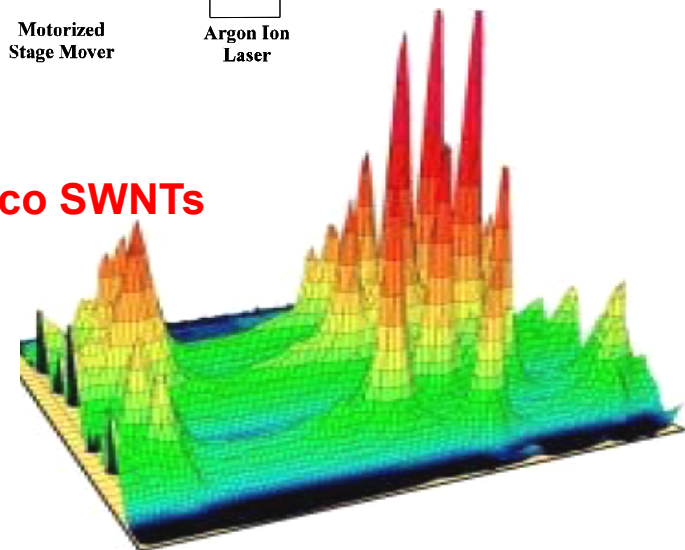


**The amount of CNTs associated with (i.e., taken up by and/or bound to) cells**

# Development of a NIR Hyperspectral Imaging System for the Direct, Label-free Detection of SWNTs



**HiPco SWNTs**



# Confocal microRaman Spectroscopy

## Direct, Label-Free Detection of CNTs

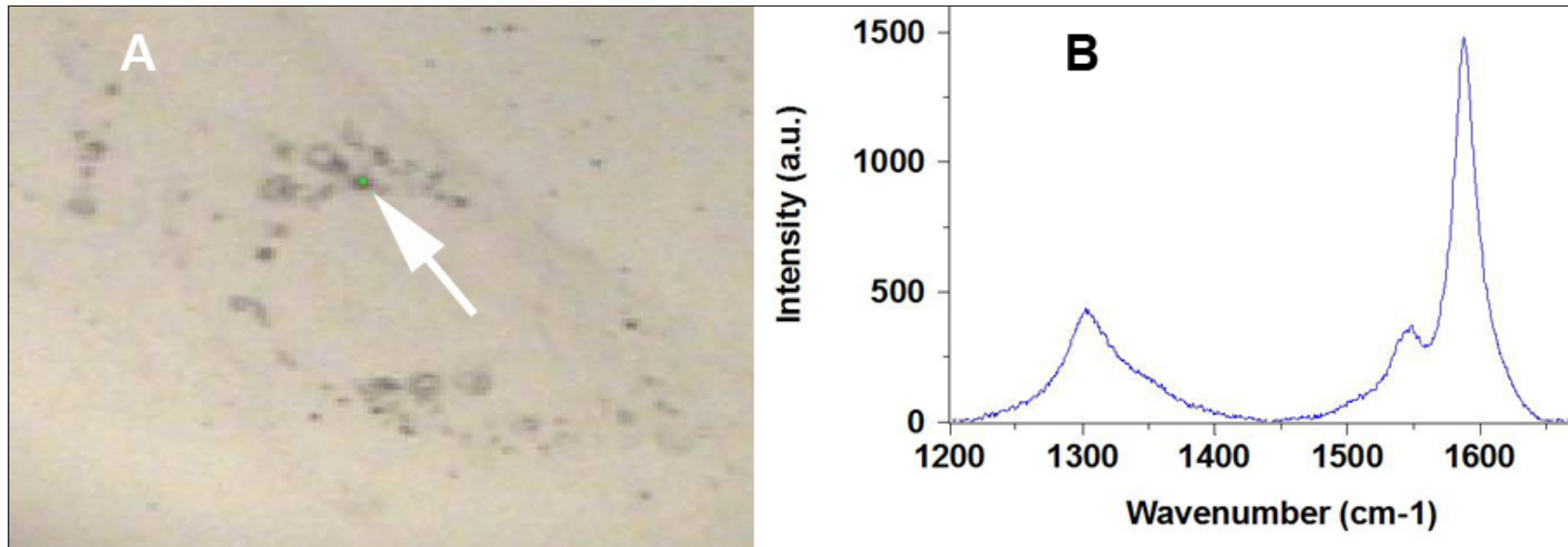
### Horiba Jobin Yvon

- 632.8 nm Laser
  - Spot size < 2  $\mu\text{m}$
- Confocal Pinhole
  - Size = 400  $\mu\text{m}$
- 50x objective
  - NA = 0.75



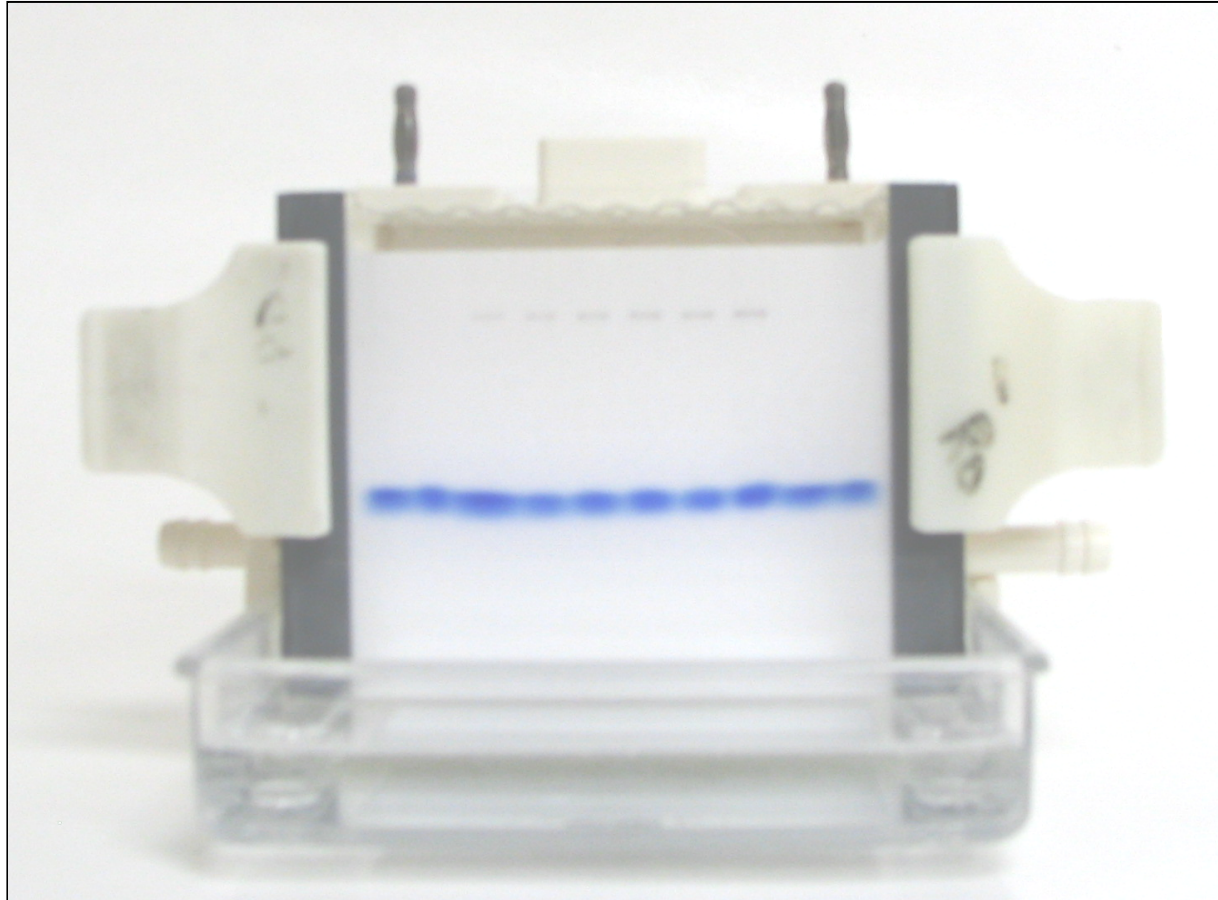
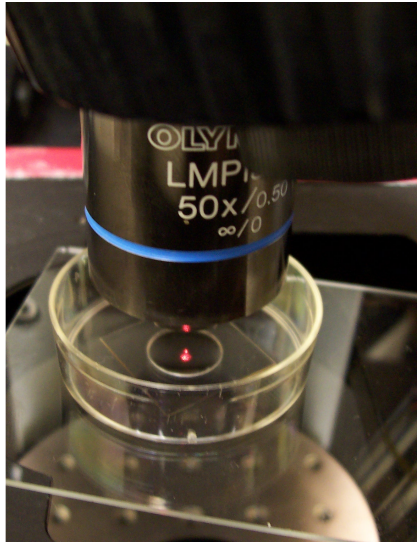
# Confocal microRaman Spectroscopy

**1-3  $\mu$  m lateral resolution - Ideal for localized measurements**



**Inexpensive, rapid, accurate, method of quantitating total intracellular SWNT concentrations from a plurality of cells**

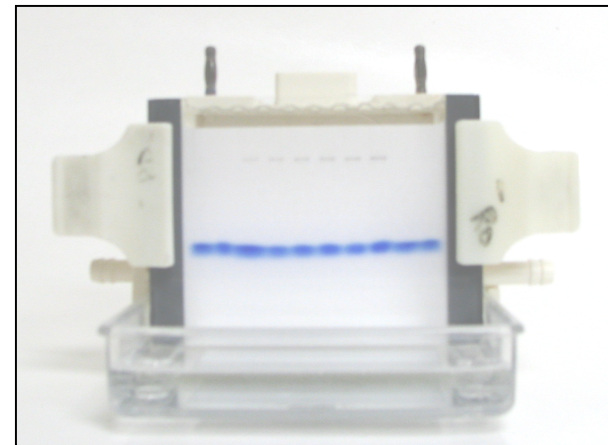
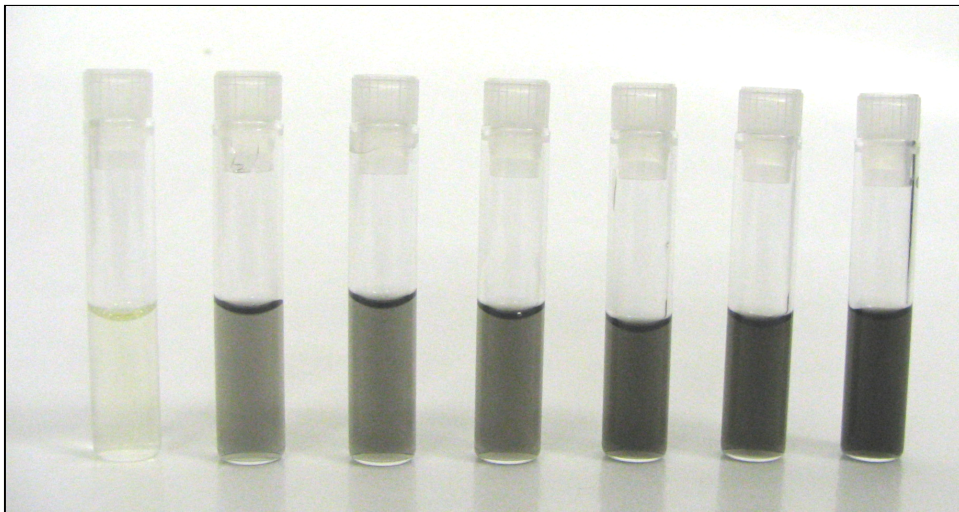
# Quantitative measurement of SWNTs taken up by $>10^4$ NRK Cells using SDS-PAGE



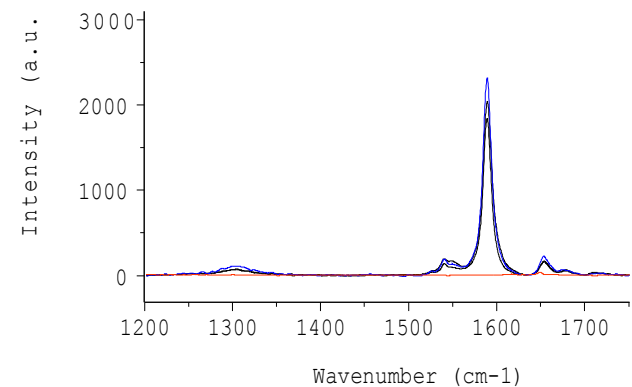
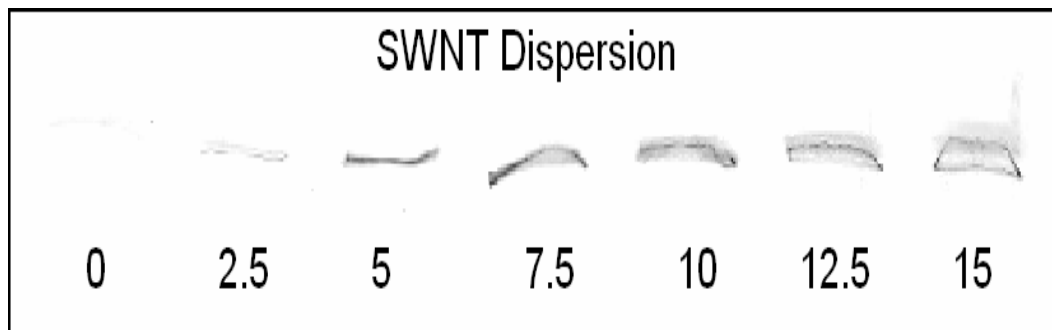
Wang, et al. *Anal. Chem.* (2009) in press.



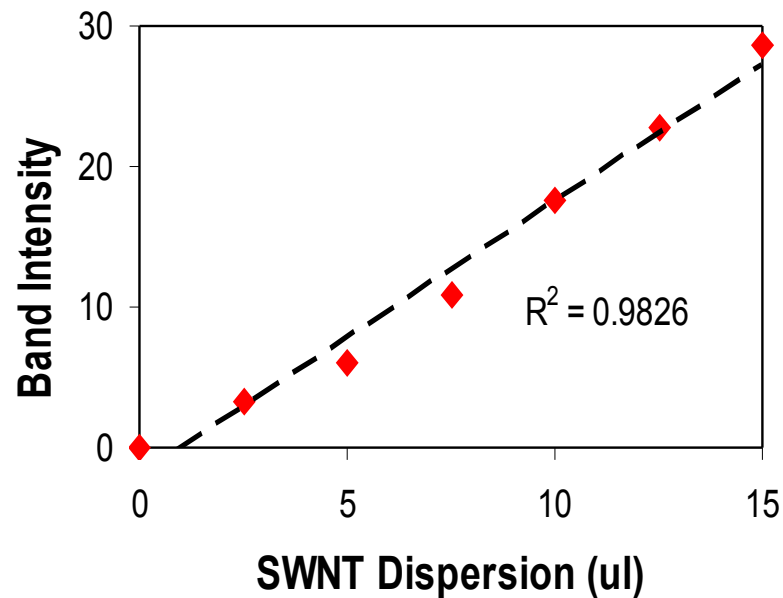
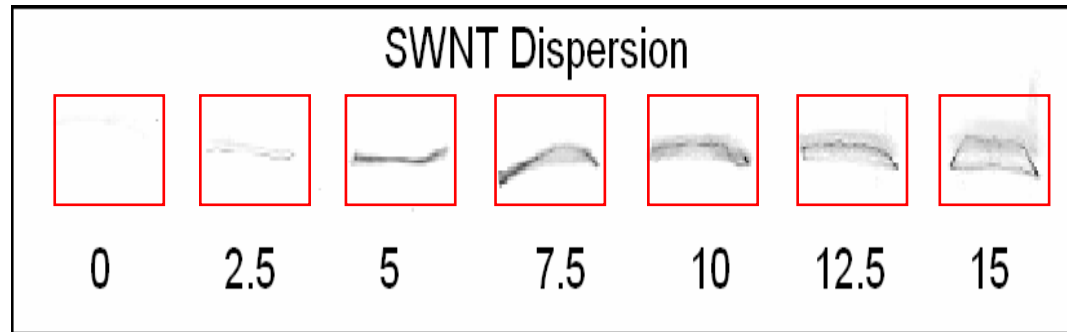
# SDS-PAGE of BSA-SWNT Dispersions



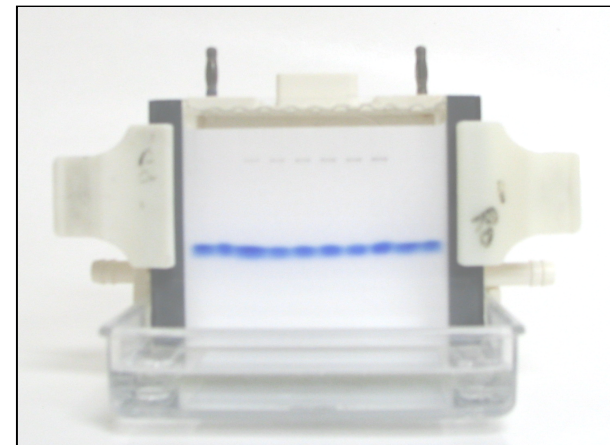
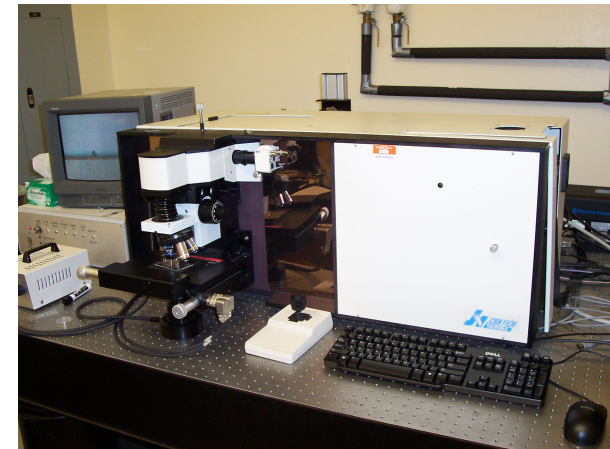
**100 V, 2 h**



# SDS-PAGE of BSA-SWNT Dispersions (band detections using a flatbed scanner)

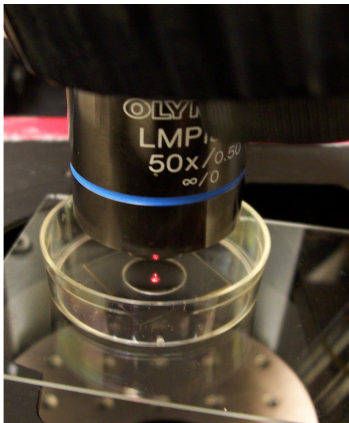


# Inexpensive, Label-free, Sensitive, At-Line Detection of CNTs from a Process Waste Stream



**Our SDS-PAGE Method:**  
**~1  $\mu$  L sample volumes and ~5 nanogram detection limits**

# Quantitative measurement of BSA-SWNTs taken up by $>10^4$ NRK Cells using SDS-PAGE

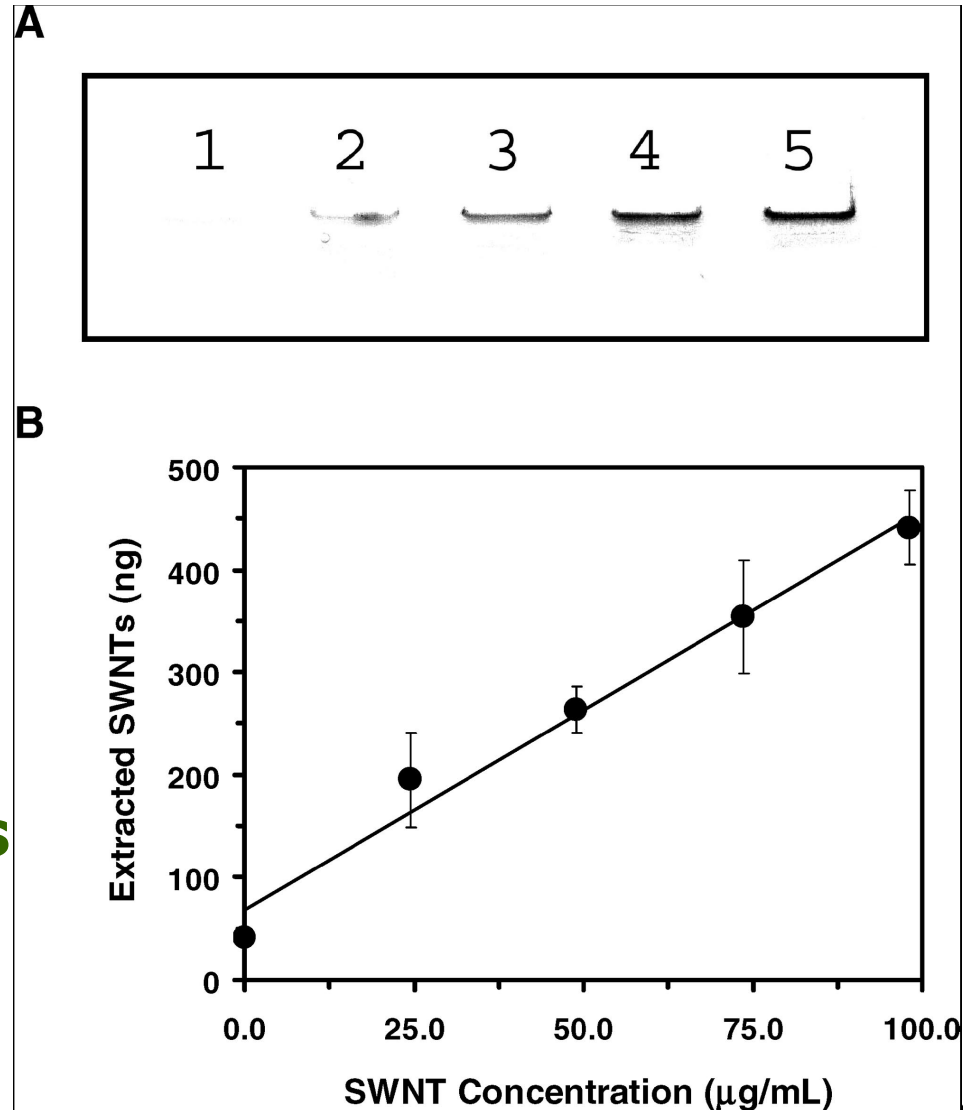


**1-day incubation**

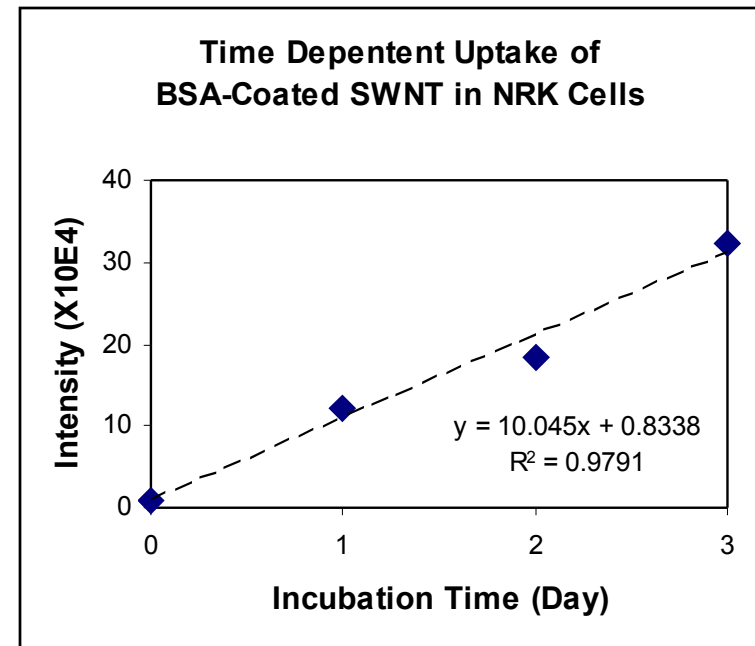
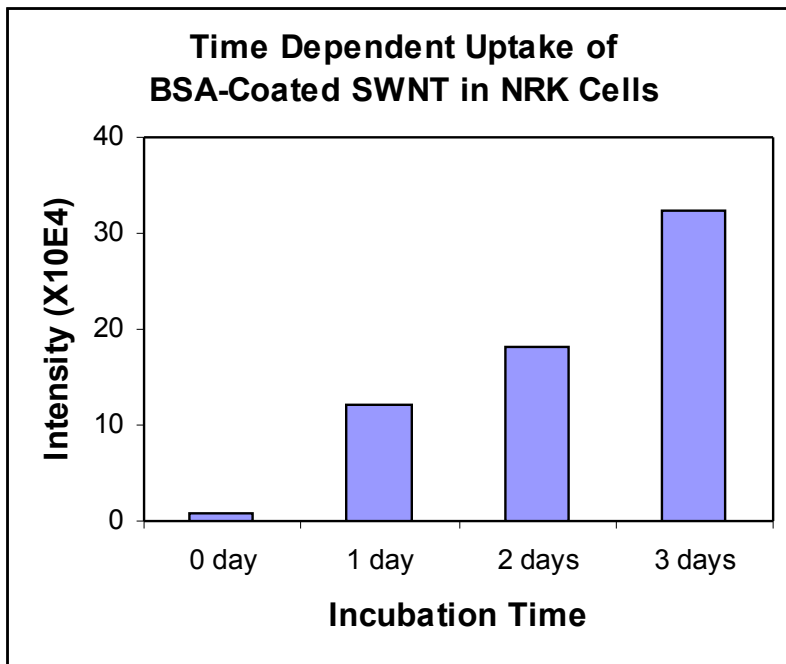
**with**

**different SWNT amounts**

**applied to cells**

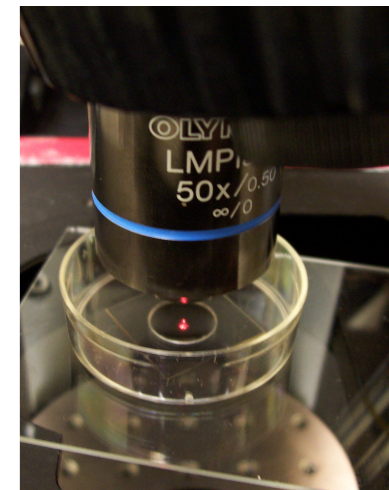
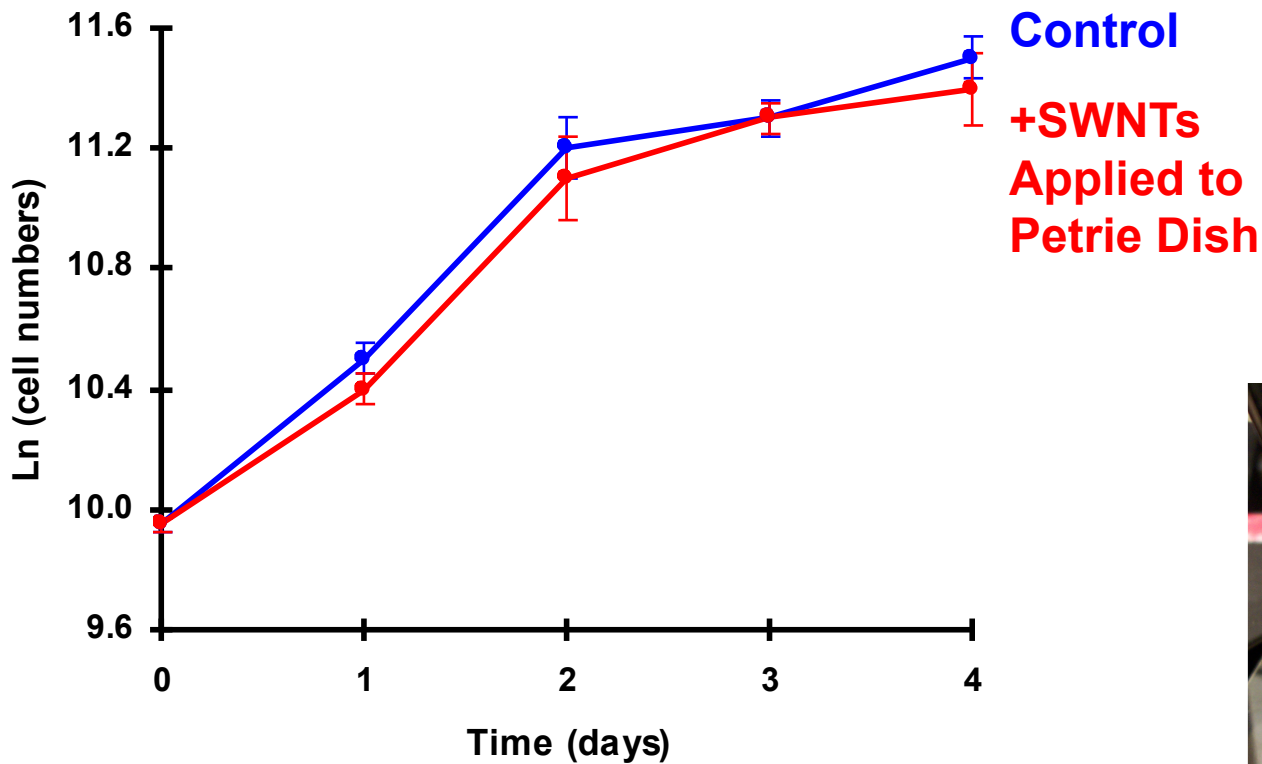


# BSA-SWNT uptake (1, 2, 3 days)

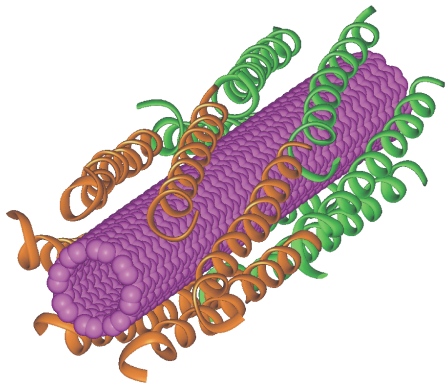
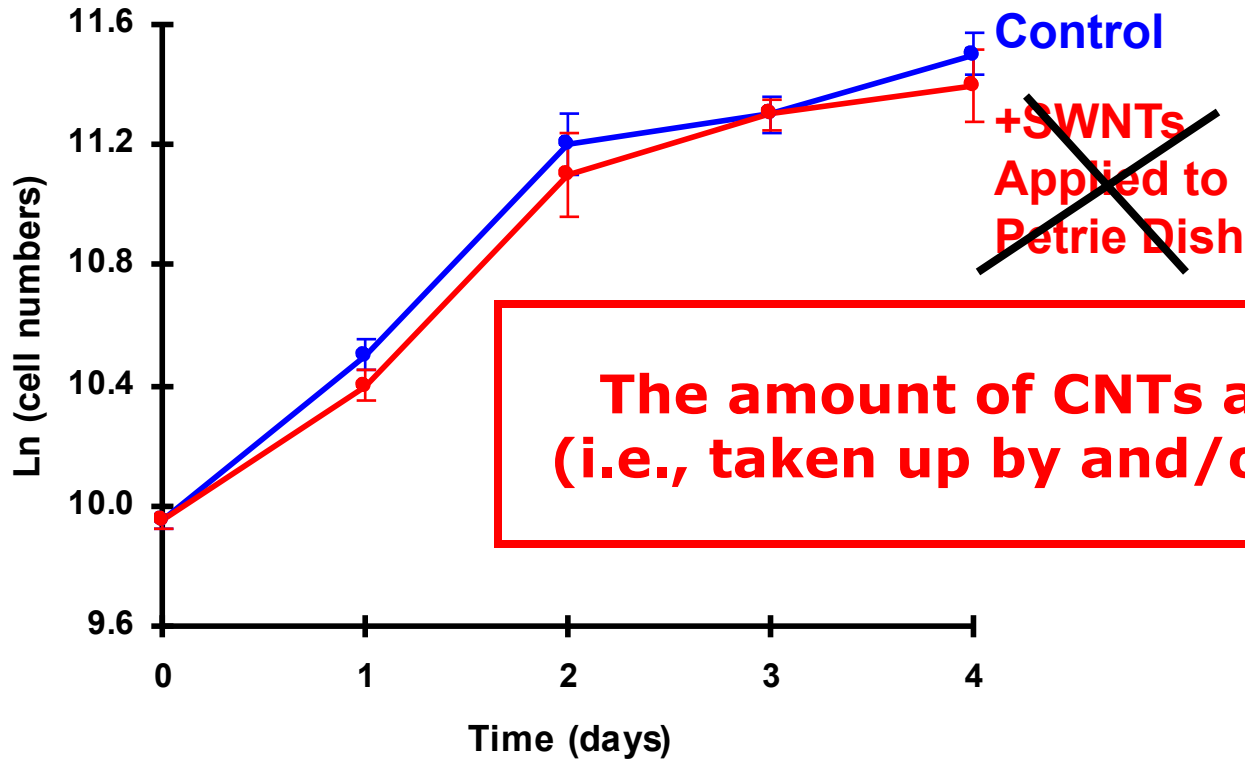


**The uptake of BSA-SWNTs by NRK cells is linear with incubation time and SWNT conc., which is consistent with fluidic-phase endocytosis mechanism**

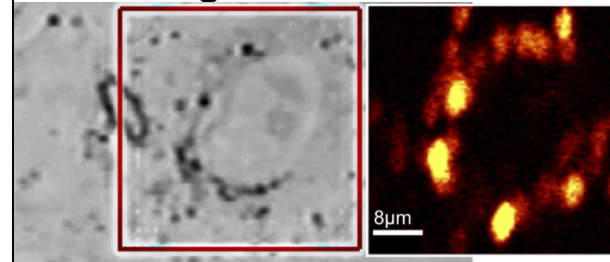
# Improved Cell Viability Data



# Improved Cell Viability Data



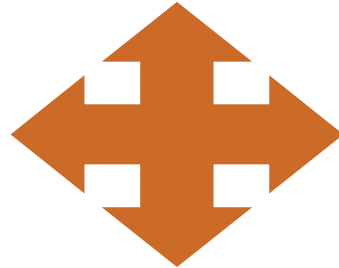
Live-cell imaging of CNTs using confocal Raman



# The UTD Bionanosciences Group

**Academia**

**Medical and  
Life Scientists**



**Chemists, Engineers,  
Physical & Materials  
Scientists**

**Business and Industry**

**Characterization of Raw CNT Materials**

**Preparation of Biocompatible CNTs**

**Intracellular Fate of CNTs and  
Biological Response of Cells**

**CNT-based Targeted Cancer Therapies**



# Predicting, Testing, and Neutralizing Nanoparticle Toxicity

