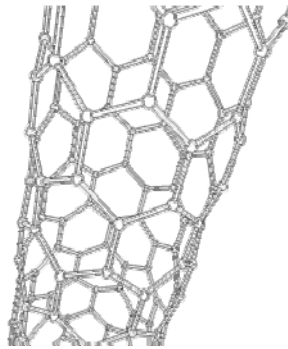




Engineering the Pharmacology & Toxicology of Nanomaterials

The Case of Carbon Nanotubes



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Centre for Drug Delivery Research
The School of Pharmacy, University of London



Carbon Nanotubes: Stuff of Dreams?

ELECTRICAL CONDUCTIVITY

Ballistic transport means that electrons in nanotubes travel much faster than in metals, and they don't dissipate. This conductivity could be useful in making electric paint, absorbing static, storing energy or replacing chips' silicon circuits.

STRENGTH

Six times lighter than steel but more than 500 times stronger.

THERMAL CONDUCTIVITY

The best material ever discovered for moving heat from one place to another, nanotubes are potentially handy for cooling confined spaces like PCs.

FLEXIBILITY

Nanotubes can be bent 120 degrees and snap back. Potential failure is therefore reduced.

SELF-ASSEMBLY

Unlike silicon circuits, which need to be "drawn," nanotubes form on their own in the presence of a catalyst.

TEAM PLAYER

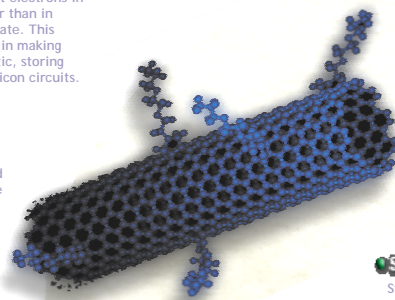
Almost chemically inert, nanotubes won't prompt reactions in other materials. That quality is potentially useful in atomic microscopes or for drug delivery.

LUMINESCENCE

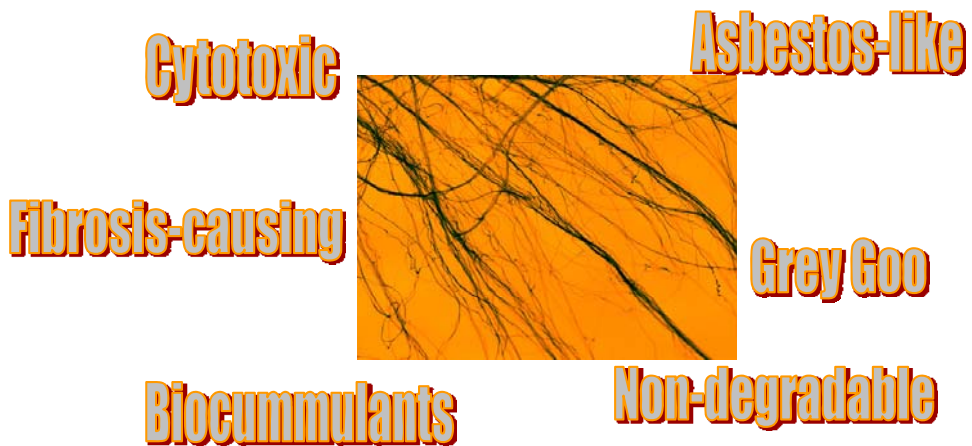
Because they emit light, nanotubes could be used in optical fiber.

SELF-RECOVERY

Strong covalent bonds mean that if an atom goes missing, the remaining carbon atoms will fill the gap.

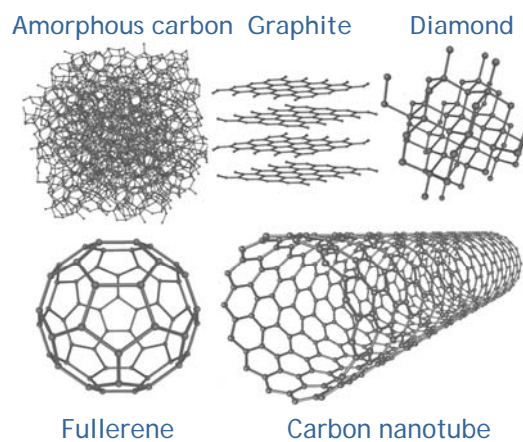


Carbon Nanotubes: Stuff from Hell?



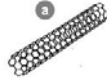
Carbon Nanotube Definition

from Amorphous Carbon to Novel Nanomaterial

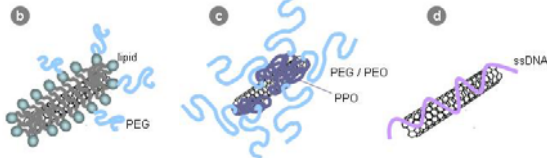


Carbon Nanotubes in Biology & Medicine

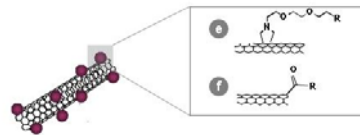
Pristine CNT



Coated CNT (non-covalent surface modification)



Functionalized CNT (covalent surface modification)

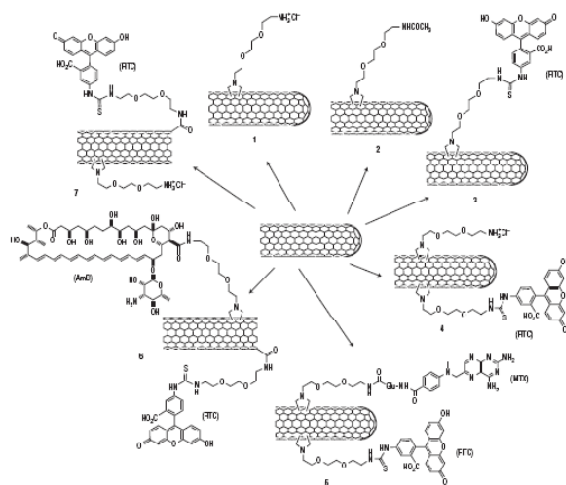


Kostarelos, Bianco, Prato. *Nature Nanotechnology*, 2009

- Only a few types of CNT used in biomedical applications
- Pristine material without surface modification should be avoided
- The fundamental needs to be achieved are:
 - aqueous and biological fluid **dispersibility**
 - nanotube **individualisation**



Universality in f-CNT intracellular uptake?



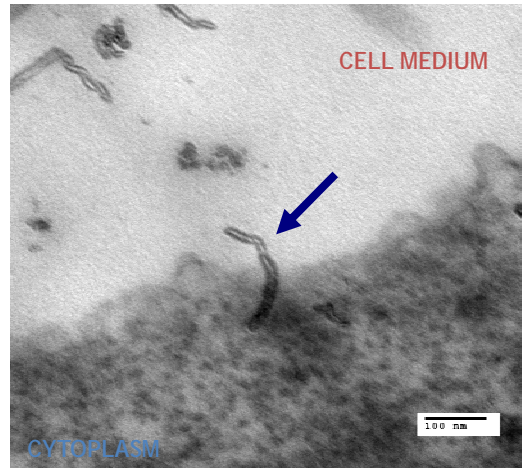
f-CNT Type	CNT characteristics (Length, diam. (nm))	Cell type	Confocal microscopy images
1	f-CMNT 0.45-0.25 f-MMNT 0.85-0.95	A549 D2 (µg ml ⁻¹) Fibroblasts HL60 C2C12 HEK293	
2	f-CMNT 0.45-0.25 f-MMNT 0.85-0.95	A549 D2 (µg ml ⁻¹) Fibroblasts HL60 C2C12 HEK293	
3	f-CMNT 0.45-0.25 f-MMNT 0.85-0.95	HeLa D2 (µg ml ⁻¹) Fibroblasts C2C12 K562 Neutrophils MCF7	
4	f-CMNT 0.95 (0.10) ^a f-MMNT 0.95 (0.10) ^b	HeLa D2 (µg ml ⁻¹) Jurlat	
5	f-CMNT 0.95 (0.10) ^a f-MMNT 0.95 (0.10) ^b	HeLa D2 (µg ml ⁻¹) Jurlat	
6	f-CMNT 0.71 (0.25) ^a f-MMNT 0.71 (0.25) ^b	HeLa D2 (µg ml ⁻¹) Jurlat	
7	f-CMNT 0.71 (0.25) ^a f-MMNT 0.71 (0.25) ^b	C. rodentium D2 (µg ml ⁻¹) E. coli S. pneumoniae	



Kostarelos et al., *Nature Nanotechnology*, 2007, 2, 108-1484



The 'Nanoneedle' Hypothesis



Pantarotto et al. *Angewandte Chemie International Edition*, 2004
Lacerda et al. *Journal of Materials Chemistry*, 2008
Lacerda et al. *NanoToday*, 2008

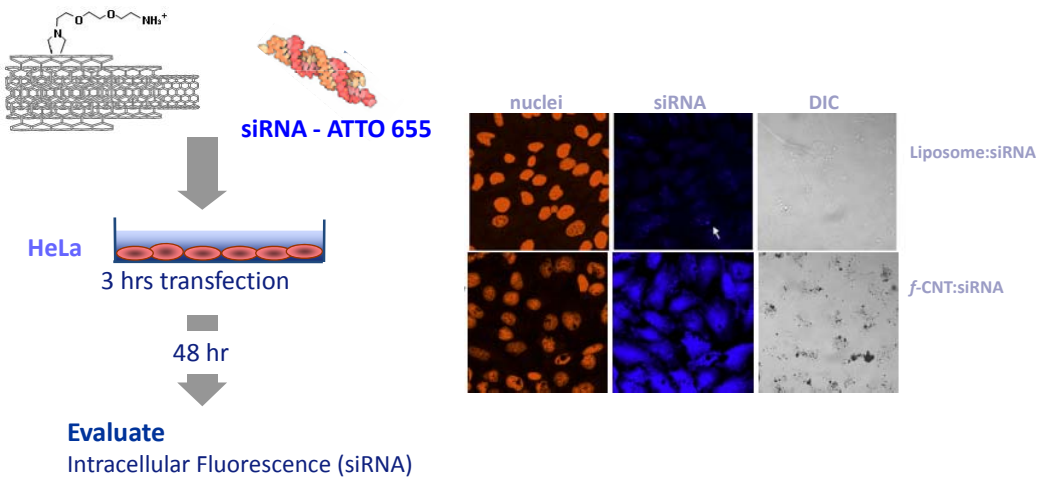


Carbon Nanotubes for Biomedicine

Why is all this interesting?



CNT-mediated siRNA delivery



Al-Jamal, K. et al., FASEB J, 2010

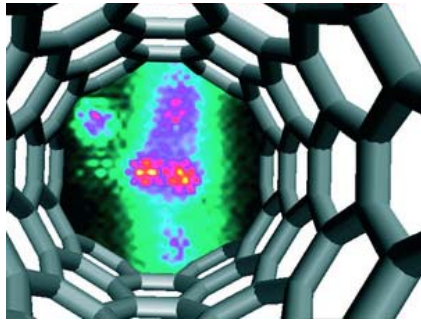
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Carbon Nanotube Pharmacology

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CNT Pharmacology

What's 'Good' and what's 'Bad'

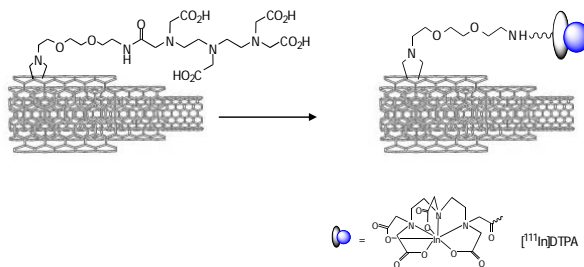


- 'Good' is long blood circulation & high degree of excretion
- 'Bad' is tissue accumulation that may lead to side effects



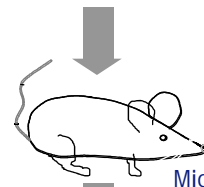
CNT Pharmacology

Radiolabelling



Administration

Intravenous (tail vein)
MWNT-DTPA [¹¹¹In]
(50 µg / 1.5-10 MBq)

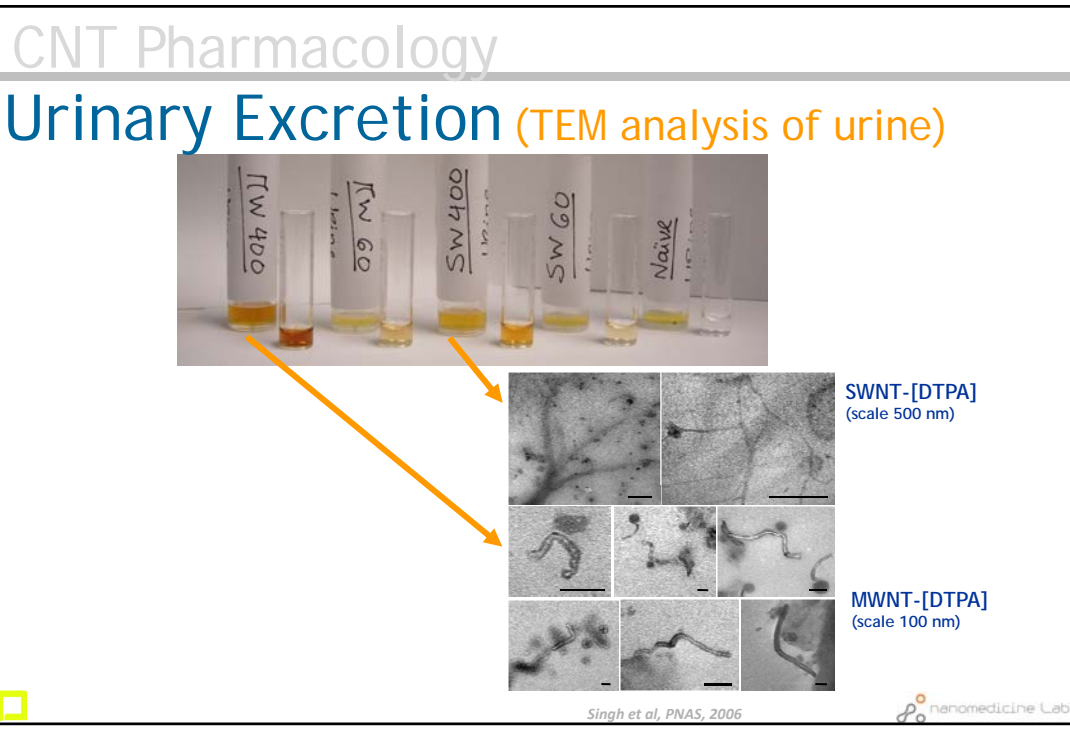
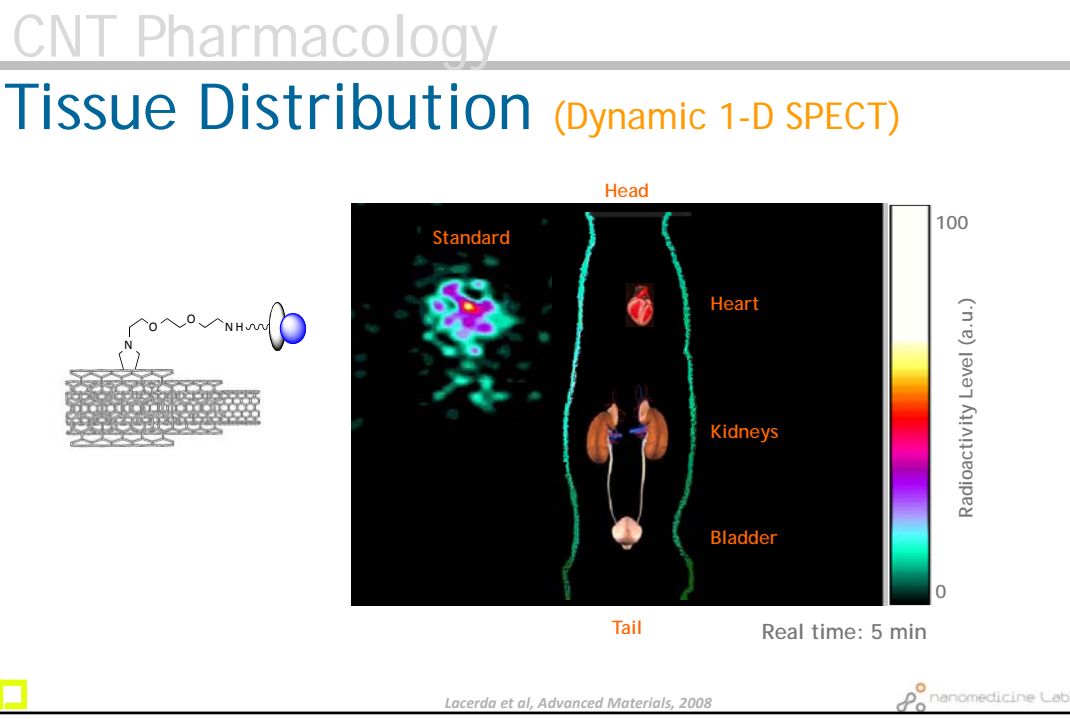


Mice / Rats

5min, 30 min, 24 hr

Evaluate
SPECT/CT imaging





CNT Pharmacology

Urinary Excretion Mechanism (kidney TEM)

Bundled MWNT found in the glomerular capillaries

500 nm

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CNT Pharmacology

Urinary Excretion Mechanism (kidney TEM)

Individual CNT

EC RBC E P BM

0.2 μ m

30 min

P E BM

0.2 μ m

5 min

Lacerda et al, SMALL, 2008

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Carbon Nanotube Toxicology

CNT Toxicology Peritoneal Model CNT Toxicity

Original Article

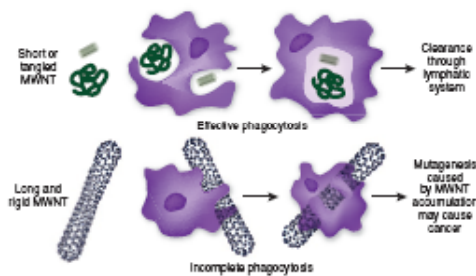
Induction of mesothelioma in p53^{-/-} mouse by intraperitoneal application of multi-wall carbon nanotube

Aleuya Takagi¹, Akihiko Hirose¹, Tetsuji Nishimura¹, Nobutaka Fukumori¹, Akio Ogata¹, Norio Ohashi¹, Satoshi Kitajima¹ and Jun Kianno¹

LETTERS

Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study

CRAIG A. POLAND¹, RODGER DUFFIN¹, IAN KINLOCH¹, ANDREW MAYNARD², WILLIAM A. H. WALLACE³, ANTHONY SEATON⁴, VICKI STONE⁵, SIMON BROWN¹, WILLIAM McNEE¹ AND KEN DONALDSON^{1*}

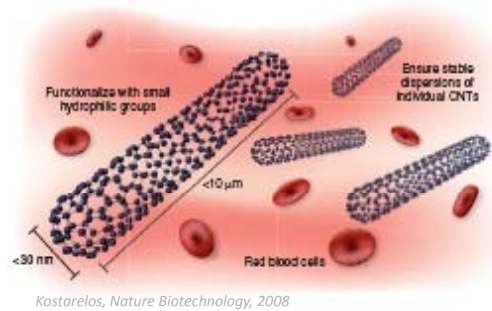


Kostarelos, *Nature Biotechnology*, 2008

- Surfactant-based dispersions of pristine, long (>20 μ m) CNT
- Compared to asbestos fibers
- Reported asbestos-like reactivity that can lead to carcinogenicity

CNT Pharmacology & Toxicology

Conclusions



- CNT interact with biological matter leading to biological activity
- CNT structural and surface characteristics determine biological profiles *in vitro* and *in vivo*
- Chemical functionalisation with small hydrophilic groups that can lead to individualised CNT can cross the glomerular filter and be excreted in urine
- Processes that can lead to shorter than 5µm CNT can completely alleviate the asbestos-like reactivity
- CNT Structure-Biological Function studies are the only way forward



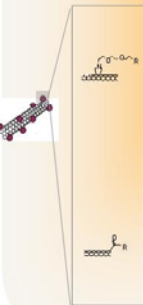


Carbon Nanotubes in Medicine into perspective...



Carbon Nanotubes in Medicine

(preclinical animal models only)

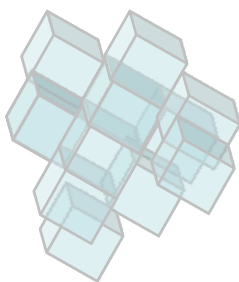
Type of Carbon Nanotube	Biomedical Application	Therapeutic/Imaging Agent	Preclinical Model
	Cancer imaging (systemic)	Radionuclide (Cu-64)	solid tumor model
	Cancer treatment (systemic)	Paclitaxel	solid tumor model
	Cancer imaging (systemic)	Intrinsic Raman & Ultrasound signal	solid tumor model
	Cancer Treatment (localised)	Hyperthermia by Radiofrequency Activation	solid tumor model
	Vaccination	FcIF7-derived Peptides	normal mice
	Vaccination	(AMA-1) Peptide	rodent malaria
	Imaging (systemic)	Radionuclide (In-111 and Y-90)	normal mice
	Cancer treatment (systemic)	Monoclonal Antibody (Rituximab)	human marrow tumor model
	Cancer treatment (localised)	Gene silencing (siRNA)	solid tumor model
	Imaging (systemic)	Radionuclide (B-123, C-14)	normal mice
	Cancer treatment (localised)	Gene silencing (siRNA)	solid tumor model
	Tumor Vaccination	Tumor lysate Protein	solid tumor model
	Cancer treatment (systemic)	Cisplatin	solid tumor model

Kostarelos et al. Nature Nanotechnology, 2009

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- Oncology is the prime indication when CNT are used in medicine
- Proof-of-principle systemic targeting of CNT (both coated and functionalised) using peptides (RGD) and antibodies shown
- Only two studies reported therapeutic efficacy to prolong survival of tumor-bearing animals
- Disease models in immunology and neurology at the proof-of-principle

The Funding



NINIVE

THALES



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