Nano/bio integrations for biosensing & drug delivery

Reema Zeineldin

Department of Pharmaceutical Sciences
Massachusetts College of Pharmacy & Health Sciences

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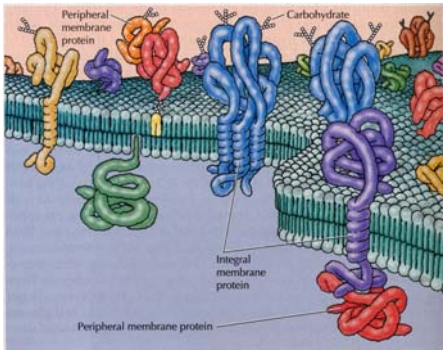
Outline

- Research interests
  - Cell & membrane biomimetics – biosensing
  - Carbon nanotubes – drug delivery

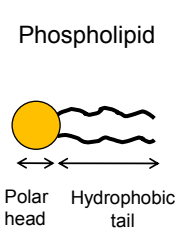
Cell and membrane mimetic systems for biosensing

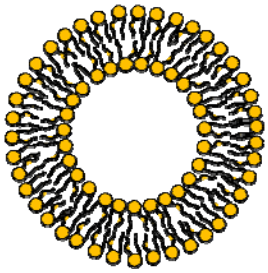
Model of cell membrane



Cooper, 1997. The cell: a molecular approach.

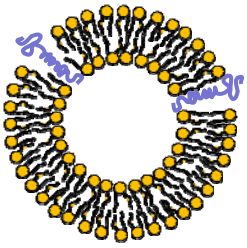
Liposomes:



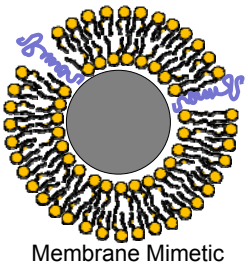


Liposomes:

Sizes: 10's nm to sub-micrometer



Membrane mimetic Liposome



Membrane Mimetic Supported lipid bilayer (SLB) on a microsphere

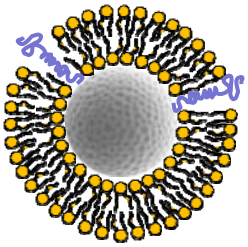
Advantages (vs. liposomes):

-Long term stability & rigidity

-Ease of handling

-Defined shapes and sizes

-Biocompatibility – drug delivery



Cell Mimetic Supported lipid bilayer (SLB) on a porous microsphere

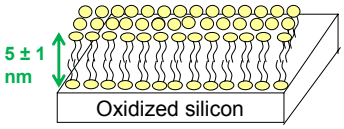
Porous microspheres:

High surface area

High pore volumes

Ordered pore network

Serve as carriers

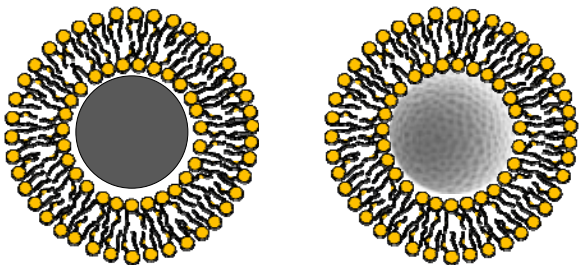


Planar substrate

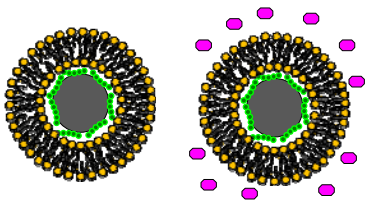
Applications of SLB

- Biomimetic platform
  - Biosensors
    Molecular interactions
    High throughput screening
  - Drug delivery (micro / nano)

Biosensors employing SLBs on microspheres for sensing interactions with membranes

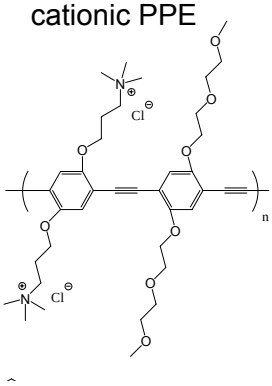


Zeineldin & coworkers Cytometry A 2006, 69:335-341
Zeineldin & coworkers Langmuir 2008, 24:4125-4131
Utility application No. 11/466,046 filed 8/21/06
Utility application No. 11/466,050 filed 8/21/06



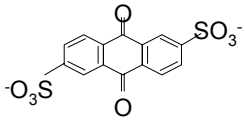
5 μm spheres

Fluorescent polymer: cationic PPE



Cationic polyelectrolyte poly(*p*-phenylene-ethynylene) (PPE) derivative

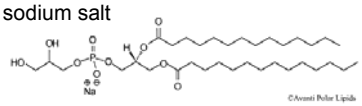
Quencher (AQ)



9,10-anthraquinone-2,6 disulfonate

DMPG (14:0) anionic

1,2-dimyristoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)] sodium salt



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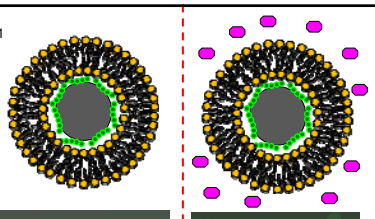
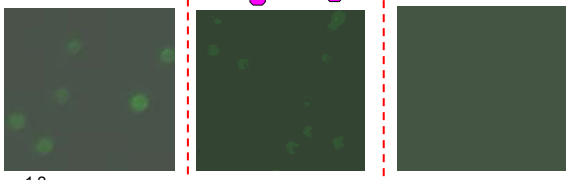
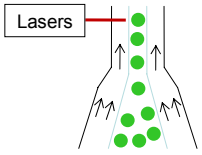


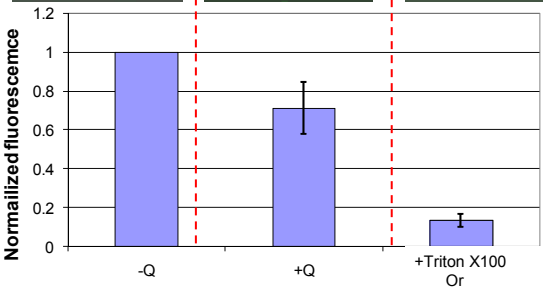
+Triton X100 or Mellitin

Fluorescence microscopy



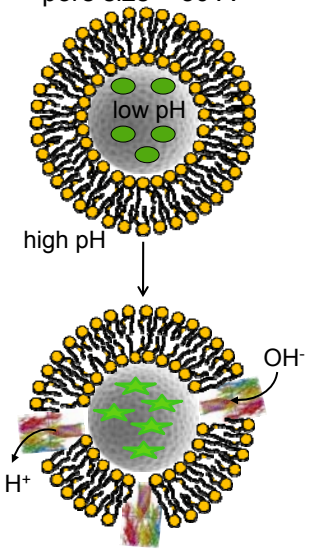
Flow cytometry





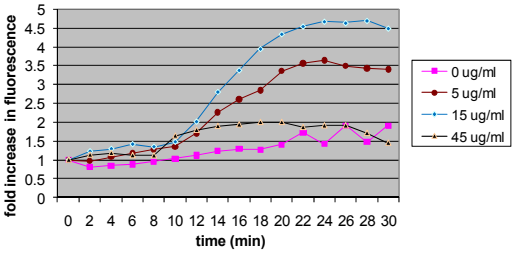
Detect interactions with SLBs on microspheres employing fluorescence quenching

Porous sphere ~ 5 µm,
pore size ~ 50 Å



↑ **fluorescence flow cytometry**

Pore-forming α-Hemolysin



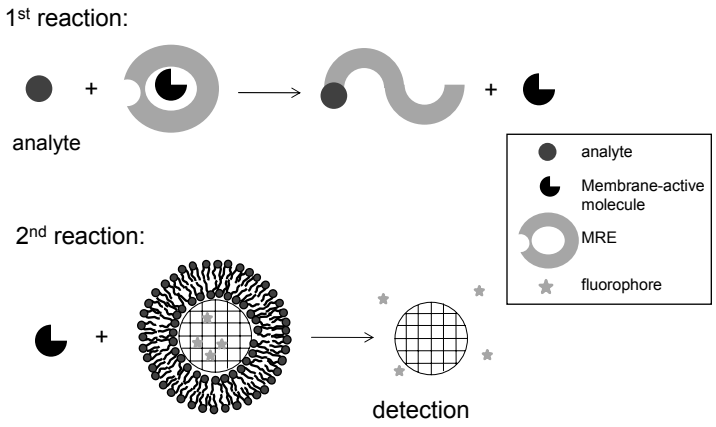
Piyasena, Zeineldin & coworkers Biointerphases 2008, 3:38-49
Utility application No. 11/466,046 filed 8/21/06
Utility application No. 11/466,050 filed 8/21/06

Detected interactions with SLB on porous microsphere using an encapsulated dye

Summary
SLBs

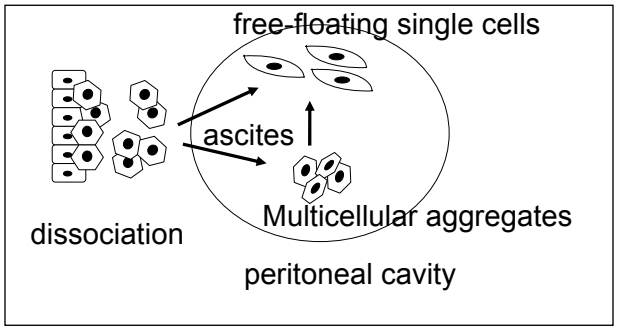
- Advantages over liposomes
- Cell mimetic – entrap & release compounds
- Applications
  - Biosensing
    - Detected interactions with SLB

Employ biomimetic microspheres for biosensing of analytes that do not interact with biomembranes



- Carbon nanotubes for targeted drug delivery to ovarian cancer

Intraperitoneal (IP) therapy in ovarian cancer (OVCA)



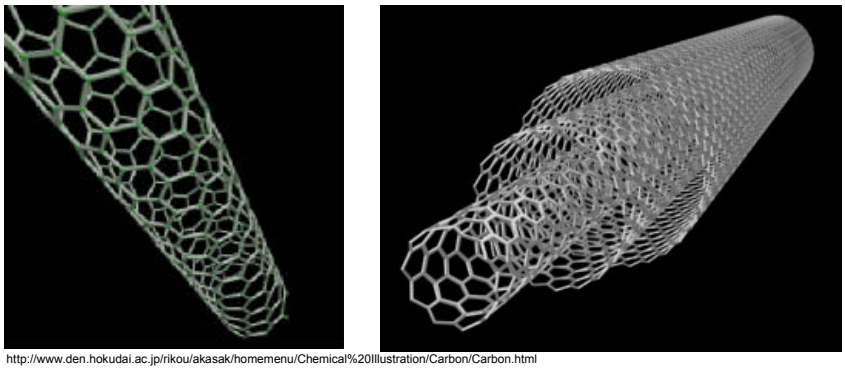
- Localized exposure to anti-neoplastic agents
  - Spare internal organs toxic effects of drugs administered intravenously
  - High [drugs]

Specificity:

Targeting OVCA through tumor markers or over-expressed receptors

- Folate receptor alpha (FRα)

Carbon nanotubes (CNTs)



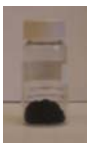
http://www.den.hokudai.ac.jp/rikou/akasak/homemenu/Chemical%20Illustration/Carbon/Carbon.html

SWNT: single-walled nanotubes

d ~ 1.2 - 1.4 nm
length nm's to μm's

MWNT: multi-walled nanotubes

d ~ 8 - 50 nm
length nm's to μm's



Dispersion

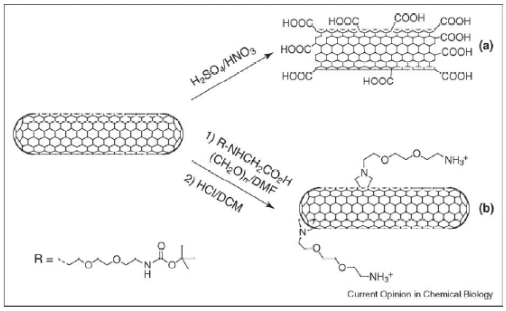
500 mg

2 mg in 500 mL

Dispersion by functionalizing CNTs:

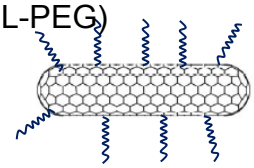
1. Chemical conjugation
2. Adsorption (involves ultrasonication)

Chemical modifications / conjugations



Bianco & coworkers 2005. Current Opinion in Chemical Biology 9:674-679

Physical adsorption
e.g. phospholipid-polyethylene glycol (PL-PEG)
ultrasonication – 1 to 2 hr



Advantages of <u>functionalized</u> CNTs for drug delivery

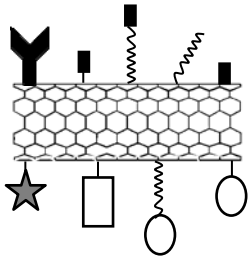
CNTs $\leq$ 1 μm deliver to cells: protein, nucleic acids, drugs

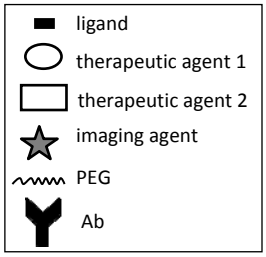
Non-immunogenic (short-term studies)

Little toxicity (short-term studies)

Advantages, cont ….

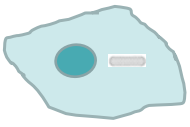
Multifunctional





Advantages, cont ….

- Cleared rapidly from body
- High thermal conductivity
- Hollow cylinders can introduce molecules into internal space
- Easy uptake



PEGylation:

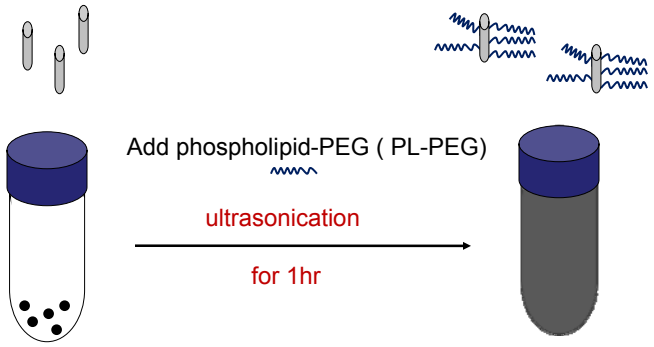
- Increases half-life in circulation
- Reduce non-specific uptake by cells
- Blocks non-specific binding to proteins

Evaluation of cellular uptake of SWNTs functionalized by adsorbing PL-PEG led to unexpected findings:

PL-PEG2000 (i.e., the MW of PEG is ~2000) to SWNTs did not reduce uptake of SWNTs

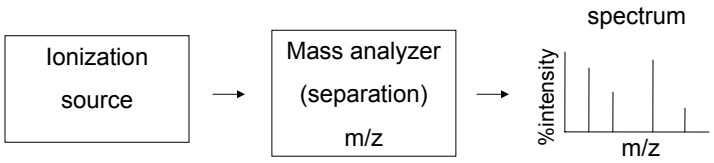
PL-PEG5000 gave contradictory results

1st question: What is the effect of ultrasonication on PEG?



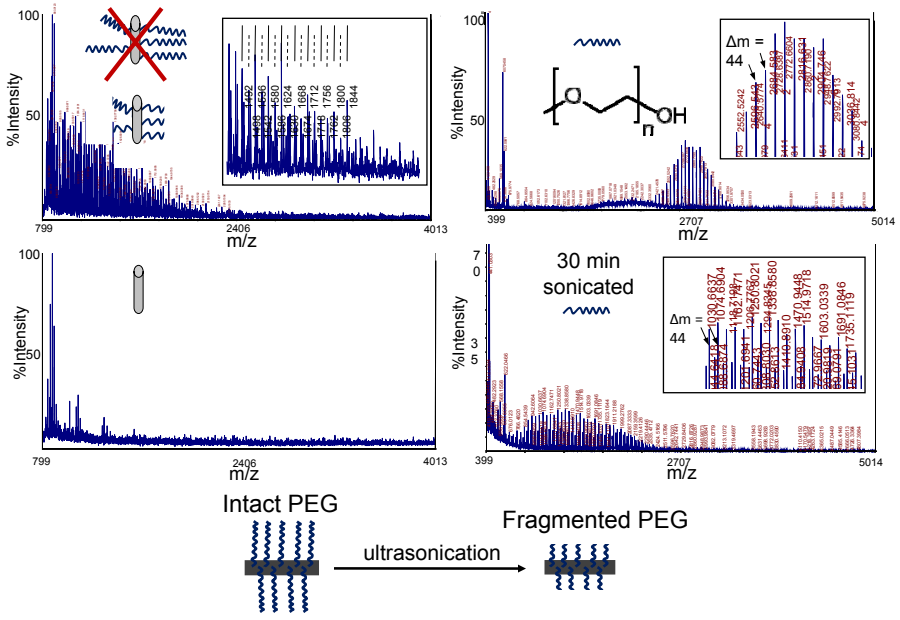
Mass spectrometry (MS)

Analytical tool for measuring molecular mass of a sample

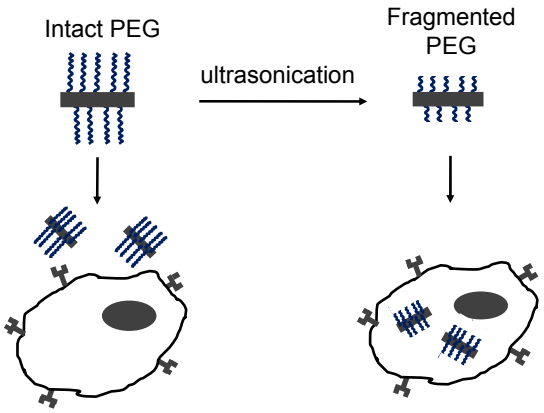


m/z = mass-to-charge ratio

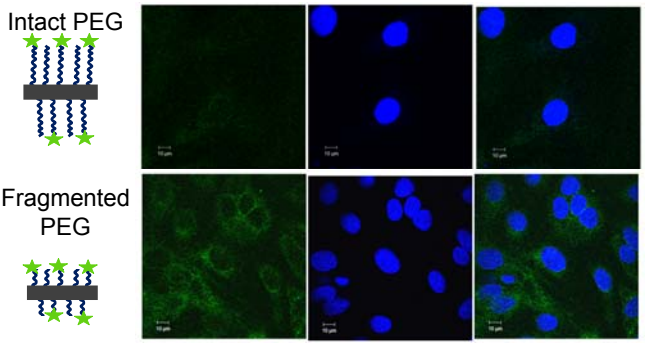
Evaluating effect of ultrasonication on PEG by MS



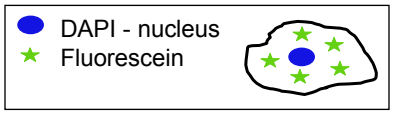
Hypothesis:



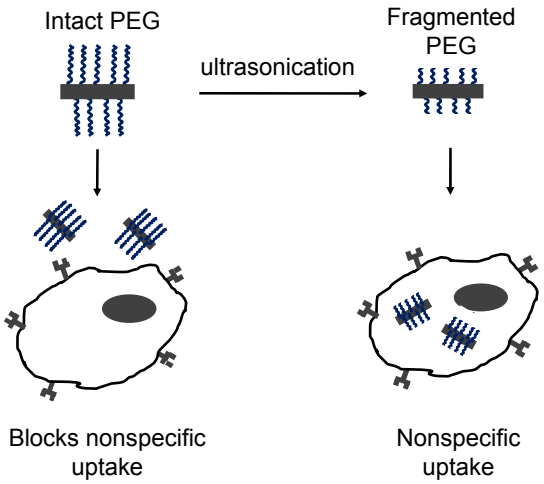
Evaluation of the effect of PEG integrity on uptake of SWNTs by cells



Zeineldin & coworkers. NanoLetters. 2009.

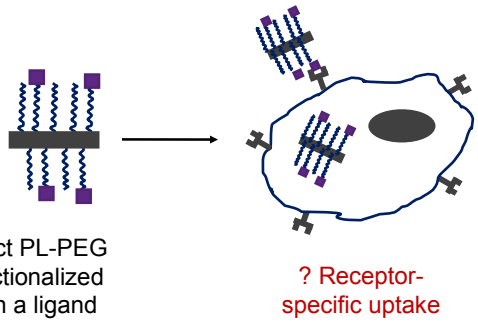


Conclusion:



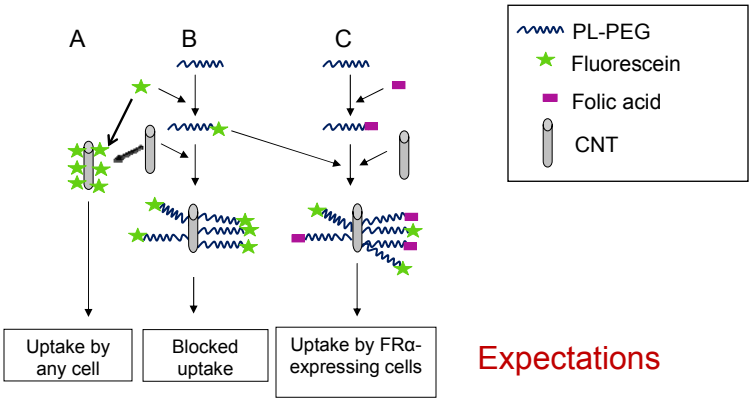
Integrity of PEG is important to prevent nonspecific uptake of SWNTs

2nd question: Can we employ intact PEG to target a cancer-specific receptor?



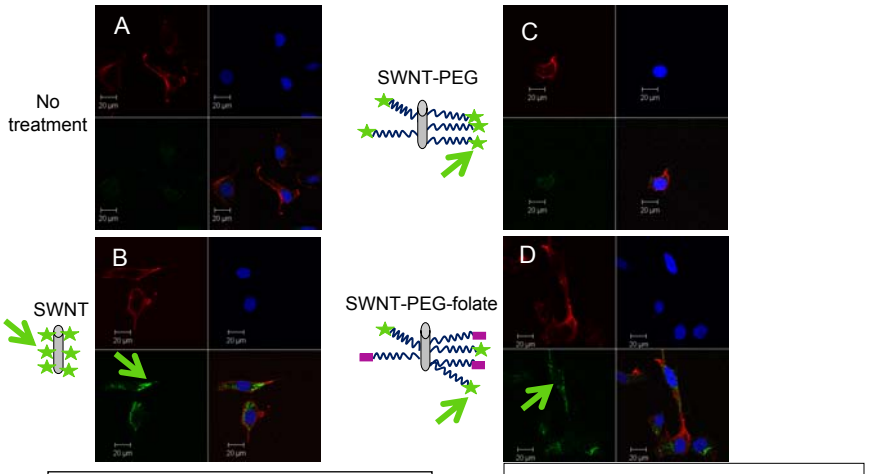
Folate receptor alpha (FRα)

Functionalizations of SWNTs



Expectations

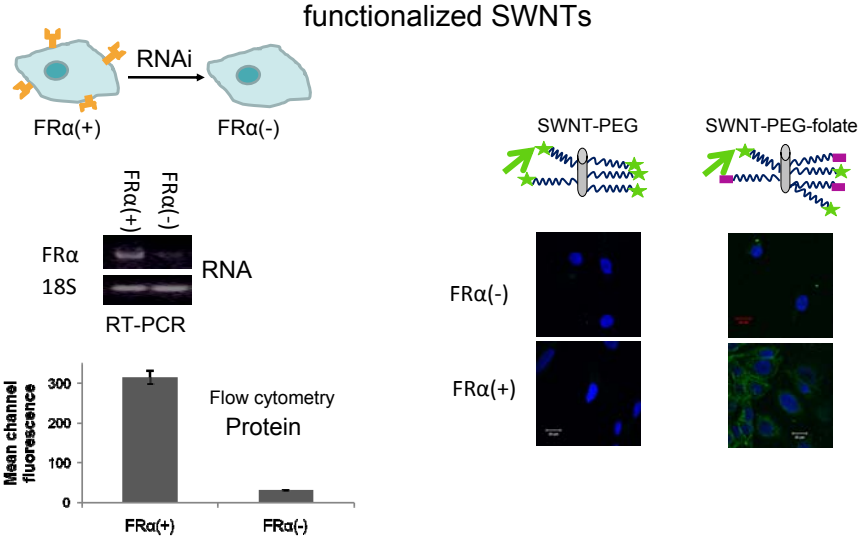
Uptake of folate-functionalized SWNTs by SKOV-3 (FR(+)) cells



	internalized
SWNT alone	Y
SWNT-PEG	N
SWNT-PEG-folate	Y

PEG blocks internalization, while folate promotes it

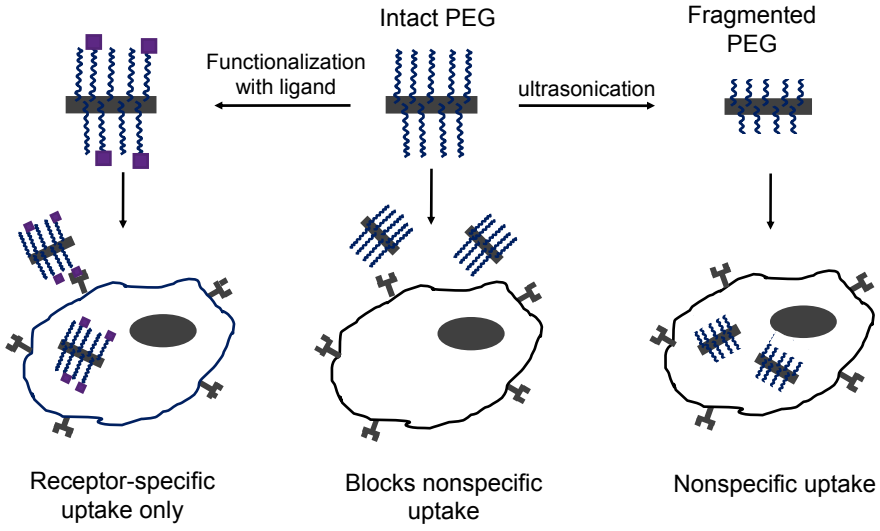
Evaluating if suppressing FRα eliminates uptake of folate-functionalized SWNTs



Folate-functionalized SWNTs were specifically taken up by FRα(+) cells but not FRα(-) cells

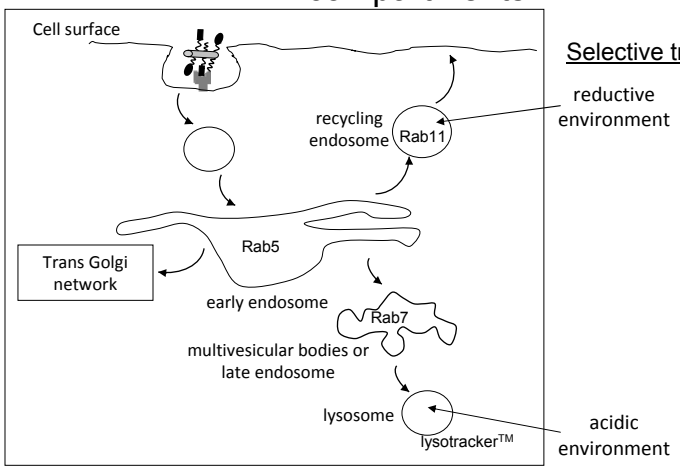
Spare normal cells

Conclusion:



Intracellular fate of targeted SWNTs

Aim: Direct carbon nanotubes to specific endocytic compartments



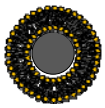
Endosomes:

- Contain targets for drugs
- Their environment may be employed for releasing drugs

Target receptors on OVCA cells:

- Folate receptor alpha (FRα)
- Epidermal growth factor receptor (EGFR)

Acknowledgements



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Dr. Tione Buranda

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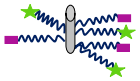
NSF-NIRT CTS 0404124 (Lopez)
ARO DAAD19-03-1-0173 (Lopez)
DTRA W911NF-07-1-0079 (Whitten)
CINT & SNL



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