Nanomedicine

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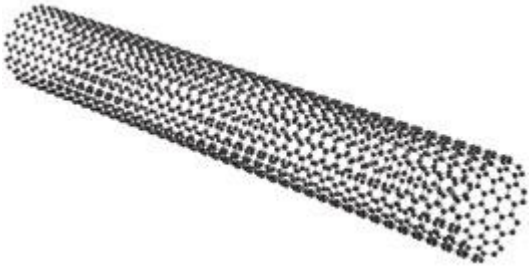
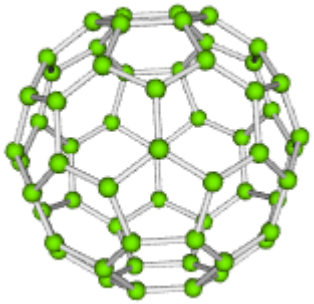
Learning Objectives

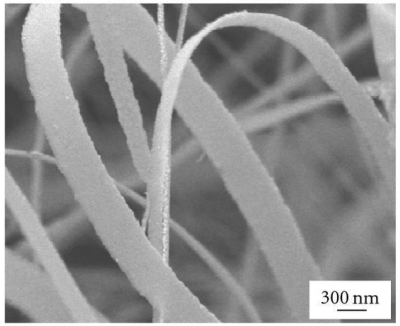
- How a nanoparticle is defined
- What they are commonly used for
- How they may benefit medicine
- How they enter the body following inhalation
- What medical applications they are being developed for
- Potential risks associated with nanoparticles

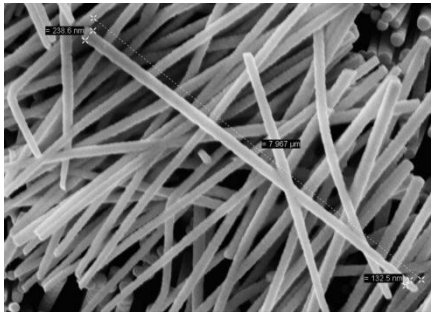
What is a nanoparticle?

A nanoparticle is a particle that has one dimension less than 100nm

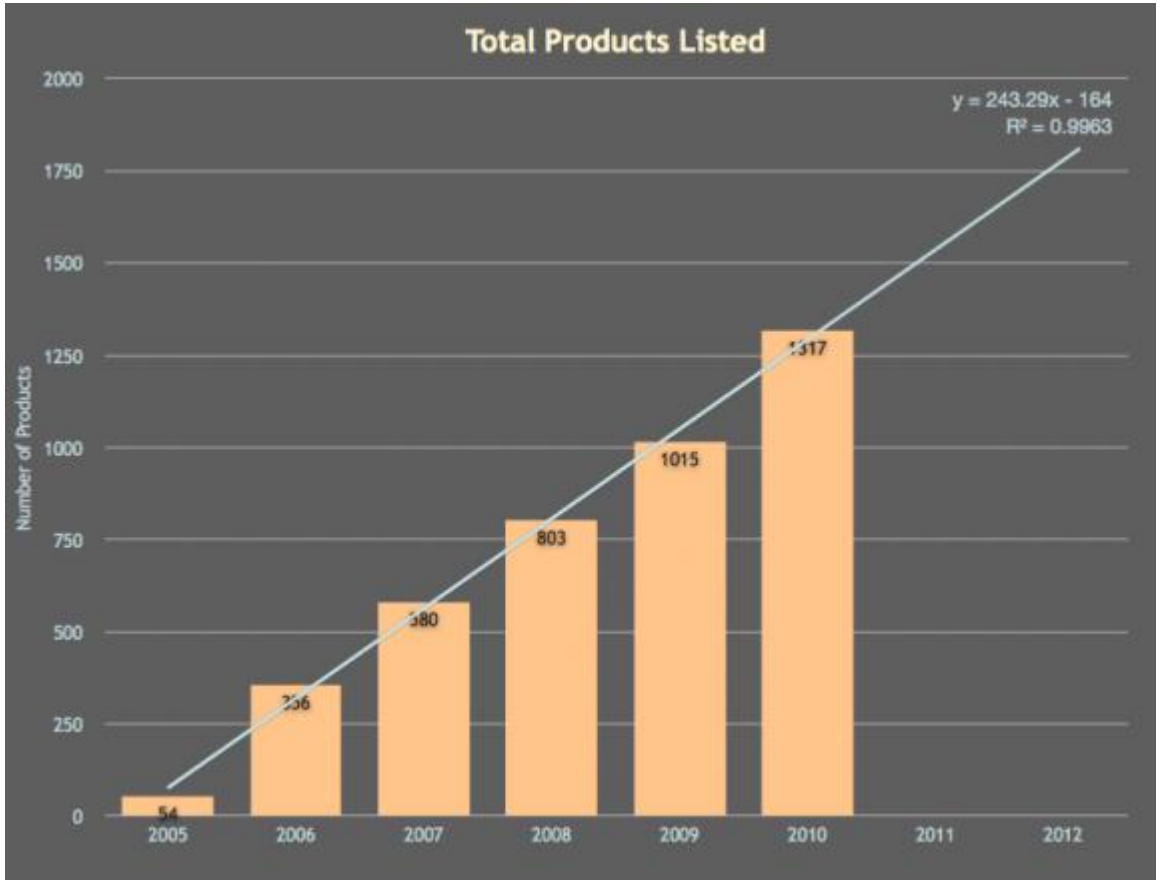




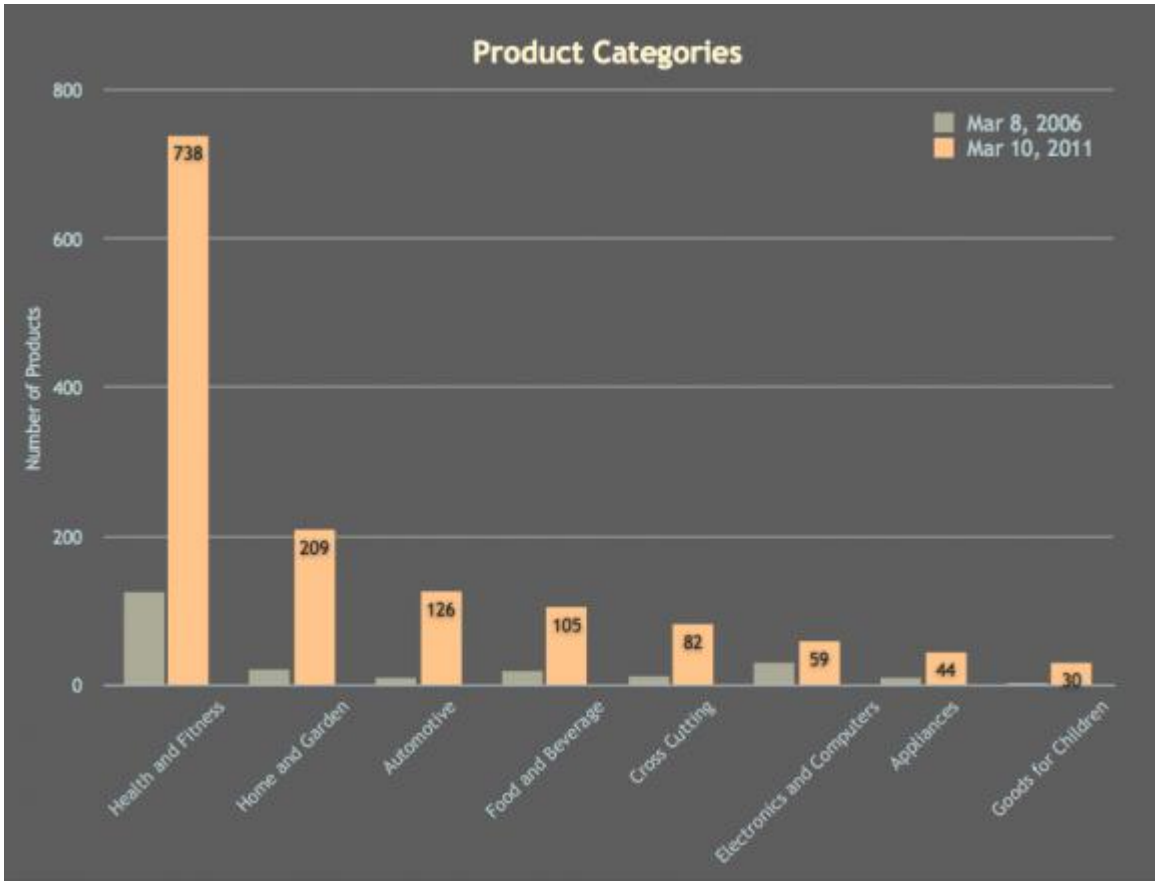




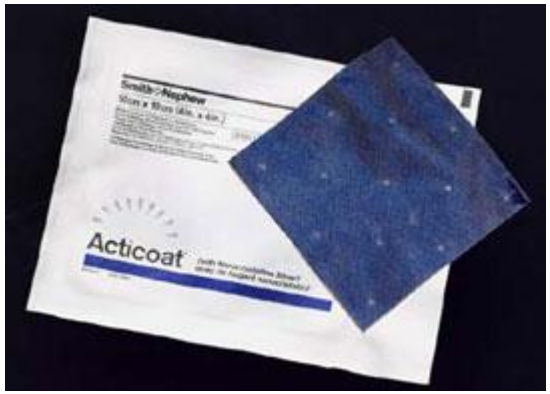
Nanoparticle use



Nanoparticle use



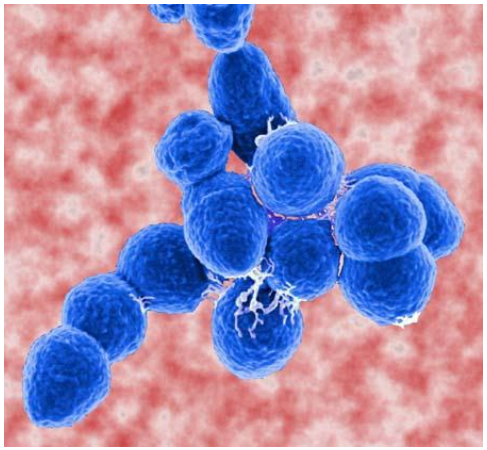
Nanoparticle use

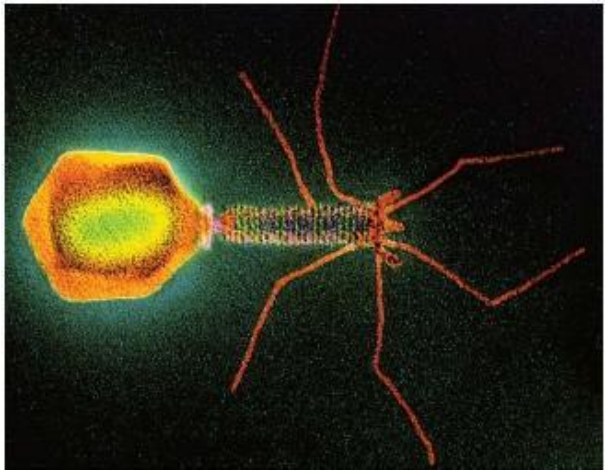


Why use nanoparticles?

- When materials enter the nano-range, their properties alter from that of their micron-sized equivalents.
- Nanoparticles have enhanced magnetic, electrical and optical properties
- As size decreases, the surface area:volume ratio increases

Why use nanoparticles?





Why use nanoparticles?

- When materials enter the nano-range, their properties alter from that of their micron-sized equivalents.
- Nanoparticles have enhanced magnetic, electrical and optical properties
- As size decreases, the surface area:volume ratio increases
- These properties can be taken advantage of for many different applications, including medicine

Inhalation

Advantages

- Relatively easy, can self administer
- Rapid onset of action
- Large surface area for absorption
- Thin basement membrane for systemic absorption
- Avoids liver first pass metabolism
- Low expression of metabolising enzymes

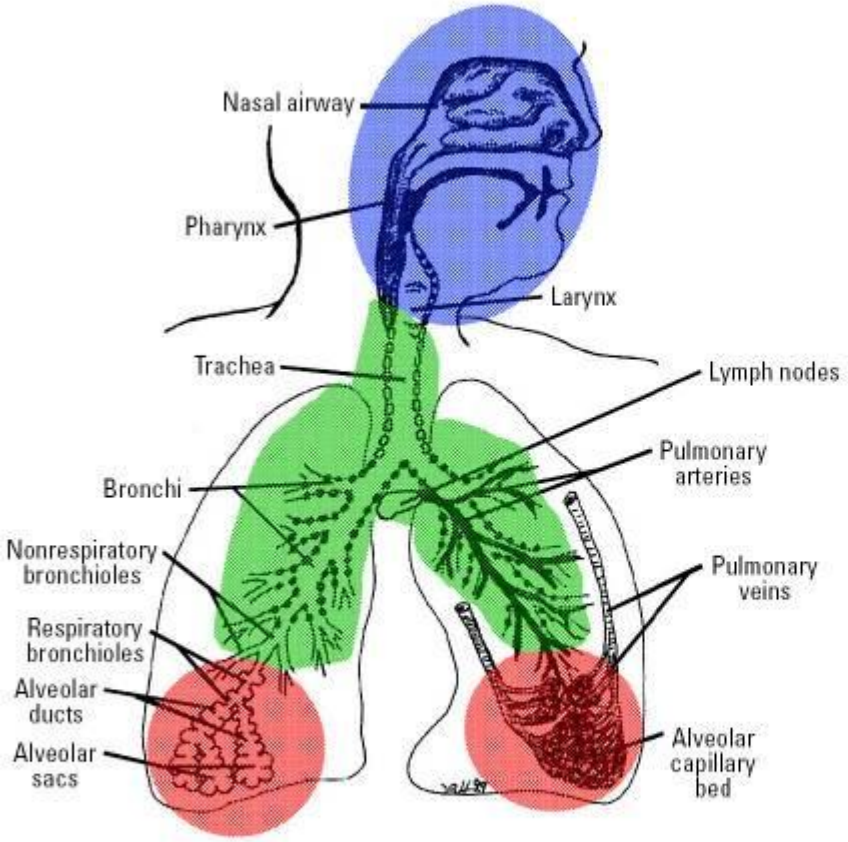
Disdvantages

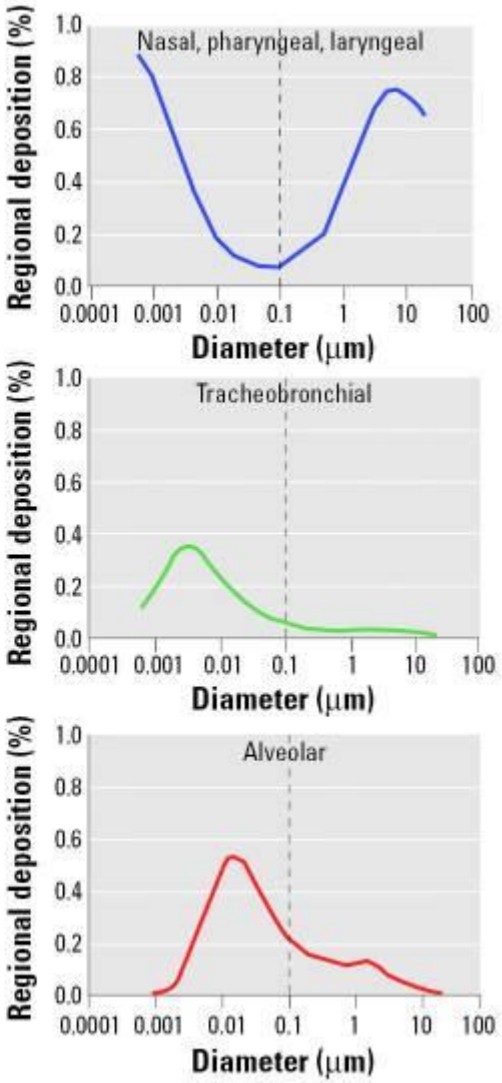
- May require some training
- Can be difficult for children and seriously ill
- Systemic side effects

Inhalation

- Inhaled particles will deposit in different parts of the lung depending on their size.
- The alveolar region is a significant site of deposition for inhaled nanoparticles

Inhalation

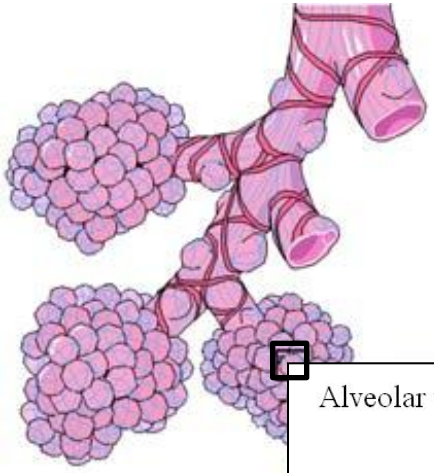

Nasal airway
Pharynx
Larynx
Trachea
Lymph nodes
Pulmonary arteries
Bronchi
Nonrespiratory bronchioles
Pulmonary veins
Respiratory bronchioles
Alveolar ducts
Alveolar sacs
Alveolar capillary bed


Nasal, pharyngeal, laryngeal
Tracheobronchial
Alveolar
Regional deposition (%)
1.0
0.8
0.6
0.4
0.2
0.0
0.0001
0.001
0.01
0.1
1
10
100
Diameter (μm)

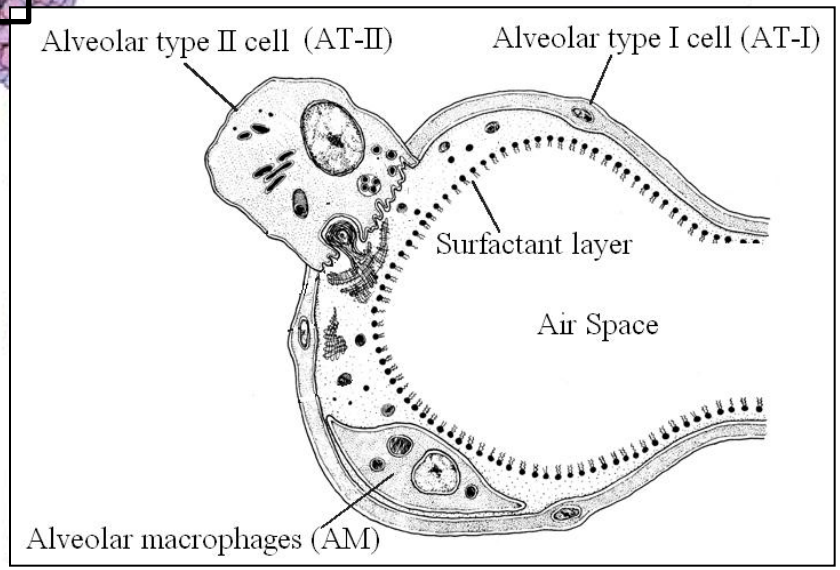
Inhalation

- Inhaled particles will deposit in different parts of the lung depending on their size.
- The alveolar region is a significant site of deposition for inhaled nanoparticles
- Take advantage of this for inhaled nanomedicine
- May be able to design particles to target specific cells/areas of the lung
- The exact mechanisms underlying nanoparticle translocation remain unclear

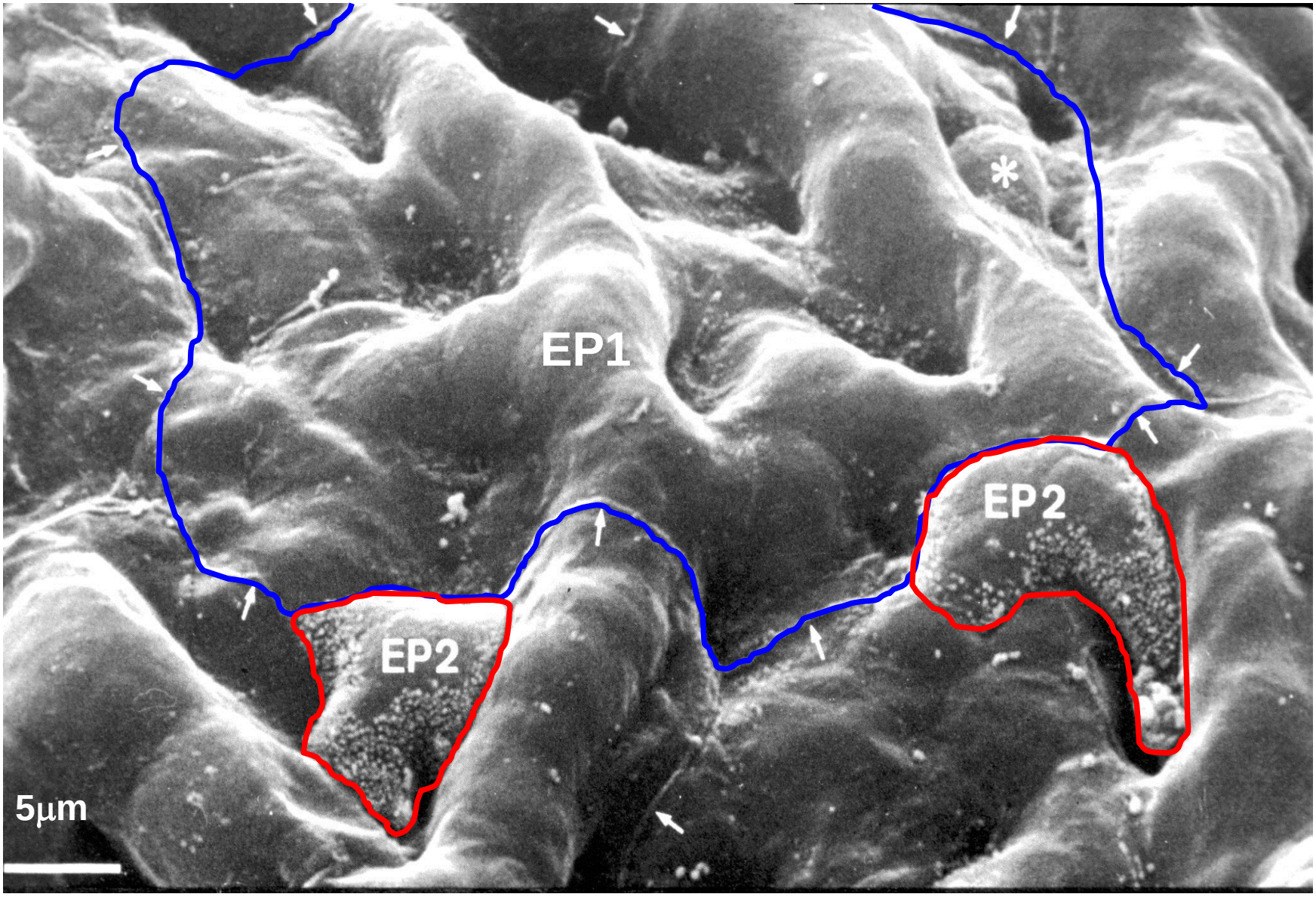
Lung Cell Biology



The air-blood barrier



Lung Cell Biology



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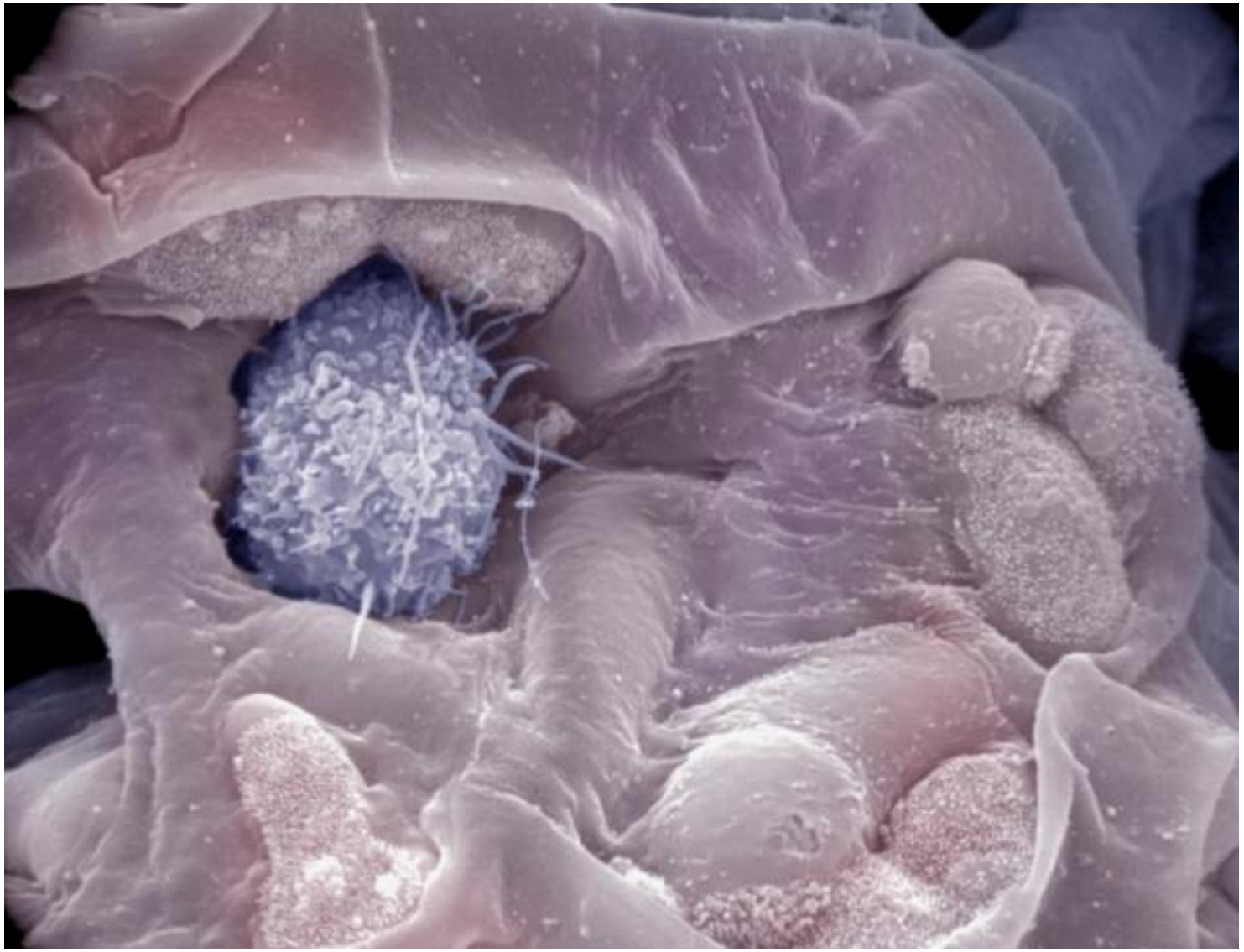
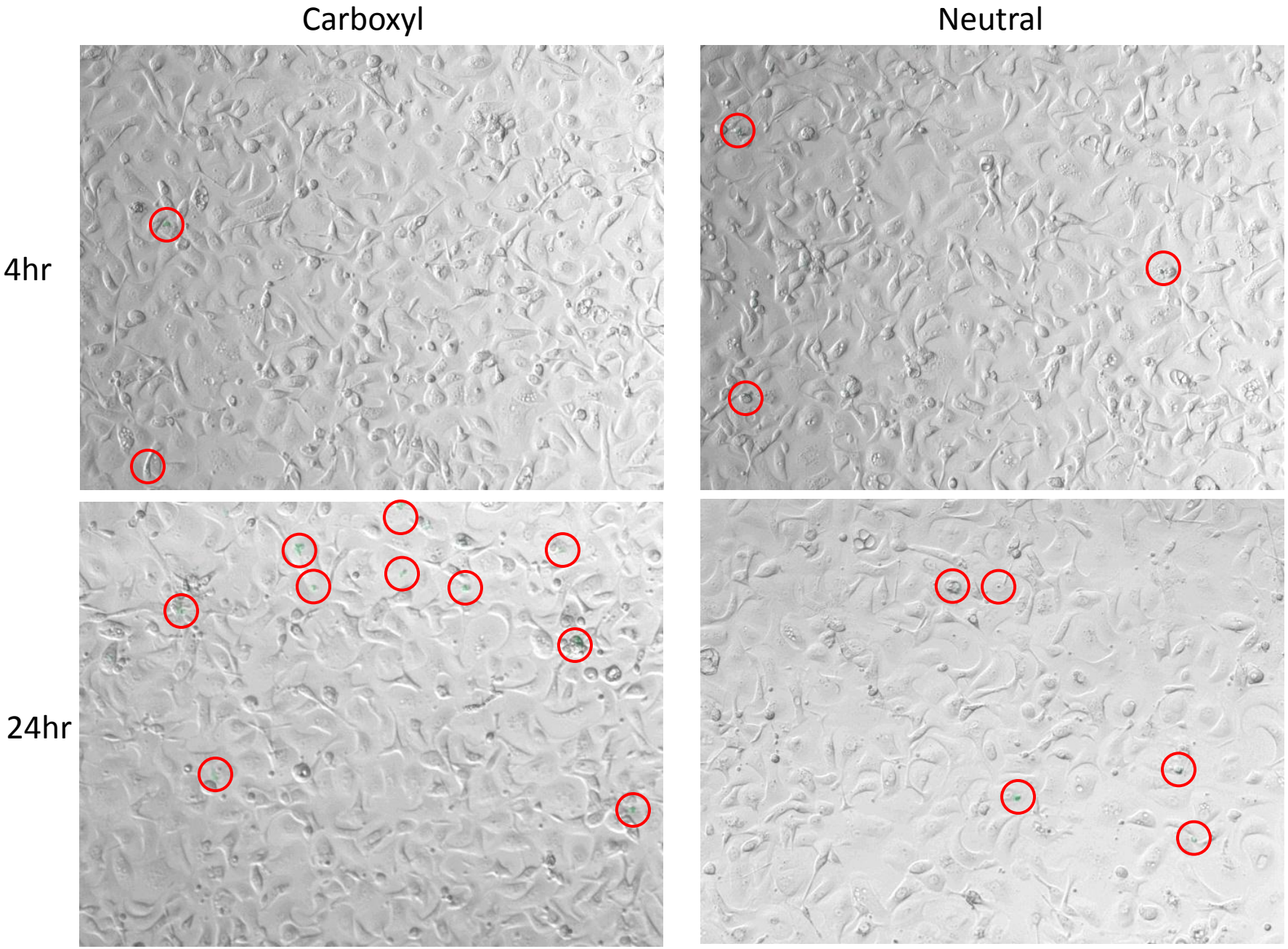


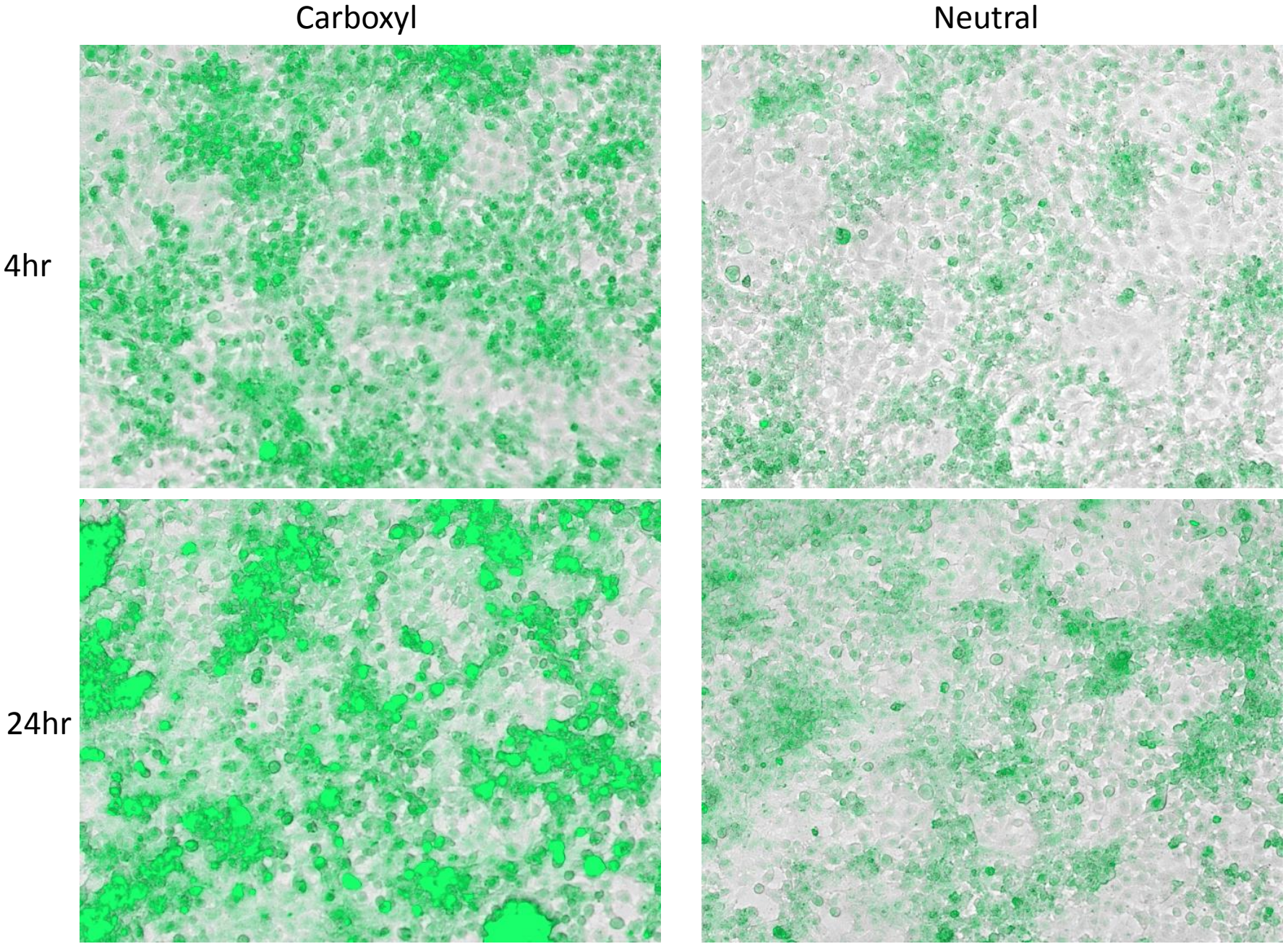
Objectives

- Are nanoparticles internalised by the alveolar epithelium?
- Do the physicochemical properties of nanoparticles influence their uptake (e.g. size and charge)?
- How do nanoparticles enter the cell?
- Does lung lining liquid influence the uptake of nanoparticles?

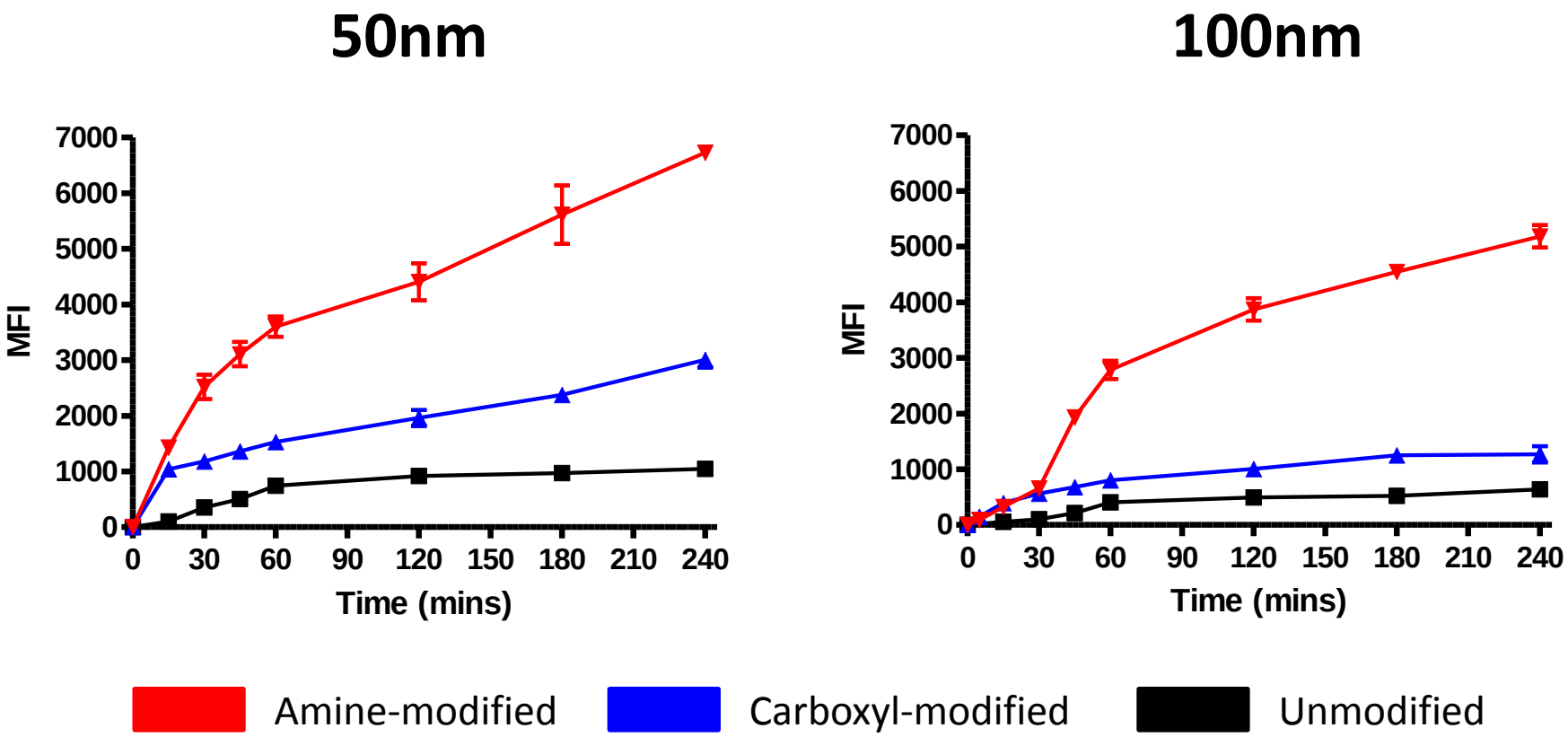
ATII cell uptake



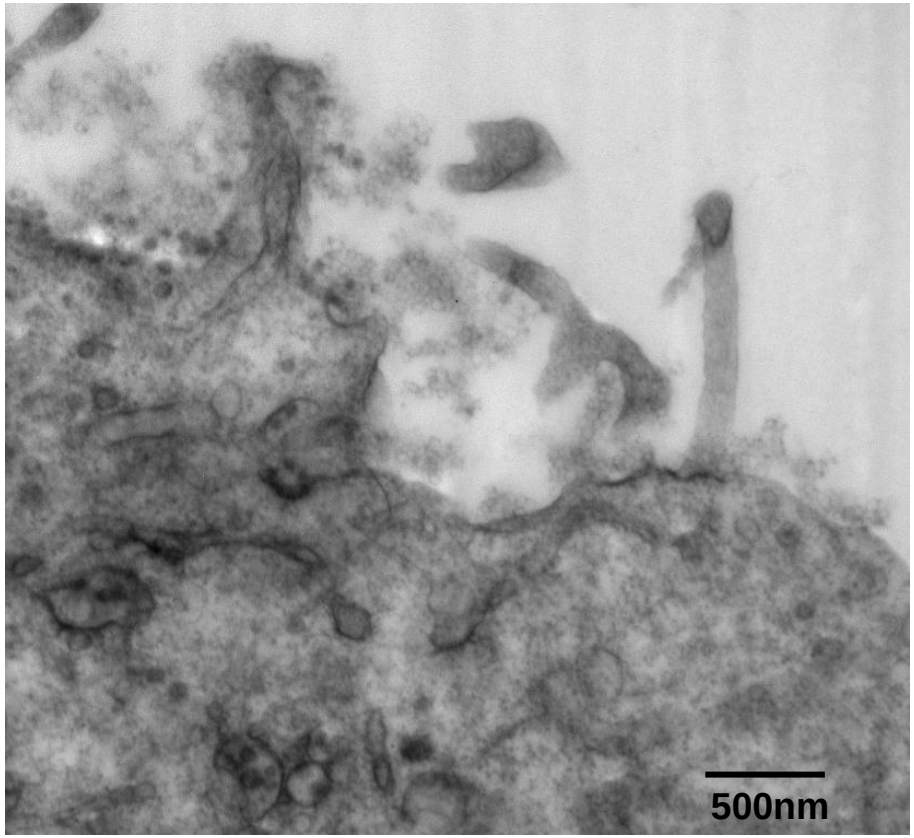
ATI cell uptake

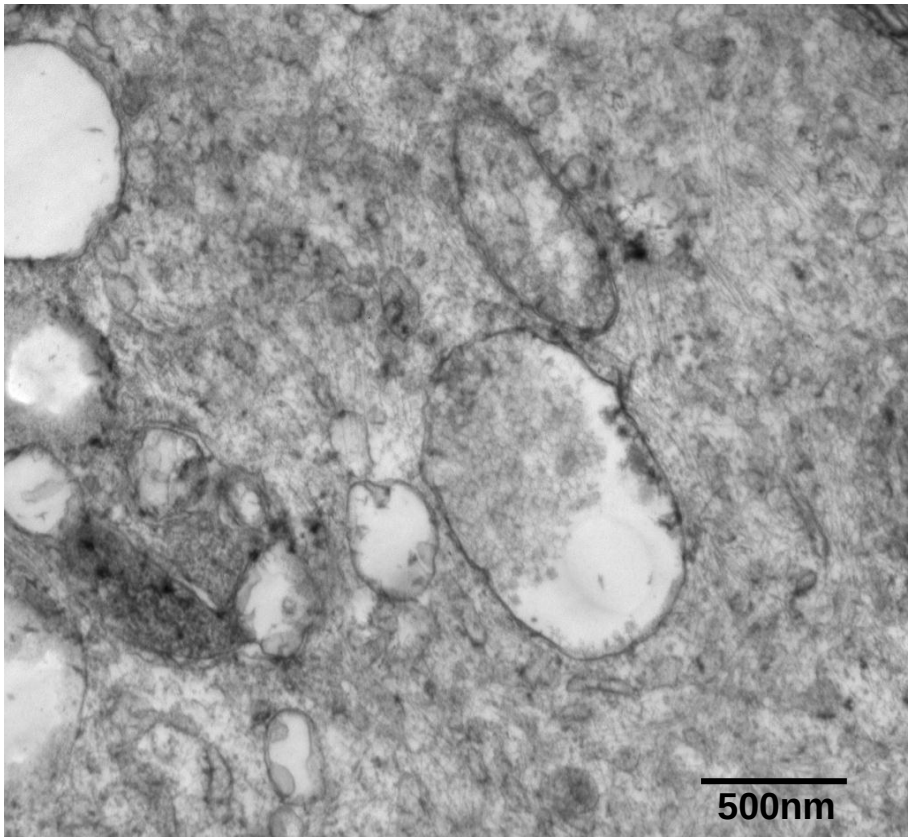


ATI cell uptake



Cellular fate of nanoparticles





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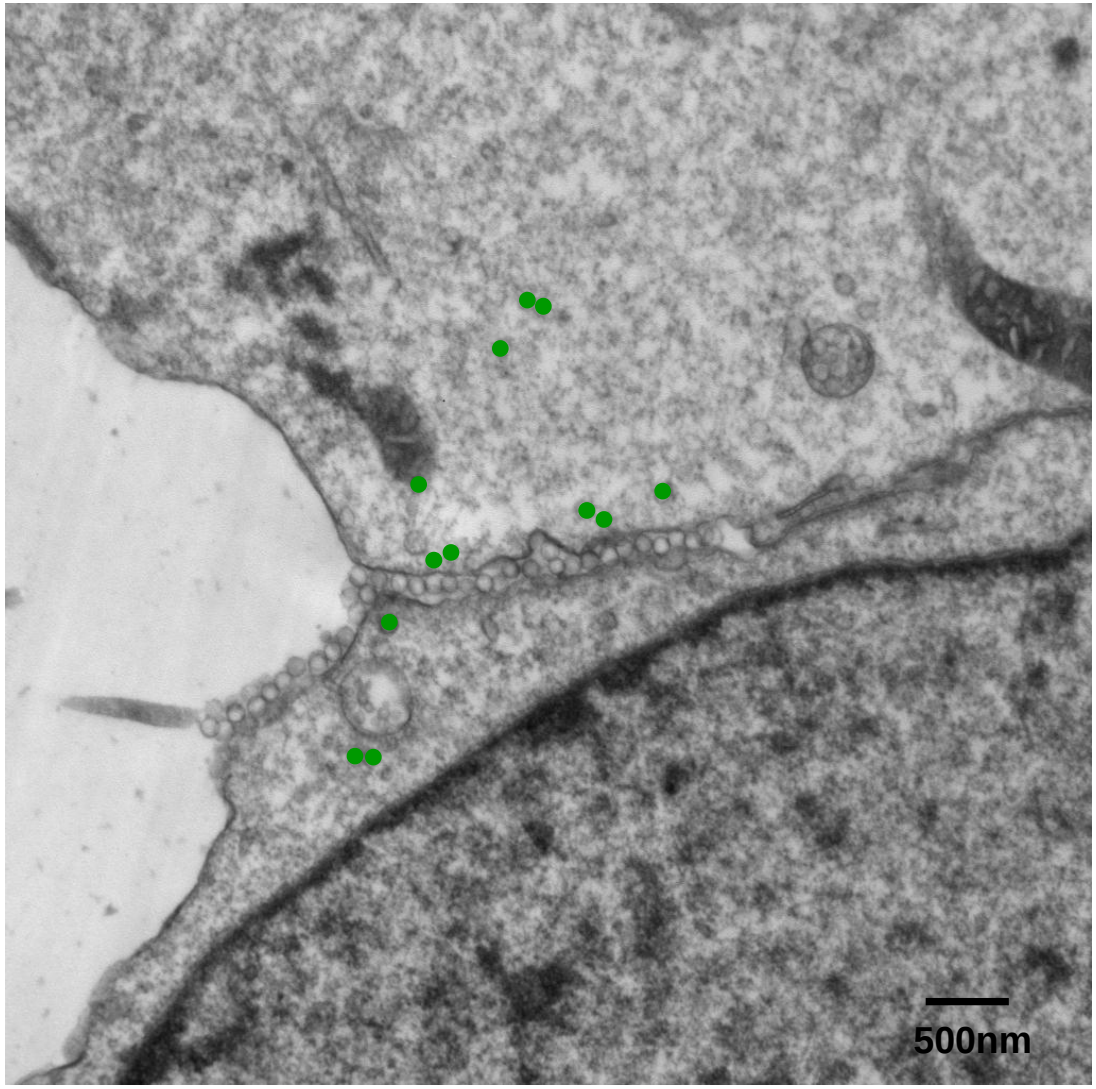
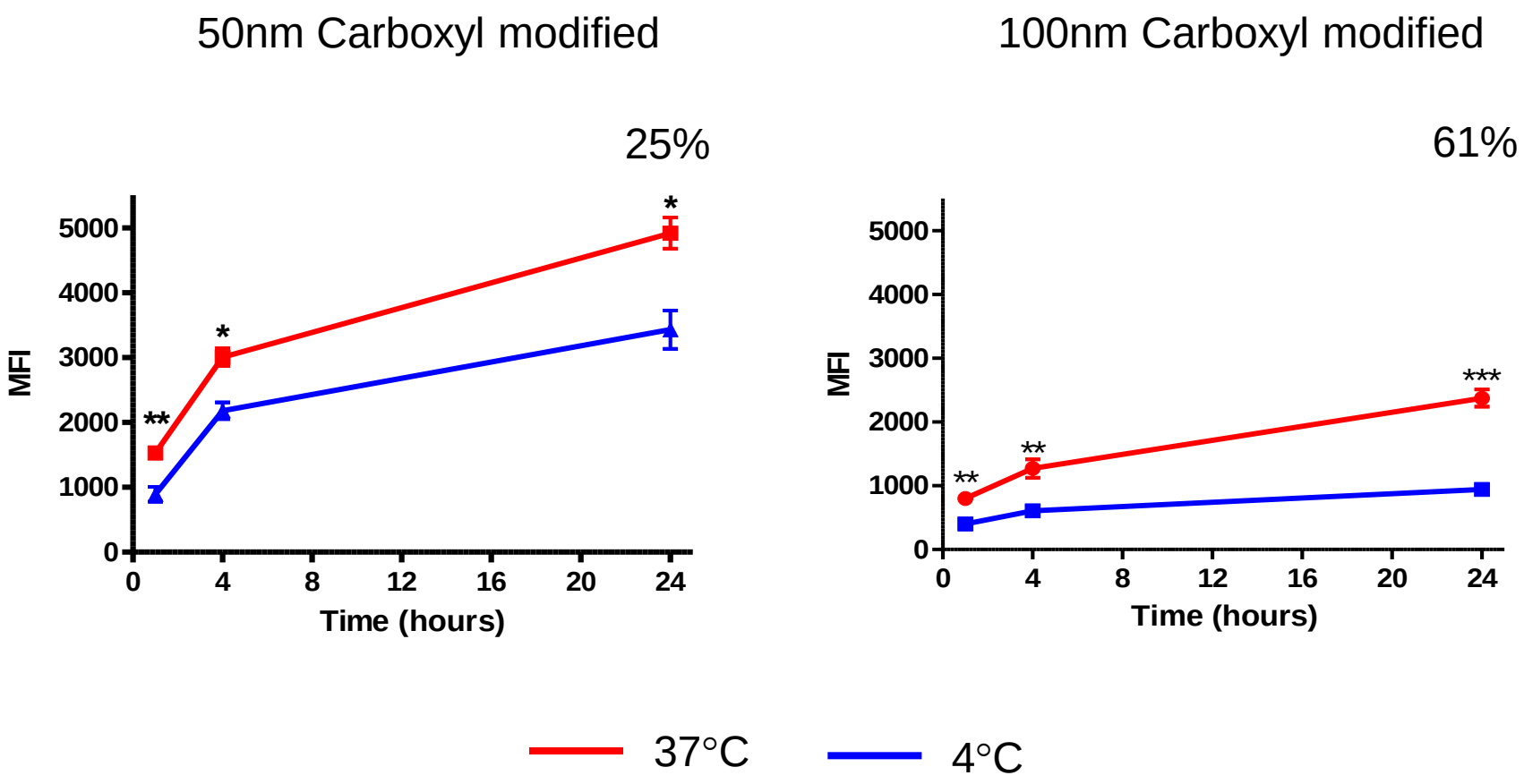


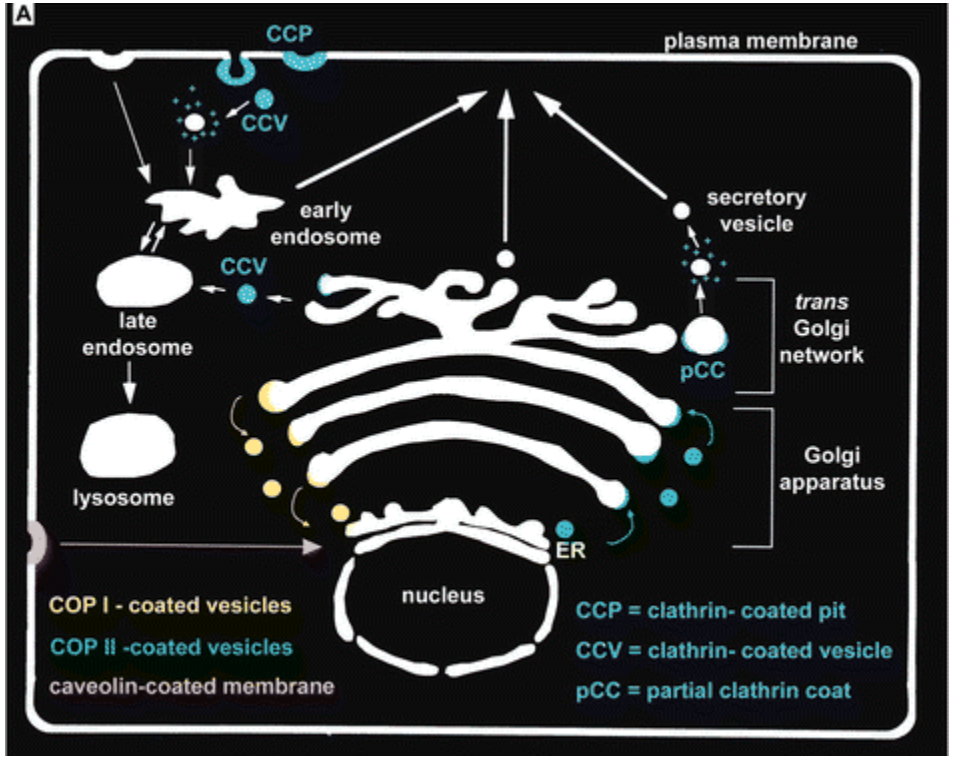
Mechanisms of nanoparticle uptake

- Interact directly with the cell membrane and enter "passively"



Mechanisms of nanoparticle uptake

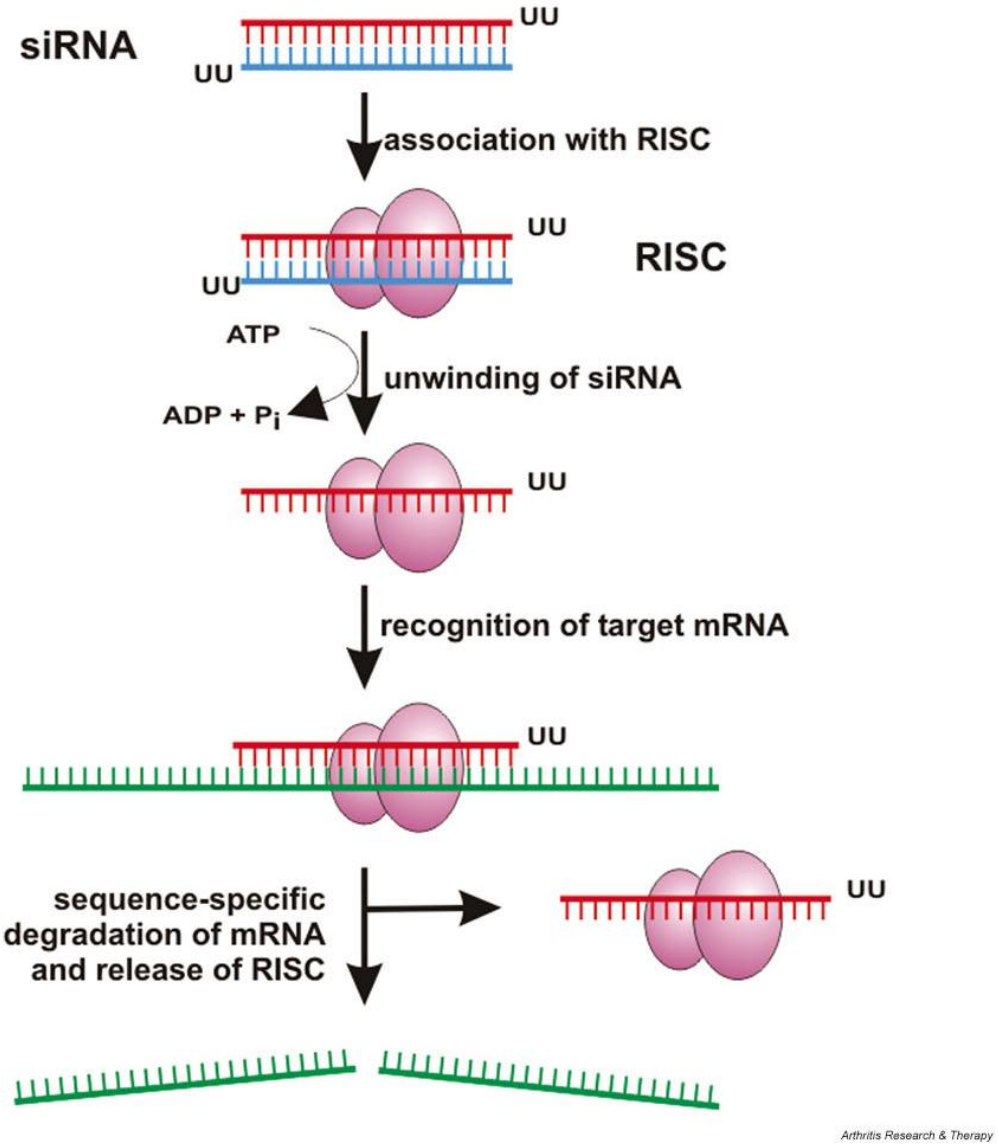
- Enter via active mechanisms e.g. endocytosis
- Endocytosis is predominantly mediated via clathrin-dependent or caveolae-dependent pathways



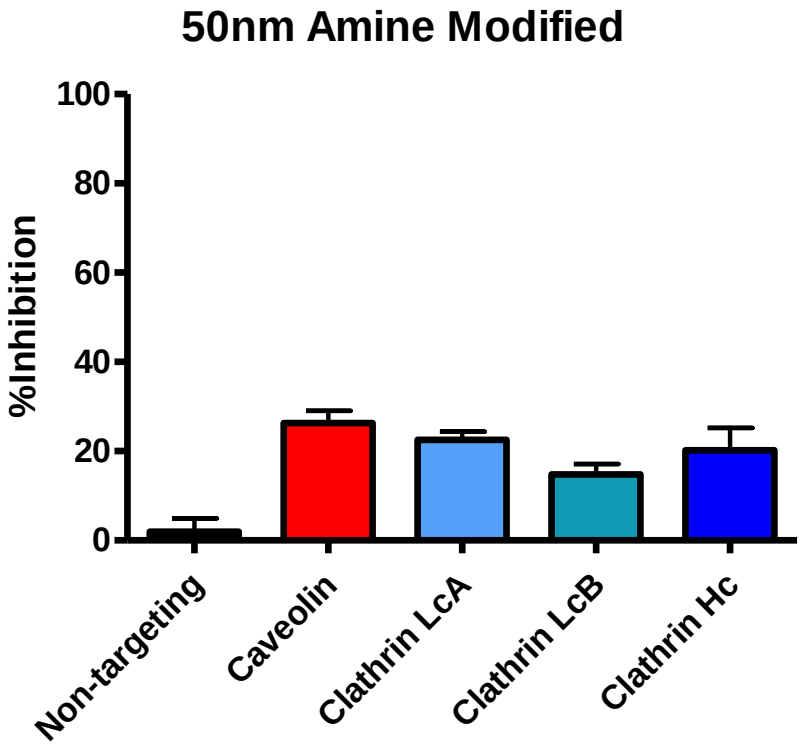
Mechanisms of nanoparticle uptake

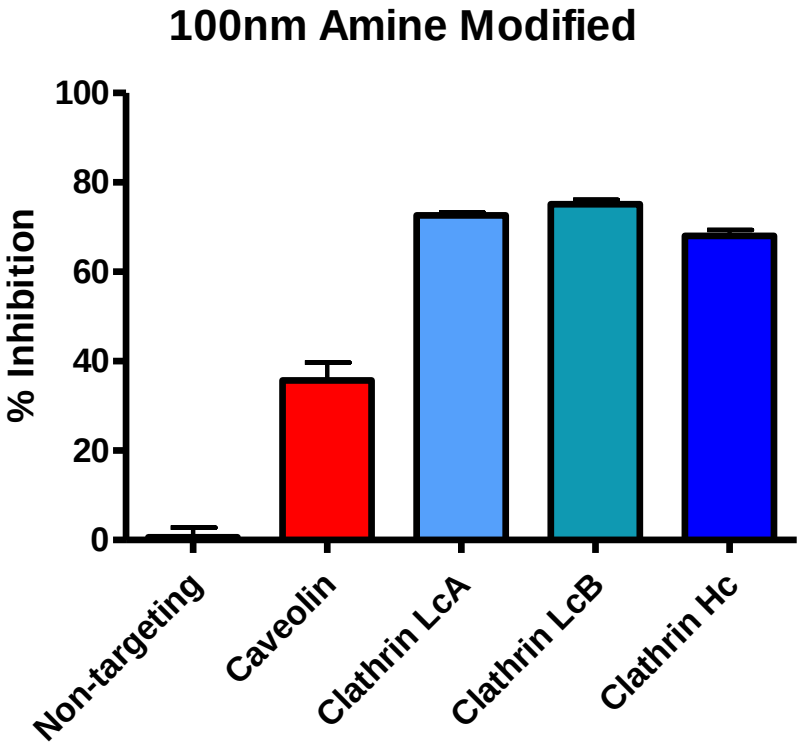
- Enter via active mechanisms e.g. endocytosis
- Endocytosis is predominantly mediated via clathrin-dependent or caveolae-dependent pathways
- These proteins are constitutively expressed by ATI cells
- Use siRNA to knockout specific proteins involved in endocytosis
- Caveolin-1, Clathrin HC, Clathrin LcA and Clathrin LcB

siRNA

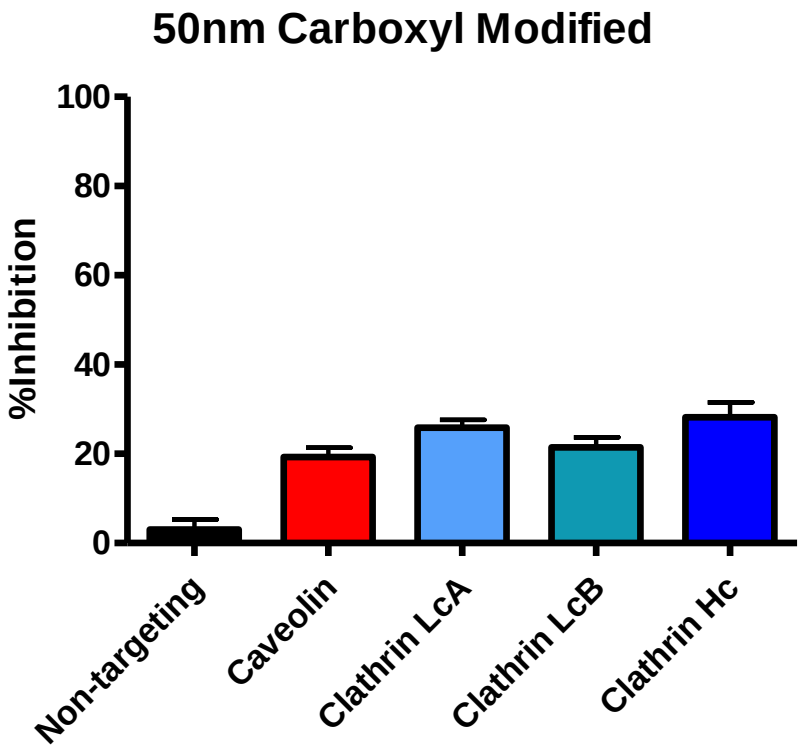

siRNA
UU
UU
association with RISC
UU
UU
RISC
ATP
ADP + Pi
unwinding of siRNA
UU
recognition of target mRNA
UU
sequence-specific
degradation of mRNA
and release of RISC
UU
Arthritis Research & Therapy

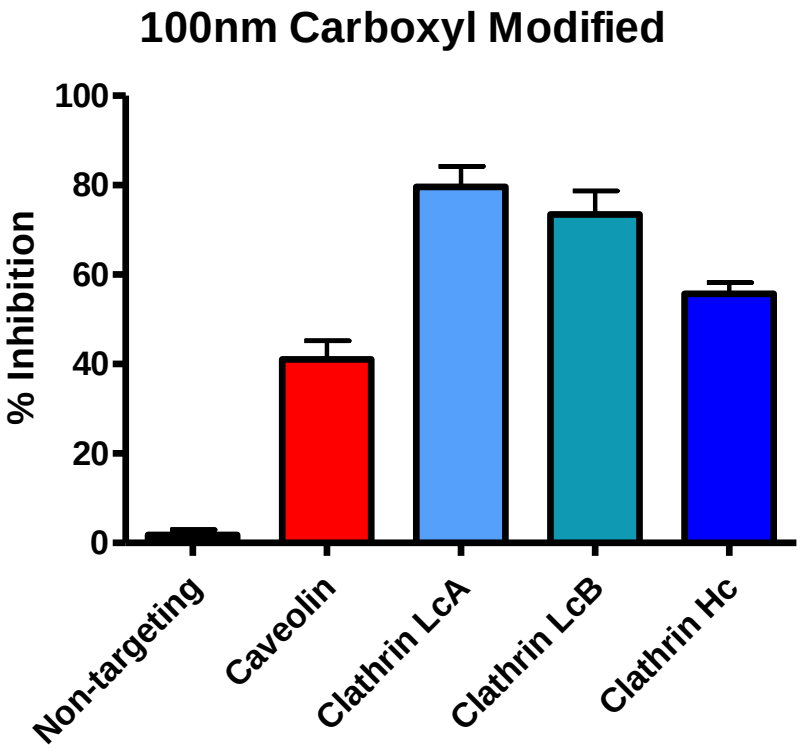
Particle uptake



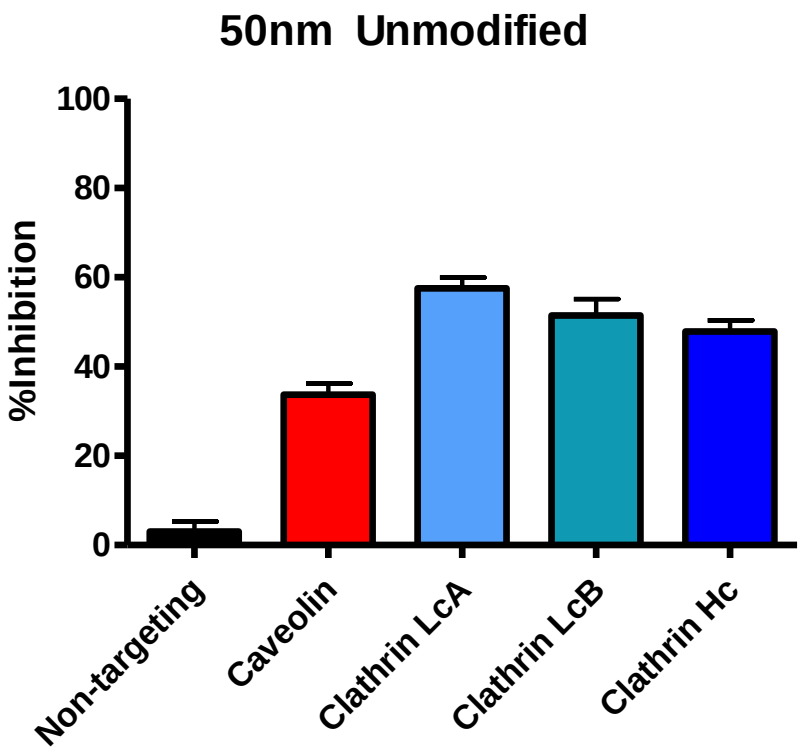


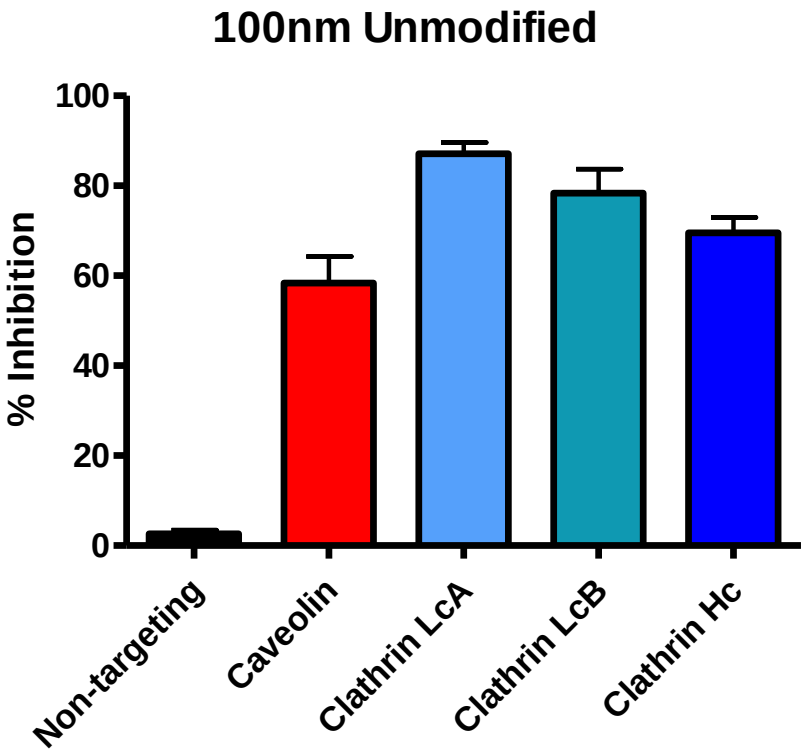
Particle uptake





Particle uptake





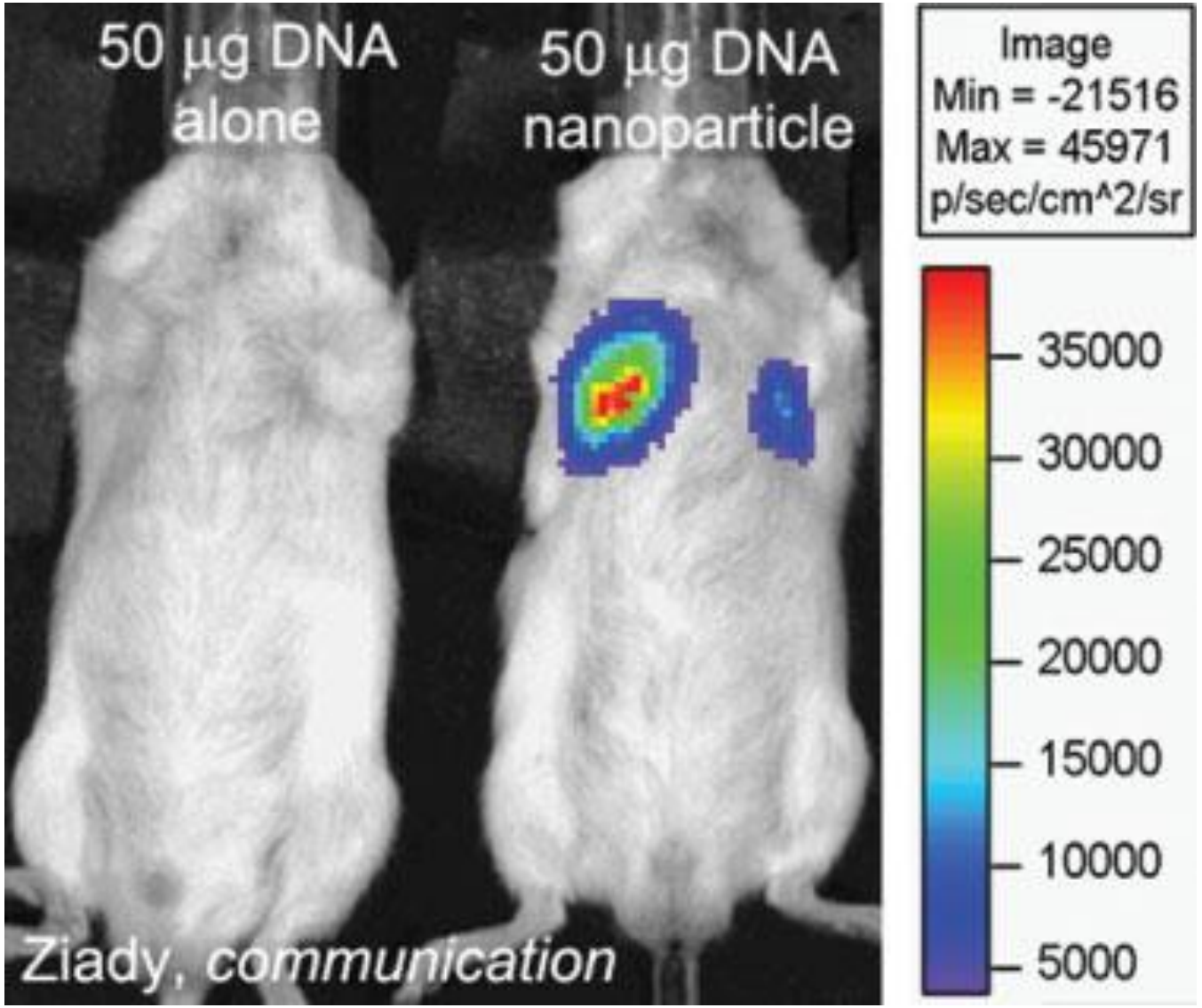
Summary

- Nanoparticles are readily internalised by ATI cells but not ATII cells
- Uptake of nanoparticles is size and surface modification-dependent
- 50 nm amine- and carboxyl- modified beads enter largely by passive diffusion across the membrane
- 50nm unmodified and particles >50nm enter by endocytosis
- Health implications –
    - Size and surface modifications can be optimised for drug delivery
    - May be suitable route of administration for systemic therapies

Inhaled nanomedicines

- Inhaled nanotherapy is particularly promising as an alternative to drugs requiring injection (e.g. insulin, heparin and human growth hormone)
- In vivo rat studies have shown that inhaled insulin can enter the systemic circulation and exert a biological effect.
- Nanoparticles also show promise for gene therapy
- May be important for developing therapies for cystic fibrosis

Inhaled nanomedicines



Inhaled nanomedicines

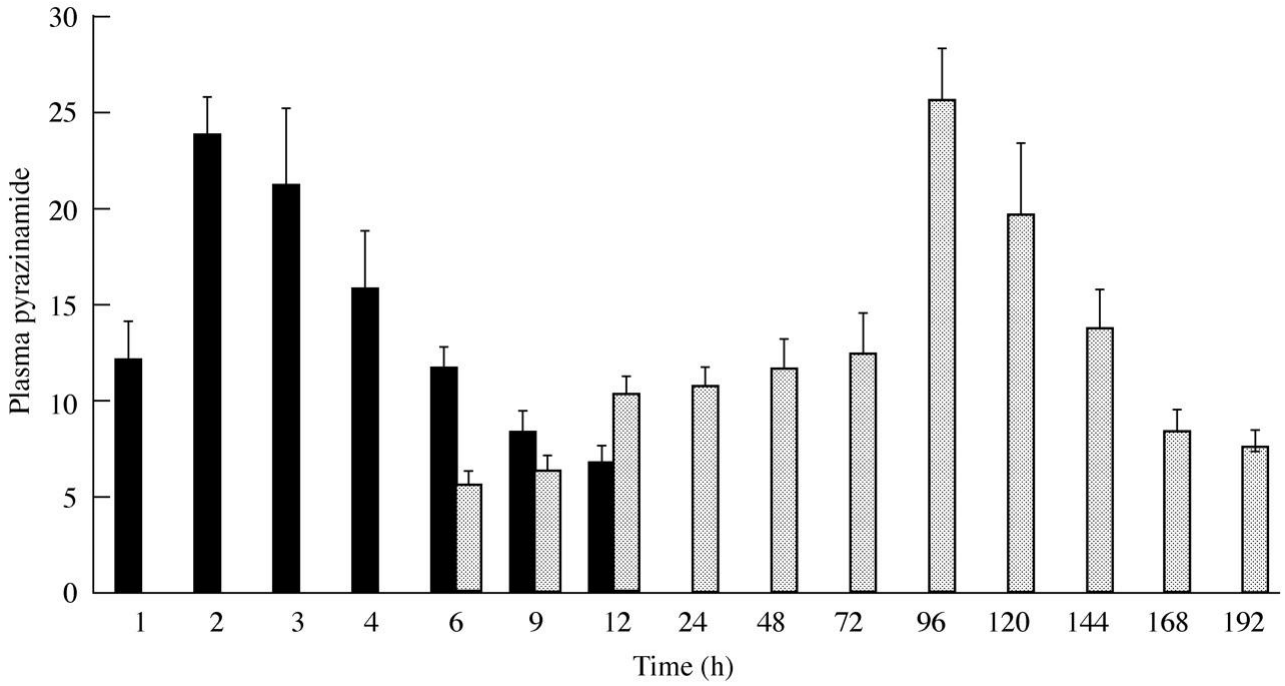
- Nanomedicine may improve the treatment of tuberculosis
- Normal therapy involves daily tablets of 3-4 separate drugs for up to six months
- Problems?
  - Poor patient compliance
  - Tablets are large and hard to swallow
  - Have to be given individually
  - Have to be taken on an empty stomach

Inhaled anti-tuberculosis nanomedicines

- Inhaled therapy better than oral therapy as it delivers straight to the site of disease
- Inhaled particles will be detected and phagocytosed by macrophages (host)
- Drugs can be formulated to be delivered together in a single dose

Inhaled anti-tuberculosis nanomedicines

- In an in vivo model of tuberculosis, guinea pigs were infected and subsequently treated with either traditional style therapy or combination therapy nanoparticles



Inhaled anti-tuberculosis nanomedicines

- Plasma concentration levels of all three drugs (rifampacin, isoniazid and pyrazinamide) were sustained for significantly longer in the inhaled nanoparticle treated animals compared to traditional oral dosed animals
- A single inhalation every ten days had the same effect as daily oral dosing
- Inhalation may prove to be a better therapy as the avoidance of large tablets along with less frequent dosing may improve patient compliance

Nanomedicine in the treatment of cancer

Intravenous

Advantages

- Rapid response
- Higher doses possible
- No barriers to systemic distribution

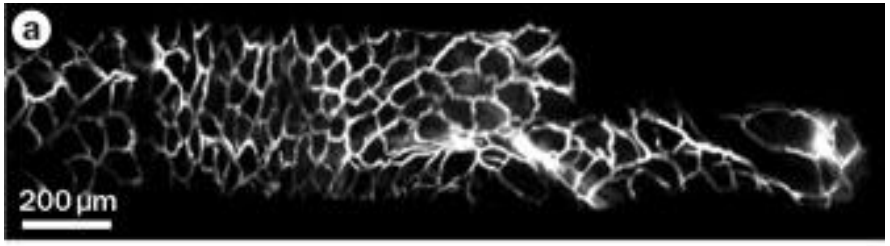
Disdvantages

- Must have suitable veins
- Needle phobia
- Requires trained personnel
- Expensive
- Must be sterile
- Systemic effects, can be non-organ specific

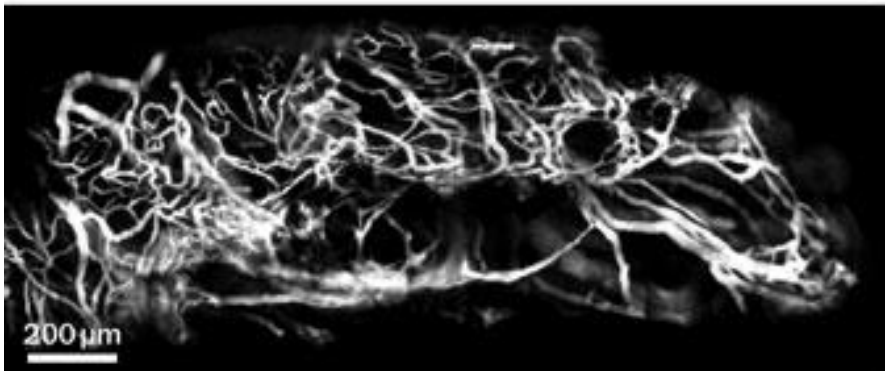
Nanotherapies for cancer

- Nanomedicine is particularly promising in cancer due to the phenomenon known as Enhanced Permeability and Retention (EPR)
- Due to the rapid growth of solid tumours, vascularisation is not well regulated and vessels grow in a disordered, poorly structured fashion

Normal Colon Vasculature

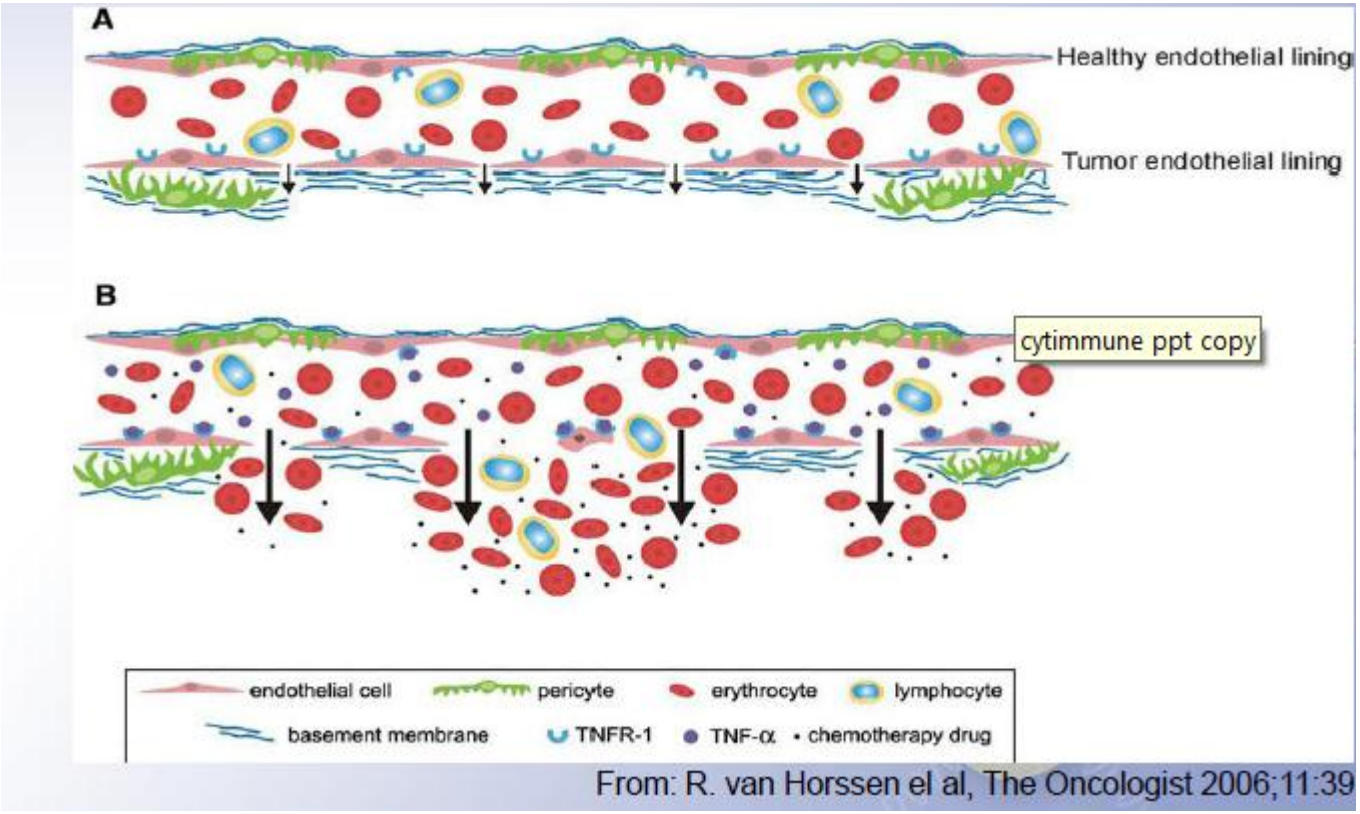


Colon Tumour Vasculature



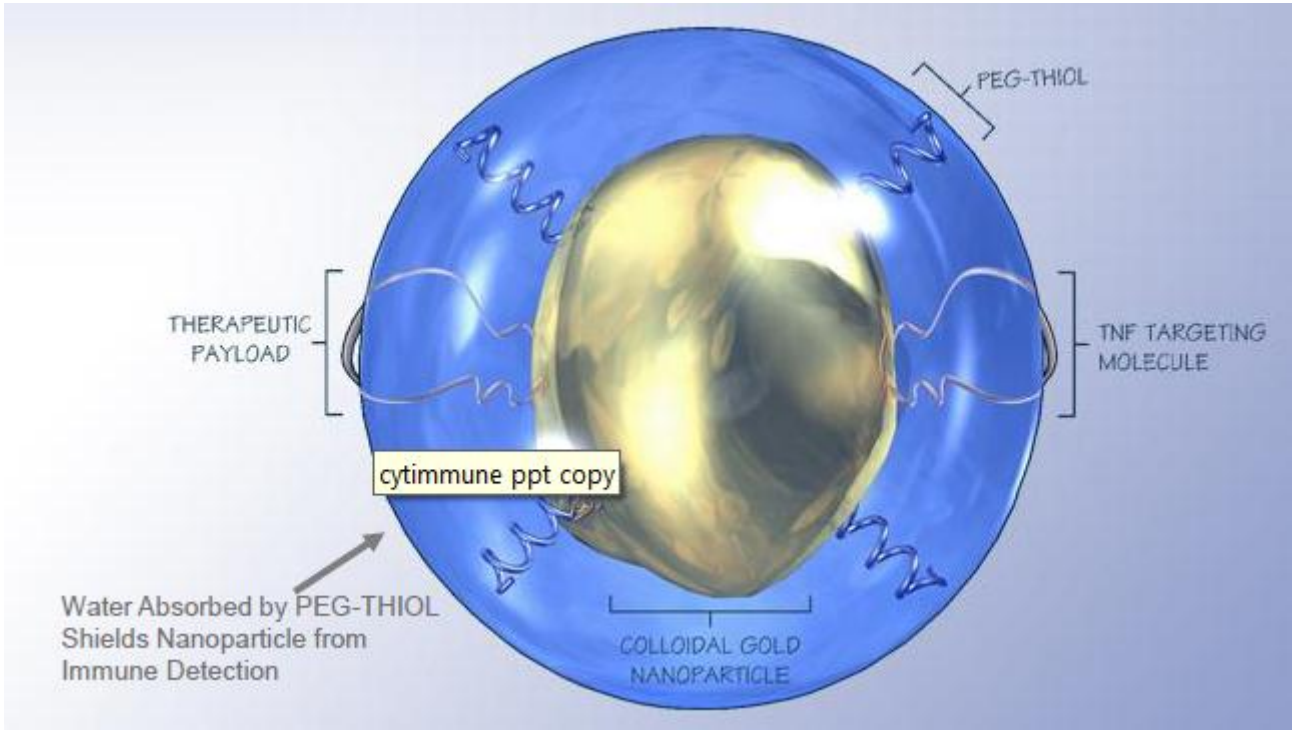
Nanotherapies for cancer

- These vessels are leaky, resulting in increased permeability to nanosized molecules



Nanotherapies for cancer

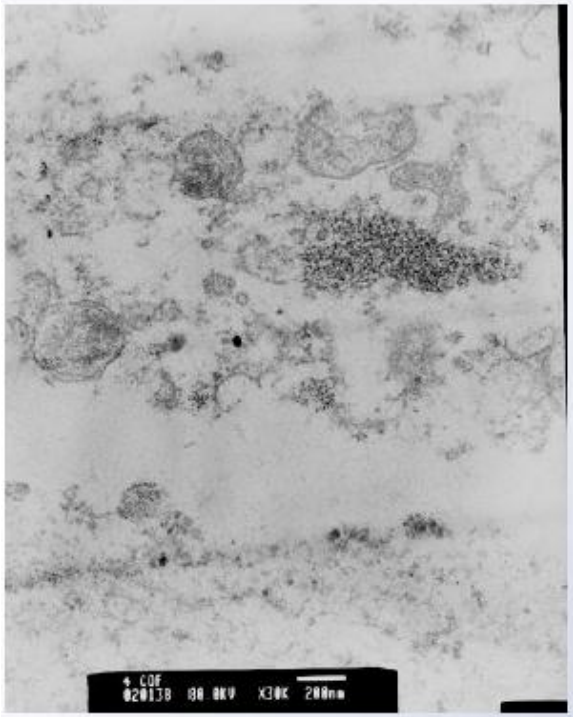
- Aurimune – TNFα coated gold nanoparticles
  - Selective targeting to tumour
  - Reduction in non-organ specific effects
  - Patients tolerate 20x higher doses



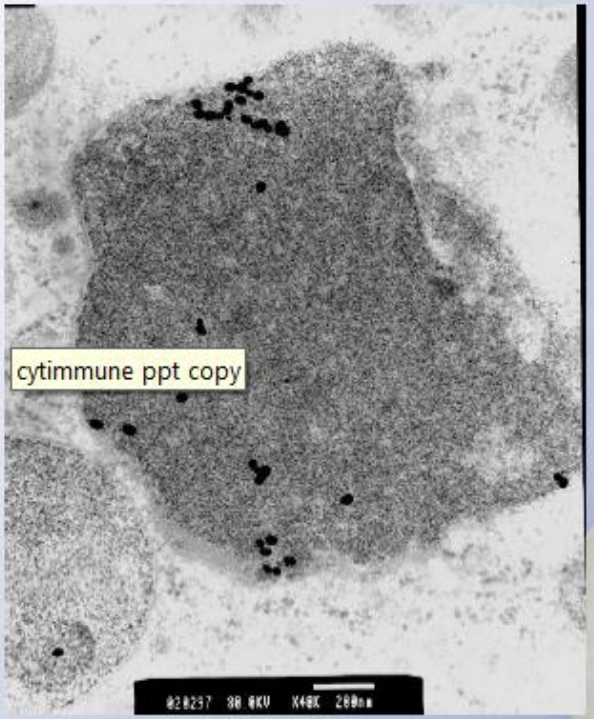
Aurimune

Murine Tumour Model

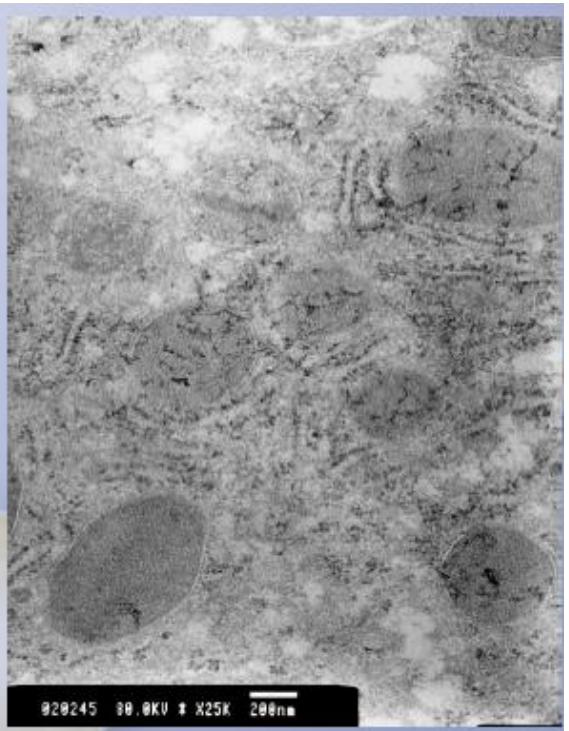
Spleen



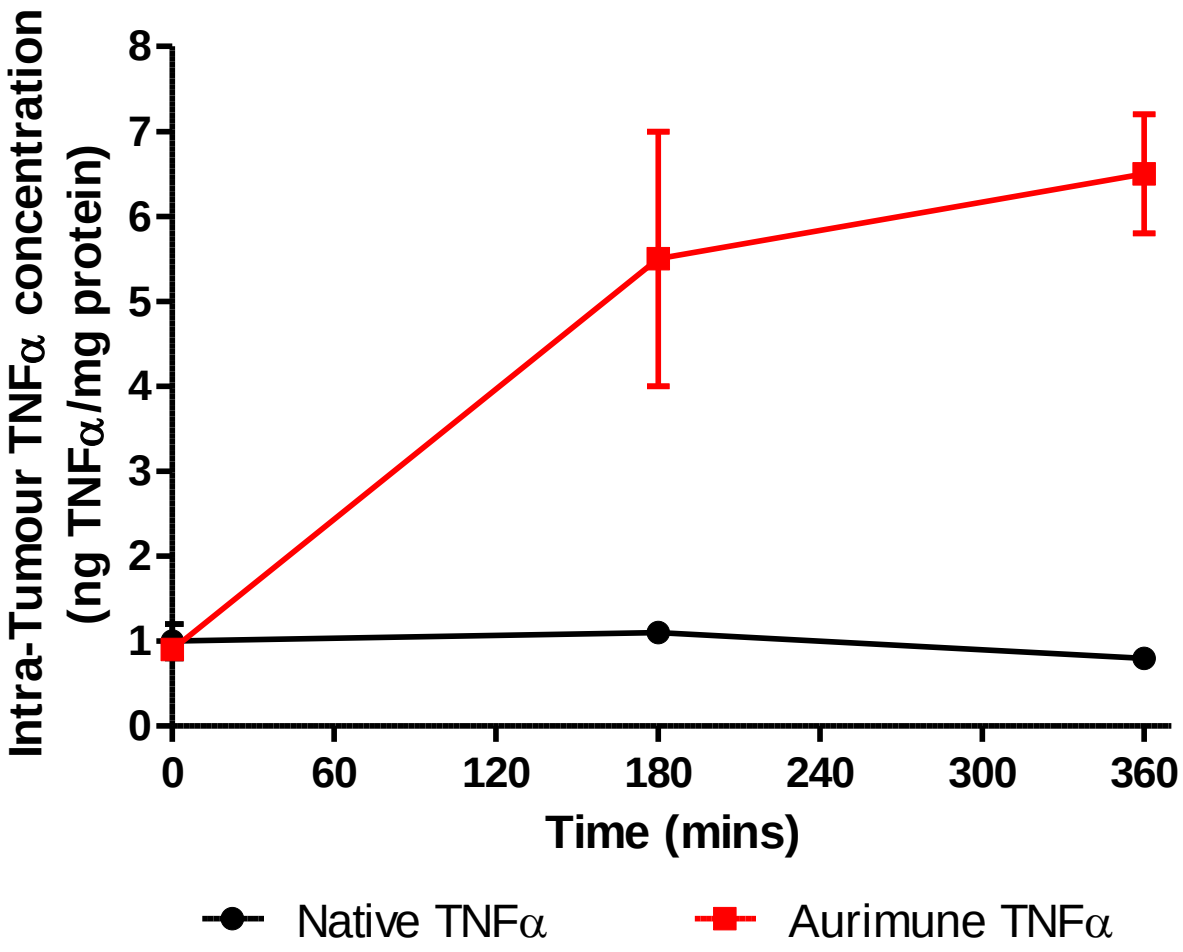
Tumour



Liver



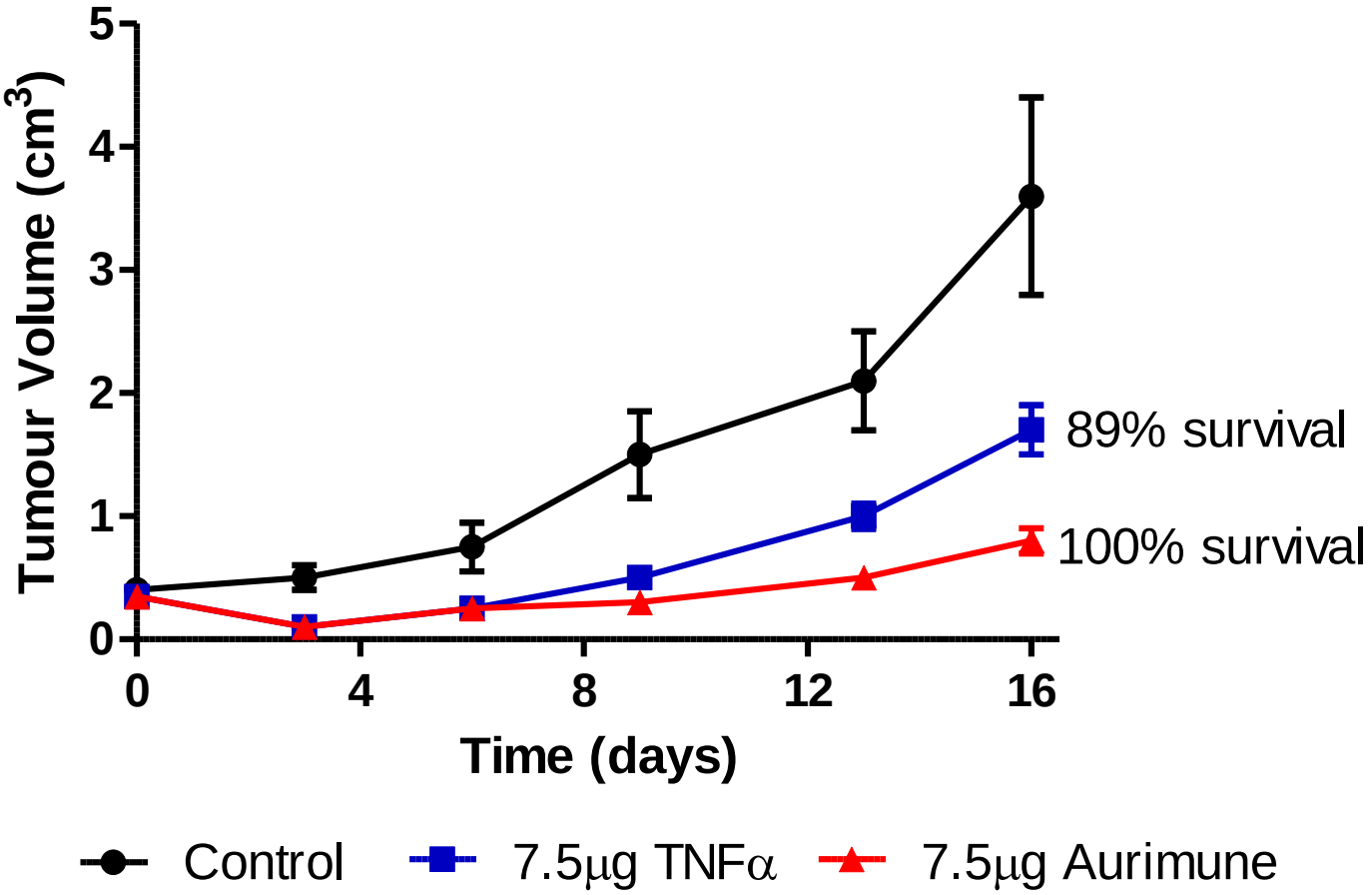
Aurimune



Tumour concentration of TNFα following IV injection of either TNFα or aurimune

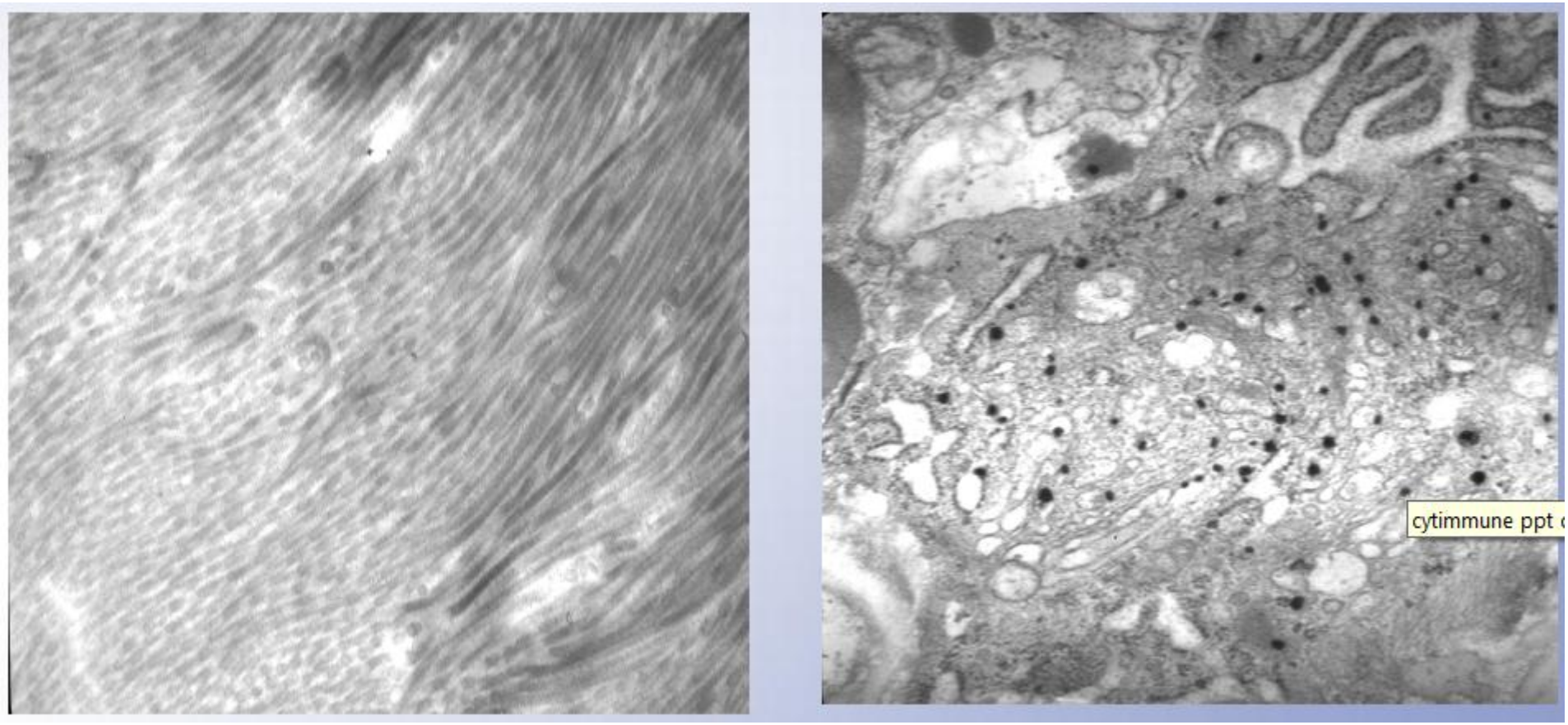
Aurimune

Effect of Aurimune and TNFα on tumour growth in mice



Aurimune – Phase 1 clinical trial

Biopsies from patient with inoperable breast cancer

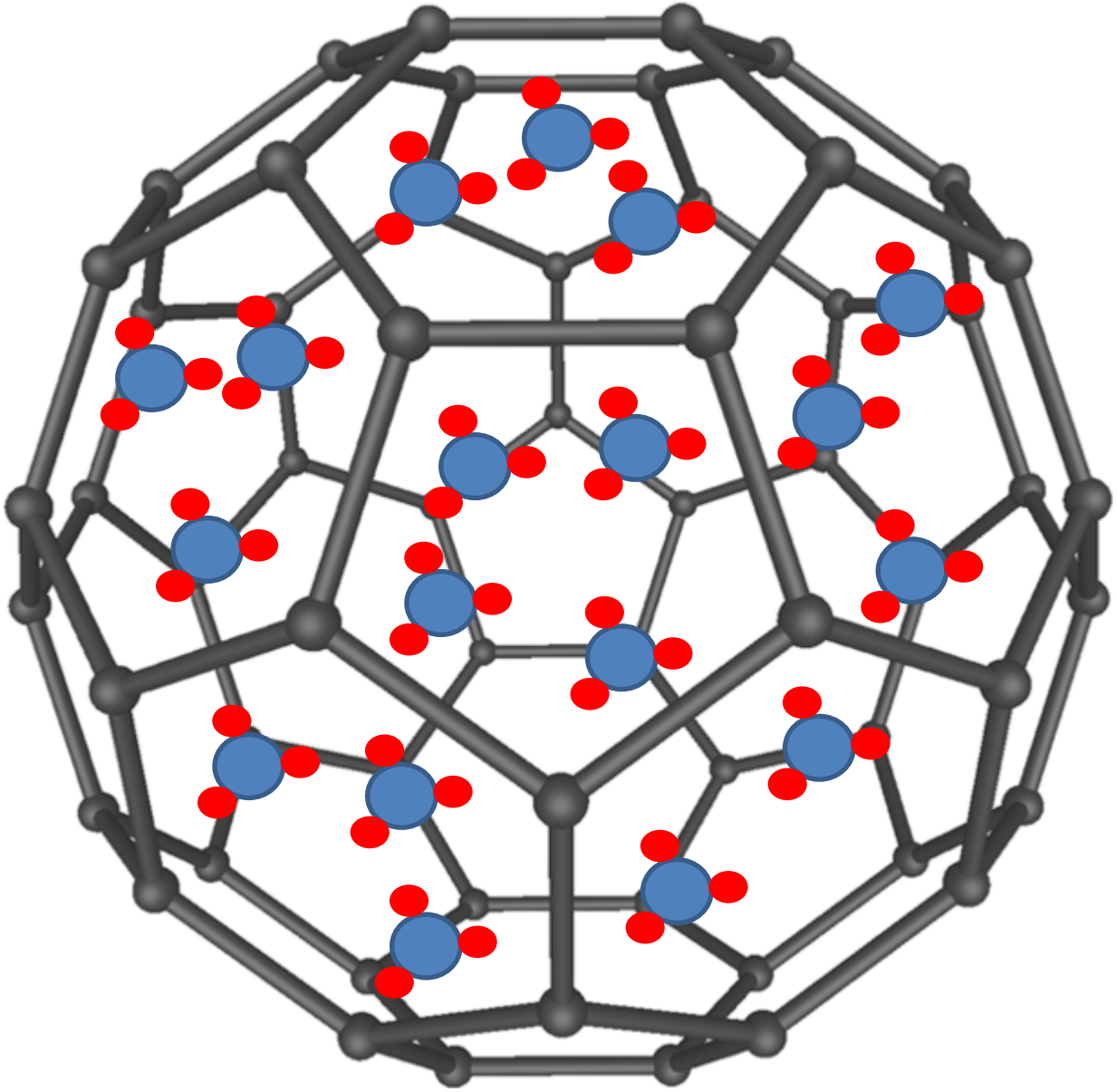


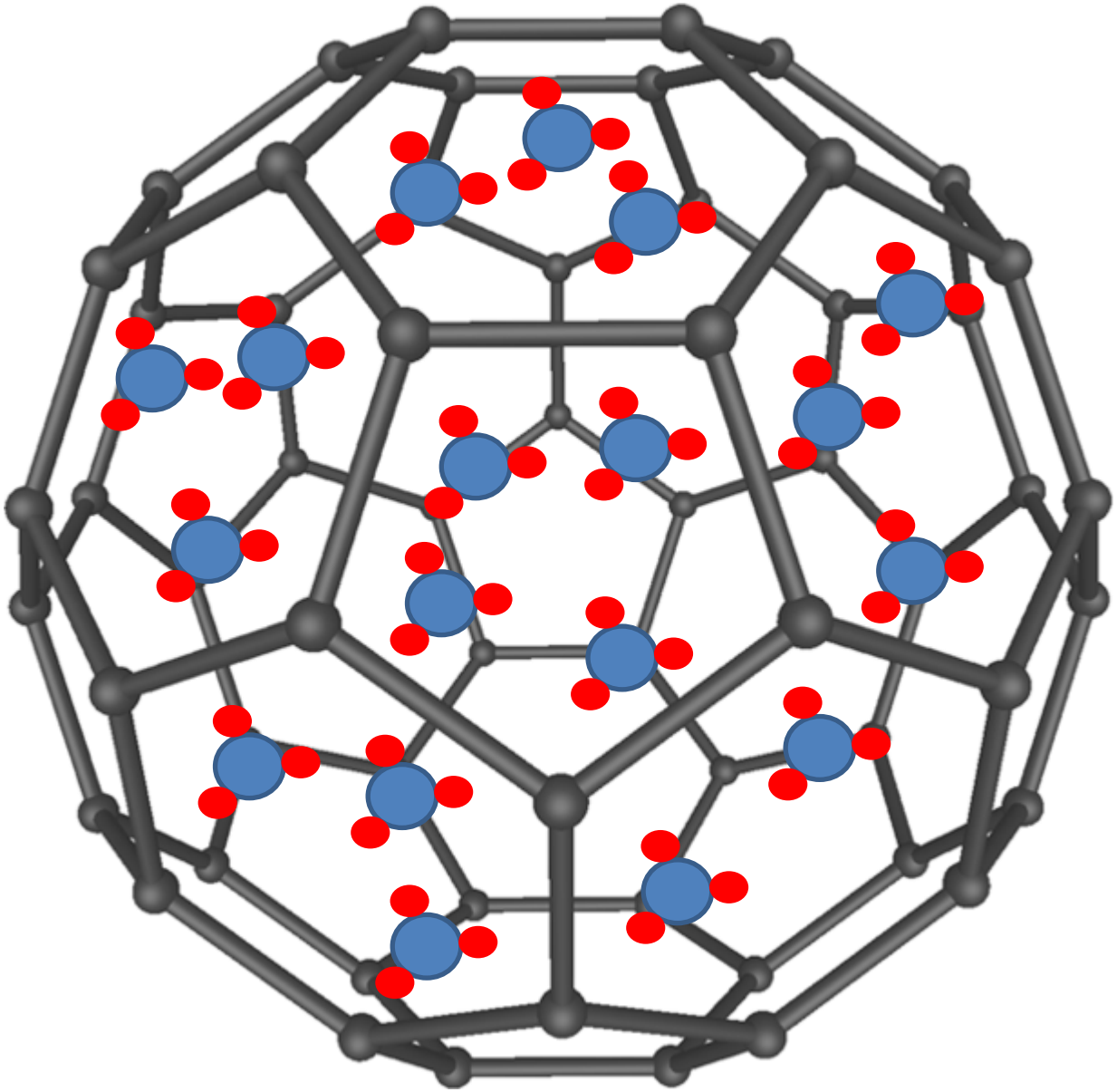
Healthy Tissue

Tumour

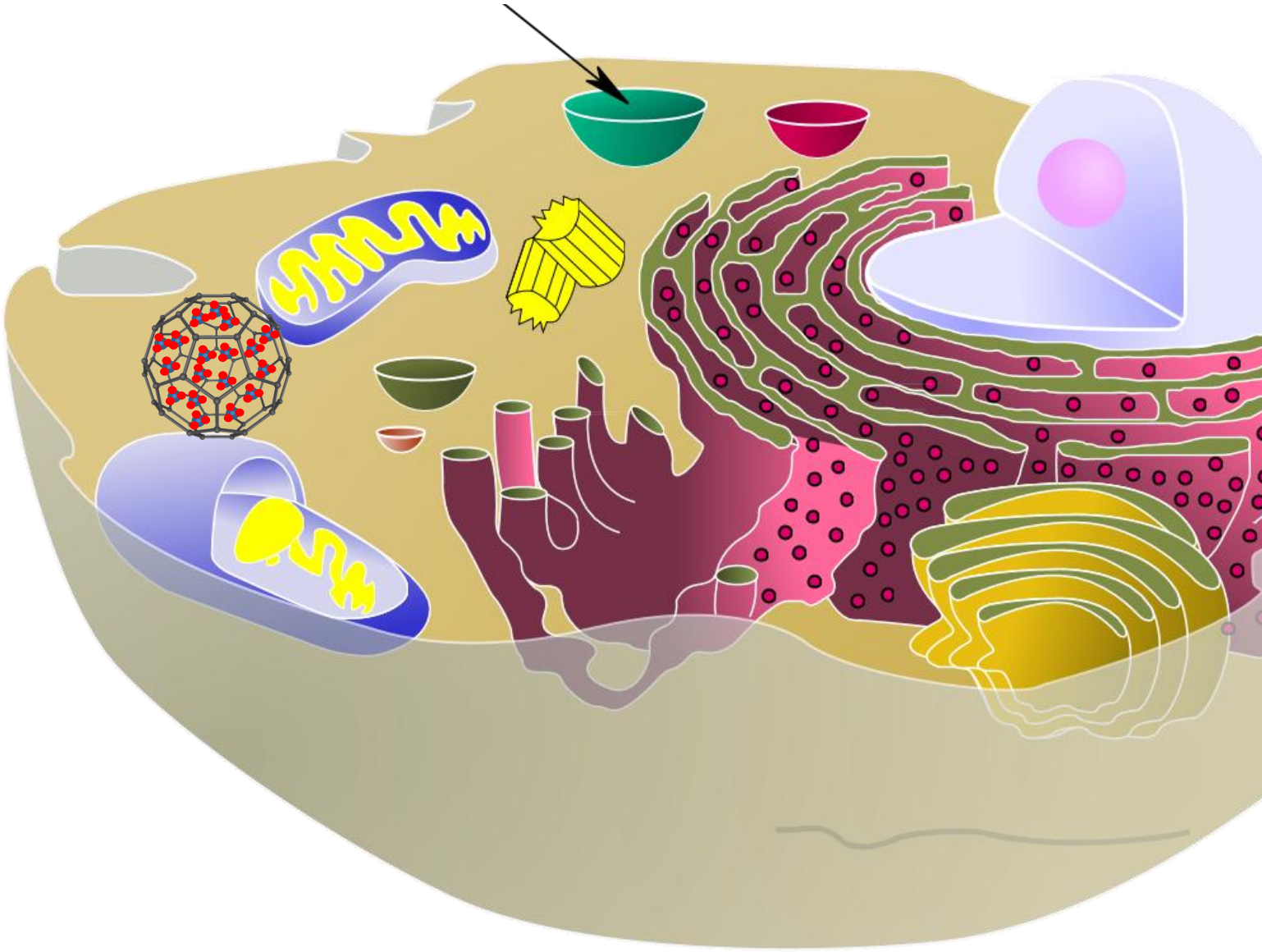
Nanotherapies for cancer

- Genexol – nano-micelles containing Paclitaxel
  - Higher doses tolerated
  - Increased efficacy
  - Fewer side effects compared to direct injection of paclitaxel





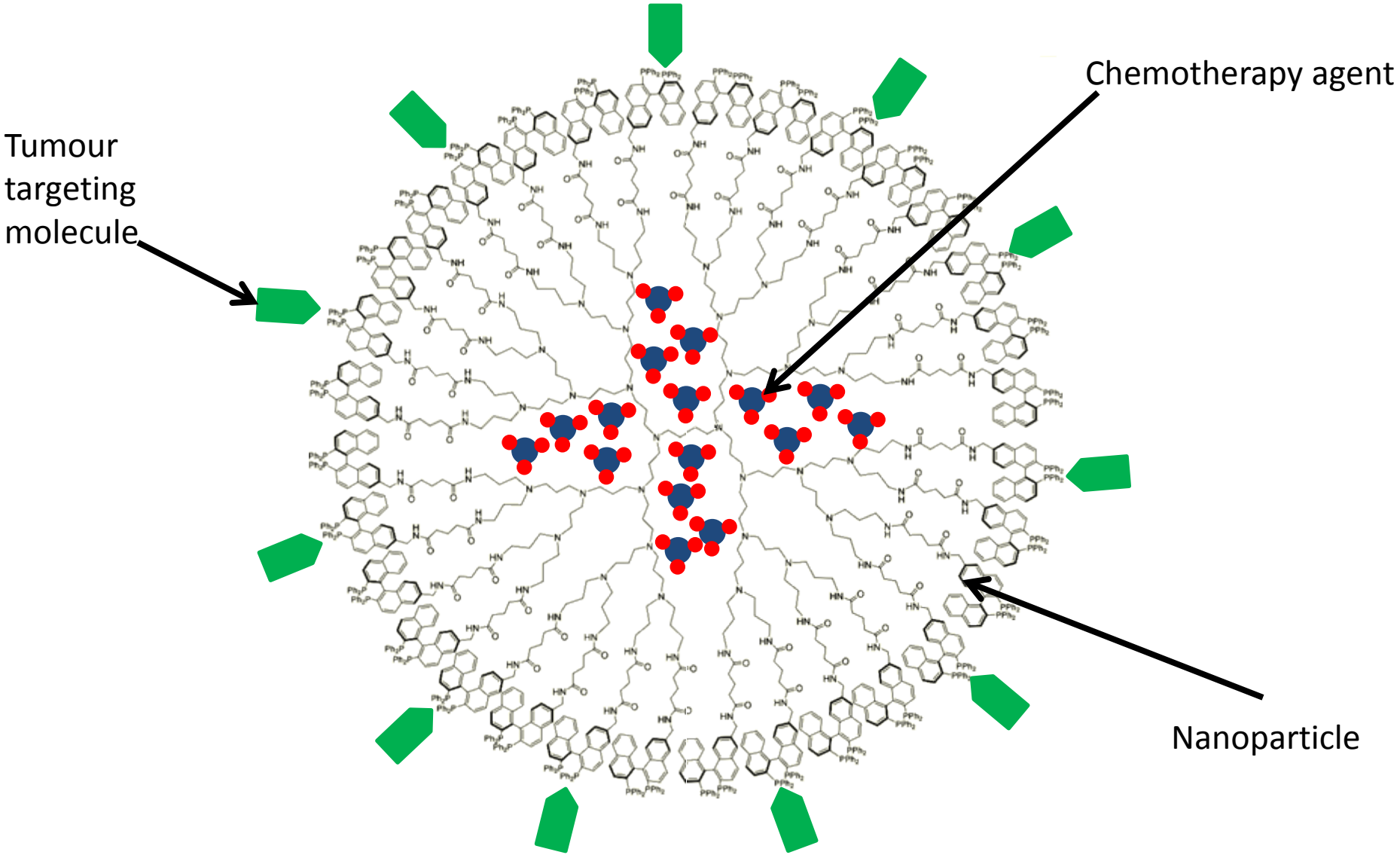
Endosome



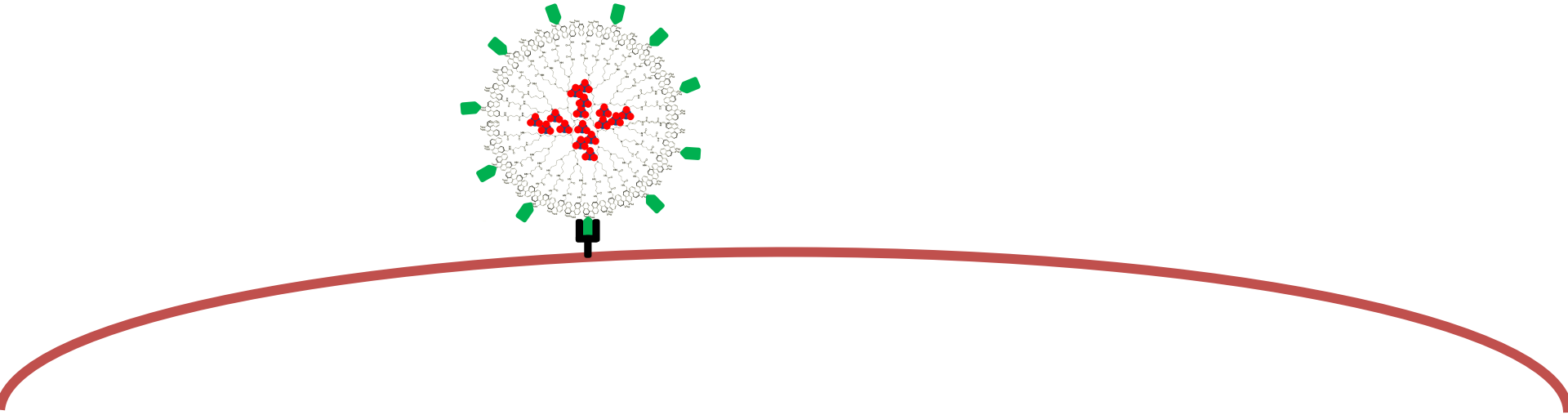
Improving delivery

- Other features of diseases and nanoparticles can be used to enhance drug efficacy
- A number of cancers are known to have abnormally high expression of specific receptors
  - HER2 receptor in breast cancer
  - Folate receptor in ovarian cancer
- Nanoparticles can be designed to break down and release their contents when heat or ultrasound is applied

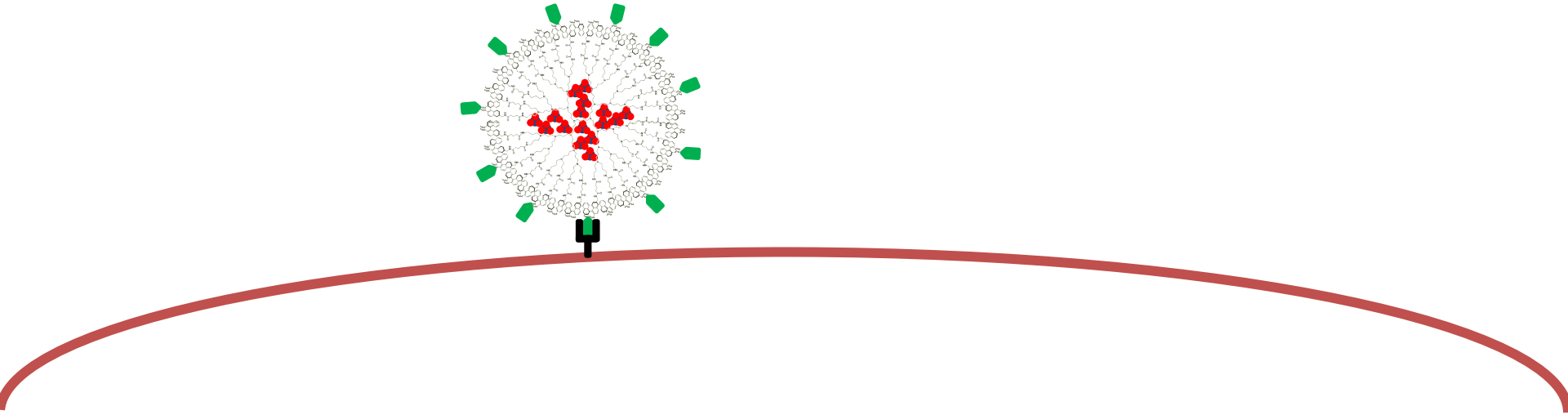
Improving delivery



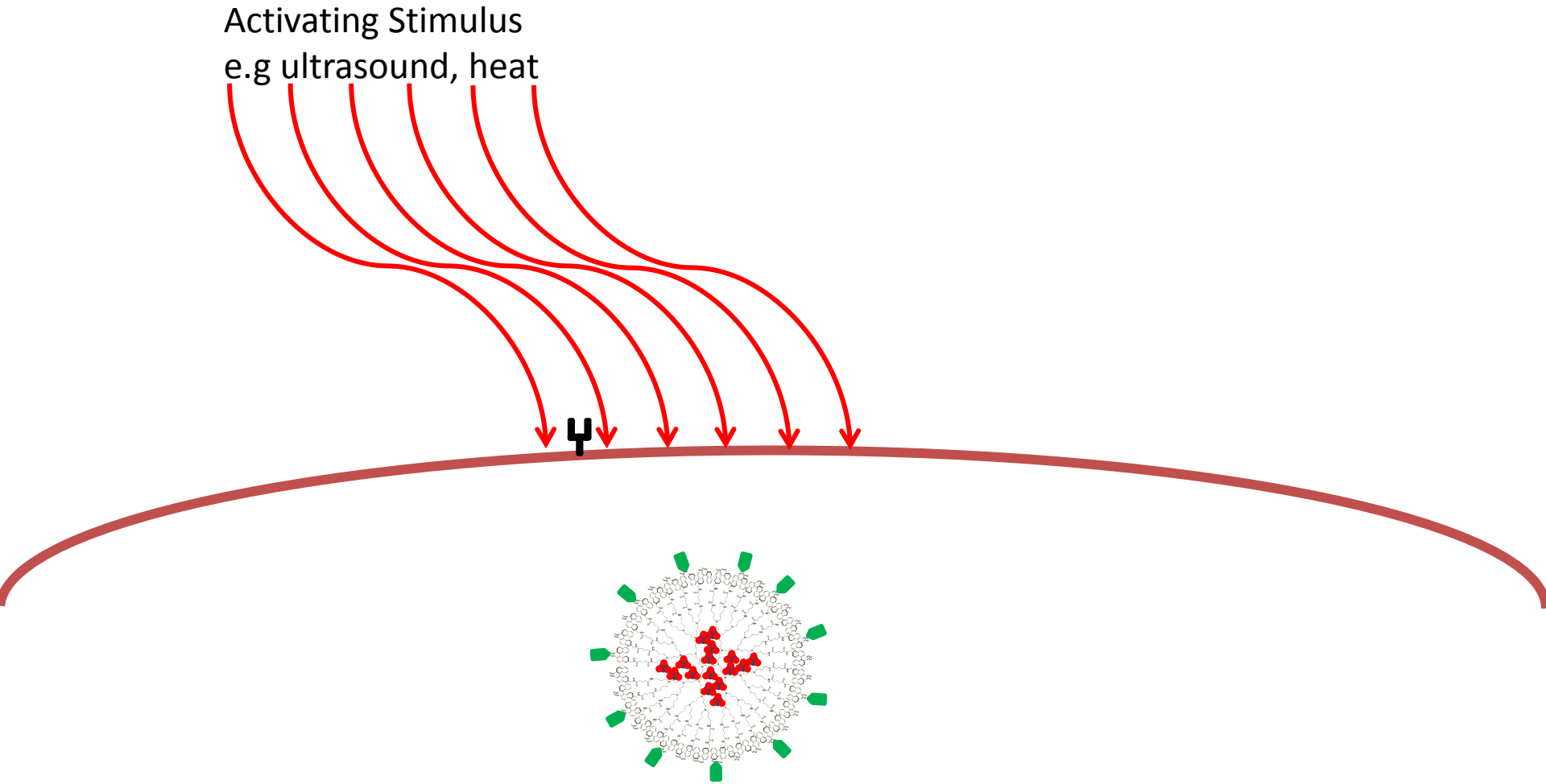
Improving delivery



Improving delivery



Improving delivery



Summary

- Nanomedicine may be a promising therapeutic field for the treatment of cancer
- Nanoparticles can selectively accumulate in tumour tissue due to leaky vasculature
- Particles can also be targeted to tumours by addition of ligands for tumour-associated receptors on the particle surface
- Particles can be designed to break down and release their contents once at the tumour site
- Reduces side effects and toxicity in non-tumour tissue
- Allows for higher doses to be administered
- Increased survival

Too good to be true?

- As with all drugs, safety testing of nanomedicines is essential
- At present non-drug-related nanomaterials incorporated in to products are not regulated
- There are no FDA guidelines for nanomedicine
- In light of studies of other man-made particles this has led to concern that nanoparticles may be harmful to health

Air pollution and health

Atopic Diseases, Allergic Sensitization, and Exposure to Traffic-related Air Pollution in Children

Verena Morgenstern[1], Anne Zutavern[1,2], Josef Cyrys[1,3], Inken Brockow[4], Sibylle Koletzko[2], Ursula Krämer[5], Heidrun Behrendt[6], Olf Herbarth[7,8], Andrea von Berg[9], Carl Peter Bauer[4], H.-Erich Wichmann[1,10], and Joachim Heinrich[1], for the GINI Study Group* and the LISA Study Group*

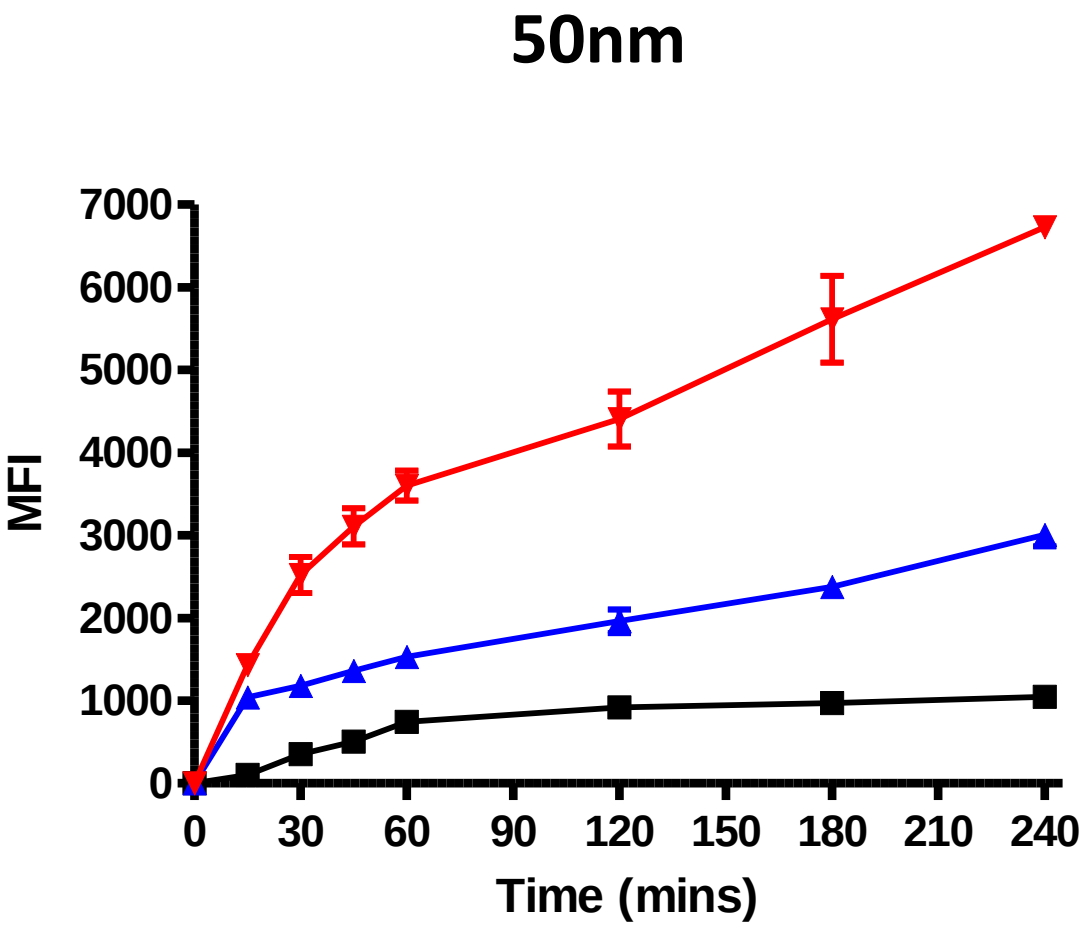
Lung Cancer, Cardiopulmonary Mortality, and Long-term Exposure to Fine Particulate Air Pollution

C. Arden Pope III, PhD
Richard T. Burnett, PhD
Michael J. Thun, MD
Eugenia E. Calle, PhD
Daniel Krewski, PhD
Kazuhiko Ito, PhD
George D. Thurston, ScD

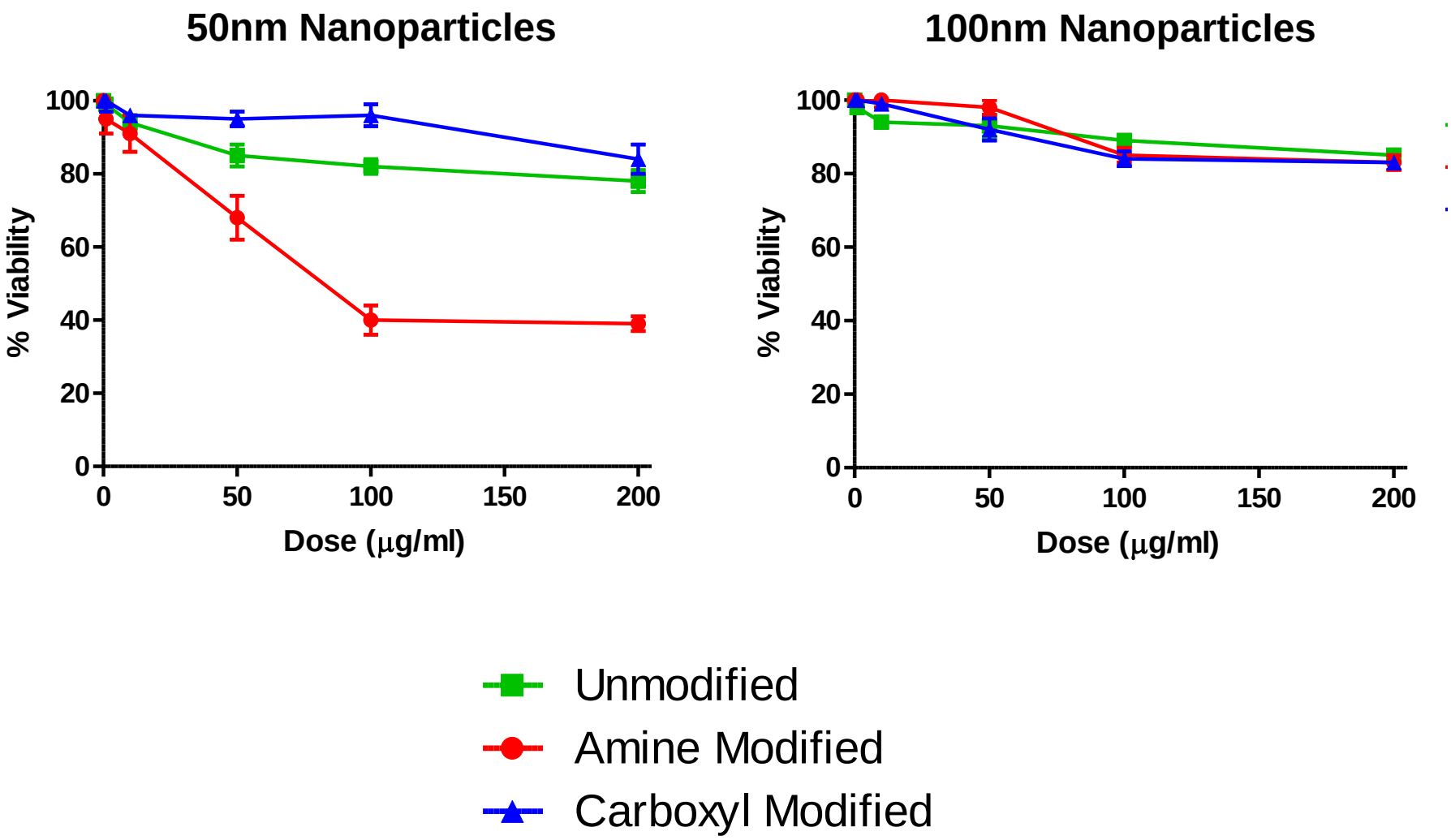
FINE PARTICULATE AIR POLLUTION AND MORTALITY IN 20 U.S. CITIES, 1987–1994

JONATHAN M. SAMET, M.D., FRANCESCA DOMINICI, PH.D., FRANK C. CURRIERO, PH.D., IVAN COURSAC, M.S., AND SCOTT L. ZEGER, PH.D.

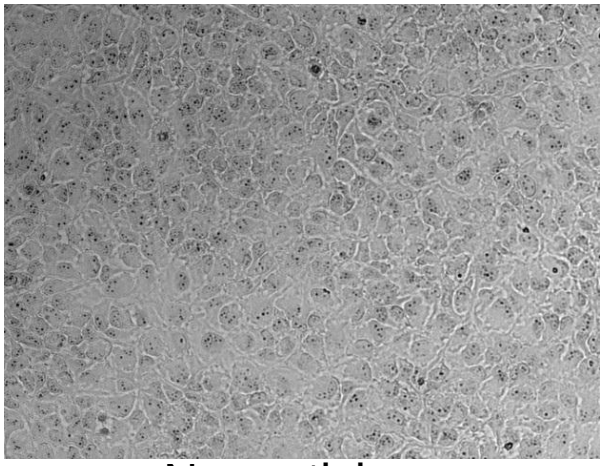
Particle cytotoxicity



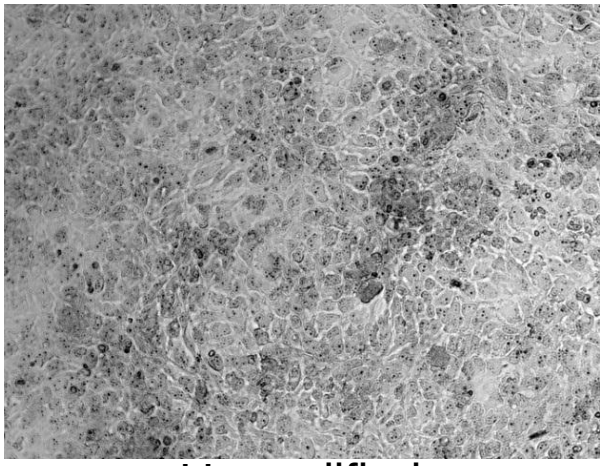
Particle cytotoxicity



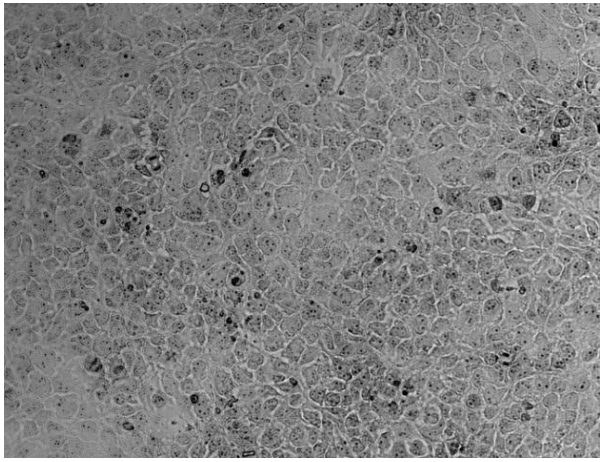
Particle cytotoxicity



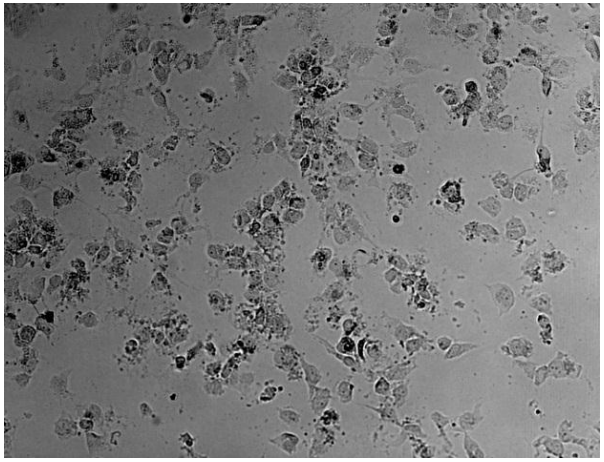
No particles



Unmodified

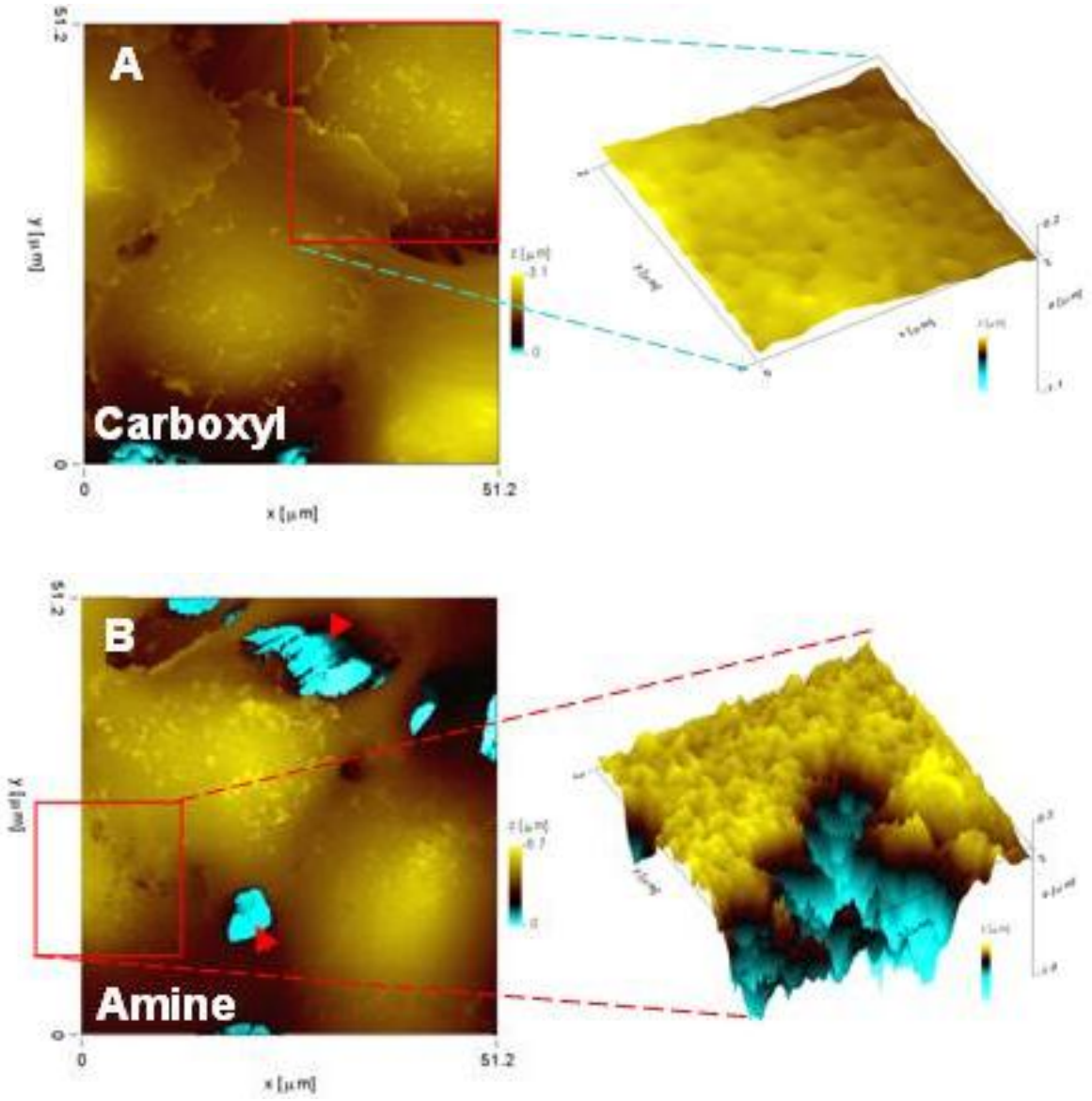


Carboxyl



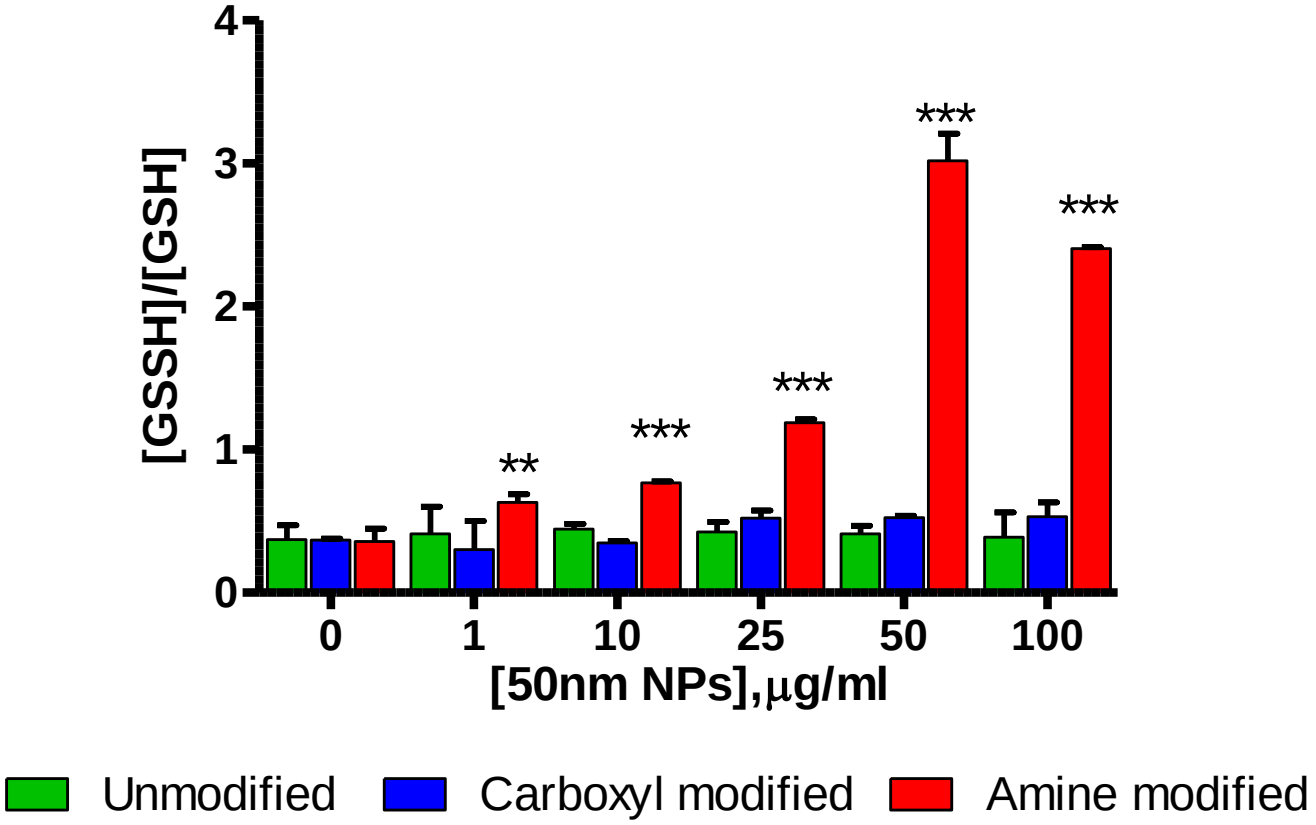
Amine

Membrane damage

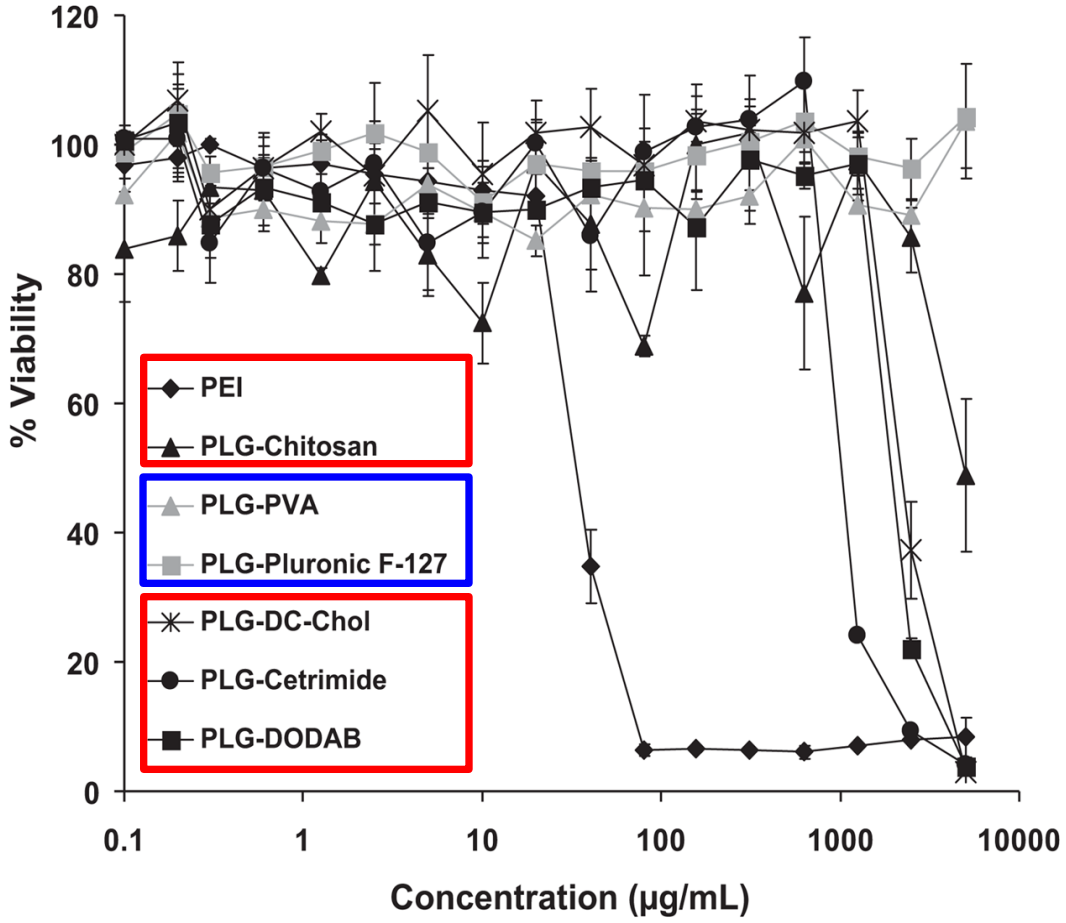


Prof Julia Gorelik Imperial College

Particle cytotoxicity



Particle Cytotoxicity



PEI – Polyethylene imine **PLG** – Poly(D,L-lactide-*coglycolide)*

Baoum, A. et al. *J Pharm Sci.* 2010; 99(5): 2413–2422

Summary

- The size and charge of particles can be modified to improve their uptake
- Properties that may improve delivery of particles to cells may also induce cytotoxicty
- Whilst a positive charge can improve delivery it can also be cytotoxic.
- Despite their desirable properties, formulation and use of nanoparticles needs to be tightly regulated