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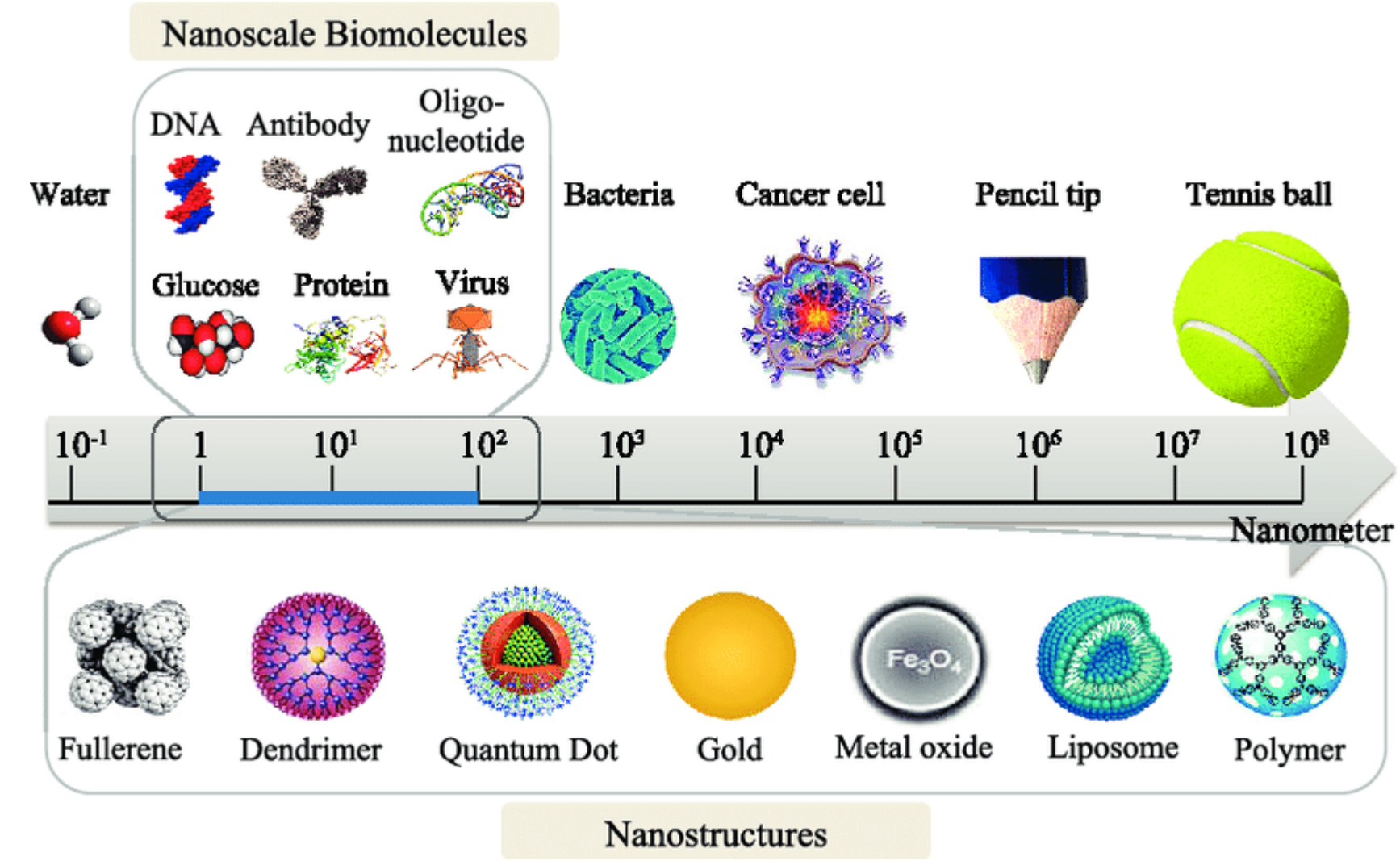
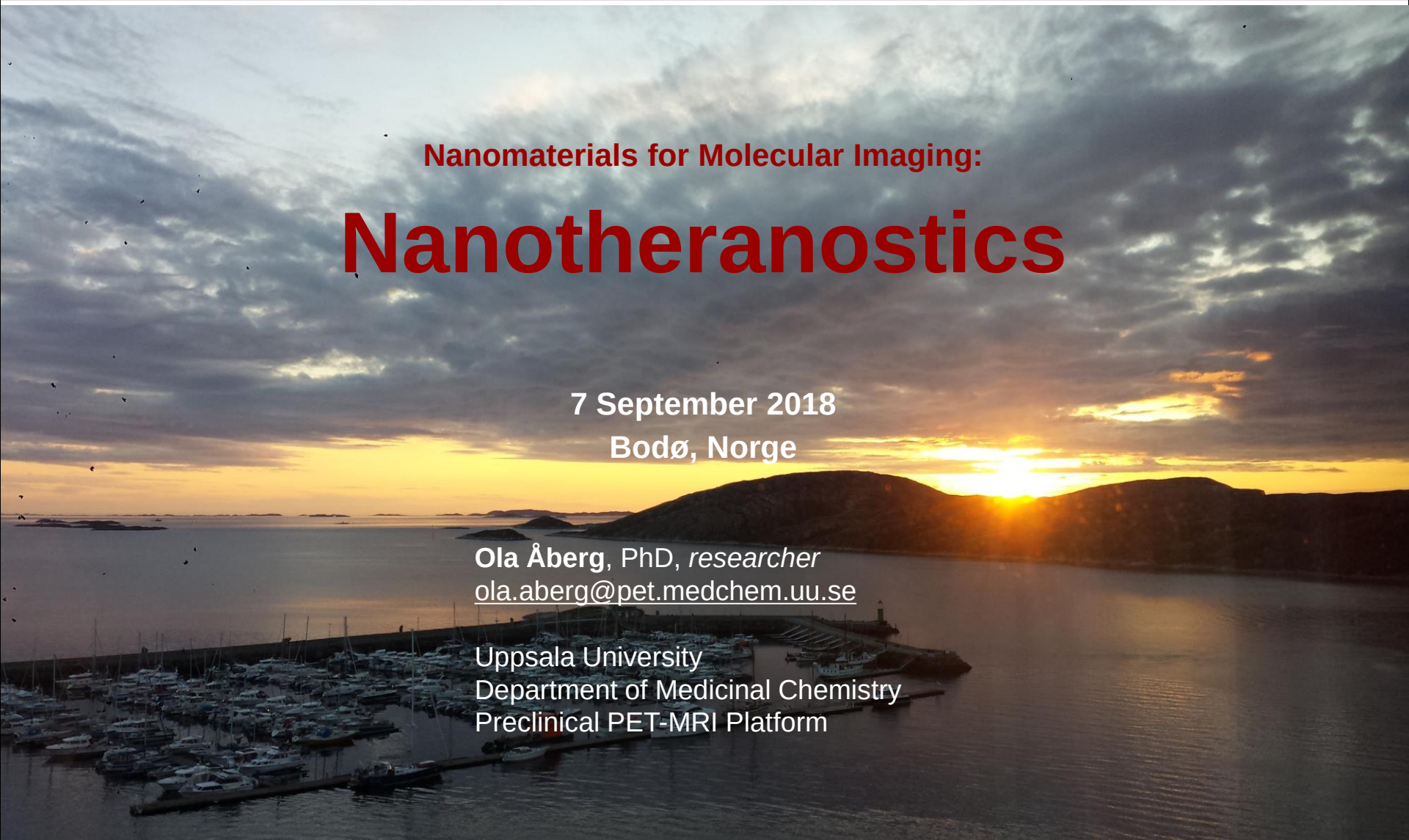
The Nanoscale





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Nanomaterials for Molecular Imaging:

Nanotheranostics

7 September 2018

Bodø, Norge

Ola Åberg, PhD, *researcher*
ola.aberg@pet.medchem.uu.se

Uppsala University
Department of Medicinal Chemistry
Preclinical PET-MRI Platform

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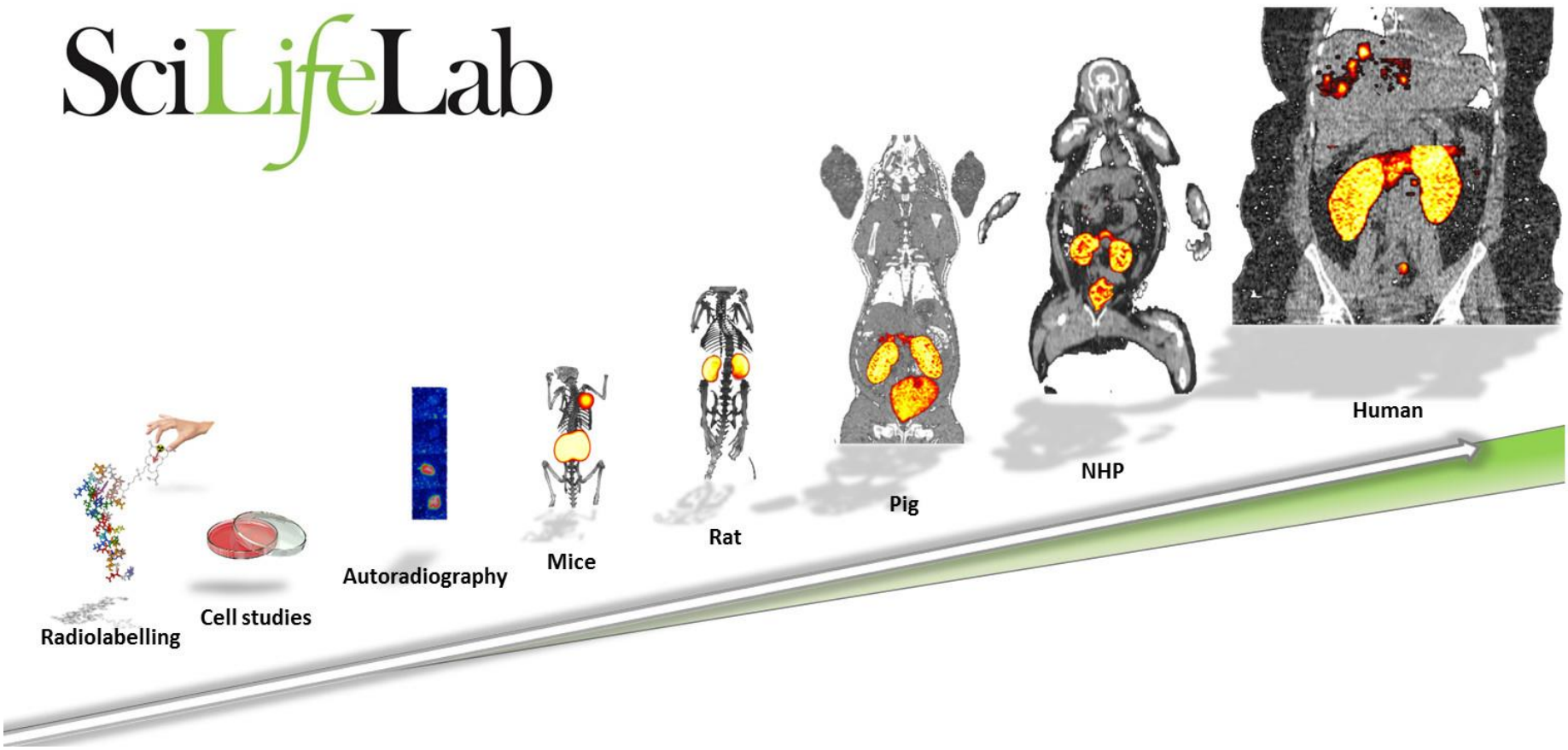
Preclinical PET-MRI Platform

SciLifeLab



Contract reserach in **molecular imaging**

https://www.ilk.uu.se/platforms/ppp_en/

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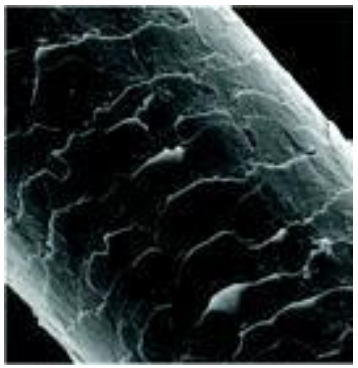
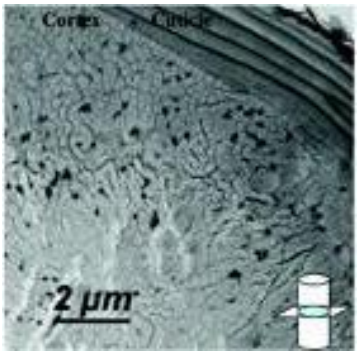
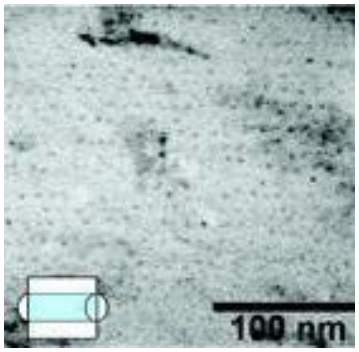
Is nanotechnology something new?







4000 years ago the Ancient Egyptians were using nanomaterials in a **black hair dye** based on a synthetic chemical process to synthesize **5 nm diameter lead sulphide (PbS)**.

Nano Lett. ***2006****;6(10):2215-9.*

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Some Nano Milestones

- 1857 Michael Faraday reports the first synthesis of a **colloidal gold solution**
- 1940 SiO_2 nanomaterial used for rubber reinforcement
- 1974 **'Nanotechnology'** coined as a term
- 2003 Samsung introduces antibacterial SilverNano™
- 2004 Merzedes-Benz, scratch resistant paint
- 2005 **Abraxane**, serum albumin NP material containing paclitaxel
- 2012 Logitech, dye senitized light powered iPad keyboard
- **Today >1800 nanotechnology based consumer products available**

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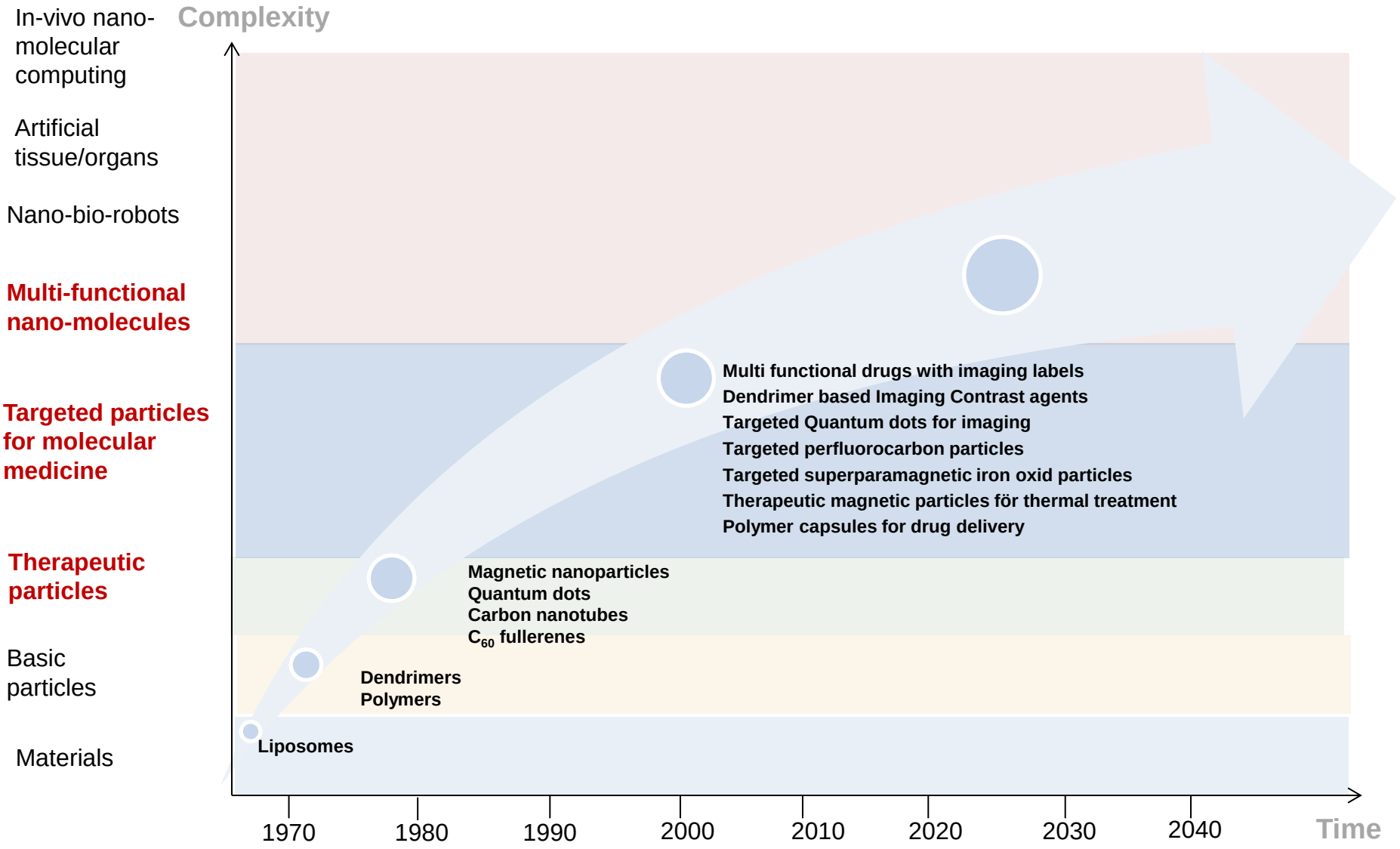
Where Are We Heading?



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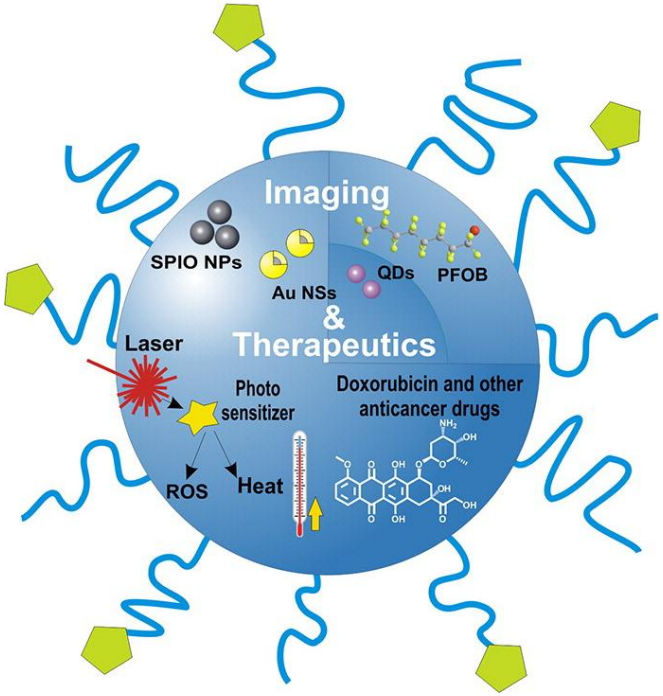
Overview

- Fundamental concepts
  - Challenges in todays cancer treatment
  - Personalised medicine
  - What is nanotheranostics?
  - The nanotheranostic platform
  - Biological barriers
  - Multi drug resistance
- Molecular imaging
  - Nuclear imaging PET & SPECT
  - Magnetic resonance imaging (MRI)
  - Fluorescence imaging
  - Remote activation of drugs
  - Image guided radiotherapy
- Examples in cancer therapy and nanomedicine



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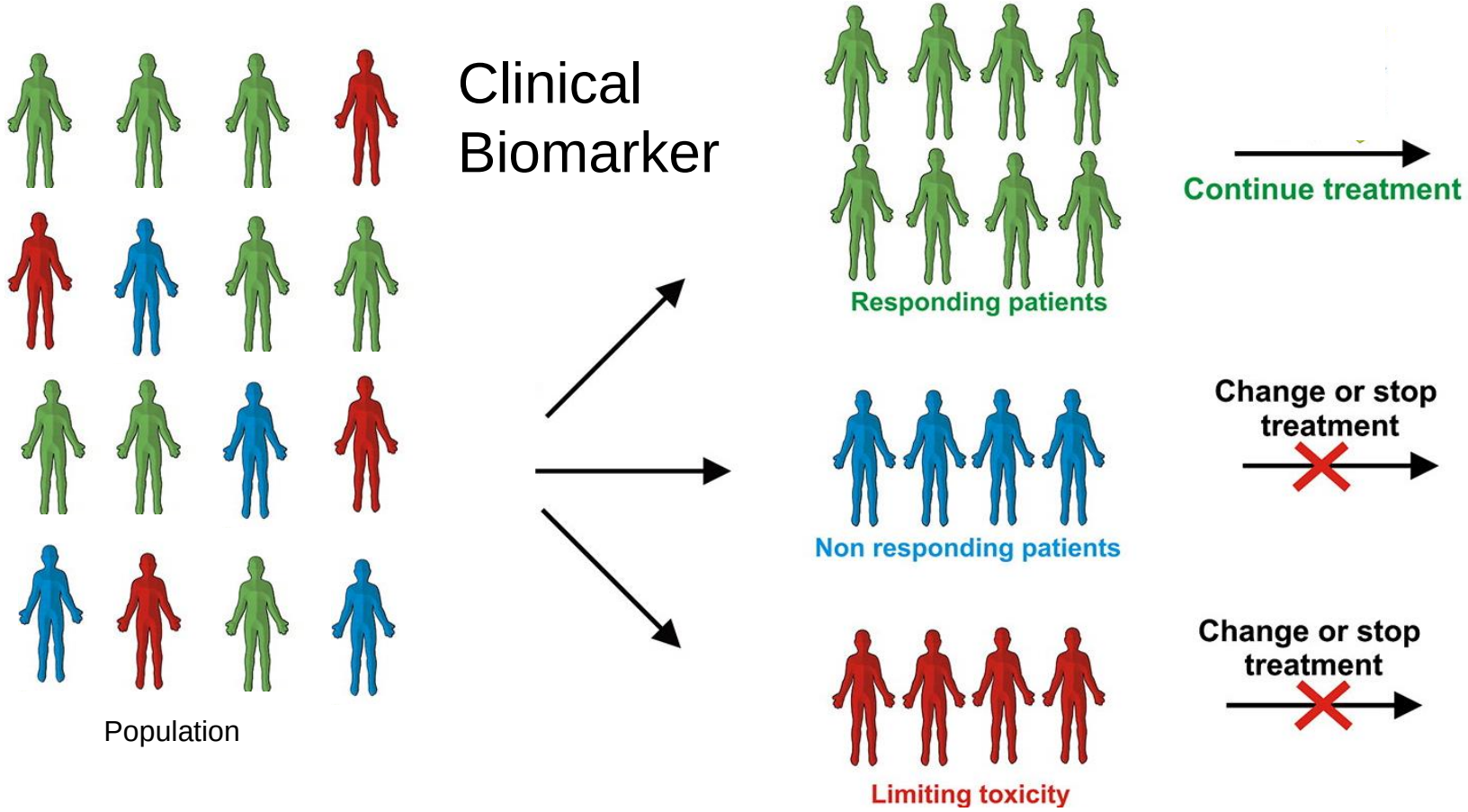
Introduction

Challanges in Todays Cancer Treatment

Treatment	Challange	Nanotechnology
Surgery	Difficult to remove all tumour tissue. Can lead to relapse.	Molecular imaging in real-time-guided surgery
Radiotherapy	Irradiation of surrounding healthy tissue.	Targeted radiotherapy
Chemotherapy	Toxic side effects. Multi drug resistance.	Image guided targeted chemo therapy
Tumour ablation	Invasive. Damage to surrounding tissues. Ineffective to larger tumours.	Non-invasive. Image guided. Controlled drug release. Heat.

Introduction

Personalised Medicine



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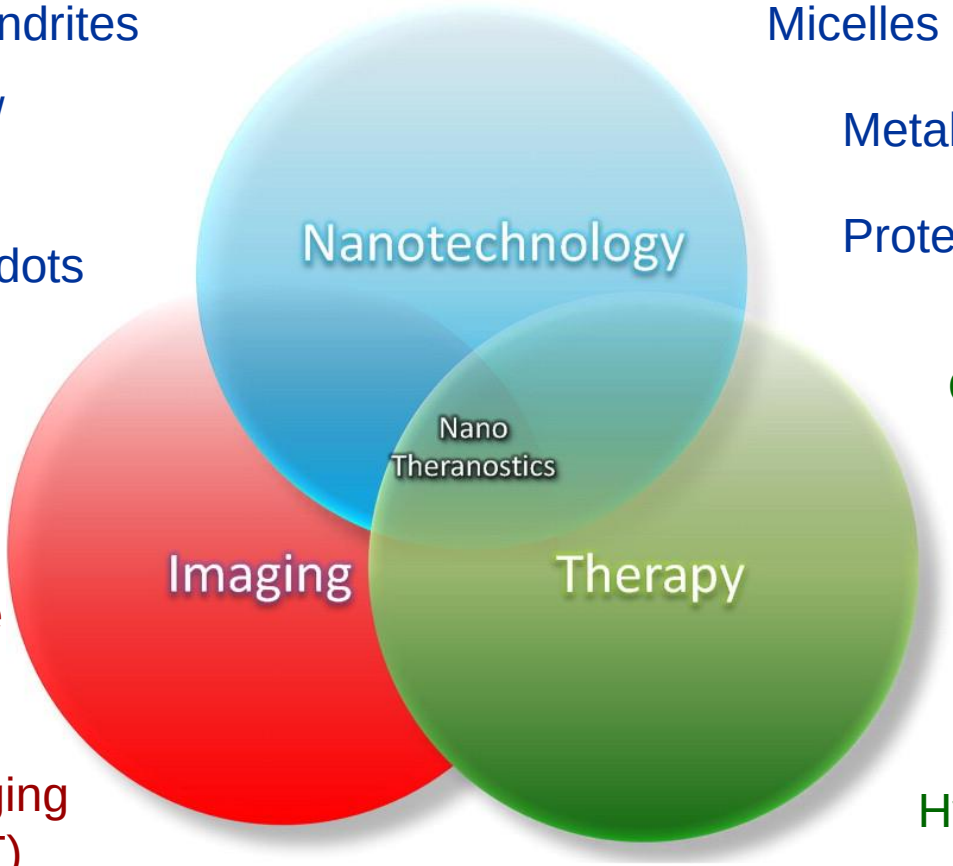
Introduction

What is Nanotheranostics?



Gold particles

Liposomes

Polymers

Dendrites

Micelles

Fullerenes/
nanotubes

Metal oxide

Protein conjugates

Quantum dots

Chemotherapy

Fluorescence
imaging

Gene therapy

Magnetic resonance
imaging (MRI)

Radiation therapy

Photodynamic

Nuclear imaging
(PET/SPECT)

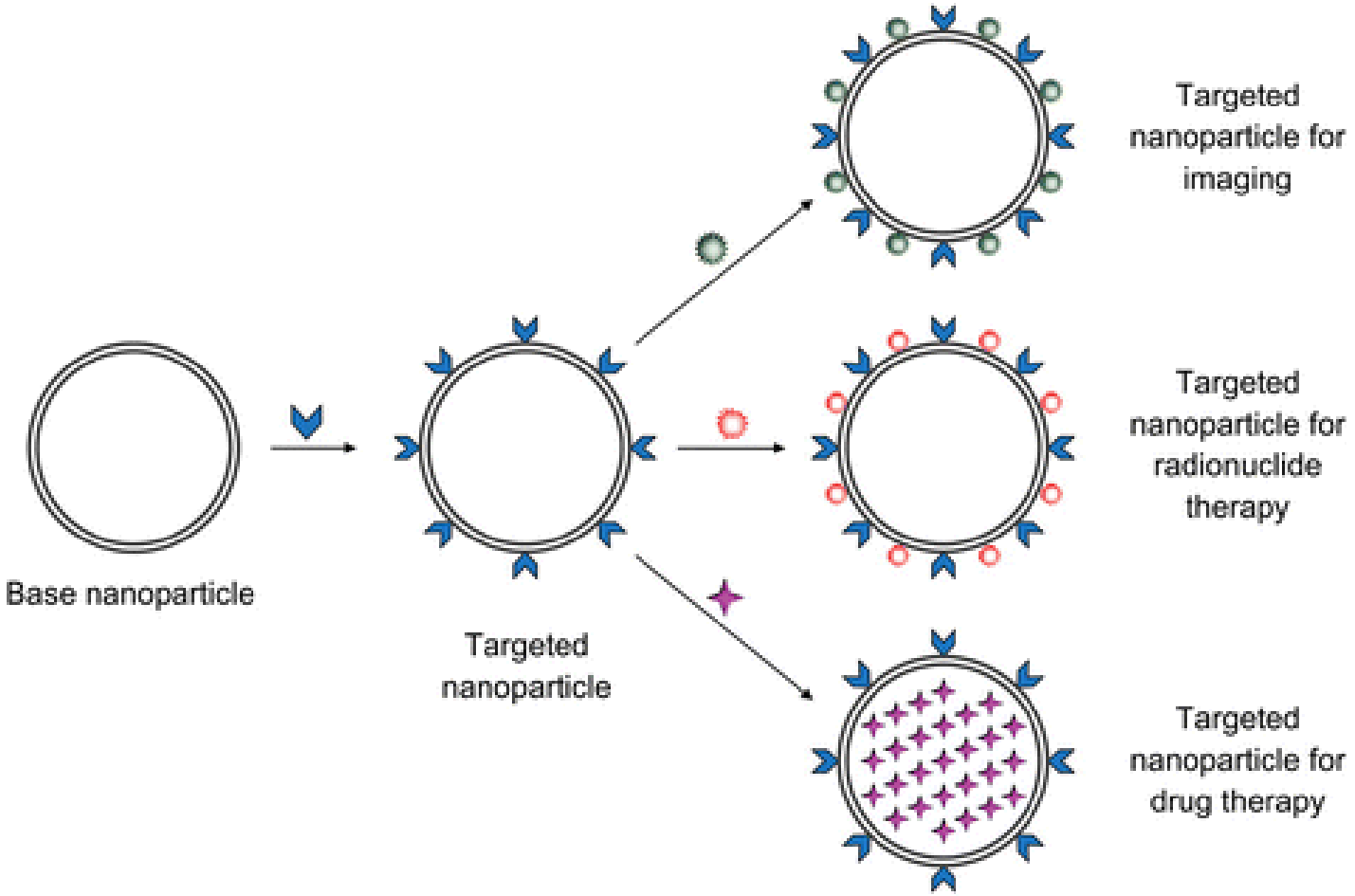
Hyperthermia

Ultrasonic imaging

Image guided surgery

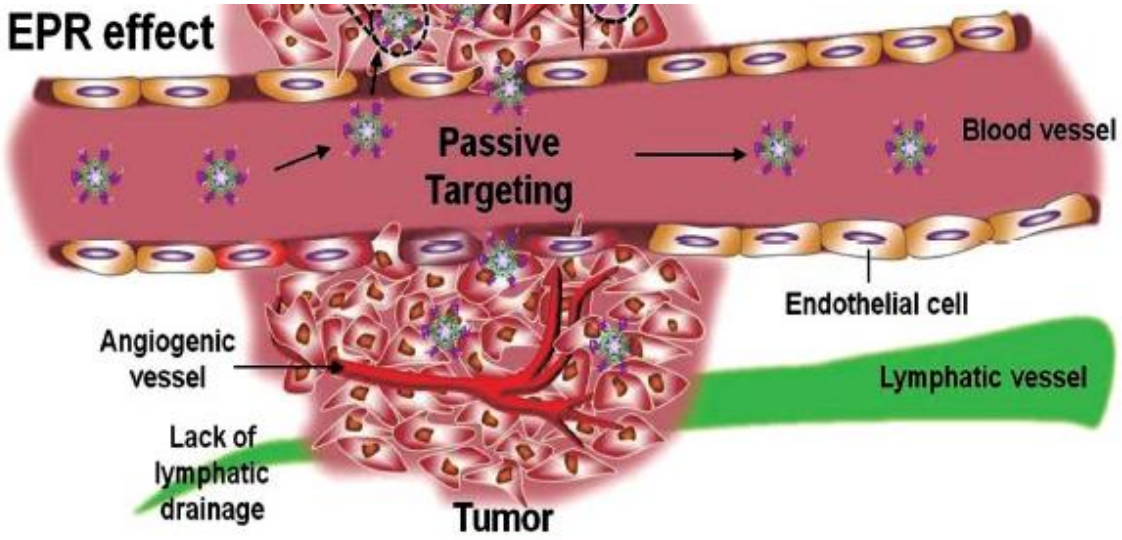
Introduction

The Nanotheranostic Platform



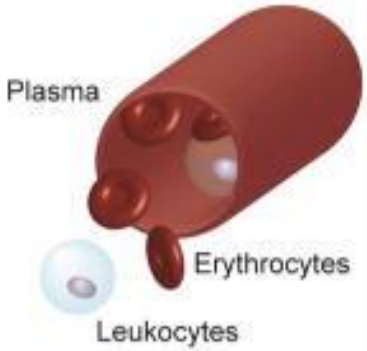
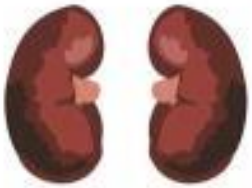
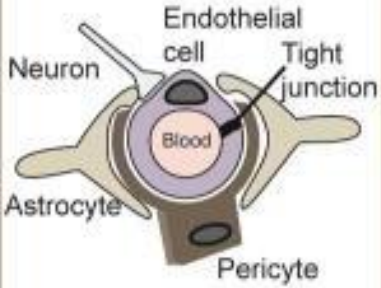
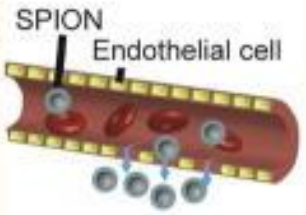
EPR Effect

- Enhanced permeability and retention (EPR) effect
  - Leaky vessels lead to **increased tumour uptake** of nanoparticles **30-100 nm**
  - NPs are retained due to poor lymphatic drainage
  - Size range of NP is very important



Maeda H. Macromolecular therapeutics in cancer treatment: The EPR effect and beyond. J Control Release. 2012

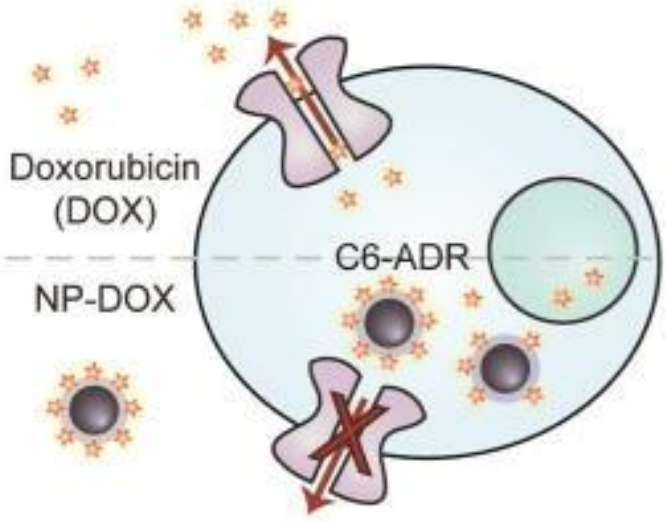
Biological Barriers and Design of NP

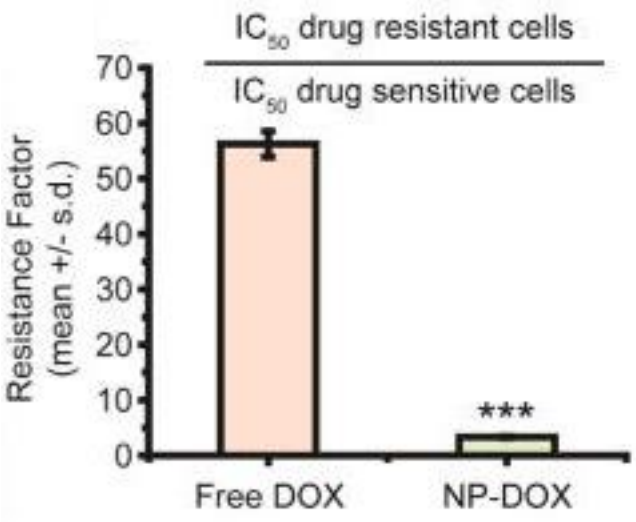
Barrier	Blood	Liver and Spleen	Kidneys	Blood-brain Barrier	Extravasation
					
Restrictions	• Highly complex fluid • Enzyme degradation • Immune recognition	• Objects larger than 100 nm recognized and removed from circulation	• Objects smaller than the 10 nm pores of the glomerulus are filtered out of the blood	• Tight junctions between endothelial cells in the brain prevent passive access	• Gaps between endothelial cells restrict material escape from the blood
Strategies	• PEGylation • Zwitterionic polymers • Encapsulation of drug or biotherapeutic	• Hydrodynamic size less than 100 nm	• Hydrodynamic size greater than 10 nm	• Osmotically shrink endothelial cells to open junctions • Active transport across vasculature	• Enhanced perm-eability and retention effect • Hydrodynamic size 30 - 100 nm

Acc Chem Res. 2011, 18;44(10):853-862

How can NP aid in overcoming multi drug resistance?

Conventional Doxorubicin therapy





NP conjugated Doxorubicin therapy

NP-conjugated Doxorubinin is effectively delivered inside the cell and recognised by the target but not by the MDR-pump→more effective treatment and less affected by drug resistance

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Molecular Imaging

”…the ***in vivo*** **characterization and measurement** of biologic processes at the cellular and molecular level”
(Weissleder and Mahmood, Radiology, 2001)

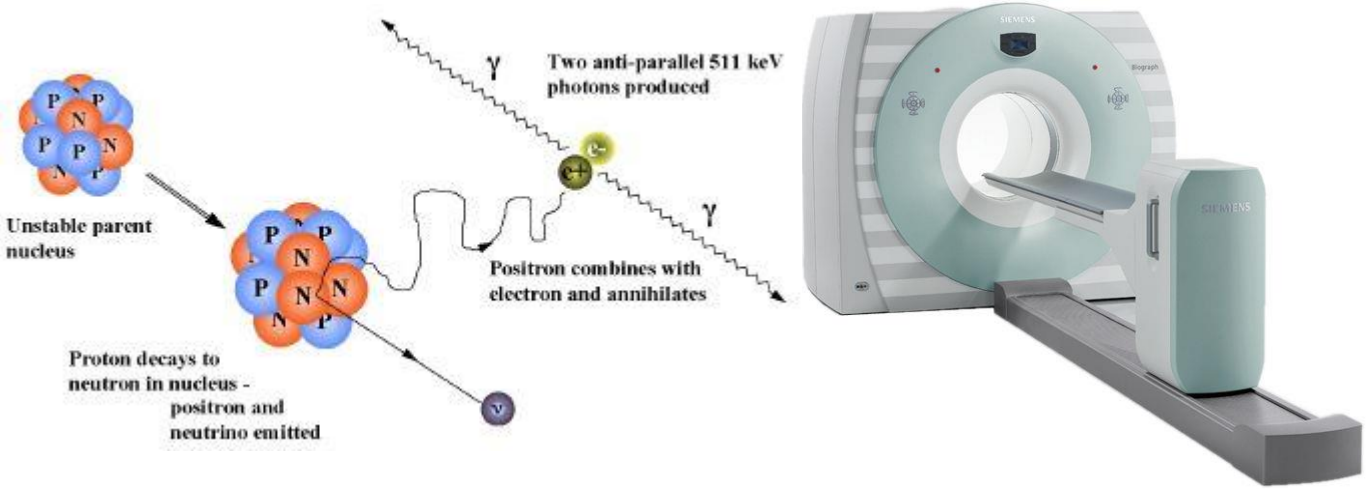
”…the visual representation, characterization, and quantification of biological processes at the cellular and subcellular levels **within intact living organisms**”
(Massoud and Gambhir, Genes & Development, 2003)

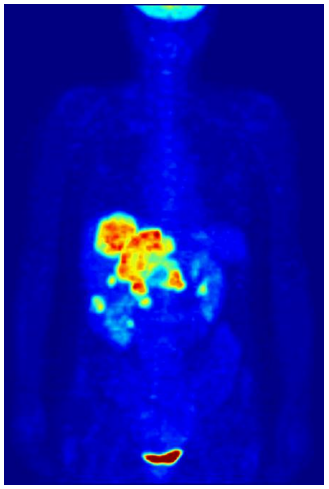
“MI techniques directly or indirectly monitor and record the spatiotemporal distribution of **molecular or cellular processes** for biochemical, biologic, diagnostic, or therapeutic applications”
(The Radiological Society of North America (RSNA) and the Society of Nuclear Medicine (SNM), April 2005)

Radionuclide imaging – PET & SPECT

Technique based on radioactive decay

- Subject is placed in a scanner
- A radiotracer for specific target is administrated, labelled with positron emitting nuclide (^{11}C, ^{18}F, ^{68}Ga, ^{64}Cu, ^{89}Zr) or gamma emitter (^{99m}Tc, ^{111}In, ^{125}I)
- The radiotracer will distribute in the subject and bind to its target
- Upon decay the radiation is detected by the detectors in the scanner
- A 3D image of the distribution of the radiotracer is reconstructed.

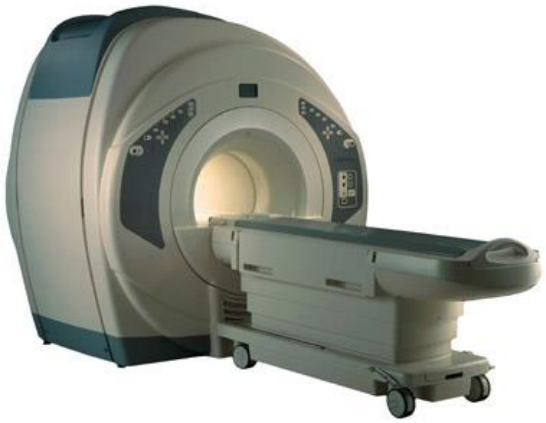


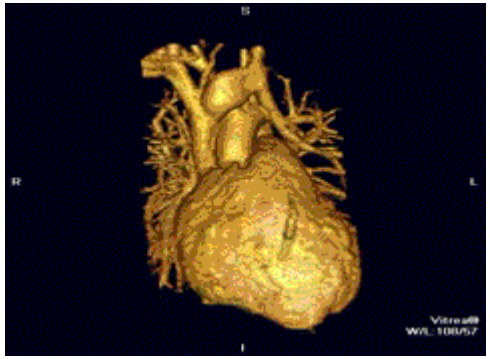


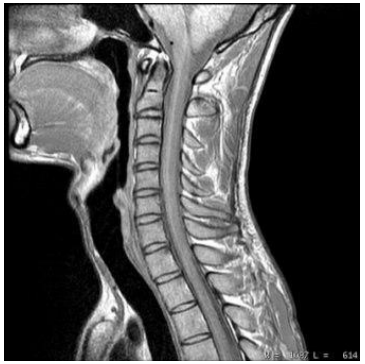
Magnetic Resonance Imaging

Technique based on behavior of unpaired nuclear spin (e.g. protons) in the presence of a strong magnetic field

- Object is placed in strong magnetic field (1-7 Tesla)
- Magnetic dipoles in the nucleus of atoms align in the field (^{1}H)
- A radiofrequency pulse is applied to change the alignment of the dipoles
- Nuclei return to their base line orientation at different rates, depending on the chemical surrounding – relaxation time
- A 3D image is reconstructed with high resolution and contrast in soft tissue
- Essentially the proton density is depicted (water content of tissues)



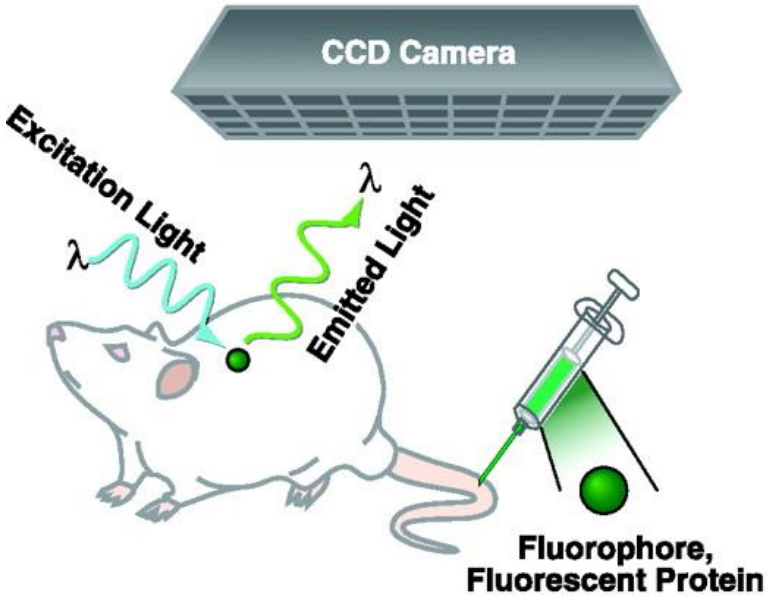




Molecular Imaging

Fluorescent Imaging

- Nanoparticle is labelled with a fluorophore
- Excitation with light -> fluorescent dye emits light of longer wavelength which is detected
- Limited by penetration depth of the light
- Used in real-time image guided surgery



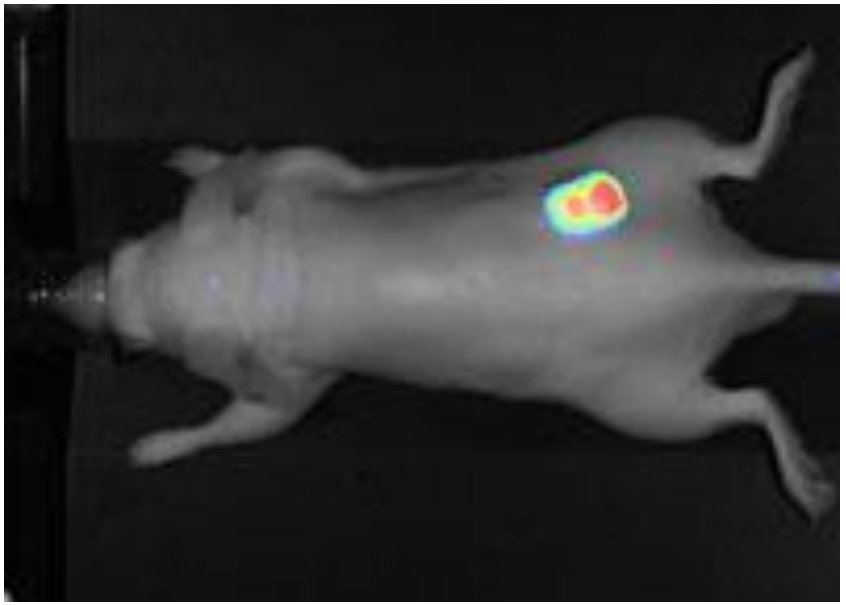


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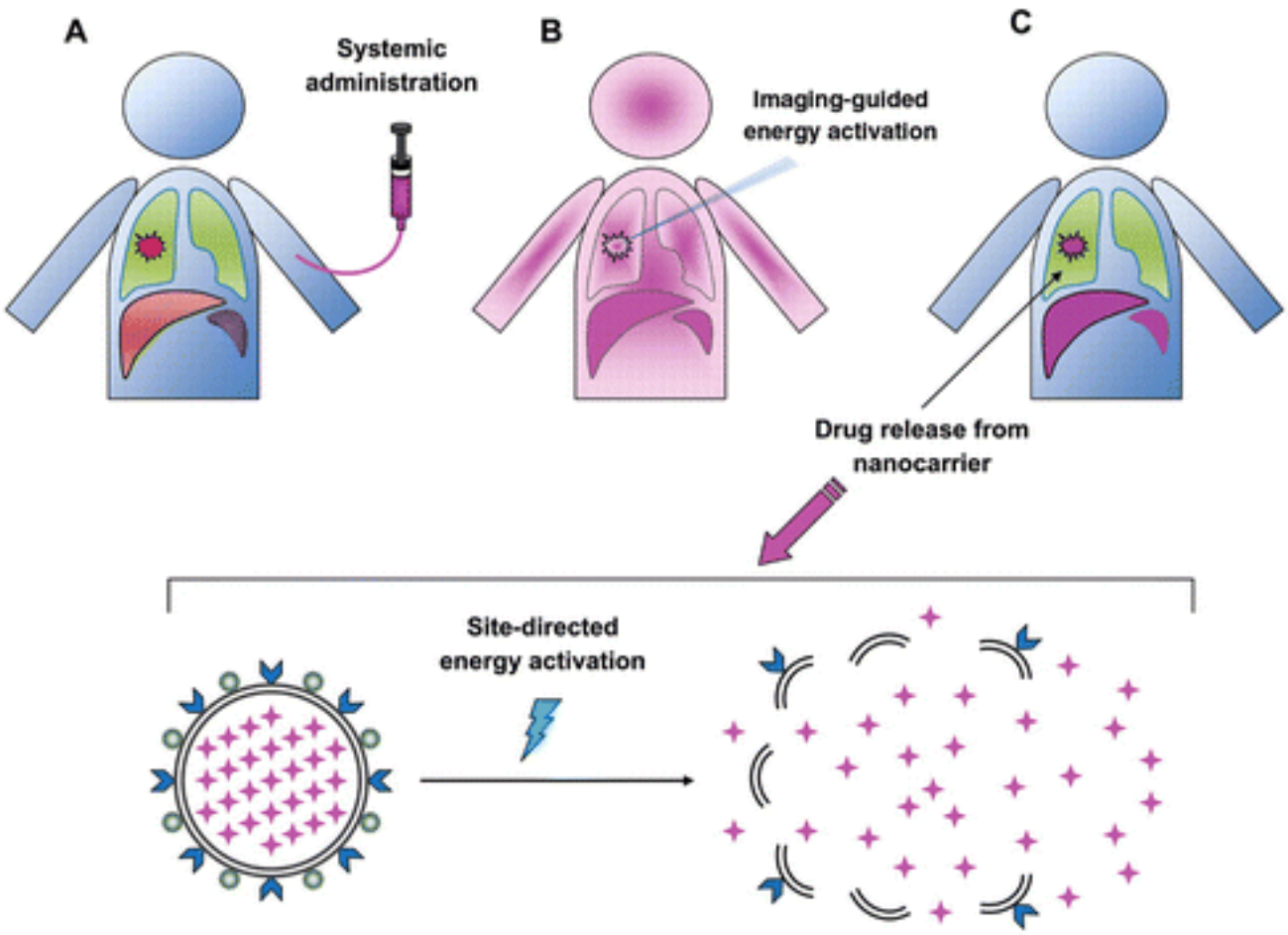
Image Guided Remote Activation of Drug Release



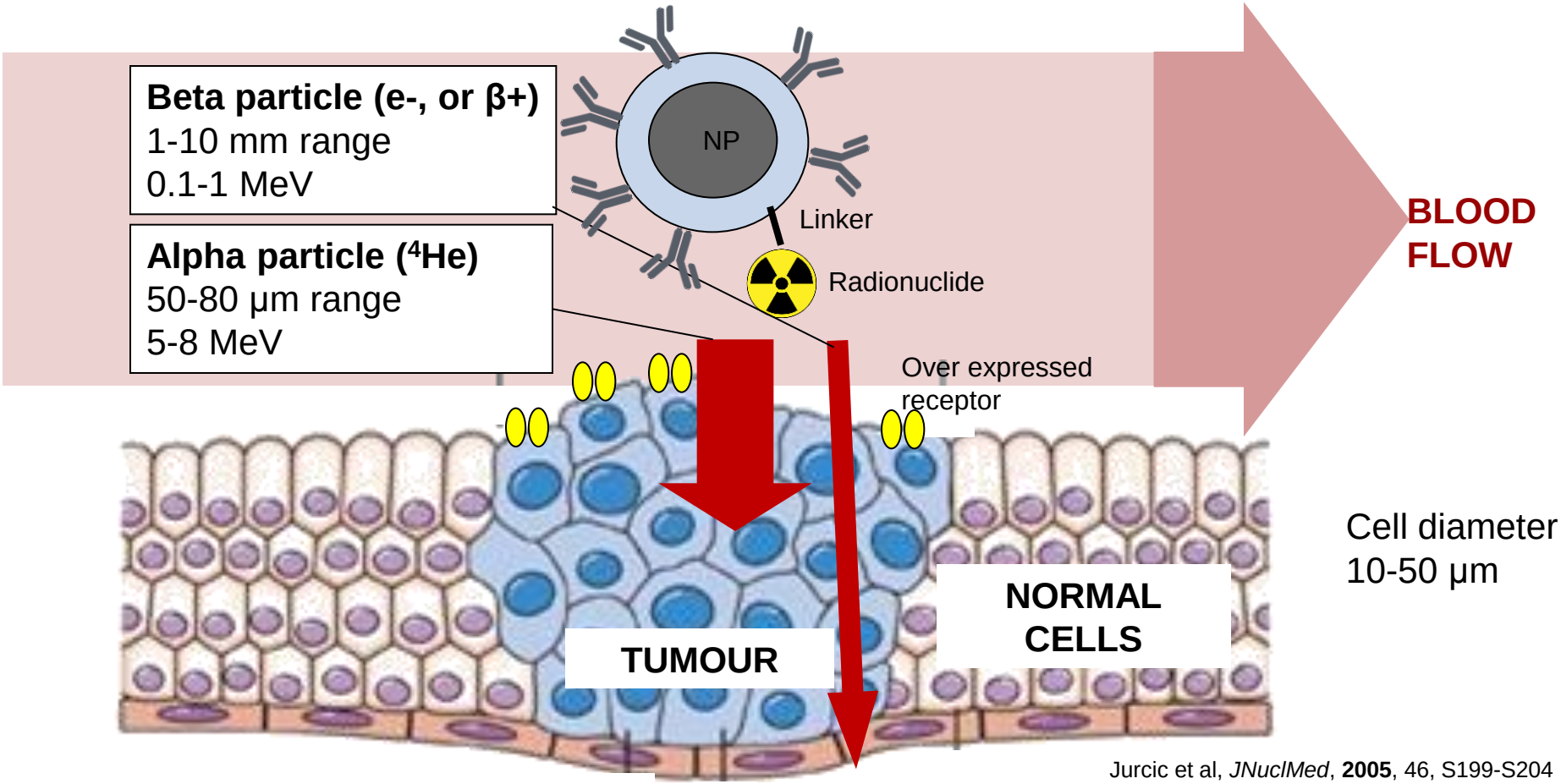
A) Systemic administration of nanomedicine to patient with lung tumor.

B) Wait for maximum tumor accumulation (follow by molecular imaging). Activation energy (*blue rays*) is applied to site of disease by imaging-guidance.

C) Activation energy causes release of drugs encapsulated in the nanocarrier. Activation step to release drugs at desired sites circumvents some of biodistribution issues of nanomedicines.

Image Guided Targeted Radiotherapy

• Close distance **internal radiation** to tumour cells could potentially be used for cancer therapy. NPs can serve as a carrier for the radionuclide (^{211}At, ^{212}Pb, ^{213}Bi, ^{225}Ac) and the targeting mAb have affinity for surface receptors that is overexpressed on the cancer cells.



Jurcic et al, *JNuclMed*, **2005**, 46, S199-S204

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Nanomaterials

Gold particles

Liposomes

Polymers

Dendrites

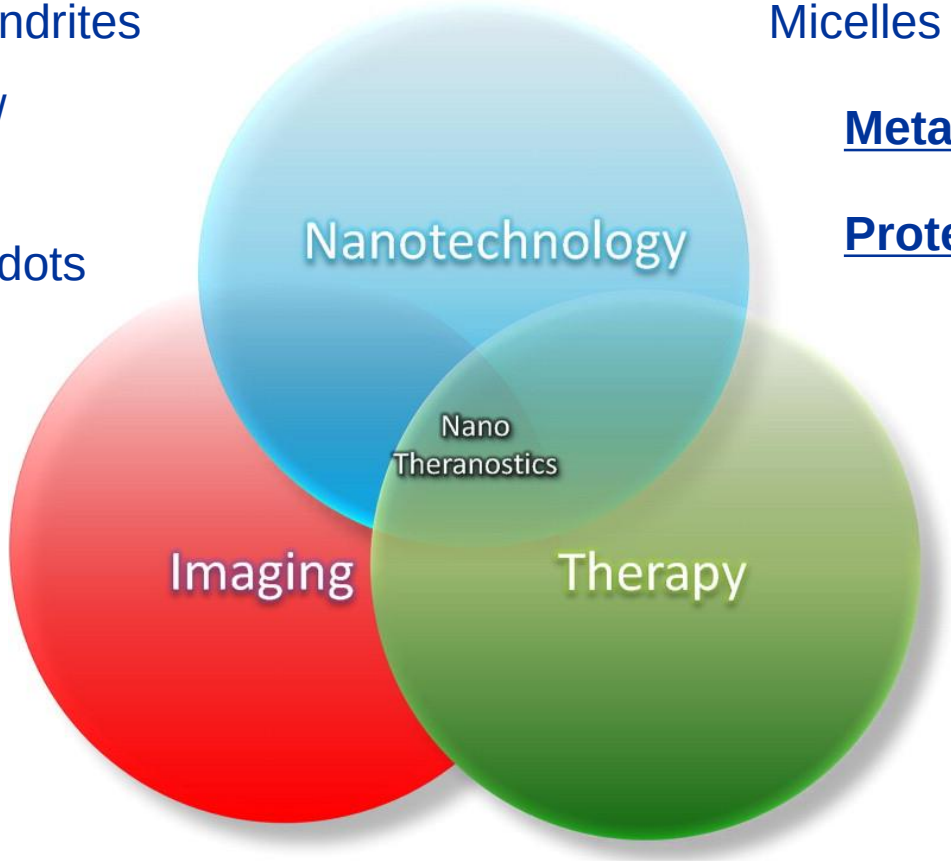
Micelles

Fullerenes/
nanotubes

Metal oxide

Protein conjugates

Quantum dots



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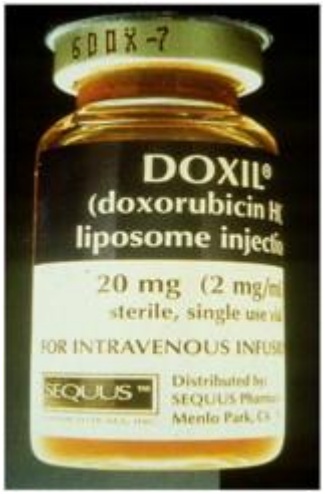
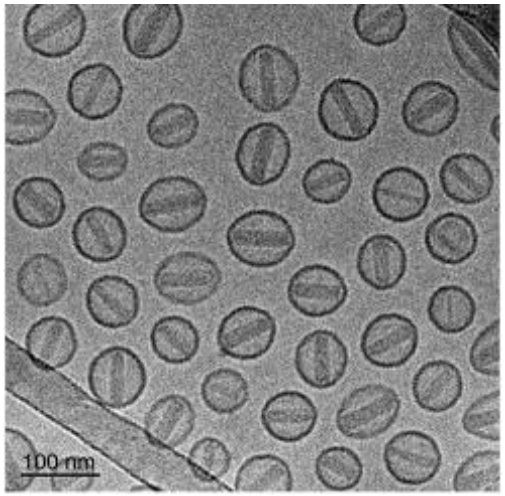
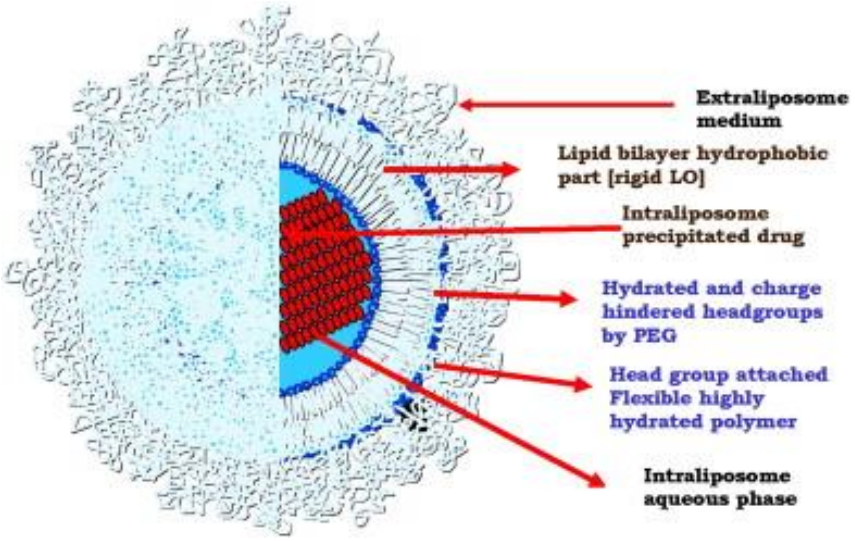
Examples

Liposomes







- Made of phosholipid bilayer
- Can be loaded with drugs
  - Doxil, liposome encapsulated doxorubicin was approved 1995 FDA, 1996 EMA
- Gases for ultrasonic imaging
- Physical and chemical instability → relatively short shelf-life (20 months for Doxil at 2-8 ^{o}C)→ increased costs

Journal of Controlled Release 160,(2), 2012, 117-134

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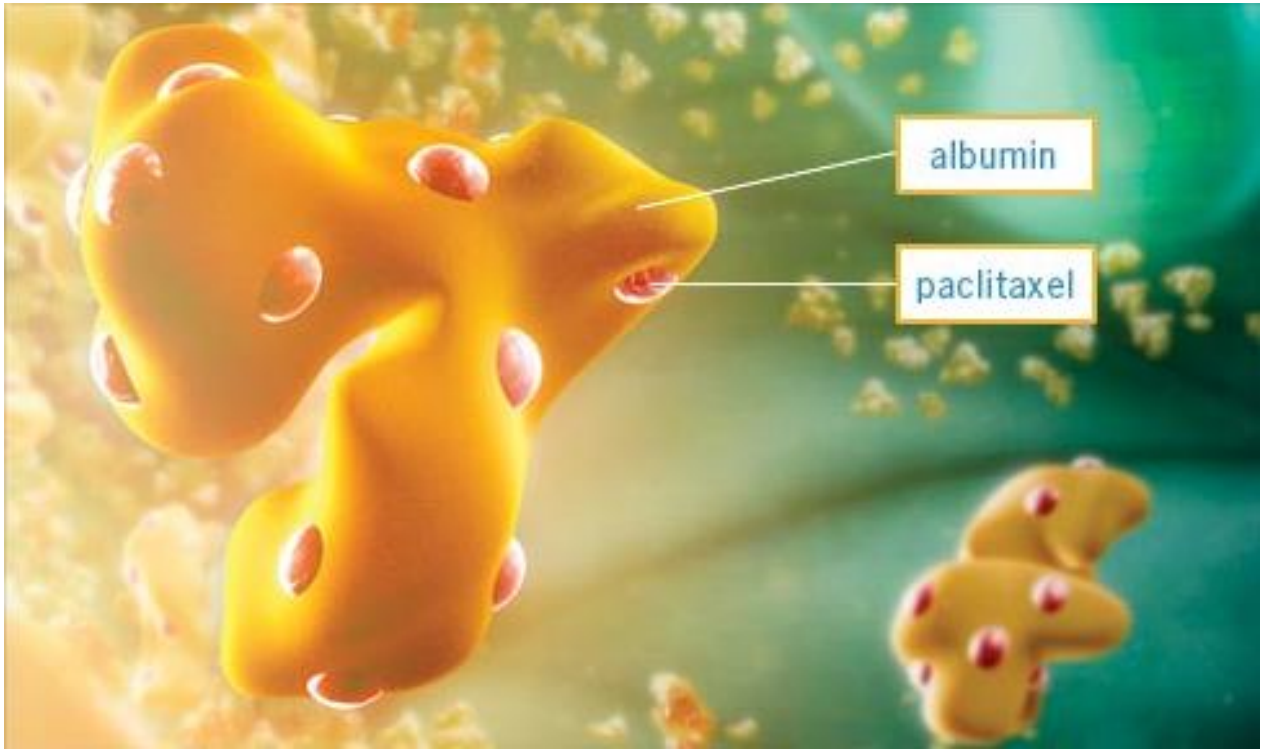
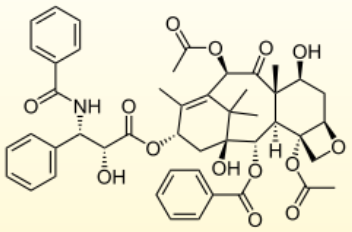
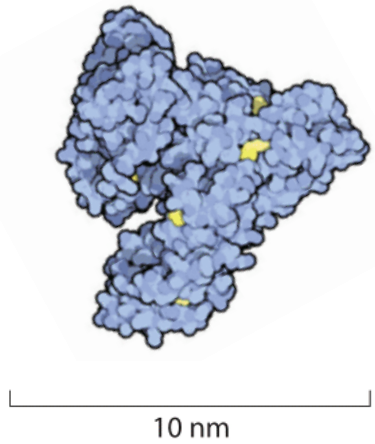
Examples

Protein conjugates





Paclitaxel



Human serum albumin

Human serum albumin loaded with Paclitaxel
FDA approved in 2005, Abraxane™

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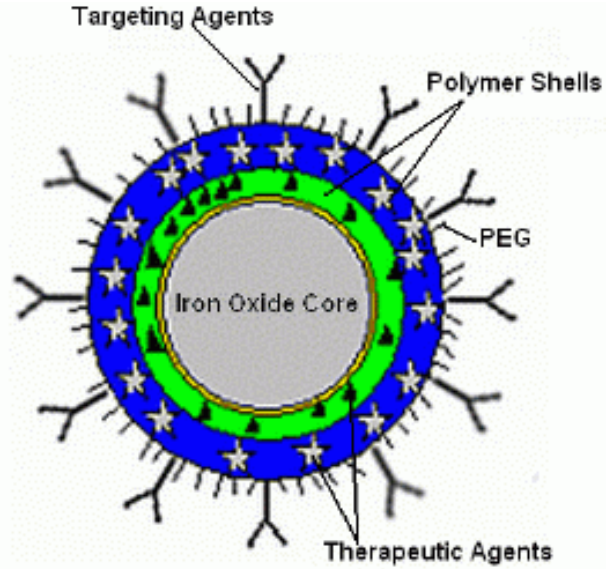
Examples

Iron oxide NPs



- Iron oxide becomes superparamagnetic in the nano-scale
- Super paramagnetism causes small inhomogeneities in an externally applied magnetic field. For MRI this means decreasing the signal and the image appears as darker
- Cheap
- Biocompatible, biodegradable
- Can generate **heat** in an altering magnetic field with no limitation in penetration depth

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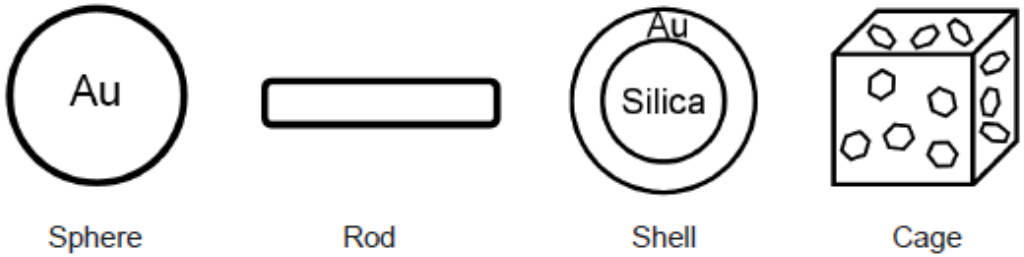
Examples

Gold NPs



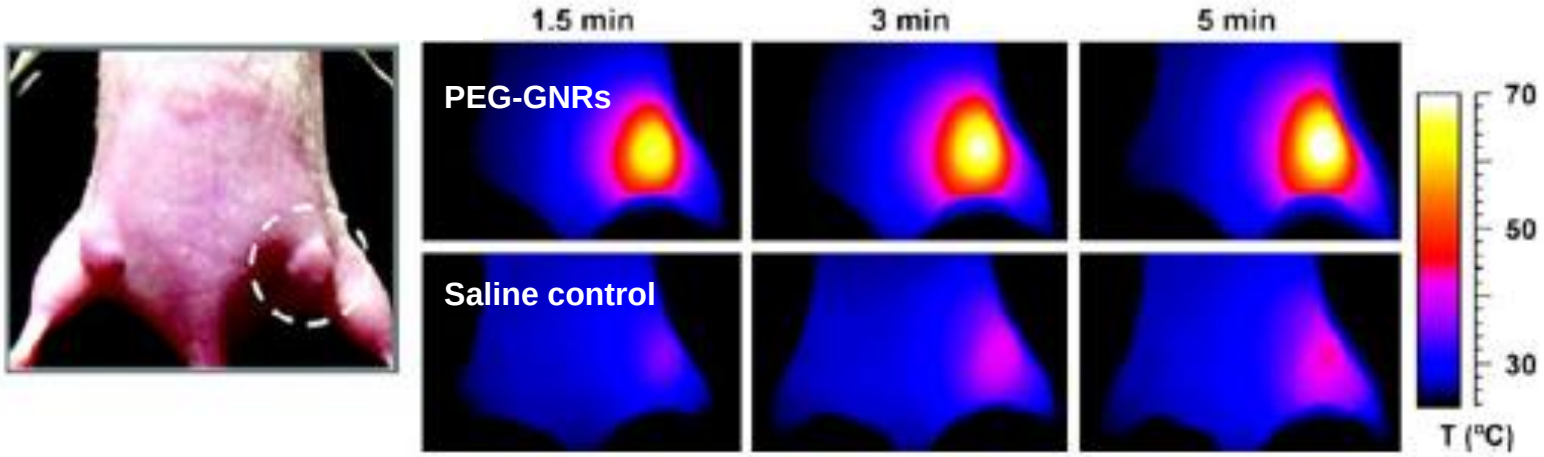
• Wide range of shapes and sizes 2 nm up to 100 nm for spheres, its optical properties can be tuned

• Penetration depths of the emitted light is a limitation but potential use as **optical probes in real-time guided surgery**

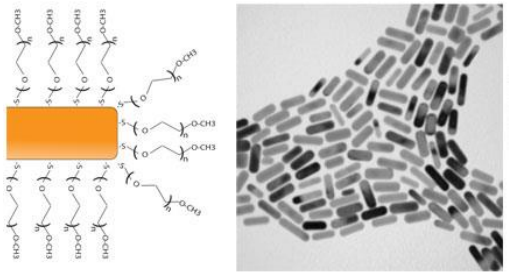
• Absorbs light which is almost 100% converted to heat → Potential use in **phototmermal therapy**

Examples

Photothermal ablation therapy with gold nanorods



1) Passive uptake in MDA-MB-435 tumour xenograft by EPR effect
2) 72 h p.i laser light (810 nm) is absorbed and transformed into heat
3) The heat (50-60 ^{o}C) ultimately kills the nearby (cancer)cells (coagulation necerosis) (>60^{o}C, instant cell death)



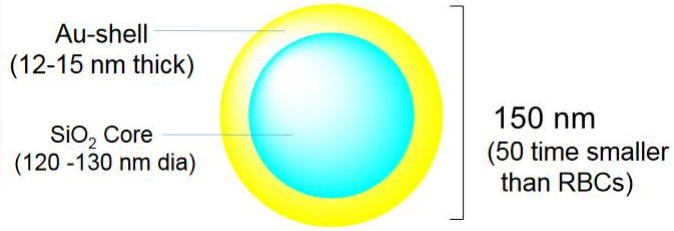
Cancer Res. **2009**, 69:3892–3900

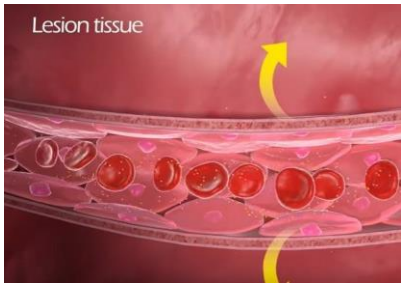
Examples

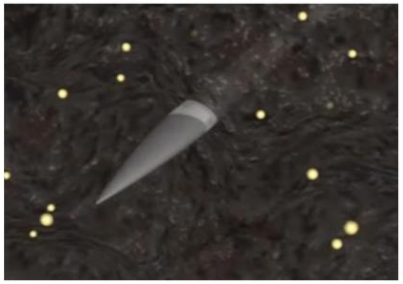
Photothermal ablation therapy with AuroLase

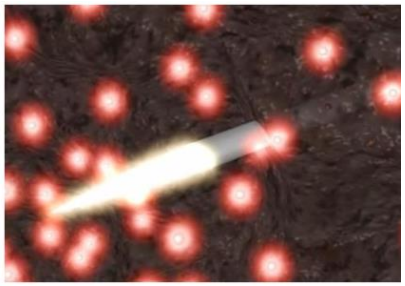
(PEG-coated silica-gold nanoshells)

Red blood cell









Near infrared light facilitated thermal ablation

1) A solution of particles is infused and allowed to be taken up in the lesion (EPR effect)
2) A laser fiber is inserted near or into the tumour and laser energy (750-800 nm) is applied
3) The particles absorb the light energy and convert it to heat
4) Cell death occurs and the tumour shrinks
5) The body reabsorb dead tissue and the lesion heals

Prostate cancer, metastatic lung cancer

Tumor Ablation and Nanotechnology, *Mol Pharm*. **2010**; 7(6): 1880–1898

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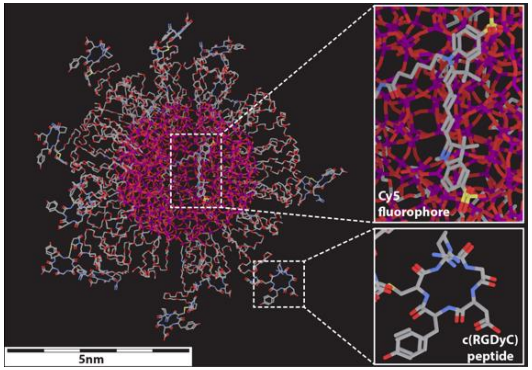
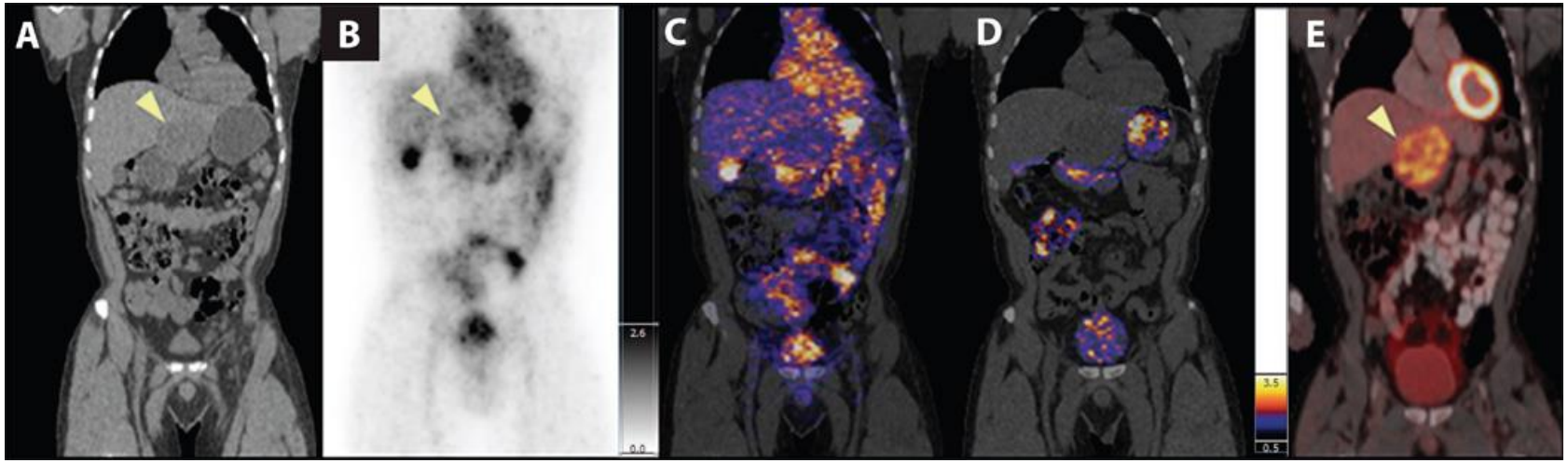
Examples

Multi-functionalised SiO_2 particles

- **Cornell Dots in clinical trials**
  - PEG coating for **solubility** and **immuno disguise**
  - cRGDY peptide for **active targeting** αvβ3 receptor overexpressed in cancers
  - ^{124}I radiolabel for **PET imaging**
  - NIR fluorophore for **fluorescent imaging**





CT | PET (^{124}I-C-dot) | PET-CT 4 h p.i (^{124}I-C-dot) | PET-CT 24 h p.i (^{124}I-C-dot) | ^{18}F-FDG PET comparison

*Science Translational Medicine 6(260),**2014,** 260ra149*

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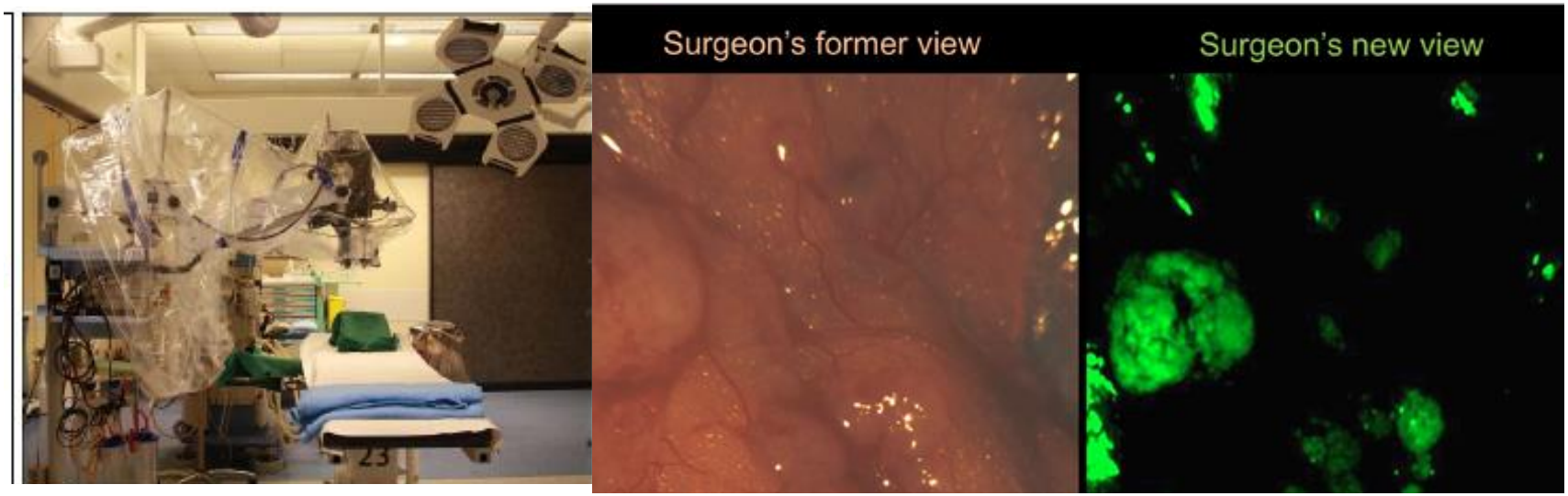
Examples

Real-time image-guided surgery using a fluorecent probe



- Real-time image-guided surgery
  - Proof-of –priniciple clinical study: a woman with ovarian cancer (2011) using a folate-fluorescein conjugate probe
  - The number of tumor deposits detected by surgeons when guided by tumor-specific fluorescence (median 34, range 8–81) was significantly higher than with visual observation alone (median 7, range 4–22, $P < 0.001$).
  - Nanotechnology applications are under development (e.g. gold nanoparticles for brain tumour imaging and therapy)

Nature Medicine, 2011, 17, 1315–1319

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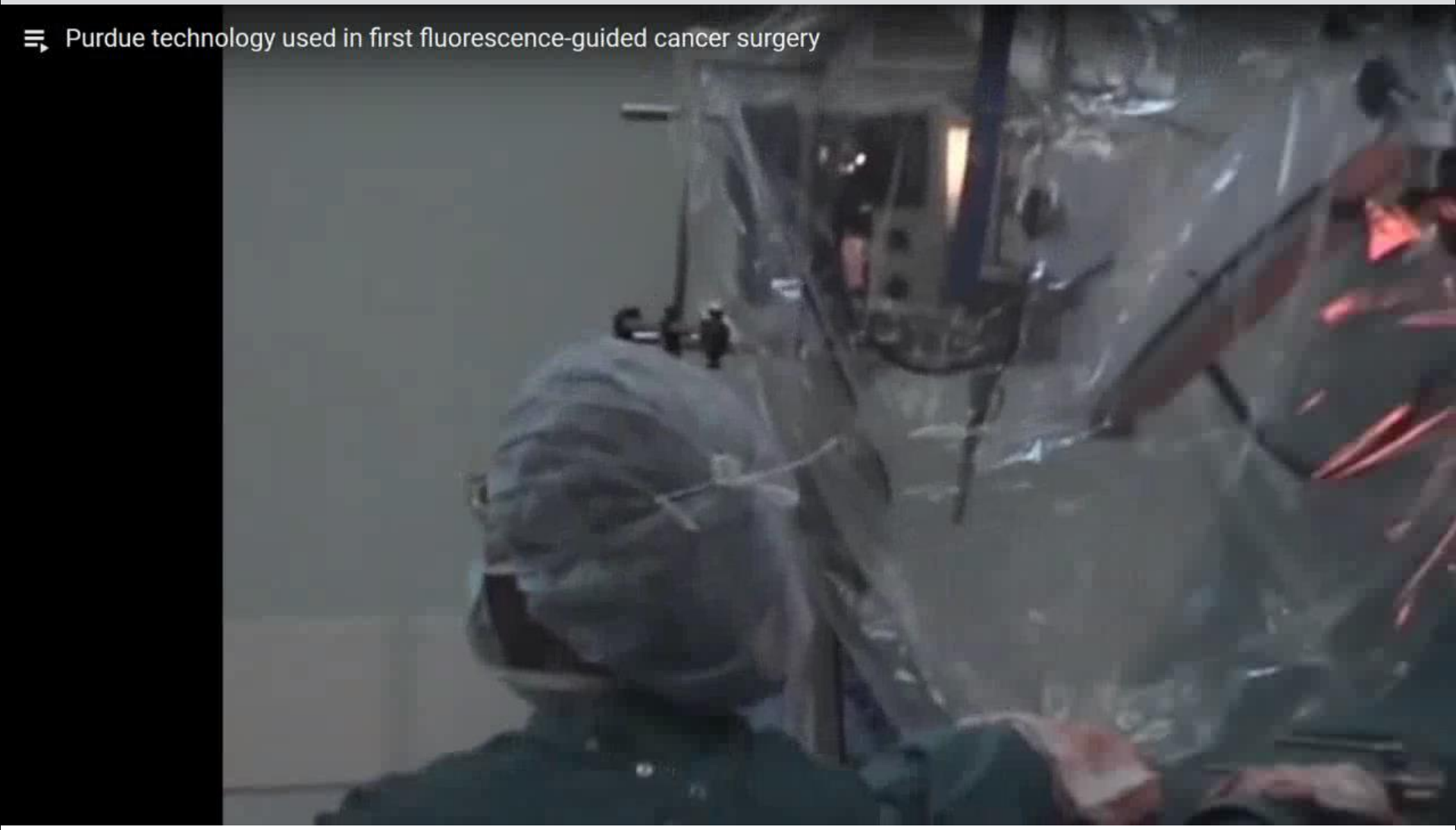
Examples

Real-time image-guided surgery using a fluorecent probe



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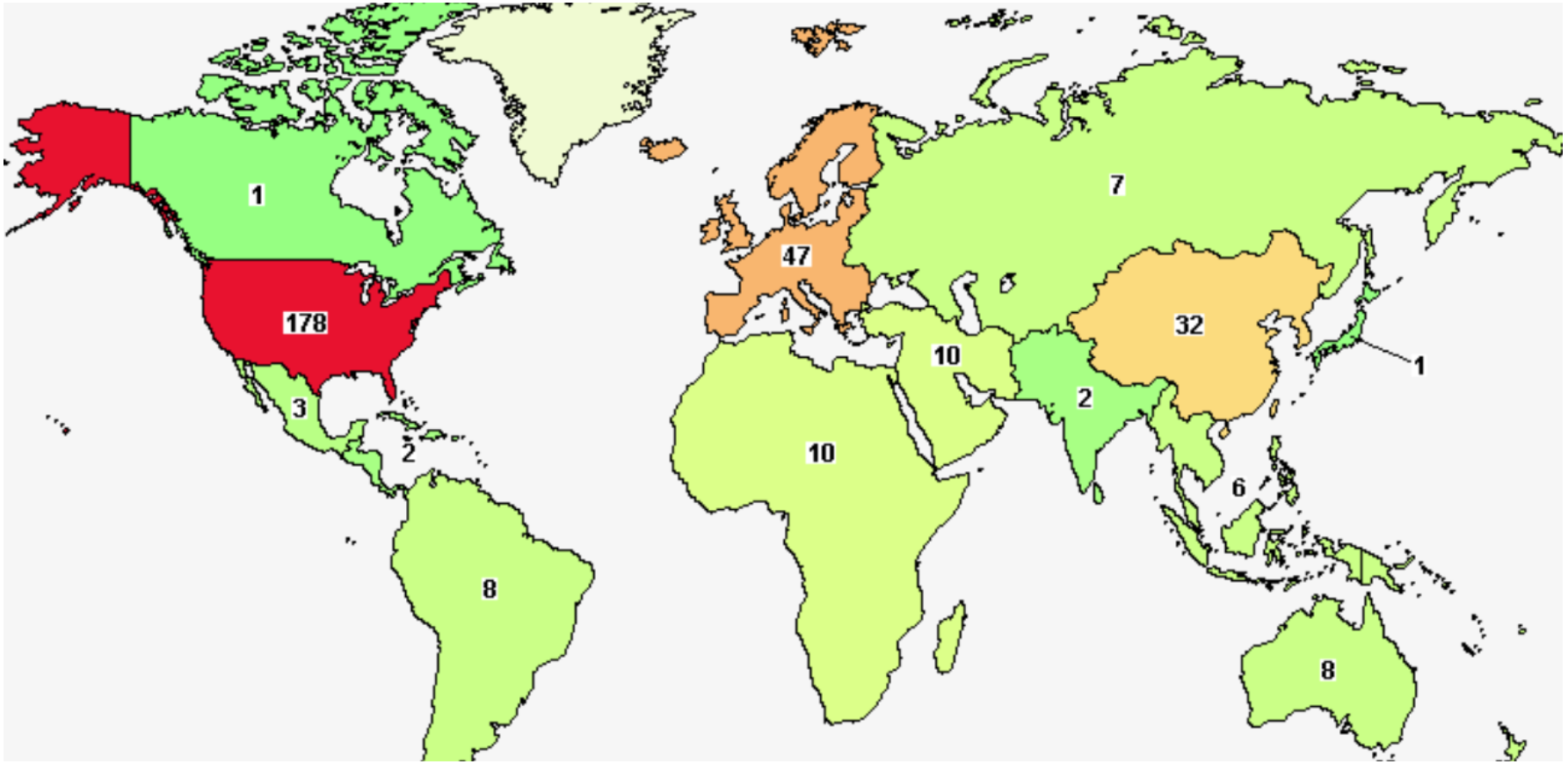
Ongoing Clinical Trials



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Take home messages

- Nanomaterials is already in use in MANY products
- Think of nanoparticles as a platform for multiple functionalities such as **delivery of drugs**, **imaging agents** and "**heat**"
- More research needed regarding long term effects (environmental and human toxicity)
- Near future: Clinical trials

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References and further reading

Nanotheranostics- Application and Further Development of Nanomedicine Strategies for Advanced Theranostics, *Theranostics* **2014**, 4(6), 660-677

Nanotheranostics for personalized medicine Expert Rev Mol Diagn. **2013**, 13(3), 257–269

Challenges to effective cancer nanotheranostics, *J Control Release*. **2012**, 164(2):177-182

Nanotheranostics for personalized medicine, *Advanced Drug Delivery Reviews*, 64(13), **2012**, 1394–1416