NANOTECHNOLOGY IN ONCOLOGY.
Radiosensitization with gold nanoparticles (GNP) as an almost perfect example

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CONFLICT OF INTEREST

NONE TO DECLARE

NANOTECHNOLOGY

(AMERICAN SOCIETY FOR TESTING AND MATERIALS)

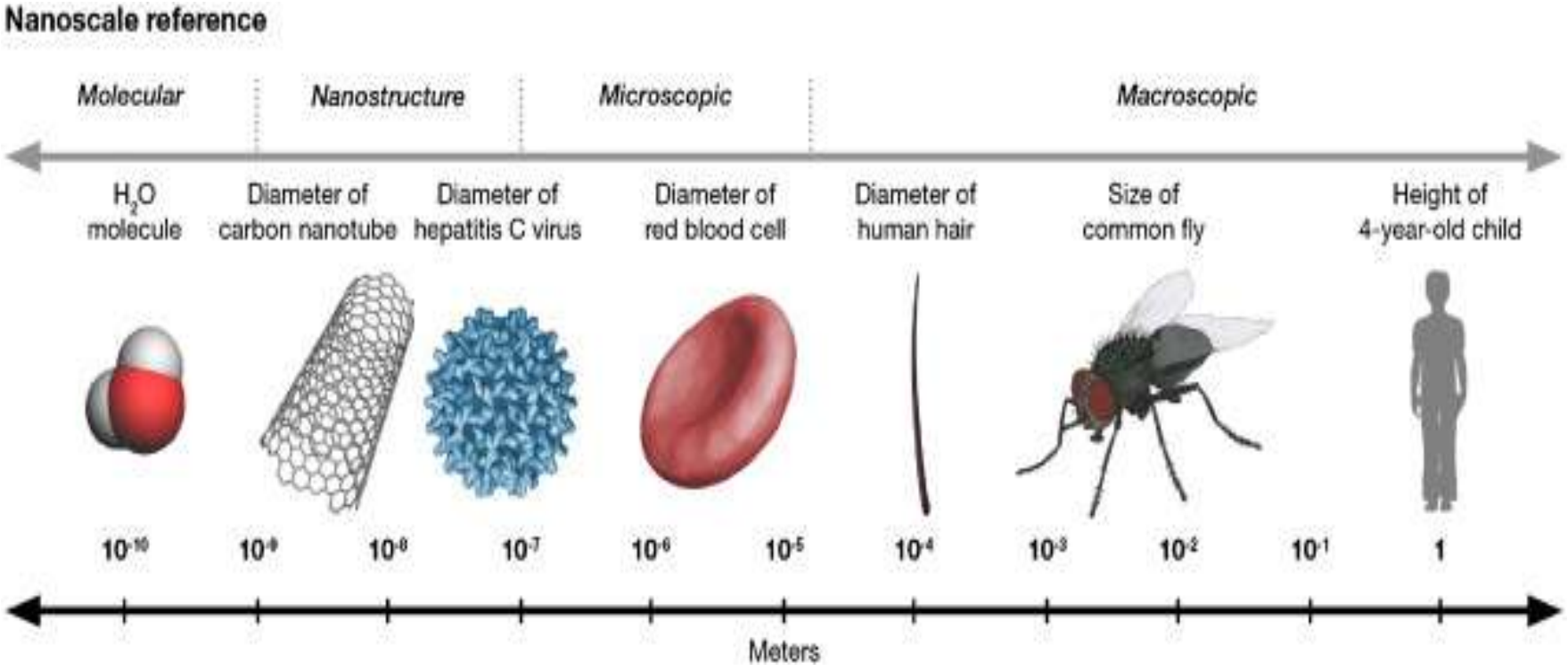
Design, characterization, production and application of

structures, devices and systems

by controlling shape and size

at a nanometric scale

Size and scale of nanostructures relative to commonly known objects.



Particles with lengths 1-100nm in 2 to 3 dimensions

Kateb et al. NeuroImage, 54, Suppl 1, 2011.

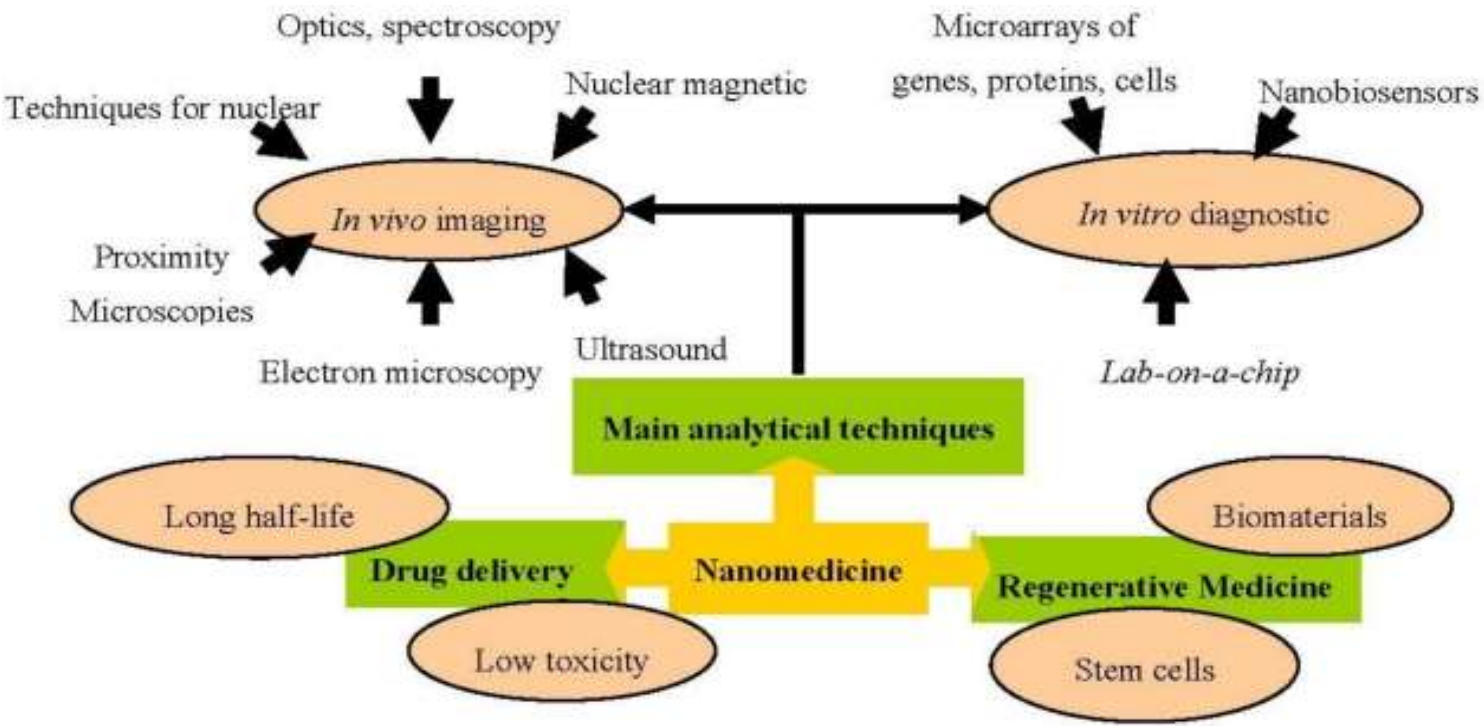
CHARACTERISTICS OF NANOPARTICLES

- DISTINCT GEOMETRIES
- SPECIFIC SURFACE PROPERTIES AND CONDUCTIVITIES
- SUSCEPTIBILITY TO VARIOUS ENVIRONMENTAL STIMULI (light or heat)

ALL CAN BE CONTROLLED!

USE OF NANOMATERIALS

- BECOME FREQUENT IN RECENT YEARS
- IMAGING, DRUG AND GENE DELIVERY



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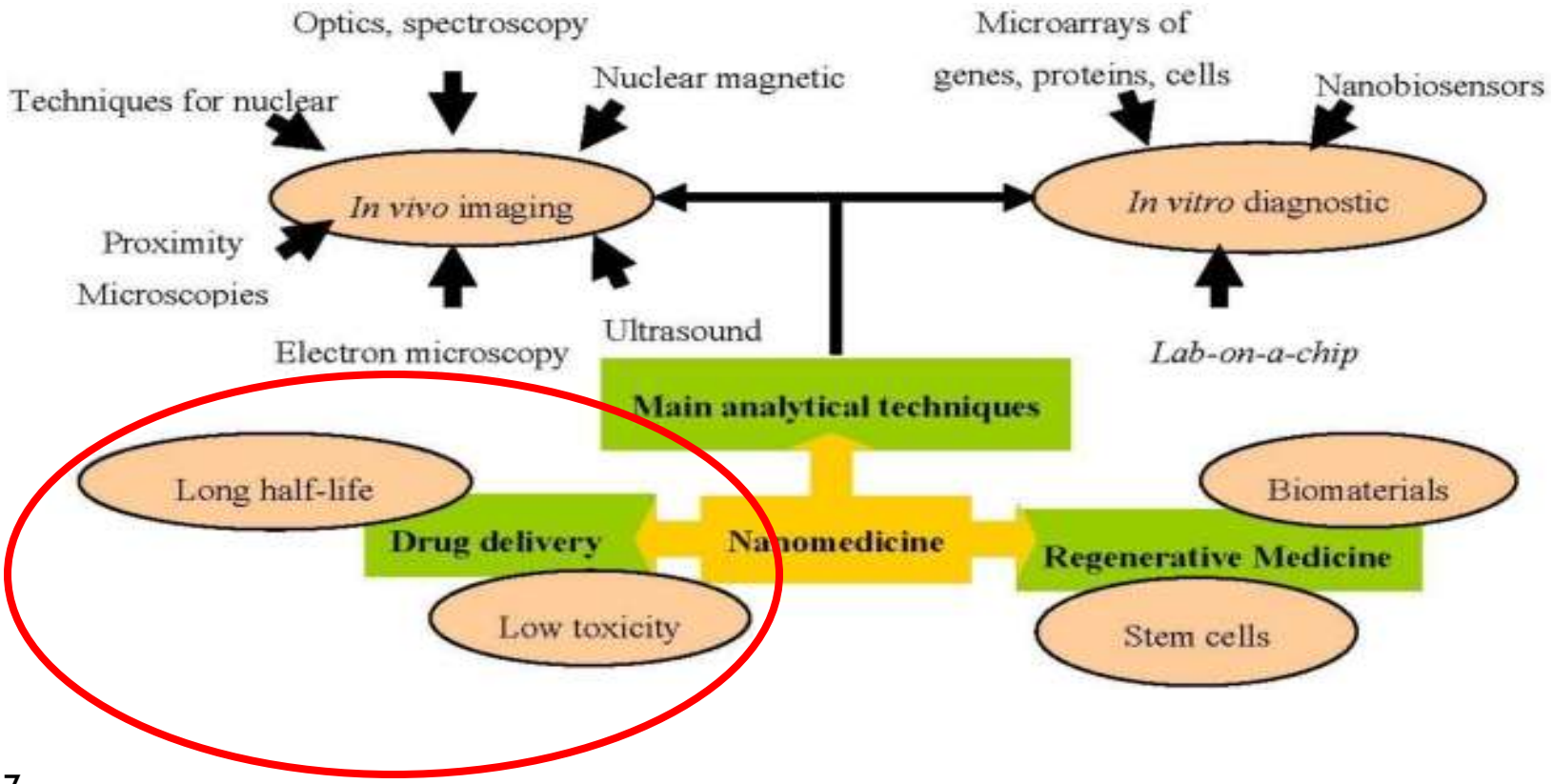
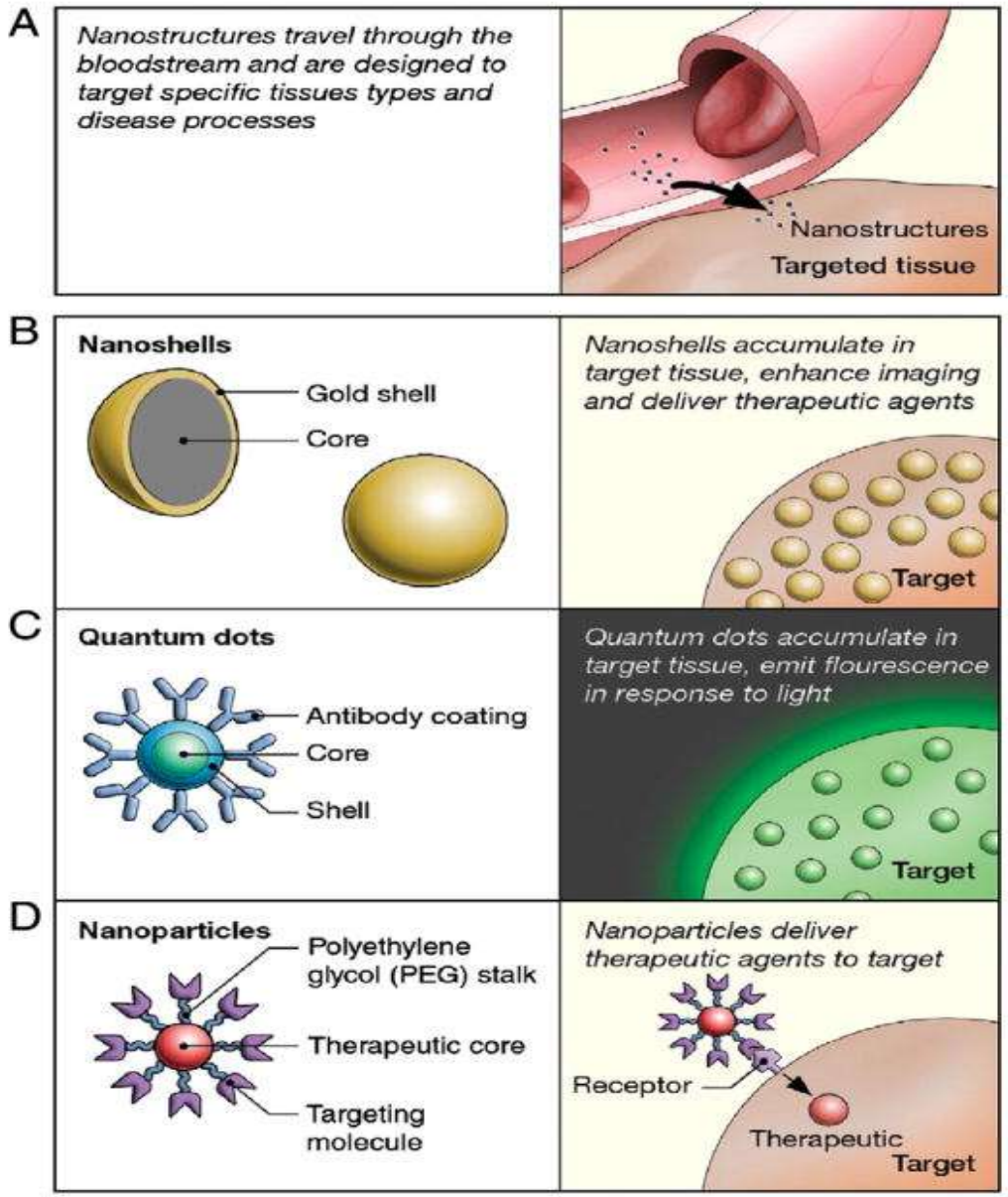


DELIVERY AND ACCUMULATION



GOLD NANOPARTICLES (GNPs)

Unique physiochemical properties

- surface plasmon resonance (SPR)
- ability to bind amine and thiol groups

Allows surface modification!

GOLD NANOPARTICLES (GNPs)

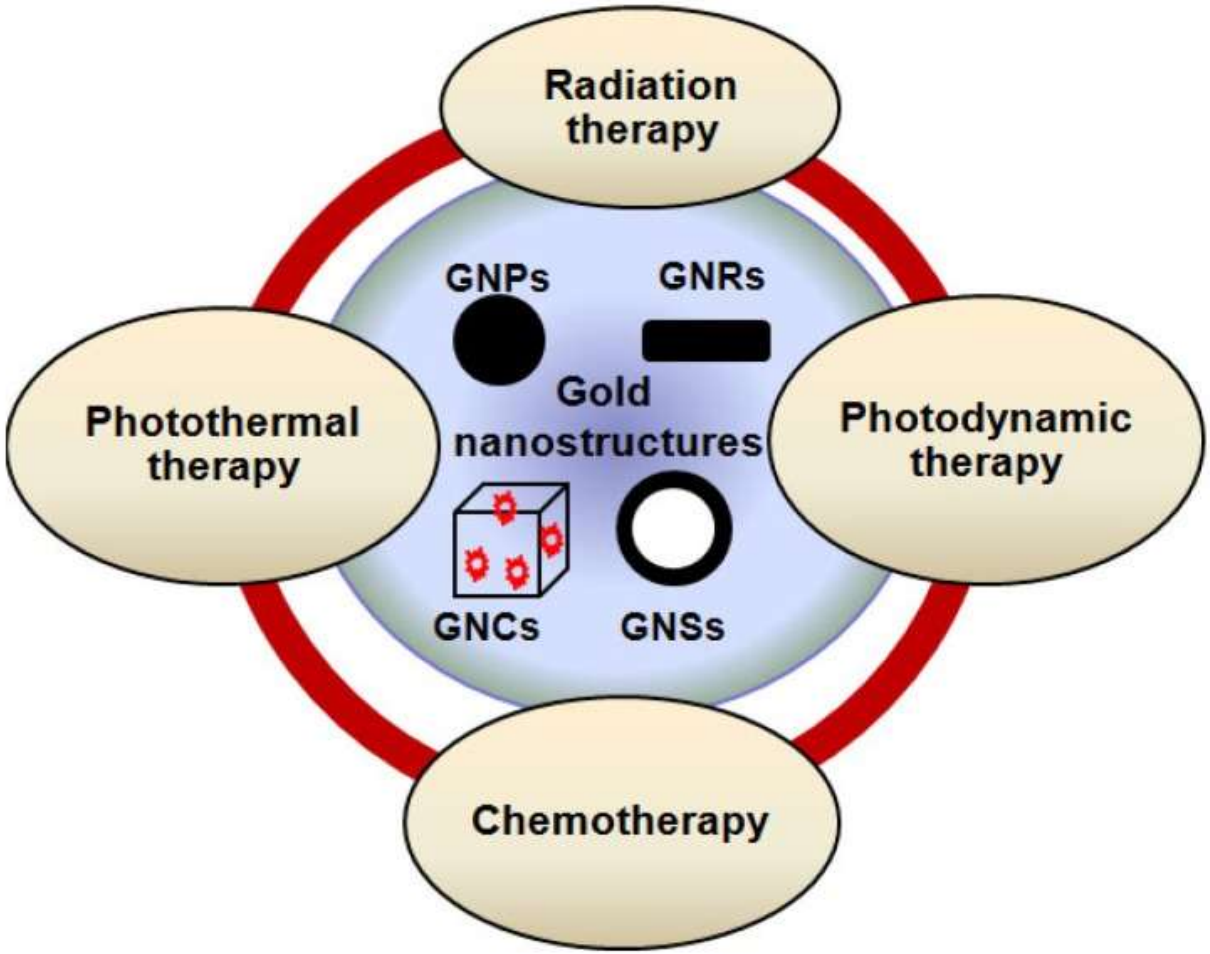
Used in various anticancer approaches

Used in metal-enhanced RT

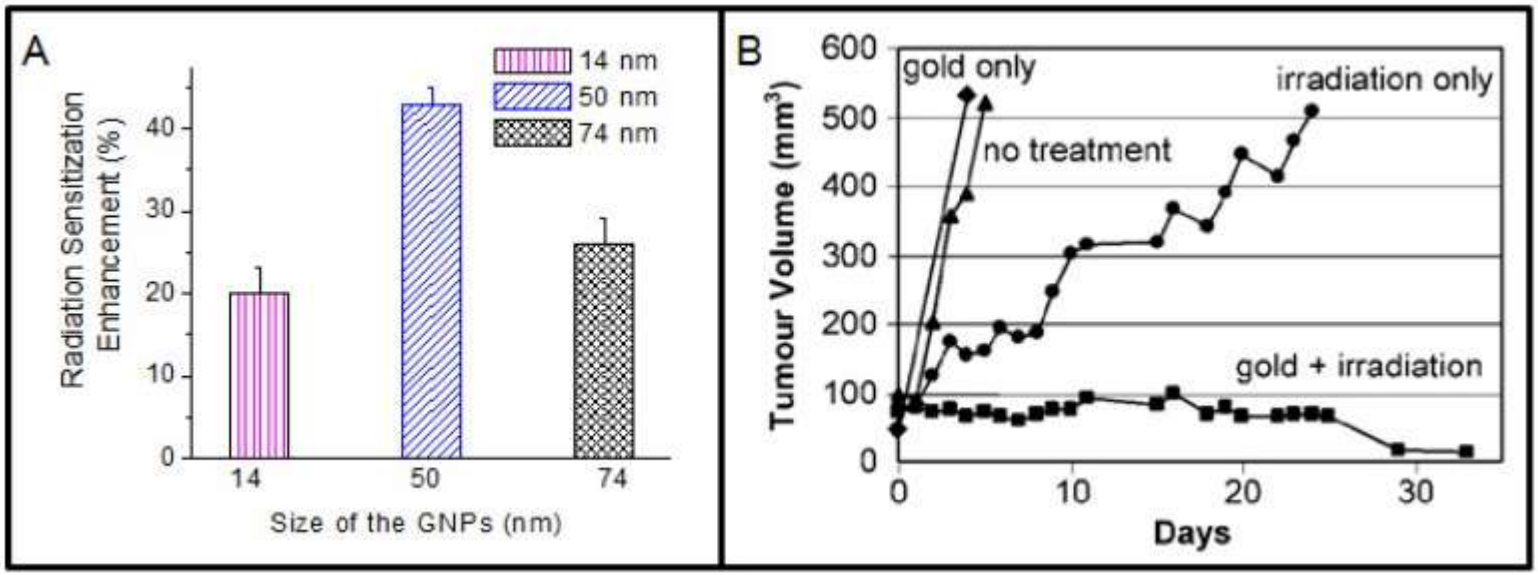
Exploits ability of high Z materials to preferentially increase photoelectric absorption of low kV RT (vs soft tissues)

Leads to enhanced – RT dose deposition at the interface of surrounding tissues

USE OF GOLD NANOSTRUCTURES



RT- GNP EFFECTS



GNPs

Presence in target cells necessary for radiosensitization

Important processes:

- intracellular uptake
- transport
- processing

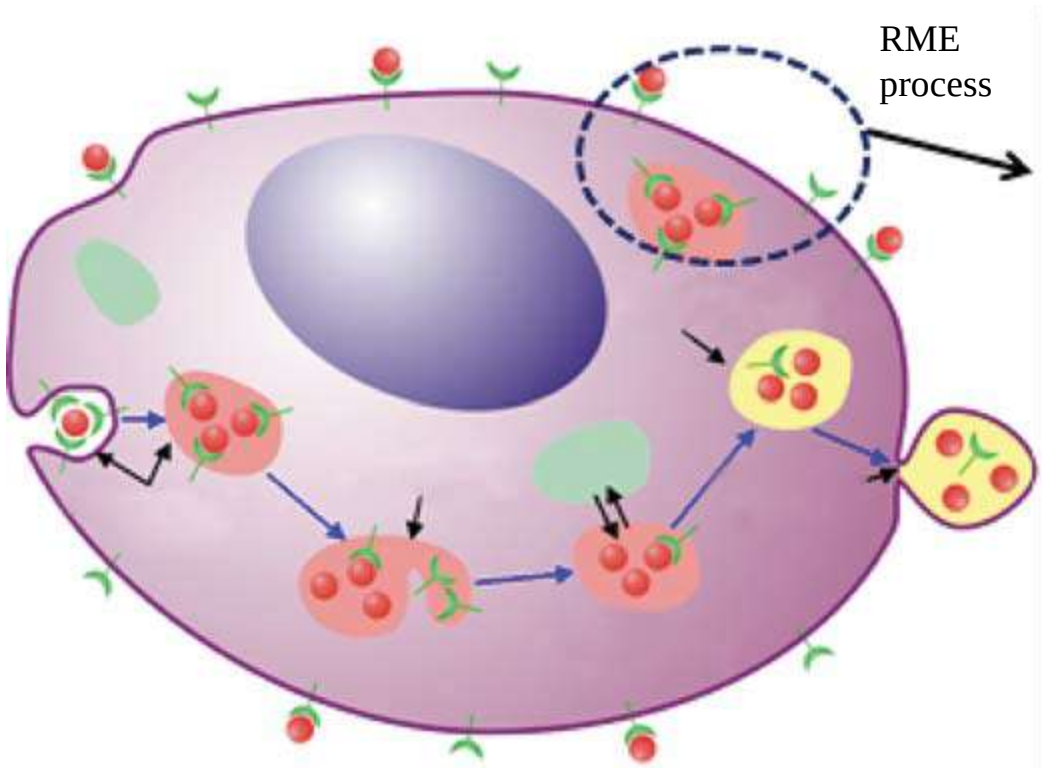
RELEVANT FEATURES OF GNP ENHANCEMENT OF RT EFFECTS

Intracellular uptake, transport and processing	**Endocytosis**	One of the major pathways for uptake Internalization is likely Receptor-mediated endocytosis (RME)
		Rate and extent of GNP uptake: size, shape, surface-coating and charge-dependent
	Intracellular processing	Processing difference between targeted and untargeted GNPs (untargeted GNPs have slower diffusion in in cell cytoplasm)
		Organelle distribution also influenced by uptake mechanism (slower diffusion time for GNPs in lysosomes than in endosomes)

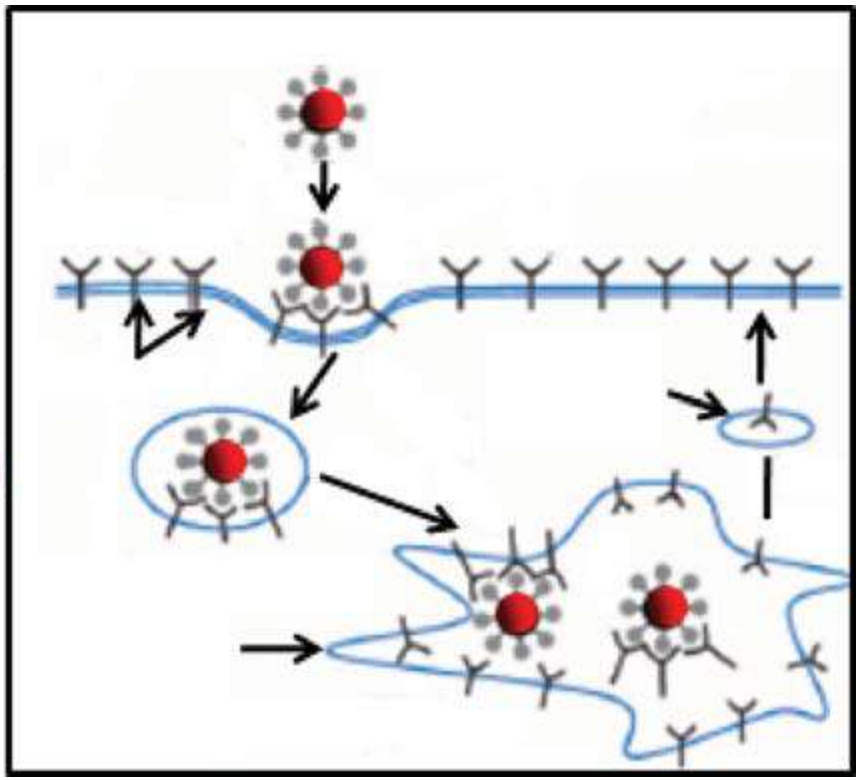
RELEVANT FEATURES OF GNP ENHANCEMENT OF RT EFFECTS

Intracellular uptake, transport and processing	**Exocytosis**	Energy-dependent process
		Dependent on time, size and shape of GNP (better and faster for smaller GNPs; better for GNRs than spherical GNPs)
	Nuclear targeting	GNP surface modification allows crossing cell membrane, but avoiding endocytosis
		Improves nuclear delivery, but needs conjugation with nuclear targeting peptides
		Size-dependent process

PATHWAYS AND PROCESSES INSIDE THE CELL



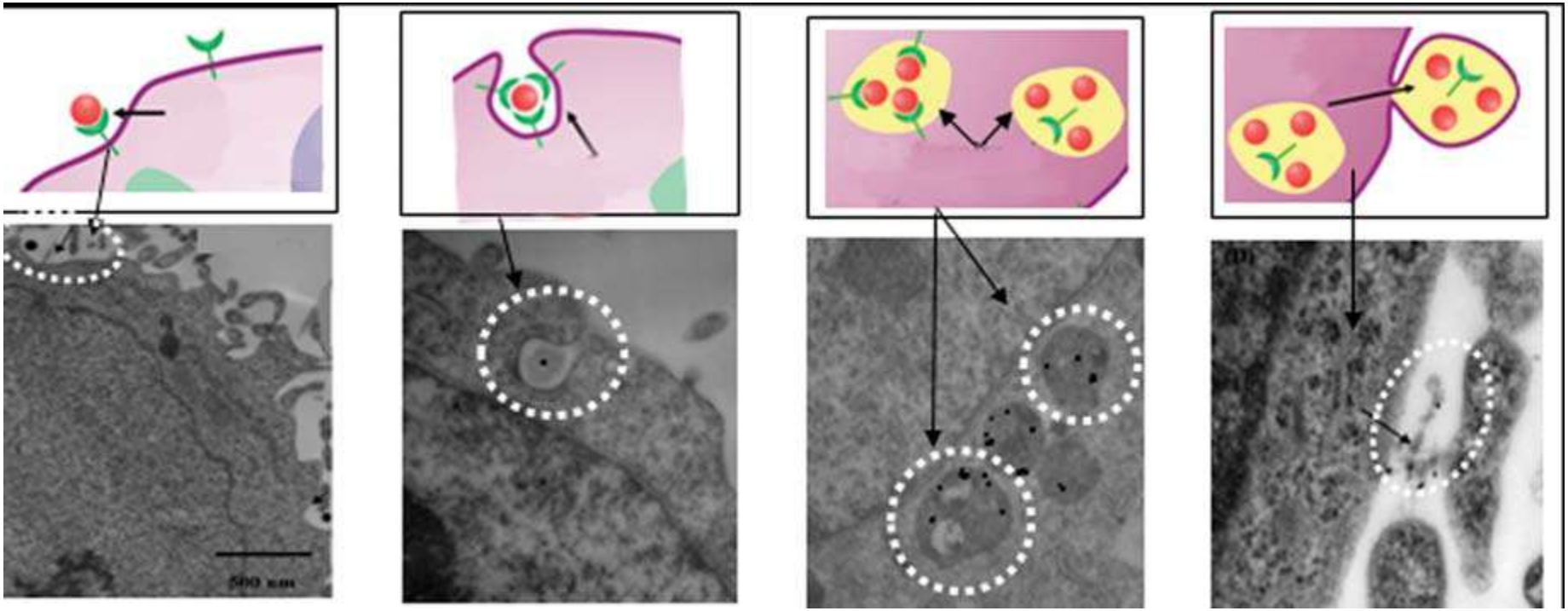
RME process



endo-lysosomal pathway of NPs inside the cell

RME process of NPs inside the cell

Different stages of NP transport through the cell

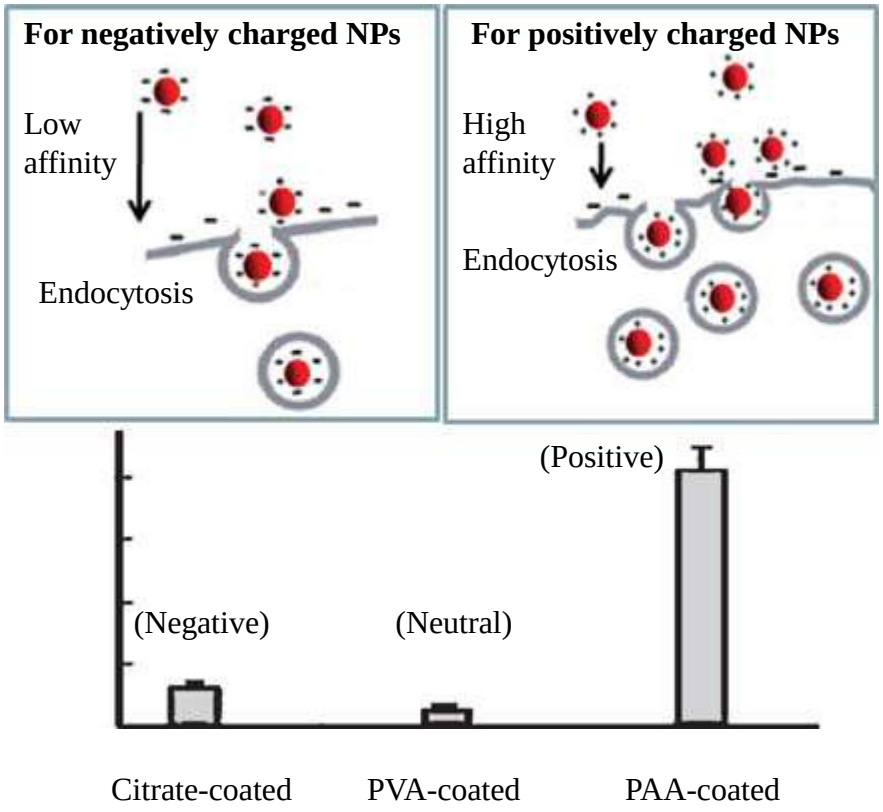


INTERACTION BETWEEN PROTEINS (LIGANDS) ON THE CELL MEMBRANE AND CELL MEMBRANE RECEPTORS

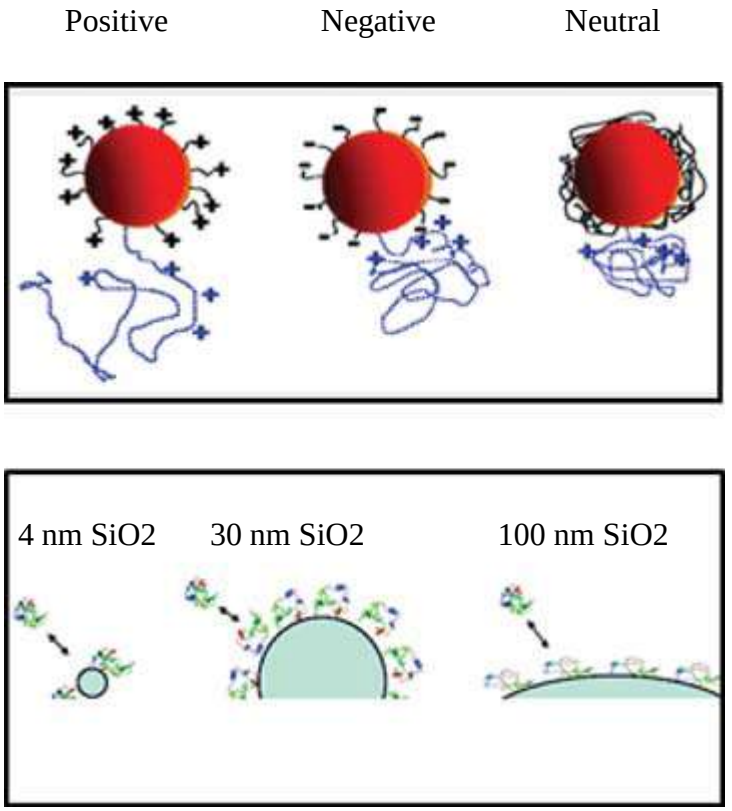
GNPs LOCALIZATION IN ENDOSOMES

FUSION WITH LYSOSOMES TO BE DEGRADED

EFFECTS OF SURFACE CHARGE AND SIZE



Effect of surface charge of GNPs on cell uptake – interactions between cell membrane interactions and GNPs with different surface charges

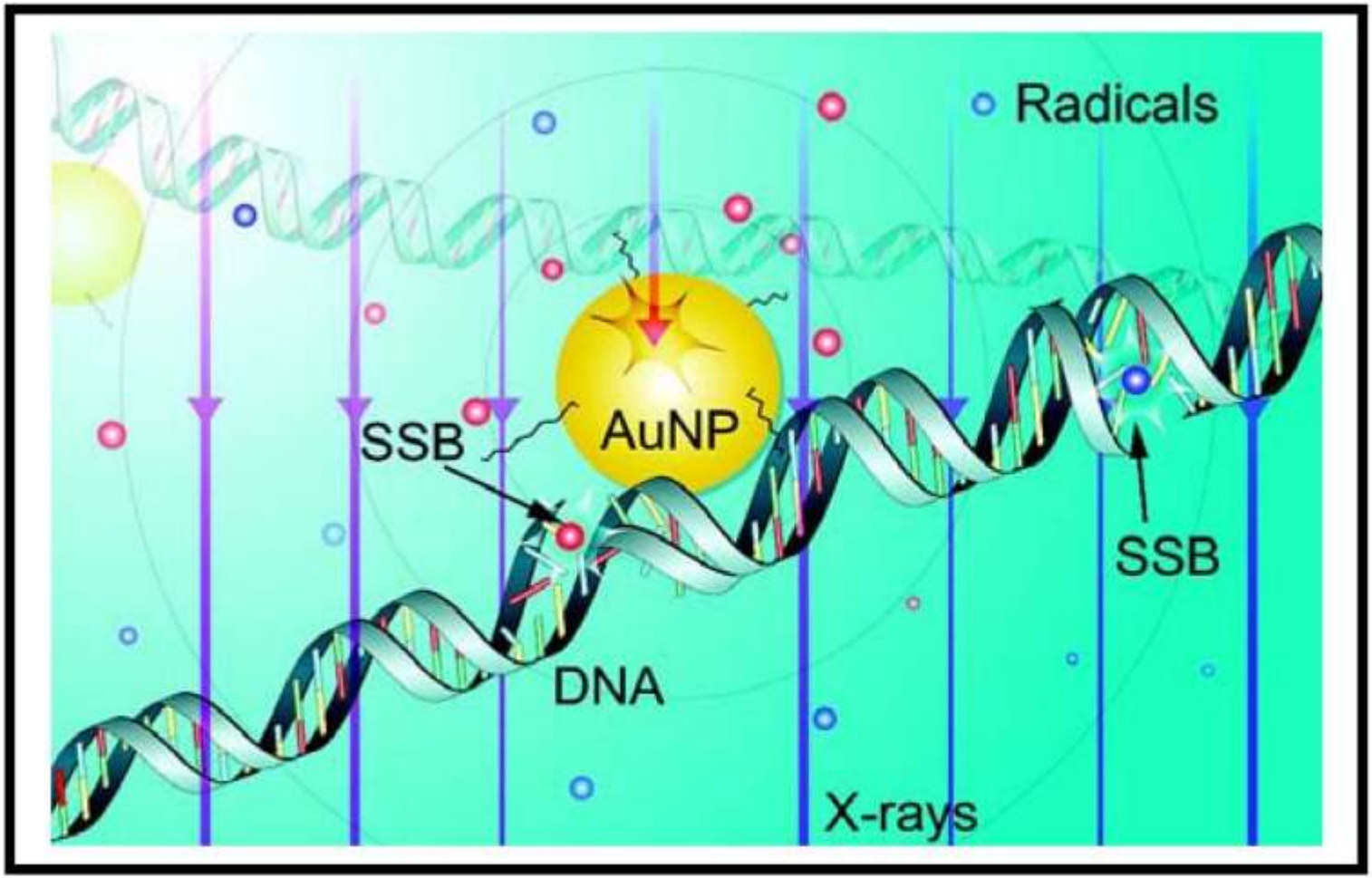


Effect of NP surface charge (top) and size (bottom) of NP on protein structure (top)

RELEVANT FEATURES OF GNP ENHANCEMENT OF RT EFFECTS

Mechanisms of GNP-RT enhancement	RT-induced cell-killing occurs after the damage to DNA, mitochondria and the cell membrane Induction of apoptosis and necrosis implicated in the process of cell damage
	Cell cycle synchronization (accumulation in G2/M) Elevated oxydative stress
	Production of low energy electrons (LEEs) (<20 to <200eV) important aspect of cell damage
	Dependent of many factors such as energy, size and concentration of Gold

Mechanisms of GNP-RT enhancement

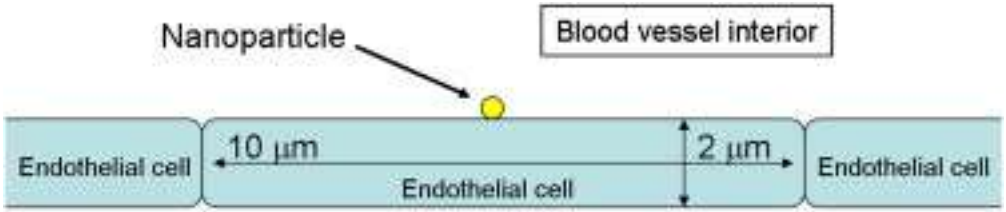


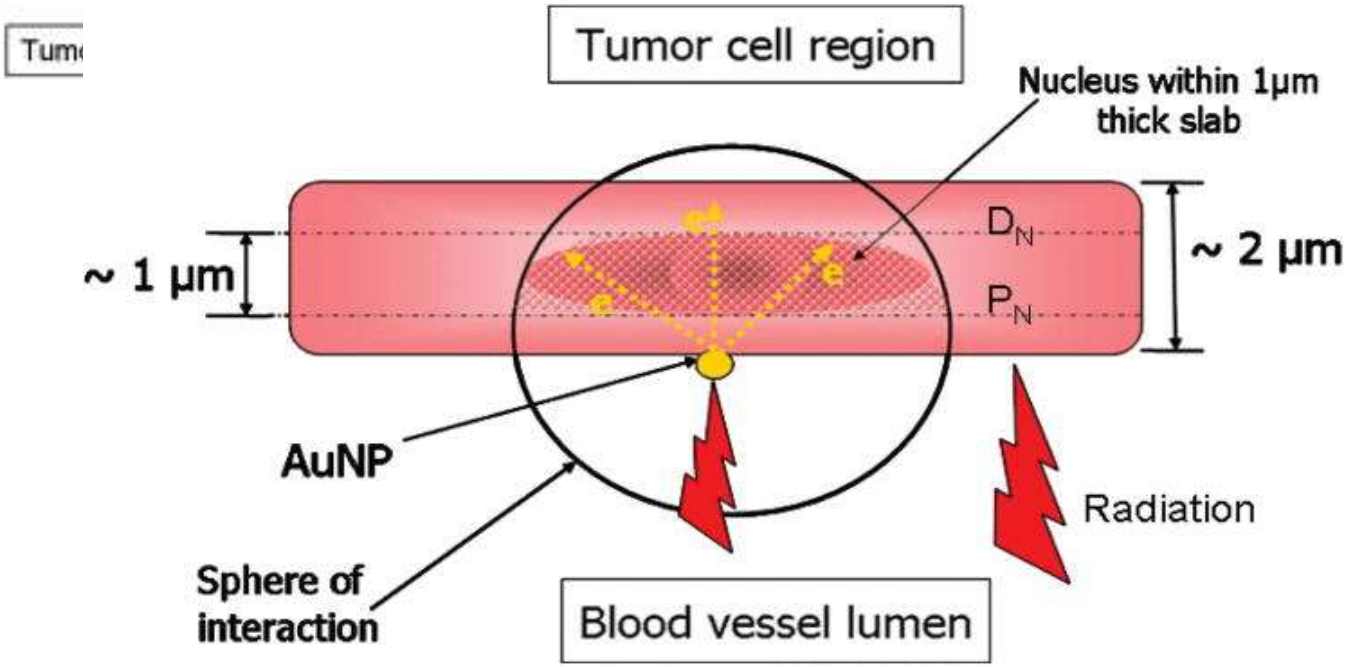
RELEVANT FEATURES OF GNP ENHANCEMENT OF RT EFFECTS

Irradiation energy	Most favorable effects of kV energies, but merging data point to the successful use of MV energies Experimental range of DEFs range: 1.01 (MV) to 2.11-7.5 (kV)
	With recently manufactured Linacs with FFF and with anticancer drugs, clinical application likely
	Dependent on many other factors such as Gold concentration, size, shape

IRRADIATION ENERGY

- Endothelial dose enhancement factor (EDEF) was 1.2 - 4.4
- It came mostly from the low energy (ca. 100 kV) spectrum



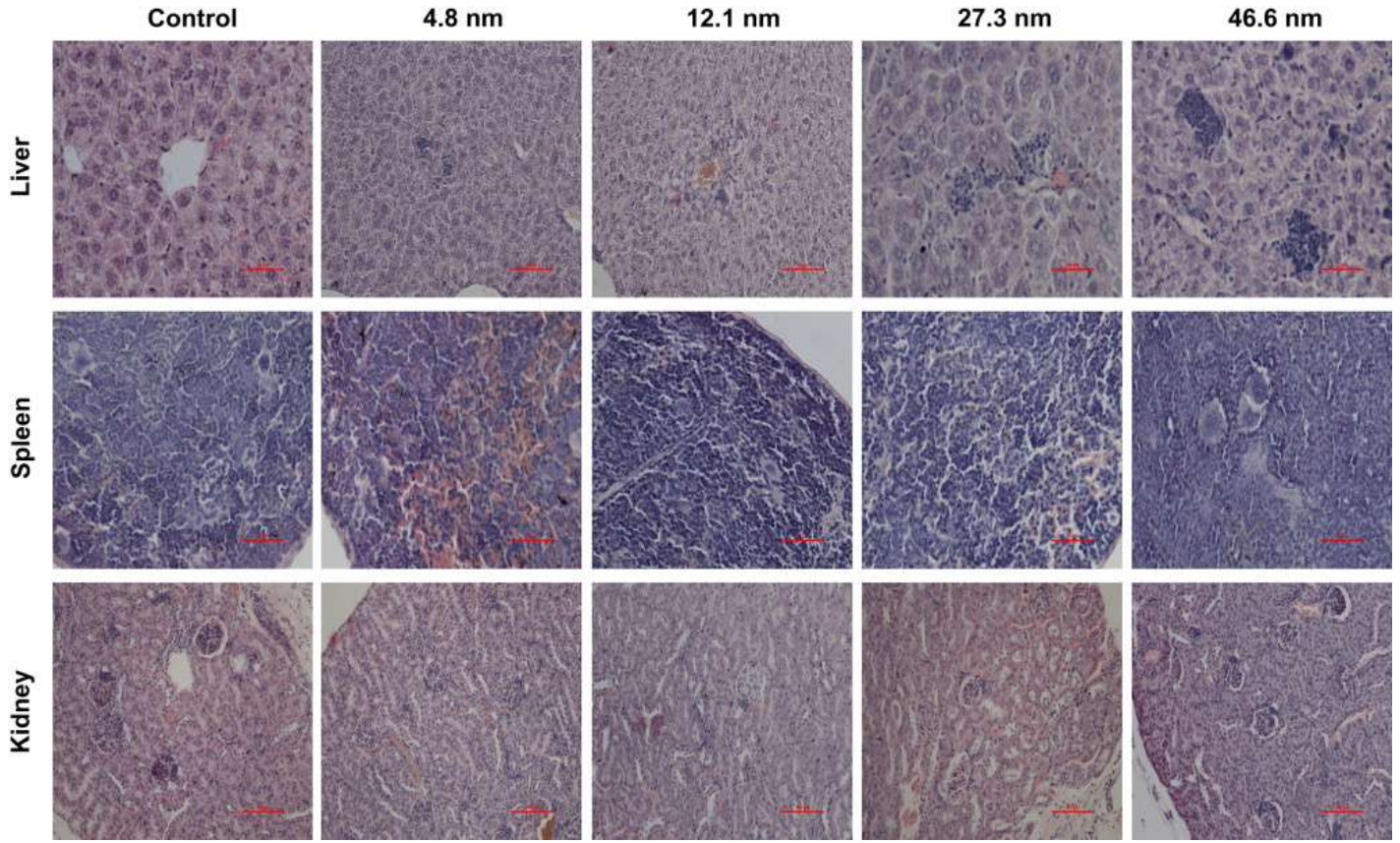


Berbeco et al, IJROBP, 81:270 – 276, 2011

RELEVANT FEATURES OF GNP ENHANCEMENT OF RT EFFECTS

GNP size, shape and toxicity	Need to compromise between GNP size, and other factors influencing their metabolism, distribution and internalization realized
	Shape and surface attachments also important factors when discussing RT-enhancement effects
	Toxicity dependent on: • shape (GNRs vs GNPs) • size (smaller GNPs can also be toxic) • surface characteristics (PEGylated without spleen/kidney damage) • dose (in vitro not toxic at < 250 mM, ionic Au toxic at 25 mM) • administration route (more in oral and IP)

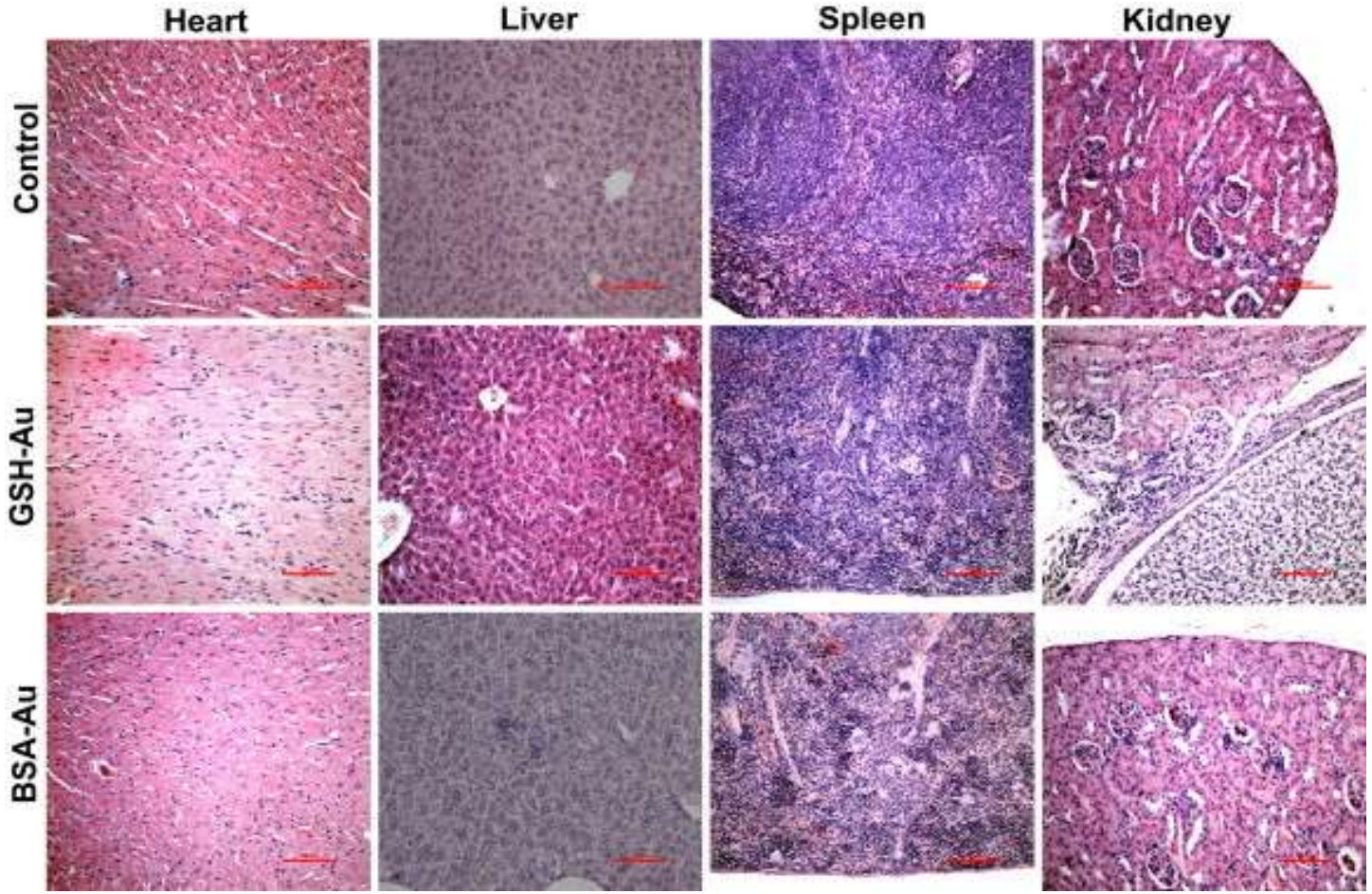
PEGylated GNPs – toxicity on various organs



Various size PEG-coated gold NPs treated mice.
Kidney and spleen don't show appreciable pathological changes, while liver does.

Zhang X-D et al, Biomaterials, 33: 6408 – 6419, 2012.

Toxicity dependence on protection type (GSH vs BSA)



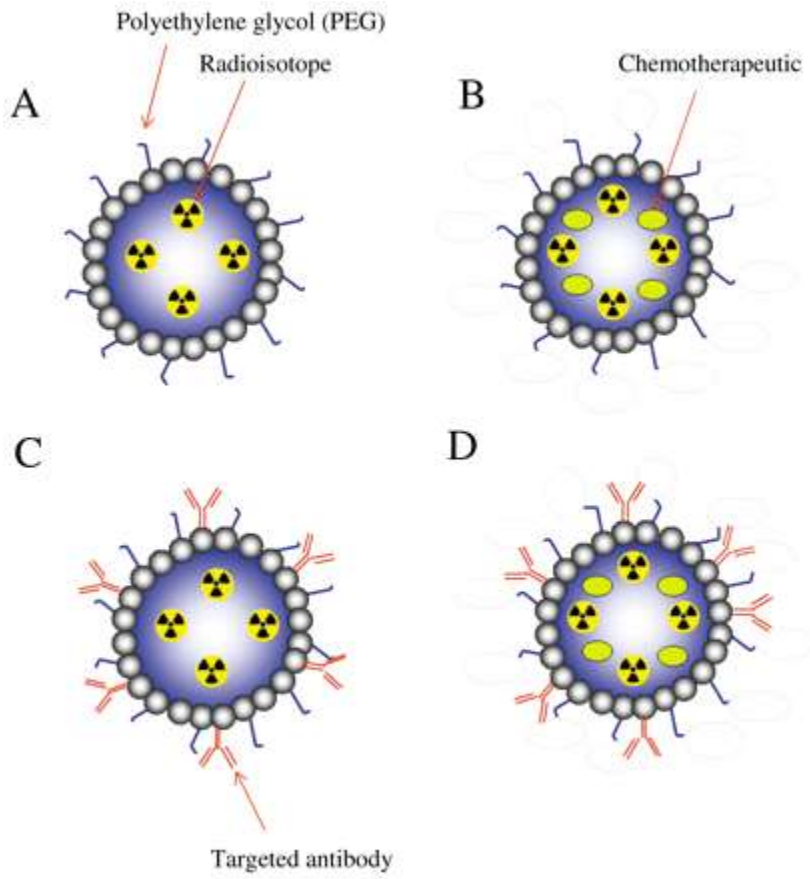
GSH- and BSA-protected Au 25 NCs after 28 days.
Appreciable pathological changes have been found only in liver in the BSA-protected Au 25 NCs.

Xiao-Dong et al. Biomaterials, 33: 4628 – 4638, 2012.

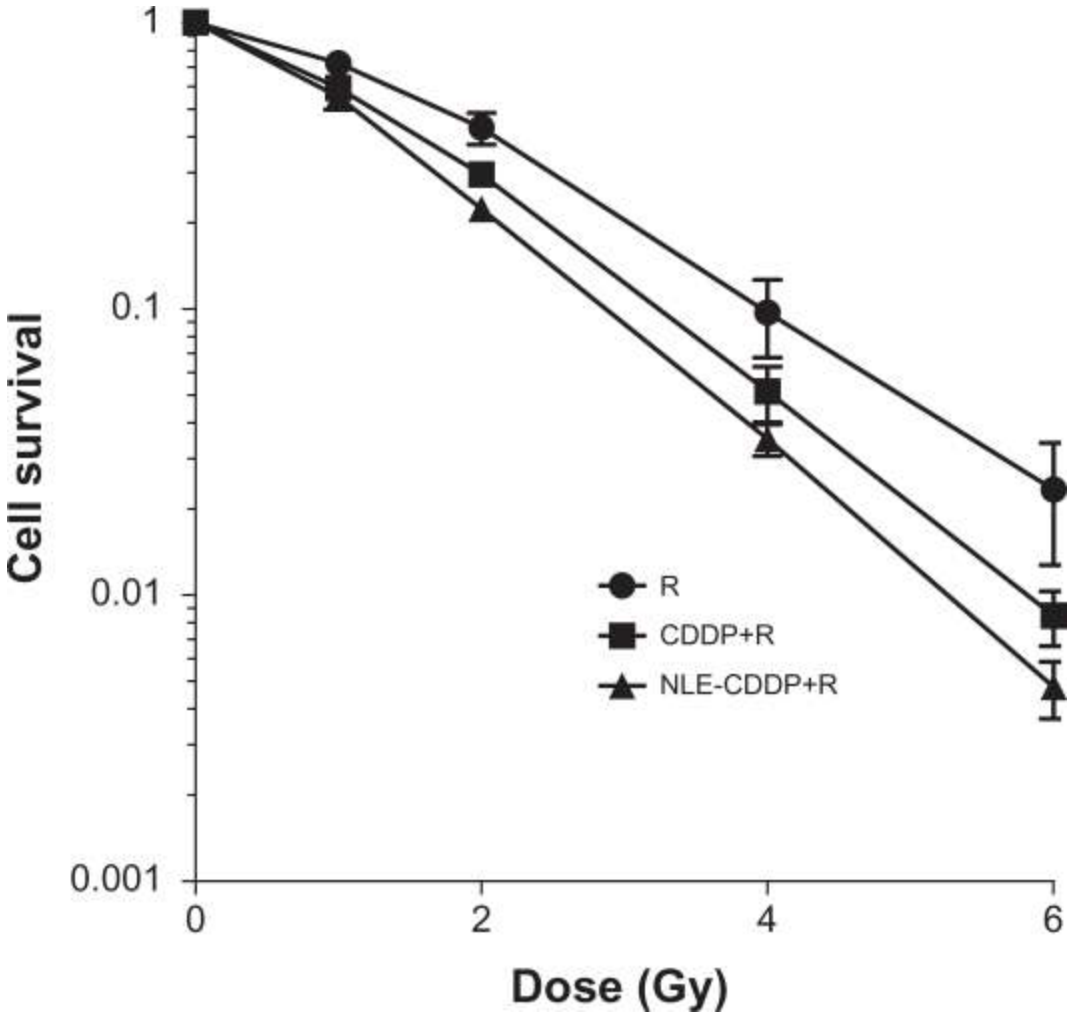
RELEVANT FEATURES OF GNP ENHANCEMENT OF RT EFFECTS

GNP-RTR-anticancer drugs	Few data available, though of potentially substantial application in daily clinical practice
	Cisplatin shown to significantly enhance RT effects Capture of LEE at the site of CDDP significantly enhanced backbone rapture CDDP-DNA complex + GNP : DEFs range 3.0 – 7.5

RT + CHEMO/TARGETED DRUGS



Radiation alone (R) vs combined with NLE-CDDP (NLE-CDDP + R) vs CDDP (CDDP + R)



P = 0.00 for CDDP vs R;
P = 0.00 for NLE-CDDP vs R;
P = 0.043 for CDDP vs NLE-CDDP

Zhang et al, In vitro and in vivo study of a nanoliposomal cisplatin as a radiosensitizer. Int J Nanomed, 6:437-444, 2011

RT-GNP - CLINICAL ASPECTS

- A phase I feasibility trial (8 pts) (Rose et al, IJROBP, 1999)
- WBRT (40Gy in 20 fx in 4 weeks) + boost of 3-5 weekly 5 Gy/fx
- IV iodine contrast administered prior to rotational RT (360 degrees, three planes, 140KV)
- Response of intracranial mets measured by weekly CT scans
- 1 CR and 4 PR, accompanied with no increase of side effects

RT-GNP - CLINICAL ASPECTS

- Libutti et al (Clin Cancer Res, 2010)
- CYT-6091, 27 nm citrate-coated GNPs bound with thiolated PEG and tumor necrosis factor-α (TNF-α)
- 29 pts with various solid cancers unresponsive to previous Tx
- TNF-α 50-600 μg/sqm with no dose-limiting toxicities
- The main side-effect being grade II fever
- 1 PR and 3 SD observed during this study

RT-GNP - CLINICAL ASPECTS

- Pilot study, IV administared Auroshell® particles with photodermal therapy
- Pts with recurrent or refractory H&N cancer
- Interstitial illumination of Auroshell® particles with 808nm laser used
- Post-treatment tumor biopsies to document both nanoparticle and tumor response.

(NCT00848042) at www.clinicaltrials.gov

RT-GNP - CLINICAL ASPECTS

- AuroLase therapy in pts with primary and/or metastatic lung tumors

- IV of AuroShell particles followed by laser illumination for photothermal ablation

(NCT01679470) at www.clinicaltrials.gov

RT-GNP – FUTURE OPTIONS

- Advantage of kV RT – skin and superficial tumours?
- Melanoma, Kaposi sarcoma, H&N nodes, chest wall recurrences, other…?
- MV RT with DEF of 1.1-1.3 means 10-30% less RT dose
- In practice, DEF of 1.2 means decrease from 72 Gy to 60 Gy
- Consider chemo as additional RT- enhancer in deep seated cancers
- Trials needed!

Gracias!