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CIBBIM - Nanomedicina

"Last approaches of nanomedicine applied to cancer"

VII Conferencia Anual de las Plataformas Tecnológicas de Investigación Biomédica: Medicamentos Innovadores, Nanomedicina Tecnología Sanitaria y Mercados Biotecnológicos
El Reto en Salud

Barcelona, 4 y 5 de Marzo de 2014

Dr. Simo Schwartz Jr

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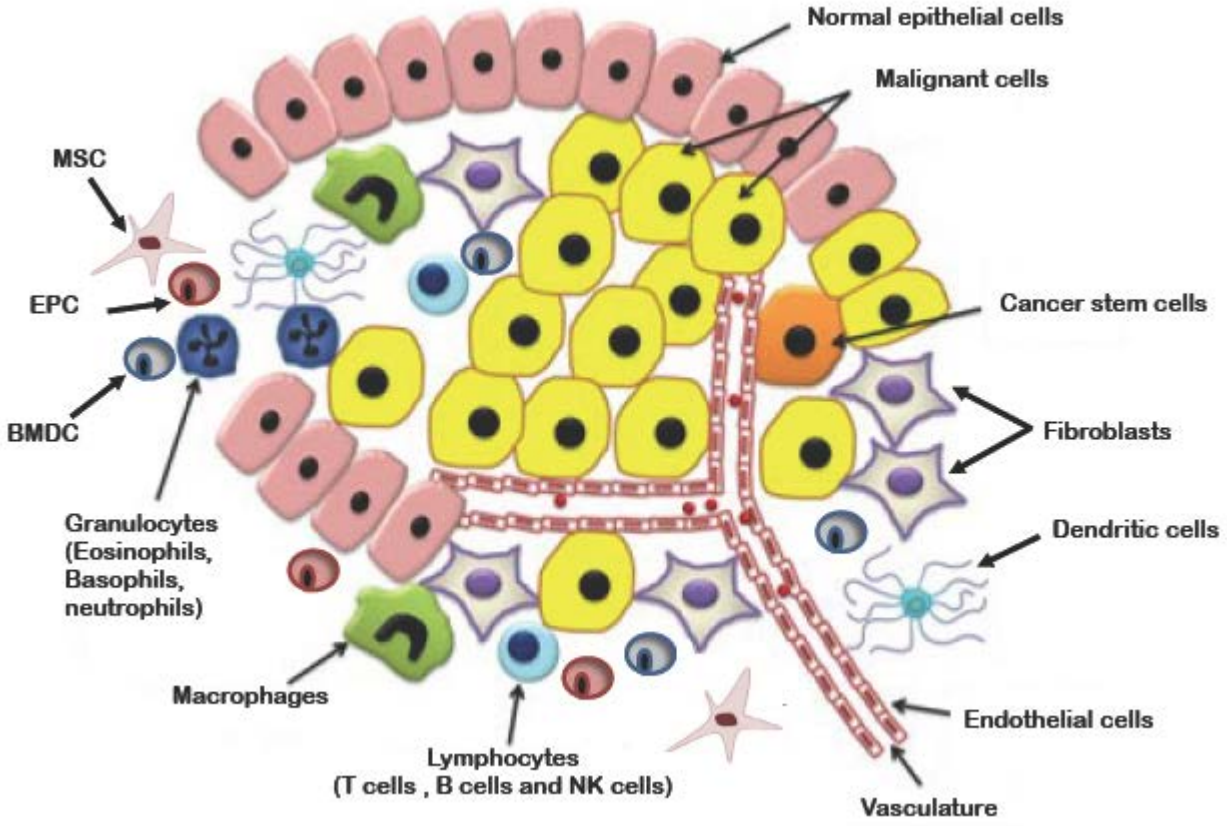
CIBBIM-Nanomedicine

www.cibbim.eu

Cancer is a complex multidimensional habitat

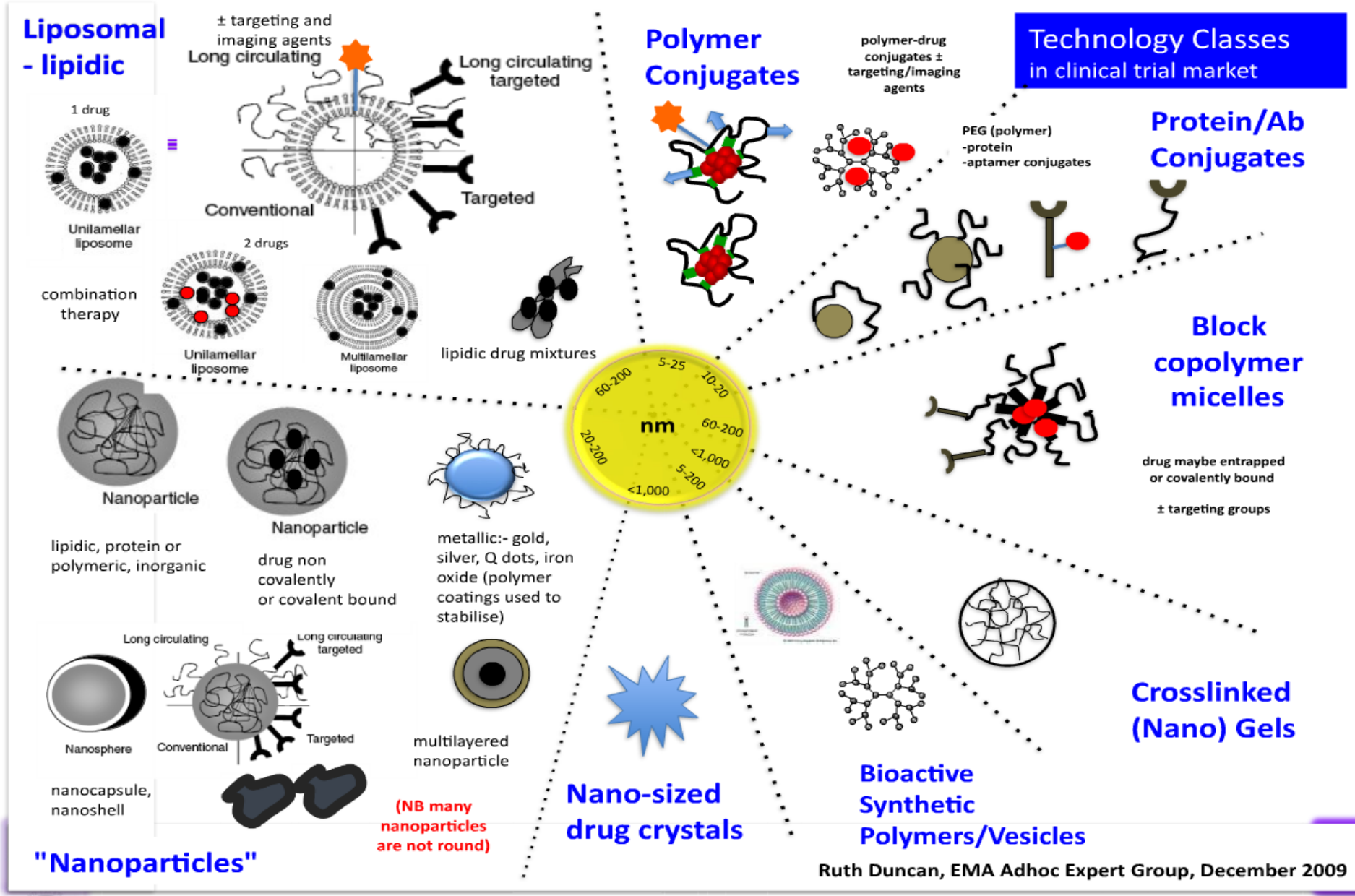


From Upreti et al., translational cancer research, 2(4) August 2013(Modified from www.Cernostics.com)

Need improved "holistic" treatments to improve Survival

Nanomedicines can be more "holistic" in many senses than classical drugs

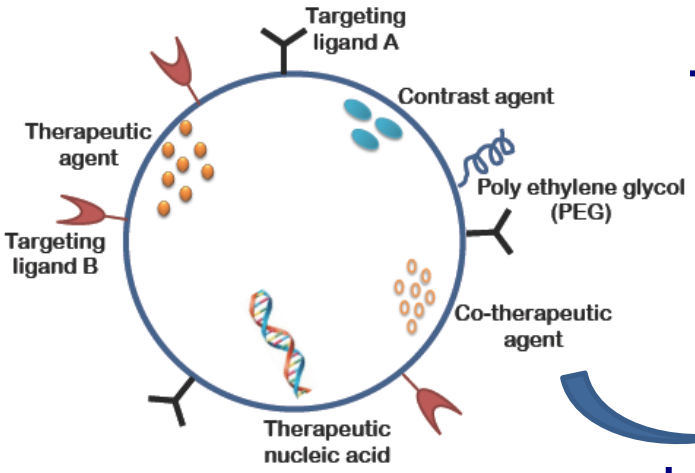
Different nanomedicines. Same goals: Therapy, Diagnostics, or Theranostics.



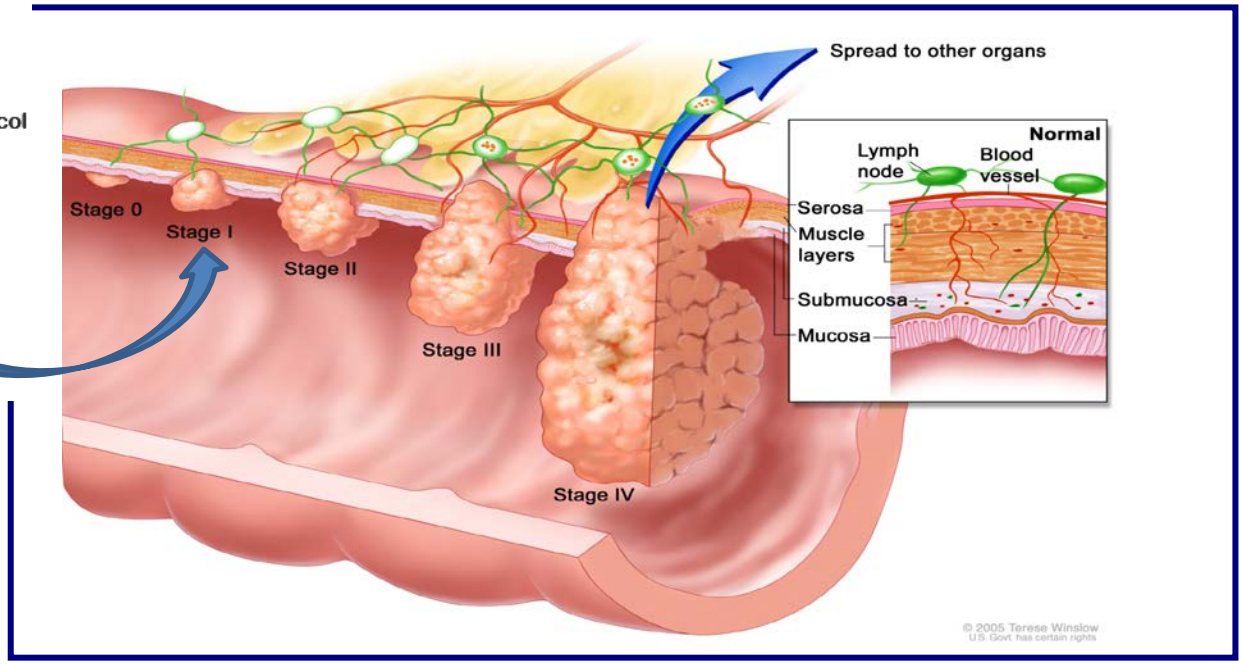
Ruth Duncan, EMA Adhoc Expert Group, December 2009

Few main Goals have to be addressed urgently:

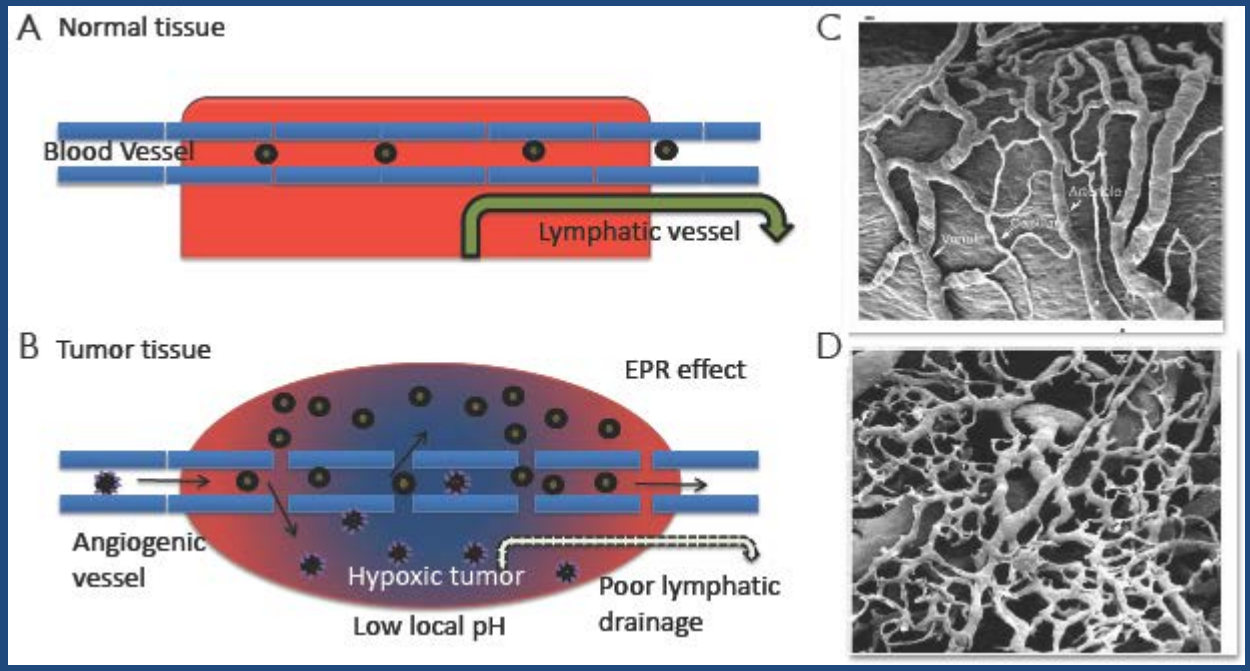
1. Avoid tumor resistance to current therapy.
2. Avoid metastatic spread of the disease.
3. Avoid system toxicity of current drugs



From Upreti et al., translational cancer research, : 2(4) August 2013



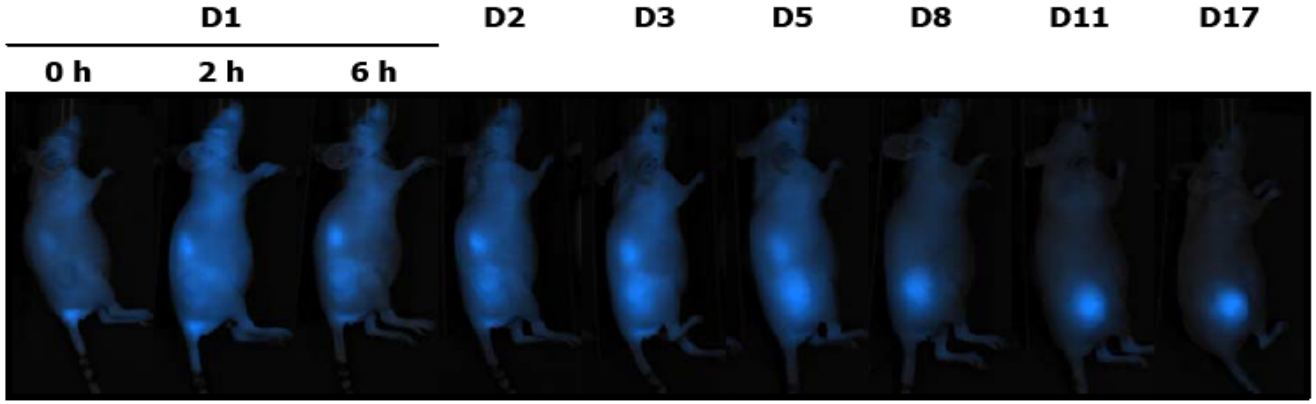
Pasive Targeting. Enhanced Permeability Retention (EPR)



From Upreti et al., translational cancer research, 2(4) August 2013

1. T-DES-polyacetal.Cy5.5 Tumor Accumulation

A)



B)

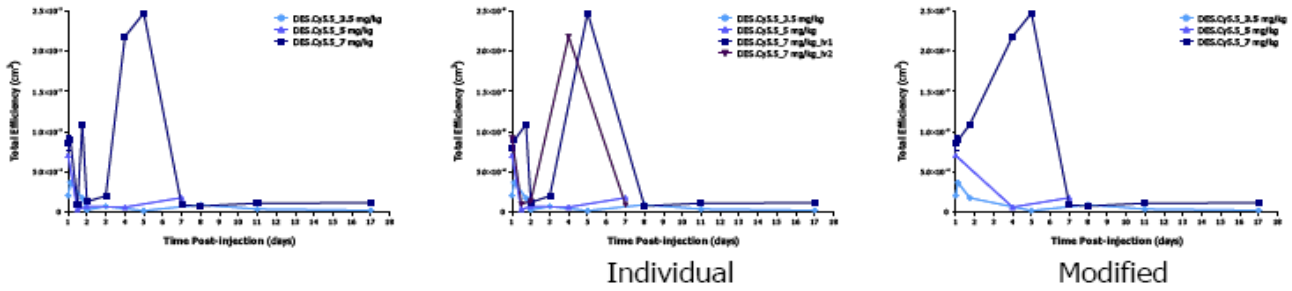
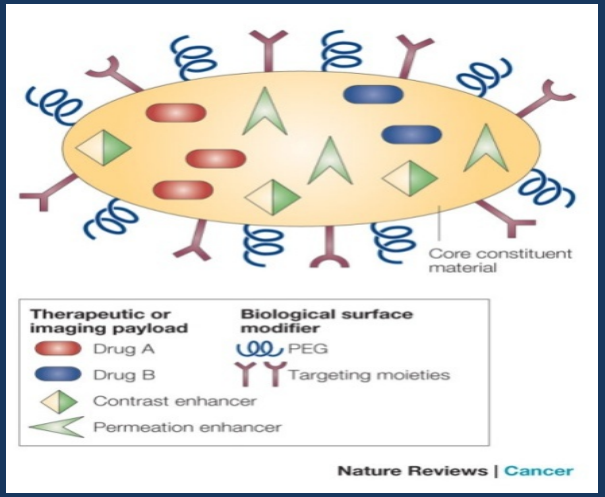
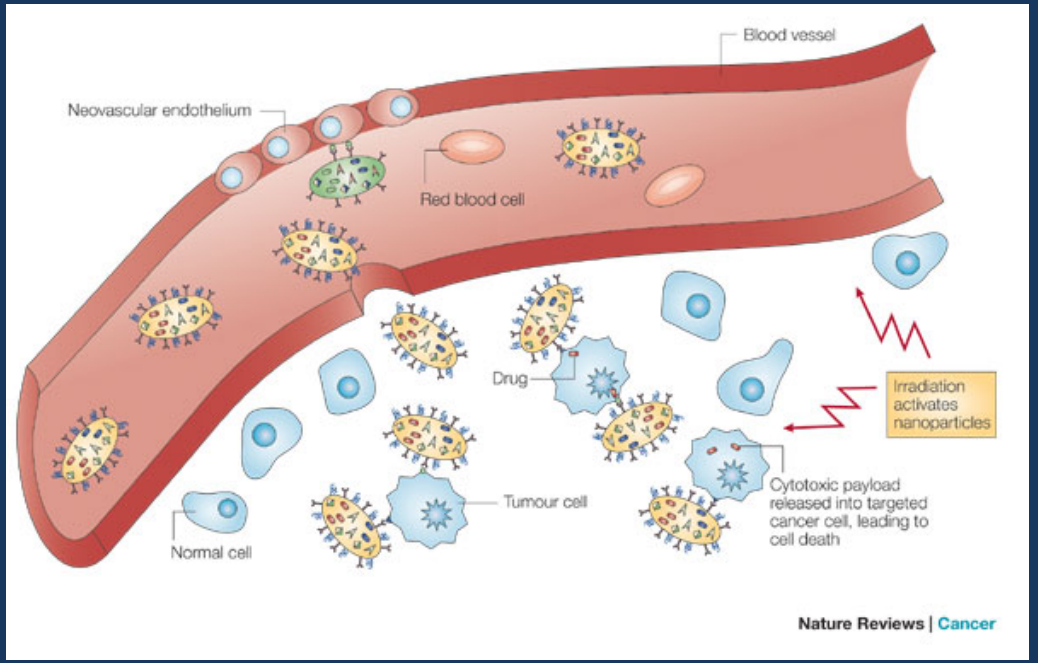


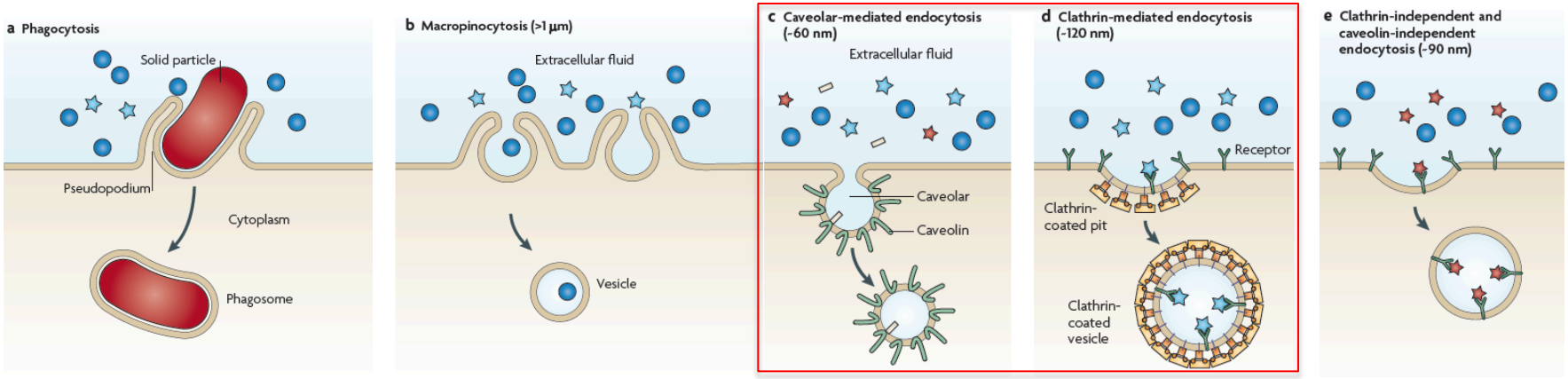
Figure 1. T-DES-polyacetal.Cy5.5 tumor accumulation. A) *In vivo* fluorescence imaging of subcutaneous HT-29 colon bearing mice after intravenous injection of 3.5, 5 and 7 mg/kg T-DES-polyacetal.Cy5.5. The tumor accumulation can be easily visualized at 6 h – 17 days postinjection. **B)** The fluorescence intensity was recorded and quantified as Efficiency over time.

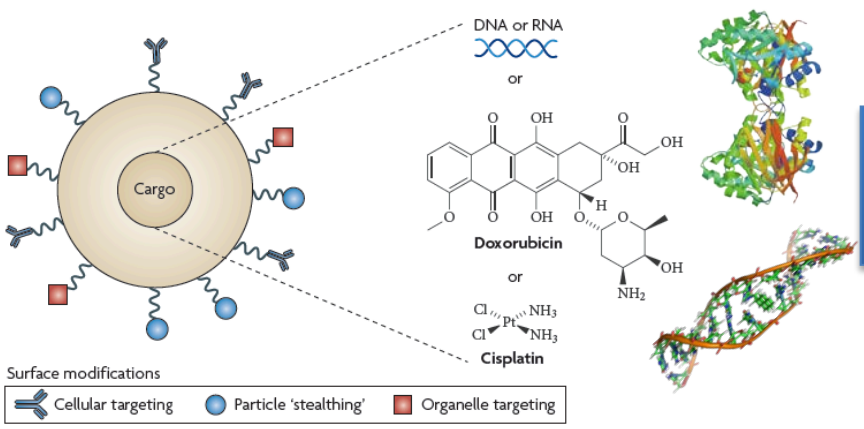
TARGETED DRUG DELIVERY

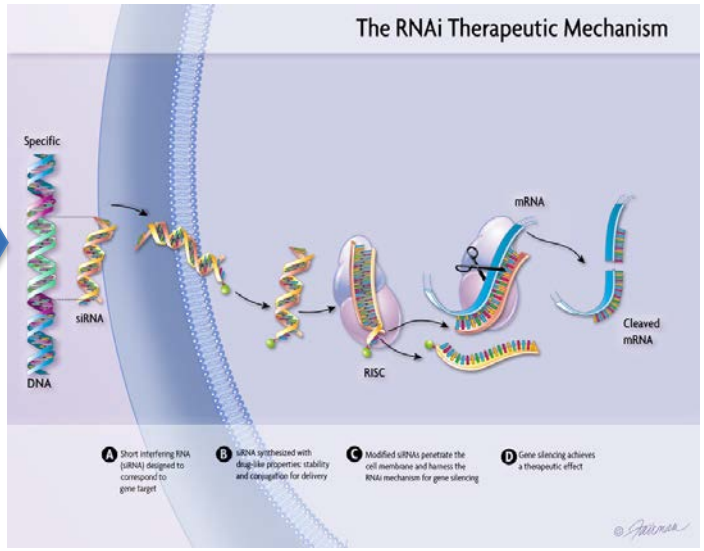


- Nanoparticles containing drugs are coated with targeting agents (e.g. conjugated antibodies)
- The nanoparticles circulate through the blood vessels and reach the target cells
- Drugs are released directly into the targeted cells

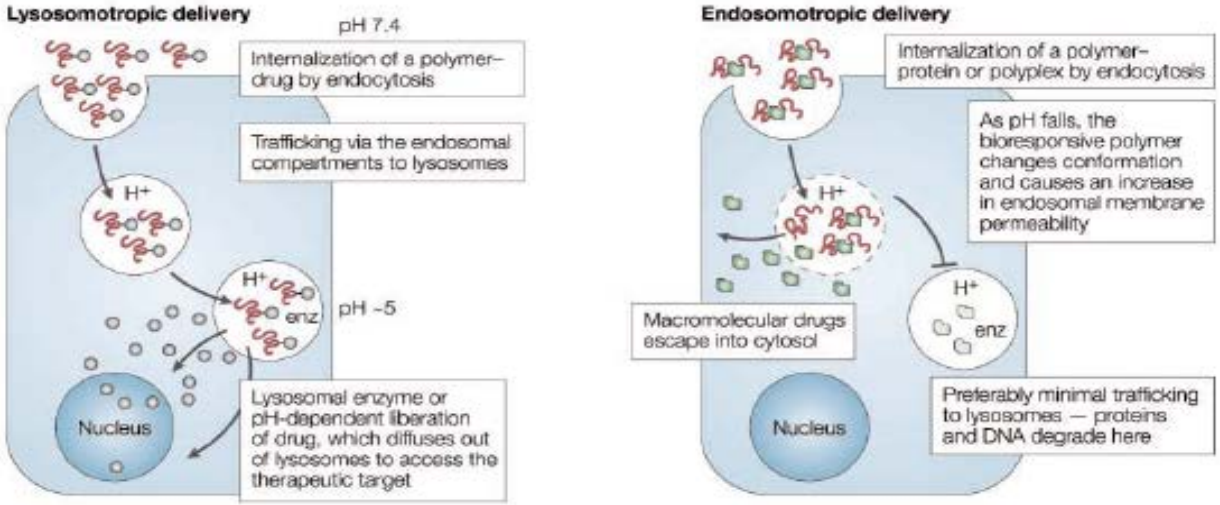








Petros and DeSimone, Strategies in the design of nanoparticles for therapeutic applications, Nature Reviews in Drug Discovery , 9(8): 615-627 (2010)
Alnylam, media-kit at http://www.alnylam.com/News-and-Events/Media-Kit.php



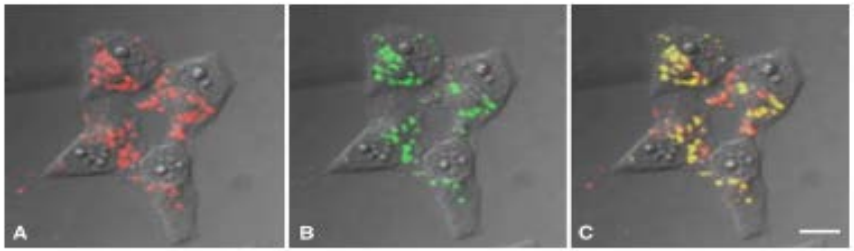
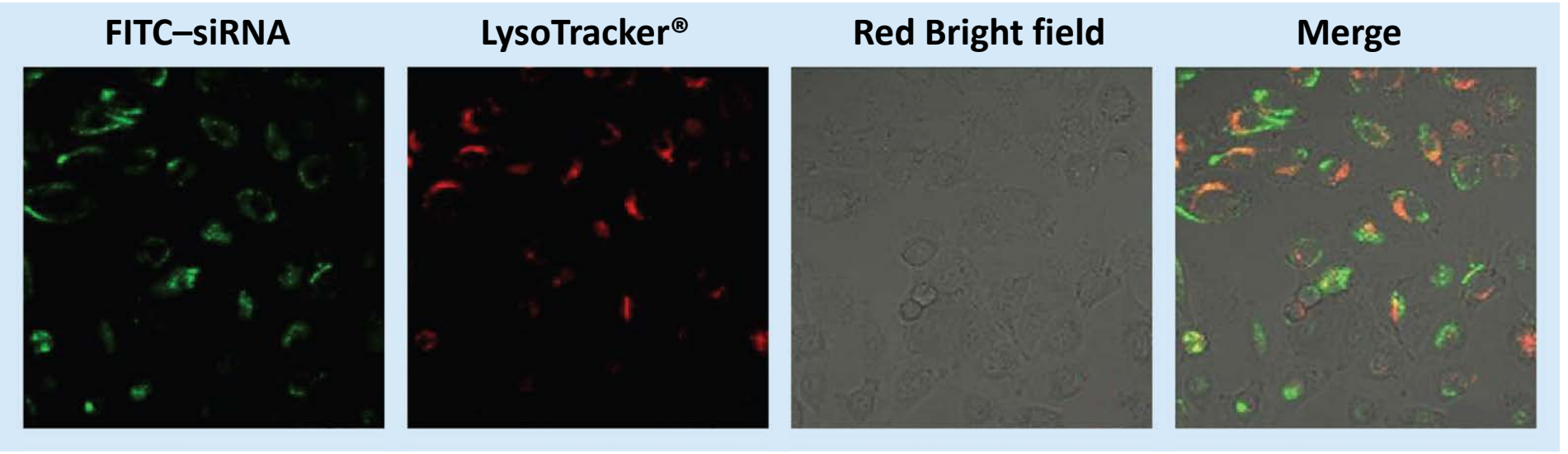
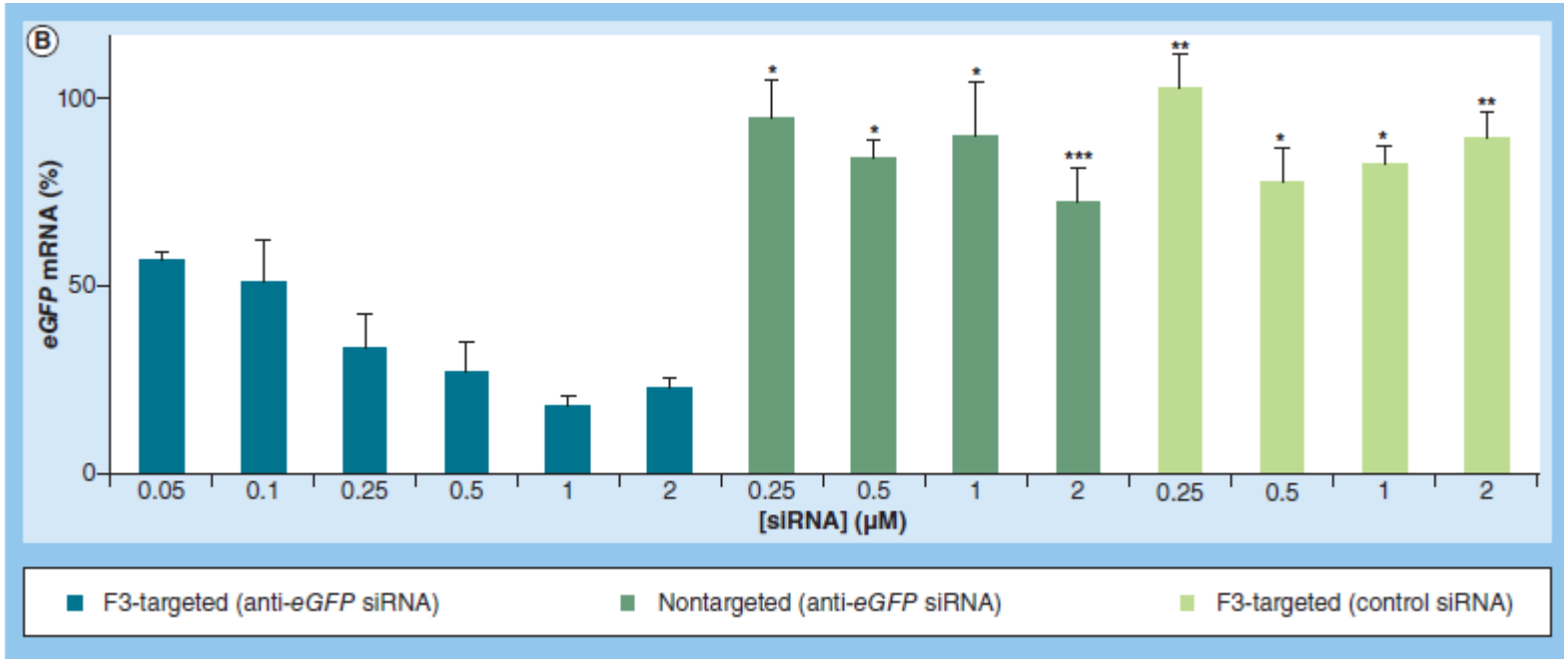


Fig 3. Localization of FNH_2SiNPs-FODNs complexes internalized in Hela cells. A, RITC indicates the position of the NH_2SiNPs; B, FITC indicates the position of the anti-ODNs; C, Merged image of A and B indicates that both fluorescent signals are superimposed and co-localized species appear as yellow. Scale bar in figure represented 10 μm.

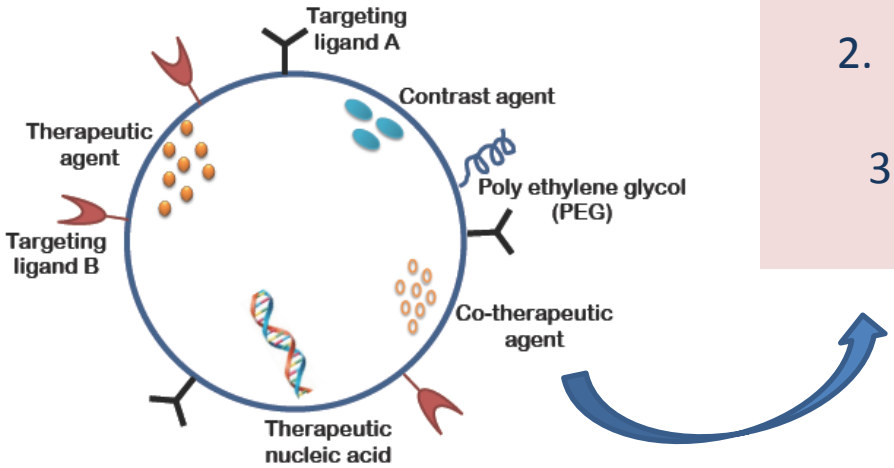
Intracellular siRNA encapsulated in F3-targeted pH-sensitive liposomes.





Gomes Da Silva et al. , Nanomedicine, in press

HOW?



From Upreti et al., translational cancer research, : 2(4) August 2013

Few main Goals have to be addressed urgently:

1. Reduce system toxicity of current drugs
2. Avoid tumor resistance to current therapy.
3. Avoid metastatic spread of the disease.

NANOMEDICINES ALLOW REDUCTION OF SYSTEMIC TOXICITY ASSOCIATED TO PHARMACOLOGICAL TREATMENT , OFTEN INCREASING THERAPEUTIC EFFICACY

AVOIDING DEGRADATION/METABOLIZATION OF CARGO IN THE BLOOD STREAM OR PERIFERAL TISSUES.

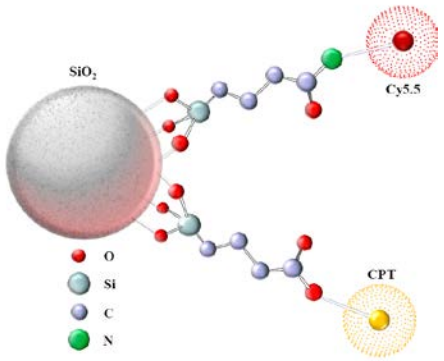
MODIFYING DRUG HALFTIME, DISTRIBUTION OR METABOLIC PATHWAYS

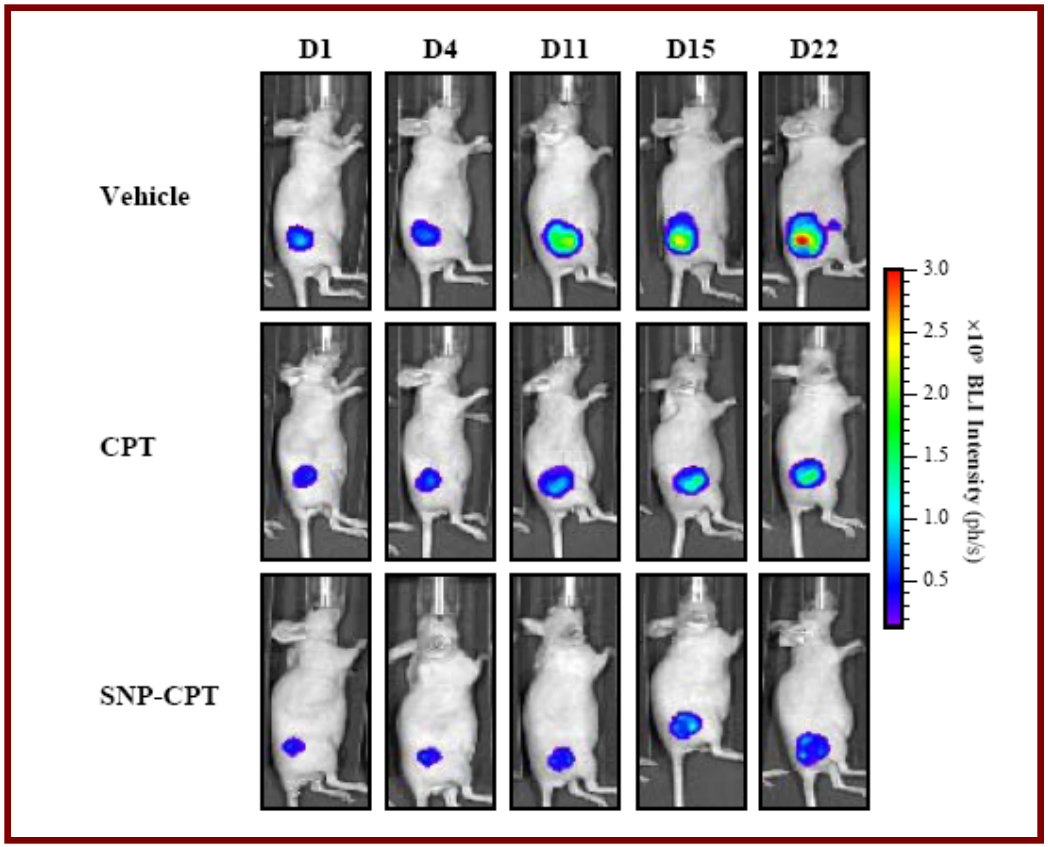
DRUGS CAN BE ADMINISTRATED SIMULTANEOUSLY (COMBINATION THERAPY)

INCREASING EFFECTIVE DOSE REACHING TARGET CELLS

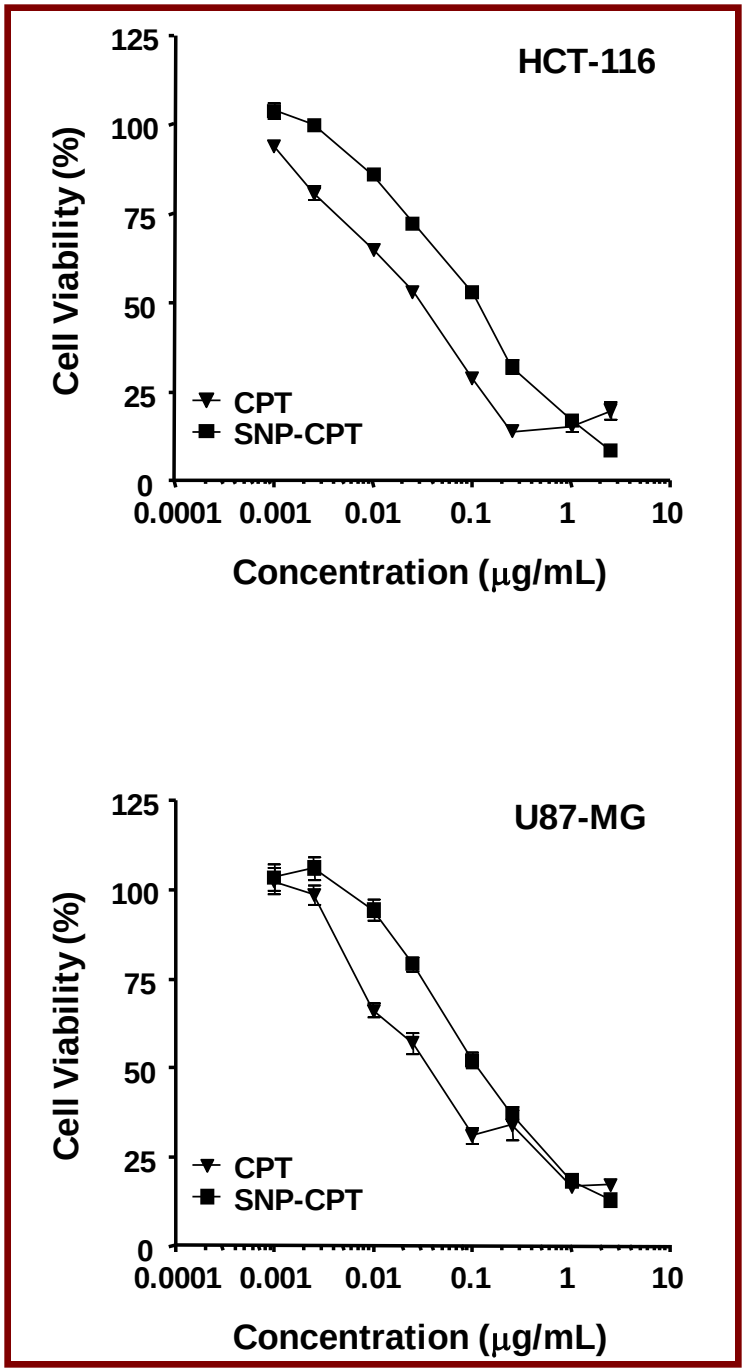
SLOW RELEASE OF DRUGS

Toxicity reduction

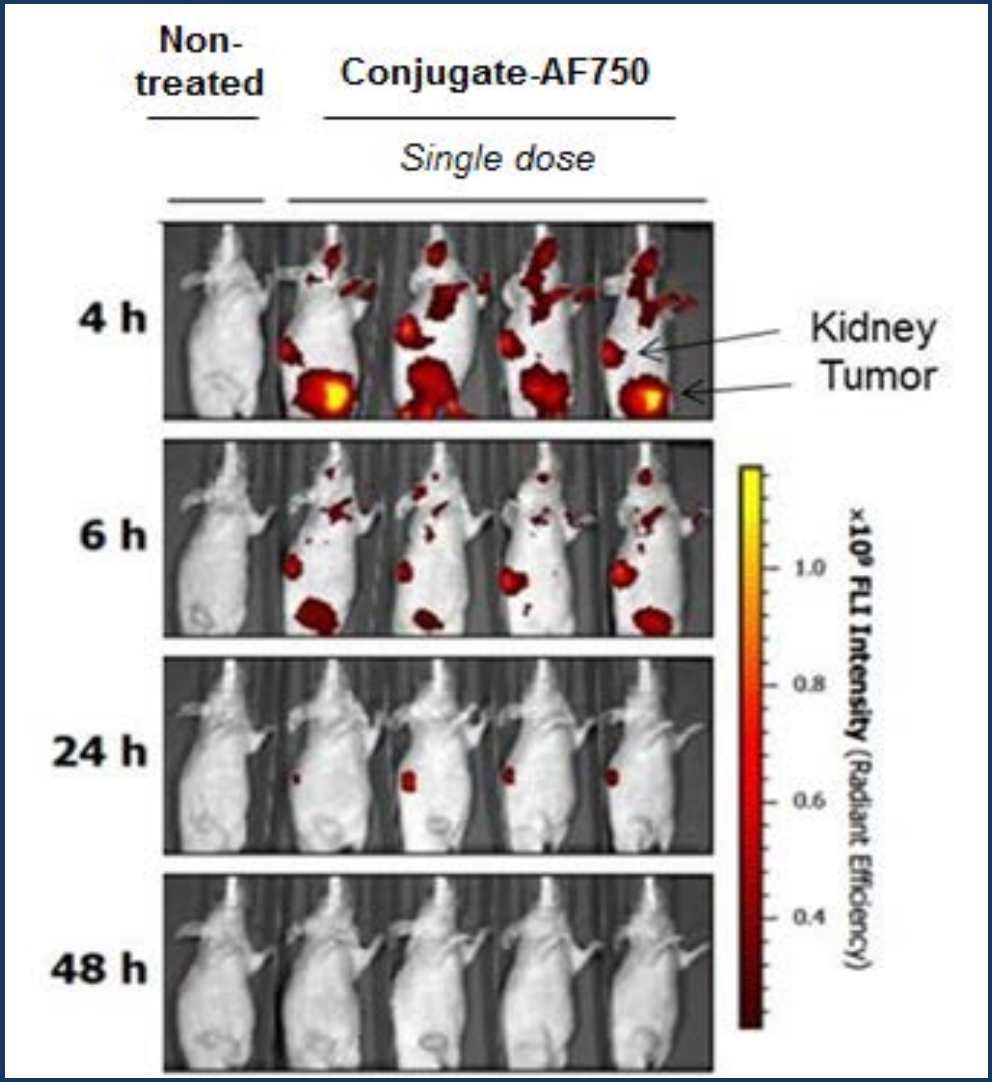




Botella P et al, J Control Release. 2011



PK data can be modified if needed



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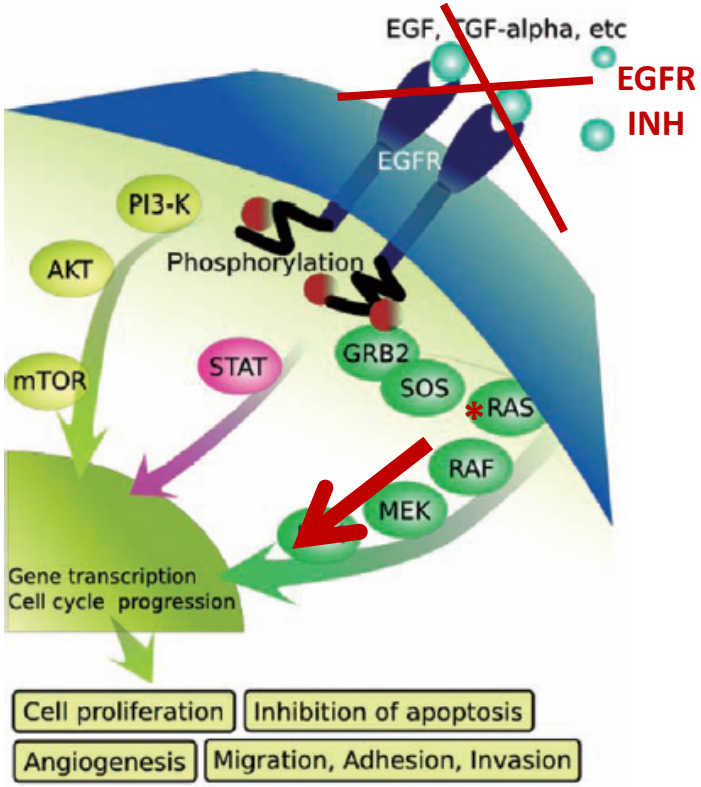
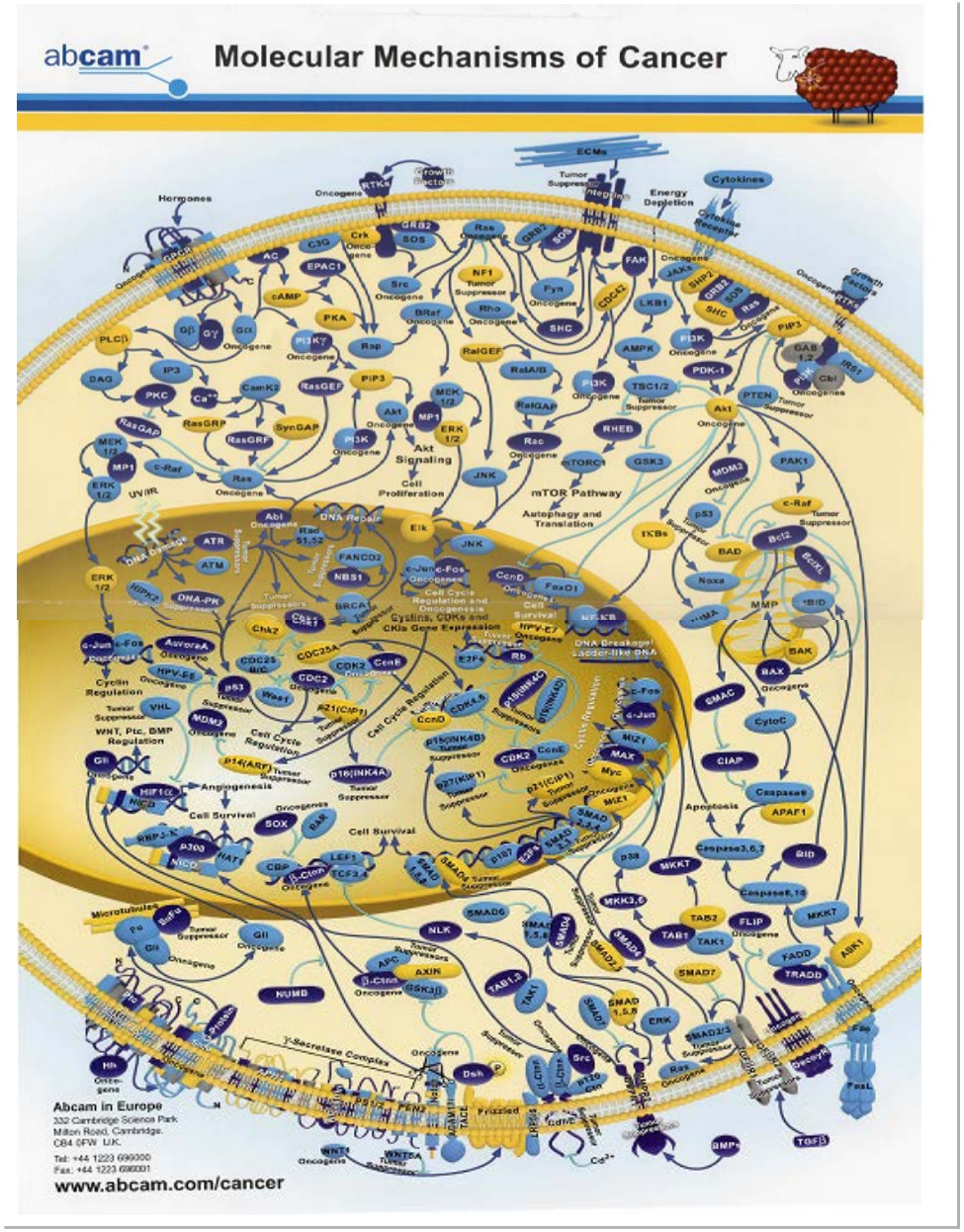
New mutations or epigenetic modifications might confer tumor resistance to current therapy





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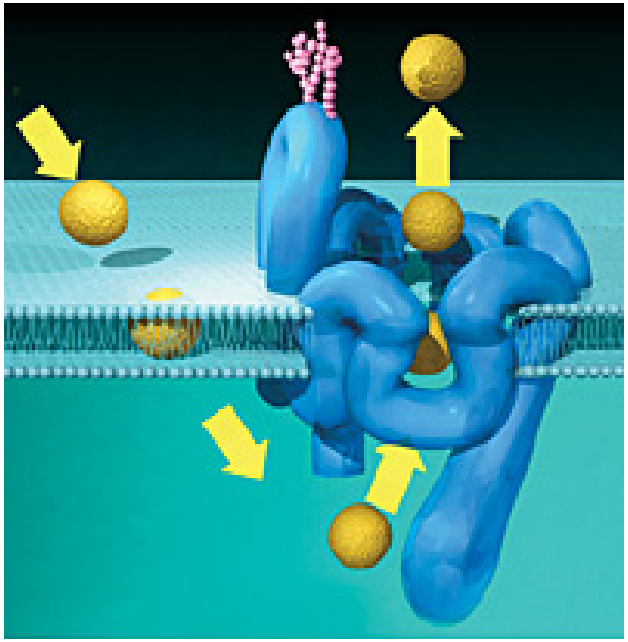
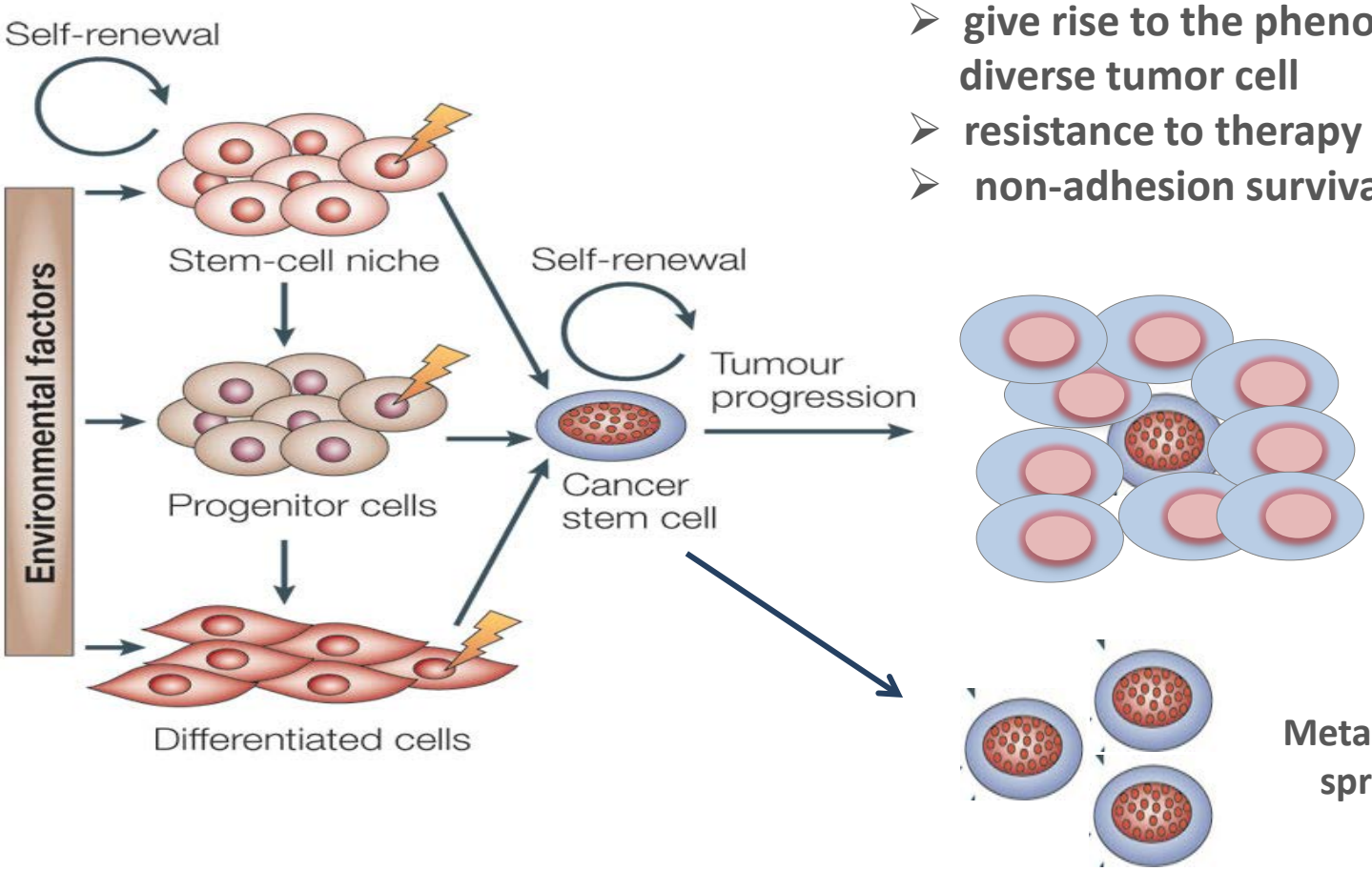
MDR complexes confer
tumor resistance to current therapy



Cancer Stem Cells allow metastatic spread and tumor resistance to current therapy

- rare cells within tumors
- high tumorigenic capacity
- self-renewal ability
- give rise to the phenotypically diverse tumor cell
- resistance to therapy
- non-adhesion survival



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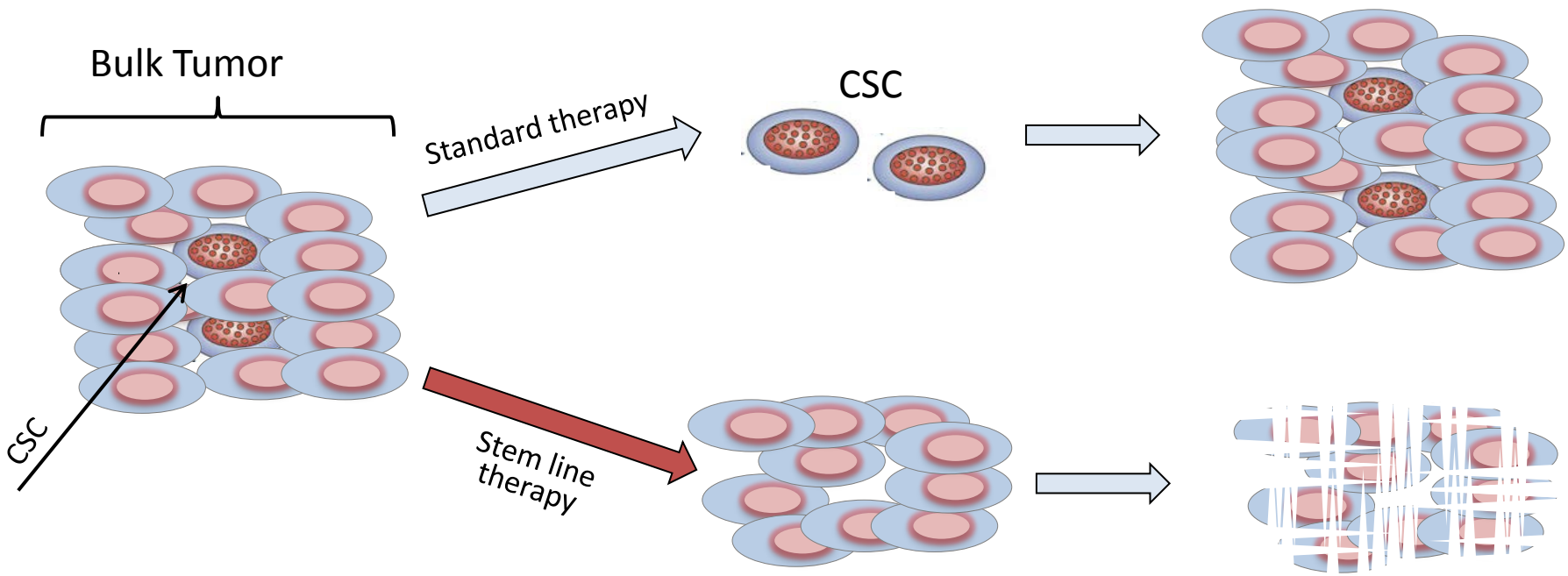

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Some needs to consider:

- Need drugs able to avoid the MDR system

- Combination therapy might overcome resistance due to new mutations/epigenetics (DDS might help to achieve feasible administration of various compounds)

- Need effective targeting to reduce metastatic spread of the disease (target CSC)

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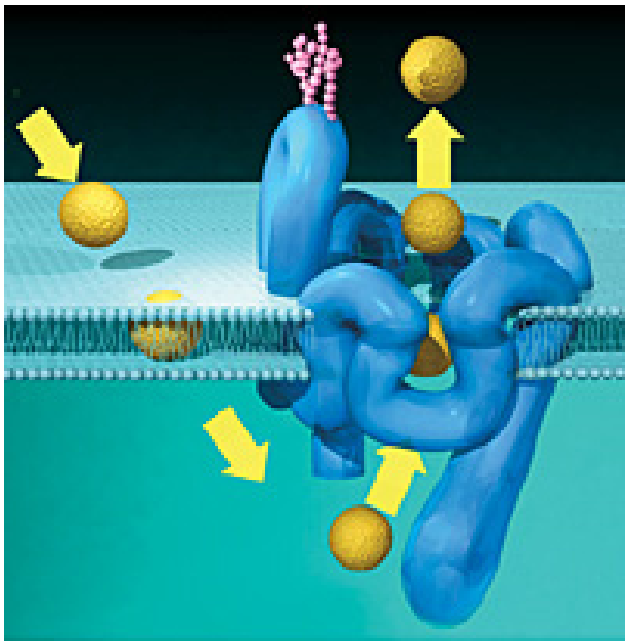
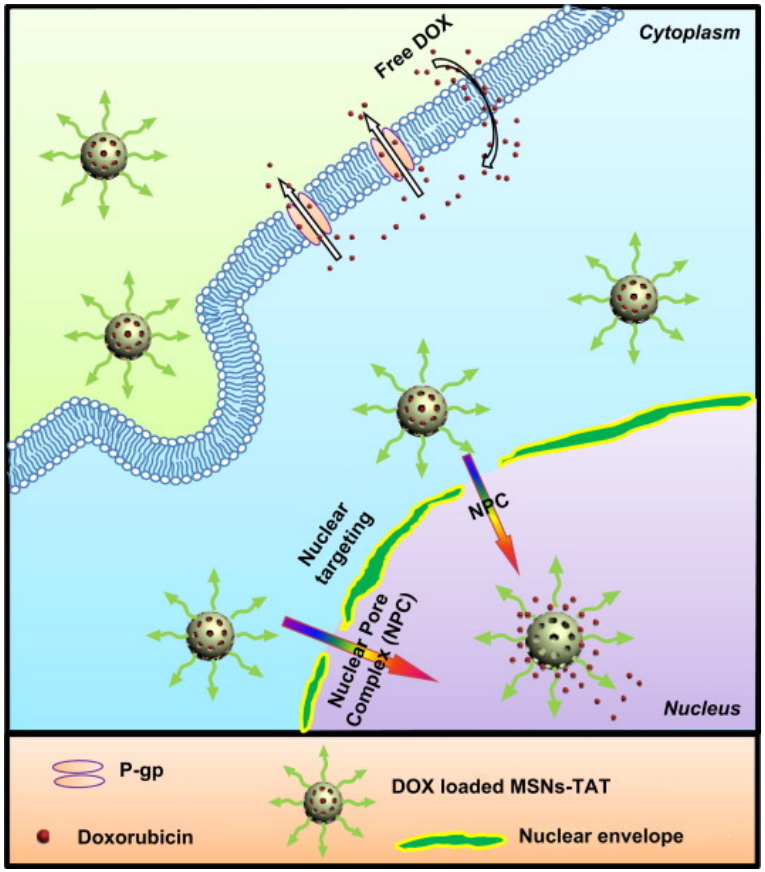
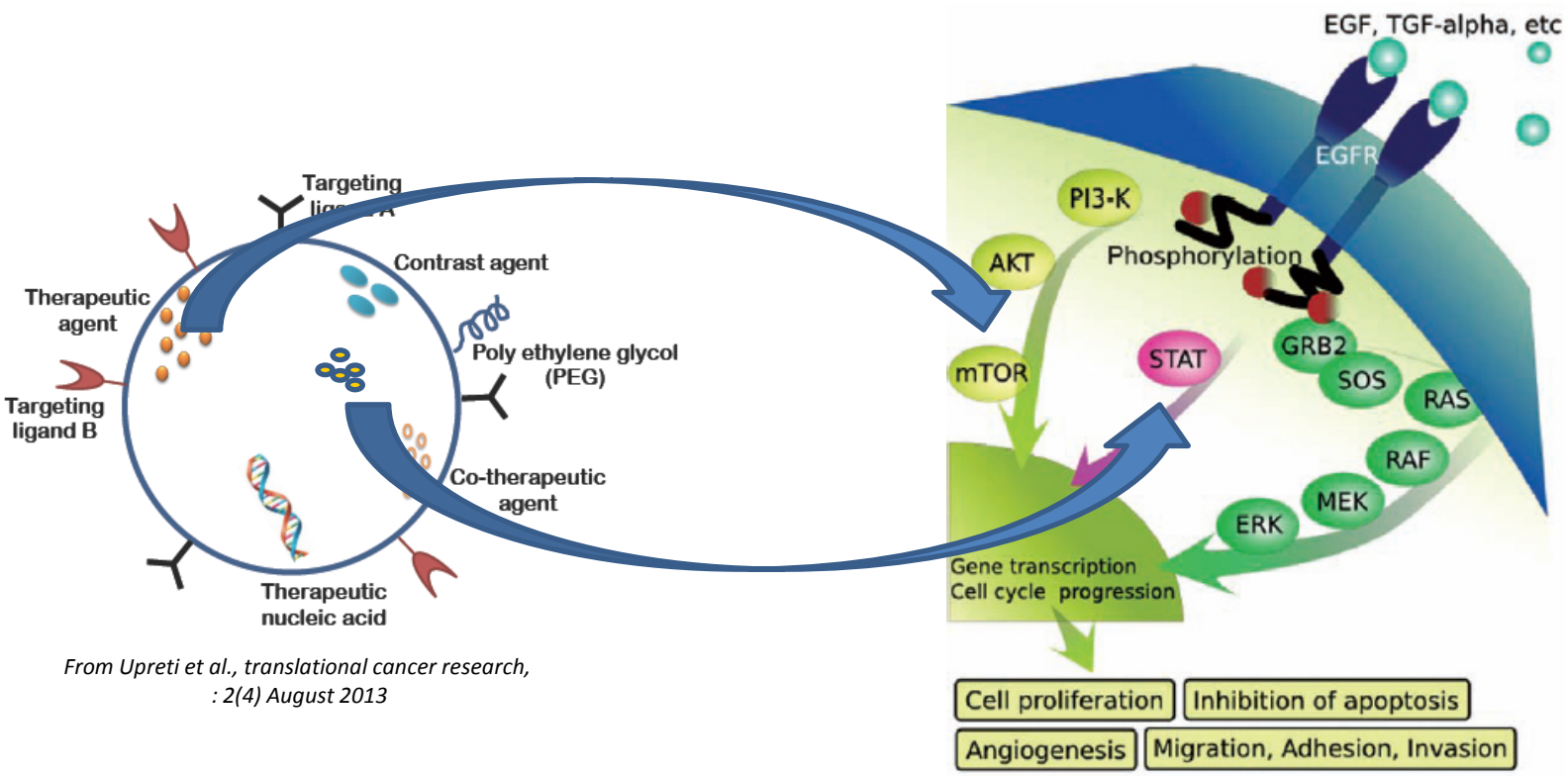




Limin Pan et al., Biomaterials 34(11) April 2013, 2719–30

Combination therapy might help to overcome resistance



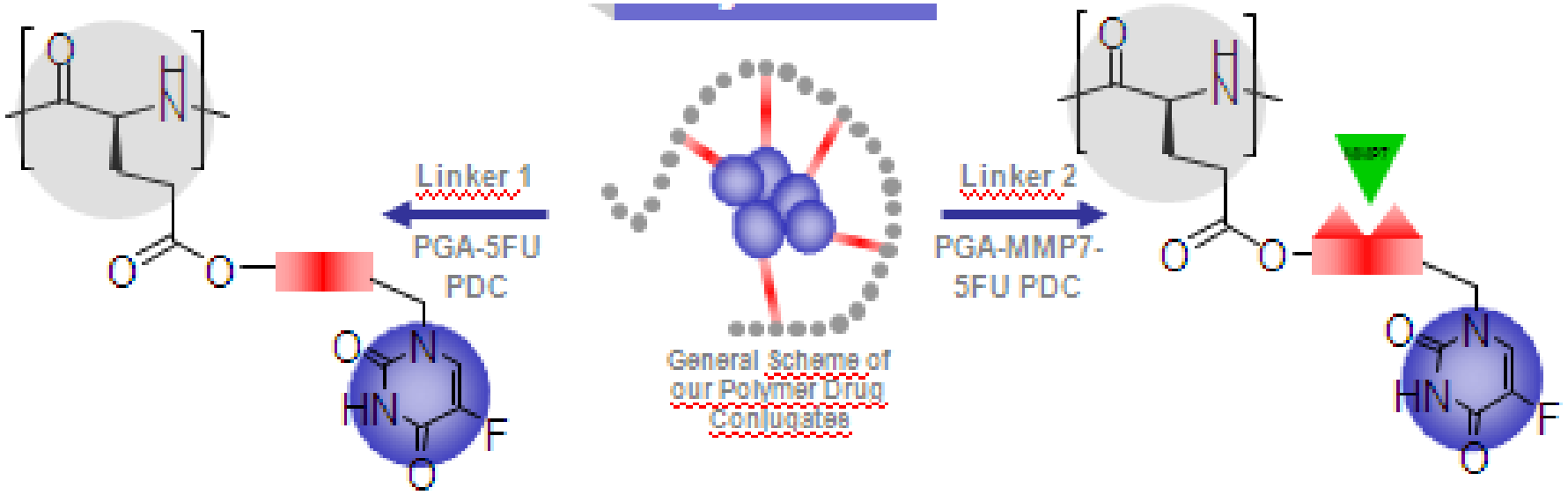
From Upreti et al., translational cancer research, : 2(4) August 2013

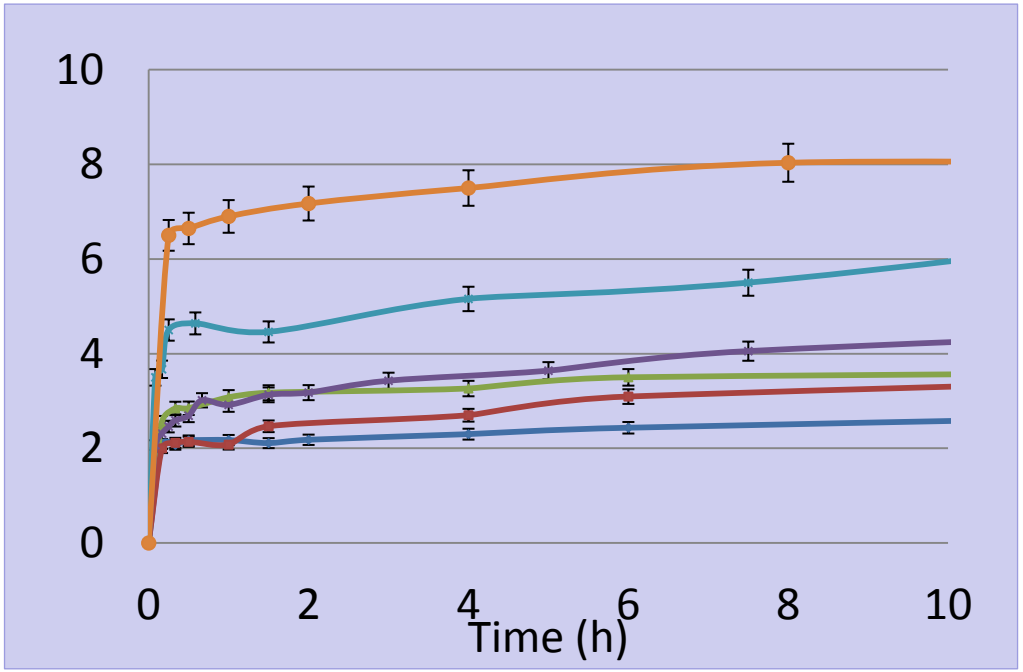
Nanoparticles help overcome Drug Resistance

- Endocytosis of DDS provide a scape mechanism from MDR complexes
- several drugs can be loaded to overcome natural tumor/disease resistance

What about targeting?

Metallotrigger Project

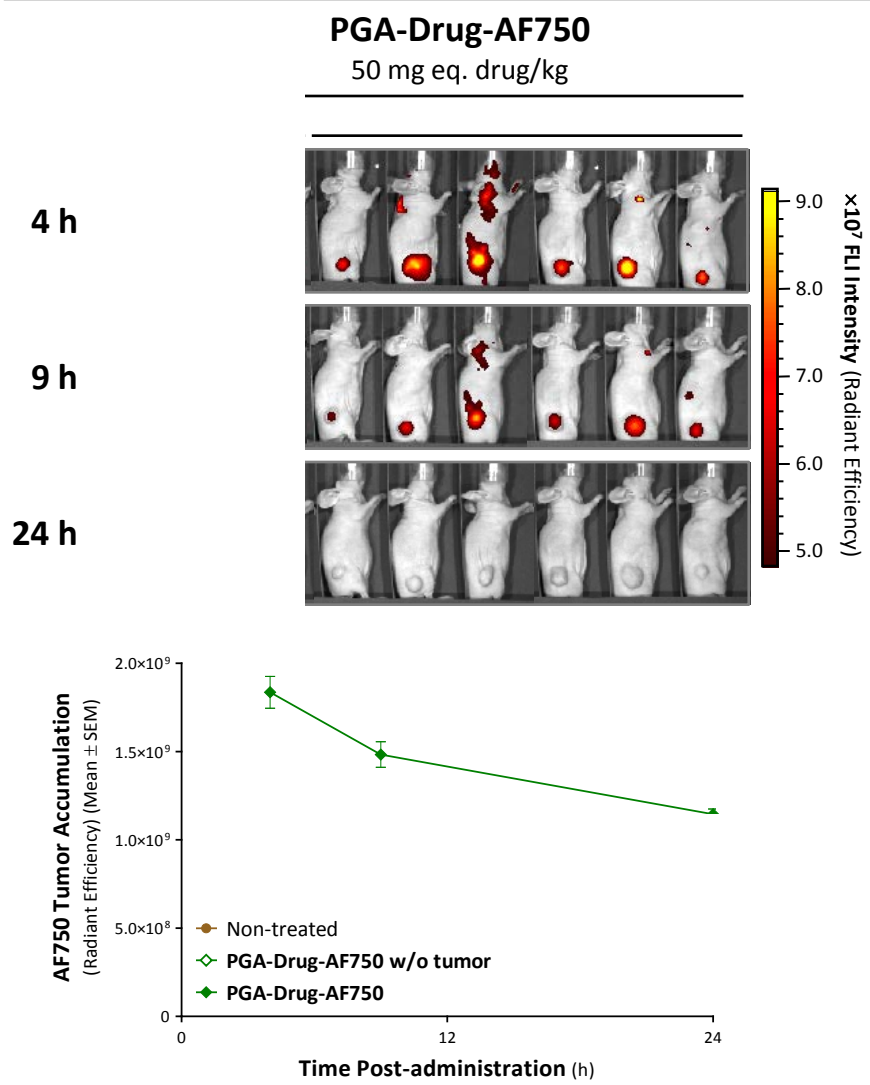




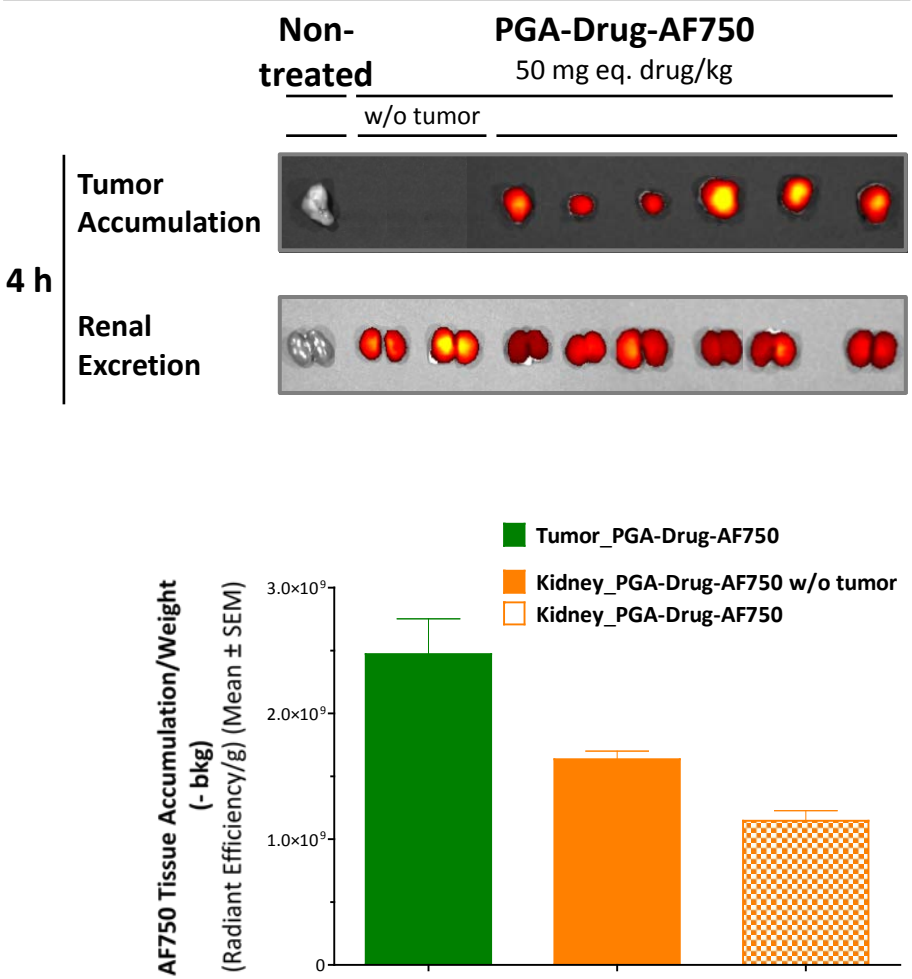
Cathepsin B

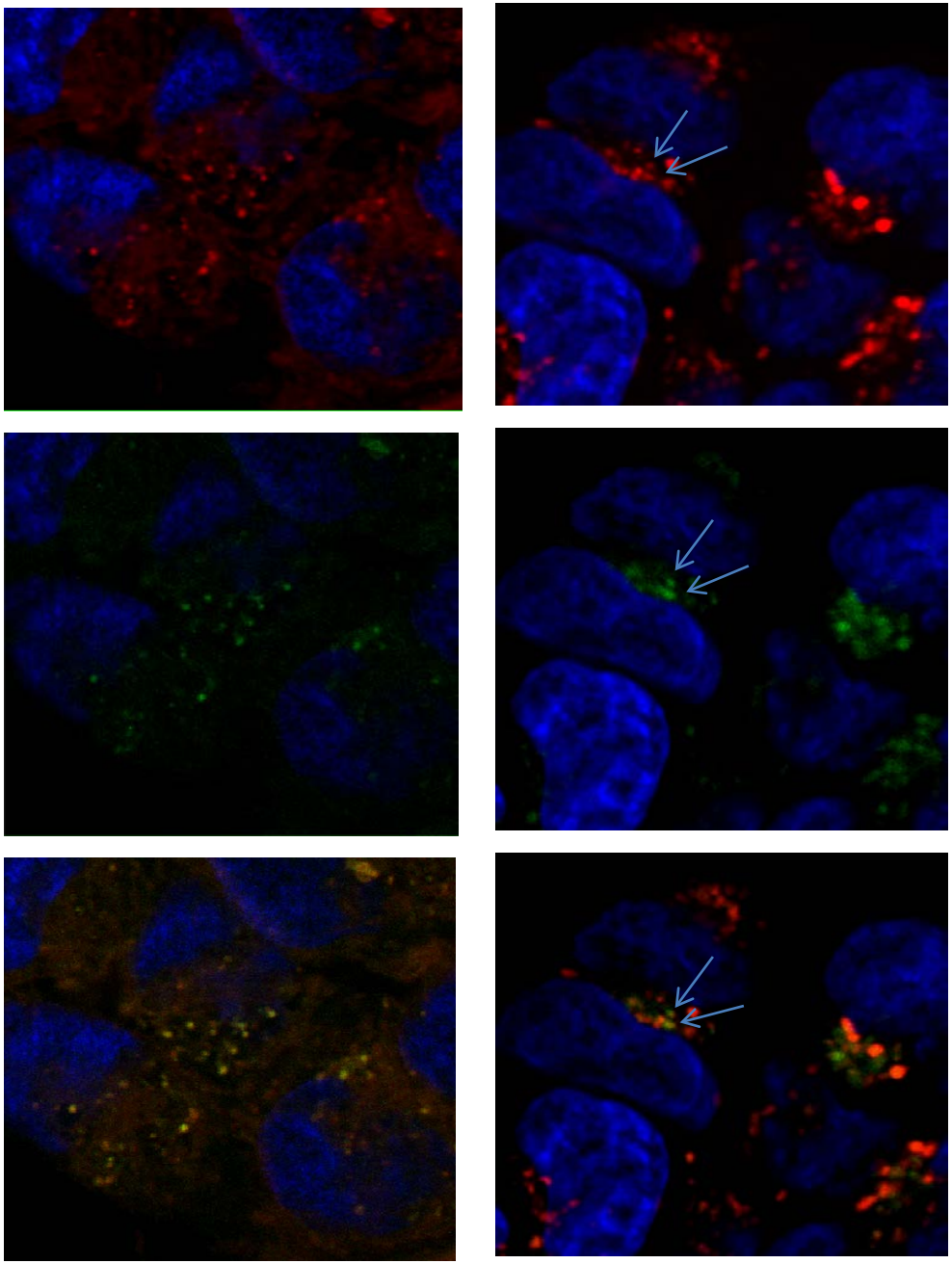
FLI: BIODISTRIBUTION. PGA-5FU-AF750

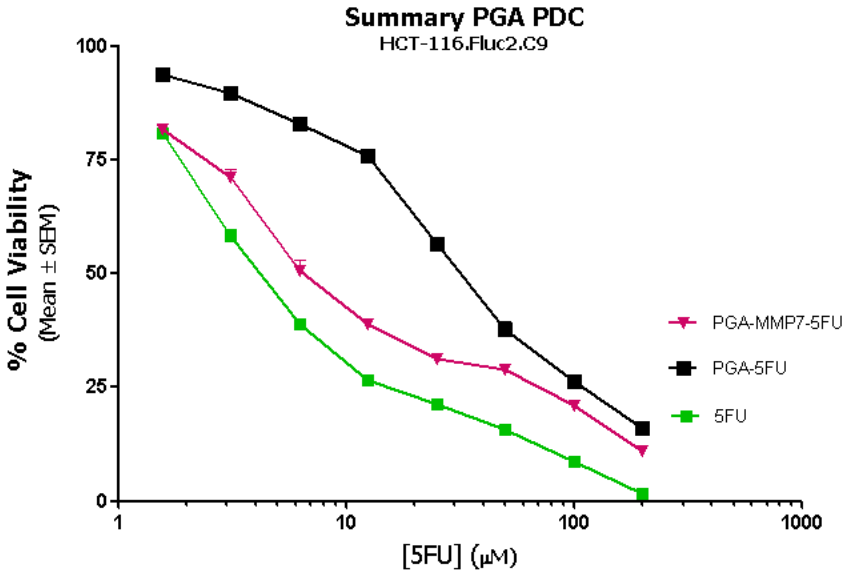
In vivo s.c. Tumor-accumulation

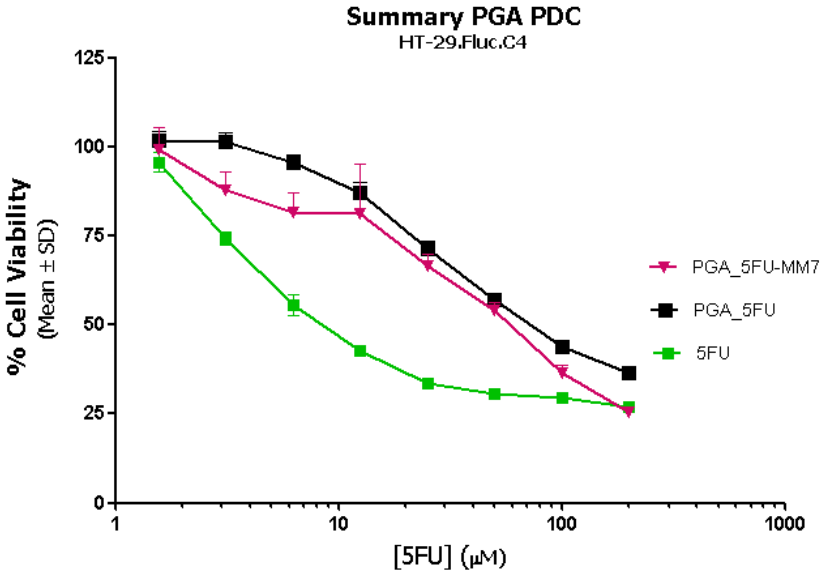


Ex vivo Tissue-accumulation









	5FU	PGA-5FU	PGA-MMP7-5FU
HCT-116.Fluc2-C9	4.88	33.38	9.11
HT-29.Fluc.C4	14.21	82.25	55.92

Cancer Stem Cells allow metastatic spread and tumor resistance to current therapy

- rare cells within tumors
- high tumorigenic capacity
- self-renewal ability
- give rise to the phenotypically diverse tumor cell
- resistance to therapy
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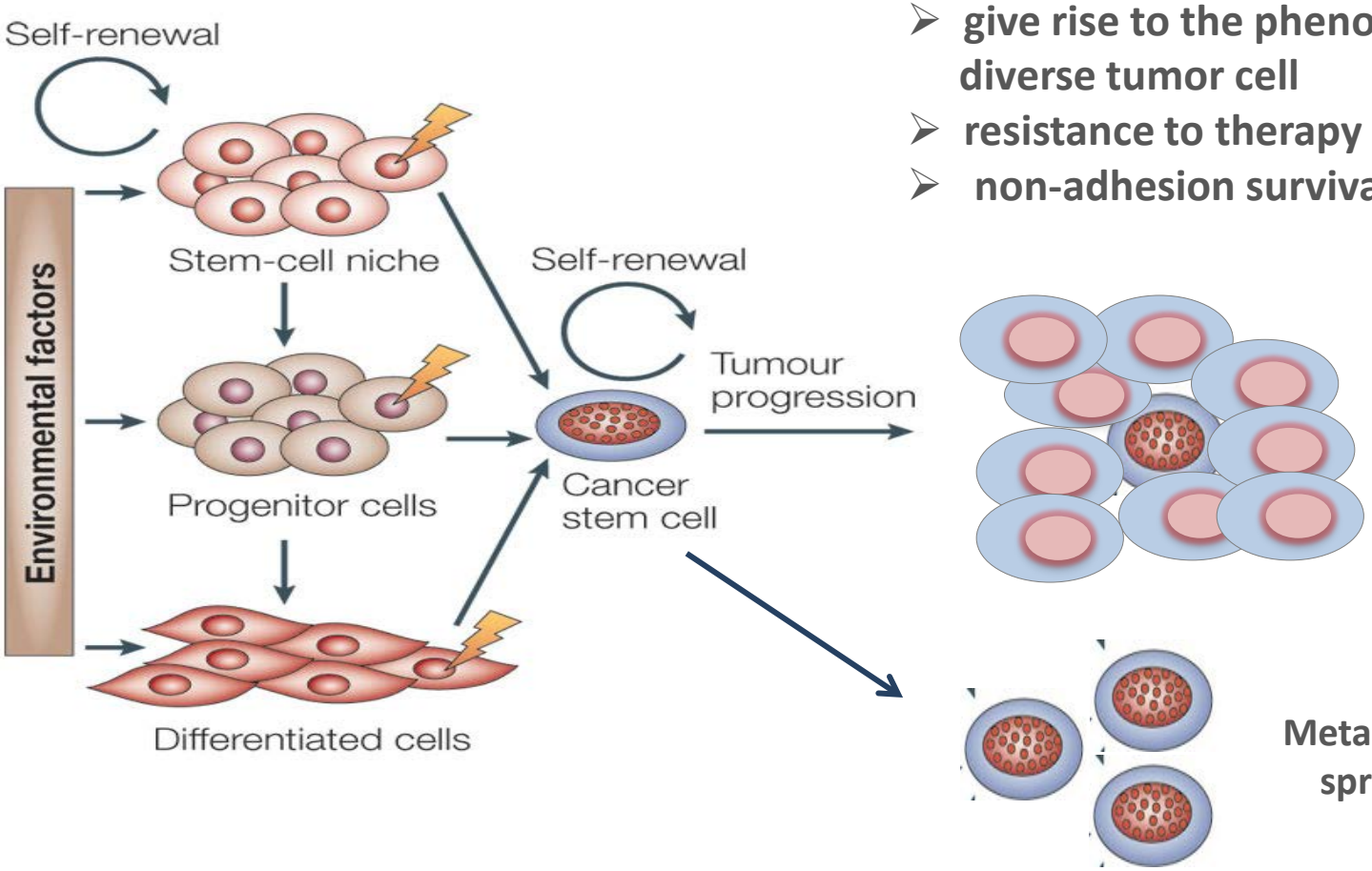
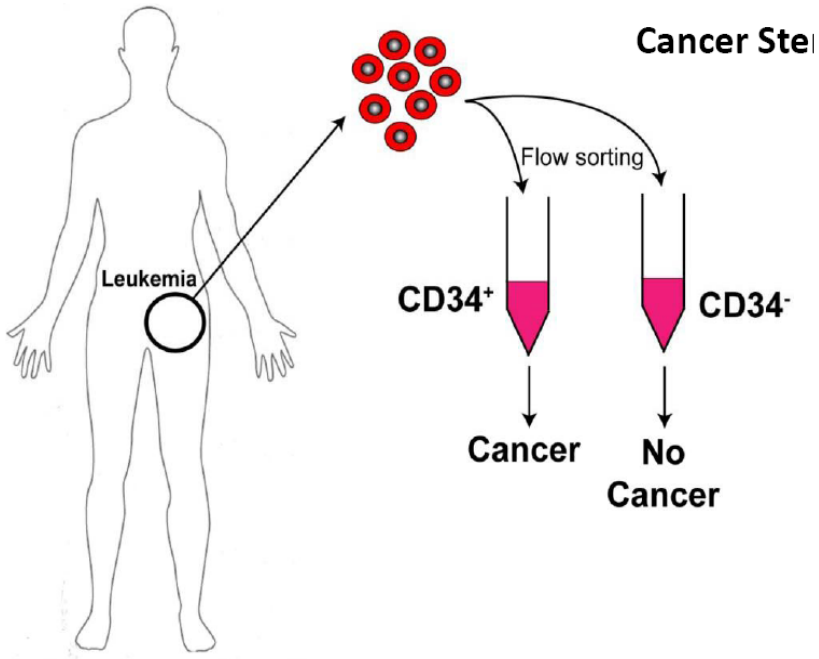


Cancer Stem Cells (CSC)



Tumor type	Cell surface markers
Acute myeloid leukemia	CD34+ CD38-
Breast cancer	CD44+ CD24-/low
Brain tumor	CD133+
Prostate cancer	CD44+
Metastatic melanoma	CD20+
Hepatic cancer	CD133+
Head and neck cancer	CD44+
Pancreatic cancer	CD44+ CD24+ ESA+

- Key assays for demonstrating CSCs
  - In vivo tumorigenic model performed in immunodeficient mice
    - More tumorigenic than the unsorted tumour population
    - Often referred to as tumor initiating cells (TICs)
  - Complemented by the in vitro "sphere forming" assay or colony forming assays

Bonnet D, Dick JE. *Nat Med*. 1997 Jul;3(7):730-7

Cancer Stem Cells (CSC)

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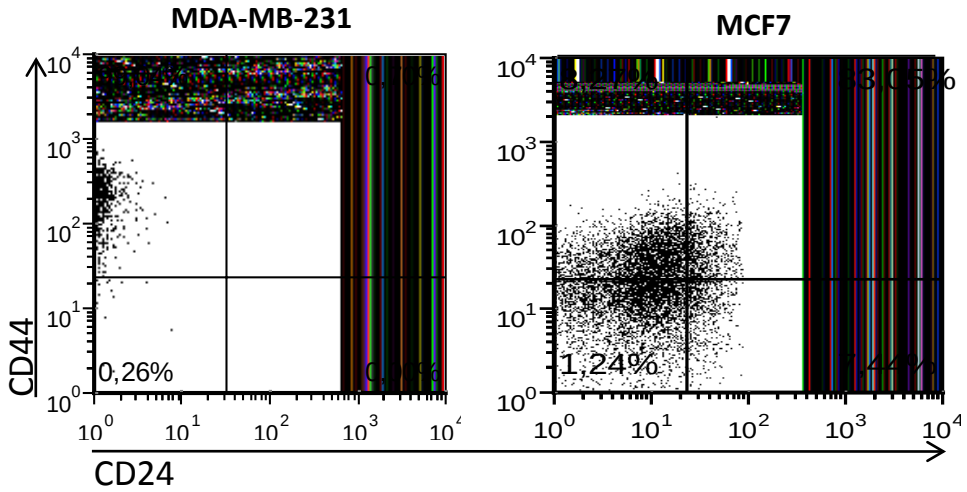
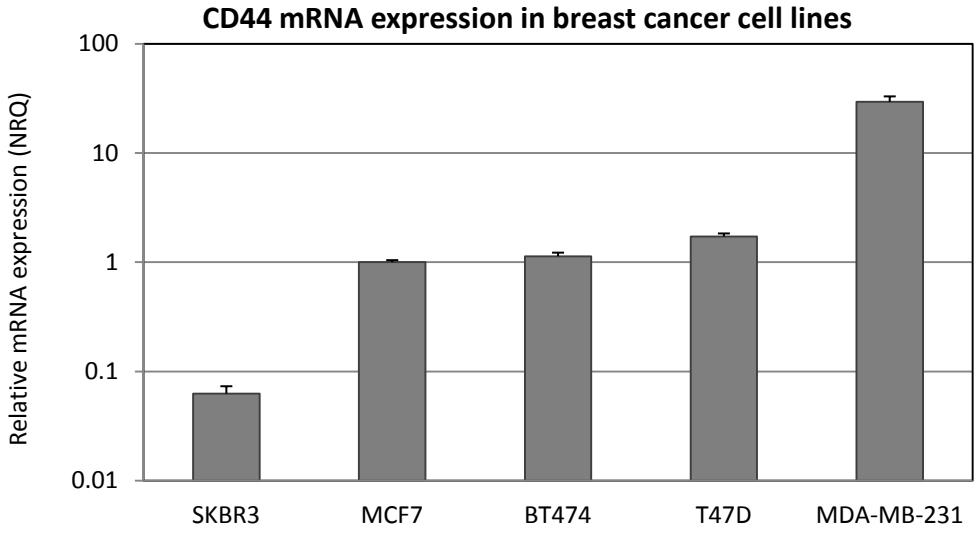
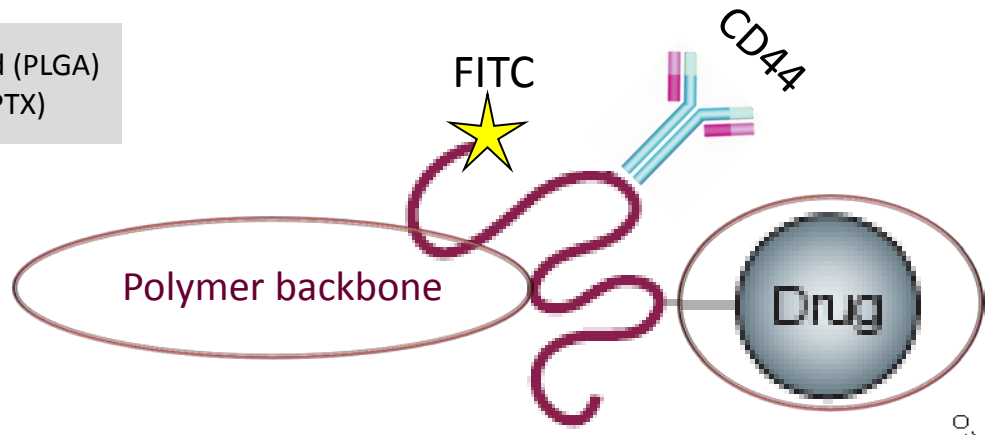




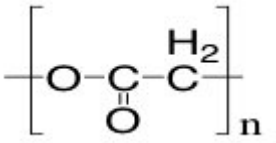
PLGA-PEG-PTX nano-DDS

In collaboration with Dr. Rogério Gaspar, Dr. Mafalda Videira,
Nanomedicine & Drug Delivery Systems Group, Faculdade de Farmácia da Universidade de Lisboa (FFUL)

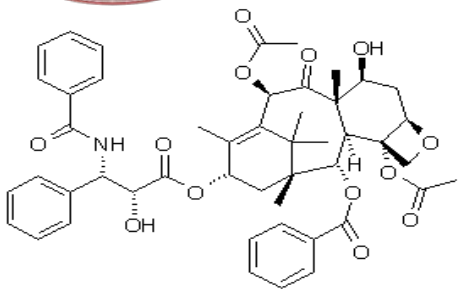
polyglycolic acid (PLGA)
Paclitaxel (PTX)



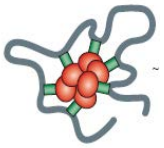
PLGA



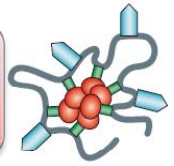
PTX



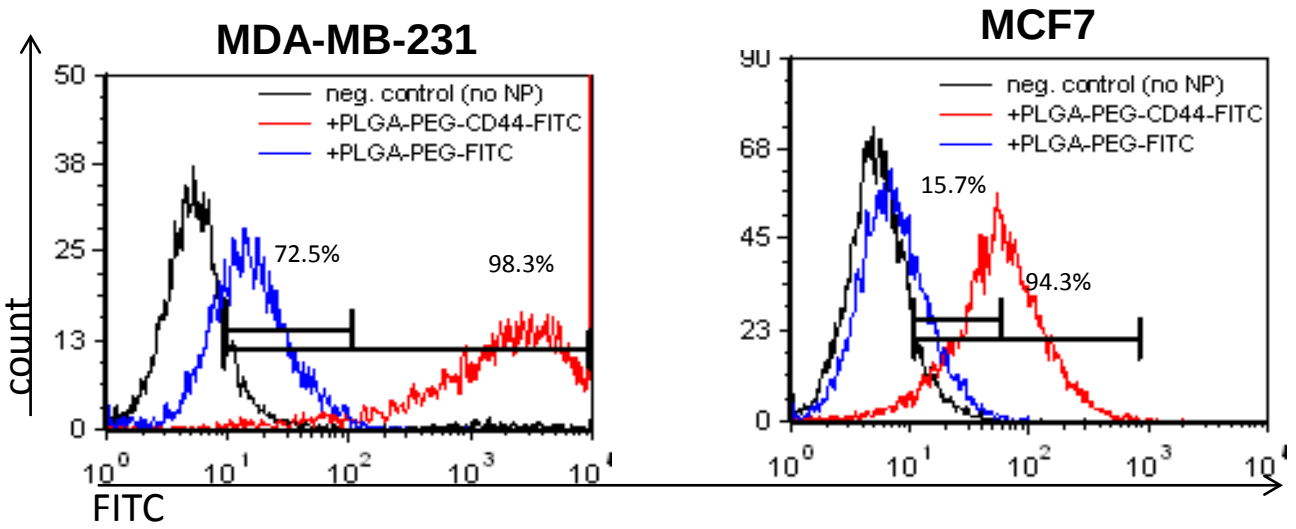
PASSIVE TARGETING
– Enhanced Permeability and Retention effect

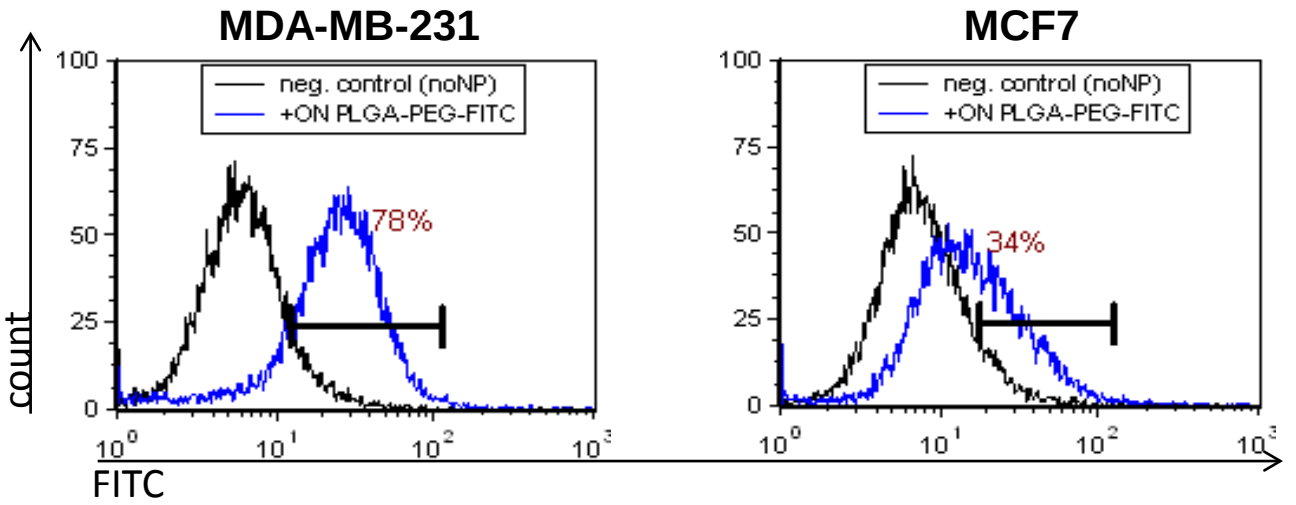


ACTIVE TARGETING
– Receptor mediated internalization



PLGA-PEG drug delivery systems: INTERNALIZATION





PLGA-PEG drug delivery systems: INTERNALIZATION

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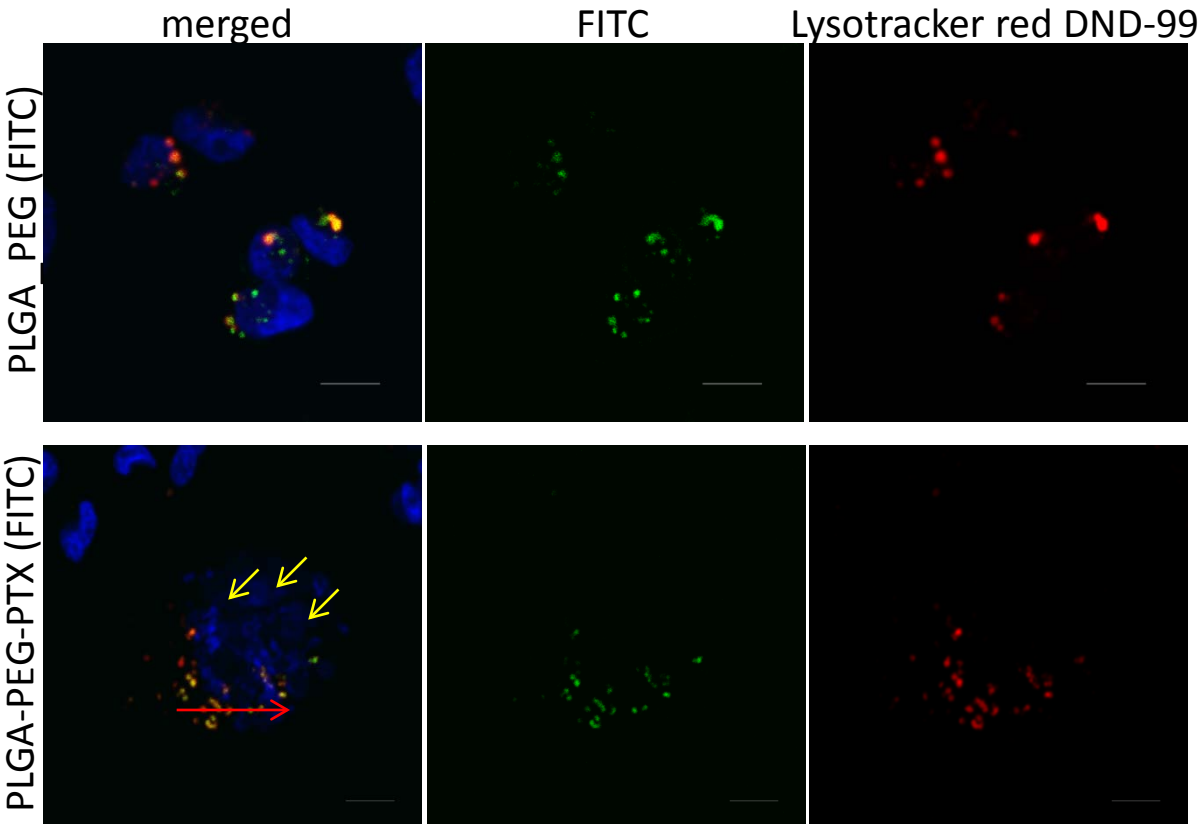
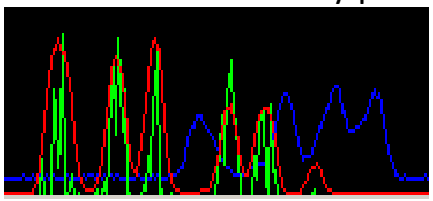
CIBBIM - Nanomedicina



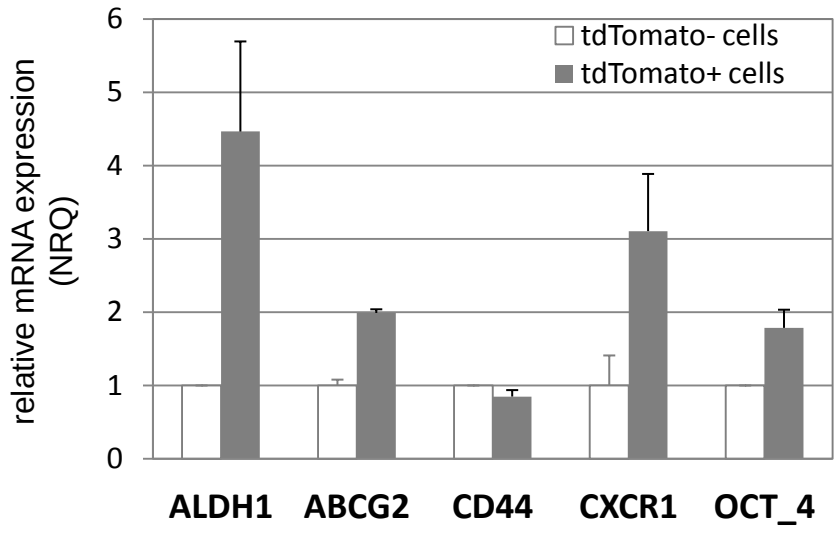
Fluorescence intensity plot



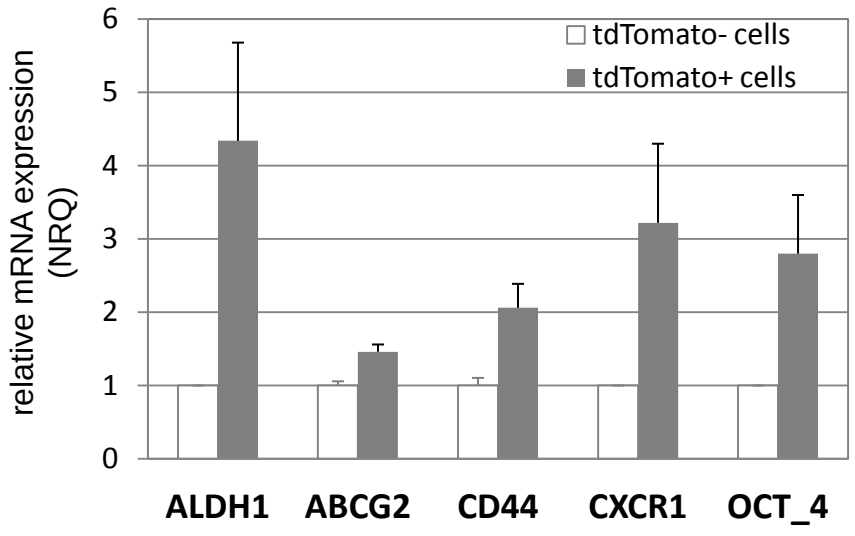
MDA-MB-231

CSC in vitro model: EXPRESSION OF STEMNESS MARKERS

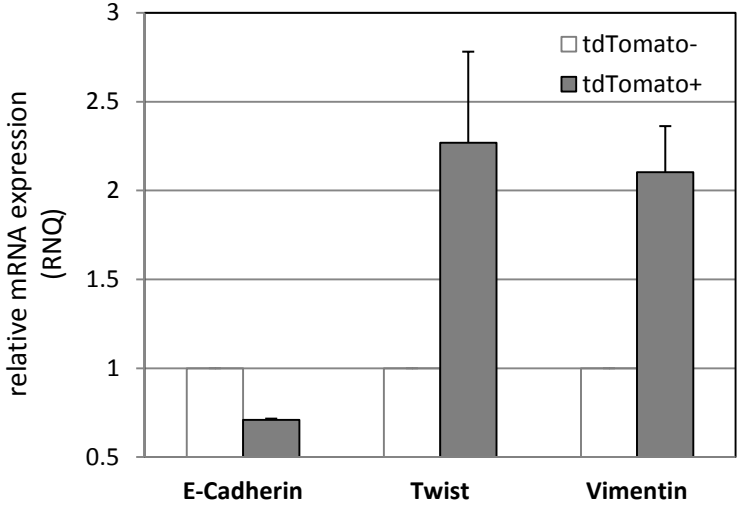
MDA-MB-231-ALDH/tdTomato



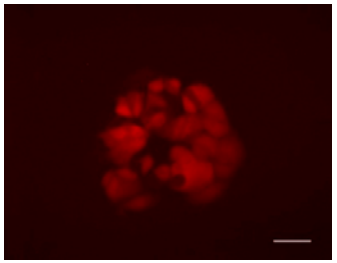
MCF7-ALDH/tdTomato



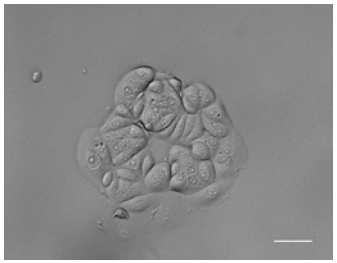
EMT transition gens



td Tomato⁺ cells



all cells



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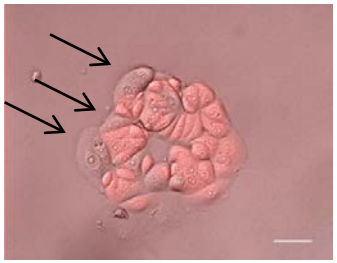
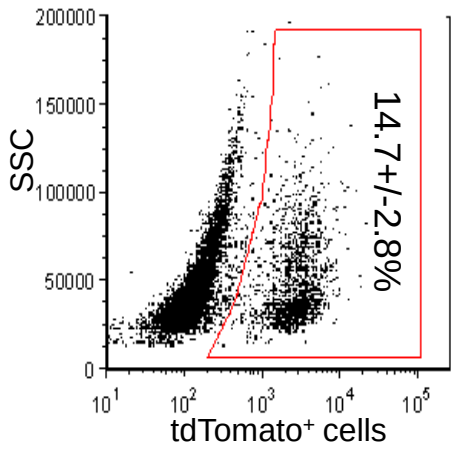
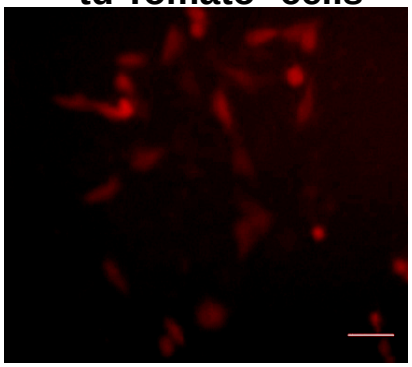


CSC in vitro model

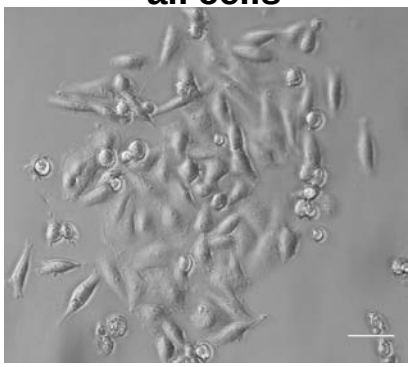
MDA-MB-231-ALDH/tdTomato



td Tomato+ cells



all cells



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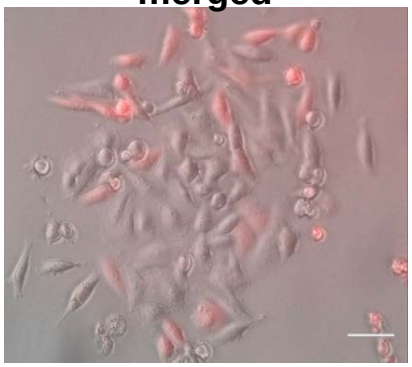
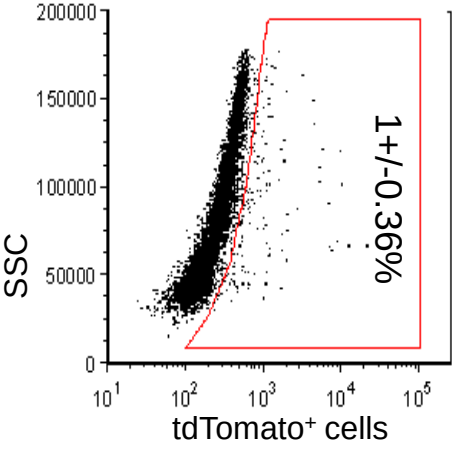
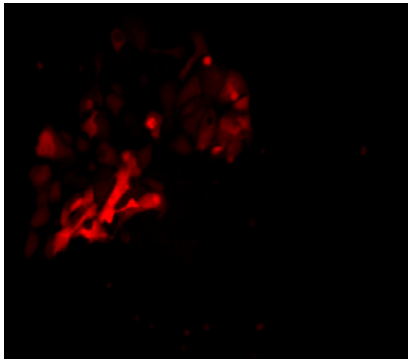


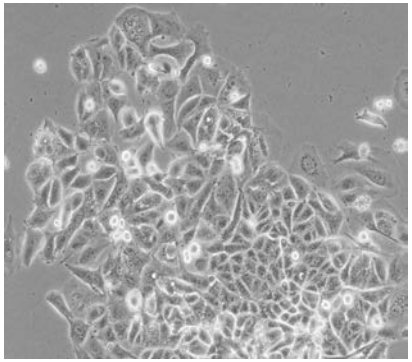
MCF7-ALDH/tdTomato



td Tomato+ cells



all cells



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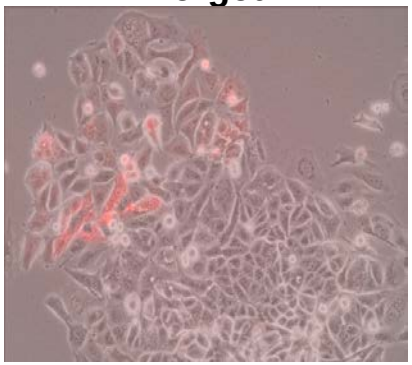


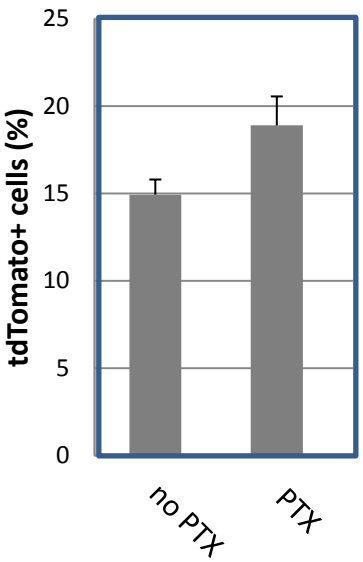
In vitro therapeutic activity of PTX-DDS in tdTomato+ CSC

Vall d'Hebron Hospital
CIBBIM - Nanomedicina

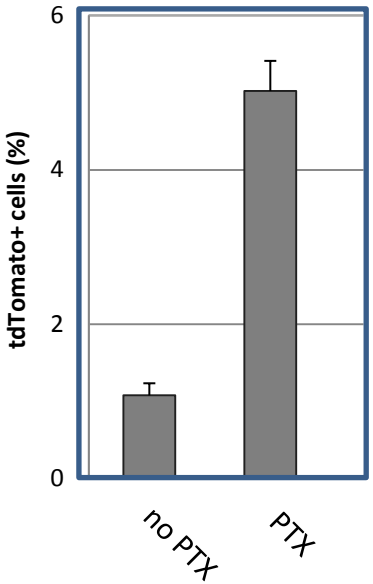
72h | 48h

Cells grow with PTX → Cells grow in PTX free medium → FACS analysis

MDA-MB-231 tdTomato+ CSC
72h PTX treatment + 48h recovery



MCF7 tdTomato+ CSC
72h PTX treatment + 48h recovery



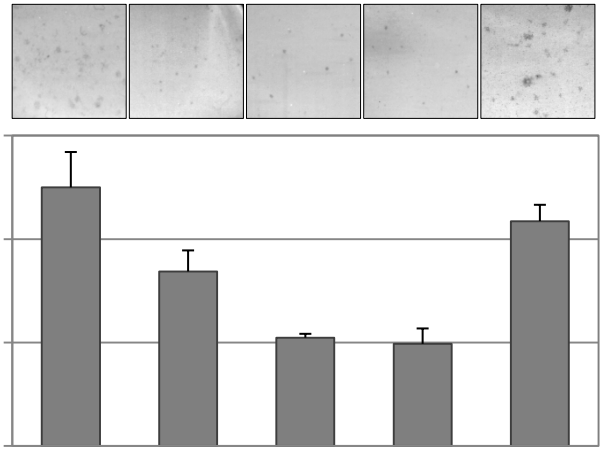
In vitro therapeutic activity of PTX-DDS in tdTomato+ CSC

Vall d'Hebron Hospital
CIBBIM - Nanomedicina

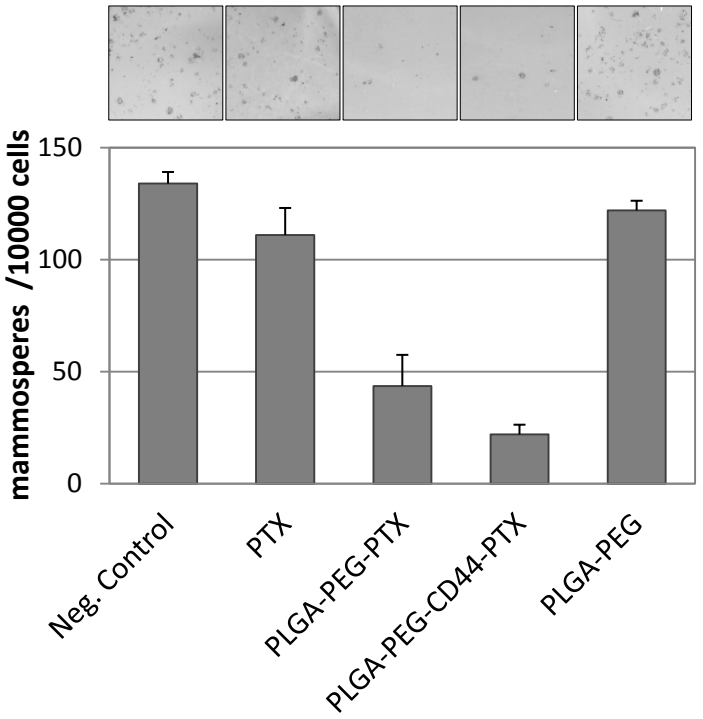
ON | 1week

Cells grow with PTX → Cells grow in PTX free medium → Count colonies

Mammosphers formation MDA-MB-231



Mammosphers formation MCF7



Drug development pipeline: *from discovery to the clinic*

Basic research → **Preclinical development** → **Clinical development**

TARGET	HIT	LEAD	DRUG CANDIDATE	Phase I	Phase II	Phase III
• Identification of molecules • Confirmation of its involvement on the pathology	• HTS • Hit Validation	• medical chemistry • Design analogs • Formulation • Efficacy and dose in animals • Acute Toxicology	• Toxicology • PK • ADME	• Toxicity	• PK • Dosis	• Efficacy

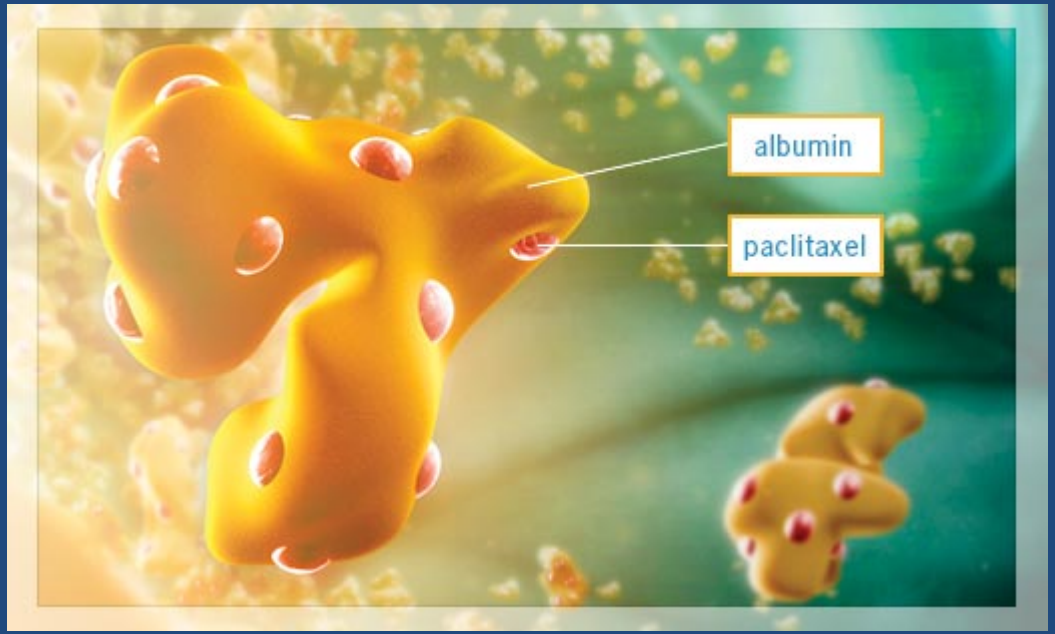
Validation in vitro - in vivo

FDA Approves Novel Abraxane Drug for Pancreatic Cancer

30% better survival when combined with Gemcitabine

originally approved for treatment of breast cancer, under the circumstances that a patient's response to conventional chemotherapy had failed, or following a relapse.

later extended to included patients with a type of lung cancer, called non-small-cell lung cancer (NSCLC).



Active targeting is mediated by SPARC

Analyst for J.P. Morgan, Geoffrey Meacham, considered Abraxane's take-up would be relatively rapid, and its use would soon become standard practice. He estimates that sales could ultimately surpass $750 million, yearly.

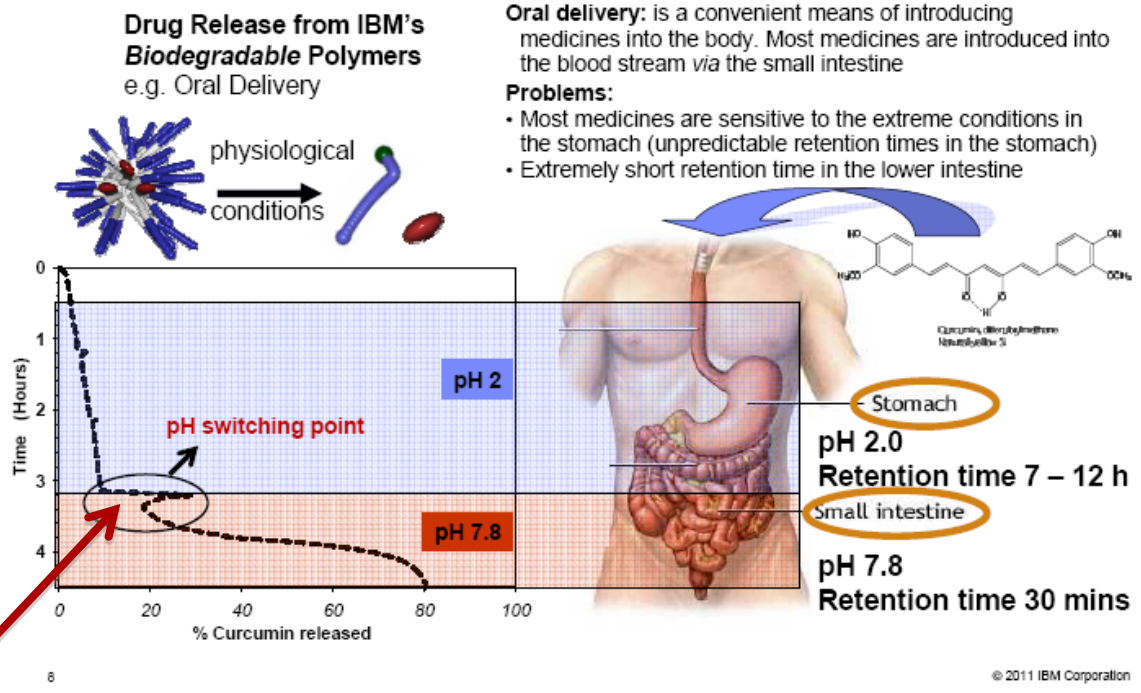
From: http://guardianlv.com/2013/09/fda-approves-novel-abraxane-drug-for-pancreatic-cancer-video/

DRUG DELIVERY SYSTEMS

CAN BE ACTIVATED

BY EXTERNAL SOURCES

Delivery of Drugs, Genetic Therapies and Pharmaceutical Combinations



From Erich Ruetsche, Nanotechnology in Medicine, IBM Research, 2011

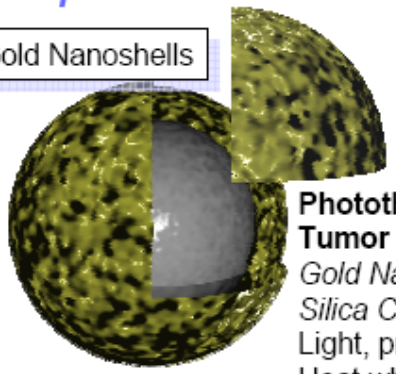
LIGHT (NIR) AS EXTERNAL SOURCE

IBM Research

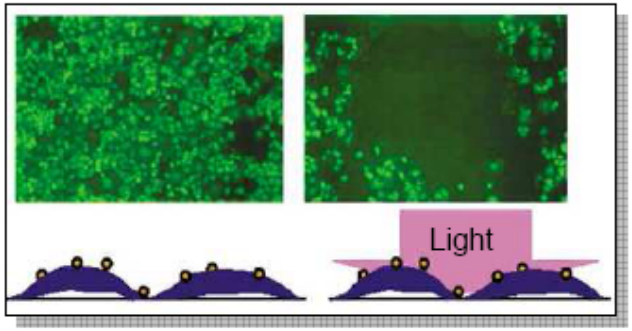
4. Theranostic Nanoparticles:

Nanoparticles that Locate, Report AND Treat Disease, Earlier and Faster

Gold Nanoshells

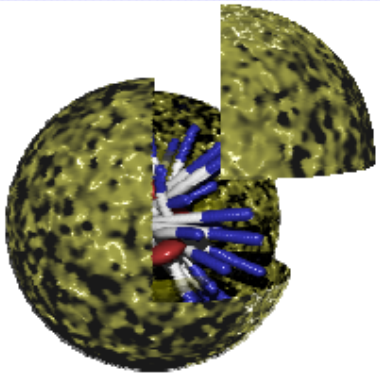


Photothermal Ablation Tumor Treatments:
Gold Nanoshells around Silica Cores Absorb NIR Light, producing Localized Heat which Kills Tumor Cells



Technol. Cancer Res. T.,2004,3(1)

Drug Loaded Gold Nanoshells @ IBM



2nd Generation Photothermal Ablation Tumor Treatments: Polymer/drug Cores

- *New: addition of secondary drug delivery capability (porous nanoshells)*
- *New: addition of secondary imaging contrast capability*
- *Cellular Targeting Surfaces*

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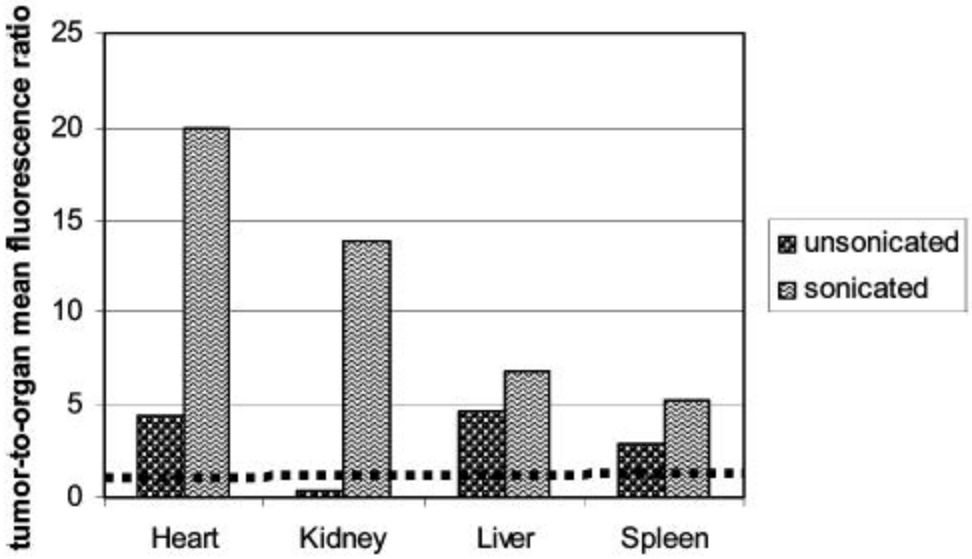
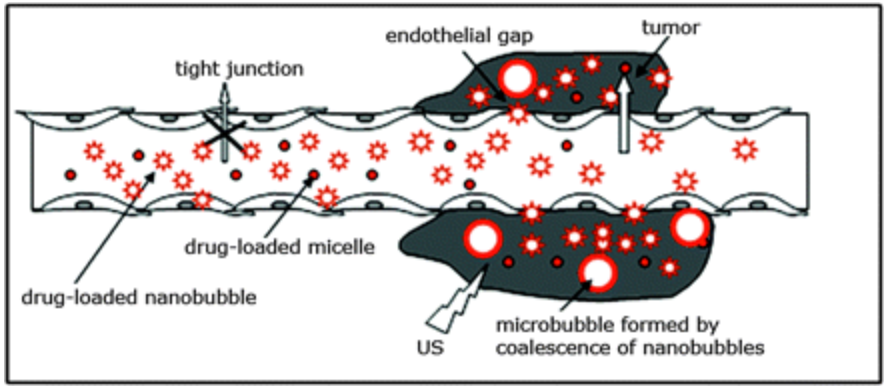
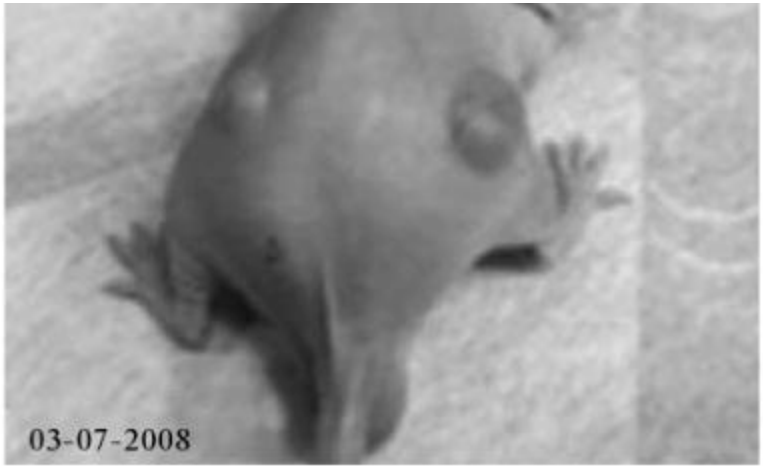
From Erich Ruetsche, Nanotechnology in Medicine, IBM Research, 2011

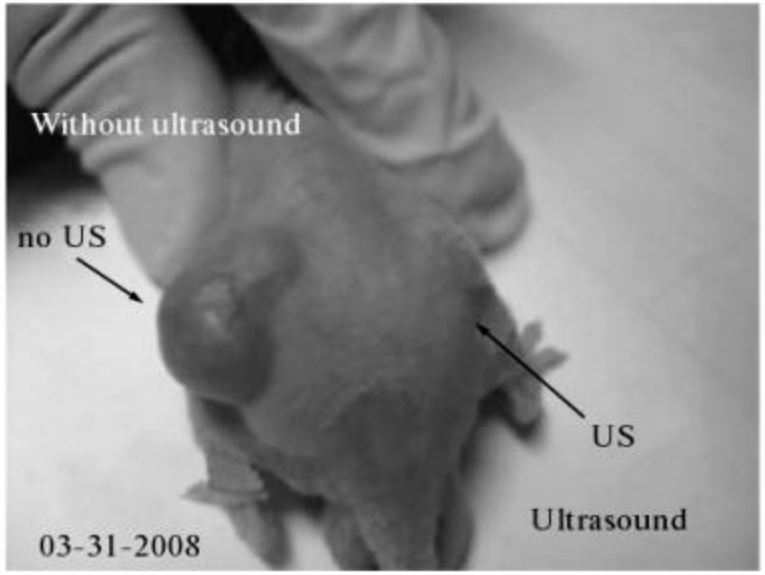
ULTRASOUNDS AS EXTERNAL SOURCE

Nanodroplets strongly retained the loaded drugs; yet, under ultrasound-mediated vaporization they released the drugs into the tumor tissue . Rapoport NY et al, Acoust Phys. 2009 Oct 1;55(4-5):594-601.



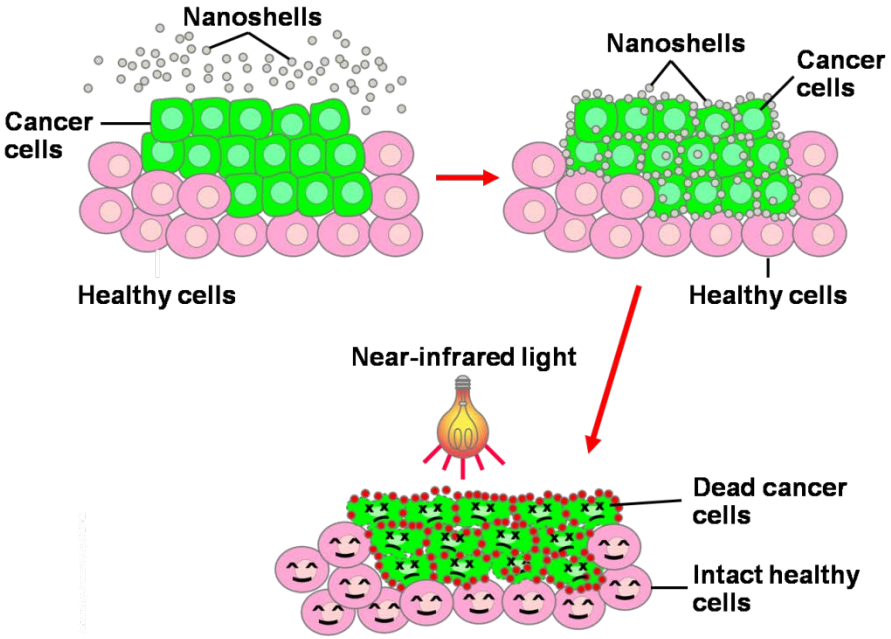






MAGNETIC FIELD AS EXTERNAL SOURCE

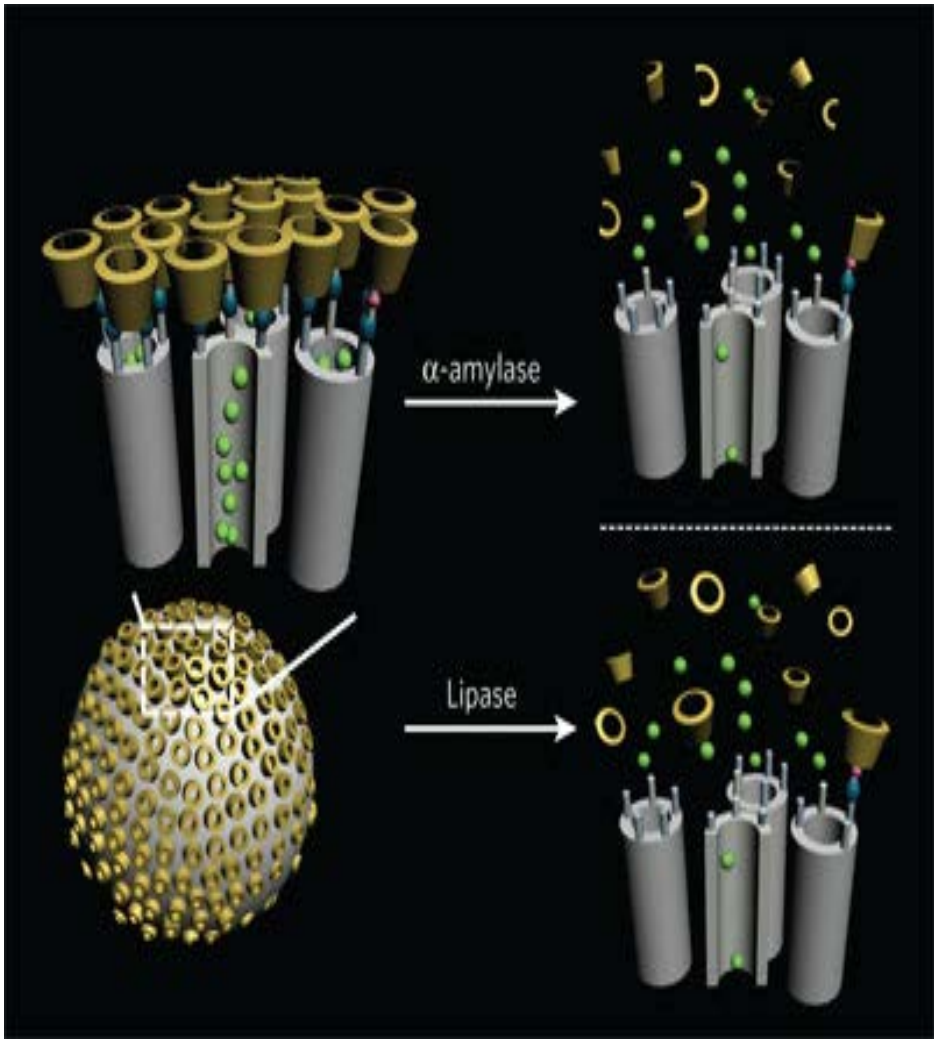
- Thermal ablation of cancer cells
  - Nanoshells have metallic outer layer and silica core
  - Selectively attracted to cancer shells either through a phenomena called enhanced permeation retention or due to some molecules coated on the shells
  - The nanoshells are heated with an external energy source killing the cancer cells

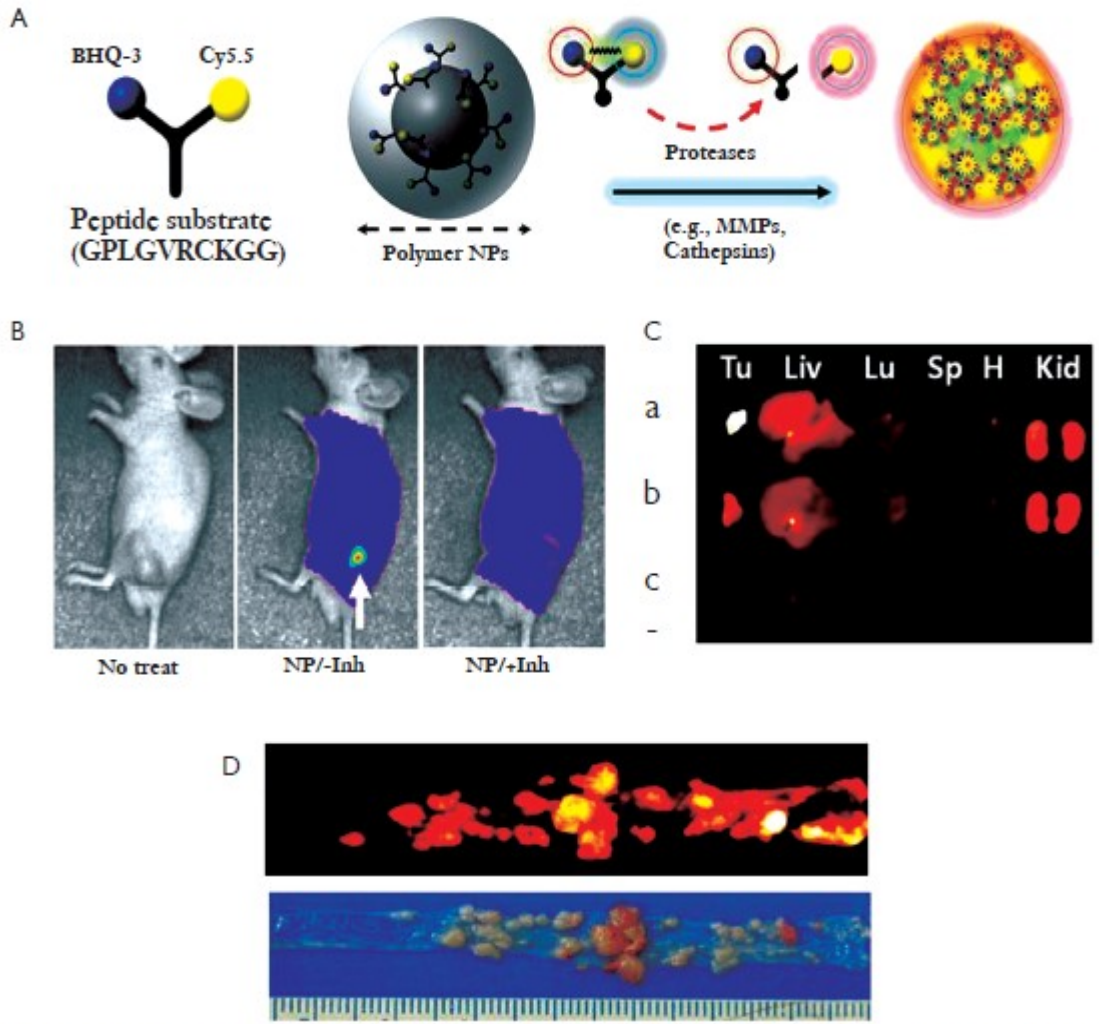


Thermal ablation of cancer cells assisted by nanoshells coated with metallic layer and an external energy source – *National Cancer Institute*

ENZYMES AS EXTERNAL SOURCE

- Nanoscience does have an impact on several areas of microbiology. It allows for the study and visualization at the molecular-assembly levels of a process.
- It facilitates identification of molecular recognition and self-assembly motifs as well as the assessment of these processes





From Kyeongsoon Park in Quantitative Imaging in Medicine and Surgery; 2(2), June 2012.

Vall d'Hebron
Hospital
CIBBIM - Nanomedicina

Thank you !!!

CIBBIM-Nanomedicine
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