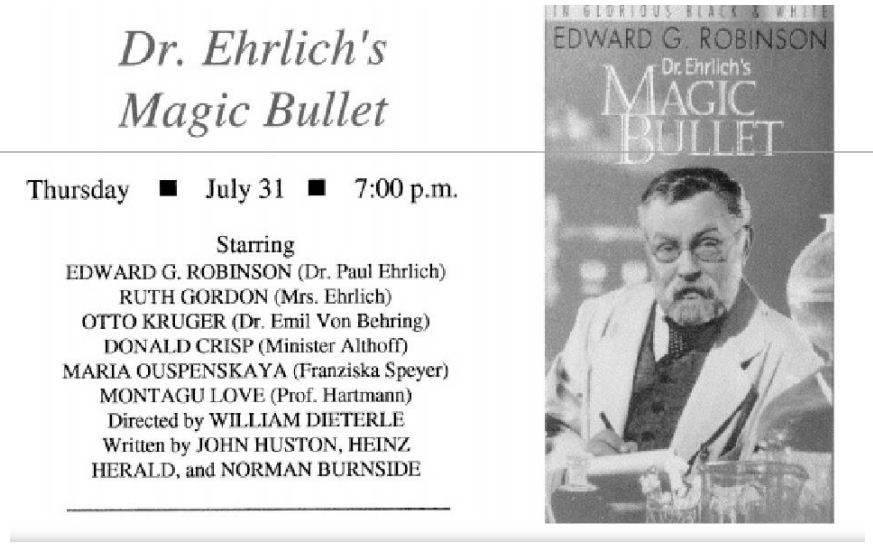
Master 2 Pharmacotechnie et Biopharmacie

Nanoscale drug delivery systems (UE 3)

Simona Mura | octobre 4, 2024 |

The magic bullet



Paul Ehrlich (1854-1915)

Magic bullet

- 1906 : “Magic bullet” (magische Kugel)
- An ideal therapeutic agent, capable of targeting the causative element of the disease

(Nano)carrier

Targeting

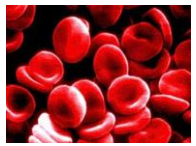
The scale of objects

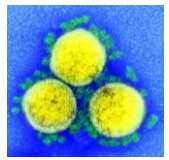
Red blood cells

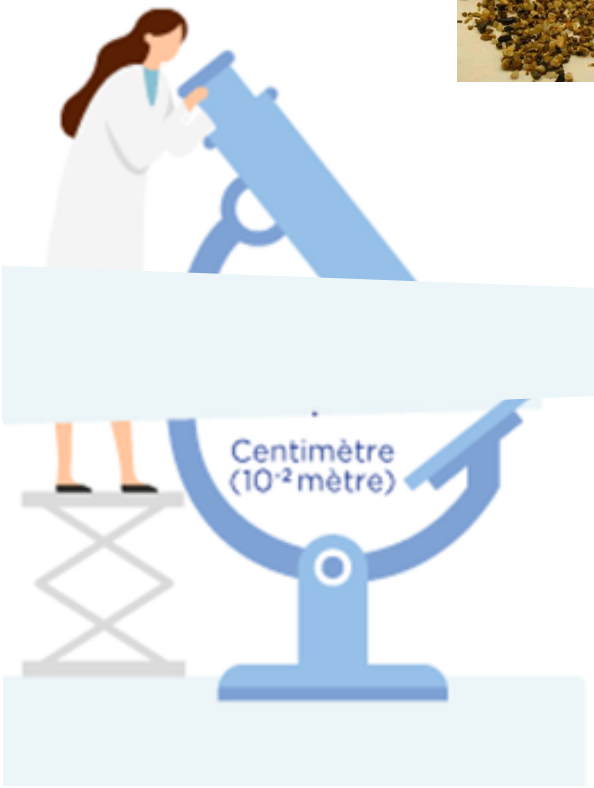
Virus
20 -400 nm

Protein 10 -20 nm

Molecule
< 10 nm





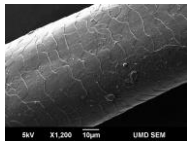


1000 nm 100 nm 1 nm

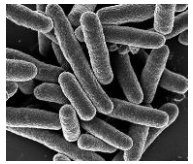
Millimeter
(10^{-3} meter)

Micrometer
(10^{-6} meter)

Nanometer
(10^{-9} meter)



Hair
10 µm



Bacteria
500 nm –10 µm

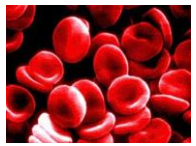
The scale of objects

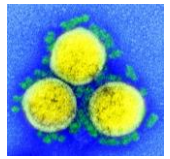
Red blood cells

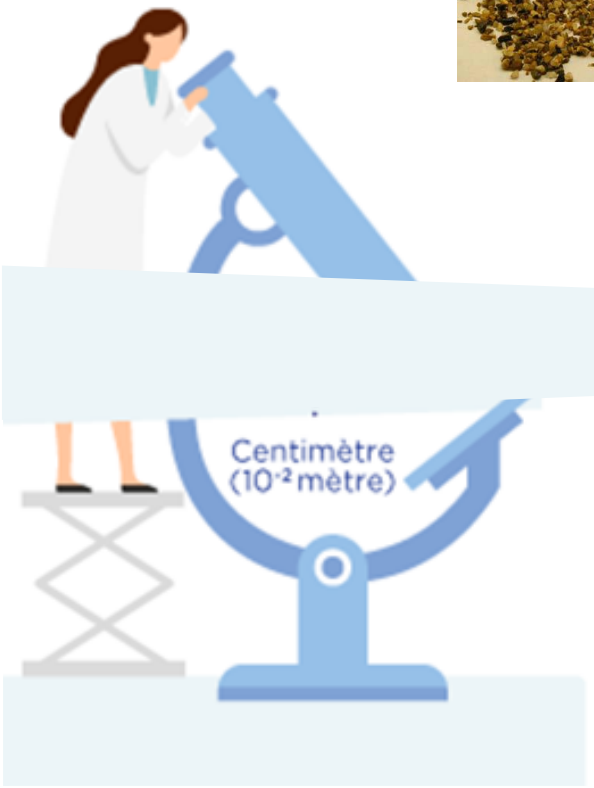
Virus
20 -400 nm

Protein 10 -20 nm

Molecule
< 10 nm







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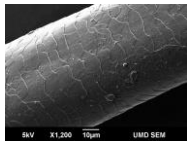
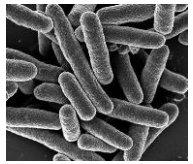
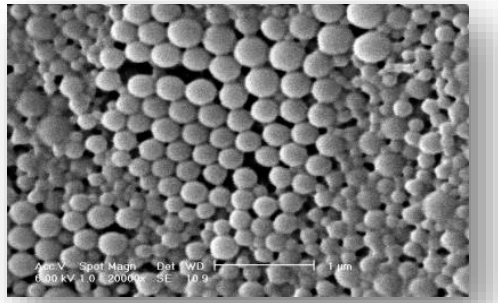


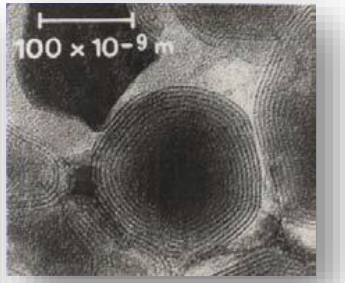
Hair
10 µm



Bacteria
500 nm –10 µm



Polymer nanoparticle

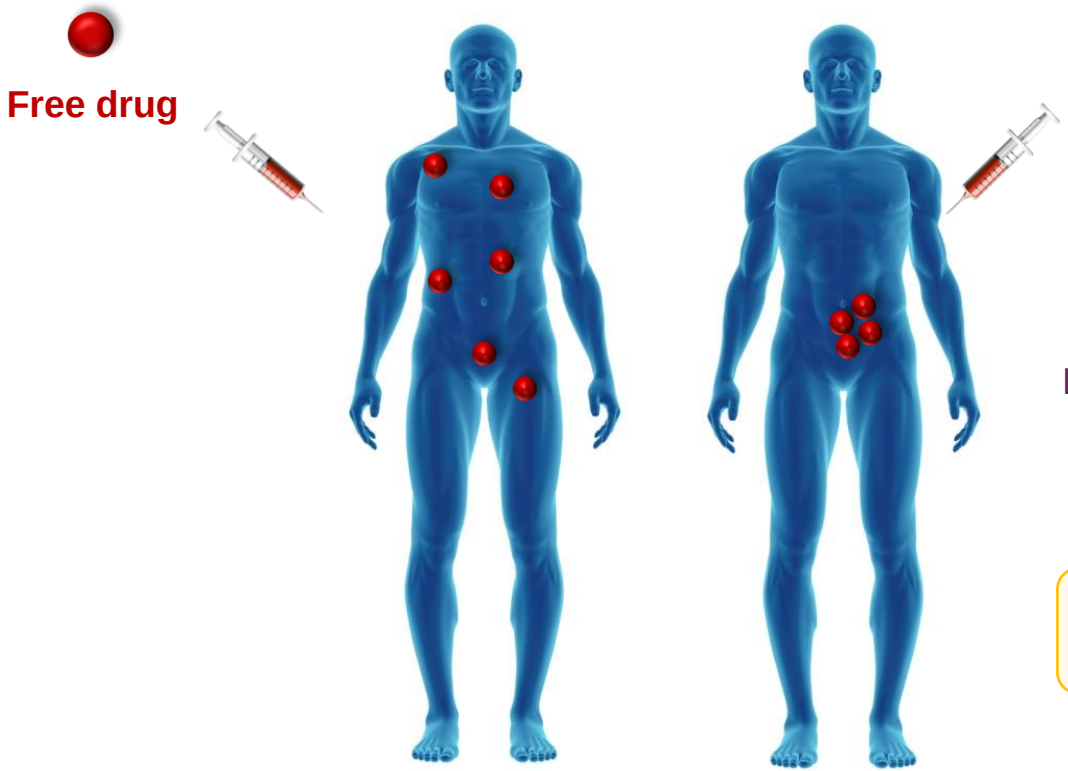


Liposomes

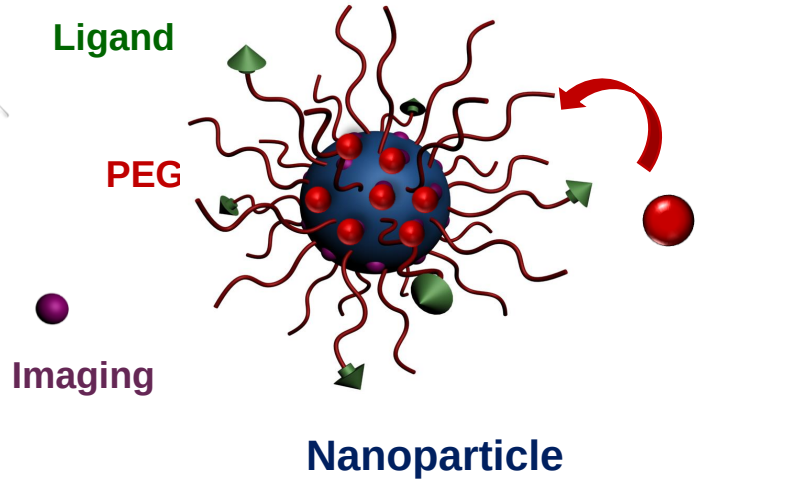
The magic bullet

Make the fate of a drug dependent from a carrier

- **Traditional chemotherapy**



- **Nanomedicines**



Distribution

- Size
- Pka
- Lipophilicity
- Binding to plasma proteins
- Biotransformations

Alternative Distribution

- Vector size
- Lipophilicity
- Stability
- Cytotropism

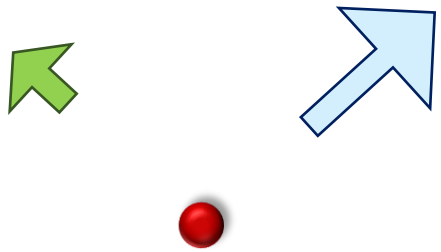
Controlled delivery

Targeting and reducing side effects

Target tissue

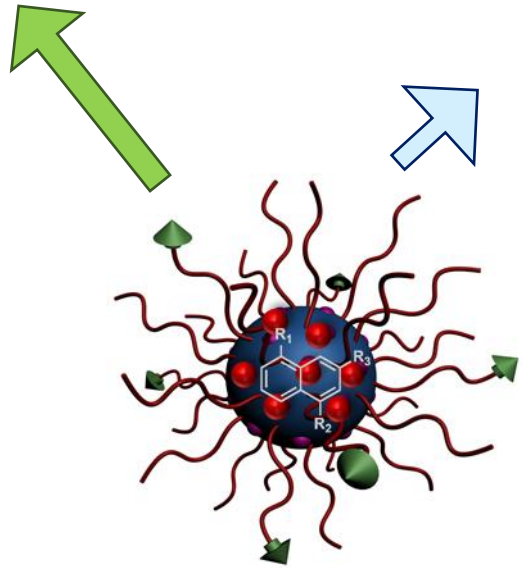
Non-specific distribution
Target of toxicity

SIDE EFFECTS



Target tissue

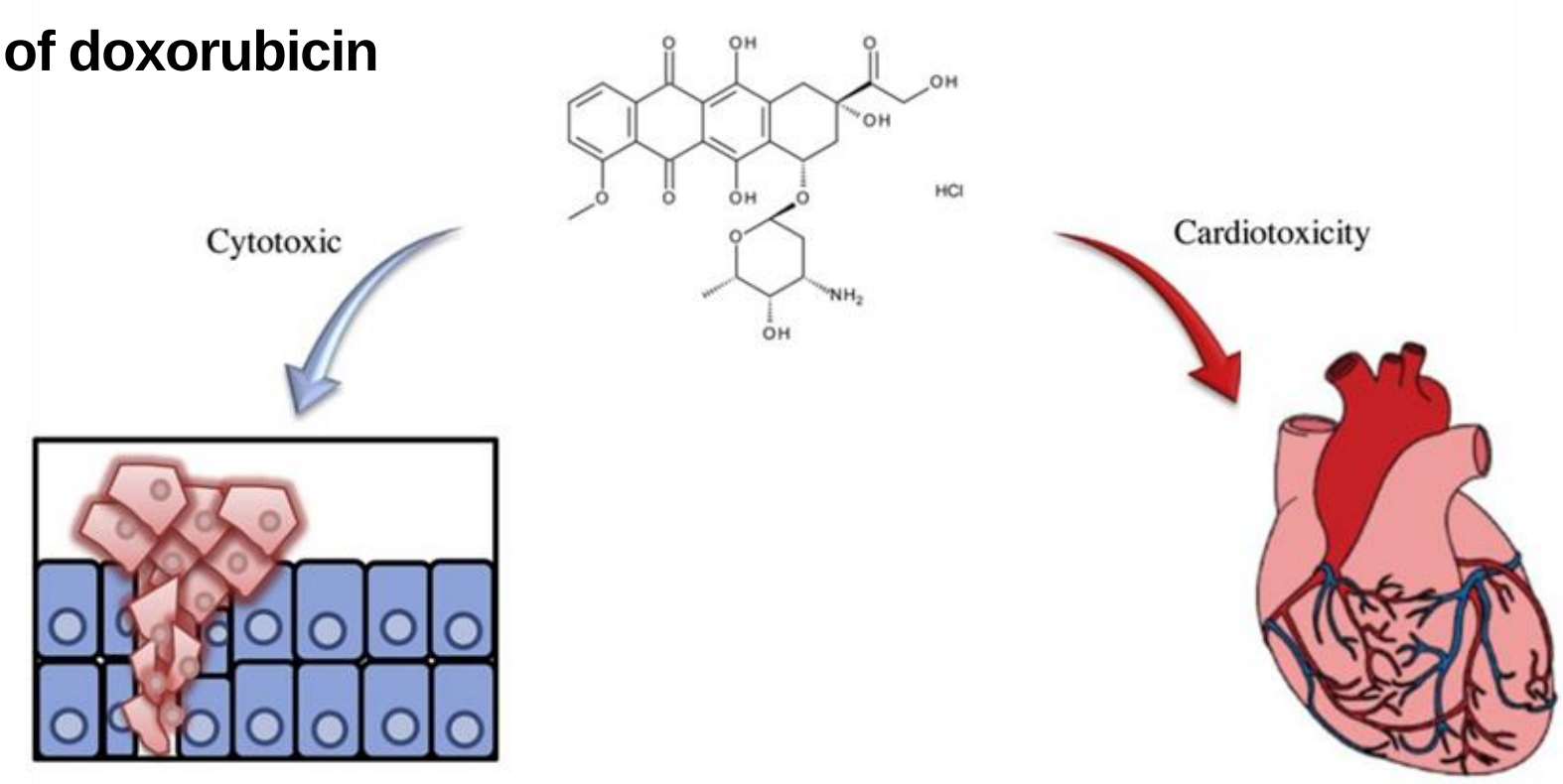
Non-specific distribution
Target of toxicity



Controlled delivery

Targeting and reducing side effects

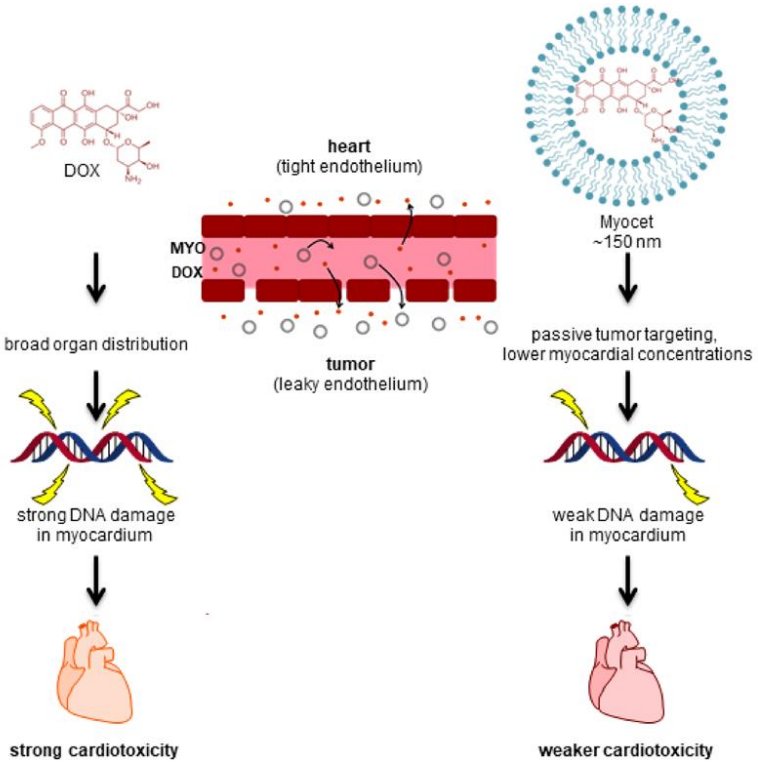
Cardiotoxicity of doxorubicin

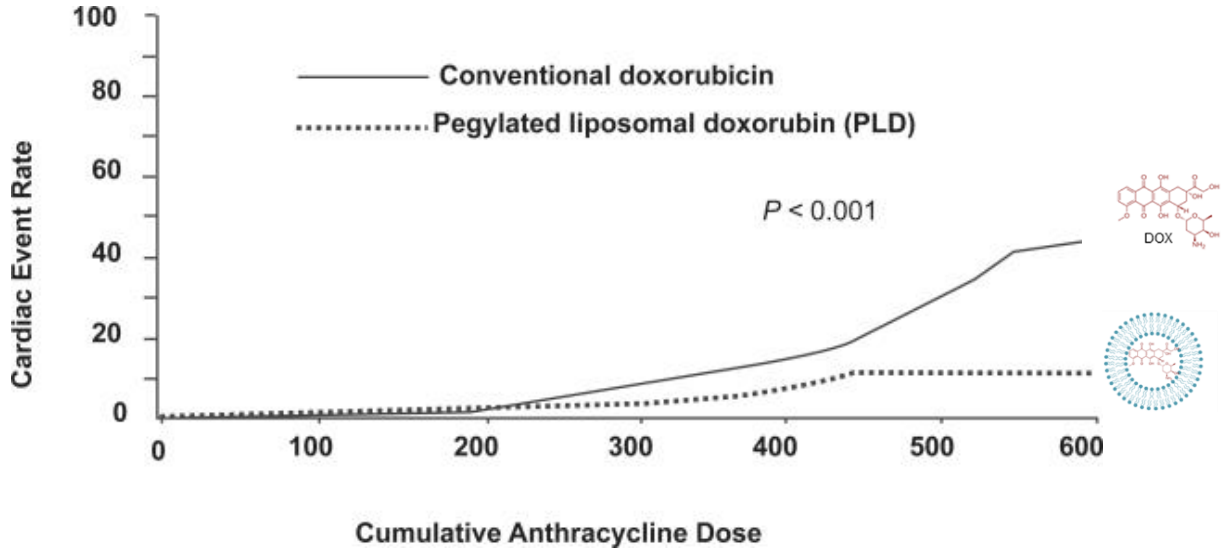


Controlled delivery

Targeting and reducing side effects

Cardiotoxicity of doxorubicin





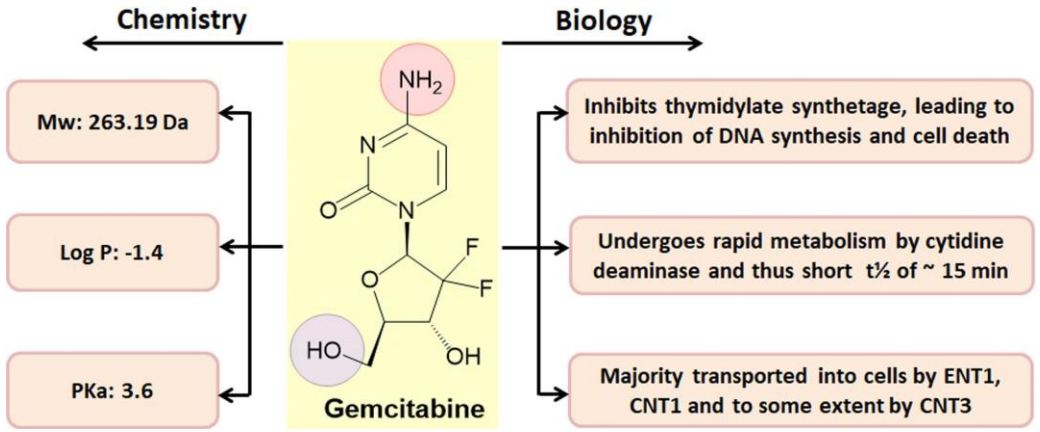
- Efficacy of CAELYX not inferior to doxorubicin
- Significantly less cardiotoxicity in first-line treatment of women with metastatic breast cancer

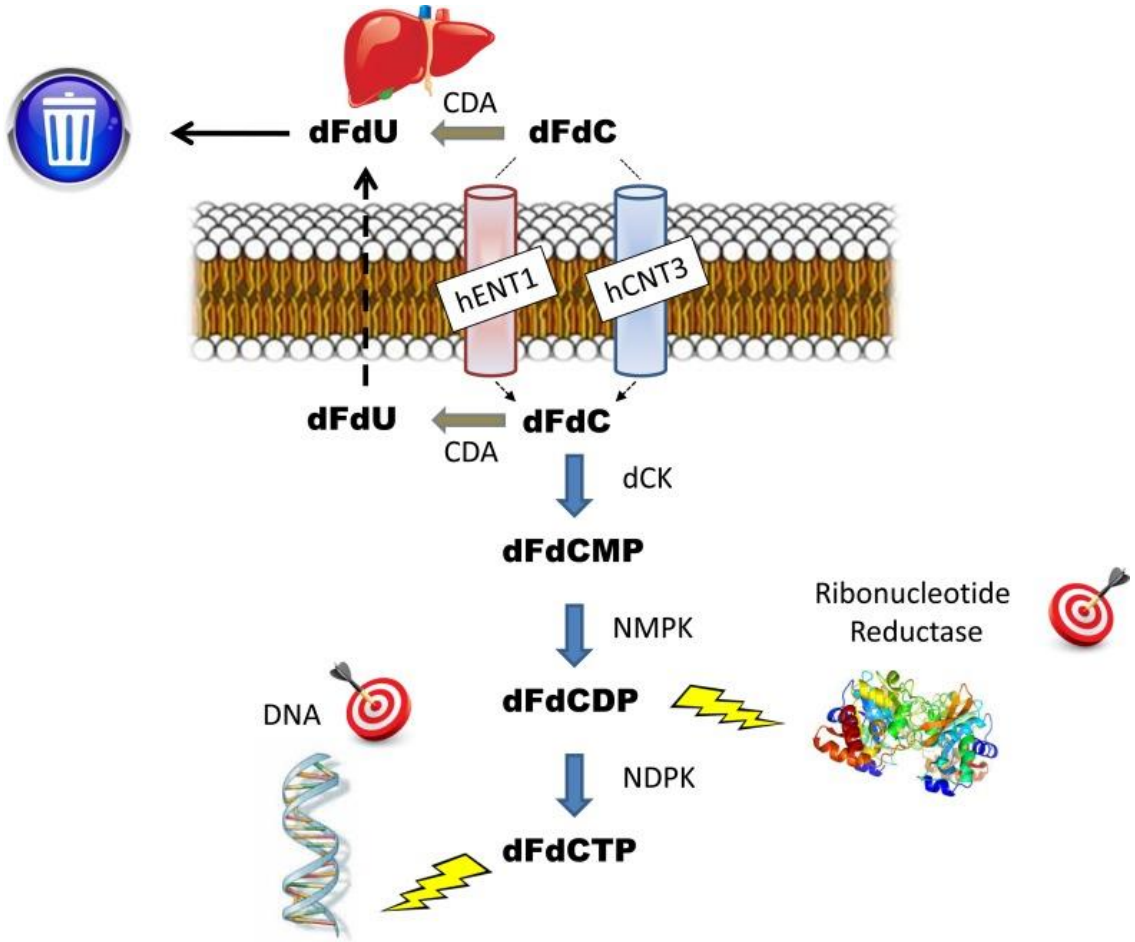
Cardiovasc Res, Volume 116, Issue 5, 1 April 2020, Pages 970–982

Rahman, Atiar M et al. International journal of nanomedicine vol. 2,4 (2007): 567-83.

Controlled delivery

Protection against degradation

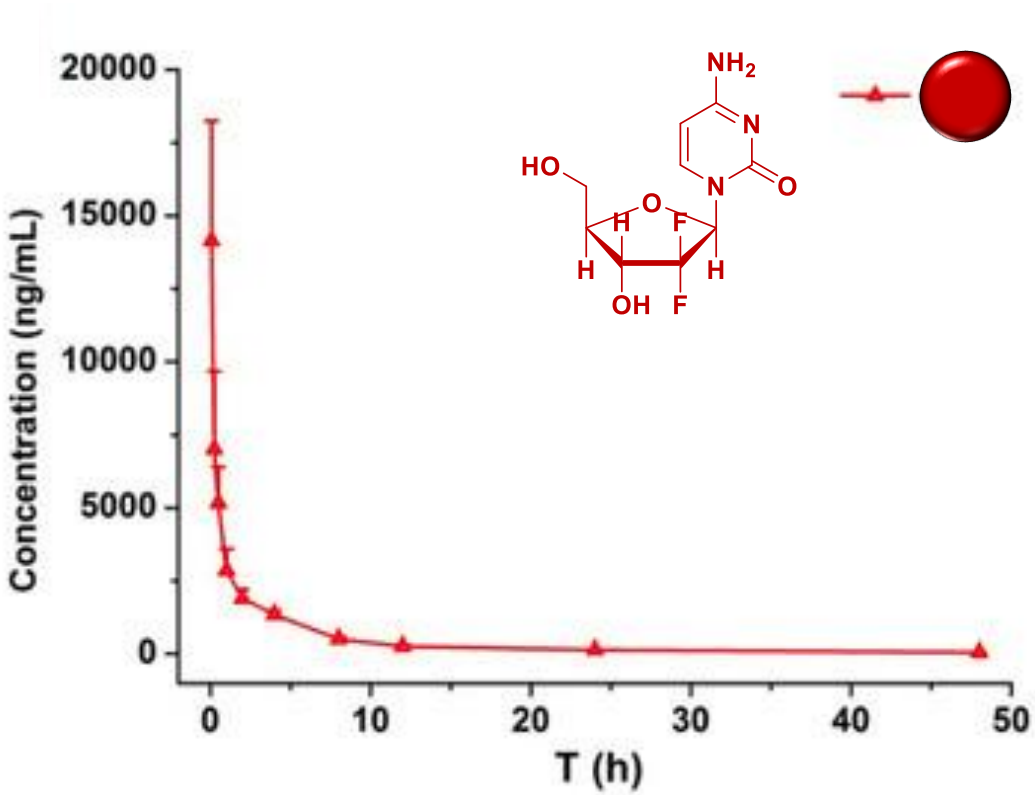


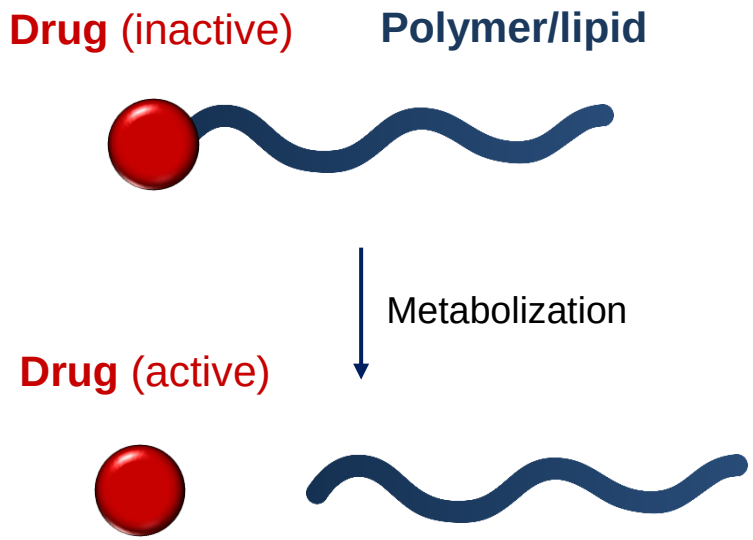


J. Ciccolini, C. Serdjebi G. J. Peters · E. Giovannetti Cancer Chemother Pharmacol (2016) 78:1–12

Controlled delivery

Protection against degradation_prodrug strategy





Advantages

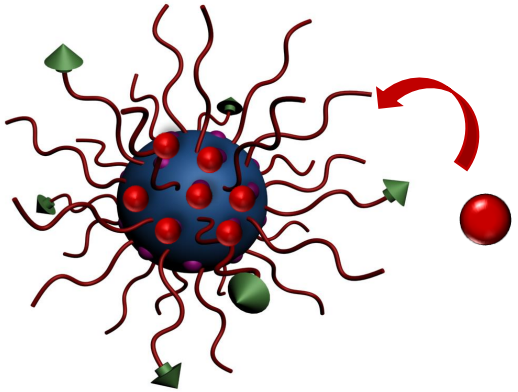
- Sustained drug release
- Increase of the drug chemical stability
- Reduced toxicity before metabolization occurs

Molecules 2020, 25(9), 2218; https://doi.org/10.3390/molecules25092218 .

The magic bullet

Make the fate of a drug dependent from a carrier

Free drug



Nanoparticle

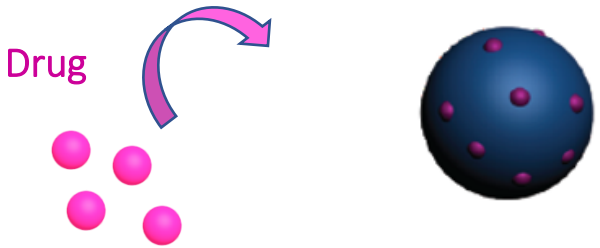
Traditional chemotherapy

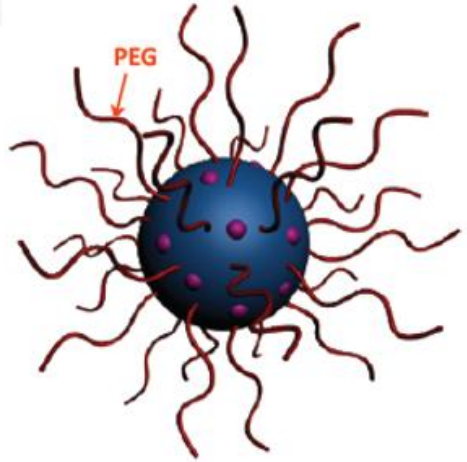
- Instability/metabolization
- Limited intracellular accumulation
- Lack of cell/tissue specificity
- Induction of resistance phenomena

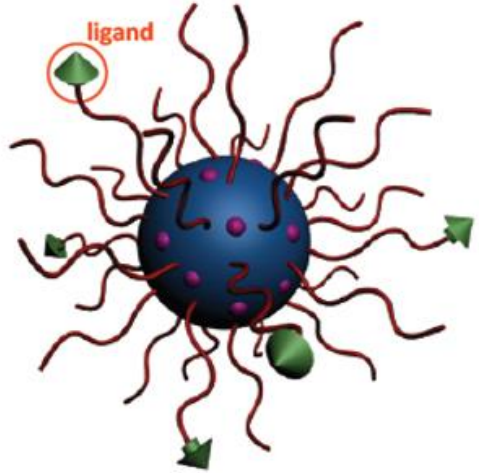
Nanomedicines

- Protection from degradation
- Increase intracellular penetration
- Cell/tissue targeting
- Overcome resistance

Nanomedicine generations







1st generation

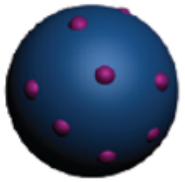
2nd generation

Stealth/Long circulating

3rd generation

Stealth/Long circulating
Surface functionalized

Nanomedicine generations



1st generation

2nd generation

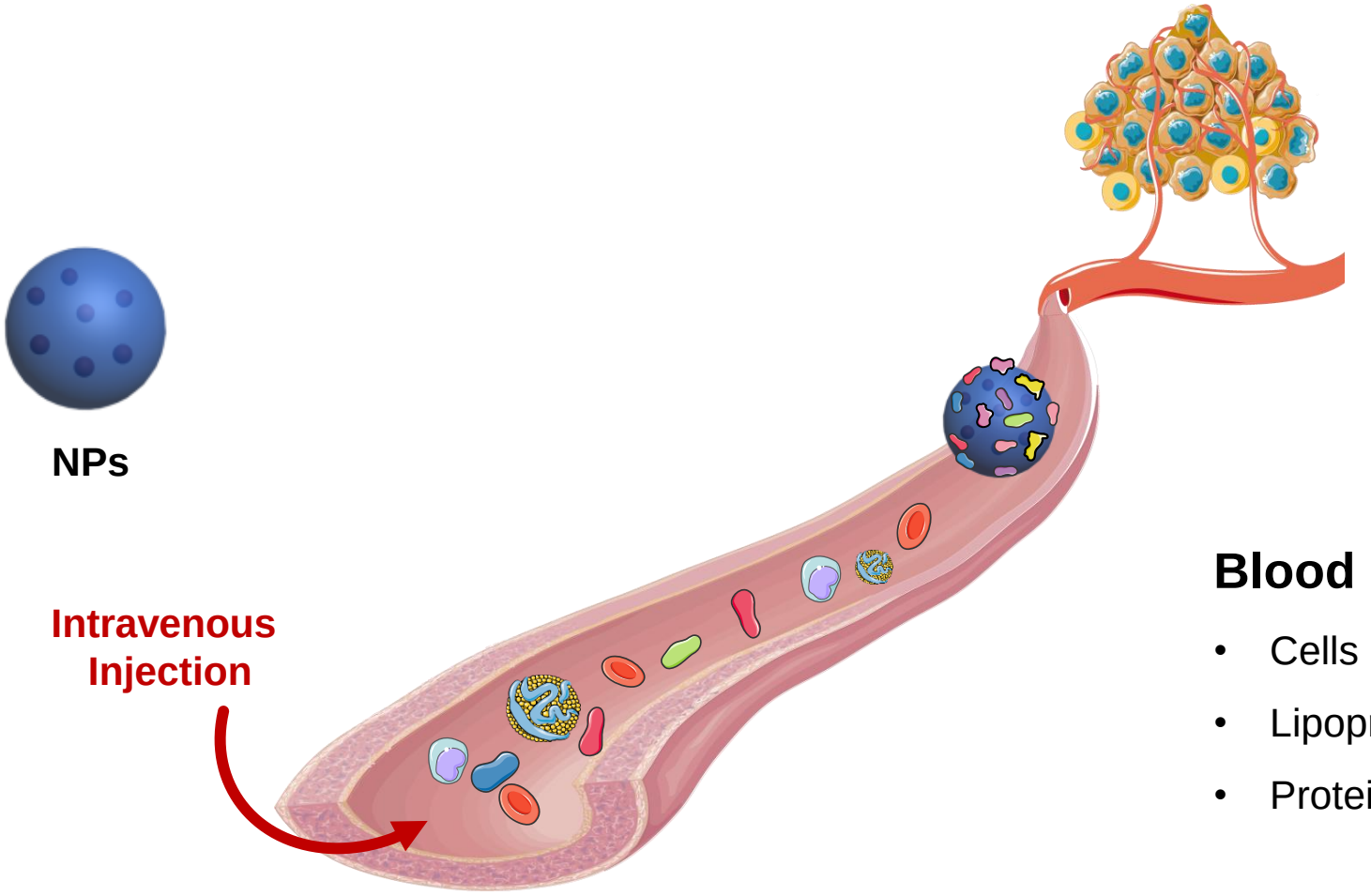
Stealth/Long circulating

3rd generation

Stealth/Long circulating
Surface functionalized

In vivo fate

Interactions in the biological medium



Blood components

- Cells
- Lipoproteins
- Proteins

Acquisition of a biological Identity

In vivo fate

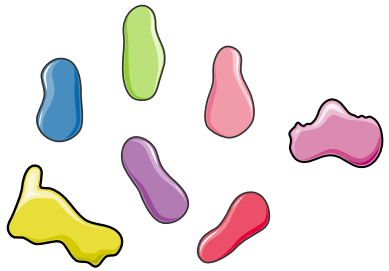
Interactions in the biological medium_the protein corona

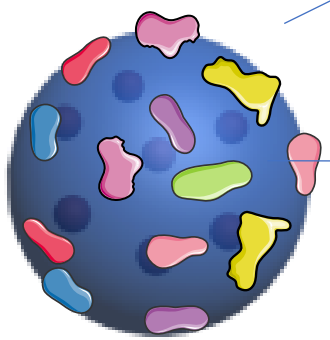
Opsonins

- Coagulation proteins : fibrinogen/kininogen-1
- Acute phase proteins
- Tissue leakage proteins
- Components of the complement system
- Immunoglobulins

NON Opsonins

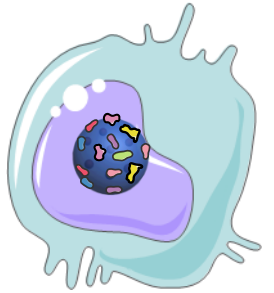
- Albumin
- Apoproteins



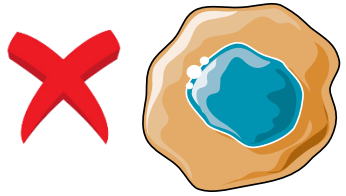


Aggregation

Elimination by macrophages



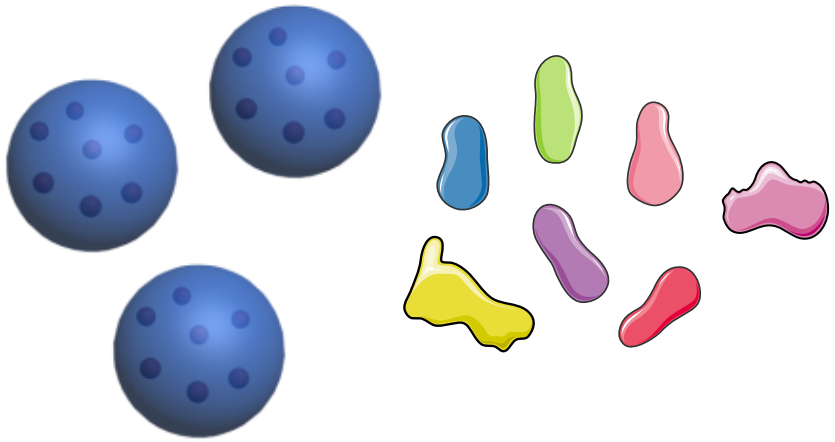
Change the interactions with the cells



Acquisition of a specific molecular signature

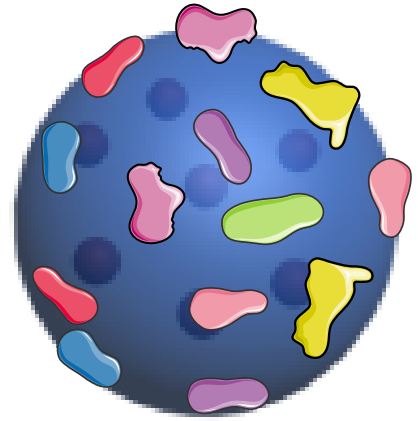
In vivo fate

Interactions in the biological medium_the protein corona



- Hydrogen bonds
- Electrostatic interactions
- Hydrophobic interactions
- Acid-base interactions

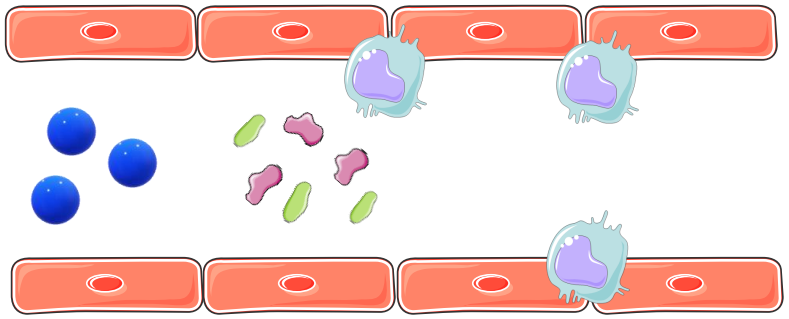
- Hydration/solvation forces
- Steric hindrance
- Electrostatic repulsion



First generation : *Fate of nanoparticles after IV administration*

- Macrophage uptake and liver accumulation

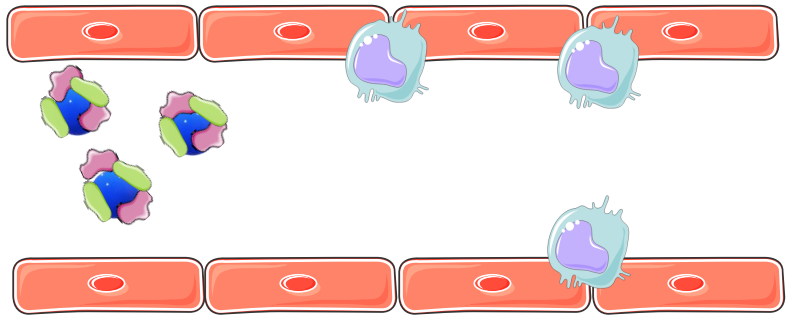
Endothelium



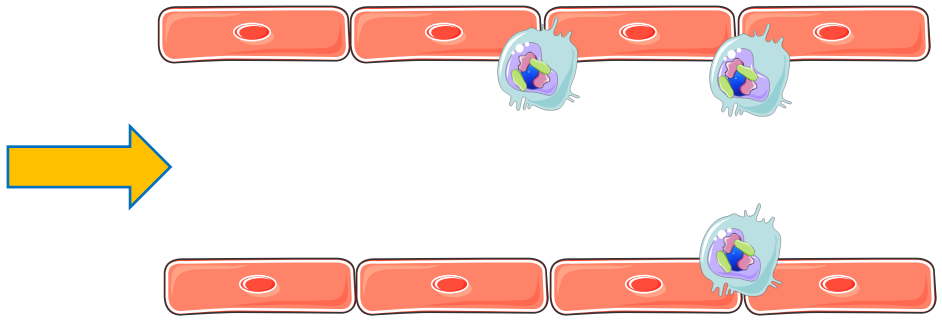
Plasma proteins

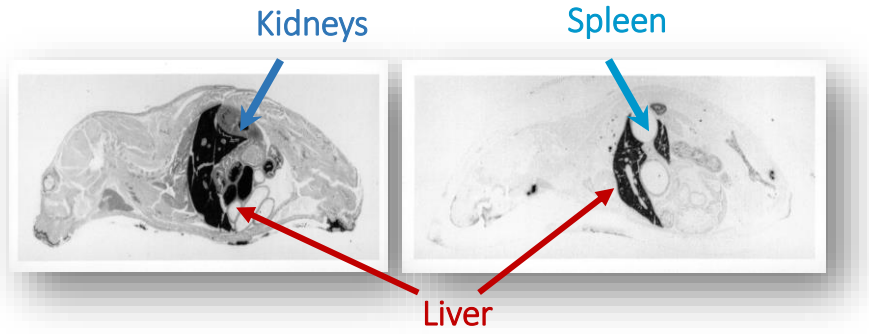
Macrophages

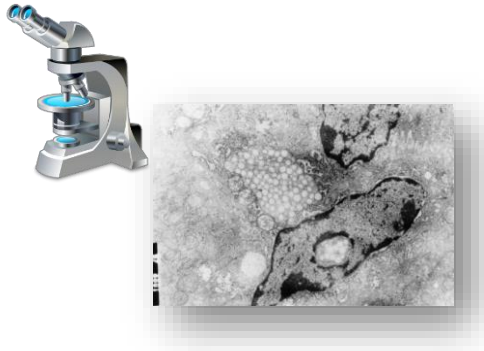
Opsonization



Internalization







Nanoparticle uptake by Kupffer cells

Rapid removal from the circulation

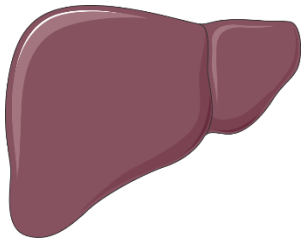
In vivo fate

Interactions in the biological medium_the protein corona

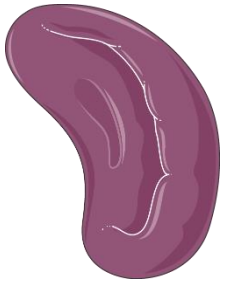
Endocytosis/Phagocytosis →

- Monocytes
- Tissue macrophages

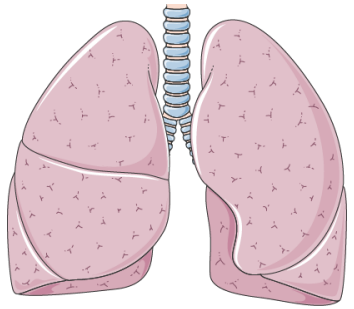
Mononuclear phagocyte system



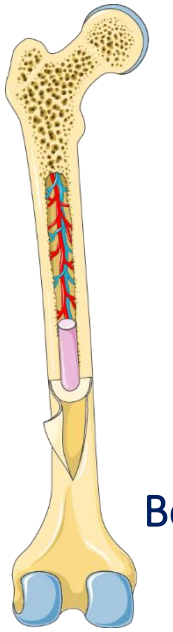
Liver



Spleen



Lungs

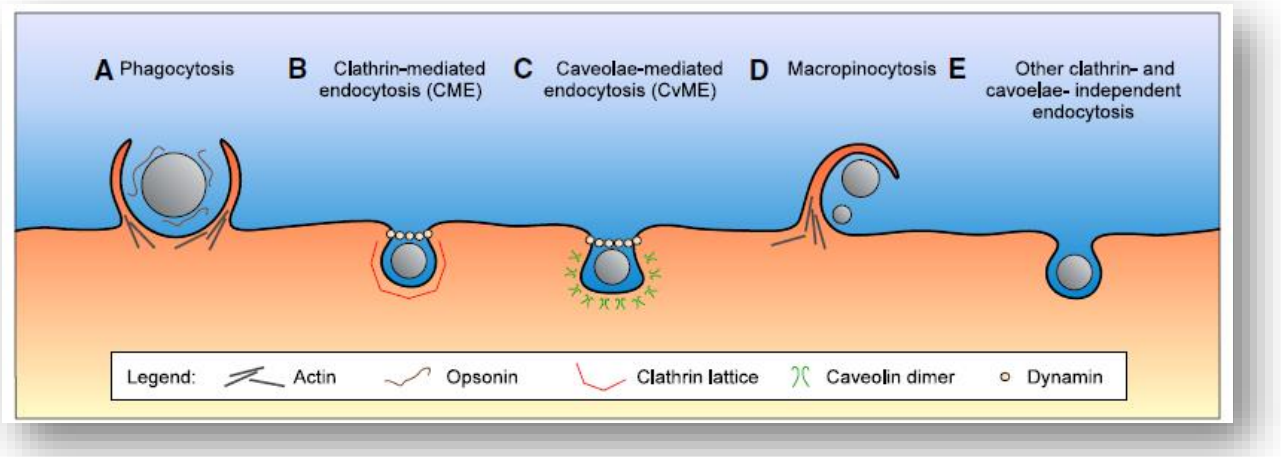


Bone marrow

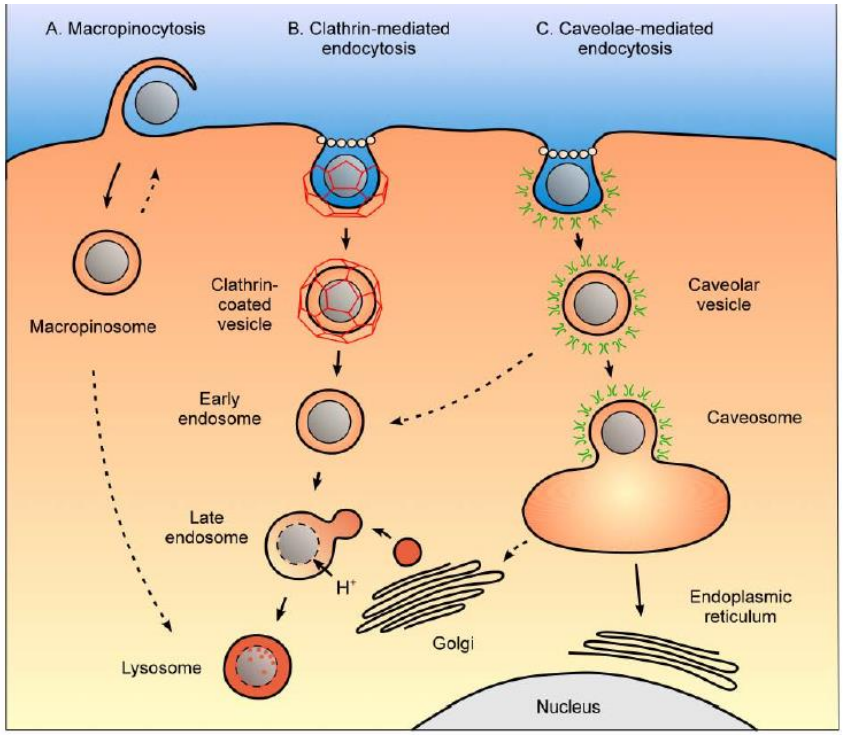
Schöttler, S. et al.,. Nature Nanotech 11, 372–377 (2016).

In vivo fate

Internalization pathways



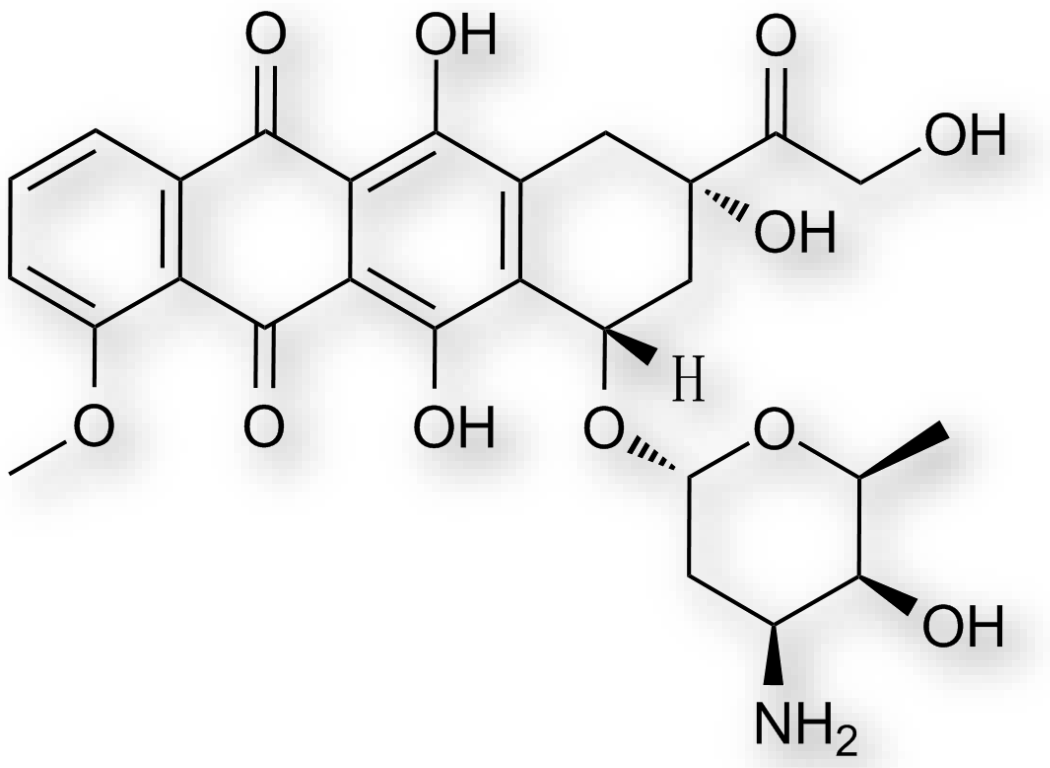
Endocytosis



Hillaireau et al., Cell. Mol. Life Sci. (2009) 66:2873–2896

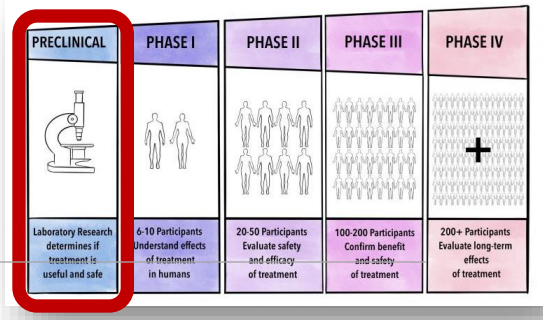
Antitumor chemotherapy

Doxorubicin

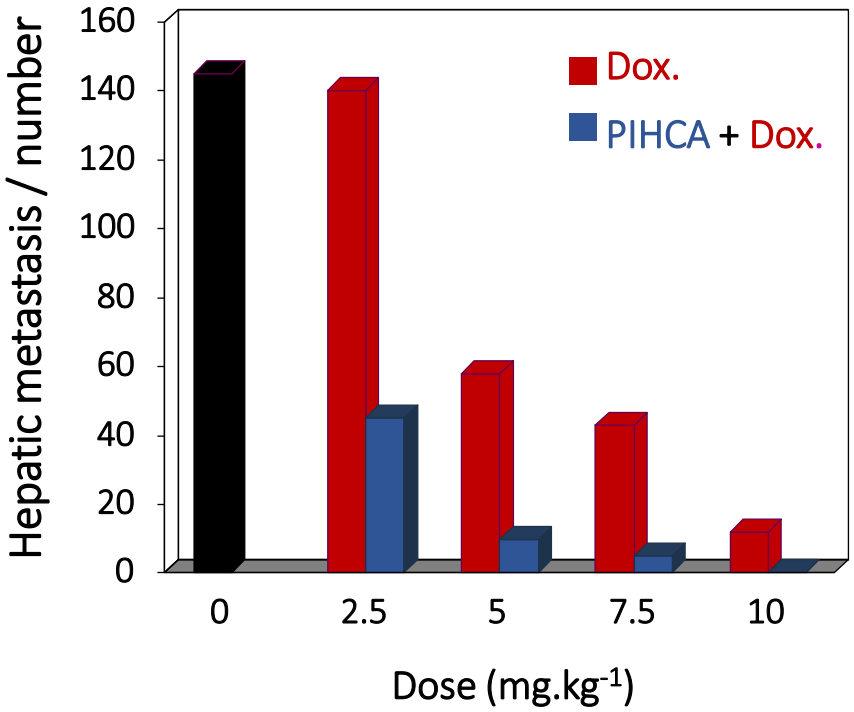


Antitumor chemotherapy

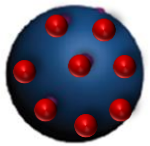
Doxorubicin _Livatag, doxorubicin transdrug



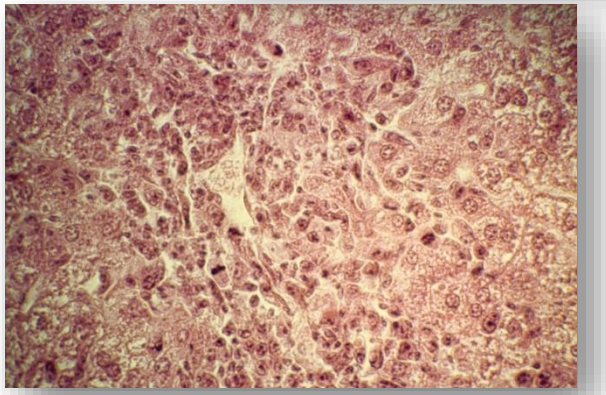
in vivo model of hepatic metastasis

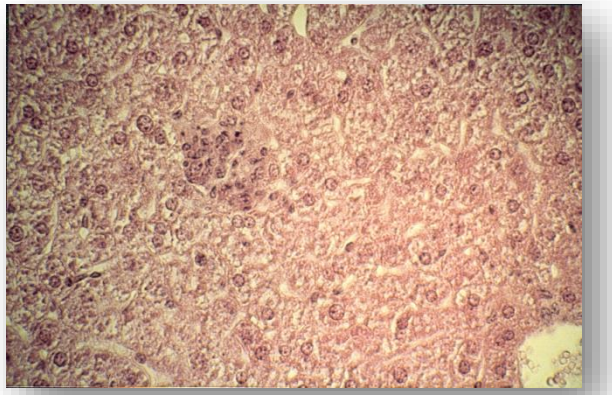


Doxorubicin



Dox-loaded
PIHCA nanoparticles



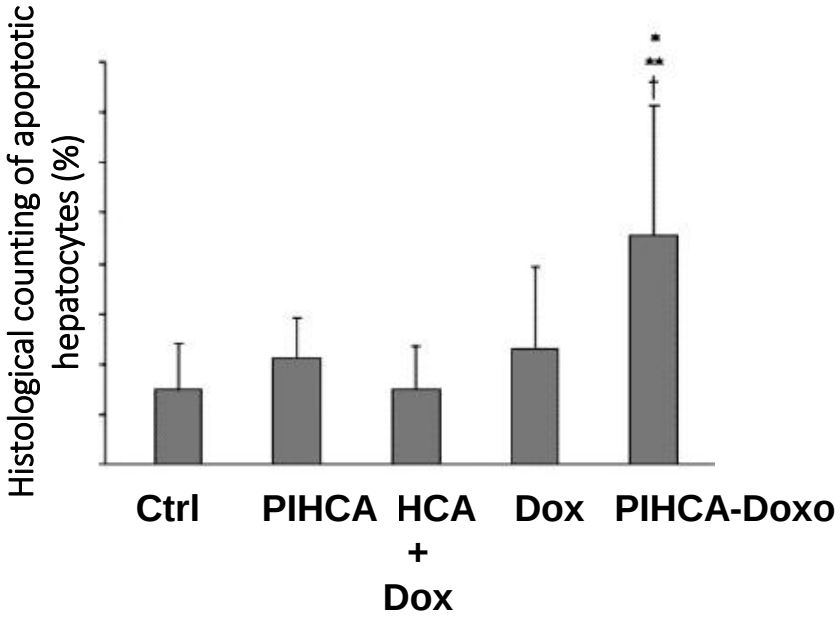


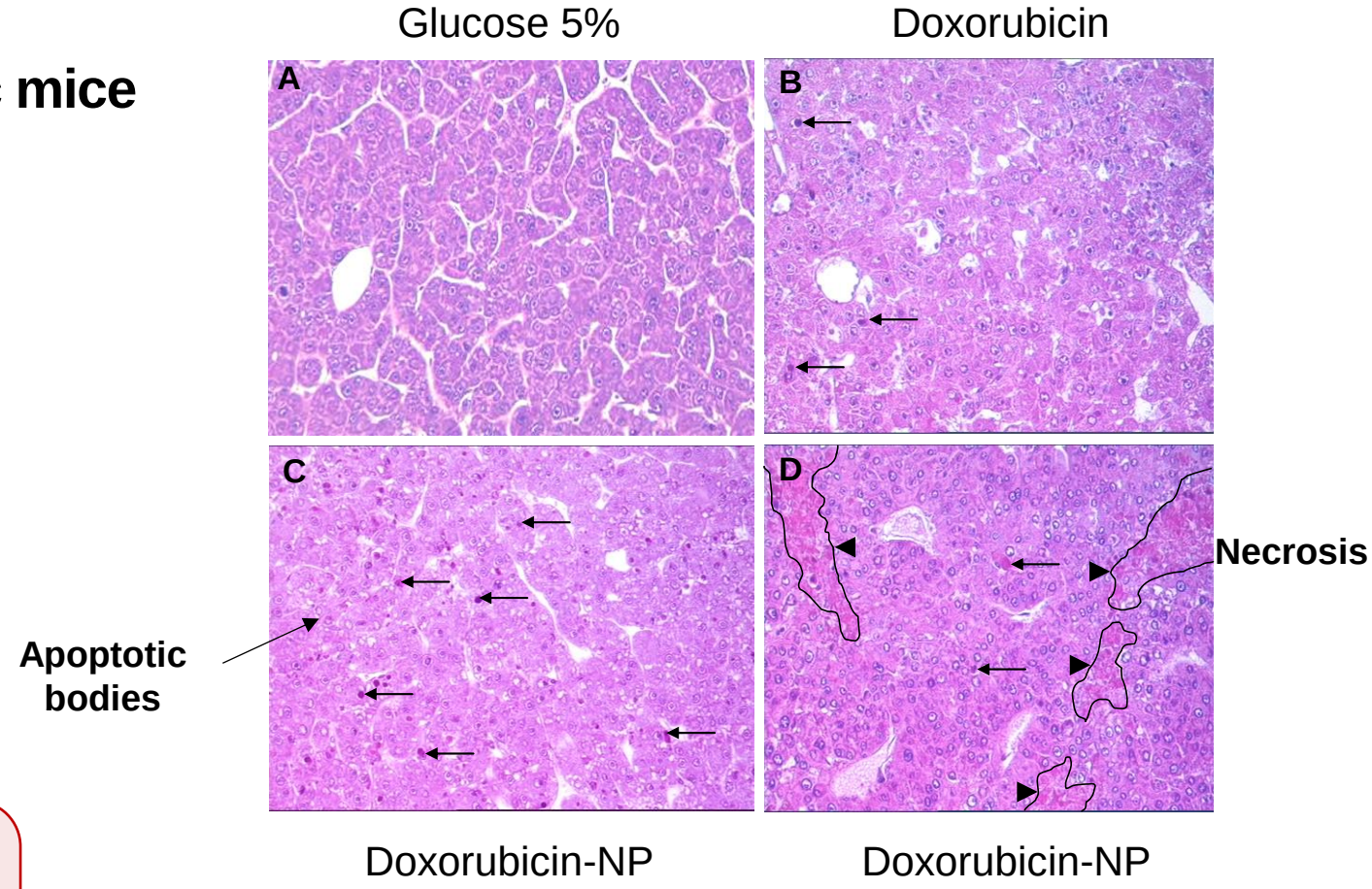
P. Couvreur *et al*, *J. Pharm. Pharmacol*. 1979, 31, 331
N. Chiannilkulchai *et al*., Sel. Cancer *Ther*. 1989, 5, 1

Antitumor chemotherapy

Doxorubicin _Livatag, doxorubicin transdrug

in vivo cytotoxicity in X/myc transgenic mice

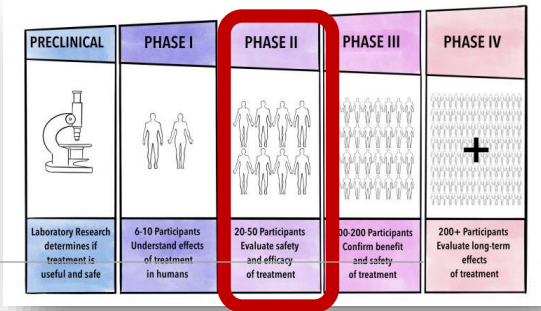




Potential breakthrough in the treatment of hepatocellular carcinoma

Antitumor chemotherapy

Doxorubicin _Livatag, doxorubicin transdrug



- PHASE II

Baseline
Tumor size 3000 mm²

intra-arterial infusion

(30 mg/m²)

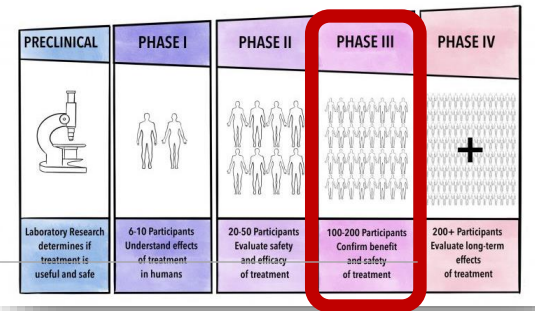
After 4 weeks
Evident necrotic area

Increased survival time 17 versus 15 months for patients getting current best of care

(transarterial chemoembolisation with a cytotoxic drug)

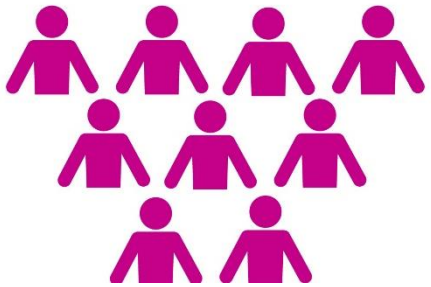
Antitumor chemotherapy

doxorubicin transdrug_ReLIVE: phase III *NCT01655693*

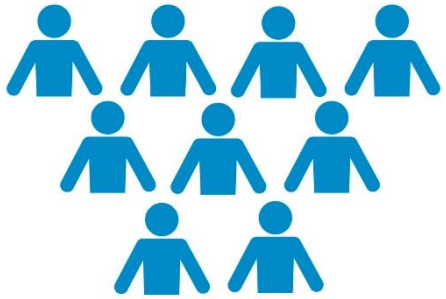


- 397 patients, 11 countries, 70 centers
- Randomized, open label, **comparative 3 parallel arms study**

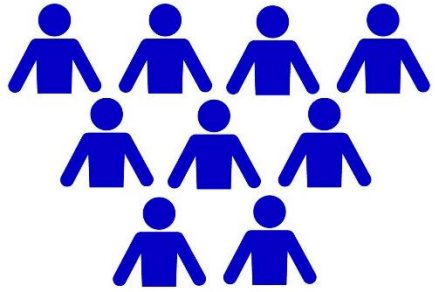
Administration through a slow 6 hours IV infusion every 4 weeks (n=263)



Best Standard Care



20 mg/m^2



30 mg/m^2

Merle et al., *Lancet Gastroenterol Hepatol* **2019,** 4, 454-465

Antitumor chemotherapy

doxorubicin transdrug_ReLIVE: phase III *NCT01655693*

Endpoints

Primary

overall survival

Secondary

Response rate & progression-free
Pharmacokinetics in selected sites

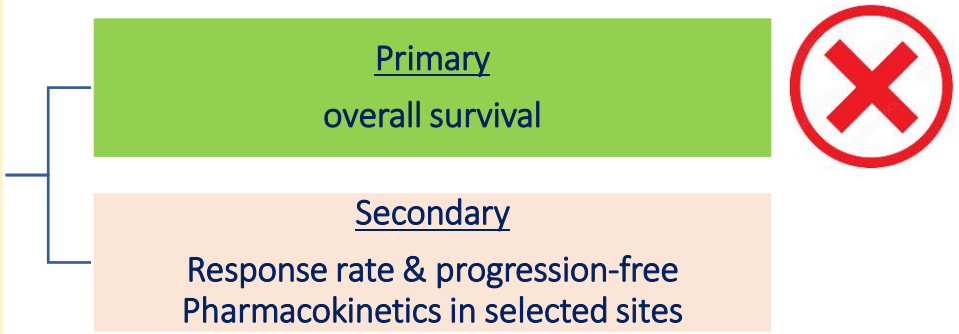
- ReLIVE: international phase III clinical study *NCT01655693*

Merle et al., *Lancet Gastroenterol Hepatol* 2019, 4, 454-465

Antitumor chemotherapy

doxorubicin transdrug_ReLIVE: phase III *NCT01655693*

Endpoints



September 11, 2017

- **Unexpected high survival** in the comparative group
- Livatag® **showed a similar effect** to the control group
- **No difference** between the two arms (20 or 30mg/m²)
- **Favorable** overall safety and tolerability

Merle et al., *Lancet Gastroenterol Hepatol* **2019,** 4, 454-465

Antitumor chemotherapy

doxorubicin transdrug_ReLIVE: phase III *NCT01655693*

Endpoints

Primary

overall survival

Secondary

Response rate & progression-free
Pharmacokinetics in selected sites

FAILED

September 11, 2017

- **Unexpected high survival** in the comparative group
- Livatag® **showed a similar effect** to the control group
- **No difference** between the two arms (20 or 30mg/m²)
- **Favorable** overall safety and tolerability

- Enrollment of patients with a better prognosis than in previous trials
- Placebo **is not** the control group
- Standard treatment is the control group *(47% gemcitabine plus oxaliplatin)*

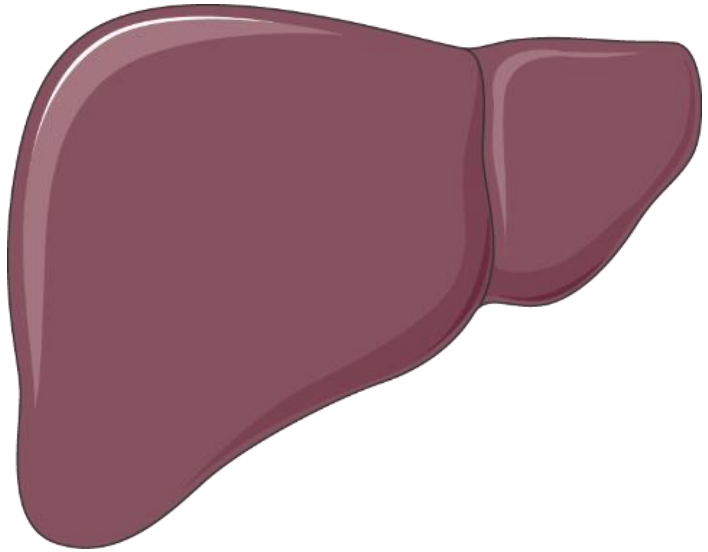
Merle et al., *Lancet Gastroenterol Hepatol* **2019,** 4, 454-465

First generation

Conclusions

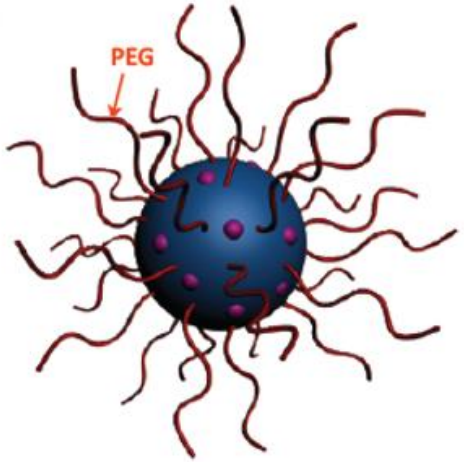
The first generation of nanocarriers was promising

The liver is always the target, so many liver diseases are likely to benefit from such targeting



Nanomedicine generations

1st generation



2nd generation

Stealth/Long circulating

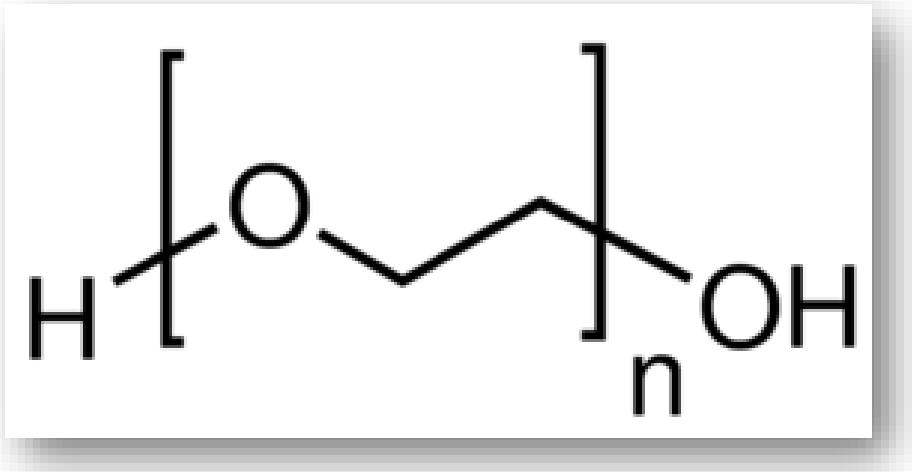
3rd generation

Stealth/Long circulating
Surface functionalized

In vivo fate

If you want to be invisible, look like water

Poly(ethylene glycol)

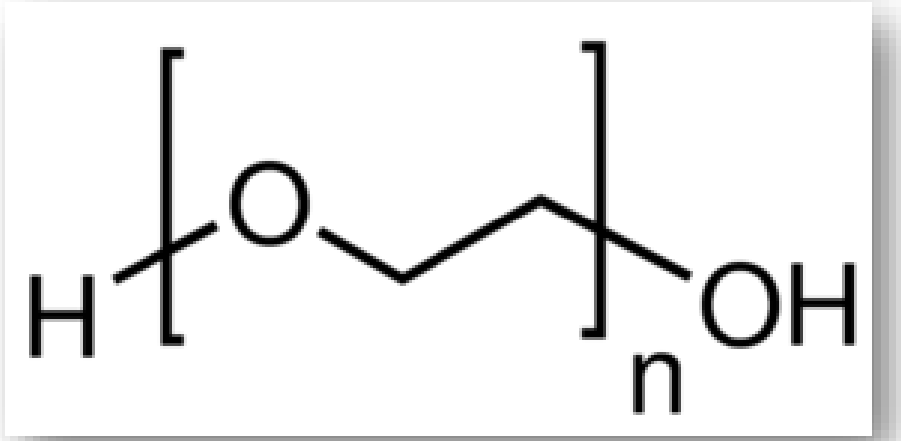


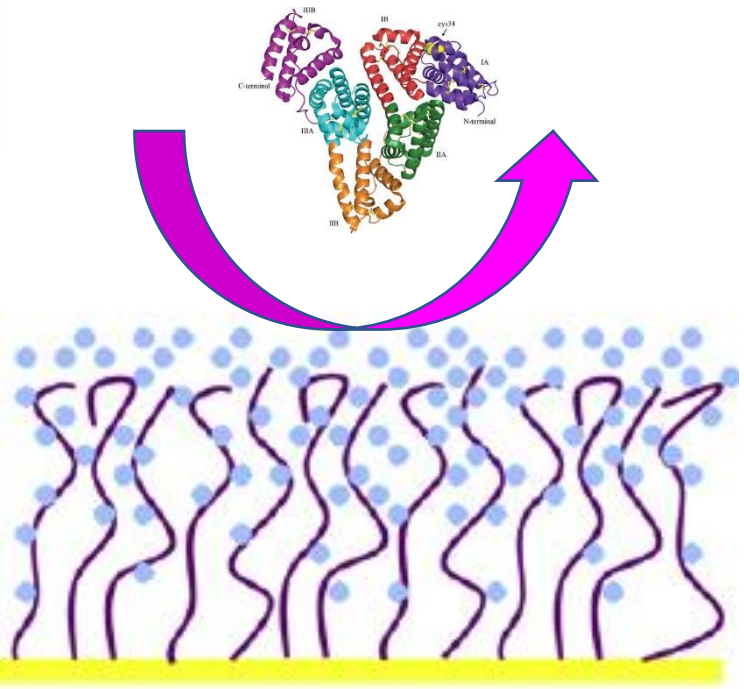
In vivo fate

If you want to be invisible, look like water

Poly(ethylene glycol)

- Non-ionic hydrophilic polymer
- Biocompatible
- Stealth effect
- Prolonged circulation

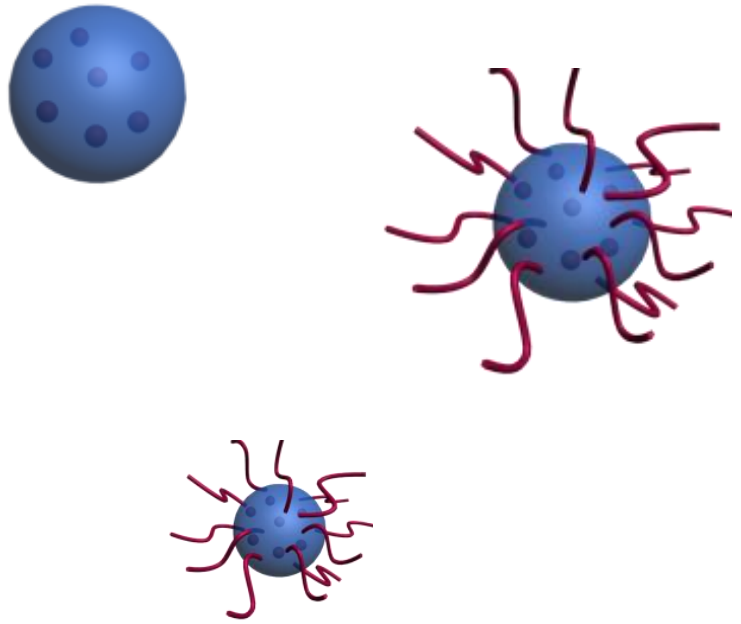




In vivo fate

Poly (methoxypolyethyleneglycol)-co-nhexadecyl cyanoacrylate NPs

Nanoparticles	Protein adsorbed (%)
PEG_{5000}-PHDCA (243 nm)	34
PEG_{5000}-PHDCA (171 nm)	23
PEG_{5000}-PHDCA (80 nm)	6
PEG_{2000}-PHDCA (172 nm)	29
PEG_{10000}-PHDCA (169 nm)	9
PHDCA (242 nm)	58
PHDCA (173 nm)	56
PHDCA (85 nm)	57



C. Fang *et al., Eur. J. Pharma. Sci.* 2006, 27, 27

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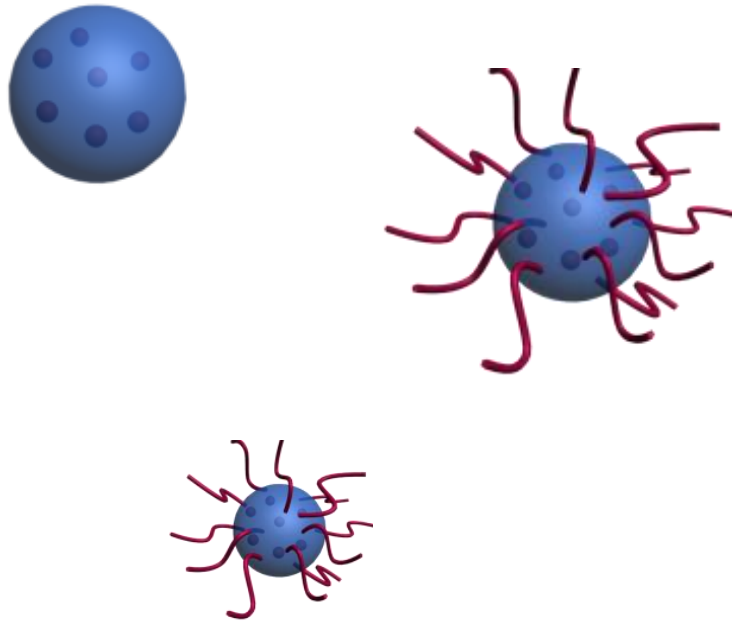
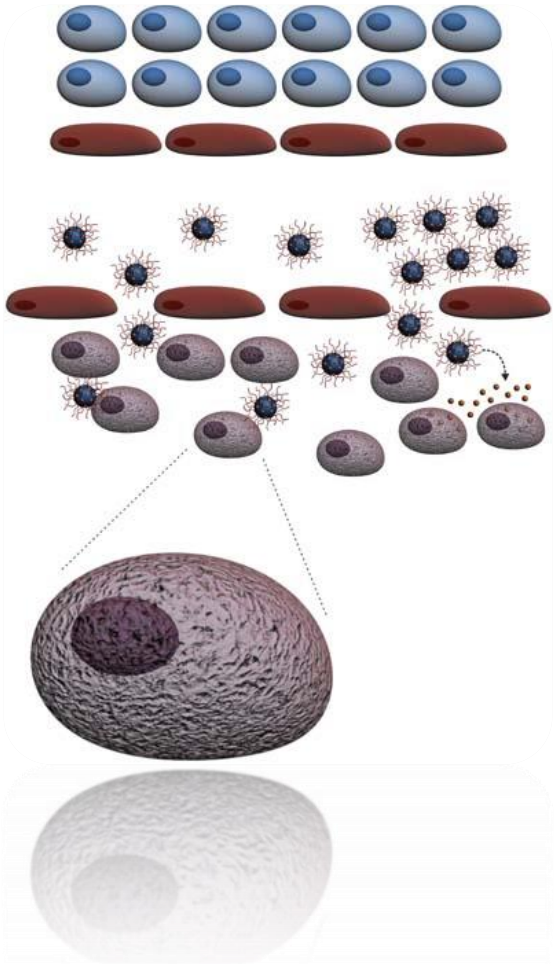


Protein adsorption is surface and size dependent

C. Fang *et al., Eur. J. Pharma. Sci.* 2006, 27, 27

Second generation

The enhanced permeability and retention effect (EPR)



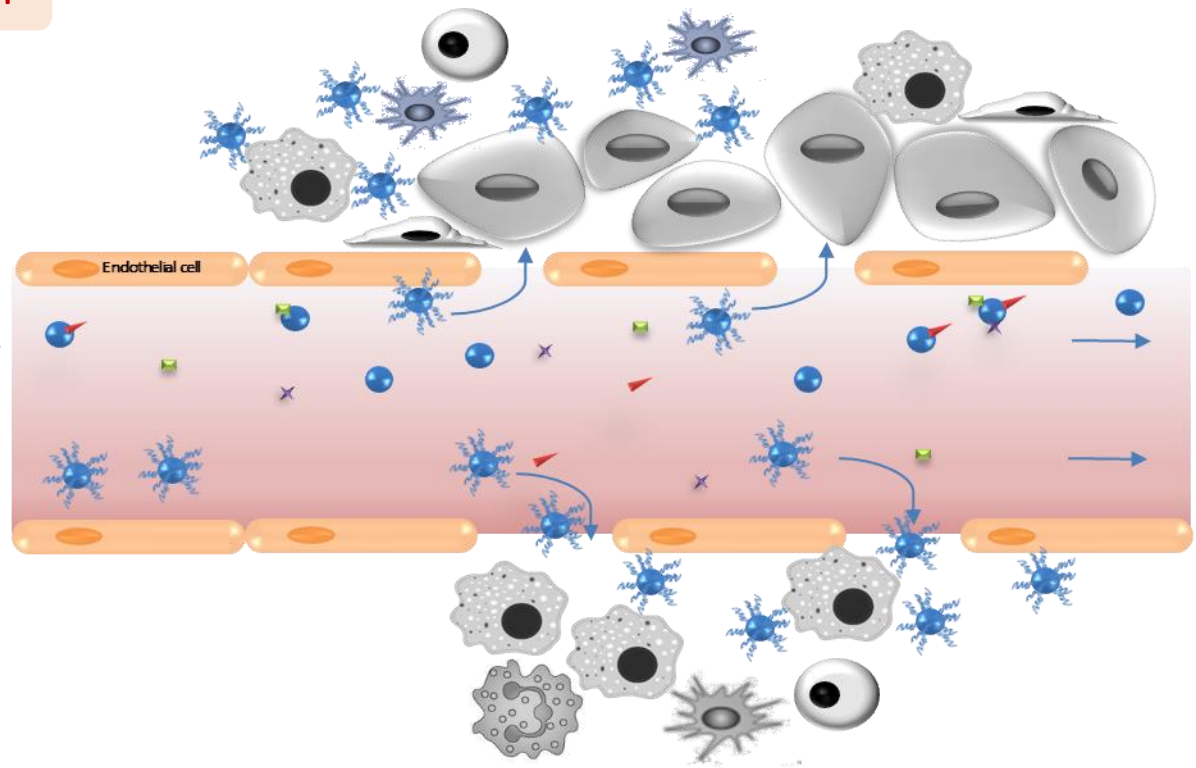
- Enhanced permeability
  - Stimulation of the blood vessel production
  - Important vascularization (blood supply)
  - Wide fenestrations, abnormal architectures
- Enhanced retention
  - Inefficient lymphatic drainage

Accumulation of nanoparticles in tumor and inflammed tissues

Second generation

The enhanced permeability and retention effect (EPR)

Tumor



Non stealth NPs

Opsonization

Stealth NPs

Prolonged blood circulation

Inflammation

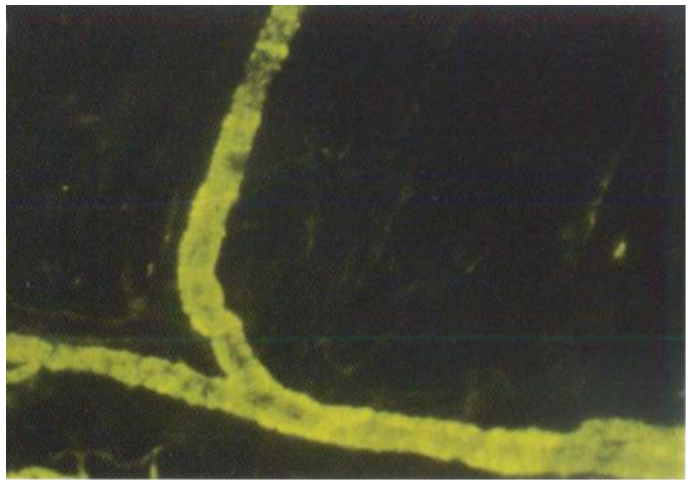
Second generation

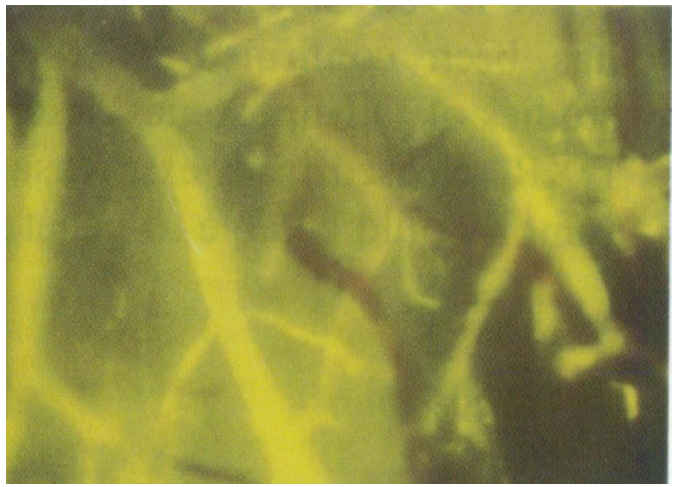
The enhanced permeability and retention effect (EPR)

Healthy tissue

Tumor tissue

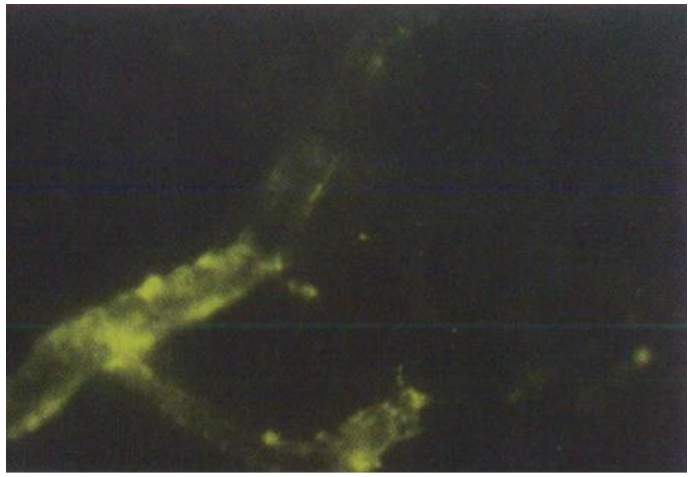
@24h

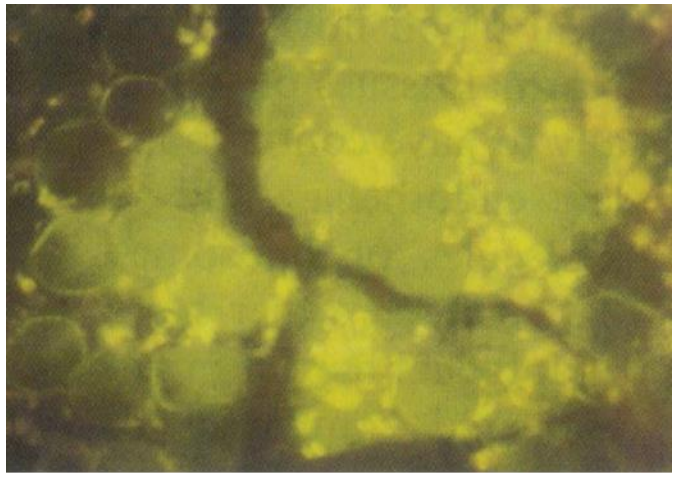




@30’

@48h



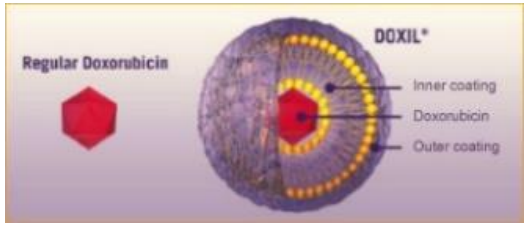


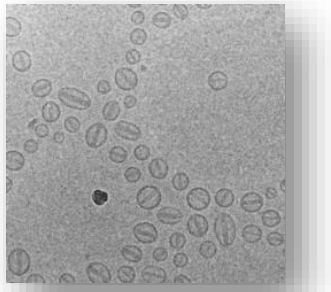
@24h

S. Unezaki *et al., International Journal of Pharmaceutics* 1996, 144, 11

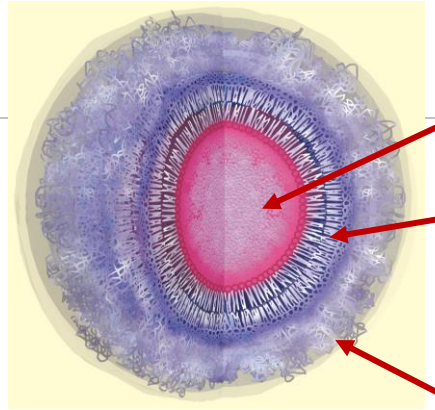
Second generation

nanomedicines in the market_Doxil (1995)





80-90 nm PEG-coated unilamellar liposomes



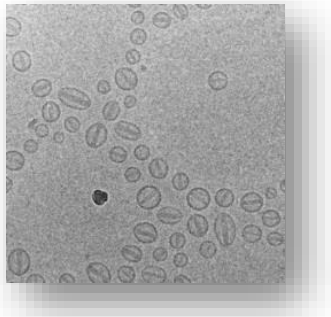
- Metastatic breast cancer
- Kaposi's sarcoma in patients with AIDS
- Multiple myeloma

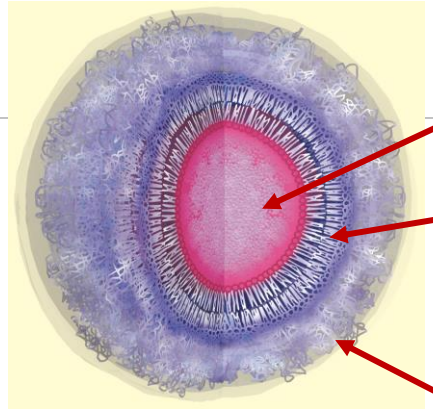
- Drug: doxorubicin

Second generation

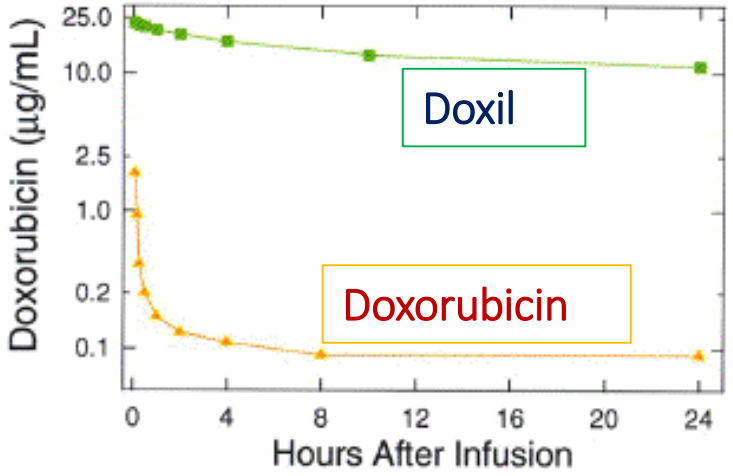
nanomedicines in the market_Doxil (1995)

80-90 nm PEG-coated unilamellar liposomes





- Plasma concentration

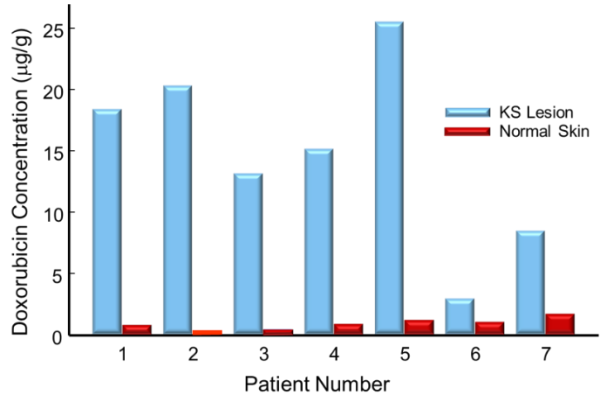


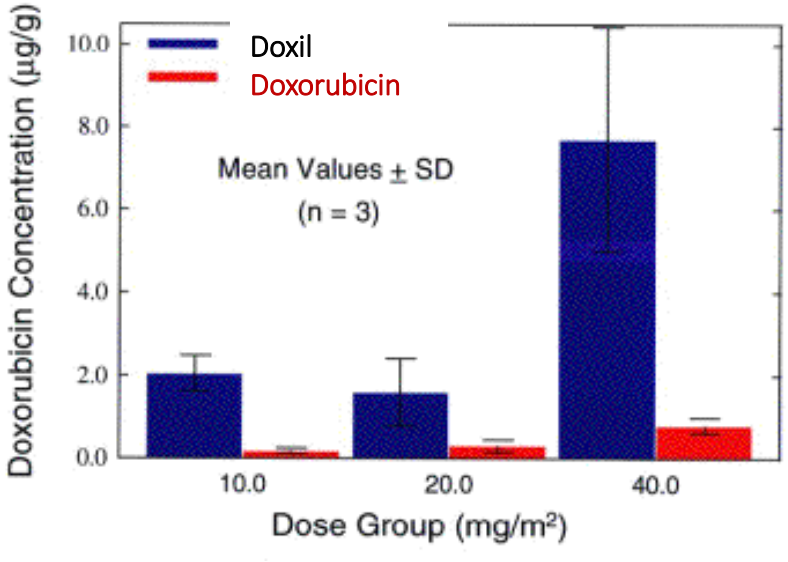
- Metastatic breast cancer
- Kaposi's sarcoma in patients with AIDS
- Multiple myeloma

- Drug: doxorubicin

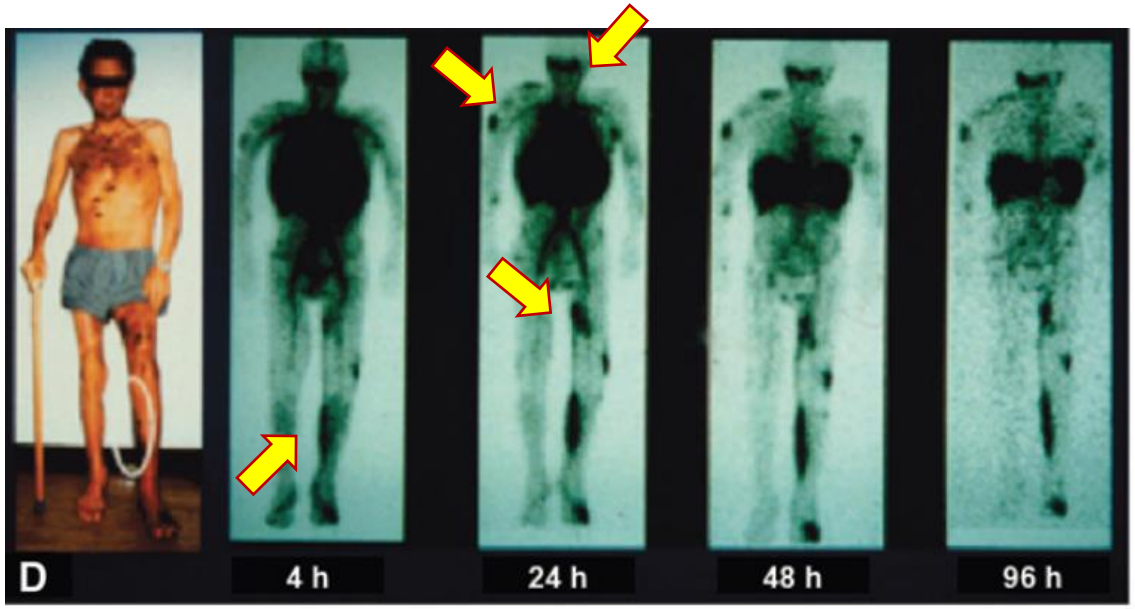
Doxil

Accumulation in KS lesions





Indium-111–labeled PEGylated liposome



Lammers T et al. Clin Cancer Res 2012;18:4889-4894

Doxil

Cardiotoxicity

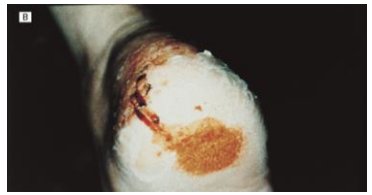
- Reduced
- Only 0.8% withdrawal due to cardiotoxicity
- Increasing dose and duration of treatment

Complement activation–related pseudo allergy

- Slower infusion rate
- Pretreat

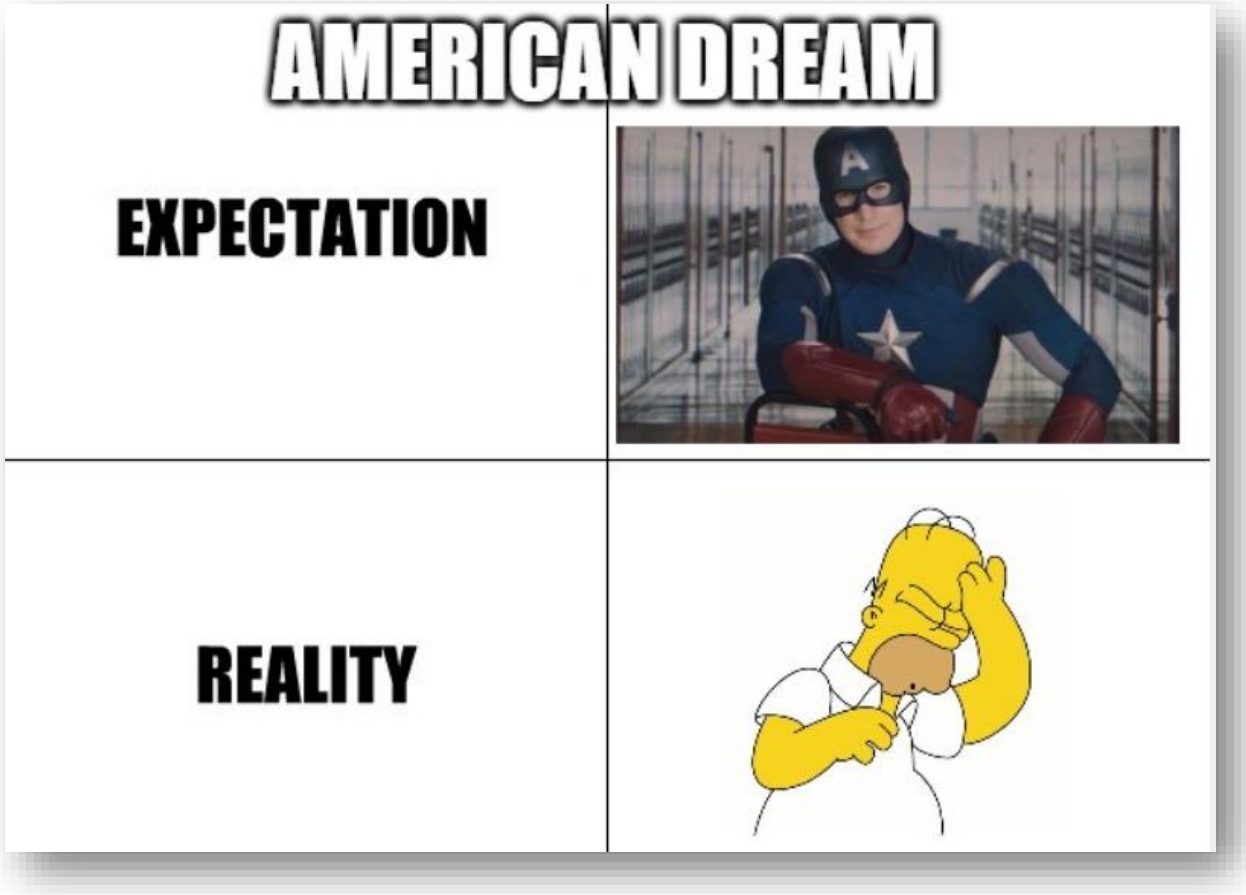
Hand-foot syndrome

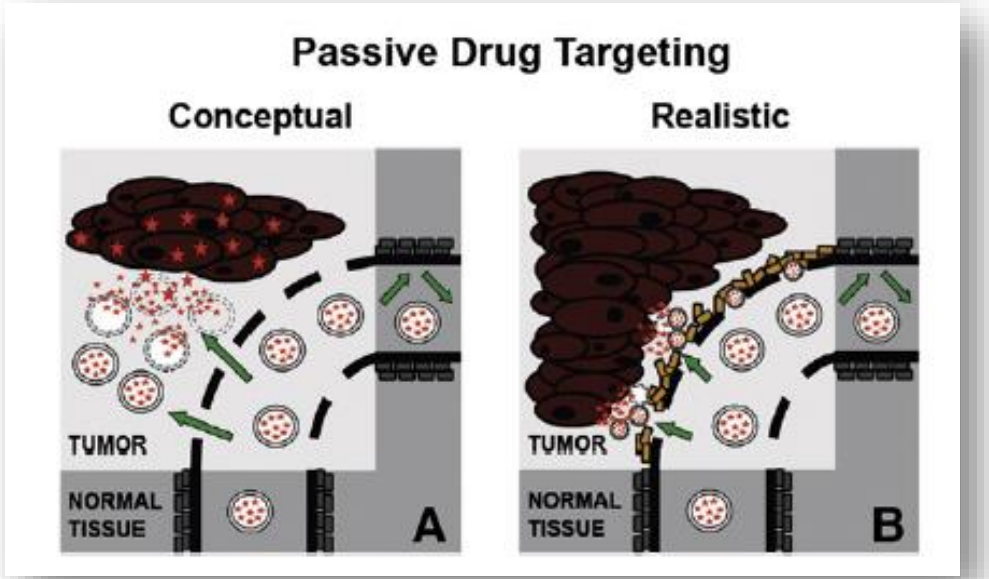
- Rich capillary network, increased blood flow
- Increased drug accumulation
- protracted slow release



Symptoms	
Grade I	Mild erythema
Grade II	Erythema with desquamation
Grade III	Blistering
Grade IV	Diffuse

Working *et al.*, JPET, 1999, 289: 1128


AMERICAN DREAM
EXPECTATION
REALITY

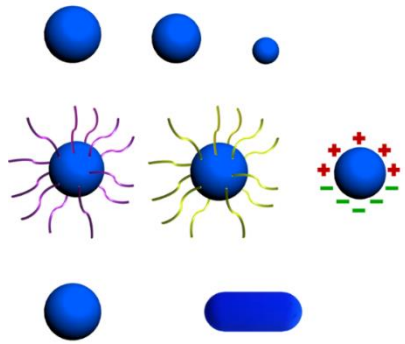


Tumor

- Extent of the EPR effect and pores cut off
- Diffusion within the extracellular matrix
- Hydrostatic pressure within the tumor

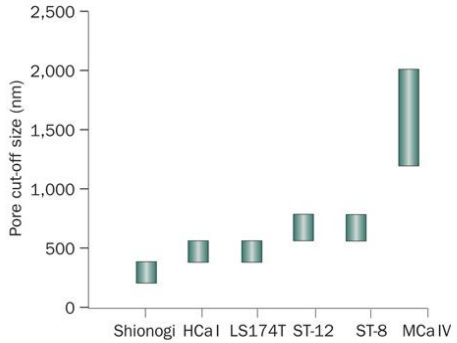
Particles

- Mean diameter
- Charge and surface chemistry
- Shape



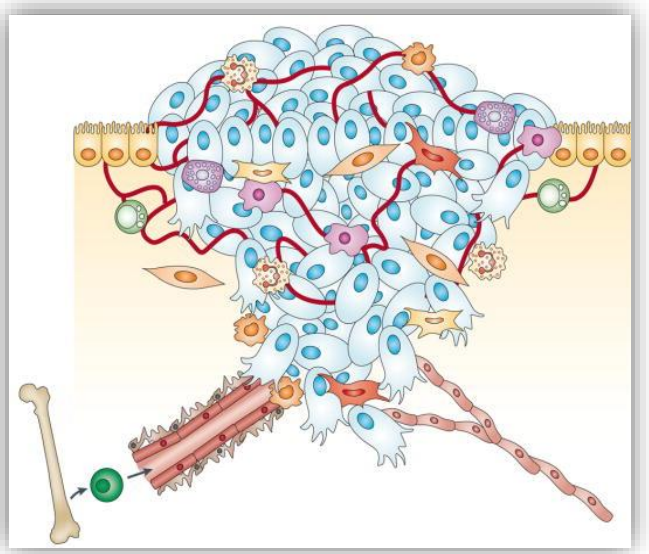
Lammers T et al., Journal of Controlled Release, 161 (2012) 175–187

Variable pore size

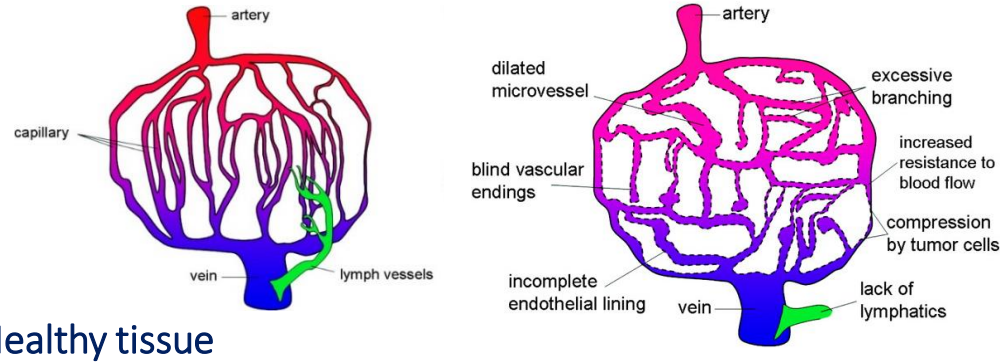


Hobbs, S. K. et al. Proc. Natl Acad. Sci. USA, 1998, 95, 4607

Heterogeneous tumor composition



Heterogeneous vasculature



Healthy tissue

Correlate EPR effect and response to treatment

Evaluate the extent of the vasculature leakage and tumor drug accumulation

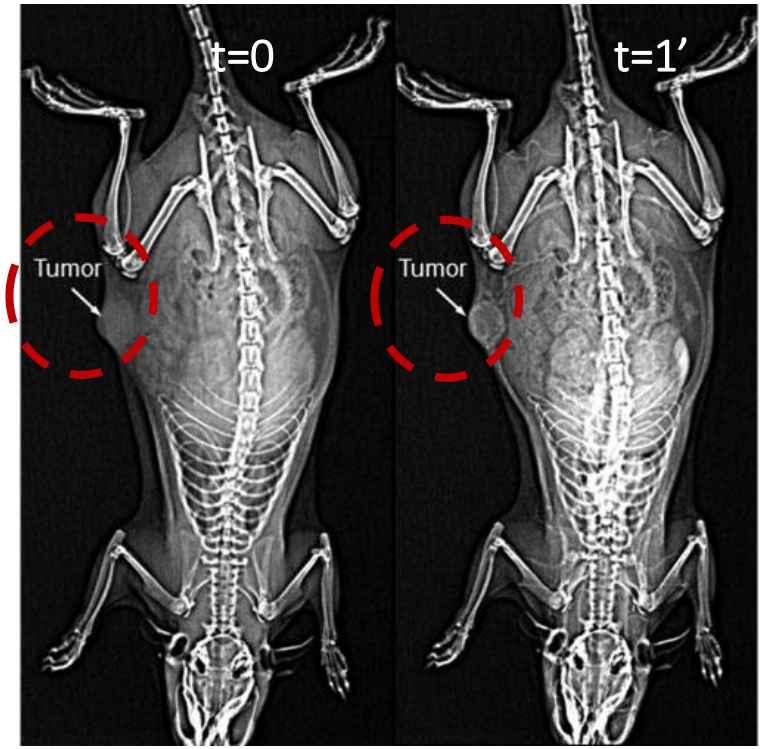
Predict the outcome of the treatment

Karathanasis *et al., Radiology* **2009**, 250, 398-406

Correlate EPR effect and response to treatment

Evaluate the extent of the vasculature leakage and tumor drug accumulation

Predict the outcome of the treatment



Iv injection of iodine-labeled liposomes

Vasculature visualization of tumor site and normal tissues

Good prognosis groups

highest X-Ray signal enhancement

Bad prognosis groups

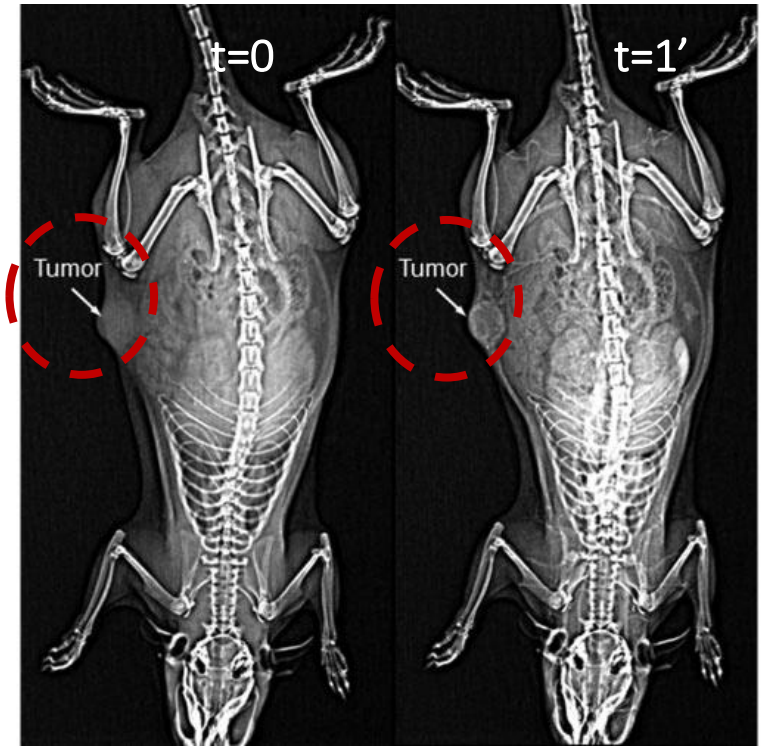
lowest X-Ray signal enhancement

Karathanasis *et al., Radiology* **2009**, 250, 398-406

Correlate EPR effect and response to treatment

Evaluate the extent of the vasculature leakage and tumor drug accumulation

→ Predict the outcome of the treatment



Iv injection of iodine-labeled liposomes

Vasculature visualization of tumor site and normal tissues

Good prognosis groups

highest X-Ray signal enhancement

Bad prognosis groups

lowest X-Ray signal enhancement

Doxorubicin-loaded liposomes treatment

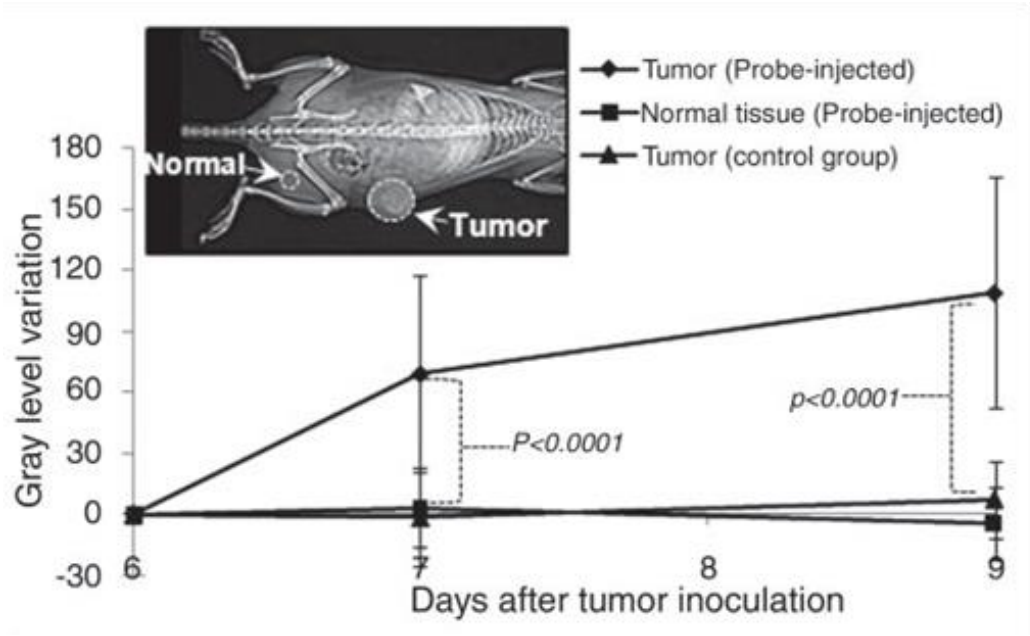
- Slower tumor grow rate
- leakier vasculature

- Faster tumor grow rate
- intact vasculature

Karathanasis *et al., Radiology* **2009**, 250, 398-406

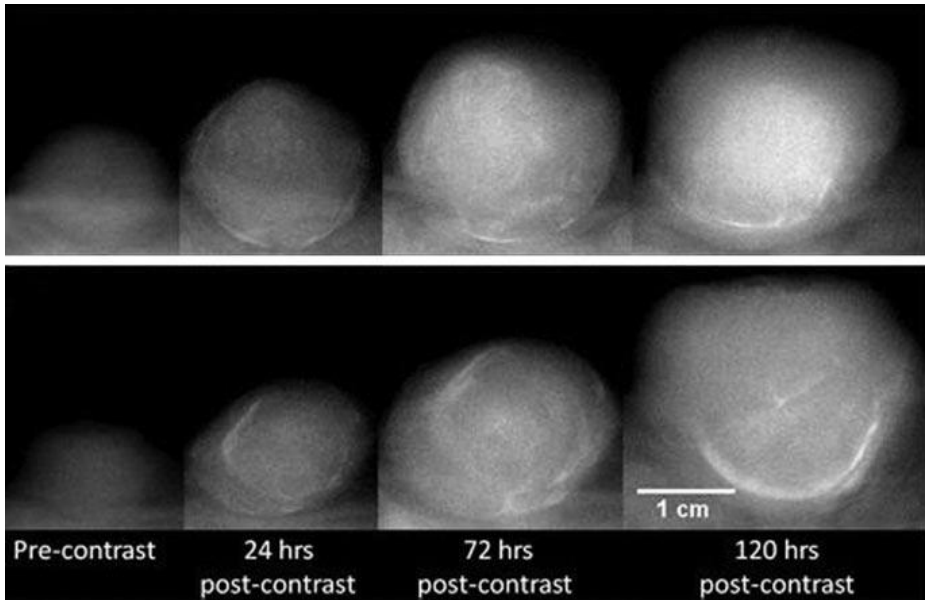
Correlate EPR effect and response to treatment

- Gray levels signal enhancement



Tumor A

Tumor B



After probe administration:

- highest enhancement in tumor tissue
- no substantial enhancement in normal tissue

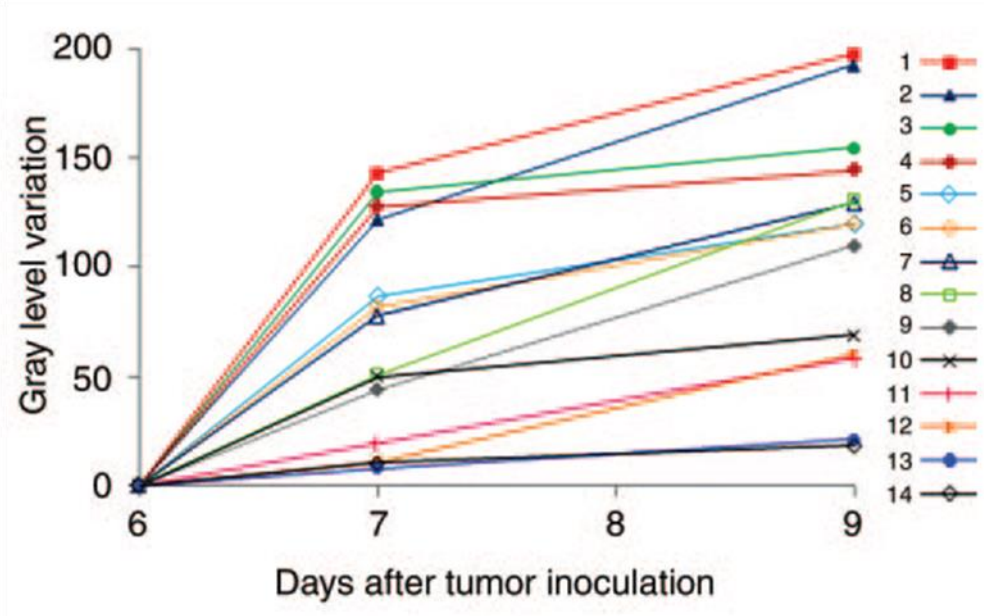
Without probe administration:

- no enhancement in tumor lesion of control group

Karathanasis *et al.*, Radiology **2009**, 250, 398-406

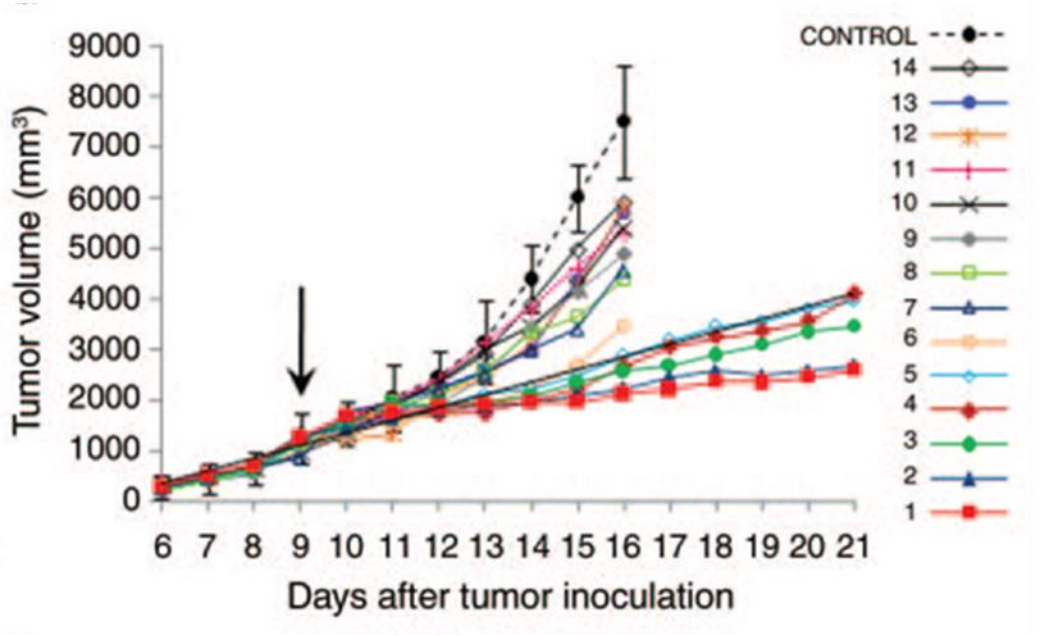
Correlate EPR effect and response to treatment

- Tumor permeability



High variability of tumor leakiness

- In vivo efficacy

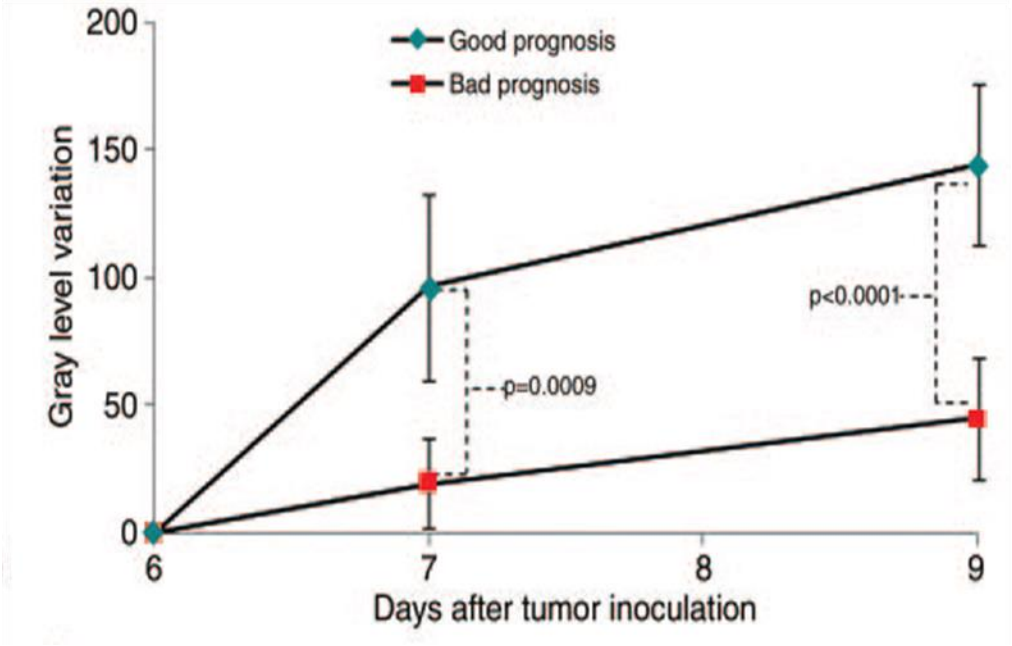


High variability of tumor response

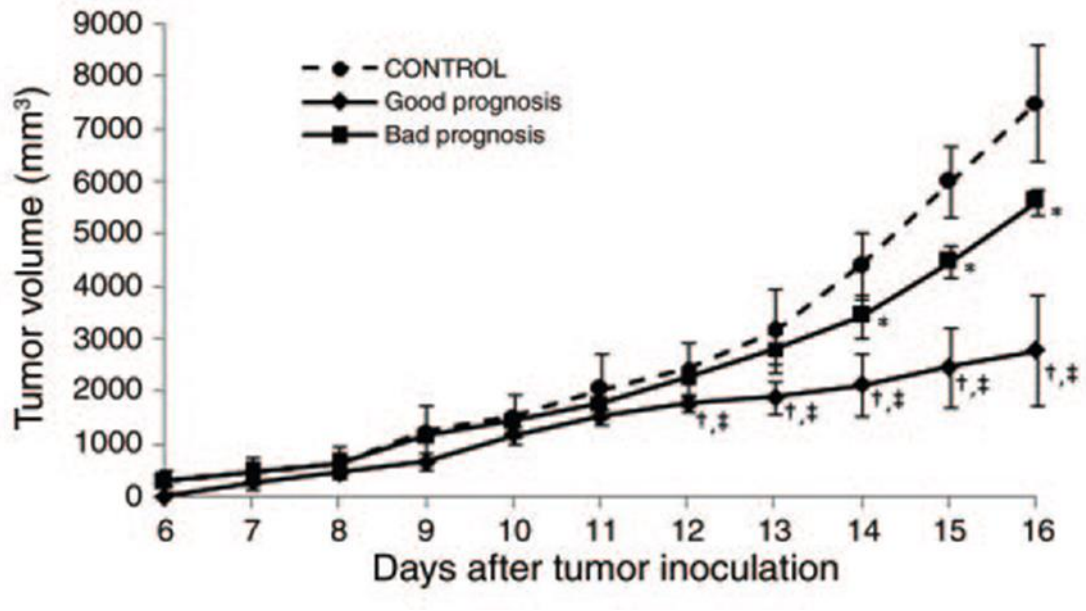
Karathanasis *et al.*, *Radiology* **2009**, 250, 398-406

Correlate EPR effect and response to treatment

- Tumor permeability



- In vivo efficacy



Significant higher response to chemotherapy of good-prognosis subgroup

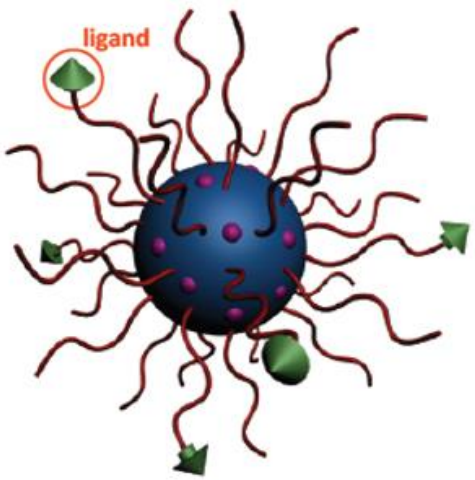
Karathanasis *et al.*, Radiology **2009**, 250, 398-406

Nanomedicine generations

1st generation

2nd generation

Stealth/Long circulating



3rd generation

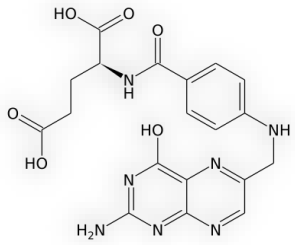
Stealth/Long circulating
Surface functionalized

Third generation

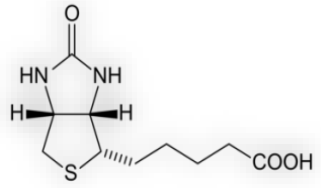
ligand mediated targeting

- **Small molecules**

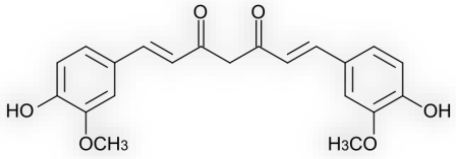
Folic acid



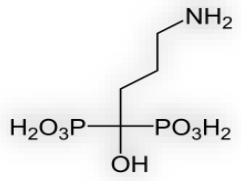
Biotin



Curcumin

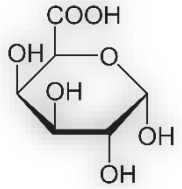


Alendronate

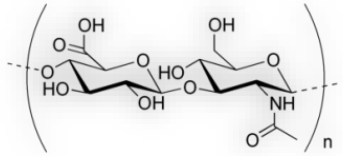


- **Carbohydrates**

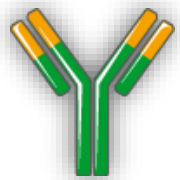
Galactose



Hyaluronan



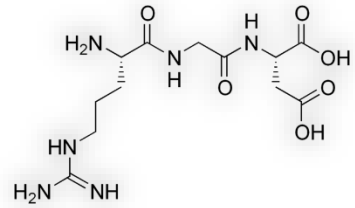
- **Antibodies**



- **Peptides/proteins**

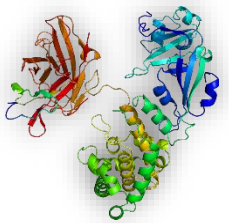
RGD peptides

GRGDS
CRGDKGPDC
Cyclo(RGDDFK)

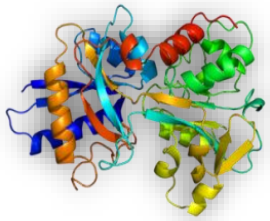


Cell penetrating peptides

EGF



Transferrin



Third generation

ligand mediated targeting

THE JOURNAL OF BIOLOGICAL CHEMISTRY
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Vol. 269, No. 5, Issue of February 4, pp. 3198–3204, 1994
Printed in U.S.A.

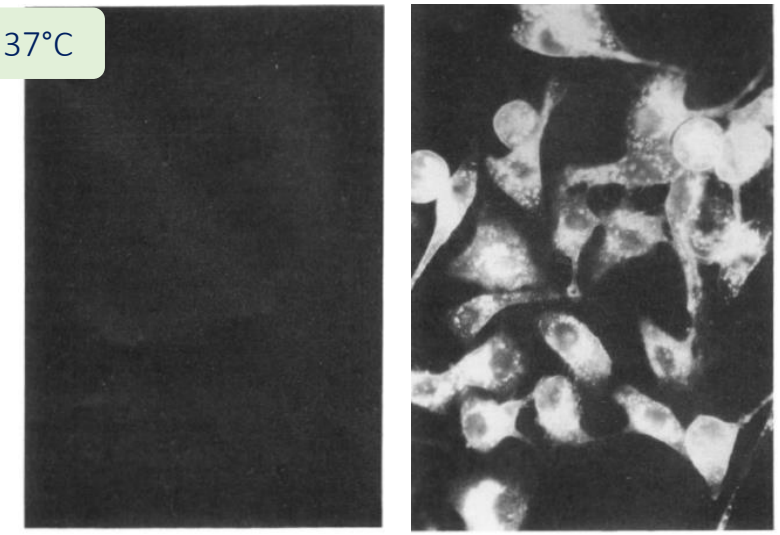
Delivery of Liposomes into Cultured KB Cells via Folate Receptor-mediated Endocytosis*

(Received for publication, June 25, 1993, and in revised form, September 1, 1993)

Robert J. Lee and Philip S. Low‡
From the Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

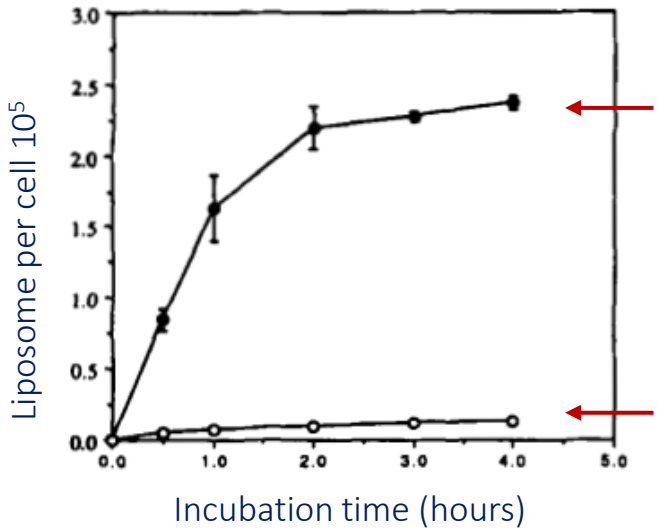
- Uptake *Confocal microscopy*

4h @ 37°C



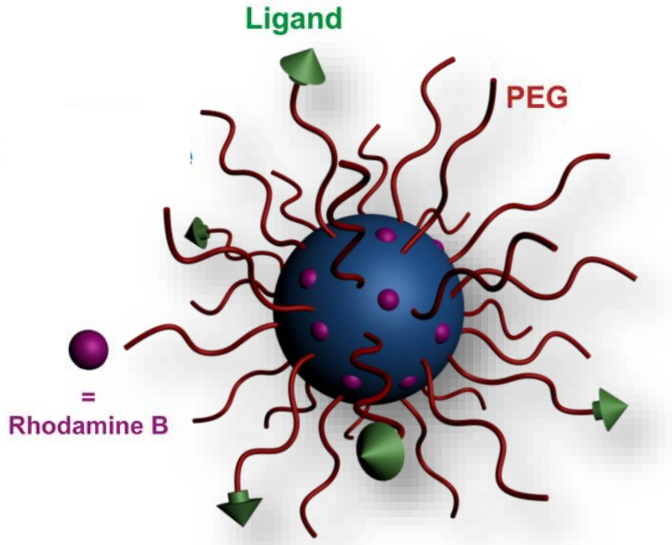
Non functionalized Folic Acid functionalized

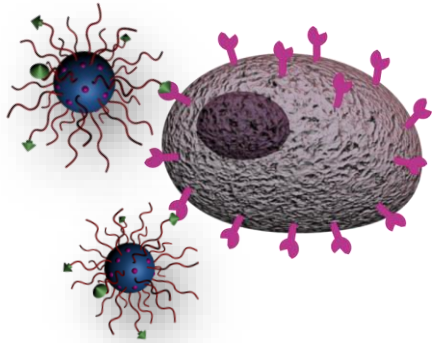
- Internalization kinetic *fluorescence spectroscopy*

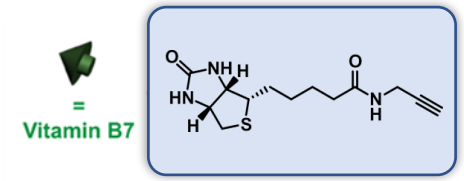


Third generation

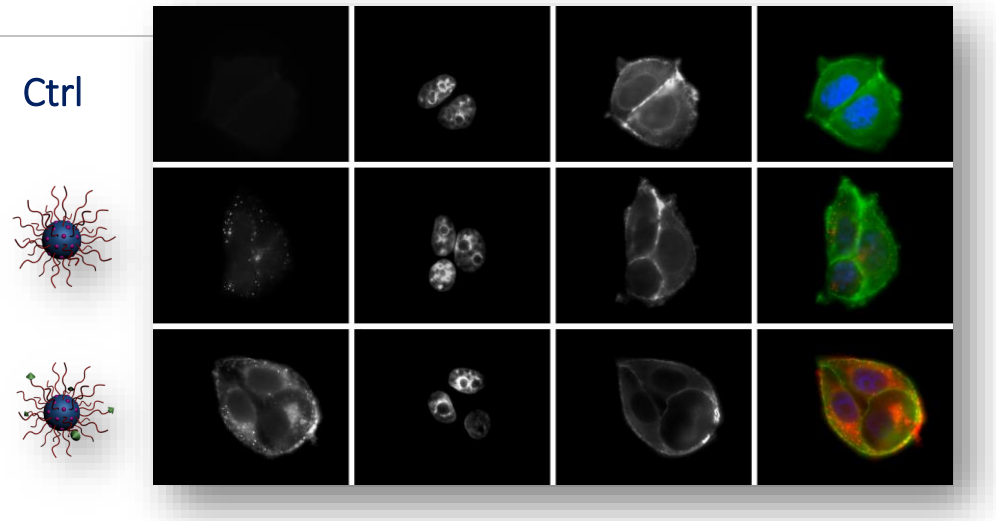
ligand mediated targeting



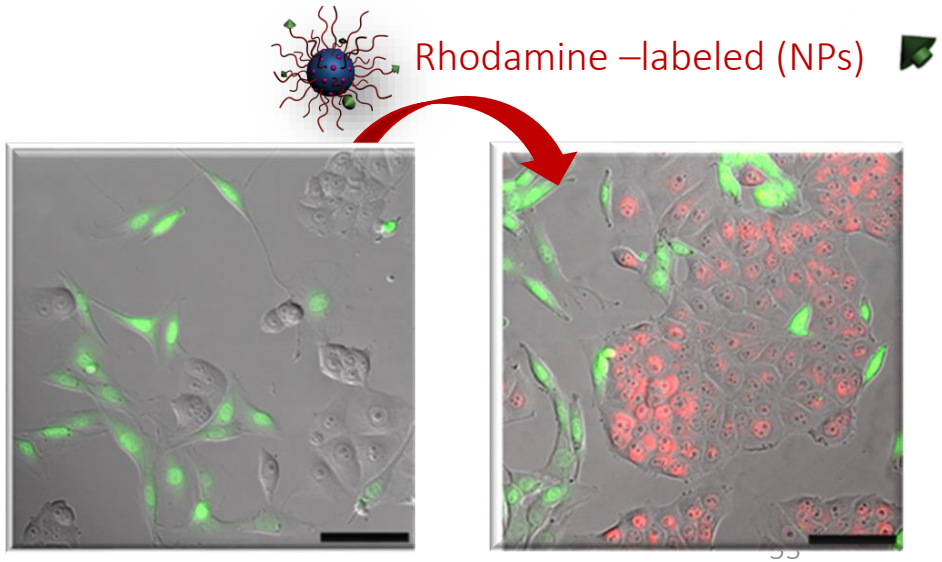




- Uptake



- Selectivity



- Green-labeled fibroblasts
- Unstained cancer cells

Brambilla *et al., Chem. Comm*. 2010, 46, 2602
Nicolas *et al.,* Soft Matter 2011, 7, 6187
Le Droumaguet *et al., ACS Nano* 2012, 6, 5866

Third generation

ligand mediated targeting

Table 1. Clinical trials for actively targeted cancer nanomedicines

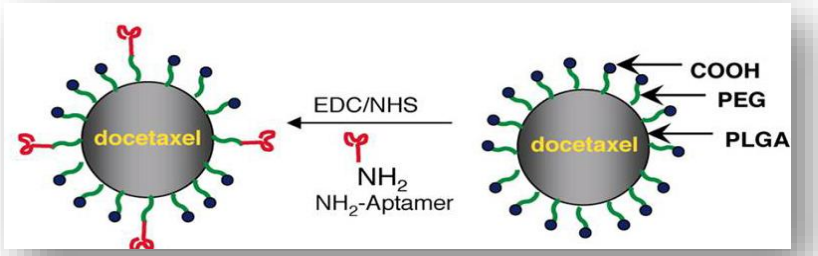
Ligand type	Name	Ligand	Target	Nanocarrier	Payload	Indication	NCT no.	Status	Ref.
Antibodies	TargomiRs	Anti-EGFR bispecific antibody	EGFR	Minicell	miR-16-based microRNA mimic	NSCLC MPM	02369198	Phase I	165
Antibody fragments	C225-ILs-DOX	Anti-EGFR Fab'	EGFR	Liposome	DOX	Solid tumors	01702129	Phase I	188
	MM-302	Anti-HER2 scFv	HER2	Liposome	DOX	Breast cancer	01304797	Phase I	189
	SGT-53	Anti-TfR scFv	TfR	Liposome	p53 plasmid	Solid tumors	00470613	Phase I	190
						Pancreatic cancer	02340117	Phase II	204
	SGT-94	Anti-TfR scFv	TfR	Liposome	RB94 plasmid	GUC	01517464	Phase I	191
	Lipovaxin-MM	Anti-DC-SIGN V_H	DC-SIGN	Liposome	Melanoma antigens and IFN-γ	Melanoma	01052142	Phase I	192
Proteins	MBP-426	Tf	TfR	Liposome	Oxaliplatin	Solid tumors	00355888	Phase I	248
						AGC or EAC	00964080	Phase I/II	249
	CALAA-01	Tf	TfR	Polymeric nanoparticles	RRM2 siRNA	Solid tumors	00689065	Phase I	251
Peptides	2B3-101	GSH	GSH transporters	Liposome	DOX	Breast cancer	01386580	Phase I/II	279
	Rexin-G	vWF-derived motif	Collagen	Retroviral vector	dn-CCNG1	Osteosarcoma	00572130	Phase II	259
						Sarcoma	00505713	Phase I/II	259
						Pancreatic cancer	00504998	Phase I/II	260

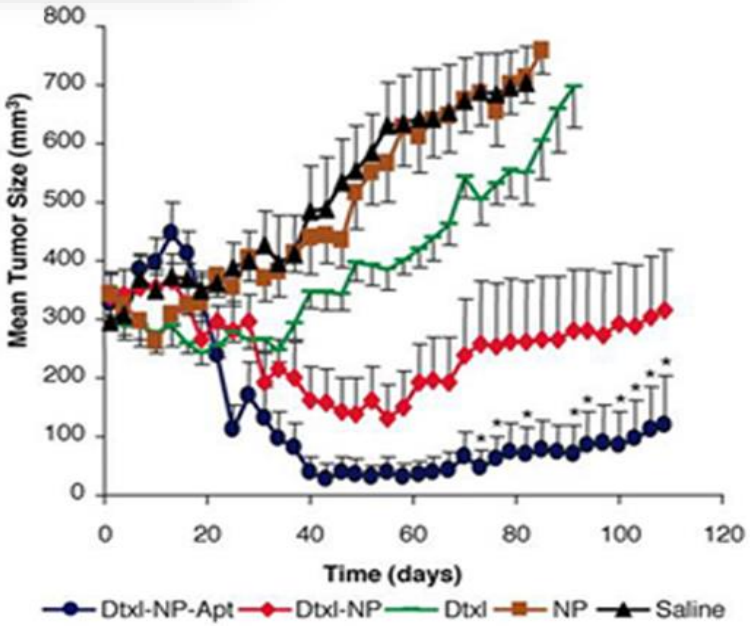
AGC advanced gastric cancer, *dn-CCNG1* dominant-negative mutant construct of cyclin G1, *DOX* doxorubicin, *EAC* esophageal adenocarcinoma, *GUC* genitourinary cancers, *MPM* malignant pleural mesothelioma, *NSCLC* non-small cell lung cancer, *Tf* transferrin, *vWF* Von Willebrand factor

Signal Transduction and Targeted Therapy (2023) 8:293

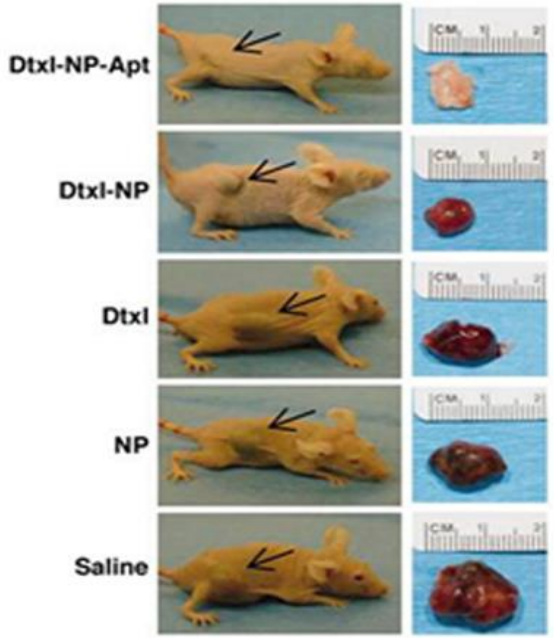
Third generation

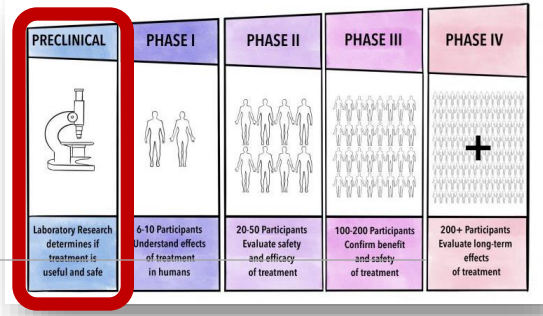
prostate specific membrane antigen (PSMA) targeting





Intratumoral injection

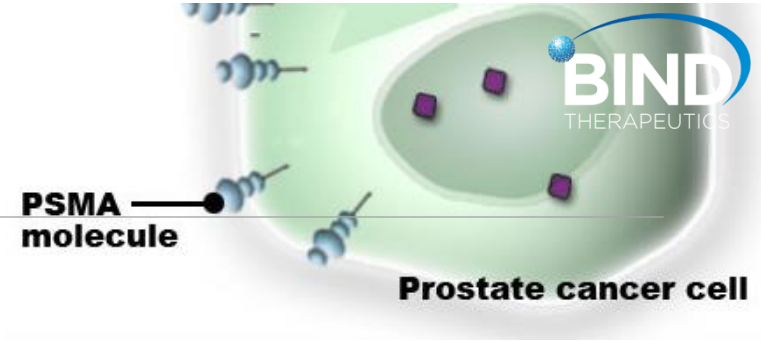




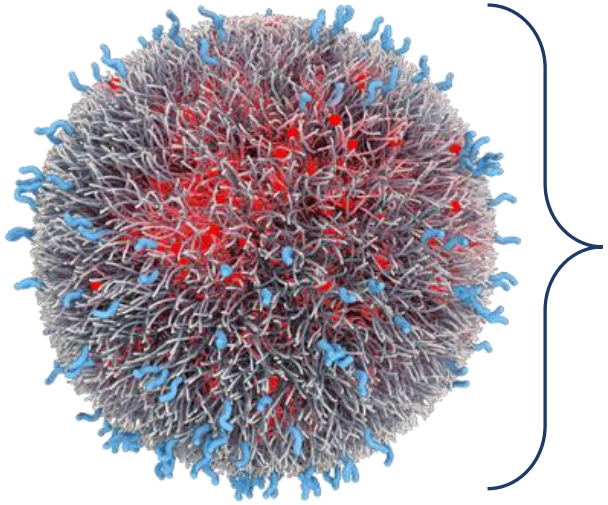
Farokhzad OC , et al.,,*Proc. Natl. Acad. Sci. U. S. A.*, **2006,** 103, 6315

Third generation

prostate specific membrane antigen (PSMA) targeting



Accurins



Targeting ligands
Stealth and protective layer
Controlled-release polymer matrix
Therapeutic payload

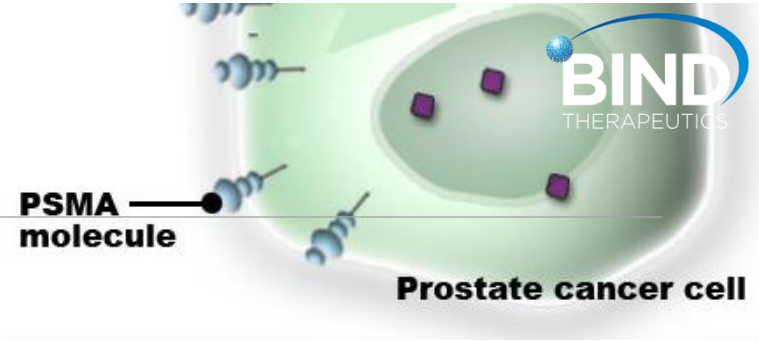
	PATIENTS EXPRESSING PSMA	
TUMOR	TUMOR CELLS	NEOVASCULATURE
Prostate	184/184 (100%)	2/12 (17%)
Breast	0/6 (0%)	5/6 (83%)
Colorectal	0/130 (0%)	110/130 (85%)
Renal Cell	0/75 (0%)	67/75 (89%)
Bladder	8/167 (5%)	167/167 (99%)
Gastric	0/119 (0%)	79/119 (66%)
Neuroendocrine	0/5 (0%)	5/5 (100%)
Melanoma	0/5 (0%)	5/5 (100%)
Pancreatic Duct	0/4 (0%)	4/4 (100%)
NSCLC	0/5 (0%)	5/5 (100%)
Soft Tissue Sarcoma	0/6 (0%)	5/6 (83%)

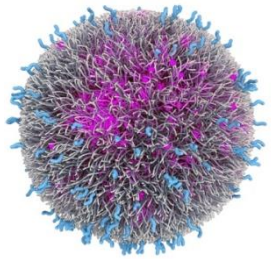
- BIND-014 (PSMA-targeted docetaxel)
- BIND-510 PSMA-targeted vincristine
- PLK1, KSP inhibitor accurins

PSMA is not found in normal vasculature

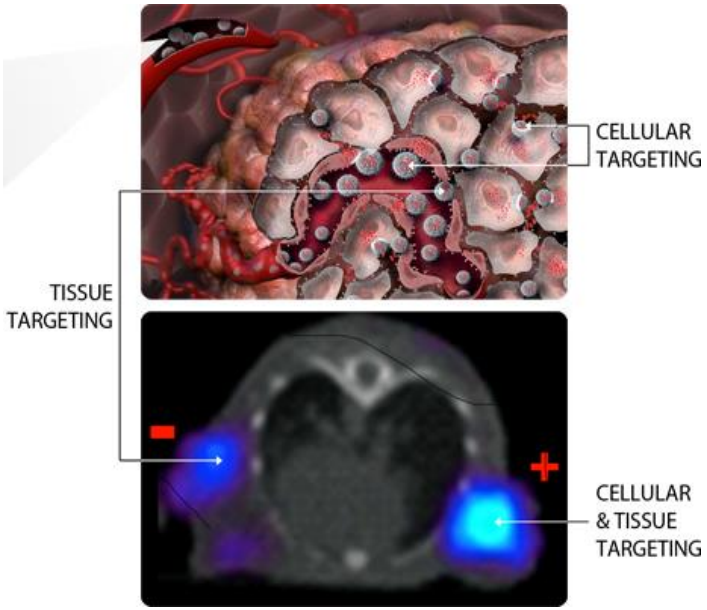
Third generation

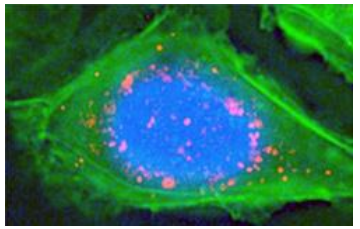
prostate specific membrane antigen (PSMA) targeting





SPECT imaging of ^{111}In-labeled PSMA-targeted nanoparticles in PSMA-positive and negative prostate tumor xenografts





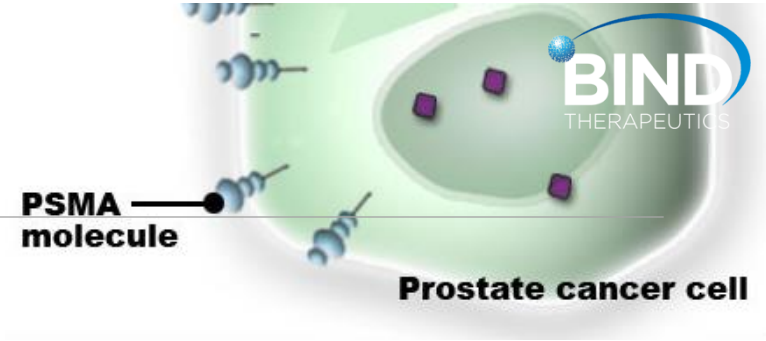
Early tests in animals and small clinical trials showed that the approach was safer than docetaxel alone

Later clinical trials disappointed

- BIND-014 failed against cervical and head-and-neck cancers
- Efficacy on lung cancer was not clear

Third generation

prostate specific membrane antigen (PSMA) targeting



Last updates February-April 2016

5 studies found for: BIND-014

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☐ Include only open studies ☐ Exclude studies with Unknown status

Rank	Status	Study
1	Completed	A Phase 2 Study to Determine the Safety and Efficacy of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension), Administered to Patients With Metastatic Castration-Resistant Prostate Cancer **Conditions:** CRPC; Prostate Cancer **Intervention:** Drug: BIND-014
2	Completed	A Study of BIND-014 Given to Patients With Advanced or Metastatic Cancer **Conditions:** Metastatic Cancer; Cancer; Solid Tumors **Intervention:** Drug: BIND-014
3	Completed	A Phase 2 Study to Determine the Safety and Efficacy of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension) as Second-line Therapy to Patients With Non-Small Cell Lung Cancer **Condition:** Non-small Cell Lung Cancer **Intervention:** Drug: BIND-014
4	Completed	A Study of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension) as Second-line Therapy for Patients With KRAS Positive or Squamous Cell Non-Small Cell Lung Cancer **Conditions:** KRAS Positive Patients With Non-small Cell Lung Cancer; Squamous Cell Non-small Cell Lung Cancer **Intervention:** Drug: BIND-014 (Docetaxel Nanoparticles for Injectable Suspension)
5	Terminated	A Study of BIND-014 in Patients With Urothelial Carcinoma, Cholangiocarcinoma, Cervical Cancer and Squamous Cell Carcinoma of the Head and Neck **Conditions:** Urothelial Carcinoma; Cholangiocarcinoma; Cervical Cancer; Squamous Cell Carcinoma of Head and Neck **Intervention:** Drug: BIND-014 (docetaxel nanoparticles for injectable suspension)

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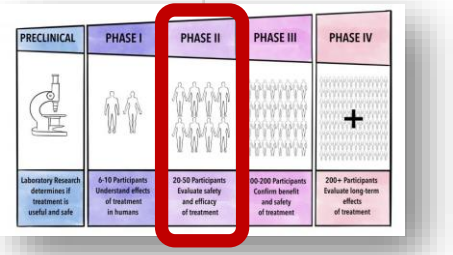
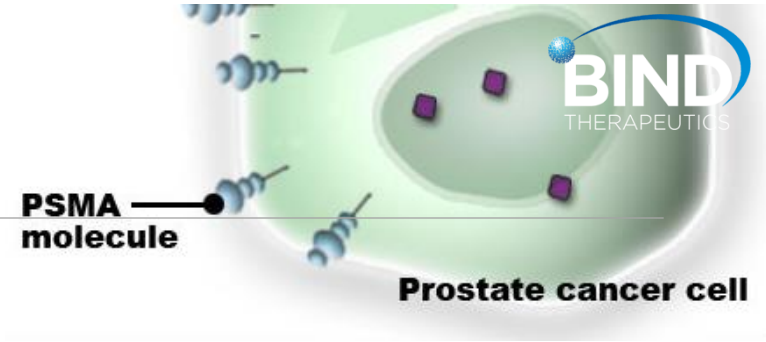


Third generation

prostate specific membrane antigen (PSMA) targeting



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☐ Include only open studies ☐ Exclude studies with Unknown status

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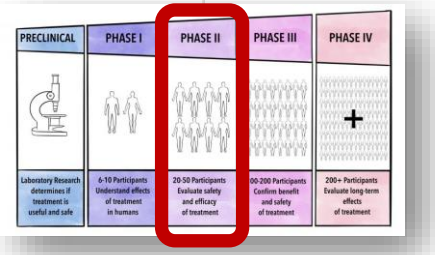
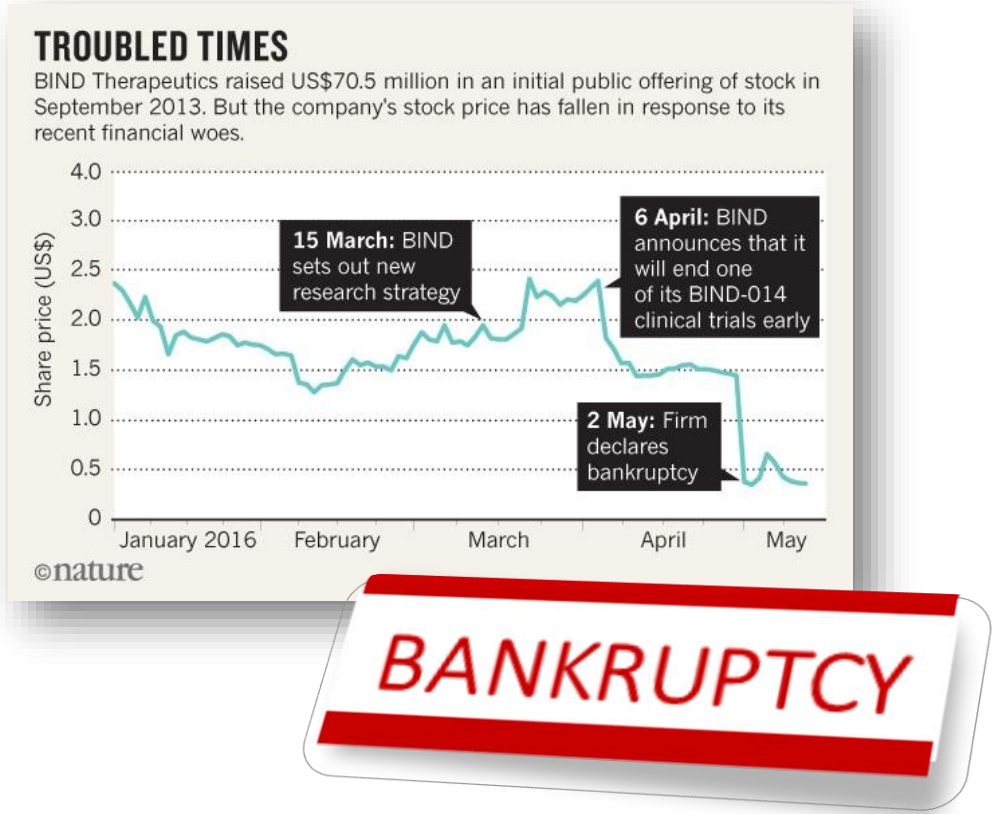


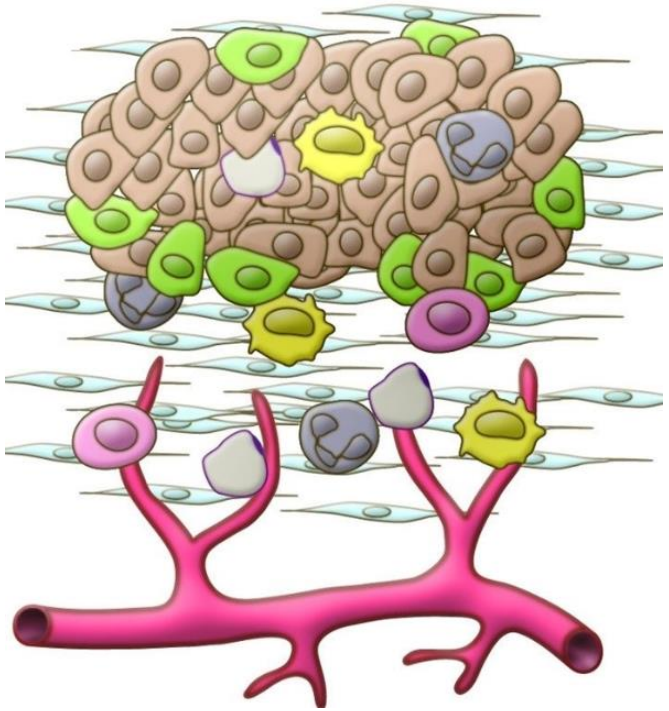


BANKRUPTCY

Need to reach the biological target

The abnormal microenvironment impairs uniform delivery and efficcacy of therapeutic agents

Transport through the microenvironnement



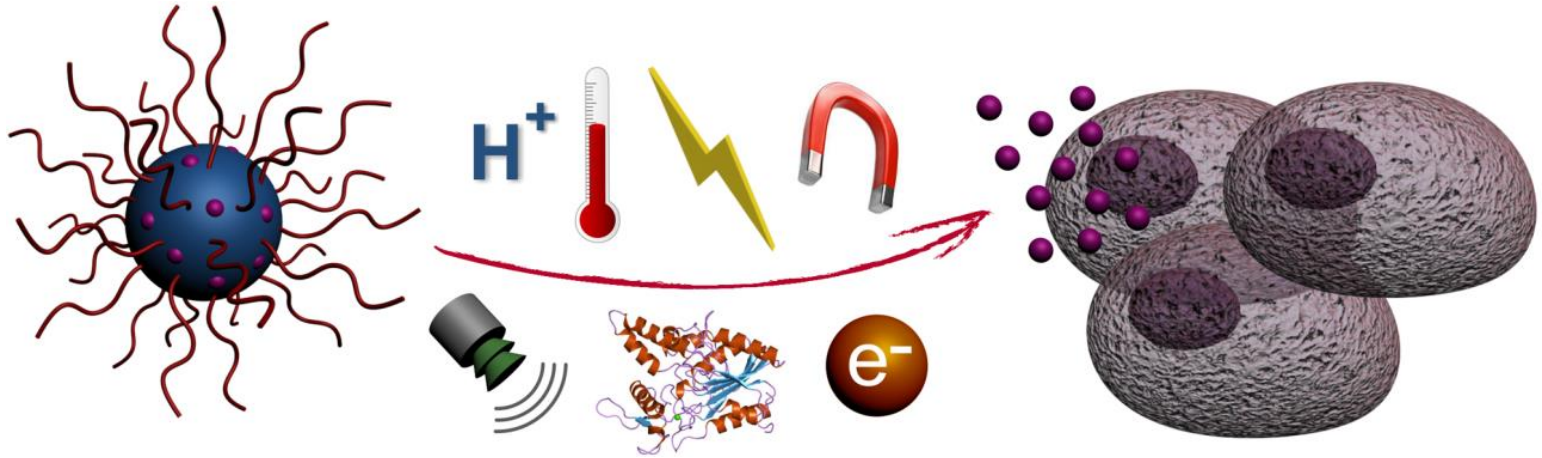
Extravasation

Efficient drug delivery to cancer cells requires crossing of multiple biological barriers

Need to have relevant predictive models

Fourth generation: stimuli responsive

Efficient spatio temporal and dosage release control



- Endogenous stimuli

  - pH
  - Redox status (glutathion concentrations)
  - Enzymatic activity

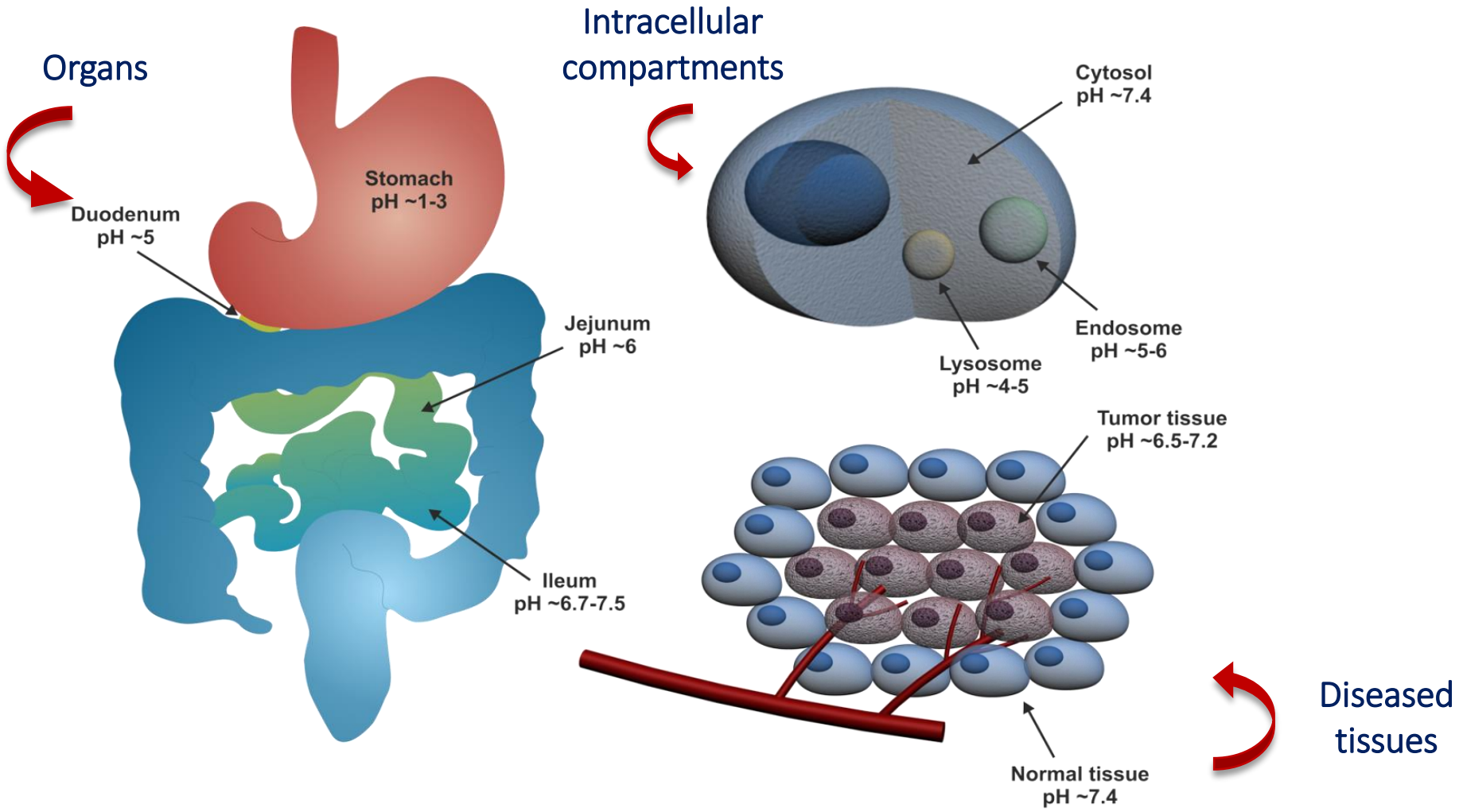
- Exogenous stimuli

  - Magnetic/electric field
  - Light
  - Ultrasound
  - Temperature

S. Mura, J. Nicolas, P. Couvreur, , *Nature Materials* 2013, 12, 991

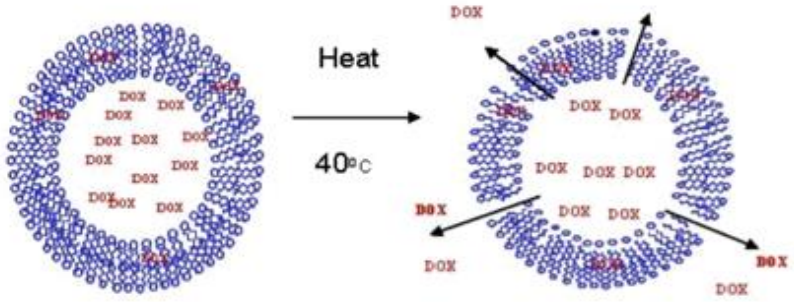
Fourth generation: pH sensitive

- Body pH variations

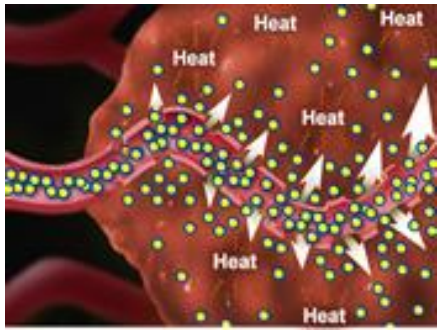


Fourth generation : temperature sensitive

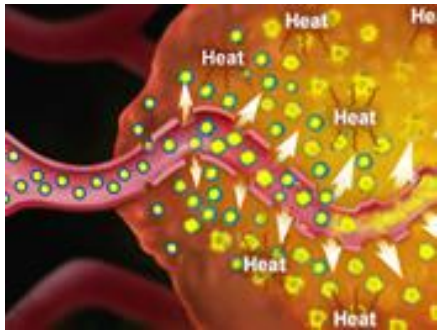
- Heat-activated doxorubicin loaded liposomes : Thermodox®



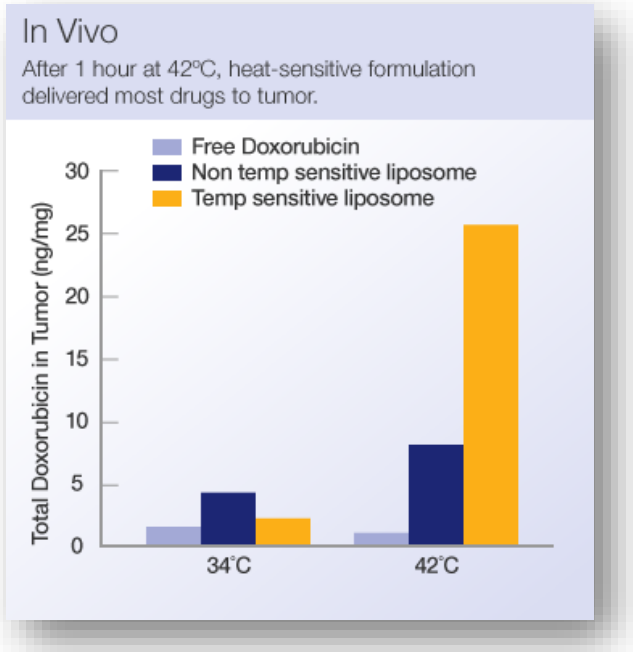
"Leaky" tumor blood Vessels



Heat adds permeability



Heat-triggered release



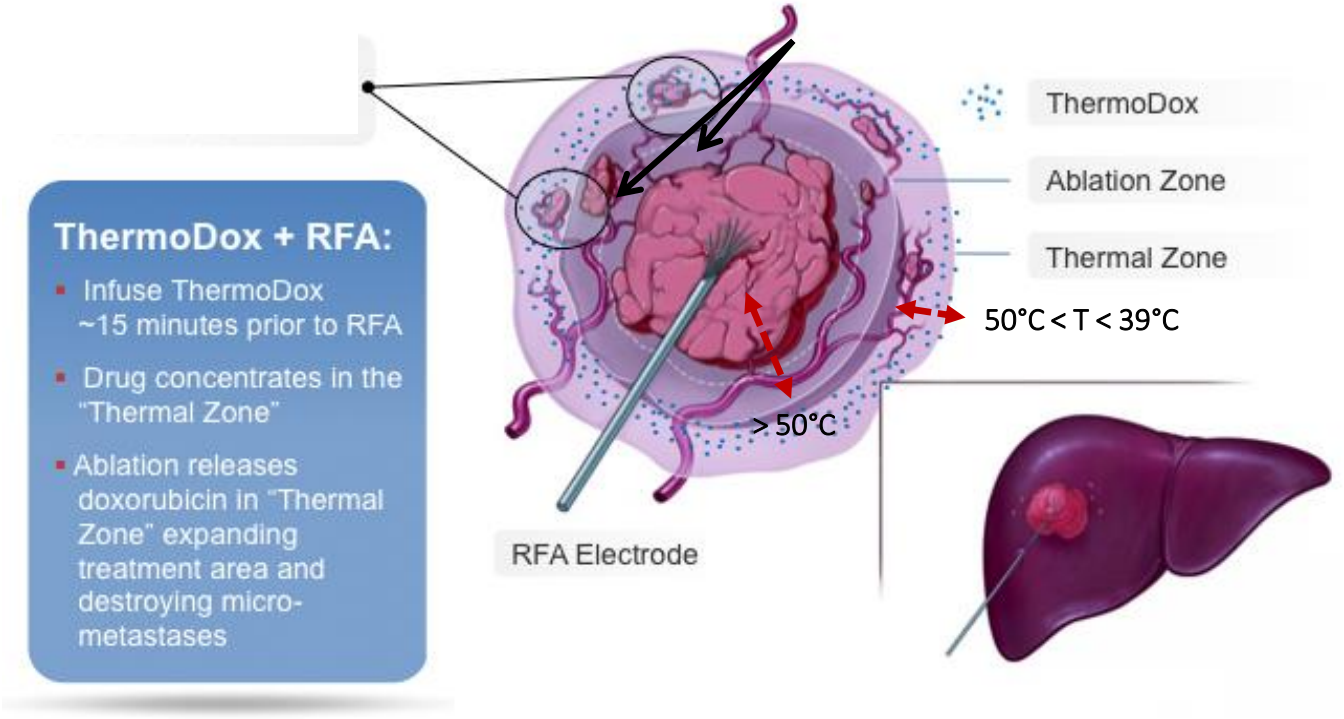
INDICATION	PRODUCT/STUDY	PRECLINICAL	PHASE 1-2	PHASE 3
Primary Liver	ThermoDox®/OPTIMA Study			
Ovarian	GEN-1/OVATION Study			
Glioblastoma	GEN-1			
Bladder	ThermoDox®			

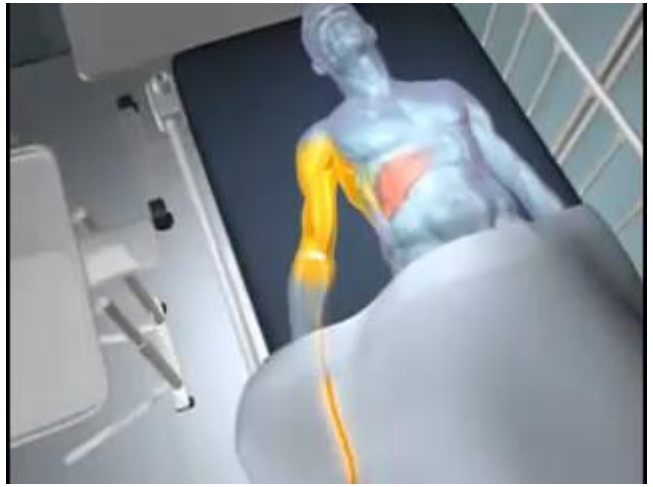
Celsion Corporation

Fourth generation: temperature sensitive

- Heat-activated doxorubicin loaded liposomes : Thermodox®

Ablated Tumor and 1 cm “tumor-free” margin

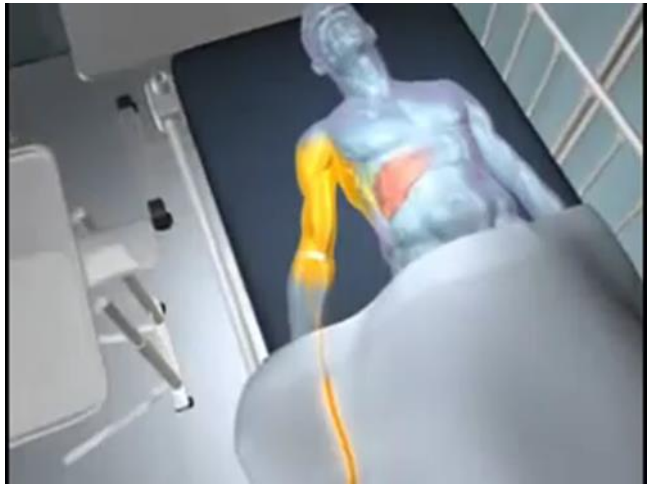




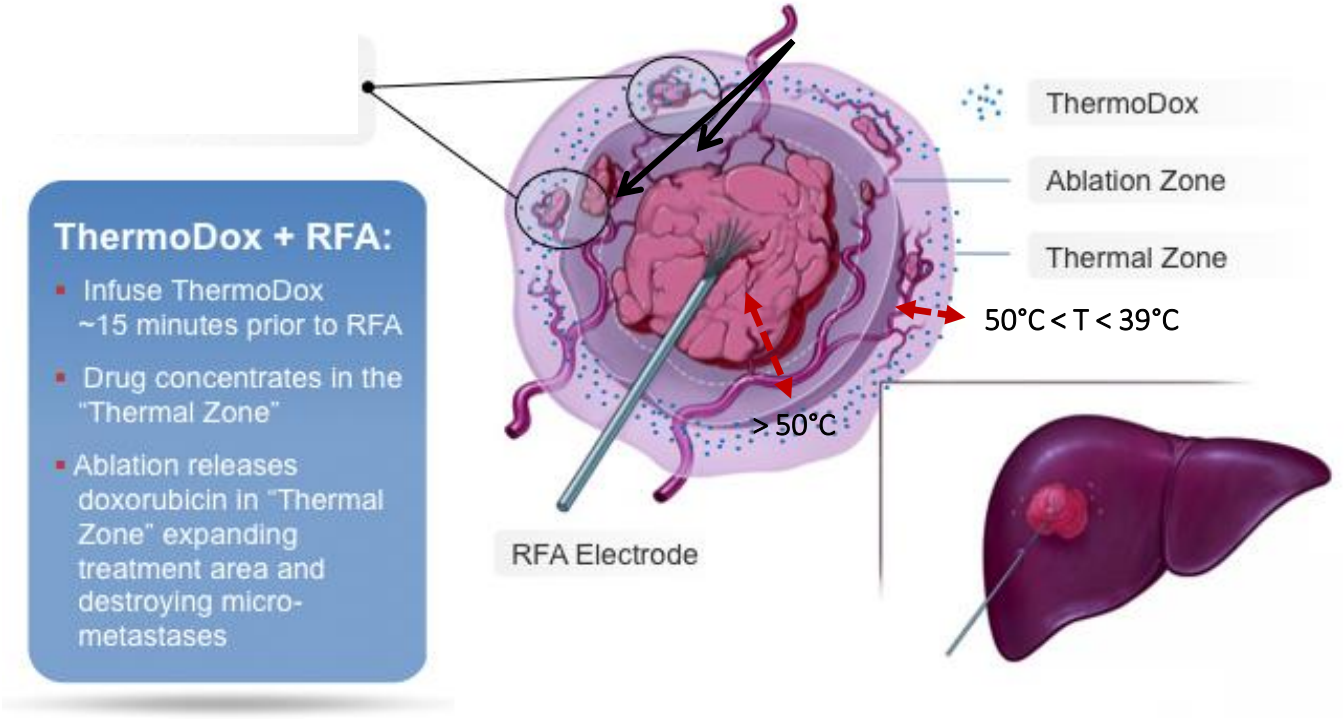
- Micro - metastasis outside the ablation zone “kill” area.
- Potential site of recurrence if not treated

Fourth generation: temperature sensitive

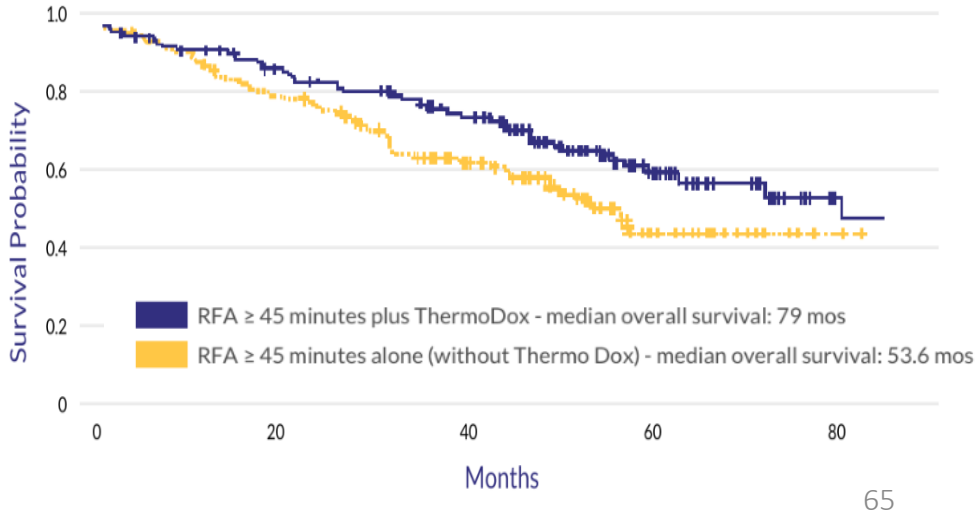
- Heat-activated doxorubicin loaded liposomes : Thermodox®



Ablated Tumor and 1 cm “tumor-free” margin

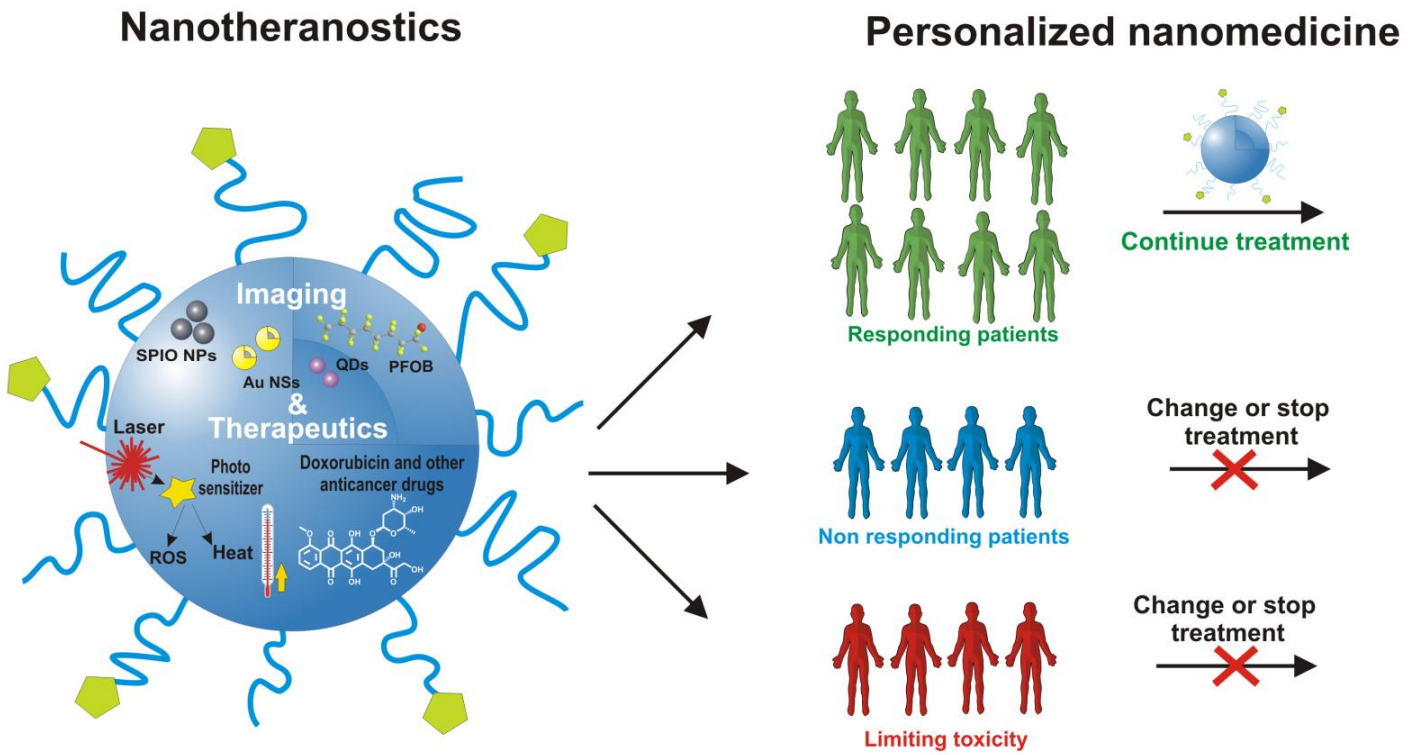


- Survival data for single-lesion patients



- Micro - metastasis outside the ablation zone “kill” area.
- Potential site of recurrence if not treated

- Moving to the personalized medicine



Combine targeted therapeutic & diagnostic functions

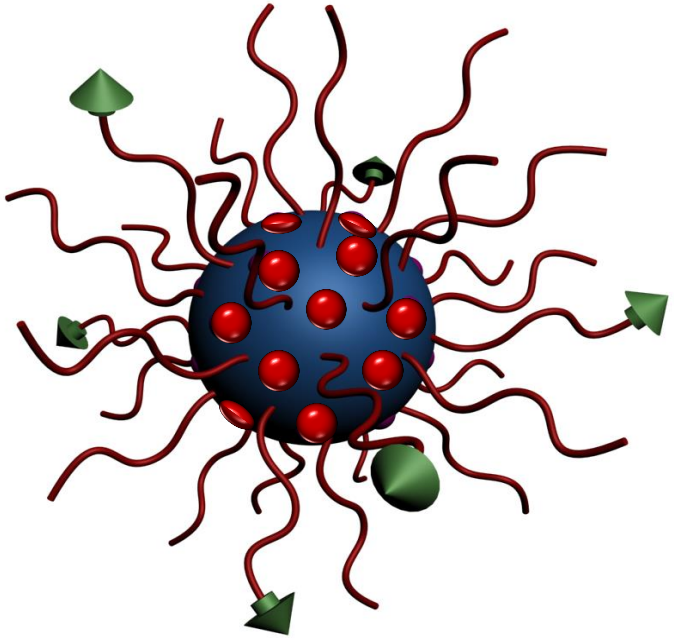
- Non invasive longitudinal monitoring
- Assessment of disease progression
- Evaluation of intervention efficacy at an early stage

Optimized and individualized treatment protocols

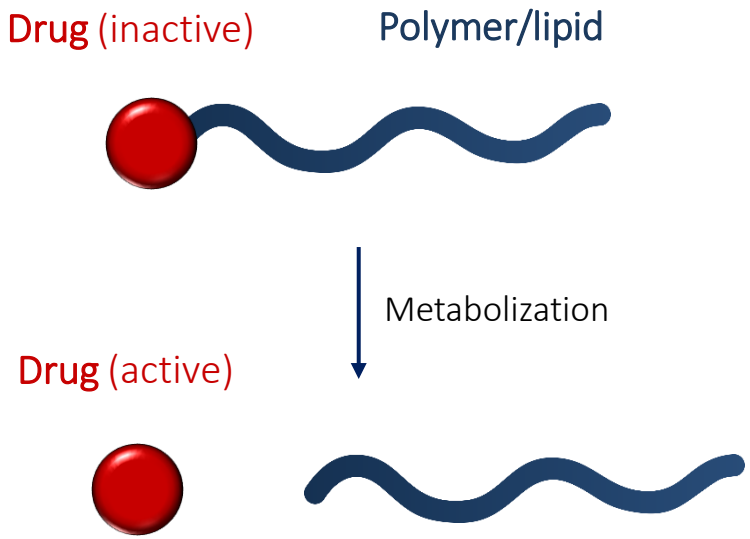
S. Mura *et al., Advanced Drug Delivery Reviews,* 2012, 64, 1394

Nanomedicine for drug delivery

Physical drug encapsulation



The prodrug strategy



Important limitations:

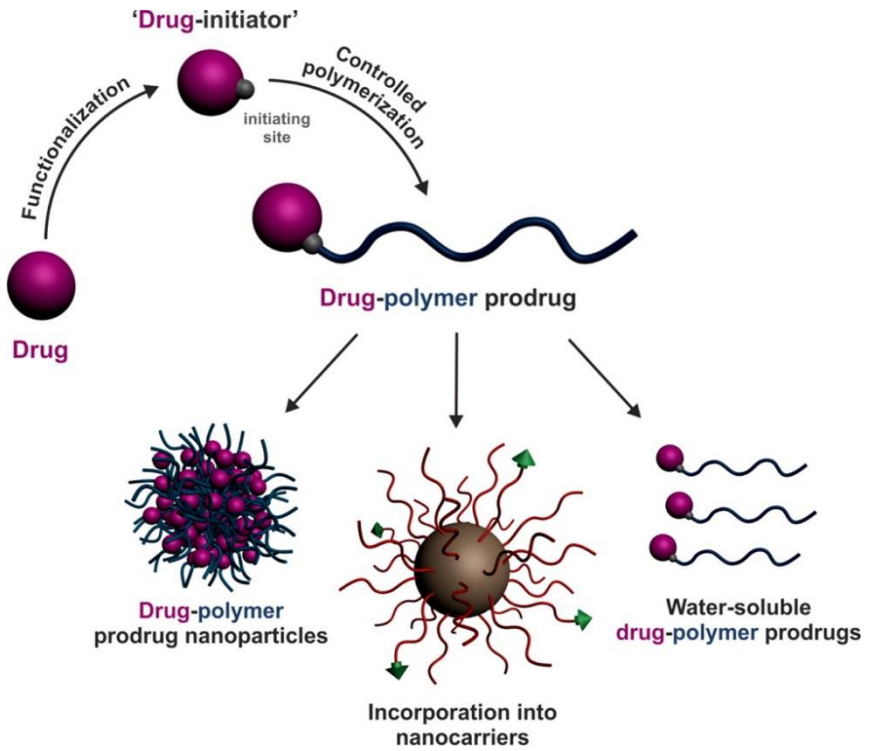
- Poor drug loading (< 5%)
- Burst release of surface adsorbed drug

Advantages:

- Sustained drug release
- Increase of the drug chemical stability
- Reduced toxicity before metabolization occurs

The prodrug approach

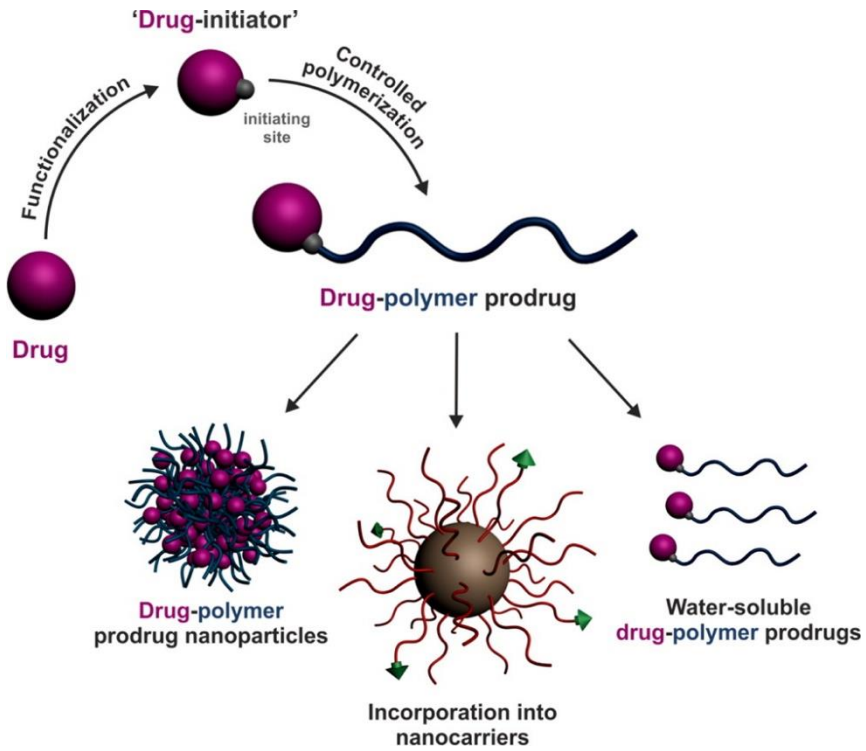
- Polymer prodrugs



Nicolas *Chem. Mater*. 2016 28, 1591; Delplace *et al*., *Polym Chem* 2014, 5, 1529

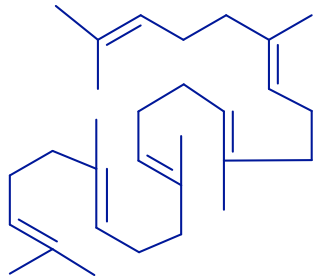
The prodrug approach

- Polymer prodrugs



- Lipid Prodrugs

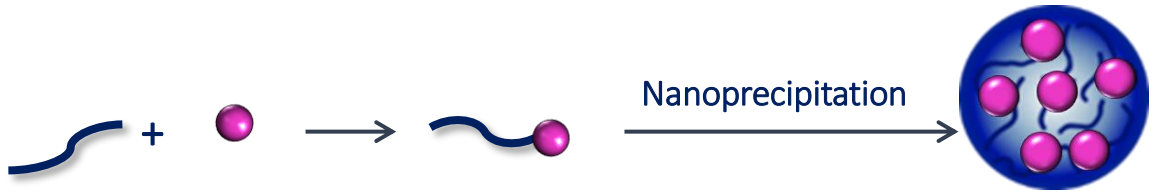
Squalene (SQ)



- Acyclic **triterpene** widely distributed in nature
- **Intermediate** in the **cholesterol biosynthetic pathway**
- Dynamically **folded conformation** in aqueous solution

The squalenoylation approach

chemical conjugation of squalene to a biologically active drug molecule leading to bioconjugates which self-assemble as nanoparticles in water

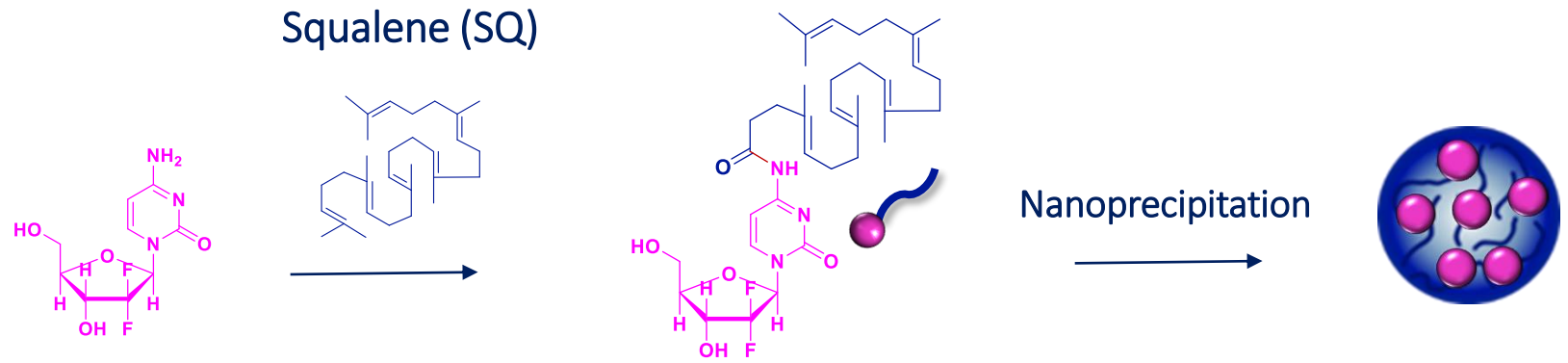


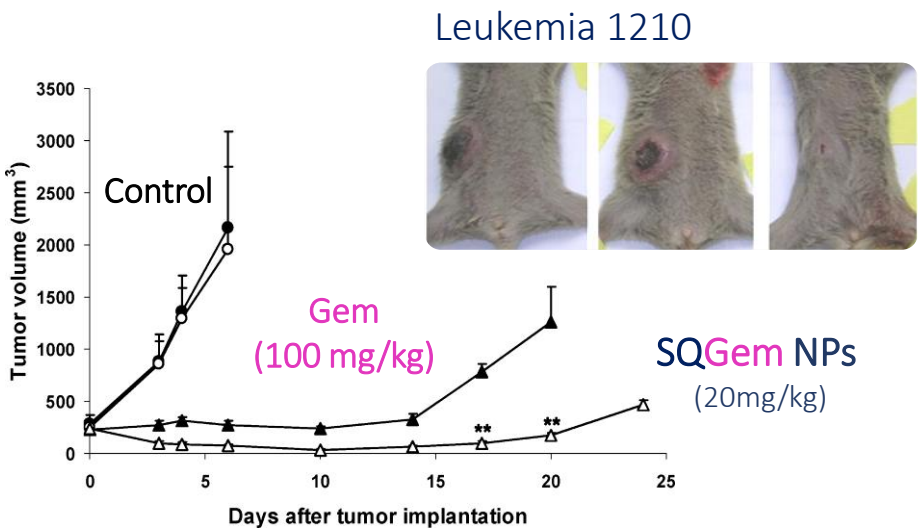
Drug SQDrug SQDrugNPs

Nicolas J. *Chem. Mater*. **2016** 28, 1591; Delplace V. *et al*., *Polym Chem* **2014,** 5, 1529

Couvreur P. *et al*., *Nano Letters*, 2006, 6, 2544; Couvreur P. *et al*., *Small*, 2008, 4, 247

The prodrug approach: squalene based





- ↑ $t_{1/2}$ (1.6 h vs. 8.6 h)
- ↑ drug loading
- Overcome resistance phenomena
- ↑ anticancer activity

Couvreur *et al.*, *Nano Letters* 2006, 6, 2544; Reddy *et al.*, *Drug Met. Disp.* 2008, 36, 1570; Reddy et al., *Mol. Pharm.* 2009, 6, 1526.

The prodrug approach: squalene based

Squalene (SQ)

Gemcitabine (Gem)

SQGem

Nanoprecipitation

SQGem

↑ $t_{1/2}$ (1.6 h vs [illegible])

↑ drug loading

No surface functionalization

Overcome resistance phenomena

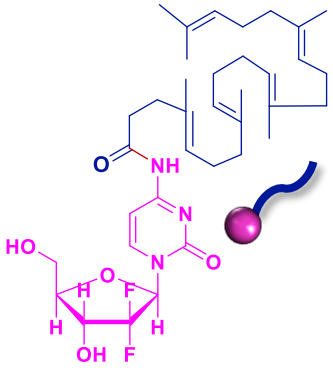
↑ anticancer activity

Leukemia 1210

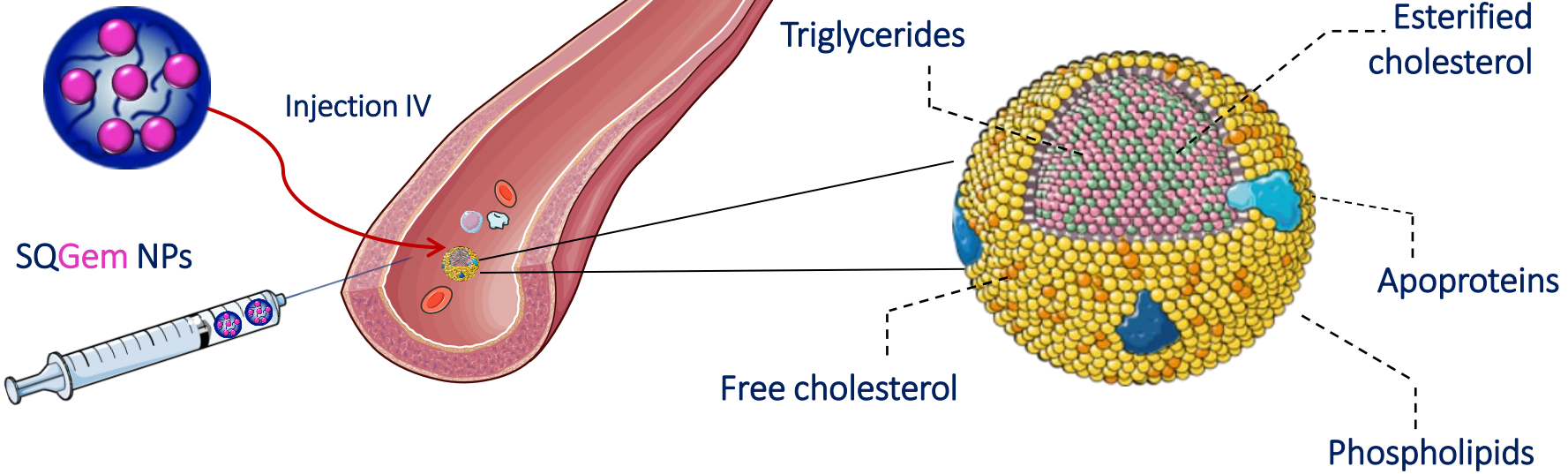
Couvreur *et al.*, *Nano Letters* 2006, 6, 2544; Reddy *et al.*, *Drug Met. Disp.* 2008, 36, 1570; Reddy et al., *Mol. Pharm.* 2009, 6, 1526.

In vivo fate of lipid prodrug-based nanoparticles (NPs)

Squalene (SQ)



Gemcitabine (Gem)



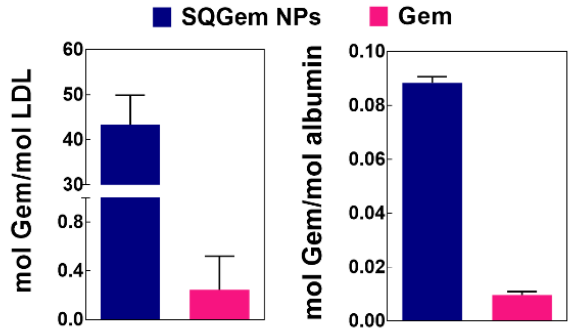
Cholesterol: transported in circulation by lipoproteins

Squalene: precursor in the cholesterol biosynthesis

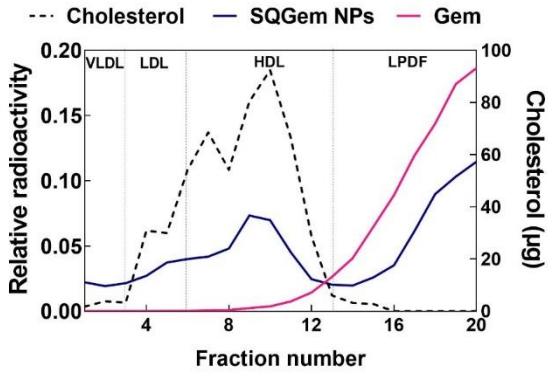
Behaviour analogy?

Lipoproteins as indirect drug carriers

- *In vitro* & *in vivo* studies



500 times higher affinity of SQGem for LDL compared to albumin



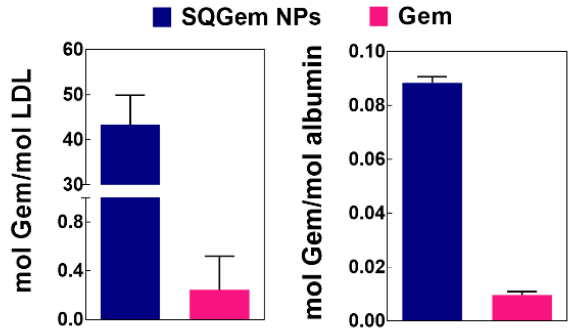
Preferential association with lipoproteins

Interaction with the main cholesterol transporters in the circulation

D. Sobot, S. Mura, S. Yesylevskyy, L. Dalbin, F. Cayre, G. Bort, J. Mougin, D. Desmaële, S. Lepetre-Mouelhi, G. Pieters, B. Andreiuk, A.S. Klymchenko, J.L. Paul, C. Ramseyer. P. Couvreur. *Nature Comm* **2017**, 8, 15678;
D. Sobot, S. Mura, M. Rouquette, B. Vukosavljevic, F. Cayre, E. Buchy, G. Pieters, S. Garcia-Argote, M. Windbergs, D. Desmaële, P. Couvreur. *Mol. Therapy* **2017**, 25, 1596

Lipoproteins as indirect drug carriers

- *In vitro* & *in vivo* studies



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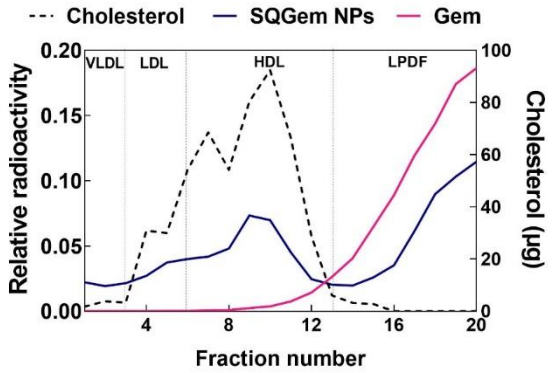

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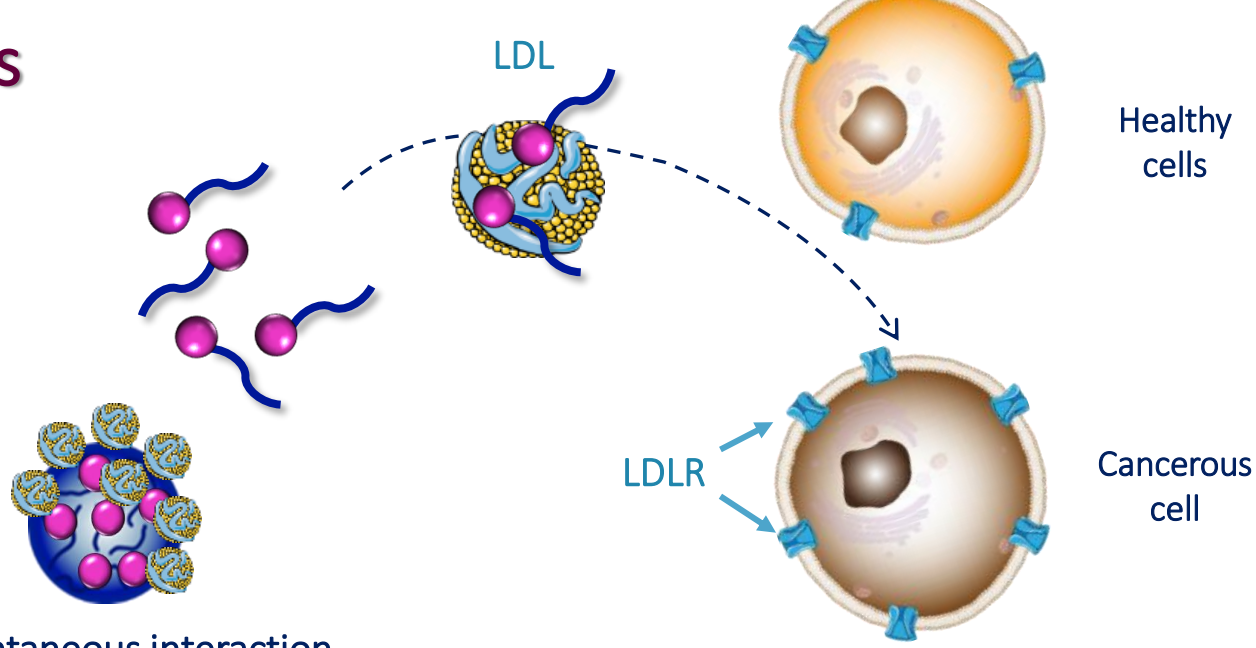
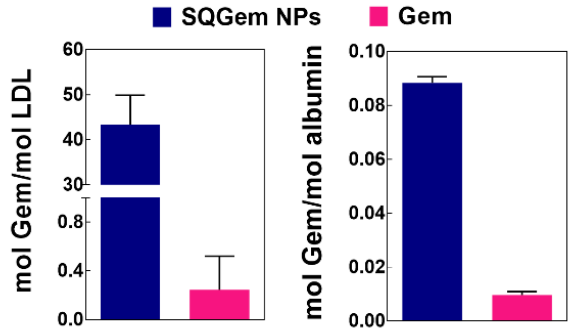


Spontaneous interaction
NP disassembly

D. Sobot, S. Mura, S. Yesylevskyy, L. Dalbin, F. Cayre, G. Bort, J. Mougin, D. Desmaële, S. Lepetre-Mouelhi, G. Pieters, B. Andreiuk, A.S. Klymchenko, J.L. Paul, C. Ramseyer. P. Couvreur. *Nature Comm* **2017**, 8, 15678;
D. Sobot, S. Mura, M. Rouquette, B. Vukosavljevic, F. Cayre, E. Buchy, G. Pieters, S. Garcia-Argote, M. Windbergs, D. Desmaële, P. Couvreur. *Mol. Therapy* **2017**, 25, 1596

Lipoproteins as indirect drug carriers

- *In vitro* & *in vivo* studies



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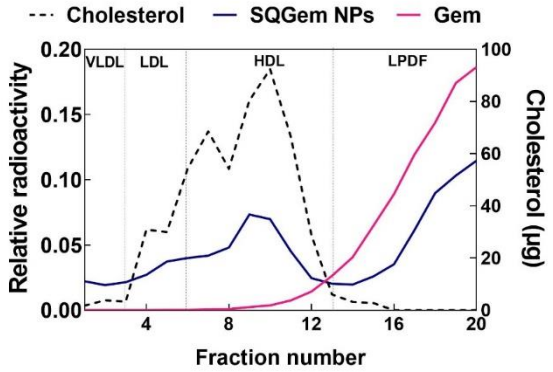
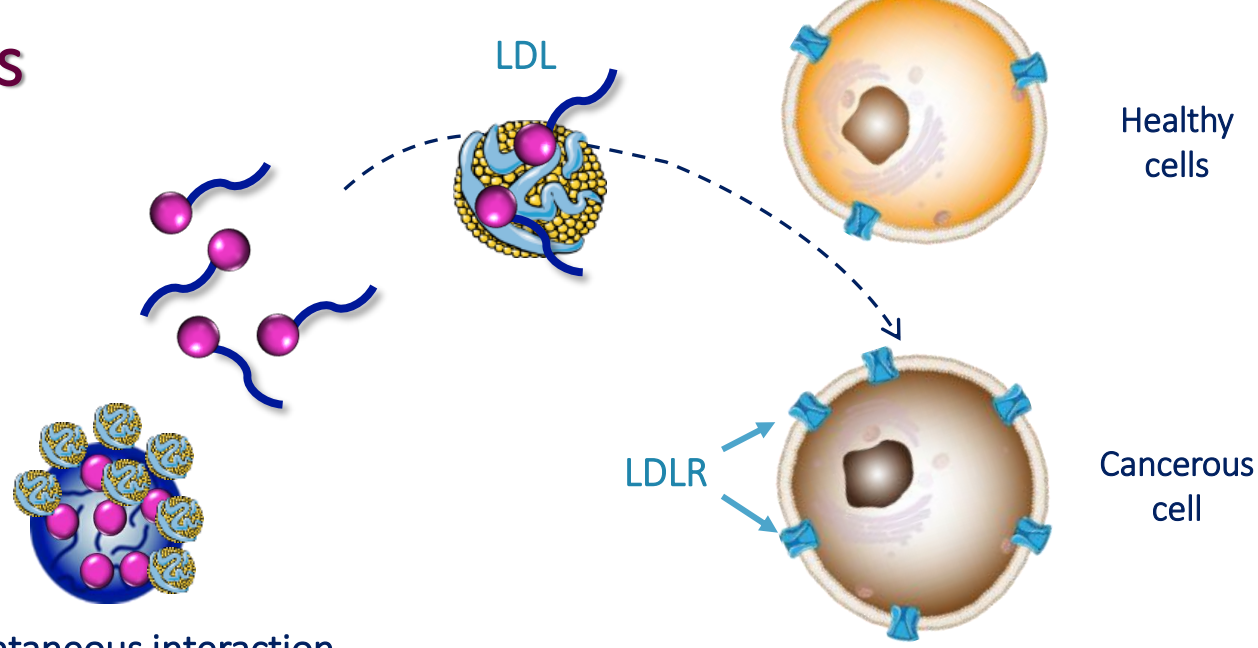


Preferential association with lipoproteins

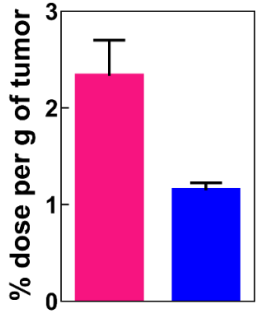
Interaction with the main cholesterol transporters in the circulation



Spontaneous interaction
NP disassembly

- Radioactivity quantification

In vivo tumor model



Uptake correlated to the extent of LDLR expression

D. Sobot, S. Mura, S. Yesylevskyy, L. Dalbin, F. Cayre, G. Bort, J. Mougin, D. Desmaële, S. Lepetre-Mouelhi, G. Pieters, B. Andreiuk, A.S. Klymchenko, J.L. Paul, C. Ramseyer. P. Couvreur. *Nature Comm* **2017**, 8, 15678;
D. Sobot, S. Mura, M. Rouquette, B. Vukosavljevic, F. Cayre, E. Buchy, G. Pieters, S. Garcia-Argote, M. Windbergs, D. Desmaële, P. Couvreur. *Mol. Therapy* **2017**, 25, 1596

Lipoproteins as direct drug carriers

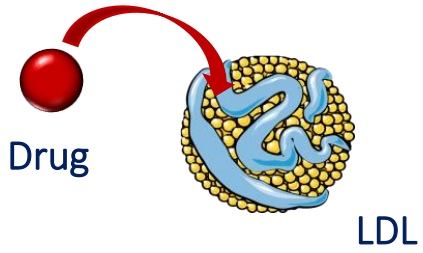
- Current loading strategies

  - Incorporation of drugs into endogenous isolated particle

  Complex LDL isolation

  Potential contamination

  Storage concerns (aggregation/degradation)

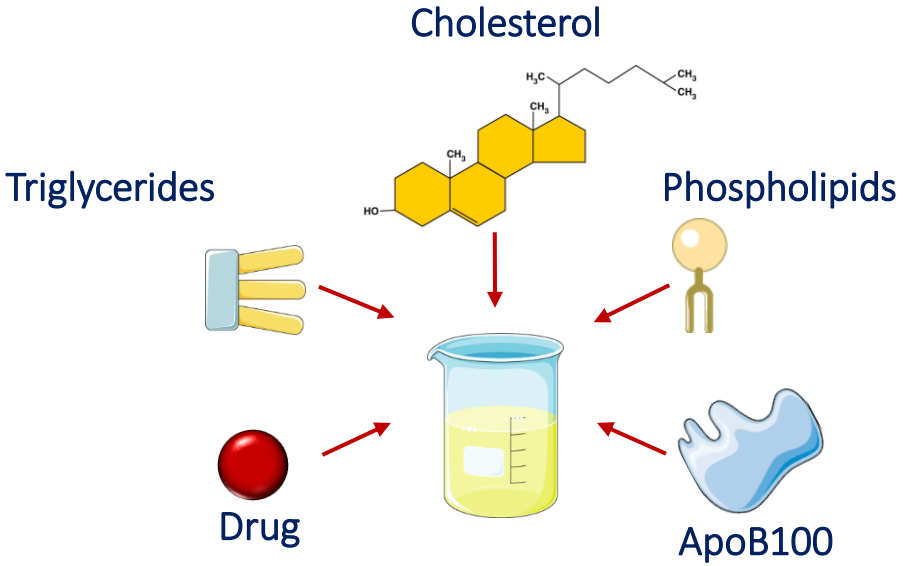


  - Design of drug loaded synthetic lipoprotein-like systems

  Batch reproducibility

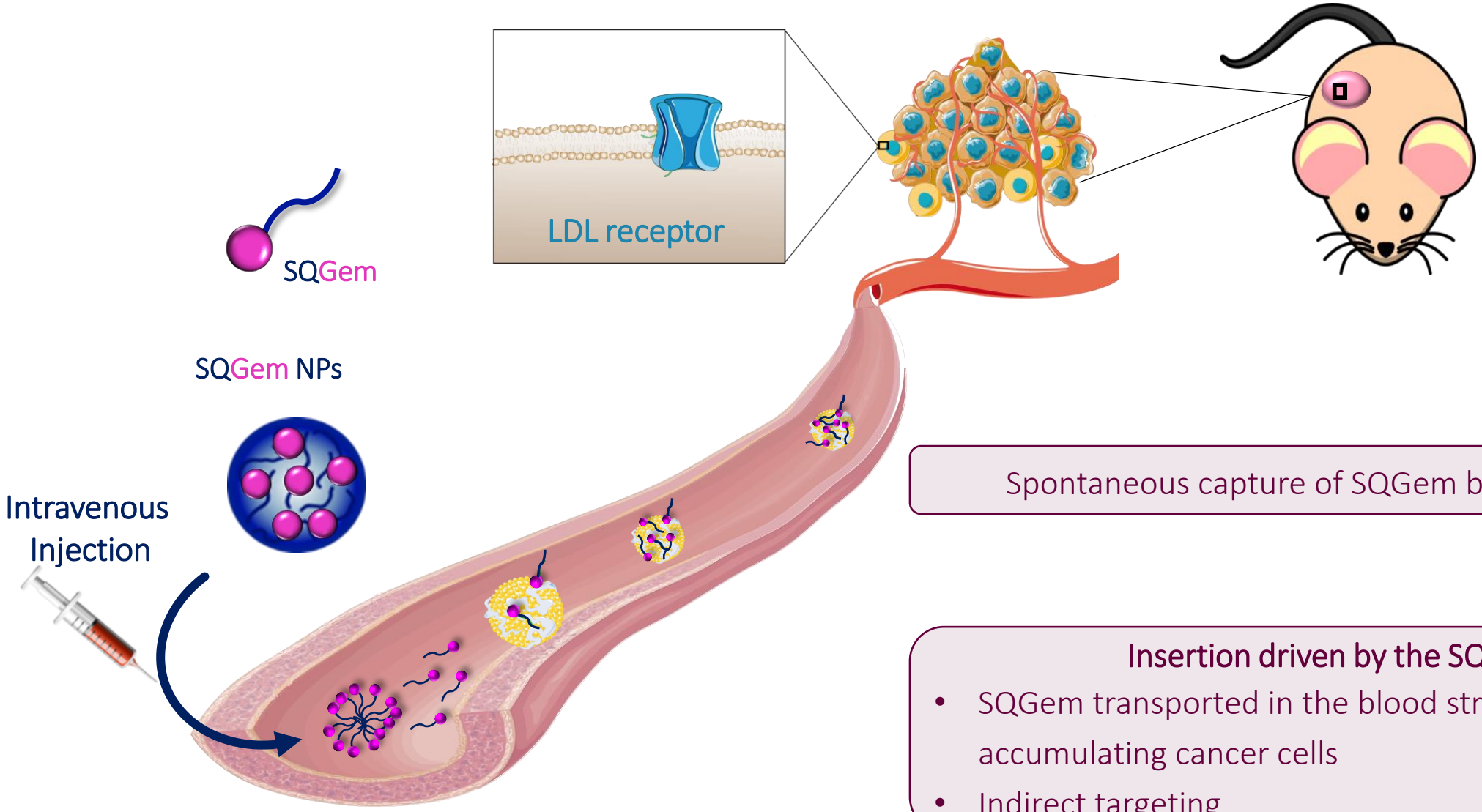
  Costs of large-scale production

  Synthetic carriers



Too many drawbacks: no industrial development

Lipoproteins as indirect drug carriers

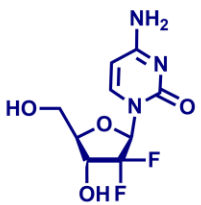


Spontaneous capture of SQGem by circulating LDL

Insertion driven by the SQ moiety

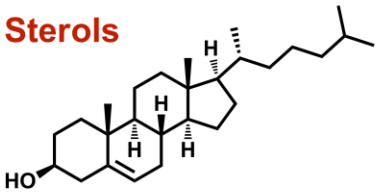
- SQGem transported in the blood stream towards LDL accumulating cancer cells
- Indirect targeting

Other lipid prodrugs



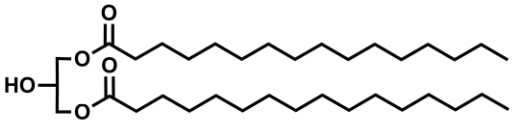
Gemcitabine

Sterols



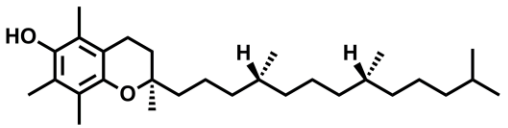
Cholesterol (Chol)

Diglycerides



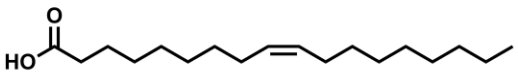
Glyceryl 1,3-dipalmitate (Digly)

Fat-Soluble vitamins

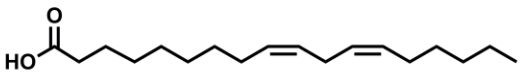


Alpha-tocopherol (VitE)

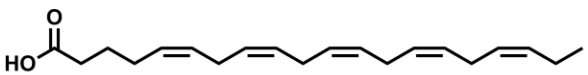
Unsaturated fatty acids



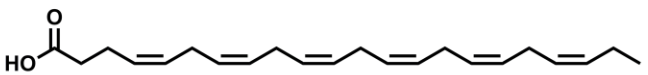
Oleic acid (OA)



Linoleic acid (LA)

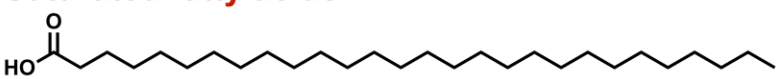


Eicosapentaeneoic acid (EPA)



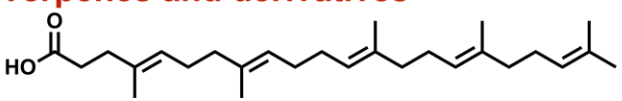
Docosahexaenoic acid (DHA)

Saturated fatty acids

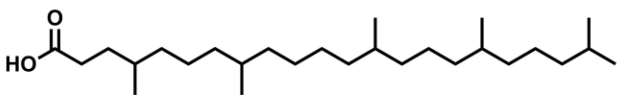


Octacosanoic acid (C28)

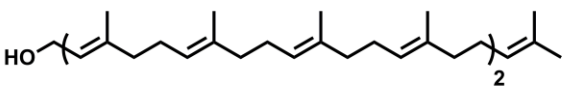
Terpenes and derivatives



Squalene (SQ)



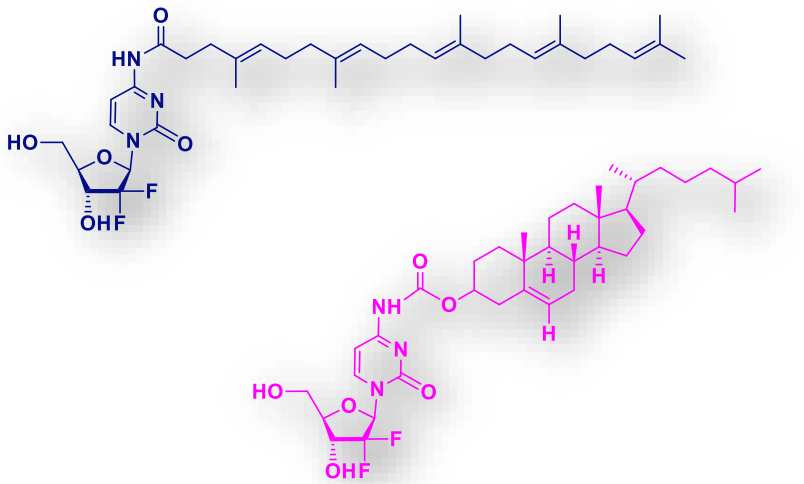
Saturated Squalenic acid (RSQ)



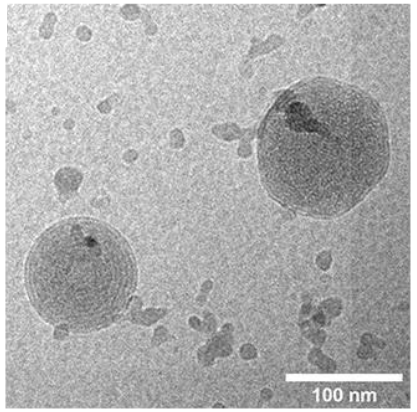
Solanesol (Sol)

E. Coppens, D. Desmaele, J. Mougin, S. Tusseau-Nenez P. Couvreur, S. Mura. *Bioconjugate Chemistry* **2021**, 32, 782

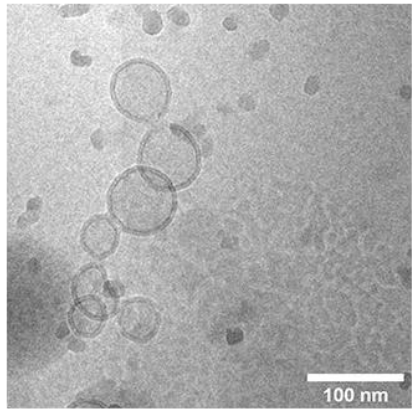
Lipid prodrugs: Cholesterol Gemcitabine



Conjugate	Mean diameter (nm)	Polydispersity index (PdI)	Zeta Potential (mV)	Drug loading (%)
SQGem	82 ± 7	0.11 ± 0.03	-20 ± 7	40.7
CholGem	97 ± 15	0.09 ± 0.02	-21 ± 7	38.9

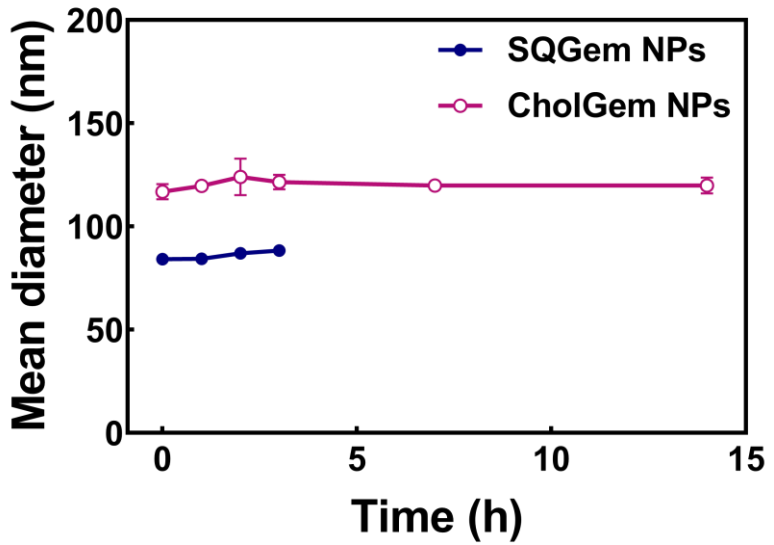


SQGem NPs



CholGem NPs

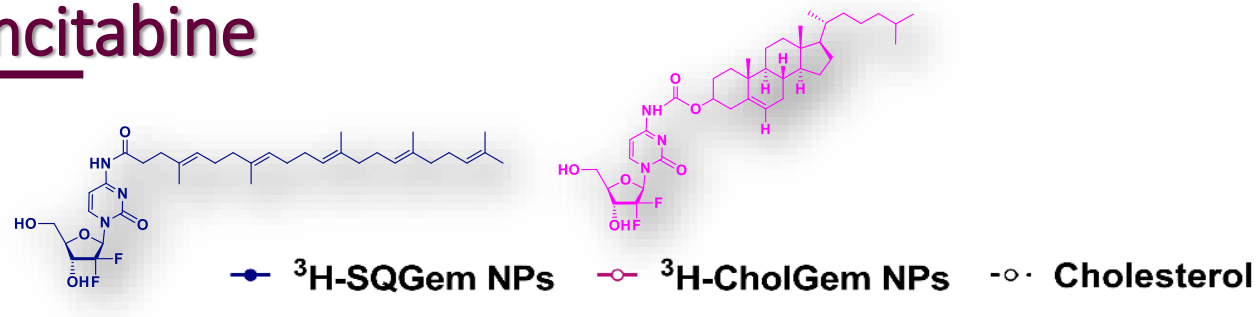
- Stability over time (RT, mQ)

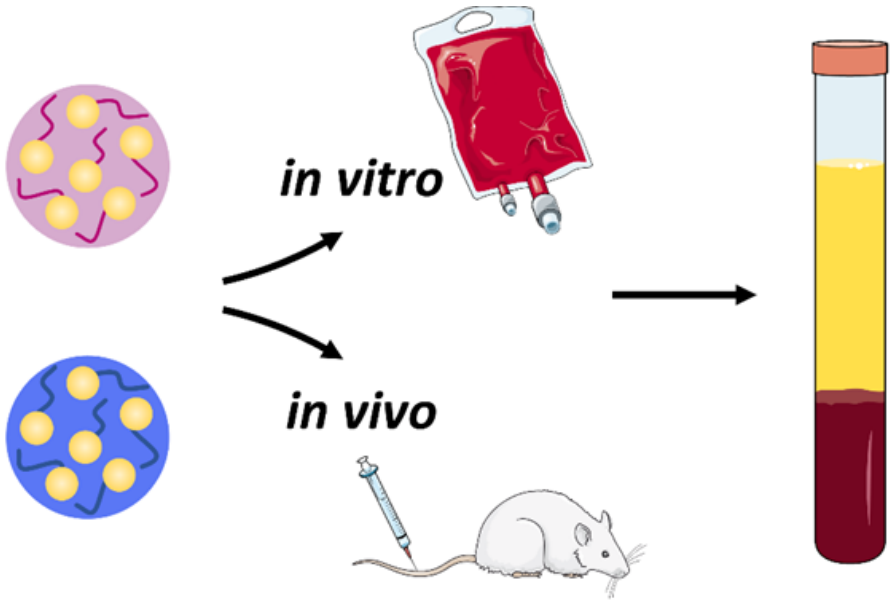


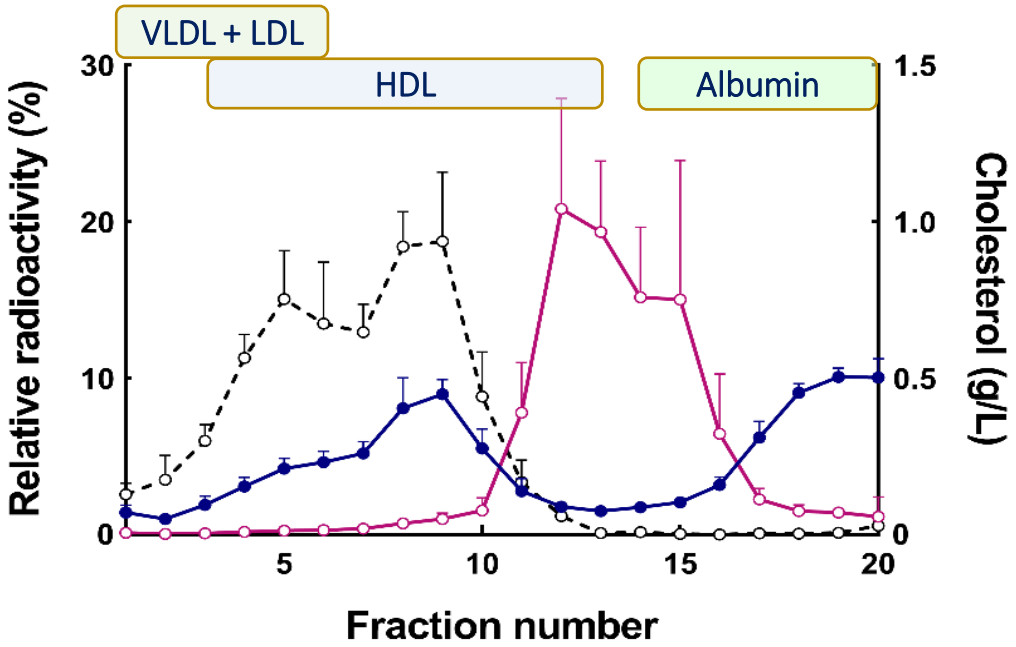
E. Coppens, D. Desmaële, T. Naret, S. Garcia Argote, S. Feuillastre, G. Pieters, C. Cailleau, J.L. Paul, B. Prost, A. Solgadi, J.P. Michel, M. Noiray, P. Couvreur, S. Mura. *Int J Pharm* **2021** 121076.

Lipid prodrugs: Cholesterol Gemcitabine

- Plasma distribution







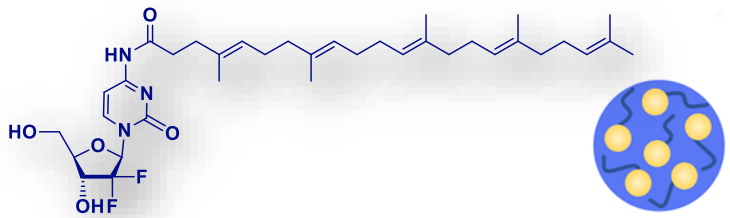
SQGem follows endogenous cholesterol profile and albumin

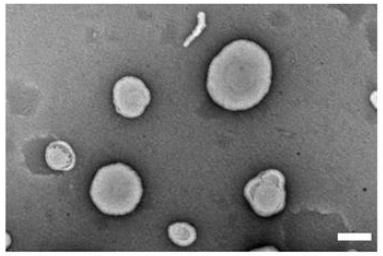
CholGem found in albumin and LP-deficient fractions

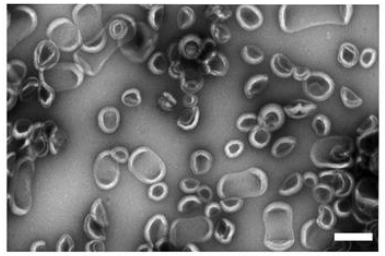
E. Coppens, D. Desmaële, T. Naret, S. Garcia Argote, S. Feuillastre, G. Pieters, C. Cailleau, J.L. Paul, B. Prost, A. Solgadi, J.P. Michel, M. Noiray, P. Couvreur, S. Mura. *Int J Pharm* **2021** 121076.

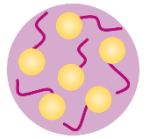
Lipid prodrugs: Cholesterol Gemcitabine

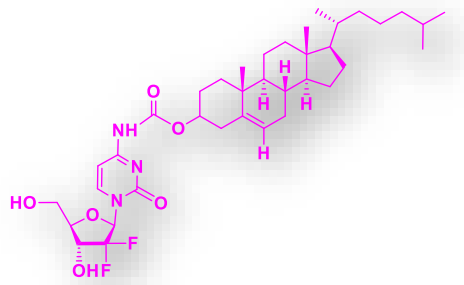
- Physical mixtures : 5’ @ 37° C





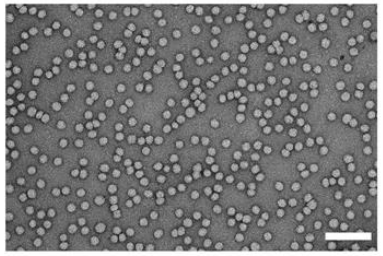


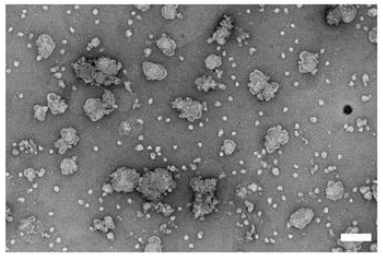


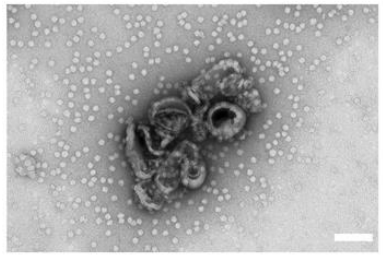


LDL

HDL

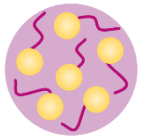






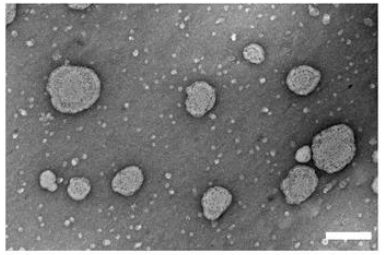
LDL

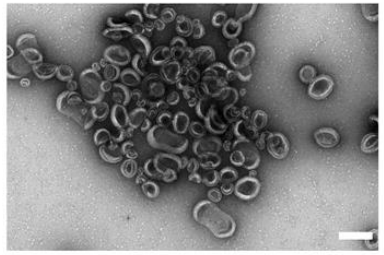
LDL



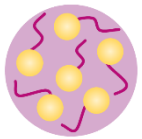
Merging of NPs & LPs

HDL





HDL

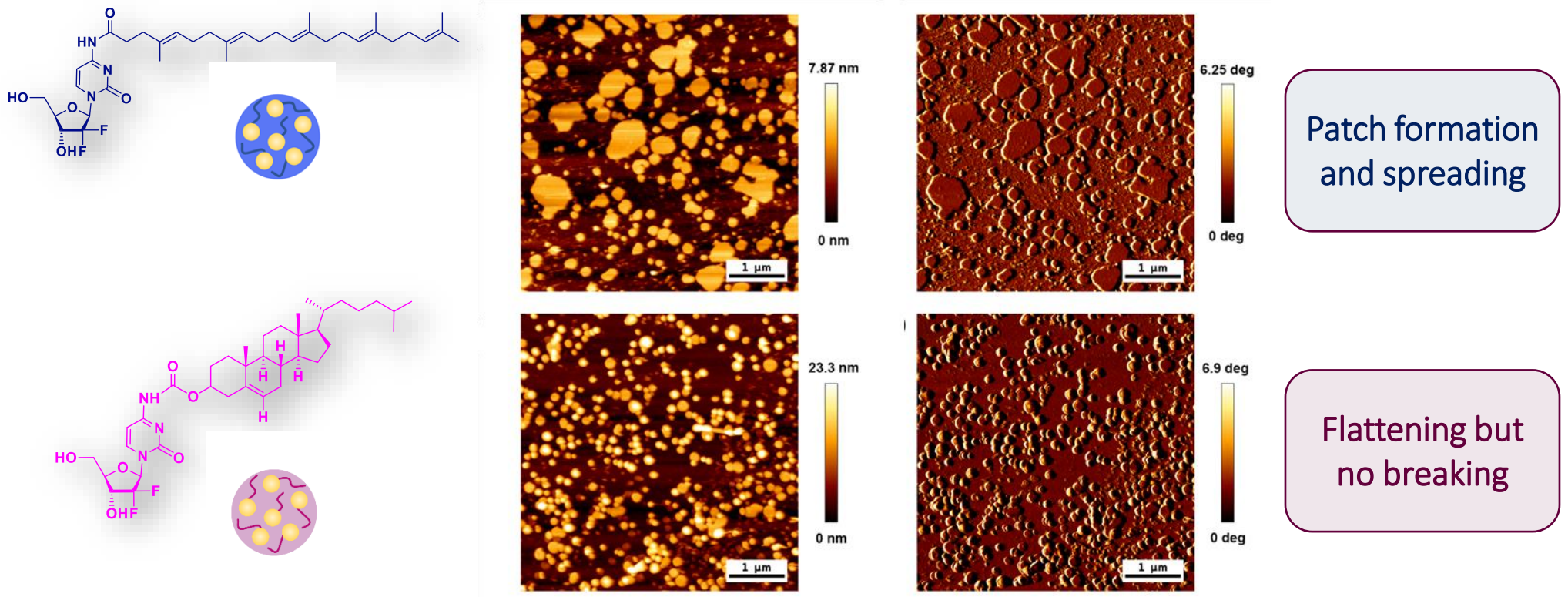


Simple co-existance

E. Coppens, D. Desmaële, T. Naret, S. Garcia Argote, S. Feuillastre, G. Pieters, C. Cailleau, J.L. Paul, B. Prost, A. Solgadi, J.P. Michel, M. Noiray, P. Couvreur, S. Mura. *Int J Pharm* **2021** 121076.

Lipid prodrugs: Cholesterol Gemcitabine

- AFM analysis: lysine-coated MICA surface



Patch formation and spreading

Flattening but no breaking

The physico-chemical properties of the NPs strongly influence the fate in the bloodstream

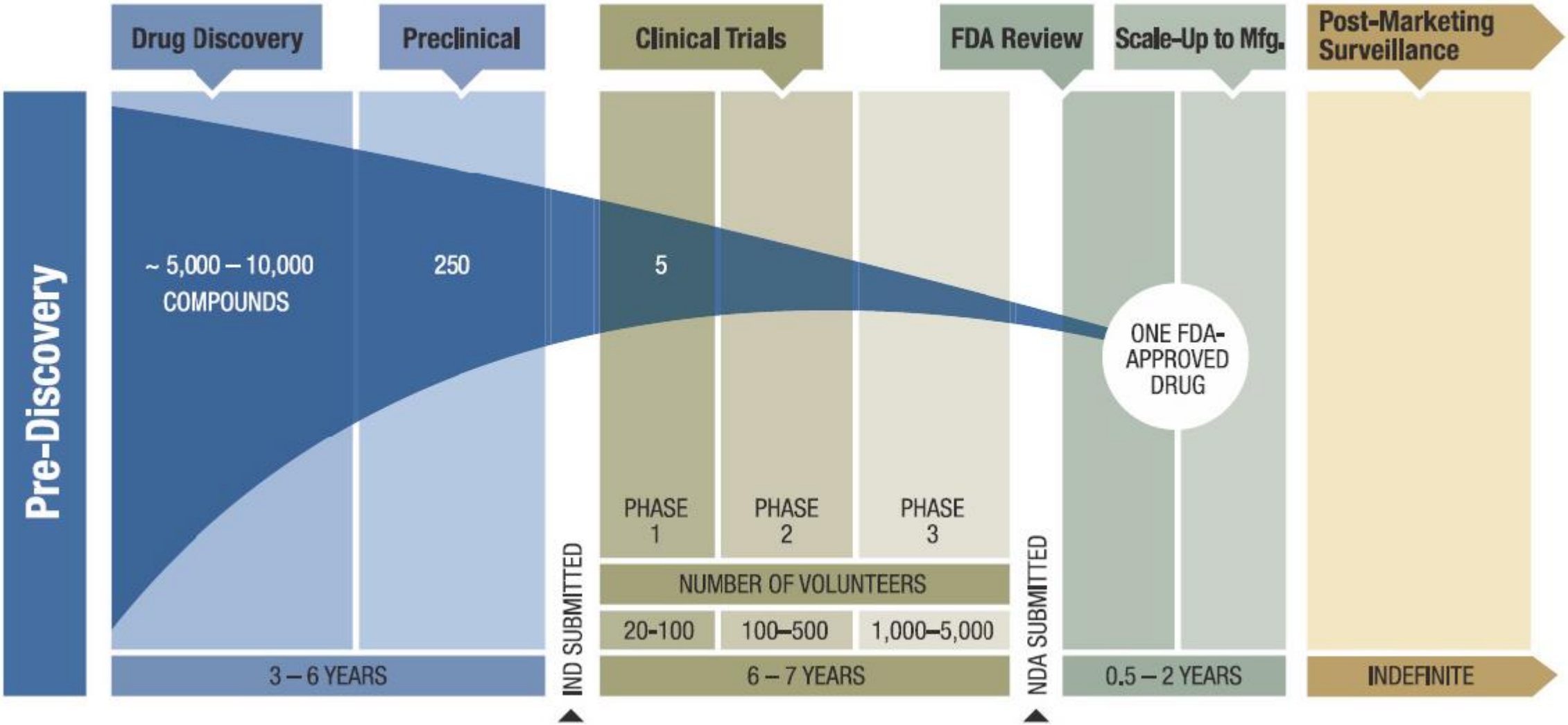
E. Coppens, D. Desmaële, T. Naret, S. Garcia Argote, S. Feuillastre, G. Pieters, C. Cailleau, J.L. Paul, B. Prost, A. Solgadi, J.P. Michel, M. Noiray, P. Couvreur, S. Mura. *Int J Pharm* **2021** 121076.

Nanoscale drug delivery systems

From the bench to the bedside

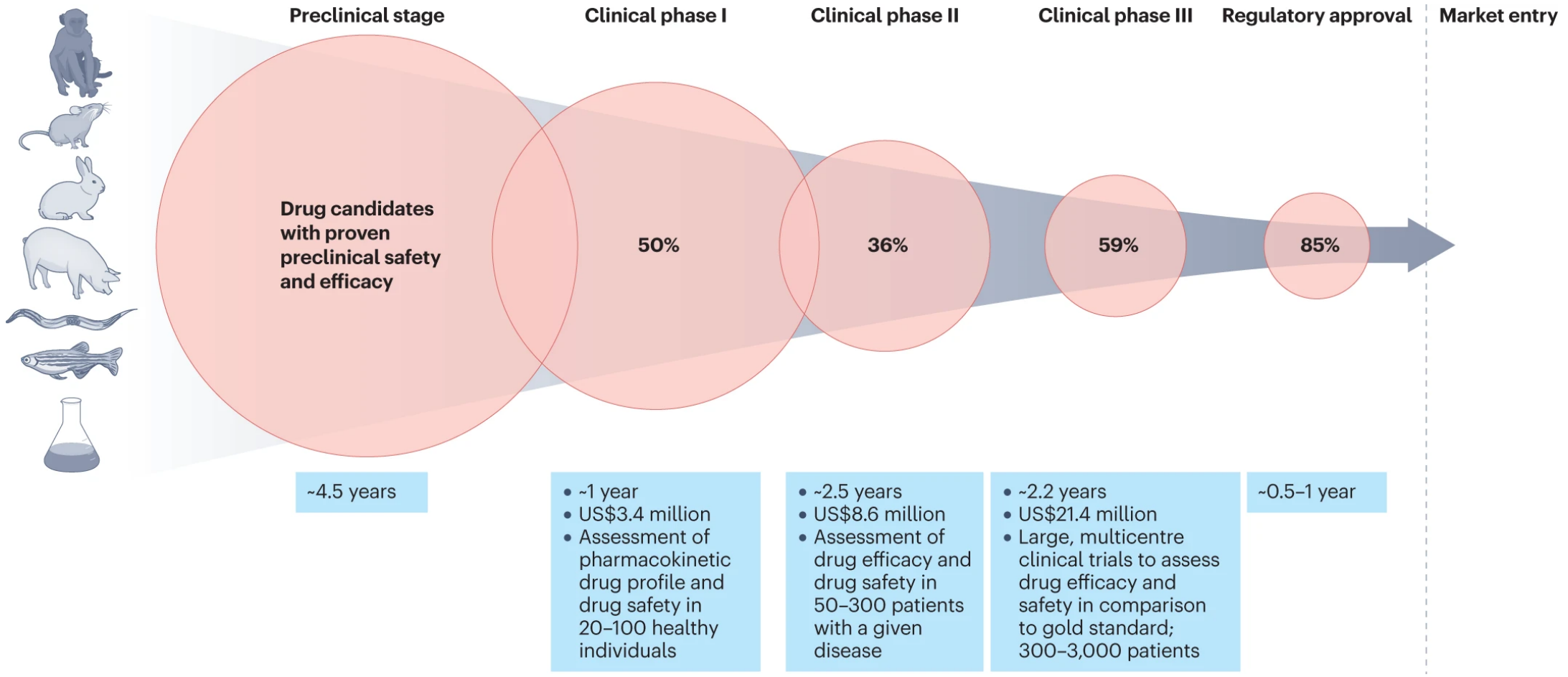
Need of a relevant preclinical evaluation (UE 3)

Drug development timeline



http://www.thepipettepen.com/what-to-expect-when-running-the-gauntlet-of-drug-development/

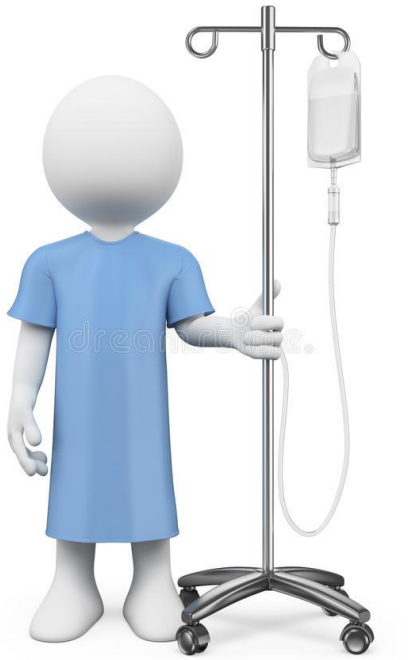
Drug development timeline



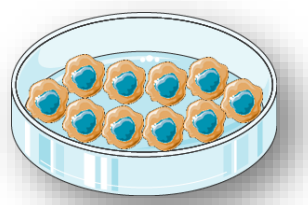
Loewa, A., Feng, J.J. & Hedtrich, S. Nat Rev Bioeng 1, 545–559 (2023).

Physiologically relevant models

- Patients



2D



Easy and convenient set-up

Highly reductionist

Flat cells, simple geometry

Lack of architecture

Less realistic drug response

- *In vivo* studies

Very useful

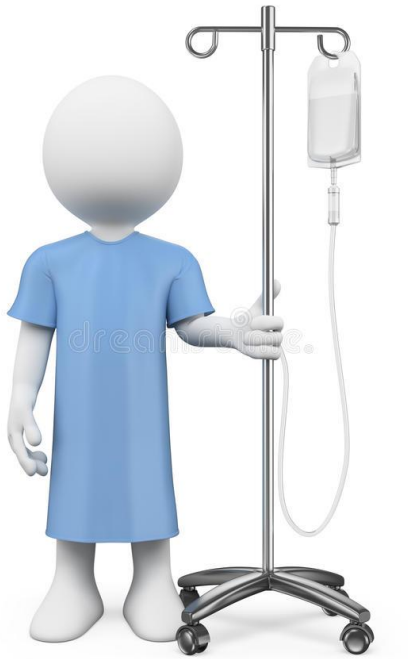
Expensive, time consuming

Specie differences

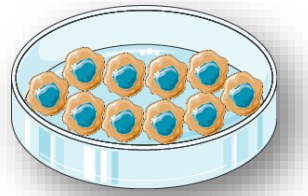
Ethical issues

Physiologically relevant models

- Patients



2D



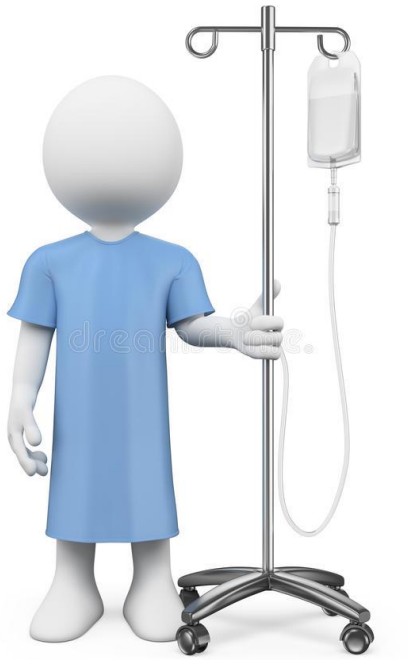
- Easy and convenient set-up
- Highly reductionist
- Flat cells, simple geometry
- Lack of architecture
- Less realistic drug response

- *In vivo* studies

- Very useful
- Expensive, time consuming
- Specie differences
- Ethical issues

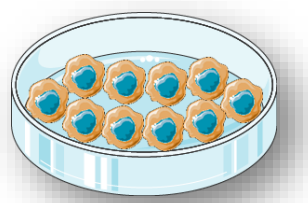
Physiologically relevant models

- Patients



- Cell-to-cell, cell-to-matrix interaction
- Oxygen, nutrient and waste gradient
- Recreation of the microenvironment
- Vascularization

2D



- Easy and convenient set-up (+)
- Highly reductionist (−)
- Flat cells, simple geometry (−)
- Lack of architecture (−)
- Less realistic drug response (−)

- *In vivo* studies

- Very useful (+)
- Expensive, time consuming (−)
- Specie differences (−)
- Ethical issues (−)

FDA Modernization Act 2.0

…make use of "certain ***alternatives to animal testing****, including cell-based assays and computer models, to obtain an exemption from the Food and Drug Administration to investigate the safety and effectiveness of a drug"…*

*"****removes a requirement to use animal studies*** *as part of the process to obtain a license for a biological product that is biosimilar or interchangeable with another biological product"*

ANIMAL RESEARCH

FDA no longer has to require animal testing for new drugs

Agency can rely on animal-free alternatives before human trials

By **Meredith Wadman**

New medicines need not be tested in animals to receive U.S. Food and Drug Administration (FDA) approval, according to legislation signed by President Joe Biden in late December 2022. The change—long sought by animal welfare organizations—could signal a major shift away from animal use after more than 80 years of drug safety regulation.

"This is huge," says Tamara Drake, director of research and regulatory policy at the Center for a Humane Economy, a nonprofit animal welfare organization and key driver of the legislation. "It's a win for industry. It's a win for patients in need of cures."

In place of the 1938 stipulation that potential drugs be tested for safety and efficacy in animals, the law allows FDA to promote a drug or biologic—a larger molecule such as an antibody—to human trials after either animal or nonanimal tests. Drake's group and the nonprofit Animal Wellness Action, among others that pushed for changes, argue that in clearing drugs for human trials the agency should rely more heavily on computer modeling, "organ chips," and other nonanimal methods that have been developed over the past 10 to 15 years.

But pro-research groups are downplaying the law, saying it signals a slow turning of the tide—not a tsunami that will remake the drug approval process overnight. Jim Newman, communications director at Americans for Medical Progress, which advocates for animal research, argues nonanimal technologies are still "in their infancy" and won't be able to replace animal models for "many, many years." FDA still retains tremendous discretion to require animal tests, he notes, and he doesn't expect the agency to change tack anytime soon.

13 JANUARY 2023 • VOL 379 ISSUE 6628

https://doi.org/10.1016/j.amjmed.2023.03.033

FDA Modernization Act 2.0

Five alternatives to animal testing

Researchers are rapidly developing non-animal alternatives that promise more accurate and cost-effective approaches to the discovery process. "I think what's going to happen is that as the field becomes more and more comfortable, confident, and experienced with using these newer methods, eventually they will completely replace the use of animals," says **Aysha Akhtar, M.D., M.P.H.**, co-founder and CEO of the Center for Contemporary Sciences, a non-profit that is working to advance research and testing approaches that are rooted in human biology.

Organoids

Organoids are cultures of stem cells capable of differentiating and spontaneously self-organizing into small 3D structures that mimic, to an extent, organs. Heart, lung, and other organoids offer screening platforms for drugs, as well as mechanistic insights. Researchers at the Center for Alternatives to Animal Testing at the Johns Hopkins Bloomberg School of Public Health have created brain organoids for studying neurodegenerative disease, electrophysiology, and even intelligence.

Human tissue

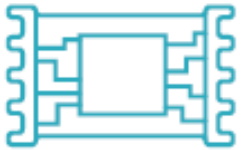
Studies on tissue derived from volunteers and surgical procedures offer opportunities to evaluate therapeutic interventions on accurate models of the disease. For example, researchers studying vitiligo, an autoimmune skin disorder, can directly assess how a potential intervention impacts autoimmune processes in skin tissue derived from people with vitiligo. Such experiments generate data that promote a level of precision medicine unattainable using animal models.

Phase 0 clinical trials

In Phase 0 trials, study participants are given sub-therapeutic levels of an investigational drug, followed by tests to identify changes in physiology. Despite the low dosage, data concerning potential toxicity and efficacy may be derived.

Organ-on-a-chip

These microfluidic devices contain tiny channels lined with living cells and are designed to reflect the architecture and physiology of an organ. This involves capturing the basic elements required for biological activity, including various cell types, structures, and microenvironments, and recreating them in a matrix. By stringing organ-on-a-chips together in a biologically relevant fashion, researchers can create multi-organ systems or even a human-on-a-chip. Such efforts recently resulted in the first FDA approval of human trials for a drug candidate without preclinical animal efficacy data.



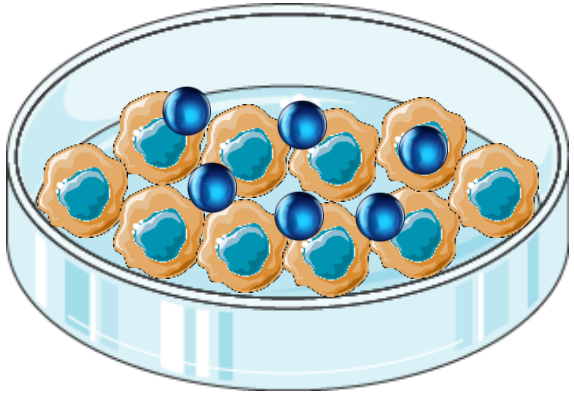
Digital twins

The application of machine learning methods takes advantage of enormous amounts of data from patient records and previous clinical trials to generate predictive models of patient response to an intervention. The creation of a "digital twin" could limit the need for animal testing and the number of patients required for a clinical trial. Theoretically, the model's accuracy would progressively increase with each subsequent trial based on the newly generated data.

Cell culture models

2D

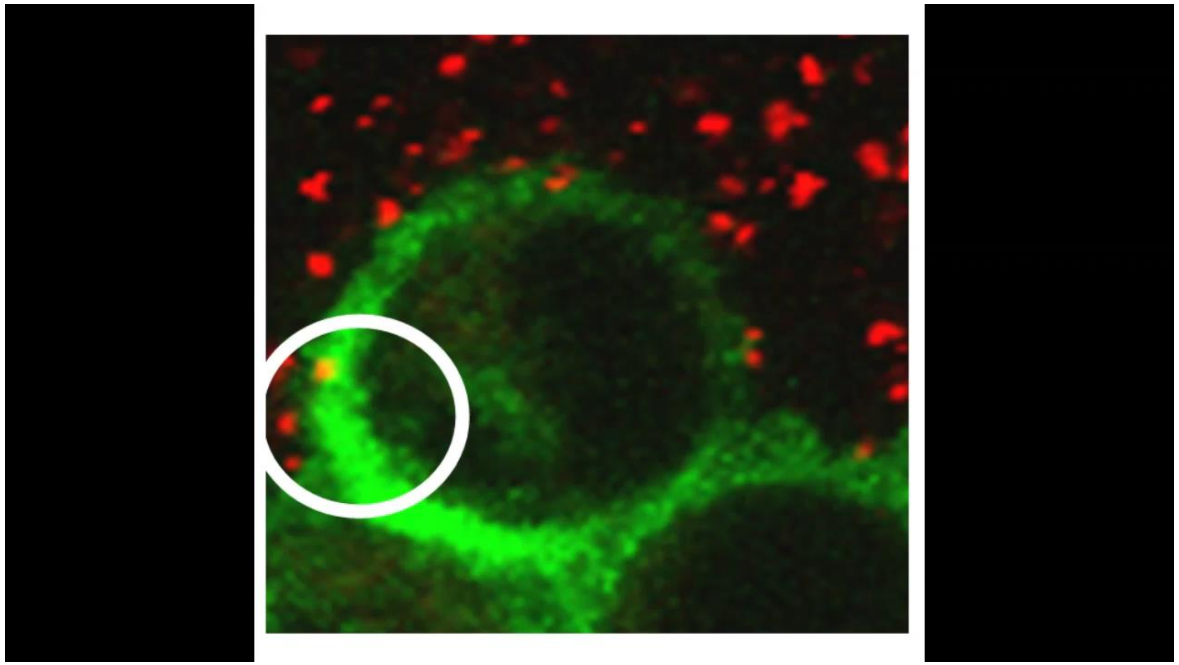
Drug / NPs



Cell-uptake studies

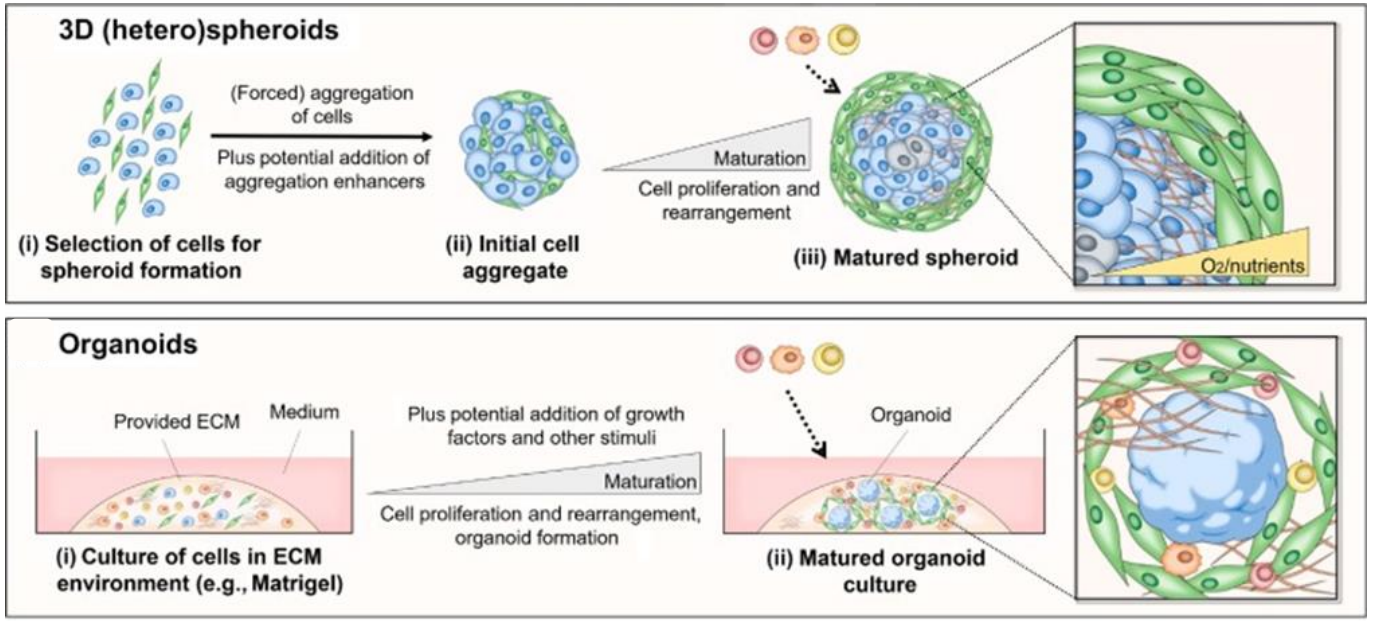
- Confocal microscopy

Uptake of fluorescently-labeled liposomes by macrophages (membrane labeled in green)



3D culture models

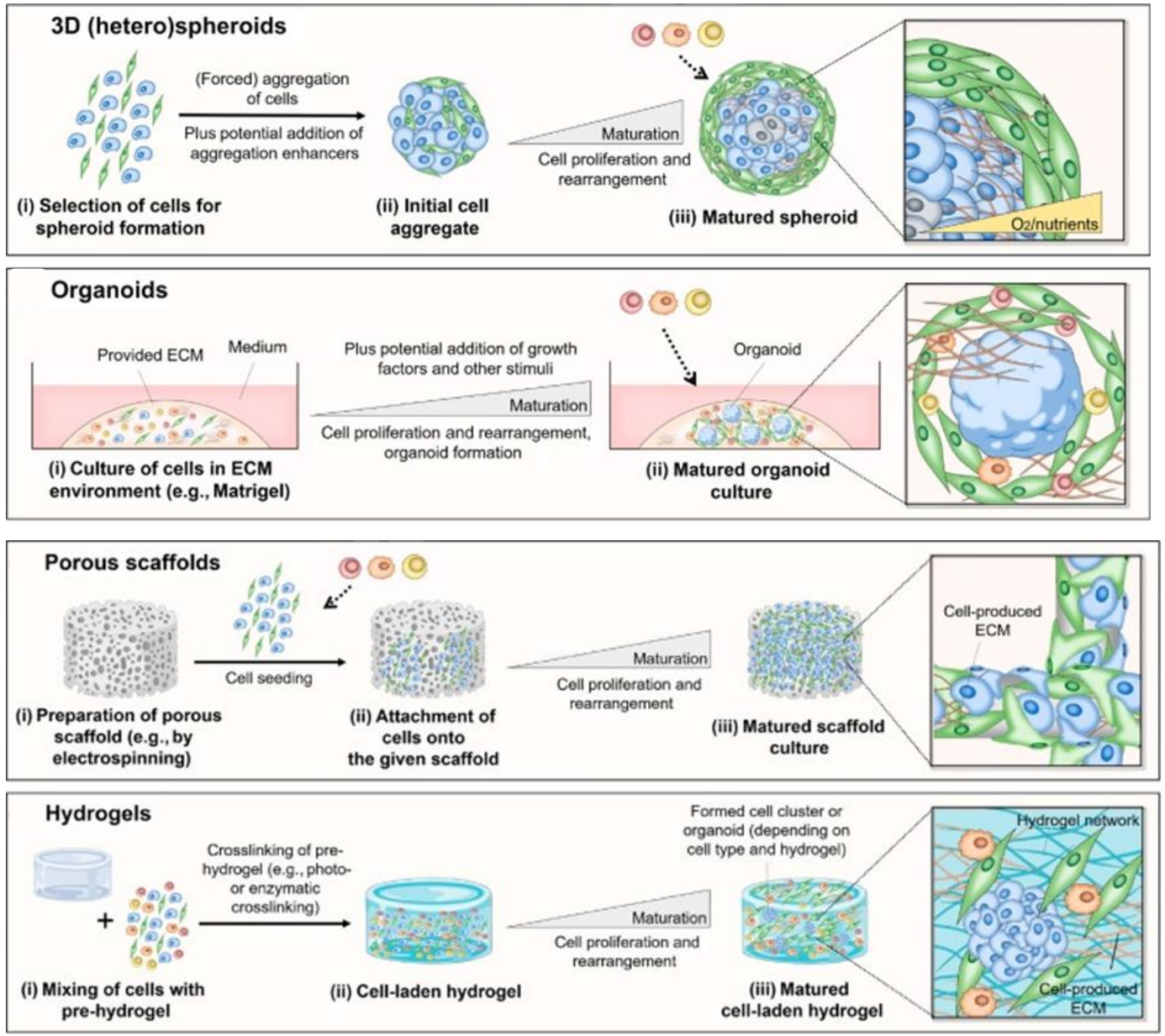
- Cell-Based



https://doi.org/10.1016/j.trecan.2020.10.009 Trends in Cancer, March 2021, Vol. 7, No. 3

3D culture models

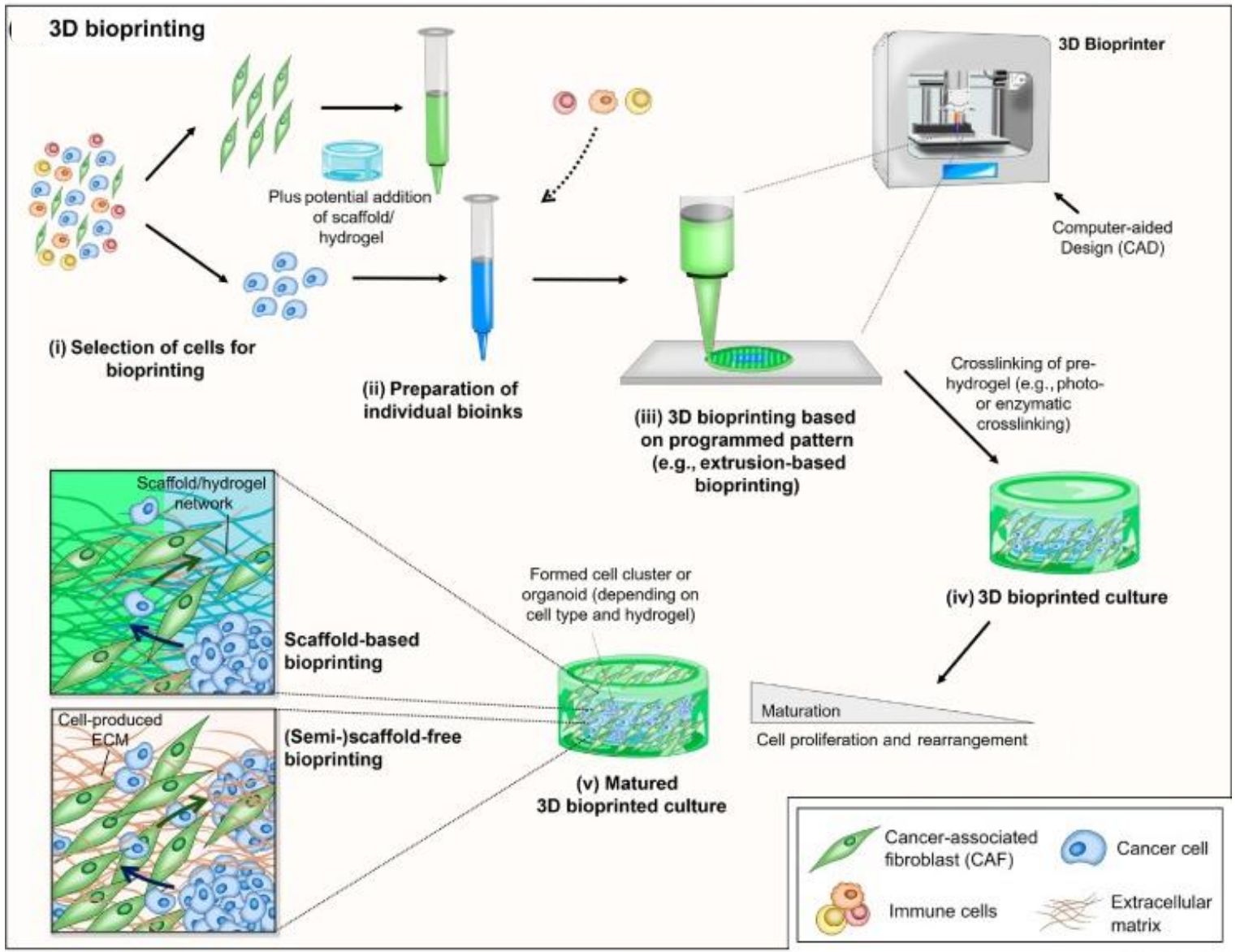
- Cell-Based
- Cell/Extracellular Matrix (ECM)-Based



https://doi.org/10.1016/j.trecan.2020.10.009 Trends in Cancer, March 2021, Vol. 7, No. 3

3D culture models

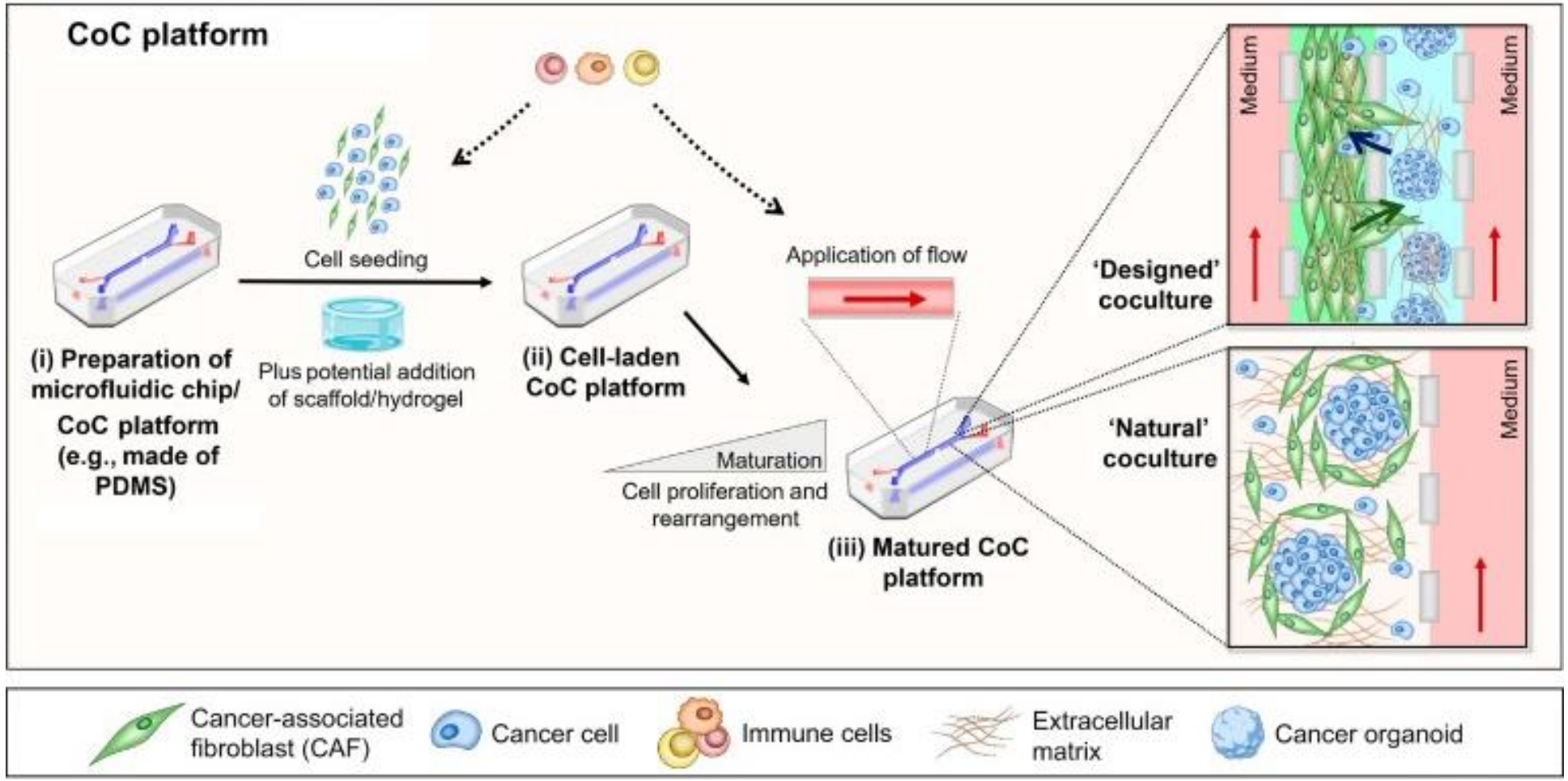
- Cell/Extracellular Matrix (ECM)-Based



https://doi.org/10.1016/j.trecan.2020.10.009 Trends in Cancer, March 2021, Vol. 7, No. 3

3D culture models

- Microfluidic Cancer-on-a-Chip (CoC)

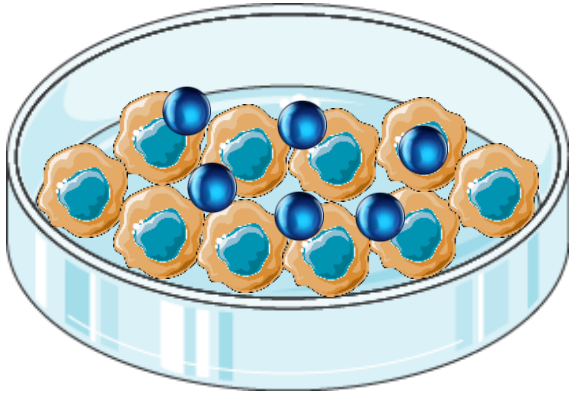


https://doi.org/10.1016/j.trecan.2020.10.009 Trends in Cancer, March 2021, Vol. 7, No. 3

Cell culture models

2D

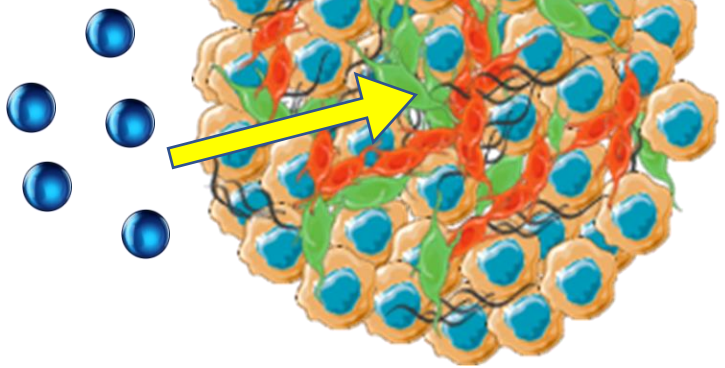
Drug / NPs



Cell-uptake studies

- Confocal microscopy

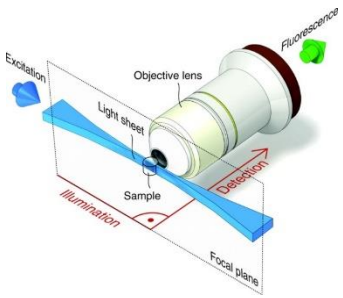
3D



Cell-uptake studies

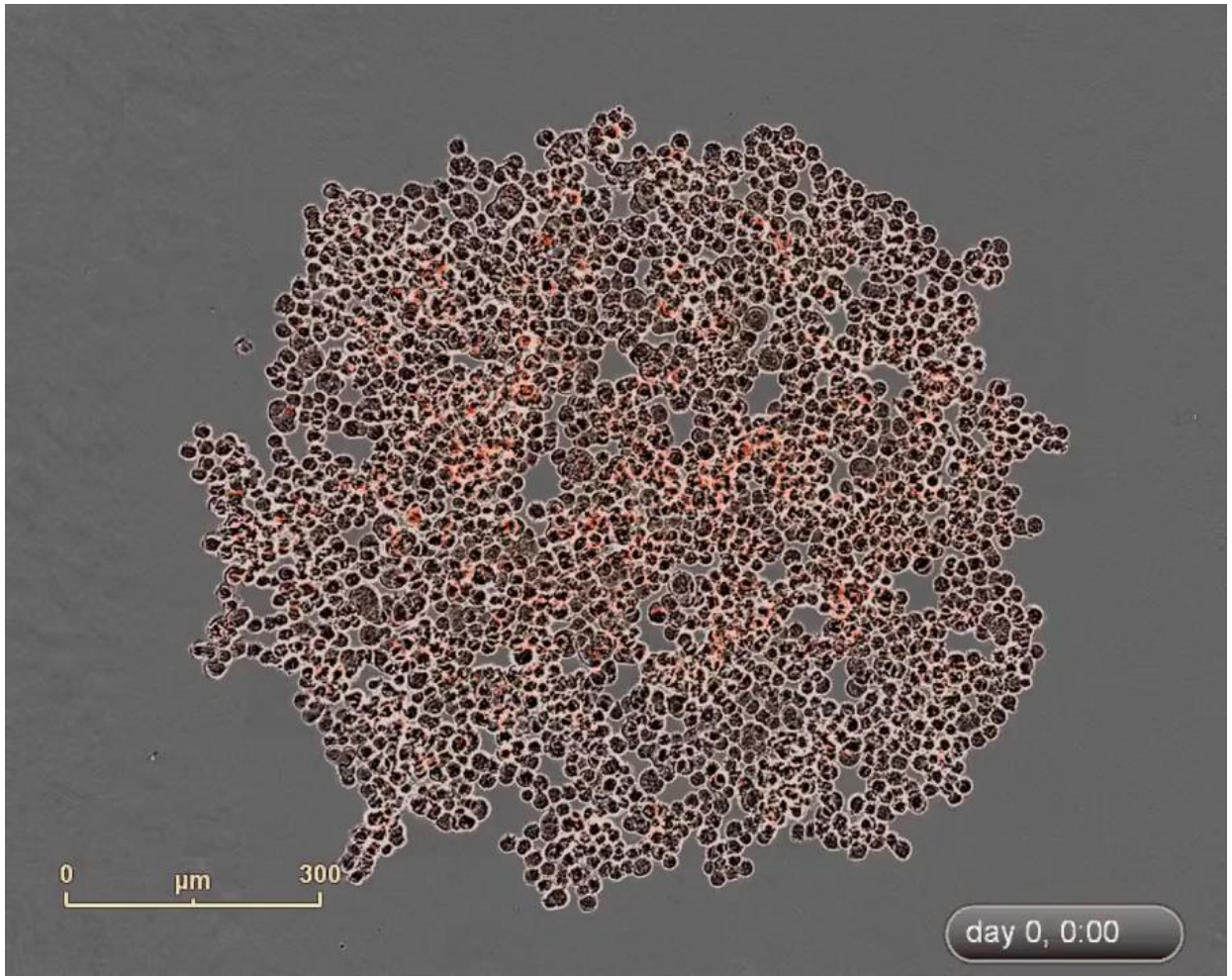
Penetration studies

- Light sheet Microscopy



Spheroids

- A549 human lung carcinoma cells stably expressing the red fluorescent protein

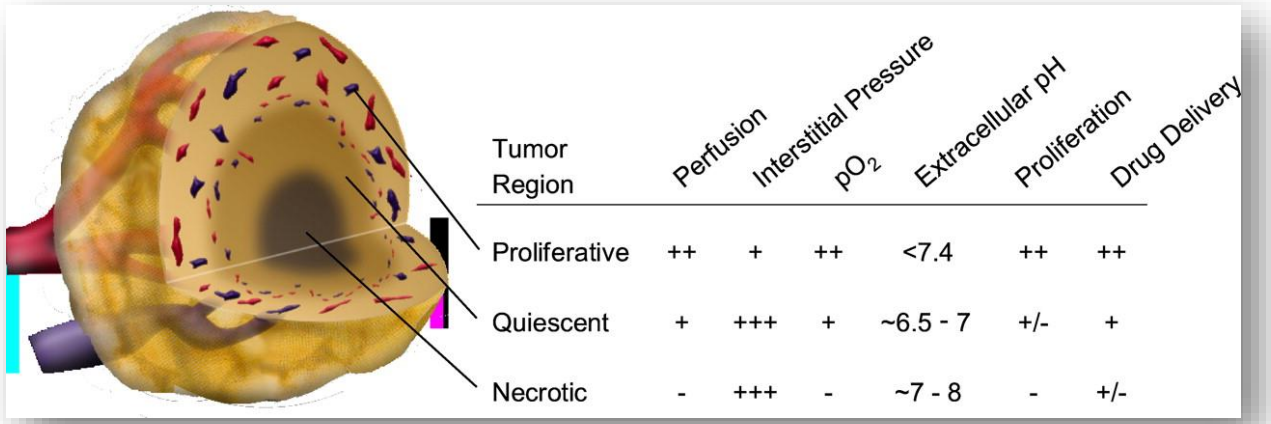


Cell aggregation and spheroid formation:
D3= 400 µm
D10= 560 µm

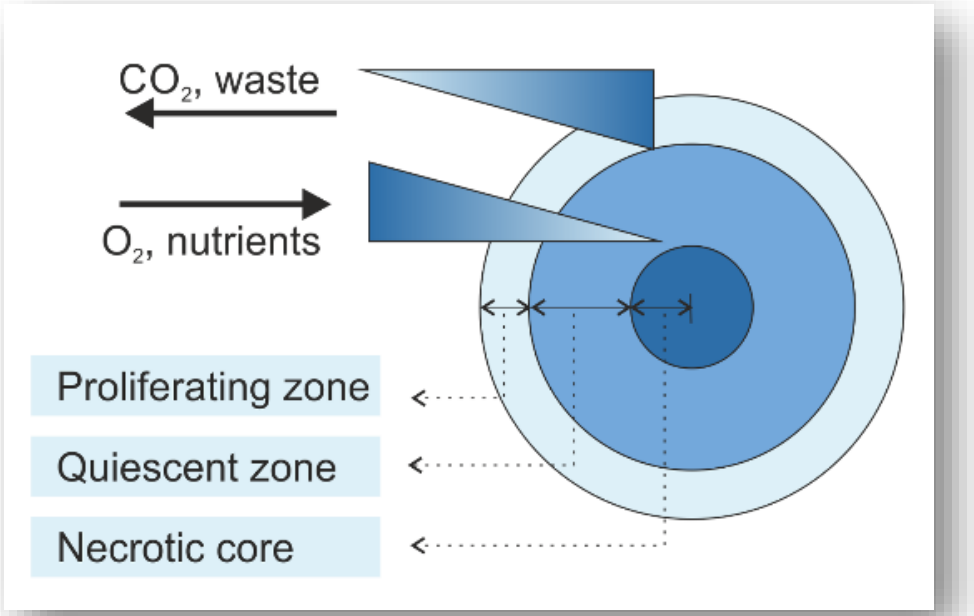
Ancorage independent

Tumor spheroids

- Common and versatile method for 3D cell culture
- Physico-chemical gradients



Tumor Region	Perfusion	Interstitial Pressure	pO_2	Extracellular pH	Proliferation	Drug Delivery
Proliferative	++	+	++	<7.4	++	++
Quiescent	+	+++	+	~6.5 - 7	+/-	+
Necrotic	-	+++	-	~7 - 8	-	+/-



Lazzari G, Couvreur P, Mura S. *Polymer chemistry* **2017**, 8, 4947

Tumor spheroids

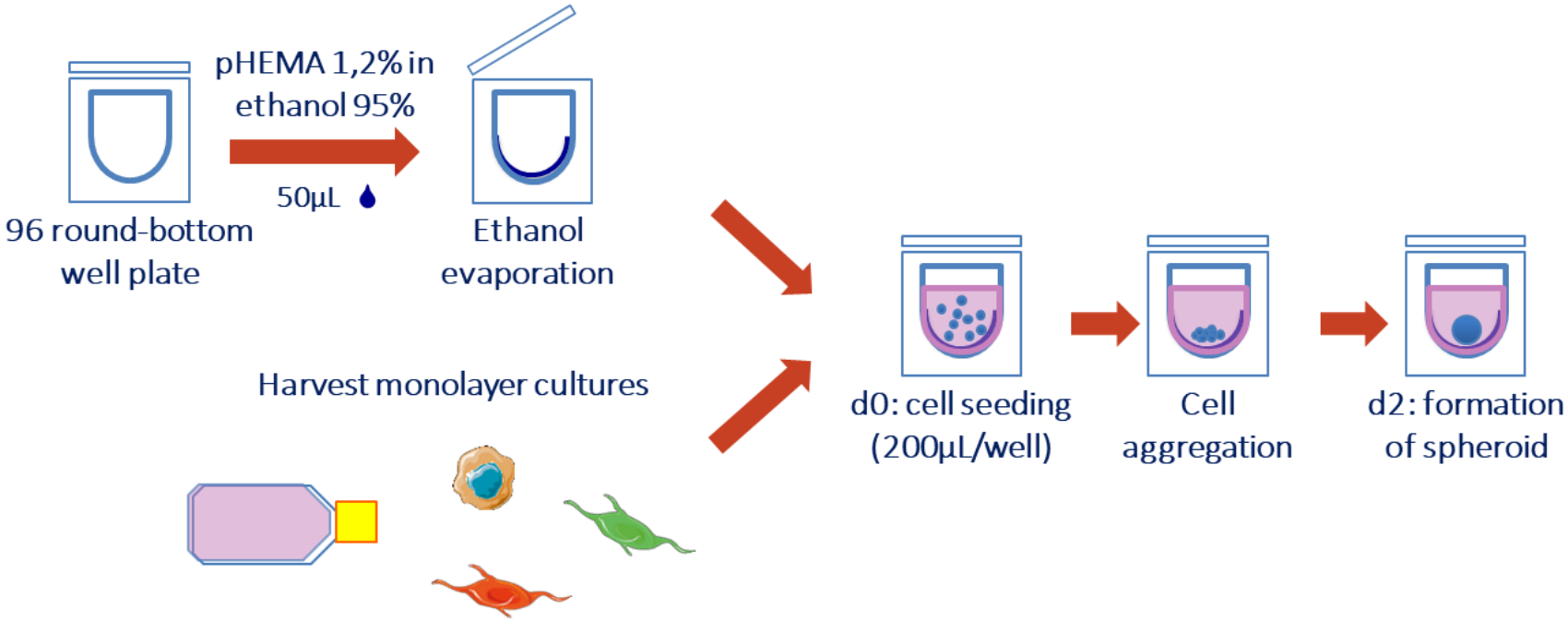
- Fabrication methods
- Liquid overlay

96 well plates

Flat bottom – Agarose coated (1.5% in DMEM) 50µl

Round bottom – polyHEMA coated (1.2% in EtOH 95%) 2*50µL

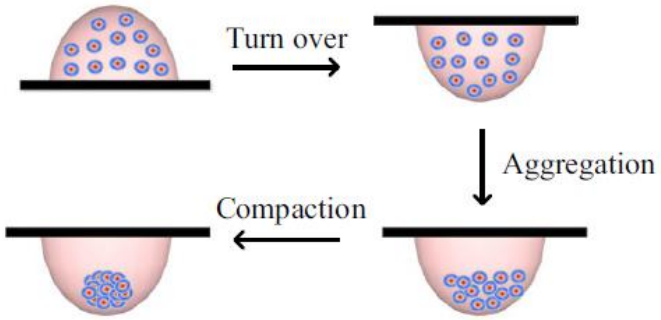
Round bottom – ultralow attachment (ULA) plates

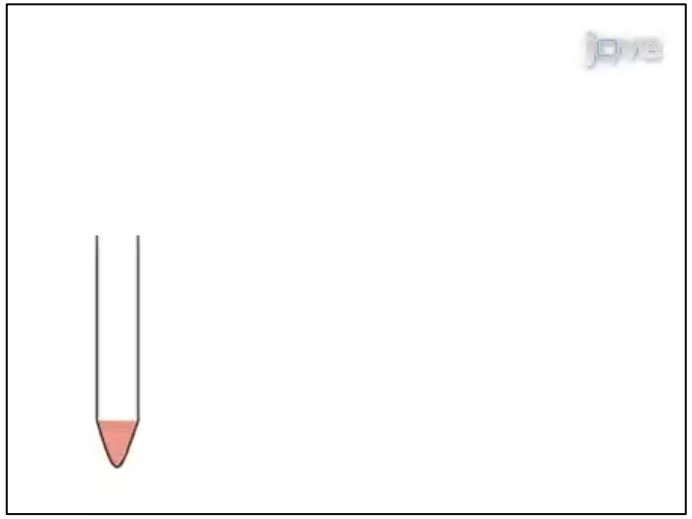


Lazzari G, Nicolas V, Matsusaki M, Akashi M, Couvreur P, Mura S. *Acta Biomaterialia* **2018**, 78, 296.

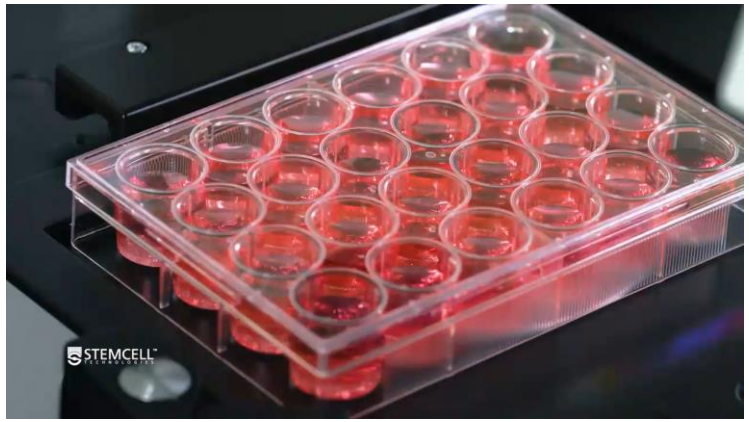
Tumor spheroids

- Fabrication methods
  - Hanging drop





  - AggreWell™

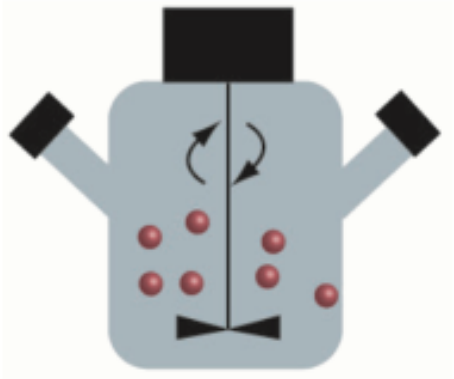


https://www.stemcell.com/products/aggrewell400.html#section-protocols-and-documentation

Tumor spheroids

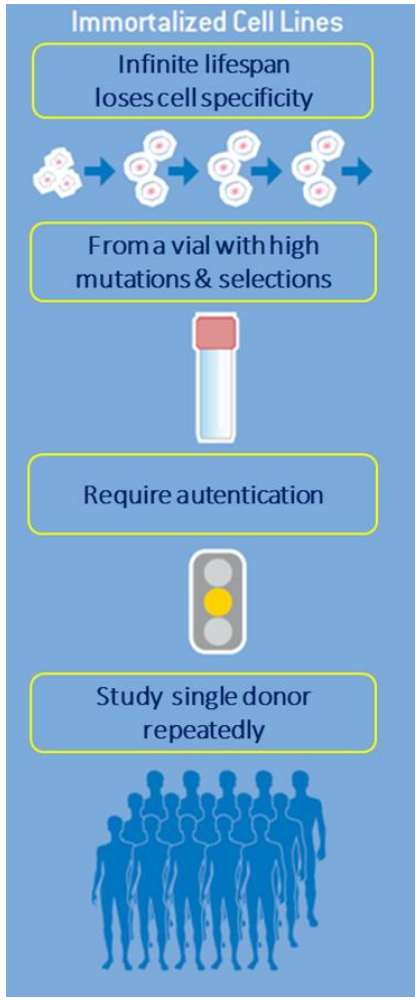
- Fabrication methods
  - Spinning Flask

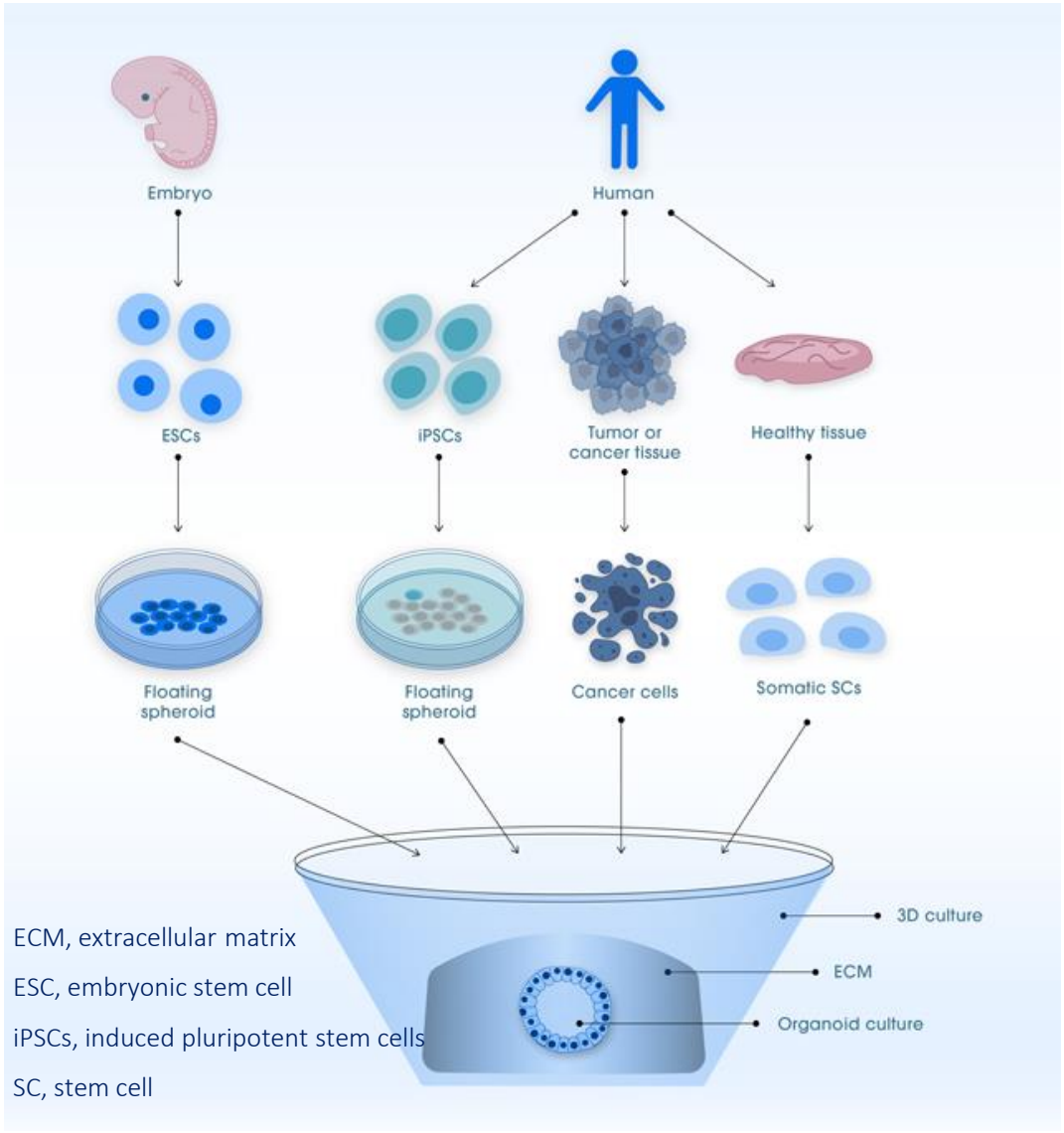
STEMCELL Technologies
10,7 k abonnés



Spheroids vs Organoids

- Three-dimensional (3D) multi-cellular, microtissues derived from human embryos, organs or tumors.



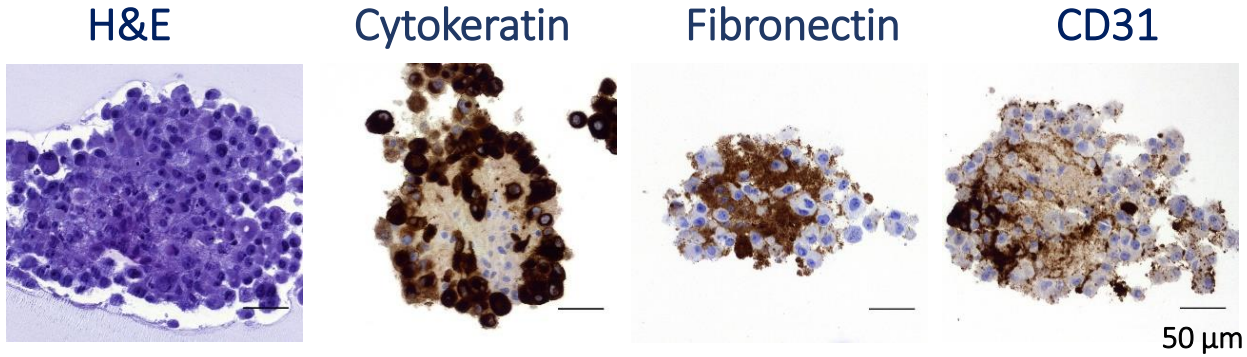


https://www.technologynetworks.com/cell-science/articles/an-introduction-to-organoids-organoid-creation-culture-and-applications-369090

Tumor spheroids

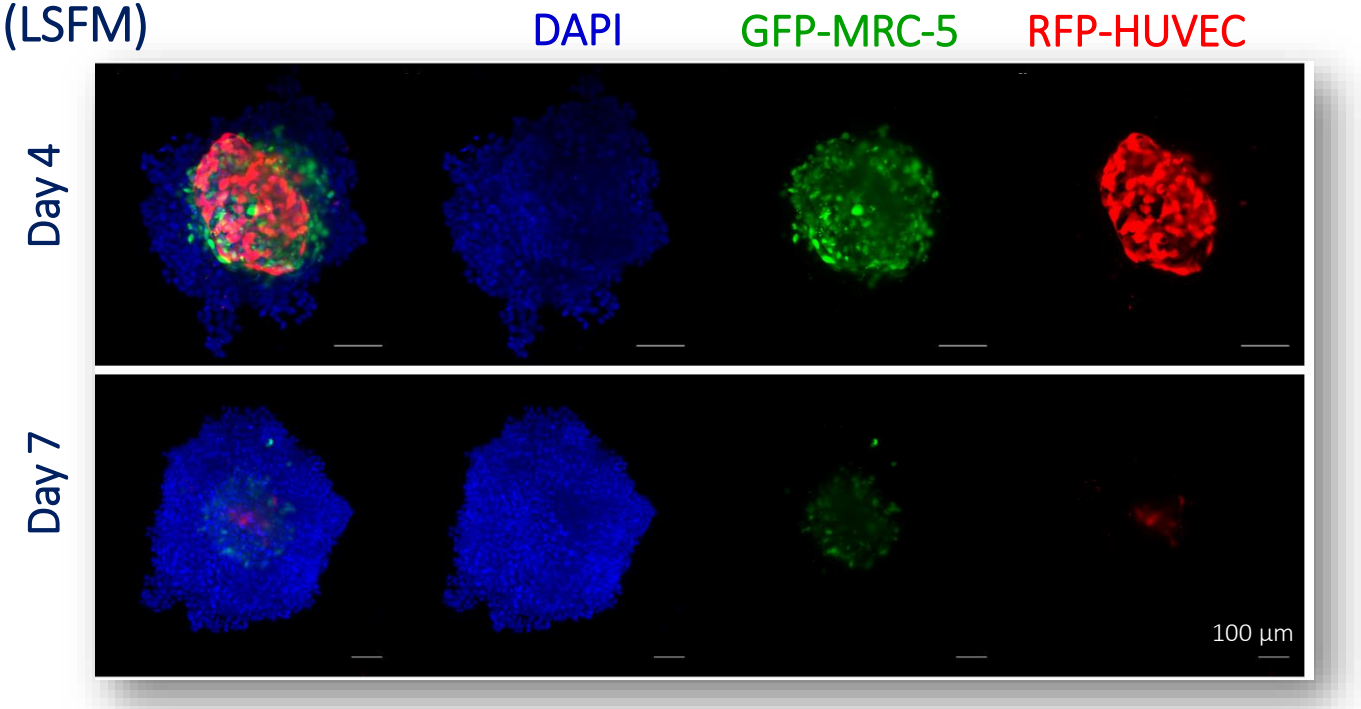
- Heterotype multicellular spheroids triple co-culture (PANC-1: MRC-5: HUVEC)

- Histology



- Liquid overlay
- LBL coating
- VEGF

- Light sheet fluorescence microscopy (LSFM)



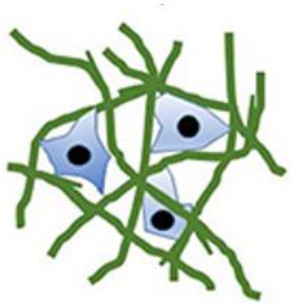
First model of triple spheroid co-culture combining tumor cells, fibrotic tissue and a collapsed vessel-like structure

3D culture models

Natural hydrogels

Animal Derived
- Collagen
- Matrigel
- Gelatin

Plant Derived
- Alginate



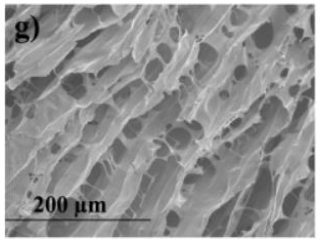
Synthetic hydrogels

Non-natural
- Polyethylene Glycol (PEG)
- Polylactic Acid (PA)
- Polyglycolic Acid (PGA)

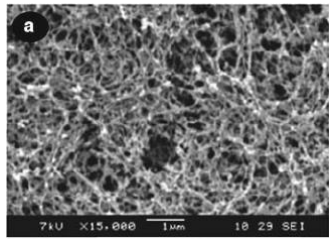
Natural
- Hyaluronic Acid (HA)
- Peptides

- ⊕ Biomimetic
- ⊕ Mimic physiological cell/material interactions
- ⊖ Batch to batch variability
- ⊖ Limited range of material properties
- ⊖ Limited cell adhesion site number

Collagen



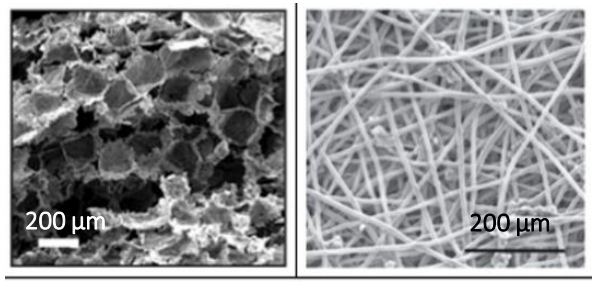
Matrigel



- ⊕ Possibility to easily tune structural properties
- ⊕ Mimic specific microenvironment features
- ⊖ Potential toxicity due to fabrication methods
- ⊖ Limited bioactivity

poly-lactic-glycolic acid

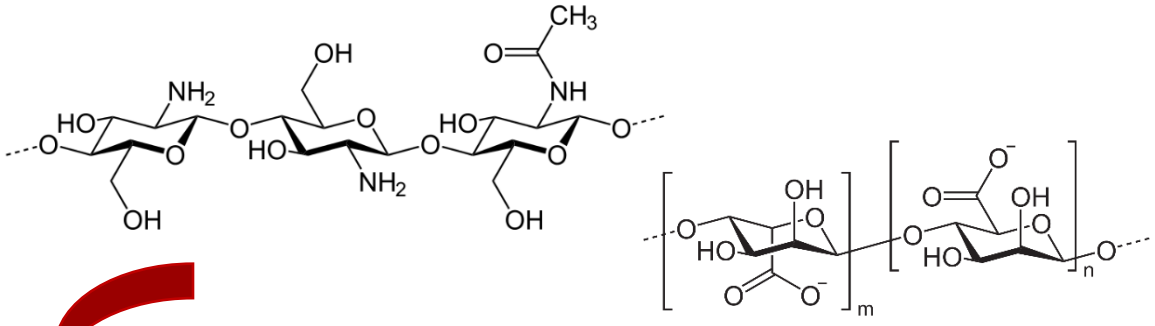
polycaprolactone

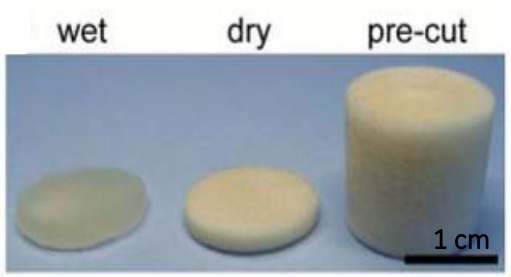


Adapted from Liu Z and Vunjak-Novakovic G, *Curr Opin Chem Eng* **2016**, 11, 94

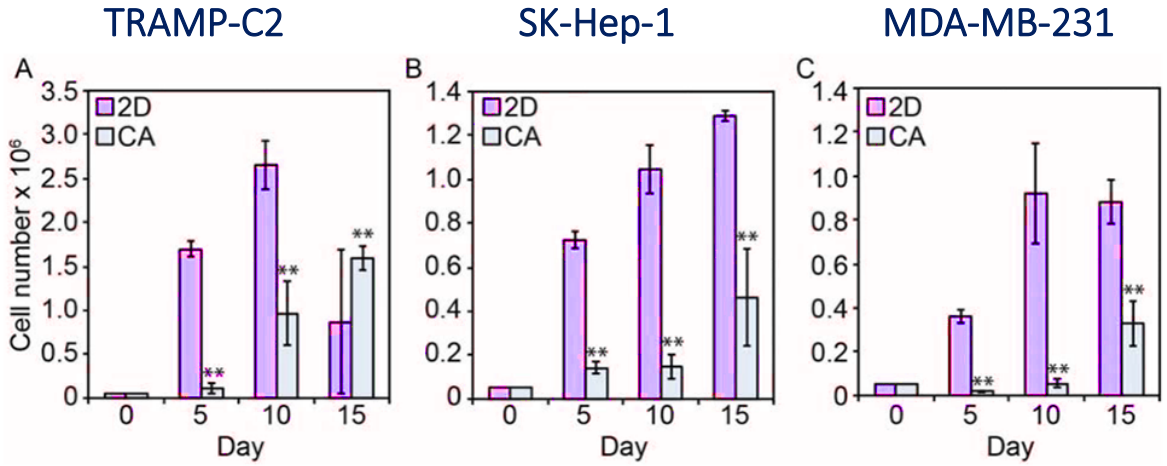
Anchorage dependent: natural hydrogels

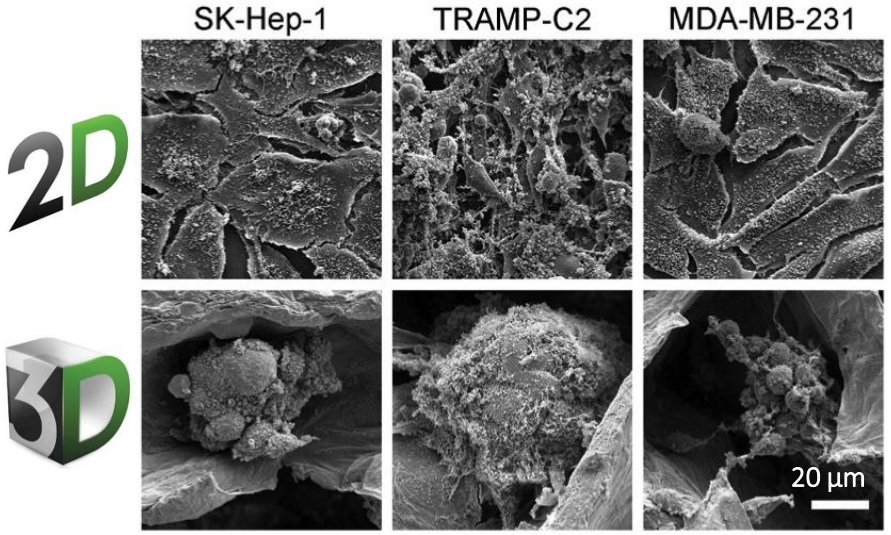
- Chitosan-alginate polyelectrolyte complex



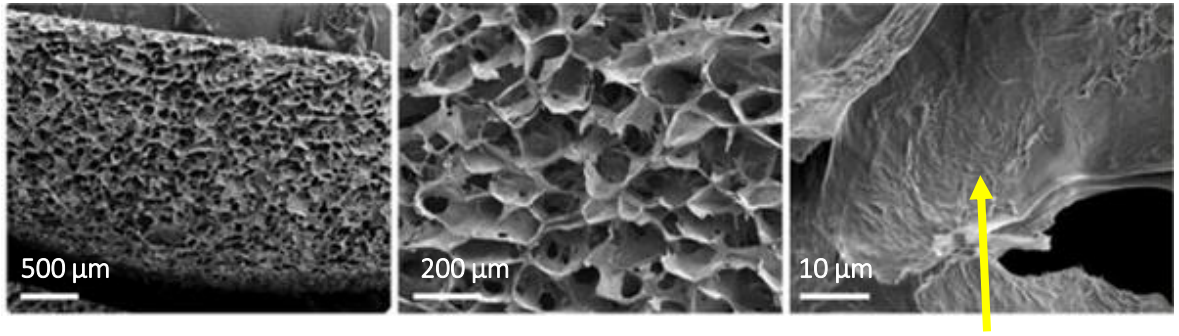


- Cell culture





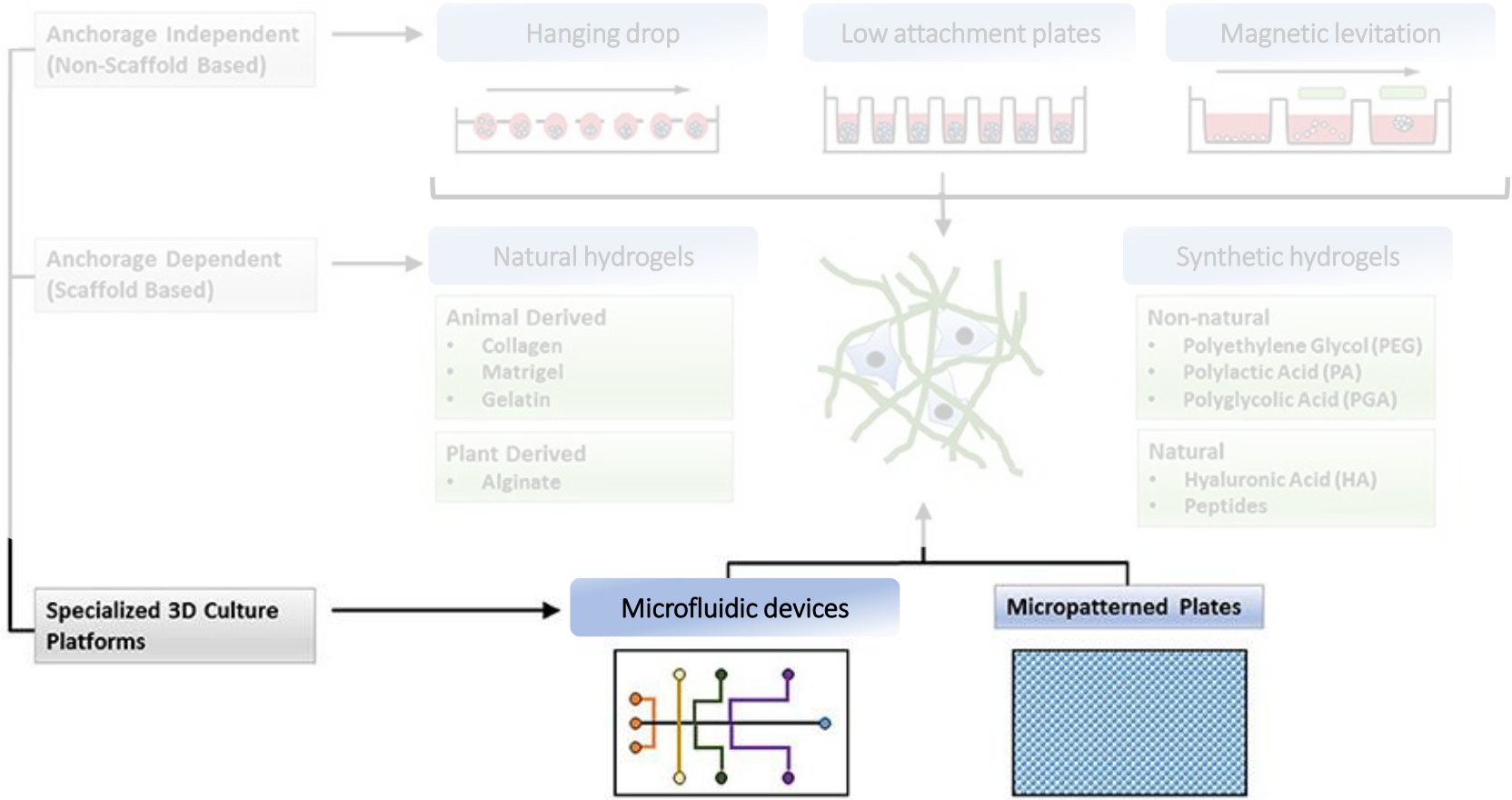
- Scaffold porosity



Uniforme | Pore morphology | Pore wall

Florczyk SJ *et al., J Mater Chem B.* **2016**; 4, 6326

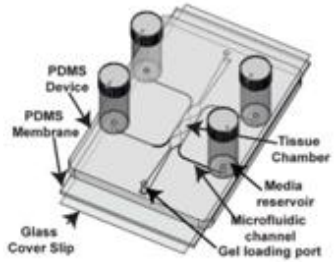
3D culture models

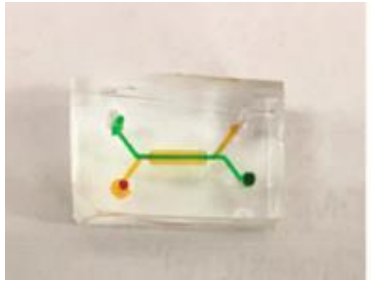


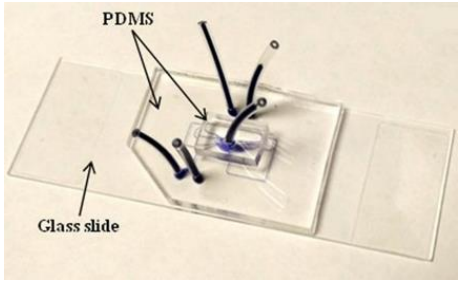
Adapted from Front. Pharmacol., 23 January 2018, https://doi.org/10.3389/fphar.2018.00006

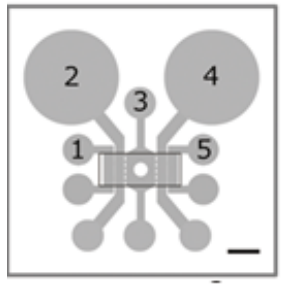
Microfluidic devices

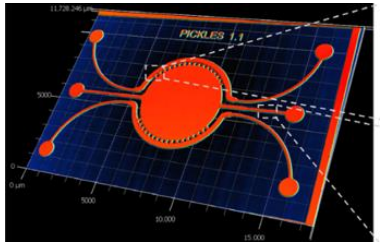
- Culturing living cells in continuously-perfused, micrometer sized chambers
- Model physiological functions of tissues and organs
- Incorporate physical forces, fluid shear stress
- Strong control of culture parameters
- Evaluation of biological responses: cell recruitment, response to drug treatment











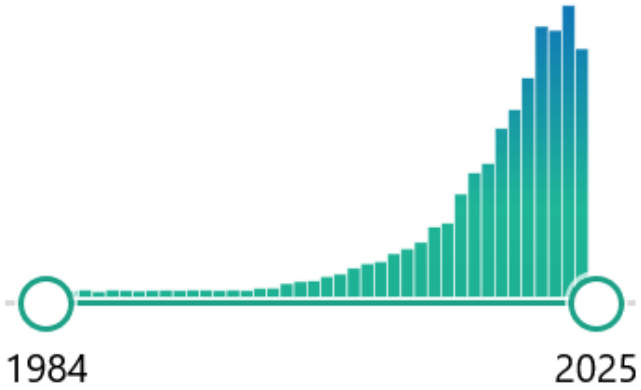
Bhatia SN, Ingber DE. *Nature biotechnology* **2014,** 32, 760

Organs-on-chips (OoCs) - microphysiological systems - tissue chips

- Integration of design, technology and biological science for more reliable models
- Provide insights into normal human organ function and disease pathophysiology
- Predict the safety and efficacy of promising new compounds and therapeutics

- Pubmed search « *organ on chip* »

5485 articles
@ 03/10/2024



- NIH, FDA and DARPA funded programs

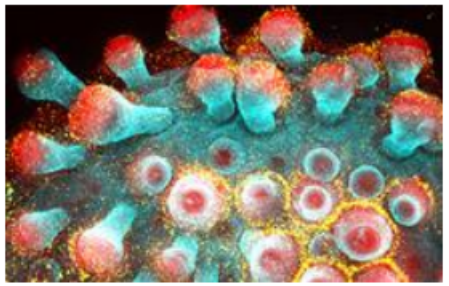
Tissue Chips for Drug Screening

develop 3D microsystems to represent multiple tissue types

Microphysiological systems programme

develop a system integrating at least 10 human organs/tissues to mimic and replicate biological crosstalk between tissues.

Organs-on-chips (OoCs) - microphysiological systems - tissue chips



CEA IRIG

FRANCE 2030 - PEPR

MED-OOC : Organes et organoïdes sur puce

Le PEPR exploratoire MED-OOC vise à réunir organoïdes, microfluidique avancée et expertise clinique pour obtenir des organes sur une puce reproduisant fidèlement la situation in vivo afin d'accélérer la découverte de médicaments, de modéliser les processus de développement et de développer des systèmes expérimentaux personnalisés ou des « jumeaux cliniques ».

Ce PEPR a été retenu en 3ème vague en 2023 et se met en place. La DRF devrait y contribuer activement par le biais de ses instituts Irig et Jacob.

Co-pilotes : CEA, CNRS, Inserm
Budget : 48 M€
Durée : 6 ans

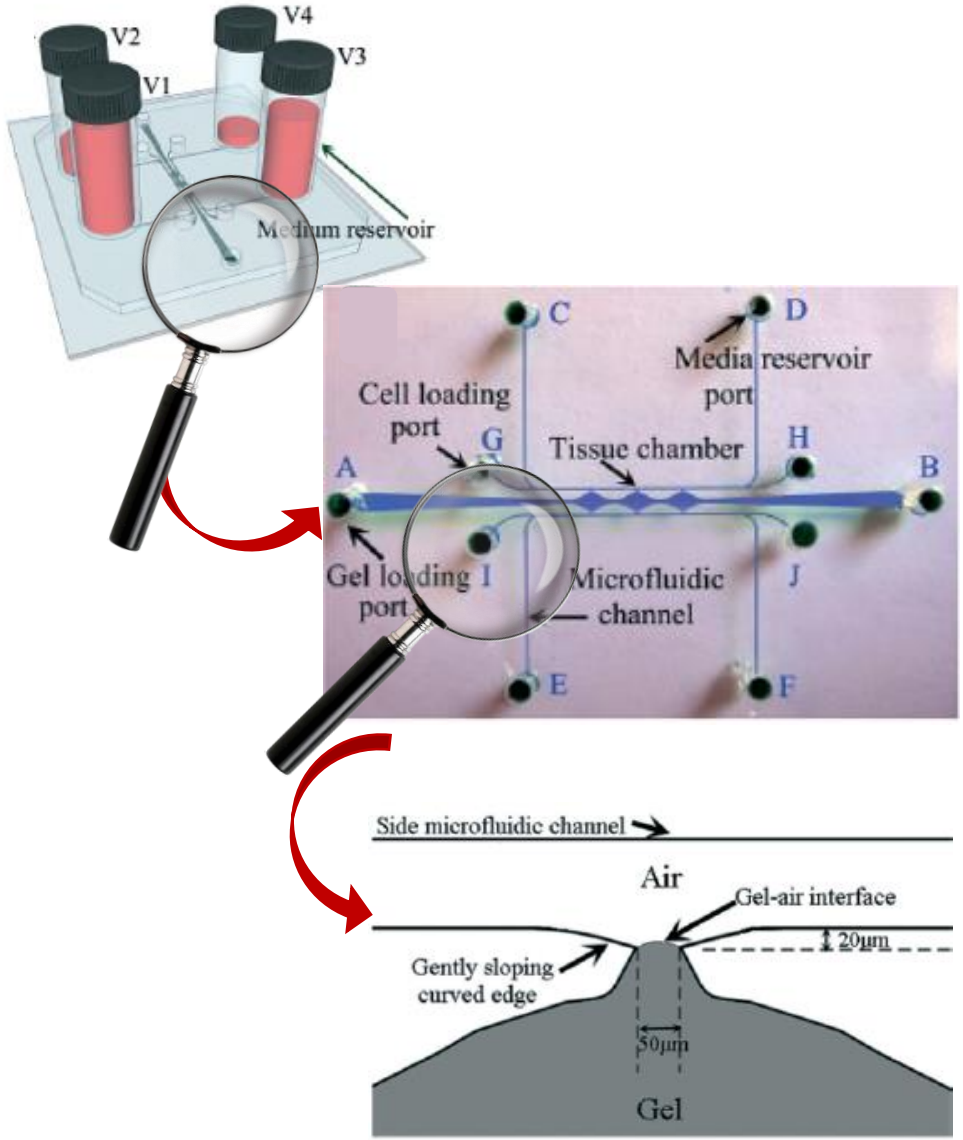
PEPR* exploratoires: *accompagner une transformation qui commence à émerger et en est à ses débuts voire à ses prémices, pour un montant prévu de 1 Md€*

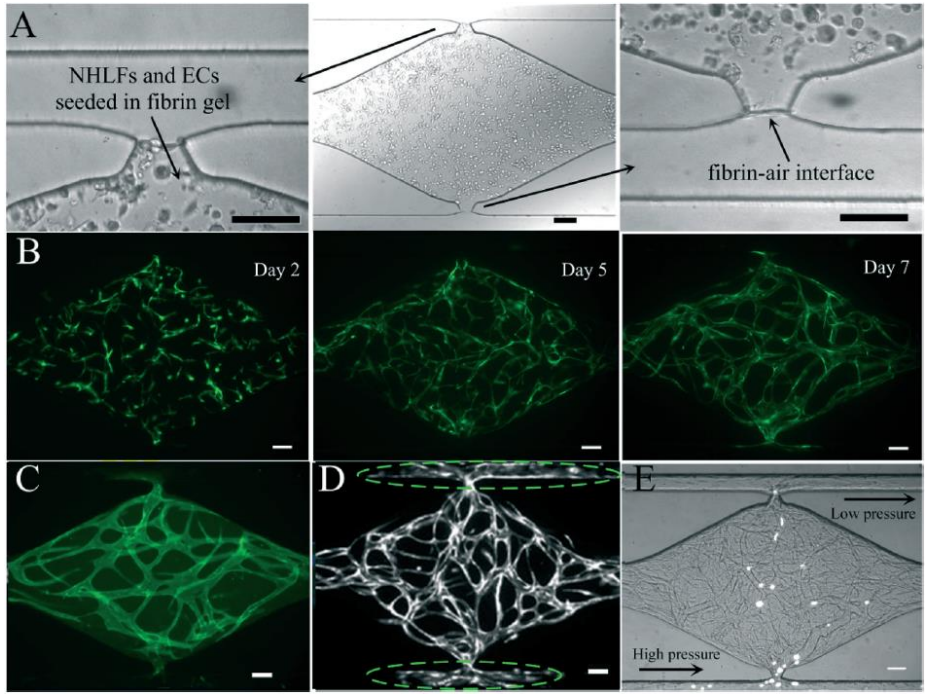
Permettre la conduite d'une politique scientifique sur des domaines d'intérêts national et européen, aux retombées pouvant être multiples

**programme et équipements prioritaires de recherche*

Microfluidic devices

- Perfusable microvascular network





Optimised pore design
- NO gel leakage
- Vasculogenesis, Sprouting & Anastomosis

Wang X et al.,. *Lab on a Chip* **2016**, 16,282; Sobrino A et al., *Scientific reports* **2016**, 6, 1.

Microfluidic devices

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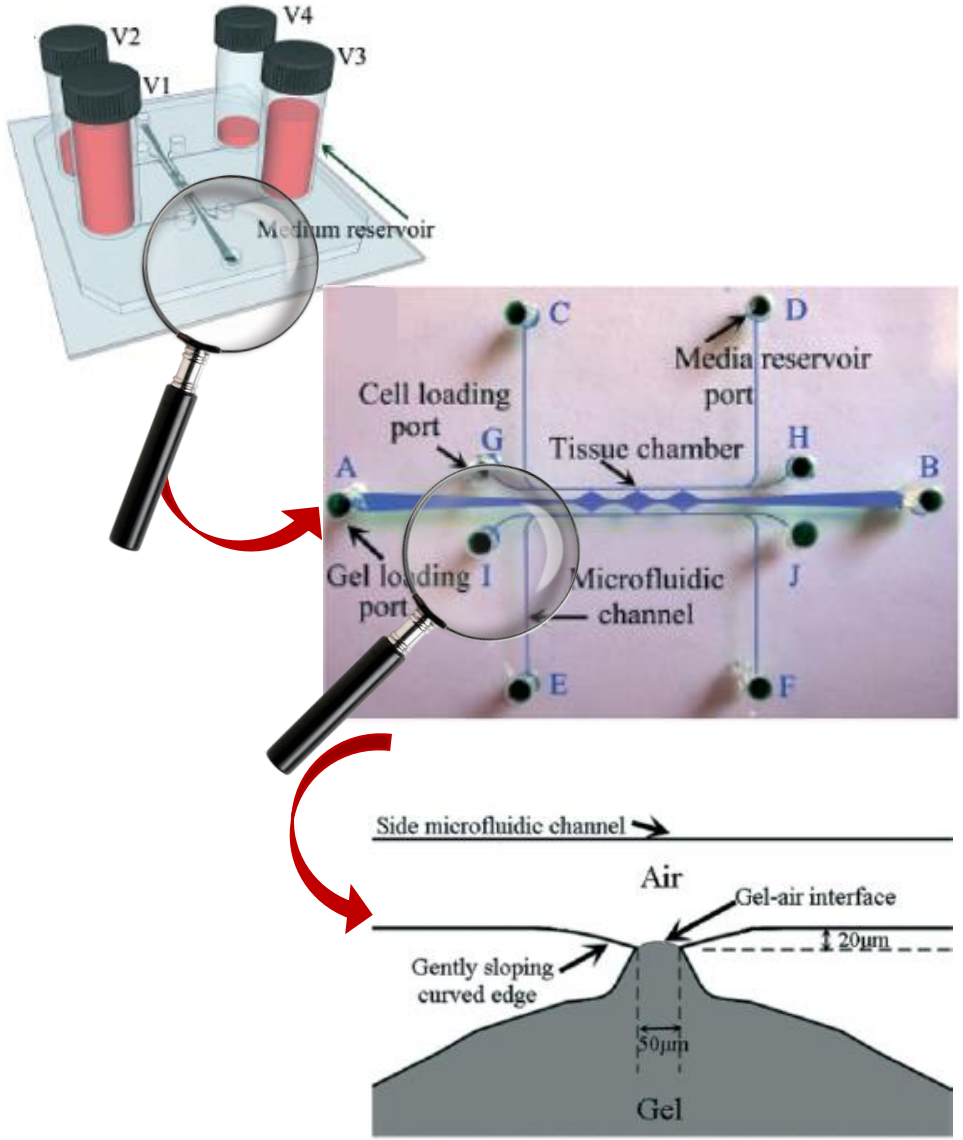

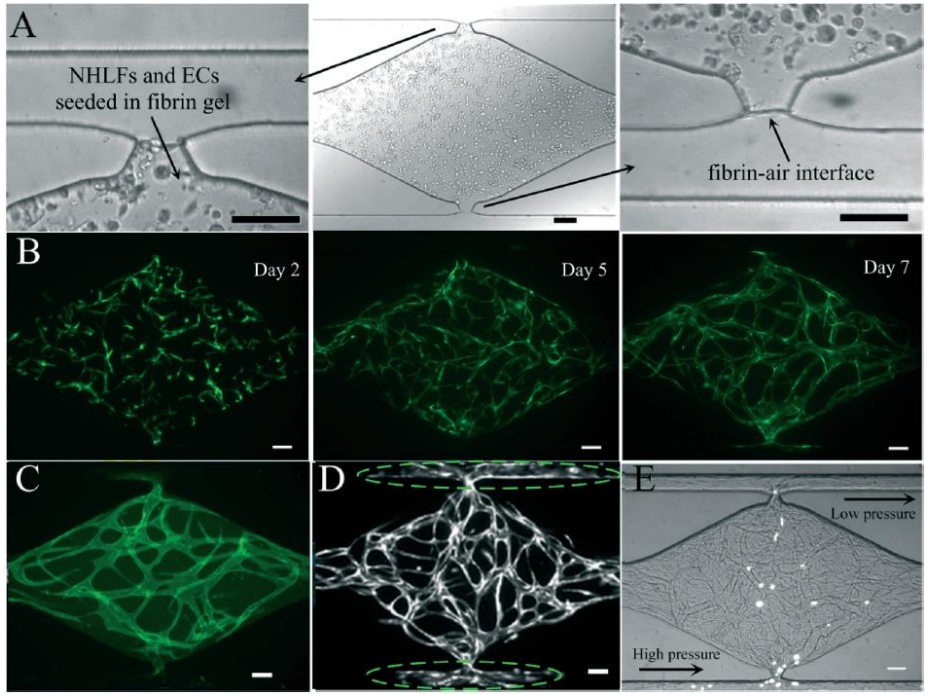

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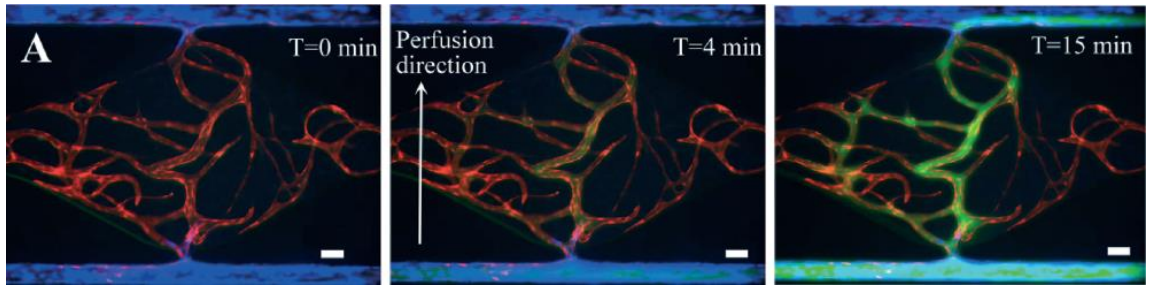
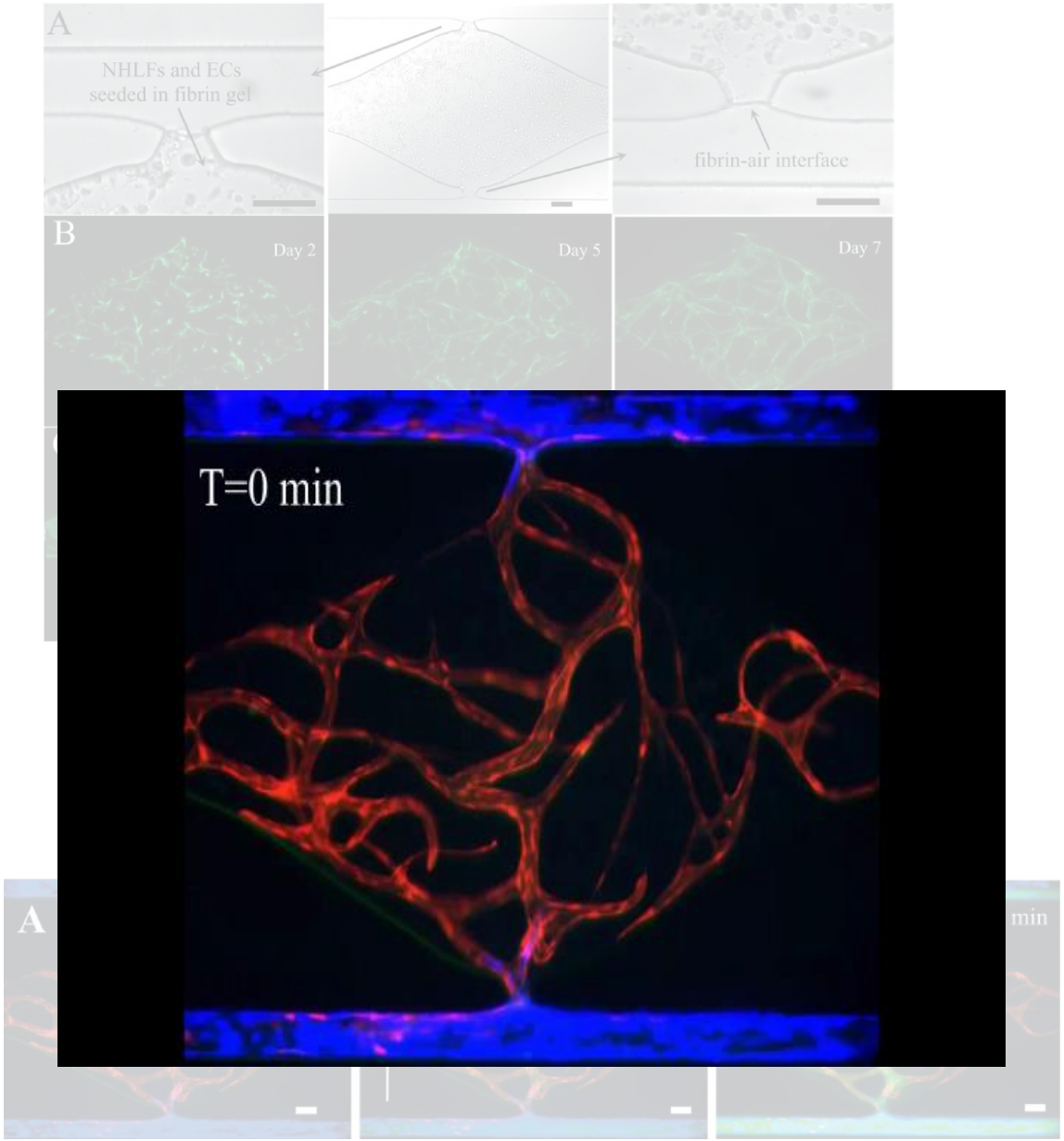


Wang X et al.,. *Lab on a Chip* **2016**, 16,282; Sobrino A et al., *Scientific reports* **2016**, 6, 1.

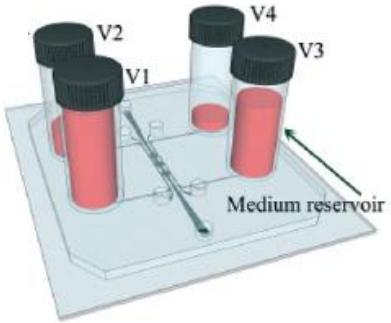
Microfluidic devices

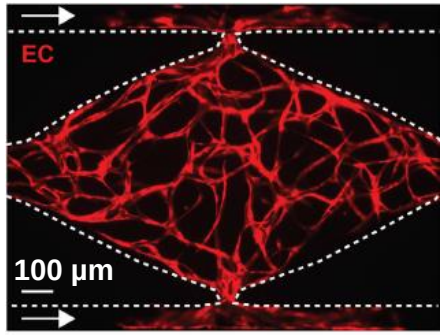


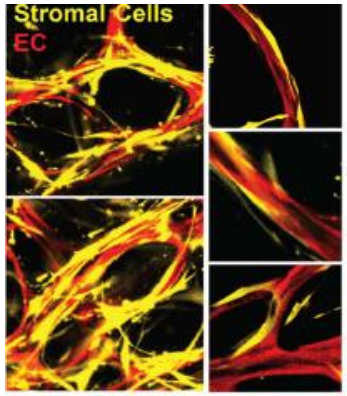
Wang X et al.,. *Lab on a Chip* **2016**, 16,282; Sobrino A et al., *Scientific reports* **2016**, 6, 1.

Microfluidic devices

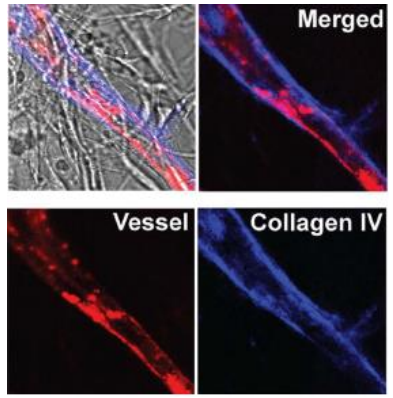
- **Perfusable microvascular network**





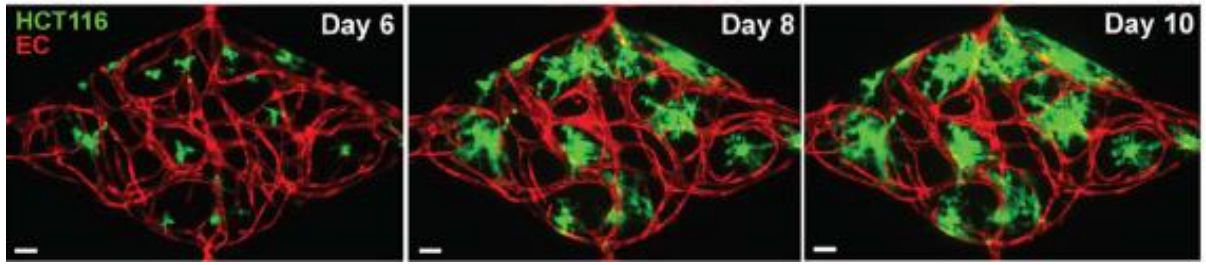


Stromal cells in perivascular position

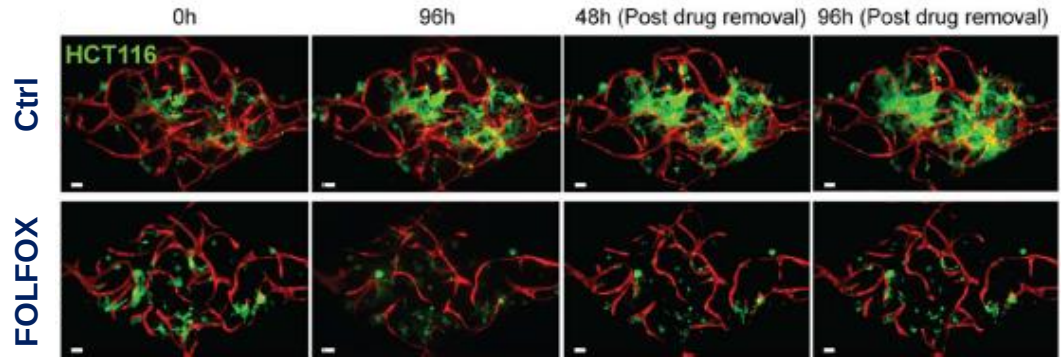


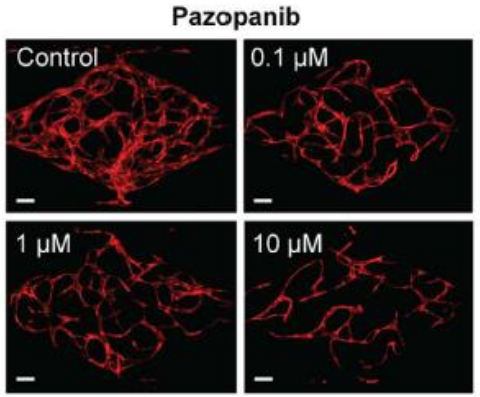
Basement membrane deposition

• Coculture with cancer cells: Vascularized Micro-Tumors



• Drug treatment: cancer or endothelial cell targeting



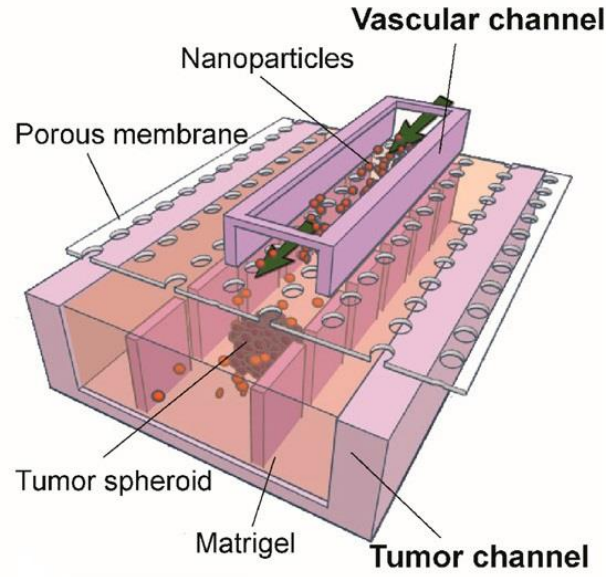


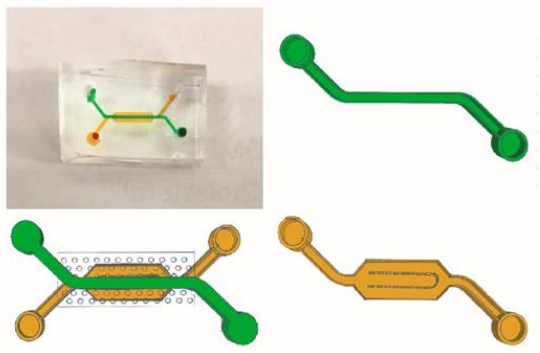
Suitable for the development of novel treatment with multiple targets

Wang X et al.,. *Lab on a Chip* **2016**, 16,282; Sobrino A et al., *Scientific reports* **2016**, 6, 1.

Microfluidic devices

- **Open top device for nanomedicine screening**
- Chip Design

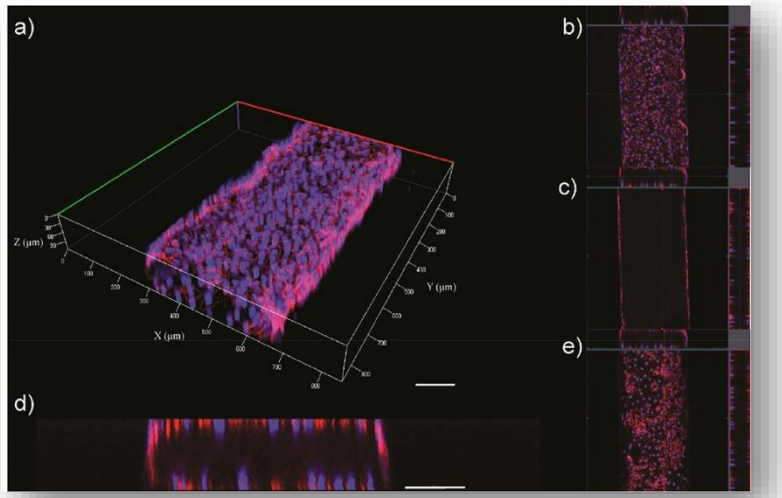




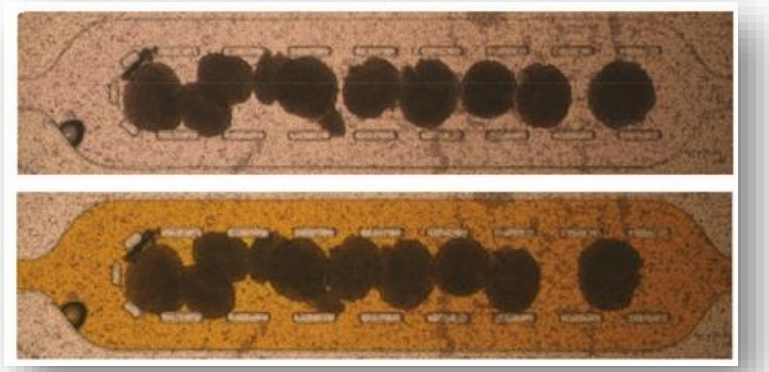
Steady medium perfusion for culturing endothelial cells

Central region for trapping tumor spheroids

- Confluent HUVEC monolayer



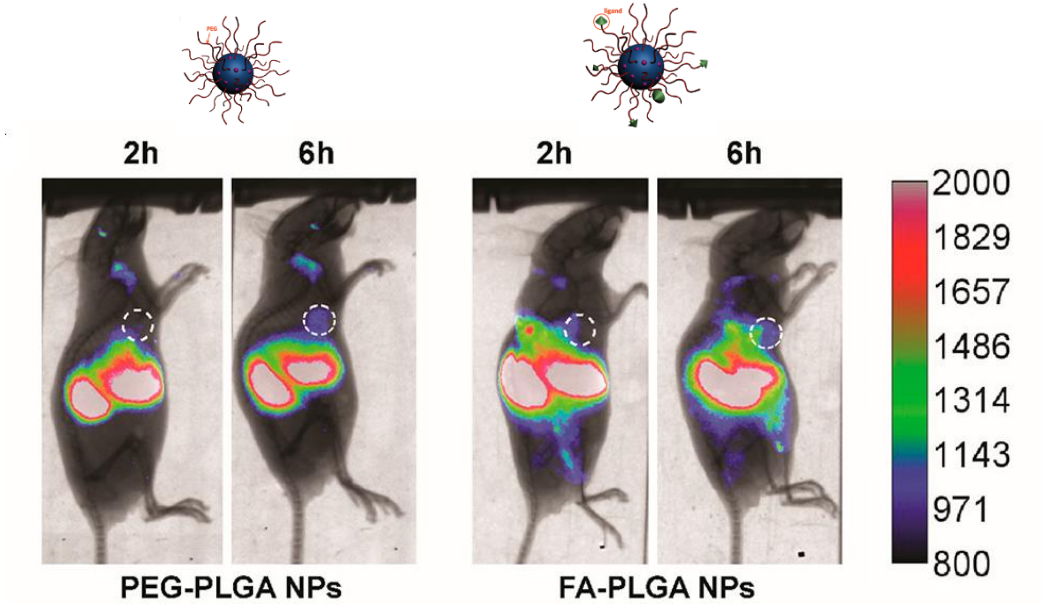
- Ovarian cancer cells (SKOV3) spheroids



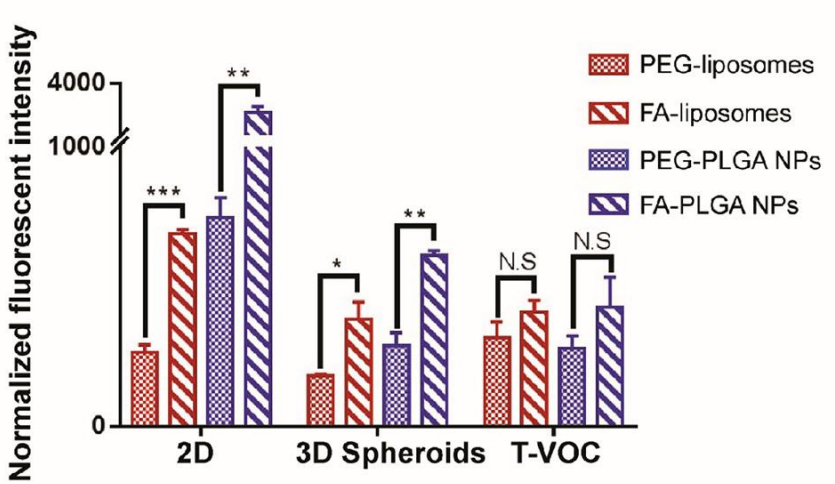
Wang HF *et al.*, *ACS Nano* ***2018***, 12, 11600

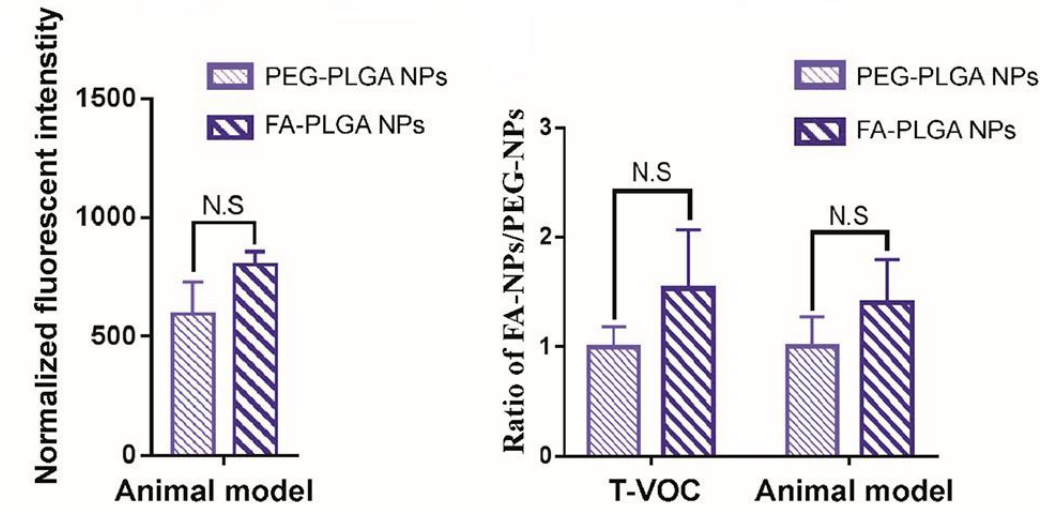
Microfluidic devices

- NP accumulation *in vivo (influence of ligands)*



Better mimicking the in vivo tumor microenvironment



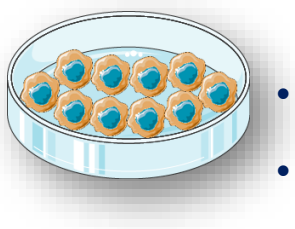


- 2D monolayer: FA-modification promotes NP uptake
- 3D tumor spheroids: less significant
- Microchip & in vivo: non-significant

Better mimicking the in vivo tumor microenvironment

Wang HF *et al., ACS Nano* ***2018***, 12, 11600

Conclusions



- Lack the organ function
- Lack structure and complexity

- Very costly and complex
- Low availability
- Some engineering skills
- Not suitable for high-throughput screening

- Lower reproducibility
- Endpoint readouts to be optimized
- Challenge to study on a single cell level
- Often limited perfusion

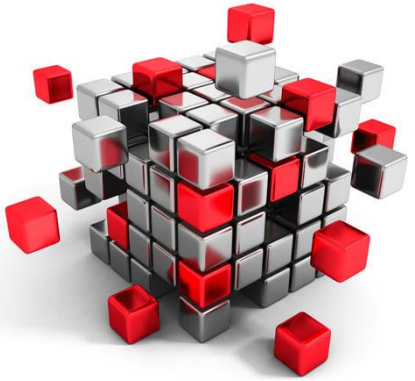
- In Vivo is not a human
- Very costly and time-consuming
- Extrapolate results to the human situation
- Limited mechanistic information

Conclusions

What is your question?

Simple question: use a simple model

Complex question: go to a more complex model



Conclusions

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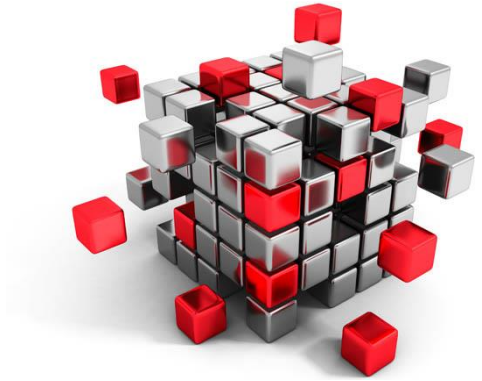

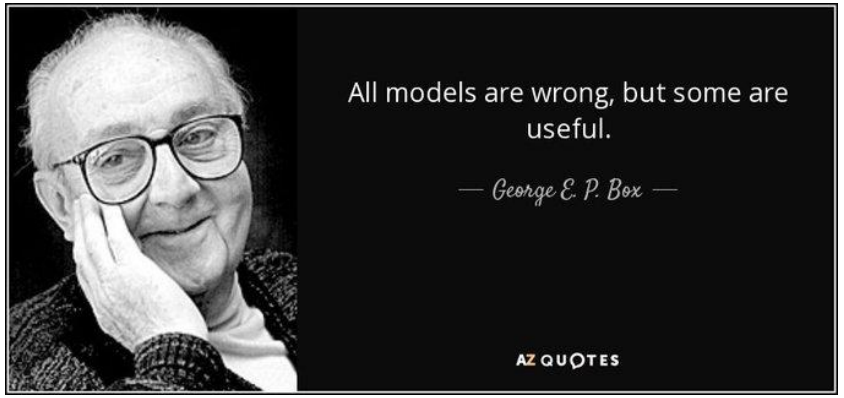

Conclusions

- Reduction of animal use in research

Ethical and economic benefits

- Proteins and molecules interaction at the surface of nanoparticles
- Perfusion and Flow pressure
- Control of the heterogeneity
- Characterization
- High throughput
- Automated techniques need to be adapted from 2D to 3D