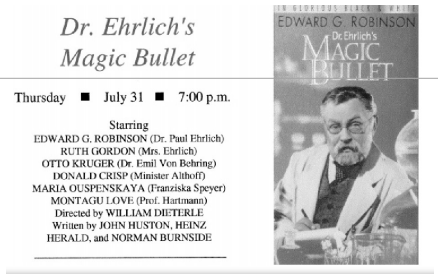
M1 Sciences du Médicament

Initiation to Drug Discovery:
The Challenges of the 21st Century (UEM 919)
Nanomedicine

Simona Mura | December 18, 2024 |

The magic bullet



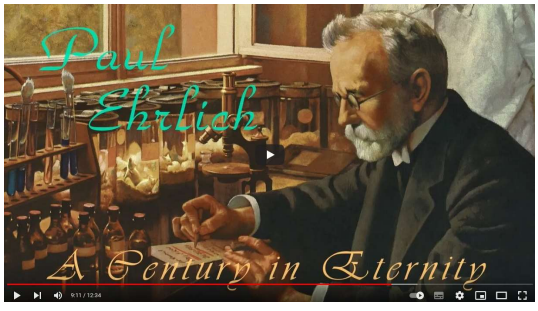
Paul Ehrlich (1854-1915)

Magic bullet

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

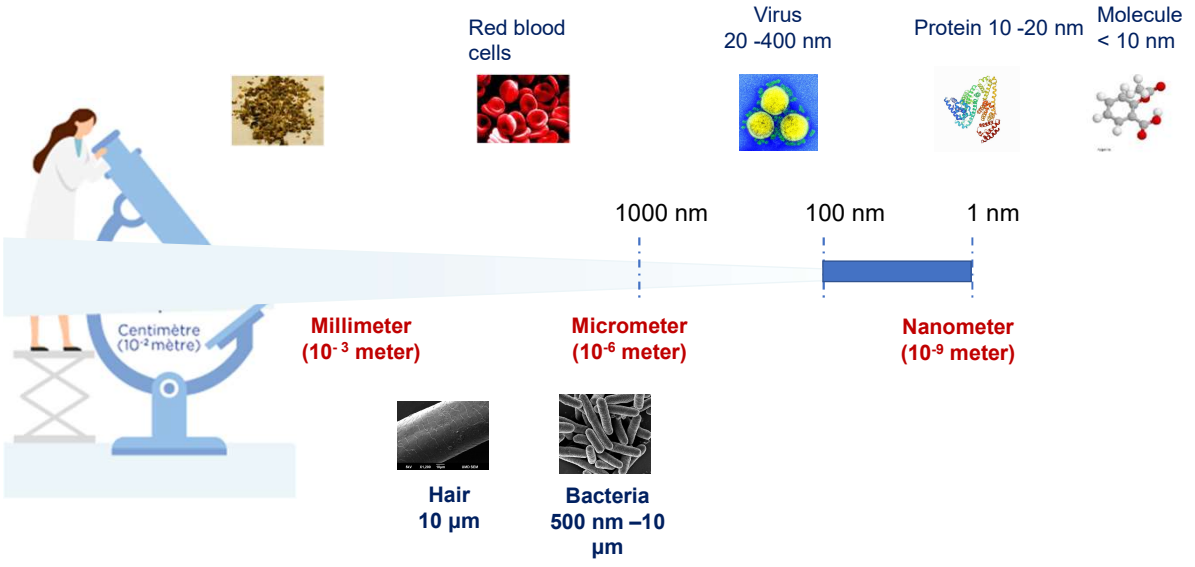
(Nano)carrier

Targeting



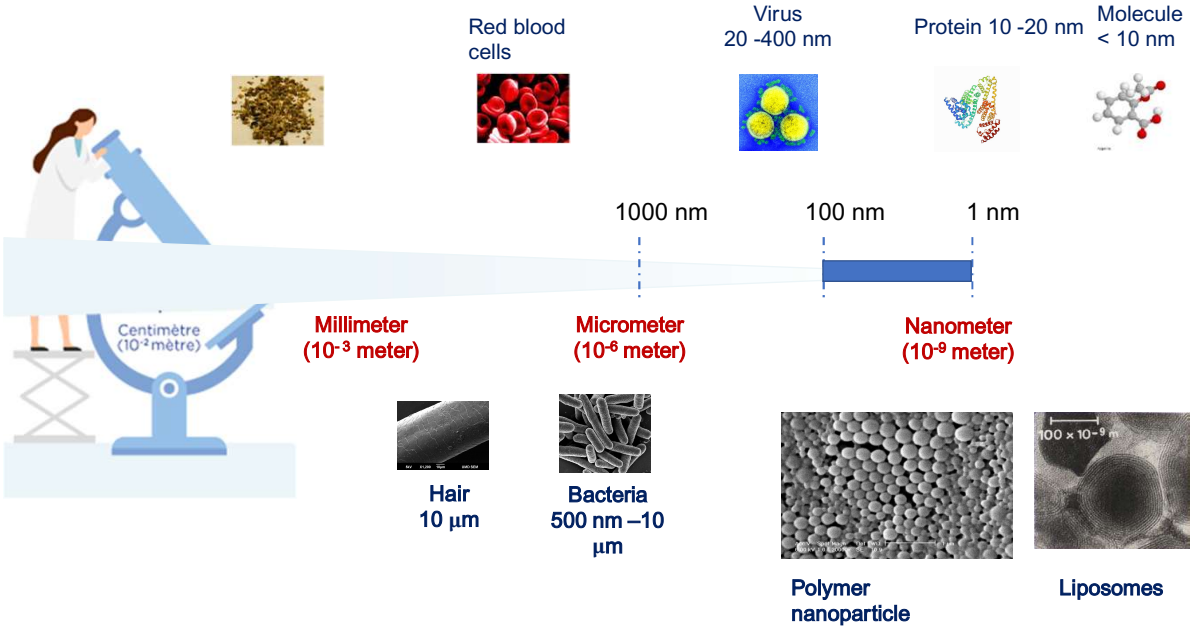
2

The scale of objects



3

The scale of objects



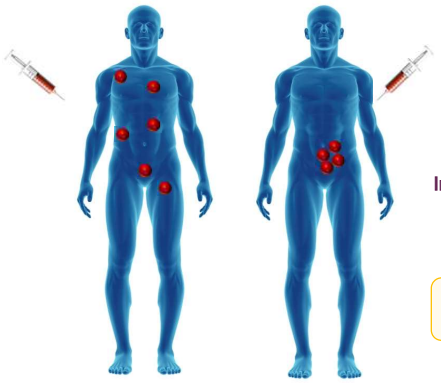
4

The magic bullet

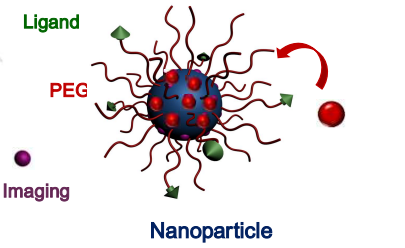
Make the fate of a drug dependent from a carrier

Traditional chemotherapy

Free drug



- Nanomedicines



Distribution

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

Alternative Distribution

- Vector size
- Lipophilicity
- Stability
- Cytotropism

5

Controlled delivery

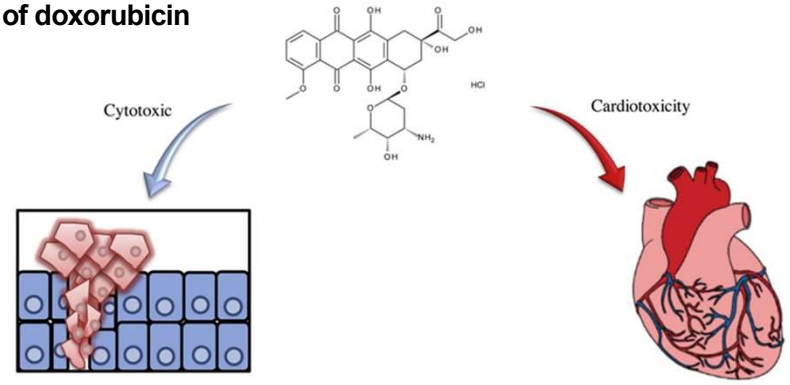
Targeting and reducing side effects

6

Controlled delivery

Targeting and reducing side effects

Cardiotoxicity of doxorubicin

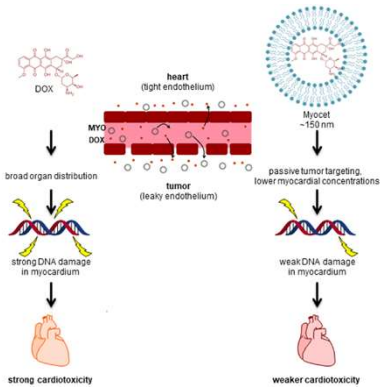


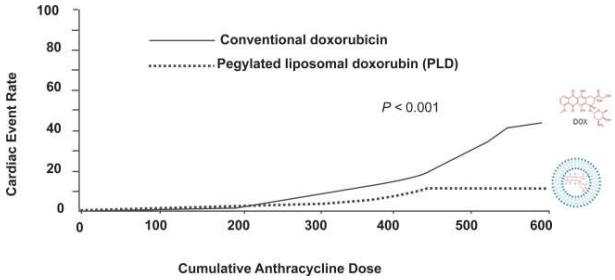
7

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

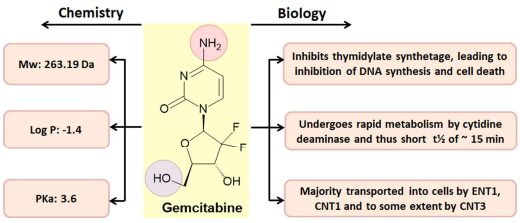
Cardiovasc Res, Volume 116, Issue 5, 1 April 2020, Pages 970–982

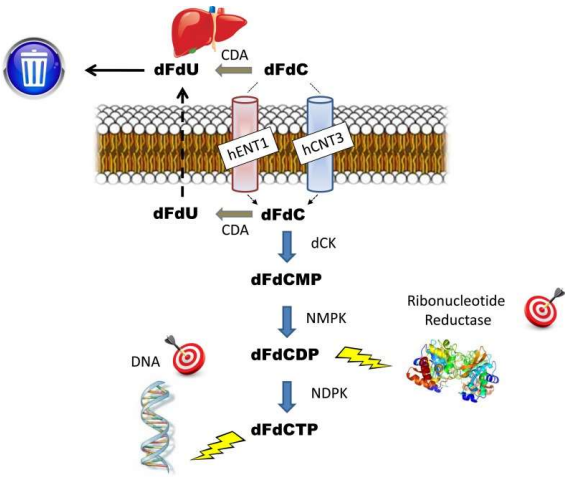
Rahman, Atiar M et al. International journal of nanomedicine vol. 2,4 (2007): 567-83.

8

Controlled delivery

Protection against degradation



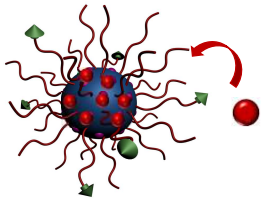


J. Ciccolini, C. Serdjebi G. J. Peters E. Giovannetti Cancer Chemother Pharmacol (2016) 78:1–12

9

The magic bullet

Make the fate of a drug dependent from a carrier



Traditional chemotherapy

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

Nanomedicines

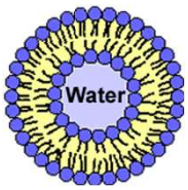
- Protection from degradation
- Increase intracellular penetration
- Cell/tissue targeting
- Overcome resistance

10

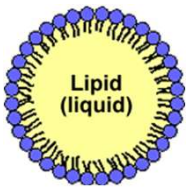
The magic bullet

Carrier structural diversity

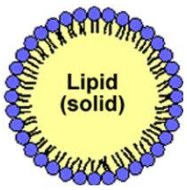
- **Lipid-based**



Liposome
- Lipid bilayer
- Aqueous cavity

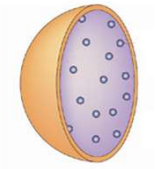


Nanoemulsion
- Lipid monolayer
- Liquid cavity

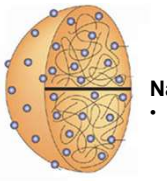


Lipid nanoparticles
- Lipid monolayer
- Solid core

- **Polymer-based**



Nanocapsule
- Polymer wall
- Liquid cavity

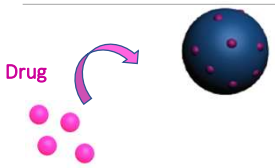


Nanosphere
- Solid polymer matrix

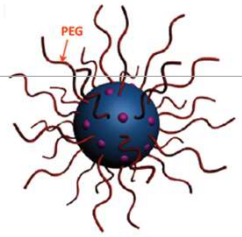
11

Nanocarriers

Carrier structural diversity

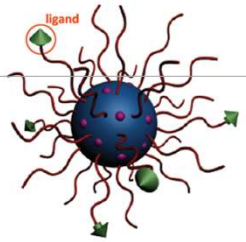


1st generation



2nd generation

Stealth/Long circulating



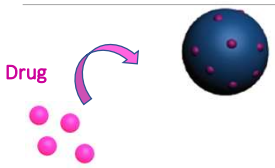
3rd generation

Stealth/Long circulating
Surface functionalized

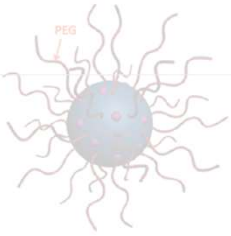
12

Nanocarriers

Carrier structural diversity

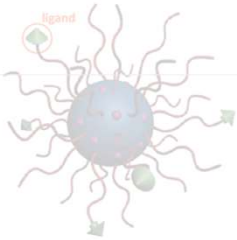


1st generation



2nd generation

Stealth/Long circulating

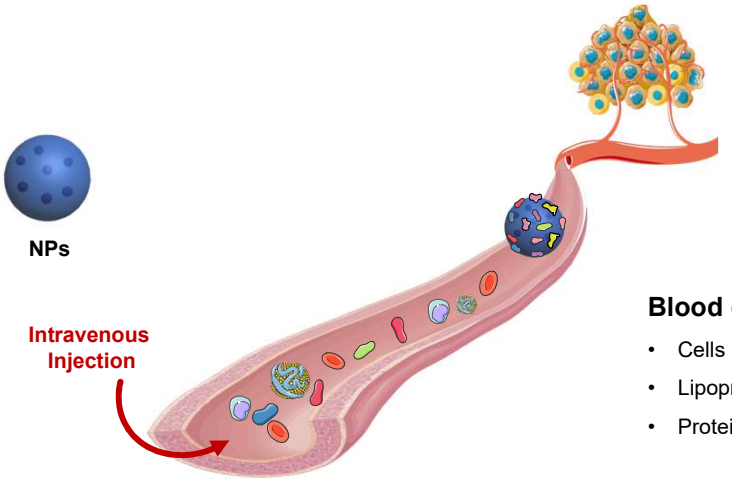


3rd generation

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

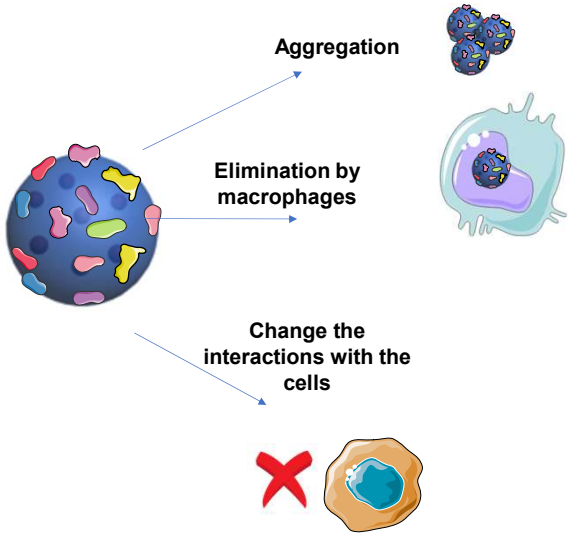
Opsonins

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

NON Opsonins

- Albumin
- Apoproteins

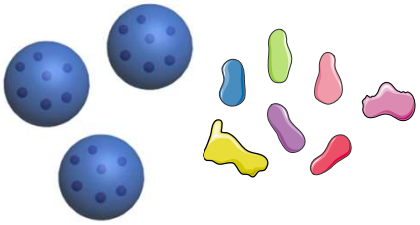
Acquisition of a specific molecular signature



15

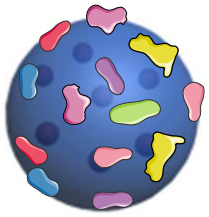
In vivo fate

Interactions in the biological medium_the protein corona



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

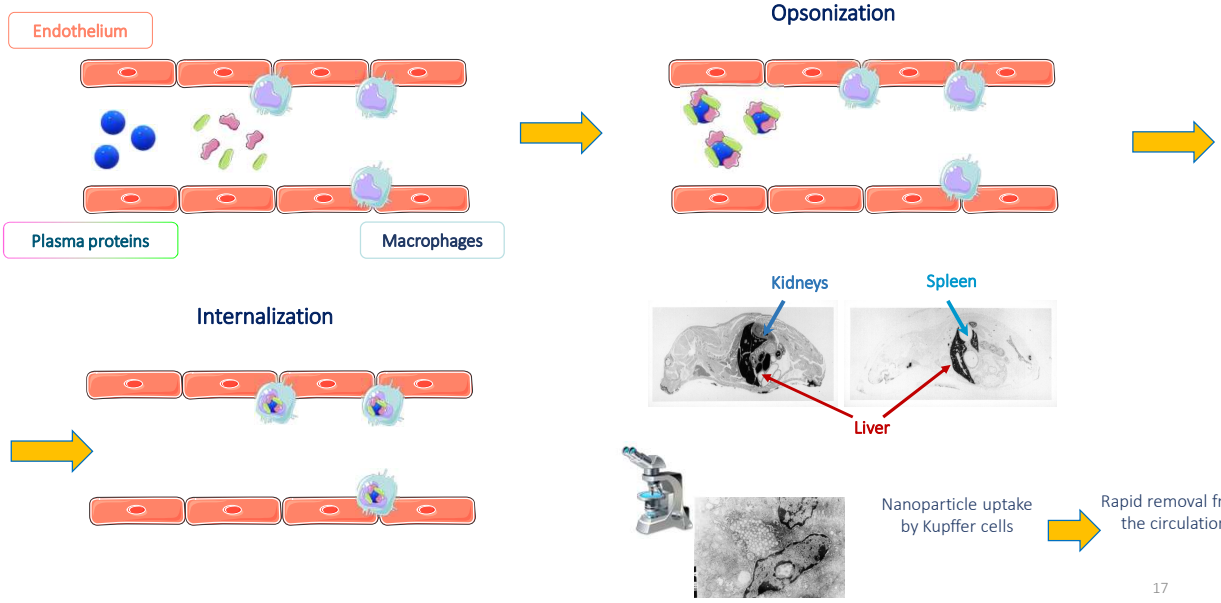
- Hydration/solvation forces
- Steric hindrance
- Electrostatic repulsion



16

First generation : *Fate of nanoparticles after IV administration*

- Macrophage uptake and liver accumulation



17

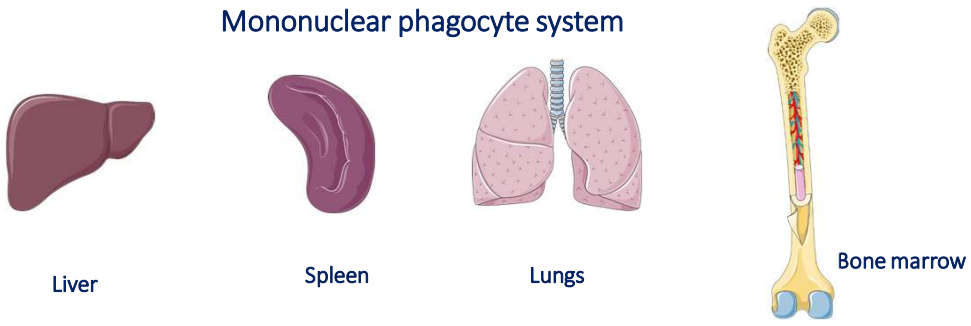
In vivo fate

Interactions in the biological medium_the protein corona

Endocytosis/Phagocytosis →

- Monocytes
- Tissue macrophages

Mononuclear phagocyte system



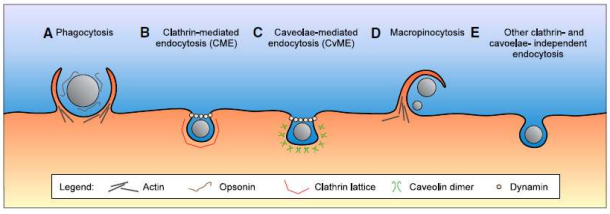
18

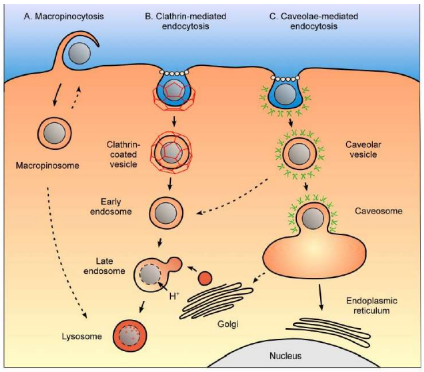
Schöttler, S. et al.,. Nature Nanotech 11, 372–377 (2016).

In vivo fate

Internalization pathways

Endocytosis



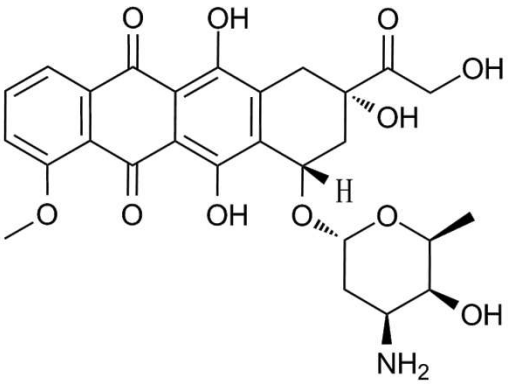


Hillaireau et al., Cell. Mol. Life Sci. (2009) 66:2873–2896

19

Antitumor chemotherapy

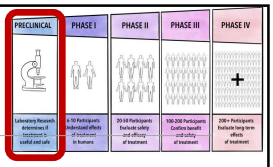
Doxorubicin



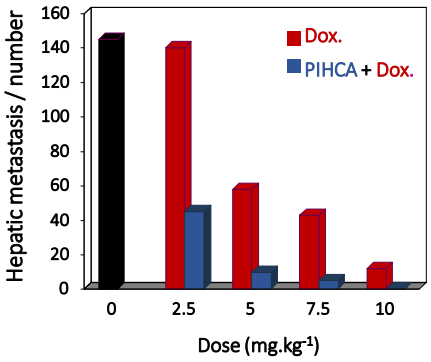
20

Antitumor chemotherapy

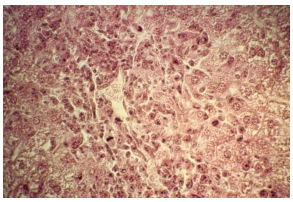
Doxorubicin _Livatag, doxorubicin transdrug



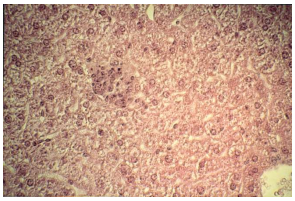
in vivo model of hepatic metastasis



Doxorubicin



Dox-loaded
PIHCA nanoparticles

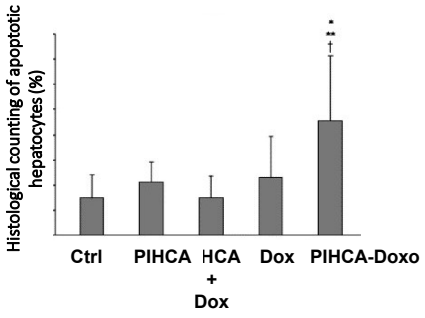


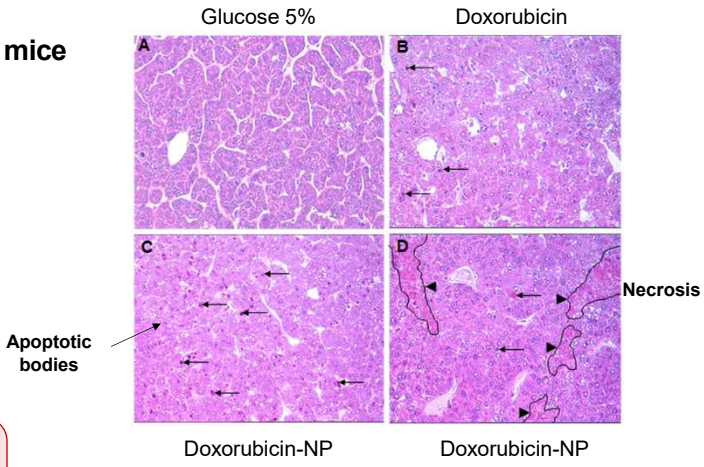
P. Couvreur *et al*, *J. Pharm. Pharmacol.* 1979, 31, 331
N. Chiannilkulchai *et al.*, Sel. Cancer *Ther.* 1989, 5, 1

Antitumor chemotherapy

Doxorubicin _Livatag, doxorubicin transdrug

in vivo cytotoxicity in X/myc transgenic mice

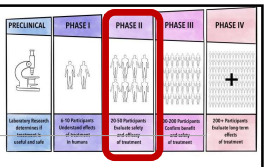


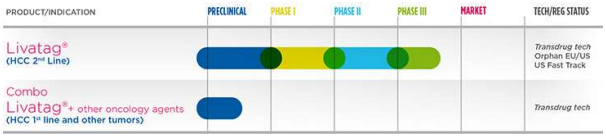


Potential breakthrough in the treatment of hepatocellular carcinoma

Antitumor chemotherapy

Doxorubicin _Livatag, doxorubicin transdrug





- PHASE II

Baseline
Tumor size 3000 mm²

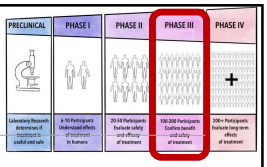
intra-arterial infusion
(30 mg/m²)

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

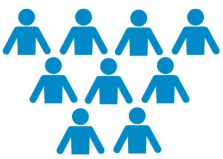
doxorubicin transdrug_ReLIVE: phase III *NCT01655693*



- 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/m²

30 mg/m²

24

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*

25

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

26

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

WHY?

- 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)*

27

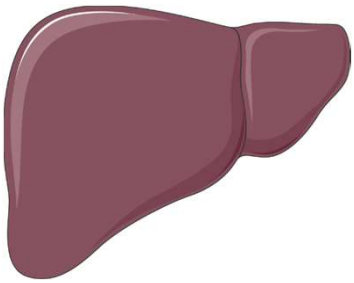
Merle et al., *Lancet Gastroenterol Hepatol* **2019,** 4, 454-465

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

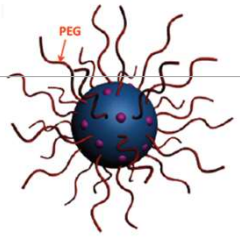


28

Nanocarriers

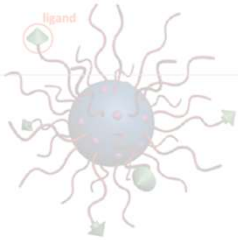
Carrier structural diversity

1st generation



2nd generation

Stealth/Long circulating



3rd generation

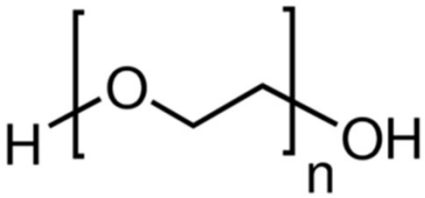
Stealth/Long circulating
Surface functionalized

29

In vivo fate

If you want to be invisible, look like water

Poly(ethylene glycol)



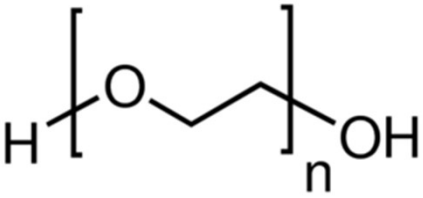
30

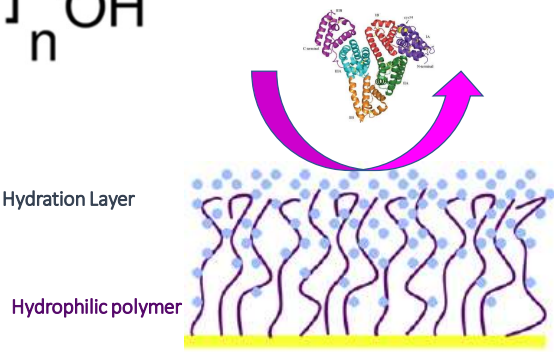
In vivo fate

If you want to be invisible, look like water

Poly(ethylene glycol)

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

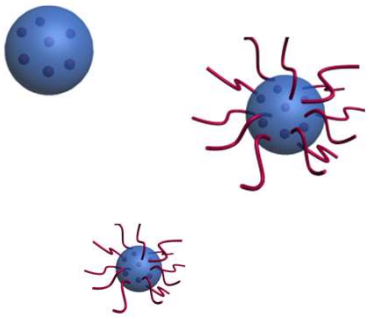




In vivo fate

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



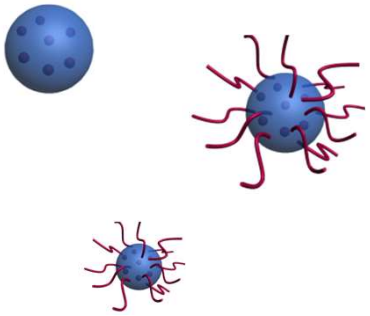
32

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

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



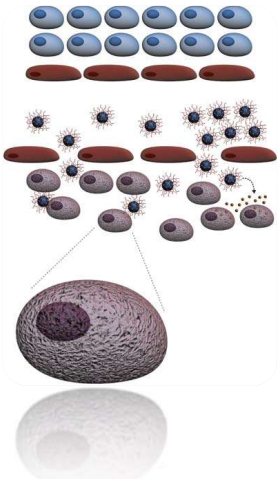
Protein adsorption is surface and size dependent

33

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

Second generation

The enhanced permeability and retention effect (EPR)



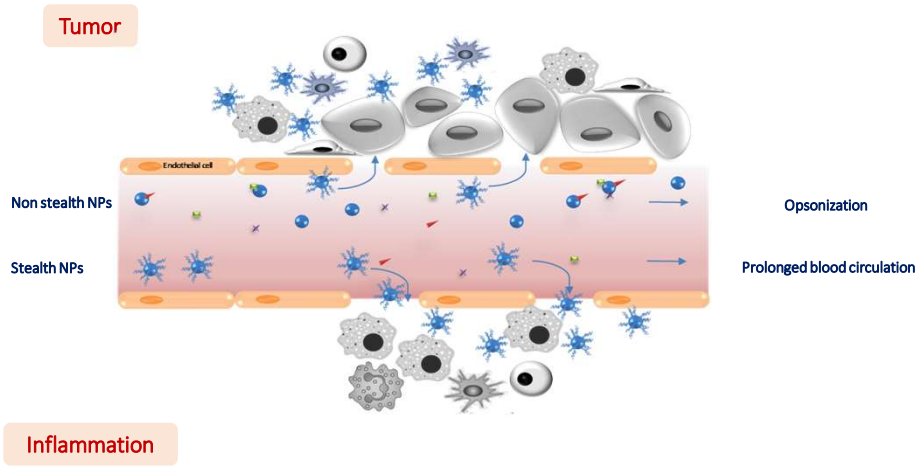
- Enhanced permeability
  - Stimulation of the blood vessel production
  - Important vascularization (blood supply)
  - Wide fenestrations, abnormal architectures
- Enhanced retention
  - Inefficient lymphatic drainage

Accumulation of nanoparticles in tumor and inflammed tissues

34

Second generation

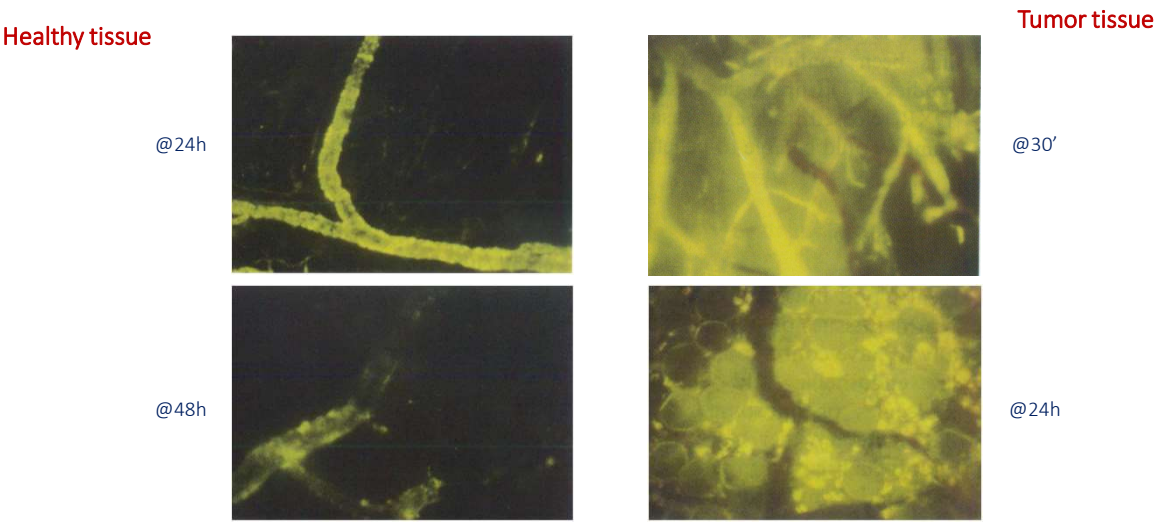
The enhanced permeability and retention effect (EPR)



35

Second generation

The enhanced permeability and retention effect (EPR)

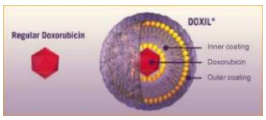


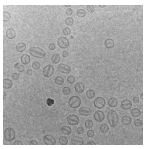
36

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

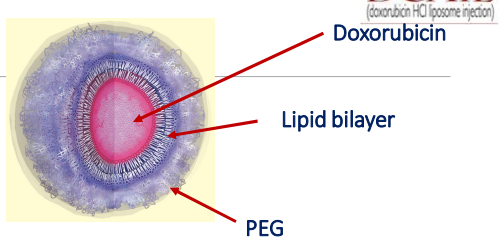
Second generation

nanomedicines in the market_Doxil (1995)





80-90 nm PEG-coated
unilamellar liposomes



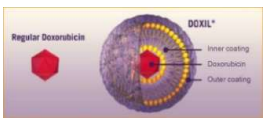
- Metastatic breast cancer
- Kaposi's sarcoma in patients with AIDS
- Multiple myeloma

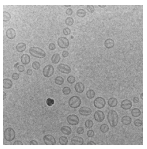
- Drug: doxorubicin

37

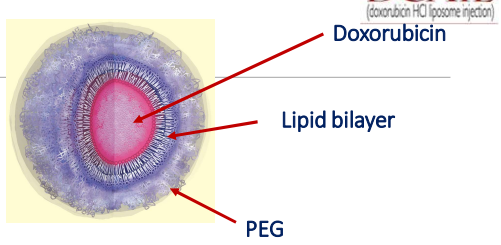
Second generation

nanomedicines in the market_Doxil (1995)





80-90 nm PEG-coated
unilamellar liposomes



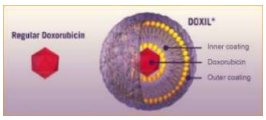
- Metastatic breast cancer
- Kaposi's sarcoma in patients with AIDS
- Multiple myeloma

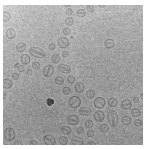
- Drug: doxorubicin

38

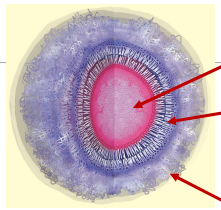
Second generation

nanomedicines in the market_Doxil (1995)

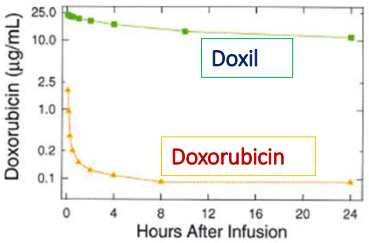




80-90 nm PEG-coated
unilamellar liposomes



- Plasma concentration



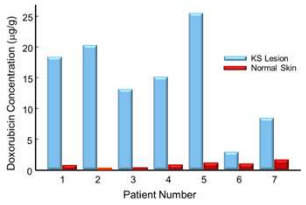
- Metastatic breast cancer
- Kaposi's sarcoma in patients with AIDS
- Multiple myeloma

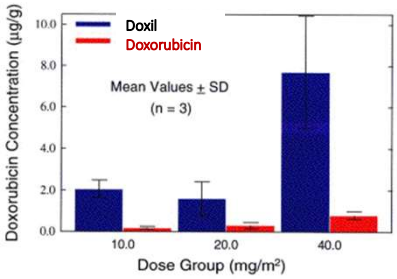
- Drug: doxorubicin

39

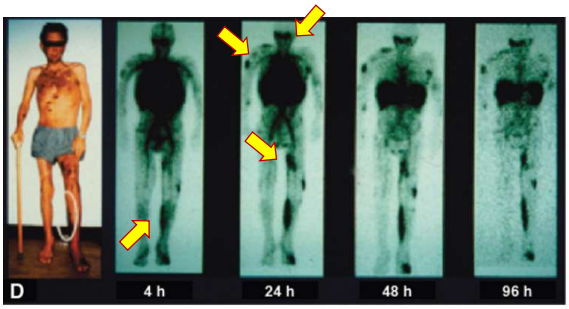
Doxil

Accumulation in KS lesions





Indium-111–labeled PEGylated liposome



40

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

Doxil

Cardiotoxicity

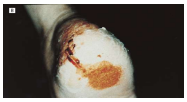
- Reduced
- Only 0.8% withdrawal due to cardiotoxicity
- Increasing dose and duration of treatment

Complement activation–related pseudo allergy

- Slower infusion rate
- Pretreat

Hand-foot syndrome

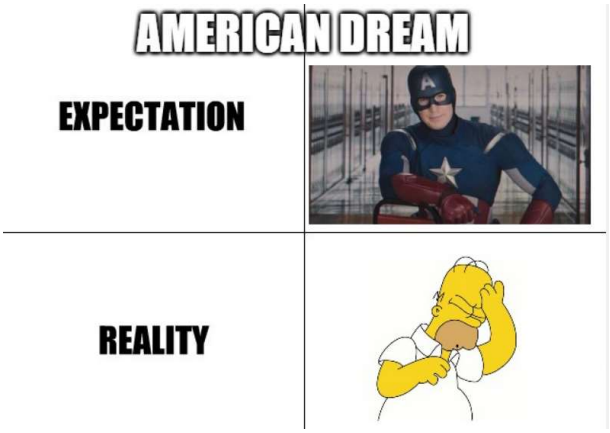
- Rich capillary network, increased blood flow
- Increased drug accumulation
- protracted slow release



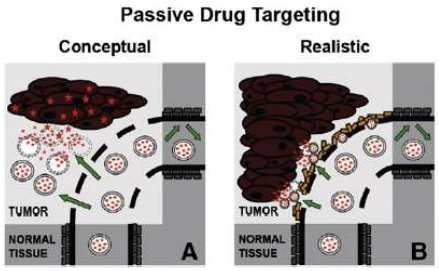
	Symptoms
Grade I	Mild erythema
Grade II	Erythema with desquamation
Grade III	Blistering
Grade IV	Diffuse

41

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



42

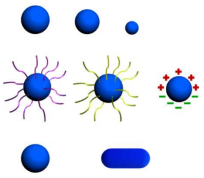


Tumor

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

Particles

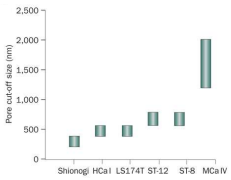
- Mean diameter
- Charge and surface chemistry
- Shape



43

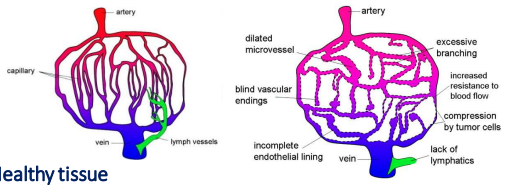
Lammers T et al., Journal of Controlled Release, 161 (2012) 175–187

Variable pore size

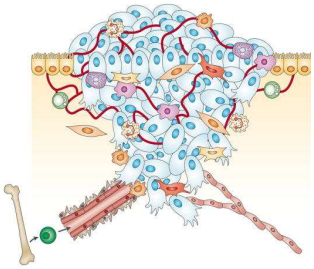


Hobbs, S. K. et al. Proc. Natl Acad. Sci. USA, 1998, 95, 4607

Heterogeneous vasculature



Heterogeneous tumor composition



44

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

45

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

46

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

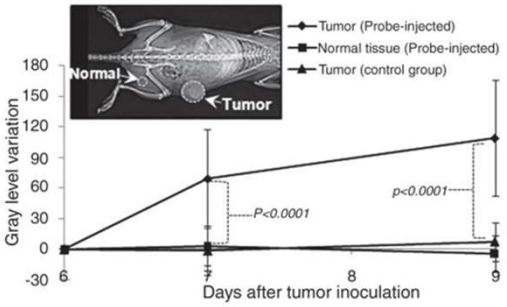
- Faster tumor grow rate
- intact vasculature

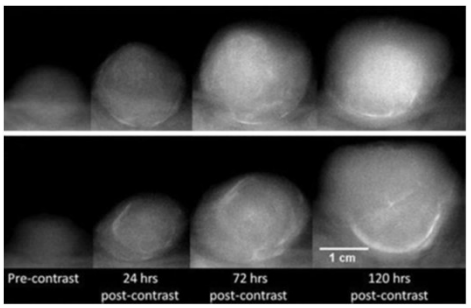
Karathanasis *et al.*, *Radiology* **2009**, 250, 398-406

47

Correlate EPR effect and response to treatment

- Gray levels signal enhancement





After probe administration:
- highest enhancement in tumor tissue
- no substantial enhancement in normal tissue

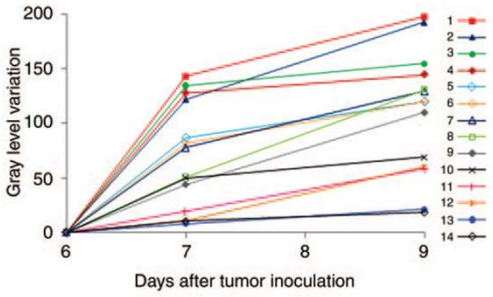
Without probe administration:
- no enhancement in tumor lesion of control group

48

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

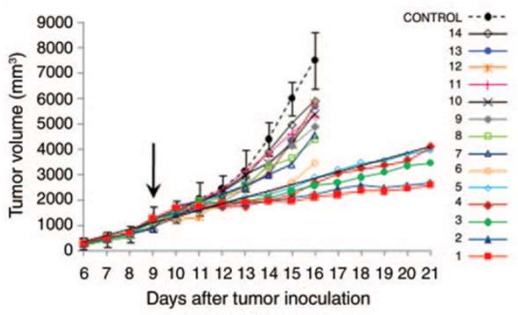
Correlate EPR effect and response to treatment

- Tumor permeability



High variability of tumor leakiness

- In vivo efficacy



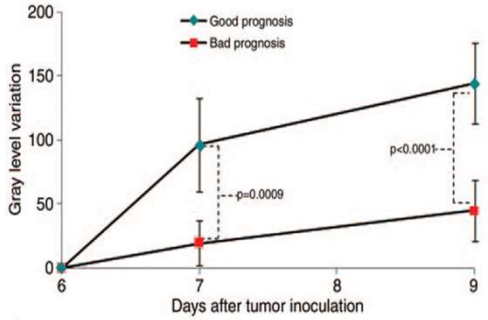
High variability of tumor response

49

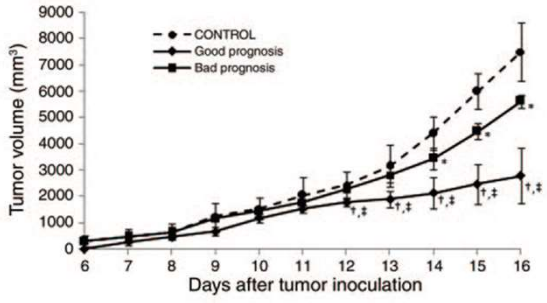
Karathanasis *et al.*, *Radiology* **2009**, 250, 398-406

Correlate EPR effect and response to treatment

- Tumor permeability



- In vivo efficacy



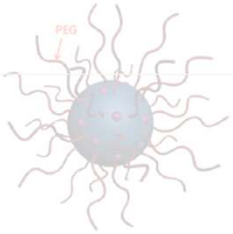
Significant higher response to chemotherapy of good-prognosis subgroup

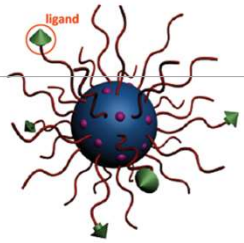
50

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

Nanocarriers

Carrier structural diversity





1st generation

2nd generation

Stealth/Long circulating

3rd generation

Stealth/Long circulating
Surface functionalized

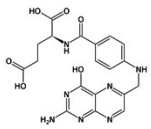
51

Third generation

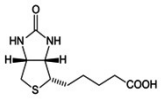
ligand mediated targeting

- **Small molecules**

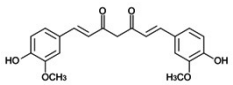
Folic acid



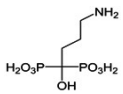
Biotin



Curcumin

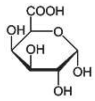


Alendronate

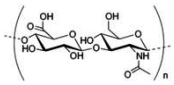


- **Carbohydrates**

Galactose



Hyaluronan

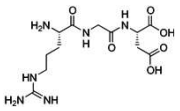


- **Antibodies**

- **Peptides/proteins**

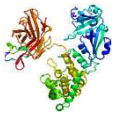
RGD peptides

GRGDS
CRGDKGPDC
Cyclo(RGDDFK)



Cell penetrating peptides

EGF



Transferrin

52

Third generation

ligand mediated targeting

THE JOURNAL OF BIOLOGICAL CHEMISTRY
© 1994 by The American Society for Biochemistry and Molecular Biology, Inc.
Vol. 269, No. 5, Issue of February 4, pp. 3198–3204, 1994
Printed in U.S.A.

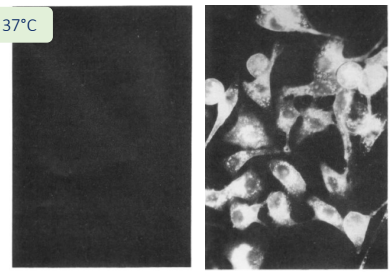
Delivery of Liposomes into Cultured KB Cells via Folate Receptor-mediated Endocytosis*

(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

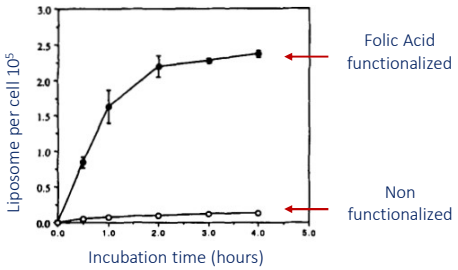
- Uptake *Confocal microscopy*

4h @ 37°C



Non functionalized Folic Acid functionalized

- Internalization kinetic *fluorescence spectroscopy*

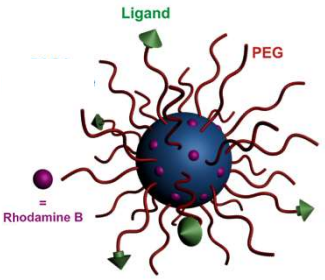


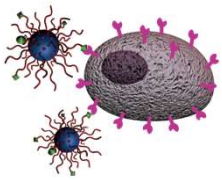
53

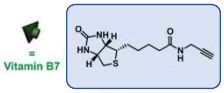
Third generation

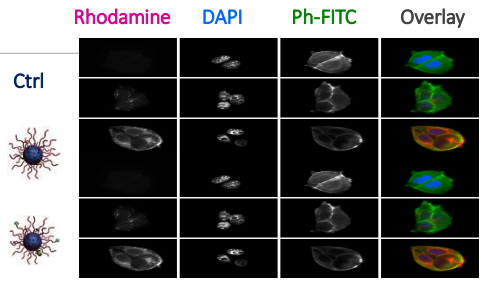
ligand mediated targeting

- Uptake

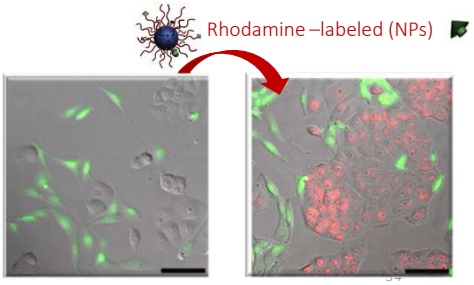








- Selectivity



- 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

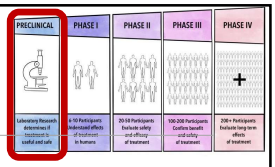
AGC advanced gastric cancer, *dn-CCNG1* dominant-negative mutant construct of cyclin G1, *DOX* doxorubicin, *EAC* esophageal adenocarcinoma, *GUC* genitourinary cancers, *MPM* malignant pleural mesothelioma, *NSCLC* non-small cell lung cancer, *Tf* transferrin, *vWF* Von Willebrand factor

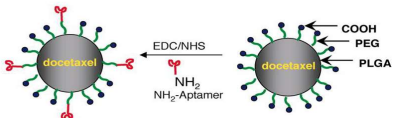
55

Signal Transduction and Targeted Therapy (2023) 8:293

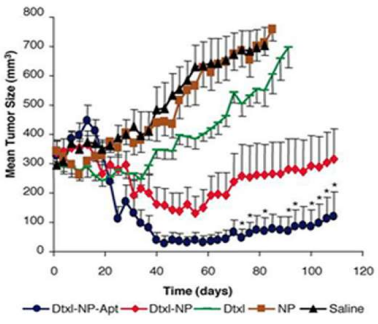
Third generation

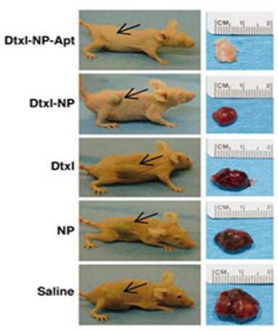
prostate specific membrane antigen (PSMA) targeting





Intratumoral injection

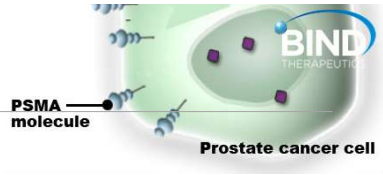




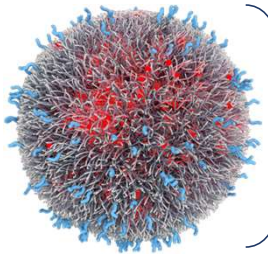
Farokhzad OC , et al.,*Proc. Natl. Acad. Sci. U. S. A.*, **2006,** 103, 6315

Third generation

prostate specific membrane antigen (PSMA) targeting



Accurins



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

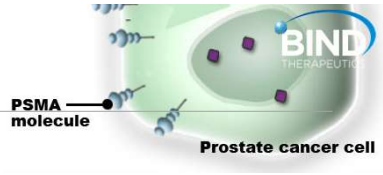
	PATIENTS EXPRESSING PSMA	
TUMOR	TUMOR CELLS	NEOVASCULATURE
Prostate	184/184 (100%)	2/12 (17%)
Breast	0/6 (0%)	5/6 (83%)
Colorectal	0/130 (0%)	110/130 (85%)
Renal Cell	0/75 (0%)	67/75 (89%)
Bladder	8/167 (5%)	167/167 (99%)
Gastric	0/119 (0%)	79/119 (66%)
Neuroendocrine	0/5 (0%)	5/5 (100%)
Melanoma	0/5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

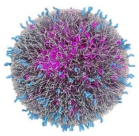
- BIND-014 (PSMA-targeted docetaxel)
- BIND-510 PSMA-targeted vincristine
- PLK1, KSP inhibitor accurins

PSMA is not found in normal vasculature

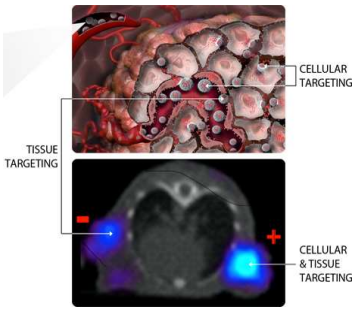
Third generation

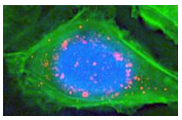
prostate specific membrane antigen (PSMA) targeting





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





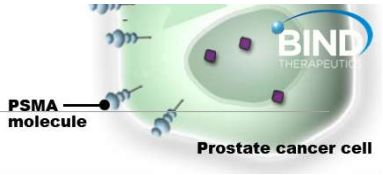
Early tests in animals and small clinical trials showed that the approach was safer than docetaxel alone

Later clinical trials disappointed

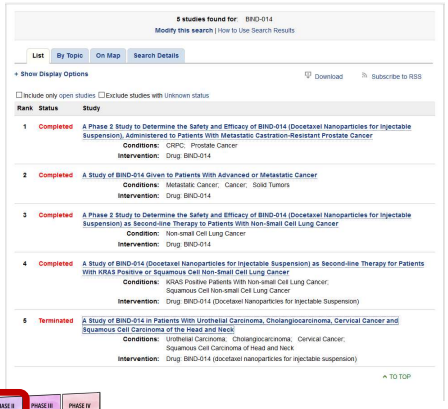
- BIND-014 failed against cervical and head-and-neck cancers
- Efficacy on lung cancer was not clear

Third generation

prostate specific membrane antigen (PSMA) targeting



Last updates February-April 2016



5 studies found for: BIND-014
Modify this search | How to Use Search Results

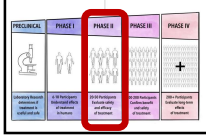
List | By Topic | On Map | Search Details

+ Show Display Options — Download — Subscribe to RSS

☐ Include only open studies ☐ Exclude studies with Unknown status

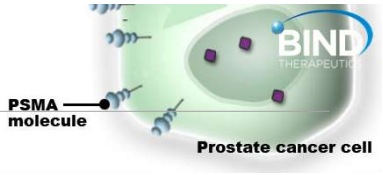
Rank	Status	Study
1	Completed	A Phase 2 Study to Determine the Safety and Efficacy of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension), Administered to Patients With Metastatic Castration-Resistant Prostate Cancer Conditions: CRPC; Prostate Cancer Intervention: Drug: BIND-014
2	Completed	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)

↑ TO TOP

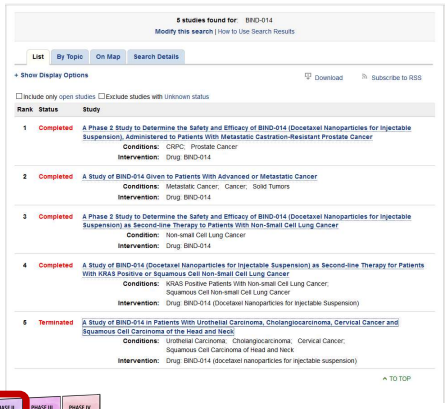


Third generation

prostate specific membrane antigen (PSMA) targeting



Last updates February-April 2016



5 studies found for: BIND-014
Modify this search | How to Use Search Results

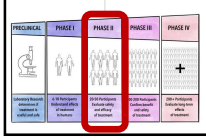
List | By Topic | On Map | Search Details

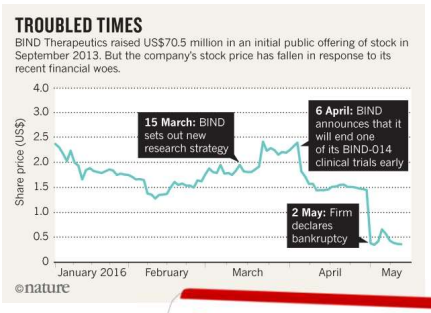
+ Show Display Options — Download — Subscribe to RSS

☐ 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)

↑ TO TOP

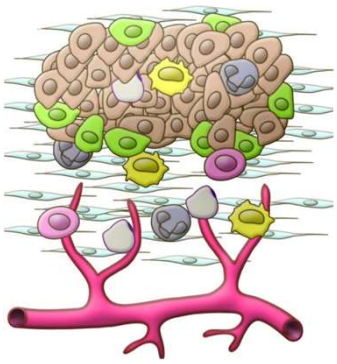




Need to reach the biological target

The abnormal microenvironment impairs uniform delivery and efficcacy of therapeutic agents

Transport through the microenvironnement



Extravasation

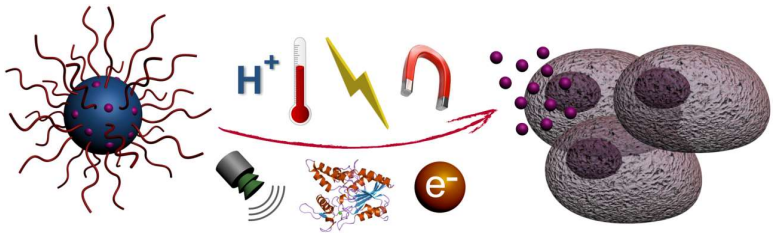
Efficient drug delivery to cancer cells requires crossing of multiple biological barriers

Need to have relevant predictive models

61

Fourth generation: stimuli responsive

Efficient spatio temporal and dosage release control



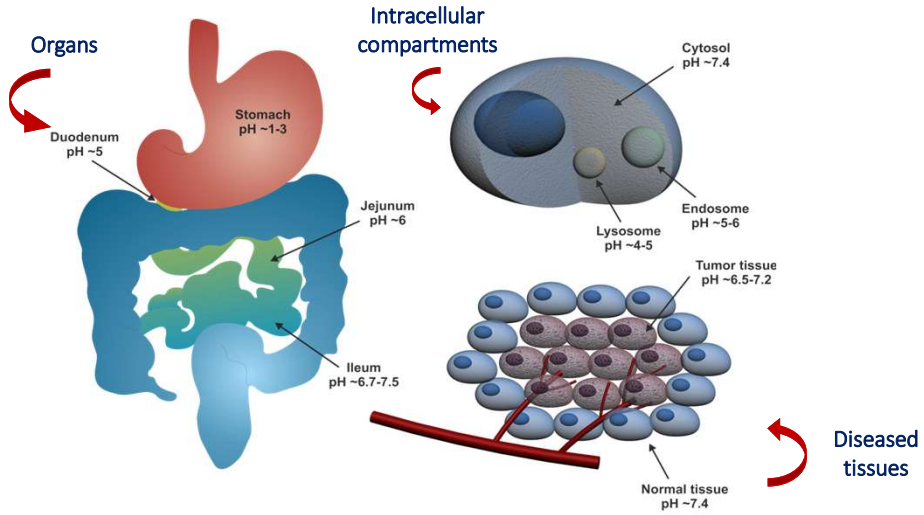
- Endogenous stimuli
  - pH
  - Redox status (glutathion concentrations)
  - Enzymatic activity
- Exogenous stimuli
  - Magnetic/electric field
  - Light
  - Ultrasound
  - Temperature

62

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

Fourth generation: pH sensitive

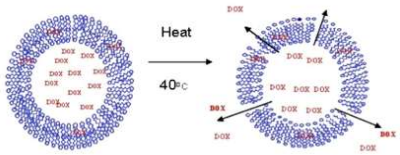
- Body pH variations

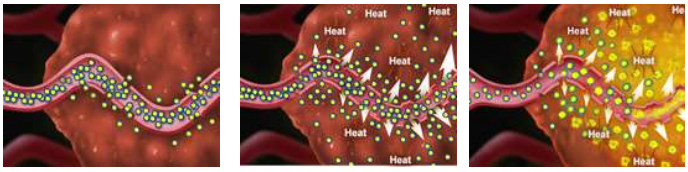


63

Fourth generation : temperature sensitive

- Heat-activated doxorubicin loaded liposomes : Thermodox®

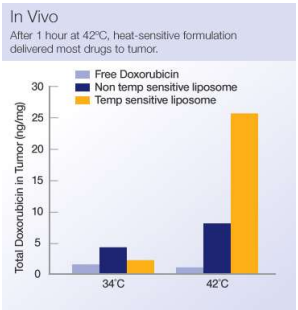


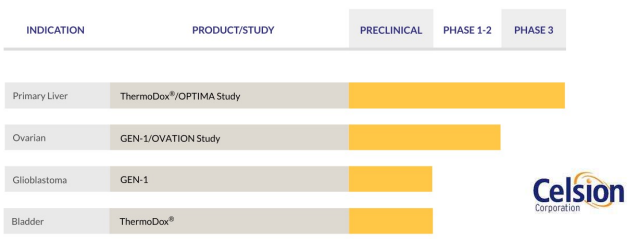


"Leaky" tumor blood Vessels

Heat adds permeability

Heat-triggered release

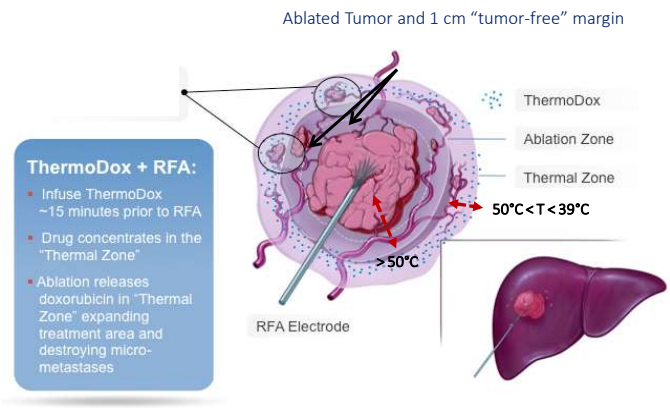


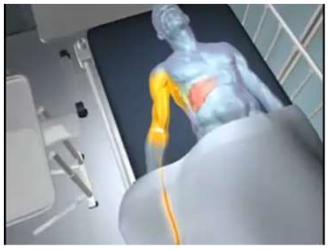


64

Fourth generation: temperature sensitive

- Heat-activated doxorubicin loaded liposomes : Thermodox®



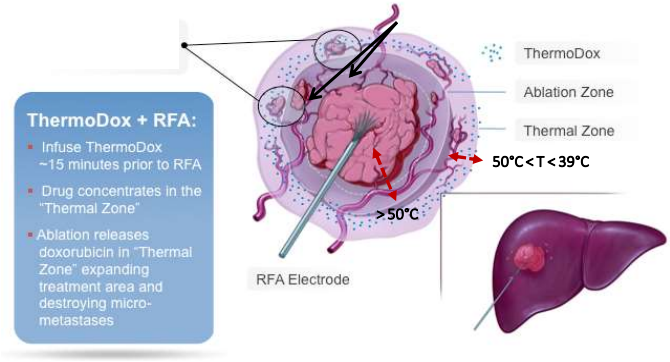


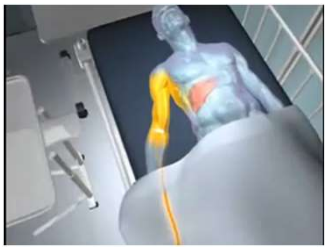
- Micro - metastasis outside the ablation zone "kill" area.
- Potential site of recurrence if not treated

65

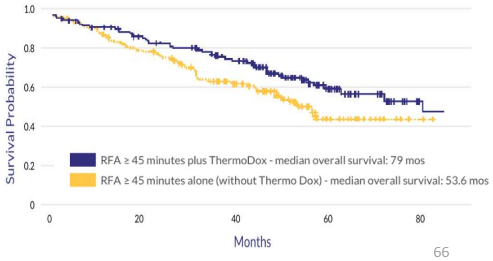
Fourth generation: temperature sensitive

- Heat-activated doxorubicin loaded liposomes : Thermodox®





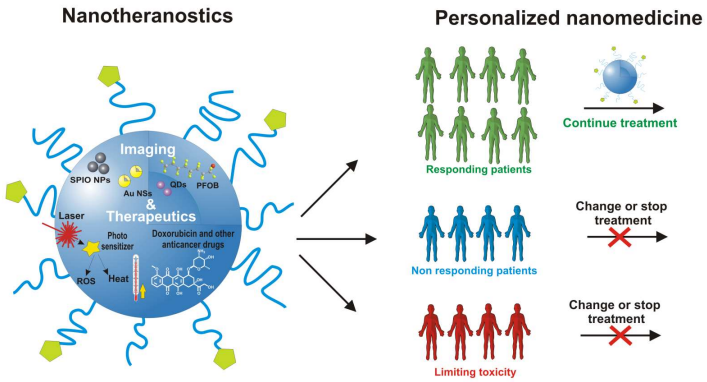
- Survival data for single-lesion patients



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

66

- 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

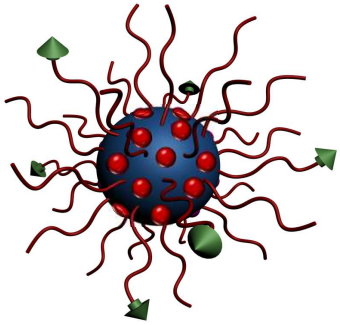
67

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

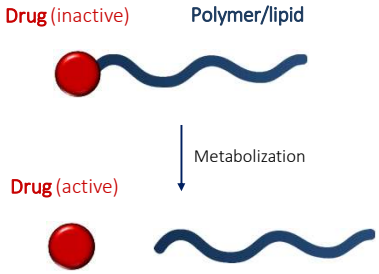
68

Nanomedicine for drug delivery

Physical drug encapsulation



The prodrug strategy



Important limitations:

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

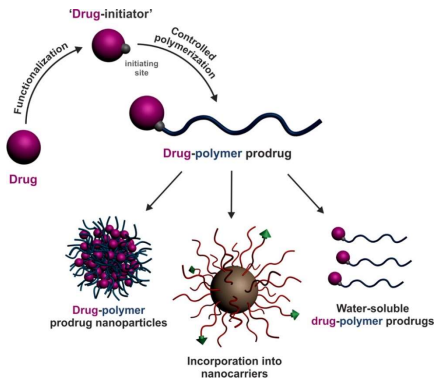
Advantages:

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

69

The prodrug approach

- Polymer prodrugs

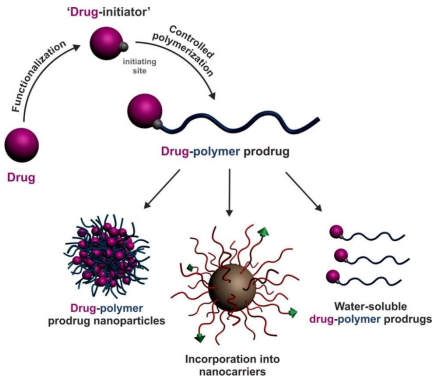


70

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

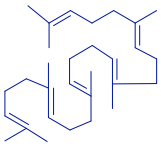
The prodrug approach

- Polymer prodrugs



- Lipid Prodrugs

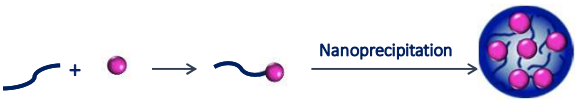
Squalene (SQ)



- 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

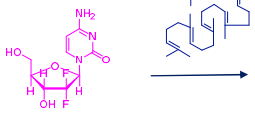
71

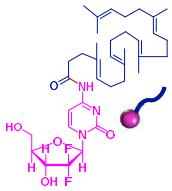
Nicolas J. *Chem. Mater.* **2016** 28, 1591; Delplace V. *et al., Polym Chem* **2014,** 5, 1529

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

The prodrug approach: squalene based

Squalene (SQ)





Gemcitabine (Gem) SQGem SQGem NPs

Leukemia 1210

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

72

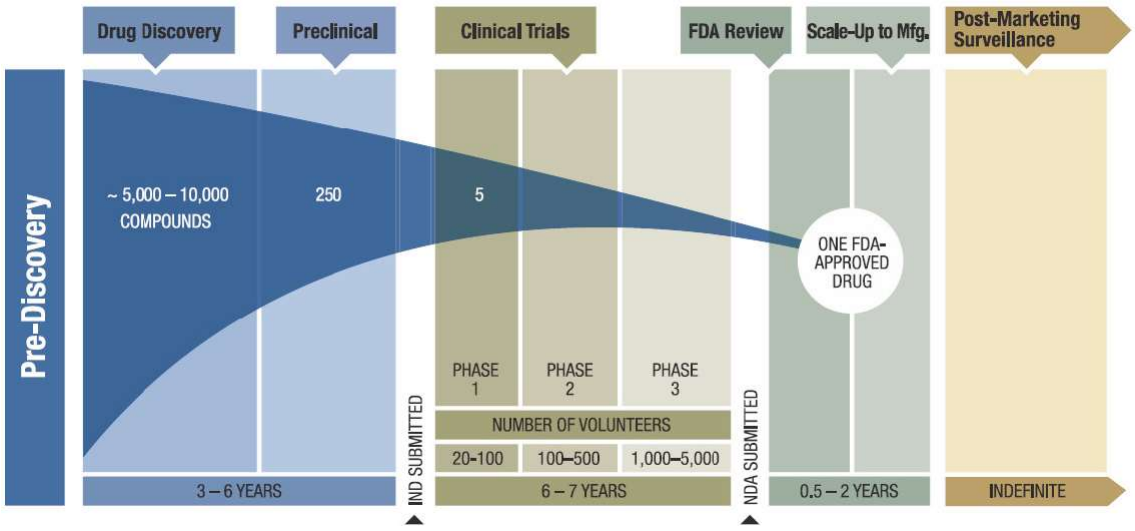
Couvreur *et al., Nano Letters* 2006, 6, 2544; Reddy *et al., Drug Met. Disp.* 2008, 36, 1570; Reddy et al., *Mol. Pharm.* 2009, 6, 1526.

M1 Sciences du Médicament

Initiation to Drug Discovery:
The Challenges of the 21st Century (UEM 919)
Relevant models for preclinical prediction

Simona Mura | octobre 4, 2024 |

Drug development timeline



74

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

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 ⊖

75

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 ⊖

76

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

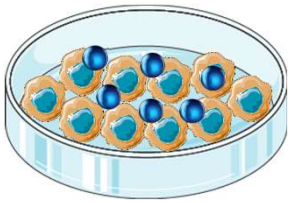
- Very useful ⊕
- Expensive, time consuming ⊖
- Specie differences ⊖
- Ethical issues ⊖

77

Cell culture models

2D

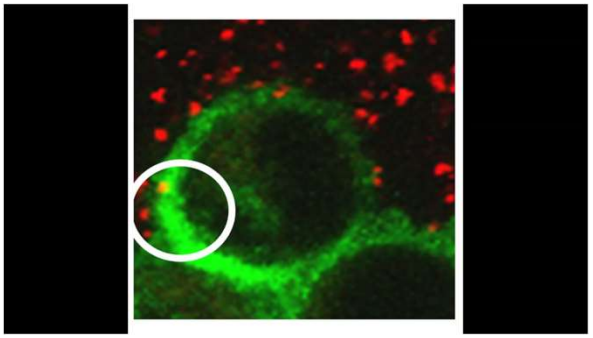
Drug / NPs



Cell-uptake studies

- Confocal microscopy

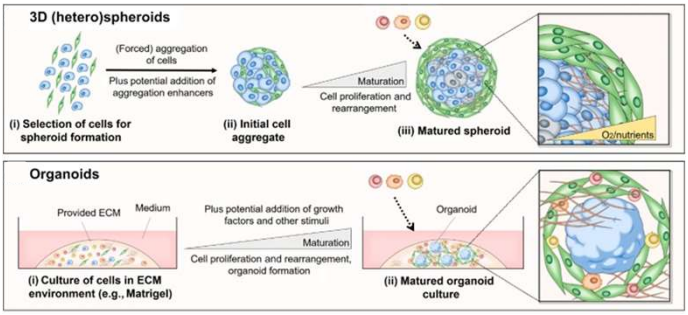
Uptake of fluorescently-labeled liposomes by macrophages (membrane labeled in green)



78

3D culture models

- Cell-Based

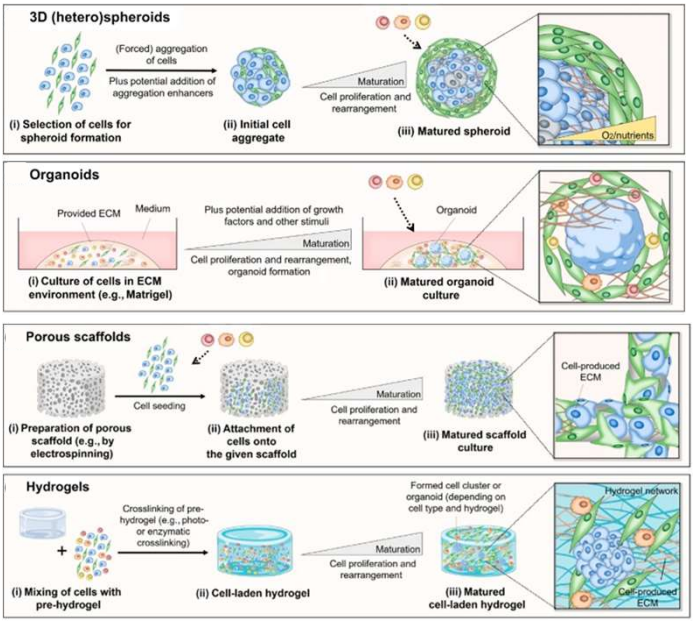


79

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

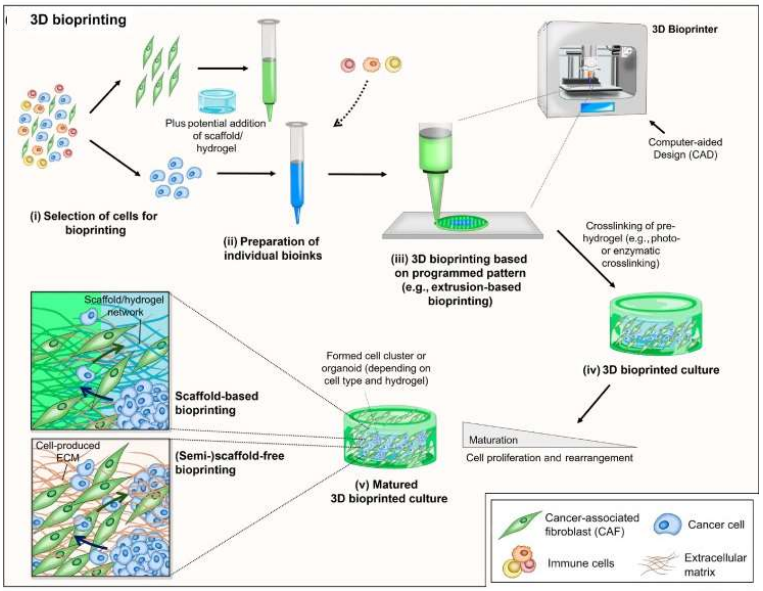


80

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

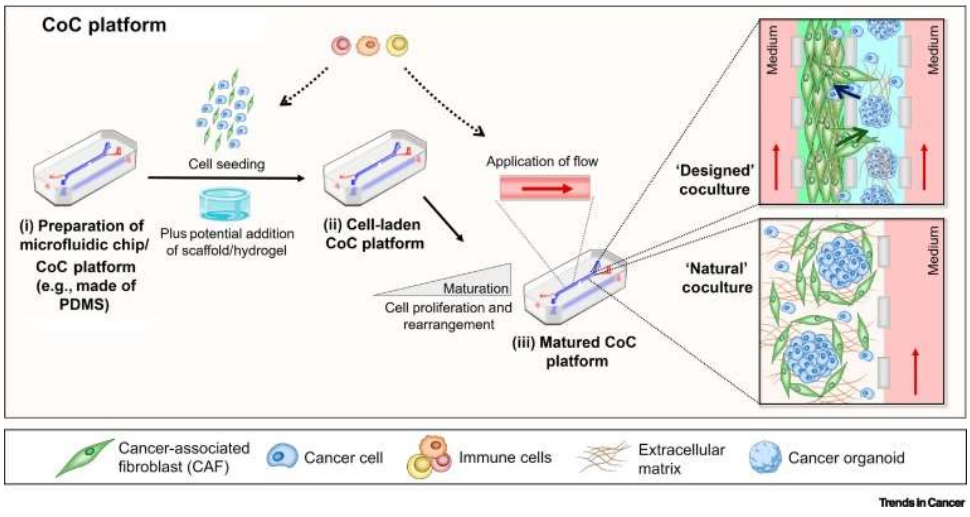


81

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)



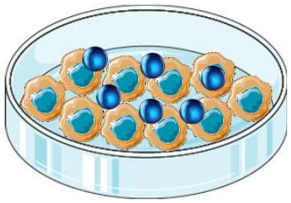
82

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

Cell culture models

2D

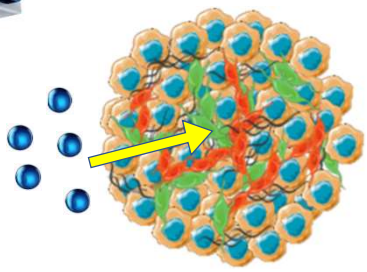
Drug / NPs



Cell-uptake studies

- Confocal microscopy

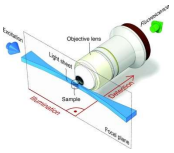
3D



Cell-uptake studies

Penetration studies

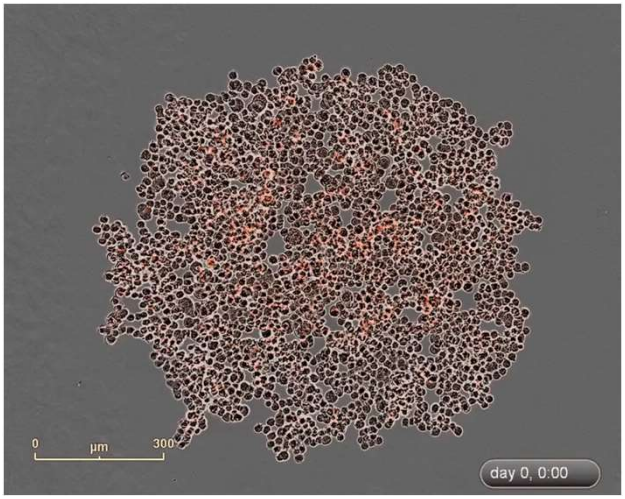
- Light sheet Microscopy



83

Spheroids

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



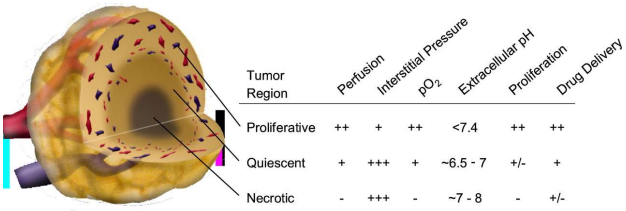
Cell aggregation and spheroid formation:
D3= 400 µm
D10= 560 µm

84

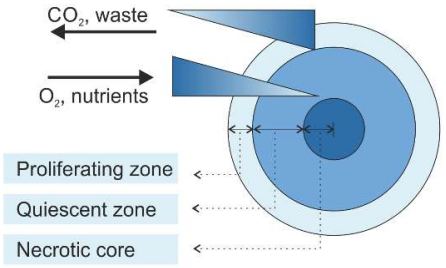
Ancorage independent

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	-	+/-



85

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

Tumor spheroids

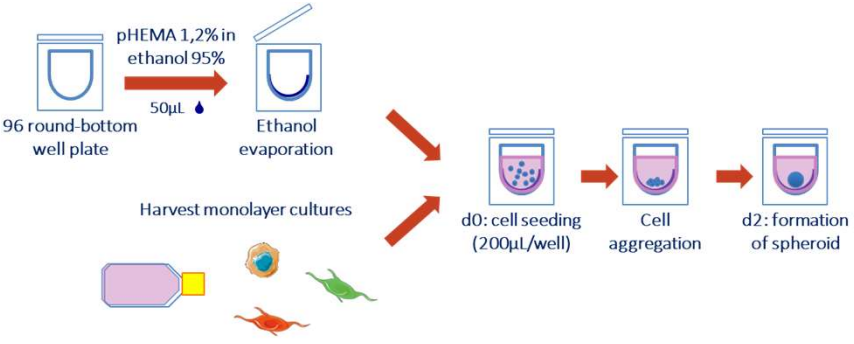
- Fabrication methods
- Liquid overlay

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

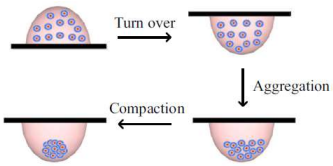


86

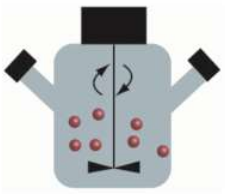
Lazzari G, Nicolas V, Matsusaki M, Akashi M, Couvreur P, Mura S. *Acta Biomaterialia* **2018**, 78, 296.

Tumor spheroids

- Fabrication methods
  - Hanging drop



  - Spinning Flask



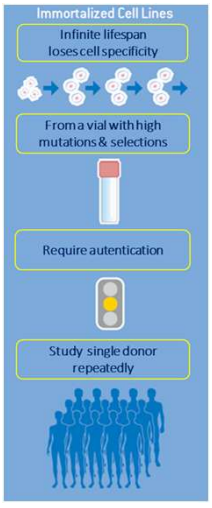
  - AggreWell™

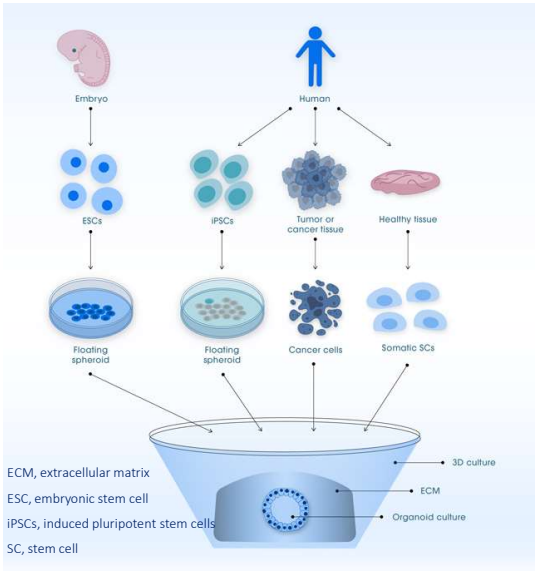
87

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

Spheroids vs Organoids

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





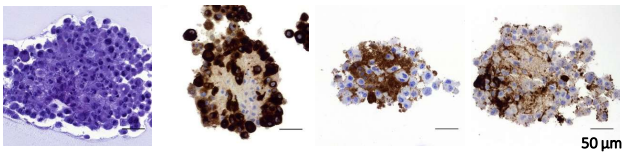
88

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

Tumor spheroids

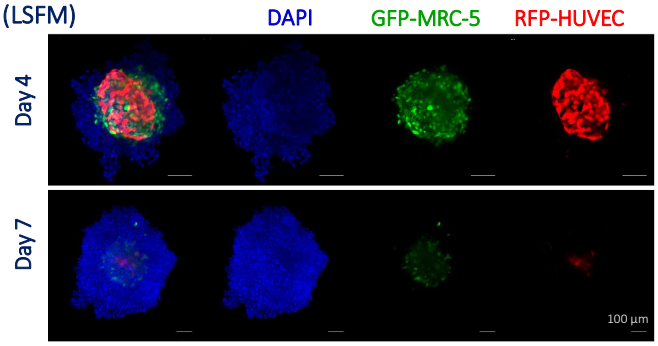
- Heterotype multicellular spheroids triple co-culture (PANC-1: MRC-5: HUVEC)

- 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

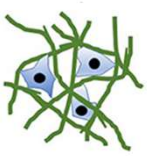
89

3D culture models

Natural hydrogels

Animal Derived
- Collagen
- Matrigel
- Gelatin

Plant Derived
- Alginate



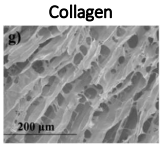
Synthetic hydrogels

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

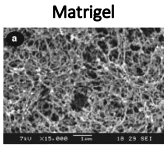
Natural
- Hyaluronic Acid (HA)
- Peptides

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

Collagen



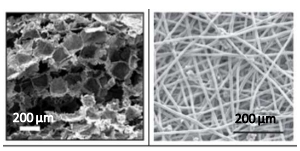
Matrigel



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

poly-lactic-glycolic acid

polycaprolactone

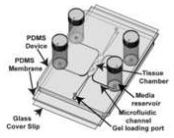


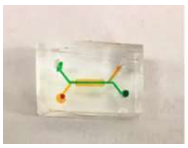
90

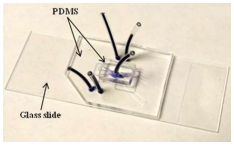
Adapted from Liu Z and Vunjak-Novakovic G, *Curr Opin Chem Eng* **2016**, 11, 94

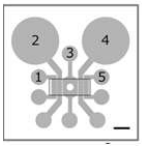
Microfluidic devices

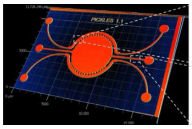
- Culturing living cells in continuously-perfused, micrometer sized chambers
- Model physiological functions of tissues and organs
- Incorporate physical forces, fluid shear stress
- Strong control of culture parameters
- Evaluation of biological responses: cell recruitment, response to drug treatment











91

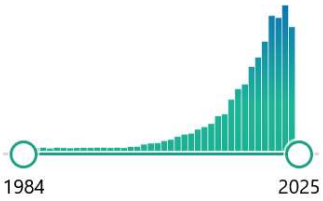
Bhatia SN, Ingber DE. *Nature biotechnology* **2014,** 32, 760

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



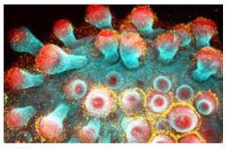
- NIH, FDA and DARPA funded programs

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.

92

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€*

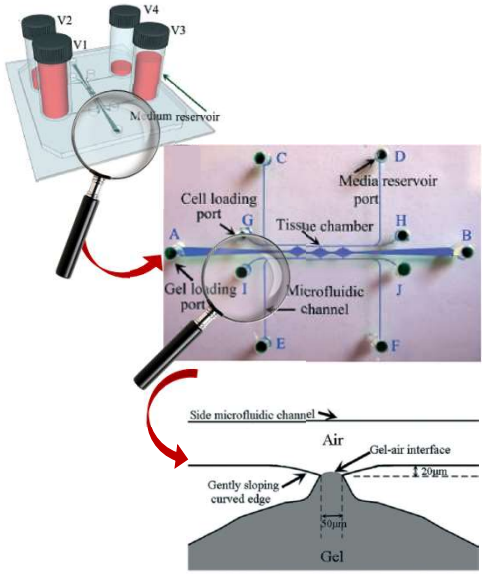
Permettre la conduite d'une politique scientifique sur des domaines d'intérêts national et européen, aux retombées pouvant être multiples

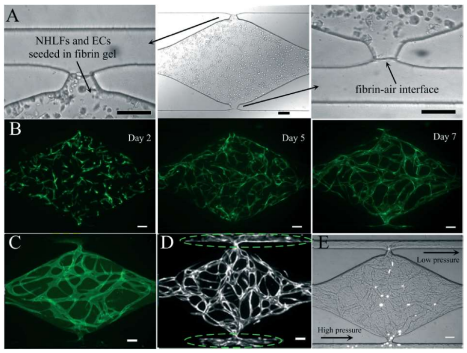
**programme et équipements prioritaires de recherche*

93

Microfluidic devices

- Perfusable microvascular network





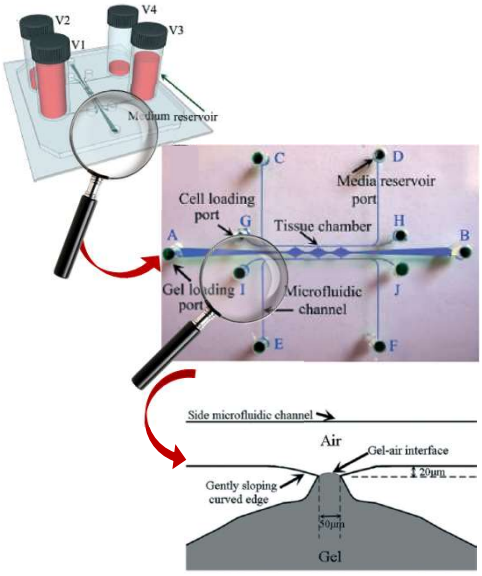
Optimised pore design
- NO gel leakage
- Vasculogenesis, Sprouting & Anastomosis

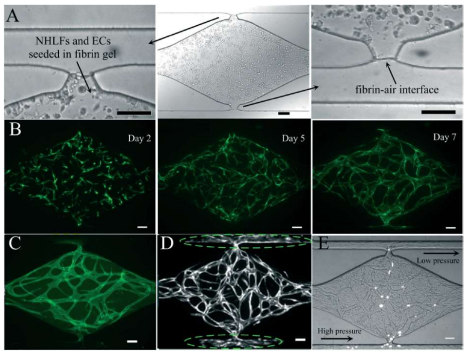
94

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

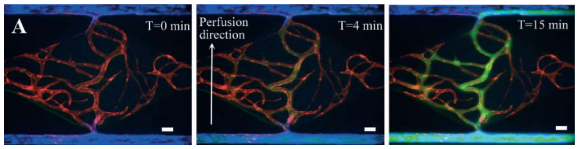
Microfluidic devices

- Perfusable microvascular network





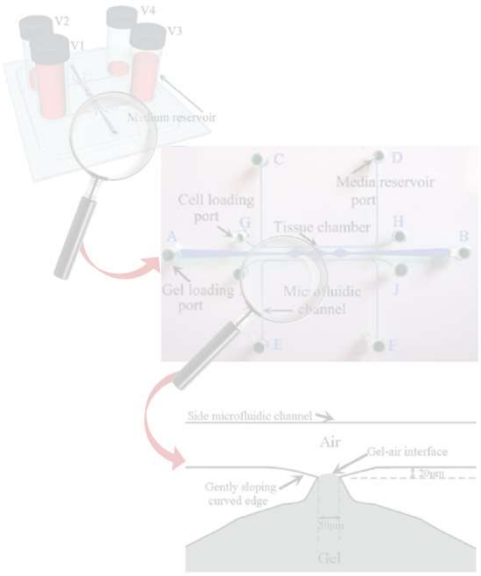
Optimised pore design
- NO gel leakage
- Vasculogenesis, Sprouting & Anastomosis

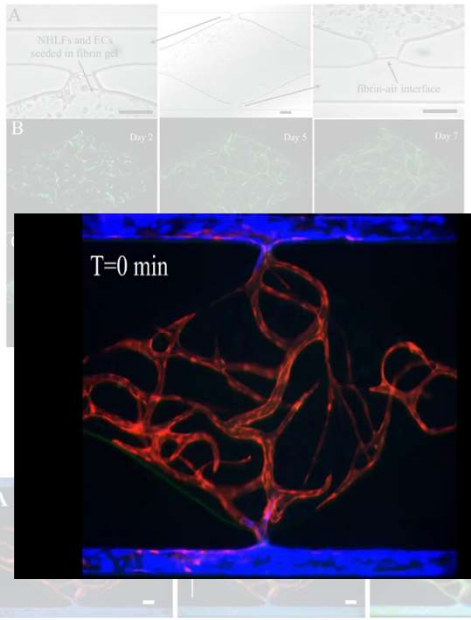


95

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

Microfluidic devices

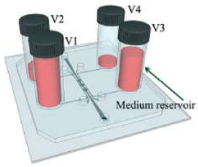


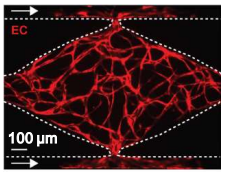


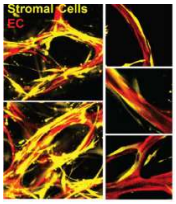
96

Microfluidic devices

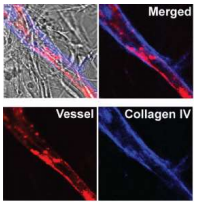
- **Perfusable microvascular network**





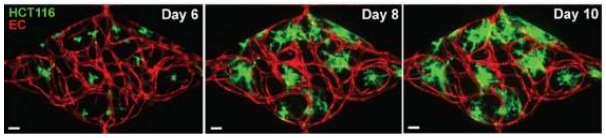


Stromal cells in perivascular position

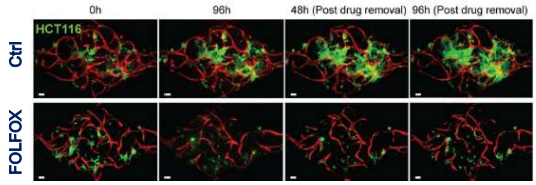


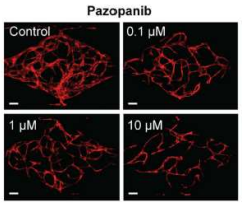
Basement membrane deposition

- Coculture with cancer cells: Vascularized Micro-Tumors



- Drug treatment: cancer or endothelial cell targeting





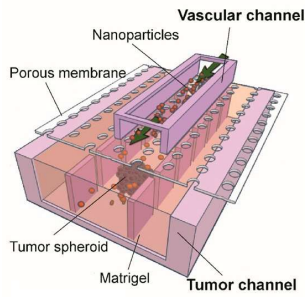
Suitable for the development of novel treatment with multiple targets

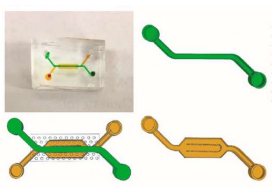
97

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

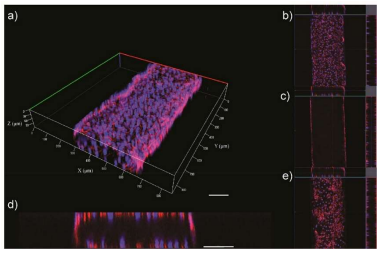




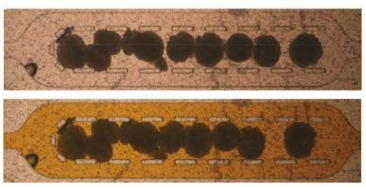
Steady medium perfusion for culturing endothelial cells

Central region for trapping tumor spheroids

- Confluent HUVEC monolayer



- Ovarian cancer cells (SKOV3) spheroids

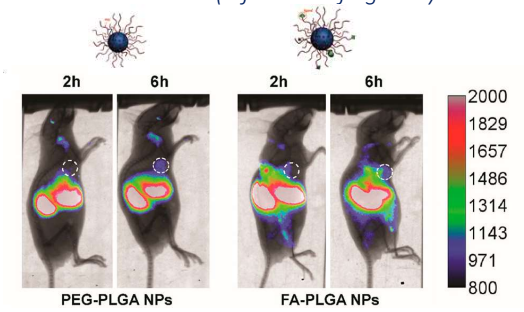


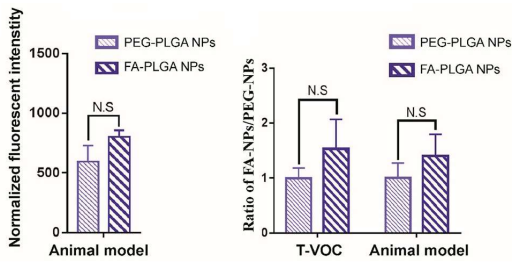
98

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

Microfluidic devices

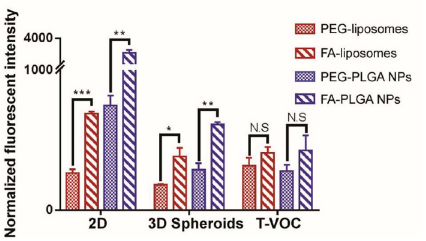
- NP accumulation *in vivo (influence of ligands)*





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

Better mimicking the in vivo tumor microenvironment

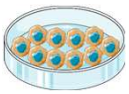


- 2D monolayer: FA-modification promotes NP uptake
- 3D tumor spheroids: less significant
- Microchip & in vivo: non-significant

Better mimicking the in vivo tumor microenvironment

99

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

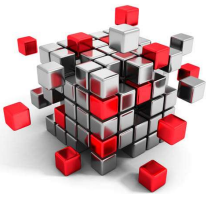
100

Conclusions

What is your question?

Simple question: use a simple model

Complex question: go to a more complex model



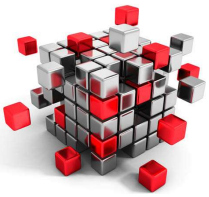
101

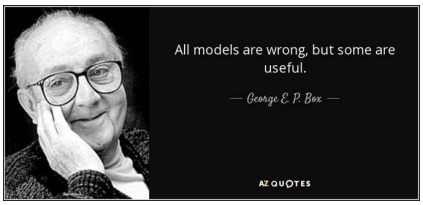
Conclusions

What is your question?

Simple question: use a simple model

Complex question: go to a more complex model





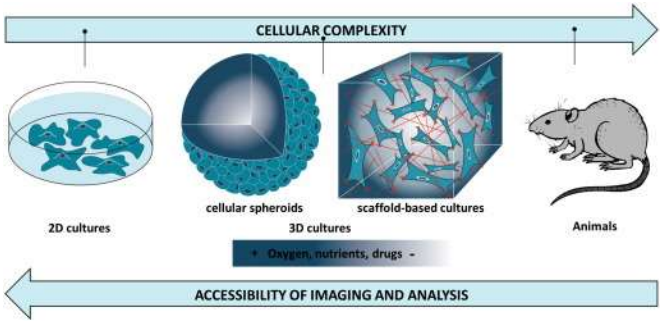
102

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



103

104

105

106