Nanomedicine:
Theranosis Toward Personalized Medicine

Summarized by
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(Cited materials available in courtesy of
Prof. S.H. Yuk @ KU and Prof. I.C. Kwon @ KIST & KU-KIST)

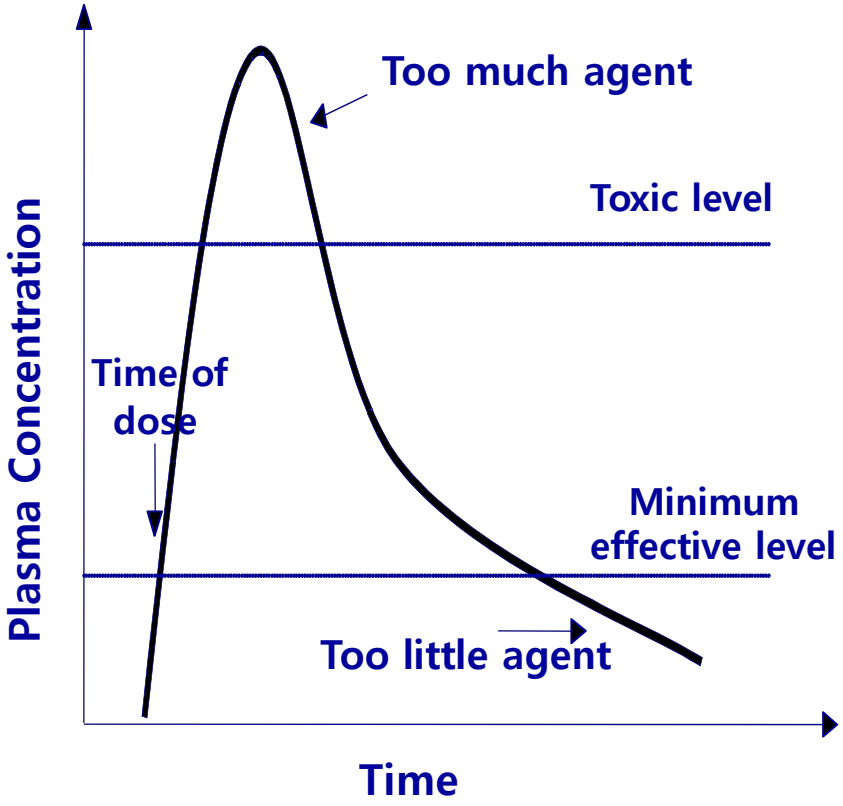
Angiogenesis

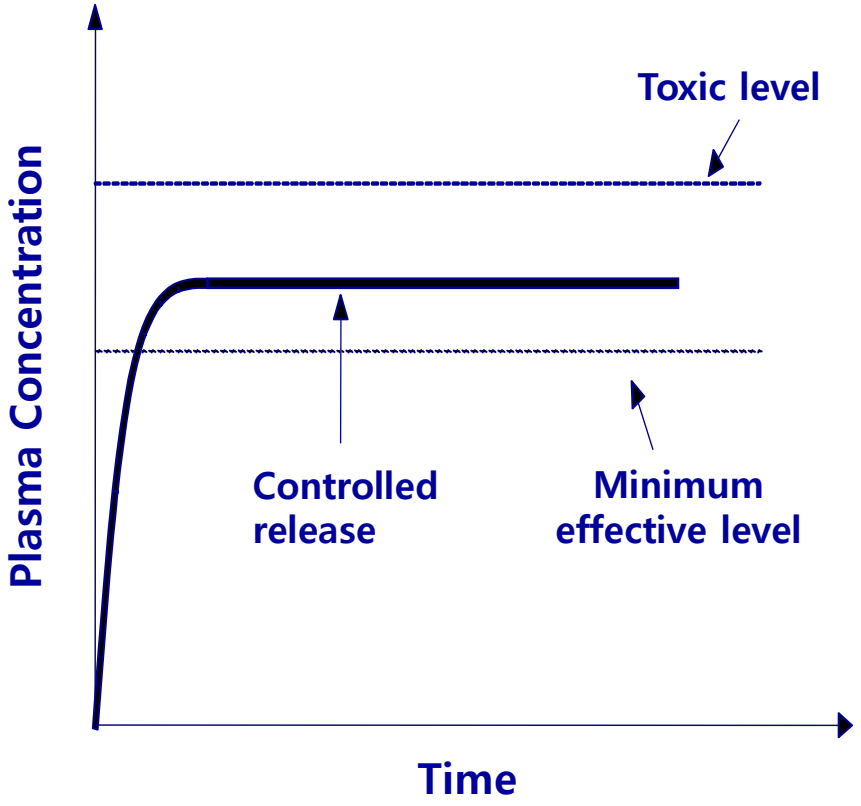
https://www.youtube.com/watch?v=LwAiyDUgALk

https://www.youtube.com/watch?v=5ps6atTqXn8

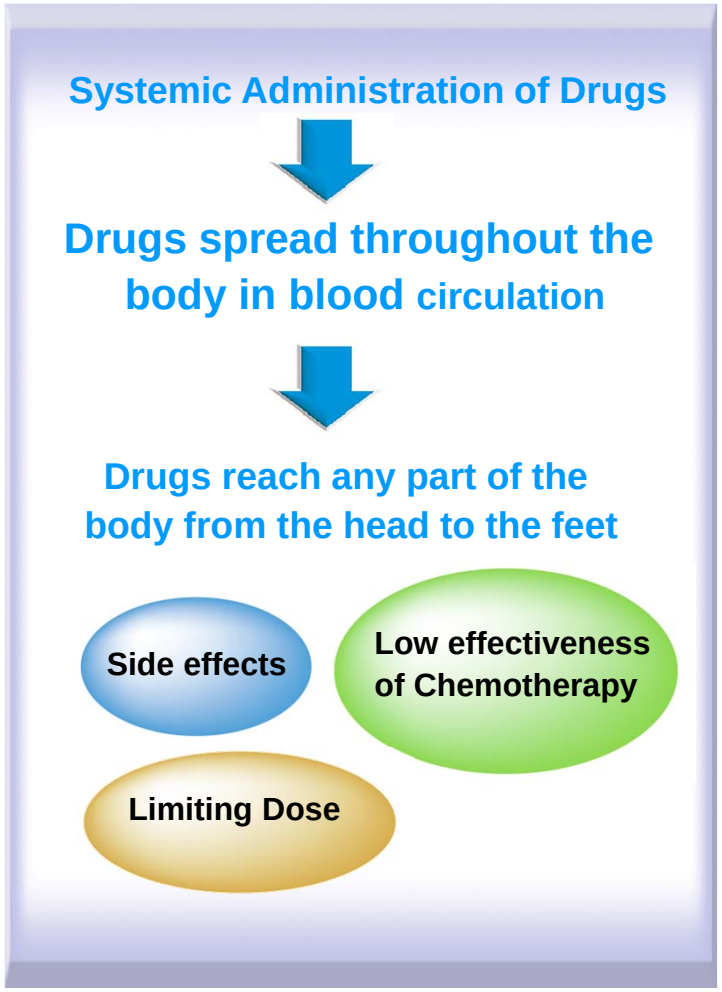
Metastasis

https://www.youtube.com/watch?v=rrMq8uA_6iA


Too much agent
Toxic level
Plasma Concentration
Time of dose
Minimum effective level
Too little agent
Time


Toxic level
Plasma Concentration
Controlled release
Minimum effective level
Time

LOCALIZATION OF THERAPEUTIC AGENTS



Two different approaches for
"Localization of Therapeutic Agents"

- **TARGETING**
- **LOCAL INJECTION**

TWO KEY TECHNOLOGIES FOR INJECTABLE DRUG DELIVERY

"Injectable Drug Delivery: Probing the Route to Growth"
reported by Datamonitor (2004)

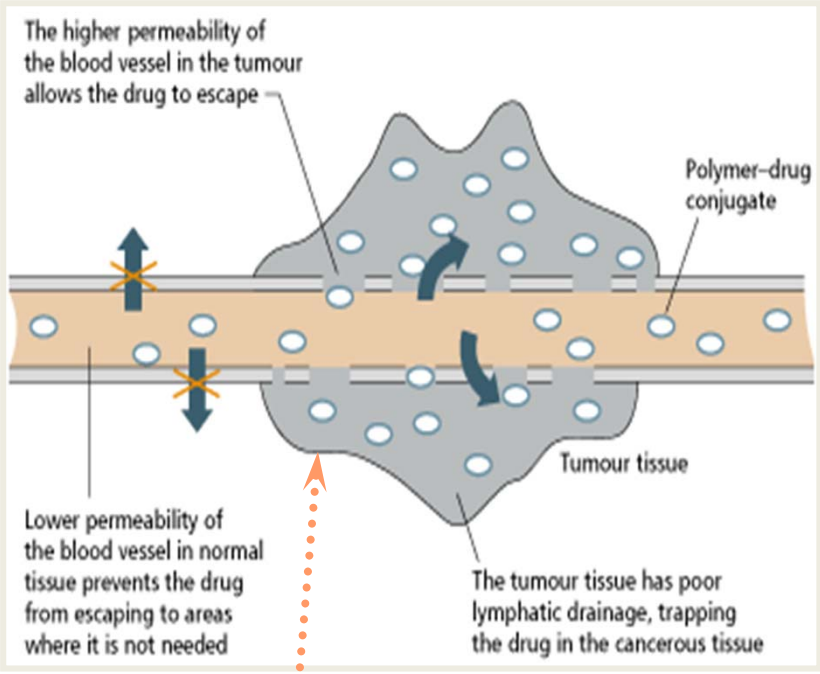
Depot Systems

- Wafers, Liposomes, Microspheres, Injectable Gels
- Sustained release of drugs
- Easily administered
- Readily accepted within the body

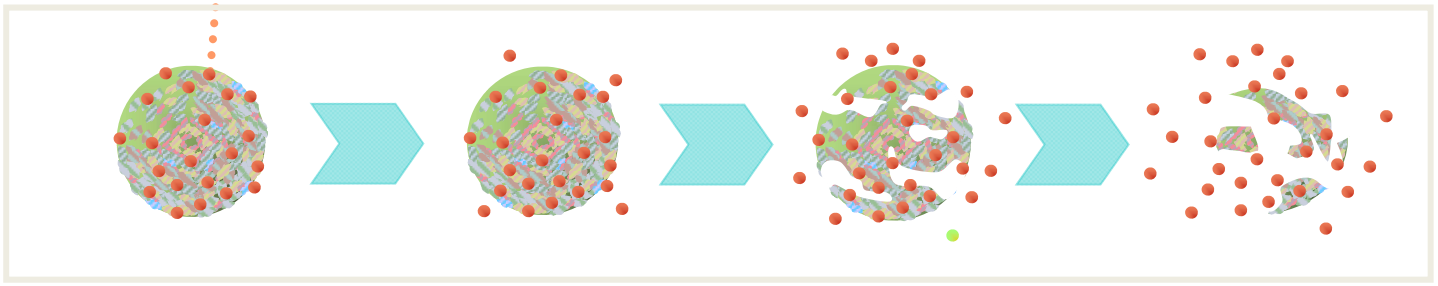
PEGylation

- Optimizing pharmacokinetics
- Increasing bioavailability
- Decreasing immunogenicity
- Decreasing dosing frequency

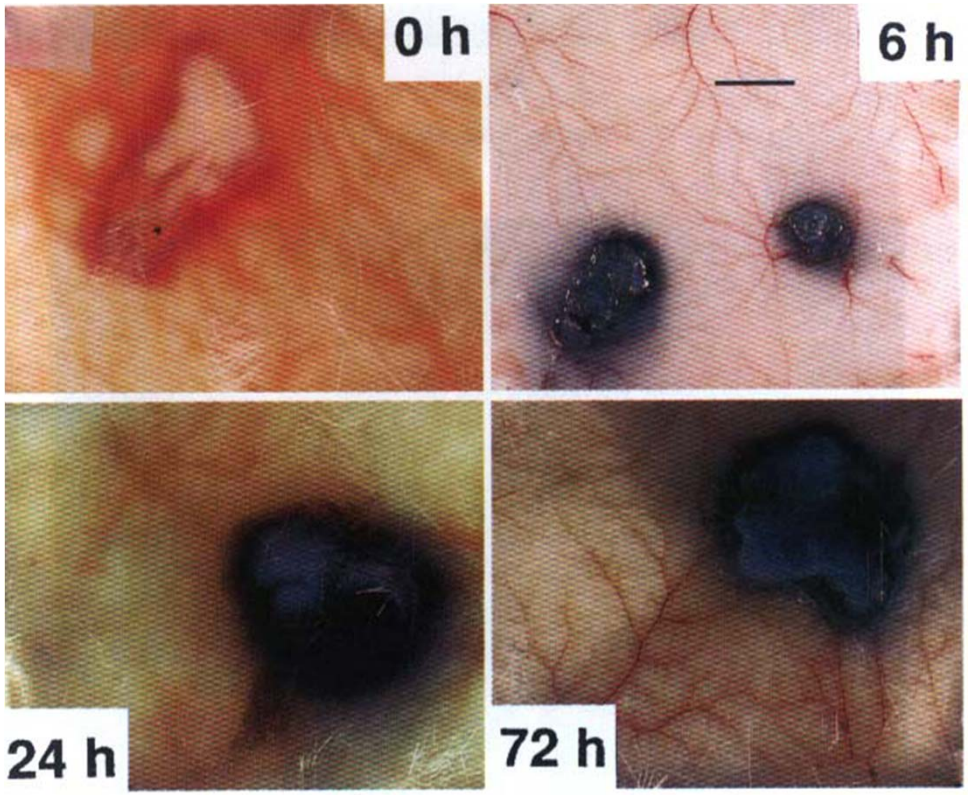
Targeting with Polymeric Nanospheres



- By considering the size of nanosphere, the possibility of the passive targeting to the specific tumor cells is under study based on the **enhanced permeation and retention (EPR) effect**.

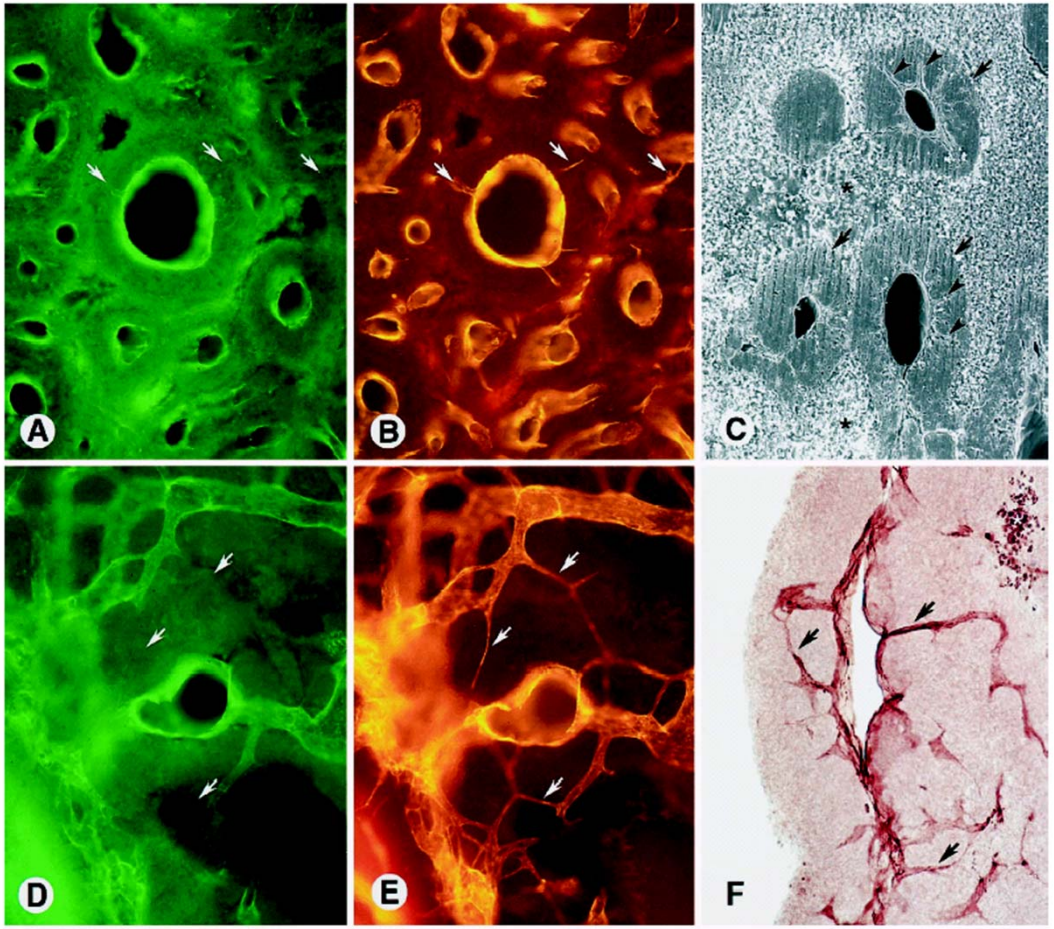


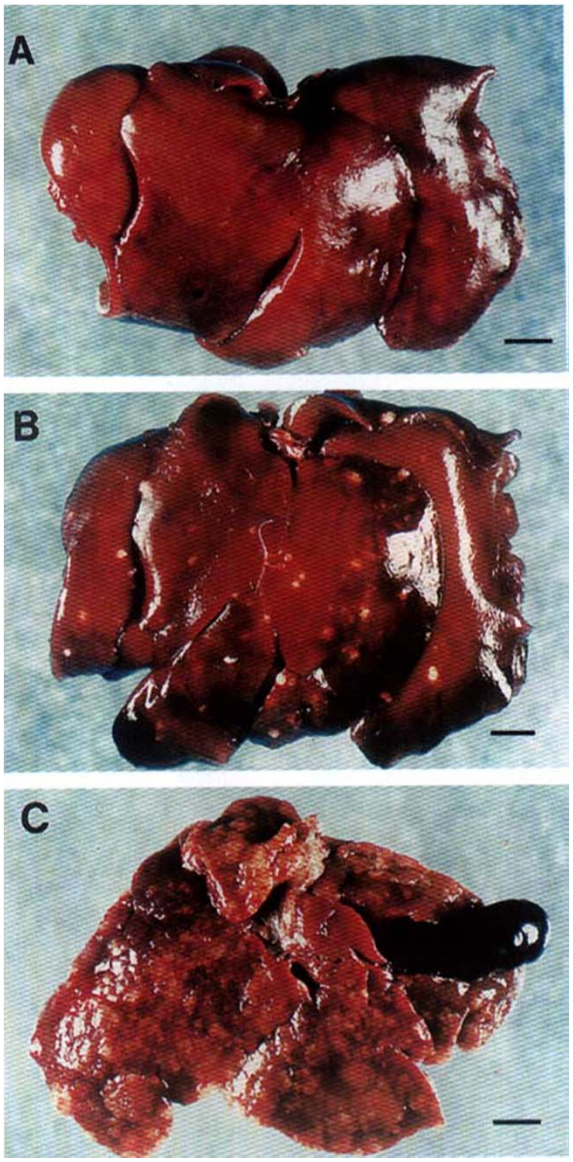
EPR effect에 의한 종양 선택성



Accumulation of Evans blue-albumin complex in tumor tissue and normal skin in tumor-bearing mice. Tumor S-180 was injected into the skin.

Blodd Vessels in MCa-IV Tumors





암조직 생성의 억제

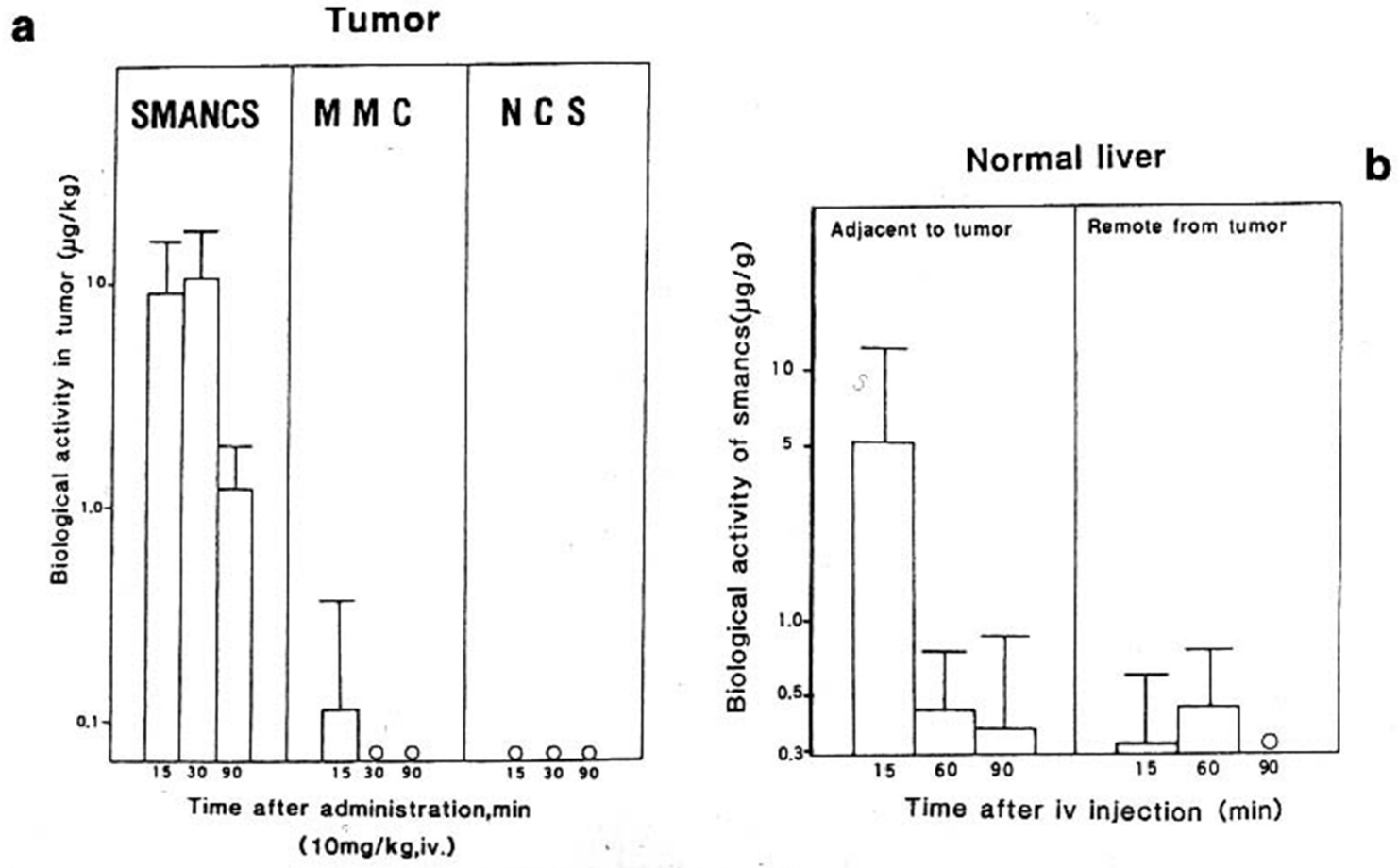
Suppression of metastatic liver tumor by Lipiodol/SMANCS

A: Lipiodol/SMANCS
(0.4mg/0.4ml/kg)

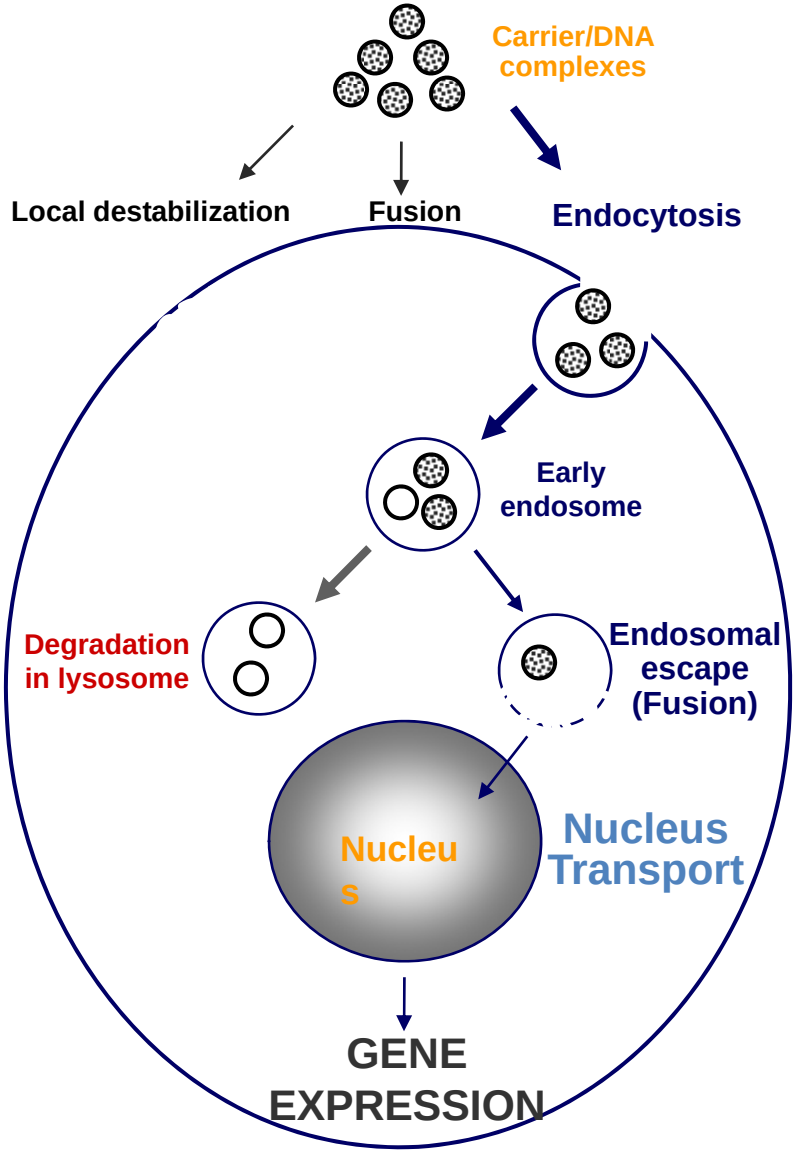
B: Lipiodol/SMANCS
plus free lipiodol
(0.4mg/0.4ml/kg)

C: No drug control
(more than 500 tumor nodule)

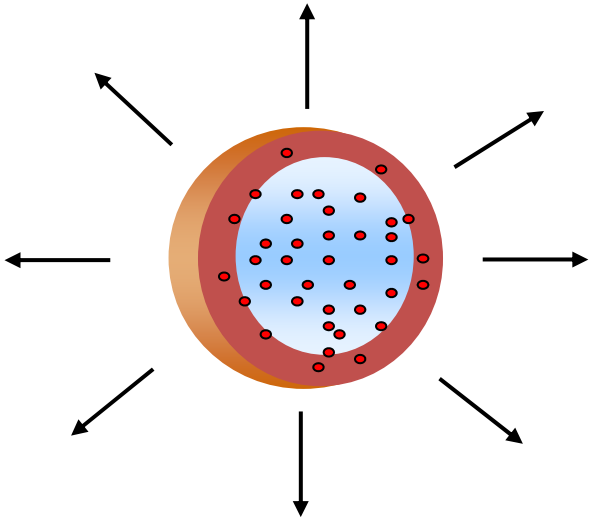
SMANCS의 암조직 선택성



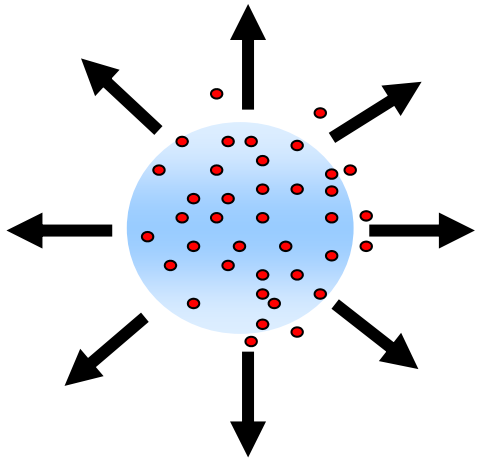
Transfection Pathways of Lipid carrier/DNA Complexes



As an effective oil-soluble drug carrier, lipid and mixed micelle have been developed. However, lipid-based drug carriers composed of a single lipid phase have several inherent problems, including the burst effect and difficulty in achieving zero order release. To overcome these difficulties, the core/shell nanoparticles with drug-loaded lipid core was prepared and characterized as a function of the thickness of polymeric shell.

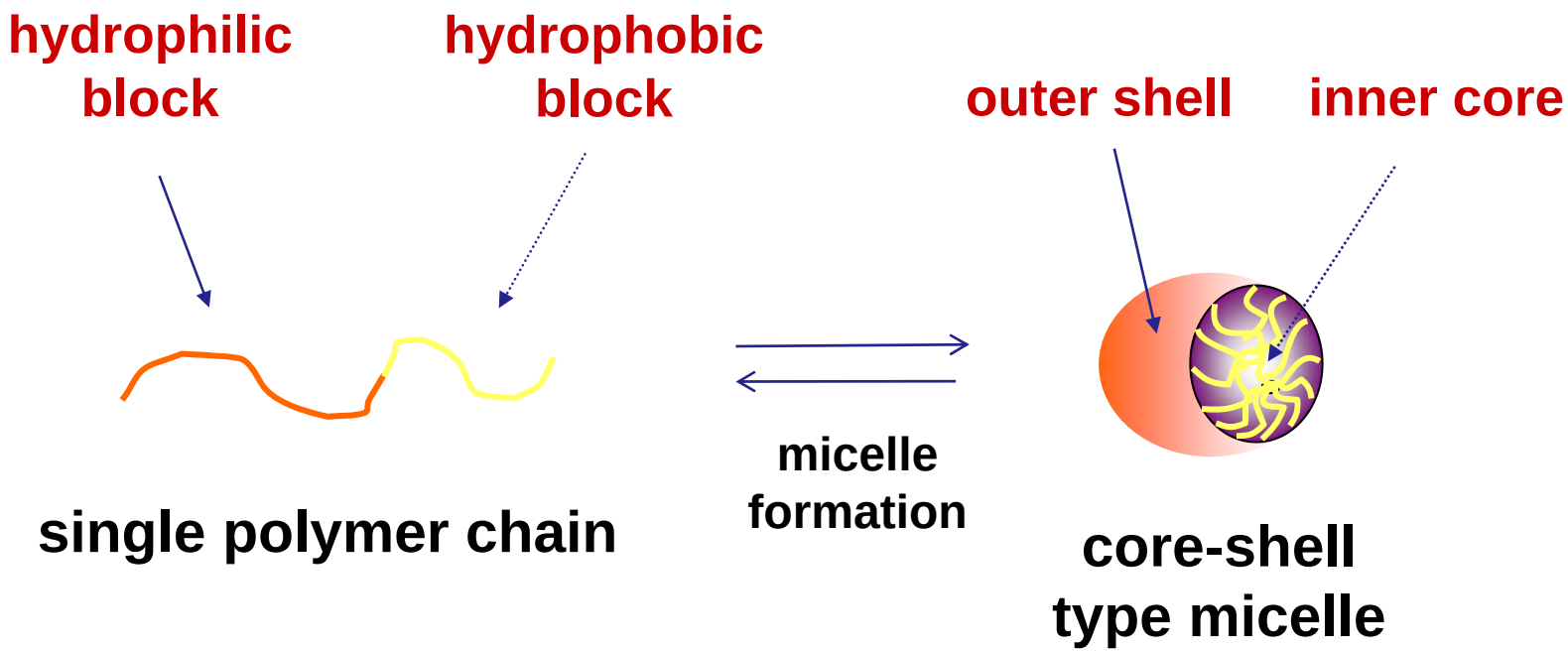


the controlled release



the burst effect

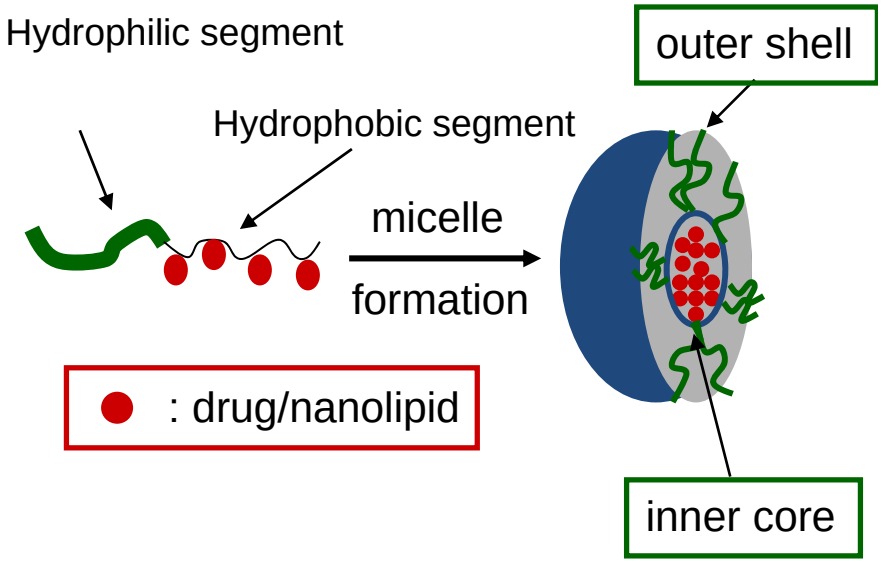
Self-Assembly of Amphiphiles into Micelles or Liposomes



Micellar Structure for Drug Delivery

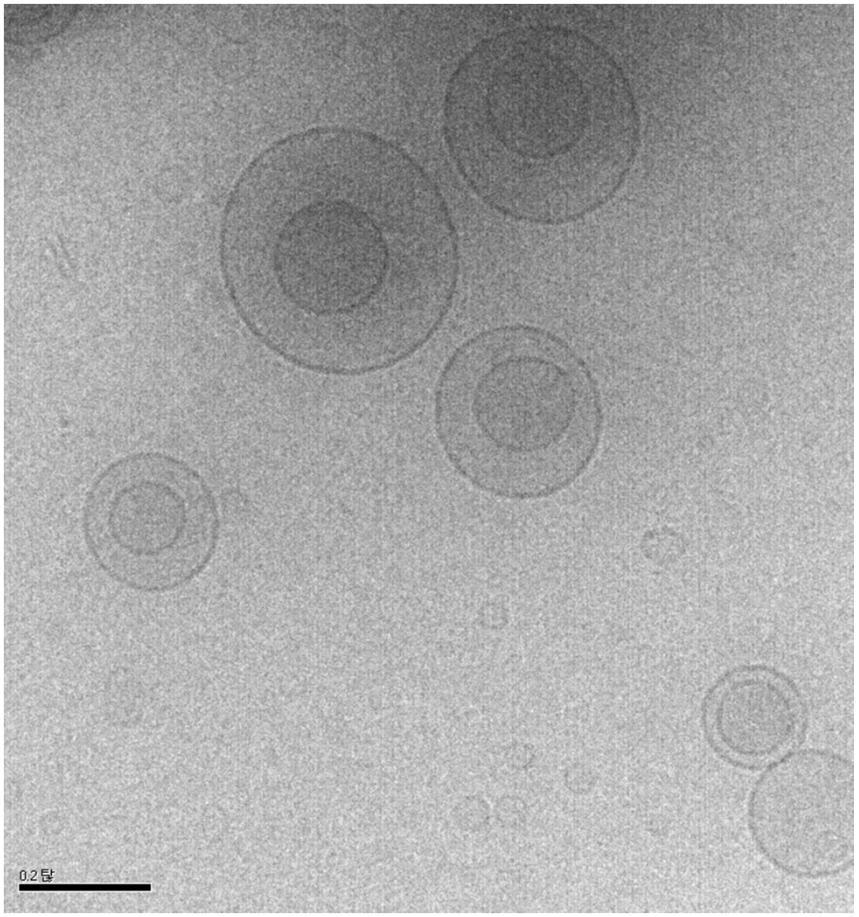
- **Micelle has unique structure which consist in hydrophilic surface an hydrophobic core.**
  - **Hydrophilic surface : Contact with aqueous millieu**
  - **Hydrophobic core : Contained hydrophobic drug**

- **Very useful of long blood circulation and passive tumor targeting**



Architecture of block copolymer micelles

Cryo-TEM Pictures

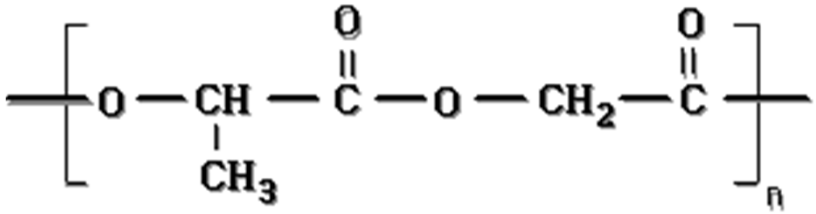


PLGA

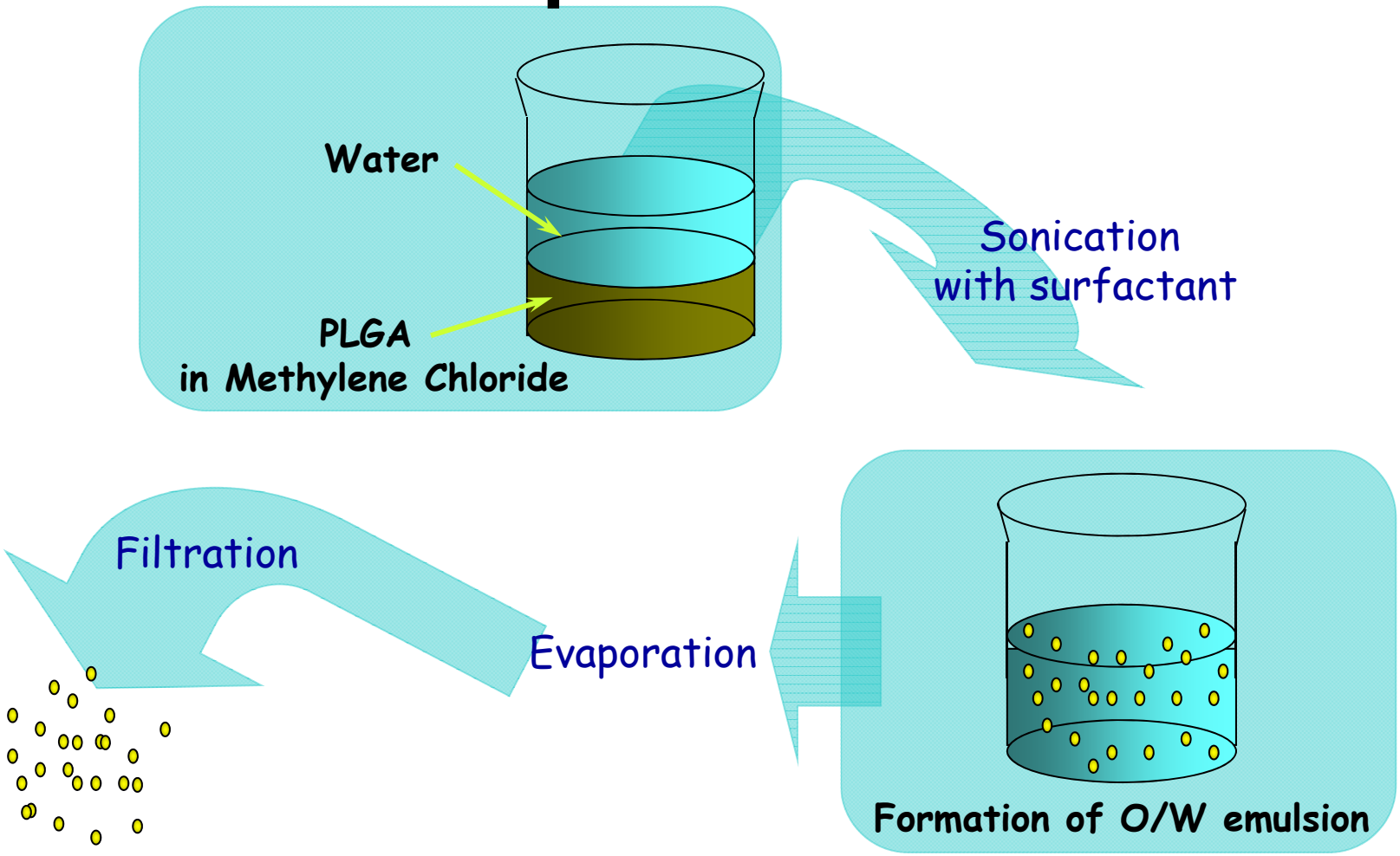
o Copolymer of lactide and glycolide: Poly(D,L-lactide-co-glycolide), Amorphous and water-insoluble polymer

o Biodegradable polymers approved by FDA for medical application such as suture

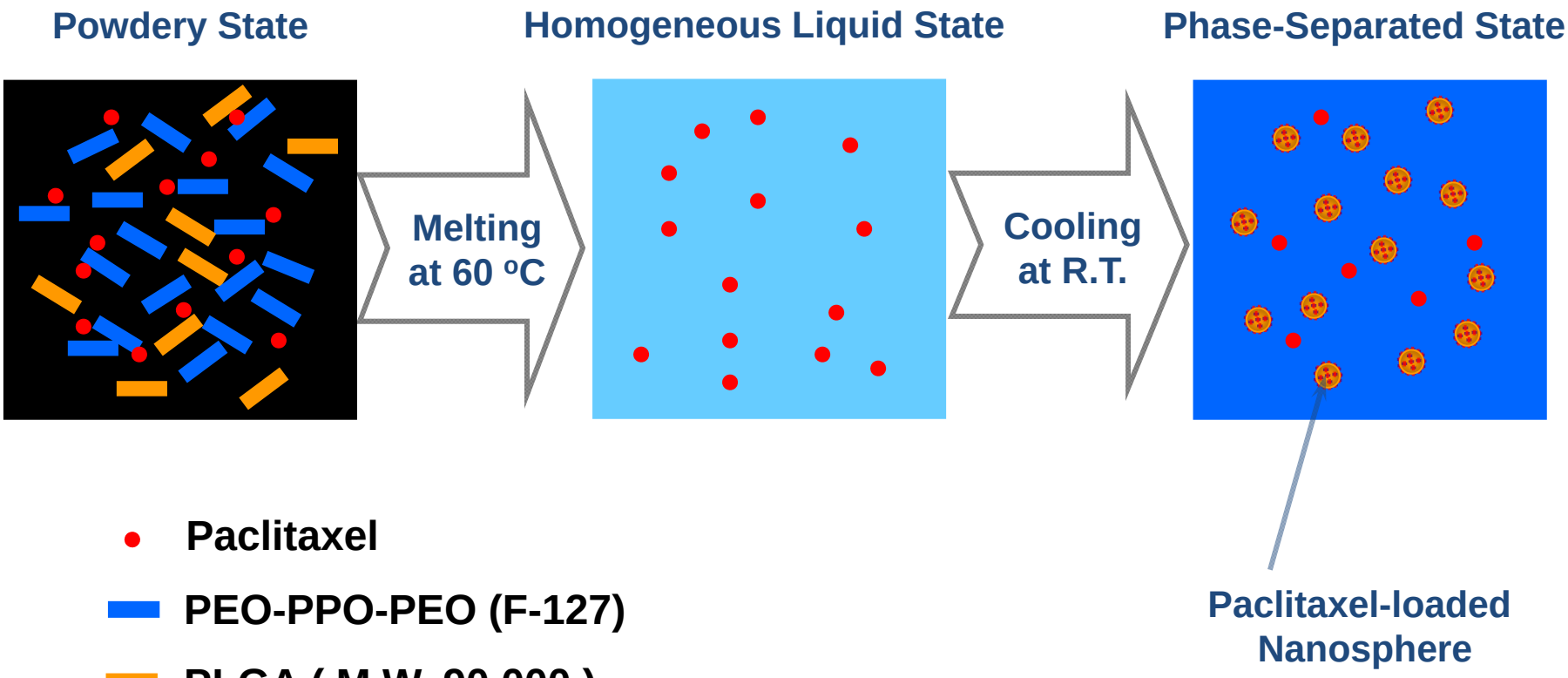
	PGA	*PLLA*	*PLGA (75 : 25)*
Degradation Time	*2~4 months*	*18~24 months*	*6 months*
Crystallinity	*Crystalline*	*Crystalline*	*Amorphous*
Glass Transition Temperature (Tg)	*35 ℃*	*45~60 ℃*	*45~55 ℃*
Melting Temp. (Tm)	*225 ℃*	*175~185 ℃*	*-*



Solvent Evaporation Method



Paclitaxel Loading



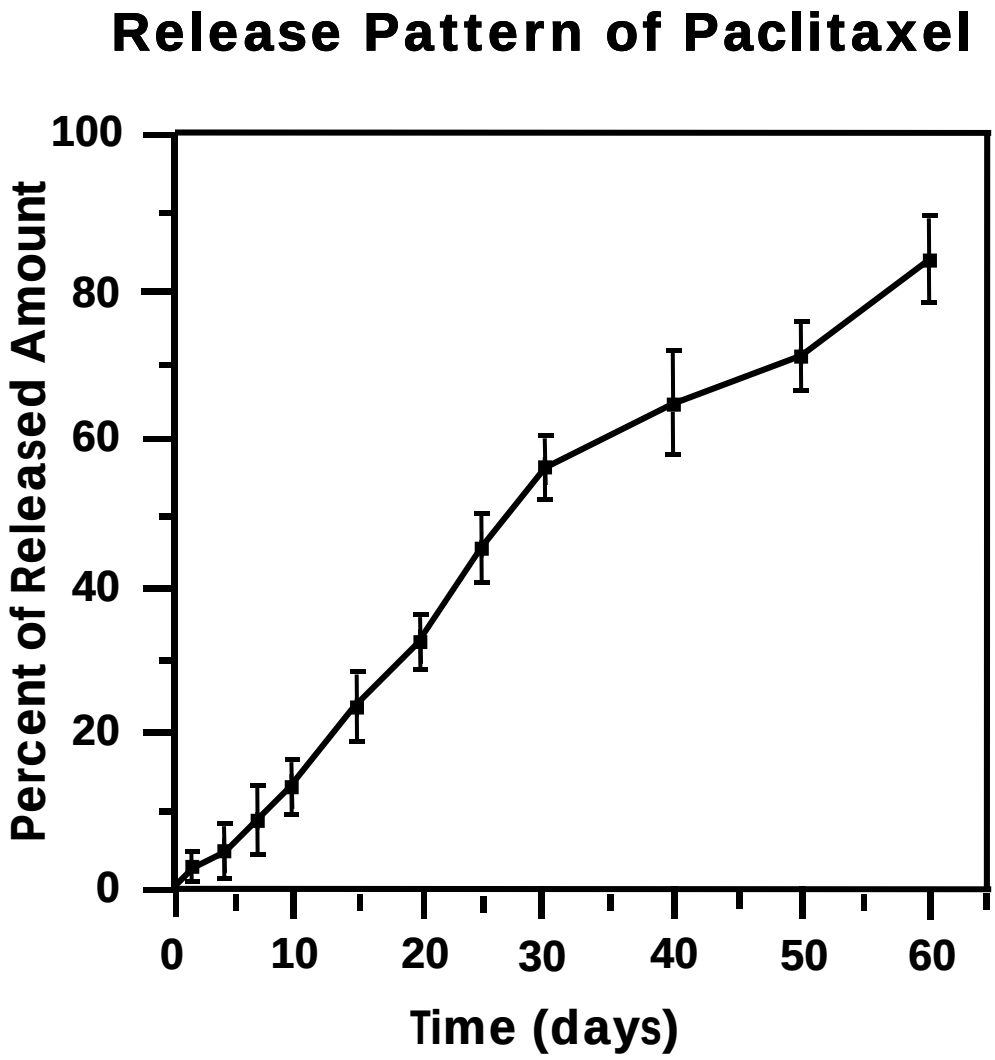
Paclitaxel Loading (Example)

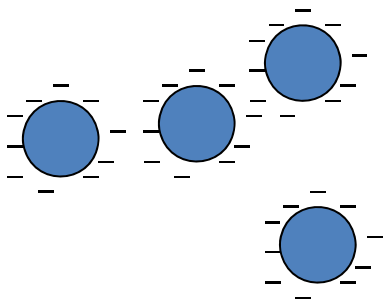
Polymer Mixture	*Characteristics*		
	Loading Amount (wt%)	*Encapsulation Efficiency*	
5/5(w/w)F-127/PLGA	-	-	×
6/4(w/w)F-127/PLGA	5.7	20.7	×/○
7/3(w/w)F-127/PLGA	9.1	21.2	○
8/2(w/w)F-127/PLGA	10.8	28.4	○
9/1(w/w)F-127/PLGA	7.4	12.3	○

Physical Loading into Self-Aggregates

(Example)

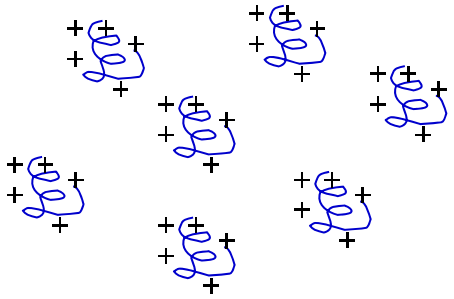
Polymer(mg)/water(ml)	DOX(mg)	Actual loading (w/w,%)	Loading efficiency (%)	Diameter 전/후(nm)
5/10 (#1)	1	18.9	94.33	238 (378)
5/10 (#2)	2	38.9	97.23	189 (342)


Release Pattern of Paclitaxel
Percent of Released Amount
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (days)

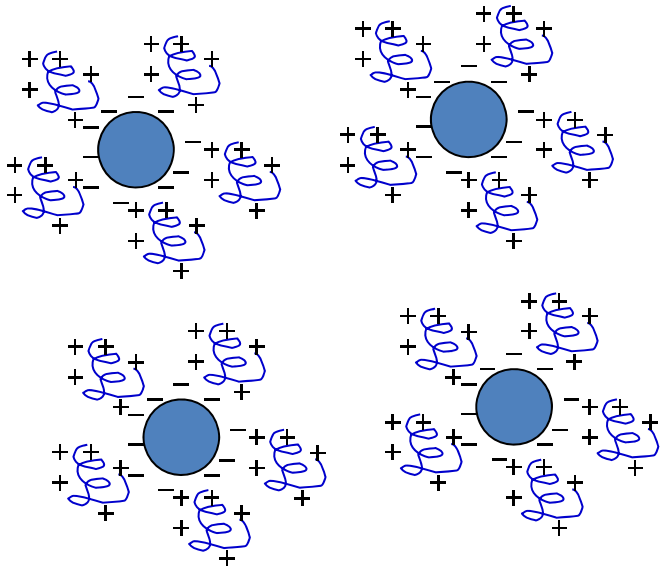


Anionic Lecithin Nanolipid

+



Proteins with high isoelectric point (>8)

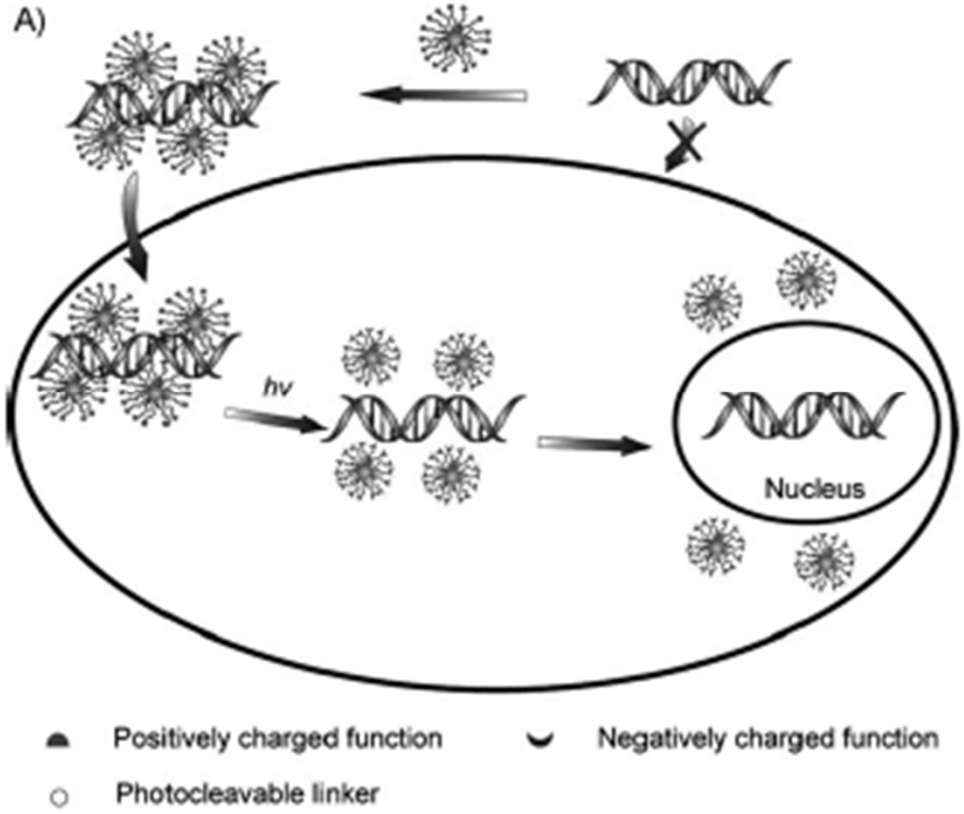


Proteins Adsorbrded Lecithin Nanolipid

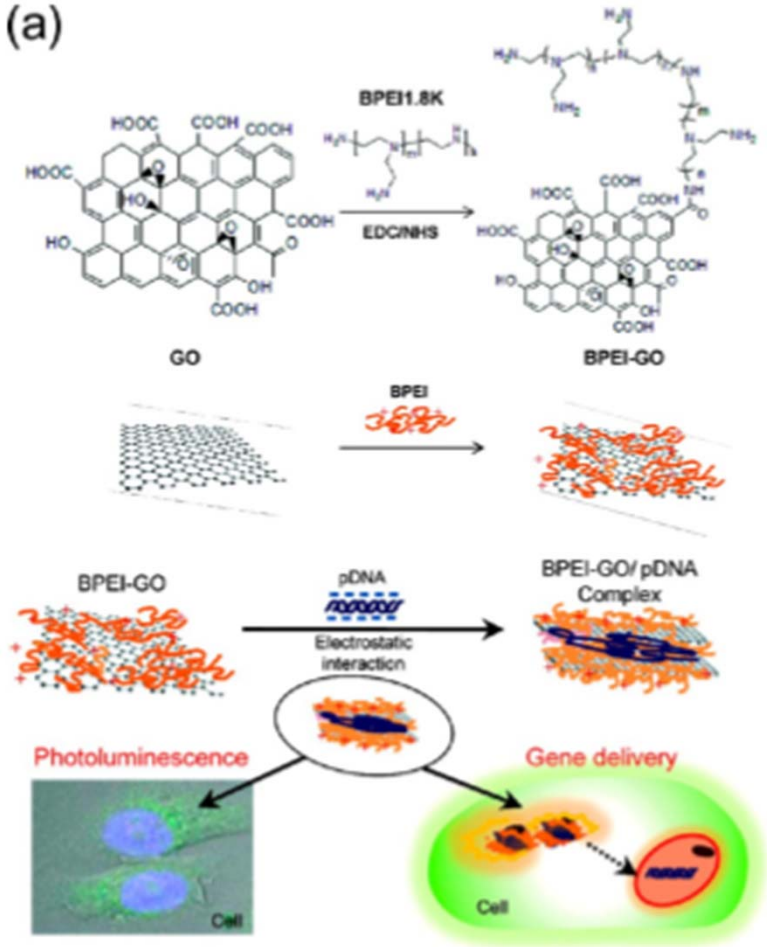
Protein-loaded Core/Shell Nanoparticles

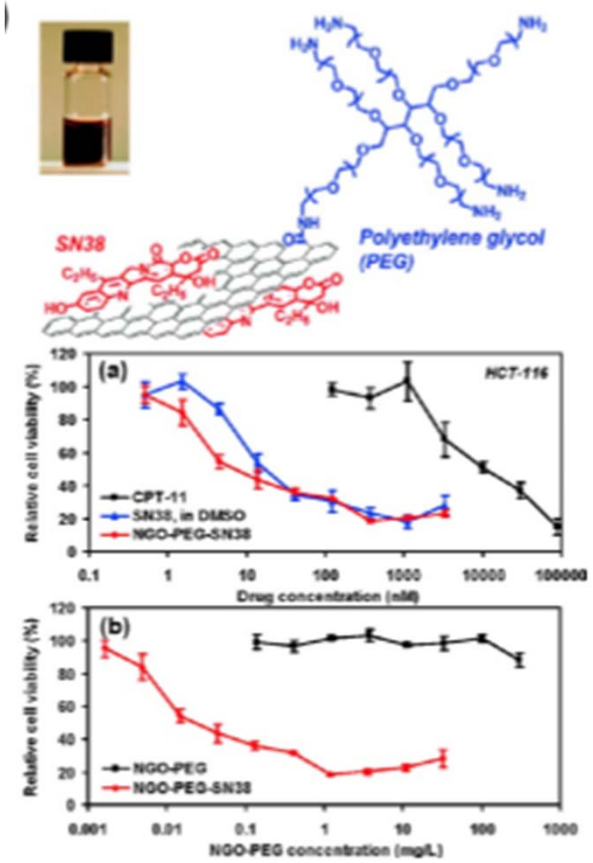
+

Gold Nanoparticles



Graphene Oxide & Graphene QD





Bio-imaging

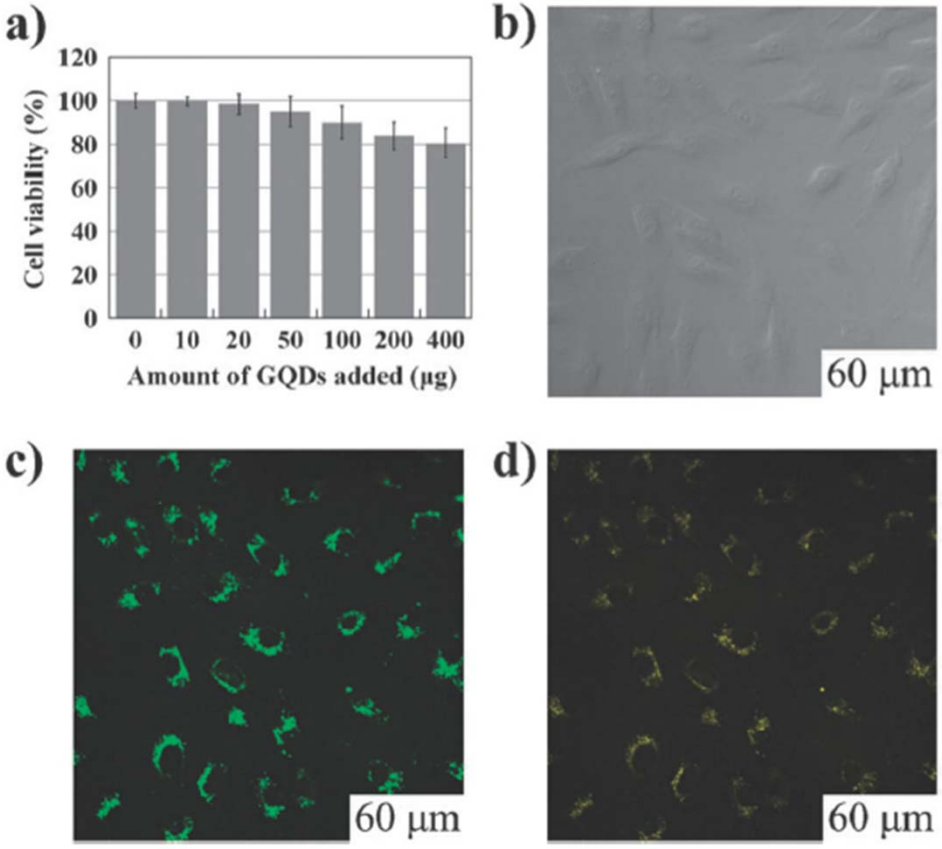
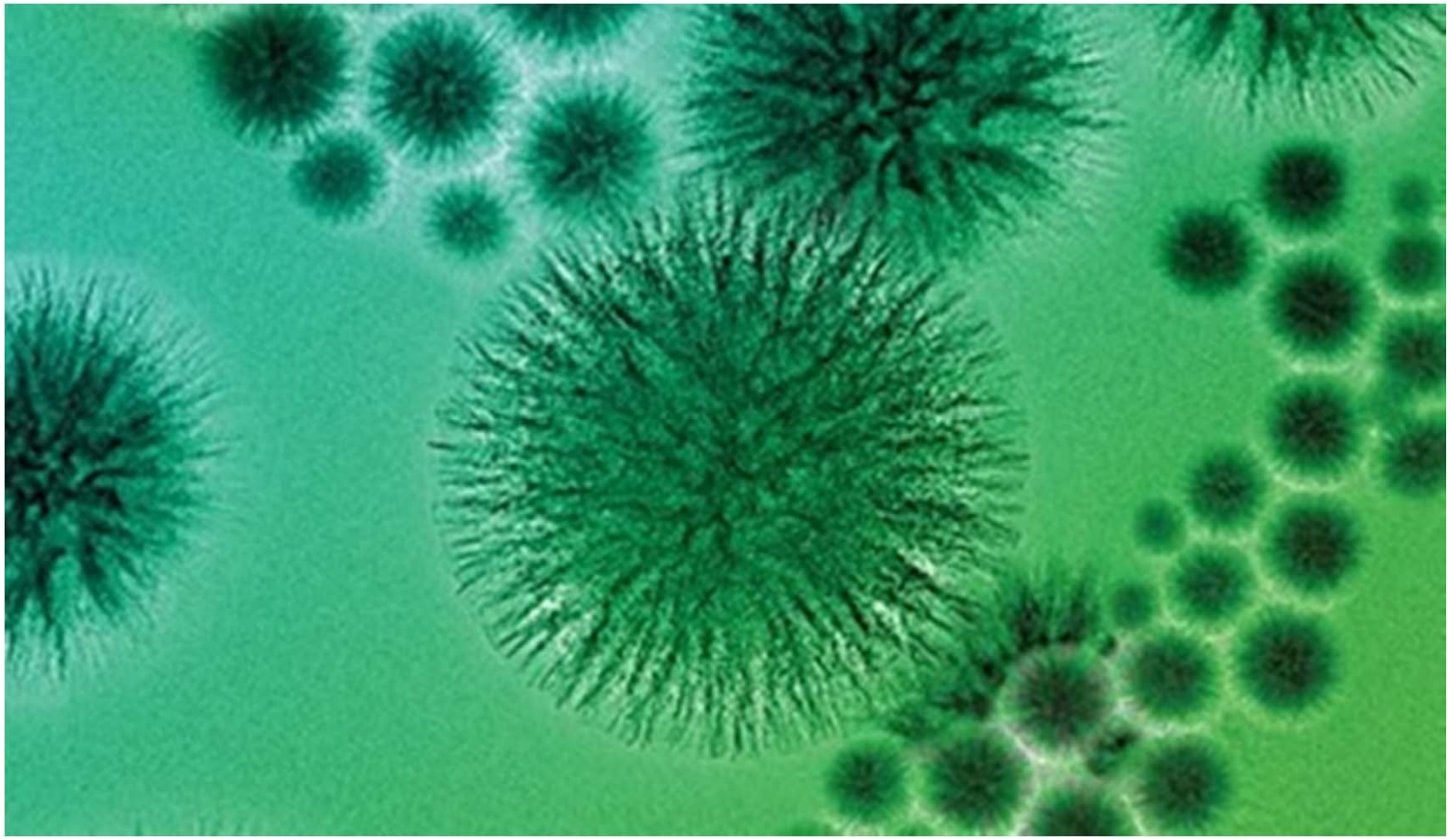
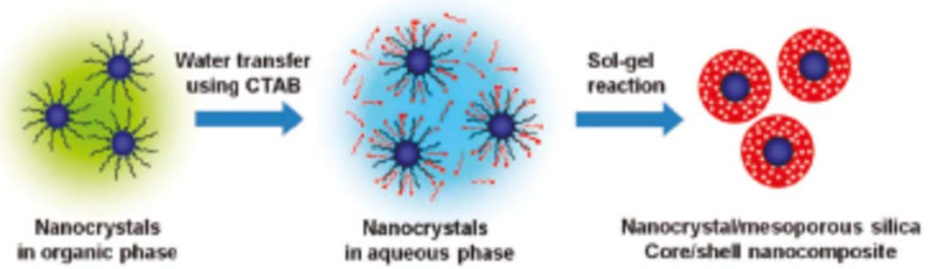
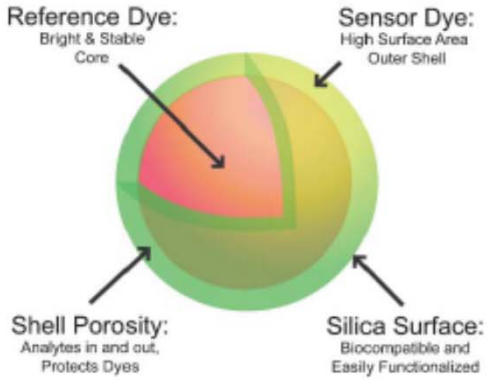


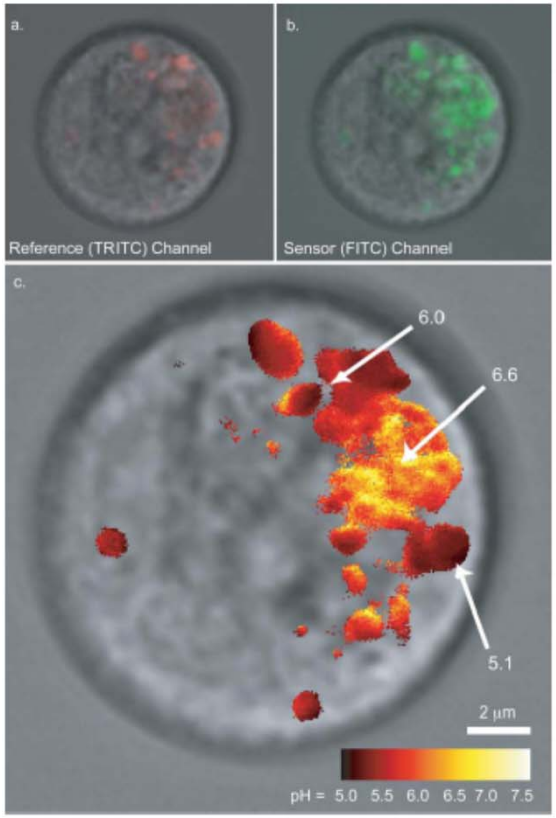
Figure 12. Cellular toxicity and cellular imaging of GQDs. a) Effect of GQDs on MG-63 cells viability. b–d) are washed cells imaged under bright field, 405 nm, 488 nm excitations, respectively. Reproduced with permission.[33] Copyright 2011, Royal Society of Chemistry.

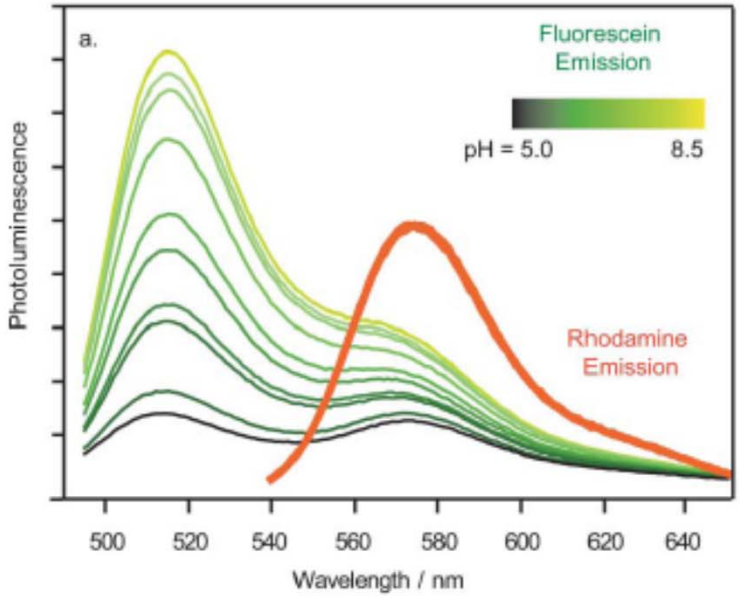
Mesoporous Silica Nanoparticles

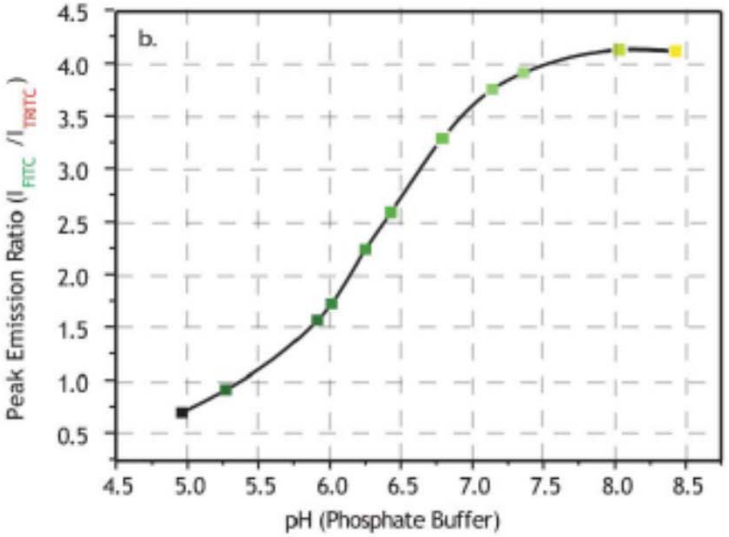





Reference Dye:
Bright & Stable
Core
Sensor Dye:
High Surface Area
Outer Shell
Shell Porosity:
Analytes in and out,
Protects Dyes
Silica Surface:
Biocompatible and
Easily Functionalized


a.
b.
Reference (TRITC) Channel
Sensor (FITC) Channel
c.
6.0
6.6
5.1
2 µm
pH = 5.0 5.5 6.0 6.5 7.0 7.5


a.
Fluorescein
Emission
pH = 5.0
8.5
Rhodamine
Emission
Photoluminescence
500 520 540 560 580 600 620 640
Wavelength / nm


b.
Peak Emission Ratio (I FITC / I TRITC)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5
pH (Phosphate Buffer)