

Research on Development and Evaluation of Delivery Systems for Precise Control of Drug Disposition

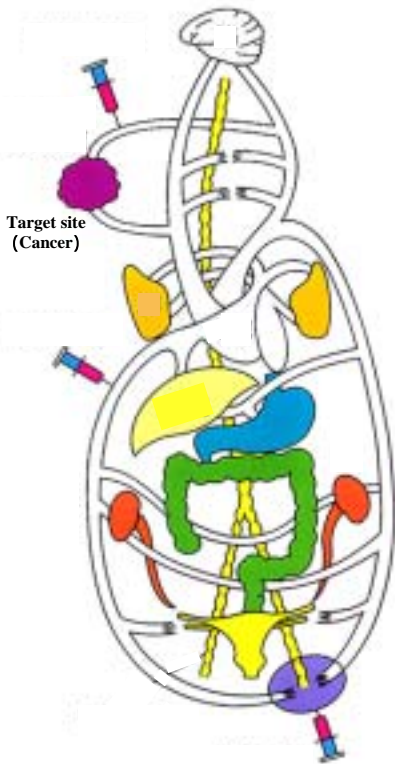
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Kyoto University

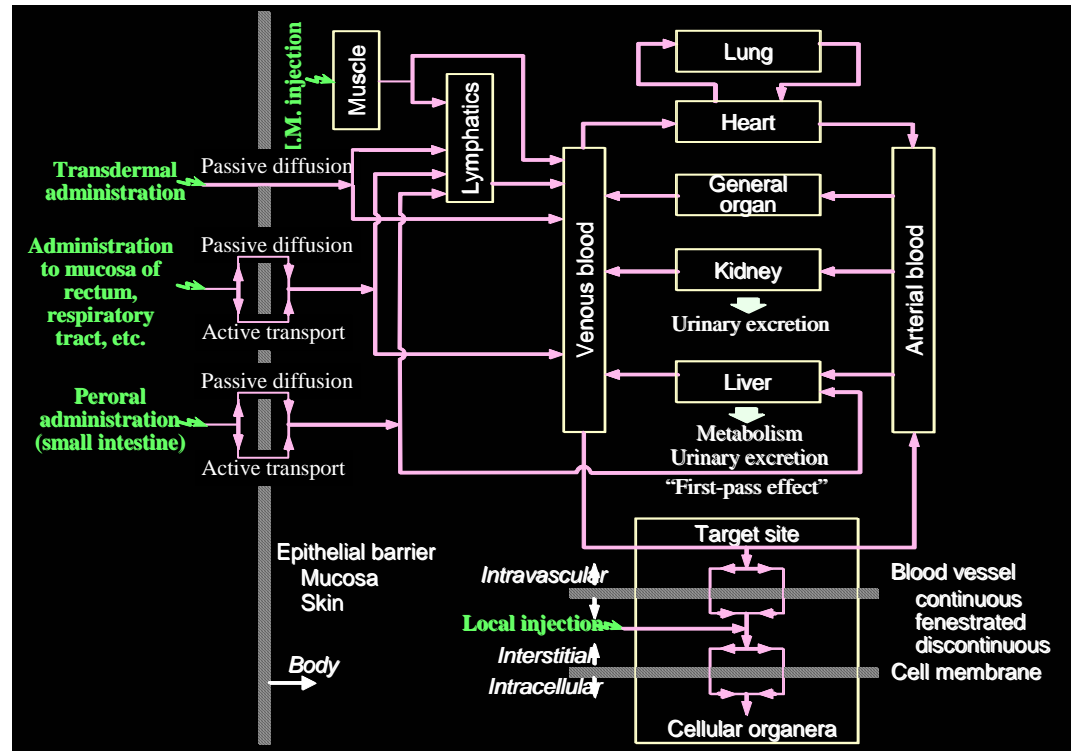
25th JSSX Annual Meeting in Tokyo
October 7 - 9, 2010

DDS (Drug Delivery System)

is a technology to control in vivo disposition of drugs precisely for achieving their optimal therapeutic efficacy

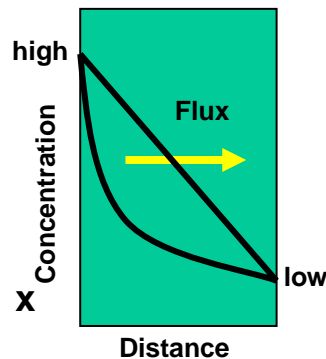


Modeling

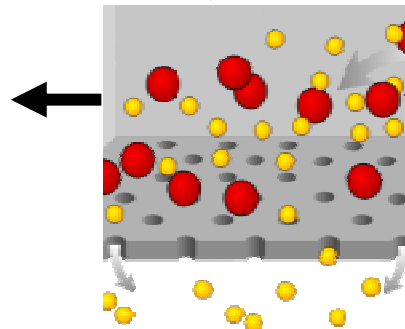


Diffusion
Fick's Law

$$C(x,t) / t = - J / x$$



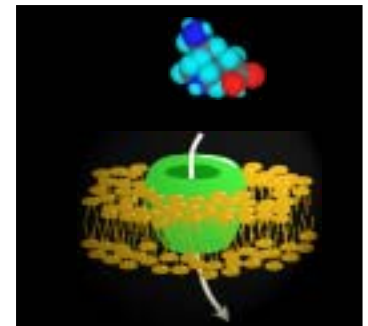
Convection and Sieving



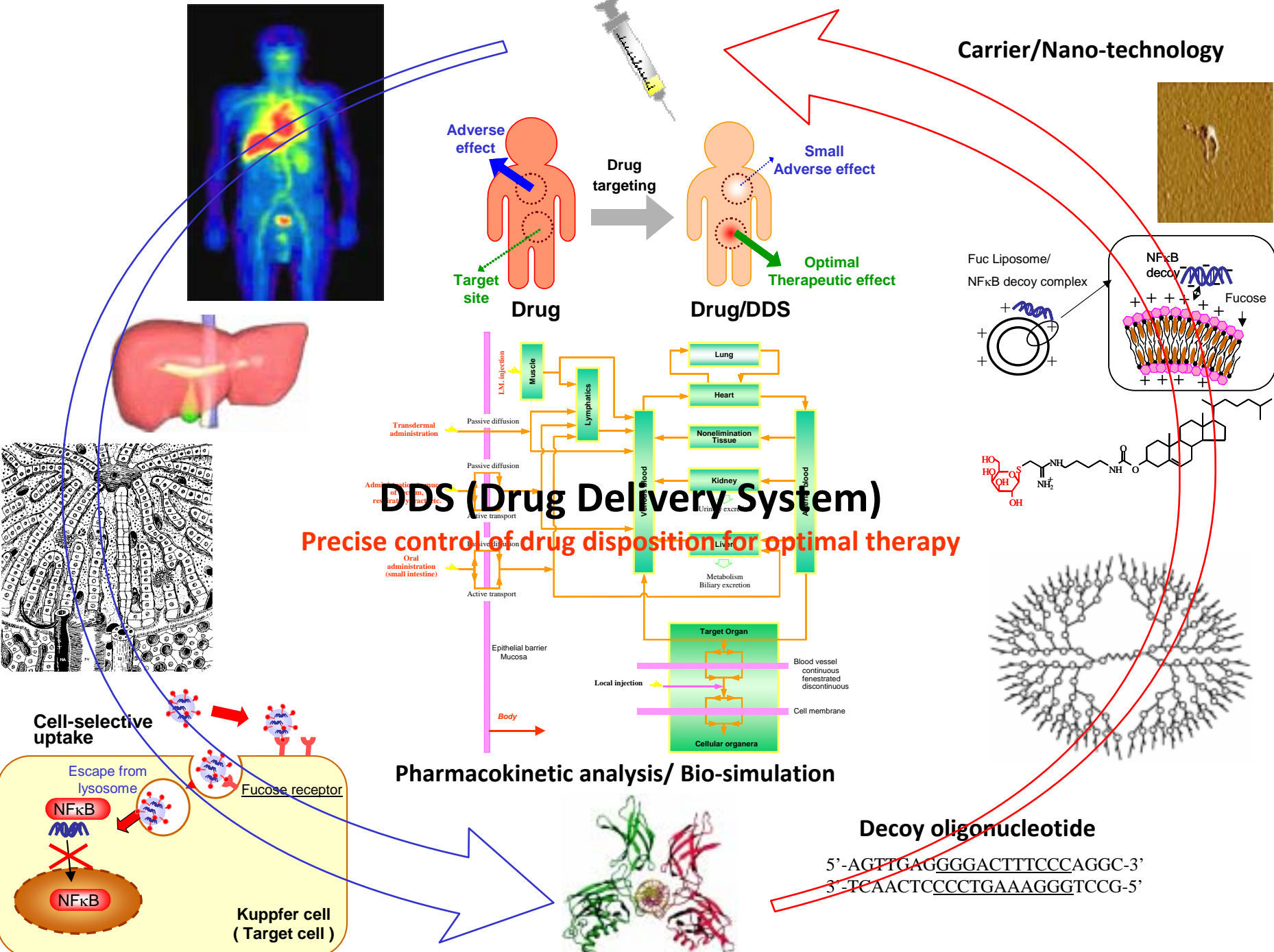
$$K = \frac{2A^2 \Delta P}{\mu \alpha c} [m^6/s]$$

$$V_0 = \frac{AR_m}{\alpha c} [m^3]$$

Active transport
By transporter



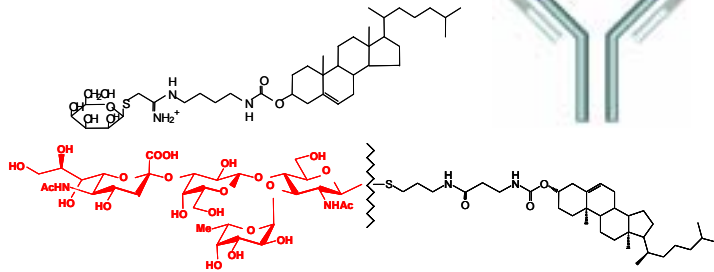
Carrier/Nano-technology



Drug Delivery for Chemo-/gene Therapy

Intracellular Delivery of Functional Materials for Cell Engineering

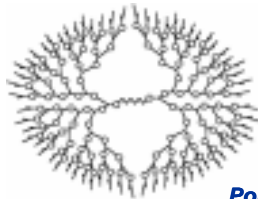
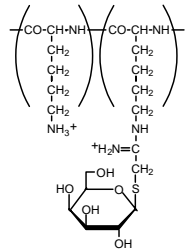
Homing Device



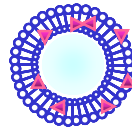
Therapeutic Drug Molecule



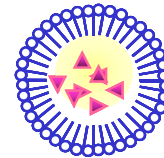
5'-GUACGUUUCAUGACCAAAA-dTdT-3'
3'dTdT-CAUGCAAAGUACUGGUUUU-5'



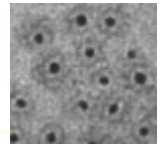
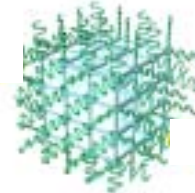
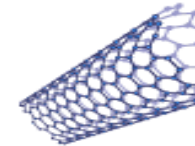
Polymeric micelles
(10-40 nm)



Liposomes
(100-130 nm)

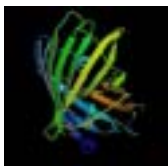


Emulsions
(130-180 nm)



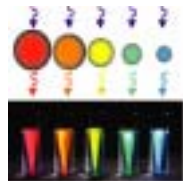
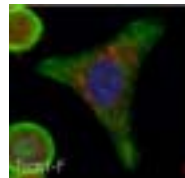
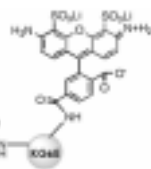
Drug Delivery → Carrier

Multi-functional Molecular Assembly → Platform



Fluorescent Protein

Fluorescent Dye



Quantum Dot

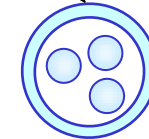


MRI
Magnetite, Gd

PET
Positron Emitter

Ultrasound
Micro-bubble

Ultrasound



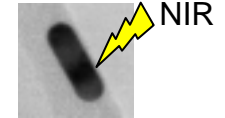
Micro-bubble

Laser beam

NIR

Carbon Nanotube

Photo-sensitizer



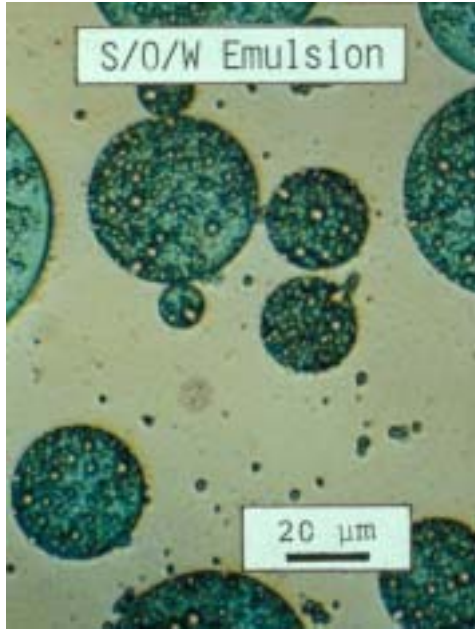
Gold nanorod

Molecule/Materials for Photo-imaging

Molecule/Materials for Diagnosis

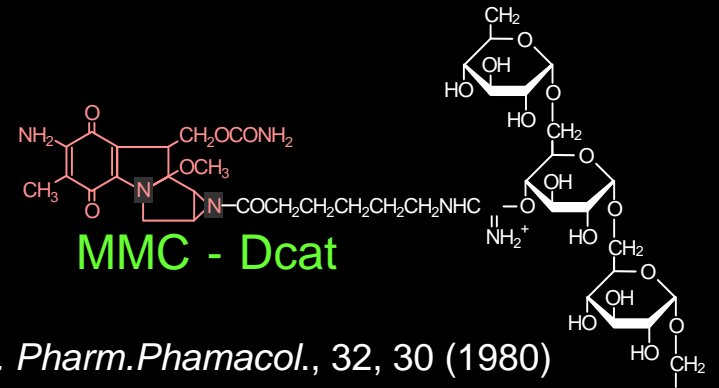
Therapeutic Material

Treatment of Cystic Hygroma by Bleomycin S/O/W Emulsion

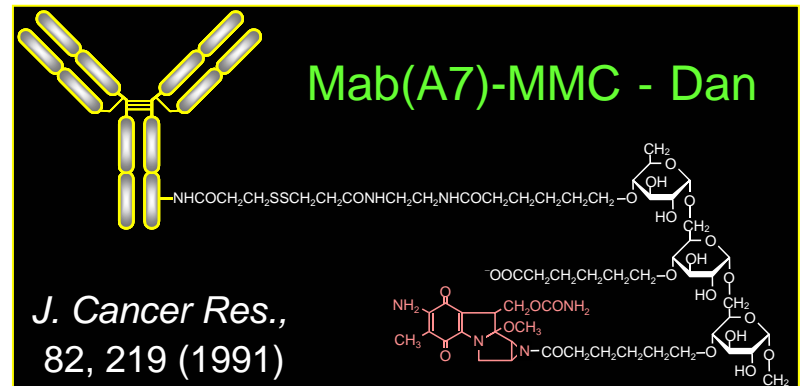


J. Pharmakokin. Biopharm. 5: 241 (1977)

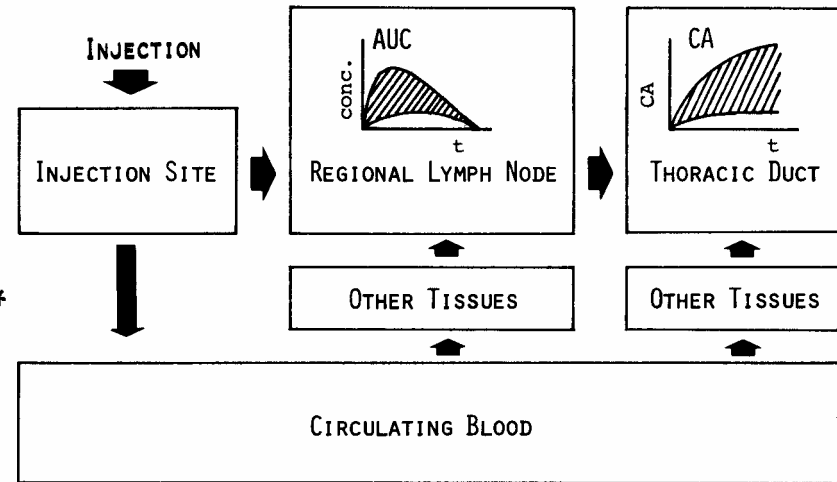
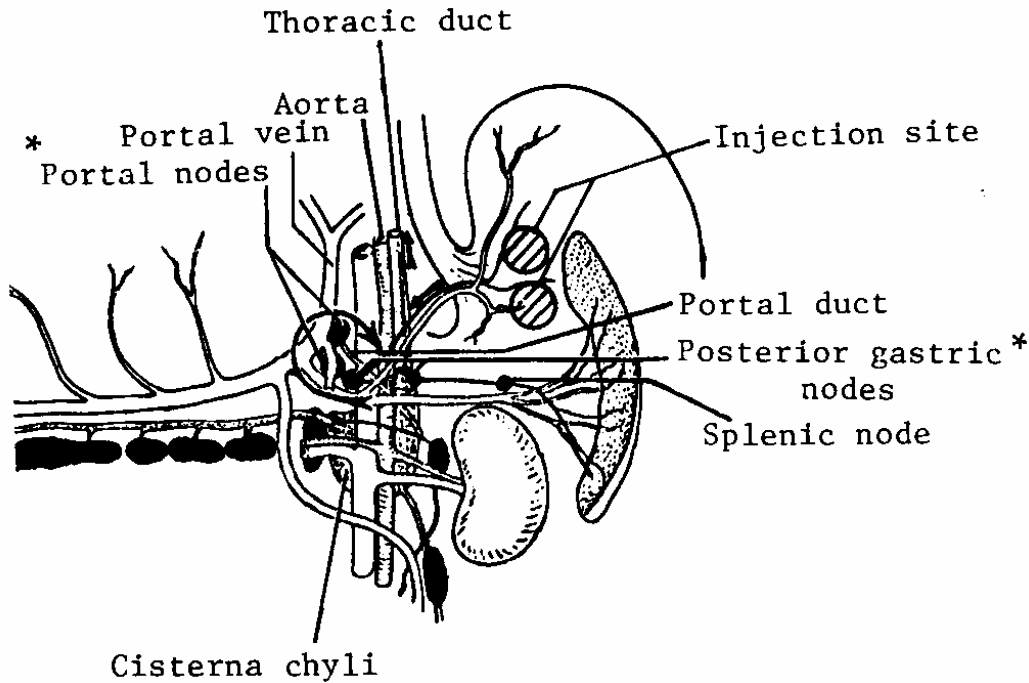
Cancer Treatment with Polymeric Produg of Mitomycin C



Cancer 60: 741 (1987)



Pharmacokinetic analysis of lymphotropicity of emulsion formulations

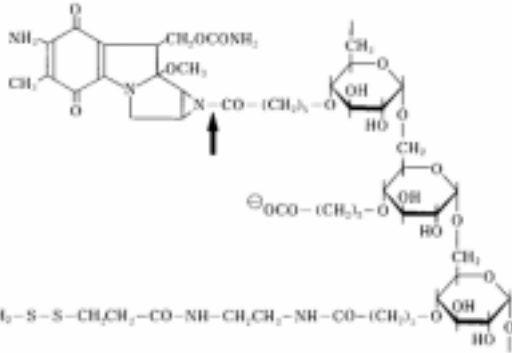


Injection Form	CA (% of dose)			
	1 hour		3.5 hours	
	Total CA	Calculated CA _{ig} -CA _{iv}	Total CA	Calculated CA _{ig} -CA _{iv}
I. V. Aqueous Solution	0.228	0	0.432	0
I. G. Aqueous Solution	0.403	0.174	0.612	0.180
W/O Emulsion	0.413	0.185	0.662	0.230
S/O Emulsion	0.712	0.484	1.121	0.690

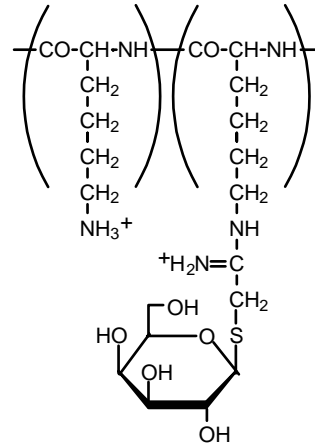
Formulation	Average Weight of Lymph Nodes(g)	Mean Transit Time (min)
Aqueous Solution	0.025	1.89
W/O Emulsion	0.023	2.80
S/O Emulsion	0.026	4.05

Polymeric Carrier

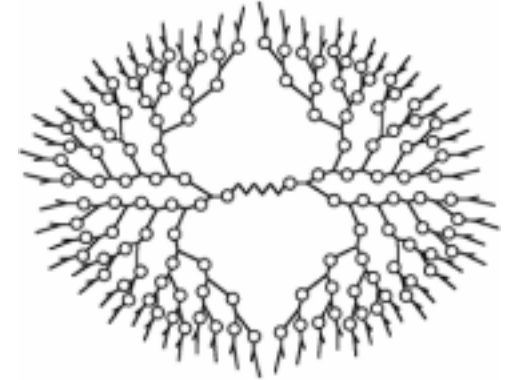
Polymer-drug conjugate



Glycosylated poly-amino acid



Amino acid dendlimer

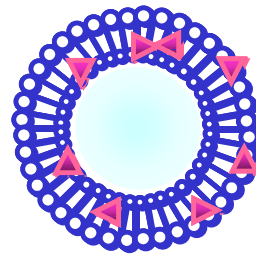


Spherical Carrier



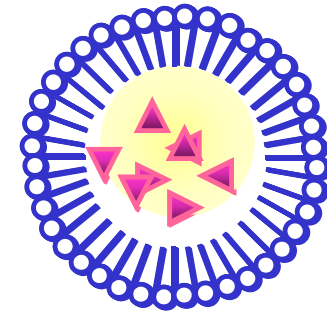
Polymeric micelles

(10-40 nm)



Liposomes

(100-130 nm)



Emulsions

(130-180 nm)

Design of Carrier

Drug Retention and Release Control

Movement Control

Escape from Non-specific Interaction

Site-specific Delivery Guidance

Theoretical Backgroud: Structure / Disposition Relationship of Macromolecular Carriers

chemical structure physicochemical/
biological properties in vivo disposition



pharmacokinetic analysis

rationalization

molecular design
(precise control of biodistribution)

Characterization of Nucleic Acid Drugs

M.W.: 8000 ~ 3000000

Polyanion

water soluble

Protein binding

(Structure dependent)

Unstability

(Structure dependent)

physicochemical properties

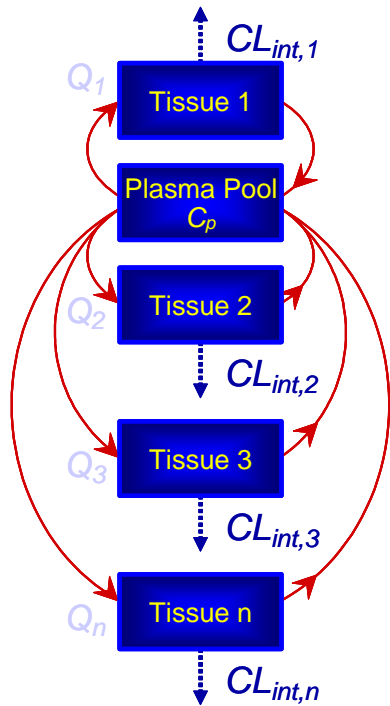
molecular size --- molecular weight, configuration

electric charge --- species, density

biological recognition mechanism (receptor-mediated endocytosis)

ligand --- structure, number, density

Organ clearances of macromolecules in the body

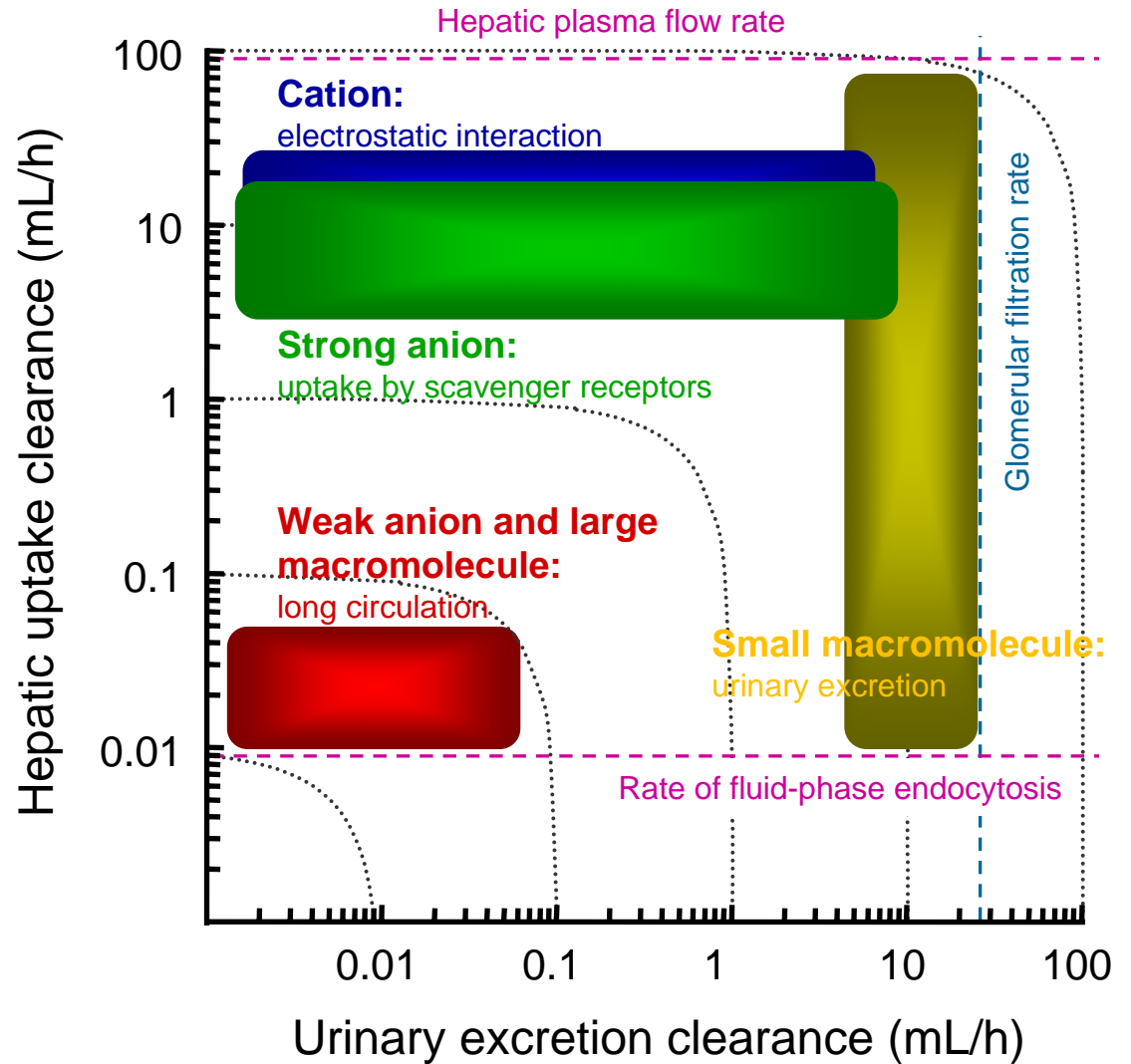


$$X_i^\infty = \frac{1}{\frac{1}{Q_i} + \frac{1}{CL_{int,i}}} AUC_p$$

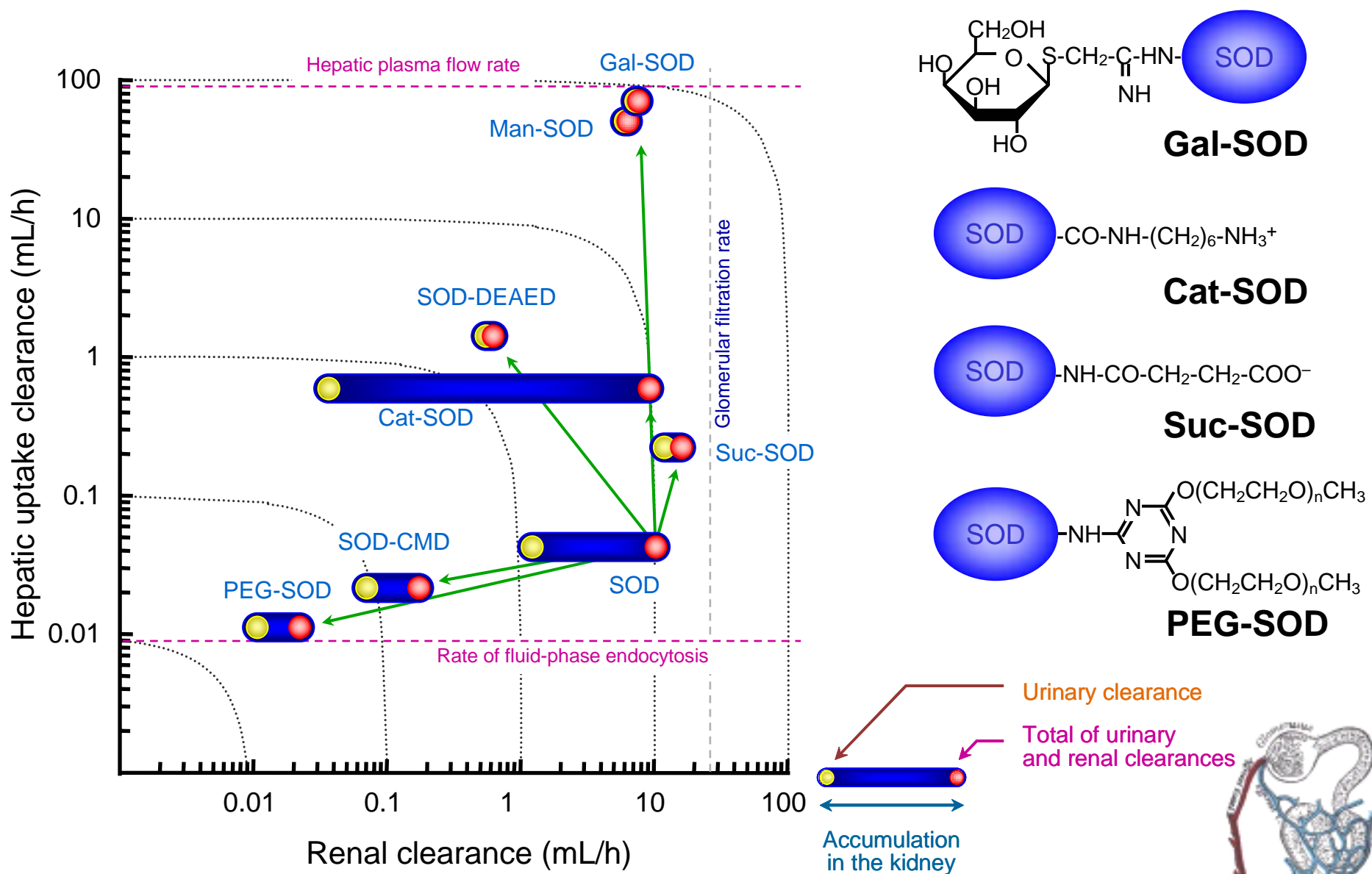
$$= CL_{org,i} \cdot AUC_p$$

X_i^∞ : total amount in organ i

AUC_p : area under plasma conc. curve



Hepatic and renal clearances of SOD derivatives in mice



Solid tumor perfusion

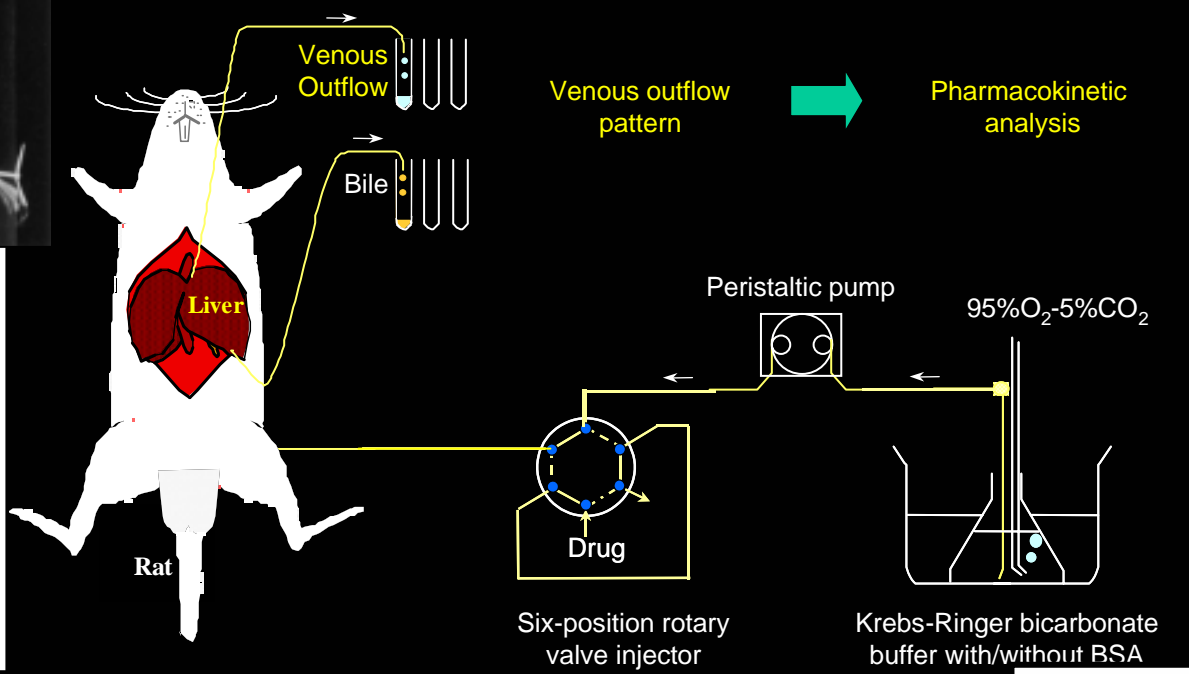
Cancer Res., **50**, 1640 (1990)

Moment analysis for local drug disposition

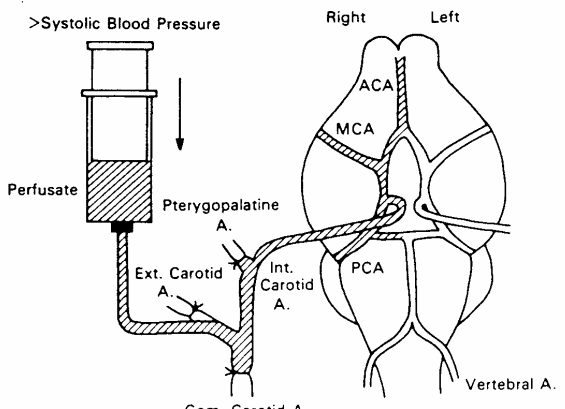
(I) Distribution	(III) Dispersion
Steady-state distribution volume: $V_i = Q_i \cdot \bar{t}_i / F_i$	Dispersion ratio: $d_i = \sqrt{\sigma_i^2 / \bar{t}_i}$
Tissue distribution ratio: $k_i = (\bar{t}_i / F) / \bar{t}_{VRS} - 1$	(IV) Clearance
Corrected mean transit time: $\bar{t}_{cor,i} = \bar{t}_i / F_i$	Intrinsic clearance: $CL_{int,i} = V_i / \bar{t}_{el,i}$
	Organ clearance: $CL_{org,i} = Q_i \cdot E_i$
(II) Elimination	
Recovery ratio: $F_i \cdot auc_i = auc_i / auc_{VRS}$	
Elimination rate constant: $k_{el,i} = 1 / \bar{t}_{el,i}$	

Rat liver perfusion experiment

Pharm. Res., **8**, 437 (1991)



J. Pharmacokin Biopharm.
13, 609 (1985)

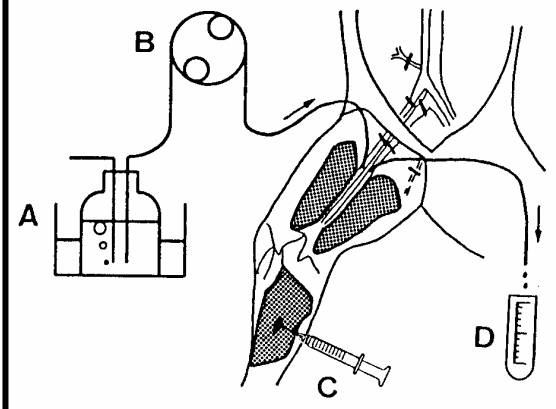


Brain perfusion

Pharm. Res., **8**, 683 (1991)

Rabbit muscle perfusion

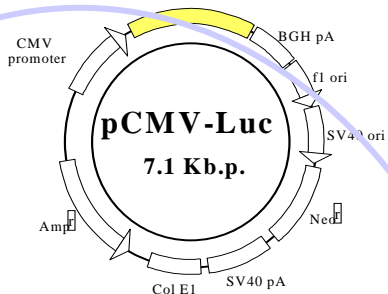
Pharm. Res., **9**, 161 (1992)



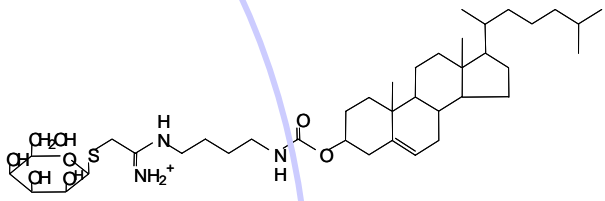
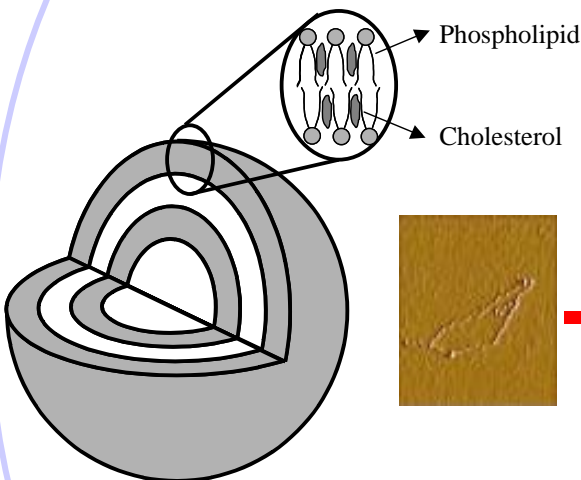
Lipoplex


Cell-specific Targeting Device (Recognition Miety)

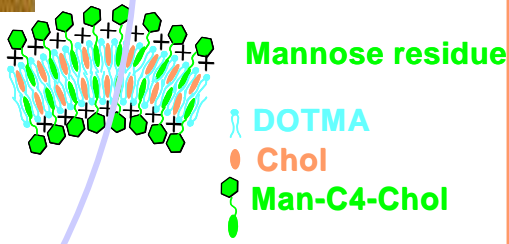
Plasmid DNA




 Fucose



 Mannose



 Galactose

Oligonucleotide

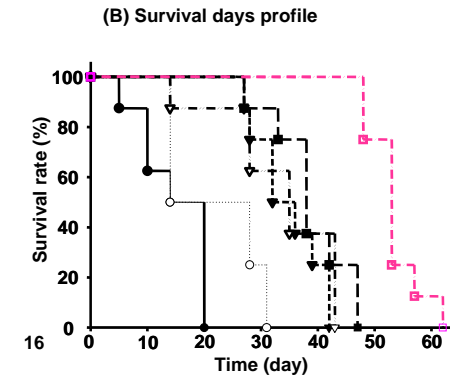
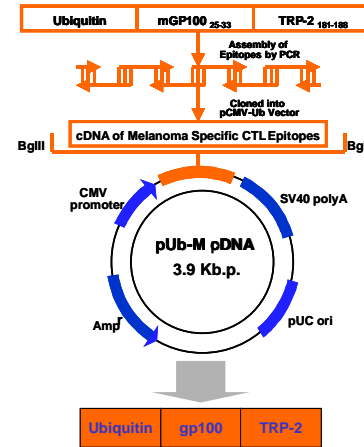
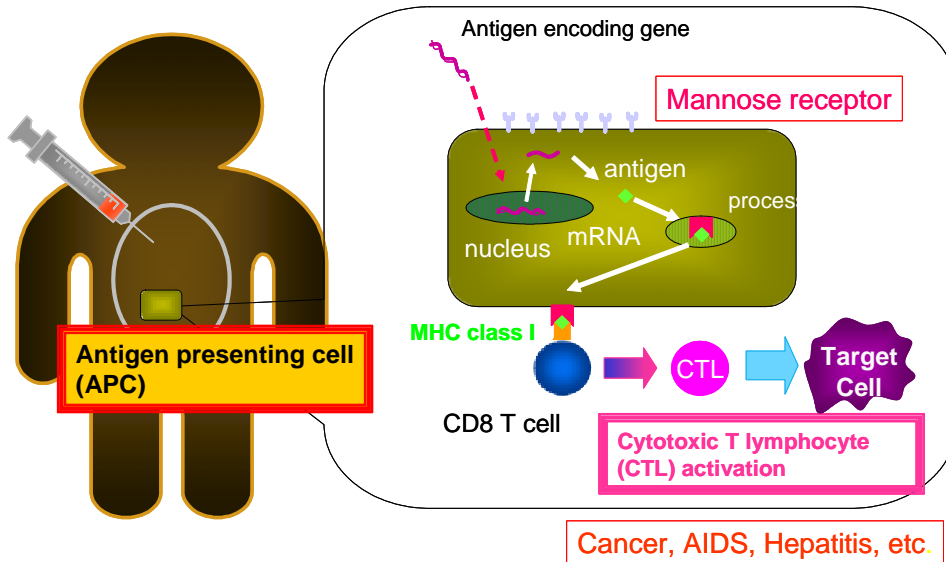


Ubc13-siRNA

5'-GUACGUUUC AUGACCAAAA-dTdT-3'
3'-dTdT-CAUGC AAAGUACUGGUUUU-5'

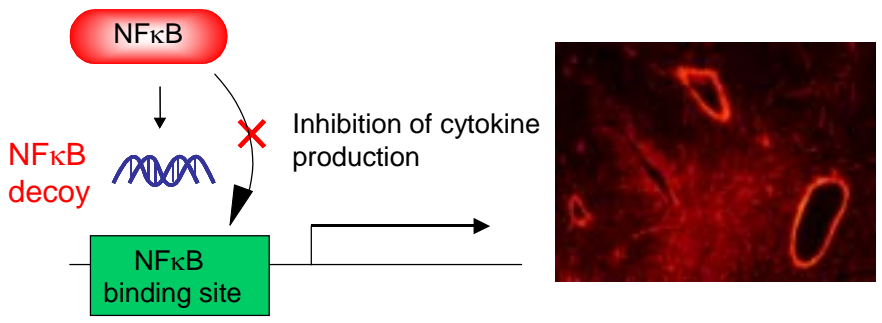


Plasmid DNA encoding target protein / Man-liposome / Antigen presenting cell / DNA vaccine



Ubiquitin fusion gp100·TRP-2 peptide
 Hattori et al. J. Control. Release 108(2-3):484-495(2005)
 Hattori et al. J. Pharmacol. Exp. Ther. 318(2):828-834(2006)
 Hattori et al. J. Gene Med. 8(7):824-834(2006)

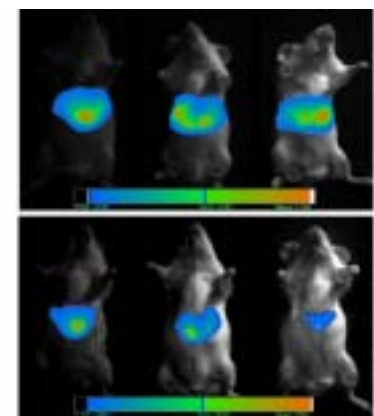
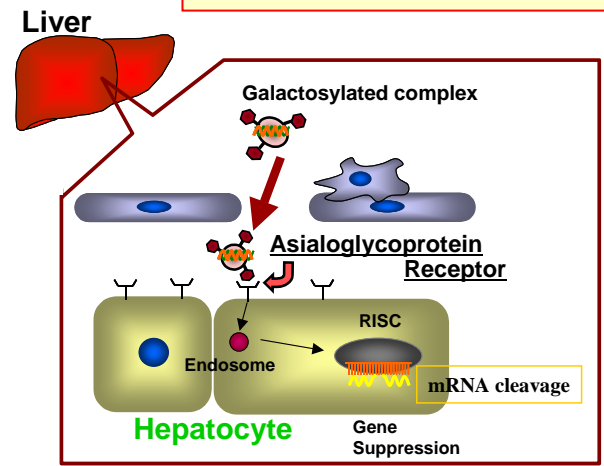
NFκB decoy / Fuc-liposome / Kupffer cell / Inflammation



5'-AGTTGAGGGGACTTTCCCAGGC-3'
 3'-TCAACTCCCTGAAAGGGTCCG-5'
 Molecular weight 13471

Kawakami et al. Biochim Biophys Acta 1524:258-265 (2000)
 Y. Higuchi et al. Biomaterials, 28: 532-539 (2007)

siRNA / Gal-liposome / Hepatocyte



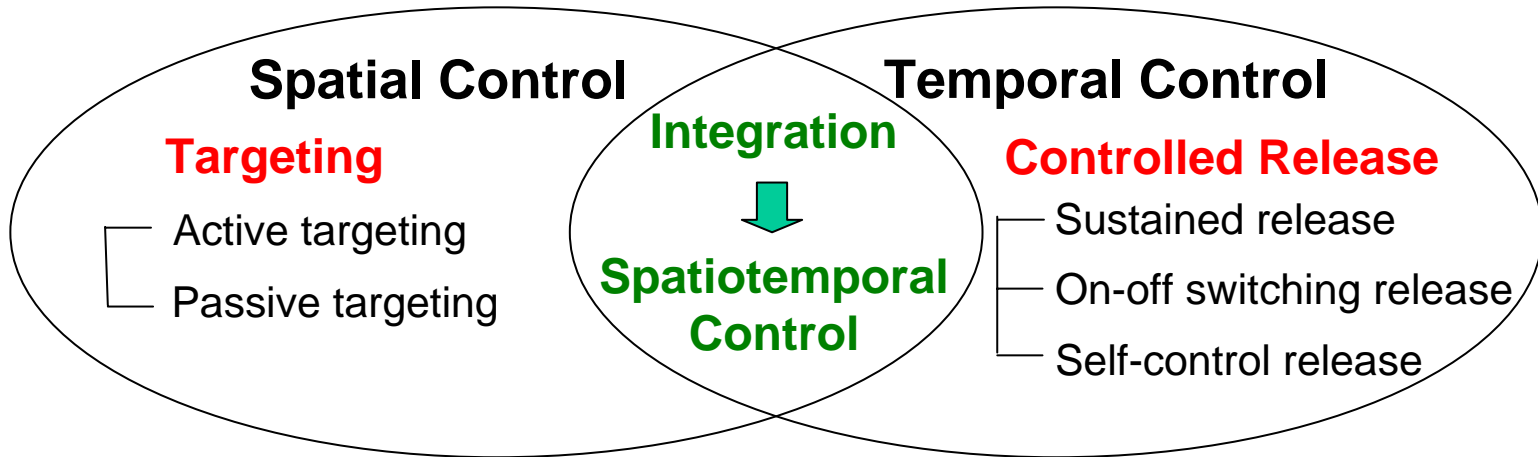
Ubc13-siRNA
 5'-GUACGUUUCAUGACCAAAA-dTdT-3
 3'-dTdT-CAUGCAAAGUACUGGUUUU-5'

A. Sato et al Biomaterials, 28: 1434-1442(2007)

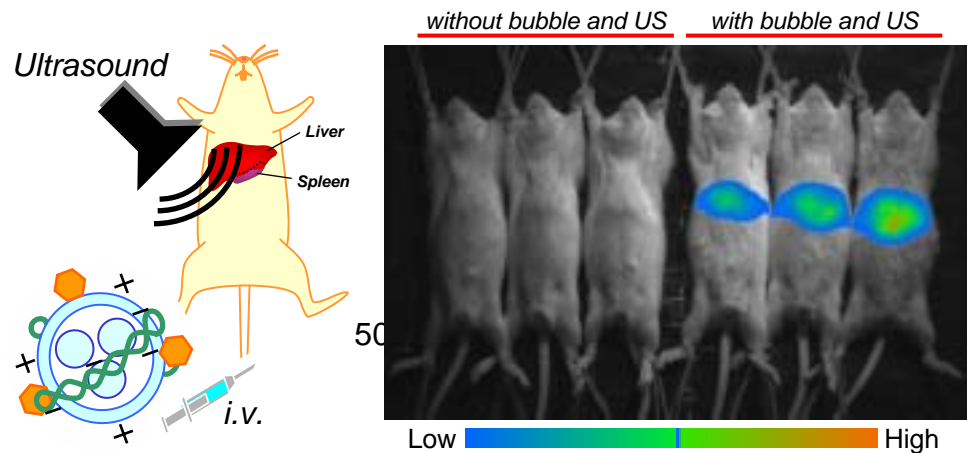
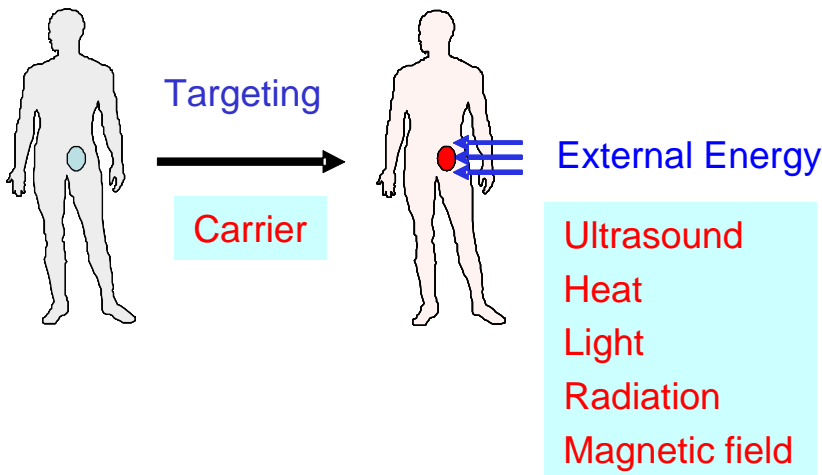
Liposome / Monoclonal antibody → Conventional formulation / therapy



New Concept of Drug Delivery System



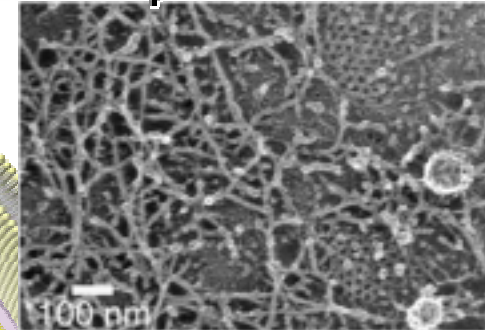
Project for R&D on Next-generation DDS Therapy Systems for Deep Therapy (NE D O)



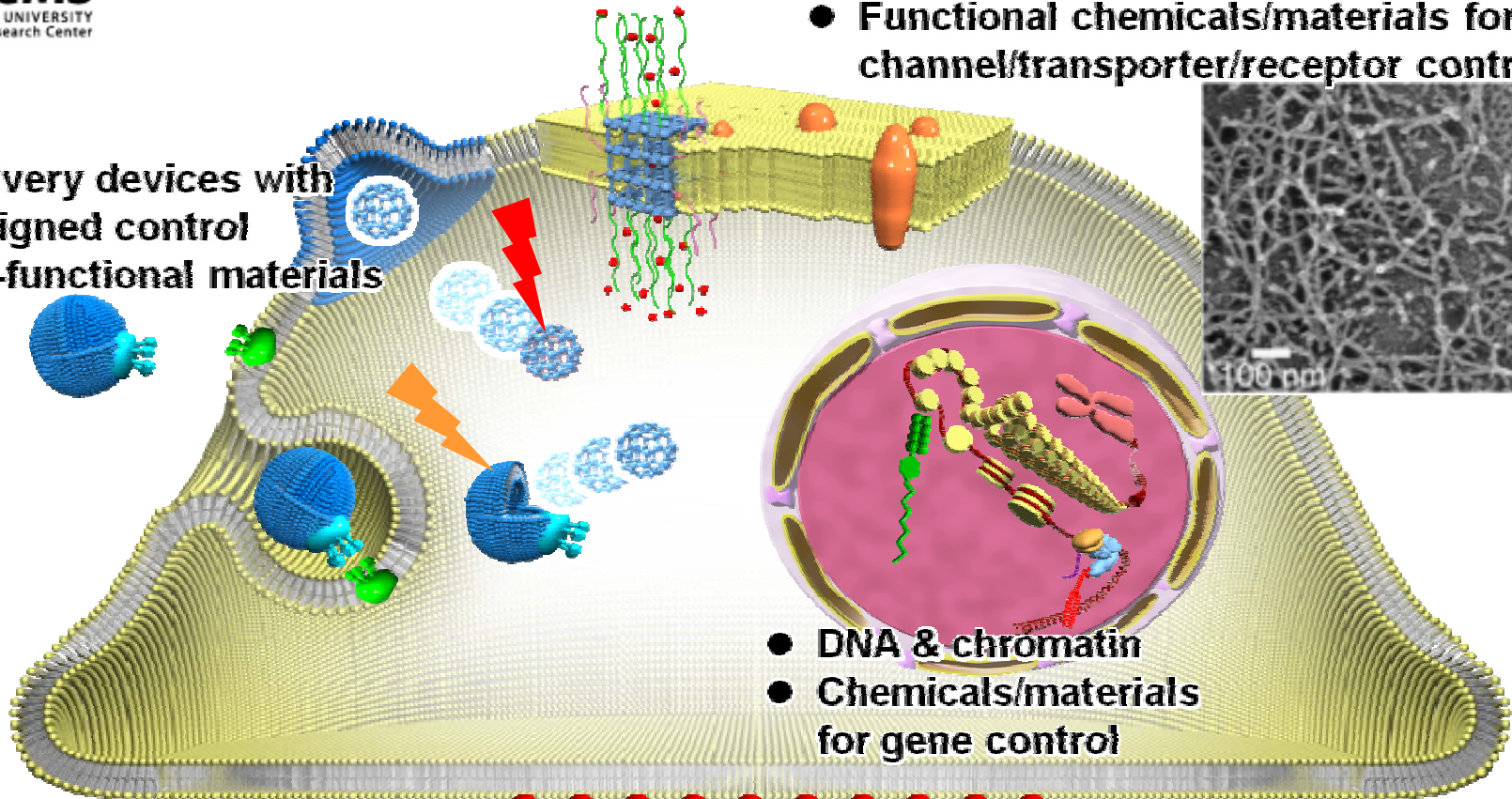
Meso-control of cellular functions by fusion of cell-material sciences



- Cell membrane meso-complex
- Functional chemicals/materials for channel/transporter/receptor control



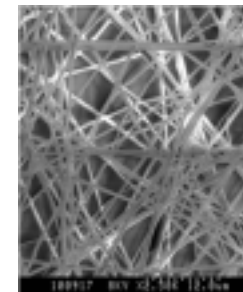
- Delivery devices with designed control
- Bio-functional materials



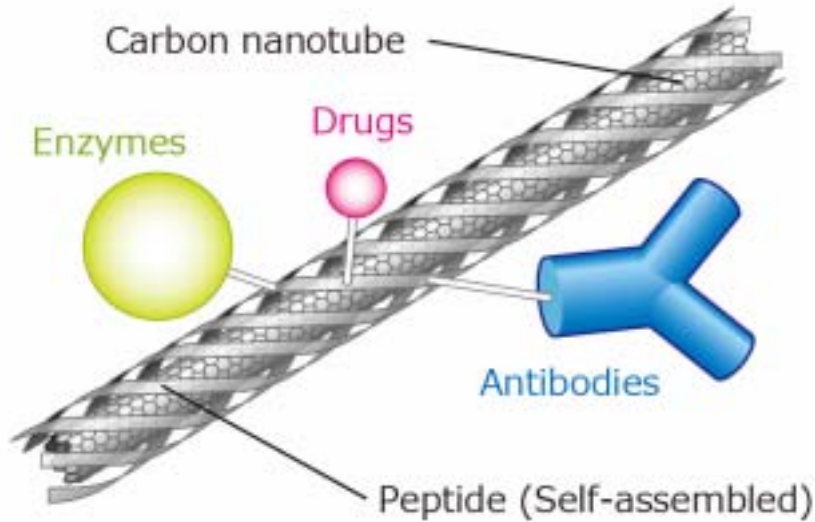
- DNA & chromatin
- Chemicals/materials for gene control



- Nano/meso/micro-engineered materials for cell environments
- Doping with bio-functional chemicals

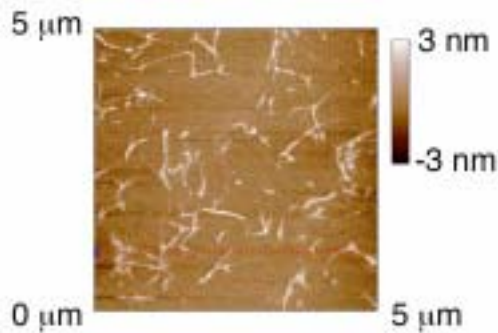


Dispersion and Biomedical Application of Carbon Nano-tube with Peptide

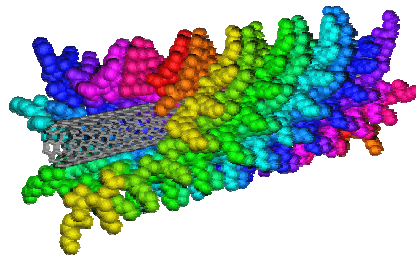


- Design of peptides
- Chemical synthesis
- Bio-production
- Purification
- Dispersion of CNT
- Characterization of CNT/peptides
- Biomedical application

AFM analysis



Computer Modeling



Photoluminescence analysis

Charge control

CNT/**Anionic peptide**

Precipitates in acidic pH

CNT/**Cationic peptide**

Precipitates in alkaline pH



← pH5.0 pH7.5 pH11 →

Cellular uptake

Gene expression (GFP)

Acknowledgements

I would like to thank all of my supervisors, seniors and friends in science, collaborators, and staffs and students of my laboratories for their encouragements and continuous support.

The Late Prof.
Hitoshi Sezaki
The Late Prof.
Takeru Higuchi

Prof. Nobuhiko Tanigawa
Prof. Koichi Tanaka
Prof. Toshio Takahashi

Prof. Shozo Muranishi
Prof. Toshikiro Kimura

Prof. Akira Yamamoto
Prof. Yoshinobu Takakura
Dr. Fumiyoshi Yamashita
Dr. Makiya Nishikawa
Dr. Shigeru Kawakami
Dr. Yuriko Higuchi



Present Member of Our Laboratory (April, 2010)