Polymeric Micelles from Bench to Bedside

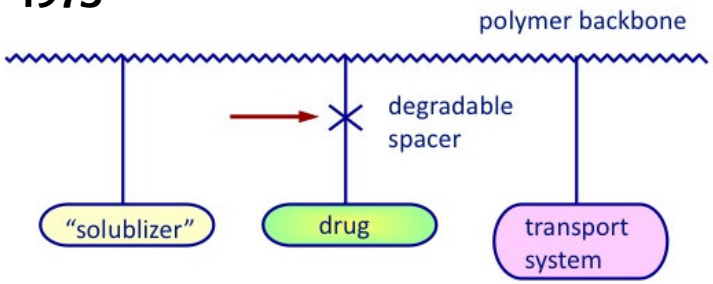
Alexander (Sasha) Kabanov

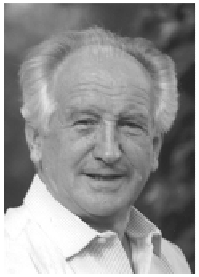
University of Nebraska Medical Center

CDDN Center for Drug Delivery and Nanomedicine

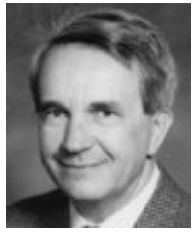
Polymeric Micelles as Drug Carriers

1975





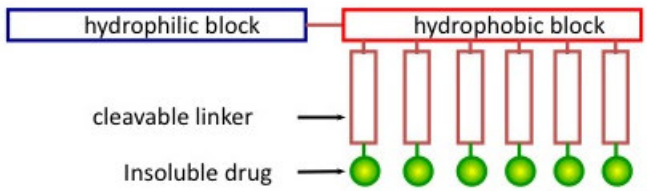
H. Ringsdorf

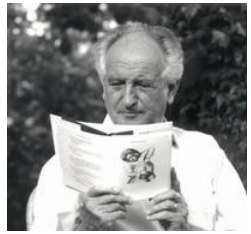


J. Kopecek

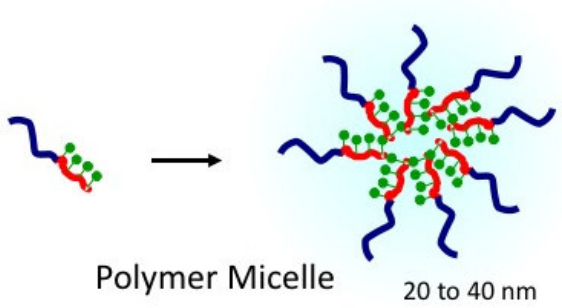
R. Duncan

1984



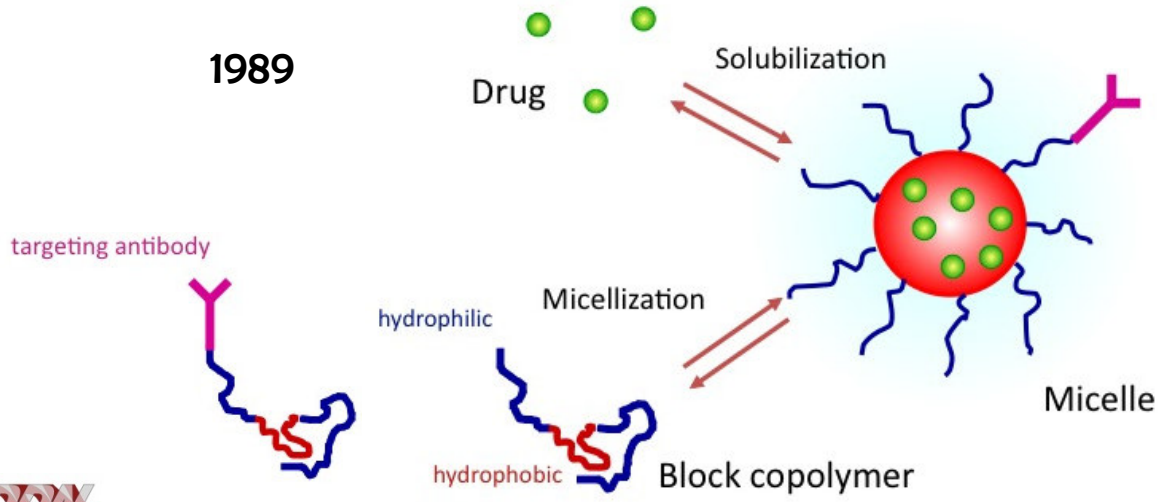


K. Kataoka



M. Yokoyama, et al. (1990) *Cancer Res*., 50: 1693

1989



Small size ca. 10-50 nm
Narrow size distribution ~ 0.1

A. Kabanov et. al *FEBS Lett.* 1989, 258:343

University of Nebraska Medical Center

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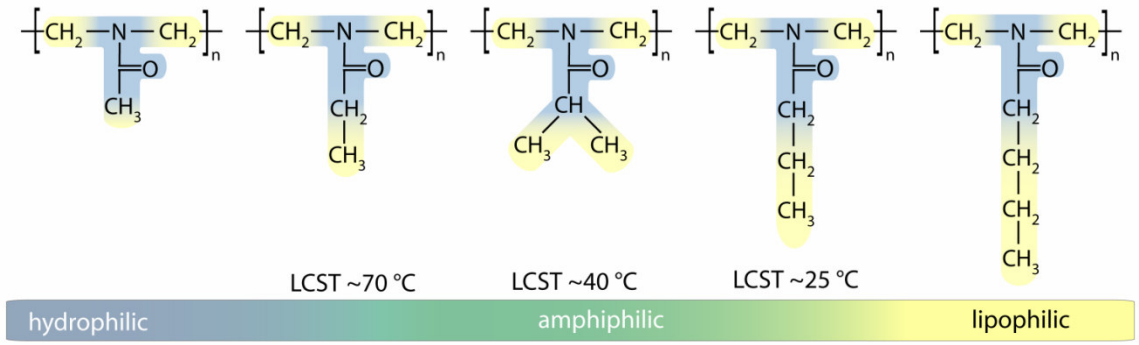
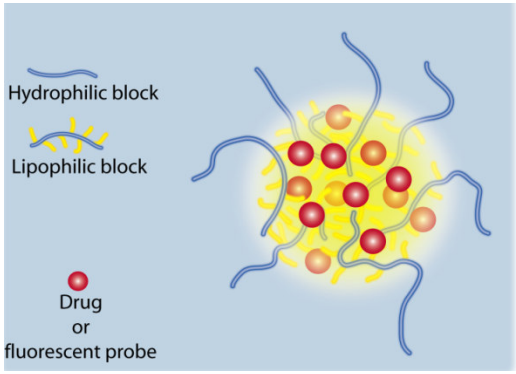
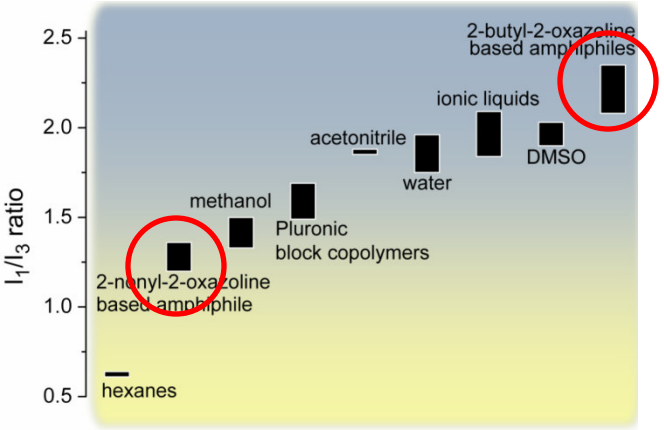
Doubly-Amphiphilic Block Copolymers based on PolyOxazolines

In collaboration with R. Luxenhofer and R. Jordan. Germany

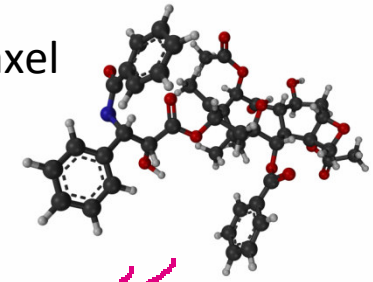




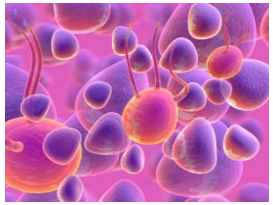
Very "polar" "hydrophobic" core



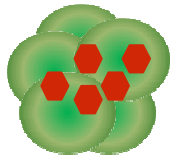
Paclitaxel



Very High Soulbilization Loading



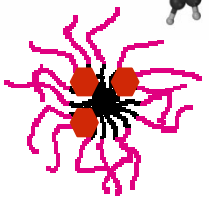
Taxol®



1%
1:100

Abraxane®

10%
1:10

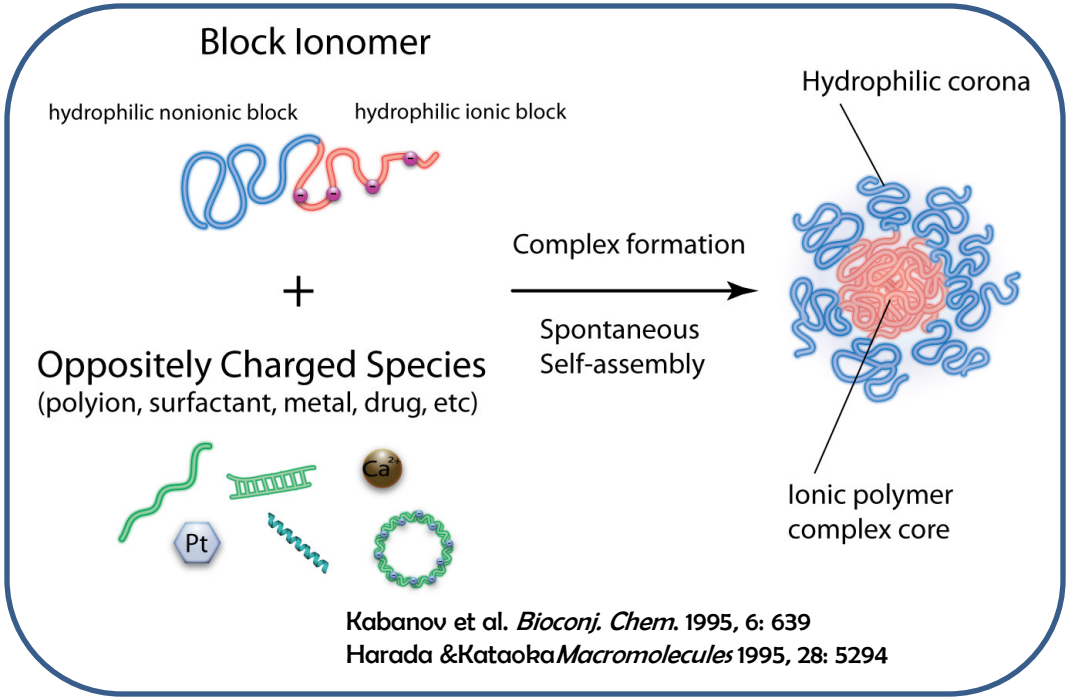


45%
1:1

POx micelles

Luxenhofer et al. *Biomaterials* 2010, 31, 4972

Block Ionomer Complexes

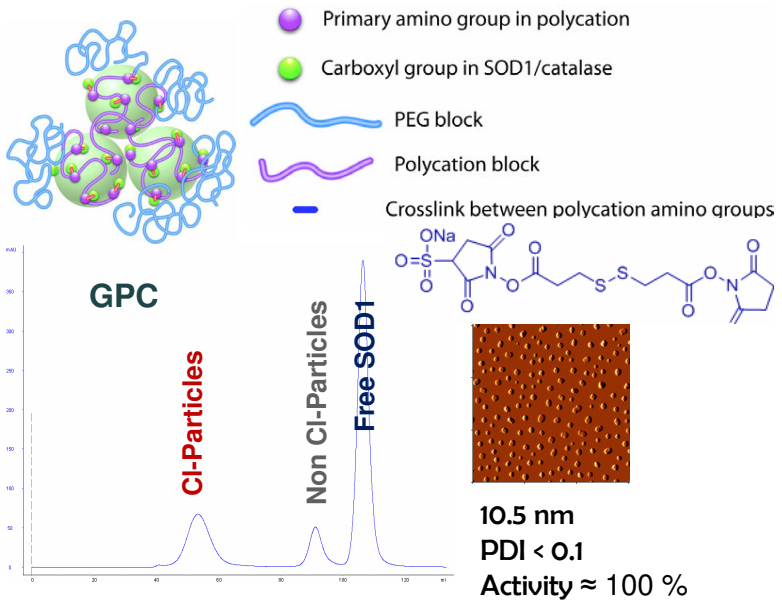


Kabanov et al. *Bioconj. Chem.* 1995, 6: 639
Harada &Kataoka*Macromolecules* 1995, 28: 5294

"nanoZYMES"

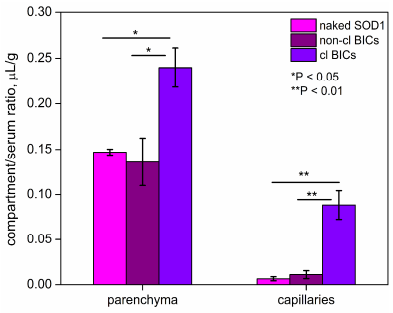

N. Klyachko


D. Manickam



10.5 nm
PDI < 0.1
Activity ≈ 100 %

CNS Delivery of SOD1 nanoZYME& Activity in MCAO Model of Stroke



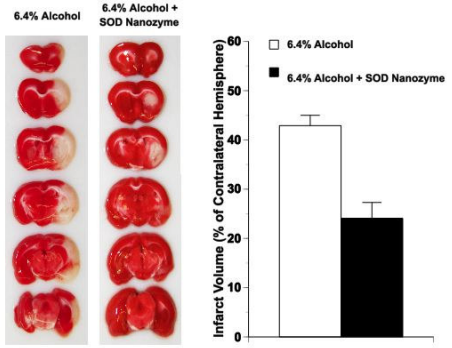
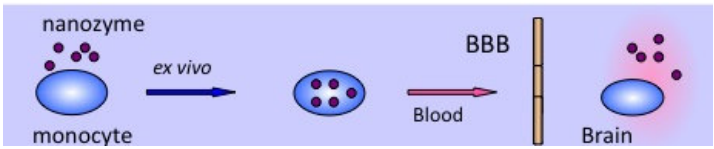
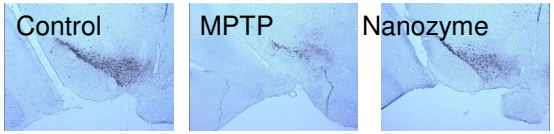


Figure 13. Effect of SOD-nanozyme on total infarct size of 6.4% alcohol-fed rats (n=2) subjected to a 2-hour right MCAO/24-hour reperfusion. Values are means ± SE.

Cell-Mediated Delivery of CatalaseNanozyme and Neuroprotection in MPTP Modelof PD

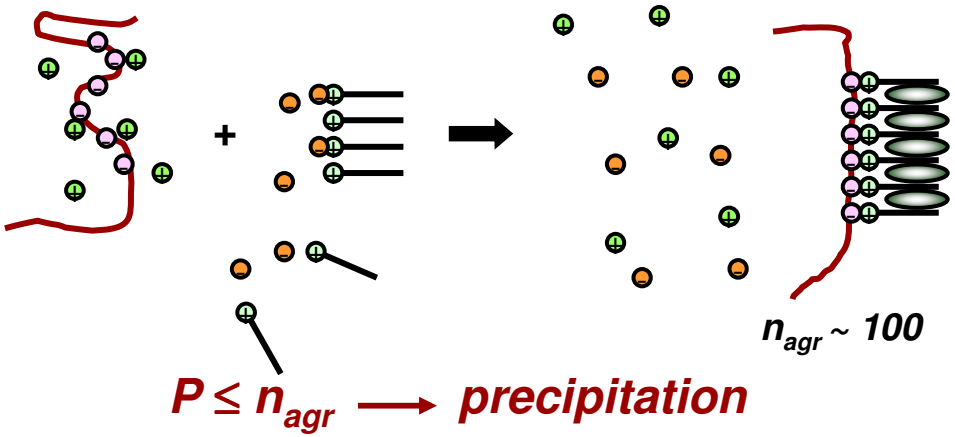

E. Batrakova



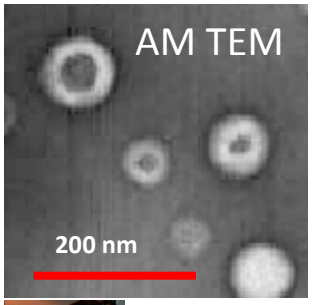


A. Brynskikhet al. *Nanomedicine (Lond.)* 2010, 53:379

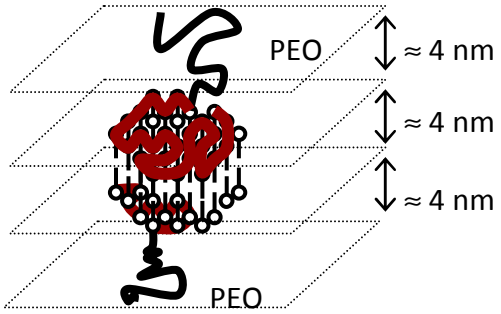
Surfactant-Based Block Ionomer Complexes



PEO-*b*-PMA/C_{16}PyBr

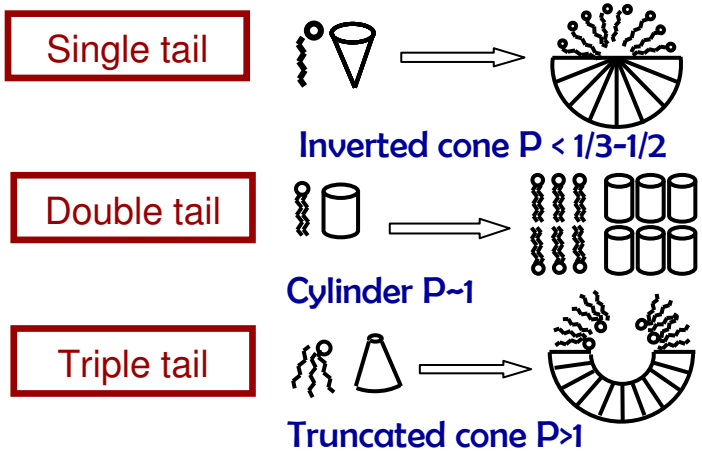


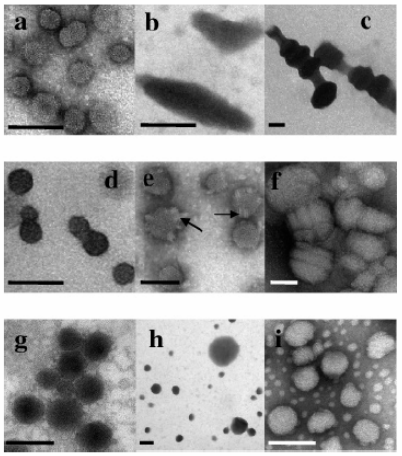
Hypothetical structure



Wall thickness 12.5 + 0.03 (TEM)

Kabanov et al. *J. Am.Chem. Soc.* 1998, 120: 9941
Bronich et al. *J. Am. Chem. Soc.* 2002, 124: 11872





Control of

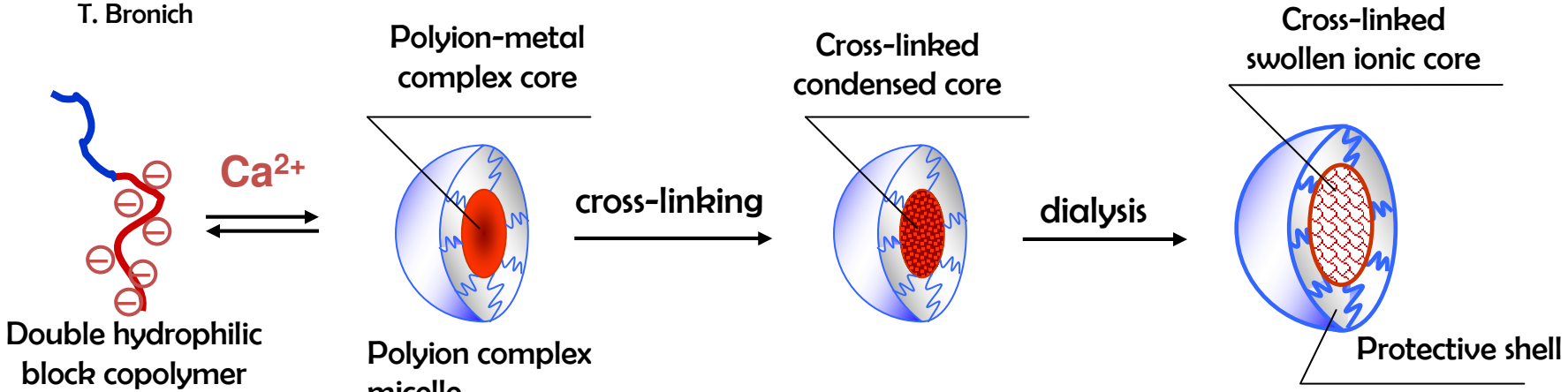
- size
- morphology
- charge
- core polarity
- solubilization
- pH-stability

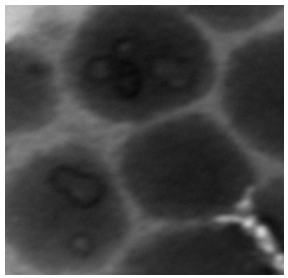
Solomatinet al. *Langmuir* 2007, 23: 2838

University of Nebraska Medical Center
COOK Center for Drug Delivery and Nanomedicine

T. Bronich

Polymer Micelles with Cross-Linked Ionic Core (cl-Micelles) = NanoGELS





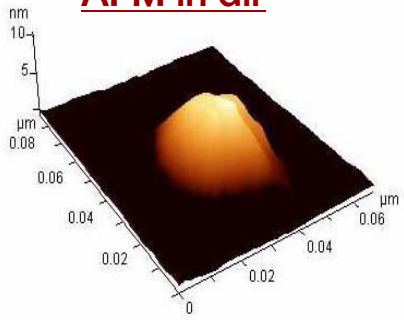
Shell thickness

TEM
7.82 + 0.24 nm (N=69)

Model of extended polymer brush

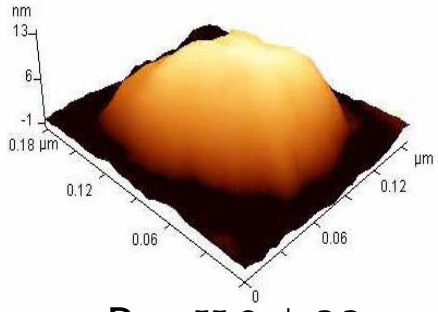
L ≅ 6.2 nm

AFM in air



D_d = 19.64 ± 0.67 nm

AFM in solution



D_{sw} = 55.0 ± 3.3 nm

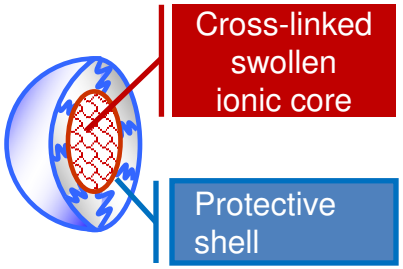
Equilibrium swelling ratio 14.5

Bronich et. al. *J. Am. Chem. Soc.* 2005, 127(23): 8236

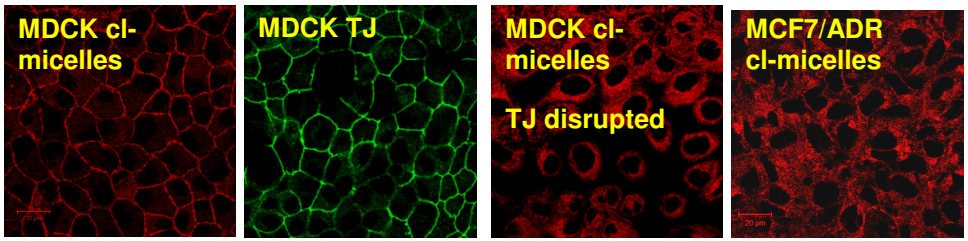
G. Sahay

J.-O. Kim

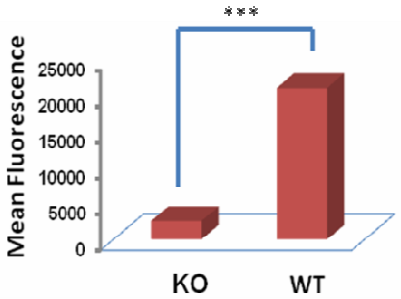
Differential Trafficking of cl-Micelles in Normal and Cancer Epithelial Cells

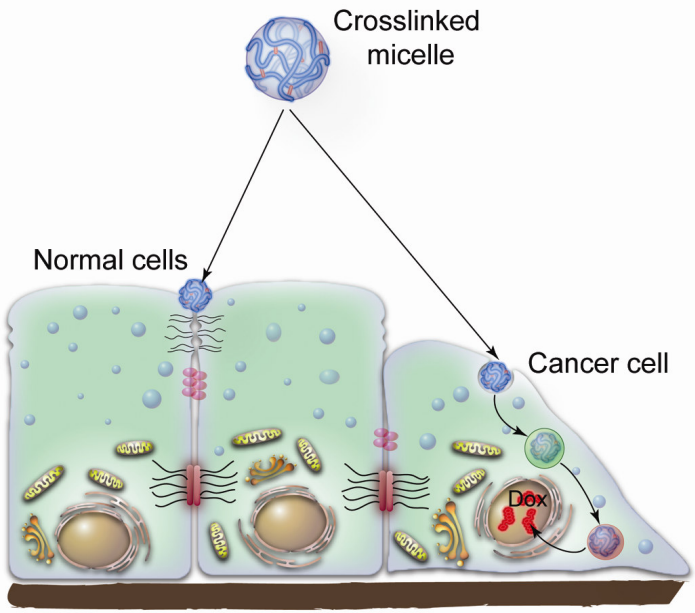


TJ and cell uptake

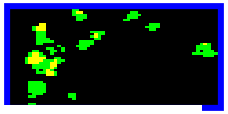


Initial entry via caveolae



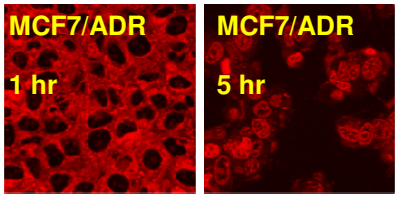


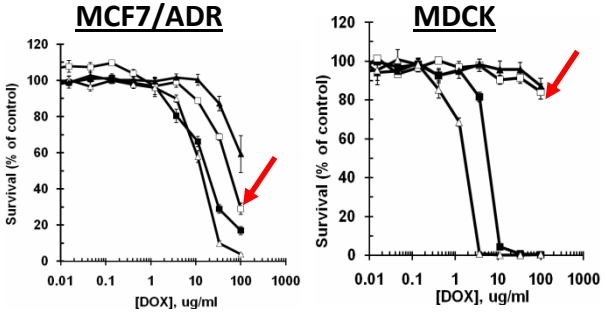
Final destination lysosomes



lysotracker, 30 min

pH-sensitive cl-micelles/Dox





G. Sahay, et al. Biomaterials, 2009, 31:923-33

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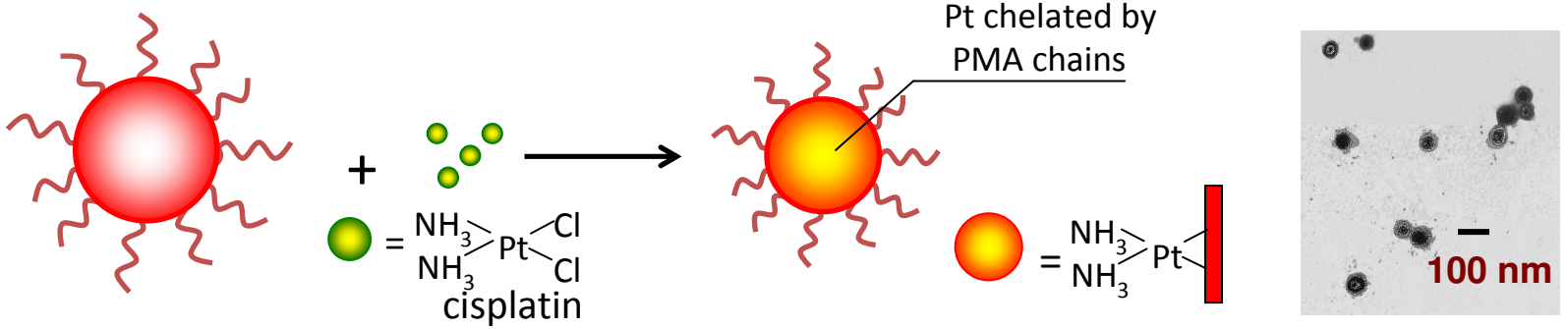
Cisplatin Loaded cl-Micelles as "Nanodrug"


T. Bronich

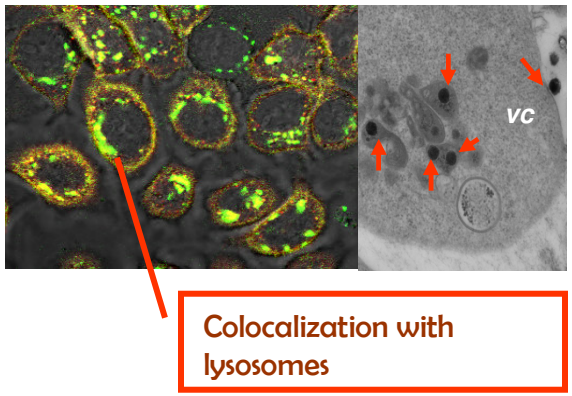

H. Oberoi


J.-O. Kim

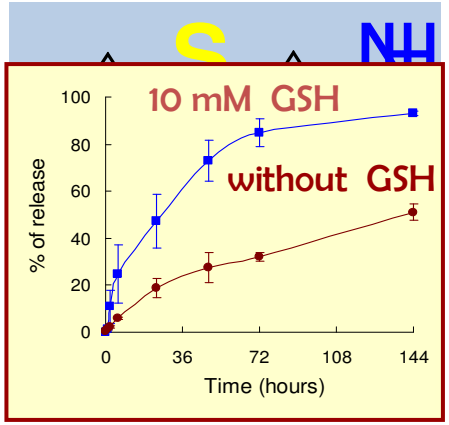


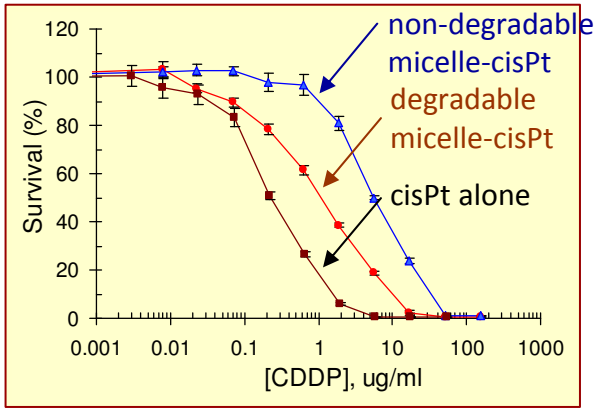
Bronich et. al. *J. Am. Chem. Soc.* 2005, 127(23): 8236

Cellular uptake of micelles



Cytotoxicity in human ovarian adenocarcinoma cells A2780





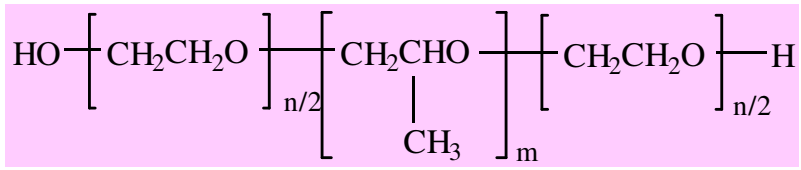
T. Bronich, J-O. Kim and H. Oberoi, 2009

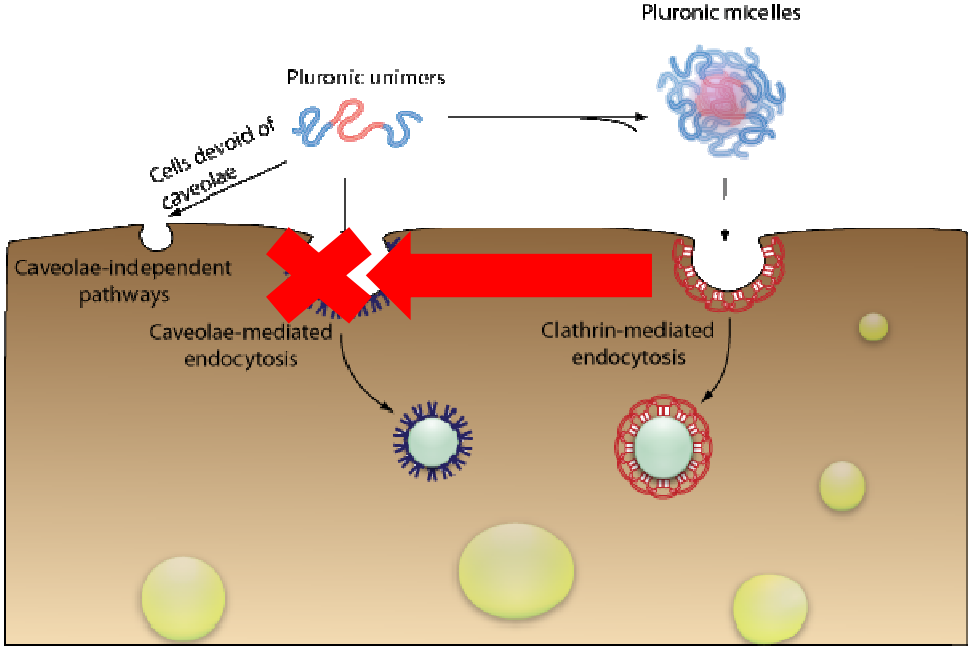
Nebraska Medical Center | UNMC Center for Drug Delivery and Nanomedicine

G. Sahay

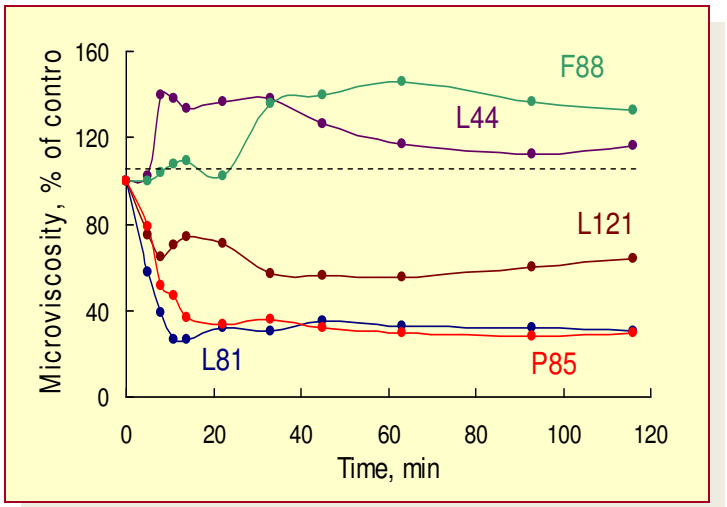
Membrane Interactions of Pluronic Block Copolymers

Pluronic block copolymers

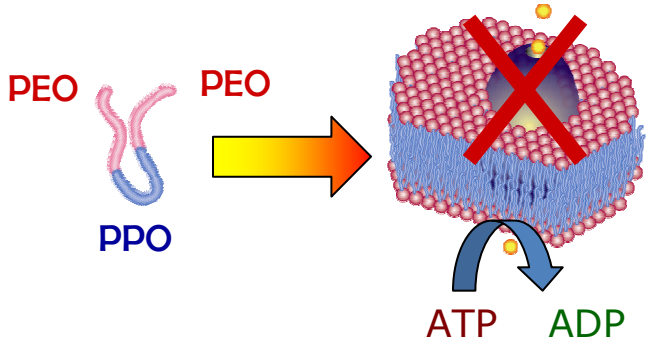




Sahay et al. *Bioconjug. Chemistry*, **2008,** 19(10):1987-94



Plasma Membrane: P-glycoprotein (Pgp)



Batrakova et al. *JPET*, **2001,** 299, 483

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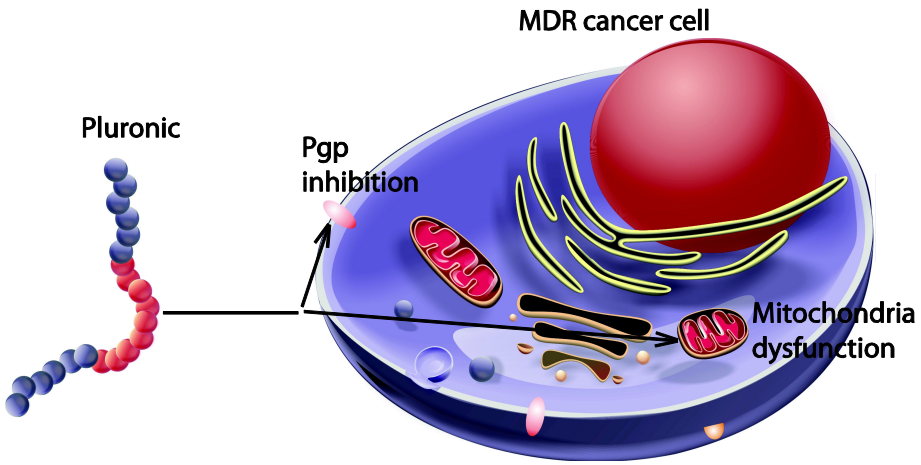
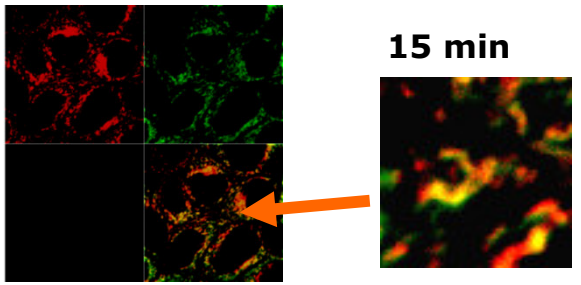
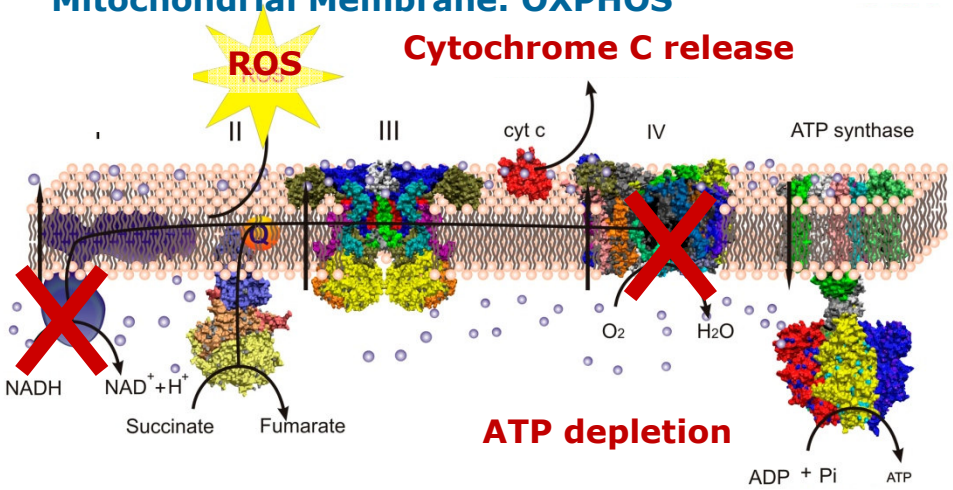
Pluronic-induced sensitization of MDR cells



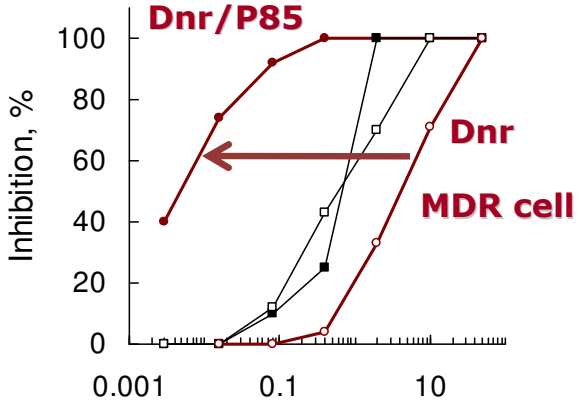
Pluronic P85 (red) Co-localization with Mitochondria (green)



Mitochondrial Membrane: OXPHOS



Pluronic/Drug cytotoxicity



Alakhova et al, *J. Contr, Release*2010, online

Alakhov et al, *Bioconjug. Chem.* 1995, 7:209-216

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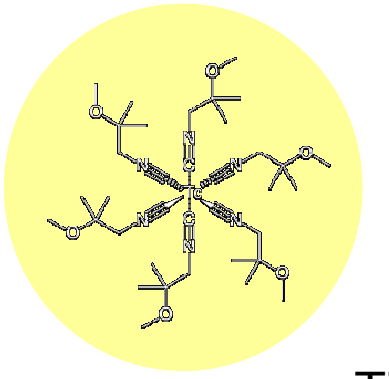
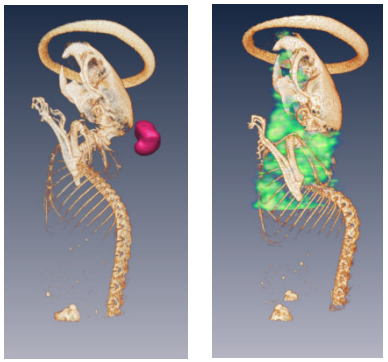
Pgp inhibition and ATP depletion *in vivo*

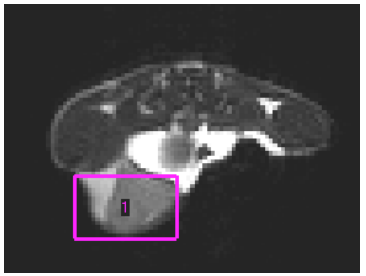
Sestamibi ^{99m}Tc CT scan





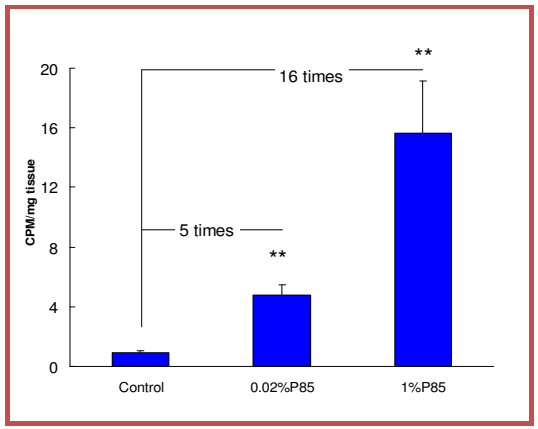
Localized ^{31}P Spectroscopy ISIS Image guided volume Selective In-vivo Spectroscopy

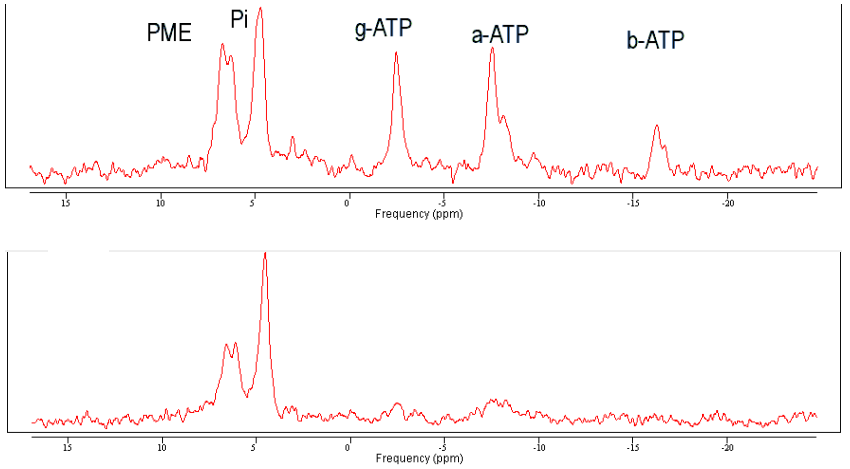
P388/ADR solid tumors



C57BL/6J mice s.c. Lewis lung carcinoma 3LL-27M

Tissue sampling





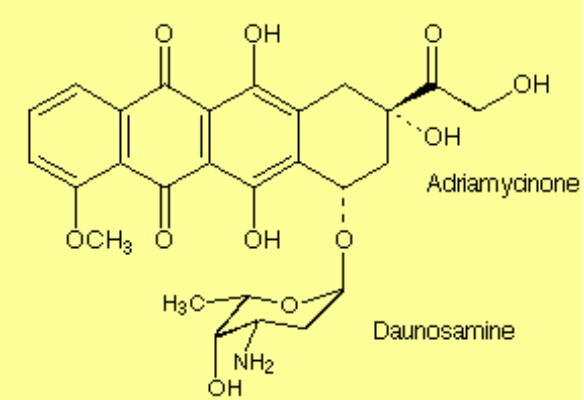
Batrakova et al, *J. Contr, Release*2010, online

Nebraska Medical Center

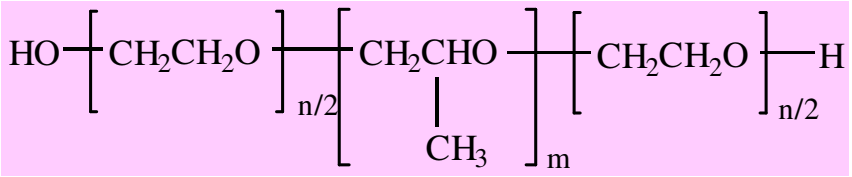
Center for Drug Delivery and Nanomedicine

SP1049C:
Pluronic Polymer Micelle Doxorubicin

Doxorubicin



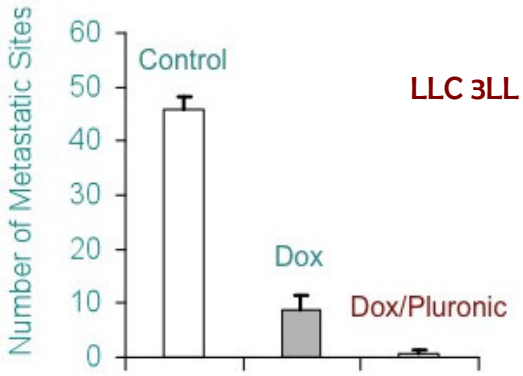
2 Pluronic block copolymers



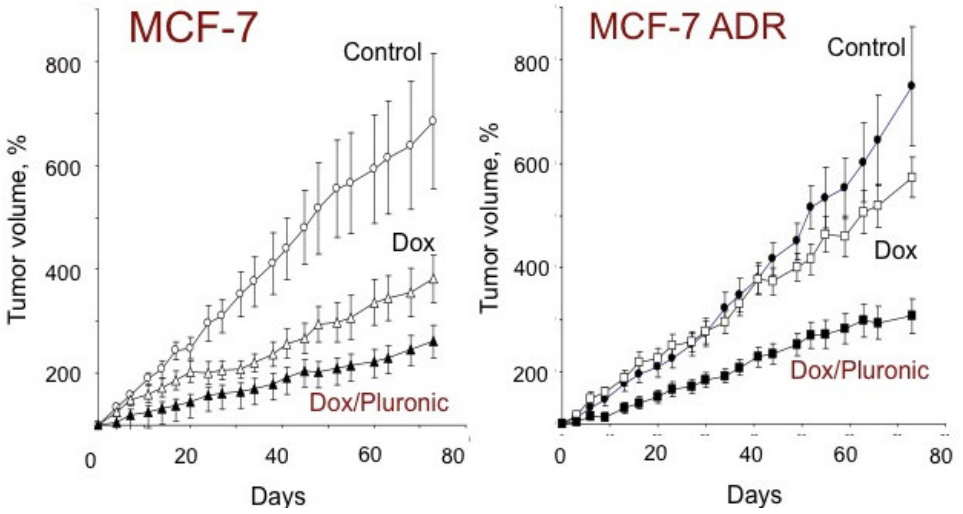
L-61 – 90% of POP, 10% of POE, Mm ~2,000Kd

F127 – 30% of POP, 70% of POE, Mm ~12,000Kd

Lung Metastasis



Tumor Volume



Alakhov et al, *Coll. Surf. B: Biointerfaces*1999, 16:113-134

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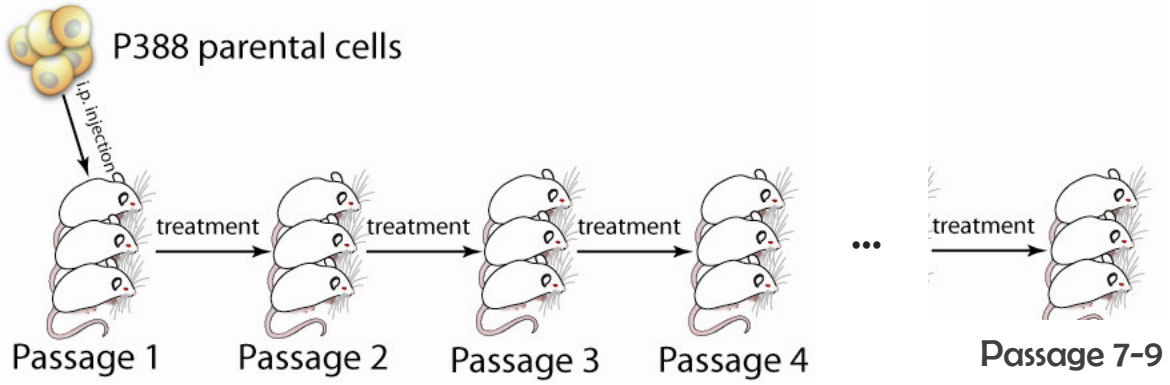
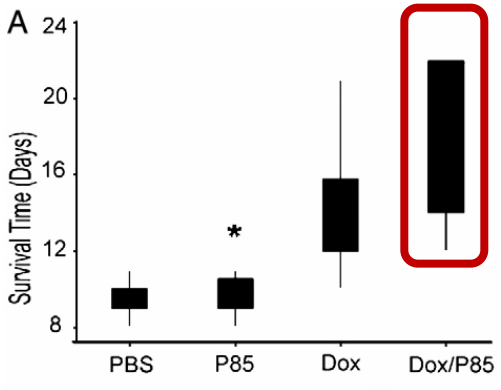
SUPRATEK PHARMA INC. The Biotransport™ Technology Company

Prevention of Development of MDR in Leukemia Cells In Vivo

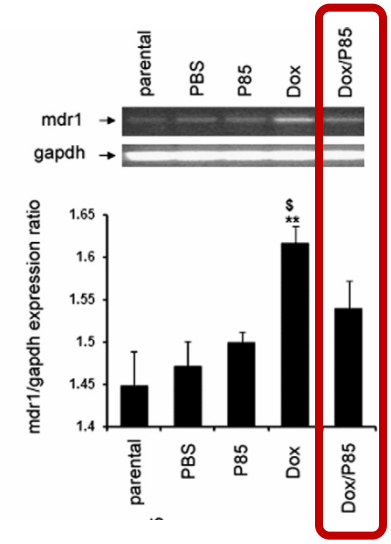


4 months
Cytotoxicity, RT-PCR mdr1, Western Blot, Rh123 uptake

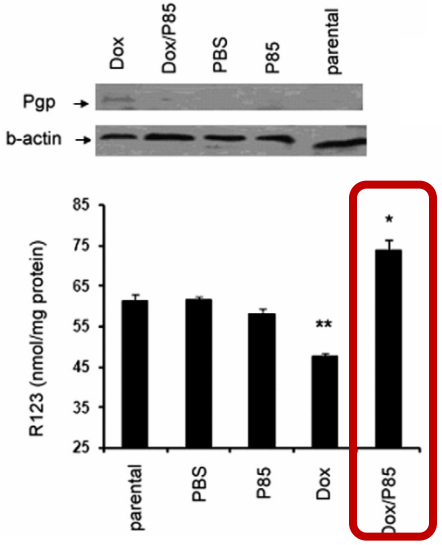
Lifespan



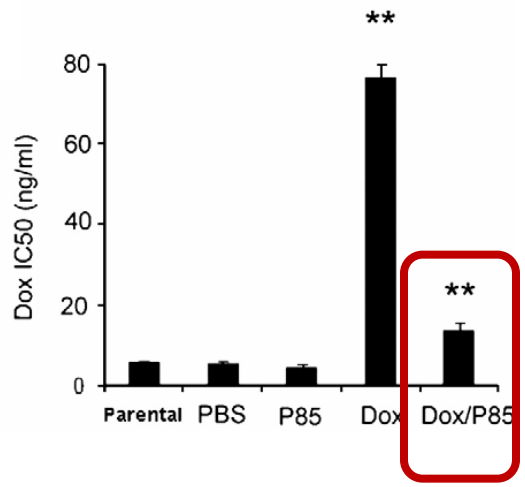
Mdr1 mRNA



Functional Pgp protein



Drug resistance (IC50)



Sharma et al. *J. Control. Release*, **2008,** 131(3):220-7

SP1049C Clinical Trial Phase I

Phase I results:

- 26 advanced stage IV cancer patients
- MTD = 70 mg/m²
- DLT = neutropeniaat 90 mg/m²
- Plasma PK - linear, dose-proportional, terminal elimination phase - circa 50 hours
- Toxicity profile similar to doxorubicin
- Activity observed in highly resistant cancer:
  - oesophageal cancer

Danson et al. *Br. J. Cancer,* 2004 90: 2085

SP1049C Clinical Trial Phase II

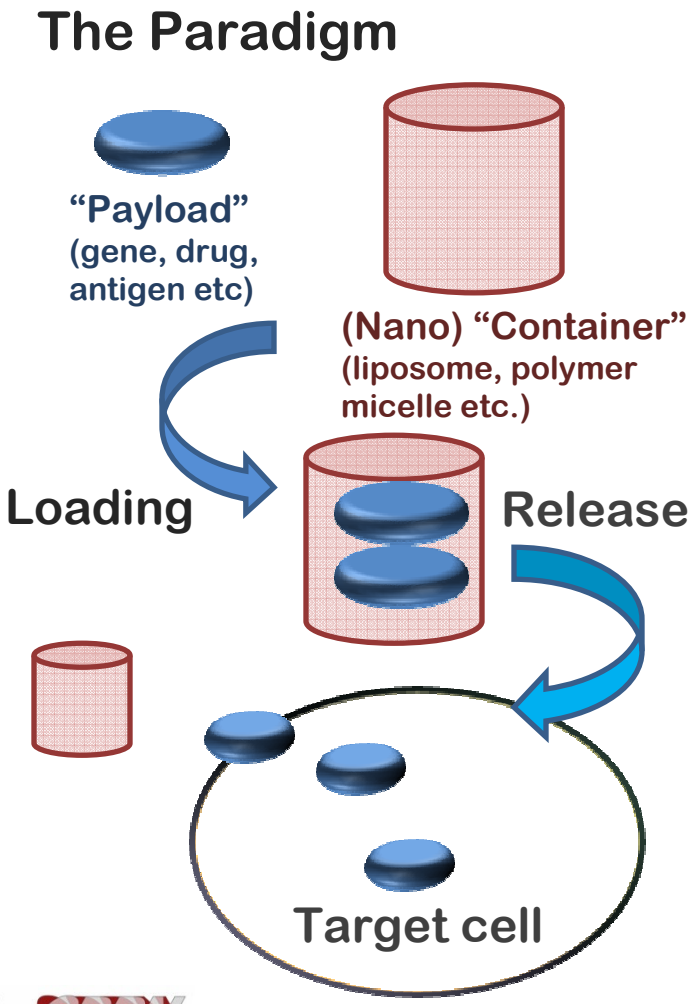
SP1049C-202-UK - open-label, phase II window

- First line therapy, adenocarcinoma of the esophagus
- 21 patients (19 evaluable)
- 75 mg/m^2 of SP1049C i.v. every 3 weeks up to 6 cycles
- SP1049C appears active in monotherapy (RR 47%)
- Median survival 9.96 months
- Toxicity profile: predominantly haematological and cardiac
- Further investigation :
  - Combination with platinum and 5FU as 1st line therapy
  - Esophagus/upper GI, vs. best supportive care after 1st line therapy

Phase III trial FDA SPA, agreed

Valle et. al. **Invest New Drugs. 2010 Feb 24.**

Drug/Gene Delivery Paradigm vs. Polymer Genomics



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Advanced Drug Delivery Reviews 58 (2006) 1597–1621
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Polymer genomics: An insight into pharmacology and toxicology of nanomedicines☆

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When physically mixed or chemically linked to biological agents such as cytotoxic drugs, DNA, antigens and the like synthetic polymers and nanomaterials can alter genomically controlled responses of cells to these agents resulting in alteration of biological response.

UNMC Nanomedicine Group

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